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Publication date
2016
Document Version
Final published version

Link to publication

Citation for published version (APA):
Tutein Nolthenius, C. (2016). *CT colonography for polyp surveillance & MRI features in Crohn's disease*. [Thesis, fully internal, Universiteit van Amsterdam].

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CT COLONOGRAPHY FOR POLYP SURVEILLANCE & MRI FEATURES IN CROHN'S DISEASE

CHARLOTTE TUTEIN NOLTHENIUS

CT colonography for polyp surveillance
&
MRI features in Crohn's disease

Charlotte Tutein Nolthenius

This thesis was prepared at the Department of Radiology, Academic Medical Center, University of Amsterdam, the Netherlands.

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The research described in chapters 2, 3, 4 and 5 was financially supported by The Dutch Cancer Society (KWF Kanker Bestrijding 2012-5698).
The research described in chapter 4 was funded by Netherlands Organisation for Health Research and Development, Centre for Translational Molecular Medicine, and the Nuts Ohra Foundation.

Printing of this thesis was financially supported by the Department of Radiology, Academic Medical Center, Amsterdam, the Netherlands; ABN Amro; Chipsoft; Crohn en Colitis Ulcerosa Fonds Nederland; AbbVie Immunology and Stichting Medisch Wetenschappelijk Onderzoek SLZ.

Printed by: Ipskamp Printing
Cover desing: Jornt van Dijk, Persoonlijkproefschrift.nl
Lay out: Jornt van Dijk, Persoonlijkproefschrift.nl
ISBN: 978-94-028-0310-5

CT colonography for polyp surveillance
&
MRI features in Crohn's disease

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties
ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op donderdag 10 november 2016, te 14:00 uur

door
Charlotte Jacoline Tutein Nolthenius
geboren te Curaçao

Promotiecommissie

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Chapter 1

General introduction & Outline of this thesis

General introduction

Part I - Surveillance CT colonography for 6-9 mm polyps in colorectal cancer screening

Colorectal cancer

Colorectal cancer is the third most common cancer diagnosed worldwide. In the Netherlands in 2014, 14,803 patients were newly diagnosed with colorectal cancer, and 4,906 patients died from the consequences of this disease (1). The large majority of colorectal cancers are adenocarcinomas, and most are thought to develop gradually from normal epithelium through adenomas into carcinomas: the adenoma-carcinoma pathway (2).

It takes many years for a carcinoma to develop from the adenoma precursor lesion, and early detection and removal of adenomas can prevent colorectal cancer (3). However, not all adenomas will eventually develop into carcinomas; in fact, only approximately 5% of all colorectal adenomas will progress to cancer (4). Adenomas with villous histology and high-grade dysplasia have a higher chance of developing into a carcinoma. In addition, there is a direct correlation between the size of an adenoma and the chance of being and/or becoming a carcinoma. Therefore, advanced adenomas (defined as adenomas ≥10 mm in size and/or villous histology ≥25% and/or high-grade dysplasia) have been considered as a subgroup of adenomas most likely to progress to carcinoma.

The last two decades an alternative precursor lesion, the serrated polyp, has gained attention. It is thought that 15-30% of colorectal cancers arise from these serrated polyps through the serrated neoplasia pathway (5-7). Serrated polyps can be subdivided into hyperplastic polyps (HPs), sessile serrated adenomas/polyps (SSPs) without dysplasia, SSPs with dysplasia and traditional serrated adenomas (TSAs) (8). This subdivision is of interest, because not all serrated subtypes have the same malignant potential. Individuals with large (≥10mm) and/or dysplastic SSPs (or high-risk SSPs) are thought to have a high risk to develop into colorectal carcinoma, and their management should be comparable to patients with high-risk adenomas (9). Screening tests should therefore be designed to not only detect adenomatous precursor lesions, but also these high-risk SSPs.

Colorectal cancer screening

In multiple European countries and in the United States of America a screening program for colorectal cancer has been implemented (10). However, there is no worldwide consensus regarding the preferred screening test. Basically, screening tests for colorectal cancer can be divided into two main groups. First, stool tests which are easy to perform and non-invasive,

but are primarily designed to detect (early) carcinoma. Second, structural examinations that visualize the entire colon, like colonoscopy or computed tomography (CT) colonography, and have the ability to not only detect invasive cancers, but also precursor lesions (adenomas and advanced adenomas). Therefore larger impact on mortality and incidence of colorectal cancer can be expected for structural examinations, but also at the cost of a higher burden caused by these structural examinations.

CT colonography in colorectal cancer screening

CT colonography is a dedicated CT examination. Carbon dioxide (CO_2) is insufflated into the rectum through a flexible, thin catheter for colonic distension. The patient is scanned in supine and prone position, allowing all segments to be optimally distended on at least one position. CT colonography has comparable sensitivity for colorectal cancer and precursor lesions of ≥10 mm to colonoscopy, and is less invasive (11). However, after a positive CT colonography, a subsequent colonoscopy is still required. During colonoscopy, early cancers and polyps can be removed and cancers, that are not endoscopically resectable, can be biopsied to confirm the diagnosis.

In the current guidelines, the role of CT colonography in colorectal cancer screening is limited to those patients in which colonoscopy was incomplete, patients at high-risk for endoscopic adverse events or patients with an explicit preference for CT colonography (12, 13). Before CT colonography could be considered as a primary screening test, there are still several aspects that require our attention.

When using CT colonography as a screening test, a selection of those patients that are supposed to be at highest risk for colorectal cancer is made and those persons are advised to undergo colonoscopy. Therefore, it is important to define the optimal colonoscopy referral strategy. Target for colorectal cancer screening are colorectal carcinomas, advanced adenomas and, as we discussed previously, high-risk SSPs. Because we cannot determine the histology of a polyp at CT colonography, the referral strategy is solely based on polyp size, as the size of a polyp directly correlates with advanced histology (Table 1) (14). Diminutive polyps (<6 mm) have a low likelihood of harboring advanced histology and can therefore be ignored and left in place (15). Large polyps (≥10 mm) are most likely relevant lesions and should be removed. Debate remains about the management of 6-9 mm polyps.

Table 1. Risk of carcinoma related to polyps' size

Size	Risk of adenoma	Risk of advanced histology	Risk of carcinoma
≤5 mm	30-50%	2%	<0.01%
6-9 mm	50-70%	7%	<1%
10-15 mm	80%	19%	1-2%

Lieberman D et al. Gastroenterology 2008 (16), O'brien MJ et al. Gastroenterology 1990 (14)

Surveillance CT colonography for small polyps

To date, US and European screening guidelines advise to refer all patients with ≥6 mm polyps detected at CT colonography for colonoscopy and polypectomy (12, 13). This policy is however mainly based on expert opinion until further evidence comes available. As an alternative to colonoscopy referral, surveillance CT colonography has been proposed for 6-9 mm polyps (17). But there is great need for determining the strength of this surveillance strategy in terms of safety, patient acceptability and subsequent (surveillance) policy after surveillance CT colonography. Little experience is at hand for leaving small polyps in situ, as gastroenterologists are used to remove all polyps at colonoscopy. Defining the optimal threshold size for endoscopy referral and polyp removal is essential for a (cost-)effective CT colonography screening strategy.

Growth of small polyps

Recent research in CT colonography has shown that growth can be predictive of the histology of a polyp, by demonstrating that almost all advanced adenomas were among the progressing polyps (18). For small polyps, the change in size between surveillance intervals is often subtle, and therefore it could be of special value to assess growth by volumetric 3D measurements, which has been shown to be more reliable than linear measurements (19, 20).

CT colonography can be read using primary 2D or primary 3D view (Figure 1 A and B). In daily practice, mostly the primary 2D view is used (reading in 2D with 3D problem solving), because this method is faster and because of unfamiliarity of the readers with the 3D images. However, 3D offers several advantages over 2D: the sensitivity for detection of 6-9 mm polyps is higher, linear polyp measurements in 3D approximate best those at colonoscopy and there is the possibility to perform volumetric measurements (Figure 1 C) (21, 22).

Assessing volumetric growth in small colonic polyps could help us understand their natural evolution, and might give us further direction in the discussion about their management. Furthermore, as the large majority of small polyps will not develop into a carcinoma, it is

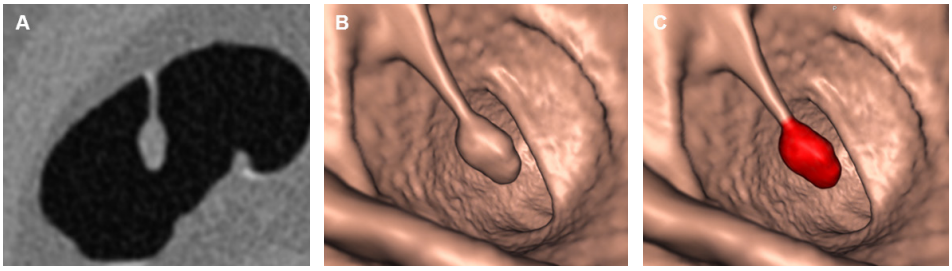

Figure 1. Advanced adenoma with tubulovillous histology. Pedunculated polyp in the descending colon on 2D view (13.7 cm) (A), 3D view (B) and 3D view with volume assessment (559 mm^3) (C).

important to assess whether there are polyp features at CT colonography that might be predictive of invasive growth.

Extra-colonic findings and patient acceptability

Although CT colonography is optimized for evaluating the colon, the entire abdomen is imaged and it is possible to encounter extra-colonic findings. This can be considered an advantage, as, for example, extra-colonic malignancies can be detected in an early stage with more favorable prognosis (23, 24). However, this also leads to additional medical examinations and costs. It is unclear if this issue is mainly an issue that primarily exists in a first round of screening with CT colonography, or whether subsequent rounds will also reveal many new extra-colonic findings.

Last but not least, the success of a screening program largely depends on patients' preference, acceptance and the willingness to return for future screening rounds. This should be taken into account when deciding on a proper screening strategy, including the role of CT colonography surveillance.

COCOS trial

In 2009/2010, a population-based randomized controlled colorectal cancer screening trial was performed, the COCOS trial (25). Individuals aged 50-75 were randomized to receive an invitation for colonoscopy or CT colonography, and participation and yield were assessed as primary endpoints. A higher participation rate in CT colonography and a higher yield in colonoscopy resulted in a similar yield for advanced neoplasia per invitee. However, in the CT colonography arm of this trial only those patients with polyp ≥10 mm at CT were referred for colonoscopy. Patients with only 6-9 mm polyps received an advice to have a surveillance CT colonography. It is only after including the yield of this surveillance population, that we can determine the actual yield of screening with CT colonography. Furthermore, the yield at

surveillance CT colonography and the following colonoscopy could give further direction to the discussion about the management of 6-9 mm polyps.

Part II - MR imaging of terminal ileum and rectum in Crohn's disease

Crohn's disease

Crohn's disease is an idiopathic, chronic inflammatory disease that can affect any part of the gastrointestinal tract from the mouth to the anus. The disease is characterized by a chronic course of relapsing inflammation and remission. The highest frequencies of Crohn's disease are found in the more industrialized parts of the world, with an incidence of 6.2 per 100,000 person-years in the Netherlands (26).

The disease is characterized by erosions, ulcerations, transmural bowel wall inflammation and the formation of non-caseating granulomas, the latter being pathognomonic for Crohn's disease. In up to 80% of patients with Crohn's disease, the small bowel is affected, mostly the terminal ileum. Bowel involvement is often segmental, with diseased segments alternating the healthy segments ('skip lesions').

At first, the disease is limited to the mucosa with neutrophilic cryptitis and lymphoid hyperplasia, lymphedema and superficial aphthoid formation. With progression of the disease, the entire bowel wall becomes involved, with ulcers extending deep into the bowel wall, predisposing to sinuses, fistulas and perienteric abscesses. In the more chronic phase, inflammation leads to fatty infiltration of the bowel wall and of fibrofatty proliferation in the adjacent (mesenteric) fat ('creeping fat'). Chronic fibrotic changes can result in strictures and bowel obstruction.

MR enterography in Crohn's disease

Both these mucosal and transmural changes can very well be visualized with MR enterography. MR enterography provides a cross-sectional view of the entire small bowel and colon with high soft-tissue contrast, without the risks of ionizing radiation. Luminal distension is mandatory for sufficient diagnostic accuracy and in enterography obtained by oral preparation. Orally administered enteric contrast is preferred over injection through a naso-jejunal tube (MR enteroclysis), because it has a lower patient burden, no fluoroscopy is needed and the in-room MRI time is shorter.

The pathophysiological changes in the bowel wall are visualized by alterations in MRI characteristics. For example, active inflammation in the bowel wall is accompanied by edema and hypervascularity, which results in a high mural signal intensity on (fat saturated) T2-weighted images and increased enhancement on post-contrast T1-weighted images, respectively. Wall thickening and length of affected segments can precisely be measured on MR enterography. More recently, the relevance of more advanced features like diffusion-weighted imaging (DWI) and its quantitative parameter apparent diffusion coefficient (ADC), and relative contrast enhancement (RCE) in small bowel Crohn's disease came to light (27-29).

With use of these MR features, multiple activity scoring systems (CDMI, London score, MaRIA, Clermont score) have been developed helping us to diagnose and quantify the degree of inflammation, each with its own advantages and disadvantages (29-31). Ideally, an activity score should be objective, easy to use, reproducible, quantifiable and non-invasive. Because each scoring system is constructed with different MR features and is developed on different reference standards (ileocolonoscopy, histopathology, clinical scores), they are difficult to compare and currently it is unknown which test is superior.

Perianal Crohn's disease

One manifestation of Crohn's disease is that of perianal disease, which includes perianal skin tags, fissures, ulcers, fistulas, abscesses and strictures. About one-third of patients will have symptoms or complications from perianal region involvement and the cumulative frequency of perianal fistulas has been reported to range from 14% to 38% (32).

Perianal fistulas in Crohn's disease may arise from penetration of fissures or ulcers in the anal canal or rectum. The most widely used classification is the Parks Classification which distinguishes four main categories of fistulas, based on their relationship to the anal sphincter (intersphincteric, transsphincteric, suprasphincteric and extrasphincteric) (33). For treatment purposes, the fistulas can also be classified as either 'simple' or 'complex', dependent on their location (superficial or deep), complexity and its relation to the external anal sphincter. In addition, active rectal Crohn's disease (proctitis) will make a fistula more complicated to manage.

MRI of the perianal region has proven its value in diagnosing perianal fistulas, with accuracies reported up to 93% in classifying fistulas and 96% in delineating abscesses (34, 35). Preoperative perianal MRI has shown its additional value by reducing recurrence rates after fistula surgery, through precisely depicting the anatomy and complexity of the fistula tract (34,

36). The concomitant presence of proctitis may complicate fistula treatment with decreased chances on healing. Therefore in case of proctitis, a more aggressive medical therapy should be started, and surgery should be avoided (37-39). Before start of treatment, many patients with perianal fistulas will undergo a perianal MRI, so diagnosing the presence of proctitis at these MRI examinations could be of additional value. Furthermore, perianal MRI might be used as a non-invasive way for monitoring treatment response. However, we do not know if the aforementioned MR features in luminal Crohn's disease will also be applicable in perianal MRI, as this MRI is limited by a different scan protocol (small FOV and less sequences) and the absence of luminal contrast for distension.

Outline of this thesis

This thesis focuses on two different topics.
Part I of this thesis focuses on surveillance CT colonography as an alternative to colonoscopy referral in patients with only 6-9 mm polyps detected at primary screening CT colonography. **Chapter 2** presents a prospective study in which patients that underwent primary CT colonography screening and had 6-9 mm polyps, underwent surveillance CT colonography after 1.5-3 years, followed by colonoscopy. Participation and yield of surveillance CT colonography were determined, as well as the overall yield of primary CT colonography screening by including the yield at surveillance to the original screening yield.

To learn more about the natural behavior of 6-9 mm polyps, in **chapter 3**, we performed per-polyp analyses in largely the same surveillance population. We established volumetric change in size in all 6-9 mm polyps and correlated this to the findings at histopathology.

About one-fifth of the colorectal cancers are thought to arise from sessile serrated polyps (SSPs). In **chapter 4** we retrospectively determined the detection rate for SSPs in our primary CT colonography screening trial, including the surveillance population. We compared this detection rate to the colonoscopy arm of the initial screening trial.

In order to determine if a procedure is suitable as a screening modality, another important factor is patient acceptance. We determined burden, pain, anxiety and stress for surveillance CT colonography in **chapter 5**. In addition, we compared burden, pain and anxiety of surveillance CT colonography with the results of the initial screening CT colonography.

Part II of this thesis focuses on the various MRI features useful in establishing disease activity in Crohn's disease in the terminal ileum and in the rectum.

Multiple activity scoring systems have been developed for diagnosing and grading Crohn's disease. In **chapter 6** we compared these scoring systems and their incorporated individual features in MR enterography of the terminal ileum with histopathology and ileocolonoscopy as standardized reference standard.

Management of patients with perianal fistulas depends on the concomitant presence of proctitis. However, the relevant MR features of proctitis at perianal MRI have not been identified yet. **Chapter 7** focuses on the identification of potential relevant MRI features in diagnosing proctitis on perianal MRI by determining reproducibility and correlation with the endoscopy.

Chapter 8 and 9 provides a summary, implications and conclusions of this thesis in English and Dutch.

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Part I

Surveillance CT colonography for 6-9 mm polyps in colorectal cancer screening

Chapter

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

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European Radiology 2016; 26(8):2762-2770

Abstract

Purpose

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

Materials and Methods

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

Results

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

Conclusion

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

Introduction

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

Recently, a population-based screening trial was performed in which the participation rate and yield of OC and CTC as primary CRC screening modalities were compared in 8,844 invitees after randomisation (COCOS trial) (8). It was shown that with higher participation in the CTC group, and higher yield in the OC group, CTC and OC have similar yields for advanced neoplasia per invitee. However, in that trial only CTC participants with lesions ≥10 mm were referred for OC. CTC participants with a largest lesion ranged between 6-9 mm were recommended a surveillance CTC. The yield of this surveillance population might give further direction to the discussion about the management of patients with small polyps. In addition, a provisional yield of CTC screening was reported (8). For a definite yield of screening with CTC, the yield of surveillance CTC should be included.

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

Materials and Methods

Study design

In a previous randomized controlled trial (RCT) participation and diagnostic yield of OC and CTC in an invitational population-based screening program of individuals aged 50-75 years

was compared (8). The overall design of the trial has been described in detail previously (10). In that population screening trial 2,920 out of 8,844 trial invitees individuals were invited for CTC (others for OC) of which 982 participated (Figure 1). All participants with only polyps measuring 6-9 mm (n=82) were advised to undergo a surveillance CTC after 1.5 or 3 years (with ≥3 or <3 polyps, respectively).

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

Participants

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

CTC

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

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

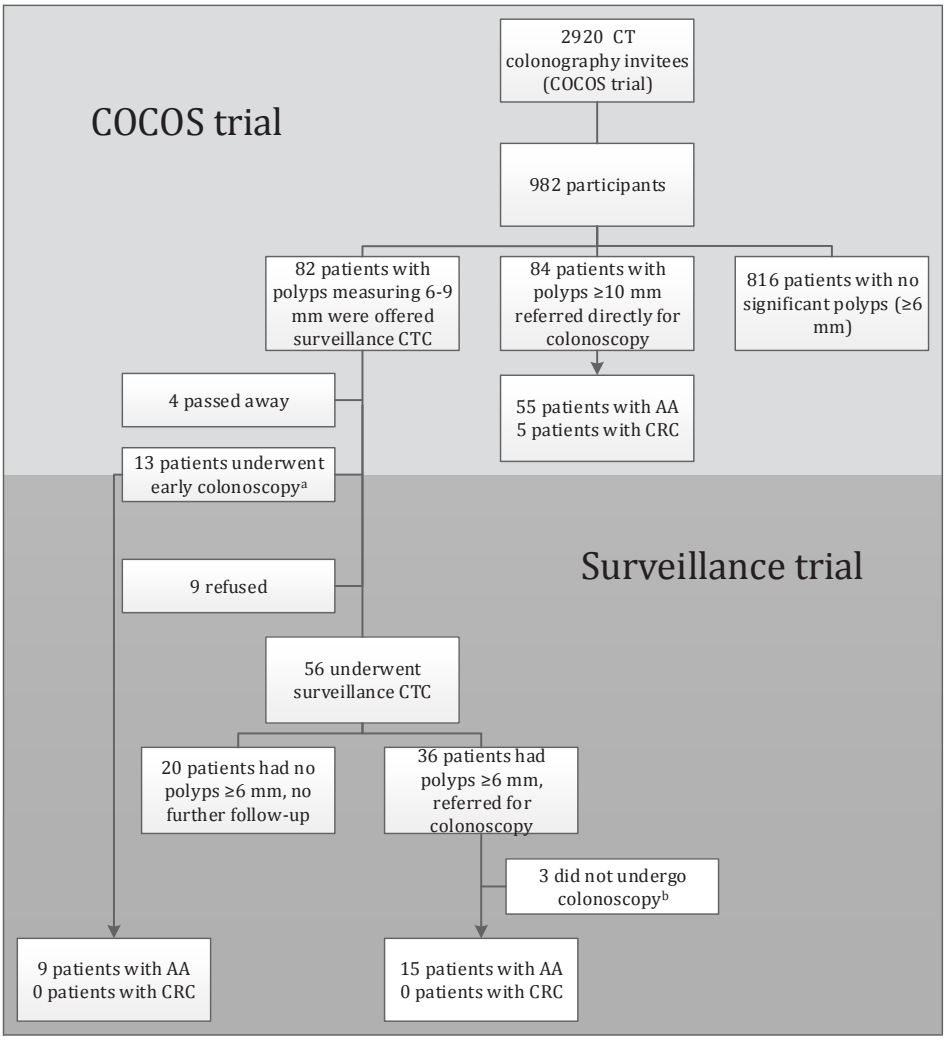

Figure 1. Participation and outcome of CTC patients in COCOS trial including surveillance CTC. [a]had OC prior to surveillance invitation, OC findings were used for our analyses. [b]2 refused (repeat) OC, 1 is still to be performed. AA = advanced adenoma, CRC = colorectal cancer.

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

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

Follow-up after a positive test result

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

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

Statistical Analysis

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

The overall diagnostic yield of CTC in the population-based trial was defined as the number of patients detected with advanced neoplasia relative to all participants and relative to all invitees of the initial trial. A McNemar test for paired observations (in 982 participants and in 2,920 invitees) was used to calculate differences between initial yield and overall yield including surveillance CTC. P-values less than 0.05 were deemed significant.

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

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

Results

Participation

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

Yield of surveillance CTC

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

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

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

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

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

97% (32/33) (95% CI 0.91-1.03). Included was the use of CAD, which had resulted in one additional OC with an advanced neoplasia.

Yield of preliminary OC

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

Yield of entire surveillance population

The per-patient yield for advanced neoplasia of our total surveillance population was 29.3 (24/82). Tables 2 and 3 summarize the characteristics of all detected adenomas and serrated lesions (see also Appendix 4).

In total 32 advanced adenomas were detected, of which 29 (91%) were at least 10 mm, 11 (34%) contained 25% or more villous component and none contained high-grade dysplasia. The other 117 neoplastic lesions included 100 tubular adenomas and 17 serrated lesions. Two patients had a large (5 and 3.5 cm) rectal carpet lesion at OC. One was under surveillance for

Table 2. Characteristics of 32 advanced adenomas

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

this lesion which measured 6-9 mm at the initial CTC; OC and polypectomy revealed a sessile polyp with tubular histology. The other had undergone an OC prior to invitation (because of complaints) showing a carpet (flat) lesion with tubulovillous histology, which was not noted on the initial CTC (interval lesion).

Overall yield of screening with CTC

At initial screening 60 CTC participants were found with at least one advanced neoplasia out of all 982 CTC participants (Table 4) (8). Adding the 24 surveillance participants with at least one advanced neoplasia, the proportion of CTC participants with at least one advanced neoplasia significantly increased to 84 of 982 participants ($p<0.001$). The overall yield per 100 CTC participants increased from 6.1 to 8.6 ($p<0.001$) and relative to those invited for CTC screening, we found an increased yield from 2.1 to 2.9 advanced neoplasia per 100 CTC invitees ($p<0.001$).

Extracolonic findings

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

Table 3. Morphology and location of detected adenomas and serrated lesions

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

Data are n(%).

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

Adverse events

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

Table 4. Most advanced lesion per participant and per invitee for primary screening and surveillance CTC

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

Note - Numbers in brackets are the actual number of individuals.
ns = not significant.

Discussion

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

To our knowledge, there has not been a previous study reporting on the yield and participation of surveillance CTC in the setting of an invitation based CRC screening program. One article has been published describing the findings of a 6-9 mm surveillance cohort of a non-invitational primary screening population of 303 patients (18). In that surveillance population of 303 patients with 6-9 mm polyps 24 advanced neoplasms resided in 23 patients (yield 7.6% (23/303)) (email correspondence PJ Pickhardt, MD; date: 2014-07-19). A possible explanation for our higher diagnostic yield is that we referred all patients with ≥6 mm polyps for OC and obtained histopathological verification of all lesions. Instead, that study referred only individuals with polyps with ≥1 mm increase in size thereby excluding stable or decreasing size ≥6 mm polyps and leaving a group of individuals (n=143) for ongoing CTC surveillance. Also, they did not present data from patients who withdrew prior to surveillance CTC, for our study inclusion of this data resulted in an additional nine patients with advanced adenomas. The participation rate in both studies was comparable (80% versus 86%).

The high yield in our CTC surveillance population showed that the earlier reported initial yield of screening with CTC has been underestimated (8). Whether the nine advanced adenomas resulting from the preliminary OCs were more likely part of the initial COCOS yield or the surveillance yield is debatable per-patient given the variety in time point of the OCs (Appendix 3). In addition, by including the seven patients with advanced adenomas which were measured ≥10 mm by one of the technologists in the surveillance yield, one might be compensating for initial misclassification by the radiologist. However, overall yield was not affected by this and is therefore probably the most representative outcome of screening for CRC with CTC.

When interpreting this overall yield one should realize that progression in growth and/or transformation from tubular to tubulovillous histology could have taken place during the surveillance interval, probably leading to a larger number of advanced adenomas. A

side-to-side comparison with the initial OC yield is therefore not possible. However, in this surveillance population all referrals for OC were for polyps already present at initial screening CTC. We believe this justifies our strategy to add the surveillance results to the initial CTC screening results leading to a significant increase in overall yield per 100 participants and per 100 invitees. As surveillance CTC for 6-9 mm polyps is a viable option in CRC screening, this surveillance yield must be taken into account when deciding on a proper screening strategy.
Debate remains regarding the policy for 6-9 mm polyps. Supportive for referral at ≥6 mm is the considerable yield of participants with advanced adenomas in our surveillance population (29.3%). On the other hand, most advanced adenomas were ≥10 mm and referral at ≥10 mm with continuing CTC surveillance for 6-9 mm polyps would have led to a decreased number of OCs and a substantial increase of PPV for advanced neoplasia (from 45% to 75%). Similar to another surveillance CTC study no interval CRC's were detected and none versus only one advanced adenoma with high-grade dysplasia in their study, suggesting a safe strategy (18). A sigmoidoscopy surveillance study for <10 mm polyps also concluded that surveillance for 6-9 mm polyps was safe (19). In an older population other health issues like life expectance have to be taken into account when advising a certain screening procedure. In our population the four deceased and one severely ill invitee probably had benefit from this non-aggressive follow-up strategy. However, the true efficacy and safety of surveillance for 6-9 mm polyps awaits a study that incorporates multiple CTC follow-up studies over a longer interval.
Extracolonic findings have been mentioned as a potential advantage as well as disadvantage of CTC (4, 20). To our knowledge, there is no data on extracolonic findings in surveillance populations after initial CTC screening. As expected, the prevalence of potentially important extracolonic findings that precipitate additional diagnostic follow-up testing in our surveillance population is lower than in a primary CTC screening population (2% versus 4.4% – 11%), as the course of time and/or previous additional investigations have proven some findings to be benign or treatment has taken place (7, 8, 21-23).

Our study has some limitations. The trial from which this surveillance population originated was powered for comparing the participation rate of CTC versus OC screening and not for evaluating CTC surveillance (10). However, for determining the overall yield of CTC in screening (including surveillance) the study population is sizeable (2,920 invitees and 982 participants). Further, the present surveillance population was already large enough to demonstrate a significant increase in yield of CTC screening. We found a relatively low PPV (45%) when only considering advanced neoplasia at OC as a true positive result, especially in comparison to the initial trial (PPV 71%). This is due to our different cut-off value for which participants were referred for OC (now ≥6 mm instead of ≥10 mm). This different cut-off value was used to learn more about small polyps' histology in surveillance. The PPV for ≥6

mm polyps was very good (97%), corresponding to a large study investigating PPV for CTC detected polyps (24). Twenty participants had no ≥6 mm polyps at surveillance CTC which could be explained by polyp regression (18), a false-positive initial CT or a false-negative surveillance CT. No OCs were performed in participants with a negative CTC, nor did we take the observations of other readers into account. This was done for consistency purposes, as to make overall yield calculations with the original COCOS trial possible. Furthermore, determining accuracy was not the purpose of this study. We did not classify serrated lesions as advanced adenomas, because of previous defined histopathology criteria in the initial trial (8). However, growing evidence shows the malignant potential and the importance of these lesions (25, 26). Including ≥10 mm serrated lesions as advanced adenomas would have increased the diagnostic yield to 31% (25/82) (27).

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

Acknowledgments

This study was funded by The Dutch Cancer Society (KWF Kanker Bestrijding 2012-5698). Philips Healthcare (Best, the Netherlands) provided the CTC workstations. Neither were involved in designing or conducting this study, had access to the data or were involved in data analysis or preparation of this manuscript.

We thank research nurses Isha Verkaik and Laurens Groenendijk for their professional research support. In addition, we would like to thank the four technologists: Cindy C.M. Beerse-Lute, Dominique Bekebrede-Kauffman, Roel J. Jansen, and Martin Poulus.

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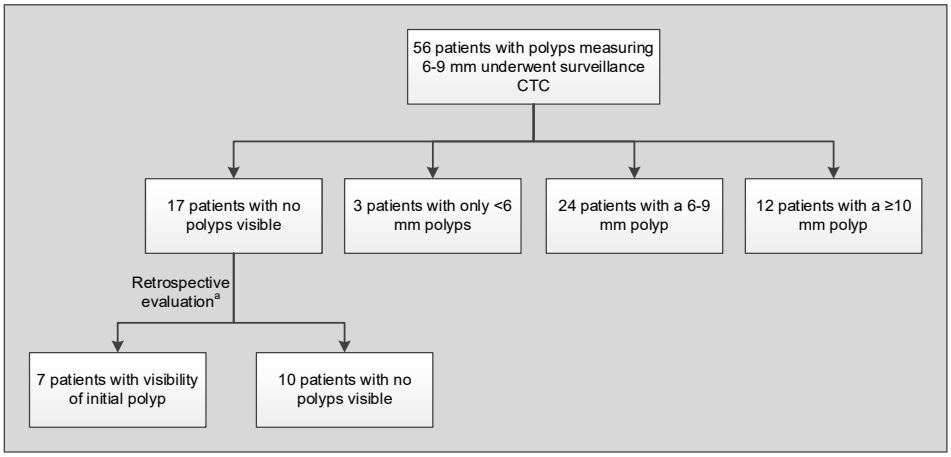
Appendices

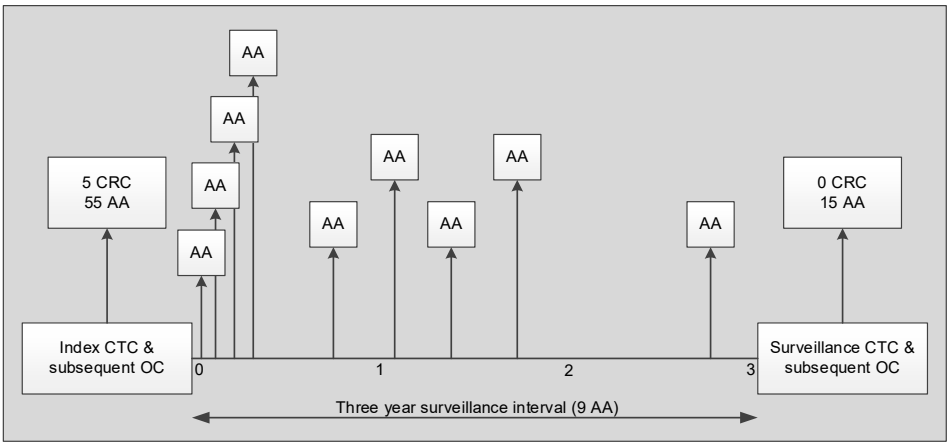
Appendix 1 Detailed explanation of OC procedure

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

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



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



Appendix 4. Histology of 132 detected adenomas

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

Data are n (%).

None of the adenomas contained high-grade dysplasia.

Chapter

Evolution of screen-detected small (6-9 mm) small polyps after a 3-year surveillance interval: assessment of growth with CT colonography compared with histopathology

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American Journal of Gastroenterology 2015 Dec;110(12): 1682-90

Abstract

Purpose

Volumetric growth assessment has been proposed for predicting advanced histology at surveillance CT colonography (CTC). We examined whether is it possible to predict which small (6-9 mm) polyps are likely to become advanced adenomas at surveillance by assessing volumetric growth.

Methods

In an invitational population-based CTC screening trial, 93 participants were diagnosed with one or two 6-9 mm polyps as the largest lesion(s). They were offered a 3-year surveillance CTC. Participants in whom surveillance CTC showed lesion(s) of ≥6 mm were offered colonoscopy. Volumetric measurements were performed on index and surveillance CTC and polyps were classified into growth categories according to ±30% volumetric change (>30% growth as progression, 30% growth to 30% decrease as stable and >30% decrease as regression). Polyp growth was related to histopathology.

Results

Between July 2012 and May 2014, 70 patients underwent surveillance CTC after a mean surveillance interval of 3.3 years (SD 0.3; range 3.0-4.6 years). Thirty-three (35%) of 95 polyps progressed, 36 (38%) remained stable and 26 (27%) regressed, including an apparent resolution in 13 (14%) polyps. In 68 (83%) of the 82 polyps at surveillance, histopathology was obtained; 15 (47%) of 32 progressing polyps were advanced adenomas, six (21%) of 28 stable polyps and none of the regressing polyps.

Conclusion

The majority of 6-9 mm polyps will not progress to advanced neoplasia within three years. Those that do progress to advanced status can in particular be found among the lesions that increased in size on surveillance CTC.

Introduction

Adenomas of ≥10 mm and/or with high-grade dysplasia and/or villousness of more than 25%, have the strongest association with malignancy (advanced adenomas) (1). For computed tomography (CT) colonography screening, size is the most important polyp feature used. Polyps ≥10 mm are most likely relevant lesions (either adenomatous or serrated) that need to be removed at colonoscopy. Diminutive polyps (<6 mm) have a very low chance of harboring malignancy and are therefore disregarded at CT colonography (2).

The probability that a 6-9 mm ("small") polyp in an asymptomatic primary screening population represents an advanced adenoma is approximately 3 - 6.6% (3-6). However, little is known about the natural course of 6-9 mm polyps and debate remains regarding the clinical relevance of these small polyps. CT colonography is probably the best method for determining longitudinal growth because during CT colonography surveillance no polyps are removed allowing for reproducible localisation and measurements.

Pickhardt et al showed that instead of assessing linear size at CT colonography, assessment of changes in volume *over time* results in a better prediction of the histology of polyps (7). They demonstrated that almost all advanced adenomas were among the progressing polyps. (7). Especially in small polyps where interval changes are often subtle, assessment of change in size is more reliable when performed by volumetric measurement (8, 9). However, current standard practice for reporting polyp size at CT colonography is linear measurement and volumetric assessment is not yet routinely used. More knowledge about polyp volumetric growth in relation to histopathology might help us to identify polyps that are at risk for harboring advanced histology. This might give direction to more (cost) effective patient management including referral for colonoscopy and polypectomy or less invasive CT colonography surveillance.

We performed a prospective study in surveillance patients derived from an invitational based screening population with only small (6-9 mm) polyps at primary screening CT colonography. The evolution of those small polyps was observed by repeat CT colonography after a 3-year surveillance interval by assessing change in volumetric size in relation to histopathology. We aimed to explore the possibility to predict which polyps at CT colonography are at risk to become advanced adenomas at surveillance by assessing volumetric growth.

Methods

Study design and patients

In a previous Dutch invitational population-based randomized screening trial participation and diagnostic yield was compared between colonoscopy and CT colonography (10). In that population screening trial 982 participated in CT colonography. For this study, we enrolled all participants from that screening trial that had one or two 6-9 mm polyps on primary CT colonography, and were advised to undergo surveillance CT colonography after three years. We excluded patients who underwent CT colonography or colonoscopy prior to the recommended surveillance CT colonography as well as those who declined participation in the study. We also excluded definite false-positive findings on index CT colonography, judged by an expert panel of three readers. We separately report on participation and yield of surveillance CT colonography on a per-patient level; per-polyp analyses and polyp growth in relation to histopathology were not evaluated.

Ethics approval from the Dutch Health Council was obtained for the COCOS trial (2009/03WBO & NTR1829, The Hague, the Netherlands), including surveillance CT colonography after three years. Patients had already given their written informed consent to be contacted for follow-up studies and consented this study.

Procedure

Patients received a non-cathartic preparation consisting of two times 50 mL of iodinated contrast agent (Telebrix Gastro, Guerbet, Aulnay-sous-Bois, France) on the day prior to CT colonography and 50 mL 1.5 h before the examination, in combination with a low-fiber diet for one day (11, 12). With an automatic insufflation of carbon dioxide (PROTOCO2L, Bracco, EZEM, Lake Success, NY, USA) colonic distention was obtained after administration of 20 mg hyoscine butylbromide intravenously (if contraindicated, 1 mg glucagon hydrochloride was used intravenously). Supine and prone position CT images were obtained on two 64-slice CT scanners (Brilliance, Philips Healthcare, Best, the Netherlands & SOMATOM Sensation, Siemens Medical Solutions, Erlangen, Germany) using a low-dose protocol; with collimation 64 x 0.625 mm, slice thickness 0.9 mm, reconstruction interval 0.7 mm, tube voltage 120 kV, and 25 reference mAs (for Brilliance) and collimation 128 x 0.6 mm, slice thickness 1.0 mm, reconstruction interval 0.7 mm, tube voltage 120 kV, and 16 ref mAs (for SOMATOM Sensation). The protocol for initial and surveillance CT colonography was identical.

CT colonography analysis

Surveillance CT colonographies were each prospectively viewed by three expert readers (one radiologist (CYN; 14 years of CT colonography experience including approximately 2000 CT colonographies) and two technologists (each >700 CT colonographies experience)) with dedicated CT colonography software (ViewForum, Philips Healthcare, Best, the Netherlands). The technologists were taking part for detection purposes only in order to minimize the possibility of false-negatives (13). The readers were not blinded to the findings of the index CT colonography and performed polyp matching (14). Linear size, morphology (sessile, flat or pedunculated), and segmental location of the polyps (cecum, ascending, transverse, descending, sigmoid and rectum) were recorded by the radiologist (CYN). Linear measurements were performed on transverse, sagittal and coronal 2D images (window setting 1500, -250 HU). The largest diameter on prone and supine was used (9). For pedunculated polyps the stalk was excluded from measurement. Quality assessment of the CT colonographies (colonic distension and fecal tagging) was performed by a research fellow (CTN) (11, 15).

Dedicated retrospective volumetric polyp assessment (Vitrea FX, ViTAL, Toshiba Medical Systems Group Company) was done by the research fellow (CTN), unaware of any colonoscopy or histopathology findings. This software system made it possible to perform semi-automated 3D volume measurements with the ability to manually correct the boundaries on the 2D axial image. Volume measurements were performed in supine and prone position, mean volumes were calculated and used for growth analysis. For pedunculated polyps the stalk was excluded from measurement.

Colonoscopy

Colonoscopy was indicated for all patients with at least one polyp measuring ≥6 mm, detected by the radiologist. A colonoscopy was performed by experienced endoscopists approximately ten weeks after a positive CT colonography. All standard quality measures were taken and standard reporting was used. A research nurse or research fellow (CTN) performed segmental unblinding of CT colonography findings. Resected lesions were classified by two expert gastrointestinal pathologists (MJV and KB) as hyperplastic lesion serrated adenoma, adenoma (non-advanced versus advanced) or carcinoma according to the Vienna classification (16). Advanced adenoma was defined as an adenoma measuring ≥10 mm (measured at endoscopy) and/or having a more than 25% villous component and/or harboring high grade dysplasia (1). Advanced neoplasia was defined as either an advanced adenoma or colorectal cancer.

Statistical analysis

Mean volume was calculated by dividing supine - prone volume measurements. The correlation coefficient (R) between supine and prone volumes of the polyps was established (R>0.80 was considered very good) (17). We assessed the volumetric change in size of each polyp in percentage over the entire surveillance interval. In order to categorize polyps into three groups (growth, stable and regression) a threshold of 30% change in polyp volume was used (with 30% or more growth classified as progression, 30% growth to 30% reduction as stable and regression as 30% or more reduction). The threshold of 30% growth or reduction was chosen because this value is beyond the expected range of CT measurement error (in semi-automated volumetric measurements) and should therefore constitute an actual change (8, 18). Associations between certain polyp characteristics and growth categories were tested for significance with Chi-square test. We related polyp growth to the histological subgroups. Different volumetric thresholds from the available literature were tested (7, 8). In addition, we reanalyzed our data using CT colonography measurement as arbiter for classifying adenomas, instead of endoscopy measurement. All statistical analyses were performed with IBM SPSS Statistics version 20.0 for Windows (SPSS, Chicago, Ill).

Results

Patient characteristics

Between July 2012 and May 2014, we invited all 93 patients with one or two 6-9 mm polyps at primary screening CT colonography for surveillance CT colonography after three years of whom 70 patients (mean age 66.1 (SD 6.6); 49% male) underwent surveillance CT colonography (Figure 1). In these 70 patients a total of 95 polyps had originally been detected on index CT colonography.

On surveillance CT colonography 82 of these 95 polyps could be detected, while 13 could not be redetected despite of good distention and good quality of fecal tagging in the relevant segments for 12 of 13 polyps (data not shown) (Figure 2). In one patient the distention of the sigmoid was considered insufficient to detect 6-9 mm polyps with certainty. However, at subsequent colonoscopy (performed for the presence of a different polyp), the polyp was not detected. Complete resolution is therefore considered in 13 (14%) of 95 polyps.

Six new ≥6 mm polyps (i.e. in retrospect not seen on index CT colonography) were detected at surveillance CT colonography, but not analyzed in this study comparing polyp growth of polyps identified on index CT colonography.

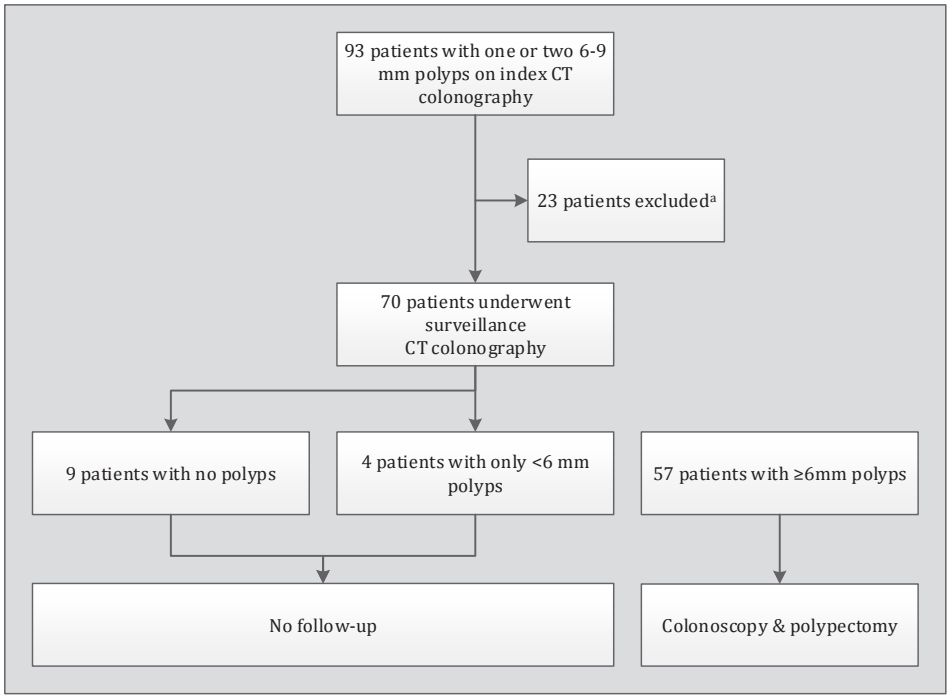

Figure 1. Patient cohort. [a]Nine refused participation in the study, ten underwent early colonoscopy, four passed away (not CRC related).

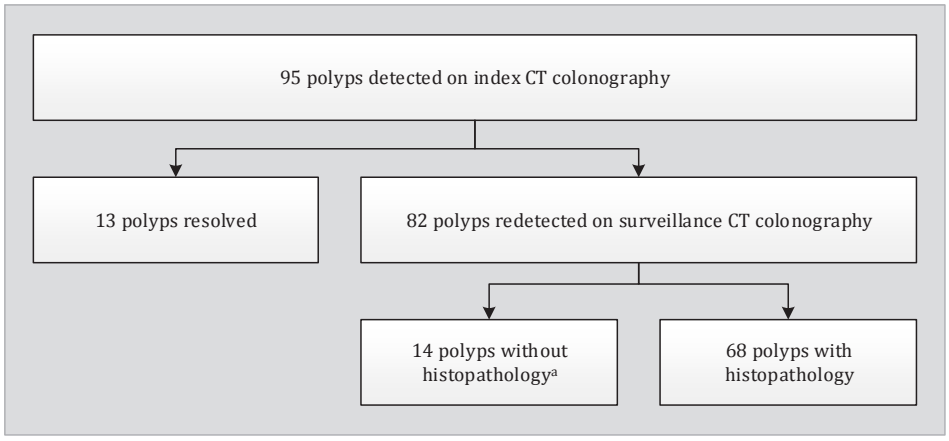

Figure 2. Polyp study cohort [a]Histopathological diagnosis not available because patients were not referred for colonoscopy (<6 mm polyp) (n=5), they refused colonoscopy (n=5) or polyps were not detected (n=3) nor retrieved (n=1) during colonoscopy.

Polyp size and evolution

The correlation coefficients (R) of supine-prone volumes of the 95 polyps on index and surveillance CT colonography were 0.91 and 0.94, respectively. This allowed us to calculated the mean volumes of each polyp. Mean polyp volume was 85.9 mm^3 (SD 62.6) on index CT colonography and mean linear size was 6.6 mm (SD 1.4) (n=95). Most polyps were sessile in morphology (79; 83%), some pedunculated (9; 9%) or flat (7; 7%). The polyps were located in the cecum (10; 11%), ascending colon (14; 15%), transverse colon (13; 14%), descending colon (9; 10%), sigmoid (34; 36%) and rectum (15; 16%).

After a mean surveillance interval of 3.3 years (SD 0.3; range 3.0-4.6 years) mean polyp volume was 127.6 mm^3 (SD 122.8) and mean linear size was 7.3 mm (SD 2.6) (n=82). According to the volumetric threshold of 30% growth or reduction, 33 polyps had progressed (35%), 36 polyps remained stable (38%) and 26 polyps regressed (27%). As mentioned above, 13 of 26 regressing polyps could not be redetected on surveillance CT colonography.

Polyp characteristics and evolution

No associations were found between the different growth categories according to the volumetric threshold of 30% growth or reduction and polyps with different morphology and location at index CT colonography (Table 1) or linear size.

Histopathology and evolution

Sixty-eight (83%) of 82 at surveillance CT colonography redetected polyps were endoscopically removed (Figure 2). Histopathology of these 68 resected polyps identified no cancers, 58 adenomas and 10 hyperplastic lesions. Twenty-one (36%) of the 58 adenomas were advanced adenomas, of which 19 were ≥10 mm (at endoscopy), 7 with tubulovillous histology and none with high-grade dysplasia (Table 2). There were 2 sessile serrated adenomas (<10 mm) and 35 non-advanced adenomas.

Of 32 progressing polyps with confirmed histology 28 (88%) were adenomas, including 15 (47%) advanced adenomas and 13 (41%) non-advanced adenomas (Figure 3). Of 29 stable polyps with confirmed histology 22 (76%) were adenomas, including six (21%) advanced adenomas and 16 (55%) non-advanced adenomas (Figure 4). Of seven regressing polyps with confirmed histology six (86%) were adenomas of which no advanced adenomas. Of two serrated adenomas one showed progression and the other one remained stable.

When using CT colonography measurements as arbiter 18% (3/17) of advanced adenomas was classified as stable, and 82% (14/17) as progressing (Appendix 1), compared to 29%

Table 1. Characteristics of all 95 polyps according to the threshold of volumetric change (±30%) during the surveillance interval

	Surveillance CT colonography		
	Progression	**Stable**	**Regression**[a]
All polyps (n=95)			
Location			
Proximal[b]	16 (48%)	15 (42%)	16 (62%)
Rectosigmoid	17 (52%)	21 (58%)	10 (38%)
Morphology			
Sessile	25 (76%)	31 (86%)	23 (88%)
Pedunculated	5 (15%)	3 (8%)	1 (4%)
Flat	3 (9%)	2 (6%)	2 (8%)
Histology			
Advanced adenoma	15 (45%)	6 (17%)	0
Non-advanced adenoma	13 (39%)	16 (44%)	6 (23%)
Serrated adenoma	1 (3%)	1 (3%)	0
Hyperplastic lesion	3 (9%)	6 (17%)	1 (4%)
Unresected	1 (3%)	7 (19%)	19 (73%)
Total	**33**	**36**	**26**
All adenomas (n=56)			
Histopathology			
Tubular	23 (82%)	20 (91%)	6 (100%)
Tubulovillous	5 (18%)	2 (9%)	0
Villous	0	0	0
Dysplasia			
Low-grade	28 (100%)	22 (100%)	6 (100%)
High-grade	0	0	0
Total	**28**	**22**	**6**

[a]Including 13 resolved polyps.

[b]Proximal is defined as descending colon, transverse colon, ascending colon or caecum (as Atkin et al).

(6/21) and 71% (15/21) when using colonoscopy measurements. With both measurements no advanced adenomas were classified as regressing. The 14 polyps of 82 redetected polyps with no histological confirmation were from patients who either refused colonoscopy (n=5), who were not referred for colonoscopy because the polyp measured <6 mm at surveillance CT colonography (n=5) or in which the polyps were not detected (n=3) nor retrieved (n=1) from the colon during colonoscopy.

Table 2. Characteristics of all confirmed advanced adenomas

			Index CTC			*Surveillance CTC*				
	Segment	**Morphology**	**Volume (mm^3)**	**Linear (mm)**	**Surveillance interval (years)**	**Volume (mm^3)**	**Linear (mm)**	**Change in volume (%)**	**Reference size at endoscopy**	**Histology[a]**
1	Rectum	Sessile	83	3.9[b]	3.9	542	11.8	550.5	15.0	Tubular
2	Rectum	Sessile	43	6.3	3.1	209	9.6	380.6	10.0	Tubular
3	Sigmoid	Sessile	144	7.2	3.2	686	15.8	376.9	18.0	Tubulovillous
4	Sigmoid	Sessile	90	8.1	3.1	360	11.3	302.4	12.0	Tubular
5	Rectum	Sessile	124	6.9	4.6	343	14.4	176.2	50.0	Tubular
6	Ascending	Sessile	46	5.8	3.2	102	11.9	123.1	10.0	Tubular
7	Cecum	Sessile	104	4.8[b]	3.0	205	9.4	97.0	10.0	Tubulovillous
8	Descending	Pedunculated	297	8.8	3.5	559	13.7	88.2	15.0	Tubulovillous
9	Sigmoid	Sessile	212	8.5	3.1	361	12.2	70.5	15.0	Tubular
10	Sigmoid	Sessile	117	8.0	3.4	199	8.1	69.9	12.0	Tubular
11	Rectum	Pedunculated	135	6.1	3.4	229	7.7	69.7	10.0	Tubular
12	Ascending	Sessile	105	7.4	3.1	163	10.3	54.9	10.0	Tubulovillous
13	Ascending	Sessile	44	6.7	3.1	67	7.7	51.9	12.0	Tubular
14	Ascending	Sessile	20	8.1	3.1	28	11.7	37.0	10.0	Tubulovillous
15	Transverse	Flat	77	6.3	3.5	103	6.9	33.6	12.0	Tubular
16	Sigmoid	Flat	150	7.6	3.0	185	8.3	23.5	15.0	Tubular
17	Sigmoid	Sessile	51	3.9[b]	3.0	57	6.4	11.9	10.0	Tubular
18	Descending	Sessile	122	7.1	3.2	122	7.5	-0.6	10.0	Tubular
19	Transverse	Sessile	157	9.4	3.1	153	9.2	-2.0	8.0	Tubulovillous
20	Sigmoid	Sessile	148	9.2	3.5	134	8.9	-9.9	7.0	Tubulovillous
21	Sigmoid	Pedunculated	448	7.7	4.3	343	8.1	-23.3	10.0	Tubular

[a]No high-grade dysplasia was present in any advanced adenoma

[b]Retrospective measurement of radiologist (CYN), prospectively measured 6-9 mm

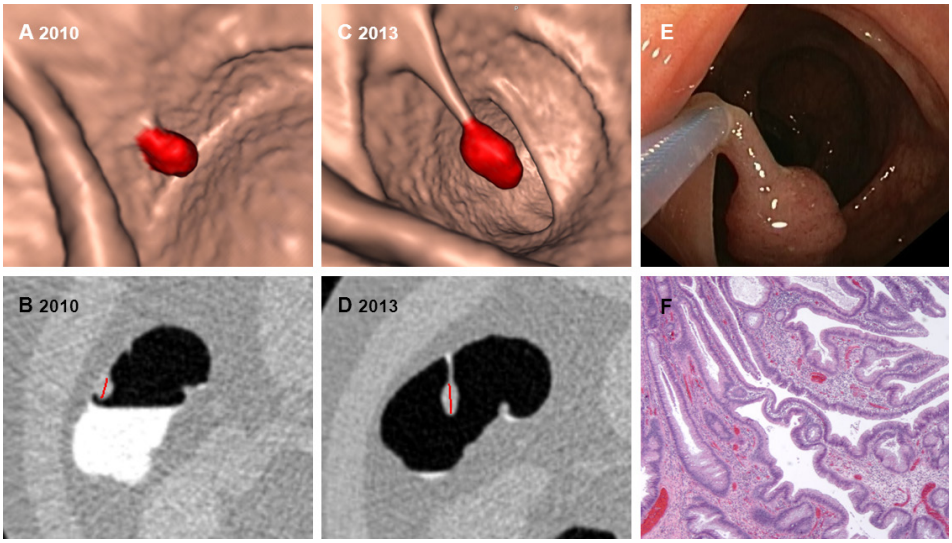

Figure 3. Progressing advanced adenoma. Pedunculated polyp in the descending colon on 3D and 2D images, measuring 296.8 mm^3 in volume and 8.8 mm in length on index CT colonography in 2010 (A and B). After a surveillance period of 3.5 years volume (558.5 mm^3; 88% growth) and length (13.7 mm) had increased (C and D). After endoscopical removal (E) histopathology revealed a tubulovillous adenoma with low-grade dysplasia (20x magnification and H&E stained sections) (F).

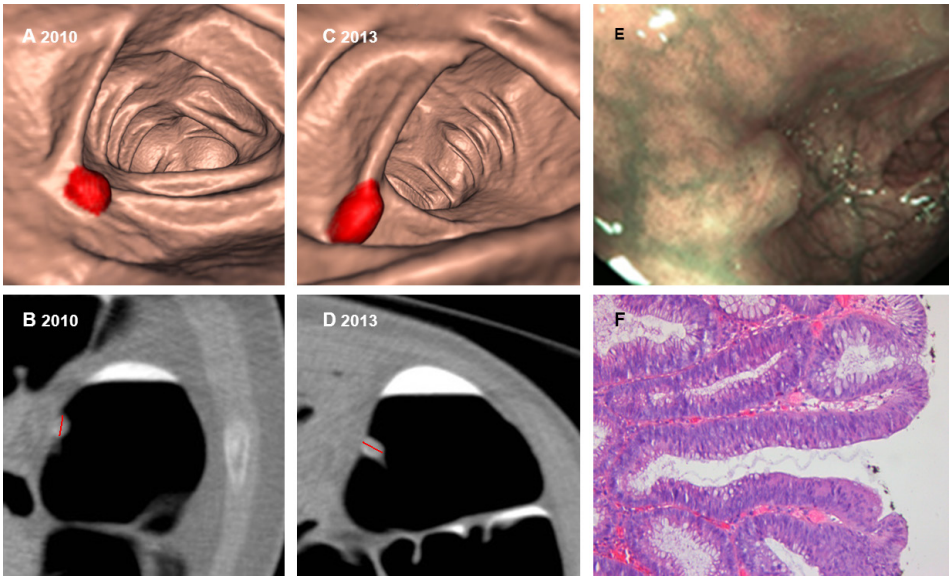

Figure 4. Stable advanced adenoma. Sessile polyp in the transverse colon on 3D and 2D images, measuring 156.6 mm^3 in volume and 9.4 mm in length on index CT colonography in 2010 (A and B). After a surveillance period of 3.1 years no interval growth took place in volume (153.4 mm^3, -2% reduction) and length (9.2 mm) (C and D). After endoscopical removal (E) histopathology revealed a tubulovillous adenoma with low-grade dysplasia (100x magnification and H&E stained section) (F).

Of the six new ≥6 mm polyps on surveillance CT colonography one was a non-advanced adenoma, two serrated adenomas, one edema in the lamina propria, and two unresected polyps (of patients who refused colonoscopy).

Testing different volumetric thresholds

The volumetric threshold of 30% growth or reduction we used classified the largest number of polyps as progressing (n=33 versus n=23 and n=24) and the largest number of advanced adenomas as progressing (n=15 versus n=12 and n=11) when compared to other volumetric thresholds available from the literature (Table 3) (7, 8, 18). When using other volumetric thresholds the distinction between growth categories was blunted with an increasing number of stable lesions (including more advanced lesions), being therefore less sensitive for the detection of growth.

Table 3. Growth categories according to different volumetric thresholds

	Volumetric thresholds		
	±30% overall[a,b]	**45 mm³ overall[b]**	**±20% per year[b]**
Progressing (n)	**33**	**23**	**24**
Advanced adenomas	15 (45%)	12 (52%)	11 (46%)
Non-advanced adenomas	13 (39%)	8 (35%)	10 (42%)
Sessile serrated adenomas	1 (3%)	0	1 (4%)
Hyperplastic lesions	3 (9%)	2 (9%)	2 (8%)
Unresected polyps	1 (3%)	1 (4%)	0
Stable (n)	**36**	**62**	**55**
Advanced adenomas	6 (17%)	8 (13%)	10 (18%)
Non-advanced adenomas	16 (44%)	27 (44%)	25 (45%)
Sessile serrated adenomas	1 (3%)	2 (3%)	1 (2%)
Hyperplastic lesions	6 (17%)	7 (11%)	8 (15%)
Unresected polyps	7 (19%)	18 (29%)	11 (20%)
Regressing (n)	**26**	**10**	**16**
Advanced adenomas	0	1 (10%)	0
Non-advanced adenomas	6 (23%)	0	0
Sessile serrated adenomas	0	0	0
Hyperplastic lesions	1 (4%)	1 (10%)	0
Unresected polyps	19 (73%)	8 (80%)	16 (100%)

[a]According to Pickhardt et al (8), [b]according to/based on Pickhardt et al (7)

Discussion

Our results show that after a 3-year surveillance interval, at CT colonography surveillance 35% of 95 small (6-9 mm) polyps demonstrated a volumetric growth of 30% or more, while 38% of polyps remained stable, 13% had a volume reduction by at least 30%, and 14% appeared to be completely regressed. No baseline polyp characteristics other than size were identified as a risk factor for advanced histology. Growing small polyps were more likely to be advanced adenomas at removal than stable or regressing polyps (45% versus 21% and 0%, respectively).

Our study has several strengths. Our study cohort was derived from an invitational population-based study and used a predefined surveillance interval of three years, which allowed us to reliably demonstrate the evolution of small polyps in a standardized way. We referred all patients with ≥6 mm polyps, including stable as well as regressing ≥6 mm polyps. The volumetric measurements of all polyps in our study were performed by one experienced reader, thereby reducing variability in growth classification.

Previous colonoscopy surveillance studies showed higher progression rates using a linear threshold of 1 mm (19, 20). However, volumetric measurements have shown to be more reliable than linear measurements in assessing small changes in size (8), and a recent CT colonography study using volumetric measurements showed a lower rate of progressing small polyps (22% versus 31% and 40% in the colonoscopy studies) (7, 19, 20). This rate is comparable to our study when applying the same volumetric threshold of 20% growth or reduction per year used in their study (25%; 24/95) and shows an overestimation of previous progression rates of small polyps.

Pickhardt et al. were the first to show that volumetric growth assessment can be a useful parameter for determining clinical importance of small polyps (7). When using the same threshold of ±20% volumetric change per year only 52% (11/21) of advanced adenomas progressed in our study versus 92% (22/24) in their study. Main differences between the studies are our predefined fixed surveillance interval of three years after which all ≥6 mm lesions were removed thereby not excluding stable lesions for analysis, compared to a variable surveillance interval from one up to seven years in their study, colonoscopy referral at 1 mm growth at interval CT colonography and a large number of (stable or regressing) polyps under continuing CT colonography surveillance at time of publication (n=142). The different volumetric thresholds used in both studies were not of influence on this different

outcome (Table 3). The sizeable group of stable advanced adenomas in our study has not been described previously and should be considered when deciding on optimal strategies for colonoscopy referral.

It is already known that 6-9 mm polyps have a low risk to harbour advanced histology at initial detection (5, 6). In this surveillance study after a 3-year interval, we did not detect adenomas with villous histology, high-grade dysplasia of invasive cancer, but only a few tubulovillous adenomas. Current US and European guidelines have pointed out that evidence on the management strategy for CT colonography detected 6-9 mm polyps is lacking. Both our study as well as the other published surveillance study advocate against the current practice to refer all patients with polyps 6 mm or larger for colonoscopy and might ask for a less aggressive approach for 6-9 mm lesions (7). However, our study focused on per-polyp analyses and when considering the results in the setting of population screening, results on a per-patient level should also be considered.

There is one major concern with establishing growth per histopathology subgroup. The division in subgroups is not solely based on histopathology, but also on size. Each adenoma ≥10 mm is defined as an advanced adenoma and in fact, the majority (67%) of the adenomas that became advanced during the surveillance interval fulfilled solely this size criterion. Among the sessile serrated adenomas we observed one progressing and one stable adenoma, which is in contrast to one decreasing serrated adenoma in the literature (7), but unfortunately these small numbers do not allow reliable analyses and/or conclusions. In our study no identifying characteristics, e.g. morphology, location or index size, were able to predict which polyps were more likely to progress. However, our subgroup analyses are limited due to small numbers.
The issue of polyp regression remains debated (19-22). We have shown that with good CT colonography quality and thorough evaluation by three expert readers, there is evidence for complete regression in 14% of polyps (13/95), which is in concordance to the 10% in the CT colonography surveillance study of Pickhardt et al (7). As in their study, we did not perform confirmative colonoscopies in those patients (7). The polyps decreasing in size in both studies are also supportive of the polyp regression concept.

Our study has a few limitations. The COCOS trial from which this population originated was powered for comparing participation rate and yield of CT colonography versus colonoscopy screening and not for surveillance CT colonography (10). This led to a relatively small surveillance study cohort of 6-9 mm polyps. However, it still remains an interesting and unique cohort of patients, as current European and US screening guidelines advice to refer all patients with ≥6 mm polyps for colonoscopy and polypectomy instead of surveillance

by CT colonography (7, 23, 24). The findings of this and another study places this strategy into perspective. Secondly, we used linear size at endoscopy as reference for classifying adenomas smaller or larger than 10 mm (1). But as seen in table 1 and as is known from the literature this can result in an over- and underestimation of linear size at CT colonography (25-28). Reanalysis of our data with CT colonography measurement as arbiter did not lead to significantly different results (Appendix 1).

What actually is the best threshold for determining a 'significant' volumetric change in size at CT colonography surveillance needs to be established. In contrast to previous literature, we presented a volumetric change over the entire surveillance period instead of volumetric change per year. This was done because, in order to calculate a growth rate per year, one must have knowledge on the growing pattern of the polyps (e.g. linear, exponential) and therefore multiple measurement points in time are needed. With a volumetric change over the entire surveillance interval we were not able to correct for the spread in surveillance interval (3-4.6 year). But as the only few outliers showed evident progression or regression we do not think this has caused bias. The threshold of 30% growth or reduction was chosen because this value is beyond the expected range of CT measurement error (in semi-automated volumetric measurements) and should therefore constitute an actual change (8, 18). For the primary aim of this study it was advantageous that volumetric measurements were performed by a single observer as volume change was outcome measure and therefore consistency was more important than determining reproducibility. In addition, reproducibility has shown to be good for volumetric polyp measurements (8).

In conclusion, the majority of small (6-9 mm) polyps will not progress to advanced neoplasia within three years. Those that do progress can in particular be found among the lesions that increased in size on surveillance CT colonography. However, one-third of advanced adenomas remained stable in size, which has not been described previously and must be taken into account when deciding on optimal referral guidelines for colonoscopy. None of the advanced adenomas regressed during 3-year CT colonography surveillance.

Acknowledgements

This study was partly funded by The Dutch Cancer Society (KWF Kanker Bestrijding 2012-5698). Philips Healthcare (Best, the Netherlands) provided the CT colonography workstations. Toshiba Medical Systems Nederland (Zoetermeer, the Netherlands) provided the workstation for volumetric measurements. Neither were involved in designing or conducting this study, had access to the data or were involved in data analysis or preparation of this manuscript.

We thank research nurses Isha Verkaik and Laurens Groenendijk for their research support. In addition, we would like to thank the four technologists: Cindy C.M. Beerse-Lute, Dominique Bekebrede-Kauffman, Roel J. Jansen and Martin Poulus.

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Appendices

Appendix 1. Characteristics of all confirmed advanced adenomas, with size at CT colonography as arbiter

			Index CTC			Surveillance CTC				
	Segment	Morphology	Volume (mm^3)	Linear (mm)	Surveillance interval (years)	Volume (mm^3)	Linear (mm)	Change in volume (%)	Size at endoscopy	Histology[a]
1	Rectum	Sessile	83	3.9[b]	3.9	542	11.8	550.5	15.0	Tubular
2	Rectum	Sessile	43	6.3	3.1	209	9.6	380.6	10.0	Tubular
3	Sigmoid	Sessile	144	7.2	3.2	686	15.8	376.9	18.0	Tubulovillous
4	Sigmoid	Sessile	90	8.1	3.1	360	11.3	302.4	12.0	Tubular
5	Transverse	Sessile	50	8.0	3.1	179	10.3	256.6	9.0	Tubular
6	Rectum	Sessile	124	6.9	4.6	343	14.4	176.0	50.0	Tubular
7	Ascending	Sessile	46	5.8	3.2	102	11.9	123.1	10.0	Tubular
8	Cecum	Sessile	104	4.8	3.0	205	9.4	97.0	10.0	Tubulovillous
9	Descending	Pedunculated	297	8.8	3.5	559	13.7	88.2	15.0	Tubulovillous
10	Sigmoid	Sessile	212	8.5	3.1	361	12.2	70.5	15.0	Tubular
11	Ascending	Flat	116	10.6	3.1	187	10.4	61.3	7.0	Tubular
12	Ascending	Sessile	105	7.4	3.1	163	10.3	54.9	10.0	Tubulovillous
13	Descending	Sessile	41	6.3	3.1	56	10.4	38.4	7.0	Tubular
14	Ascending	Sessile	20	8.1	3.1	28	11.7	37.0	10.0	Tubulovillous
15	Sigmoid	Sessile	180	7.2	3.3	207	11.1	14.9	8.0	Tubular
16	Transverse	Sessile	157	9.4	3.1	153	9.2	-0.2	8.0	Tubulovillous
17	Sigmoid	Sessile	148	9.2	3.5	134	8.9	-9.9	7.0	Tubulovillous

[a]No high-grade dysplasia was present in any advanced adenoma.

[b]Retrospective measurement of radiologist (CYN), prospectively measured 6-9 mm.

chapter
3

Chapter 4

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

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Abstract

Objectives

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

Methods

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

Results

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

Conclusions

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

Introduction

Colorectal cancer (CRC) is a major cause of cancer related morbidity and mortality worldwide (1). CRC arises from precursor lesions in the course of many years and detection and resection of these lesions can prevent CRC (2). Research from the last two decades has suggested that 15-30% of CRCs arise from serrated polyps, via the serrated neoplasia pathway, rather than from adenomas (3-5). This has caused a paradigm shift in CRC prevention strategies, as not only adenomas, but also all premalignant serrated polyps should be detected and resected during colonoscopy (6). According to the most recent World Health Organization guideline, serrated polyps are subdivided into hyperplastic polyps (HPs), sessile serrated adenomas/polyps (SSPs) without dysplasia, SSPs with dysplasia and traditional serrated adenomas (TSAs) (7). This classification seems to be of importance, as not all serrated polyp subtypes possess an identical malignant potential (6, 8). Mainly, SSPs have been associated with CRC, whereas distally located and/or smaller HPs are considered innocuous lesions (6, 8). The US Multi-Society Task Force on Colorectal Cancer acknowledged that individuals with dysplastic and/or large (≥10 mm) SSPs have a high risk of developing CRC and should be managed comparable to patients with high-risk adenomas (9). Therefore, CRC screening strategies should not only be designed to detect high-risk adenomas and early CRC, but should also be able to identify those individuals with dysplastic and/or large SSPs, referred to as high-risk SSPs (10).

Colonoscopy has been widely acknowledged as the reference standard to detect colonic polyps as well as CRC, while other modalities are also accepted as CRC screening techniques (11). In a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology, it was stated that computed tomography colonography (CTC) is the radiological examination of choice for CRC screening in average-risk adults aged 50 years and above (11). In the most recent European guideline, CTC is not recommended as a primary test for population screening. However, it may be proposed as a CRC screening test on an individual basis providing the screenee is adequately informed about test characteristics, benefits, and risks (12). Although a large number of studies have reported on the performance of CTC in the detection of high-risk adenomas and CRC, studies that assess the performance of CTC in the detection of high-risk SSPs are lacking to our knowledge (13). The aim of this study was to compare the performance of CTC with colonoscopy for the detection of large and/or dysplastic SSPs.

Methods

Study design and population

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

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

Procedures

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

CTC

Participants allocated to receive primary CTC screening were prepared with a reduced bowel preparation consisting of two times 50 mL iodinated contrast agent (Telebrix Gastro, Guerbet, Aulnay-sous-Bois, France) the day before the examination and one identical bottle 90 minutes before examination, accompanied by a low fiber diet. Distension of the colon was achieved with

an automatic carbon dioxide insufflator (PROTOCO2L, Bracco, EZEM, Lake Success, NY, USA). Directly before distension, 20 mg of hyoscine butylbromide was administrated intravenously as bowel relaxants, or if contraindicated, was substituted for 1 mg of glucagon hydrochloride intravenously. No medication was given if both agents were contraindicated. Each CTC was read within two weeks by three readers: one of three experienced radiologists (≥800 examinations) and two of four experienced radiological technologists, who all underwent an extensive and structured training program including 175 training cases and 25 test cases. A more detailed description of the CTC reading procedure was reported earlier (15, 16). The readers were instructed to report all polyps ≥6 mm and ignore smaller polyps.

Follow-up advice after CTC depended on the size of the largest lesion. All individuals who were diagnosed with at least one large lesion at CTC (≥10 mm in size) were referred for a colonoscopy. All individuals with a largest lesion sized 6-9 mm at CTC were recommended surveillance CTC. Individuals with three or more lesions of 6-9 mm were recommended surveillance CTC after 1.5 years, and individuals with one or two lesions of 6-9 mm were recommended surveillance CTC after three years. Individuals without lesions ≥6 mm did not receive follow-up. In case of any discrepancy in CTC reading by the three individual readers (one radiologist and two technologists for each CTC), the most stringent advice was pursued. Earlier research from our group showed that a reading strategy of three readers without consensus resulted in the most effective strategy considering diagnostic yield of CTC (16).

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

Colonoscopy

All colonoscopies were executed according to the standard quality indicators (17). Pre-procedure bowel cleansing was obtained by a combination of 2 L of clear fluids and 2 L of hypertonic polyethylene glycol solution (Moviprep; Norgine bv, Amsterdam, the Netherlands), accompanied by specific diet instructions. Colonoscopy was performed under conscious sedation using intravenous fentanyl (Bipharma, Weesp, the Netherlands) and midazolam (Dormicum, Actavis, Baarn, the Netherlands), dosed to the preference of the endoscopists as well as the participant. Cecal intubation was confirmed by still images of the standard landmarks (ileocecal valve as well as the appendiceal orifice) and/or by intubation of the

terminal ileum. Quality of bowel cleansing was evaluated using the validated Ottawa bowel preparation score (18). Colonoscopies were rescheduled in case of an inadequate bowel preparation. All detected polyps were immediately removed and obtained for histological assessment, irrespective of polyp location and/or optical polyp diagnosis. If resection of the detected polyp was not directly possible, biopsies were taken to enable histopathological assessment. Characteristics of all detected polyps were obtained during colonoscopy, i.e., size (measured compared to an open forceps of 7mm), location (colonic segment), morphology (pedunculated (Paris Ip), sessile (Paris Is), flat (Paris IIa, IIb) or depressed (IIc)), and optical diagnosis (carcinomatous, adenomatous, hyperplastic).

Histopathology

All tissue samples were evaluated according to the Vienna criteria by one designated expert gastrointestinal pathologist per hospital (19). Adenomatous polyps were classified based on the presence of a villous component (tubular, tubulovillous or villous) and on their severity of dysplasia (low-grade or high-grade). Serrated polyps were subdivided into HPs, SSPs without dysplasia, SSPs with dysplasia or TSAs. Predominantly, a SSP was defined based on distortion of the crypts as well as the presence of (hyper-)serration up to the base of the crypts (7). A TSA was predominantly defined based on the presence of prominent serration, aberrant crypt formation, a distorted tubulovillous or villous configuration and diffuse cytoplasmic eosinophilia (7). A high-risk adenoma was defined as an adenoma of at least 10 mm in size at colonoscopy, with at least a 25% villous component and/or with high-grade dysplasia. A high-risk SSP was defined as a SSP containing dysplasia and/or ≥10 mm in size and a HP of at least 10 mm was regarded as a high-risk SSP, in agreement with the recent US guidelines (6, 9).

Statistical analysis

The primary outcome measure of this study was the detection rate of ≥1 high-risk SSP for CTC as compared with colonoscopy as method for opportunistic screening in average-risk individuals. Because of imposed restrictions by the Dutch Health Council in the COCOS-trial only those individuals with a lesion ≥10 mm were initially referred for colonoscopy. Individuals with lesions 6-9 mm in size were offered surveillance CTC, followed by a colonoscopy in case a lesion ≥6 mm was detected at surveillance CTC. To mimic international referral guidelines (referral for colonoscopy in case of a polyp ≥6 mm detected at CTC), the yield of initial CTC screening together with the yield of CTC surveillance for all individuals with a polyp 6-9 mm at initial CTC was aggregated and used to calculate the detection rate of CTC as screening strategy (11, 12). Lesions detected in individuals in the CTC group that underwent a colonoscopy before the recommended CTC surveillance interval were also added to the detection rate of CTC screening.

Both the overall detection rate of all serrated polyp subtypes as well as the detection rate of all serrated polyp subtypes as most advanced lesion per individual were evaluated. CRCs as well as high-risk adenomas were considered as more advanced lesions than high-risk SSP, whereas all other adenomas were regarded as less advanced lesions. Low-risk SSPs as well as HPs were considered as less advanced lesions than any type of adenoma. Multiple logistic regression, adjusted for gender and age, was used to statistically compare the detection rate of colonoscopy versus CTC based screening. Difference was presented as odds ratio with 95% confidence interval (CI). A two-sided p-value <0.05 was considered significant in this study. Analyses were performed using SPSS statistics version 21 (Chicago, IL, USA).

Results

In total 8,844 individuals aged 50-75 years were invited to participate, of which 2,920 were randomized to CTC and 5,924 to colonoscopy (Figure 1). Of the CTC invitees, 982 (34%) participated and were eligible for inclusion. Mean age of CTC participants was 60.3 years (SD 6.4) and 507 were male (52%). Of the colonoscopy invitees, 1,276 individuals (22%) participated and were eligible for inclusion in this study. Mean age of colonoscopy participants was 60.1 years (SD 6.2) and 652 were male (51%). Reasons for non-participation have been described in detail earlier (15).

Of the 982 individuals that underwent a CTC, 96 had at least one ≥10 mm polyp and were referred for colonoscopy, 104 had a largest polyp of 6-9 mm and were offered surveillance CTC and 782 had no ≥6 mm polyps and therefore required no follow-up (16). Of the 104 individuals referred for surveillance, five died within the surveillance interval (four for other reasons than CRC and one unknown), 11 did not want to participate due to various reasons and 10 already underwent a colonoscopy within the surveillance interval. As a result, 78 individuals underwent surveillance CTC at three years, of which 57 were referred for colonoscopy because of a colonic lesion ≥6 mm. Of these individuals, 50 underwent a colonoscopy in one of the participating academic centers, three underwent a colonoscopy in another hospital and four did not want to participate (Figure 1). The data on all polyps collected in 96 initial colonoscopies and 63 surveillance colonoscopies in the CTC arm were compared with polyp data collected in 1,276 colonoscopies in the primary colonoscopy arm.

Detection rate of high-risk SSPs

In table 1, the detection rate for colonoscopy as well as CTC as primary CRC screening modality in average-risk adults is presented.

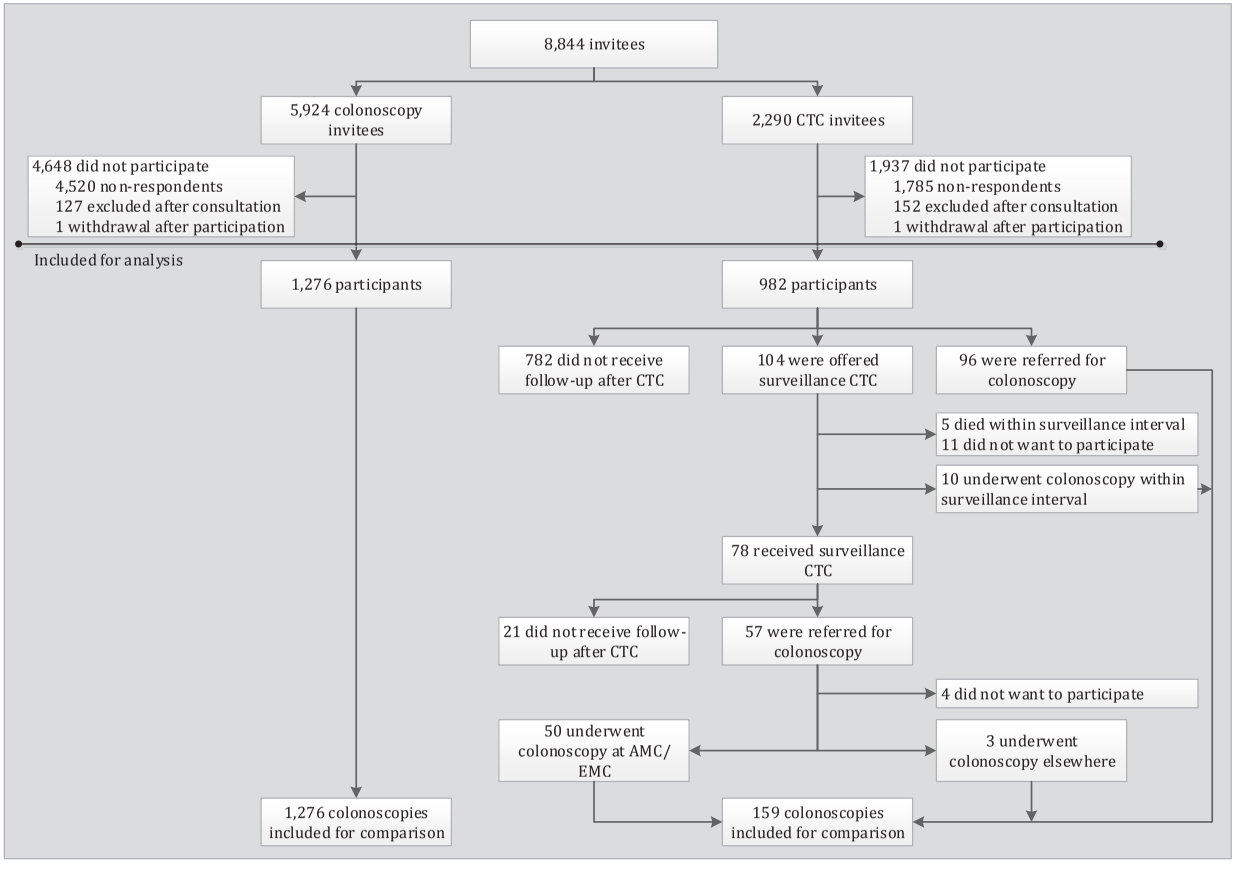

Figure 1. Study flowchart

Table 1. Per individual detection rate of serrated polyps

	CT colonography (n=982)	Colonoscopy (n=1,276)	*p* value
Overall			
High-risk SSP, n (%)	8 (0.8)	55 (4.3)	<0.001
SSP ≥10 mm	7 (0.7)	36 (2.8)	0.001
SSP with dysplasia	1 (0.1)	23 (1.8)	0.005
All SSP (high and low risk), n (%)	21 (2.1)	83 (6.5)	<0.001
Hyperplastic polyp, n (%)	68 (6.9)	316 (24.8)	<0.001
As most advanced lesion			
High-risk SSP, n (%)	4 (0.4)	39 (3.1)	<0.001
Low-risk SSP, n (%)	3 (0.3)	13 (1.0)	0.06
Hyperplastic polyp, n (%)	7 (0.7)	172 (13.5)	<0.001

SSP= sessile serrated adenoma/polyp

In the primary colonoscopy arm, 55 individuals (4.3%) were diagnosed with at least one high-risk SSP, compared with eight individuals (0.8%) in the CTC arm (p<0.001). This corresponds to an adjusted odds ratio of 5.5 (95% CI 2.6-11.6) to detect at least one high-risk SSP for colonoscopy compared to CTC. In total, 39 individuals (3.1%) in the colonoscopy arm were diagnosed with at least one high-risk SSP as most advanced lesion, compared with four individuals (0.4%) in the CTC arm. This corresponds to a significantly higher detection rate for colonoscopy (p<0.001), with an adjusted odds ratio to detect at least one high-risk SSP as most advanced lesion of 7.7 (95% CI 2.7-21.6).

Characteristics of high-risk SSPs

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

Table 2. Histology of detected serrated polyps (per polyp analysis)

	CT colonography n (%)	Colonoscopy n (%)
Serrated polyps ≥10 mm		
SSP with dysplasia	0 (0)	5 (11.6)
SSP without dysplasia	8 (100)	38 (88.4)
TSA	0 (0)	0 (0)
Total	**8**	**43**
Serrated polyps 6-9 mm		
SSP with dysplasia	0 (0)	8 (10.0)
SSP without dysplasia	8 (30.8)	14 (17.5)
TSA	0 (0)	0 (0)
Hyperplastic polyp	18 (69.2)	58 (72.5)
Total	**26**	**80**
Serrated polyps <6 mm		
SSP with dysplasia	1 (0.7)	17 (3.0)
SSP without dysplasia	18 (12.2)	42 (7.3)
TSA	0 (0)	1 (0.2)
Hyperplastic polyp	128 (87.1)	512 (89.5)
Total	**147**	**572**
Overall		
Total number of serrated polyps	181	695
Total number of high-risk SSPs	9	68

SSP=sessile serrated adenoma/polyp, TSA=traditional serrated adenoma

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

	CT colonography n (%)	Colonoscopy n (%)
Morphology		
Flat	0 (0)	17 (25.0)
Sessile	9 (100)	51 (75.0)
Total	**9**	**68**
Location		
Cecum	0 (0)	9 (13.2)
Ascending colon	1 (11.1)	23 (33.9)
Transverse colon	0 (0)	19 (27.9)
Descending colon	0 (0)	1 (1.5)
Rectosigmoid	8 (88.9)	16 (23.5)
Total	**9**	**68**

Discussion

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

All available data were collected in a large prospective randomized controlled setting, and both colonoscopies as well as CTCs were performed according to the most up-to-date quality guidelines (12, 17). General colonoscopy quality was described in a previous study (20). Yet, a number of limitations have to be acknowledged in this study. As mentioned before, the current US guideline recommends that every individual with a lesion ≥6 mm at CTC should be referred for colonoscopy (11). However, due to imposed restrictions by the Dutch Health Council in the COCOS-trial only those individuals with a lesion ≥10 mm were initially referred for colonoscopy. Individuals with lesions 6-9 mm in size were offered surveillance CTC, followed by a colonoscopy in case of a lesion ≥6 mm detected at CTC. To mimic the current referral guideline, initial CTC screening and surveillance data of CTC followed by colonoscopy for all polyps ≥6 mm were aggregated in this study, imposing a potential risk for biased results. For this reason, the diagnostic yield in the setting of population-based screening was beyond the scope of this study, and we decided to restrict our conclusions to the main outcome parameter, the detection rate of high-risk SSPs per participating individual. Because of the extent of the detected difference and the underlying quality of this study, we believe that, irrespective of the potential bias, the external validity of our results is amply sufficient for the assessment of the primary outcome measure.

To our knowledge, no earlier studies have been performed that compared the detection rate of high-risk SSPs of CTC with colonoscopy as primary screening modalities in average-risk adults. Nevertheless, this study can be related to earlier findings in the literature. Of specific importance with regard to the detection of SSPs is the fact that these lesions tend to be small and inconspicuous lesions and have a sessile or flat morphology (21). More advanced SSPs often do not tend to be larger than less advanced SSPs and do not differ in morphology (22, 23). For instance, Bouwens et al. showed that SSPs with dysplasia are as often 1-5 mm in size as SSPs without dysplasia (22). Furthermore, Rosty et al. showed that the mean polyp size

of SSPs with invasive malignancy ranged from 8-11 mm (23). In line with these results, we showed that 37% of the high-risk SSPs detected in the colonoscopy arm were smaller than 10 mm, whereas 25% were 1-5 mm in size. In total, 75% of high-risk SSPs were sessile, whereas 25% were flat. These characteristics of high-risk SSPs might have largely contributed to the significantly lower detection of high-risk SSPs in the CTC arm, compared to the colonoscopy arm. First, because of the stepwise approach, referring only those individuals with a lesion ≥6 mm at CTC, a substantial number of 1-5 mm SSPs with dysplasia will have remained *in situ* with the CTC-based screening strategy. This threshold for referral is standard in CTC practice as the accuracy measures are low for 1-5 mm lesions (24, 25). Second, several studies suggested that the sensitivity of CTC for the detection of flat and/or 6-9 mm lesions might be suboptimal compared to colonoscopy, although these results widely differ (26-29). In the largest multicenter CTC screening trial to date (n=2,600 individuals), the diagnostic accuracy of CTC was compared with colonoscopy for the detection of adenomas and CRC (29). The sensitivity for the detection of lesions above 10 mm in diameter was 90%, whereas the sensitivity for the detection of lesions ≥6 mm dropped to 78%. Unfortunately, no sub-analysis was performed, stratified for polyp morphology. A recent retrospective study suggested that the sensitivity of CTC to detect flat adenomas ≥10 mm was 70.6% (26). Another prospective study showed that the sensitivity of CTC for the detection of flat adenomas of ≥20 mm in size was only 32% (27). In a large prospective study in one expert center, however, a sensitivity of 93.3% was reported for the detection of flat lesions ≥6 mm (28). A third potential reason for a low detection rate of high-risk SSPs at CTC is the fact that serrated polyps tend to flatten during distention of the colon, described as the visual "disappearing phenomenon" (30, 31). As distension of the cecum and ascending colon is relatively the widest during CTC, which is also the most prevalent location of SSPs, this might explain why high-risk SSPs in the proximal colon were more often left undetected (32). Although this phenomenon will also occur during colonoscopy, the overlying mucus cap of SSPs still supports their identification (33). Because of this mucus cap, surface contrast coating might also enable a better visualization of SSPs with CTC (34). Contrast coating has been described as the phenomenon where the oral contrast adheres to the polyps' surface, making it more susceptible for detection (35). Previous research showed this was especially seen in flat polyps located in the proximal colon. Although the mechanism of this phenomenon remains speculative, the authors believe the oral preparation including different agents is responsible (34). Therefore, a fourth explanation for the lower detection rate of serrated polyps with CTC could be the bowel preparation used in our study, consisting of only one iodinated agent.

The results from our study might have implications for the value of CTC as opportunistic screening modality for average-risk individuals. As mentioned before, The US Multi-Society

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

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

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Chapter

Burden of waiting for surveillance CT colonography in patients with screen-detected 6-9 mm polyps

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European Radiology 2016 April 8 [Epub ahead of print]

Abstract

Purpose

We assessed the burden of waiting for surveillance CT colonography (CTC) performed in patients having 6-9 mm colorectal polyps on primary screening CTC. Also, we compared the burden of primary and surveillance CTC.

Materials and Methods

In an invitational population-based CTC screening trial, 101 persons were diagnosed with <3 polyps 6-9 mm, for which surveillance CTC after 3 years was advised. Validated questionnaires regarding expected and perceived burden (5-point Likert scales) were completed before and after index and surveillance CTC, also including items on burden of waiting for surveillance CTC. McNemar's test was used for comparison after dichotomization.

Results

Seventy-eight (77%) of 101 invitees underwent surveillance CTC of which 66 (85%) completed the expected and 62 (79%) the perceived burden questionnaire. The majority of participants (73%) experienced waiting for surveillance CTC never or only sometimes as burdensome. There was almost no difference in expected and perceived burden between surveillance and index CTC. Waiting for the results after the procedure was significantly more burdensome for surveillance CTC than for index CTC (23% vs. 8%;p=0.012).

Conclusion

Waiting for surveillance CTC after primary CTC screening caused little or no burden for surveillance participants. In general, burden of surveillance and index CTC were comparable.

Introduction

Debate remains regarding the management of individuals with 6-9 mm polyps at screening, and an option is surveillance CT colonography, because of the low malignancy risk and slow growing rate of these polyps (1-4). Successful surveillance with CT colonography is amongst other factors dependent on patients' adherence, which is likely related to previous experiences with CT colonography and expectations towards the surveillance examination. Furthermore, screening for cancer may cause relevant side effects, such as discomfort, anxiety and distress. Especially waiting for a follow-up examination, with the idea of having a lesion that may progress to cancer, and waiting for the results of the surveillance examination may cause considerable negative psychological consequences. The consequences of awaiting surveillance CT colonography are currently unknown and have to be weighed against CT colonography benefits (5). Further, one can speculate about potential differences in experience between first and second CT colonography, as patients should know better what to expect the second time.

In this prospective study we evaluated the burden of waiting three years for the procedure and the results of a surveillance CT colonography in patients having one or two small (6-9 mm) polyps at primary screening CT colonography. We also assessed the burden, pain and embarrassment of surveillance CT colonography in comparison to index CT colonography in our previously performed randomized population-based screening trial (6).

Materials and methods

Study design and participants

We enrolled asymptomatic 50-75 year adults with no prior or family history of CRC or adenomatous polyps, who underwent CT colonography in the context of an invitational population-based screening program (COCOS trial) (7, 8). Eligible patients had one or two 6-9 mm polyps that were prospectively identified at screening CT colonography, and were advised to undergo surveillance CT colonography after three years. At that time, management after surveillance CT colonography was not clear.

Ethics approval from the Dutch Health Council (2009/03WBO, The Hague, the Netherlands) was obtained for the COCOS trial, in which the surveillance CT colonography was included. Patients had already given their written informed consent to be contacted for follow-up studies and consented this study.

Invitation

Invitations for surveillance CT colonography were sent by mail and patients were asked to contact one of the researchers by phone. In case of no response, a reminder letter was sent after four weeks and if no response to the reminder letter, the person was contacted by phone once after another four weeks. Patients who underwent a CT colonography or colonoscopy in the time between the index CT colonography and the advised surveillance CT colonography were excluded. Study information was sent to all included patients willing to participate. Non-participation reasons were summarized (9).

Procedure

CT colonography preparation, colonic distention and scan protocol were identical to the index CT colonography examination (see for detailed description Appendix 1). Briefly, patients underwent a non-cathartic preparation the day before the examination and 1.5 hours prior to the examination (total of 3x50 mL of iodinated contrast agent; Telebrix Gastro, Guerbet, Aulnaysous-Bois, France) in combination with a low-fibre diet for 1 day (10, 11). Before colonic insufflation, 20 mg intravenous hyoscine butylbromide (Buscopan; Boehringer-Ingelheim, Ingelheim, Germany) was administered, after which colonic distention was achieved with automated pressure controlled carbon dioxide insufflation (PROTOCO2L, Bracco, EZEM, Lake Success, NY, USA) through a thin flexible rectal tube. When distension was considered sufficient at the scout image, a breath-hold supine and prone CT was performed using a 64 multi-detector-row CT scanner (Brilliance, Philips Healthcare, Best, the Netherlands; SOMATOM Sensation, Siemens Medical Solutions, Erlangen, Germany). Patients received no sedation or analgesics. Expert readers evaluated all CT colonographies within two weeks after the procedure. Patients were informed about the results within two weeks after the surveillance CT colonography by phone. Colonoscopy was done if a lesion ≥6 mm was reported.

Questionnaires

The expected burden questionnaire (EBQ) and perceived burden questionnaire (PBQ) were identical to those used at index CT colonography and are based on previous Dutch faecal occult blood test (FOBT) screening pilots and on studies investigating the acceptance of CT colonography and patient perception of diagnostic tests for faecal incontinence (12-15). For all included EBQs and PBQs we retrieved the corresponding EBQs and PBQs of index CT colonography and the questions for index and surveillance CT colonography were compared.

Expected burden questionnaire (EBQ)

A pre-procedural questionnaire was sent to the participants to assess the expectations towards the CT colonography within four weeks before the procedure. They were asked to complete the questionnaire prior to the screening procedure and to return it by mail in a prepaid envelope (which was identical for index CT colonography). The EBQ contained items regarding expected embarrassment, pain and burden of the bowel preparation and the examination itself. All but two items were scored on 5-point Likert scales (1=not at all; 2=slightly; 3=some; 4=rather; 5=extremely) (16). Two items regarding thoughts in the past three years were scored on 4-point Likert scales (1=never; 2=sometimes; 3=regularly; 4=often). Expected burden questionnaires completed after surveillance CT colonography were excluded from analysis.

Perceived burden questionnaire (PBQ)

The perceived burden, pain and embarrassment of CT colonography and different procedural aspects were assessed using a post-procedural questionnaire, sent by mail after the participants had been informed about the CT colonography result. The PBQ contained items regarding the perceived embarrassment, pain and burden of the bowel preparation, the examination itself and the overall burden of the CT colonography examination (same 5-point Likert scale as pre-procedural (16)). We also collected information on the willingness to return to future screening rounds. PBQs that were completed after 12 weeks from the surveillance CT colonography were excluded from analysis as we considered this time interval too long for an accurate representation of the perceived burden (for index CT colonography this was six weeks)

Surveillance specific questions

In addition to the EBQ for the index CT colonography, items regarding the burden and fear for waiting for (the results of) surveillance CT colonography were included. All but two items were scored on 5-point Likert scales. Two items regarding thoughts in the past three years were scored on 4-point Likert scales (1=never; 2=sometimes; 3=regularly; 4=often). The PBQ included additional items on the most burdensome aspect of the surveillance CT colonography (waiting for surveillance CT colonography, preparation, examination, abdominal symptoms afterwards or waiting for the results) and of the entire CT colonography screening procedure ((results of) index or surveillance CT colonography).

Impact of Event Scale (IES)

The colorectal cancer (CRC)-specific distress was assessed using the Impact of Event Scale (IES) sent together with the EBQ (IES-I) and PBQ (IES-II) (17-19). The 15 IES items were

tailored to the specific "event": "a diagnosis of colorectal cancer". All items were scored on 4-point Likert scales whether this was present (0=not at all; 1=rarely; 3=sometimes; 5=often) during the past 7 days. The summary score of the total scale could range 0 to 75, with a higher score indicating more cancer-specific distress (0-8: no meaningful impact; 9-25: impact event; 26-43 powerful impact event; 44-75 severe impact event). The IES was found to be sufficiently reliable (Cronbach α for IES-I and IES-II was 0.87 and 0.89, respectively) to allow these analyses to be performed.

Statistical analysis

Demographics and items specific for surveillance CT colonography were described. Corresponding questions on EBQs and PBQs were compared between index and surveillance CT colonography, only paired data were used. Answers to questions with 4-points and 5-points ordinal scales were first dichotomized (totally agree/agree versus disagree/totally disagree and not at all/slightly versus some/rather/extremely) and differences were assessed using the McNemar test for paired proportions. One question regarding expectations towards surveillance CT colonography required a different dichotomization because of different response categories (better/slightly better/as expected versus slightly worse/worse than expected). We used Mann-Whitney U tests to test the significance of differences in the mean IES scores by sex and surveillance CT colonography result. To test for differences in IES over time, paired Wilcoxon signed-rank test were conducted. A p-value of <0.05 was considered significant. To determine the clinical relevance of the significant difference between means, we used the minimal important difference (MID), which is defined as half of a standard deviation. SPSS V.20.0 for Windows (SPSS, Chicago, Ill) was used to perform all statistical tests.

Results

Response and respondent characteristics

Between July 2012 and May 2014 101 patients were invited to undergo surveillance CT colonography (Figure 1). Twenty-three (23%) of 101 invitees were excluded for surveillance CT colonography (four passed away; ten underwent a colonoscopy examination prior to the invitation of the surveillance CT colonography of which five at own request (Appendix 2); nine did not wish to participate, the most common reason mentioned was other health problems).

Seventy-eight patients (77%) underwent a surveillance CT colonography (median age 63.5 IQR [60.0-72.0]; 53% male) at a mean surveillance interval of 3.3 years (SD 0.3; range 3.0-4.6 years) (Table 1). The EBQ was completed in time by 66 (85%) surveillance participants,

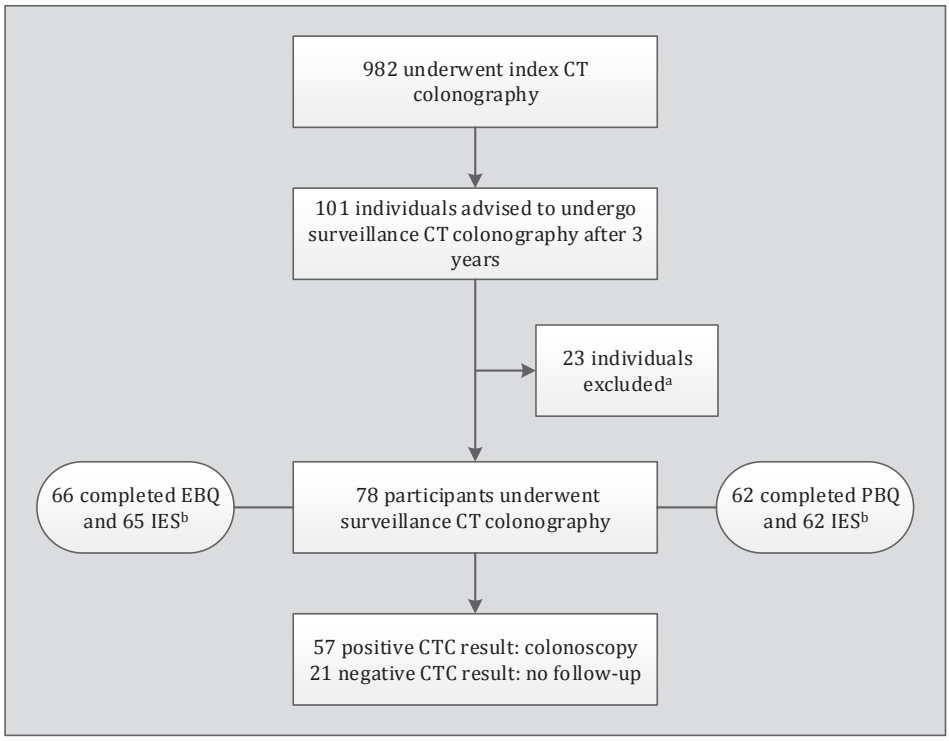

Figure 1. Overview of response to the expected and perceived burden questionnaire (EBQ and PBQ) including Impact of Event Scale (IES) among 101 surveillance CT colonography participants. [a]Four passed away, ten underwent a colonoscopy prior to invitation for surveillance CT colonography and nine did not wish to participate for various reasons. [b]Completed the EBQ & IES-I and PBQ & IES-II in time (prior to the surveillance CT colonography and within 12 weeks of surveillance CT colonography, respectively).

the IES-I in 65 (83%) participants. The PBQ and IES-II were returned within 12 weeks of surveillance CT colonography by 62 patients (79%). Sixty-four EBQs and 48 PBQs of index and surveillance CT colonography were available for a head-to-head comparison.

Waiting for the surveillance CT colonography

The vast majority of the respondents never or only sometimes thought about the colonic polyp(s) (89%; 57/64) or the recommended surveillance CT colonography (84%; 54/64) (Figure 2).

Thoughts about the presence of the colonic polyp(s) or the waiting for surveillance CT colonography were for the majority of participants not at all or only slightly burdensome (75%; 47/63 and 73%; 46/63, respectively). Waiting for surveillance CT colonography did

Table 1. Baseline characteristics of CT colonography surveillance participants

	Participants surveillance CT colonography (n=78)
Age in years (median, IQR)	64 (60-72)
Gender (% male)	41 (53%)
Married/lived together (%)[a,b]	59 (81%)
Socioeconomic status (mean, SD)[a,b,c]	2.8 (SD 1.4)
Education[a,b]	
- *Elementary (%)*	5 (7%)
- Secondary (%)	45 (62%)
- *Tertiary and postgraduate (%)*	23 (32%)
Previous experience (%)[b]	
- *CT colonography*	1 (2%)
- *Colonoscopy*	4 (6%)

[a]At time of index CT colonography

[b]As not all respondents completed the questinos on their maritial status, education and prior endoscopy experience, the percentages mentioned for these items are not based on the total number of respondents, but on the total number of participants who answered those questions

[c]Socioeconomic status was categorised as very low, low, medium, high and very high (1-5).

not result in anxiety or slight anxiety in 86% (54/63). The vast majority expected the waiting for the results to be not at all or only slightly burdensome (70%; 45/64) or expected to be not at all or only slightly anxious (72%; 46/64) for the waiting for the results of surveillance CT colonography.

Expected burden in comparison to index CT colonography

Expected burden for surveillance CT colonography was rated similar as for index CT colonography, with the exception that the bowel preparation was expected to be not or only slightly embarrassing by a larger proportion of participants for surveillance CT than for index CT (87%; 55/63 versus 71%; 45/63, respectively; p=0.031) (Figure 3).

The proportion of participants who thought that the evaluation of extracolonic structures on CT colonography was advantageous was larger at surveillance than at index CT colonography (98%; 63/64 versus 89%; 57/64; p=0.031) (Appendix 3).

Perceived burden in comparison to index CT colonography

Items on perceived burden of bowel preparation, CT colonography examination, abdominal complaints in the weeks of the examination and the entire screening procedure were rated

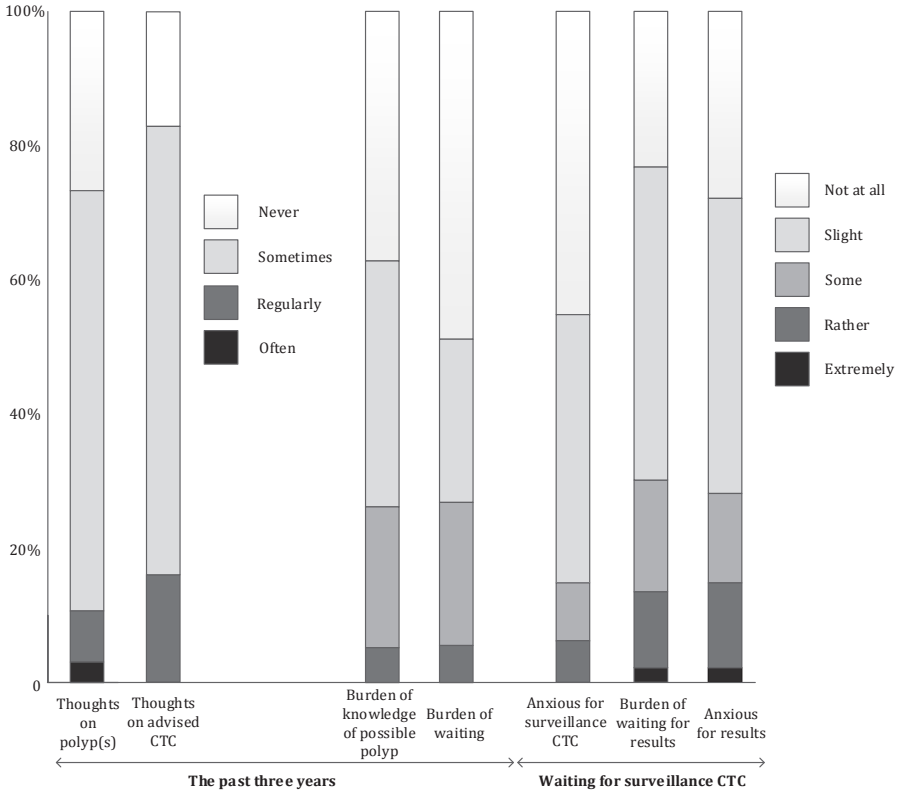

Figure 2. Thoughts on colonic polyps and experienced burden in the period between the index and surveillance CT colonography (the past three years). Anxiety and expected burden while waiting for (the results of) surveillance CT colonography.

comparable for index CT colonography, with the CT colonography examination itself as the most burdensome part and insufflation of CO_2 as the most burdensome/painful part of the CT examination (Appendix 4). Two items differed: Waiting for the results was considered some, rather or extremely burdensome by 23% (11/47) in surveillance CT colonography versus 6% (3/47) of participants in index CT colonography (p=0.021) (Figure 4). The surveillance CT colonography was experienced as expected by 31% (15/48) and worse than expected by 6% (3/48), versus 15% (7/48) and 23% (11/48), respectively in index CT colonography (p=0.011).

Evaluation entire screening procedure

The most burdensome part of the surveillance CT colonography procedure was considered the CT examination itself (33%; 16/48) followed by bowel complaints (25%; 12/48) and

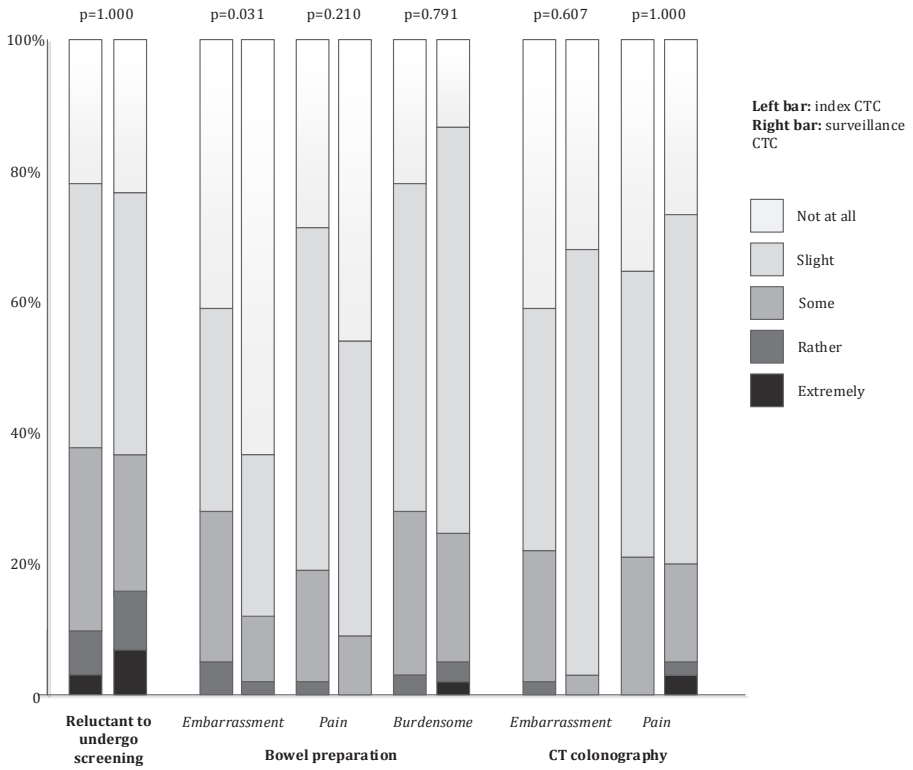

Figure 3. Reluctancy to undergo index (screening) CT colonography and surveillance CT colonography, and expected embarrassment, pain and burden of bowel preparation and CT colonography of both examinations. P values of McNemar's test after dichotomization are presented on top of the bars.

waiting for the results (25%; 12/48). For index CT colonography the bowel preparation was indicated as the most burdensome part (35%; 17/48), followed by the examination itself (29%; 14/48) and the bowel complaints (25%; 12/48). Waiting three years for surveillance CT colonography was indicated as the most burdensome part by only 8% (4/48) of invitees. There was no significant difference between surveillance and index CT colonography for proportion of participants who would recommend CT colonography in screening (96%; 46/48 versus 98%; 47/48; p=1.000) and who would participate in future screening rounds (98%; 46/47 versus 94%; 44/47; p=0.625).

Psychological distress

Fifty-five paired IES scores were available for analysis. The total IES scores were significantly higher for women than for men prior to and after surveillance CT colonography (9.4 (SD 9.8)

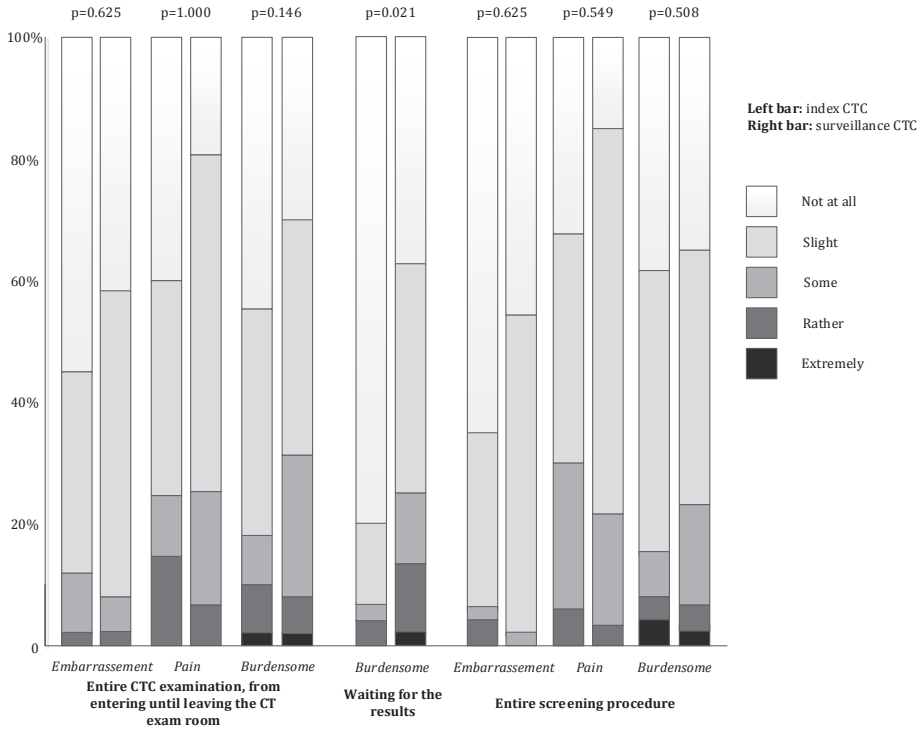

Figure 4. Perceived burden of the entire CT colonography examination, waiting for the CT colonography results and entire screening procedure with surveillance CT colonography, in comparison to index CT colonography. P-values of McNemar's test after dichotomization are presented on top of the bars.

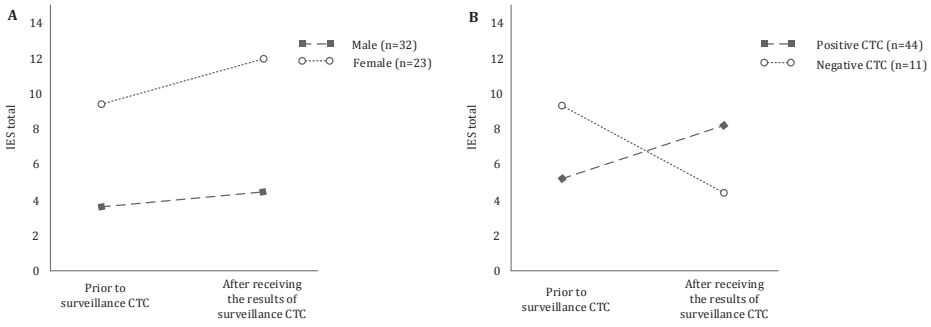

Figure 5. CRC specific distress score (Impact of Event Scale [IES] total) over time. **A** IES scores separated by gender. Total IES scores in women were significantly higher than for men prior to and after surveillance CT colonography (p=0.006 and p=0.012, respectively). **B** IES scores separated by result of the surveillance CT colonography. Total IES score of the group with a positive CT colonography result increased (p=0.006). Total IES scores of the group with a negative result decreased (p=0.655).

and 3.6 (SD 5.3); p=0.006 and 11.9 (SD 11.9) and 4.3 (SD 4.7); p=0.012, respectively) (Figure 5A). Differences were larger than the MID and therefore considered to be clinically relevant. The total IES score of the group of patients with a positive CT colonography result significantly increased over time (from 5.2 SD (6.6) to 8.2 (SD 10.1); p=0.006) (Figure 5B). The difference was smaller than the MID and therefore not considered to be clinically relevant.

Discussion

This study demonstrated that the knowledge of having a 6-9 mm colonic polyp and therefore being under surveillance caused little or no burden. It furthermore showed that waiting for surveillance CT colonography in screening for CRC caused little to no anxiety or burden in the vast majority of participants. In general, expectations towards and perceived burden of surveillance CT colonography were similar to index CT colonography three years before. Only waiting for the CT colonography results after the surveillance CT colonography was considered significantly more burdensome than for index CT colonography (23% versus 8%). The surveillance CT colonography less often turned out to be worse than expected than the index CT colonography, 6% versus 23%, respectively. Surveillance for CRC with CT colonography appeared to have no major impact on most patients; women did experience significantly more distress than men. The large majority of participants would recommend participating in CT colonography for CRC screening (96%) and would participate again in the future (98%).

To the best of our knowledge, our study is the first to evaluate the burden of waiting for surveillance CT colonography in patients with one or two 6-9 mm polyps detected at primary screening CT colonography. Our study design with identical questionnaires made a head-to-head comparison between expected and perceived burden of index and surveillance CT colonography possible. Both questionnaires had been validated in previous CRC screening pilots.

Patients did not seem to worry too much about the possible presence of colonic polyp(s) or did not found the knowledge of having this/these polyp(s) burdensome, which also can be concluded from the small fraction of patients (8%) who considered waiting for surveillance CT colonography the most burdensome aspect of the entire screening procedure. One must realize that our study population does not represent a random selected group of persons. Individuals chose to participate in the initial CRC screening trial and, in exchange for being informed about their health, they accepted certain consequences, for example (the burden of)

surveillance CT colonography. In addition, there were ten excluded patients that underwent a preliminary colonoscopy of which five at their own request, it seems likely that anxiety or worry was a barrier for waiting three years for surveillance CT colonography and that they were probably more prone to psychological stress.

In addition to the selection bias described above, a number of other potential limitations should be acknowledged. The surveillance population originated from a primary screening trial (COCOS trial), which was powered for comparing the participation rate and yield of CT colonography versus colonoscopy screening and not for evaluating burden in surveillance CT colonography, therefore leading to a relatively small surveillance population (10). In addition, we only used paired data for solid comparison analyses resulting in the exclusion of more questionnaires. Because of those limited number of patients, we chose a relatively wide interval (12 weeks) in which the PBQ could be returned, to maintain as much questionnaires for analyses as possible. This possibly could have affected patients' evaluation. An assessment of PBQ and cancer-specific distress (IES) before receiving the results of surveillance CT colonography might have showed higher burden scores and/or distress, as waiting for the results was reported as burdensome in 25%. Also, an extra assessment later in time (after the results of the colonoscopy) could have provided us with information about the duration of higher distress experienced by certain patients (20). Because of the associated questions (e.g. three questions on bowel preparation, for pain, burden and embarrassment), there is a chance of eventually finding a significant difference on one question/outcome, as was probably the case with the expected embarrassment on bowel preparation given the comparable expectations on all other items.

Waiting for the results of a (screening) study is burdensome (5). The significantly higher proportion of patients considering waiting for the results of surveillance CT colonography some, rather or extremely burdensome in comparison to index CT colonography (23% versus 8%), is most likely related to the knowledge of having a colonic polyp that may have grown. However, the waiting time for the results of the surveillance CT colonography in our study was unusually long (two weeks), as the CT was evaluated by multiple observers within the framework of a different study. In daily practice the wait will be shorter and this might decrease the burden. At colonoscopy patients are directly informed on the results, which is very much appreciated by patients (6).

The significantly larger proportion of patients reporting surveillance CT colonography to be better than or as expected compared to index CT colonography (94% versus 77%) was in accordance with our hypothesis that patients previously had underestimated certain

elements of index CT colonography (6). As the study information and guidance during the CT colonography was identical to index CT colonography, the more realistic expectations are most likely due to the previous experience with CT colonography. This was however not accompanied by a higher expected or lower perceived burden in surveillance CT colonography. The CT colonography examination itself was identified as the most burdensome part of the entire screening procedure when participants were forced to choose one aspect alone, and in line with previous studies the colonic insufflation with CO_2 was considered the most burdensome and painful part of CT colonography (6, 21). Although analgesia has shown to reduce total procedural pain and burden in CT colonography (22), this use of it remains a matter of practical hurdles, side effects and costs.

The Impact of Event Scale (IES) has been used in the psycho-oncology literature as a measure of cancer-related anxiety, amongst other in screening populations (5, 23, 24). Although we noticed a significant increase of the total IES score in patients with a positive result, we did not notice any clinically relevant changes in cancer-specific distress, which was in accordance to other screening studies (5, 23). The higher distress scores in women than in men was also reported in other studies (5, 25, 26). This should be considered when supplying information and providing counselling for CRC screening.

In conclusion, waiting for surveillance CT colonography caused little discomfort. In general, the expected and perceived burden of surveillance and index CT colonography were comparable. Since waiting for the results for surveillance CT colonography showed to be burdensome, minimizing the waiting time for the test result is recommended. It is reassuring that also after surveillance CT colonography almost every patient would participate again in future screening rounds.

Acknowledgments

This study was funded by The Dutch Cancer Society (KWF Kanker Bestrijding 2012-5698). Philips Healthcare (Best, the Netherlands) provided the CT colonography workstations. Neither were involved in designing or conducting this study, had access to the data or were involved in data analysis or preparation of this manuscript.

We thank research nurses Isha Verkaik and Laurens Groenendijk for their research support.

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Appendices

Appendix 1

Detailed description of CT colonography procedure.

A non-cathartic preparation consisting of two times 50 mL of iodinated contrast agent (Telebrix Gastro, Guerbet, Aulnaysous-Bois, France) was given on the day before the examination, and another 50 mL was given 1.5 hour prior to the examination (total 150 mL) in combination with a low-fibre diet for one day (10,11).

All CT colonography examinations were performed by experienced radiologic technologists. Both supine and prone position CT images were obtained on two 64-slice CT-scanners (Brilliance, Philips Healthcare, Best, the Netherlands; SOMATOM Sensation, Siemens Medical Solutions, Erlangen, Germany) using a low-dose protocol; with collimation 64 x 0.625 mm, slice thickness 0.9 mm, reconstruction interval 0.7 mm, tube voltage 120 kV, and 25 reference mAs (for Brilliance) and collimation 128 x 0.6 mm, slice thickness 1.0 mm, reconstruction interval 0.7 mm, tube voltage 120 kV, and 16 ref mAs (for SOMATOM Sensation). Before colonic insufflation 20 mg intravenous hyoscine butylbromide was administered (if contraindicated, 1 mg of glucagon hydrochloride was used intravenously), Distention of the colon was obtained via a thin flexible rectal catheter using automatic insufflation of carbon dioxide (PROTOCO2L, Bracco, EZEM, Lake Success, NY, USA).

All CT colonographies were evaluated within two weeks after the procedure by an experienced abdominal radiologist using primary 2D (window setting 1500, -250 HU) with 3D problem solving (Amsterdam: View Forum, Philips, Best, the Netherlands) and two of four trained technologists (experience of all four approximately ±1200 CT colonographies), using primary 2D read and followed by 3D (7). All readers finished with computer-aided detection (CAD) evaluation. Patients were informed about the results within two weeks of the CT colonography. Colonoscopy was done if at least one of the observers reported a lesion ≥6 mm.

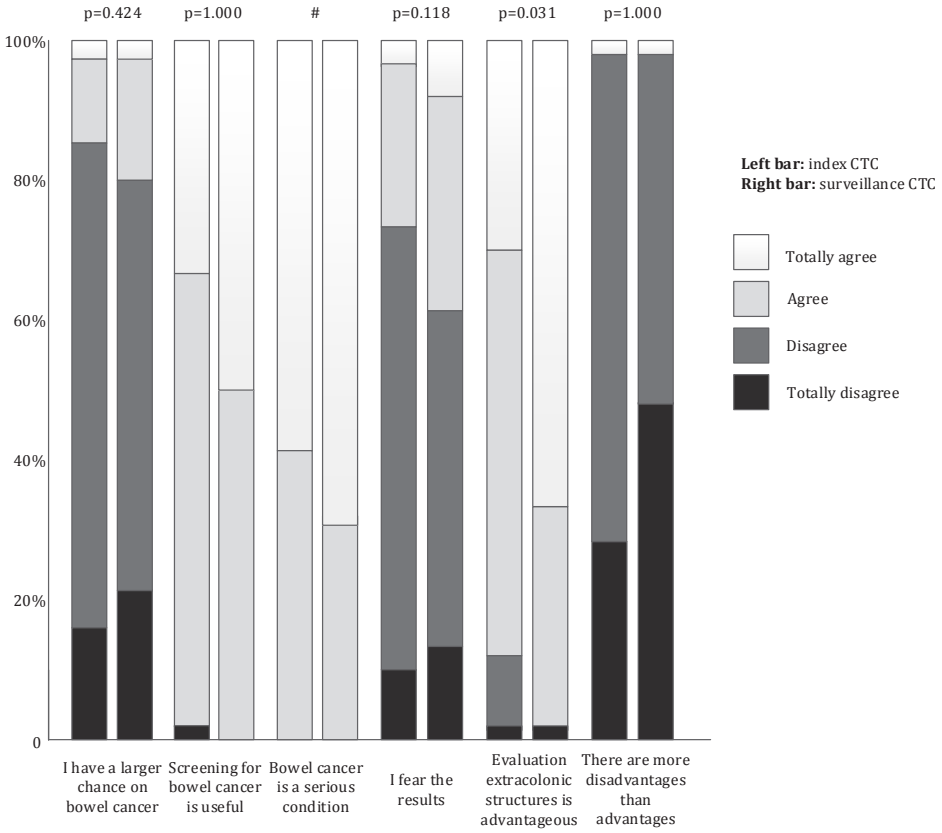
Appendix 2

Reasons for early surveillance CT colonography or colonoscopy instead of the advised surveillance CT colonography at three years

	Number of patients
Surveillance CT colonography at 1.5 years	
Preferrance directly after initial CT colonography at screening trial	2
Early colonoscopy	
Preferrance directly after initial CT colonography at screening trial	2
Abdominal complaints	4
Worries about the presence of polyps	1
Refused to give information	1
Total	10

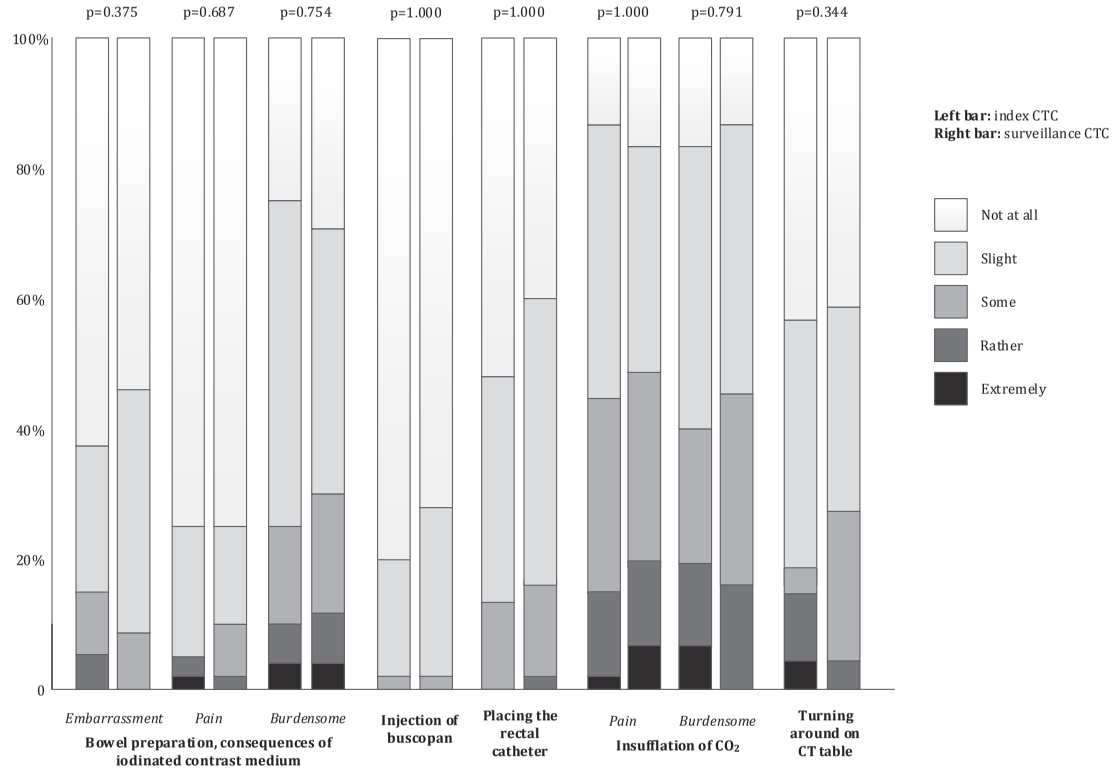
Appendix 3

General statements on bowel cancer screening in index and surveillance CT colonography. P-values of McNemar's test after dichotomization are presented on top of the bars.



Appendix 4

Perceived burden of bowel preparation and different aspects of surveillance CT colonography in comparison to index CT colonography. P-values of McNemar's test after dichotomization are presented on top of the bars.



Part II

MR imaging of terminal ileum and rectum in Crohn's disease

Chapter 6

Comparison of MRI activity scoring systems and features for the terminal ileum in Crohn's disease patients

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Abstract

Purpose

To evaluate several magnetic resonance imaging (MRI) activity scoring systems for diagnosis and grading of Crohn's disease (CD) in the terminal ileum (TI) against a histopathological and ileocolonoscopic reference standard.

Material and methods

Ethics approval and written informed consent were obtained. Suspected/proven CD subjects were prospectively recruited from December 2011 until August 2014. Each patient underwent MRI and ileocolonoscopy with standardized TI biopsies within two weeks. Four MRI scoring systems (CDMI, London, MaRIA and Clermont) and the incorporated individual features were calculated for the TI by two observers. MRI features and scoring systems were correlated to the histopathological eAIS score (0–6) and Crohn's Disease Index of Severity (CDEIS) (0-44). Reproducibility (weighted kappa and intra class coefficient (ICC)) and diagnostic accuracy (active disease eAIS≥2 and CDEIS≥3) were evaluated for MRI features and scoring systems.

Results

A total of 114 patients (mean age 31 years; female 55%) were included. All four scoring systems showed good reproducibility (ICC: 0.72–0.78), moderate correlation to eAIS (r=0.47–0.57) and strong correlation to CDEIS (r=0.65–0.73). Sensitivity and specificity for scoring systems ranged from 79% and 69–73% for observer 1 and from 74–76% and 62–67% for observer 2 against eAIS. Sensitivity and specificity against CDEIS ranged from 80–84% and 72–81% for observer one and from 77–80% and 71–78% for observer two. Reproducibility, correlation coefficients and diagnostic accuracy did not differ significantly between the scoring systems.

Conclusion

All four scoring systems were comparable in terms of reproducibility, correlation to the histopathological and ileocolonoscopic reference standard and diagnostic accuracy. Therefore, the choice may be based on other aspects such as personal preference, experience and practical considerations.

Introduction

Magnetic resonance imaging (MRI) is widely used for evaluating Crohn's disease (1-3). Grading of disease activity is important to optimally determine treatment strategy and thereafter monitor response to treatment. Extensive research has revealed multiple MR features that are useful in assessing disease activity (4-7). Using these features, several grading systems (MaRIA, Clermont, London and CDMI score) have been developed and validated particularly in the terminal ileum (4, 6, 8-10). Ideally, an activity score should be objective, easy to use, reproducible, quantifiable and non-invasive. The available scoring systems incorporate different features and were developed based on different reference standards (histopathologic and endoscopic scores), which complicate their comparison. There is a clinical need, however, to determine the strengths of each scoring system and the incorporated features.

The terminal ileum is the most commonly affected part of the gastrointestinal tract in Crohn's disease. The ileocecal valve (or ileocecal anastomosis in post-operative patients) is a relevant landmark both at ileocolonoscopy and MRI, making it and its surrounding area an optimal location for accurate correlation between disease features on MRI and endoscopic or histopathologic inflammation. In this respect, a fixed location histopathologic reference standard would provide the most robust measurements and fair comparison to MRI. However, ileocolonoscopy provides an overview of disease extent, which better resembles the evaluation by MRI.

The aim of this prospective study was to compare multiple scoring systems for grading of Crohn's disease activity in the terminal ileum and evaluate individual MRI parameters using a histopathological and endoscopic reference standard.

Materials and methods

Patients

From December 2011 until August 2014, a multicenter trial in two tertiary referral centers (1. Academic Medical Center, Amsterdam, the Netherlands and 2. University College London Hospitals, London, United Kingdom) was performed with patients with suspected or proven Crohn's disease (based on endoscopy or histopathology) (≥18 years of age) who underwent MRI and ileocolonoscopy (within two weeks) as part of their clinical work-up (VIGOR++ study). For the current study, we included all patients in which a complete ileocolonoscopy with terminal ileum biopsies was performed. The following exclusion criteria were used: general

contraindications for MRI (claustrophobia, pregnancy, renal insufficiency, pacemaker), an incomplete scan protocol or if no biopsies from the terminal ileum were taken (e.g. in case of incomplete colonoscopy due to impassable strictures). Ethical permission was obtained from the hospitals' medical ethics committee and all patients gave written informed consent.

Reference standard

As the MaRIA and Clermont score were developed using the CDEIS as a reference standard, and the CDMI and London score were developed using the eAIS (4, 6, 9), both reference standards were used for analysis in order to strengthen the comparison between the scoring systems, by minimizing the influence of the chosen reference standard on the correlation with each respective scoring system.

eAIS Ileocolonoscopy was performed according to standard quality indicators by either a gastroenterologist or a senior resident in gastroenterology under direct supervision of a gastroenterologist using a standard endoscope (model CF-160L, Olympus). Sedation was administered intravenously at the discretion of the endoscopist. For proper matching to MRI, two to four biopsies were taken from a fixed location. In case of disease, the most inflamed area within the distal 5 cm of the terminal ileum was biopsied. If no disease was present, biopsies were taken approximately 2 cm proximal to the ileocecal valve or anastomosis in case of previous ileocecal resection. The terminal ileum biopsies were examined in consensus by two experienced pathologists (LB and MRJ), who were unaware of clinical or radiologic findings. Each biopsy was examined on at least three slices and graded according to the endoscopic biopsy acute inflammation score (eAIS) (4). This grading system describes the presence of six histological features (erosion or ulceration, polymorphs in lamina propria, cryptitis, crypt abscess formation, inflammatory exudates (luminal pus) and granulomas; one point for each feature) with a maximum total score of six. For each patient, the biopsy with the highest eAIS was used for analysis.

CDEIS The Crohn's Disease Endoscopic Index of Severity (CDEIS) was determined in the last 20 cm of the terminal ileum by the gastroenterologist/supervisor (11). Therefore, disease activity on MRI was also evaluated by all observers in the last 20 cm of the terminal ileum (in addition to the evaluation of the distal 5 cm).

MRI protocol

For the VIGOR++ study an extended MRI protocol with specialized sequences and additional bowel preparation for colonic distention was performed. The preparation consisted of four hours of fasting prior to the examination and oral ingestion of 800 ml Mannitol solution

(2.5%; Baxter, Utrecht, the Netherlands; Thetford, United Kingdom) three hours prior to the examination (to fill the colon), followed by an additional 1600 ml Mannitol solution (2.5%) in one hour prior to the examination (to fill the small bowel). All MRI examinations were performed at 3.0 T (Philips Intera or Ingenia, Philips, Best, the Netherlands) with a 16-channel torso phased-array body coil. The protocol consisted of coronal balanced gradient-echo (GE) and dynamic coronal balanced turbo field echo (BTFE) sequences, followed by coronal and axial T2-weighted single-shot fast spin-echo (SSFSE) sequences, the latter with and without fat saturation (Appendix 1). An axial DWI sequence (b values = 0, 300, 600 s/mm^2) was then performed, followed by a coronal fat-saturated 3D T1-weighted spoiled gradient-echo (SPGE) sequence. Subsequently, a dynamic contrast-enhanced (DCE) coronal 3D T1-weighted fast SPGE sequence was performed. These DCE images were acquired in the setting of a different study and not evaluated as part of the current report as DCE evaluation is not incorporated in any widely accepted scoring system. Sixty seconds after the start of the dynamic sequence intravenous gadolinium contrast medium was administered using the standard contrast agent in the participating centers (Gadovist 1.0 mmol/L, Bayer Schering Pharma, Berlin, Germany; Dotarem 0.5 mmol/L, Guerbet, Paris, France). Subsequently, contrast-enhanced coronal and axial T1-weighted SPGE images were acquired, for approximately seven minutes after contrast injection. To reduce bowel peristalsis, three separate doses of 10 mg butylscopolamine bromide (Buscopan, Boehringer Ingelheim) were applied at equal intervals during the examination (Appendix 1).

Image analysis

In each MRI examination the distal terminal ileum (last 5 cm) was evaluated for the presence and severity of disease activity by two out of four experienced abdominal radiologists blinded to clinical findings. The first pair (observer 1) consisted of two radiologists (CYN and JS) with 18 years of experience (>1100 MR enterography examinations) and 21 years (>800 MR enterography examinations), respectively. CYN evaluated the scans from the first center, while JS evaluated all scans from the second center. The second pair (observer 2) consisted of two radiologists (DP and ST) with 5 years of experience (>500 MR enterography examinations) and 13 years of experience (>1500 MR enterography examinations) and evaluated scans from the first and second center, respectively.

The features used in the different scoring systems (CDMI, London, MaRIA and Clermont score) were assessed in the most affected part of the last 5 cm of the terminal ileum (full definitions given in Appendix 2): wall thickness in millimeters, mural T2 signal intensity, perimural T2 signal, T1 enhancement. In addition, the presence of edema and ulcers were scored (4, 5, 8).

Additionally, luminal distention, defined as the percentage of adequate distension of the distal terminal ileum, was graded on a 5-point scale (<20%, 20-40%, 40-60%, 60-80%, >80%).
Two research fellows (CTN, >200 MR enterographies; and CP, >100 MR enterographies), who were blinded to clinical information and findings from the observers, obtained quantitative apparent diffusion coefficient (ADC) values from the distal 5 cm of the terminal ileum by drawing a region of interest (ROI) of 0.3-1.0 cm^2 in the area of the highest signal intensity on DWI. To determine the uniformity in ADC value between patients, an ROI of at least 2.5 cm^2 was drawn in the erector spinae muscles. Additionally, wall signal intensity (SI) was measured on pre- and post-contrast sequences by ROI placement in area with most pronounced enhancement.

Relative contrast enhancement (RCE) was calculated from wall SI values using a modified formula as described by Rimola et al (Appendix 2) (6). In our experience, using the background noise (SD) correction is not suitable for correction of the signal noise ratio (SNR). We found that SDnoise values outside the body are highly dependent on the distance of the ROI from the body and gave inconsistent measurements.

For all RCE and a subset of ADC measurements, a scan specific scaling correction was applied (12).

The different MRI scoring systems (CDMI, London, MaRIA and Clermont score) were calculated using the formulas described in Appendix 2 (4, 6, 9).

Statistical analysis

Interobserver agreement was calculated for ordinal data using a weighted kappa coefficient, for binominal data using a multirater kappa coefficient, and for continuous data using a multirater intraclass correlation coefficient. Kappa and intraclass correlation coefficient values were interpreted using the following criteria: ≤0.20, poor; ≥0.21–0.40, fair; ≥0.41–0.60, moderate; ≥0.61–0.80, good; ≥0.81–1.00,very good (13).

Spearmans rank correlation for non-normal distributions was used to test associations between MRI features, calculated scoring systems, histologic eAIS and CDEIS. Non-normality was assessed by visual interpretation of histograms and descriptive statistics. Interpretation of Spearmans correlation coefficient was done as follows: >0-<0.20, very weak; ≥0.20-<0.40, weak; ≥0.40-<0.60, moderately; ≥0.60-<0.80, strong; ≥0.80-<1.00, very strong. Cut off points for active disease as assessed by MRI scoring systems were obtained from the literature: 3 for CDMI score, 4.1 for London score, 7 for MaRIA score and 8.4 for Clermont score (4, 8, 10).

To evaluate the ability to predict active disease the eAIS was dichotomized using a cut-off ≥2 (4). For CDEIS a cut-off of ≥3 was used (14). Steiger Z-test was used to compare correlations between the different scoring systems and eAIS/CDEIS for each observer. Sensitivity, specificity and accuracy were compared using the McNemar test.

A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics version 22.0 for Mac (SPSS, Chicago, III, USA) and Vassarstats.com (Richard Lowry, Poughkeepsie, NY, USA).

Results

Patients

Of the 171 patients eligible for participation, 57 patients were excluded for the following reasons: >14 days between MRI and colonoscopy (n=7), did not drink first 800 ml Mannitol (n=6), MRI performed at 1.5 T (n=13), cancelled or aborted colonoscopy (n=5), missing MRI sequences (n=7), severe contaminated colonoscopy (n=1), severe language barrier (n=1), no terminal ileum biopsies were taken (n=16) and in one patient (reactive) ischemia was seen by the pathologists. Finally, 114 underwent complete ileocolonoscopy with biopsies in the distal terminal ileum and were included in the present study. All of these patients underwent the complete MRI protocol, except for five patients, where the ADC map was missing (n=2) or the distal terminal ileum was not in the FOV of the DWI sequence (n=3). These patients were not excluded for analyses of the other features. Of the 114 included patients, 98 (86%) had a final diagnosis of Crohn's disease, while others were diagnosed with ulcerative colitis (n=2), irritable bowel syndrome (n=7), resolved infection (n=1), diverticulosis (n=2), intestinal malrotation (n=1), unclear diagnosis (n=1) or no disease (n=2). Baseline characteristics of all included patients are described in Table 1.

The eAIS ranged from 0 to 4 with a median of 2 (IQR:0-2) (no biopsies were graded with score 5 or 6). Segmental CDEIS ranged from 0 to 36, with a median of 4.9 (IQR:0-14.1).

Mean luminal distention values for observer 1 and observer 2 were 3.41 (SD: 0.891) and 3.40 (SD: 0.85), respectively.

MRI scoring systems

Reproducibility – All four scoring systems showed good interobserver variability, with the highest ICC of 0.78 for the CDMI (Table 2).

Table 1. Baseline characteristics of the study population

Total no. of patients	**114**
Gender, female, n (%)	63 (55)
Age at MRI in years, median (IQR)	31 (24-41)
Disease duration in years, median (IQR)	8 (4-15)
Days between ileocolonoscopy and MRI, median (IQR)	4 (2-7)
History of ileocecal resection, n (%)	30 (26)
Therapy	
Anti-tumor necrosis factor, n (%)	28 (25)
Steroids, n (%)	19 (17)
Purine-antagonists, n (%)	19 (17)
5-ASA, n (%)	19 (17)
Methotrexate, n (%)	5 (4)
Harvey-Bradshaw index, median (IQR)	5 (2-8)
Harvey-Bradshaw index >4, n (%)	64 (56)
CRP (mg/L), median (IQR)	3.6 (1.0-10.9)

5-ASA: 5-aminosalicylic acid, CRP: C-reactive protein, eAIS: acute inflammation score, IQR: interquartile range, MRI: magnetic resonance imaging

Table 2. Reproducibility and correlation for all four scoring systems to eAIS and to CDEIS

Reproducibility	**ICC (95% CI)**			
CDMI score	0.78 (0.69-0.84)			
London score	0.73 (0.63-0.81)			
MaRIA score	0.72 (0.62-0.80)			
Clermont score	0.72 (0.62-0.80)			
	Observer 1		**Observer 2**	
Correlation to eAIS	**Coefficient**	***p-Value***	**Coefficient**	***p-Value***
CDMI score	0.57	<0.001	0.52	<0.001
London score	0.57	<0.001	0.50	<0.001
MaRIA score	0.51	<0.001	0.47	<0.001
Clermont score	0.53	<0.001	0.50	<0.001
	Observer 1		**Observer 2**	
Correlation to CDEIS	**Coefficient**	***p-Value***	**Coefficient**	***p-Value***
CDMI score	0.66	<0.001	0.73	<0.001
London score	0.68	<0.001	0.71	<0.001
MaRIA score	0.65	<0.001	0.69	<0.001
Clermont score	0.68	<0.001	0.70	<0.001

ICC:intraclass coefficient, CI: confidence interval, eAIS: acute inflammation score, CDMI: Crohn's disease MRI index, MaRIA: Magnetic Resonance Index of Activity

Correlation to eAIS – All four scoring systems showed moderate correlation to the eAIS for both observers (Table 2).

Correlation to CDEIS – All four scoring systems showed strong correlations to CDEIS for both observers (Table 2), while no significant differences were found between the correlation coefficients (all p-values for observer 1>0.4; all p-values for observer 2≥0.1).

Diagnostic accuracy – For both observers, similar sensitivity, specificity, PPV, NPV and accuracy for diagnosing active disease at histopathology (eAIS≥2) and ileocolonoscopy (CDEIS≥3) was seen all four scorings systems (Table 3). No significant differences in sensitivity and specificity were found (p>0.05), except for a higher sensitivity for MaRIA compared to Clermont score for the CDEIS for observer 1 (84% versus 80%, p=0.03). Specificity and accuracy were higher for Clermont compared to MaRIA, but this difference was not significant (p>0.05).

MRI features

Reproducibility – Interobserver agreement of the individual MRI features incorporated in the different scoring systems is described in table 4. Enhancement, perimural T2 signal, ADC and RCE showed good interobserver agreement (ICC: 0.68 (95% CI: 0.55-0.80), 0.68 (95% CI: 0.57-0.78), 0.70 (95% CI: 0.56–0.80) and 0.70 (95% CI 0.59–0.78), respectively). ADC erector spinae measurements for observer 1 and observer 2 showed mean values of 1617 (SD: 132, range: 1194–1893) and 1617 (SD: 204, range: 1216–2491).

Correlation to eAIS and CDEIS – Wall thickness, mural T2 signal, enhancement, mural edema and ADC showed moderate correlation to eAIS for both observers (r=0.40-0.60), while other individual features showed weak or no correlation (r<0.40) (Table 5). Wall thickness, mural T2 signal and enhancement showed strong correlation to CDEIS (r=0.60–<0.80), while mural edema showed moderate-to-strong correlation (r=0.40–<0.80). ADC and RCE showed moderate correlation (r=0.40–<0.60), while ulcers and perimural T2 signal showed weak-to-moderate correlation (r=0.20–<0.60) to CDEIS.

Table 3. Diagnostic accuracy for observer 1 and observer 2 for all scoring systems

eAIS		Observer 1					Observer 2				
Scoring systems	**Cut off point**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
CDMI score	3[a]	79%	73%	75%	77%	76%	74%	67%	70%	71%	71%
London score	4.1[a]	79%	73%	75%	77%	76%	74%	67%	70%	71%	71%
MaRIA score	7[b]	79%	69%	73%	76%	74%	74%	64%	68%	70%	69%
Clermont score	8.4[c]	79%	69%	73%	76%	74%	76%	62%	68%	71%	69%

CDEIS		Observer 1					Observer 2				
Scoring systems	**Cut off point**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
CDMI score	3[a]	82%	78%	80%	80%	80%	77%	78%	80%	75%	77%
London score	4.1[a]	82%	78%	80%	80%	80%	77%	78%	80%	75%	77%
MaRIA score	7[b]	84%	72%	77%	80%	78%	80%	74%	78%	77%	77%
Clermont score	8.4[c]	80%	81%	83%	77%	80%	80%	71%	80%	71%	76%

CDMI=Crohn's Disease MRI index, MaRIA=Magnetic Resonance Index of Activity, PPV=positive predictive value, NPV=negative predictive value

[a]Steward et al. Eur J Radiol 2012, [b]Rimola et al. IBD 2011, [c]Hordonneau et al. Am J Gastroenterol 2014

Table 4. Interobserver agreement between observer 1 and observer 2 for all MRI features

MRI features	
	Weighted kappa (95% CI)
Wall thickness (0-3)	0.54 (0.43-0.64)
Mural T2 signal	0.50 (0.39-0.61)
Perimural T2 signal	0.68 (0.57-0.78)
Enhancement	0.68 (0.55-0.80)
	Multirater kappa
Mural edema	0.63 (0.49-0.77)
Ulcer	0.28 (0.07-0.48)
	ICC (95% CI)
Wall thickness (in mm)	0.58 (0.33-0.74)
Apparent diffusion coefficient (ADC)	0.70 (0.56-0.80)
Relative contrast enhancement (RCE)	0.70 (0.59-0.78)

ICC: intraclass coefficient, CI: confidence interval

Table 5. Correlation between MRI features and eAIS and between MRI features and CDEIS

	eAIS				**CDEIS**			
	Observer 1		**Observer 2**		**Observer 1**		**Observer 2**	
MRI features	**r**	***p Value***	**r**	***p Value***	**r**	***p Value***	**r**	***p Value***
Wall thickness (0-3)	0.59	<0.001	0.49	<0.001	0.69	<0.001	0.67	<0.001
Mural T2 signal	0.54	<0.001	0.49	<0.001	0.61	<0.001	0.69	<0.001
Perimural T2 signal	0.34	<0.001	0.44	<0.001	0.30	<0.01	0.53	<0.001
Enhancement	0.53	<0.001	0.50	<0.001	0.65	<0.001	0.70	<0.001
Mural edema	0.44	<0.001	0.44	<0.001	0.52	<0.001	0.64	<0.001
Ulcer	0.14	0.14	0.31	0.001	0.29	<0.01	0.50	<0.001
Wall thickness (in mm)	0.57	<0.001	0.48	<0.001	0.69	<0.001	0.63	<0.001
Apparent diffusion coefficient (ADC)	-0.45	<0.001	-0.49	<0.001	-0.47	<0.001	-0.47	<0.001
Relative contrast enhancement (RCE)	0.19	0.048	0.22	0.02	0.42	<0.001	0.43	<0.001

Note - all coefficients were calculated using the Spearman rank correlation

Discussion

In this study we evaluated and compared four available MRI scoring systems and their incorporated MRI features for diagnosis and grading of inflammation in Crohn's disease. All four scoring systems were comparable in terms of interobserver agreement (ICC: 0.72–0.78), correlation to the histopathological reference standard (r: 0.51–0.57 and 0.47-0.52 for observers 1 and 2, respectively) and diagnostic accuracy (accuracy 74%–76% and 69%–71% for observers 1 and 2, respectively). Also the correlation to the CDEIS and diagnostic accuracy was comparable. Enhancement, perimural T2 signal, ADC and RCE showed good reproducibility (ICC: 0.68–0.70). The individual features showed at best a moderate correlation to the eAIS, but strong correlation to the CDEIS.

To our knowledge, this is the first study that compared four available MRI scoring systems and validated the MaRIA and Clermont score using the eAIS as the reference standard. The benefit of the approach in which we obtained this histopathological reference standard is the use of a standardized location for biopsies providing a more accurate location matching between MRI and histopathologic results. Furthermore, the robustness of the reference standard was improved by an objective evaluation of the biopsies by two experienced pathologists in consensus, who were blinded to any clinical or endoscopy information. Within a large multi-center cohort of patients with suspected and proven Crohn's disease, we correlated MRI features and scoring systems in the last 5 cm of the terminal ileum to this standardized and objective histopathological diagnosis of terminal ileum biopsies. Additionally, to take into account that the scoring systems that were developed using different reference standards (MaRIA and Clermont score using CDEIS, CDMI and London score using eAIS), we also correlated the scoring systems and features in the terminal ileum with CDEIS. To simulate the clinical practice of MR enterography examination, both suspected and known Crohn's disease patients were included in the analysis, of which some received a final diagnosis other than Crohn's disease (n=16). Although there is a risk of skewing correlation statistics around zero, the high prevalence of terminal ileum disease in our population minimizes this influence.
Previously reported interobserver agreement for the London score was high compared to our data (0.90 versus 0.73) (4). In that study exemplary reference images were available of qualitative MR features which in part may explain the high interobserver agreement. We did not include key images, as we wanted a fair and equal comparison, comparable to daily practice in many centers. Furthermore, our readers had considerable experience in reading MR features in Crohn's disease and scoring systems, both in daily clinical practice and research. However, use of key images in clinical practice could potentially improve feature and

scoring system reliability. Almost perfect reproducibility has been previously reported for the MaRIA and Clermont score by Coimbra et al. (0.97 for MaRIA) and Hordonneau et al. (0.99 and 0.98, respectively), whereas we found relatively lower reproducibility in our data (0.72 and 0.72, respectively) (10, 15). Another study reported similar interobserver agreement for the CDMI between experienced radiologists (0.80 versus 0.78 in our study) and a slightly higher agreement for the MaRIA (0.80 versus 0.72 in our study) (7). In summary, higher reproducibility was found particularly by the research groups that developed these scoring systems (4, 15, 16). This underlines the importance of validation on an independent patient cohort as was presented in the current study.

Only one study reported on the correlation of MRI features or MRI scoring systems to the eAIS. In the development study for the London score, Steward et al. reported lower correlations to the eAIS (0.40 versus 0.57/0.50 in our study) (4) which is encouraging for the utility of this score. The correlation values for MaRIA to the CDEIS were comparable to the research group that developed this scoring system (observer 1: 0.65, observer 2: 0.69 in our study versus 0.70 and 0.81 in two studies from that research group) (8, 16). Interestingly, the CDMI and London scores, although developed using histopathology, achieved a similar correlation to the CDEIS as the MaRIA score.

Tielbeek et al. reported lower correlations to CDEIS than those found in our study (MaRIA: 0.51; CDMI: 0.59) (7). To the best of our knowledge, the Clermont score has only been correlated to MaRIA, and not to a non-MRI reference standard. Although the intention of using a second reference standard was merely for excluding the influence of the chosen reference standard on our outcome, interestingly all four MRI scoring systems showed a better correlation to CDEIS than to histopathological eAIS. This higher correlation could be related due to the similarity in macroscopic assessment by ileocolonoscopy and MRI, compared to the focal microscopic evaluation by histopathology.

In our study, we found a poor correlation between RCE and eAIS, despite the application of a corrected scaling. However, we found high reproducibility for RCE, which was expected considering the optimal circumstances of confining the area of measurement to the last 5 cm of terminal ileum. Compared to Rimola et al., our study differed in that we used post-contrast sequences in the delayed phase (7 minutes post-injection), instead of sequences in the portal-venous phase (70 seconds post-injection). This might have influenced the height of maximum enhancement at time of measurement, although this is not expected to be a major influence, as the first peak after rapid enhancement is followed by a (albeit lowered) plateau phase, known from multiple DCE studies (17, 18). On the other hand, a recent study did find

that a high increase in enhancement between 70 seconds and 7 minutes is associated with higher levels of fibrosis (19). Thus, enhancement on delayed phase acquisition might have lower differentiating capability between inflammation and fibrosis. Despite these potential limitations and poor results for RCE, we did find a moderate correlation between subjective enhancement and eAIS. In addition, Scardapane et al. showed that a modified MaRIA score (without the RCE) was comparable to MaRIA in the evaluation of disease activity in Crohn's disease (20). However, for optimalization of the modified score, the weightings of the remaining features should be revised using linear regression.

Current limitations of quantitative measurements, such as scanner and interscanner variability, different technical factors and methods of measurement, were addressed by Kim and Park (21, 22). The variability produced by these limitations was confirmed in our study by a wide range of ADC values in the erector spinae muscle. Furthermore, the cut-off values determined for quantitative parameters are subject to spectrum bias, which means the numerical ADC values are individual and study-specific and therefore not generalizable (21).

MRI scoring systems have been increasingly used in research studies and might be included as outcome for clinical trials in the near-future. In contrast, daily practice has not yet seen major uptake of MRI scoring systems, despite the promising abilities for quantification of inflammatory activity and treatment response monitoring. This limited application can in part be explained by unfamiliarity with the scoring systems or some of their features, their supposedly time-consuming determination and the diversity of available scoring systems without the knowledge of their strengths and limitations. Based on our results, we cannot conclude about other factors that could influence the choice of scoring systems, such as the time needed for feature measurement and score calculation. However, we should note that the necessary scaling corrections for RCE and ADC on Philips scanner systems requires considerable technical expertise and, to our knowledge, cannot be done automatically.

Our study has several limitations. Firstly, while DWI should ideally be evaluated without contrast-enhanced sequences (and vice versa), our observers had access to all sequences during evaluation, which possibly influenced scoring of the individual MR features. However, this procedure is best comparable to daily clinical practice. Secondly, our conclusions are limited to evaluation of the terminal ileum, as biopsies were only taken from this segment. However, colonic biopsies would have provided less accurate location matching due to the absence of visual landmarks on endoscopy.

For all four scoring systems the interobserver agreement, diagnostic accuracy and the correlation to the histopathological and endoscopic reference standard were comparable. Given these comparable results, the choice for usage may be based on other aspects such as personal preference, experience and practical considerations.

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Appendix 1. scan protocol

AMC	*Balanced GE*	*BTFE dynamic*	*T2-w SSFSE*	*T2-w SSFSE*	*T2-w SSFSE*	*DWI sequence*	*3D T1-w SPGE*	*DCE sequence* [a]	*3D T1-w SPGE*	*3D T1-w SPGE*
Plane	Coronal	Coronal	Coronal	Axial	Axial	Axial	Coronal	Coronal	Coronal	Axial
Fat saturation	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
TR (ms)	2.5	2.1	628	759	967	2972	2.4	2.9	2.4	2.3
TE (ms)	1.25	1.03	60	119	50	60	1.06	1.8	1.06	1.1
Flip angle (°)	60	45	90	90	90	90	10	15	10	10
Slice thickness/gap (mm)	5/1	10/0	4/1	4/1	7/1	7/1	2/0	2.5/0	2/0	2/0
Slices	15	Variable	40	60	3x15	20	90	30	90	90
Field of view (mm)	380x380	380x380	380x380	400x400	380x302	380x260	380x380	380x380	380x380	380x380
Acquisition matrix	252x209	192x158	240x211	256x198	292x189	152x101	192x188	128x128x15	192x188	204x205x45
Reconstruction matrix	400x400	192x192	384x384	528x528	320x256	288x196	192x192	224x224x30	192x192	384x384x90
UCLH	*Balanced GE*	*BTFE dynamic*	*T2-w SSFSE*	*T2-w SSFSE*	*T2-w SSFSE*	*DWI sequence*	*3D T1-w SPGE*	*DCE sequence* [a]	*3D T1-w SPGE*	*3D T1-w SPGE*
Plane	Coronal	Coronal	Coronal	Axial	Axial	Axial	Coronal	Coronal	Coronal	Axial
Fat saturation	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
TR (ms)	2.5	1.97	661	759	1314	4975	2.2	2.9	2.2	2.1
TE (ms)	1.25	0.98	60	119	50	48	1.02	1.8	1.02	1.03
Flip angle (°)	60	45	90	90	90	90	10	15	10	10
Slice thickness/gap (mm)	5/1	10/0	4/1	4/1	7/1	7/1	2/0		2/0	2/0
Slices	15	Variable	40	60	3x15	20	90	30	90	90
Field of view (mm)	380x380	380x380	380x380	400x400	380x302	380x260	380x459	380x439	380x459	380x380
Acquisition matrix	252x211	192 x 158	236x210	252x198	292x189	152x101	192x230	128x145x15	192x230	196x197x45
Reconstruction matrix	400x400	192x192	400x400	528x528	320x320	288x196	200x240	192x224x30	200x240	384x384x90

Buscopan was administered at three time point: (1) before the coronal T2-w SSFSE sequence, (2) before the DWI sequence, and (3) before the contrast-enhanced coronal 3D T1-w SPGE sequence. [a] Use of contrast agents: BLINDED (1.0 mmol/mL; 0.1 mL/kg; 5 mL/s; Gadovist, Bayer Schering Pharma); BLINDED (0.5 mmol/mL; 0.2 mL/kg; 3 mL/s; Dotarem, Guerbet). AMC=Academic Medical Center; BTFE=Balanced Turbo Field-Echo;DCE=Dynamic Contrast Enhancement; DWI=Diffusion Weighted Imaging; GE=Gradient-Echo; SPGE=Spoiled Gradient-Echo; SSFSE=Single-Shot Fast Spin Echo; UCLH=University College London Hospital.

Appendix 2 Calculation of different MRI-based activity scoring systems.

A. CDMI score

Table. Definitions of the qualitative CDMI score[a]

Score	0	1	2	3
Mural thickness	1-3 mm	>3-5 mm	>5-7 mm	>7 mm
Mural T2 signal	Equivalent to normal bowel wall	Minor increase in signal - bowel wall appears dark grey on fat saturated images	Moderate increase in signal - bowel wall appears light grey on fat saturated images	Marked incease in signal - bowel wall contains areas of white high signal approaching that of luminal content
Perimural T2 signal	Equivalent to normal mesentery	Increase in mesenteric signal but no fluid	Small fluid rim (≤2 mm)	Larger fluid rim (>2 mm)
Enhancement	Equivalent to normal bowel wall	Minor enhancement - bowel wall signal greater than normal small bowel but significantly less than nearby vasular structures	Moderate enhancement - bowel wall signal increased but somewhat less than nearby vascular structures	Marked enhancement - bowel wall signal approaches that of nearby vascular structures

[a]Steward et al Eur J Radiol 2012

B. London score (features are scored using CDMI table)

*1.79 + 1.34*mural thickness + 0.94*mural T2 score*

C. MaRIA score

*1.5*mural thickness (mm) + 0.02*RCE + 5*edema + 10*ulceration*

The following formula was used to calculate RCE values:

RCE = (SI post-contrast - SI pre-contrast) / SI pre-contrast

D. Clermont score

*1.646*mural thickness (mm) – 1.321*ADC + 5.613*edema + 8.306*ulceration*

chapter
6

Chapter

MRI characteristics of proctitis in Crohn's disease on perianal MRI

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Abdom Radiol (NY). 2016 Oct;41(10):1918-30

Abstract

Purpose

Multiple features have been described for assessing inflammation in Crohn's disease (CD) in MR enterography, but have not been validated in pelvic magnetic resonance imaging (MRI). Retrospectively, we studied which MRI features are valuable in assessing proctitis.

Materials and Methods

CD patients (≥18 years) who underwent colonoscopy (reference standard) and perianal fistula MRI within eight weeks were included. Seventeen MRI features were blindly scored by three observers and correlated to endoscopy (regression analysis). Reproducibility (multirater kappa, intraclass correlation coeffient) was determined for all three observer pairs. MRI features were considered relevant when significantly correlated to endoscopy for ≥two observers, and reproducibility was ≥0.40 for ≥two observer pairs.

Results

Perianal MRI of 58 CD patients were included. Wall thickness, rectal mural fat, creeping fat and size of mesorectal lymph nodes showed a significant correlation with endoscopy for ≥two observers (p=0.000-0.023, p=0.011-0.172, p=0.007-0.011 and p=0.000-0.005, respectively) with a kappa/intraclass correlation coefficient of ≥0.60 for ≥two observer pairs. Perimural T2 signal and perimural enhancement significantly correlated to endoscopy (all p values ≤0.05) for all three observers and the reproducibility was ≥0.40 for ≥two observer pairs. Mural T2 signal and degree and pattern of T1 enhancement showed significant correlation to endoscopy for two observers, but with poor to moderate reproducibility.

Conclusion

Wall thickness, mural fat and mesorectal features (perimural T2 signal, perimural enhancement, creeping fat and size of mesorectal lymph nodes) had significant correlation to endoscopy and were reproducible in diagnosing proctitis. Some established luminal features in MRE were considered not useful.

Introduction

Magnetic Resonance Imaging (MRI) of the perianal region has proven to be a valuable tool in diagnosing perianal fistulas in patients with Crohn's disease, with accuracies reported up to 93% in classifying fistulas and 96% in delineating abscesses (1, 2). The anatomy and complexity of the fistula tract can precisely be depicted which is important for treatment planning (3). Preoperative MRI has shown to reveal additional and clinically relevant information, thereby reducing recurrence rates after fistula surgery (1, 4). Another important issue in treatment planning is the concomitant presence of proctitis. Proctitis is defined as an inflammation of the rectum, approximately 12 to 15 cm from the dentate line. In the presence of proctitis the chance of fistula healing is reduced, therefore, a more aggressive medical therapy should be started and surgery should be avoided (3, 5, 6).

Extensive research revealed multiple MRI features and scoring systems able to accurately assess inflammation in luminal Crohn's disease (7-9). These features have been assessed on MR enterography or MR colonography, and have not been tested in dedicated pelvic MRI, which is limited by a different scan protocol (small FOV, other sequences) and the absence of luminal contrast. As many patients with perianal fistulas will undergo a pelvic MRI before start of treatment, diagnosing the presence and degree of proctitis on this MRI could be of additional value (2, 3).

In our retrospective study we aimed to identify the MRI features of proctitis on a dedicated pelvic MRI, and to determine the reproducibility of the different MRI features.

Materials and Methods

Patients

From January 2001 until February 2014, we searched the endoscopy database (EndoAlpha Documentation, Olympus Nederland BV, Zoeterwoude, the Netherlands) of the Academic Medical Center, Amsterdam, the Netherlands, for patients (≥18 years of age) with known Crohn's disease who underwent a proctoscopy, sigmoidoscopy or colonoscopy and who also underwent a dedicated pelvic MRI according to our standard MRI perianal fistula protocol within either eight weeks prior to or after endoscopy. We chose this eight-week interval balancing inclusion versus a satisfactory interval. Patients were included if the endoscopy report mentioned the rectum, either with regard to the diagnosis of proctitis, rectal inflammation or rectitis or with regard to no signs of rectal inflammation at all. Patients could

only be included once. In that case, the most recent MRI was chosen. For consistency, MRI's performed with an endocoil or with an incomplete scan protocol were excluded. Electronic medical records were searched by a research fellow (CTN) and relevant information was noted (time of diagnosis, use of medication during the examinations, previous surgery). Patients with change in therapy, either medical or surgical, in the period between endoscopy and MRI were excluded. All included MRI scans were blinded and randomly ordered.

The requirement for review by the Medical Ethical Committee or informed consent was waived because of the retrospective nature of this study with pre-existing data.

Reference standard

With no access to clinical information or MRI scans, we evaluated the endoscopy reports of all included patients and performed a classification of lesion severity by considering three categories: grade 1) absence of lesions; grade 2) presence of inflammatory lesions without ulceration, including erythema, oedema, pseudopolyps, and aphthae; and grade 3) presence of superficial or deep ulcerations (10). The presence or absence of fistulas and anal stenosis was also noted. Uncertainties were resolved by the expert opinion of a gastroenterologist (CYP; 20 years of experience), with inflammatory bowel disease as subspecialty, with access to all endoscopical information, including endoscopy images.

MRI protocol

All MRI's were performed at 1.5 T (Signa Horizon Echospeed, LX 9.0, General Electric Medical Systems, Milwaukee, WI, USA and MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany) and at 3 T (INTERA, Philips Medical Systems, Best, the Netherlands) without bowel preparation, except four hour fasting. Patients were scanned in supine position using a torso phased-array surface coil. Sagittal, coronal, and transversal sequences were performed with the coronal and transversal sequences angulated parallel and perpendicular to the anal canal, respectively. The scan protocol consisted of T2-weighted Turbo Spin Echo sequences in the sagittal, coronal, and transversal planes, a fat suppressed transversal T2-weighted TSE sequence and a fat suppressed transversal T1-weighted TSE sequence after intravenous gadolinium. For a detailed description of all MRI parameters see appendix 1.

Observers

All MRI scans were blinded and retrospectively evaluated by three abdominal radiologists with different relevant experience level. No clinical or endoscopy findings were provided, except for the presence or absence of perianal fistulas. Observer 1 (BM; abdominal radiologist for 9 years including approximately 500 perianal fistula MRIs and 500 MR enterographies)

years, observer 2 (AS; radiologist for 20 years including approximately 300 perianal fistula MRIs and 300 MR enterographies), and observer 3 (JS; abdominal radiologist for 21 years including approximately 1300 perianal fistula MRIs and 800 MR enterographies). Before start, the observers read a document explaining the different MRI features to be evaluated with examples obtained from the previous literature and cases from a different dataset followed by a joined session discussing the features led by a fellow researcher (CTN) and the most experienced abdominal radiologist (observer 3: JS) (Figure 1) (7, 11-14). Five example cases from a different dataset were discussed. For evaluation of all cases, a digital questionnaire was developed (proctitis.co.nr).

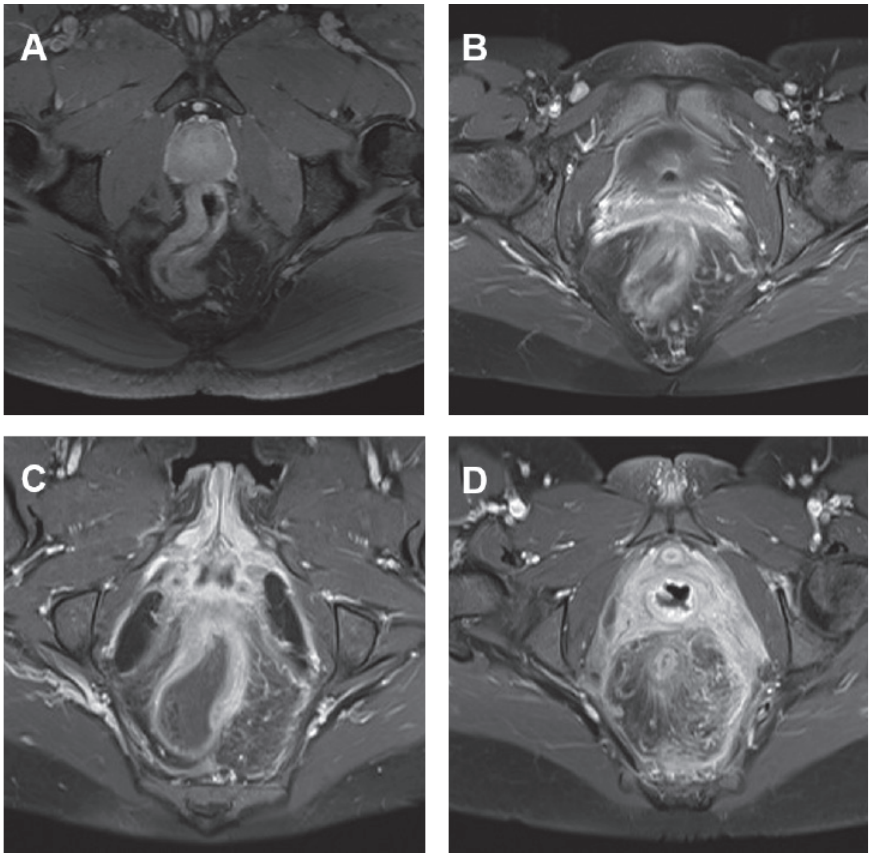

Figure 1. Axial oblique fat-saturated post-contrast T1-weighted images of four different patients with Crohn's disease with different degrees of perimural enhancement. (a) Equivalent to normal fat tissue. (b) Minor enhancement. There is blurred demarcation of the bowel wall with or without mild increase of perimural fat tissue signal. (c) Moderate enhancement. Increase of perimural fat tissue signal but less than nearby vascular structures. (d) Marked enhancement. Perimural fat tissue signal approaches that of nearby vascular structures. Mesorectal fascia enhancement can be noted.

MRI features

Quality of the scan and rectal distention were evaluated by the most experienced observer as poor (non-diagnostic), adequate (artifacts, but sufficient diagnostic quality) and good (no artifacts) and none (completely collapsed rectum), moderate (some distension but no convex contours of the rectal wall) and good (convex contours of the rectal wall) assessed in the least distended part of the rectum, respectively. Seventeen MRI features (Table 1) were evaluated by all three readers. Features were selected according to MRI features described in the literature and those used in two published scoring systems on MRI in luminal Crohn's disease (7, 10, 11). Definitions of certain features were adapted to be applicable in perianal MRI (Table 1). Additional items according to expert opinion were added: enhancement of perimural fat tissue (see Table 1 and Figure 1 for definition), creeping fat was defined as an increased amount of perirectal fat tissue and the comb sign as increased vascular structures in the perirectal fat, both scored on the sagittal images. The most affected part of the rectum was evaluated. Shortest axis of the largest lymph node per station was measured.

Statistical analysis

The maximum number of eligible patients in the given time period were included, no sample size calculations were therefore performed. Extension of this time period to earlier period was not desirable, as the MRI protocol was different before 2001 (use of endocoil) and thereby not reflecting the practice nowadays.

Normality of continuous data was tested by visual assessment of the data. Normally distributed data were presented with means with SD. For non-normally distributed data, medians with interquartile ranges (IQR) were given.

Interobserver agreement

Several multirater analyses were performed for all features individually. To test the level of interobserver agreement for the separate MRI features between the three different pairs of radiologists the appropriate measure was used. For all ordinal data, a weighted kappa coefficient was calculated per two raters. For the binominal data, a kappa coefficient was used calculated per two raters. For continuous data, an intraclass correlation coefficient was determined per two raters. Both kappa and intraclass correlation coefficient values were interpreted as follows: 0-0.20, poor; 0.20-0.40, fair; 0.40-0.60, moderate; 0.60-0.80, good; 0.80-1.00, very good (15).

Table 1. MRI features, evaluated in the most affected part of the rectum

MRI features				
Wall thickness in mm[1]				
Largest regional lymph node in mm (mesorectal, obturator, iliac, inguinal)				
% of circumference involved	0-25%	26-50%	51-75%	76-100%
Mural T2 signal[2]	Equivalent to normal bowel wall	Minor increase - bowel wall appears dark grey on fat saturated images	Moderate increase - bowel wall appears light grey on fat saturated images	Marked increase - bowel wall contains areas of white high signal approaching that of nearby vascular structures
Perimural T2 signal[2]	Equivalent to normal fat tissue	Increase in signal but no fluid	Small fluid rim (≤2 mm)	Larger fluid rim (>2 mm)
T1 enhancement[2]	Equivalent to normal bowel wall	Minor enhancement - bowel wall signal increased but significantly less than nearby vascular structures	Moderate enhancement - bowel wall signal increased but somewhat less than nearby vascular structures	Marked enhancement - bowel wall signal approaches that of nearby vascular structures
T1 enhancement pattern[2]	N/A[a]	Homogeneous	Mucosal	Layered
Enhancement of perimural fat tissue	Equivalent to normal fat tissue	Minor enhancement - blurred demarcation of the bowel wall with/without mild increase of perimural fat tissue signal	Moderate enhancement - increase of perimural fat tissue signal but less than nearby vascular structures	Marked enhancement - perimural fat tissue signal approaches that of nearby vascular structures. Mesorectal fascia enhancement can be noted
Mural fat	Absent	Present		
Ulcers[1]	Absent	Present		
Supralevatoric fistula	Absent	Present		
Supralevatoric abscess	Absent	Present		
Creeping fat	Absent	Present		
Comb sign	Absent	Present		

[1]According to Rimola et al IBD 2011, [2]According to Steward at al EJR 2012.

Comparison of observers with reference standard

Endoscopical reference standard was dichotomized in absence of lesions (grade 0) versus proctitis (grade 1 and 2) because of limited size of study population. Associations were tested using regression analyses for ordinal or binominal MRI parameters. Comparison of continuous MRI parameters and endoscopical reference standard was performed using the Mann-Whitney U test, as data were not normally distributed.

Relevant MRI features

MRI features with a significant correlation (p value of ≤0.05) between the reference standard and at least two of three observers, and with a (weighted) kappa/intraclass correlation coefficient value of ≥0.60 for at least two of three observer pairs, were identified and considered potentially relevant in diagnosing proctitis. In post hoc analysis, threshold for the kappa/intraclass correlation in considering a feature relevant was changed to ≥0.40, because this concerns an initial study aimed at identifying potential relevant features and therefore sufficient features should be identified to be used in a future validation study.

All statistical analyses were performed with IBM SPSS Statistics version 20.0 for Windows (SPSS, Chicago, Ill, USA) and Vassarstats.com (Richard Lowry, Poughkeepsie, NY, USA).

Results

Patient and MRI characteristics

Between January 2001 and February 2014, 106 Crohn's disease patients were extracted from the database who underwent perianal MRI within eight weeks of endoscopy (Figure 2). After exclusion, a total of 58 patients remained (Figure 2) of which 21 (36%) male and a mean age of 38.7 (SD 12.6) at time of MRI. The median time between MRI and endoscopy was 12 days ([IQR 6-21]; range 0-44). Thirty-two (55%) had no signs of proctitis at endoscopy and 26 (45%) had signs of proctitis, of which 19 (33%) had non-ulcerative proctitis and 7 (12%) ulcerative proctitis. Table 2 summarized the demographic and clinical data of patients included in the study.

Quality of the MRI scans was considered good in 74.1% (43/58) and adequate in 25.9% (15/58). There was no rectal distention in 43.1% (25/58), moderate distention in 34.5% (20/58) and good distention in 22.4% (13/58).

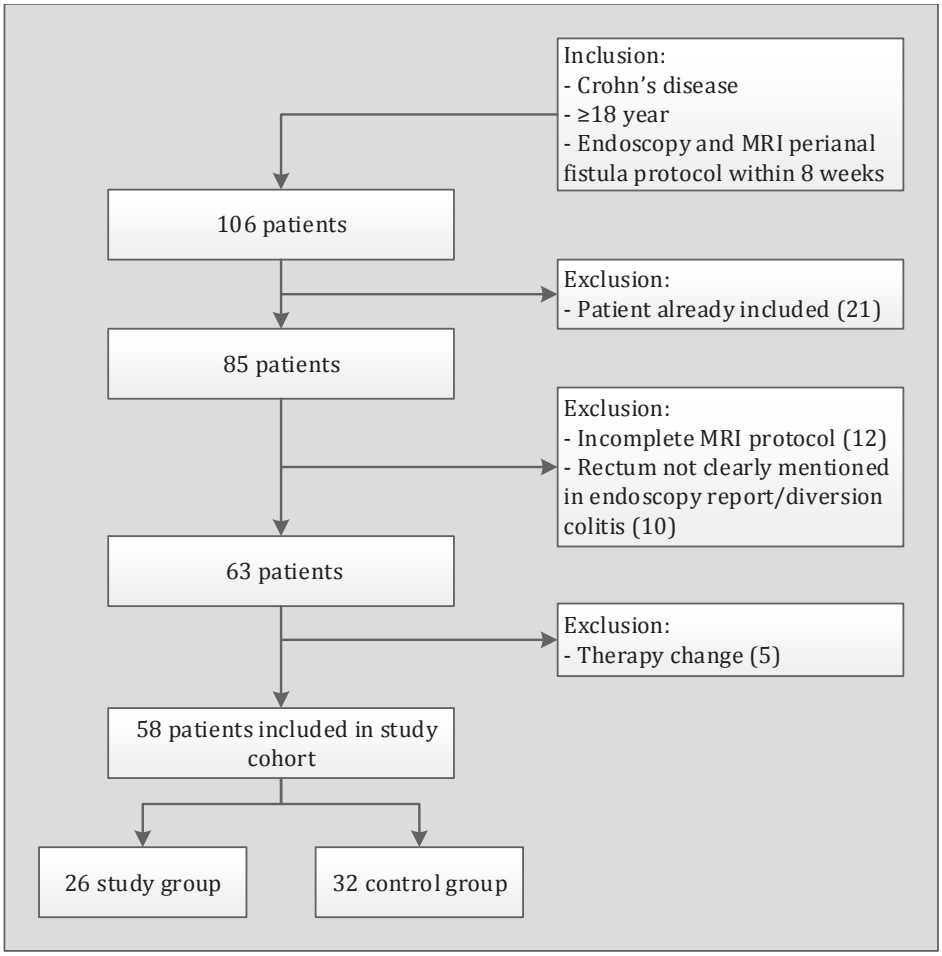

Figure 2. Flow chart of search in hospitals' patient database.

Interobserver agreement

Agreement between the three observer pairs is presented in table 3. For size of mesorectal lymph nodes the agreement for all three pairs ranged between good to very good (0.78 and 0.83). Wall thickness, mural fat and creeping fat showed for two of three observer pairs good agreement (0.70-0.58-0.69, 0.67-0.57-0.64 and 0.48-0.69-0.76, respectively). Perimural T2 signal, supralevatoric extension of fistula and abscess showed for all three observer pairs at least moderate agreement (≥0.40). Perimural enhancement and size of inguinal lymph nodes showed at least moderate agreement for two of three observer pairs (0.46-0.34-0.59 and 0.65-0.38-0.43).

Table 2. Demographic characteristics of the study population

	Study group	Control group
No. (%) of patients	26 (55)	32 (45)
Men (%)	13 (50)	8 (25)
Women (%)	13 (50)	24 (75)
Age at time of imaging (y), median (IQR)	40 (27-51)	37 (28-47)
Disease duration (y), median (IQR)	7 (4-11)	7 (3-21)
Days between endoscopy and MRI, median (IQR)	13 (7-23)	11 (4-20)
Previous surgery, no. (%) of patients	16 (62)	22 (69)
Maintenance therapy, no. (%) of patients	18 (69)	23 (72)
Antitumor necrosis factor, no. (%) of patients	5 (19)	11 (34)
Steroids, no. (%) of patients	8 (31)	3 (9)
Immunosuppressant, no. (%) of patients	12 (46)	12 (38)
5-Aminosalicylic acid medications, no. (%) of patients	1 (4)	7 (22)
Vedolizumab, no. (%) of patients	1 (4)	0
Presence of fistula (on MRI)		
None, no. (%) of patients	3 (12)	8 (25)
Simple, no. (%) of patients	11 (42)	16 (50)
Complex, no. (%) of patients	12 (46)	8 (25)
Endoscopy diagnosis		
Absence of lesions, no. (%) of patients	0	32 (100)
Non-ulcerative lesions, no. (%) of patients	7 (27)	0
Ulcerations, no. (%) of patients	19 (73)	0

Note - IQR=interquartile range

Comparison of observers with reference standard

In table 4 the comparison of continuous variables (upper part) and ordinal variables (lower part) with the reference standard are presented. Wall thickness was significantly smaller for all three observers in patients without proctitis than in patients with proctitis (observer 1: 6.0 mm vs. 9.0 mm, p=0.000; observer 2: 8.0 mm vs. 11.0 mm, p=0.023; observer 3: 4.0 mm vs. 10.0 mm, p=0.000).

Mesorectal lymph nodes were smaller for all three observers in patients without proctitis than with proctitis (observer 1: 3.0 mm vs. 5.0 mm, p=0.001; observer 2: 4.0 mm vs 6.0 mm, p=0.005; observer 3: 3.0 mm vs 6.0 mm, p=0.000).

Percentage of circumference involved, perimural T2 signal, perimural enhancement and the presence of the comb sign showed also a significant correlation between all three observers and the endoscopy reference standard (Table 4).

Table 3. Multirater Kappa and intraclass correlation coefficient values between the observer pairs

MRI features	1 vs 2	2 vs 3	1 vs 3
Wall thickness	0.70 (0.54-0.81)	0.58 (0.38-0.73)	0.69 (0.53-0.81)
Mesorectal lymph nodes	0.83 (0.72-0.89)	0.78 (0.66-0.87)	0.83 (0.72-0.89)
Obturator lymph nodes	0.31 (0.06-0.53)	0.26 (0.00-0.48)	0.27 (0.01-0.49)
Iliac lymph nodes	0.38 (0.14-0.58)	0.23 (-0.03-0.46)	0.24 (-0.01-0.47)
Inguinal lymph nodes	0.65 (0.48-0.78)	0.38 (0.14-0.58)	0.43 (0.20-0.62)
% of circumference involved	0.16 (0.03-0.29)	0.17 (0.06-0.27)	0.47 (0.27-0.67)
Mural T2 signal	[a]26% (15/58)	[a]43% (25/58)	[a]41% (24/58)
Perimural T2 signal	0.50 (0.34-0.67)	0.57 (0.41-0.73)	0.71 (0.58-0.85)
T1 enhancement	0.13 (0.03-0.24)	0.14 (0.01-0.27)	0.39 (0.22-0.56)
T1 enhancement pattern	0.13 (0.02-0.25)	0.25 (0.12-0.38)	0.43 (0.25-0.61)
Perimural enhancement	0.46 (0.29-0.64)	0.34 (0.17-0.50)	0.59 (0.42-0.76)
Mural fat	0.67 (0.44-0.90)	0.57 (0.34-0.81)	0.64 (0.37-0.90)
Ulcers	[a]64% (37/58)	0.13 (0-0.39)	0.25 (0-0.57)
Supralevatoric fistula	0.48 (0.24-0.72)	0.57 (0.31-0.82)	0.59 (0.39-0.79)
Supralevatoric abscess	0.53 (0.21-0.86)	0.53 (0.24-0.82)	1
Creeping fat	0.48 (0.18-0.77)	0.69 (0.46-0.92)	0.76 (0.53-0.98)
Comb sign	0.18 (0.01-0.34)	0.20 (0.03-0.36)	0.55 (0.32-0.78)

[a]Proportion of agreement calculated instead of kappa, because observed concordance is smaller than mean-chance concordance.

Mural T2 signal, T1 enhancement, T1 enhancement pattern and creeping fat showed a significant correlation for two of three observers. Ulcers and supralevatoric extension of fistula and abscess did not show a significant correlation to the reference standard for all three observers.

Relevant MRI features

Based on predefined criteria, the following MRI features were considered most relevant in diagnosing proctitis (Table 3 and Table 4): wall thickness, size of mesorectal lymph nodes, mural fat and creeping fat showed a significant correlation between at least two of three observers and the endoscopy reference standard, as well as a kappa/intraclass correlation coefficient of ≥0.60 for at least two of three observer pairs (Figure 3 and 4).

Table 4. Comparison of observers with reference standard

		Observer 1		Observer 2		Observer 3	
MRI Features		**Median (IQR)**	***P* Value**	**Median (IQR)**	***P* Value**	**Median (IQR)**	***P* Value**
Wall thickness (mm)	Normal	6.0 [4.0-8.0]	0.000	8.0 [7.0-12.0]	0.023	4.0 [3.0-6.8]	0.000
	Proctitis	9.0 [7.0-10.5]		11.0 [9.8-12.0]		10.0 [7.0-12.3]	
Mesorectal lymph nodes (mm)	Normal	3.0 [2.0-4.8]	0.001	4.0 [0.0-5.8]	0.005	3.0 [0.5-5.0]	0.000
	Proctitis	5.0 [4.0-7.0]		6.0 [4.8-7.3]		6.0 [4.0-8.0]	
Obturator lymph nodes (mm)	Normal	5.0 [4.0-7.0]	0.647	5.0 [0.0-6.0]	0.535	4.0 [3.0-5.0]	0.905
	Proctitis	6.0 [2.3-7.0]		5.0 [2.3-6.0]		4.0 [3.0-5.3]	
Iliac lymph nodes (mm)	Normal	5.0 [0.0-7.0]	0.375	5.0 [4.0-7.0]	0.855	0.0 [0.0-4.0]	0.403
	Proctitis	6.0 [4.0-7.0]		6.0 [0.0-7.0]		0.0 [0.0-4.3]	
Inguinal lymph nodes (mm)	Normal	8.0 [7.0-9.8]	0.442	8.0 [7.0-9.8]	0.427	8.0 [6.0-10.0]	0.575
	Proctitis	7.0 [6.0-10.0]		7.0 [6.0-9.0]		7.0 [6.0-10.0]	
		Exp(B) (95% CI)	***P* Value**	**Exp(B) (95% CI)**	***P* Value**	**Exp(B) (95% CI)**	***P* Value**
% of circumference involved		14.18 (3.60-55.87)	0.000	12.65 (2.60-61.65)	0.002	9.90 (2.96-31.09)	0.000
Mural T2 signal		4.34 (1.58-11.91)	0.004	3.16 (1.07-9.37)	0.038	3.90 (1.07-16.30)	0.062
Perimural T2 signal		20.43 (4.13-100.99)	0.000	4.79 (1.72-13.34)	0.003	20.25 (4.95-85.76)	0.000
T1 enhancement		3.10 (1.15-8.18)	0.025	2.16 (1.30-6.10)	0.145	2.69 (1.01-7.17)	0.049
T1 enhancement pattern		2.48 (1.05-6.46)	0.064	6.28 (2.00-19.71)	0.002	2.89 (1.11-7.57)	0.030
Perimural enhancement		11.70 (3.27-41.85)	0.000	9.06 (2.81-29.22)	0.000	17.76 (4.35-74.07)	0.000
Mural fat		6.67 (1.28-34.92)	0.025	2.23 (0.71-7.06)	0.172	16.41 (1.91-140.75)	0.011
Ulcers		0.47 (0.11-2.02)	0.307	1.11 (0.34-3.60)	0.868	9.30 (1.04-83.13)	0.046
Supralevatoric fistula		1.25 (0.44-3.56)	0.673	1.60 (0.46-5.52)	0.460	1.93 (0.57-6.51)	0.291
Supralevatoric abscess		5.64 (0.59-53.93)	0.133	3.11 (0.82-11.86)	0.096	5.64 (0.60-53.93)	0.133
Creeping fat		[a]		7.09 (1.71-29.35)	0.007	16.41 (1.91-140.75)	0.011
Comb sign		7.00 (1.91-25.67)	0.003	5.96 (1.48-23.97)	0.012	13.18 (3.18-54.57)	0.000

[a]Not calculated because of the presence of a zero in the crosstab

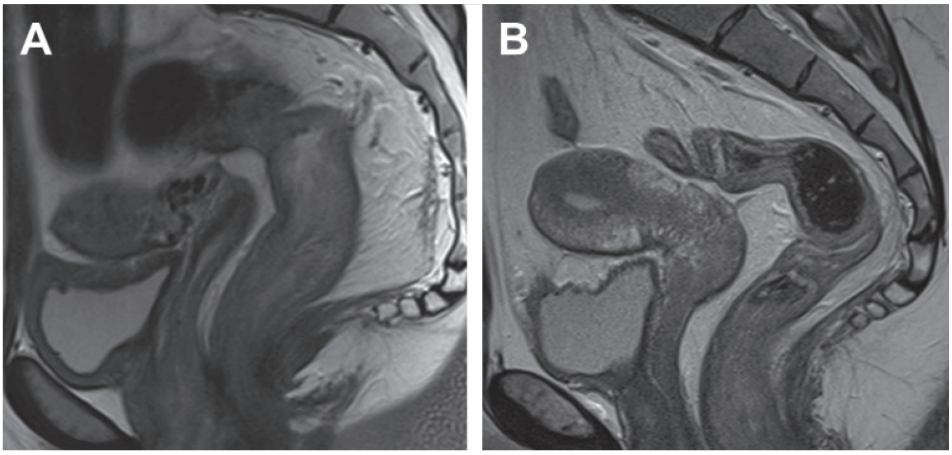

Figure 3. Sagittal T2-weighted image of two different patients with Crohn's disease. (a) 25-year old female with ulcerative proctitis at endoscopy. The image shows increased amount of mesorectal fat tissue (creeping fat) and a subtle increase of perimural vascularity ('comb sign') in addition to rectal wall thickening. (b) 24-year old female with no signs of proctitis at endoscopy. There is no increased amount of mesorectal fat tissue and the rectum shows no abnormal MRI features.

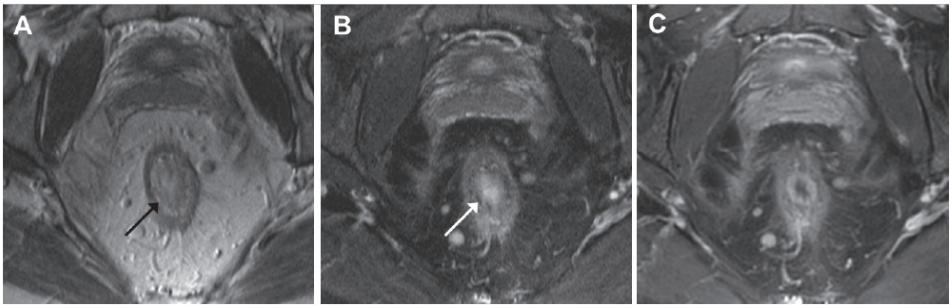

Figure 4. 53-year old female with Crohn's disease and ulcerative proctitis at endoscopy. (a) Axial oblique T2-weighted image shows high mural signal intensity and (b) low signal intensity on axial oblique fat-saturated T2-weighted image corresponding to mural fat (arrow). (c) Axial oblique fat-saturated post-contrast T1-weighted images shows moderate enhancement of the rectal wall and perimural fat tissue. In addition, wall thickening and multiple mesorectal lymph nodes are present.

In post hoc analysis, a kappa/intraclass coefficient threshold of ≥0.40 was considered, which included perimural T2 signal and perimural enhancement as they showed a moderate interobserver agreement for two of three observer pairs, and a significant correlation with the reference standard for all three observers (Appendix 2) (Figure 5).

All other features (all other lymph nodes, % of circumference involved, T1 enhancement (pattern), ulcers, supralevatoric fistula and abscess and comb sign) did not fulfill our

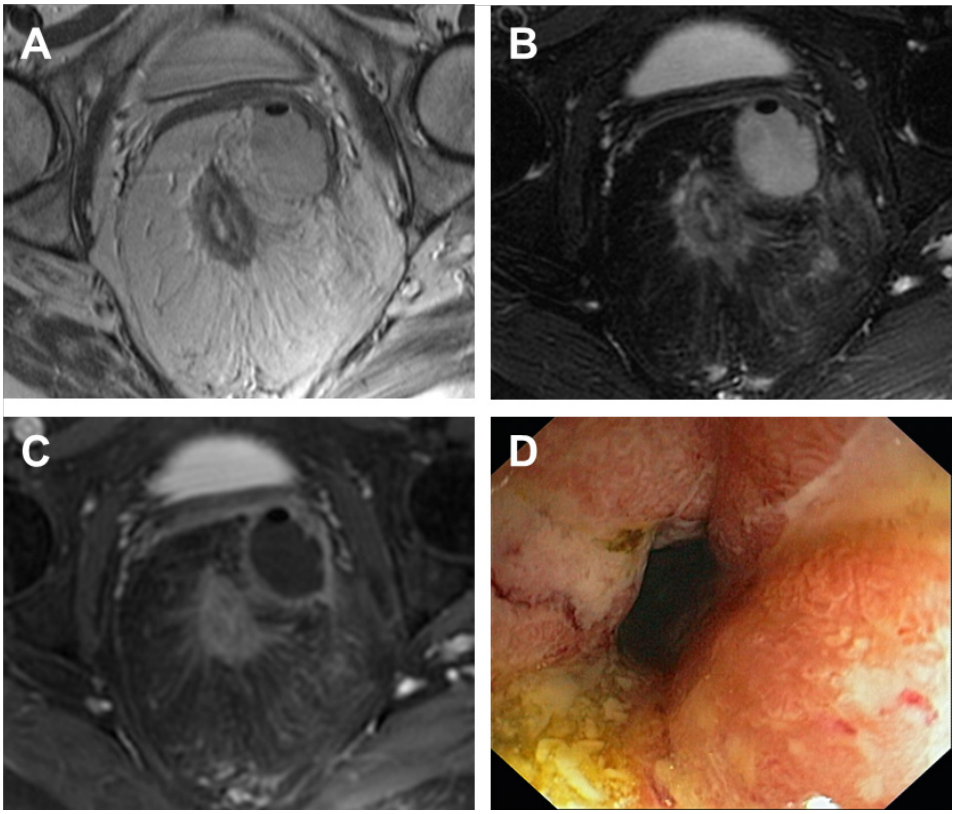

Figure 5. 49-year old female with Crohn's disease. (a) Axial oblique T2-weighted image and (b) axial oblique fat-saturated T2-weighted image show rectal wall thickening, a marked increase of T2 signal intensity and a perimural large fluid rim (>2 mm). (c) Axial oblique fat-saturated post-contrast T1-weighted images obtained at the same level shows a moderate enhancement of the rectal wall and the perimural fat tissue. In addition, there is creeping fat and a supralevatoric abscess left anterolateral of the rectum on all three images. (d) Endoscopy showed ulcerative proctitis.

predefined criteria for relevancy. Although the correlation with endoscopy was significant for two observers, mural T2 signal and T1 enhancement (pattern) showed poor to moderate agreement.

Discussion

MRI features rectal wall thickness, mesorectal lymph nodes, mural fat and creeping fat were considered relevant in diagnosing proctitis on perianal MRI, as they showed a significant correlation between at least two observers and the endoscopy reference standard, and at least a good interobserver agreement for at least two of three observer pairs. Perimural T2 signal

and perimural enhancement showed a significant correlation for all three observers and at least a moderate interobserver agreement for at least two of three observer pairs. Mural T2 signal and T1 enhancement degree and pattern showed poor to moderate reproducibility.

This is to our knowledge the first study reporting on the specific MRI features associated with proctitis on a dedicated pelvic MRI. Previous research did study rectal involvement in Crohn's disease patients, but this was done using MR enterography or MR colonography (8-10). No specific rectal and/or perirectal features were described. Van Assche developed a MRI based-score of perianal Crohn's disease severity with rectal wall thickening as the sole indicator for rectal inflammation, which can be used for evaluation of response to treatment (16, 17). Our results confirmed the correlation between rectal wall thickening and inflammation, in addition, a moderate to good interobserver agreement was observed. Most features considered relevant in diagnosing proctitis involved the mesorectal fat tissue (Figures 4 and 5). This is in contrast to a study that showed only fair reproducibility for perimural features on MR enterography (11). Crohn's disease is known for its transmural inflammation and subsequent perimural involvement. In the rectum this perimural involvement was often quite prominent. This might be related to the isolated localization of the rectum surrounded by mesorectal fat tissue and therefore perimural changes are somewhat easier appreciated than when multiple loops of bowel are closely aligned. Further, the rectum was not or moderately distended in most cases, which might result in the perirectal features becoming more apparent. This rectal collapse might have led to increased wall thickness measurements. Even so, there was a significant difference in wall thickness in proctitis versus no proctitis as observed by all three observers. Further research should focus on the predictive value of the individual MRI features identified in our study, and the clinical use in monitoring treatment response as a non-invasive alternative to endoscopy and in case of severe anal stenosis.

In contrast, luminal features already proven to be useful in establishing disease severity on MR enterography and MR colonography, for example T2 signal intensity and T1 enhancement (pattern and degree), were considered not useful in our study (7-9). In order to decide if a certain feature is considered normal or increased, one must be able to compare it to other colonic loops, which were almost never included in the field of view of the T1-weighted and T2-weighted fat saturated sequences that was only performed in the axial oblique plane. Also, in our standard perianal fistula protocol no T1-weighted pre-contrast images for comparison were performed. For the T2 signal intensity of the rectal wall in almost all cases (normal or proctitis) observers scored the T2 signal intensity of the rectal wall at least as slight, but mostly as moderately increased (Figure 6).

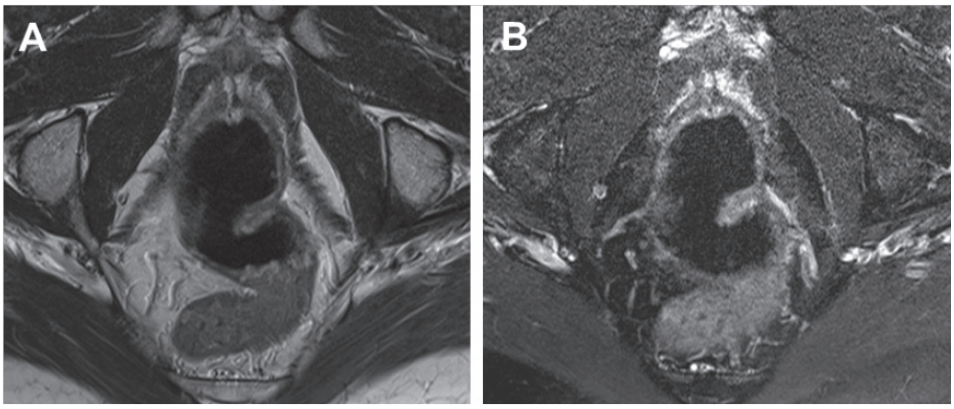

Figure 6. 45-year old male with Crohn's disease and no signs of proctitis at endoscopy. (a) Axial oblique T2-weighted image and (b) axial oblique fat-saturated T2-weighted image obtained at the same level shows a moderate increase of T2 signal intensity of the rectal wall.

This suggests that the normal rectal signal intensity on T2 fat-saturated images is already light grey and that the grading scale used for luminal disease was not adequate for the rectum. Furthermore, MR enterography and colonography use luminal contrast to obtain bowel distention.

We do not have a balanced explanation for the lack of correlation between the supralevatoric extension of fistula and/or abscess and the presence of proctitis as one might have expected. Only our most experienced observer showed a significant correlation for the presence of ulcerations. A limitation for this feature is that in the proctitis group, we combined the patients with non-ulcerative and ulcerative proctitis because of low number of patients in each group. As the number of ulcerative proctitis cases was low, a possible correlation in ulcerative proctitis might not be identified. Combining ulcerative and non-ulcerative proctitis, also prevented us to rule on disease severity. For the features 'presence of creeping fat' and 'comb sign' we had no circumscribed definitions or grading, and observers had to score these features according to their expert opinion rendering it susceptible for subjectivity. Although the comb sign did show a significant correlation with endoscopy, the interobserver agreement was very low for two of three observer pairs, probably because of unfamiliarity with this feature (Figure 7).

Increased wall thickness is not only seen in the active phase of Crohn's disease, but also in the chronic stage of the disease. Also, the presence of mural fat and creeping fat are signs of chronic disease. The significant correlation to active inflammation at endoscopy for these

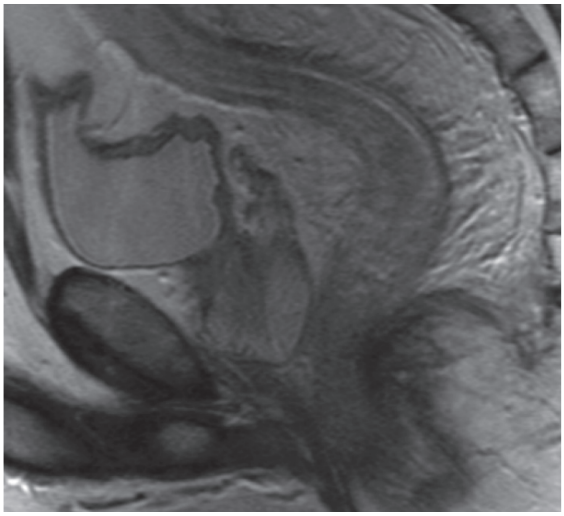

Figure 7. 43-year old male with Crohn's disease and ulcerative proctitis at endoscopy. Sagittal T2-weighted image shows the increased perimural vascularity perpendicular to the rectum ('comb sign') in addition to the wall thickening of the entire rectum.

features is inherent to Crohn's disease with a chronic course of relapsing and remitting inflammation, where features of chronic disease coexists with acute inflammatory changes.

Our study has several limitations. First, endoscopy reports were retrospectively analyzed in order to determine the reference standard. However, only reports with evident mentioning of the rectum were included and evaluated using a predefined clear-cut scoring system (10) and an experienced gastroenterologist was involved. Because of only including patients with mentioning of the rectum in the endoscopy report, our patient population was subject to selection bias creating a disease-enriched population. Second, the time between the MRI and the endoscopy examination ranged from 0 to 44 days. In this time frame disease activity could have been altered because of natural course. However, since we excluded all patients with change in medical or surgical therapy during the time interval this possibility was minimized. Third, the use of a kappa/intraclass coefficient value of ≥0.60 would have strengthened our study, but at initial evaluation of our data too little features remained. In this first phase of identifying possible relevant features we wanted to include as much features as possible, in order to make a further selection in a future validation study. Fourth, the introductory session for the observers regarding the different MRI features was held by the same expert abdominal radiologist (JS) who was also one of the readers in this study, which could have increased reproducibility. We did not notice higher agreement between the observer pairs including this expert abdominal radiologist than the other observer pair.

In conclusion, for diagnosing proctitis in Crohn's disease in perianal MRI, MRI features involving the mesorectal tissue, perimural T2 signal, perimural T1 enhancement, presence of creeping fat and size of mesorectal lymph nodes, were most valuable, as they showed a significant correlation with endoscopical findings and were reproducible. Established luminal features like mural T2 signal and T1 enhancement may be less helpful in perianal MRI. In addition, rectal wall thickness and presence of mural fat were relevant as well. Future research should focus on these MRI features by validating them in a prospective study, and for defining thresholds for continuous variables.

Acknowledgments

We would like to thank research nurse Jitteke de Jong for her help performing the search in the hospitals' patient database and physician A.J. Nederveen for his help extracting the MRI scan parameters from the DICOM headers.

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Appendices

Appendix 1. Range of MR scan parameters performed on three different MR scanners

1.5 T (Siemens, Avanto), 33 MR scans	*Sagittal T2-weighted TSE*	*Coronal T2-weighted TSE*	*Axial T2-weighted TSE*	*Axial T2-weighted TSE with fat sat.*	*Axial T1-weighted TSE with fat sat. + iv contrast enhancement*
Field of View (cm)	300	300/320	220/300	220/300	300-450
No. of slices	28-40	25-42	28-45	28-42	28-42
Repetition time (ms)	2500-4000	2500-4000	2500-4000	2500-4000	600-718
Echo time (ms)	69/70	70-121	70-121	70-121	9,4/11
Image matrix	512x231-512x578	256x297-512x575	256x297-512x578	256x297-512x575	256x288-512x256
Slice thickness (mm)	3/4	3/4	3/4	4	4
Slice gap (mm)	0.4	0-0,4	0-0.4	0/0.4	0-0,4
NSA	1-3	1/2	1/2	1/2	1-4
Flip angle	90/150	90/150	90/150	90/150	90/150
1.5 T (Signa, GE), 20 MR scans	*Sagittal T2-weighted TSE*	*Coronal T2-weighted TSE*	*Axial T2-weighted TSE*	*Axial T2-weighted TSE with fat sat.*	*Axial T1-weighted TSE with fat sat. + iv contrast enhancement*
Field of View (cm)	300	300	300	300	300/450
No. of slices	32	32	31/32	28-32	31/32
Repetition time (ms)	2500	2500	2500	2500-4500	560/600
Echo time (ms)	69/70	71/72	69	69-83	10.8
Image matrix	512x200	512x200	512x200	256x100	256x100
Slice thickness (mm)	4	4	4	4	4
Slice gap (mm)	0.4	0.4	0.4	0.4	0.4
NSA	1	1	1	1	2
Flip angle	90	90	90	90	90
3 T (Philips), 5 MR scans	*Sagittal T2-weighted TSE*	*Coronal T2-weighted TSE*	*Axial T2-weighted TSE*	*Axial T2-weighted TSE with fat sat.*	*Axial T1-weighted TSE with fat sat. + iv contrast enhancement*[a]
Field of View (cm)	230-360	240-400	240-400	240-400	300/400
No. of slices	30-41	30-37	32-45	35-45	40-45
Repetition time (ms)	2689/3000	2689-3000	2689-3000	3000/4626	550-786
Echo time (ms)	70-100	70-100	70-100	70/100	10
Image matrix	256x198-528x361	400x246-528x400	400x395-528x361	300x287-768x287	248x248-512x255
Slice thickness (mm)	3/4	3/4	3/4	3/4	3/4
Slice gap (mm)	0-1	0/0.3	0/0.3	0/0.3	0/0.3
NSA	2/4	1/4	1/4	1/2	1/2
Flip angle	90	90	30	90	90

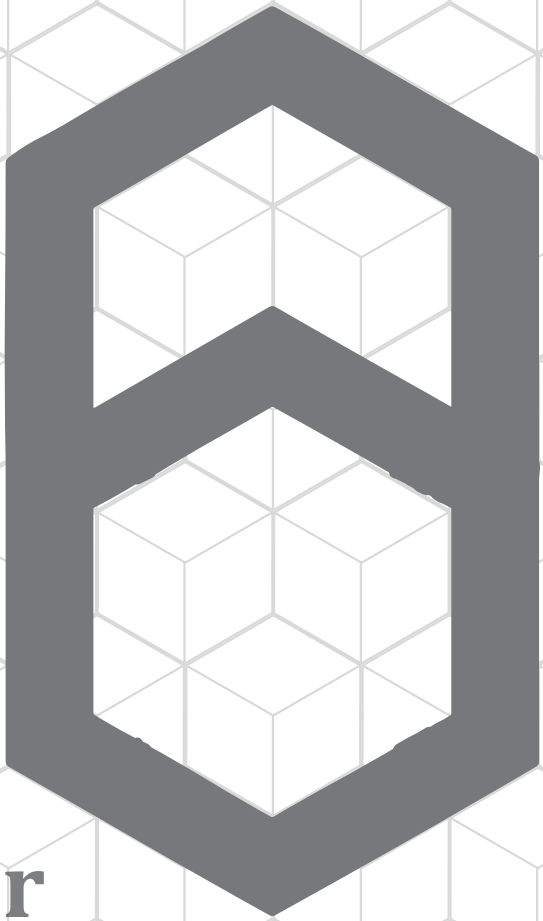
[a]With the exception of one SENSE dixon post-contrast serie: FOV 400, no. of slices 480, TR 0, TE 0, matrix 512x207, slice thickness 1.5, gap 0, averages 1, flip angle 8.

Appendix 2. Combined results of interobserver agreement and correlation between observers and reference standard

MRI features	Significant correlation between observer and reference standard (p≤0.05)			Kappa or intraclass coefficient ≥0.40			Relevant MRI feature
	Observer 1	Observer 2	Observer 3	1 vs 2	2 vs 3	1 vs 3	
Wall thickness	yes	yes	yes	yes	yes	yes	**yes**
Mesorectal lymph nodes	yes	yes	yes	yes	yes	yes	**yes**
Obturator lymph nodes	no	no	no	no	no	no	**no**
Iliac lymph nodes	no	no	no	no	no	no	**no**
Inguinal lymph nodes	no	no	no	yes	no	yes	**no**
% of circumference involved	yes	yes	yes	no	no	yes	**no**
Mural T2 signal	yes	yes	no	no	no[a]	no[a]	**no**
Perimural T2 signal	yes	yes	yes	yes	yes	yes	**yes**
T1 enhancement	yes	no	yes	no	no	no	**no**
T1 enhancement pattern	no	yes	yes	no	no	yes	**no**
Perimural enhancement	yes	yes	yes	yes	no	yes	**yes**
Mural fat	yes	no	yes	yes	yes	yes	**yes**
Ulcers	no	no	yes	no[a]	no	no	**no**
Supralevatoric fistula	no	no	no	yes	yes	yes	**no**
Supralevatoric abscess	no	no	no	yes	yes	yes	**no**
Creeping fat	[b]	yes	yes	yes	yes	yes	**yes**
Comb sign	yes	yes	yes	no	no	yes	**no**

[a]Proportion of agreement calculated, because observed concordance is smaller than mean-chance concordance. Assuming kappa ≤0.40

[b]Not calculated because of the presence of a zero in the crosstab



Chapter

Summary, Implications & Conclusions

Part I - Surveillance CT colonography for 6-9 mm polyps in colorectal cancer screening

Summary

In screening for colorectal cancer with CT colonography, size is the most important polyp feature used to decide which individuals should be referred for colonoscopy and polypectomy. As the size of a polyp correlates with advanced histology (high-grade dysplasia or cancer), it is generally accepted that large polyps (≥10 mm) should be removed and diminutive polyps (<6 mm) can be ignored. Debate remains however on the clinical relevance and management of 6-9 mm ('small') polyps. Despite the low probability of harboring advanced histology in 6-9 mm polyps (3-6.6% in an asymptomatic screening population), to date all US and European screening guidelines advise to refer all individuals with ≥6 mm polyps at CT colonography for colonoscopy and polypectomy (1, 2). This policy is mainly based on expert opinion until further evidence comes available. In addition to size, other polyp features might be predictive for advanced histology, such as location, morphology or growth. To establish growth, CT colonography surveillance is very suitable as polyps remain in situ, localization is easy, and there is the possibility to perform measurements.

As an alternative to colonoscopy, surveillance CT colonography was proposed for patients with 6-9 mm polyps. However, studies to determine the (cost-) effectiveness and safety of such a CT colonography surveillance strategy are scarce. In chapter 2, we describe a cohort of patients that underwent CT colonography as a primary screening method for CRC and only had 6-9 mm polyps. In this setting, all persons with polyps ≥6 mm were referred for colonoscopy. We assessed participation, yield and extra-colonic findings at surveillance CT colonography after 3 years. In addition, we assessed the overall yield of screening with CT colonography, as previously only a provisional yield could be reported based on findings in only those persons that underwent colonoscopy. We report that participation rate in surveillance CT colonography was high at 86.2%. The yield for advanced adenomas was substantial at 29.3% and mostly based on polyp size ≥10 mm. Importantly, no colorectal cancers or adenomas with high-grade dysplasia were detected, suggesting this strategy is safe. Detection of new important extra-colonic findings was rare (1.8%). Including this yield at surveillance in the primary yield of screening CT colonography, led to an increased yield CT colonography in population-based screening per 100 participants (from 6.1 to 8.6; $p<0.001$), as well as per 100 invitees (from 2.1 to 2.9; $p<0.001$).

In chapter 3, we studied the evolution of 6-9 mm polyps, aiming to learn more about the natural behavior of 6-9 mm polyps and to identify characteristics that might help us to determine which polyps are at risk of becoming advanced and should be removed. In patients with one or two 6-9 mm polyps, we assessed volumetric change in size on CT colonography during a 3-year surveillance period. We used volumetric measurements as these have shown to be more reliable than linear measurements, especially in assessing small changes in size, as is often the case in small polyps. We showed that at CT colonography surveillance after 3 years, 35% of 95 small polyps demonstrated a volumetric growth of 30% or more, 38% of polyps remained stable, 13% had a volume reduction by at least 30%, and 14% seemed completely regressed. No baseline polyp characteristics (location, morphology, size at index CT colonography) other than growth were identified as a risk factor for advanced histology. When correlating growth categories to histopathology, growing small polyps were more likely to be advanced adenomas at removal than stable or regressing polyps (45% versus 21% and 0%, respectively).

In the last two decades, the clinical relevance of serrated adenomas came to light, as an estimated 15-30% of colorectal carcinomas arise from sessile serrated polyps (SSPs) through the so-called serrated neoplasia pathway. Therefore, colorectal cancer screening modalities should also aim to detect high-risk SSPs (SSPs with dysplasia and/or SSPs ≥10 mm in size). In chapter 4, we retrospectively determined the yield of high-risk SSPs in our primary screening population, comparing the yield in the CT colonography arm (*including* surveillance CT colonography) with the yield in the colonoscopy arm. We observed a significantly higher detection rate of high-risk SSPs in colonoscopy screening than in CT colonography screening, with a relative risk to detect at least one high-risk SSP of 5.3 (95% CI 2.5-11.1; $p<0.001$), and at least one high-risk SSP as most advanced lesion of 7.9 (95% CI 2.8-22.1; $p<0.001$). As compared with the findings in the colonoscopy arm, especially flat SSPs located in the proximal colon were detected less often with CT colonography. As this is the first study to report low detection rates of serrated polyps for CTC, we are awaiting the results of other large screening trials.

Patients' acceptance and willingness to return in future screening rounds is essential for the success of a screening program. In chapter 5, we evaluated the burden of waiting three years for (the results of) surveillance CT colonography, as well as the expected and perceived burden of the surveillance CT colonography procedure, and compared these parameters to index CT colonography. We observed that waiting for a surveillance CT colonography caused little discomfort. However, waiting for the results after having undergone a CT colonography was considered more burdensome for surveillance than for index CT colonography (23% versus

8%). The surveillance CT colonography less often turned out worse than expected compared to the index CT (6% versus 23%). It was reassuring that after surveillance CT colonography, almost all patients were willing to participate again in future screening rounds with CTC.

Implications

In the Netherlands recently an invitational colorectal cancer screening program has been introduced by biennial Fecal Immunochemical Test (FIT). However, structural examinations that visualize the entire colon (like colonoscopy and CT colonography), have the ability to not only detect invasive cancers, but also precursor lesions (adenomas and advanced adenomas), and might therefore have a larger impact on mortality and incidence of colorectal cancer than a FIT-based program (considering a comparable participation rate). CT colonography is a promising and evolving technique and has several advantages over colonoscopy. One of the issues to be addressed, however, is the optimal referral strategy for colonoscopy.

Current CT colonography screening guidelines refer a high percentage of patients for colonoscopy, i.e. all individuals with polyps of ≥6 mm, and many patients are over-treated when considering that an estimated very low number of 5% of all colorectal adenomas will ever progress to cancer in 10-15 years (3). By refining CT colonography referral guidelines to more accurately identify patients with advanced neoplasia, we might be able to optimize the colonoscopy yield and reduce the costs. With the results described in this thesis, we provide ground for a large population-based screening study in which patients with 6-9 mm polyps at CT colonography will be randomized for the current policy of immediate colonoscopy and a surveillance CT colonography. This latter less aggressive strategy would not only increase colonoscopy yield, but would also especially benefit the older and more fragile screenees as the burden and risks of CT colonography are lower than those for colonoscopy (4, 5). At the first surveillance CT colonography at 3 years, all patients with growing polyps reaching the 10 mm threshold will be referred to colonoscopy for polypectomy, and patients with smaller polyps can be kept in a CT colonography surveillance schedule. Focus of research should be to explore the (cost-) effectiviness and safety of extending CT colonography surveillance intervals for these small polyps.

Natural evolution of small polyps

As it takes an estimated 10-15 years for an adenoma to progress to a colorectal carcinoma, it is not surprising that in a 3-year surveillance interval only a third of the polyps 6-9 mm showed progression, and there were no polyps with high-grade dysplasia or carcinoma. By leaving

small polyps in place and keeping them under continuing CT surveillance, we can obtain more knowledge on their natural evolution. For example, with multiple measurement points in time we can establish growing curves (for example linear or exponential), potentially predictive for their histopathology and helpful in determining which polyps should be removed.

Determination of polyp size

Volumetric measurements might be an effective method to measure growth and to identify which patients should be referred for colonoscopy. However, these measurements are not yet routinely used in daily practice as most hospitals nowadays do have 3D software for virtual colonoscopy, but are not equipped with the possibility of performing volumetric measurements. In addition, different methods for volumetric measurements are available (automated, semi-automated, manually), each having their own advantages and disadvantages regarding reproducibility, usage and accuracy, making a uniform policy difficult (6, 7). Determining the accuracy of volumetric measurements is complicated by the lack of a reliable reference standard. How can one measure the actual volume of a polyp as it shrinks once it is removed? A robust technique to perform (automated) volumetric measurements would facilitate decision-making in colonoscopy referral for small polyps and could optimize a surveillance CT colonography strategy.

Serrated adenomas

Considering the clinical relevance of high-risk SSPs, one of the main challenges for a screening program using CT colonography is to increase the detection rates of SSPs. Several explanations have been discussed in this thesis and especially the concept of barium coating deserves more attention (8). This phenomenon describes the adherence of oral contrast to the polyps' surface, while it washes away from the normal colonic mucosa. It is especially seen in large, flat polyps located in the proximal colon (9, 10). The SSPs of interest are typically large, located in the proximal colon and have a flat morphology, which are therefore precisely the lesions that are most likely to be coated by oral contrast. The working mechanism of this contract coating is explained by the fact that the positively charged barium within the oral preparation is attracted by the negatively charged overlying mucin cap, particularly seen in serrated and hyperplastic polyps, creating the contrast coat seen at CT colonography (9). Therefore, the influence of each of the different contrast agents in the oral preparation, and especially the effect of the addition of barium sulfate, should be further investigated.

Molecular markers for growth

Although growth itself is not predictive for an adenoma to develop into cancer, the size of an adenoma does correlate with the chance of harboring advanced histology. At CT colonography

only parameters like size and growth are available. As size is one of the criteria for the definition of an advanced adenoma, the relationship between growth and becoming an advanced adenoma (based on the size criterium alone) can be described as a self-fulfilling prophecy. That is why there is need for an independent marker to identify (volumetric) growth potential of adenomas, and with that, the risk assessment of becoming a colorectal cancer. Colorectal cancer is the result of accumulation of genetic abnormalities and perhaps molecular markers can provide a reliable assessment to identify lesions at high risk to develop into cancer (3). Our polyp data set (tissue samples) is currently under investigation for DNA analysis, and the genetic profile will be correlated to the volumetric change in size. Hopefully this analysis will bring more understanding as to why some polyps are more prone to progression and if volumetric growth on CT colonography can be used as a selection tool for polyp removal.

And more

Before surveillance CT colonography can be considered the management of choice for 6-9 mm polyps, other aspects deserve further attention as well. Firstly, the detection of extra-colonic findings on CT colonography has been considered an advantage as well as a disadvantage. Proponents would emphasize the mortality reduction of detecting asymptomatic aortic aneurysms, opponents would advocate the additional (potentially harmful) examinations and costs for non-relevant findings. The fact that in CT colonography performed for surveillance-purposes, less newly diagnosed extra-colonic lesions are expected as indicated in this thesis, would shine new light on this discussion.

Exposure to ionizing radiation is another concern regarding the use of CT colonography. For primary CT colonography screening with an interval of 5 years, the benefit of prevented colorectal cancers is thought to outweigh the estimated radiation-induced cancers (11). Especially when considering the continuing decrease in radiation dose established by new developments, the risk of radiation for CT colonography screening is considered extremely low and negligible (12). However, previous research did not take into account the influence of a shorter surveillance interval, namely the 3-year surveillance for 6-9 mm polyps. This would inevitably increase the lifetime effective dose for a small portion of screenees. Research on the duration of follow-up of 6-9 mm polyps would determine if this increase is going to be significant.

The cost-effectiveness of a surveillance CT colonography strategy for 6-9 mm polyps is currently under investigation and this should be compared to a colonoscopy referral strategy. First results of this modeling study, based on the COCOS trial data, showed that the most cost-

effective CT colonography strategy was a strategy with immediate referral to colonoscopy for all ≥6 mm lesions (not yet published).
Furthermore, another very interesting focus of further research would be patients' preference; surveillance CT colonography or colonoscopy. At the primary COCOS trial, patients with 6-9 mm polyps were advised to undergo surveillance CT colonography. However, some of them chose not to wait, but underwent colonoscopy earlier on their own initiative (5%; 4/82). What if all patients were offered a choice? Although we showed that acceptance for surveillance CT colonography was high and burden was low, maybe patients would have preferred to have their polyps directly removed.

Conclusions

By further specifying the different aspects of surveillance CT colonography in screening, we are one step closer at implementing this surveillance strategy as management of choice for 6-9 mm polyps.

In this thesis we demonstrated that surveillance CT colonography is a viable alternative to colonoscopy referral for patients with 6-9 mm polyps as it is safe and patients' acceptance is high. Especially in a screening population, this less-invasive and less-aggressive strategy might benefit this older patient population that may have multiple co-morbidities. Volumetric measurements can be a helpful tool in deciding which patients should be referred for colonoscopy, as all advanced adenomas were among the progressing or stable polyps as detected by volumetric measurement. A major challenge remains to identify the cause(s) of the under detection of SSPs in CT colonography compared to colonoscopy.

Part II - MR imaging of terminal ileum and rectum in Crohn's disease

Summary

MRI has proven its use in diagnosing and monitoring Crohn's disease. Extensive research has revealed numerous MR features useful in assessing inflammation in Crohn's disease. Using MR Enterography or MR colonography, multiple scoring systems have been developed to diagnose and quantify the degree of inflammation in those patients (13-15). Every research group has its own preference and expertise, and there was no study comparing all these scoring systems. Debate remains on the most useful MRI scoring system.

In chapter 6 we performed a prospective study of MR enterography, in which we compared four MRI scoring systems for disease activity in the terminal ileum and the individual features that are incorporated in the different scoring systems. We determined interobserver agreement and the correlation to the histopathological (eAIS) and ileocolonoscopic (CDEIS) reference standard. Our findings show that in our patient population with suspected or proven Crohn's disease all scoring systems had good interobserver agreement (ICC ranging from 0.72 to 0.78), correlations to the histopathological reference standard were moderate (r: 0.51–0.57 and 0.47-0.52 for observers 1 and 2, respectively) and diagnostic accuracies were 74%–76% and 69%–71% for observers 1 and 2, respectively. The correlation to the CDEIS and diagnostic accuracy was also comparable. Of the individual MRI features, enhancement, perimural T2 signal, ADC and RCE showed good reproducibility (ICC: 0.68–0.70). To the eAIS, the individual features showed at best a moderate correlation and to the CDEIS a strong correlation. As the four scoring systems were comparable in reproducibility, correlation and diagnostic performance, the choice for use in daily practice may be based on other aspects such as personal preference, experience and practical considerations.

In case of perianal fistulas, a frequent problem in Crohn's disease, patients will undergo perianal MRI. Perianal MRI has a limited scan protocol (smaller FOV, less sequences and the absence of luminal contrast) than in luminal Crohn's disease and it was unknown whether the features used to assess disease activity in MR enterography or MR colonography, would also be applicable to assess rectal inflammation on this specific perianal MRI. But for treatment planning, determining the absence or presence of proctitis is very relevant. Therefore, in chapter 7, we performed a retrospective study to determine which MRI features were useful in diagnosing proctitis on perianal MRI. Seventeen features were evaluated, comparing all MR features to the endoscopy reference standard and assessing reproducibility. MRI features were considered relevant when significantly correlated to endoscopy for ≥two observers, and reproducibility was ≥0.40 for ≥two observer pairs. Wall thickness, mural fat and four features related to the perimural fat tissue (perimural T2 signal, perimural enhancement, presence of creeping fat and size of mesorectal lymph nodes) fulfilled these criteria and were potentially relevant in diagnosing proctitis. Mural T2 signal and T1 enhancement degree, proved less helpful as the reproducibility was poor for all three observer pairs. In contrast to assessment of disease activity at MR enterography or MR colonography, on perianal MRI perirectal features are more helpful in establishing rectal inflammation than established luminal features.

Implications

Grading of disease activity on MRI in Crohn's disease has shown its value to monitor treatment response in daily practice. For this purpose, we have multiple MRI features and scoring systems at our disposal. A major limitation of conventional MRI features, however, remains the difficulty in the objective grading of disease activity. Inevitably, when evaluating one separate feature the radiologist is influenced by the findings on other sequences as well. With the advent of newer techniques, more advanced quantitative features have been developed, promising with respect to reproducibility and objectivity, but often at cost of time-consuming measurements and evaluations.

A major problem with the interpretation of quantitative parameters like ADC and RCE is that it is subject to multiple sorts of variabilities: there is within scanner variability, inter scanner variability and the difference in method of measurement (size and position of ROI, selection of representative value (highest, establishing mean by drawing multiple ROIs)). Furthermore, the cut off values determined for quantitative parameters are subject to spectrum bias, which means the numerical values are individual and study-specific and therefore not generalizable (16, 17). In fact, an alliance, QIBA (Quantitative Imaging Biomarkers Alliance) was formed with its main goal to understand and improve the value and practicality of quantitative imaging biomarkers. We also encountered those variabilities in our study, coming to light because of large differences in numerical ADC values in a relatively stable structure (erector spinae muscle) between the two participating hospitals, but even within the hospitals. As long as no uniform policy exists on how to deal with these variabilities, the generalization of results is extremely difficult and therefore the usage of these quantitative parameters (and scoring systems including those parameters) are not yet ready for daily practice.

A solution to the influence of observers' subjectivity when evaluating qualitative features, could be the use of novel software solutions like (semi-)automated measurements. Research from our study group has shown promising results with semi-automatically generated features (bowel wall thickness and disease volume), requiring minimal user input, showing high correlation with subjective radiologist measurement and improving reproducibility. A new scoring system, also incorporating semi-automated features could potentially improve performance compared to existing MRI activity scoring systems.

In perianal MRI not all MRI features are available to us, due to the limited scan protocol with less sequences than commonly used for MR enterography or MR colonography. The currently available features have shown different diagnostic value. A substantial difference with MR enterography or MR colonography is the absence of luminal contrast to achieve luminal

distention, which results in an often collapsed lumen making a precise evaluation of the wall difficult. However, the point of our study was to see if we could rule on the presence of inflammation with the existing limited scan protocol. Other differences apply to the anatomy of the mesorectum with the isolated localization of the rectum surrounded by a substantial amount of fat tissue, the latter being even more pronounced when the amount of fat has increased by disease activity (creeping fat phenomenon), both accentuating the perirectal features. The relevance of these features specific for rectal inflammation came to light in this thesis, and should be confirmed in a prospective study and thresholds for continuous variables should be determined.

Although Crohn's disease is characterized by transmural inflammation, it can very well present with only superficial (mucosal) lesions. Because of a relatively small patient population we were forced to group the patients in those with and those without proctitis. It would be interesting to know if the perirectal features would also manifest in patients with non-ulcerative proctitis (only superficial lesions). We would suggest a new study overcoming the imperfections of our study: a prospective setting with a larger patient cohort, a maximum time interval of two weeks between MRI and endoscopy and at least a kappa/intraclass coefficient of 0.60 for considering a feature relevant. Furthermore, the endoscopy reference standard should be an assessment of disease severity, considering different grades of disease severity (ulcerative versus non-ulcerative) and possibly a subdivision should be made to separate active from recurrent/chronic inflammation. An easy-to-add sequence would be the DWI, as this is a short sequence that would cause no additional patient burden, and is probably easy to evaluate in the isolated rectum.

Conclusions

Patients with Crohn's disease would benefit from non-invasive ways of establishing disease activity and severity, mainly in the setting of treatment response monitoring, but also for diagnostic purposes in patients intolerable to endoscopic examinations.

In this thesis, we showed that for MR enterography or MR colonography the CDMI and London score, both consisting of conventional MRI features, seem the most suitable for this purpose. At this moment, the quantitative parameters are subjected to too much technical difficulties, in addition to their time-consuming aspect, to use in daily practice.

In contrast to previously established luminal features on MR enterography or MR colonography, we discovered that on perianal MRI, the diagnosis of proctitis is mostly based on perirectal features.

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Chapter

Samenvatting, Implicaties & Conclusies

Deel I – Surveillance CT-colografie voor 6-9 mm poliepen bij screening voor colorectaal carcinoom

Samenvatting

Bij screening op colorectaal carcinoom met behulp van CT-colografie, is de grootte van de poliep het belangrijkste kenmerk om te bepalen welke patiënten verwezen moeten worden voor coloscopie en poliepectomie. Omdat de grootte van een poliep correleert met de aanwezigheid van hooggradige histologie (hooggradige dysplasie of carcinoom), is het algemeen geaccepteerd dat grote poliepen (≥10 mm) verwijderd moeten worden en dat *diminutive* poliepen (<6 mm) genegeerd kunnen worden. Er blijft discussie omtrent de klinische relevantie en het beleid bij de 6-9 mm ('kleine') poliepen. Ondanks de lage kans op hooggradige histologie bij 6-9 mm poliepen (3-6.6% in een asymptomatische screeningspopulatie), adviseren de huidige Amerikaanse en Europese richtlijnen om alle personen met ≥6 mm poliepen op CT-colografie te verwijzen voor coloscopie (1, 2). Dit beleid is voornamelijk gebaseerd op de mening van experts totdat er meer bewijs tot onze beschikking komt. In aanvulling op grootte, zijn er mogelijk andere poliepkenmerken voorspellend voor hooggradige histologie, zoals morfologie, locatie en groei. Om groei vast te stellen, is CT-colografie surveillance heel geschikt omdat poliepen in situ blijven, makkelijk zijn te lokaliseren en vergelijken, en er is de mogelijkheid om metingen te verrichten.

Als een alternatief voor coloscopie, is surveillance CT-colografie voorgesteld voor personen met 6-9 mm poliepen. Echter, studies die de (kosten-) effectiviteit en veiligheid van zo'n CT-colografie surveillance strategie testen zijn schaars. In hoofdstuk 2, beschrijven we een surveillance cohort met personen die een CT-colografie ondergingen als primaire screenings strategie in het kader van een proefbevolkingsonderzoek naar colorectaal carcinoom en die alleen 6-9 mm poliepen hadden. We hebben participatie, opbrengst en extracolonische bevindingen op surveillance CT-colografie na 3 jaar vastgesteld. Ook hebben we de totale opbrengst berekend van screening met CT-colografie, aangezien er eerder alleen een voorlopige opbrengst berekend kon worden, gebaseerd op de bevindingen bij personen die na de primaire CT-colografie voor coloscopie werden verwezen. We vonden een hoge participatie in surveillance CT-colografie van 86.2%. De opbrengst voor advanced adenomen was substantieel (29.3%), en grotendeels gebaseerd op poliepen ≥10 mm. Belangrijk is dat er geen colorectale carcinomen of adenomen met hooggradige dysplasie werden gedetecteerd, hetgeen suggereert dat dit een veilige strategie is. Het detecteren van nieuwe belangrijke extracolonische bevindingen was zeldzaam (1.8%). Het incorporeren van deze nieuwe

surveillance opbrengst, heeft geleid tot een hogere totale opbrengst van screenen met CT-colografie in het kader van een bevolkingsonderzoek, zowel per 100 participanten (van 6.1 naar 8.6; p<0.001), als per 100 uitgenodigden (van 2.1 naar 2.9; p<0.001).

In hoofdstuk 3, hebben we de natuurlijke evolutie van 6-9 mm poliepen bestudeerd, in een poging meer te leren over het natuurlijk gedrag van deze poliepen en om karakteristieken te identificeren die ons zouden kunnen helpen bij het bepalen welke poliepen *at risk* zijn om hooggradig te worden en dus verwijderd zouden moeten worden. In patiënten met één of twee 6-9 mm poliepen, hebben we de volumeverandering van de poliepen op CT-colografie bepaald na een surveillance periode van drie jaar. We hebben hiervoor volumemetingen gebruikt, omdat is gebleken dat deze metingen betrouwbaarder zijn dan lineaire metingen, zeker als het gaat om het aantonen van kleine verschillen in grootte wat vaak het geval is bij deze kleine poliepen. We hebben aangetoond dat op de surveillance CT-colografie na 3 jaar 35% van de 95 kleine poliepen een volume toename lieten zien van 30% of meer, 38% van de poliepen stabiel bleef, 13% een volume reductie onderging van tenminste 30% en dat 14% compleet in regressie ging. Behalve groei werden er geen andere poliepkarakteristieken geïdentificeerd als risicofactor voor hooggradige histologie. Wanneer groei gecorreleerd werd aan histopathologie, waren groeiende poliepen meer waarschijnlijk advanced adenomen bij het verwijderen dan stabiele of kleiner wordende poliepen (45% versus 21% en 0%, respectievelijk).

De laatste 20 jaar is de klinische relevantie van serrated adenomen duidelijk geworden: geschat wordt dat ongeveer 15-30% van de colorectale carcinomen ontstaat uit sessiele serrated poliepen (SSPs) via de zogenaamde 'serrated neoplasia pathway'. Screeningsmodaliteiten voor colorectaal carcinoom moeten er daarom ook op gericht zijn om de hoog risico SSPs (SSPs met dysplasie en/of SSPs ≥10 mm in grootte) te detecteren. In hoofdstuk 4, hebben we retrospectief de opbrengst van hoog-risico SSPs bepaald in onze primaire screenings populatie, en de opbrengst in de CT-colografie arm (surveillance CT-colografie geïncludeerd) vergeleken met de opbrengst in de coloscopie arm. We vonden een significant hogere detectiegraad van hoog-risico SSPs bij coloscopie screening dan bij CT-colografie screening, met een relatief risico om tenminste één hoog-risico SSP te detecteren van 5.3 (95% CI 2.5-11.1; p<0.001), en tenminste één hoog-risico SSP als de meest hooggradige poliep van 7.9 (95% CI 2.8-22.1; p<0.001). In vergelijking met de resultaten in de coloscopie arm, zagen we dat met name vlakke SSPs gelokaliseerd in het proximale colon minder vaak gedetecteerd werden dan met CT-colografie. Omdat dit de eerste studie is die een lage detectiegraad rapporteert van serrated poliepen in CT-colografie, zijn we erg benieuwd naar de resultaten van andere grote screeningsstudies.

Onderdeel van een succesvolle screenings procedure, is de acceptatie van patiënten en de bereidheid om terug te keren in toekomstige screeningsrondes. In hoofdstuk 5 evalueerden we de belasting van het drie jaar wachten op (de resultaten van) surveillance CT-colografie. Ook evalueerden we de verwachte en ervaren belasting van de surveillance CT-colografie en vergeleken die met de initële CT-colografie. We observeerden dat het wachten op de surveillance CT-colografie weinig onbehagen veroorzaakte. Maar het wachten op de resultaten na het ondergaan van de surveillance CT-colografie, werd als meer belastend ervaren bij surveillance dan bijde initiële CT-colografie (23% versus 8%). De surveillance CT-colografie viel minder vaak tegen dan de initiële CT-colografie (6% versus 23%). Het is geruststellend dat na surveillance CT-colografie bijna alle patiënten bereid waren wederom te participeren in toekomstige screenings rondes.

Implicaties

In Nederland is recent het bevolkingsonderzoek naar colorectaal carcinoom geïntroduceerd middels de tweejaarlijkse Faecal Immunochemical Test (FIT). Echter, structurele onderzoeken die het gehele colon in beeld brengen (zoals coloscopie en CT-colografie), hebben als eigenschap dat ze niet alleen de invasieve carcinomen kunnen detecteren, maar ook de *precursor* afwijkingen (adenomen en advanced adenomen). Daarom hebben deze onderzoeken mogelijk een grotere impact op de mortaliteit en incidentie van het colorectale carcinoom dan een bevolkingsonderzoek middels de FIT (ervan uitgaande dat de participatie graad gelijk is tussen de modaliteiten). CT-colografie is een veelbevolende en zich ontwikkelende techniek en heeft een aantal voordelen ten opzichte van de coloscopie. Eén van de punten die echter nog geadresseerd moeten worden, is de optimale coloscopie verwijzingsstrategie.

Huidige CT-colografie screeningsrichtlijnen sturen een hoog percentage patiënten door voor coloscopie, namelijk alle patiënten met poliepen van ≥6 mm, en gezien het feit dat maar een geschat zeer laag percentage van 5% van alle colorectale adenomen zich zal ontwikkelen tot een carcinoom in 10-15 jaar, worden veel patiënten dus overbehandeld (3). Door de verwijsrichtlijnen voor CT-colografie verder te specificeren om beter de patiënten met hooggradige neoplasieën te kunnen identificeren, kunnen we mogelijk de coloscopie opbrengst optimaliseren en de kosten verlagen. Met de resultaten naar voren gebracht in dit manuscript, hebben we een basis gelegd voor een groot bevolkingsonderzoek waarbij de patiënten met 6-9 mm poliepen gerandomiseerd worden tussen het huidige beleid van directe coloscopieverwijzing en een surveillance CT-colografie. Deze laatste, minder agressieve strategie zal niet alleen de coloscopie opbrengst verhogen, maar zal met name ten

goede komen aan de oudere en kwetsbare gescreenden, aangezien de belasting en risico's van CT-colografie lager zijn dan die van coloscopie (4, 5). Bij de eerste surveillance CT-colografie, na 3 jaar, worden alle groeiende poliepen die de 10 mm drempel bereiken verwijderd, en patiënten met kleine poliepen kunnen onder CT-colografie surveillance blijven. Focus van het onderzoek moet zijn de (kosten-) effectiviteit, en de veiligheid van het verlengen van het surveillance interval voor deze kleine poliepen.

Natuurlijke evolutie van kleine poliepen

Aangezien het ongeveer 10-15 jaar duurt voordat een adenoom zich ontwikkelt tot een carcinoom, is het niet verwonderlijk dat in een 3-jaar surveillance interval maar één-derde van de 6-9 mm poliepen progressie liet zien, en dat er geen poliepen waren met hooggradige dysplasia of carcinoom. Door de kleine poliepen in situ te laten en ze onder continue CT surveillance te houden, kunnen we meer kennis vergaren over hun natuurlijke evolutie. Bijvoorbeeld, met meerdere meetpunten in de tijd kunnen we groeicurves maken (bijvoorbeeld lineair of expontentieel), mogelijk voorspellend voor de histopathologie van de poliep en daarmee nuttig voor het bepalen welke poliepen verwijderd moeten worden.

Het bepalen van de poliepgrootte

Volume metingen zijn mogelijk een effectieve methode om groei te bepalen en te identificeren welke patiënten verwezen moeten worden voor een coloscopie. Echter deze metingen worden in de dagelijkse praktijk nog niet routinematig gebruikt, omdat de meeste ziekenhuizen, hoewel tegenwoordig wel uitgerust met 3D software voor virtuele coloscopie, niet de mogelijkheid hebben om daarmee ook volume metingen te verrichten. Tevens zijn er verschillende methoden voor volumemetingen beschikbaar (automatisch, semi-automatisch, manueel), met ieder zijn voor- en nadelen ten aanzien van reproduceerbaarheid, gebruik en accuratesse, wat een uniform beleid lastig maakt (6, 7). Het bepalen van de accuratesse van de volume metingen wordt tevens gecompliceerd doordat er geen betrouwbare referentiestandaard beschikbaar is. Hoe kan het echte volume van een poliep gemeten worden, als deze krimpt zodra hij verwijderd wordt? Een robuuste techniek om (automatische) volume metingen te verrichten zal de besluitvorming ten aanzien van coloscopieverwijzingen voor kleine poliepen kunnen vergemakkelijken en de CT-colografie surveillancestrategie kunnen optimaliseren.

Serrated adenomen

Gezien de klinische relevantie van high-risk SSPs, is één van de belangrijkste uitdagingen voor een screeningsprogramma met CT-colografie de detectie van SSPs te vergroten. Diverse verklaringen zijn bediscussieerd in dit manuscript en met name het concept van 'contrast coating' verdient meer aandacht (8). Dit fenomeen beschrijft hoe het orale contrast vast blijft

kleven aan het oppervlak van de poliep, terwijl het weg wast van de normale mucosa van het colon. Het wordt met name gezien in grote, vlakke poliepen gelokaliseerd in het proximale colon (9, 10). De relevante SSPs zijn typisch groot, gelokaliseerd in het proximale colon en hebben een vlakke morfologie, waarmee ze precies de laesies zijn die meest waarschijnlijk gecoat worden door het orale contrast. Het werkingsmechanisme achter de contrastcoating wordt verklaard door het feit dat het positief geladen barium, wat onderdeel is van de orale voorbereiding, aangetrokken wordt door de negatief geladen overliggende slijmkap, met name te zien in serrated en hyperplastische poliepen. Hierdoor wordt de contrastcoat gecreëerd welke te zien is op CT-colografie (9). Daarom moet de invloed van elk van de verschillende contrastmiddelen in de orale voorbereiding, en met name het effect van de toevoeging van bariumsulfaat, verder worden onderzocht.

Moleculaire markers voor groei

Hoewel groei op zich niet voorspellend is voor een adenoom om zich tot een carcinoom te ontwikkelen, correleert de grootte van een adenoom wel met de kans om hooggradige histologie te bevatten. Op CT-colografie zijn alleen parameters als grootte en groei beschikbaar. Aangezien grootte één van de criteria is voor de definitie van een advanced adenoom, kan de relatie tussen groei en de overgang naar een advanced adenoom (gebaseerd op alleen het criterium van grootte) beschreven worden als een self-fulfilling prophecy. Daarom is er behoefte aan een onafhankelijke marker om de (volumetrische) groeipotentie van adenomen te identificeren, en daarmee het risico op een colorectaal carcinoom te voorspellen. Colorectaal carcinoom is het resultaat van een accumulatie van genetische afwijkingen en waarschijnlijk kunnen moleculaire markers een betrouwbare inschatting maken om afwijkingen te identificeren die een hoog risico hebben om zich te ontwikkelen tot kanker (3). Onze dataset van poliepen (weefselmonsters) wordt op het moment aan de hand van DNA analyse onderzocht, en het genetische profiel zal worden gecorreleerd aan de volume verandering van de poliepen. Hopelijk zullen deze analyses ons meer inzicht verschaffen waarom sommige poliepen meer neiging tot groei vertonen, en of volumemetingen op CT-colografie gebruikt kunnen worden als een selectiemiddel om poliepen te verwijderen.

En meer

Voordat surveillance CT-colografie overwogen kan worden als eerste keus behandeling bij 6-9 mm poliepen, moet er aandacht zijn voor andere aspecten. Ten eerst, de detectie van extracolonische bevindingen kan gezien worden als een voordeel maar ook als een nadeel. Voorstanders zouden de mortaliteitsreductie benadrukken ten gevolge van tijdig gedetecteerde asymptomatische aorta-aneurysma's, tegenstanders zouden de (potentieel schadelijke) extra onderzoeken aanvoeren, en de kosten voor niet-relevante bevindingen.

Het feit dat als CT-colografie uitgevoerd wordt in het kader van surveillance er minder nieuw gediagnosticeerde extracolonische bevindingen te verwachten zijn, zoals blijkt uit dit proefschrift, zet deze discussie in een nieuw daglicht.

Blootstelling aan ioniserende straling is een andere zorg met betrekking tot het gebruik van CT-colografie. Voor primaire screening CT-colografie met een interval van 5 jaar, weegt het voordeel om colorectaal carcinoom te voorkomen op tegen de verwachte stralings-geïnduceerde carcinomen (11). Zeker als men ervan uitgaat dat er een continue daling is in stralingsdosis ten gevolge van nieuwe ontwikkelingen, wordt het risico van de straling van een CT-colografie beschouwd als extreem laag en verwaarloosbaar (12). Echter, eerdere onderzoeken namen niet de invloed mee van een korter surveillance-interval, namelijk de 3 jaar surveillance voor 6-9 mm poliepen. Onvermijdelijk zou dit de levenslange dosis voor een kleine deel van de gescreenden doen toenemen. Onderzoek naar de duur van follow-up voor 6-9 mm poliepen zal moeten bepalen of deze toename significant zal zijn.

De kosteneffectiviteit van een surveillance CT-colografie strategie voor 6-9 mm poliepen wordt op het moment onderzocht en dit zal vergeleken moeten worden met een coloscopie verwijsstrategie. De eerste resultaten van deze modelleerstudie, gebaseerd op data van de COCOS-trial, laten zien dat de meest kosteneffectieve CT-colografie strategie een strategie is waarbij alle patiënten met ≥6 mm laesies direct voor coloscopie verwezen worden (data nog niet gepubliceerd).

Een ander zeer interessant onderwerp voor toekomstig onderzoek zou zijn de voorkeur van patiënten; surveillance CT-colografie of coloscopie. Bij de primaire COCOS trial werden patiënten met 6-9 mm poliepen geadviseerd om een surveillance CT-colografie te ondergaan. Maar sommige van hen kozen ervoor om niet te wachten, maar ondergingen vervroegd een coloscopie op eigen initiatief (5%; 4/82). Wat als aan alle patiënten de keus was voorgelegd? Ondanks dat we hebben laten zien dat de acceptatie voor surveillance CT-colografie hoog was en de belasting laag, zou het kunnen zijn dat patiënten er een voorkeur voor zouden hebben om hun poliepen direct te laten verwijderen.

Deel II- MR Imaging van het terminale ileum en rectum bij de ziekte van Crohn

Samenvatting

De MRI heeft zijn nut bewezen in het diagnosticeren en monitoren van de ziekte van Crohn. Uitgebreid onderzoek heeft talrijke MRI karakteristieken geïdentificeerd, bruikbaar in het vaststellen van ontsteking bij de ziekte van Crohn. Op MR enterografie en MR colografie zijn er meerdere scoringssystemen ontwikkeld om de mate van ontsteking te diagnosticeren en te kwantificeren bij deze patiënten (13-15). Elke researchgroep heeft zijn eigen voorkeur en expertise, en er zijn geen studies die deze verschillende scoringssystemen met elkaar vergelijken. Er blijft discussie omtrent het meest nuttige MRI scoringssysteem.

In hoofdstuk 6 hebben we een prospectieve studie met MR enterografie verricht, waarin vier MRI scoringssystemen vergeleken worden op het gebied van ziekteactiviteit in het terminale ileum en de individuele karakteristieken welke opgenomen zijn in deze verschillende systemen. Van deze scoringssystemen en individuele karakteristieken bepaalden we de interobserver agreement en de correlatie met de histopathologie (eAIS) en ileocoloscopie (CDEIS) referentiestandaard. Onze resultaten laten zien dat in onze populatie van patiënten met verdenking op, of met bewezen ziekte van Crohn, alle scoringssystemen een goede interobserver agreement hadden (ICC tussen 0.70 en 0.78), correlaties met de histopathologie referentiestandaard matig waren (r: 0.51–0.57 en 0.46-0.52 voor observers 1 en 2, respectievelijk) en de diagnostische accuratesse 74%–77% en 69%–72% was voor observers 1 en 2, respectievelijk. De correlatie met de CDEIS en diagnostische accuratesse was ook vergelijkbaar. Van de individuele MRI karakteristieken, lieten aankleuring, perimuraal T2 signaal, ADC en RCE een goede reproduceerbaarheid zien (ICC: 0.68–0.70). Met de eAIS, was er maximaal een matige correlatie voor de individuele karakteristieken en met de CDEIS een sterkte correlatie. Aangezien de vier scoringssystemen vergelijkbaar waren in reproduceerbaarheid, correlatie en diagnostische prestatie, kan de keus voor het gebruik in de dagelijkse praktijk gebaseerd worden op andere aspecten zoals persoonlijke voorkeur, ervaring en praktische overwegingen.

In het geval van perianale fistels, een veel voorkomend probleem bij de ziekte van Crohn, zullen patiënten een perianale MRI ondergaan. Perianale MRI heeft een gelimiteerd scan protocol (kleiner FOV, minder sequenties en de afwezigheid van luminaal contrast) ten opzichte van luminale ziekte van Crohn en het is nog onbekend of de karakteristieken die gebruikt worden om ziekteactiviteit op MR enterografie of MR colografie vast te stellen, ook bruikbaar zijn om ontsteking van het rectum vast te stellen op deze specifieke perianale MRI. Maar voor

het bepalen van een behandeling, is het vaststellen van de aan- of afwezigheid van proctitis zeer zeker relevant. Daarom hebben we in hoofdstuk 7, een retrospectieve studie verricht om vast te stellen welke MRI karakteristieken bruikbaar zijn in het diagnosticeren van proctitis op perianale MRI. Zeventien karakteristieken zijn geëvalueerd; de MRI karakteristieken zijn vergeleken met de endoscopie referentiestandaard en de reproduceerbaarheid werd vast gesteld. MRI karakteristieken werden relevant geacht, als ze significant correleerden met de endoscopie van ≥2 observers, en als de reproduceerbaarheid ≥0.40 voor ≥2 observerparen was. Wanddikte, muraal vet en vier karakteristieken gerelateerd aan het perimurale vetweefsel (perimuraal T2 signaal, perimurale aankleuring, aanwezigheid van *creeping fat* en de grootte van mesorectale lymfeklieren) beantwoordden aan deze criteria en waren potentieel relevant in het diagnosticeren van proctitis. Muraal T2 signaal en T1 aankleuring bleken minder nuttig aangezien de reproduceerbaarheid slecht was voor alle drie de observer paren. In tegenstelling tot de beoordeling van ziekteactiviteit op MR enterografie of MR colografie, zijn op perianale MRI perirectale karakteristieken meer bruikbaar in het vaststellen van ontsteking van het rectum dan reeds gevestigde luminale karakteristieken.

Implicaties

Het graderen van ziekte activiteit op MRI bij de ziekte van Crohn heeft waarde bij het monitoren van response op behandeling in de dagelijkse praktijk. Voor dit doel staan er meerdere MRI karakteristieken en scoringssystemen tot onze beschikking. Echter, een belangrijke beperking van de conventionele MRI karakteristieken is het objectief graderen van de ziekte-activiteit. De radioloog die de ene karakteristiek moet evalueren wordt onvermijdelijk beïnvloed door de bevindingen op andere sequenties. Met de komst van nieuwe technieken zijn er meer geavanceerde kwantitatieve karakteristieken ontwikkeld. Deze zijn veelbelovend op het gebied van reproduceerbaarheid en objectiviteit, maar dit gaat vaak ten koste van tijdrovende metingen en evaluaties.

Een groot probleem met de interpretatie van kwantitatieve parameters, zoals ADC en RCE, is dat deze onderhevig zijn aan meerdere variabiliteiten: er is variabiliteit binnen de scanner, tussen de scanners en er zijn verschillende methoden van metingen (grootte en positie van ROI, selectie van representatieve waarde (de hoogste, vaststellen van een gemiddelde waarde door meerdere ROIs te tekenen). Bovendien zijn de cut off-waarden vastgesteld voor kwantitatieve parameters onderhevig aan spectrumbias, wat betekent dat numerieke waarden individu- en studiespecifiek zijn en daarom niet generaliseerbaar (16, 17). Sterker nog, een alliantie, QIBA (Quantitative Imaging Biomarkers Alliance), is samengesteld met als

voornaamste doel de waarde en uitvoerbaarheid van kwantitatieve imaging biomarkers te begrijpen en te verbeteren. In onze studie kwamen we ook deze variabiliteiten tegen, welke aan het licht kwamen door grote verschillen in numerieke ADC waarden in een relatief stabiele structuur (musculus erector spinae) tussen de twee deelnemende ziekenhuizen, maar ook binnen de ziekenhuizen. Zolang er geen uniform beleid bestaat over hoe om te gaan met deze variabiliteiten, is het generaliseren van resultaten extreem moeilijk en daarom is het gebruik van deze kwantitatieve parameters (en van de scoringssystemen welke gebruik maken van deze parameters) nog niet geschikt voor de dagelijkse praktijk.

Een oplossing voor de subjectiviteit van een observer bij het evalueren van kwalitatieve karakteristieken zou het gebruik van (semi-) geautomatiseerde metingen kunnen zijn. Onderzoek van onze studiegroep heeft veelbelovende resultaten laten zien met semi-automatisch gegenereerde karakteristieken (darmwanddikte en ziektevolume): minimale gebruikersinput, hoge correlatie met subjectieve metingen van de radioloog en verbeterde reproduceerbaarheid. Een nieuw scoringssysteem, welke ook semi-geautomatiseerde karakteristieken incorporeert, kan potentieel de prestatie verbeteren vergeleken met de bestaande MRI activiteit-scoringsssytemen.

In perianale MRI zijn niet alle MRI karakteristieken beschikbaar, door het gebruik van een gelimiteerd scan protocol met minder sequenties dan gebruikt wordt bij MR enterografie of MR colografie. De huidig beschikbare karakteristieken verschilden in diagnostische waarde. Een substantieel verschil met MR enterografie en MR colografie is de afwezigheid van luminaal contrast om luminale distentie te bewerkstelligen. Dit resulteert vaak in een gecollabeerd lumen wat een precieze evaluatie van de wand bemoeilijkt. Echter, het doel van onze studie was om te zien of we de aanwezigheid van ontsteking konden bepalen, juist met het bestaande, gelimiteerde scanprotocol. Andere verschillen hebben betrekking op de anatomie van het mesorectum met de geïsoleerde locatie van het rectum omgeven door een substantiële hoeveelheid vetweefsel, hetgeen nog meer wordt geprononceerd als de hoeveelheid vet toeneemt in geval van ziekte activiteit (creeping fat fenomeen). Hierdoor worden de perirectale karakteristieken geaccentueerd. De relevantie van deze karakteristieken specifiek voor ontsteking van het rectum kwam aan het licht in dit manuscript en moeten bevestigd worden in een prospectieve studie, waarin ook de drempelwaarden voor continue variabelen bepaald zullen moeten worden.

Hoewel de ziekte van Crohn gekarakteriseerd wordt door transmurale ontsteking, kan het zich ook presenteren met alleen oppervlakkige (mucosale) laesies. Door de relatief kleine patiëntenpopulatie werden we gedwongen de patiënten te verdelen in degene mét en degene

zonder proctitis. Het zou interessant zijn om te weten of de perirectale karakteristieken zich ook zo zouden manifesteren in patiënten met niet-ulceratieve proctitis (alleen oppervlakkige laesies). We stellen een nieuwe studie voor zonder de tekortkomingen van onze studie: een prospectieve studie met een groter patiëntencohort, een maximaal tijdsinterval van twee weken tussen MRI en endoscopie en teminste een kappa/intraclass coefficient van 0.60 om een karakteristiek als relevant te beschouwen. Bovendien dient de endoscopie referentiestandaard een beoordeling te zijn van de ernst van de ziekte, rekening houdend met verschillende gradaties van ernst (ulceratief versus niet-ulceratief) en mogelijk dat er een onderscheid gemaakt zou kunnen worden tussen actieve en recidiverende/chronische inflammatie. Een makkelijk toe te voegen sequentie zou de DWI kunnen zijn. Dit is een korte sequentie welke geen extra patiëntenbelasting veroorzaakt, en waarschijnlijk makkelijk te beoordelen is in het geïsoleerde rectum.

Conclusies

Patiënten met de ziekte van Crohn hebben voordeel bij niet-invasieve manieren van het vaststellen van ziekteactiviteit en -ernst, voornamelijk in de setting van het vervolgen van response op behandeling maar ook voor diagnostische doeleinden bij patiënten die endoscopie-onderzoeken niet goed verdragen.

In dit manuscript hebben we laten zien dat voor MR enterografie of MR colografie de CDMI en London score, beide opgebouwd uit conventionele MRI karakteristieken, het meest geschikt lijken voor dit doel. Afgezien nog van het tijdrovende aspect zijn op dit moment kwantitatieve parameters nog onderhevig aan te veel technische moeilijkhedenom te gebruiken in de dagelijkse praktijk.

In tegenstelling tot gevestigde luminale karakteristieken op MR enterografie of MR colografie, hebben we gezien dat op perianale MRI, de diagnose proctitis voornamelijk gebaseerd is op perirectale karakteristieken.

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chapter
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Chapter 10

Abbreviations

Dankwood

List of publications

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Curriculum vitae

Abbreviations

AA	Advanced adenoma
ADC	Apparent diffusion coefficient
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDEIS	Crohn's disease endoscopic index of severity
CDMI	Crohn disease MRI index
CRC	Colorectal cancer
CRP	C-reactive protein
CTC	Computed tomography colonography
CI	Confidence interval
DWI	Diffusion-weighted imaging
eAIS	Acute inflammation score in endoscopic biopsies
EBQ	Expected burden questionnaire
FOBT	faecal occult blood test
FOV	Field of view
FIT	Faecal immunochemical test
HP	Hyperplastic polyp
IES	Impact of event scale
IQR	Interquartile range
MaRIA	Magnetic resonance index of activity
MID	Minimal important difference
MRI	Magnetic resonance imaging
OR	Odds ratio
PBQ	Perceived burden questionnaire
R	Correlation coefficient
RCE	Relative contrast enhancement
ROI	Region of interest
SD	Standard deviation
SSP	Sessile serrated polyp
TI	Terminal ileum
TSA	Traditional serrated adenoma

Dankwoord

Veel mensen hebben mee geholpen aan de totstandkoming van dit proefschrift. Vanzelfsprekend wil ik de patiënten bedanken die hebben mee gedaan aan de verschillende studies, zonder hun medewerking waren deze studies nooit gelukt.

Graag zou ik een aantal mensen in het bijzonder willen bedanken:
De promotoren, prof. dr. J. Stoker en prof. dr. E. Dekker. Beste Jaap, dit boek zou er niet zonder jou geweest zijn. Niet alleen door je uitgebreide kennis en ervaring, maar ook door me het goede voorbeeld te geven hard te werken en zo de vaart erin te houden. Hoe druk je ook was, ik kon altijd op snelle reacties rekenen en ik waardeer je flexibele houding als mijn tijd (mede) door de opleiding beperkt was. Ik ben geen geboren wetenschapper, maar heb er door jou wel een liefde voor ontwikkeld. Beste Evelien, ik heb onze samenwerking altijd als enorm plezierig ervaren. Jouw kritische en klinische blik was onmisbaar bij de totstandkoming van mijn artikelen.

Mijn co-promotor, dr. A.D. Montauban van Swijndregt. Beste Alexander, ik herinner me nog als de dag van gisteren ons eerste gesprek over een eventueel promotietraject, en kijk wat er van gekomen is. Dank voor je steun en rotsvast vertrouwen in mij. Erik-Jan en Hanny, dank voor jullie flexibiliteit en hulp bij de roosterplanning als ik weer eens een extra onderzoeksdagje nodig had. En natuurlijk wil ik de gehele maatschap radiologie van het OLVG bedanken die dit promotietraject überhaupt mogelijk hebben gemaakt. Maar met name voor de geweldige opleidingstijd die ik in het OLVG gehad heb. Met pijn in mijn hart verlaat ik de afdeling.

De leden van mijn promotiecommisie, voor het beoordelen van mijn proefschrift.

Mijn lieve paranimfen, Julie en Floortje. Julie, wat een geluk dat mijn zus hetzelfde vak uitoefent! Met zoveel plezier deel ik met jou al jaren mijn onzeker- en onwetendheden en voel me gesterkt door jouw steun als oudere, wijze zus. Dank voor je oneindige support bij de opleiding, de presentaties, het promoveren, het solliciteren en natuurlijk het gewone leven! Floortje, ik bewonder je optimisme, vrolijkheid en intelligentie en ben ontzettend blij je te hebben leren kennen. Dank voor je altijd oprechte interesse, goede gesprekken en natuurlijk een geweldige week in Chicago. Het geeft me een gerust gevoel dat je op 10 november naast me staat!

De mede-auteurs van de artikelen in dit proefschrift. In het bijzonder wil ik Thierry en Margriet bedanken voor jullie altijd snelle en kritische evaluatie van mijn artikelen. En natuurlijk Shandra, door jou zag ik door de waas van de statistiek weer het licht.

De radiologen van het AMC en in het bijzonder Yung Nio, Banafsche Mearadji en Anje Spijkerboer, die dankzij het scoren mijn studies mogelijk hebben gemaakt.

Laurens, Isha, Caroline, Martin, Dominique, Cindy en Roel, zonder jullie inspanningen bij de inclusies en het scoren van de CT's zou er überhaupt geen studie geweest zijn.

De onderzoekers van G1, Henk-Jan, Cheima, Jurgen, Olvert, Anne, Shira, Nus, Laura, Floortje, Jordi, Jos, Carl, Martine, Charlotte, Anouk, Kilian, Ivo, Sofieke, Marloes, Daan en Sjoerd. Dank voor de altijd hartelijke en stimulerende sfeer op de afdeling. Carl, wat een leuke afsluiter van mijn onderzoekstijd, een artikel met mijn neef te kunnen schrijven. Het voelt als de kroon op mijn werk om naast een artikel met je vader er nu ook een met jou te hebben geschreven. Wat zou Boppi trots op ons geweest zijn!

De IT-mannen, Jean-Paul, Martin, en Jan in het bijzonder, die altijd klaar stonden met hun technische vernuftigheden.

Ann-Sophie, jij wist altijd waardevolle tijd voor me vrij te maken in de drukke agenda van Jaap.

Aart Nederveen, dank voor al je hulp bij de technische MRI problemen waar ik tegenaan liep. Alle arts-assistenten radiologie van het OLVG en AMC, wat heb ik een ongelooflijk leuke tijd gehad tijdens mijn opleiding, en dat heb ik voor een groot deel aan jullie te danken. Ik hoop jullie nog vaak te zien.

Lieve oom Juul, jouw aanstekelijk enthousiasme heeft er al jaren geleden voor gezorgd dat ik gekozen heb voor het vak radiologie en daar ben ik je nog iedere dag dankbaar voor. Ik kan me geen mooier beroep wensen. Dat enthousiasme is natuurlijk al een generatie eerder begonnen. Ik ben blij dat Boppi nog heeft mogen meemaken dat in ieder geval twee van zijn kleinkinderen opgeleid werden tot radioloog. En het worden er vast meer!

Lieve vriendinnen, dank voor het geduldig aanhoren van alle onderzoeksperikelen en jullie opbeurende woorden. In het bijzonder: Loet, mijn grootste en trouwste supporter, eigenlijk bij alles in mijn leven. Fleur, onze wekelijkse ontbijtjes zijn me heel dierbaar; gedurende deze

heb jij mij wegwijs gemaakt in de wereld van een promovendus, het moederschap en in nog zo veel meer. Faye en Mariek, verschillende carrièrekeuzes en grote afstanden hebben jullie er nooit van weerhouden precies op de hoogte te zijn van het reilen en zeilen in mijn leven. Veel dank voor alles!

Lieve schoonfamilie, wat ben ik gezegend met jullie. Altijd oprecht geïnteresseerd en bereid tot hulp, in welke vorm dan ook. Onlosmakelijk verbonden hiermee ben en blijf jij, lieve Nikki. Je wordt dan ook ontzettend gemist.

Lieve familie, altijd even enthousiast bij de kleine en grote mijlpalen in mijn promotietraject en mijn leven. Julie, Heleen en Boeli, ik voel me gezegend met de hechte band tussen ons en de steun en vriendschap die daaruit voortkomt. Lieve pap en mam, ik wil jullie danken voor het warme nest en jullie onvoorwaardelijke liefde. Jullie gaven mij het goede voorbeeld en het doorzettingsvermogen dat ik nodig had om dit promotietraject tot een goed eind te brengen. Jullie hebben me, zoals altijd in mijn leven, op alle mogelijke manieren ondersteund en uit de brand geholpen. Mam in het bijzonder, onvermoeibaar en met de grootste precisie heb je mijn teksten gelezen en verbeterd en mee gezocht naar oplossingen voor de vele 'problemen' die tijdens zo'n promotietraject langs komen. Ik kan jullie niet genoeg bedanken. Ik hou van jullie!

Lieve mannen van mijn leven, het is af en mijn volledige aandacht kan eindelijk weer naar jullie. Ik kijk uit naar de toekomst, binnenkort met z'n vieren!

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IJspeert JEG, **Tutein Nolthenius CJ**, Kuipers EJ, van Leerdam ME, Nio CY, Thomeer MGJ, Biermann K, van de Vijver MJ, Dekker E, Stoker J.
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Inter-observer agreement for abdominal CT in unselected patients with acute abdominal pain.
Eur Radiol. 2009 Jun; 19(6):1394-407.

Portfolio

Name PhD student:	Charlotte Jacoline Tutein Nolthenius, MD
PhD Period:	December 2012 - November 2016
Promotor:	Prof. dr. J. Stoker, Prof. dr. E. Dekker
Co-promotor:	Dr. A.D. Montauban van Swijndregt

	Year	Workload (ECTs)
General Courses		
BROK (Basic Course Legislation and Organization of Clinical Researchers)	2013	0.9
Practical Biostatistics	2013	1.1
Clinical Data Management	2013	0.3
Specific Courses		
Basic MSK Ultrasound Course, LUMC, Leiden	2011	11.5
Cursus Echo en CT bij acute buik, MCH, Den Haag	2011	12
Interactieve workshop 'de pols, anatomie en functie', AMC	2012	1
CT colonography course (NVvR)	2013	40
MR Enterography in Crohn's disease course (NVvR)		
Basic	2013	10
Advanced	2015	6
Cursus praktische neuroanatomie en neuroradiologie, VUMC, Amsterdam	2013	12
HRCT cursus, Leuven, België	2015	11.5
EMRI course - Abdominal and Urogenital, Brussel, België	2016	21
Teaching		
Tutor for CT colonography course (NVvR)	2013-2014	
Presentations		
Radiologendagen, 's-Hertogenbosch	2014	0.5
European Congress of Radiology, Vienna	2015	0.5
Radiologendagen, 's-Hertogenbosch	2015	0.5
Radiological Society of North America, Chicago	2015	0.5
European Congress of Radiology, Vienna	2016	0.5
Congress of European Crohn and Colitis Ulcerosa, Amsterdam	2016	0.5

Awards

Best scientific paper presentation award ECR within the topic “GI Tract”	2015
European Radiology ESGAR Gold Award	2015
Dr. Keeman Wetenschapsprijs 2016	2016

Curriculum vitae

Charlotte Tutein Nolthenius is geboren op 10 november 1983 in Willemstad te Curaçao. Zij doorliep het gymnasium aan het Lorentz Casimir Lyceum in Eindhoven. In 2001 ging zij, na uitgeloot te zijn voor geneeskunde, biomedische wetenschappen studeren aan de Universiteit van Amsterdam. In 2002 werd zij alsnog ingeloot, en startte zij haar studie geneeskunde aan het Academisch Medisch Centrum (AMC) in Amsterdam. Tijdens de doctoraalfase heeft zij onderzoek gedaan op de afdeling radiologie naar de reproduceerbaarheid van zowel de CT abdomen als de conventionele buikoverzicht opname bij patiënten die zich presenteren met een acute buik op de eerste hulp. Zij volgde keuze co-schappen chirurgie in het St Elisabeth Hospitaal te Curaçao en radiologie aan het UCLA, Los Angeles, USA. Na haar afstuderen in 2009 ging zij werken als ANIOS chirurgische specialismen in het BovenIJ Ziekenhuis te Amsterdam.

In 2010 begon zij met de opleiding Radiologie aan het OLVG, locatie Oost te Amsterdam onder leiding van dr. A.D. Montauban van Swijndregt en dr. E.J.T. Krul/A. Driessen-Waaijer. Na haar academische stage in het AMC, is zij tijdens de opleiding gestart met een promotieonderzoek bij prof. dr. J. Stoker met als onderwerpen de surveillance CT-colografie van kleine poliepen in het kader van screening, en MRI karakteristieken bij de ziekte van Crohn, en dan specifiek in het terminale ileum en het rectum. Begin augustus 2016 heeft zij de opleiding tot radioloog afgerond en 1 september 2016 is zij gestart als fellow abdominale radiologie in het St. Antonius ziekenhuis te Nieuwegein.

Zij woont in Amsterdam met haar man Joris Albers en hun zoon Splinter.

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