The Sahlgrenska Academy

CT Colonography: implementation and technical developments

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It is not the mountain we conquer but ourselves. ~Edmund Hillary

CONTENTS

ABSTRACT

CT Colonography: implementation and technical developments

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Background: Computed tomographic colonography (CTC) is a minimally invasive imaging method for the detection of colorectal neoplasms. Uncertainty about its diagnostic performance, optimal visualization method, long learning curve and radiation exposure are among problems with CTC, affecting its implementation in routine health care. Potential means of improvements include novel three-dimensional (3D) CTC displays, such as "Perspective-filet view" (3D Filet), and computer-aided detection (CAD). Increasing awareness of radiation doses in CT promotes low-dose techniques, the effects of which on the prevalence of noise-related artefacts and lesion perception on 3D images are unknown.

Aims: I. To determine the availability and technical performance of CTC in Sweden. II. To compare lesion detection by inexperienced CTC readers using primary 3D Filet analysis versus primary 2D analysis and to evaluate the effect of combined 3D Filet+2D analysis. III. To investigate whether CAD applied to 3D Filet improves the inexperienced reader´s performance compared to CAD-unassisted 3D Filet and 2D. IV.To compare the prevalence of noise-related artefacts and lesion perception on 3D Filet at standard and low radiation doses.

Methods: I. Questionnaires on CTC implementation and technical performance were sent to all radiology departments in Sweden in 2005 and in 2009. II. Fifty symptomatic patients were prospectively enrolled and examined with CTC followed by same-day colonoscopy with segmental unblinding. An experienced reader prospectively performed 3D Filet analysis, followed by complete 2D analysis (3D Filet+2D). Two inexperienced readers, blinded to CTC and colonoscopy findings, performed 3D Filet analysis and, after 5 weeks, 2D analysis. True positives ≥6 mm detected by the inexperienced readers with 3D Filet and/or 2D were combined to obtain 3D Filet+2D. III. Four months later, the inexperienced readers re-read the cases only evaluating CAD marks on 3D Filet. IV. Forty-eight patients underwent CTC at standard and at low radiation dose. Noise-related artefacts and perception of polyps on 3D Filet images were evaluated at standard dose, original low dose and modified low dose, i.e. after manipulation of opacity on 3D images.

Results: I. In 2009, CTC is performed in 42% of the radiology departments, i.e. 18 additional departments compared to 2005. Attitudes of radiologists are increasingly in favour of CTC. II. For the inexperienced readers, there was no significant difference between 3D Filet and 2D analysis regarding sensitivity and reading time. III. CAD applied as second reader on 3D Filet increased the sensitivity by inexperienced readers, but also the number of false positives, compared to CAD-unassisted 3D Filet and 2D, thus not improving overall performance, i.e. the ability to distinguish between lesions and non-lesions. IV. The mean effective dose was 3.9±1.3 mSv at standard dose and 1.03±0.4 mSv at low dose. Image quality was significantly affected on 3D Filet at low dose compared with standard dose. Reduction of the effective radiation dose to 1 mSv did not significantly impair the perception of lesions ≥6 mm.

Conclusions: CTC is increasingly available in Sweden as an alternative to barium enema and complement to colonoscopy. Lesion detection by inexperienced readers does not seem to be influenced by the choice of the display method. It can be improved by the use of CAD. At low-dose CTC corresponding to 1 mSv effective dose, image quality is worsened, but detection of clinically important lesions is not significantly affected.

Keywords: X-ray Computed Tomography; Computed Tomographic Colonography; Computer-Assisted Image Processing; Three-Dimensional Imaging; Colonoscopy; Colon; Rectum; Colorectal neoplasms; Computer-Assisted Diagnosis; Ionizing Radiation. ISBN-: 978-91-628-7842-9 http://hdl.handle.net/2077/20454

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Fisichella V, Hellström M.
Availability, indications, and technical performance of computed tomographic colonography: a national survey.
Acta Radiologica 2006;47(3):231-7

II. Fisichella VA, Hellström M.
Survey update on implementation, indications and technical performance of CT colonography in Sweden
Acta Radiologica 2009. In press

III. Fisichella VA, Jäderling F, Horvath S, Stotzer P-O, Kilander A, Hellström M.
Primary 3D analysis with perspective-filet view versus primary 2D analysis: evaluation of lesion detection by inexperienced readers at CT colonography in symptomatic patients
Acta Radiologica 2009;24:1-12

IV. Fisichella VA, Jäderling F, Horvath S, Stotzer P-O, Kilander A, Båth M, Hellström M.
Computer-aided detection (CAD) as second reader using perspective-filet view at CT colonography: effect on performance of inexperienced readers
Clinical Radiology 2009. In press

V. Fisichella VA, Båth M, Johnsson AÅ, Jäderling F, Bergsten T, Persson U, Mellingen K, Hellström M.
Evaluation of image quality and lesion perception by human readers on 3D CT colonography: comparison of standard and low radiation dose
European Radiology 2009. In press.

ABBREVIATIONS

AUC	Area under the curve
BMI	Body Mass Index
CAD	Computer-aided detection
CI	Confidence interval
CRC	Colorectal cancer
CT	Computed tomography
CTC	Computed tomographic colonography
CTDIvol	Computed tomography index volume
DCBE	Double-contrast barium enema
DLP	Dose-length product
E	Effective dose
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
FOBT	Fecal occult blood test
FOM	Figure-of-Merit
FP	False positive
FROC	Free-Response Receiver Operating Characteristic
HU	Hounsfield units
IQR	Interquartile range
JAFROC-1	Jackknife Free-Response Receiver Operating Characteristic-1
kV	Kilovolt
LD	Low dose
mA	Milliampere
mAs	Milliampere second
MDCT	Multidetector row computed tomography
mGy	Milligray
min	Minutes
ml	Milliliter
MLD	Modified low dose
mm	Millimeter
MPR	Multiplanar reconstruction
mSv	MilliSievert
ns	Non-significant
OC	Optical colonoscopy
OLD	Original low dose
ROC	Receiver Operating Characteristic
ROI	Region-of-interest
Rot	Rotation
s	Second
SD	Standard deviation
STD	Standard dose

3D	Three-dimensional
3D Filet	Three-dimensional analysis with perspective-filet view
2D	Two-dimensional
TP	True positive
VGC	Visual grading characteristics
Vs	Versus

INTRODUCTION

COLORECTAL CANCER AND POLYPS

Colorectal cancer (CRC) is the second most common cancer in women and the third in men in Sweden, corresponding to 8% of the total number of cancer diagnoses in 2007, with a total of approximately 4600 new cases (1). Although the 5-year survival rate has improved in the last two decades and nowadays is approximately 60% (2), due to more effective chemotherapeutic agents and improved surgical techniques, CRC is still the second ranked cause of cancer-related deaths in Sweden. A possible explanation is that CRC is often diagnosed at an advanced stage.

Most cases of CRC develop from previously benign neoplastic polyps, i.e. adenomas, according to the "adenoma-carcinoma sequence" concept (3). The endoscopic removal of adenomas (secondary prevention) plus post-polypectomy surveillance are associated with a substantial reduction of incidence and thus mortality from CRC (4-7).

The likelihood of malignant transformation of an adenomatous polyp is positively related to its size, the amount of villous tissue and the grade of dysplasia. In CRC screening the target lesion is the "advanced adenoma". It corresponds to a polypoid lesion with one or more of the following characteristics: size of at least 1 cm; high-grade dysplasia; substantial villous component (8). It is associated with a risk of developing cancer in 10-25% of cases (9). It has been reported that in screening populations, advanced histology is present in 30% of large polyps (≥10 mm). Concerning medium-sized polyps (6-9 mm), studies have reported the presence of advanced dysplasia in 3-20% (10-12) and the presence of cancer in 0.5-1%, with the risk increasing with the number of adenomas (≥3) (13). Most of the small polyps (≤5 mm) are hyperplastic, only 1.7% have advanced histology (11) with a risk of developing cancer far below 1%. Also for small lesions, the risk increases if more than three adenomas are present.

As radiological examinations cannot give information about the histology (except in case of lipomas if performing a computed tomography (CT)), the size and the number of polyps are considered as surrogate markers for possible advanced histology (10) and clinical significance. As the risk of cancer

transformation is reported to be low for polyps of 5 mm and less, “clinically significant polyps” are usually defined as polyps that are at least 6 mm. However, there is controversy about how to define a polyp as clinically significant on the basis of its size (14, 15). Thus, for patients with polyps 5 mm and smaller, there is no agreement on the optimal management strategy, e.g. if small lesions should be reported at radiological examinations or not, and in case they are reported, if one should recommend endoscopic removal or surveillance.

DIAGNOSTIC TESTS

Diagnostic tests should be able to detect early CRC and adenomatous polyps.

a. *Fecal occult blood tests (FOBT)*

FOBT detect the presence of blood in the stool, which might be caused by a bleeding CRC or large polyps. Large trials have shown that screening with FOBT, followed by colonoscopy with removal of detected polyps, reduces CRC mortality by 15-33% and reduces CRC incidence by 20% (16-18). However, FOBT have highly variable sensitivity and specificity, depending on the type of test (low-sensitivity or high-sensitivity FOBT (19)). For CRC and avanced adenomas, the high-sensitivity FOBT have a reported sensitivity of 64-80% and 41%, respectively, and a specificity of about 87% (20, 21). FOBT should be repeated every year or every 2 years as CRC or large polyps can bleed only intermittently. Subjects with positive FOBT need to undergo colonoscopy.

b. *Sigmoidoscopy*

Sigmoidoscopy is an endoscopic procedure where only the distal part of the colon and the rectum is examined. No sedation is required. As at least one third of polyps are located in more proximal parts of the colon (22), it can not be considered a complete diagnostic test. However, it may have some predictive value regarding the proximal colon, as patients with an adenoma in the distal colon or rectum have a higher risk of advanced neoplasia in the proximal colon compared with patients with no adenomatous polyps in the distal colon or rectum. It is therefore recommended that patients with adenomas found at sigmoidoscopy undergo complete colonoscopy.

c. *Double-contrast barium enema (DCBE)*

DCBE is a radiological procedure performed after rectal administration of a radiopaque contrast medium (barium sulphate) and air. The barium coats the colorectal mucosa while air distends the lumen. Multiple radiographs are taken

with the patient turning in several positions under fluoroscopy. No sedation is required. DCBE has a relatively high sensitivity and specificity for CRC, around 85%, (23-25), but quite low sensitivity for polyps (23).

d. *Optical colonoscopy (OC)*

OC is considered the "gold standard", although not infallible, as it has a very high sensitivity and specificity for detection of CRC and polyps, and also allows visual inspection of inflammatory changes. During OC it is also possible to perform biopsies and resect polyps. However, OC is an invasive procedure that often requires the use of sedative and/or analgesic medication in order to reduce patient pain and discomfort. Half of all severe adverse events during OC are reported to be cardiopulmonary events such hypotension, oxygen desaturation and cardiac arrythmias, some of which are related to sedation (26). OC is associated to a low risk of perforation, approximately 0.1% (27). In addition, it has been reported that OC fails to depict the whole colon in approximately 3-13% of patients (28, 29), and up to 23% in a study from the United Kingdom (30), due to e.g. pain and discomfort, or technical problems like colon tortuosity, strictures or fecal material. Although OC is the most accurate diagnostic test to screen for CRC and polyps, the compliance of individuals to endoscopic screening has been reported to be low (31).

CT COLONOGRAPHY

Computed tomographic colonography (CTC) is a relatively recent radiological examination that uses CT technique and dedicated interactive three-dimensional (3D) and two-dimensional (2D) imaging software to evaluate the colon. Since its introduction in 1994 by Vining et al. (32), CTC has undergone extensive clinical assessment and technological advancements.

As with OC and DCBE, patients should undergo colon cleansing prior to the examination. The colon is distended by insufflation of air or carbon dioxide, via a small plastic rectal tube. Antispasmodic agents (Buscopan or Glucagon) and/or contrast media may be administered intravenously before the CT scan. Recently, the use of oral contrast agents (such as barium, water-soluble low-osmolar iodine or gastrografin) has been introduced. The oral contrast medium opacifies residual stool or fluid, thus allowing discrimination from polyps, resulting in so called "fecal" or "fluid tagging". Additionally, it is possible to perform an "electronic cleansing", i.e. the CTC software recognizes areas with high density

(corresponding to oral contrast mixed with stool or fluid) and subtracts it from the images.
The CT scan is performed in supine and prone positions during breath-holding. No sedation or analgetics are required.

Studies on CTC Performance

CTC has emerged as a potential alternative or complement to OC and DCBE in the detection of CRC and polyps.
CTC is more sensitive and more specific than DCBE concerning polyps ≥ 6 mm (33-36). Concerning comparison of CTC versus OC, several meta-analyses suggest that CTC has excellent average sensitivity concerning identification of patients with CRC (96%, range 80-100%) and very good average sensitivity (82-93%, range 48-100%) and specificity (97%) concerning patients with large adenomas (34, 37, 38). Accuracy of CTC diminishes with decreasing polyp size, with an average sensitivity for polyps <5 mm of only 50%.
Some conflicting results on CTC performance have, however, been published. Pickhardt et al (39) had excellent results on 1233 screening individuals with a sensitivity of 94% for CTC concerning patients with large adenomas, even higher than for OC (87.5%). Two subsequent large studies by Cotton et al and Rockey et al had, however, disappointing results with CTC sensitivity for patients with large polyps ranging from 55% to 64% (35, 40). A retrospective analysis of the data from Rockey et al showed that most of the polyps missed were perceptual errors, i.e. observer-related (41). A criticism toward those two studies was raised concerning the lack of experience and inadequate training of the readers.
Further multicenter trials have recently been performed in order to assess the potential of CTC. In the ACRIN (American College of Radiology Imaging Network) trial (42) on 2531 screening individuals, the radiologists who read the CTC datasets had an experience of at least 500 CTC or were trained and had to pass a test of their diagnostic ability before participating the trial. More than half of the readers had to undergo additional training in order to pass the test. The newly published IMPACT trial (Italian Multicenter Polyp Accuracy CTC trial) was performed on 937 individuals including asymptomatic individuals at higher than average risk and individuals with positive FOBT (43). Radiologists with experience of at least 50 CTCs could participate. The ACRIN and IMPACT trials reported per-patient sensitivity of 90% and 85%, respectively, for large polyps and per-patient specificities over 85%. These results suggest that CTC is

an accurate test for detection of CRC and large polyps when performed by trained readers.

CTC Indications

CTC is currently performed in symptomatic patients in cases of failed or incomplete OC (44), which may be due to an obstructing colorectal cancer, diverticular disease, redundant colon, adhesions, residual colonic content, patient intolerance to OC because of excessive pain or discomfort. CTC can visualize the colon proximal to a stenosing cancer and can thus evaluate any synchronous colonic lesions and at the same time evaluate the abdomen for local tumor spread, and liver or lymph node metastases for staging. CTC can preferably be performed the same day as the failed OC in order to avoid a second bowel preparation.

CTC is preferred also in patients where OC is contraindicated (patients with cardio-pulmonary disease, bleeding disorders or anticoagulant therapy, elderly frail patients) or who refuse OC.

CTC has less complications compared with OC, with a reported perforation rate between 0.03% and 0.009% (45). Most of the studies on patient discomfort show either better acceptance of CTC than of OC (46-48), or no difference between the two methods (49, 50). However, this issue is complex and depends not only on the actual experience of pain and discomfort during the examination but also on factors such as the use and effects of analgetics and sedatives at OC, and how patients are informed beforehand about the procedures and the potential need for follow-up examinations.

There is a general consensus that CTC should replace DCBE as the radiological investigation of choice for the diagnosis of CRC and polyps (51, 52). Unlike DCBE, CTC does not require turning the patient in different positions and is better tolerated by the patients (48, 49, 53, 54).

CTC is not indicated in inflammatory bowel disease (Crohn, ulcerative colitis) because it cannot give information on superficial ulcerations. Furthermore, patients with inflammatory bowel disease are at higher risk of developing CRC *ex novo*, i.e. which does not follow the adenoma-carcinoma sequence. CTC can however, be considered in such cases where OC is incomplete due to severe stricture of a colonic segment.

In the USA, CTC has recently been suggested by the American Cancer Society as alternative imaging method for colorectal cancer screening (19). In Europe, CTC is increasingly used in symptomatic patients. A survey in the United

Kingdom showed that CTC is performed especially in cases of failed whole-colon examinations and as an alternative to DCBE in frail patients (55).
In the Nordic countries, CTC has attracted attention primarily for detecting symptomatic colon cancer.
Implementation of new technologies is complex, since interpretation of e.g. scientific evidence, local traditions, individual preferences, costs, vendor marketing and multitudes of technical solutions influence the process. The introduction of CTC as a replacement for DCBE or as a complement to OC may affect costs for the referring clinic, as well as investments for the radiology departments.

Reader experience and training

Some of the key factors that affect the quality of CTC interpretation are reader experience and specific skills such as care to details. Expert consensus recommend specific CTC training with hands-on courses and the interpretation of a minimum of 50 colonoscopy-verified CTC cases (51). However, it has been shown that such training might not be enough and that experienced readers have a significantly better performance than novice readers trained on 50 CTC cases (56, 57).
The lack of standards for training and the limited number of experienced readers are still some of the factors that might limit the widespread use of CTC (58). In the UK, a significant percentage of radiologists reporting CTC in clinical settings have limited training and experience (59). Also in the USA, the number of highly trained CTC readers seems to be limited compared to the potential demand of CTC as a screening method (60). Therefore, efforts should be made to obtain CTC training for a higher number of radiologists and to find ways to improve the performance of inexperienced readers.

Image analysis: 2D vs 3D

For colon visualization at CTC, a combined two-dimensional (2D) and three-dimensional (3D) approach is recommended as it utilises the strengths of both medhods (51). Using only traditional axial 2D images for diagnosis is not considered adequate. Depending on ones own experience and preference, CTC datasets can thus be evaluated as follows:

1. by a primary 2D reading with axial slices (using multiplanar reconstructions, MPR, in the coronal and sagittal planes and/or 3D views for problem-solving),
2. by a primary 3D reading (with axial images and/or MPR for problem-solving),
3. by a complete 3D and complete 2D reading.

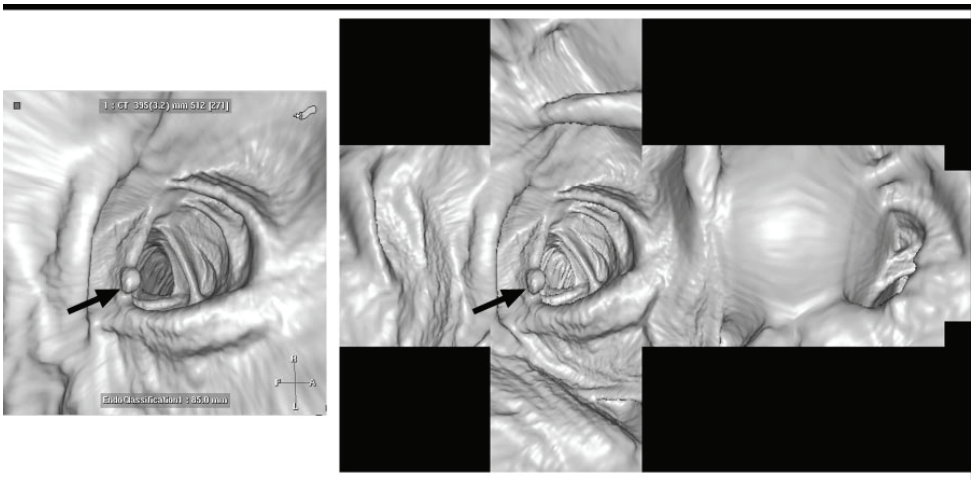
The advantages of 2D (and disadvantages of 3D) reading are:
- radiologists are used to 2D reading
- density (Hounsfield units) can be measured directly in order to differentiate polyps from lipomas or stool
- it allows visualisation of the thickness of the colonic wall (useful for evaluation of flat lesions)
- it allows immediate evaluation of reasons for incomplete visualisation (fluid, poor distension, tumour)

On the other hand, disadvantages of 2D (and advantages of 3D) are:
- looking at axial slices is a complex reading mode with two simultaneous moments:
  1. to follow the tortuous bowel anatomy by scrolling up and down the images;
  2. at the same time look for polyps
- less "time to see" lesions, compared to 3D, when the image stack is scrolled, which could hamper the perception of small lesions
- some areas, such as bulbous folds, can be difficult to distinguish from polyps on 2D.

The traditional 3D software display used for CTC reading is called "endoluminal fly-through" (Figure 1a). It allows a virtual navigation inside the colonic lumen (from here the denomination of CTC as "virtual colonoscopy"). Endoluminal fly-through provides an intuitive viewing of the colonic inner surface, but it requires both an antegrade and a retrograde evaluation in order to look behind the haustral folds. If a primary 3D reading with endoluminal fly-through is chosen, the radiologist has thus to perform a virtual 3D colon navigation 4 times (twice for the supine scan and twice for the prone scan), which is time-consuming.

In order to overcome the limitations of endoluminal-fly-through, several 3D visualisation displays based on different concepts have been introduced.

The “unfolded cube” is a 3D display that renders six planar projections at 90° viewing angles from points on the central path (61) (Figure 1b). It has been shown that with the conventional 3D method (endoluminal fly-through) 93.8% of the colon surface could be viewed, while the unfolded cube method visualized 99.5% of the colon surface in the same data set (61).



a. b.

Figure 1: polyp visualised on endoluminal fly-through display (**a**) and on unfolded cube display (**b**). From ref. (61) with permission.

“Split colon view” is another 3D display where the colon is cut in two perpendicular sections, an anterior and a posterior section. A virtual camera is then positioned perpendicular to the colon axis, flying over the anterior and posterior sections, respectively, and showing the colonic mucosa en face (62).

Another recent 3D display is the “virtual colon dissection”. In the “virtual colon dissection”, the full circumference of the colon is virtually unfolded allowing a global view of the colonic inner wall, with the appearance similar to a dissection specimen (63) (Figure 2).

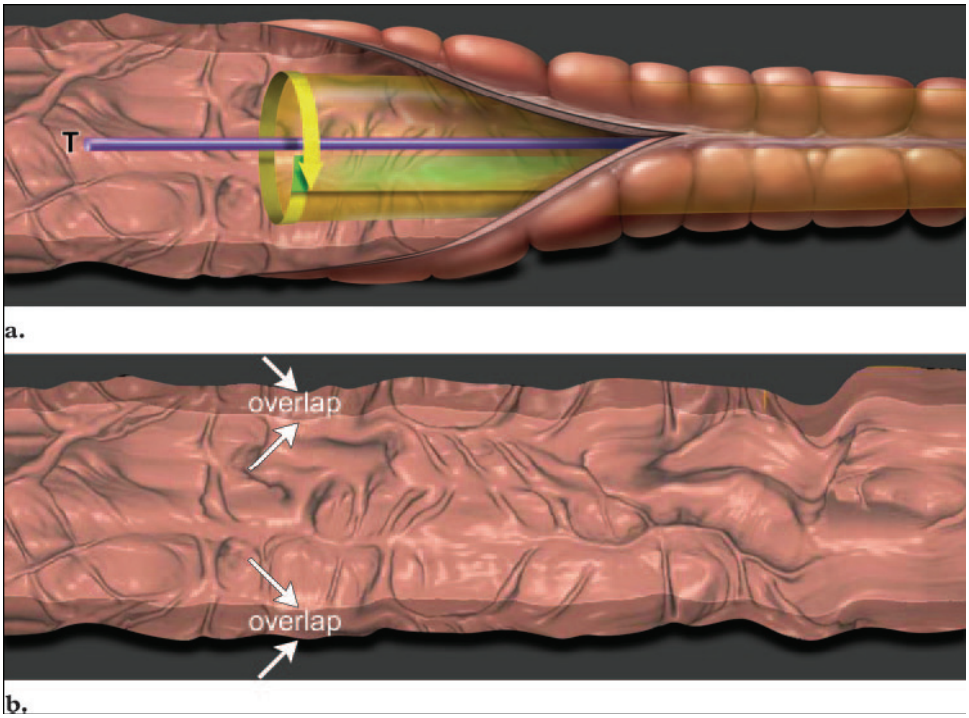


Figure 2. Virtual colon dissection. **(a)** The virtual dissection software slices the colon open and unfolds it longitudinally by reconstructing the axial CT source image data from the perspective of a virtual camera with an orientation perpendicular to the midline of the colonic tract *(T)*. **(b)** A 360° view of the inner colonic surface is presented as a flattened 3D panel with a few degrees of overlap at the edges (arrows). From ref. (63) with permission

A further development of "virtual dissection" is the "Perspective-Filet view" (Figure 3). The main difference from virtual dissection is that the image is not flat but rather a perspective projection that allows viewing of the three surfaces of folds (anterior, posterior, on top). In this way, perspective-filet view allows a 360 degree visualisation of the colonic inner surface, including the difficult areas in between tight folds and complex anatomy (63-66). As a result, only a single unidirectional evaluation is needed (63). Supine and prone reconstructions can be simultaneously displayed, thus comparing the position of endoluminal lesions. A drawback of virtual dissection and perspective-filet view is the distortion of the normal anatomy, such as haustrae, particularly in angulated anatomic areas, such as the colonic flexures or cecum.

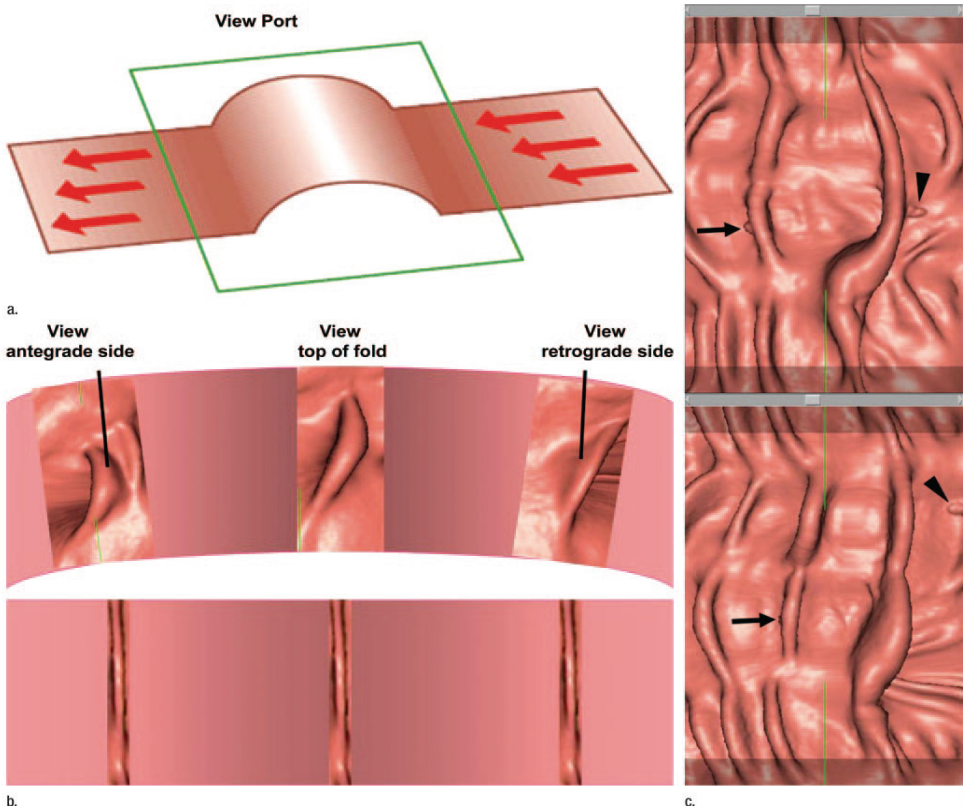


Figure 3. Perspective-Filet View. (a) The dissected colon is viewed as if the viewing area is pushed across a tube, rounding the center of the viewing area. (b) Top: The Perspective-Filet View software allows the user to see both the retrograde and the antegrade sides of the fold. Bottom: In contrast, with other dissection methods, the view of the colon is flat and shows only the top of the folds. Consequently, these methods do not allow the user to see around the folds; thus, a lesion on a fold could be easily missed. (c) Supine (top) and prone (bottom) 3D Perspective-Filet View images. Each 10° area at the top and bottom of the image is added to the 360° view of the colonic surface and displayed with a transparently shaded color so as not to miss any lesion. Note that the polyp (arrows) remains unchanged on both images, but the lump of feces (arrowheads) changes in position. Modified from ref. (66) with permission.

Some studies on primary 3D analysis with virtual dissection or perspective-filet view have shown sensitivities for detection of colorectal lesions similar to those of primary 2D analysis (66-68) or primary 3D analysis with endoluminal fly-through (64, 65) with reduced interpretation time (64-67). In those studies, virtual dissection and perspective-filet view were evaluated by experienced observers. It is not known if radiologists with long experience of conventional CT reading but limited experience of CTC would benefit from a primary 3D or primary 2D approach. One of the major sources of errors for less-experienced readers seems to be perception errors (69, 70) which could depend on the choice

of the reading method. 3D display allows views of larger parts of the colon mucosa, thus potentially enhancing lesion visibility, as compared to 2D (71, 72). On the other hand, radiologists accustomed to conventional CT reading may be more comfortable using a primary 2D approach.
Uncertainty about the optimal visualization method, long learning curves and extensive interpretation times are among remaining problems with CTC.

Computer-Aided Detection (CAD)

CAD is a computer program that uses a mathematical algorithm to identify abnormal patterns on medical images. It is used as an aid or second opinion to the doctors´ interpretation by drawing the attention to areas that might be overlooked.
The first research studies on CAD appeared in the 1960s, but it was only in 1998 that the first CAD product gained approval of the US Food and Drug Administration. It was a program to detect microcalcifications and masses in mammograms. CAD in medical imaging is an evolving field. Nowadays there are CAD programs available for e.g. mammography, thoracic radiology, CTC, scintigraphy, PET-CT, breast MRI and echocardiography.
CAD algorithms for CTC have been developed for the automated detection of polyps in order to overcome the difficulties in CTC interpretation. With the latest developments of multidetector CT scanners, allowing generation of thin slices, the number of images per CTC examination has increased considerably, and commonly exceeds 1000 images. The high number of images and the complex reading due to evaluation of both supine and prone scans and combinations of 2D and 3D displays cause long interpretation times at CTC, leading to reader fatigue, potentially affecting diagnostic performance. The long interpretation times increase radiologist´s time, thus increasing costs. There is a high variability of sensitivity among CTC readers, probably due to the long learning curve for accurate interpretation of CTC. Furthermore, the conspicuity of polyps may depend on the display method used. All these factors might increase the possibility of perception errors, especially for inexperienced readers, but also for experienced ones.
CAD used as a support for interpretation of CTC might decrease human readers´ perception errors and variability in diagnostic performance. CAD highlights suspected lesions, but each CAD mark has to be interpreted by the reader and classified as stool or a real lesion. Several studies have described improved

sensitivity with the use of CAD applied on CTC, especially for inexperienced readers (73-77).

Most of the CAD schemes consist of four steps: 1. extraction of the colonic wall, 2. detection of polyp candidates, 3. elimination of false positive candidates, 4. display of detected polyps (78-80). In step 1, a region containing the colonic wall is extracted from the CTC dataset using the contrast (difference in CT values) between the colonic wall and the gas in the colonic lumen. In step 2, polyp candidates are detected by evaluating geometric features that characterize polyps at each point in the colonic wall. Polyps have bulbous, cap-like shape, while folds are elongated and the colonic wall is a flat, cup-like structure. Various methods have been developed in order to differentiate polyps from folds and colonic wall by evaluating such shape differences. In step 3, false positive detections (more often prominent folds and stool, less often the ileo-cecal valve or the rectal tube tip) must be differentiated from polyps. Differentiation of folds is based mainly on the difference in appearance, as folds usually are much more elongated structures than polyps. Differentiation of stool is based on the distribution of CT attenuation values which is inhomogeneous in stool (because of the internal gas and fat content) while it is homogeneous in polyps. A statistical classifier is then applied generating a decision boundary that separates the polyp class from the false positives class. In step 4, the polyps detected by CAD are displayed to the radiologist on the workstation, either on the 2D dataset or on the 3D dataset, or on both.

There are three ways to integrate CAD in the workflow. CAD can be used as first, concurrent or second reader. In the first reader approach, the CAD program is activated before any human reading takes place. The first reader approach is the most time efficient as only the CAD marks are evaluated. The detection of lesions is, however, limited to the performance of the CAD algorithm. In the concurrent reading approach, CAD marks are displayed during the radiologist´s evaluation. In the second reader approach, CAD is applied only after the radiologist (first reader) has performed a full, complete CTC evaluation. It is more medico-legally acceptable than the first reader approach and more sensitive than concurrent reading (81, 82), although more time consuming.

CAD for CTC thus appears to be an important technical development with potential to help readers reduce perception errors. However, little is known

about its efficiency when applied to novel 3D visualization softwares, such as perspective-filet view. In particular, its effects on the diagnostic performance of novices should be evaluated, considering its potential role in shortening the learning curve and providing feedback for readers.

Radiation dose

One of the drawbacks of CTC, especially in a screening setting, is the exposure to ionizing radiation. There is uncertainty, however, about the potential harms derived from multiple CT examinations as there is not enough scientific evidence for health risks at the limited radiation doses commonly used in medical imaging.

A recent survey among research institutions that performed CTC showed that the median effective dose of paired (supine and prone) CTC scans was 5.7 mSv for screening protocols and 9.1 mSv for daily-practice protocols (83), i.e. doses comparable to DCBE (84). In a position statement by the Health Physics Society (a non profit scientific professional organization chartered in the United States), it was stated that " below 5-10 rem [corresponding to 50-100 mSv, i.e. much lower than the dose given during CTC] which includes occupational and environmental exposures, the risk of health effects are either too small to be observed or are nonexistent " (85). Nevertheless, current radiation protection practices are based on the ALARA (As Low As Reasonably Achievable) principle, based on the hypothesis that any radiation dose could cause detrimental health effects, with the risk being directly proportional to the dose received. As more individuals are examined with multiple diagnostic radiological examinations, there is an increasing concern about the risk that for some individuals the dose over a lifetime could be sufficiently high to induce cancer. Therefore, in 2006 the American College of Radiology recommended use of low-dose protocols for screening CTC (86). The estimated lifetime risk for cancer induction in any site from paired CTC scans (performed with the following parameters: slice thickness 8x1.25 mm, pitch 1.35, 65 mAs, 120 kV; resulting in a dose of 7-13 mSv) is small, i.e. 0.14% (1/700) for a 50-year-old individual and about half that for a 70-year-old (87). With ultra-low dose protocols these values could probably be reduced with a factor 5-10. It is, in fact, possible to reduce the radiation dose at CTC to very low levels, despite the associated increase in image noise, because of the high contrast (difference in density) between the colonic wall and the luminal air or carbon dioxide.

Previous feasibility studies of low-dose CTC showed moderate to good detection of medium and large polyps (88-96). In only two of these studies, a primary 3D reading approach was used to interpret the low-dose CTC examinations (89, 91). When performing a primary 3D reading of CTC examinations, endoluminal colonic lesions first have to be perceived on 3D and thereafter characterized on 2D. At low radiation dose CTC, noise-related artefacts depending on the reduced x-ray tube current might affect image quality more on 3D than on 2D (91), thus potentially affecting polyp detection. To our knowledge, there are no previous studies where noise-related artefacts on 3D have been systematically analysed and compared at standard and low dose in clinically performed CTC, or where their role for the perception of lesions on 3D has been investigated.

In those few studies (89, 91) where primary 3D reading was used, the CTC examinations were performed with fixed tube current, which gives an inhomogeneous image noise and consequently inhomogeneous image quality in different parts of the body, depending on the varying density of the examined body structures. Newer CT scanners are equipped with automatic tube current modulation, which adapts tube current and thus radiation dose to the thickness of the patient, in order to keep image quality constant. A dose reduction of 20% can be achieved with attenuation-based tube current modulation, regardless of the mAs preset (97). Only one study (98) has evaluated image quality on 3D on low-dose CTC performed with tube current modulation. That study showed good image quality on 3D at 40 mAs in one body position resulting in a mean effective dose of 1.61 mSv. The effect of this low-dose technique on polyp detection was not studied.

RATIONALE

CTC is gaining large interest world-wide and is increasingly being introduced into clinical practice. Introduction of a new technology may, however, be complex and is often influenced by factors other than scientific evidence regarding its diagnostic accuracy and proper utilisation. It therefore seemed motivated to assess the present status of CTC regarding its implementation and technical performance, as related to state-of-the art knowledge, in order to ascertain an evidence-based introduction.

CTC reading is complex and associated with considerable inter-observer variation and long learning curves. Thus, ways to improve and facilitate CTC reading, such as improved 3D visualisation methods and CAD, should be searched for and tested. Parallel to this development, increasing awareness of the radiation hazards associated with CT, including CTC, has prompted the introduction of low-dose CTC techniques. However, it is not known how dose reduction in CTC affects image quality and lesion detection using the new display methods.

These issues formed the rationale for the studies presented in the present thesis.

AIMS

The general aim of this thesis was to assess the present status of CTC in routine clinical practice and to assess the impact of new technical developments, such as a novel 3D display method, CAD and low radiation dose CTC technique, on readers´ performance.

To achieve this, the following specific aims were defined:

1. To evaluate the availability, indications and technical performance of CT colonography in Sweden.

2. To evaluate whether lesion detection by inexperienced readers can be improved by primary 3D analysis with the novel 3D image display "perspective-filet view" (3D Filet), as compared with primary 2D analysis.

3. To evaluate whether CAD applied as second reader to perspective-filet view improves diagnostic performance of inexperienced readers in comparison to the performance with CAD-unassisted 3D Filet or CAD-unassisted 2D analysis. Furthermore, to compare the CAD-assisted performance of the inexperienced readers with the performance of an experienced reader.

4. To evaluate whether image quality and lesion perception can be maintained at low radiation dose CTC performed with automatic dose modulation. In particular, to evaluate the prevalence of noise-related artefacts and lesion perception on 3D Filet images at standard radiation dose, original low radiation dose and modified low radiation dose, i.e. after manipulation of opacity at 3D volume rendering.

MATERIAL AND METHODS

OVERVIEW

In **Paper I and II,** we performed a survey on CTC by sending a questionnaire to all radiology departments in Sweden. We investigated indications for CTC, technical performance, reasons for non-availability of CTC and opinions on its future role in colorectal imaging.

In **Paper III,** we performed a prospective CTC study on symptomatic patients referred for OC. A radiologist with previous experience of CTC evaluated the CTC studies before same-day OC, by performing a primary 3D analysis with perspective-filet view (3D Filet), immediately followed by a complete 2D analysis and after that, by evaluating marks highlighted by a CAD system (CAD evaluation was further studied in **Paper IV**). The reference standard was OC performed with segmental unblinding, i.e. with re-examination of colon segments in which CTC had shown lesions not seen by first-look OC. Afterwards, two inexperienced readers, blinded to OC findings, separately read the CTC studies, first by performing a primary 3D Filet analysis, as the experienced reader, and after several weeks by performing a primary 2D analysis. The results of the inexperienced readers concerning the primary 3D Filet analysis were compared with those of their primary 2D analysis and with the results of the primary 3D Filet analysis by the experienced reader.

In **Paper IV,** the same two inexperienced readers as in paper III evaluated CAD marks shown on 3D Filet several months after the study described in paper II. We investigated if CAD applied to 3D Filet improved their performance by comparing the results of CAD-assisted 3D Filet analysis with those of CAD-unassisted 3D Filet or 2D analysis.

In **Paper V,** we blindly compared image quality and perception of polyps on 3D Filet images from scans performed at standard radiation dose versus scans performed at low radiation dose. The low radiation dose scan was obtained in supine immediately after the standard dose scan in 48 out of the 50 patients studied in paper II and III. Furthermore, the low radiation dose scan ("original low dose") was manipulated by changing opacity settings on 3D in order to reduce noise-related artefacts, thus obtaining "modified low dose" 3D Filet images. Image quality on 3D Filet was evaluated for all 48 patients by two experienced CTC readers in consensus. The presence of polyps on 3D Filet was

evaluated by five experienced CTC readers. The results obtained at standard dose were compared with the results obtained at original low dose and modified low dose.

QUESTIONNAIRE (Paper 1)

In May 2004, a structured self-assessed questionnaire was mailed to all radiology departments in Sweden except those sub-specialized in thoracic, pediatric, or neuro-radiology. Departments were identified from the registry of the National Board of Health and Welfare. A total of 119 questionnaires were sent out, along with a pre-stamped and pre-addressed reply envelope with return deadline for the end of May 2004. Eighty-seven replies were received within the deadline. In October 2004, the same questionnaire was sent again to departments that had not replied. Twelve replies were received by the beginning of 2005. Thus, a total of 99 radiology departments answered the questionnaire, resulting in a final response rate of 83%. All except one of the non-responding departments were small or middle-sized county hospitals or small radiology departments in private enterprise clinics.

The questionnaire was divided into three sections:

1. A general section about the total number of radiological examinations performed per year at each department and the general availability of OC, DCBE and CTC;
2. A short section for departments that did not perform CTC, including questions on the reasons why they did not offer the service;
3. A more detailed section for those that did perform CTC, including questions on indications for CTC, the number of examinations performed, type of CT equipment, patient preparation routines, use of fecal tagging and intravenous contrast administration, the use of room air or carbon dioxide for bowel distension, CT scanning parameters, and preferred mode of image interpretation.

All responders (department heads or section heads) were also asked to give their views on the future role of CTC for colon imaging.

Follow-up telephone interview

In June 2005, a follow-up telephone interview was performed with departments that, according to their answers on the questionnaire, intended to start a CTC service in the near future. They were asked whether a CTC service had started,

the total number of CTC examinations performed, how often these were done, and on what indications.

SURVEY UPDATE 2008-2009 (Paper II)

In December 2008, a structured, self-assessed questionnaire regarding implementation, indications and technical performance of CTC was mailed to all radiology departments (regardless of size, including private centres) in Sweden except those sub-specialized in thoracic, pediatric, or neuroradiology.
The questionnaire was similar to the one used in the survey in 2004-5, but contained some additional questions: number of performed DCBE examinations per week, use of CAD, double-reading and number of radiologists who read CTC in each department. In February and March 2009, those departments that had not replied until then were contacted by e-mail or by telephone. All contacted (100%, 119/119) radiology departments answered the questionnaire.

SUBJECTS (Papers III-V)

The studies were performed at Sahlgrenska University Hospital, Gothenburg, Sweden, between October 2006 and May 2007.
Fifty patients (32 women; mean age 66.4 years; range 50 to 86 years) at high risk for colorectal cancer, referred for OC at the Gastrointestinal Endoscopy Department, were prospectively enrolled.
Inclusion criteria were: rectal bleeding and/or iron deficiency-related anemia and/or positive FOBT. Exclusion criteria were: age less than 50 years, suspicion of inflammatory bowel disease and patients with colostomy. Sixty-two patients who fullfilled the inclusion criteria were asked to participate in the study. Inclusion was intended to be consecutive, but this could not always be achieved, depending on lack of availability of CTC room facility or difficulties with same-day CTC-OC booking coordination. Ten patients fulfilled the inclusion criteria but did not provide informed consent. Fifty-two fulfilled the inclusion criteria and agreed to participate. Two patients were eventually excluded because OC could not be performed due to vasovagal reaction and large amounts of residual bowel content, respectively.
The studies were performed according to the Declaration of Helsinki and were approved by the Regional Ethical Review Board. Study IV was also approved

by the Radiation Protection Committee of the Sahlgrenska University Hospital. All patients who participated in the studies gave written informed consent.

BOWEL PREPARATION (Papers III-V)

Patients underwent CTC followed by same-day OC, taking advantage of the same bowel preparation, which was performed according to the clinical routines of the endoscopy unit. All patients underwent colonic preparation with low-fibre diet 3 days prior to the CTC examination and 4 litres of oral polyethylene glycol solution (Laxabon, Biophausia, Stockholm, Sweden), administered the day before the CTC. No fecal tagging, i.e. oral contrast, was given to the patients.

CTC TECHNIQUE (Papers III-V)

The CTC preceded the OC by approximately 2 hours.
All examinations were performed using a 64-row multi-detector CT (MDCT) scanner (LightSpeed VCT, GE Healthcare, Chalfont St-Giles, UK).
Before rectal gas insufflation, a spasmolytic agent was administered intravenously; 20 mg of Hyoscine-N-butylbromide (Buscopan, Boheringer Ingelheim, Ingelheim, Germany; *n=40*) or 1 mg of glucagon (Glucagon, Novo Nordisk Scandinavia, Malmö, Sweden; *n=8)*. No spasmolytic agent was given in 2 patients due to contraindications.
Carbon dioxide was automatically insufflated (ProtoCOl™, E-Z-EM, Lake Success, N.Y., USA) via a thin plastic rectal tube with a balloon cuff. Insufflation pressure was adjusted according to patients´ tolerance. Colon gas distribution was assessed on the scout view. CT of the entire abdomen and pelvis was performed, first in supine (non-contrast-enhanced) at standard radiation dose and immediately afterwards at low radiation dose, and then in prone position (contrast-enhanced) only at standard radiation dose. Intravenous contrast medium (Visipaque 320 mgI/ml, GE Healthcare, Chalfont St-Giles, UK) was administered according to body weight at a rate of 2.8 ml/sec. Images were acquired after a delay of 75 seconds from the start of injection.
In **papers III-IV,** the radiologists evaluated the scans obtained in supine and prone at standard radiation dose. In **paper V**, only the CTC scans obtained in supine at standard and low dose were compared. Scanning parameters were: 64x0.625 mm collimation; 0.625 mm reconstruction interval; table speed 39.37 mm/rot; pitch 0.984; tube rotation time 0.5 second; tube voltage kV 120;

automatic tube current modulation (predefined tube current settings : 40-160 mA for standard dose; 10-50 mA for low dose). In **paper V**, the first two patients were scanned at lower doses than described above (predefined tube current settings: 10-30 mA), but the presence of artefacts on 3D was considered to affect image quality to a high degree, thus making these low dose examinations nondiagnostic and they were excluded from the present study. The remaining 48 patients were examined at tube current 10-50 mA. A total of 48 CTC examinations were thus included in **paper V**.

OPTICAL COLONOSCOPY (Papers III-V)

The OC examinations were performed by one of two experienced endoscopists (>5000 colonoscopies each) using a standard endoscope (Fujinon EC 450WL5, Saitama City, Japan; Olympus CF160 AL, Tokio, Japan). OC were complete to the caecum in all patients. Segmental unblinding was applied (39), meaning that lesions of any size detected by CTC but not at OC necessitated OC re-examination of that colon segment before proceeding to the next segment.
Lesion size was measured in situ using a measurement device graded in 2 mm intervals. The anatomical location and macroscopic appearance of findings (sessile, pedunculated, flat, stenosing or other appearance) was documented in order to facilitate matching with CTC. All OC findings were considered as true positive unless histologically classified as normal colon mucosa.

CTC IMAGE EVALUATION (Papers III, IV)

Image evaluation was performed on a dedicated workstation (Extended Brilliance 3.0.1, Philips Medical Systems, Cleveland, Ohio, USA) using CTC software (Perspective Filet View).

Experienced reader
A radiologist (Reader 1) with previous experience in CTC using the dedicated workstation (>200 CTC studies) evaluated the CTC examinations before same-day OC.
1. Primary 3D analysis using perspective-filet view (3D Filet) (**Paper III-IV**)
First, primary 3D analysis with perspective-filet view **(**3D Filet**)** was performed. Supine and prone data sets for each patient were simultaneously reviewed with the 3D Filet views side by side. This allowed anatomical synchronisation,

thereby facilitating the comparison of location of endoluminal findings in relation to colonic folds. When findings were suspected on 3D Filet, the corresponding 3D endo-fly-through views and related 2D images were used for problem-solving. Lesion characteristics (size, location, shape and density before and after intravenous contrast) were reported on the study protocol. The maximal diameter of the lesion was measured on 3D. The location of the lesions was specified (rectum, sigmoid, descending, left flexure, transverse, right flexure, ascending, caecum). Interpretation time was recorded.

2. Additional complete 2D analysis (3D Filet + 2D) (**Paper III**)

Immediately after completing the evaluation form of the 3D Filet analysis, the experienced reader performed a complete 2D analysis, exhibiting supine and prone datasets side-by-side. A window width of 1400 Hounsfield Units (HU) and a window level of -500 HU, but also dynamic window settings, e.g. to evaluate internal lesion inhomogeneity, were used. Lesions suspected on the axial images but not on 3D Filet, were further evaluated on multiplanar reconstructions (MPR) and on related Filet view or endo-flythrough views. Interpretation time was recorded.

3. CAD (**Paper IV**)

Once the 3D Filet+2D analysis was completed, CAD software was applied. CAD marks that did not coincide with previously described findings on 3D Filet+2D were evaluated on 3D Filet, using endo-fly-through or 2D for problem-solving. With this approach, we aimed to perform a careful prospective CTC evaluation, including CAD marks, thereby also optimizing segmental unblinding at same-day OC.

Inexperienced readers

Two radiologists blinded to the patient data, OC and CTC findings separately reviewed the CTC studies. Reader 2 (intermediately trained CTC reader) was a specialist with 5 years experience of general radiology including CT and had attended a hands-on course on CTC and reviewed 30 CTC cases on a dedicated software different from the one used in the study, i.e. with no 3D Filet view. Before interpretation of the study cases, Reader 2 had additional training on 15 OC-proven CTC studies on the workstation used in the study. Reader 3 (least trained CTC reader) was a specialist with 15 years experience of general radiology and special interest in abdominal CT. Reader 3 received course material and review articles on CTC in order to get the theoretical basics of CTC

interpretation and had training on 15 OC-proven CTCs on the workstation used in the study.

1. Primary 3D analysis using 3D Filet view (3D Filet) (**Paper III-IV**)

The inexperienced readers individually reviewed the cases using the same 3D Filet approach as described above, with 2D and 3D endo-fly-through views only for problem-solving. The cases were evaluated during 8-10 sessions.

2. Primary 2D analysis (**Paper III-IV**)

At least 5 weeks later, the inexperienced readers individually and blindly evaluated the cases in random order, using a primary 2D analysis, i.e. by simultaneously reviewing the axial supine and prone slices and using MPR, 3D Filet or endo-fly-through views only for problem-solving. Lesion size was measured on 2D using the largest diameter (window width 1400 HU, window level -500 HU).

No performance feedback was given to the inexperienced readers during the course of the study.

3. Combined 3D Filet + 2D analysis (**Paper III**)

The OC-proven (true positives) findings ≥6 mm described with 3D Filet and/or 2D were combined to obtain 3D Filet+ 2D results.

4. CAD as "second reader" (3D Filet+CAD) (**Paper IV**)

Unlike the experienced reader who used CAD after 3D Filet+2D, the inexperienced readers used CAD as additional aid for a 3D Filet analysis.

Four months after performing the 2D analysis, the inexperienced readers re-read the CTC studies in random order using CAD, i.e only reviewing CAD marks shown on 3D Filet. No additional full evaluation of the CTC studies was performed. Readers checked if CAD marks matched with their own findings previously recorded in the study protocol for 3D Filet. CAD marks that did not match (lesion location and characteristics) with previously registered findings were further evaluated on 3D Filet, with 3D endo-fly-through and 2D views for problem-solving. The image number, body position, lesion characteristics of such CAD marks suspected of being true lesions were recorded and CAD interpretation time was registered.

MATCHING OF FINDINGS (Paper IV)

Detection of colorectal lesions with 3D Filet for all readers, with 2D for inexperienced readers and with 3D Filet + 2D for all readers were evaluated and

compared on a per-lesion and per-patient basis, using OC with segmental unblinding as a reference. Lesions were considered as true positive matches between CTC and OC when present in the same or adjacent colorectal segment and when the maximum lesion diameters on CTC and OC were within a 50% margin of error. A patient was considered a true positive case (per patient analysis) when at least one true positive lesion in a given size category was found.

A fourth reader (previous experience of >500 CTC) and Reader 1 retrospectively evaluated all false negatives ≥6 mm by reviewing the CTC data sets on 3D Filet and 2D, the OC reports and photographs and pathology reports of biopsied or surgically resected lesions. Location, shape and visibility in supine and prone were assessed.

The quality of bowel preparation and distension for all datasets, including segments where false negatives were located, was evaluated according to the technique described in a previous study (99), taking fluid collections (complete/incomplete redistribution), stool interference (no/limited/moderate/ extensive) and gas distension (not/partly/completely gas filled) into consideration.

CAD ALGORITHM (Paper IV)

We used a commercially available CAD software that shows CAD colour-marks on 3D Filet (Colon CAD, Extended Brilliance 3.0.1, Philips Healthcare, Cleveland, OH, USA). The Colon CAD segmentation algorithm scans the colon wall to identify convex elevated tissue regions, where the surface has a positive curvature in all directions. The following features are considered in deciding if a certain region should be marked as a lesion or not: morphology (including size, convexity and compactness) and density (Hounsfield Units, HU) average and standard deviation. The Colon CAD application assigns a confidence level to each identified lesion candidate based on the above mentioned features, e.g if the candidate has a high positive curvature and also falls within the HU range of polyps (tissues), it gets a higher confidence score. Based on this, Colon CAD has 5 different “filter sensitivity” settings, ranging from 1 (lowest sensitivity) to 5 (highest) and 3 different polyp size threshold (≥3 mm, ≥6 mm, ≥10 mm). In our study we used “Medium filter sensitivity” and lesion size at the lowest level, i.e. ≥3 mm.

EVALUATION STRATEGY OF CAD FINDINGS (Paper IV)

The CTC data sets were evaluated according to the ”external validation” methodology (100, 101), i.e. all data sets were previously unknown to the CAD software and not related to the development of the CAD algorithm. All 50 patients included in the study, with or without lesions, were evaluated. CAD colour-marks were compared with findings at OC with segmental unblinding, the reference standard. A finding was considered a true positive match with OC if located in the same or adjacent colonic segment and within 50% size error. The false negative CTC findings of the experienced reader were retrospectively evaluated with help of the OC study report protocol and in-situ OC lesion photographs and checked whether they were visible on CTC and marked by CAD or not. CAD colour-marks that matched with the reference standard were considered true positives if marked on either supine or prone scan position. The size of lesions at OC was used as the reference for size measurements of true positives. The characteristics of CAD true positives (image number, segment location, shape, density) were recorded and then compared with CAD findings described by the inexperienced readers.

EFFECTIVE DOSE ASSESSMENT (Paper V)

The effective dose is an approximate indicator of the potential detrimental risk due to radiation exposure (102).

A broad estimate of the effective dose (E) from standard dose and low dose scanning, respectively, in the supine position was calculated according to the formula:

$$E = E_{DLP} \times DLP\ (mSv) \quad (103)$$

where DLP is the dose-length product and E_{DLP} is a region-specific effective dose conversion factor (104). The DLP was automatically calculated by the CT system.

IMAGE NOISE MEASUREMENTS (Paper V)

Image noise was measured by placing a region-of-interest (ROI) with an area of 1.5-4 cm² in the colonic lumen at four anatomical levels, as reported by Graser et al (98): level 1, at the portal vein; level 2, at the renal hilum; level 3, cephalad to the iliac crest; level 4, in the pelvis cephalad to the acetabulum. The standard deviation (SD) in Hounsfield Units of the measured attenuation values at standard and low doses were considered as noise measurements.

IMAGE QUALITY EVALUATION (Paper V)

CTC examination images were transferred to a dedicated workstation (Extended Brilliance 3.0.1, Philips Healthcare, Cleveland, OH, USA). For each patient four low dose and four standard dose 3D Filet images, corresponding to the four anatomical levels where image noise was measured, were saved. In addition, low dose images were manipulated by subjectively modifying the opacity map settings until any "snow" artefacts disappeared (modified low dose images). Opacity assignment is a function of 3D volume rendering algorithms that allows alteration of the opacity of each attenuation value in an image volume (105). By choosing a certain opacity threshold, it is possible to decrease visible noise by making images smoother or eliminating snow artefacts (92). Thus, a total of 576 images (192 images at the standard dose, original low dose and modified low dose, respectively) were saved. The images were then transferred to a computer where ViewDEX 2.19, a dedicated software program designed to display radiological images in observer performance studies (106), had been installed. Image quality was assessed according to visual grading characteristics (VGC) analysis (107). We aimed to assess important anatomical structures visible on 3D rendering, i.e. the colonic inner surface between folds and the aspect of folds. In particular, with regard to the colonic inner surface, we evaluated if the inner surface appeared smooth or if it had a diffuse nodular pattern (cobblestone artefact) (108). We also evaluated the presence of so-called "snow" artefacts, i.e. linear or punctate endoluminal noise-induced structures that obscure the underlying inner colonic surface. The images were evaluated in random order, in a blinded fashion, by two experienced radiologists (>300 and >500 CTC, respectively) in consensus. The radiologists responded to questions with regard to the presence of artefacts (1. cobblestone artefacts of the inner colonic surface between folds (Fig. 4); 2. snow artefacts (Fig. 5); 3. irregularly delineated

colonic folds (Fig. 5)) and graded them according to a four step scale (1. no artefacts, 2. mild artefacts, 3. moderate artefacts, 4. severe artefacts).

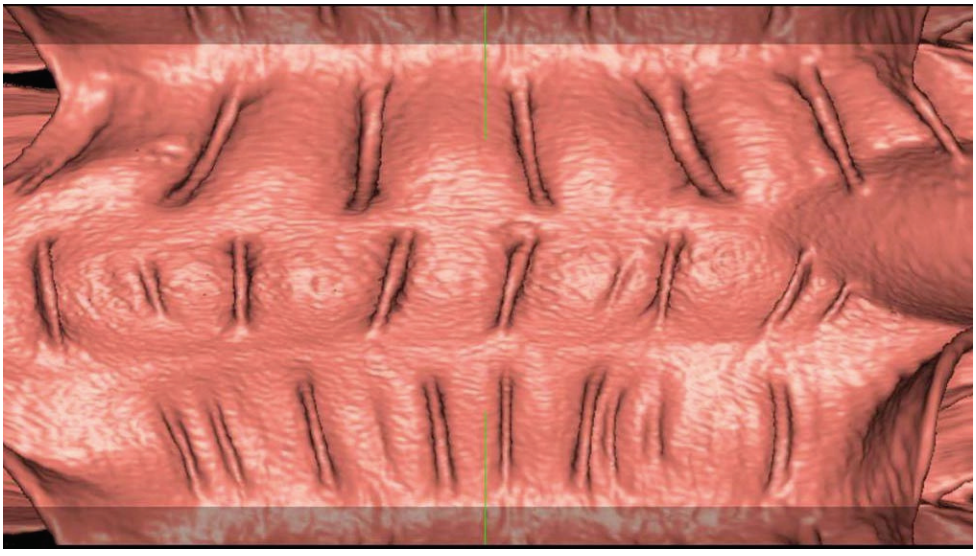


Figure 4 3D Filet image showing moderate cobblestone artefacts, i.e. diffuse nodular pattern between colonic folds

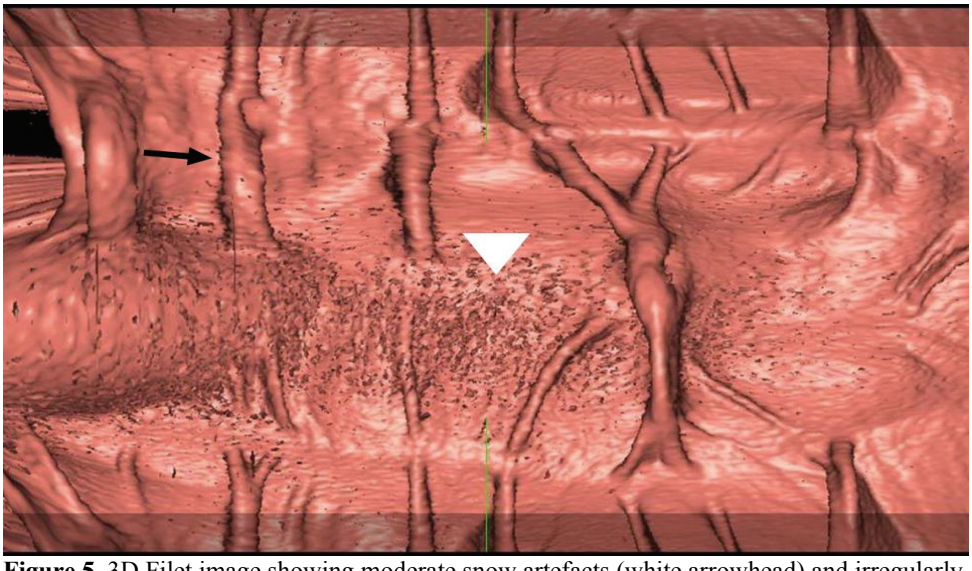


Figure 5 3D Filet image showing moderate snow artefacts (white arrowhead) and irregularly delineated folds (black arrow)

POLYP DETECTION STUDY (Paper V)

Reference standard

The experienced radiologist who performed the prospective CTC evaluation before OC identified those polyps that were visible at the standard dose in the supine position by reviewing the CTC data sets on 3D Filet and 2D. Only polyps that were confirmed by the reports from the segmentally unblinded OC, lesion photographs and pathological reports of biopsied or surgically resected lesions were included. One polyp of 5 mm was excluded, as the polyp-containing colonic segment was partly collapsed in one of the two supine body positions obtained for low dose and standard dose images. A total of 46 polyps were identified and the corresponding 3D Filet images, obtained at the standard dose and the low dose in the supine position, were saved. Efforts were made to ensure that the colonic segments containing the polyps were anatomically as identical as possible (ray projection angle, centring of polyps) on images obtained at the low dose and the standard dose, respectively. Eleven polyps measured ≥10 mm, 10 polyps 6-9 mm, 25 polyps 3-5 mm. Polyp location was as follows: rectum (5; 11%), sigmoid colon (16; 35%), descending colon (5; 11%), transverse colon (11; 24%), right flexure (3; 6.5%), ascending colon (4; 8.5%), caecum (2; 4%).
For the purposes of the study, 31 additional colonic segments without polyps (to be randomly mixed with polyp-containing segments) were selected, using the same technique as described above.

Readers

Five board certified radiologists with previous experience of CTC and of 3D Filet interpretation took part as readers (experience of Reader 1: 100 CTC, Reader 2: 180 CTC, Reader 3: 200 CTC, Reader 4: 300 CTC, Reader 5: >500 CTC). Each reader independently reviewed 74 3D Filet images showing colonic segments with polyps (43 images, 46 polyps) or without polyps (31 images), obtained at the standard dose, the original low dose and the modified low dose, for a total of 222 images. The images were scrutinised blindly and in a random order, using the ViewDEX computer software display. Readers were not informed about the prevalence of polyps. They marked suspected polyps on the images with a digital cursor and graded their degree of diagnostic confidence for each polyp according to a four step scale where 1 corresponded to the highest degree of confidence (very likely a polyp) and 4 represented the lowest degree of confidence (probably not a polyp), according to the free-response receiver

operating characteristics (FROC) paradigm. At the same time, the 5 readers also assessed image quality (according to the criteria described above) for the 74 images at the standard, modified and original low doses, respectively. The image quality evaluation by the 5 readers was performed in order to check for possible differences in image quality of this smaller group of images compared with the evaluation of all patients and all anatomical levels performed by the 2 radiologists in consensus.

STATISTICAL METHODS

General statistical approaches

The data are presented as absolute numbers, percentage of total or as mean ± standard deviation (SD) or median and interquartile range (IQR) (25% to 75%), as appropriate. Comparisons between groups were done by means of chi-square test concerning nominal data or by Student's t test concerning continuous variables (**paper I**).

The McNemar test was used for a comparison of nominal data for the case of two related samples (**paper II**, **III**). The Wilcoxon signed rank test was used for a comparison of continuos variables for the case of two related samples (**paper III, IV, V**). The Mann-Whitney test was used for a comparison of continuous data in two-sample cases (**paper III**).

A p-value of less than 0.05 was considered as significant. SPSS 11.0 for Windows (SPSS Inc, Chicago, Ill., USA) was used for statistical analysis.

ROC, FROC and JAFROC-1 analysis (papers IV, V)

In CT colonography studies, the ability of the reader in detecting individual lesions in patients (per-lesion analysis) or in detecting patients with or without lesions (per-patient analysis) is commonly measured by sensitivity and the number of false positives (per-lesion analysis) or by sensitivity and specificity (per-patient analysis), respectively. Sensitivity and number of false positives (FP), or specificity, are closely correlated to each other and depend on the decision threshold of the reader. A change in the decision threshold would alter the level of sensitivity, resulting in a change of specificity. This dependence on decision threshold leads to difficulties when comparing different modalities or readers by only analyzing sensitivity or specificity *per se*.

In receiver operating characteristic (ROC) analysis, the relationship between sensitivity and specificity, according to each choice of decision threshold of the reader, is taken into consideration. This relationship can be displayed by a curve, the ROC curve, plotting sensitivity (or true positive-rate) on the y-axis and specificity (or false-positive rate) on the x-axis (Fig. 6).

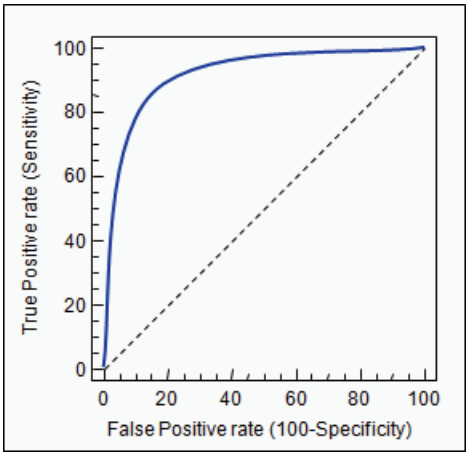


Figure 6: ROC curve. Sensitivity and false positive rate are expressed in % in the figure.

Each point on the ROC curve represents a sensitivity/specificity pair associated with a specific decision threshold of the reader (109). As sensitivity and specificity are related, an increase in sensitivity will be accompanied by a decrease in specificity. The closer the curve is to the left-hand border and the top border of the ROC space, the better the test, as it shows a high sensitivity at a low false-positive rate. The area under the ROC curve (AUC) can also be calculated as a measure of test accuracy, i.e. the probability to correctly classify cases. An AUC of 0.5 indicates that the diagnostic test or reader is not informative, corresponding to the diagonal line in figure . The larger the AUC, the more accurate is the test. An AUC of 1 represents an excellent test performance. In CTC studies, ROC analysis can be performed in order to assess the ability of the readers in distinguishing patients with no lesions from patients with lesions (per-patient analysis). In **paper IV**, thus, we performed a ROC analysis to evaluate the ability of readers to correctly identify patients with lesions ≥6 mm, i.e. those patients for whom colonoscopy usually is recommended. In particular, we compared the AUC of each inexperienced reader when using three different reading modes (3D Filet, 2D, 3D Filet+CAD). In addition, we compared the AUC of the CAD-assisted inexperienced readers

(3D Filet+CAD) with the AUC of the CAD-unassisted experienced reader (3D Filet). Readers had to express their confidence level of suspicion for lesions on CTC examinations on a scale from 1 (= very uncertain) to 4 (= absolutely certain). If the reader did not identify any lesion, the confidence rating was set to 0. The highest confidence rating for lesions was used to represent the reader´s confidence level for each patient. If the reader did not describe any lesion, the confidence rating was set to 0.

A limitation of ROC analysis is that the correct identification of a patient with a lesion is not necessarily based on the correct identification of a lesion. Thus, a reader might correctly classify a patient as having a lesion (i.e. true positive patient) although erroneously describing a false positive lesion and missing the real lesion (false negative lesion). This limits the role of ROC analysis in evaluating the ability of readers in detecting lesions (per-lesion analysis). This limitation is overcome by the free-response receiver operating characteristic (FROC) analysis where the readers have to state the presence, the number and the location of suspected lesions. The location of suspected lesions is compared with that of the reference standard. Free-response data are thus defined as true positives (TP) if the locations of the suspected lesions correspond to those of the lesions detected by the reference standard (110). FROC analysis can thus be used to evaluate per-lesion performance, i.e. the ability of distinguishing between lesions and non-lesions. Such an approach is easily applied in CTC studies where suspected lesions on CTC have to be compared to colonoscopy according to predefined matching criteria (i.e. location, size).

In **paper IV and V** we assessed per-lesion performance by using a recent development of FROC methodology, the so called jackknife free-response receiver operating characteristic (JAFROC-1) analysis (111, 112).
JAFROC analysis is a non-parametric method intended to evaluate free-response data. It has been used in recent detection studies by human observers in mammography and thoracic radiology (113, 114). The JAFROC-1 software (111) calculates a figure-of-merit (FOM), i.e the probability that a TP is rated higher than the highest rated FP in a case. The FOM thus gives information on the relationship between sensitivity and FP, similar to the area under the curve in ROC analysis, but with higher statistical power as it gives information on the *location* of *multiple* lesions and not just on the detection of *any* lesion independently of the location, as in ROC (112). In particular, in **paper IV** we

evaluated the FOM of the inexperienced readers with the different reading modes (3D Filet, 2D, 3D Filet+CAD). In addition, the FOM of the inexperienced readers with or without CAD assistance concerning lesions ≥6 mm were compared with the FOM of the experienced reader using 3D Filet. In **paper V** we assessed the FOM of each of the 5 experienced readers and the reader-averaged FOM at different radiation dose techniques (standard dose, original low dose, modified low dose).

In **paper IV and V**, in order to graphically show the per-lesion performance, FROC curves were determined, using Proproc software (115-117). The FROC curve has characteristics similar to a ROC curve. The FROC curve is a plot of per-lesion sensitivity along the y-axis versus the number of FP/number of patients (named FP-rate in the following text) along the x-axis (118), for different confidence thresholds. It is characterized by a steep high confidence region starting at (0,0), a shoulder corresponding to the middle confidence region, and a plateau in the lowest confidence region (111) (Fig. 7).

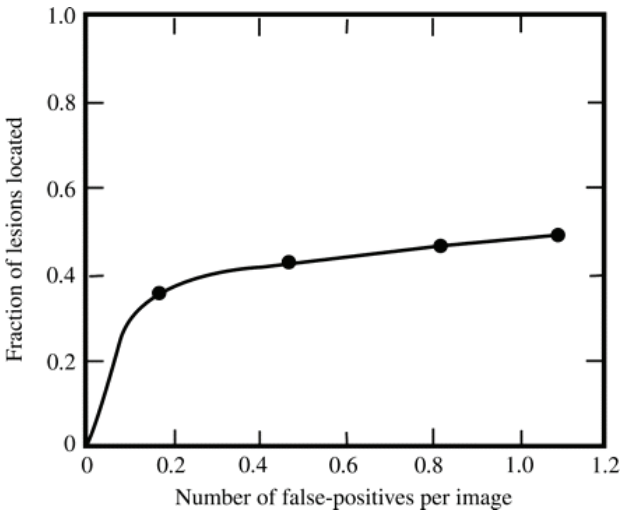


Figure 7: FROC curve (119). The dots on the curve correspond to the different confidence thresholds used by the readers: symbols on the extreme left represent the highest degree of confidence (e.g. very likely a lesion), while symbols on the extreme right represent all the degrees of confidence.

Visual Grading Characteristics (VGC) analysis (paper V)

In **paper V**, image quality was evaluated with VGC analysis (107), a novel statistical method. In visual grading analysis (VGA) studies, readers are asked to evaluate diagnostically relevant anatomical structures, as the possibility to detect pathology depends on how good the anatomy is reproduced on the images. There are no published guidelines on quality criteria for CTC. We used as image quality criteria important anatomical structures depicted on 3D Filet, such as the smoothness of the inner surface among colonic folds, the delineation of folds, and the visualisation of the lumen. As in ROC analysis, readers have to rate their confidence level about the fulfillment of an image quality criterion.

As opposed to VGA where the ratings of the readers are treated as numerical values, in VGC the ratings are treated as ordinal values. VGC is thus a hybrid method that contains the strengths of both VGA and ROC analysis (107). Data are thus analysed in a manner similar to that used in ROC analysis, so that an AUC is obtained as a measure of the difference in image quality between e.g. two radiation dose techniques (standard dose versus modified low dose; original low dose versus modified low dose). An AUC of 0.5 indicates that the two compared techniques are equal. AUC and SD were calculated with ROCFIT software (Kurt Rossmann Laboratories for Radiologic Image Research at the University of Chicago) for the 2 readers in consensus and by LABMRMC (117), for the 5 readers. P-values were calculated by Z-test.

RESULTS

PAPER I

Data from the structured self-assessed questionnaire

Out of the 99 departments that replied, 23 (23.2%) offered a CTC service. A DCBE and OC service was locally available in 89 (89.9%) of the hospitals. DCBE and OC were performed in all hospitals where there was a CTC service. Consequently, CTC was performed in 25.8% (23/89) of the departments where a DCBE service was offered. Seventy-three departments out of 76 answered the question about their reasons for non-implementation of CTC (Table 1).

Table 1. Reasons for non-implementation of CTC

	No. of departments (%)
Lack of CTC training and expertise	34/73 (46.6%)
Non-availability of multidetector row CT scanner	33/73 (45.2%)
Non-availability of appropriate software	31/73 (42.5%)
Lack of doctor´s time	28/73 (38.4%)
Awaiting further scientific documentation on CTC	19/73 (26.0%)
Limited CT lab capacity	17/73 (23.3%)
Non-availability of spiral CT scanner	13/73 (17.8%)
Non-availability of appropriate workstation	13/73 (17.8%)
Not economically motivated	4/73 (5.5%)
Not medically motivated	2/73 (2.7%)

Out of 76 departments that did not perform CTC, 30 (39.5%) stated that they intended to start in the near future (Fig. 8).

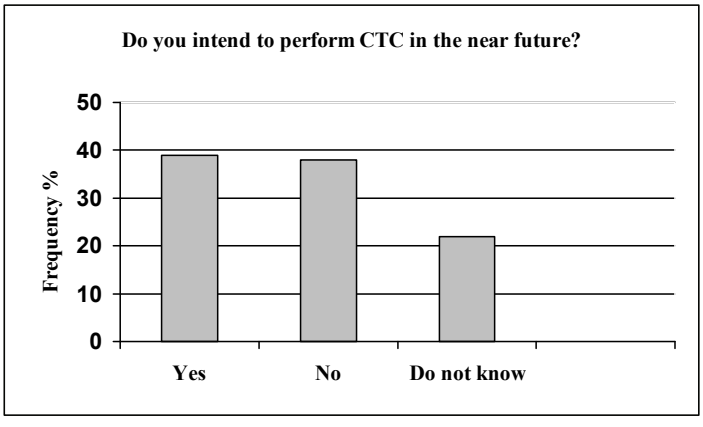


Figure 8.

These departments performed more (P<0.001) radiological examinations annually (mean 66,179 ± 37,807) than departments not intending to start a CTC

service (mean 30,489 ± 27,885). Departments not intending to carry out CTC in the near future reported the lack of a spiral-CT scanner as the reason in 9/29 cases (32%), while departments intending to start a CTC service reported lack of a spiral-CT scanner in 2/30 cases (6.6%).

On the question ‘‘Do you believe that CTC will, in the future, replace double-contrast barium enema?’’ 55/99 departments (55.6%) answered either ‘‘Yes, absolutely’’ or ‘‘Yes, probably’’. The expressed expectation that CTC was to replace DCBE did not depend on local CTC service availability (Fig. 9).

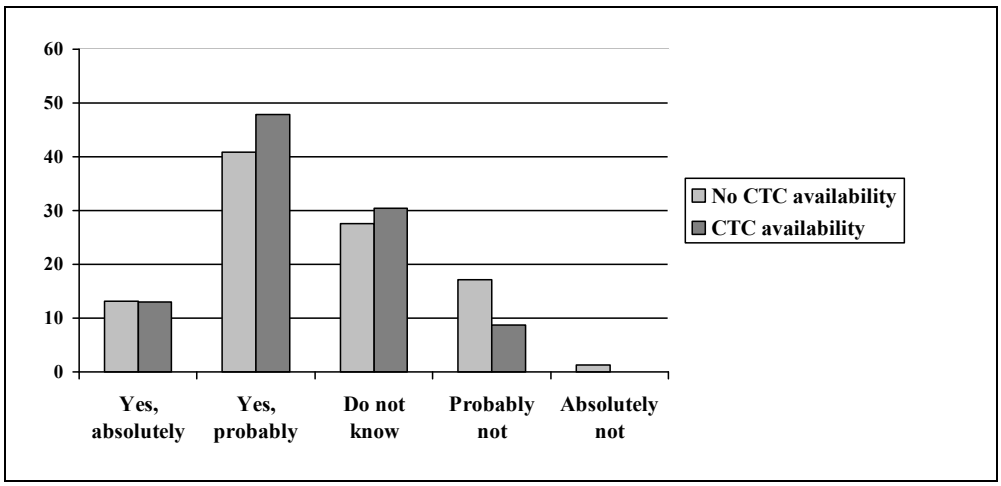


Figure 9. Frequency data on y-axis are expressed in %.

Out of 23 departments that performed CTC, 8 (34.8%) did less than one examination per month; 5 (21.7%) did 1–4 examinations per month, 5 (21.7%) did 1–2 per week, 3 (13%) did 3–5 per week, and 2 (8.7%) did more than 5 examinations per week. At the time of completion of the questionnaire, 6 (26.1%) departments had performed 1–5 examinations, 2 (8.7%) departments 6–10 examinations, 3 (13%) departments 11–20 examinations, 2 (8.7%) departments 21–50 examinations, 1 (4.3%) department 51–100 examinations, 5 (21.7%) departments 101–200 examinations, and 4 (17.4%) departments more than 200 examinations. Ten (43.5%) departments used a 16-slice multidetector row CT, while 4 (17.5%) used an 8-slice MDCT, 8 (34.8%) a 4-slice MDCT, and 1 (4.3%) a single-slice CT.

Indications for CTC are given in Table 2.

Table 2. Indications for computed tomography colonography(CTC)

	No. of departments (%)
Complement to an incomplete colonoscopy	21/23 (91.3%)
Patients who are expected to have difficulties going through colonoscopy or barium enema due to old age or physical disability	14/23 (60.9%)
Patients who refuse colonoscopy or barium enema	12/23 (52.2%)
Complement to an incomplete barium enema	11/23 (47.8%)
Follow-up after previous polypectomy	3/23 (13.6%)
Preoperative examination in patients with known colorectal cancer	3/23 (13%)
Alternative examination to barium enema regardless of history	3/23 (13%)
Alternative examination to colonoscopy regardless of history	2/23 (8.7%)
Within research project	2/23 (8.7%)
Screening in asymptomatic individuals with high risk of colon cancer	1/23 (4.3%)
Other indication	1/23 (4.3%)

Incomplete OC was the indication most commonly stated (21/23 departments; 91.3%).

Examinations of choice in the event of suspected colorectal cancer in hospitals with a CTC practice are shown in Fig. 10.

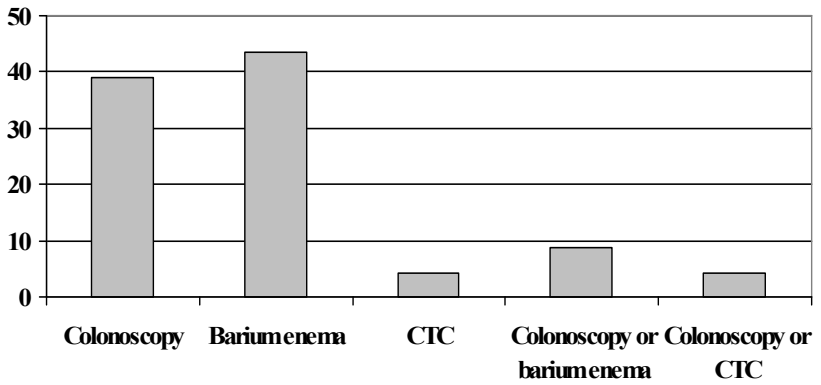


Figure 10. Frequency data on y-axis are expressed in %.

Full bowel preparation was routinely performed with phosphosoda in 11/23 (47.8%) departments, while polyethylene glycol solution was preferred in 7/23 (30.4%). Phosphosoda or polyethylene glycol solution was used in 3/23 (13%) departments, bisacodyl in 1/23 (4.3%), and bisacodyl and magnesium citrate in 1/23 (4.3%). One (4.3%) out of 23 departments used fecal tagging with barium.

Dual patient positioning (supine and prone) and room air insufflation were routine maneuvers in all departments (100%). Intravenous contrast material

was routinely administered in 9/23 (39.1%) departments.
Out of 23 active centers, 8 (34.7%) used a CT collimation of 2.5 mm, 7 (30.4%) a collimation of 1.25 mm, 3 (13%) used 0.75 mm, 2 (8.6%) used 1.5 mm, 2 (8.6%) used 1 mm, and 1 (4.3%) did not specify. The median (interquartile range) of mAs used in the supine position was 125 (100–165), while in the prone position it was 100 mAs (50–130). All the departments that replied used 120 kV.
At 13/23 (56.5%) centers, radiologists performed the air insufflation, while in 10/23 (43.5%) centers this was done by radiology technicians/nurses. In 18/23 (78.3%) departments, a radiologist reviewed the scout view to judge the quality of air insufflation, while in 5/23 (21.7%) this was done by a radiology nurse/technician.
Primary 2D analysis (with 3D endoluminal views for problem-solving) was the preferred routine at 14/23 (60.9%) centers, while primary 3D analysis (with 2D images for problem-solving) was the preferred method in 1/23 (4.3%) departments. Both 3D and 2D images (3D+2D) were primarily reviewed in 8/23 (34.8%) centers.
The mean estimated interpretation time for a CTC study was 10–15 min in 5 (21.7%) departments, 16–20 min in 6 (26.1%) departments, 21–30 min in 8 (34.8%) departments, and more than 30 min in 4 (17.4%).

Data from follow-up telephone interviews
Of the 30 departments that in 2004 (according to questionnaire answers) had intended to start a CTC service in the near future, 9 (30%) had done so by June 2005. Thus, including the 23 CTC centers and the 9 departments that on the follow-up telephone interview reported starting CTC, a total of 32 (32.3%) of the 99 responding departments had started CTC by June 2005.

A total of between 1 and 5 CTC examinations had been performed by 3 (33.3%) of the 9 departments, 6–10 examinations by 1 (11.1%) department, 21–50 by 3/9 (33.3%) departments, and 51–100 by 2/9 (22.2%) departments. Between 1 and 4 CTC examinations per month were performed in 4/9 (44.4%) departments, between 1 and 2 per week in 2/9 (22%) departments, and between 3 and 5 per week in 3/9 (33.3%) departments.
Indications for CTC included difficulty performing OC or DCBE because of old age or physical disability in 5/9 (55.6%) departments, incomplete OC in 3/9 (33.3%), incomplete DCBE in 2/9 (22.2%), alternative examination to DCBE

regardless of history in 2/9 (22.2%), alternative examination to OC regardless of history in 2/9 (22.2%), research project in 1/9 (11.1%).

PAPER II

CTC is currently performed in 50 of 119 (42%) departments, i.e. 18 additional departments compared to 2005. With regard to those departments that do not perform CTC, 23 out of 60 responding departments (38%) stated that they intend to start in the near future. DCBE is currently performed in 77 of the 119 (65%) departments, 12 departments less compared to 2005. The median number of DCBE examinations performed per week is 8 (IQR 3-15).

Reasons for non-implementation of CTC are shown in Table 3. Non-availability of CT equipment was reported to be reason for non-implementation of CTC in 6% (5/77) of departments performing DCBE in 2009, as compared to 29% (26/89) in 2005. Compared to the departments who replied in 2005, a significantly smaller number of departments stated in 2009 that they are "awaiting further scientific documentation on CTC" (p=0.002).

Table 3. Reasons for non-implementation of CTC

	No. of departments (%)	
	2008-2009	2004-2005
Non-availability of spiral CT scanner	26/64 (41%)	13/73 (18%)
Non-availability of multidetector row CT scanner	25/64 (39%)	33/73 (45%)
Lack of doctors time	22/64 (34%)	28/73 (38%)
Lack of CTC training and expertise	18/64 (28%)	34/73 (47%)
Non-availability of appropriate software	14/64 (22%)	31/73 (42%)
Limited CT lab capacity	14/64 (22%)	17/73 (23%)
Awaiting further scientific documentation on CTC	2/64 (3%)	19/73 (26%)
Not economically motivated	3/64 (5%)	4/73 (6%)
Not medically motivated	2/64 (3%)	2/73 (3%)

Previous and current indications for CTC are shown in Table 4. The number of departments that stated that CTC is indicated in patients who refuse colonoscopy or DCBE has increased (p=0.01) in 2009 compared to the answers given by the same departments in 2005.

Table 4. Indications for CTC

	No. of departments (%)	
	2008-9	2004-5
Complement to an incomplete colonoscopy	48/50 (96%)	21/23 (91%)
Patients who are expected to have difficulties going through colonoscopy or barium enema due to old age or physical disability	39/50 (78%)	14/23 (61%)
Patients who refuse colonoscopy or barium enema	39/50 (78%)	12/23 (52%)
Alternative examination to barium enema regardless of history	30/50 (60%)	3/23 (13%)
Complement to an incomplete barium enema	19/50 (38%)	11/23 (48%)
Preoperative examination in patients with known colorectal cancer	18/50 (36%)	3/23 (13%)
Follow-up after previous polypectomy	15/50 (30%)	3/23 (14%)
Alternative examination to colonoscopy regardless of history	14/50 (28%)	2/23 (9%)
Screening in asymptomatic individuals with high risk of colon cancer	7/50 (14%)	1/23 (4%)
Within research project	2/50 (4%)	2/23 (9%)

The proportion of departments that perform at least 3 CTC examinations per week has increased from 25% (8/32) in 2005 to 70% (35/50) in 2009. More than half of the CTC centres (59%, 29/49) have performed more than 200 CTC until 2009 compared to 13% (4/32) of CTC centres in 2005. About half of the CTC centres (55%, 27/49) use 64-slice multidetector-row CT in 2009, while in 2005 the most used CT machine for CTC was 16-slice MDCT (44%, 10/23). In 2009, no departments perform CTC with single-slice CT. As in 2005, all CTC centres use a slice collimation of 2.5 mm or less. In 2009, the median mAs used in the supine position was 150 (95-205), while in the prone position it was 80 mAs (50–100). As in 2005, all CTC centres use a tube voltage of 120 kV.

As in 2005, the majority of CTC centres (64%, 28/44) uses phosphosoda as laxative, followed by polyethylene glycol (30%, 13/44).

Out of 49 responding CTC active centres, 11 (22%) use fecal or fluid tagging in 2009 while in 2005 only 1 of 23 CTC centres used tagging. Three of the centres use barium, 7 centres use gastrografin and 1 centre uses low-osmolar iodine contrast. Intravenous contrast material is routinely administered in almost all CTC centres (86%, 42/49) while in 2005 it was routinely administered in less than half of CTC centres (39%, 9/23). Carbon dioxide is currently used to distend the colon in 44 centres (90%) while in 2005 room air was used to distend the colon in all CTC centres. A radiology technician/nurse currently performs colon insufflation in 86% (42/49) of the centres (44%, 10/23 in 2005) and reviews the scout view in 78% (38/49) of the centres to judge the quality of colon distension (22%, 5/23 in 2005).

While in 2005 primary 2D reading was the most used interpretation method (61%, 14/23), in 2009 both 2D and 3D images are primarily reviewed in the majority of CTC centres (56%, 27/48), followed by primary 2D reading (21%, 10/48), primary 3D reading (15%, 7/48) and only 2D reading (8%, 4/48).

Computer-aided detection (CAD) is used in 16/48 CTC centres (33%), of which it is "always" used in 5 centres and "often" in 11 centres.
Double-reading is "always" performed in 26 of 49 (53%) CTC centres and "often" performed in 15 (31%) CTC centres.
The median number of radiologists reading CTC per centre is 3 (IQR 2-5).

On the question ''Do you believe that CTC will, in the future, replace double-contrast barium enema?'' almost all responding departments (93%, 93/100) answered either ''Yes, absolutely'' or ''Yes, probably'' in 2009, while in 2005 about half of the departments (56%, 55/99) gave similar answers.
With regard to those departments that replied in 2005 and in 2009, a significantly larger proportion stated in 2009 that they believe CTC will "absolutely" or "probably" replace DCBE, as compared to 2005 (93%, 80/86 in 2009 versus 60%, 52/86 in 2005; $p<0.001$).

PAPER III

OC findings
At OC with segmental unblinding a total of 113 polyps and 3 cancers in 34 (68%) out of 50 patients were detected; 16 lesions were ≥10 mm in diameter (9 pedunculated, 5 sessile, 2 flat), 19 lesions measured 6-9 mm in diameter (2 pedunculated, 15 sessile, 2 flat), 81 lesions were ≤5 mm (1 pedunculated, 80 sessile). Distribution of lesions was as follows: rectum, 23 (20%); sigmoid colon, 37 (32%); descending colon, 8 (7%); left flexure, 3 (2%); transverse colon, 18 (16%); right flexure, 8 (7%); ascending colon, 10 (9%); caecum, 9 (8%). The three cancer lesions (3 patients) were >2 cm. In 25 (50%) of the 50 patients, 48 adenomatous polyps were detected. Ten adenomas were ≥10 mm, 7 measured 6-9 mm, 31 were ≤5 mm. The remaining polyps were classified as hyperplastic polyps. One lipoma was identified.
Per-lesion sensitivity and per-patient sensitivity and specificity of first-look OC are shown respectively in Tables 5 and 6.

Table 5. Per-lesion sensitivity and number of false positives, respectively, of Reader 1 (experienced) with 3D Filet and additional complete 2D (3D Filet + 2D), and of first-look optical colonoscopy.

	Reader 1				**Optical Colonoscopy**	
	3D Filet		**3D Filet+2D**			
	Sensitivity	FP	Sensitivity	FP	Sensitivity	FP
Any lesion						
≥10 mm	75 (12/16)	2	81 (13/16)	3	100 (16/16)	-
≥6 mm	77 (27/35)	17	83 (29/35)	20	94 (33/35)	-
6-9 mm	79 (15/19)	15	84 (16/19)	17	89 (17/19)	-
≤5 mm	48 (39/81)	41	56 (45/81)	52	94 (76/81)	4
Any size	57 (66/116)	58	64 (74/116)	72	94 (109/116)	4
Adenoma or carcinoma						
≥10 mm	69 (9/13)		77 (10/13)		100 (13/13)	
≥6 mm	80 (16/20)		85 (17/20)		95 (19/20)	
6-9 mm	100 (7/7)		100 (7/7)		86 (6/7)	
≤5 mm	52 (16/31)		55 (17/31)		94 (29/31)	
Any size	63 (32/51)		67 (34/51)		94 (48/51)	

Note. Sensitivity is expressed in percentage. Numbers in parentheses are the proportions of true positive lesions. FP: number of false positive lesions

Table 6. Per-patient sensitivity and specificity, respectively, of Reader 1 (experienced) with 3D Filet and additional complete 2D (3D Filet + 2D), and of first-look optical colonoscopy

	Reader 1				**Optical Colonoscopy**	
	3D Filet		**3D Filet+2D**			
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Any lesion						
≥10 mm	75 (9/12)	95 (36/38)	83 (10/12)	95 (36/38)	100 (12/12)	100 (38/38)
≥6 mm	75 (15/20)	80 (24/30)	85 (17/20)	73 (22/30)	90 (18/20)	100 (30/30)
Any size	80 (27/34)	56 (9/16)	85 (29/34)	50 (8/16)	100 (34/34)	94 (15/16)
Adenoma or carcinoma						
≥10 mm	75 (9/12)		83 (10/12)		100 (12/12)	
≥6 mm	81 (13/16)		87 (14/16)		94 (15/16)	
Any size	80 (20/25)		88 (22/25)		96 (24/25)	

Note. Sensitivity and specificity are expressed in percentages. Numbers in parentheses are the proportions of patients with lesions (sensitivity) and without lesions (specificity)

normal mucosa at histology) were reported. At a patient level, there was one false positive OC examination, reporting a finding <5 mm.

CTC Per-lesion analysis

The sensitivity for lesions ≥10 mm with 3D Filet was 75% for the experienced reader and 69% and 62%, respectively, for the inexperienced readers (Table 7).

Table 7. Per-lesion sensitivity and number of false positives of Reader 1 (experienced) with 3D Filet and of Readers 2 and 3 (inexperienced) with 3D Filet and 2D.

	Experienced		***Inexperienced***							
	Reader 1		Reader 2				Reader 3			
	3D Filet		**3D Filet**		**2D**		**3D Filet**		**2D**	
	Sensitivity	FP	Sensitivity	FP	Sensitivity	FP	Sensitivity	FP	Sensitivity	FP
Any lesion										
≥10 mm	75 (12/16)	2	69 (11/16)	1	81 (13/16)	1	62 (10/16)	3	62 (10/16)	1
≥6 mm	77 (27/35)	17	51 (18/35)	8	57 (20/35)	8	40 (14/35)	7	43 (15/35)	4
6-9 mm	79 (15/19)	15	37 (**7**/19)	7	37 (7/19)	7	21 (4/19)	4	26 (5/19)	3
≤5 mm	48 (39/81)	41	38 (31/81)	38	37 (30/81)	44	32 (26/81)	8	22 (18/81)	4
Any size	57 (66/116)	58	42 (49/116)	46	43 (50/116)	52	34 (40/116)	15	28 (33/116)	8
Adenoma or carcinoma										
≥10 mm	69 (9/13)		77 (10/13)		77 (10/13)		62 (8/13)		62 (8/13)	
≥6 mm	80 (16/20)		55 (11/20)		60 (12/20)		50 (10/20)		45 (9/20)	
6-9 mm	100 (7/7)		14 (1/7)		29 (2/7)		29 (2/7)		14 (1/7)	
≤5 mm	52 (16/31)		45 (14/31)		45 (14/31)		39 (12/31)		29 (9/31)	
Any size	63 (32/51)		49 (25/51)		51 (26/51)		43 (22/51)		35 (18/51)	

Note. Sensitivity is expressed in percentage. Numbers in parentheses are the number of true positive lesions detected at CTC with 3D Filet or 2D/the total number of polyps detected at colonoscopy. FP: number of false positive lesions

Compared with the inexperienced readers, the experienced reader detected one and two more lesions ≥10 mm, respectively, and a significantly higher number of polyps 6-9 mm ($p<0.05$), adenomatous or not, and of polyps of any size ($p<0.05$). All 3 cancer lesions were detected by the experienced reader with 3D Filet.

With 3D Filet + 2D (Table 5), the experienced reader detected a significantly higher number of polyps ≤5 mm (p=0.03) than with 3D Filet alone, but the number of detected adenomas in this subgroup was not significantly different.
Concerning comparison between 3D Filet and 2D for inexperienced readers (Table 7 and Fig. 11), there was no statistically significant difference in sensitivity for detection of polyps or adenomas of any size subgroups. There was a trend (p=0.07) for Reader 3 to detect more polyps ≤5 mm with 3D Filet than with 2D.

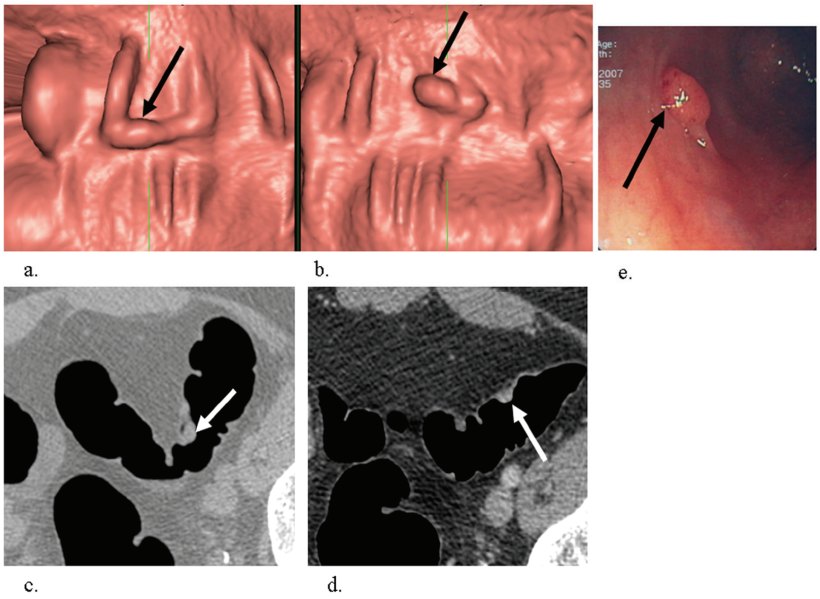


Figure 11 Pedunculated polyp of 1 cm in the sigmoid colon of a 53-year-old man. The lesion was identified by the experienced reader with 3D Filet and by the inexperienced readers both with 3D Filet and with 2D. 3D Filet supine view (A) and 3D Filet prone view (B) show the polyp (arrow). (C) Axial 2D image in supine shows the pedunculated polyp (arrow) hanging from the ventral part of the sigmoid wall. (D) Axial 2D image in prone with contrast enhancement shows the polyp (arrow). (E) Optical colonoscopy image. Histology revealed adenoma.

Combining 3D Filet+2D, the sensitivity of the inexperienced readers for lesions ≥6 mm increased to 63% (22/35) (compared with 51% with 3D Filet alone, and 57% with 2D alone) for Reader 2 and to 51% for Reader 3 (18/35) (compared with 40% with 3D Filet alone and 43% with 2D alone) (Fig.12).

Regarding polyp morphology, there was no statistically significant difference in sensitivity between the review methods.

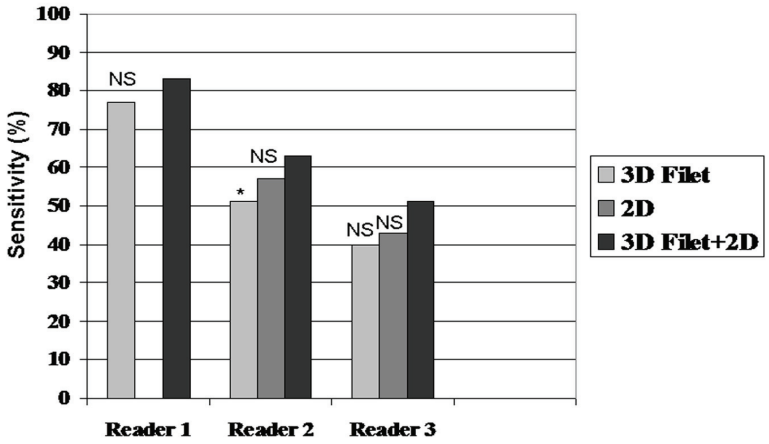


Figure 12. *Per-polyp sensitivities for lesions ≥ 6 mm*
Reader 1 (experienced) performed 3D Filet followed in the same reading session by additional complete 2D (3D Filet+2D). A separate primary 2D analysis was not performed.
Readers 2 and 3 (inexperienced readers) read the CTC cases with 3D Filet and in a separate reading session with 2D. In addition, true positives described with 3D Filet and/or 2D were combined to obtain 3D Filet+ 2D.
* = statistically significant (p=0.02) difference between 3D Filet and 3D Filet+2D
NS= not statistically significant difference compared to 3D Filet+2D at the significance level p<0.05

CTC Per-patient analysis

Per-patient sensitivity for lesions ≥10 mm with 3D Filet was 75% for the experienced reader and 75% and 62% for the inexperienced readers (Table 8). For patients with lesions ≥6 mm, the experienced reader had higher sensitivities compared to the inexperienced readers with 3D Filet but the difference was not statistically significant. The additional 2D evaluation slightly improved per-patient sensitivity of the experienced reader regardless of lesion size (Table 6).

For inexperienced readers, per-patient sensitivity and specificity concerning patients with polyps ≥10 mm or ≥6 mm or any size did not differ significantly between 3D Filet and 2D (Table 8).
With combined 3D Filet+2D for lesions ≥6 mm, the per-patient sensitivity of the inexperienced readers would increase from 65% (13/20) to 80% (16/20) for Reader 2 and from 50% (10/20) to 60% for Reader 3 (12/20).

Table 8. Per-patient sensitivity and specificity of Reader 1 (experienced) with 3D Filet, and of Readers 2 and 3 (inexperienced) with 3D Filet and 2D

	Experienced		***Inexperienced***							
	Reader 1		Reader 2				Reader 3			
	3D Filet		**3D Filet**		**2D**		**3D Filet**		**2D**	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Any lesion										
≥10 mm	75 (9/12)	95 (36/38)	75 (9/12)	97 (37/38)	83 (10/12)	100 (38/38)	67 (8/12)	92 (35/38)	67 (8/12)	97 (37/38)
≥6 mm	75 (15/20)	80 (24/30)	65 (13/20)	87 (26/30)	70 (14/20)	87 (26/30)	50 (10/20)	87 (26/30)	55 (11/20)	90 (27/30)
Any size	80 (27/34)	56 (9/16)	74 (25/34)	44 (7/16)	79 (27/34)	62 (10/16)	62 (21/34)	75 (12/16)	59 (20/34)	75 (12/16)
Adenoma or carcinoma										
≥10 mm	75 (9/12)		75 (9/12)		67 (8/12)		83 (10/12)		67 (8/12)	
≥6 mm	81 (13/16)		62 (10/16)		56 (9/16)		69 (11/16)		62 (10/16)	
Any size	80 (20/25)		64 (16/25)		64 (16/25)		76 (19/25)		56 (14/25)	

Note. Sensitivity and specificity are expressed in percentages. Numbers in parentheses are the proportions of patients with lesions (sensitivity) and without lesions (specificity)

Clinically significant (≥6 mm) false negatives at CTC

The majority (approximately 70% for each reader) of false negatives (FN) ≥6 mm, were missed both on 3D Filet and 2D by the experienced and the inexperienced readers. None of the 4 flat lesions (two adenomas and two hyperplastic polyps) were described by any reader with any reading method. Of these lesions, only two adenomas of 1 cm and 3 cm could be identified retrospectively. In addition, the inexperienced readers missed 7 and 11 lesions, respectively, with both reading methods, most of them were sessile polyps between 6 and 9 mm in diameter. The majority of these FN (6/7 polyps (86%) for Reader 2 and 7/11 (64%) for Reader 3) were visible in only one body position, being submerged by fluid or located in collapsed segments in the other body position.

Approximately 30% of all false negative lesions ≥6 mm were missed by only one of the reading methods. Thus, Reader 2 detected all three cancers with 2D but missed one with 3D Filet (Fig. 13), while Reader 3 detected all cancers with 3D Filet but missed one with 2D (Fig. 14).

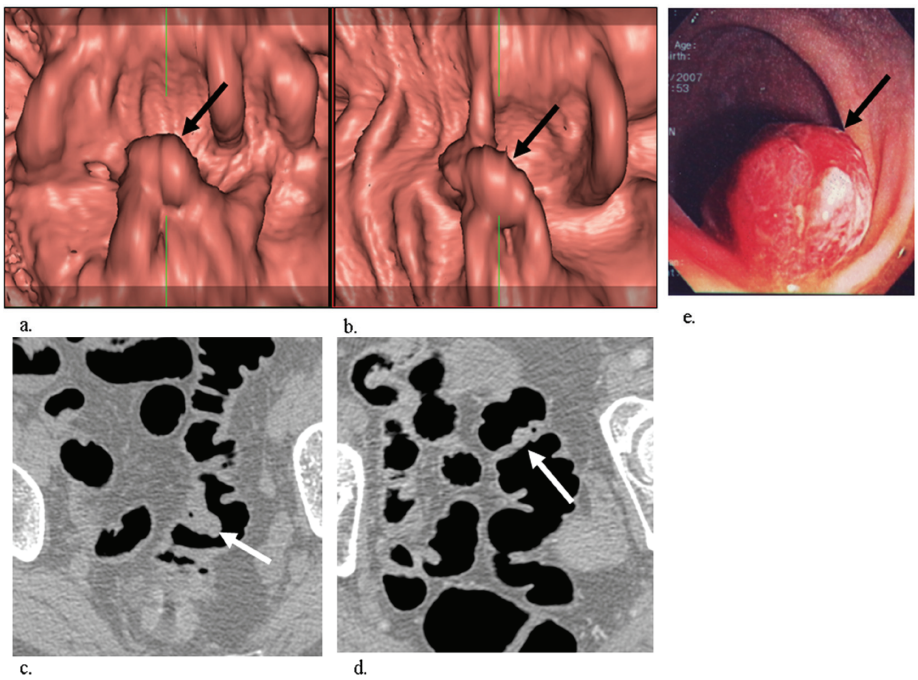


Figure 13: Pedunculated polyp of 2 cm in the sigmoid colon of a 67-year-old woman. The lesion was missed by Reader 2 with 3D Filet but detected with 2D. Supine (A) and prone (B) 3D Filet views show the polyp (arrow) lying on a colonic fold. Supine (C) and prone (D) 2D axial CTC images show the mobile head (arrow) of the polyp while the stalk is not clearly visible. Note that the colonic segment where the polyp was located was clean and adequately

distended. Optical colonoscopy (E) shows the head (arrow) of the pedunculated polyp. Biopsy revealed non-invasive adenocarcinoma.

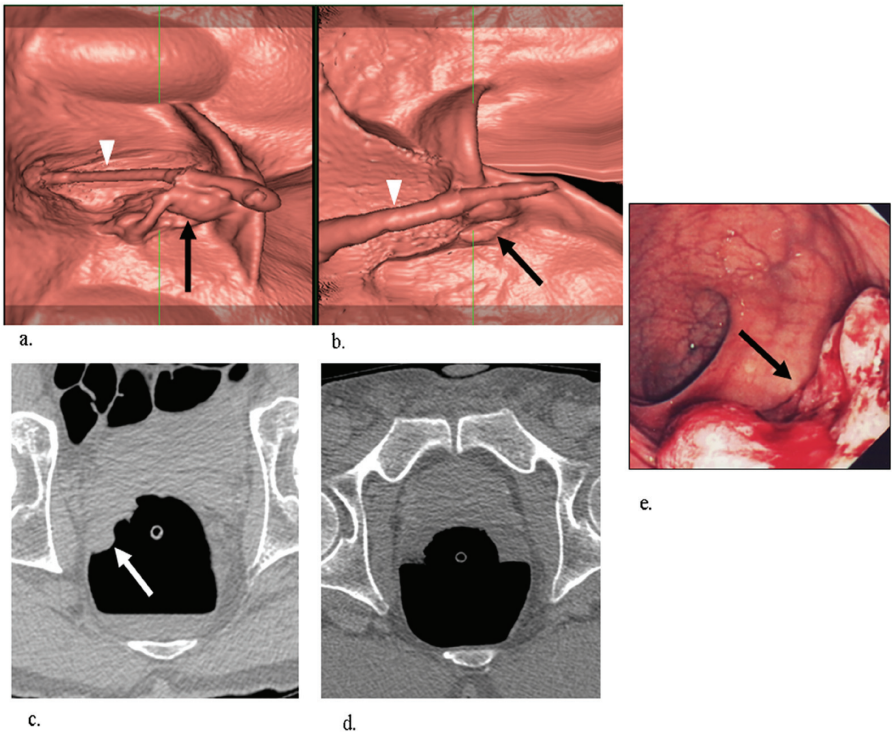


Figure 14: Rectal cancer of 3 cm in a 73-year-old man. The lesion was missed by Reader 3 with 2D but detected with 3D Filet. Supine (A) and prone (B) 3D Filet views show the lobulated cancer (arrows) close to the rectal tube (arrowheads). Supine (C) 2D axial CTC image clearly shows the lobulated sessile cancer (arrow). In prone (D) 2D axial CTC image the cancer is submerged by residual fluid. Optical colonoscopy (E) image shows the presence of the lesion (arrow). The final histopathologic diagnosis was ulcerated adenocarcinoma.

False positives (FP) at CTC

Tables 5 and 7 show the number of FP per reading method and per polyp size for the experienced and the inexperienced readers, respectively.

The mean number of FP per patient for the experienced reader was 1.2 with 3D Filet and 1.5 with 3D Filet+2D. In terms of FP ≥6 mm, the difference was not statistically significant (0.4 FP/patient compared to 0.3 FP/patient).

Concerning inexperienced readers, the mean number of FP/patient with 3D Filet and 2D was 0.9 and 1.0, respectively, for Reader 2 and 0.3 and 0.2, respectively,

for Reader 3. Regarding FP ≥6 mm, the mean number/patient was 0.2 and 0.2, respectively, for Reader 2 and 0.1 and 0.1, respectively for Reader 3. The differences in the number of FP between 3D Filet and 2D were not statistically significant for any lesion size subgroup.

Bowel wall visualisation

In 20 (40%) patients all colon segments were completely gas filled both in supine and prone. Fluid levels were present in 48 (96%) patients with complete fluid redistribution in all patients and all segments. In combined review of supine and prone positions, all colon segments were gas filled in 45 (90%) patients. No stool interference was present in 30 (60%) patients. There was limited stool interference in 16 (32%) patients and in 29/400 segments. Moderate stool interference was present in 3 patients and 3 segments and extensive interference in one patient and one segment.

Interpretation times

Median (interquartile range, IQR) interpretation times with the different reading methods were as follows: *Reader 1*, 15 minutes (12-26 min) with 3D Filet, and 12 minutes (8-16 min) for the additional 2D evaluation; *Reader 2,* 24 minutes (17-31 min) with 3D Filet, 22 minutes (15-30 min) with 2D; *Reader 3,* 39 minutes (29-49 min) with 3D Filet, 34 minutes (24-48 min) with 2D. The differences between 3D Filet and 2D were not statistically significant. Cases with no OC-proven polyps required significantly less evaluation time for Reader 2 on 3D Filet (median 20 min, IQR 12-22 min) than on 2D (median 23 min, IQR 14-26 min) (p=0.007), while there was a trend in favour of 3D Filet (p=0.07) for Reader 3 (3D Filet: median 29 min, 21-40 min; 2D: 34 min, 24-48 min).

PAPER IV

Lesions

Only lesions ≥3 mm detected at OC were included in the evaluation since CAD minimum filter size was 3 mm.

A total of 103 lesions (mean lesion size 7 mm, range 3-50 mm) were detected in 34 patients at OC with segmental unblinding. Sixteen lesions were large (≥10 mm), 19 lesions medium-sized (6-9 mm), and 68 lesions small (3-5 mm). Sixteen patients had no polyps. Among patients with polyps, the mean number

of polyps per patient was 3 (median 2; range: 1-12). Twenty of the 50 patients had one or more lesion ≥6 mm.
Distribution of lesions was as follows: rectum, 19 (18%); sigmoid colon, 36 (35%); descending colon, 8 (8%); left flexure, 3 (3%); transverse colon, 14 (13%); right flexure, 6 (6%); ascending colon, 9 (9%); caecum, 8 (8%). In 3 patients, 3 cancers >2 cm were detected. Two cancers were sessile and ulcerated located respectively in the rectum and caecum, and one cancer was pedunculated, located in the sigmoid colon.

CAD stand-alone performance
Per-lesion sensitivity of the CAD algorithm was 89% (31/35) and 73% (75/103) for lesions ≥6 mm and ≥3 mm, respectively. CAD detected all 3 cancers. Concerning lesions ≥6 mm, all except two flat 6 mm lesions were visible in retrospect on CTC. CAD marked at least one suspected lesion ≥6 mm in all patients with or without lesions at OC. CAD correctly identified at least one lesion ≥6 mm in 18 of 20 patients (per-patient sensitivity 90%). The mean number of FP CAD marks per patient was 12.8 in supine (median 8, IQR 5.5-16.5) and 11.4 (median 8, IQR 5-14.5) in prone. Of the FP, approximately 80% were fecal residues, 10% bulbous haustral folds, 5% ileocecal valve, 3% rectal tube tip, 2% extrinsic impressions.

Experienced reader (Reader 1) assisted by CAD
With CAD assistance, Reader 1 correctly identified 1 additional medium-sized polyp and 4 additional small polyps. Thus, sensitivity for lesions ≥6 mm increased from 83% (29/35), at a FP-rate of 0.40 (*3D Filet+2D*), to 86% (30/35) (*3D Filet+2D+CAD*), at a FP-rate of 0.44. Concerning lesions ≥3 mm, Reader 1 increased the sensitivity from 66% (68/103) at a FP-rate of 1.54 (*3D Filet+2D*) to 71% (73/103) at a FP-rate of 1.60 (*3D Filet+2D+CAD)*. At a per-patient level, AUC did not differ significantly between 3D Filet+2D (0.87) and 3D Filet+2D+CAD (0.86) ($p>0.05$).

Performance of the inexperienced readers (Readers 2 and 3) assisted by CAD
Per-lesion sensitivity
Table 9 shows sensitivity values concerning lesions ≥6 mm and ≥3 mm by the inexperienced readers with 3D Filet, 2D and 3D Filet+CAD.

Table 9

Per-lesion sensitivity of Reader 2 and 3 (inexperienced readers) with primary 3D with perspective-filet view analysis (3D Filet), primary 2D analysis (2D) and CAD as second reader using perspective-filet view (3D Filet+CAD).

	Lesions ≥ 6 mm		**Lesions ≥ 3 mm**	
	Reader 2	**Reader 3**	**Reader 2**	**Reader 3**
3D Filet	51 (18/35)	40 (14/35)	47 (49/103)	38 (39/103)
2D	57 (20/35)	43 (15/35)	44 (45/103)	32 (33/103)
3D Filet+CAD	57 (20/35)	57 (20/35)*	58 (60/103)*†	48 (50/103)*†

Note: data show sensitivity expressed in %. Numbers in parentheses are the number of true positives /the total number of lesions.

*= statistically significant difference ($p<0.05$) between 3D Filet+CAD and 3D Filet

†= statistically significant difference ($p<0.05$) between 3D Filet+CAD and 2D

Concerning lesions ≥6 mm, there was a statistically significant increase of sensitivity with 3D Filet+CAD for the least inexperienced Reader 3 compared with 3D Filet.

Concerning lesions ≥3 mm, both inexperienced readers had a statistically significant increase in sensitivity with 3D Filet+CAD compared with 3D Filet and 2D.

Reader 2 correctly identified 11 additional lesions with 3D Filet+CAD, as compared with unassisted 3D Filet: 1 large, 1 medium-sized (Fig. 15), 9 small lesions. Although highlighted by CAD, a pedunculated cancer was not described on 3D Filet+CAD, while it was identified on 2D.

Also Reader 3 correctly identified 11 additional lesions with 3D Filet+CAD: 2 large (Fig. 16), 4 medium-sized, 5 small lesions. Of the 2 lesions ≥1 cm detected with 3D Filet+CAD, one was a pedunculated polyp that had been missed both on 3D Filet and 2D

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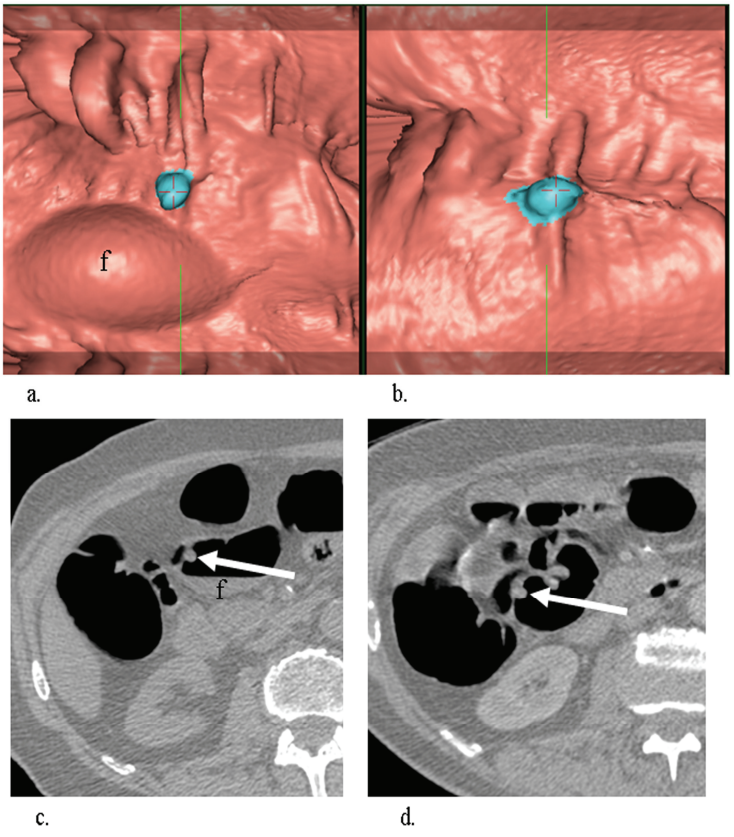

Figure 15. Sessile 6 mm polyp on a fold in the right flexure of an 84-year-old man. The lesion was missed by Reader 2 (inexperienced reader) with 3D Filet and 2D but detected with 3D Filet+CAD, while Reader 3 (inexperienced reader) missed it with all review methods. Supine (a) and prone (b) 3D Filet views show the polyp, marked in blue by CAD. Note the presence of fluid (f) close to the polyp in supine. Corresponding supine (c) and prone (d) 2D axial CTC images show the polyp (arrow) on a fold. Biopsy revealed adenoma.

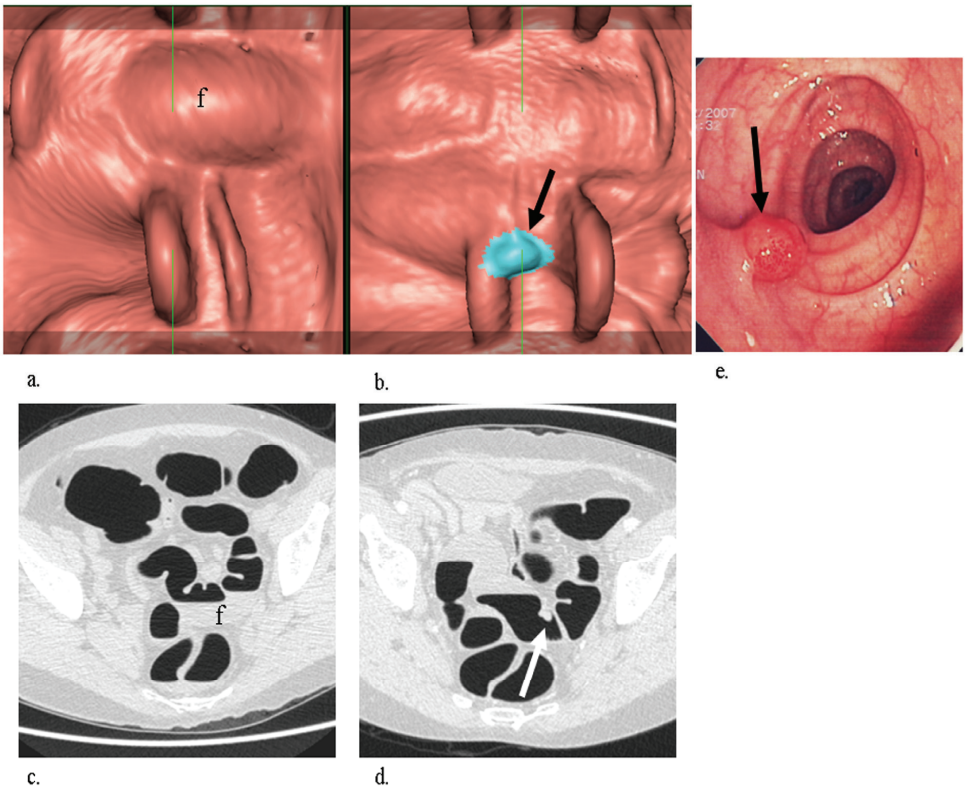

Figure 16. Pedunculated 1 cm polyp in the sigmoid colon of a 69-year-old woman. The lesion was missed by Reader 3 (inexperienced reader) with 3D Filet and 2D but it was detected with 3D Filet+CAD. Supine (a) 3D Filet view image shows the presence of fluid (f) under which the polyp head is submerged. Prone (b) 3D Filet view image shows the mobile polyp head (arrow) marked in blue by CAD, lying between two colonic folds. Supine (c) and prone (d) 2D axial CTC images show respectively the presence of fluid and the mobile head (arrow) of the polyp lying between two folds. Optical colonoscopy (e) shows the pedunculated polyp. Biopsy revealed adenoma.

JAFROC-1 analysis

There was no statistically significant difference in performance, as expressed by FOM, among reading modes for the inexperienced readers concerning lesions

≥6 mm (p=0.4) or ≥3 mm (p=0.8) (Table 10). Concerning lesions ≥6 mm, the FOM of the two inexperienced readers using 3D Filet+CAD became identical (0.72) (Table 10) and was slightly lower than that of the experienced reader using 3D Filet (0.79; p=0.8).

Table 10

Results of JAFROC-1 analysis concerning lesions ≥6 mm and ≥3 mm by Reader 2 and Reader 3 (inexperienced readers) with primary 3D with perspective-filet view analysis (3D Filet), primary 2D analysis (2D) and CAD as second reader using perspective-filet view (3D Filet+CAD). Data show the figure-of-merit (FOM), i.e. the probability that a true positive is rated higher than the highest rated false positive in a case.

	Lesions ≥ 6 mm		**Lesions ≥ 3 mm**	
	Reader 2	**Reader 3**	**Reader 2**	**Reader 3**
3D Filet	0.71	0.66	0.55	0.60
2D	0.74	0.69	0.55	0.59
3D Filet+CAD	0.72	0.72	0.55	0.58

FROC curves

FROC curves showed that at a constant diagnostic confidence level, both per-lesion sensitivity for lesions ≥3 mm and ≥6 mm and the FP-rate increased with 3D Filet+CAD compared with 3D Filet for both inexperienced readers (Fig. 17 and 18). Also compared with 2D, 3D Filet+CAD had a higher sensitivity and higher FP-rate (Figure 17 and 18), except for Reader 2 and the subgroup of lesions ≥6 mm where sensitivity with 3D Filet+CAD was identical to 2D, but at a higher FP-rate (Figure 17).

With 3D Filet+CAD, the FP-rate ≥3 mm increased by 41% and 26% compared with 3D Filet and by 71% and 200% compared with 2D for Reader 2 and 3, respectively.

Concerning lesions ≥6 mm, both inexperienced readers using 3D Filet+CAD reached a sensitivity of 57% (20/35) at a FP-rate of 0.26 and 0.22, respectively, while the experienced reader had a sensitivity of 77% (27/35) at a FP-rate of 0.34 with 3D Filet (Figure 19).

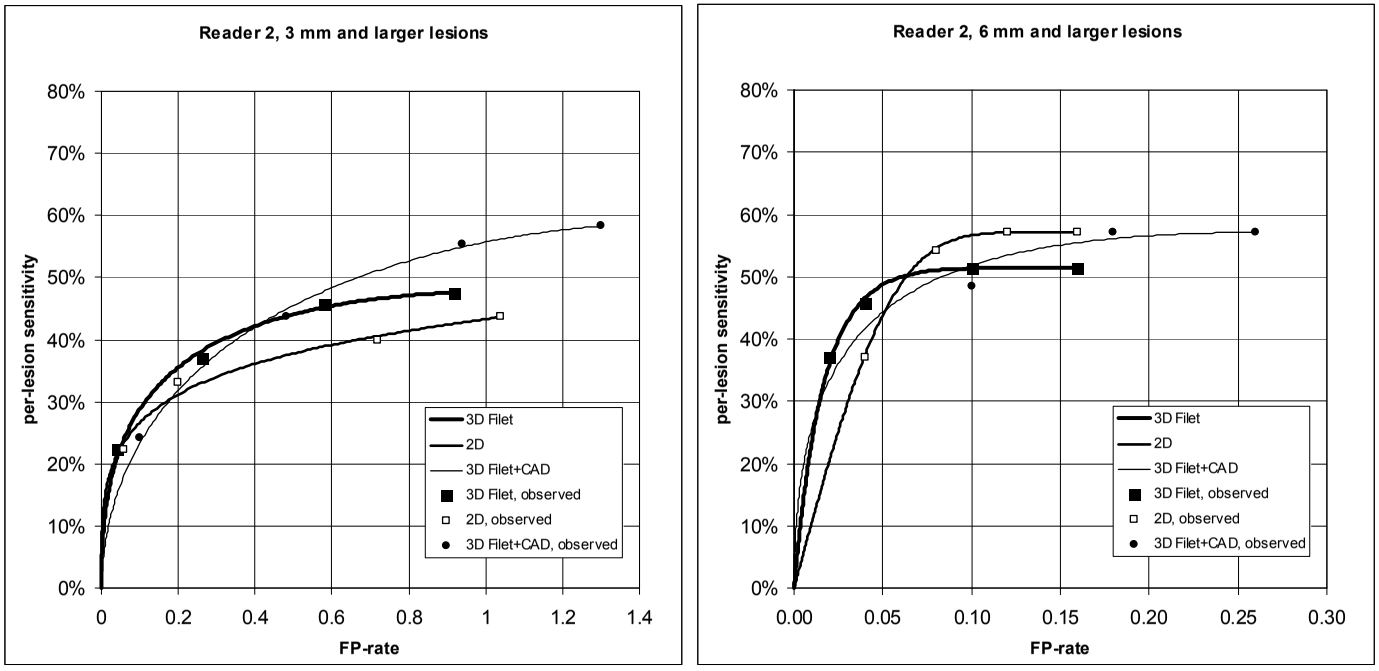

Figure 17. Free-response receiver operating characteristic (FROC) curves of Reader 2 (inexperienced) concerning lesions ≥3 mm and lesions ≥6 mm with 3D Filet, 2D and 3D Filet+CAD.

At a constant diagnostic confidence level, 3D Filet+CAD had higher per-lesion sensitivity for lesions ≥3 mm and ≥6 mm and higher FP-rate compared to 3D Filet. Also compared with 2D, 3D Filet+CAD had a higher sensitivity and higher FP-rate, except for lesions ≥6 mm where sensitivity with 3D Filet+CAD was identical to 2D, but at a higher FP-rate.

Footnote: per lesion-sensitivity = true positives findings/total number of lesions

FP-rate= false positive findings/total number of patients

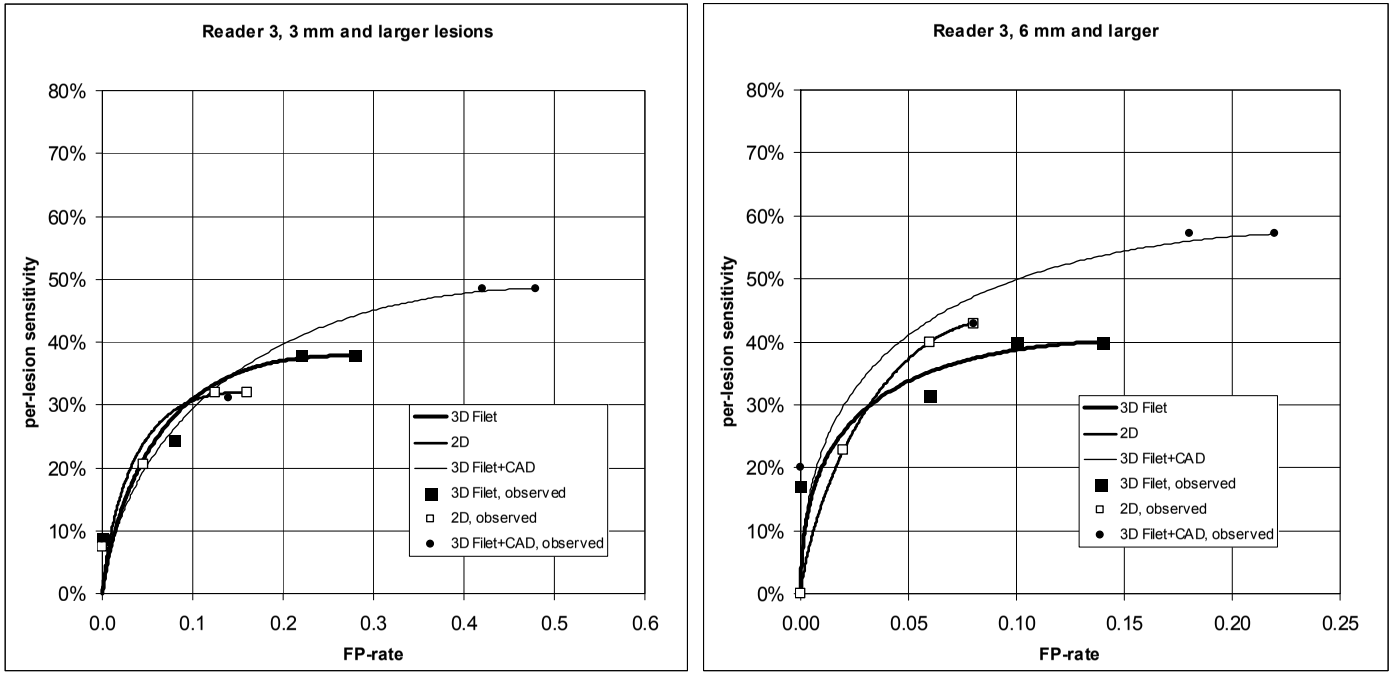

Figure 18. Free-response receiver operating characteristic (FROC) curves of Reader 3 (inexperienced) concerning lesions ≥3 mm and lesions ≥6 mm with 3D Filet, 2D and 3D Filet+CAD.

At a constant diagnostic confidence level, 3D Filet+CAD had higher per-lesion sensitivity for lesions ≥3 mm and ≥6 mm and higher FP-rate compared both with 3D Filet and with 2D.

Footnote:

per lesion-sensitivity = true positive findings/total number of lesions

FP-rate= false positive findings/total number of patients

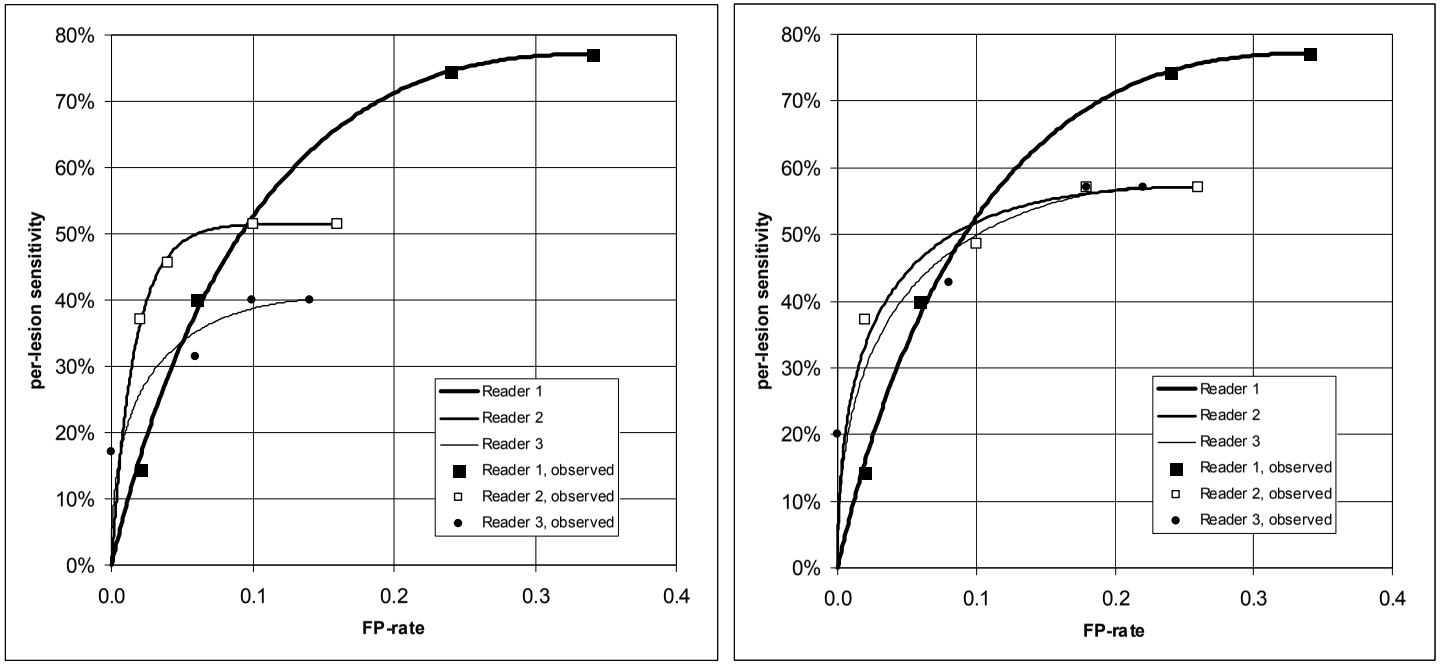

Figure 19. (a) Free-response receiver operating characteristic (FROC) curves for lesions ≥6 mm of the experienced (Reader 1) and the inexperienced readers (Reader 2 and 3) performing 3D Filet. (b) FROC curves of Reader 1 with 3D Filet and of Readers 2 and 3 with 3D Filet+CAD.
With 3D Filet+CAD the inexperienced readers (Reader 2 and 3) increased their sensitivity for lesions ≥6 mm compared to 3D Filet, reaching the value of 57% (20/35). The sensitivity of the inexperienced readers with CAD-assisted reading was, however, considerably lower than the per-lesion sensitivity of 77% (27/35) of the experienced reader (Reader 1) with CAD-unassisted 3D Filet.

Per-patient analysis

AUC values of the inexperienced readers concerning patients with or without lesions ≥6 mm, did not differ significantly between 2D or 3D Filet, or 3D Filet+CAD (Table 11).With 3D Filet+CAD, AUC of the inexperienced readers was similar to that of the experienced reader using 3D Filet (AUC=0.85, 95% CI: 0.73-0.96).

Table 11

Results of the receiver operating characteristic (ROC) analysis concerning patients with/without lesions ≥6 mm. Data shows the area under the ROC curve (AUC) of Readers 2 and 3 (inexperienced readers). 95% confidence intervals are shown within brackets.

	AUC Reader 2	**AUC Reader 3**
3D Filet	0.78 [0.64-0.92]	0.72 [0.57-0.87]
2D	0.73 [0.58-0.87]	0.69 [0.53-0.84]
3D Filet+CAD	0.78 [0.64-0.92]	0.78 [0.65-0.92]

Interpretation times

The additional interpretation times (median, IQR) used for CAD assistance for the inexperienced readers were as follows: 9 min (5-15 min) for Reader 2; 11 min (7-17 min) for Reader 3.

PAPER V

Radiation dose

For the standard dose protocol, the mean effective dose to the patients was 3.9 ± 1.3 (SD) mSv (range 1.6-6.8 mSv). For the low dose protocol, the mean effective dose was 1.03 ± 0.4 mSv (range 0.4-1.9 mSv). Thus, a 73.6% mean radiation dose reduction was obtained with the low dose protocol.

Image noise

Table 12 shows the mean image noise at anatomical levels 1-4 and the mean total image noise at all anatomical levels with the standard dose and the low dose protocol. The mean total image noise for the low dose protocol was 72.7% higher than for the standard dose protocol. With both the standard dose and the low dose, there was significantly more noise at level 4 (pelvis) and level 1 than at level 2 and level 3 ($p<0.05$).

Table 12 Image noise with the standard dose and the low dose at anatomical levels 1-4 and the total for all anatomical levels. Values are expressed by mean, median within parenthesis and ±SD.

	Standard dose	Low dose	p-value
Level 1	24.8 (24) ±6.2	44.9 (44) ±10.1	0.0001
Level 2	22 (20.9) ±4.7	39.2 (37.9) ±8.8	0.0001
Level 3	21.4 (19.5) ±6.6	37.6 (34.9) ±10.4	0.0001
Level 4	30.3 (30.7) ±6.1	48.3 (45.1) ±11.7	0.0001
Mean total	24.6 (23.3) ±4.3	42.5 (41.2) ±6.7	0.0001

Image quality with regard to all patients and all 4 anatomical levels

Table 13 shows the prevalence and severity of artefacts.

Table 13 Prevalence and severity of artefacts on 3D Filet images at any anatomical level with regard to all 48 patients. Data correspond to the number of images at standard dose (STD), modified low dose (MLD) and original low dose (OLD) techniques.

Cobblestone artefacts				*Snow artefacts*			*Irregularly delineated folds*		
	STD	MLD	OLD	STD	MLD	OLD	STD	MLD	OLD
No artefacts	153	11	2	183	171	8	177	90	18
Mild artefacts	36	119	125	9	21	85	14	85	95
Moderate artefacts	3	58	61	0	0	73	1	15	63
Severe artefacts	0	4	4	0	0	26	0	2	16

The number of images with cobblestone artefacts was significantly higher with the modified low dose and with the original low dose than with the standard dose ($p<0.0001$). Most of the cobblestone artefacts with modified low dose images were mild (62%, 119/192) followed by moderate severity (30%, 58/192). The manipulation of low dose images (modified low dose) did not significantly alter the presence of cobblestone artefacts compared with the original low dose images ($p=0.1$).

Moderate and severe "snow" artefacts were present on 51% (99/192) of original low dose images and on 4% (9/192) of standard dose images. Snow artefacts were intentionally eliminated on the modified low dose images, but mild snow artefacts were still present on 11% (21/192) of these images.

The number of modified low dose images with irregularly delineated folds was significantly higher compared with standard dose images ($p<0.0001$) and significantly lower compared with original low dose images ($p<0.0001$). Forty-seven percent (90/192) of the modified low dose images had no irregularly delineated folds. Slightly irregularly delineated folds were present in 44% (85/192) of the modified low dose images versus 7% (14/192) of the standard dose images The manipulation reduced the number of images with moderately or severely irregularly delineated folds, respectively, from 33% (63/192) and 8% (16/192) with the original low dose to 8% (15/192) and 1% (2/192) with the modified low dose.

Severe cobblestone or snow artefacts or severely irregularly delineated folds were present at all anatomical levels with the original and modified low doses in 1 extremely obese patient with a BMI of 41 and waist circumference of 142 cm,

and also in an obese patient with BMI of 30 and waist circumference of 116 cm. The moderate artefacts present at some anatomical levels with the standard dose occurred in the extremely obese patient mentioned above.

Image quality with regard to 3D images used in the polyp detection study
The image quality assessed by the 5 readers in the polyp detection study showed similar differences in the prevalence of artefacts between the standard and modified low doses and between the original and modified low doses, as those described in the overall image quality evaluation performed by the two radiologists in consensus (see above), except that also the difference in cobblestone artefacts at the modified low dose compared with the original low dose was statistically significant ($p<0.0001$) in the detection study analysis (Table 14).

Table 14 Image quality assessed by the 5 readers with regard to images with polyps (n=43) and without polyps (n=31) at the standard dose and original low dose relative to the modified low dose. Data correspond to AUC values.

	Standard dose versus modified low dose	p-value	**Original low dose versus modified low dose**	p-value
Cobblestone artefacts	.8524	<0.0001	.3417	<0.0001
Snow artefacts	.5691	0.4	.0703	<0.0001
Irregularly delineated folds	.7637	<0.05	.2284	<0.05

Polyp detection study
The JAFROC-1 analysis showed that the mean overall performance regarding polyp detection, as expressed by the reader-averaged figure-of-merit (FOM), was significantly higher at the standard dose than at the original low dose ($p=0.02$) (Fig.20). The image manipulation improved the performance, so that the difference between the modified low dose and the standard dose no longer reached statistical significance.

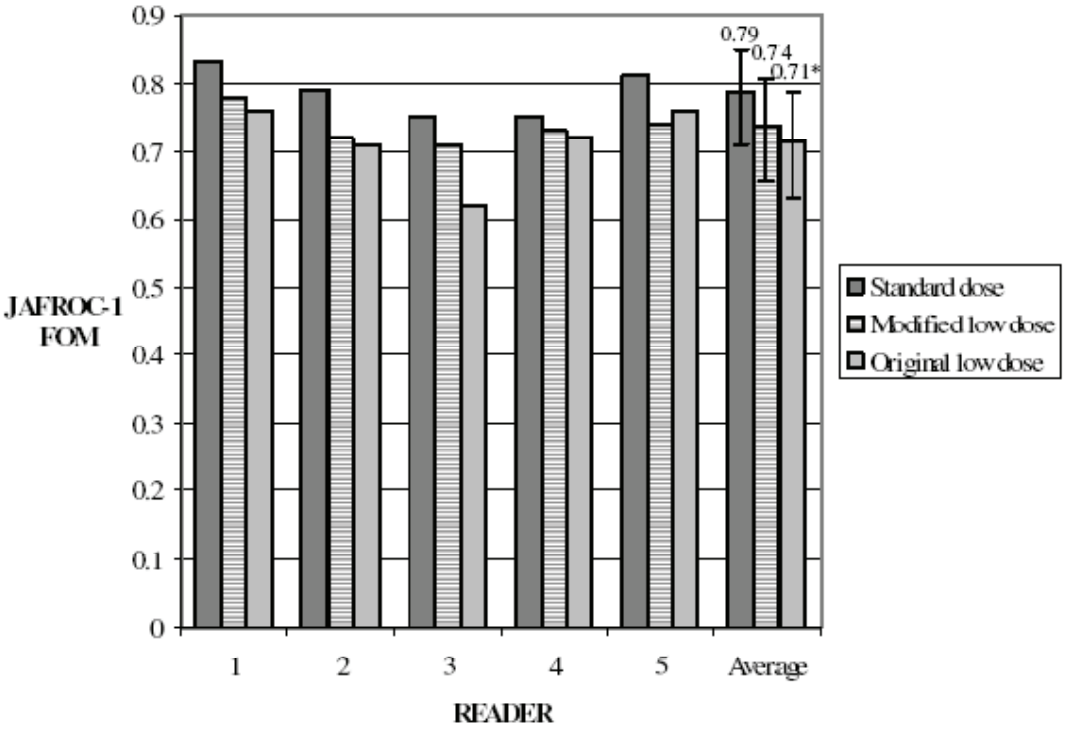

Figure 20 Results of JAFROC-1 analysis regarding polyp detection: Figure-of-merit (FOM) for each reader and technique and Reader Averaged FOM for each technique (standard dose, modified low dose, original low dose). Error bars represent 95% confidence intervals.
* Statistically significant difference (p=0.02) of Reader Averaged FOM between standard and original low dose images

FROC curves for each reader are shown in Fig. 21.

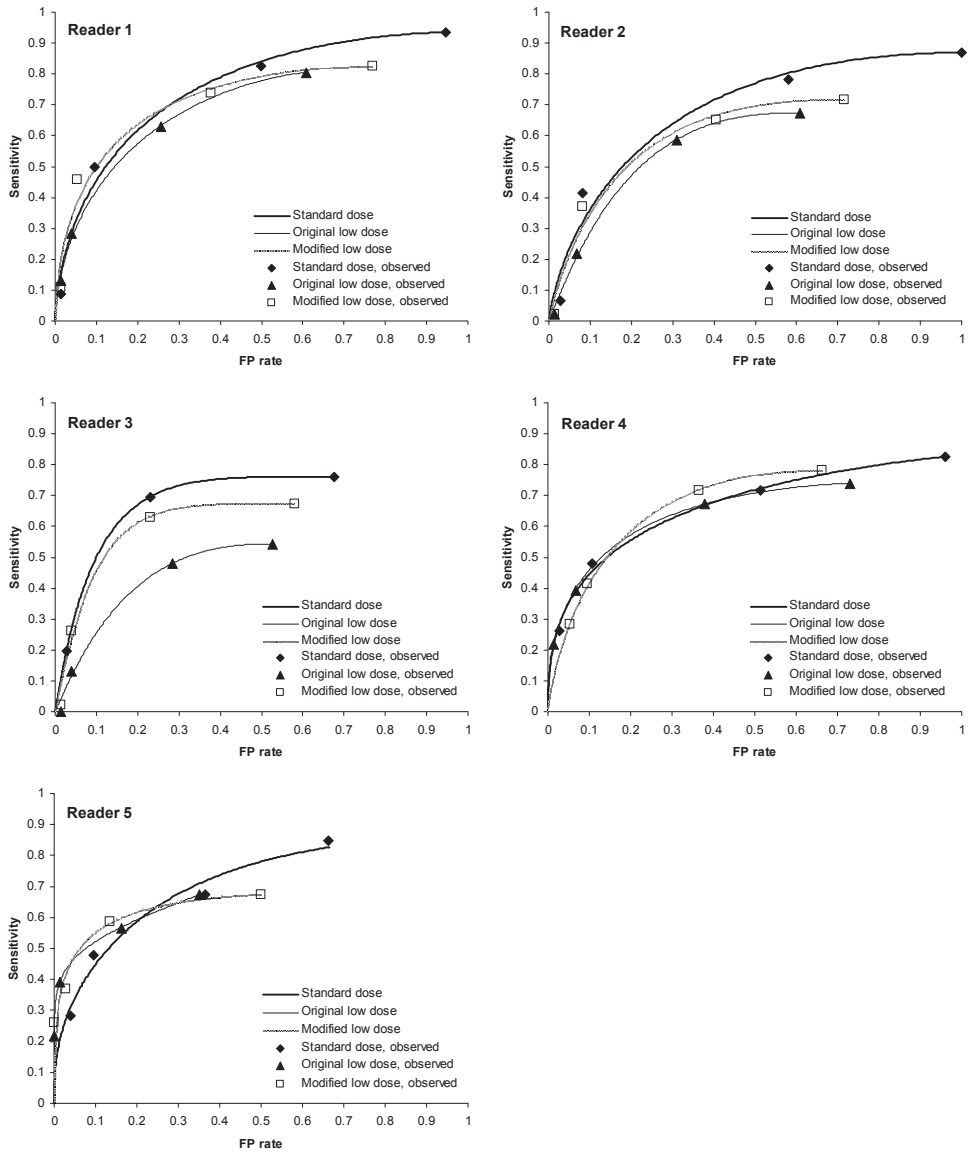

Figure 21 Free-Response Operating Receiver Characteristics (FROC) curves for readers 1-5 with regard to the standard dose, original low dose and modified low dose. Sensitivity (%) is represented on the y-axis and the false-positive (FP) rate (total of FP/number of images) is represented on the x-axis. The sensitivity and the FP rate at each of the four observed

operating points (corresponding to the four different thresholds used by the reader) are presented in the figure with symbols labelled "observed": symbols on the extreme left represent the highest degree of confidence (very likely a polyp), while symbols on the extreme right represent all the degrees of confidence.

FROC curves show that at the observed operating points, readers in general had, with the standard dose, a higher overall sensitivity and a higher FP rate compared with original and modified low dose images. There was a tendency among the readers to report slightly more lesions at the modified low dose than at the original low dose, resulting in slightly higher sensitivity and FP rate. The mean overall sensitivity, i.e. for all polyps, was 84.3% for the standard dose and it decreased to 73.9% for the modified low dose (p=0.03) and to 69.1% for the original low dose (p=0.002). With regard to polyp size subgroups, there was a statistically significant difference in mean per-polyp sensitivity between the standard dose and the original low dose (p=0.01) and between the standard and modified low doses (p=0.04) with regard to 3-5 mm polyps but not with regard to ≥6 mm polyps (Fig. 22).

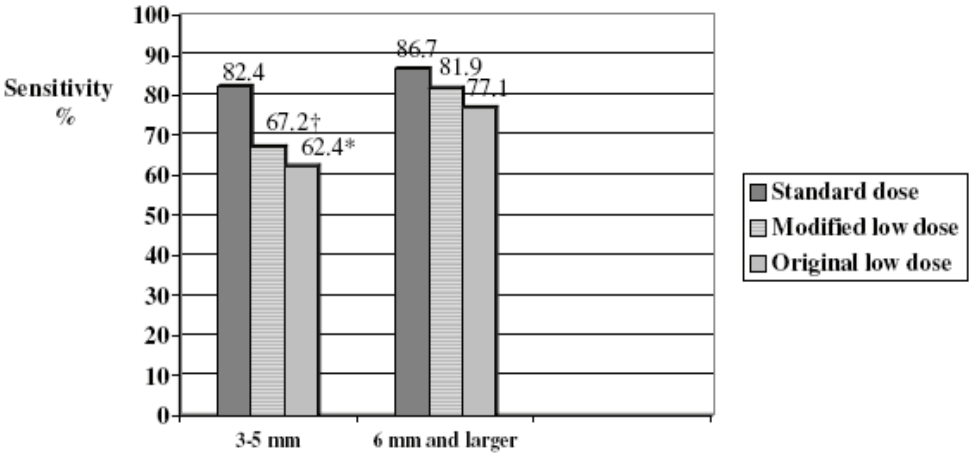

Figure 22 Mean sensitivity (Readers 1-5) for detection of polyps, stratified by size, with the standard dose, modified low dose and original low dose, respectively.
† Statistically significant difference in mean sensitivity for detection of 3-5 mm polyps between standard and modified low dose (p=0.04)
* Statistically significant difference in mean sensitivity for detection of 3-5 mm polyps between standard and original low dose (p=0.01)

The mean number of FP was significantly lower at the modified low dose compared with the standard dose (p=0.02), but no statistically significant difference was found between modified and original low doses (p=0.3).

DISCUSSION

The main results in the present studies will be combined and discussed briefly below and compared with findings in the literature.

1. AVAILABILITY, INDICATIONS AND TECHNICAL PERFORMANCE OF CTC IN SWEDEN (I, II)

The national survey performed in 2005 (**paper I**) reflected a relatively limited diffusion of CTC practice in Sweden, with CTC performed by one-third of the responding radiology departments, mostly in a small scale. The survey update (**paper II**) in 2009 shows an increased CTC availability in Sweden over a four-year period, and a parallel reduction of DCBE availability, although DCBE is still more widely available than CTC.

In our national surveys in 2005 and in 2009, about 40% of the responding radiology departments reported non-availability of a multi-slice CT scanner as major reasons for not implementing CTC. Although good CTC results have been obtained with single-slice CT equipment (120), the limited speed of image acquisition and cumbersome image post-processing are arguments for non-implementation of CTC using older equipment. In Sweden, as in other developed countries, most of single-slice scanners have been replaced by multi-slice scanners with appropriate software, providing a much wider platform for CTC implementation in the near future.

In those departments with CT equipment, lack of CTC training and expertise was the most stated reason for the non-implementation of CTC in 2005. Unlike many other new applications of CT, CTC includes several technical and interpretative aspects not previously handled by most radiologists. Since 2003, several workshops on CTC have been offered throughout Europe and the USA. The availability of training courses is reflected in our survey update in 2009 where the most stated reason for non-implementation of CTC in those departments where CT is available was lack of doctor´s time. Thus, as most of the departments currently performing DCBE also have CT equipment, the transition to CTC in radiology departments does not seem to depend only on availability of CT equipment. The indications for CT have increased

dramatically over the past decade; these include e.g. pulmonary embolism, acute abdomen, ureteric colic and cardiac imaging. This means increased competition for CT machine time, thus affecting the availability of CT for colorectal imaging and increasing the workload of the radiologist. In order to further implement CTC, a sufficient number of radiologists with interest in CTC should be recruited and trained. It seems desirable that radiology residents undergo basic training in CTC, by attending courses and by reading CTC in those centres where a high number of CTC examinations are performed. A reasonable compromise between educational demands and clinical efficiency might be achieved by primary reading by a resident and final reading by an experienced CTC specialist. New technical developments, such as CAD, may, in the future, improve the accuracy of inexperienced readers and may limit the need of double-reading, although CAD cannot substitute for training, as shown by **paper IV**.

Noteworthy, compared to 2005, less departments currently claim "Awaiting further scientific documentation on CTC" as a reason for not implementing CTC. While previous CTC studies on symptomatic patients have shown mixed results for large and medium sized lesions, recent large CTC trials on screening populations (42, 121) have shown good results for detection of adenoma or cancer of at least 1 cm with sensitivities similar to those of colonoscopy.

Compared to 2005, a larger number of departments perform CTC with state-of-the art techniques such as the use in all centres of MDCT with thin collimation, the use of carbone dioxide for bowel distension in 90% of the centres and intravenous contrast medium in 86%. In over 90% of CTC centres, a combination of 2D and 3D views are used for CTC interpretation. The technical parameters are thus in agreement with guidelines for CTC performance suggested by the European Society of Gastrointestinal Radiology (ESGAR) experts consensus in 2007 (51). Recent developments in CTC techniques, such as fecal/fluid tagging and CAD, have been suggested to improve CTC performance, but are at presently used by a minority of centres according to our survey.

Compared to 2005, the attitudes of radiologists seem now to have dramatically changed in favour of CTC. The majority of departments in 2009 believe that CTC will replace DCBE in the future, while a similar answer was given by only

half of the responding departments in 2005. This increased acceptance of CTC probably reflects the results of recent large multicenter studies showing high diagnostic accuracy of CTC as compared to colonoscopy with regard to large and medium-sized lesions (42, 43, 121).

In 2004, DCBE was stated by nearly half of the departments offering a CTC service as being the first-line colon imaging method in patients with clinically suspected colon cancer, despite the fact that this technique has been shown to be less accurate than both colonoscopy and CTC (23, 33). Although these figures may be biased because only radiologists were asked, it is apparent that DCBE is still a common examination. In fact, even in 2009 DCBE is still largely available, probably because of insufficient availability of endoscopists and insufficient large scale experience of CTC. As suggested by the literature and experts, it seems reasonable to completely replace DCBE by colonoscopy and/or CTC. Traditions and local imaging cultures among radiologists do not seem to be major obstacles for the transition from DCBE to CTC (51).

The most common indications for CTC both in 2005 and 2009 were failed whole-colon examination (colonoscopy or DCBE) and old age or physical disability, i.e. frail or immobile patients. These indications are in accordance with those of a national survey in the UK (55) and other published recommendations (122). Noteworthy, an increased proportion of departments perform CTC as “alternative to colonoscopy regardless of history”, probably as a consequence of the long waiting lists for colonoscopy.

Based on the results of the surveys, one may consider centralization of CTC to departments with the most experience of the procedure, in order to ensure high CTC diagnostic performance. However, the examination is easy to perform and the expected further spread of multi-slice CT scanners makes it suitable for decentralized performance. Nevertheless, it is mandatory that CTC is performed with state-of-the art techniques and that radiologists perform a defined number of CTC per year, in order to maintain CTC skills at an acceptable level. For centres with a limited number of CTC examinations, double reading by digital communication networks with more experienced centres could be helpful. Close collaboration with gastroenterologists and colorectal surgeons is also necessary for feedback and follow-up.

2. PRIMARY 3D FILET ANALYSIS VS PRIMARY 2D ANALYSIS BY INEXPERIENCED READERS (III)

In **paper III**, we have shown that primary 3D Filet analysis is comparable to primary 2D analysis in terms of lesion detection when used by inexperienced readers. Our results are thus in accordance with previous studies (66-68) performed on experienced readers, showing no significant difference in detection rate between 3D Filet or virtual dissection mode and 2D mode.

The experienced reader in our study had, with 3D Filet, a sensitivity of 80% for adenomas ≥6 mm and detected all 3 cancers. These results are similar to those of a previous study (66) where experienced readers used the same 3D Filet software. The inexperienced readers in our study, on the other side, missed one cancer with either review method and detected about half of the adenomas ≥6 mm with 3D Filet. In most of the cases, the missed lesions were medium-sized (6-9 mm) and were retrospectively visible in only one body position, due to residual fluid, fecal material or insufficient distension. This might have contributed to diagnostic uncertainty among the inexperienced readers. Clearly, bowel cleansing and distension are critical to the results of CTC, perhaps more so for inexperienced than for experienced readers.

As in previous studies, the sensitivities for small lesions were low for all readers (up to 60%), despite the use of state-of-the-art equipment. This suggests that factors other than CT hardware are responsible for the difficulties in identifying diminutive lesions.

Our results highlight the need to focus on training of inexperienced readers independently of the interpretation method. The least trained reader (Reader 3) had in fact lower detection rate with any review method compared with the more trained Reader 2, who had read 45 CTCs before start of the study. Interpretation of CTC examinations is difficult and has a long learning curve. Expert consensus recommend training with a minimum of 50 OC-verified cases (51), but studies have shown that for some individuals competence may not be attained even after 50 cases (57). A recent survey in the UK (59) showed that 41% of the radiologists performing CTC deemed their CTC training inadequate. Most of the patients undergoing CTC in the UK (55) and in Sweden are examined in non-academic hospitals. A study conducted in the UK (123) on gastrointestinal radiologists reading CTC in day-to-day clinical practice in a non-academic environment, and with no previous formal training, showed a

wide variability of performance with an overall sensitivity of 65% for large lesions, i.e. similar to the results of the least trained reader in our study. Efforts should be done to establish a standardized training program for novice readers with focus both on primary 2D analysis and on primary 3D analysis. Trained readers could be tested and certified prior to reading CTC in clinical practice, in order to guarantee a high quality level.

If patients with colonic lesions found at CTC are routinely referred to OC, the per-patient sensitivity and specificity is of interest. In identification of patients with clinically significant lesions with 3D Filet, the experienced reader had higher sensitivity (75%) than the inexperienced ones (65% and 50%, respectively). On the other hand, per-patient specificities for the inexperienced readers were high with both review methods, i.e. 87% with 3D Filet and between 87% and 90% with 2D. These findings suggest that only a limited number of patients without clinically important polyps would be unnecessarily referred for OC after CTC.

Since we aimed to perform a prospective evaluation of CTC, a separate blinded primary 2D analysis could not be performed by the experienced reader. Instead, immediately after 3D Filet, a complete 2D search was performed (3D Filet+2D) in order to evaluate if any lesion missed on 3D Filet could be detected on 2D. With 3D Filet+2D, sensitivity improved slightly for lesions ≥6 mm, while it increased significantly for small lesions. Of the large lesions missed on 3D Filet and on 2D, two were flat polyps. As previously reported (124), flat lesions are difficult to detect on CTC. In fact, 2 of the four flat lesions in our study were not seen even in retrospect.

Unlike the experienced reader, the inexperienced readers in our study did not perform a combined reading with complete 3D Filet and 2D in the same session. In the 3D Filet+2D analysis for the inexperienced readers we considered the true positive findings described by at least one of the reading methods. Our results show that a combined 3D Filet+2D analysis would improve per-lesion and per-patient sensitivity up to 15 percentage points for lesions ≥6 mm by the inexperienced readers and all cancers would be detected. Thus, it seems likely that to some extent, certain polyps are easier to detect with either 2D or 3D, depending on their location, size, shape and other characteristics, and perhaps depending on the reader. However, we do not know if decision-making would have been influenced by reading with both methods in the same session.

Complete reading in both 2D and 3D is time-consuming, but may be useful in training inexperienced readers, provided that appropriate feed-back is obtainable by double-reading together with more experienced radiologists (67), or by feedback from OC and surgery. Interestingly, complete reading in both 2D and 3D was stated to be the preferred reading method by the majority of CTC centres in 2009 (**Paper II**).

Other options to improve performance of inexperienced readers could be the use of faecal tagging, but further studies are needed to prove this. Slater et al (70) showed no significant differences in diagnostic performance of novices without or with faecal tagging, but few data sets were examined. From our own clinical experience, it is obvious that fecal tagging may facilitate the differentiation between fecal material and real lesions in many patients.

In contrast to previous studies with experienced readers, we did not find any significant difference in evaluation time between 3D Filet and 2D for inexperienced readers. This could probably be explained by the high prevalence of colorectal lesions in our patient group, since 68% of the patients had at least one lesion (mean 3.4 polyps) with a range of 1-12 polyps. On the other hand, primary evaluation with 3D Filet was significantly faster in patients without polyps than in patients with polyps compared with 2D, thus suggesting the potential advantage of 3D Filet in screening populations with low frequency of pathology.

Some limitations were present in our study.
First, there was a limited number of patients. However, a relatively large number of polyps were present in this symptomatic population, providing a reasonable study material for the purpose of the study.
Another limitation was that the inexperienced readers re-read the CTC datasets on 2D after 3D Filet. Despite reading the cases in random order and with an interval of at least 5 weeks between 3D Filet and 2D, and without knowledge of the OC results, it is possible that some recall-bias was present when re-reading the cases by 2D. This might have contributed to the marginally higher detection rate of polyps ≥6 mm with 2D compared with 3D Filet, although the difference was not statistically significant.
Another potential limitation was that the inexperienced readers did not receive any feedback during the course of the study. Furthermore, they read an average

of 8 cases per day which may have caused a certain degree of reader's fatigue. In clinical routine work, it is generally recommended not to schedule CTC reading for an entire work day, in order to avoid perception errors from fatigue.
Finally, we did not compare 3D Filet with 3D endo-fly-through. A drawback of virtual dissection and 3D Filet is the image distortion, especially in lower rectum, colonic flexures and caecum (63, 125). Endo-fly-through display may be more intuitive, but despite bidirectional evaluation, visualisation of all colonic mucosa may not be achieved unless a dedicated software showing "blind spots" is used (126). In contrast, unidirectional 3D Filet allows visualisation of all colonic mucosa, with potentially shorter reading times than 3D endo-fly-through. Thus, it remains to be determined which of these visualization techniques is to be preferred in clinical work.

3. EFFECT OF CAD ON PERFORMANCE OF INEXPERIENCED READERS (IV)

There are several commercially available CAD programs for CTC. Such programs have been tested by the producing companies before introduction in the market. However, the interaction of the CAD algorithm with readers must be clinically evaluated. Although a CAD algorithm might have a good stand-alone sensitivity, it is not known in which way and to what extent readers might benefit from it.

The CAD algorithm we used in **paper IV** had a very good stand-alone sensitivity for detection of clinically significant lesions, with sensitivity values comparable to those of an experienced reader. The median number of false positive CAD marks was, however, quite high, 8 per patient in prone as well as in supine, and false positives occurred in all patients without lesions at colonoscopy. These results are in line with previous studies in which other CAD algorithms were used (127-130), emphasizing the limitation of using CAD as stand-alone diagnostic method.

In **paper IV**, we showed that the inexperienced readers significantly improved their overall sensitivity with CAD-assisted 3D Filet in comparison with CAD-unassisted 3D Filet or 2D, with an increase in sensitivity of 10-11 percentage points compared to 3D Filet and of 14-16 percentage points compared to 2D. Sensitivities with CAD-assisted reading in our study were lower than in a

previous study (77) where inexperienced readers using CAD as concurrent reader applied to virtual dissection software had a sensitivity of 70% (compared to 58% and 48% in the current study), with lower number of false positives. The very low proportion of small lesions and the use of fecal tagging in that study might explain the better performance as compared with our results.
Also concerning lesions ≥6 mm in our study, there was an improvement in sensitivity for both inexperienced readers with CAD-assisted reading, which was statistically significant for the least experienced Reader 3. Interestingly, the sensitivity for the inexperienced Reader 2 for lesions ≥6 mm was the same with 3D Filet+CAD as with 2D, but with a higher number of false positives. A possible explanation for this could be the fact that Reader 2, who had some previous experience with CTC using 2D reading, probably was more familiar with this approach.

With CAD assistance, the difference in performance between the inexperienced readers for lesions ≥6 mm was eliminated, suggesting the potential beneficial role of CAD as a mean to reduce inter-observer variability, as previously suggested (75, 131).
FROC analysis indicated that the inexperienced readers assisted by CAD increased per-lesion sensitivity but also the number of false positives compared to CAD-unassisted reading. This suggests that although CAD facilitates the perception of lesions, characterization still remains a problem. The parallel increase of sensitivity and of the false positive-rate explains the fact that the overall diagnostic performance (i.e. the ability to distinguish between lesions and non-lesions) of CAD-assisted reading did not differ significantly from that of the CAD-unassisted reading. An increase in sensitivity for an observer can be obtained both by an increase in detectability (the FROC curve is shifted upwards) and by an altered reporting threshold confidence level (the curve is shifted to the right as more uncertain findings are described, causing an increase in the false positive-rate, as in our study). In the first case, the increase in sensitivity reflects a better differentiation between lesions and non-lesions, while in the second, it does not.

Despite the large number of false positive CAD marks that had to be scrutinized, the false positive-rate of the inexperienced readers concerning the subgroup ≥6 mm was low (0.26 and 0.22, respectively). The ability in distinguishing patients with clinically significant lesions (i.e. ≥6 mm) from patients without clinically

significant lesions did not significantly differ with CAD-assisted reading as compared to CAD-unassisted reading. This is in accordance with a previous study (131) where the high number of false-positives did not significantly impair radiologist´s specificity even when almost 30 false-positives CAD marks were shown. Thus, when using CAD as second reader it is our clinical experience that many of the false positive CAD marks can be easily dismissed, as it is often obvious that they represent e.g. fecal material, the ileocecal valve or the rectal tube. However, CAD as a second reader might be impractical and too time-consuming in those cases where the colon preparation is suboptimal, due to a lot of residual feces and thus a lot of CAD-marks to scrutinize.

Even with CAD assistance, however, the sensitivities of the inexperienced readers for lesions ≥6 mm were low (57%) compared with that of the experienced reader with 3D Filet (77%). A previous study showed that one day of training seems to improve sensitivity of inexperienced readers assisted by CAD integrated to primary 2D viewing software, but not of all readers and generally not to an adequate diagnostic level (73). Hock et al (77) showed a significant improvement of performance of inexperienced readers after training using virtual dissection. Further studies are needed to better understand the process of learning and inter-individual variation in perception and interpretation of CTC findings.

Although marked by CAD, the inexperienced readers did not describe some large lesions using 3D Filet without or with CAD assistance while they detected them on 2D. All of these lesions were pedunculated polyps (of which one proved to be a cancer, missed by one inexperienced reader). Probably the lack of familiarity with the distorted shape of a mobile pedunculated lesion on 3D Filet could have influenced their final decision. On the other hand, with CAD assistance the inexperienced readers detected one large lesion each that had been missed both on 2D and 3D Filet.

Using CAD as second reader applied on 3D Filet would probably be less time-consuming for inexperienced readers than performing a complete 3D Filet and a complete 2D analysis (**paper III**). The potentially beneficial role of CAD in the CTC learning process should also be mentioned, although this issue was not studied in the present thesis.

This study has some limitations. First, we did not use fecal or fluid tagging, which potentially could have improved diagnostic performance, although its effects on identification and characterisation of lesions using various CAD systems have not been studied. Second, a potential limitation was the fact that in the CAD reading session only CAD marks not corresponding to lesions previously registered on 2D or 3D Filet were analysed, while previous findings were not re-evaluated. Finally, the small number of inexperienced readers makes generalization of our results uncertain. Being the first study of CAD used on 3D Filet, our results should be confirmed in larger materials.

4. IMAGE QUALITY AND LESIONS PERCEPTION ON 3D CTC AT STANDARD AND LOW RADIATION DOSE (V)

In **paper V** we showed that a reduction of the effective radiation dose down to 1 mSv significantly affects image quality on 3D CTC, although this can be partly compensated for by changing opacity settings at 3D volume rendering. The perception of clinically significant lesions on 3D was not significantly reduced at low doses, while smaller polyps were difficult to see at low doses compared with the standard dose protocol. Our results suggest that patient doses at CTC can be lowered substantially, but further clinical studies are necessary to confirm our data.

By modifying the opacity map settings at 3D volume rendering on the low dose series, it was possible to drastically reduce "snow" artefacts and the irregularities of the delineation of the colonic folds on modified low dose images compared with original low dose images. However, even after manipulation, low dose images still had significantly worse image quality with regard to irregular folds compared with standard dose images, although most of these artefacts were classified as slight. Also cobblestone artefacts, i.e. the nodular pattern of the colonic inner surface, were mild on most of the modified low dose images. In our study, the manipulation of the opacity settings was arbitrarily and subjectively performed, because the virtual colonoscopy software we used in the study did not allow a predefined choice of specific numerical window (Hounsfield unit) threshold settings for opacity. Care should be taken when changing the opacity settings on volume rendering, as in the case of improper settings, shine-through artefacts and other artefacts might appear, degrading

image quality even more. Previous studies (91-93) have described the use of dedicated de-noising filters to smooth CT images at very low doses (less than 6.3 mAs). We did not use such filters in our study as we did not deem it essential at the dose levels we used. The role of such filters in clinical routine remains to be determined.

To our knowledge, our study is the first to assess image quality on standard and low dose CTC using VGC analysis (107). With this method, the observers are asked to express their confidence with regard to the visibility of diagnostically relevant structures, such as the colonic inner surface or folds. In previous studies, on the other hand, image quality on low dose CTC has been assessed simply by expressing an overall impression of the CTC examination (for example: not diagnostic, moderate, good or excellent for diagnosis) (89, 90, 96). With such an approach, the observer can choose any criteria he or she finds appropriate to judge image quality, which may add to the subjectivity. In addition, in VGC analysis data are analysed in a manner similar to ROC analysis, enabling a statistically valid method of evaluating ordinal data. VGC analysis might thus be more appropriate than previously used statistical methods where the ordinal grading rates were converted into numerical values, such as means (89, 98).

With regard to human perception of colonic lesions on 3D, our results show that the overall performance was significantly reduced with the original low dose since a significantly smaller number of lesions was detected compared with the standard dose. This caused a decrease in the mean overall sensitivity from 84.3% at the standard dose to 69.1% at the original low dose. The manipulation of low dose images, and thus the subjective improvement of image quality, improved the performance compared with the original low dose images so that the mean overall sensitivity increased to 73.9%. This shows that the smoothing effect of modifying opacity settings at low doses did not negatively affect the perception of polyps. The perception of what are commonly considered as clinically significant lesions, on the other hand, was not significantly different for the different dose levels. Our results are thus in agreement with previous studies where standard and low doses were compared, indicating that the detection of large and medium size polyps at low dose CTC is not impaired (89, 91, 96). In our study, however, the sensitivity of small lesions (3-5 mm) was significantly reduced at low doses (original low dose and modified low dose

images). Although the risk of developing cancer in diminutive lesions ≤5 mm is very low, there is no consensus among gastroenterologists on the management of patients with such lesions.

The mean effective dose for the low dose images in our study was comparable to previous studies with an effective dose of around 1 mSv in one body position (90, 92, 98). Although the CTC examinations in our study were performed using automatic tube current modulation, there was significantly higher noise at anatomical levels with higher attenuation, such as level 4 (pelvis) and level 1 (upper abdomen). This was due to the narrow range of mA settings selected for the standard dose protocol and even more so for the low dose protocol, which was necessary for the desired dose reduction.

There are some limitations to our study. Our results cannot be automatically generalised to a clinical setting as the readers did not perform a full colon evaluation with interactive virtual colon navigation and correlations of findings on 2D to further enhance detection and characterisation of lesions as polyps or faecal material. Thus, per patient sensitivity and specificity, which are important data when deciding whether or not to recommend a subsequent colonoscopy, could not be evaluated. Limitations in patient radiation dose prohibited double supine and double prone imaging. Nevertheless, our study is the first to compare low dose and standard dose CTC performed in the same individual, as opposed to previous studies where low dose series were simulated (89, 91, 96). When using a single body position, CTC differentiation between polyps and faecal material is limited (mobility of suspected faecal material cannot be confirmed, re-distribution of disturbing fluid and gas is not possible). The results of such an approach do therefore not reflect the true sensitivity and specificity of low tube current CTC. In addition, on 2D images it is very difficult for readers to remain unaware of which patient has received the low- versus the standard tube current, as the image noise will be obvious on low dose images. In order to avoid such bias, we therefore evaluated the perception of lesions on 3D only, without 2D correlation. An additional limitation for the generalizability of the study for 3D evaluation is that only perspective-filet view was tested.

CRITICAL ISSUES

In order to put CTC in a wider perspective together with other currently available diagnostic tests for colorectal neoplasms, some critical issues should be considered, as follows:

Patient selection

A structured selection of patients for colorectal examination, based on the presence and severity of symptoms, is necessary. While there is unanimous agreement that alarm symptoms such as rectal bleeding, iron-deficiency anemia and positive FOBT require further examinations, there is no consensus on how to manage patients with unspecific general symptoms such as increased meteorism, mild abdominal pain or altered bowel habits. For example, patients with unspecific bowel symptoms are, in Sweden, often examined with DCBE, which rarely shows any significant findings in such patients. The present trend is to replace DCBE with CTC. By referring patients with unspecific abdominal symptoms to CTC, there is a potential risk of unnecessarily creating worry in case of incidental extracolonic findings or incidental small polyps, which might require further follow-up, thus increasing costs and anxiety.

It is thus important to have guidelines on which patients should be investigated for suspected colorectal disease. Such guidelines can be of help for primary care physicians, and these guidelines must be known also by radiologists.

Selection of diagnostic method

Once selection of patients for further examination, such as suspected CRC, is made, it is important to select the proper diagnostic method for colorectal examination (rectoscopy, sigmoidoscopy, DCBE, OC, CTC or combinations thereof). The choice should depend on patient´s characteristics, such as severity of symptoms, age, comorbidity, family history of CRC, compliance, and on availability of diagnostic methods (local expertise, waiting lists).

Definition of clinically important lesions

There is still no general agreement on the importance of small polyps, e.g. how to handle colorectal lesions that are 5 mm or less at CTC. As CTC cannot give information on the histology of lesions (neoplastic or hyperplastic), lesion size is the critical parameter at CTC. The choice of diagnostic method is therefore

dependent on the need to detect lesions of a defined size. The definition of a clinically significant lesion, and the risk-stratification, must, however, depend not only on the lesion size per se, but also on the patient age, symptoms and comorbidity. Thus, detection of polyps below 5 mm in size is probably of minor importance in an 80-year old with clinical symptoms of colon cancer. If lesions smaller than 5 or 6 mm are important to look for in younger age groups, or in screening, the further development of CTC must be directed towards improved detection of such lesions.

Thus, agreement between radiologists and gastroenterologists on what constitutes important colorectal lesions in different patient groups is necessary, in order to make proper and wise use of the different available diagnostic modalities.

Follow-up of findings

If small polyps are detected and described at CTC, how should they be managed by the referring clinician? Should patients undergo OC and polyp removal? Or should they be followed up by CTC and at what time-interval? Present guidelines recommend that findings measuring less than 5 or 6 mm should not be reported at CTC, unless there are 3 or more such polyps. Follow-up strategies for colorectal lesions found at CTC should be designed and conveyed to the physicians, including the radiology community.

Incidental findings

Extracolonic findings are common and often require further investigation. The incidence of extracolonic findings must be taken into account when referring for a CTC. Agreements should be made between clinicians and radiologists on how incidental findings should be reported and handled.

As CTC becomes increasingly available, CTC radiologists should be aware of the above-mentioned problems while gastroenterologists and colorectal surgeons should be aware of the potential and limitations of CTC. A close collaboration between radiologists, gastroenterologists and colorectal surgeons, hopefully in a multidisciplinary setting, is therefore needed in order to propose guidelines that are evidence-based and that take local situations into consideration.

SUMMARY AND CONCLUSIONS

1. CTC is increasingly available in Sweden as an alternative imaging method for colorectal neoplasms, although DCBE is still performed by the majority of radiology departments. The most common indications for CTC are in line with published recommendations. The majority of departments perform CTC with state-of-the art techniques. DCBE should be replaced by colonoscopy and CTC, but the transition requires both human and economical resources.

2. Lesion detection and interpretation times by inexperienced readers were similar when using primary 3D analysis with Perspective Filet-view (3D Filet) as when using primary 2D analysis. With regard to clinically significant polyps (≥6 mm), combining the polyps detected with primary 3D Filet with those detected with primary 2D (3D Filet+2D) analysis, would improve detection rate of inexperienced readers, but not to the level of an experienced reader using 3D Filet alone.

3. CAD applied as second reader on 3D Filet increased the sensitivity of the inexperienced readers compared with unassisted 3D Filet and 2D, although it did not improve the overall performance since also the number of false positive findings increased. CAD seems thus to improve perception of lesions of inexperienced readers, but training on characterization of lesions remains vital. Sensitivity of inexperienced readers for lesions ≥6 mm with CAD-assisted 3D Filet did not reach the level of an experienced reader using unassisted 3D Filet.

4. Performing low dose CTC with reduction of the effective radiation dose down to 1 mSv, affects significantly image quality on 3D, but this can be partly compensated for by changing opacity settings at 3D volume rendering. Most of the artefacts on modified low dose images were in fact mild.The perception of clinically significant lesions on 3D, on the other hand, is not significantly reduced at low doses, compared with the standard dose technique.

FUTURE PERSPECTIVES

CTC is gaining increasing popularity both among clinicians and radiologists. Increased public demand for CTC can be expected, and it will likely continue to replace DCBE. However, improved training and further technical developments are necessary to increase its diagnostic accuracy, to shorten the learning curve and to reduce reading times. Such measures will probably accelerate its further diffusion. Training courses with test of reader ability and certification of CTC competence are possible scenarios.

Important technical advancements requiring further research include the limited or eliminated use of laxatives prior to CTC. One of the most uncomfortable parts of the CTC procedure is the rigorous colon cleansing (132). If CTC can be performed without conventional bowel preparation it could become a very appealing imaging technique, increasing patient compliance also for colon cancer screening. Some studies have shown the feasibility of performing CTC with reduced bowel preparation or even with no bowel preparation, while mantaining diagnostic accuracy. The residual fecal material can be "tagged" by the oral administration of contrast media, but the degree of tagging of feces might vary, resulting in a mixture of tagged and untagged stool. Although both fecal and fluid tagging are already used in clinical practice, the optimal tagging regime has not been determined.

CAD is another area where an important technical development is expected. Further improvements should be done on detection by CAD of non-polypoid lesions. Not all colorectal masses protrude into the lumen. Some masses can, in fact, appear as a local wall thickening or imitate a collapsed colonic region and therefore might not be detected by CAD (133). Minimally elevated (flat) neoplasms are difficult to detect at CTC and easily missed at OC. Also, it would be desirable to improve sensitivity of CAD for detection of lesions smaller than 6 mm, as there is evidence that multiple small adenomas in a patient may constitute a high risk for colorectal cancer development. The use of fecal tagging can be challenging for a CAD algorithm as the presence of high-density intraluminal contrast can artificially alter the density and the shape of adjacent material, such as polyps, which might then go undetected by CAD (133). The electronic removal of the fecal tagging agent, on the other hand, creates artifacts on the colonic inner surface which can cause false-positives at CAD. Only

preliminary studies have been performed when combining CAD and fecal tagging, showing high sensitivity and a moderate false-positive rate with CAD (133), however further larger studies are needed.

With increasing awareness of the radiation burden caused by the increasing use of CT, low-dose techniques will continue to develop for CTC. Developments of automatic dose modulation, taking individual patient parameters into account, will continue. Preliminary studies have shown promising results with CAD applied to low dose CTC with high sensitivity for large and medium-sized lesions (134) but low sensitivity for small lesions (135). Future studies will determine to what degree radiation doses can be lowered, depending on the target lesion size in different clinical settings.

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