CT colonography in faecal occult blood test positives

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Introduction and outline of the thesis

INTRODUCTION

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

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

Anatomy & pathology of the colon

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

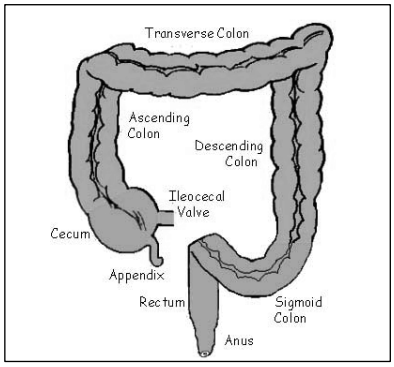

Fig. 1 Colonic segments

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

adenomas.[12,13] In fig. 2 a pedunculated and sessile polyp are shown, both with zones of carcinomatous cells.

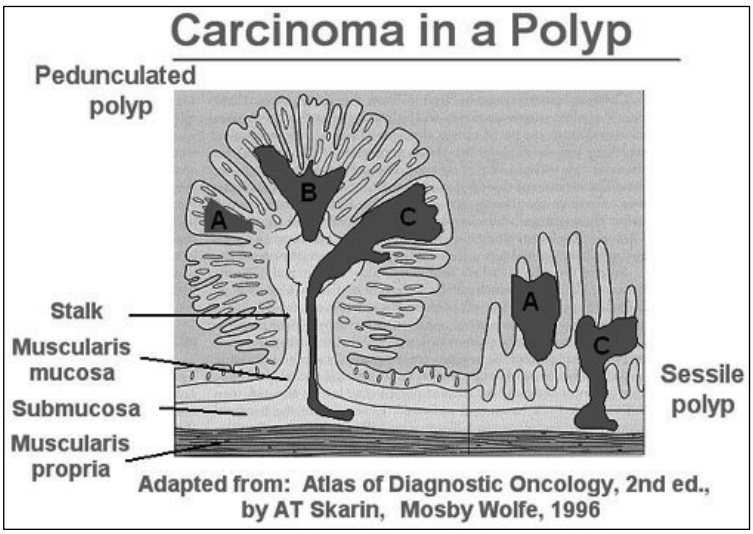

Fig. 2 Drawing of a pedunculated and sessile polyp. All dark areas represent zones of carcinoma. Zone B and C show invasion into the submucosa of the bowel wall and are therefore called invasive carcinomas. http://www.cancer.gov/

SCREENING ON COLORECTAL CARCINOMA

In several countries population screening programs for colorectal cancer have been started. The goal of cancer screening is to reduce mortality from this disease through early detection of cancer and its precursors, preventing or limiting the development of advanced disease. A number of tests are available for colorectal cancer screening. These screening tests are grouped into those that primarily detect cancer early and those that can detect cancer early as well as adenomatous polyps.[2]

The *first category*, tests that detect cancer early, comprises the stool tests: the guiac faecal occult blood test (G-FOBT), the immunochemical faecal occult blood test (I-FOBT) and the DNA stool tests. The G-FOBT detects blood in the stool through pseudoperoxidase activity of haeme of haemoglobin, while immunochemical-based tests react to human globin. The advantage of the FOBT as a screening test is that it is a very cheap and simple test and therefore suitable for population screening.[2,14] It has been demonstrated that G-FOBT significantly reduces disease-related mortality and is cost effective. Disadvantages are a low sensitivity and a high number of false positives (a PPV of less than 50% for carcinomas and adenomas).[15,16] Therefore a large part of the FOBT positive participants will receive an unnecessary colonoscopy with subsequent burden and risks on complications. A test performed in FOBT positives that can triage only the positives with relevant lesions that need colonoscopy could avoid those unnecessary examinations.

The *second category* consists of tests that do not only detect colorectal carcinomas, but also adenomatous polyps. To this category of tests belong the sigmoidoscopy, colonoscopy, double contrast barium enema (DCBE) and CT colonography.[2] A major advantage of colonoscopy that it is not only a diagnostic test but that polypectomy and biopsy can be performed in one examination. All other tests need a colonoscopy as a second procedure. Disadvantages are that colonoscopy is an invasive test that requires extensive bowel preparation, its performance depends on the skills of the endoscopist and colonoscopy is not a perfect reference standard, 2% of adenomas ≥10mm and 13% of adenomas between 6 and 9mm are missed.[17] A fairly new imaging technique of the colon is CT colonography. This technique is described in the paragraphs hereafter.

CT COLONOGRAPHY (VIRTUAL COLONOSCOPY)

In 1983 the first article was published on computerized radiology of the colon.[18] Until 1996 this new technique remained relatively undeveloped. Vining was the first to publish an article on Virtual Endoscopy after this period.[19] From that time the technique has developed enormously and a large amount of research has been performed in this field. Several studies have been performed to evaluate the accuracy of adenoma and carcinoma detection in symptomatic, surveillance and screening patients. Furthermore developments have been made to reduce the radiation dose and bowel preparation.

Technique of CT colonography

CT colonography is performed on a multislice CT scanner (MSCT), preferentially 16-slice or more MSCT. A small collimation can then be used which makes small polyps more easy to detect, while scanning times can be short (5-10 seconds for 64-slice scanners).[20,21] Most recent studies used a collimation of 1 mm and a tube current of 50 mAs or less when no intravenous contrast agent was administered. To distend the colon prior to scanning, air or preferably CO_2 has to be insufflated. An automated insufflator, instead of manual insufflation, can be used to for a pressure controlled inflow of CO_2.[21] For an optimal examination, scans have to be made in two positions, the supine and the prone position. When distension in one part of the colon is not optimal or a polyp is covered by faeces, the other position might help visualizing this colonic part.

Bowel preparation

For optimal imaging of the colon, the colon should be cleansed using laxative agents, or residual faeces has to be 'tagged' with an oral contrast agent.[21] Recent studies have shown that using an oral contrast agent only gives good results regarding image quality and polyp detection.[22-25] The two types of oral contrast agent that are used for tagging are iodine and barium. Barium mixes well with solid stool particles and does not cause diarrhoea.[24] A disadvantage is that barium mixes badly with aqueous solutions resulting in a more difficult interpretation of images. Iodine on the other hand mixes well with liquid stools and a homogeneous mixing can be obtained. Because most iodine contrast agents are hyperosmotic, patients will have diarrhoea after ingestion.[25]

Accuracy of CT colonography

CT colonography can be considered as a good alternative to colonoscopy in case of similar sensitivity and specificity in the detection of polyps and carcinomas. Two large meta-analyses have evaluated the accuracy of CT colonography.[26,27] The per-patient sensitivity of CT colonography for the detection of colorectal carcinomas was 96%, for polyps ≥10mm this was 85-93% and for polyps between 6 and 9 mm 70-86%. These were predominantly studies in symptomatic patients. Two recent studies that used CT colonography as a population screening tool for colorectal cancer, showed that the detection of colorectal neoplasia at CT colonography was nearly equal to that of colonoscopy. Kim et al. found that in two equally sized groups of patients the number of detected colorectal neoplasms was similar; 123 advanced neoplasms were found in the CT colonography group and 121 in the colonoscopy group.[28] Johnson et al. evaluated the accuracy of CT colonography in a screening population and found a per-patient sensitivity of 90% for the detection of adenomas and carcinomas ≥10mm and a specificity of 86%.[29] Up till now no randomized trial for screening with CT colonography has been performed and the effects on mortality reduction are not clear yet. One study has assessed the accuracy of CT colonography in FOBT positives (no screening participants). A high sensitivity of 87% for detection of advanced neoplasia was found.[30]

Extracolonic findings

Although a CT colonography is primarily performed for inspection of the colon, extracolonic structures such as the kidneys, liver and the aorta are also displayed. A consensus proposal has been published that classifies extracolonic findings in an E-RADS scoring system.[31] E4 findings are highly important findings that need intervention. In a systematic review it was found that 14% of all patients that received a CT colonography had extracolonic findings that needed follow-up, while Pickhardt et al. found a prevalence of 7.2% relevant lesions in screening participants.[32,33] Studies that evaluated the costs of extracolonic findings also reported different results on cost-effectiveness, some in favour of CT colonography and others not.[34-36]

Radiation dose

An issue that is often debated when CT colonography is considered as screening option for colorectal carcinoma is the risk on radiation induced cancer. Hall and Brenner calculated that the lifetime cancer risk induced by a CT colonography in a 50 year old patient is 0.14%.[37,38] Numerous comments were made on these calculations, for example that a linear no-threshold hypothesis was used which means that every minimal radiation dose could induce cancer. When BEIR VII data on health risks from exposure from low level radiation are used, a CT colonography with a 3 mSv effective dose results in a risk of 0.01-0.02% for a 50 year old and 0.006-0.008% for a 75 year old.[39] Currently, efforts are being made to reduce the radiation dose for CT colonography as much as possible.[40,41]

Reading methods and experience

Two different reading methods exist for reading a CT colonography examination; a primary 2D read with 3D images for verification or a primary 3D read using 2D for verification. Several studies have been performed to test which reading method is most effective. It

however appeared in most studies that there was no difference in sensitivity when using the primary 2D versus the primary 3D method.[42-44] In a study of Pickhardt et al. experienced readers performed significantly better in 3D reading.[45] An additional tool to improve the detection of polyps by a reader is the use of Computer Aided Detection (CAD). This software algorithm automatically detects polyps by identifying voxels along the wall of the colon and measuring the shape index of the wall to classify the wall locally into polypoid and nonpolypoid (i.e. normal) areas.[46,47] Previous studies have shown that especially inexperienced readers benefited from the use of CAD software and their sensitivity was significantly increased.[48-51] CAD used by experienced readers does not seem to result in a higher sensitivity.[50,52]

The amount of experience in reading CT colonographies to become an expert reader with a high sensitivity and specificity is not clear. It has been shown that after a training course with 50 CT colonographies a reader does not obtain an accuracy equal to an experienced reader.[53,54] Training does improve the accuracy of a reader, but the necessary amount of training cases to become an expert reader has not been established yet.

OUTLINE OF THE THESIS

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

In **chapters 5 and 6** the results of a large CT colonography triage study are described. Positive FOBT screening participants were asked to undergo a CT colonography before colonoscopy. In **chapter 5** we evaluated the effectiveness of CT colonography as a triage method after FOBT. The positive and negative predictive values of CT colonography, the number of extracolonic findings, the patient acceptance and the participation rate are presented. Furthermore we calculated the sensitivity and specificity of adenoma and carcinoma detection in **chapter 6**.

When CT colonography is used in a population screening setting it is important to minimize the radiation dose in order to lower the risk of obtaining radiation induced cancer. In **chapter 7** we made an extensive inventory of used radiation doses among all institutions that perform CT colonography for research purposes. The median radiation doses of CT colonographies performed for daily practice and screening purposes were calculated.

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

Chapter 10 we describe a study on matching of polyps found at CT colonography with polyps found at colonoscopy by expert readers. In all studies that evaluate the accuracy of CT colonography compared to colonoscopy, a matching procedure is performed. When this procedure is performed differently by CT colonography readers, this will have influence on the outcomes of accuracy. The purpose of the study in this chapter was to evaluate if differences in matching between expert readers exist.
In **chapter 11 and 12** we provide a summary, general discussion and implications for patient care and future research.

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