CT colonography for screening of patients at increased risk for colorectal cancer: accuracy, patient acceptance and radiation issues
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Chapter

Introduction and Outline of the Thesis

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Introduction

Epidemiology of colorectal cancer Invasive colorectal cancer was diagnosed in 9157 patients in the year 2000, and in the same year 4274 patients died as a result of colorectal cancer in the Netherlands (1). Although the mortality is stable over the last ten years, colorectal cancer incidence has increased (figure 1). After breast cancer, colorectal cancer currently is the second most diagnosed cancer for both sexes combined in the Netherlands, with a similar distribution among men and women. Patients with a personal or family history of colorectal polyps or cancers are well known to be at increased risk to develop colorectal cancer.

![Figure 1. Colorectal cancer incidence and mortality 1989-2000 (1).](image)

Figure demonstrates colorectal cancer incidence (●) and mortality (□) in the Netherlands (1989-2000). Incidence of colorectal cancer increases, but mortality is stable.

Etiology of colorectal cancer It has been estimated that as much as 95% of colorectal cancers arise from pre-existing adenomatous polyps (2), which may appear as pedunculated, sessile or flat masses. Adenomatous polyps are very common, and have an increasing incidence with age. It is believed that 5% of adenomas will progress to malignancy, a process that may take ten years (3). Environmental factors and genetic predispositions play a role in the development of colorectal cancer. Genetic predispositions in the form of inherited germline mutations lead to a very high risk of colorectal cancer in a selected subgroup of
patients. In addition there are less well defined patterns of colorectal cancer.

Environmental factors include diet (low in fibre, vegetables and folate and high in fat, red meat and alcohol) a sedentary life-style and cigarette smoking.

**Molecular genetics** Fearon and Vogelstein were the first to describe a molecular genetic model of colorectal cancer as a multi-step process of carcinogenesis, consisting of the accumulation of genetic mutations (4). There is a progressive accumulation of mutations in oncogenes and tumor suppressor genes, which underlies the stepwise progression of small tubular adenomas to large villous adenomas, and subsequently invasive carcinoma over time (figure 2) (5). Mutations that are involved in this process were described in the last twenty years, and this knowledge may provide new diagnostic opportunities such as the detection of mutant genes from faecal DNA (6-9). In addition, germline mutations in genes that are involved in the development of colorectal cancer have been identified in families with a high risk for colorectal cancer, which enables the identification of individuals that require follow-up.

**Figure 2.** Accumulation of mutations in genes that are associated with the development of colorectal cancer

<table>
<thead>
<tr>
<th>Normal epithelium</th>
<th>Hyperproliferative epithelium</th>
<th>Adenoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC mutations</td>
<td>k-ras mutations</td>
<td>DCC</td>
<td>p53 mutations</td>
</tr>
</tbody>
</table>

The loss of tumor suppressor genes (eg. P53, APC, DCC), the induction of oncogenes (k-ras), the loss of miss match repair genes (eg. hMLH1, BAT 26), and the induction of modifier genes (COX-2) offer growth advantages for the mucosal epithelium of the colon, resulting in the development of adenomatous polyps, and eventually, colorectal cancer (5, 55).

**Colorectal cancer prevention** Several studies have demonstrated that screening for and removal of colorectal adenomas results in a reduction of colorectal cancer incidence (10-15) and mortality (13; 16-24).

Controversy remains as to the appropriateness of and preferred methods for screening an asymptomatic population(25). There is, however, more consensus about the need for screening people known to be at increased risk, such as those with a personal or family
history of colorectal polyps or cancer. Many organizations recommend colonoscopic screening/surveillance for patients at increased risk for colorectal cancer (26), but even in these groups utilization of colorectal screening varies widely (27-32).

Colonoscopy is the preferred investigation for patients with a personal or family history of colorectal polyps or cancer. Disadvantages of colonoscopy are the attendant discomfort, a reason that is frequently mentioned to decline screening (33), and the small but definite risk for complications (34). Ideally, its use should be targeted at patients with polyps who are pre-selected by means of a less invasive test.

Innovative screening methods Two fundamentally different new approaches to detect colorectal adenomas and cancer have emerged in the last ten years and may benefit screening for colorectal cancer in the future: CT colonography, aimed at the detection of morphologic abnormalities of the colon mucosa, and genetic stool tests, aimed at the detection of common mutations of genes in colorectal adenomas and cancers.

CT colonography This method enables the examination of the entire colon mucosa with two-dimensional (2D) and three-dimensional (3D) high-resolution images. The CT colonography examination is performed with a spiral CT scanner and comprises the scanning of the air-distended colon in supine and prone position after use of thorough laxative bowel preparation. Colon distension is achieved via rectal insufflation of room air or carbon dioxide and is preceded by an intravenous injection of hyoscine butyl bromide (buscopan) or glucagon to reduce bowel spasms.

The role of CT colonography in colorectal cancer screening or surveillance, would be the pre-selection of patients with polyps that would profit from further endoscopic diagnostics or treatment. As adenomas ≤ 5 mm and 6-9 mm rarely contain high-grade dysplasia (0.9% and 4.4%, respectively(35)) when compared to adenomas ≥ 10 mm (16.2%(35)), it is generally agreed to focus on large polyps in the framework of screening (36). Accordingly, pre-selection with CT colonography should be primarily aimed at patients with large polyps.

The accuracy and patient acceptance of CT colonography has been repeatedly reported in the past 9 years. Except for two studies that were hampered by sub optimal technique and learning curves (37; 38), many early reports were enthusiastic: the sensitivities and specificities for patients with large polyps ranged from 75% to 100% and 73% to 96%, respectively (39-42).

Early studies on patient acceptance of CT colonography demonstrate conflicting results.
with some indicating that CT colonography is preferred by patients and others indicating the opposite (43-48). Most likely this variability is the result of differences in provision of premedication for CT colonography (buscopan/glucagon to reduce bowel spasms or not) or for colonoscopy (sedatives and analgesics or not).

The existing studies on accuracy and patient acceptance are predominantly performed in patient groups that partly comprised subjects with positive screening tests and subjects that were primarily evaluated for symptoms. Such high-risk patients are known to have a higher prevalence of (pre)malignant colorectal polyps and a more severe disease spectrum than average risk or increased risk patients. Accuracy studies in high risk patients may produce higher sensitivity results due to the fact that in these patients generally more and larger polyps are present (39-41). Studies on patient acceptance in such populations may have an influence on the preference as it concerns patients that are aware of the fact that colonoscopy will be required to remove the already diagnosed abnormality. As for them the need for pre-selection is unnecessary, there will be a tendency to prefer colonoscopy.

Therefore the available accuracy and patient acceptance results may not apply to patients at increased-risk or average-risk for colorectal cancer, the populations that may benefit most from implementation of CT colonography.

The present thesis comprises studies on the accuracy and patient acceptance of CT colonography in patients that are screened for personal or family history of colorectal polyps or cancer. Additionally, several studies address key issues that surround CT colonography at present.

**Genetic stool assays** Based on the premise that mucosal DNA sheds into the feces, investigators have demonstrated the feasibility to detect mutated genes in stool that are commonly present in colorectal cancers (figure 2). Although this method is an attractive non-invasive screening method, its use is currently hampered by technical limitations (6-9).

Future studies focusing on the ability of genetic markers in stool to identify patients with colorectal adenomas and cancers in a screening setting will indicate the role of this technique in colorectal cancer prevention.

**CT colonography: current issues in CT colonography research** As stated above, the available data on the sensitivity and specificity of CT colonography may not apply to patients that are screened for a personal or family history of colorectal polyps or cancer (increased risk). The studies presented in this thesis aim to investigate the ability
to identify patients with large polyps with CT colonography and its patient acceptance in consecutive patients at increased-risk for colorectal cancer. As utility of colorectal cancer screening and surveillance varies widely among patients with a personal or family history of colorectal polyps or cancer, this population might benefit from an accurate and non-invasive pre-selection method.

**Accuracy** To date, colonoscopy is the gold standard for the detection of colonic polyps and therefore virtually all studies that investigate the diagnostic value of CT colonography use this method as reference. It is widely known, however, that this test is imperfect and the miss rate for large polyps as determined by back-to-back colonoscopy is estimated to be 0-6% (49; 50). In fact, the miss rate may be even higher because these proportions are the result of studies in which colonoscopy is compared with a second colonoscopy, which has the same limitations. Due to the miss rate of colonoscopy the sensitivity and specificity of CT colonography may be underestimated, because an unknown number of CT colonography findings may be labelled false positive while in fact these are true positive polyps that were missed with colonoscopy.

**Patient acceptance** Patient acceptance is a major determinant of the effectiveness of colorectal cancer screening, and has been the most important anticipated advantage of CT colonography over colonoscopy. Comparison of preferences between CT colonography and colonoscopy may reflect the relative acceptance of CT colonography and may indicate whether attendance rates may be higher or lower than for screening colonoscopy.

The majority of available preference comparisons of CT colonography and colonoscopy are performed in high-risk patients and may not apply to patients that are screened for an increased-risk of colorectal cancer (43-48). Moreover, these studies all measured preferences within three days after the examination under stressful circumstances (hospital, physical discomfort, aftereffects of sedatives)(43-48). As adverse reactions towards tests tend to temper in time (47), however, preferences might preferably be assessed some time after the examinations. It can be expected that the last measurement is a more faithful reflection of future behavior, than measurements obtained directly after the examinations.

**Radiation dose** Current estimates demonstrate that 0.6-1.8% of the cumulative risk of cancer to age 75 could be attributable to diagnostic X-rays, among which CT imaging (51). When CT colonography is to be implemented in colorectal cancer screening and surveillance, and high numbers of patients are exposed to ionizing radiation, the number
of patients with CT-induced cancer may increase. The risk due to radiation is uncertain, and must always be considered in the light of the potential benefit of the diagnostic procedure. In a clinical setting the benefit generally outweighs the risks. In case of screening, this balance is more delicate due to the low potential benefit.

The risk to induce a fatal cancer due to exposure to ionizing radiation relates proportionally to its magnitude, and is dependent on the patient’s age. For CT colonography the generally used effective dose is unknown and consequently no estimation of the radiation related risk associated with CT colonography can be made.

To reduce radiation risks to the bare minimum, investigations should be focussed on the lowest dose that is compatible with polyp detection. Although it has been anticipated that the effective dose for CT colonography can be substantially decreased due to the high contrast between air and the bowel wall, no data exist on the lowest dose that can be used without affecting the ability to detect polyps.

**Review of CT data** CT colonography is performed with a spiral CT scanner that produces volumetric data. These data can be reviewed with 2D and 3D methods. Generally, radiologists review the data either primarily with two-dimensional or with three-dimensional methods. The *primary 2D* review method comprises the evaluation of axial CT images and the selective use of 3D endoluminal images to elucidate difficult anatomical structures. The *primary 3D* review traditionally comprises volume rendered forward and backward 3D movies, combined with 2D images for additional information.

The endoluminal 3D review method that comprises this method is adopted from conventional colonoscopy, and suffers from the same limitations: the colon surface that is situated between haustral folds cannot easily be visualized (figure 3). The resulting blind spots are either neglected, or require additional time-consuming interactive viewing. The primary 3D review method is infamous for the long review times, which can be up to 40 minutes (52). Development of time efficient primary 3D review methods may be beneficial for the performance of CT colonography.

A prior study demonstrated that 2D review combined with selected conventional 3D endoluminal viewing to elucidate difficult structures results in a similar performance as an entire 2D and an entire ‘conventional’ 3D review (figure 3) together(53). On the other hand, some small studies indicated that detection of polyps is more accurate with comprehensive 3D methods than with 2D methods, when corrected for the visibility of lesions (54). Based on practical grounds, the majority of researchers currently use primary 2D methods to review CT colonography. As it can be expected that the accuracy of CT colonography is dependent
on the visualization method, development of new comprehensive time-efficient display modes is crucial.

Outline of the thesis

In chapter 2, we evaluate the diagnostic value of CT colonography in consecutive patients with a personal or family history of colorectal polyps or cancer. In this study a second-look colonoscopy was performed when large false positive findings could not be explained based on review of the videotaped colonoscopy. In this way we were able to place the results with regard to identification of patients with large polyps of CT colonography in the perspective of the results of colonoscopy.

Figure 3. Schematic display of conventional endoluminal 3D display mode for CT colonography.

In chapter 3, we investigated the patient preferences for either CT colonography or colonoscopy in the same patient group, in a five-week follow-up study. Additionally we performed multivariate analyses to elucidate the determinants of preference. With this study we aimed to gain insight in preferences of patients after immediate inconvenience due to the examinations had disappeared and the patients had most likely returned to normal life. Additionally, we were interested in the possible changes in determinants of preference that may occur in the follow-up time.

Chapter 4 is an inventory of effective doses used for CT colonography in reported studies, updated by information from the departments that published these studies, as obtained by questionnaires. In this study we additionally analyzed trends in time based on a literature study. The outcome of this study may be of importance for patients, physicians and public
health authorities when in the future decisions on implementation must be taken, and
risk estimates must be available.

In chapter 5 we investigate the possibility to reduce the effective dose for CT colonography
in identical patient groups. Using a simulation method we were able to produce scans of a
lower effective dose based on the raw transmission measurements. This study investigated
effective doses in the range that was achievable on CT scanners at the conception of this
study.

Chapter 6 is directly related to the result of chapter 5. As polyp detection rates were unimpaired
at the lowest dose that was assessed, we wanted to gain insight in the lowest (theoretical) dose
that is compatible with unimpaired polyp detection. Therefore, using a comparable simulation
method, this study deals with doses ranging from medium to ultra-low.

In chapter 7 we validated an innovative primary 3D review method, the unfolded cubic
projection, which was developed by the Pattern Recognition Group from the Technical
University of Delft. In this study we compared time efficiency and colon surface visibility
between the unfolded cubic projection and a conventional 3D display mode.

Chapter 8 was performed as the unfolded cubic display mode passed the test of chapter
7. In this study we compared accuracy and inter-observer agreement between the unfolded
cubic projections and the current standard for CT colonography data review, the primary
2D review method.
References


