CT colonography as surveillance technique for patients at increased risk for colorectal cancer
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Introduction and Outline of the Thesis
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Introduction

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

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

![Figure 1. Adenoma-Carcinoma Sequence](image)

The adenoma-carcinoma sequence is a well-described pathway of mutational events that characterize the transition from normal colon epithelium to premalignant adenoma and then invasive adenocarcinoma. This process may take up to 10 to 15 years.

Current data indicates that over ninety-five percent of colorectal cancers arise in adenomatous polyps which develop and grow slowly in the colon and take approximately ten to fifteen years to turn into a carcinoma, this is called the adenomatous-carcinoma sequence (figure 1) [6, 7, 8].
Although the occurrence of adenomas is relatively frequent (twenty to thirty percent) in individuals fifty years and older [9], it has been estimated that only a small proportion of adenomas will eventually develop into a carcinoma [10]. Size is an important predictor of malignancy (table 1) [11-14].

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>Prevalence (%)</th>
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<tr>
<td>≥20</td>
<td>30&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
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<tr>
<td>≥10</td>
<td>10&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
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<td>&lt;10</td>
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<td>&lt;6</td>
<td>0.1&lt;sup&gt;4&lt;/sup&gt;</td>
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<sup>4</sup>Waye JD et al. Am J Gastroenterol 1988; 83:120-122

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

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

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

Figure 2. Reconstructed three-dimensional CT colonography image

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

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

**Figure 3. Example of two flat adenomatous polyps**

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

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

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

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

**Outline of the Thesis**

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

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