COLORECTAL CANCER PREVENTION

Surveillance of adenoma patients

towards more efficient guidelines

ELSE-MARIËTTE BEATRICE VAN HEIJNINGEN

Colorectal Cancer Prevention

Surveillance of adenoma patients – towards more efficient guidelines

Else-Mariëtte Beatrice van Heijningen

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Surveillance of adenoma patients – towards more efficient guidelines

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Chapter 1

General introduction

Colorectal Cancer

Colorectal cancer epidemiology

Colorectal cancer (CRC) is a significant public health problem. It is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world.[1] In the Western-world it even ranks third or second as cancer-related death in both men and women. [2 3] Worldwide, approximately 1.4 million new colorectal cancer cases were diagnosed and almost 700,000 related deaths occurred in 2012. [4] The burden of CRC is expected to increase to more than 2.2 million new cases and 1.1 million cancer deaths by 2030. [1] The increase is linked to ongoing societal and economic developments in many low- and middle-income countries. Highly developed countries where rates remain among the highest in the world, show stabilizing or decreasing trends. In the Netherlands, 13,043 people were diagnosed with CRC in 2013 increasing to 15,192 in 2014 with introduction of population screening, and almost 5,000 people die per year from this disease. [5] The incidence of CRC increases with age and is higher in men compared to women. [5 6]

Natural history

Most colorectal cancers develop from benign precursor colonic lesions or polyps. The majority of cancers (65-95%) are believed to develop through the so-called adenoma-carcinoma sequence: from adenomatous polyps (adenomas) to cancer *(Figure 1,* [7]*)*. Estimated progression time from adenoma onset to cancer is approximately 20 years. [8 9] A minority of cancers develops through alternative pathways, in particular through the serrated neoplasia pathway (5-33%). [10]

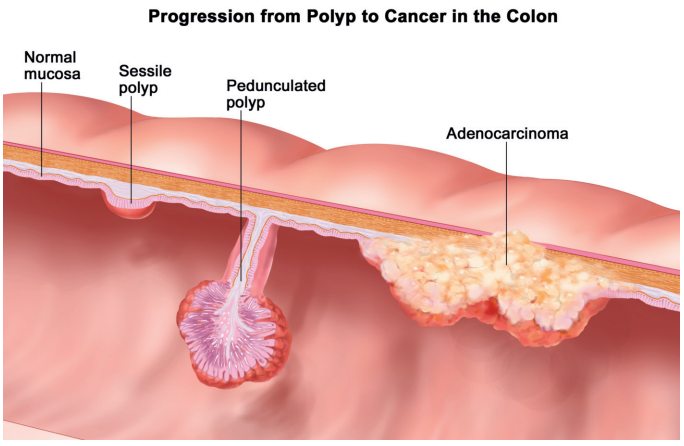

Figure 1. Schematic overview of the adenoma-carcinoma sequence. For the National Cancer Institute © 2018 Terese Winslow LLC, U.S. Govt. has certain rights. [7]
With permission.

The shape of adenomas can vary from pedunculated (stalked) to broad-based, flat or depressed. Adenomas can have tubular (<25% villous component), tubulovillous (25-75% villous component), or villous (>75% villous component) histology, and vary in size. Adenomas are generally classified as having low-grade or high-grade dysplasia. [11-13] Images of adenoma histology and dysplasia are presented in *Figure 2.* [14 15] An adenoma large in size (≥10 mm), with (tubulo)villous histology, or high-grade dysplasia (HGD) is assumed to have elevated risk to develop into CRC. An adenoma with at least one of these characteristics is therefore called an advanced adenoma. An adenoma without these characteristics is called a non-advanced adenoma. Approximately 30-50% of people will develop one or more adenomas throughout their life, however only about 3-5% of people develop CRC. [6 16]

Serrated lesions include sessile serrated adenoma or polyps (SSA/P), traditional serrated adenomas (TSA) and hyperplastic polyps, [17] and are morphologically characterized by a serrated ("saw-tooth") architecture *(Figure 3,* [15]*)*. Hyperplastic polyps were originally believed to be benign, however over the past years this opinion has changed. Now some pathologists believe that a subset of hyperplastic polyps can develop into SSA/P that are considered to have malignant potential. [10 18] The serrated neoplasia pathway was first described in 1996, [19] and only found traction over the last 15 years. SSA/P have only recently accurately been captured and reported in community practice. The study on which this thesis is based was initiated prior to that time and captures data starting in 1990 – 2002. Therefore serrated lesions are not specifically discussed in this thesis.

CRC staging

The progression from adenoma to carcinoma includes invasion through layers of the colon wall. The stage of cancer depends on the depth of invasion (and spread of malignant tissue). From the inside colon (lumen) to the pericolorectal tissue, the layers of the colonic wall are: mucosa, lamina propria, muscularis mucosae (thin muscle layer), submuscosa, muscularis propria (thick muscle layer), subserosa, and serosa. Cancers are classified on the basis of 1) the depth of invasion of the primary tumour, 2) presence of metastases in lymph nodes, and 3) presence of metastases in distant organs (TNM-classification). Based on this classification cancer stages are defined by the American Joint Committee on Cancer (AJCC). Adenomas or polyps are lesions that do not invade further than the lamina propria or muscularis mucosae, including carcinoma in situ. Stage I cancers are local tumours that invade into the submucosa or muscularis propria

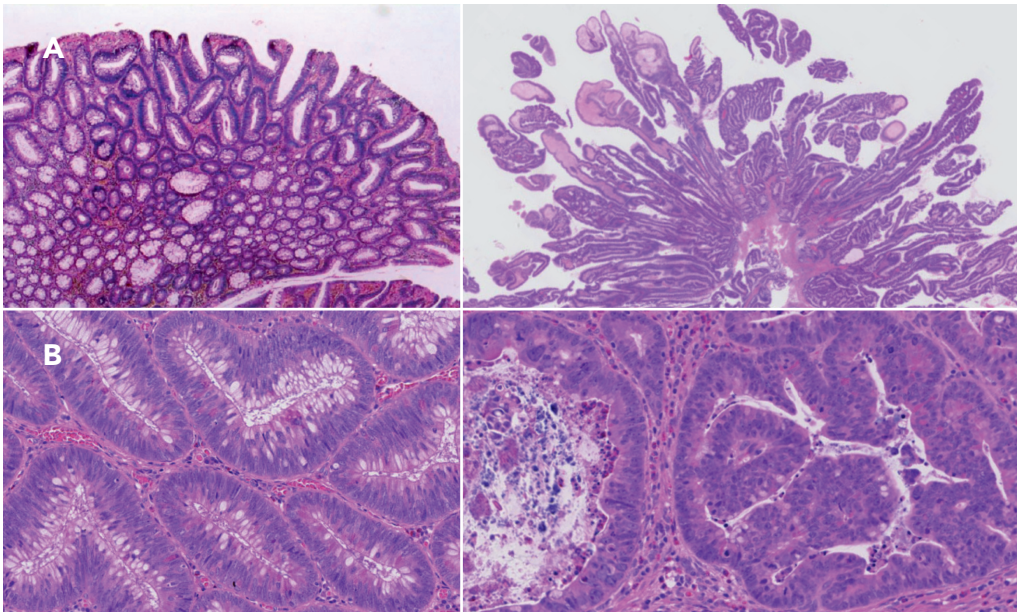

Figure 2. Microscopic images of (A) histological types of adenomatous polyps: tubular adenoma (left) [14] *and villous adenoma (right)* [15]*; and (B) adenomatous tissue with low-grade dysplasia (left) and high-grade dysplasia (right)* [15]*. With kind permission.*

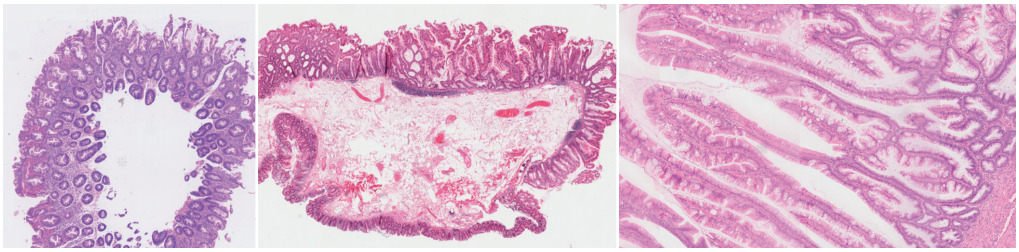

Figure 3. Microscopic images of serrated polyps: hyperplastic polyp, sessile serrated lesion, and traditional serrated adenoma [15]*. With kind permission.*

(muscle layer). Stage II cancers invade the (sub)serosa or pericolorectal tissues and potentially penetrate the outer layer of the colorectum. Stage III cancers affect one or more lymph nodes. Stage IV cancers have metastases in distant organs [13]. Images of cancer stages I-IV are given in *Figure 4.* [7] In the Netherlands, the 5-year survival ranges from 94% in patients with stage I cancer to approximately 12% in those with stage IV cancer. [5]

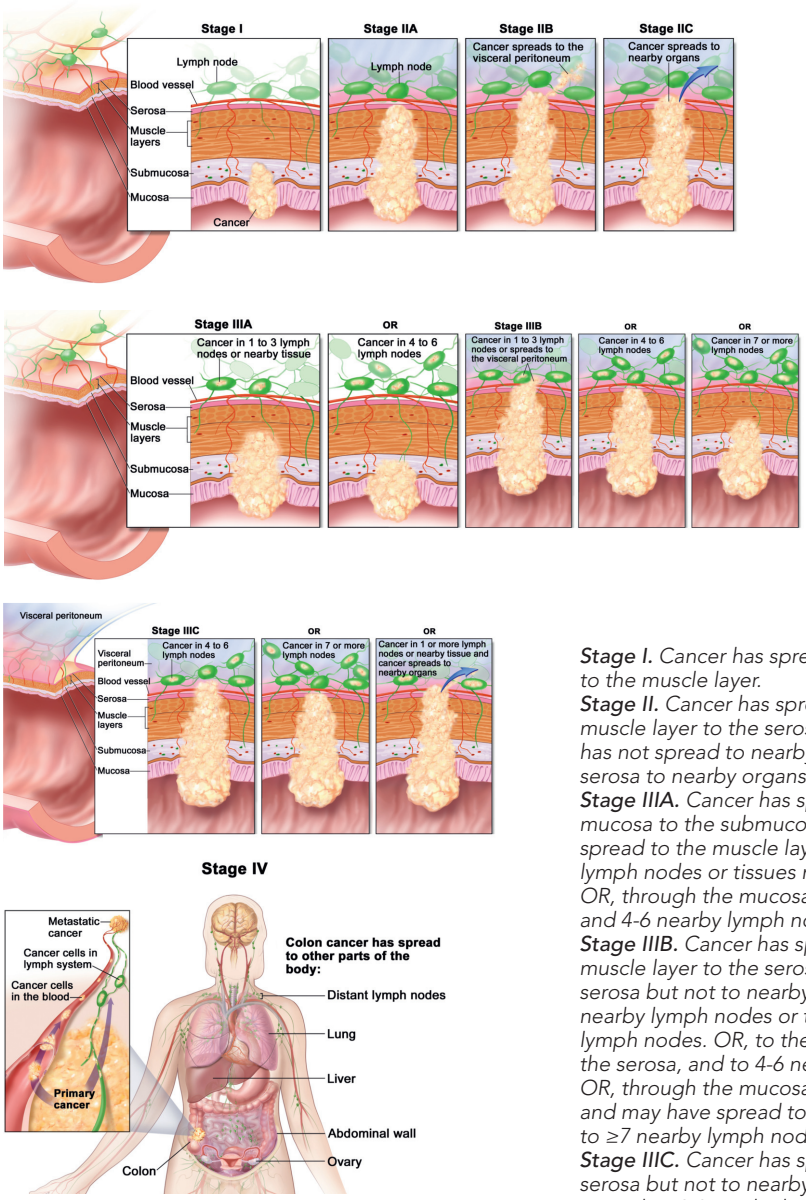

Figure 4. Colorectal cancer stages I-IV. For stages I-III, showing the layers of the colon/rectal wall. For stage IV, the inset shows cancer cell spreading. For the National Cancer Institute © 2018 Terese Winslow LLC, U.S. Govt. has certain rights.[7] *With permission.*

Stage I. *Cancer has spread from the mucosa to the muscle layer.*
Stage II. *Cancer has spread through: the muscle layer to the serosa (IIA); the serosa but has not spread to nearby organs (IIB); the serosa to nearby organs (IIC).*
Stage IIIA. *Cancer has spread: through the mucosa to the submucosa and may have spread to the muscle layer, and to 1-3 nearby lymph nodes or tissues near the lymph nodes. OR, through the mucosa to the submucosa and 4-6 nearby lymph nodes.*
Stage IIIB. *Cancer has spread: through the muscle layer to the serosa or through the serosa but not to nearby organs; and to 1-3 nearby lymph nodes or to tissues near the lymph nodes. OR, to the muscle layer or to the serosa, and to 4-6 nearby lymph nodes. OR, through the mucosa to the submucosa and may have spread to the muscle layer; and to ≥7 nearby lymph nodes.*
Stage IIIC. *Cancer has spread through the serosa but not to nearby organs; cancer has spread to 4-6 nearby lymph nodes. OR, cancer has spread through the muscle layer to the serosa or has spread through the serosa but not to nearby organs; cancer has spread to ≥7 nearby lymph nodes. OR, cancer has spread through the serosa to nearby organs and to one or more nearby lymph nodes or to tissues near the lymph nodes.*
Stage IV. *The cancer has spread to other parts of the body, such as the lymph nodes, lung, liver, abdominal wall, or ovary.*

In the Netherlands, the stage distribution before the introduction of a national CRC screening program was 18%, 31%, 29%, and 23%, for stages I, II, II and IV respectively. [5] After the introduction of the screening program, a shift in stage distribution is expected towards more early stage cancers. In 2015, after the introduction of screening more lower stage cancers were diagnosed for screen-detected CRCs compared to symptom-detected CRCs, the distribution of cancers in stages I, II, III and IV were 48%, 19%, 27%, and 6% versus 17%, 23%, 35%, and 26%, respectively. [20]

Prevention of colorectal cancer

There are three forms of prevention: primary, secondary and tertiary. Below, these three types of prevention are described. In this thesis the emphasis is on secondary prevention of CRC.

Primary prevention

Lifestyle and nutritional factors influence CRC risk. It is assumed that 18-32% of CRC cases can be prevented through modification of dietary and lifestyle factors. [21 22] Meta-analyses of observational studies have been performed, but large randomized trials are lacking. Factors associated with higher risk of CRC include obesity (especially abdominal fatness), tobacco smoking, alcohol consumption and consumption of red or processed meat. [22 23] The pooled relative risk (RR) for obese vs. normal BMI (body mass index) is 1.33 (95%CI, 1.25 – 1.42) and for waist circumference (highest vs. lowest category) 1.46 (95%CI, 1.33 – 1.60). [24 25] Smoking (ever smokers vs. never smokers) increased CRC incidence and mortality, pooled RR = 1.18 (95%CI, 1.11- 1.25) and RR = 1.25 (95%CI, 1.14- 1.37), respectively. [26] Also, former smokers are at increased risk compared to never smokers and the association with smoking is higher for rectal cancer than for colon cancer. [27] Compared to non-drinkers, the pooled RR for alcohol consumption was 1.16 (95% CI, 0.99 to 1.36) for persons who consumed 30 to less than 45 g/d, and 1.41 (95%CI, 1.16 – 1.72) for those who consumed 45 g/d or more. [28] Red meat consumption increased the CRC incidence by 17-28% per 100-120 g/day (pooled RR, 1.17; 95% CI 1.05–1.31 and pooled RR, 1.28; 95% CI 1.18–1.39) and processed meat per 30-50 g/day by 9-18% (pooled RR, 1.09; 95% CI 1.05–1.13 and pooled RR, 1.18; 95% CI 1.10–1.28). [29 30]

Factors that may decrease CRC risk include physical activity, chemoprevention by means of NSAIDs (use of aspirin), and possibly high intake of fruits and vegetables. Physical activity may decrease CRC incidence by 24% (pooled RR, 0.76; 95% CI, 0.72–0.81) [31] and (daily) aspirin use may reduce long-term CRC risk after 10-20 years by 40% (pooled RR, 0.60; 95% CI, 0.52 – 0.86). [32]

Secondary prevention

The CRC incidence and mortality can be reduced by secondary prevention through screening and surveillance. Since progression time from adenoma to carcinoma is substantial, it leaves considerable room for early detection and removal of (early stage) cancers and precursor lesions (adenomas). Therefore CRC is well suited for screening.

Screening

Screening aims to detect the disease at an earlier stage with a more favourable prognosis (preventing the number of deaths due to the disease or leading to prolonged survival time), before onset of clinical signs or symptoms. Unfortunately, screening also has disadvantages. It can lead to over-diagnosis and overtreatment (detection and treatment of cancers or adenomas that would have never been found without screening). Also, serious complications of screening have been reported, like colonic perforation after colonoscopy and even death.

Various screening methods for CRC are available. They can be classified into stool tests, endoscopic or imaging tests and other tests. Stool tests are self-tests requiring participants to collect one or more samples of their stool and send it to a laboratory for analysis. There are three types of stool tests currently on the market: guaiac faecal occult blood tests (gFOBT), faecal immunochemical tests (FIT), and stool-DNA tests (sDNA). In the laboratory, the stool samples are investigated for the presence of haem (gFOBT), globin (FIT) or DNA mutations (sDNA). A positive stool test requires follow-up with colonoscopy to evaluate the presence of polyps or cancer.

Colonoscopy *(Figure 5)* and sigmoidoscopy are both endoscopic tests, during which a flexible tube with a videochip digital camera is inserted via the anus to visualize the colorectum. During the procedure cancers can be biopsied and polyps or adenomas can be removed. Both invasive procedures require bowel preparation, but the preparation for colonoscopy is considerably more burdensome. Sigmoidoscopy only visualizes the distal part of the colon (rectum, sigmoid and descending colon), while colonoscopy visualizes the full colon. As a consequence sigmoidoscopy cannot detect proximal lesions.

Computed tomography colonography (CTC) is a non-invasive imaging technique of the colorectum. Scans are made to construct two- or three dimensional images that are used to search for presence of neoplastic lesions. CTC requires a burdensome bowel cleansing as preparation, like colonoscopy. When tested positive, it requires follow-up with colonoscopy.

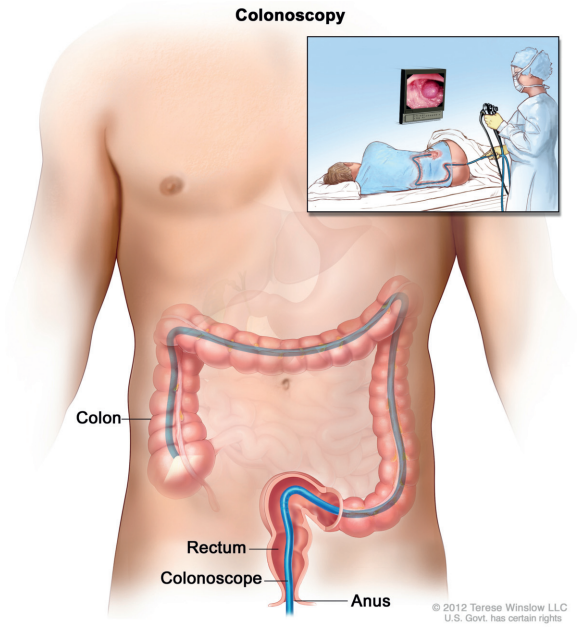

Figure 5. *Colonoscopy. A thin, lighted tube is inserted through the anus and rectum and into the colon to look for abnormal areas. For the National Cancer Institute © 2018 Terese Winslow LLC, U.S. Govt. has certain rights.* [7] *With permission.*

Two other tests, not yet standard use in current practice, are colon capsule endoscopy (CCE) and blood tests. With CCE the colon is visualized though an ingestible capsule with a video camera at both ends for imaging as it progresses through the gastrointestinal tract. CCE requires good or excellent bowel preparation similar to colonoscopy. [33 34] With blood tests a routine sample of blood is collected and analysed for tumour markers (circulating protein biomarkers and tumour-specific mutations in circulating DNA). [35] Also these tests require follow-up after a positive screen test with colonoscopy.

So far, the only evidence for effectiveness of screening from randomized controlled trials is available for gFOBT and sigmoidoscopy, showing a CRC mortality reduction of 11-33% with repeated biennial gFOBT [36-40] and 22-33% after single sigmoidoscopy. [41-45] However, given similarities between FIT and gFOBT (specificity) and better performance characteristics of FIT (sensitivity), FIT is considered superior to gFOBT. [46-50] Observational studies suggested that the mortality reduction after FIT was at least as of the same magnitude as with gFOBT, ranging from 32-80%. [51-53] Similarly, colonoscopy is expected to be more effective than sigmoidoscopy because these are both endoscopic examinations with a further reach for colonoscopy. However, colonoscopy is also more burdensome. Overall, there is no consensus on which screening test is best. Currently, several RCT's are underway comparing colonoscopy and FIT. [54 55]

As a consequence of differences in CRC incidence, the impact of the disease relative to other health problems, the capacity to treat the disease, economic resources, healthcare structure and infrastructure to support screening (e.g. ability to identify the target population at risk and the availability of a cancer registry), there are widely different CRC screening practices across the world, see *Figure 6* [56]. The national CRC screening program in the Netherlands uses biennial FIT screening. More information on the Dutch screening program can be found below under *'CRC screening in the Netherlands'. (page 18)*

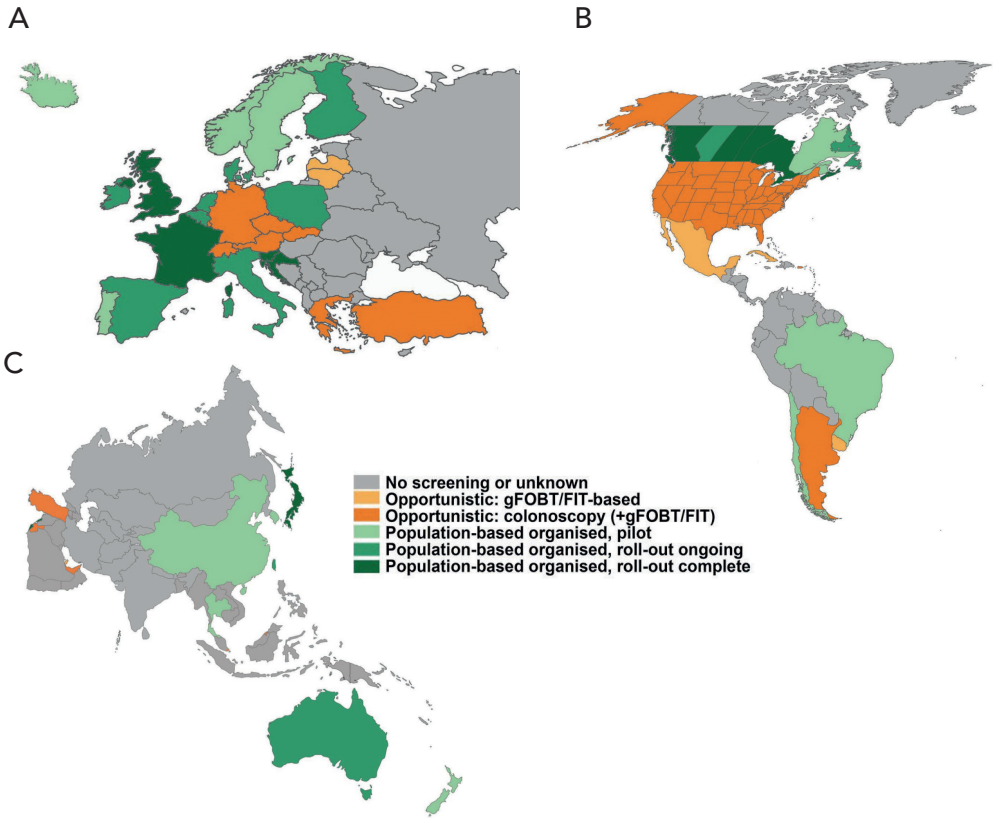

Figure 6. *Overview of various screening practices across the world in 2014. Regional differences with in one country are, except for North-America, not taken into account in these figures. (A) Overview of screening programmes in European region. (B) Overview of screening programmes in regions of the Americas. (C) Overview of screening programmes in Western Pacific, South-East Asia and Eastern Mediterranean region. FIT, Faecal immunochemical test for haemoglobin; gFOBT, Guaiac faecal occult blood test.* [56] *With permission.*

Surveillance colonoscopy

Individuals in whom adenomas have been detected and removed (as a result of colonoscopy screening, colonoscopy follow-up after a positive screen test or during colonoscopy indicated for symptoms) have an increased risk for CRC compared with the general population, even after adenomas have been removed. [57 58] Patients with adenoma are therefore recommended to undergo regular surveillance colonoscopy. [59-63] In this thesis we focused on risk stratification of adenoma patients and intervals for surveillance colonoscopy for further guideline development. For more information on surveillance colonoscopy: effectiveness, burden, (international) guidelines, its shortcomings and adherence to guidelines, see below under heading *'Surveillance in adenoma patients'. (page 18)*

Tertiary prevention: CRC treatment

Over the last two decades CRC treatment has improved disease outcome and extended a patients' survival time. [6] Depending on cancer stage and location, treatment of CRC include local treatment (surgery and/or radiotherapy) and/or systemic treatment (chemotherapy, targeted therapy and immunotherapy). [64] Treatment of rectal cancer varies somewhat from colon cancer, differences include surgical technique, the use of radiation therapy, and the method of chemotherapy administration. [65]

Usually stage I-II colon cancers and stage I rectal cancers are treated locally with surgery. More advanced cancers require combinations of treatments, for stage II-III rectal cancers preoperative chemo radiation therapy is the preferred treatment (combination of chemo- and radiation therapy). Neoadjuvant chemotherapy and radiation therapy aim to shrink tumours and kill cancer cells. [64 65] Treatment for stage III colon cancers involves surgery with adjuvant chemotherapy. Adjuvant chemotherapy is used to kill any cancer cells that might have been left behind as well as cancer cells that might have escaped from the main tumour and settled in other parts of the body. Commonly used drugs for chemotherapy are 5-Fluorouracil (5-FU), capecitabine (Xeloda), irinotecan (Camptosar), oxaliplatin (Eloxatin), and trifluridine and tipiracil (Lonsurf). [64] For stage IV colon and rectal cancers treatment involves a combination of surgery, chemotherapy and targeted therapy. [65] Targeted therapy include drugs that either target blood vessel formation to stop tumours to form new blood vessels (examples are bevacizumab (Avastin), ramucirumab (Cyramza), and ziv-aflibercept (Zaltrap)), or target cancer cell growth (examples are cetuximab (Erbitux) and panitumumab (Vectibix)). A drug that targets both is regorafenib (Stivarga). [64] In addition, immunotherapy can be used to stimulate or suppress the immune system to help the body fight cancer. [65] It can

shrink tumours or slow down their growth. Examples are pembrolizumab (Keytruda) and nivolumab (Opdivo). [64]

Colonoscopy

Colonoscopy is key in the prevention and management of CRC. Colonoscopy is either used as primary screening test or for diagnostic follow-up for all other CRC screening tests, for surveillance after polyp or adenoma removal (polypectomy), and is also the gold standard for detection of lesions in people with abdominal symptoms. In patients over 50 years old, about 50-60% of all colonoscopies are performed for screening and surveillance purposes. [66 67] Colonoscopy is the most sensitive method for the detection of CRC and its precursor lesions. The estimated sensitivity of colonoscopy is 95% for CRC and 85% for medium sized (6-9 mm) adenomas, the specificity is assumed to be 86%. [68 69] However, the effectiveness of colonoscopy depends strongly on its quality. The introduction of colorectal cancer screening programs has led to a growing interest in quality assurance for colonoscopy practices. High-quality colonoscopies are complete procedures with cecal intubation, having a withdrawal time of at least 6 minutes and a good bowel preparation (Boston Bowel Preparation Score ≥6), at which all relevant lesions/polyps are detected and radically (completely) removed. [70-72] Missed or incompletely removed lesions may result in interval cancers after colonoscopy (post-colonoscopy colorectal cancers). These cancers are detected after colonoscopy and before the date of the next recommended colonoscopy or screening. [73] Interval cancer reduces the effectiveness of a screening or surveillance program and is an indicator of sensitivity.

Complications of colonoscopy

Although colonoscopy is the most accurate test of the available screening tests for CRC, the procedure is not without risk of complications. Major reported complications are bleeding, colonic perforation and even death. Widely differing complication rates have been reported [74 75], e.g. perforation rates ranging from 2.2 to 11.4 per 10,000 colonoscopies. Since the colonoscopy is one of the most commonly performed examinations, several gastrointestinal societies adopted safety standards to control the quality of the colonoscopy. The latest recommendation of the American Society for Gastrointestinal Endoscopy (ASGE) and the American College of Gastroenterology (ACG) aims for a maximum of 20 perforations in 10,000 colonoscopies. [76] For screening colonoscopies, no more than 10 perforations in 10,000 colonoscopies is acceptable. [76 77]

The demand for colonoscopy is increasing, mainly due to the implementation of colorectal screening programs. [78] The absolute number of individuals exposed to colonoscopy is dependent on the chosen screening and surveillance programme. In order to make an optimal choice which stategy is prefered several characteristics should be taken into account like participation rates, costs, harms and benefits. Especially in screening programs, it is important that the participants are aware of both benefits and risks of the procedures, so that an informed decision can be made whether or not to undergo colonoscopy. For quality control purposes, a regular review of complication rates of colonoscopy in the screening and clinical settings is essential.

CRC screening in the Netherlands

In the Netherlands, biennial FIT screening was introduced nationally in 2014 for men and women aged 55-75 years. The program is implemented gradually by age group over a period of 5 years, allowing for timely increase in colonoscopy capacity. In 2019 the program covers the full age range (55-75), targeting a population of 2.2 million annually. [79 80]

In the first 3 years of the Dutch program almost 3.4 million individuals were invited (for first and/or second round), over 2.4 million participated by returning a FIT test which led to 151,411 positive test results and to at least 121,481 individuals undergoing colonoscopy. Of individuals undergoing colonoscopy, about 9,900 individuals were diagnosed with CRC and almost 79,000 (approximately 65%) with adenoma, of whom two-third with advanced adenoma. [81-83] The proportion of patients with advanced adenoma was 44% in the first screening round and 36% in the second screening round. A large proportion of patients with adenoma is recommended a surveillance colonoscopy and will return for colonoscopy within the next 5 years.

Surveillance of adenoma patients

Adenoma patients in whom adenomas have been removed are believed to be still at elevated risk of CRC compared to the general population. [57 84] Within 3-5 years of follow-up, 20-50% of adenoma patients will have adenoma recurrence. [84-87] Due to the presumed elevated CRC risk adenoma patients are generally advised to undergo regular surveillance colonoscopy. [61 62] Compared to the general population, CRC mortality was reduced by 53% in patients with colonoscopy with polypectomy after a follow-up period of up to 23 years (median follow-up was 16 years). [88] However, other studies found a smaller effect on CRC incidence and mortality reduction in adenoma patients undergoing surveillance colonoscopy. [58 89 92]

Surveillance colonoscopy should be targeted at adenoma patients most likely to benefit and should be minimized to the lowest frequency needed to protect against CRC. According to two meta-analyses, risk of advanced neoplasia recurrence is higher when adenomas at index colonoscopy had the following characteristics: large size (>=10 mm), villous histology and proximal location. [90 91] Patients with these characteristics warrant more intense surveillance. This is confirmed by a study of Løberg and Kalager et al. showing a higher risk of CRC mortality in high-risk adenoma patients within a median follow-up period of 7.7 years (standardized incidence-based mortality ratio = 1.16 (95% CI 1.02 – 1.31) compared to the general population. [92]

Surveillance colonoscopies are estimated to constitute 13%–40% of all colonoscopies performed. [66 93-95] This proportion may increase in the near future due to the adoption of population screening, unless the introduction of screening is accompanied by introduction of more selective surveillance guidelines.

Guidelines for surveillance of adenoma patients

Internationally, risk stratification of adenoma patients in guidelines for surveillance colonoscopy is predominately based on adenoma multiplicity and categorization of an adenoma as advanced or non-advanced *(Table 1)*. [61 62 96] Similar to the 2012 US guideline, the 2013 European (European Society of Gastrointestinal Endoscopy, ESGE) guideline classifies patients as high-risk if either 3 or more adenomas or at least one high-risk adenoma is removed (i.e., a large adenoma or an adenoma with (tubulo)villous histology or high grade dysplasia). [61 62] Three-year surveillance intervals are recommended for high-risk patients and five to ten year intervals for low-risk patients. [61 62] The UK, Scottish, Australian, and other European Union guidelines distinguish 3 categories, with the distinction of recommending a 1-year surveillance interval for patients with 5 adenomas, [59 60 96 97] very large (20 mm) adenomas [59] or in case of 3 or more adenomas with at least one large (≥10 mm). [60 97] Patients with 10 or more adenomas should be referred for genetic counselling. [61 96]

In the Netherlands, the first guideline for surveillance of adenoma patients was issued in 1988. This guideline recommended a repeat colonoscopy within 1 year to check for complete removal of polyps in all patients, and subsequently a 3 year or 5 year interval for patients with multiple or a single adenoma, respectively. [99] In 1998 the guideline-workinggroup concluded that a repeat colonoscopy one year after removal of an initial single adenoma was no longer indicated, and could safely be perfomed after 2-3 years. [100] In 2002, the surveillance guideline recom-

Table 1. Risk stratification and interval recommendations for surveillance after polypectomy according to various guidelines

Guideline	Interval based on adenoma characteristic	Surveillance interval		
		1 year	3 years	5-10 years *
ESGE 2013 [61]	Number or advanced (Size/ HGD/ Villous)		• ≥3 • ≥10 mm • HGD • Villous • SP, HGD • SP, ≥10 mm	• 1-2, <10mm, Tub, LGD • <10 mm SP, LGD
US 2012 [62]	Number or advanced (Size/ HGD/ Villous)	• >10[1]	• ≥3 – 10 • ≥10 mm • HGD • Villous • SP, HGD • SP, ≥10 mm • TSA	• 1-2, <10mm, Tub, LGD • SP, <10 mm, no dysplasia[2] • HP, <10 mm[2]
European Union 2012 [59]	Number & size	• ≥5, <10 mm • ≥20 mm	• 3-4, <10 mm • 10-<20 mm • Villous[3] • HGD[3]	• 1-2, <10mm • Tubular & LGD[3]
UK 2010 [60]	Number & size	• ≥5 • ≥3 & ≥1 ≥10 mm • SP, ≥10 mm	• 3-4, <10 mm • 1-2, ≥10 mm	• 1-2, <10mm
Scottish 2011 [97]	Number & size	• ≥5 • ≥3 & ≥1 ≥10 mm	• 3-4, <10 mm • 1-2, ≥10 mm	• 1-2, <10mm, LGD
Australian 2011 [96]	Number or advanced (Size/ HGD/ Villous)	• ≥5 • SP, ≥10 mm	• ≥3 • ≥10 mm • TV/ Villous • HGD	• 1-2, <10 mm, Tub, LGD
Dutch 2002 [63]	Number		• ≥3	• 1-2
Dutch 2013 [98]	Number, size, location & villous		• Risk score 3-5	• Risk score 1-2

HGD = high-grade dysplasia, LGD = low-grade dysplasia, Tub = tubular, TV = tubulovillous, TSA = traditional serrated adenoma, SP = serrated polyp, HP=hyperplastic polyp
** ESGE 2013 [61]: Return to screening or colonoscopy in 10 years; US 2012 [62]: 5-10 years; European Union 2012 [59]: Routine screening; UK 2010 [60]: 5 years or no screening; Scottish 2011 [97]: 5 years: Australian 2011 [96]: 5 years: Dutch 2002 [63]: 6 years; Dutch 2013 [98]: 5 years for patients with risk score 1-2, FIT screening after10 years for patients with risk score 0.*
[1] surveillance interval < 3 years
[2] Surveillance interval 5 years for SP, 10 years for HP
[3] Optional additional criteria.

mended patients with three or more adenomas to have surveillance colonoscopy after three years, and patients with less than three adenomas after six years. [63] At the time the 2002 guidelines were set, a more specific guideline was not possible, because of lack of sufficient data. At the initiation of this thesis,

a survey had indicated discomfort of gastroenterologists with the existing guidelines. Their recommended surveillance intervals differed from the guideline, because they felt that important risk factors for adenoma recurrence were not considered. They assumed a higher perceived risk for adenoma patients with presence of other risk factors than solely adenoma number. This discomfort and lack of adherence formed the basis for our study, called Surveillance After Polypectomy – Towards Efficient Guidelines (SAP-study), and the resulting change in guideline in 2013 (see *Chapter 8, Figure 1* for more detail).

Shortcomings in guidelines for surveillance in adenoma patients

In general, all international surveillance guidelines are based on very little empirical evidence. No randomized controlled trials have evaluated the benefit of surveillance compared to no surveillance or have evaluated effectiveness of surveillance in a setting with screening and only two studies compared CRC risk at different surveillance intervals. [84 101] The largest, the National Polyp Study, compared two surveillance schemes for patients with newly diagnosed adenomas, surveillance at 1 year plus at 3 years versus surveillance at 3 years only, and concluded that the interval for colonoscopy surveillance can be extended to 3 years after complete removal of initial polyps for most patients. [84]

There are more observational studies concerning surveillance of adenoma patients. Some have assessed independent predictors of advanced neoplasia at surveillance. Predictors of advanced neoplasia are studied, as a proxy for CRC risk, to better target colonoscopies to those patients who benefit most from the procedure. These studies consistently showed that adenoma multiplicity, size and villous histology are each independent predictors of advanced adenoma recurrence. [90 91] Despite these findings, guidelines do not incorporate a higher risk level for patients in whom multiple risk factors are present. Furthermore, several additional predictors for recurrent advanced colorectal neoplasia, such as older age, male sex, and proximal location of the adenoma(s) are generally not considered at all. [91] Additionally, most recommended intervals for surveillance in guidelines are based on expert opinion, not on formal decision analysis (cost-effectiveness). Formal decision analysis is needed to take into account costs and harms, besides effectiveness.

Adherence to surveillance guidelines

For optimal effectiveness of CRC prevention and limitation of resource depletion, adherence to surveillance guidelines is required. Surveys show that gastroenterologists often advise shorter surveillance intervals than recommended

by guidelines. [102-105] However, results from surveys are indicators of adherence, but may be too optimistic. These results reflect gastroenterologists' intention immediately after the colonoscopy, which is only one factor on whether or when surveillance colonoscopy will take place. Also, they may be prone to bias because of desirable answers. Few studies have assessed actual adherence to surveillance guidelines in clinical practice. [106-108] Most were either relatively small single-centre studies or based on self-reported patient survey. The proportion of patients not having surveillance was often not assessed. Adherence to surveillance guidelines is generally poor, with mainly too frequent surveillance in low-risk adenoma patients and too little surveillance in high-risk patients. [104 106 107 109]

Aim and research questions (outline of this thesis)

The aim of this thesis is to propose more efficient guidelines for surveillance of adenoma patients in the Netherlands. This thesis is divided into three parts answering the following research questions:

Part I: Complications of colonoscopy

1. What are perforation and mortality rates of colonoscopy according to literature over the past 30 years? *(Chapter 2)*

Part II: Predictors of (advanced) neoplasia recurrence and more efficient surveillance of adenoma patients

2. What are adenoma and colonoscopy-related predictors of (advanced) colorectal neoplasia recurrence at surveillance examinations? *(Chapter 3)*
3. How can we improve risk stratification of adenoma patients? *(Chapter 4)*
4. What are cost-effective strategies for surveillance of adenoma patients with different risk profiles? *(Chapter 5)*

Part III: Adherence to and acceptance of guidelines for surveillance of adenoma patients

5. What are actual adherence rates to recommended surveillance intervals in clinical practice? What is the influence of a recent change in the guideline? *(Chapter 6)*
6. Is the new risk-stratified surveillance guideline feasible for gastroenterologists? What difficulties do gastroenterologists have regarding guideline interpretation or compliance? *(Chapter 7)*

Chapter 8, the general discussion, concludes this thesis with the answers to and discussion of the above mentioned research questions.

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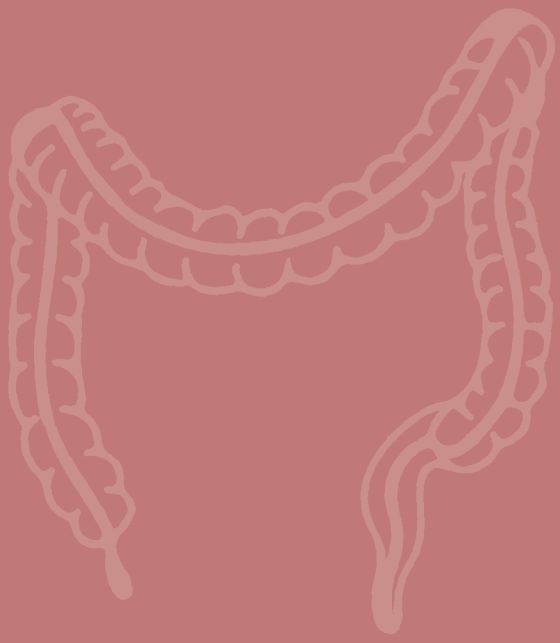
Part I

Complications of colonoscopy



Chapter 2

Perforation and mortality rates for colonoscopy – systematic review and meta-analysis

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Submitted

Abstract

Background: Colonoscopy use has increased dramatically in many countries, partly due to the introduction of colorectal cancer screening programs. Colonoscopy is considered a safe procedure, but it is not free from complications. To inform patients, accurate estimates for major complication rates are required.

Objective: To estimate pooled rates of colonoscopy perforation and mortality and how these rates are associated with study characteristics.

Design: Systematic review and meta-analysis of prospective and retrospective studies published between 1991 and April 2017 reporting complication rates for ≥5,000 colonoscopies. A literature search was performed using PubMed and EMBase. Random Effects Poisson-Normal modeling was used to calculate pooled complication rates and to assess relationships with study characteristics.

Patients and Interventions: Adult population undergoing colonoscopy.

Main outcome measures: Outcomes considered were colonoscopy related rates of perforation and mortality.

Results: A total of 92 studies were included. The overall perforation rate (PR, 95%CI) was 5.7 (4.7 – 6.8) per 10,000 coloscopies. The PR was higher for colonoscopies with therapeutic intervention (mainly polypectomy) (9.7, 95%CI 6.8 – 16.8 per 10,000) than for colonoscopies without therapeutic intervention (3.4, 95%CI 2.4 – 4.9 per 10,000; $p<0.01$). PRs decreased significantly over time (RR = 0.96 per year; 95%CI 0.93 – 0.98). The pooled mortality rate (95%CI) was 0.13 (0.05 – 0.34) per 10,000 colonoscopies. Year of data collection was the sole study characteristic associated with PR.

Limitations: Significant heterogeneity existed across studies.

Conclusion: This meta-analysis shows that perforation and mortality rates with colonoscopy are low and below the currently accepted thresholds in quality guidelines. Moreover, rates are improving over time, suggesting that quality thresholds can be more stringent.

Introduction

Colonoscopy is one of the most commonly performed medical procedures.[1] It is used for a wide range of indications to diagnose, treat or screen for colorectal diseases.[2 3] The demand for colonoscopy is rising dramatically, with reported increases of 250% over 10 years for some settings.[4] Due to ongoing implementation of colorectal cancer screening programs, the end to the rise in colonoscopy demand is not expected soon.[5 6]

In general, colonoscopy is considered a safe procedure, but major complications can occur. Major complications include bleeding, colonic perforation and even death. Studies show large variation in complication rates. Even between studies in large populations, 10-fold variation in perforation rates has been reported, ranging from 1.3 – 12.1 per 10,000 colonoscopies.[7 8]

Several gastrointestinal societies adopted quality thresholds to control the safety of colonoscopy. The latest recommendation from the American Society for Gastrointestinal Endoscopy (ASGE) and the American College of Gastroenterology (ACG) on complication rates aims for an incidence of perforations of less than 1 in 500 colonoscopies; and for primary screening colonoscopies of less than 1 in 1,000 colonoscopies.[9] The latter is also recommended by the European Society of Gastrointestinal Endoscopy (ESGE).[10]

Both for patients as for professional quality control purposes, a regular review of complication rates of colonoscopy in the screening and clinical settings is essential. It is important that set quality thresholds are met, especially in screening programmes, targeted primarily at healthy individuals. It is important that the participants are aware of both benefits and harms of the procedures, so that an informed decision can be made whether or not to undergo colonoscopy. However, complication rates in various screening populations (e.g. primary screening colonoscopy; follow-up colonoscopy after a positive faecal immunochemical test, or surveillance colonoscopy) are unclear. Since major complications are relatively rare, a large study population is required to obtain reliable estimates of risk. One way to achieve this is to pool results from existing studies.

In this systematic review and meta-analysis, we aim to examine pooled rates of major colonoscopy complications (perforation and mortality) over the past 30 years and assess rates stratified by type of procedure (therapeutic/ diagnostic) and type of population (primary screening, follow-up after a positive screen test and mixed patient or symptomatic), and a combination of both (type of procedure within type of population). In addition, we evaluated which study characteristics were associated with complication rates.

Methods

Search strategy

The MEDLINE/PubMed and EMBase databases were searched from January 1991 to April 2017 to identify relevant studies published in English or Dutch. Search strategies included the following terms: *colonoscopy, complications, hemorrhage, bleeding, (intestinal) perforation, adverse (effects), mortality, death, mass screening, early detection (of cancer), and colorectal neoplasms.* The exact search strategies are presented in *Appendix 1*.

Selection criteria

Intervention and outcome

Included studies reported on the number of colonoscopies and the number of complications resulting from the procedure, with a minimum sample size of 5,000 colonoscopies. We only considered major complications, which we defined as colonic perforation and death. Deaths were included when related to colonoscopy. A colonoscopy was defined as diagnostic colonoscopy when no therapy or only cold biopsy was performed. Therapeutic colonoscopy included colonoscopies with any performed intervention during the procedure, such as polypectomy, dilatation, angiocoagulation and placement of stents.

Population

Adults, including asymptomatic populations that underwent colonoscopy for primary screening, as follow-up after a positive screen test (other than colonoscopy), or for post-polypectomy surveillance, as well as patient populations (case mix). We excluded studies that focused on: children or adolescents (age <18), upper GI endoscopy (duodenoscopy and gastroscopy), patients with gastrointestinal diseases (inflammatory bowel diseases, colorectal cancer, hereditary colorectal cancer syndromes (e.g. FAP and HNPCC)), patients with previous bowel resections, and patients with specific co-morbidities or specific patient populations (e.g. with HIV/AIDS, psychological conditions).

Study

Randomized controlled trials (RCTs) and observational studies were included. Review articles were only used to find original research studies (RCTs or observational studies) reporting complications of colonoscopy. Case reports, letters, comments, historical articles and case-control studies were excluded. When articles used data from the same source population, the most relevant article was selected if it fo-

cused on complications and otherwise based on (largest) sample size.
First, we screened all titles resulting from the search strategy, followed by abstracts and eventually full texts if potentially relevant. In full text articles, we screened the results-section, then the methods section, and finally, other sections when relevant. Three reviewers (E.M.B.H., R.Massl, E. Karakoc) screened studies for inclusion. Data of all included articles were checked by A.K.

Data extraction

Variables of interest were number of colonoscopies and number of complications (perforation or death). In addition, for stratification purposes and regression analysis, data was extracted on publication year, mid-period year of data collection, complications as primary study endpoint, population (screen, screen follow-up or patient population), type of colonoscopy (diagnostic or therapeutic), study design (prospective or retrospective), continent of data collection (western or non-western), type of center (academic or other), days of follow-up on complications, mean age of the study population (median if mean age was not reported) and percentage male participants, all to the extent available. When a study report mentioned that no (fatal) adverse events had occurred, this was interpreted as no perforations and no deaths by colonoscopy.

Statistical analysis

A funnel plot was created to assess the presence of publication bias. Cochran's Q-statistic was used to assess heterogeneity across included studies. In addition, we calculated the I^2 measure of the proportion of variation across studies due to heterogeneity rather than chance. [11]

Random Effects Poisson-Normal modeling without covariates was used to calculate pooled perforation and mortality rates with 95% confidence intervals (95% CI). Next to overall pooled perforation and mortality rates, we assessed pooled perforation rates for subgroups of studies; period of data collection (1980-1989, 1990-1999, 2000-2009, >2010) and study population (primary screening, follow-up after FOBT screening, and mixed patient or symptomatic). Additional stratified analyses were performed for studies that separately reported number of colonoscopies and perforations according to age group, sex or type of colonoscopy (therapeutic and diagnostic procedures). The results of these stratified analysis were presented in a figure or forest plot. We calculated stratified pooled PR for type of colonoscopy within study population. Statistical differences between stratum-specific estimates were tested using the Z-score (Wald test), with a p-value of $p<0.05$.

Associations of perforation and mortality rates with relevant study characteristics were assessed by adding one or more covariates to the Random Effect Poisson-Normal regression models. In multivariable regression analysis, covariates were excluded if they were strongly correlated to another covariate (coefficient >.75), if that covariate may not be representative for all observations within the study or was not statistically significantly associated with the outcome (mean/median age, proportion male and proportion therapeutic colonoscopies). The number of covariates in the multivariate analysis should not exceeded $\sqrt{n}$, where n is the number of included studies. A minimum of 25 studies was required for application of multivariable analysis. A p-value of $p<0.05$ was considered statistically significant in all analyses. All analyses were performed in R statistical software using the metafor package. [12 13]

Results

Selected studies and study characteristics

The search strategy identified 2,560 articles. Reasons for exclusion of articles are given in *Figure 1*. Screening of reference lists of relevant papers led to 11

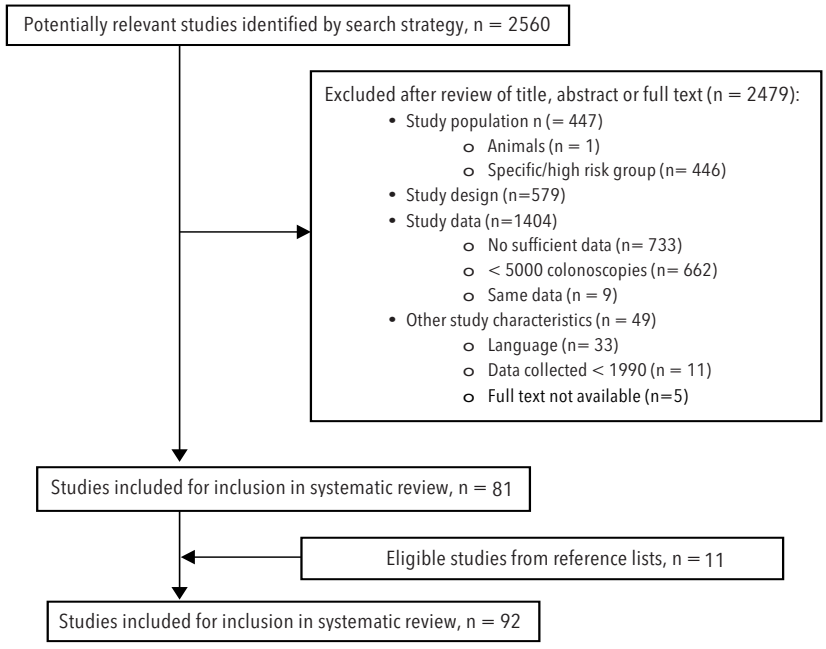


Figure 1. *Flowchart to identify articles for inclusion*

additional relevant papers. Eventually, 92 studies were identified as eligible and included in the meta-analysis (study details are presented in *Appendix 2*). In total, the studies comprised 10,970,892 colonoscopies, with the number of colonoscopies per study varying from 5,120 to 2,315,126. [14 15] We included 64 retrospective studies and 28 prospective studies. Thirty-four studies were European, 36 North American (USA & Canada), 21 Asian, and one was from Australia. Six studies reported colonoscopy complications specifically in elderly patients (75 years and older). Seventy-nine studies focused on a mixed or symptomatic patient population, whereas 7 studies involved a population undergoing screening colonoscopy, 4 studies a population undergoing colonoscopy for follow-up after a positive screen test (Fecal Occult Blood Test, FOBT), and 2 studies combined screening colonoscopy and follow-up colonoscopy. Thirty-six studies were performed in an academic medical center, 54 in other settings and in 2 studies the setting was unclear. A subset of 41 studies reported the number of diagnostic and/or therapeutic colonoscopies and corresponding perforations. Median or mean age varied from 47 to 76 years old and the proportion male varied from 36 to 94%.

Pooled rates of major complications of colonoscopy

Perforation rate

All 92 studies reported on perforations following colonoscopy. The perforation rate (PR) varied from 0 – 39.5 per 10,000 colonoscopies. [16-18] The pooled overall PR was 5.7 per 10,000 (95%CI 4.7 – 6.8), which represents 1 perforation per 1,754 colonoscopies *(Figure 2)*. There was significant heterogeneity across included studies (Q= 2,129, p < 0.01; I^2=97.0%, *Figure 2)*. This was confirmed by the funnel plot *(Appendix 3)*.

Over time the PR decreased from 11.3 (95%CI 6.2 – 20.4) in the period 1980 - 1989 to 3.5 (95%CI 1.8 – 6.8) in the more recent years (> 2010). The PRs according to population are 1.8 (95%CI 0.9– 3.4) per 10,000 screening colonoscopies, 8.1 (95%CI 3.7 – 17.6) per 10,000 follow-up colonoscopies after screening, and 6.3 (95%CI 5.3 – 7.5) per 10,000 colonoscopies in a mixed or symptomatic patient population.

Within studies that reported outcome by type of colonoscopy, the pooled PR was higher for therapeutic colonoscopies (9.7 per 10,000; 95%CI 6.8 – 14.0) than for diagnostic colonoscopies (3.4 per 10,000 (95%CI 2.4 – 4.9); p<0.001), *Figure 3*. Significant heterogeneity persisted when separating out both subtypes of colonoscopy (Q= 559, P < 0.01; I^2=96.0% and Q= 724, p < 0.01; I^2=96.0%, respectively).

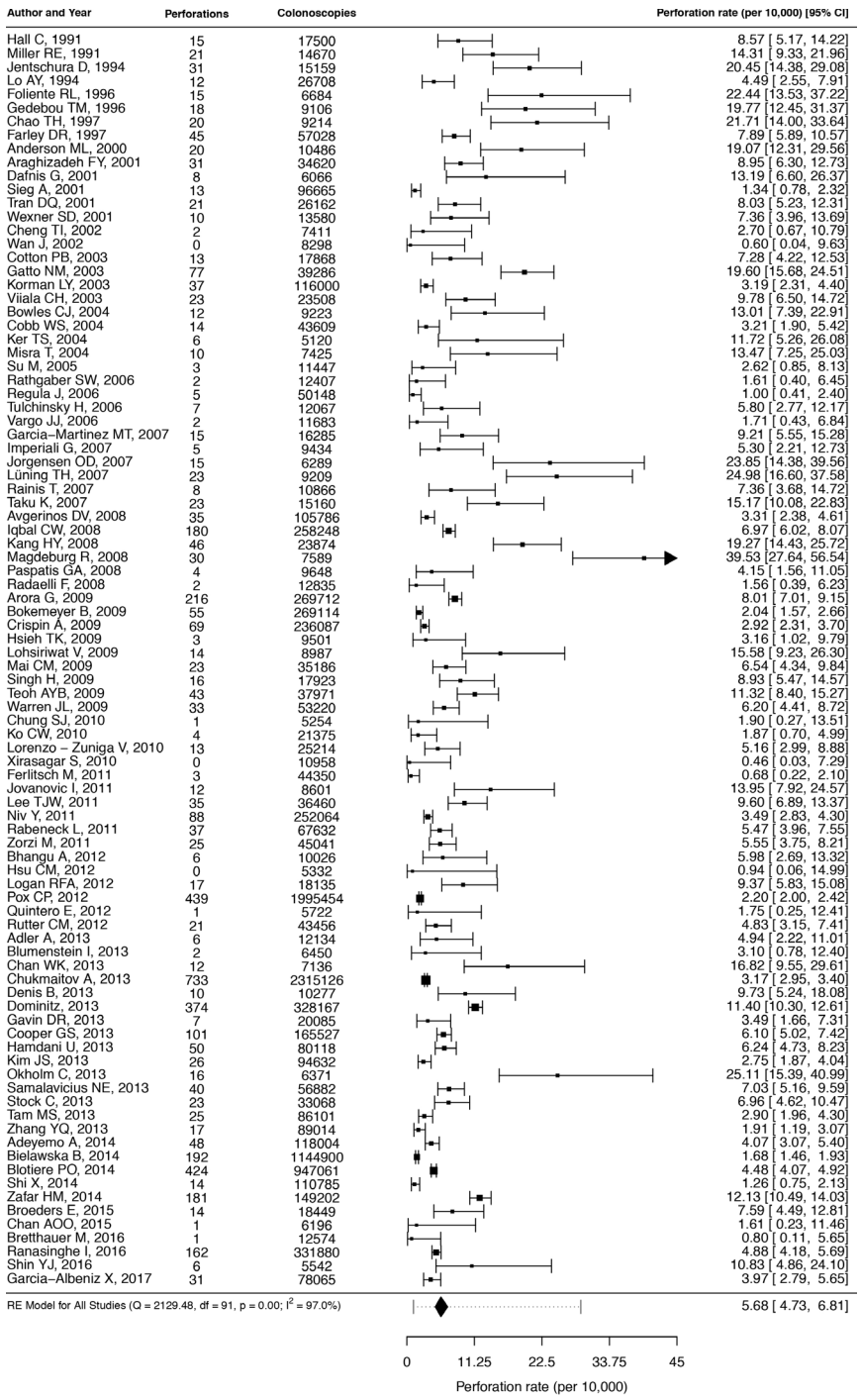


Figure 2. *Forest plot of the perforation risk in all included studies and types of exams.*

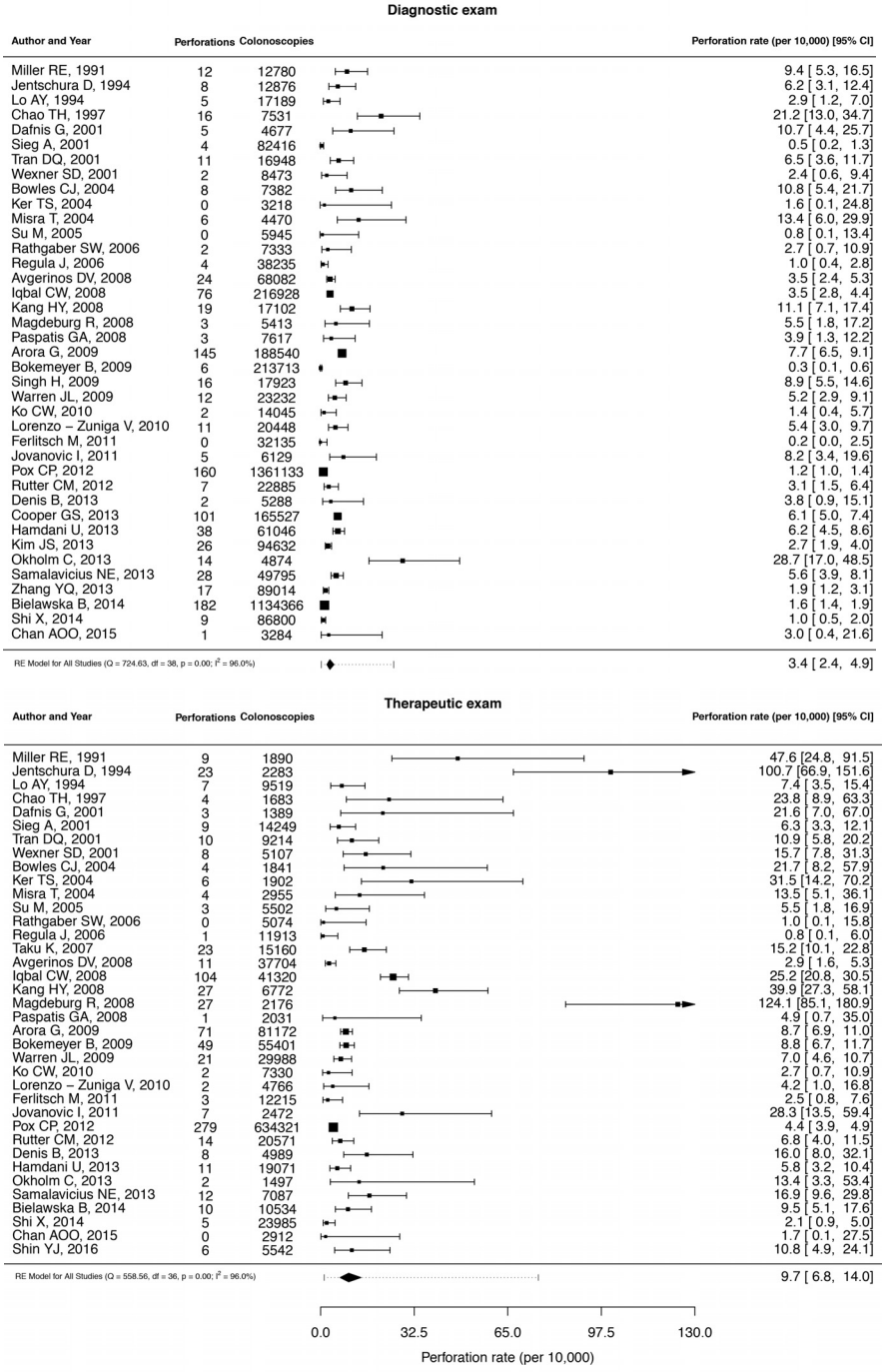


Figure 3. *Forest plots of the perforation risk in diagnostic and therapeutic exams.*

Table 1. Study characteristics in relation to perforation and fatal complication risk

Study characteristics	N studies[a]	Perforation		Mortality
		Univariate analysis RR (95% CI)	Multivariate analysis[b] RR (95% CI)	Univariate analysis RR (95% CI)
Publication year	92/28	0.95 (0.93 – 0.98)*	x	0.91 (0.13 – 1.09)
1990-1999		Ref.		
2000-2009		0.50 (0.28 – 0.92)*		Ref.
> 2010		0.34 (0.18 - 0.61)*		0.28 (0.06 – 1.31)
Median year of data collection	88/26	0.96 (0.93 - 0.98)*	0.95 (0.93 – 0.99)*	0.90 (0.78 – 1.05)
1980-1989		Ref.		No deaths[§]
1990-1999		0.72 (0.36 – 1.44)		Ref.
2000-2009		0.43 (0.23 – 0.82)*		0.37 (0.09 – 1.54)
>2010		0.31 (0.12 - 0.76)*		No deaths[§]
Complications PE study	92/28			
No		Ref.		Ref.
Yes		1.93 (1.30 – 2.88)*	x	1.42 (0.27 – 7.60)
Prospective study design	92/28			
No		Ref.	Ref.	Ref.
Yes		0.57 (0.38 – 0.84)*	0.7 (0.4 – 1.3)	0.67 (0.13 – 3.58)
Continent[^]	92/28			
Non-Western		Ref.	Ref.	Ref.
Western		1.13 (0.73 – 1.74)	0.95 (0.5 – 1.8)	1.07 (0.13 – 8.52)
Population	92/28			
Symptomatic		Ref.	Ref.	Ref.
Screening[c]		0.48 (0.29 – 0.82)*	1.3 (0.5 – 3.1)	0.06 (0.008 – 0.42)*
Type of center	92/28			
Other		Ref.	Ref.	Ref.
Academic		1.64 (1.15 – 2.34)*	1.3 (0.8 – 2.2)	3.40 (0.29 – 40.32)
Number of days after colonoscopy[d]	52/16	1.00 (0.98 – 1.02)	1.0 (0.99 – 1.03)	1.04 (0.94 – 1.16)
1-3		Ref.		Ref.
4-7		1.69 (0.89 – 3.21)		No deaths[§]
8-30		1.49 (0.89 – 2.50)		1.45 (0.05 – 39.28)

[a] *The number of studies included studies in the univariable analysis for perforation and mortality, respectively.*
[b] *Multivariable regression analysis were performed including only one of two strongly correlated covariates. Pubyear was strongly correlated to median year of data collection, and primary endpoint was inversely associated with prospective study design. Multivariable analysis included 49 studies.*
[c] *Screening, including primary colonoscopy and follow-up colonoscopy after a positive screening test (e.g. FOBT).*
[d] *This term refers to perforation and mortality.*
** statistically significant at 5% significance level.*
[^] *Western continent includes North-America and Europe. Non-western continent includes Asia (incl Middle-East) and Australia/ Oceania.*
[§] *No estimate due to zero deaths within the subgroup.*

Table 2. Comparison of (pooled) perforation and mortality rates (per 10,000) with results from other reviews or a very large study

Subgroup (no. of studies)	Our study	Wang et al[25]	Reumkens et al[22]	Lin et al (syst review USPSTF)[25]	Niv et al[24]	Panteris et al[21]
Perforation rates						
Overall (92)	5.7 (4.7 – 6.8)		5 (4 – 7)	5 (4 – 7)		7 (-)
Diagnostic (39)	3.4 (2.4 – 4.9)		4 (2 – 8)	4 (2 – 8)		
Therapeutic (37)	9.7 (6.8 – 14.0)		8 (6 – 10)	8 (6 – 10)		10 (-)
Primary screening colonoscopy *(7)*	1.8 (0.9 – 3.4)	4.9 (4.5 – 5.2)*	3 (2 – 5)	3 (2 – 5)	1 (0.6 – 2)	
Diagnostic (4)	0.5 (0.2 – 1.3)[a]	2.9 (2.5 – 3.3)*				
Therapeutic (4)	3.4 (1.2 – 9.3)[a]	6.3 (5.8 – 6.8)*				
FU colonoscopy ^ *(4)*	8.1 (3.7 – 17.6)		x	x		
Diagnostic (1)	3.3 (0.4 – 26.8)[b]					
Therapeutic (1)	15.2 (2.1 – 109.6)[b]					
Symptoms/patient mix *(79)*	6.3 (5.3 – 7.5)	7.2 (6.7 - 7.7)	13 (6 – 23)	13 (6 – 23)		
Diagnostic (31)	4.5 (3.4 – 6.1)	4.8 (4.3 – 5.3)				
Therapeutic (31)	11.6 (8.1 – 16.8)	10.8 (9.9 – 11.7)				
Mortality rate						
Overall *(28)*	0.1 (0.1 -0.3)		0.3 (0.1 – 0.6)	0.3 (0.1 – 0.6)		

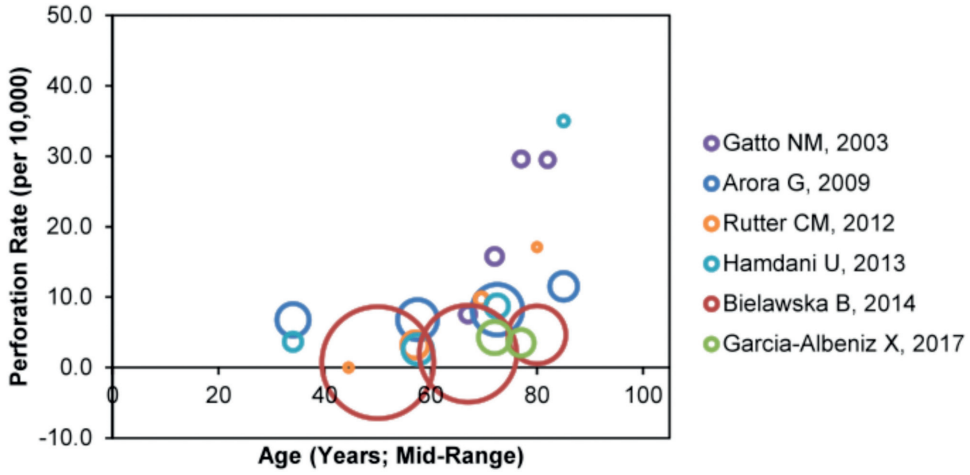
** Includes primary colonoscopy screening and surveillance colonoscopy*
^ After screening with fecal occult blood test
[a] Based on 4 studies [19 26-28]
[b] Based on 1 study [29]

In *Table 2* we present PRs according to type of colonoscopy among subsets of studies by type of patient population. The pooled PRs were 0.5, 3.3 and 4.5 per 10,000 diagnostic colonoscopies for primary screening, follow-up after a positive screen test and mixed or symptomatic patient population, respectively. The pooled PRs were 3.4, 15.2 and 11.6 per 10,000 therapeutic colonoscopies for a population undergoing primary screening, follow-up after a positive screen test and mixed or symptomatic patient population, respectively.

The association between PR with age and sex are presented in *Figures 4a* and *4b*. Higher perforation rates are observed in older age groups. The pooled PR was somewhat higher in women than in men (7.0 [95%CI 3.1 – 16.0] vs. 5.5 [95%CI 2.2 – 13.8]), but not significant.

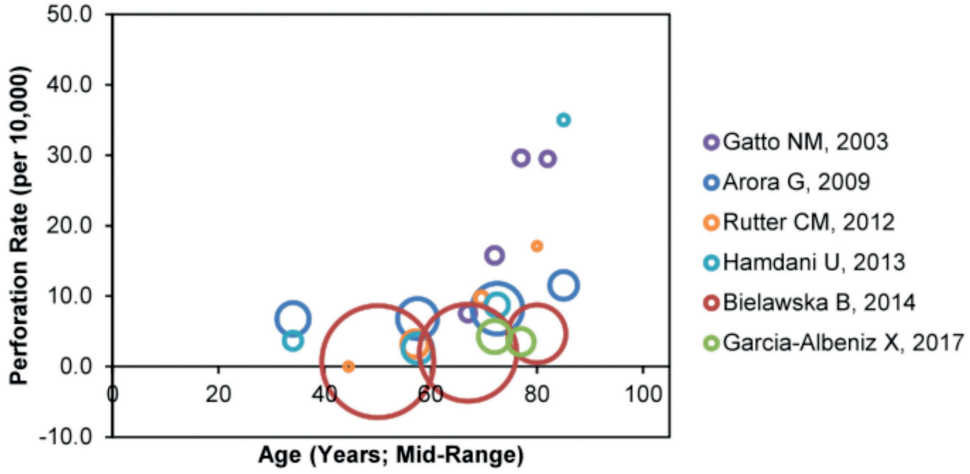
Mortality rate

Figure 5 represents 28 studies that reported on mortality related to colonoscopy. There was significant heterogeneity across included studies (Q= 86, $p < 0.01$; I^2=74.5%). Mortality rates varied from 0 – 6.5 per 10,000 colonoscopies.[19 20] The pooled mortality rate was 0.13 per 10,000 (95%CI 0.05 – 0.34), or 1 death per 76,923 colonoscopies.



The size of the circles reflect study sample size.

Figure 4a. *Crude perforation rate by age in studies that stratified by age category*



The size of the circles reflect study sample size.

Figure 4b. *Crude perforation rate by sex in studies that stratified by sex.*

Associated study characteristics

Table 1 presents associations of study characteristics with perforation and mortality risk. In univariable regression analysis, study characteristics significantly associated (RR [95% CI]) with lower perforation rate were: more recent year of

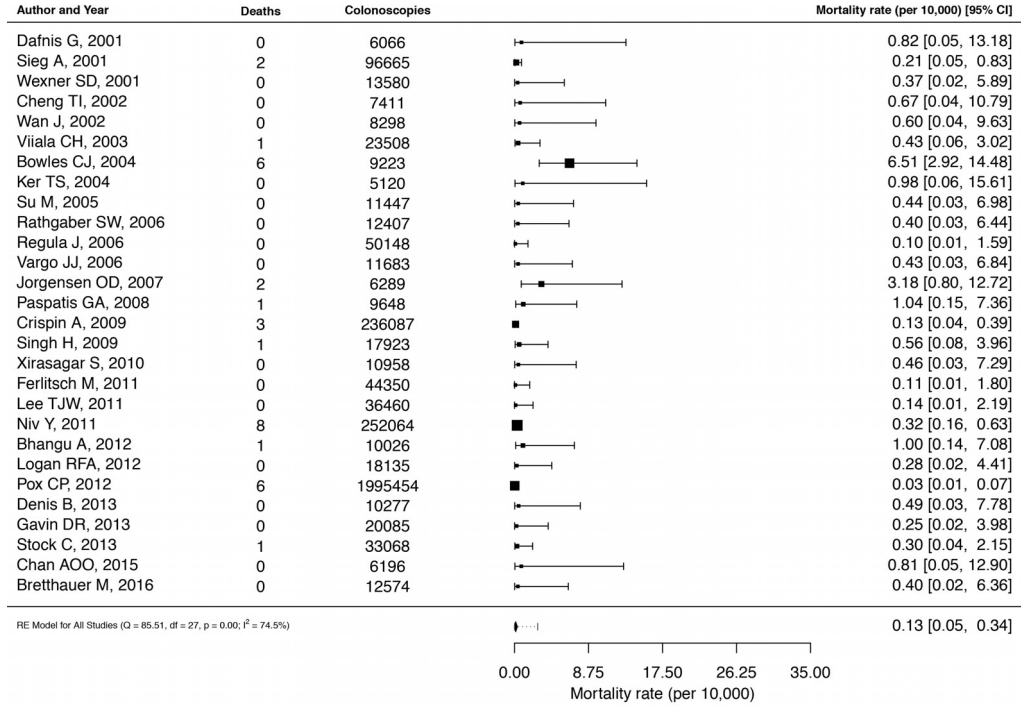


Figure 5. *Forest plot of the fatal complication risk in all included studies and types of exams*

publication (0.95 [95%CI, 0.93 – 0.98] per year per 10,000 colonoscopies); more recent year of data collection (0.96 [95%CI, 0.93 - 0.98] per year per 10,000 colonoscopies); prospective design (0.57 [95%CI, 0.38 – 0.84] per 10,000 colonoscopies); and screening populations (undergoing screening colonoscopy or colonoscopy follow-up after screening with (g)FOBT) (0.48 [95%CI, 0.29 – 0.82] per 10,000 colonoscopies). Characteristics associated with higher perforation rates were studies having complications as primary study endpoint (1.93 [95%CI, 1.30 – 2.88] per 10,000 colonoscopies) and colonoscopy in academic centers (1.64 [95%CI, 1.15 – 2.34] per 10,000 colonoscopies). In multivariate analysis, only year of data collection maintained a significant inverse association with perforation risk (RR = 0.95 [95%CI, 0.93- 0.99] per year per 10,000 colonoscopies).

Mortality rates were inversely associated with a population undergoing colonoscopy for primary screening or follow-up after a positieve screen test compared to a sympthomatic or patient mix population, in the univariable analysis. This finding could not be corroborated in multivariable analysis, since this was not performed due to an insufficient number of studies reporting more than zero fatal colonoscopy-related complications resulting in invalid estimates for subgroups with zero deaths.

Discussion

Main results

This review and meta-analysis showed an overall pooled PR of 5.7 per 10,000 colonoscopies with a decreasing trend over time, from 11.3 in the period 1980 - 1989 to 3.5 in the more recent years (> 2010). The pooled PR was higher for therapeutic colonoscopies (9.7 per 10,000) than for diagnostic colonoscopies (3.4 per 10,000). The PR was lowest in a population undergoing primary screening colonoscopy (1.8 per 10,000), and higher for a mixed patient or symptomatic population (6.3 per 10,000 colonoscopies) and in a population undergoing follow-up colonoscopy after a positive screen test (8.1 per 10,000). The trend of lower PR in therapeutic vs. diagnostic colonoscopies was also observed within population subgroups. The pooled mortality rate was only 0.1 per 10,000 colonoscopies.

Our results suggest that colonoscopy has become safer over time, which is likely due to increased colonoscopy quality, by means of improved endoscopy techniques and more experienced endoscopists (larger volumes per endoscopist), and potentially the shift in population undergoing colonoscopy from patients with symptoms with higher comorbidity to a more healthy population with colonoscopy for (primary) colorectal cancer screening and surveillance. The PR was relatively similar for a population with follow-up colonoscopy after a positive screen test and a mixed patient or symptomatic population, but considerably higher compared with a population undergoing primary colonoscopy screening. The explanation is likely in the nature of the findings during colonoscopy. The yield of (advanced) neoplasia after a positive screen test, especially after Faecal Immunochemical Test, is much higher than in a primary colonoscopy screening population. Therefore the proportion of therapeutic colonoscopies will also be higher, which we showed to be significantly associated with a higher PR compared to diagnostic colonoscopies. The lower PR for therapeutic colonoscopies in a population undergoing primary screening compared with those undergoing colonoscopy follow-up after a positive screen test, may be related to the larger proportion of patient with therapeutic interventions for non-advanced lesions holding a lower risk of perforations.

Comparison to literature

To our knowledge, our study is the first study that has estimated PR according to various populations and type of procedure. Our overall pooled PR is in line with results from other reviews or meta-analyses *(Table 2)*.[21-23] According to pa-

tient population, our pooled PR for primary screening colonoscopies (2 per 10,000) [22 24] and for follow-up colonoscopies after a positive screen test (8 per 10,000) are in line with literature (PR range: 1-3 and 8 per 10,000, respectively) [23], but our PR is substantially lower than reported for colonoscopies mixed patient or symptomatic population (6 vs. 13 per 10,000). [22] The latter may be related to larger studies that we included and the observed lower PR in larger studies. A recent very large US study showed a more similar PR in a symptomatic population (7 per 10,000 colonoscopies). [25] This study reported a PR of 5 per 10,000 colonoscopies for primary screening and surveillance. Unfortunately, this large study did not make a distinction between primary screening and surveillance colonoscopies and did not report on complication rates for follow-up colonoscopies after screen test. As far as we know, only one review reported a pooled mortality rate, in which the presented rate was higher compared to our result *(Table 2)*, which may be related to the smaller studies that they included reporting cases of death. [22]

Strengths and limitations

Our study is one of the few reviews including large (> 5,000) international observational studies, comprising almost 11 million colonoscopies, to examine pooled complication rates over a long period of time (more than 30 years), with univariable and multivariable analysis assessing study-related factors. An important strength of our study is that it considered colonoscopy perforation rates for three separate populations: primary screening, follow-up after positive screen test and mixed patient or symptomatic, including a subdivision according to type of procedure *(Table 2)*. This could help patients make an informed decision about undergoing colonoscopy. Our study also has several limitations. First, we only included large studies comprising at least 5,000 colonoscopies to limit the number of included studies in this review and meta-analysis. This may have resulted in some selection bias, because we may have missed studies focusing on specific subgroups or centers that perform fewer colonoscopies. On the other hand, our selection may have limited the potential for publication bias, which may be more likely to affect small studies, however this cannot be observed from our funnel plot *(Appendix 3)*.

Second, there was a marked variability in characteristics of the included studies (e.g. population, colonoscopy indication, study design, definition of type of colonoscopy, and method of assessment of complications), which explained only part of the statistically significant heterogeneity for the PRs. No patient-level characteristics could be evaluated, which may explain some of the residual

heterogeneity. Missing values on study characteristics resulted in inclusion of fewer studies in the multivariable analysis of associated study characteristics.

Third, the number of days of follow-up after colonoscopy in which the complications were measured varied among studies; from during or immediately after colonoscopy (within 24 hours) to 30 days after the procedure. Although an underestimation of complications may be expected for studies with a short post-colonoscopy follow-up, we did not find a statistically significant difference in perforation rate when comparing various ranges of follow-up time. A recent study reported that most perforations occur within 14 days. [25] More than half of the studies in our analysis covered 14 days of follow-up.

Finally, not all studies had complications as first outcome of interest (primary endpoint). Pooled perforation rates were higher in studies with complications as primary endpoint than in the other studies. This may imply that complications are underreported in regular practice and we may have therefore underestimated the complication rate.

Generalizability, implications and future research

Presented colonoscopy mortality and perforation rates can be used to inform individuals selected to undergo colonoscopy about the risks of the procedure and can serve as benchmark for endoscopy units. The pooled perforation rates we presented in this review are well below the currently formulated quality standards with a maximum of 20 perforations in 10,000 colonoscopies for a mixed patient or symptomatic population and 10 in 10,000 colonoscopies for primary screening colonoscopies. [9] According to these standards, colonoscopy can be regarded as a safe procedure. Our results even imply that current quality thresholds for perforation rates can be more stringent, since our pooled rates are remarkably lower.

Monitoring complications of colonoscopy in clinical practice should be a mainstay of quality control. Especially in settings where a large number of (healthy) individuals is exposed to potential harms of colonoscopy (colonoscopies indicated for CRC screening or surveillance) and when technically more advanced excisions of lesions are performed. These more advanced polypectomy techniques, like endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), may harbor a higher risk of complications. Currently, the ESGE guideline advises excision of large polyps by expert endoscopists before referral for surgery. [10] To accurately monitor the safety of colonoscopy, use of complication registries and complete and uniform registration is essential. Complication registries may include more complications than those related to

the endoscopic procedure. Therefore, it would be good to register the likelihood of the complication to be related to the procedure. More uniform standards for reporting on quality indicators will be needed to further improve the prediction of complication risk at the individual patient level.

Complication registries with the possibility of linkage of data with other registries on the individual level may be useful for future research, like linkages with a registry of causes of death and registries of colonoscopy reports. Complications can then be related to characteristics of colonoscopy and polypectomy, to better inform patients on potential harms of colonoscopy procedures and can make endoscopists and health professionals aware of factors associated with a higher risk of complications. Feedback to gastroenterologist on quality- as well as safety indicators is essential, especially in screening programs. To limit the number of complications, endoscopists' awareness (of complication rates, risk factors, signs and symptoms, and preventive actions to take) and experience are important factors. [21]

Ideally, complications rates should be adjusted for background risk of complications in the general population. Therefore studies that include control populations to correct for risk of certain complications are desired, especially in case of mortality. However, this requires studies with very large sample sizes.

In conclusion, mortality and perforation rates after colonoscopy reported in literature vary substantially, but pooled rates are below the thresholds for colonoscopic complications as set by the Societies for Gastrointestinal Endoscopy. We therefore conclude that colonoscopy is a safe procedure and that quality thresholds may even need to be more stringent to ensure that colonoscopy remains as safe in the future and that these thresholds relate to type of procedure and population. Since the demand of colonoscopies and polypectomies is likely to keep increasing in the near future, especially due to the expansion of colorectal cancer screening programs and because endoscopic techniques keeps evolving, monitoring of complications in clinical practice should be a mainstay of quality control.

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Appendix 1 Search strategies

Medline/PubMed search, 2017-03-14:

1) colonoscopy[ti] AND (complications[sh] OR hemorrhage[mh] OR intestinal perforation[mh] OR adverse effects[sh] OR death[mh] OR mortality[mh]) AND humans[mh] AND adult[mesh] AND (eng[la] OR ger[la] OR dut[la]) AND 1991:3000[dp]
   =>results: n = 1113
2) colonoscopy[mh] AND (complications[sh] OR hemorrhage[mh] OR intestinal perforation[mh] OR adverse effects[sh] OR death[mh] OR mortality[mh]) AND humans[mh] AND adult[mesh] AND (eng[la] OR ger[la] OR dut[la]) AND (clinical trial[pt] OR randomized controlled trial[pt] OR controlled clinical trial[pt]) AND 1991:3000[dp]
   => results: n = 497
3) (mass screening[mh] OR early detection of cancer[mh]) AND colorectal neoplasms[mh] AND humans[mh] AND adult[mesh] AND (eng[la] OR ger[la] OR dut[la]) AND (clinical trial[pt] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR multicenter study[pt]) AND 1991:3000[dp]
   => results: n = 731
4) ((colonoscopy/ae[mesh] AND ((("Randomized controlled trials as Topic"[mesh] OR "Randomized controlled trial"[pt] OR "randomized controlled trial"[tw] OR "randomised controlled trial"[tw] OR "randomized controlled trials"[tw] OR "randomised controlled trials"[tw] OR "Random allocation"[mesh] OR "Double blind method"[mesh] OR "Single blind method"[mesh] OR "Clinical trial"[pt] OR "Clinical Trials as Topic"[mesh] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR ((singl*[tiab] OR doubl*[tiab] OR treb*[tiab] OR tripl*[tiab]) AND (blind*[tiab] OR mask*[tiab])) OR Placebos[mesh:noexp] OR placebo*[tiab] OR (random*[tiab] AND allocat*[tiab])) NOT ("case report"[tiab] OR Letter[pt] OR "Historical article"[pt])) OR ("epidemiologic studies"[mesh] OR "case control studies"[mesh] OR "cohort studies"[mesh] OR "case control"[tw] OR ((cohort[tw] OR follow-up[tw] OR followup[tw] OR observation*[tw]) AND (study[tw] OR studies[tw] OR analys*[tw] OR analyt*[tw]) OR longitudinal[tw] OR retrospective[tw] OR "cross sectional"[tw] OR "cross-sectional studies"[mesh])))) OR ((colonoscop*[tiab] OR coloscop*[tiab) AND (complicat*[tiab] OR adverse[tiab] OR hemorrhag*[tiab] OR haemorrhag*[tiab] OR bleeding[tiab] OR mort*[tiab] OR death[tiab] OR perforat*[tiab]) NOT medline[sb])) AND (adult[mesh] OR adult*[tiab] OR aged[tiab]) AND (eng[la] OR ger[la] OR dut[la]) AND 1991:3000[dp]
   => results: n = 668

EMBASE search, 13-4-2017: 'coloscopy'/exp/dd_ae AND [1991-2017]/py =>
n = 285
dd_ae = subheading adverse effects

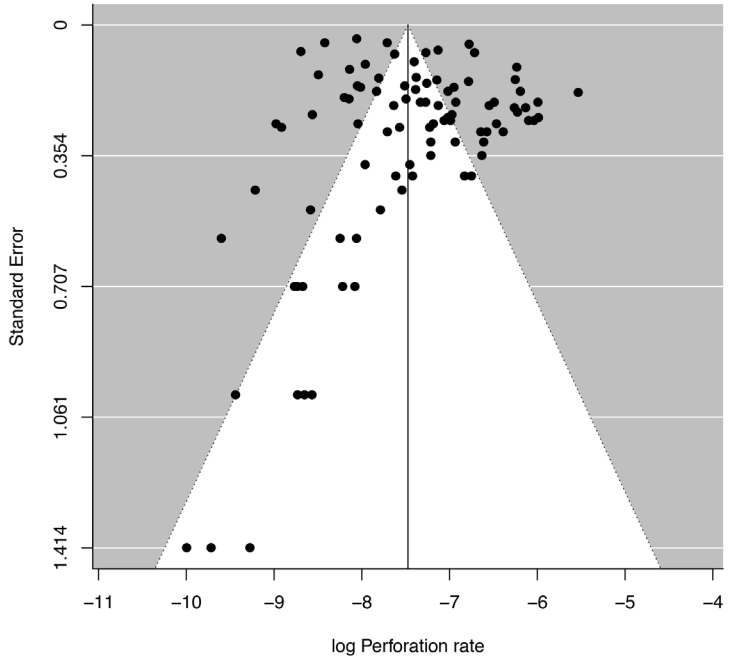
Total (undoubled) articles in search PUBMED + EMBase: n = 2560

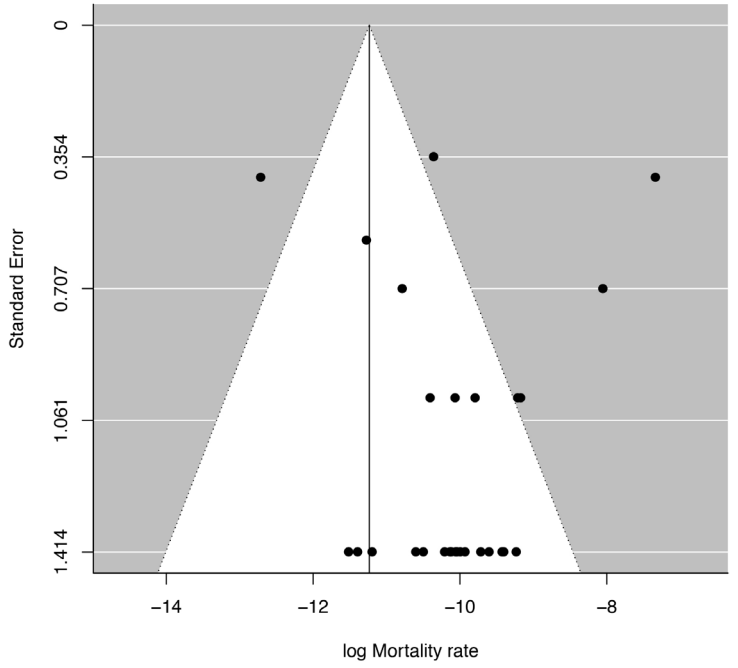
Appendix 2 Characteristics of included studies

Author	Publication year	Primary endpoint is complications	Country	Study design	Population category	Type of centre	Median year of data collection	Age (median)	Age (mean)	Gender (% male)	Number of colonoscopies	Distinction between diagnostic and therapeutic colonoscopies	Number of days of reported complications	Number of reported perforations	Distinction between caused by diagnostic or therapeutic colonoscopies	Stratification for age	Number of deaths related to colonoscopy
Adeyemo [30]	2014	yes	western	retrospective	patient mix	academic	2008	60,6	NA	46,3	118004	no	NA	48	no	no	NA
Adler [31]	2013	yes	western	prospective	screening	other	2007	NA	64,5	47	12134	no	30	6	yes	no	NA
Anderson [32]	2000	yes	western	retrospective	patient mix	academic	1992	NA	NA	NA	10486	no	15	20	yes	no	NA
Araghizadeh [33]	2001	yes	western	retrospective	patient mix	academic	1983	NA	NA	NA	34620	no	2	31	yes	no	NA
Arora [34]	2009	yes	western	retrospective	patient mix	other	2000	NA	64,2	36,3	269712	yes	7	216	yes	yes	NA
Avgerinos [35]	2008	yes	western	retrospective	patient mix	academic	1997	NA	NA	NA	105786	yes	NA	35	yes	no	NA
Bhangu [36]	2012	no	western	prospective	patient mix	other	2008	64	NA	50,2	10026	no	30	6	yes	no	1
Bielawska [37]	2014	yes	western	retrospective	patient mix	other	2005	NA	NA	52,1	1144900	yes	1	192	yes	yes	NA
Blotiere [38]	2014	yes	western	retrospective	patient mix	other	2010	NA	58,2	44,4	947061	yes	3	424	no	no	NA
Blumenstein [39]	2013	no	western	prospective	patient mix	other	2010	NA	66,7	43,5	6450	no	NA	2	yes	no	NA
Bokemeyer [26]	2009	no	western	prospective	screening	other	2005	NA	65,5	44,3	269114	yes	NA	55	yes	no	NA
Bowles [20]	2004	no	western	prospective	patient mix	other	NA	NA	58	50,4	9223	yes	30	12	yes	no	6
Bretthauer [40]	2016	no	western	prospective	patient mix	other	2012	60	NA	51,6	12574	no	30	1	no	no	0
Broeders [41]	2015	yes	western	retrospective	patient mix	academic	2009	NA	NA	NA	18449	no	NA	14	yes	no	NA
Chan AOO [42]	2015	yes	non-western	prospective	patient mix	other	2012	NA	53,7	49,3	6196	yes	30	1	yes	no	0
Chan WK [43]	2013	yes	non-western	retrospective	patient mix	academic	2008	NA	NA	NA	7136	no	NA	12	yes	no	NA
Chao [44]	1997	yes	non-western	retrospective	patient mix	other	1988	NA	NA	NA	9214	yes	NA	20	yes	no	NA
Cheng [45]	2002	no	non-western	prospective	screening	academic	1999	NA	46,8	55	7411	no	NA	2	no	no	0
Chukmaitov [14]	2013	yes	western	retrospective	patient mix	other	2001	NA	60,8	45,8	2315126	yes	30	733	no	no	NA
Chung [46]	2010	no	non-western	retrospective	screening	academic	2006	NA	48	65,8	5254	no	NA	1	yes	no	NA
Cobb [47]	2004	yes	western	retrospective	patient mix	academic	2000	NA	NA	NA	43609	no	3	14	yes	no	NA
Cooper [48]	2013	yes	western	retrospective	patient mix	other	2005	NA	75,5	45	165527	yes	30	101	yes	no	NA
Cotton [49]	2003	no	western	retrospective	patient mix	other	1996	NA	NA	50	17868	no	NA	13	no	no	NA
Crispin [50]	2009	yes	western	retrospective	patient mix	other	2006	61	NA	43,3	236087	yes	NA	69	no	no	3
Dafnis [51]	2001	yes	western	retrospective	patient mix	other	1987	60	NA	NA	6066	yes	30	8	yes	no	0
Denis [29]	2013	yes	western	prospective	FU-screen	other	2007	NA	62,7	NA	10277	yes	30	10	yes	no	0
Dominitz [52]	2012	no	western	retrospective	patient mix	other	2003	NA	74,1	42,3	328167	no	30	374	no	no	NA
Farley [53]	1997	yes	western	retrospective	patient mix	academic	1987	NA	NA	NA	57028	no	NA	45	yes	no	NA
Ferlitsch [27]	2011	no	western	prospective	screening	other	2009	60,7	NA	49	44350	yes	NA	3	yes	no	0
Foliente [54]	1996	yes	western	retrospective	patient mix	academic	1990	NA	NA	NA	6684	yes	NA	15	no	no	NA
Garcia-Albeniz [55]	2017	no	western	prospective	patient mix	other	2004	NA	72,4	50,1	78065	no	30	31	no	yes	NA
Garcia-Martinez [56]	2007	yes	western	retrospective	patient mix	academic	1999	NA	NA	NA	16285	no	6	15	yes	no	NA
Gatto [57]	2003	yes	western	retrospective	patient mix	other	1995	NA	74,4	43	39286	no	7	77	no	yes	NA
Gavin [58]	2013	no	western	prospective	patient mix	other	2011	NA	NA	NA	20085	no	8	7	yes	no	0
Gedebou [59]	1996	yes	western	retrospective	patient mix	academic	1991	NA	NA	NA	9106	no	NA	18	yes	no	NA
Hall [60]	1991	yes	western	retrospective	patient mix	other	NA	NA	NA	NA	17500	no	3	15	yes	no	NA
Hamdani [61]	2013	yes	western	retrospective	patient mix	other	2006	NA	59,1	46,7	80118	yes	7	50	yes	yes	NA
Hsieh [62]	2009	yes	non-western	retrospective	patient mix	other	2002	NA	51,17	58,4	9501	no	3	3	yes	no	NA
Hsu [63]	2012	no	non-western	retrospective	patient mix	academic	2008	NA	49,5	56	5332	no	NA	0	yes	no	NA
Imperiali [64]	2007	no	western	prospective	patient mix	other	2003	NA	NA	NA	9434	no	NA	5	yes	no	NA
Iqbal [65]	2008	yes	western	retrospective	patient mix	academic	1993	NA	NA	NA	258248	yes	30	180	yes	no	NA
Jentschura [66]	1994	yes	western	prospective	patient mix	academic	1986	62,2	NA	65,5	15159	yes	8	31	yes	no	NA
Jorgensen [67]	2007	no	western	prospective	patient mix	academic	1990	NA	60,5	58,2	6289	no	NA	15	yes	no	2
Jovanovic [68]	2011	yes	western	retrospective	patient mix	academic	2005	NA	NA	NA	8601	yes	0	12	yes	no	NA
Kang [69]	2008	yes	non-western	retrospective	patient mix	academic	2003	NA	NA	NA	23874	yes	2	46	yes	no	NA
Ker [15]	2004	yes	western	retrospective	patient mix	-999	1996	NA	63	54	5120	yes	4	6	yes	no	0
Kim [70]	2013	yes	non-western	retrospective	patient mix	academic	2006	NA	NA	NA	94632	yes	NA	26	yes	no	NA
Ko [71]	2010	yes	western	prospective	screening & FU-screen	other	NA	NA	63,2	55	21375	yes	30	4	yes	no	NA
Korman [72]	2003	yes	western	retrospective	patient mix	other	1999	NA	NA	NA	116000	no	4	37	yes	no	NA
Lee [73]	2012	no	western	prospective	FU-screen	other	2008	NA	66	61,6	36460	no	30	35	no	no	0
Lo [74]	1994	yes	western	retrospective	patient mix	academic	1989	NA	NA	NA	26708	yes	NA	12	yes	no	NA
Logan [75]	2012	no	western	prospective	FU-screen	other	2007	NA	NA	60,5	18135	no	NA	17	no	no	0

Author	Publication year	Primary endpoint is complications	Country	Study design	Population category	Type of centre	Median year of data collection	Age (median)	Age (mean)	Gender (% male)	Number of colonoscopies	Distinction between diagnostic and therapeutic colonoscopies	Number of days of reported complications	Number of reported perforations	Distinction between caused by diagnostic or therapeutic colonoscopies	Stratification for age	Number of deaths related to colonoscopy
Lohsiriwat [76]	2009	yes	non-western	prospective	patient mix	academic	2006	NA	NA	NA	8987	no	30	14	yes	no	NA
Lorenzo-Zuniga [77]	2010	yes	western	retrospective	patient mix	academic	2001	NA	57,4	NA	25214	yes	NA	13	yes	no	NA
Lüning [78]	2007	yes	western	retrospective	patient mix	academic	1998	NA	NA	NA	9209	no	NA	23	no	no	NA
Magdeburg [16]	2008	yes	western	retrospective	patient mix	academic	2005	NA	NA	NA	7589	yes	NA	30	yes	no	NA
Mai [79]	2010	yes	non-western	retrospective	patient mix	other	2003	NA	NA	NA	35186	no	NA	23	yes	no	NA
Miller [80]	1991	yes	western	retrospective	patient mix	academic	1981	NA	NA	NA	14670	yes	6	21	yes	no	NA
Misra [81]	2004	yes	western	retrospective	patient mix	academic	1999	NA	NA	NA	7425	yes	14	10	yes	no	NA
Niv [82]	2011	yes	non-western	retrospective	patient mix	other	2003	NA	NA	NA	252064	no	NA	88	no	no	8
Okholm [83]	2013	yes	western	retrospective	patient mix	other	2008	NA	NA	NA	6371	yes	NA	16	yes	no	NA
Paspatis [21]	2008	yes	western	retrospective	patient mix	other	2001	62	NA	48,8	9648	yes	30	4	yes	no	1
Pox [19]	2012	no	western	prospective	screening	other	2006	NA	NA	NA	1995454	yes	NA	439	yes	no	6
Quintero [84]	2012	no	western	prospective	screening & FU-screen	other	NA	NA	NA	NA	5722	no	NA	1	no	no	NA
Rabeneck [85]	2011	yes	western	retrospective	patient mix	other	2002	NA	NA	NA	67632	no	30	37	yes	no	NA
Radaelli [86]	2008	no	western	prospective	patient mix	other	2004	63	NA	53	12835	yes	1	2	no	no	NA
Rainis [87]	2007	no	non-western	retrospective	patient mix	academic	2002	NA	NA	45	10866	no	1	8	no	no	NA
Ranasinghe [88]	2016	yes	western	retrospective	patient mix	other	2010	NA	74,2	46	331880	no	7	162	no	no	NA
Rathgaber [89]	2006	yes	western	retrospective	patient mix	other	2003	NA	59,7	47,8	12407	yes	30	2	yes	no	0
Regula [28]	2006	no	western	prospective	screening	other	2003	NA	55,2	35,9	50148	yes	30	5	yes	no	0
Rutter [90]	2012	yes	western	retrospective	patient mix	other	2002	NA	60,1	49	43456	yes	30	21	yes	yes	NA
Samalavicius [91]	2013	yes	western	retrospective	patient mix	other	2009	NA	NA	NA	56882	yes	NA	40	yes	no	NA
Shi [7]	2014	yes	non-western	retrospective	patient mix	academic	2006	NA	67,14	50	110785	yes	6	14	yes	no	NA
Shin [92]	2016	yes	non-western	retrospective	patient mix	academic	2013	NA	NA	NA	5542	yes	5	6	yes	no	NA
Sieg [93]	2001	yes	western	prospective	patient mix	other	1998	NA	NA	NA	96665	yes	3	13	yes	no	2
Singh [94]	2009	yes	western	retrospective	patient mix	other	2005	NA	NA	NA	17923	yes	30	16	yes	no	1
Stock [95]	2013	yes	western	retrospective	patient mix	other	2005	NA	61	44	33068	no	30	23	yes	no	1
Su [96]	2005	no	non-western	retrospective	patient mix	academic	2001	NA	53	62,3	11447	yes	NA	3	yes	no	0
Taku [97]	2007	yes	non-western	retrospective	patient mix	academic	2001	NA	NA	NA	15160	yes	NA	23	yes	no	NA
Tam [98]	2013	yes	western	retrospective	patient mix	academic	2003	NA	NA	NA	86101	no	30	25	no	no	NA
Teoh [99]	2009	no	non-western	retrospective	patient mix	other	2002	NA	NA	NA	37971	no	NA	43	yes	no	NA
Tran [100]	2001	yes	western	retrospective	patient mix	academic	1996	NA	NA	NA	26162	yes	NA	21	yes	no	NA
Tulchinsky [101]	2006	yes	non-western	retrospective	patient mix	academic	1998	NA	NA	NA	12067	no	1	7	yes	no	NA
Vargo [102]	2006	no	western	prospective	patient mix	other	2001	NA	60,8	43,1	11683	no	NA	2	no	no	0
Viiala [103]	2003	yes	non-western	retrospective	patient mix	other	1995	61	NA	45	23508	no	30	23	yes	no	1
Wan [17]	2002	no	non-western	prospective	patient mix	-999	1992	NA	70,5	94,1	8298	no	NA	0	yes	no	0
Warren [104]	2009	yes	western	retrospective	patient mix	other	2003	NA	74,8	41,7	53220	yes	30	33	yes	no	NA
Wexner [105]	2001	yes	western	prospective	patient mix	other	1999	NA	NA	NA	13580	yes	NA	10	yes	no	0
Xirasagar [18]	2010	no	western	retrospective	patient mix	other	2004	NA	58,3	48	10958	no	NA	0	yes	no	0
Zafar [8]	2014	yes	western	retrospective	patient mix	other	2008	NA	74,4	45,3	149202	no	30	181	no	no	NA
Zhang [106]	2013	yes	non-western	retrospective	patient mix	academic	2009	NA	NA	NA	89014	yes	1	17	yes	no	NA
Zorzi [107]	2011	no	western	prospective	FU-screen	other	2009	NA	NA	NA	45041	no	NA	25	yes	no	NA

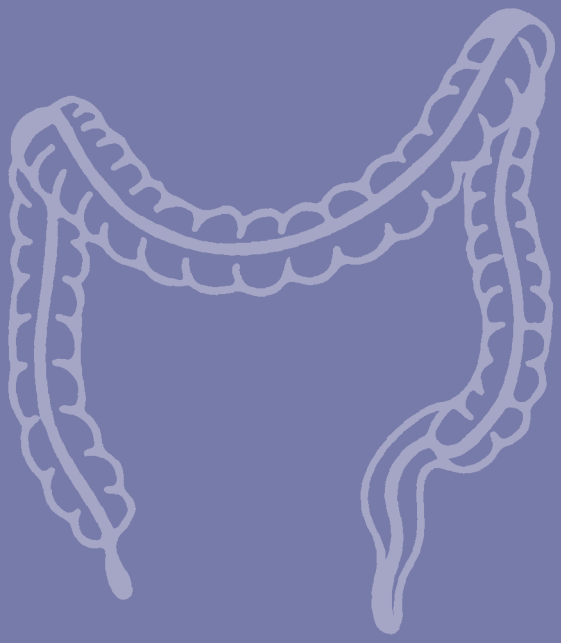
Appendix 3 Funnel plots of studies with perforation rates (upper) and mortality rates (lower).





Part II

Predictors of (advanced) neoplasia recurrence and more efficient surveillance of adenoma patients



Chapter 3

Features of adenoma and colonoscopy associated with recurrent colorectal neoplasia based on a large community-based study

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Abstract

Background & Aims: We investigated adenoma and colonoscopy characteristics that are associated with recurrent colorectal neoplasia based on data from community-based surveillance practice.

Methods: We analyzed data on 2990 consecutive patients (55% male; mean age 61 years) newly diagnosed with adenomas from 1988 to 2002 at 10 hospitals throughout the Netherlands. Medical records were reviewed until December 1, 2008. We excluded patients with hereditary colorectal cancer (CRC) syndromes, a history of CRC, inflammatory bowel disease, or without surveillance data. We analyzed associations among adenoma number, size, grade of dysplasia, villous histology, and location with recurrence of advanced adenoma (AA) and non-advanced adenoma (NAA). We performed a multivariable multinomial logistic regression analysis to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: During the surveillance period, 203 (7%) patients were diagnosed with AA and 954 (32%) patients with NAA. The remaining 1833 (61%) patients had no adenomas during a median follow-up of 48 months. Factors associated with AA during the surveillance period included baseline number of adenomas (ORs ranging from 1.6 for 2 adenomas; 95% CI: 1.1–2.4 to 3.3 for ≥5 adenomas;95% CI: 1.7–6.6), adenoma size ≥10 mm (OR = 1.7; 95% CI: 1.2–2.3), villous histology (OR = 2.0; 95% CI: 1.2–3.2), proximal location (OR = 1.6; 95% CI: 1.2−2.3), insufficient bowel preparation (OR = 3.4; 95% CI: 1.6-7.4), and only distal colonoscopy reach (OR = 3.2; 95% CI: 1.2-8.5). Adenoma number had the greatest association with NAA. High-grade dysplasia was not associated with AA or NAA.

Conclusions: Large size and number, villous histology, proximal location of adenomas, insufficient bowel preparation, and poor colonoscopy reach were associated with detection of AA during surveillance based on data from community-based practice. These characteristics should be used jointly to develop surveillance policies for adenoma patients.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the Western world.[1, 2] Detecting and removing (early-stage) cancers and precursor lesions (adenomas) can reduce CRC incidence and mortality.[3-5] Individuals in whom adenomas are detected have an increased risk of CRC developing compared with the average population, even after the adenoma has been removed.[4, 6-9] Therefore it is recommended that adenoma patients undergo regular surveillance colonoscopy.[10-14] Surveillance colonoscopy currently presents a considerable burden for individuals and demand on endoscopy units. To increase the efficacy of surveillance, risk stratification based on advanced adenoma (AA) recurrence rates with well-allocated surveillance intervals is needed. Patients with high-risk adenomas, so called "advanced adenomas", or with >2 adenomas are especially known for higher advanced adenoma recurrence rates.[4, 9, 15, 16] Advanced adenomas are usually defined as adenoma(s) with at least one of the following characteristics size ≥10mm, high-grade dysplasia (HGD), and (tubulo)villous histology.

Currently recommended surveillance intervals differ between countries and institutions, and are predominantly based on adenoma multiplicity and categorization of an adenoma as advanced or nonadvanced.[11-13] None of the surveillance guidelines have incorporated recommendations when specific combinations of the various aspects (ie, size ≥10mm, villousness, HGD) of advanced adenomas are present. Previous studies suggested that these adenoma characteristics are independent predictors of adenoma recurrence, but these studies were often small or assessed the adenoma predictors one at a time.[17-19] Two meta-analyses explored the predictive effect of individual adenoma characteristics on AA recurrence.[9, 19] These studies included data from clinical trials performed in the United States, often with high quality examinations and per-protocol surveillance intervals. Most studies included patients with prior adenomas and without certain medical conditions, and approximately half of the population included also underwent a dietary or chemopreventive intervention. The aim of the present study was to determine independent adenoma-related and colonoscopy-related predictors and their associated odds ratios for (advanced) colorectal adenomas during clinical surveillance practice in a large community-based study.

Methods

Data collection

We used the nationwide registry of histopathology and cytopathology (PALGA) to select patients with newly diagnosed adenoma between 1988 and 2002 from 10 hospitals (3 academic and 7 nonacademic) in The Netherlands. Participating hospitals were selected on the basis of long-term availability of electronic medical records and geographical distribution throughout The Netherlands. Years of inclusion of adenoma patients depended on the availability of electronic medical records per hospital. Local hospital medical records, mainly endoscopy and pathology reports, were reviewed until December 1, 2008 to collect information on patient characteristics and adenoma characteristics at index colonoscopy and surveillance endoscopies. Patients with any of the following criteria were excluded: age at index colonoscopy younger than 40 years; (suspected) hereditary CRC syndromes, such as Lynch syndrome (hereditary nonpolyposis colorectal carcinoma), familiar adenomatous polyposis, Peutz-Jeghers syndrome, juvenile polyposis, or mutYH-polyposis; personal history of CRC or CRC at index colonoscopy; inflammatory bowel disease; hyperplastic polyps (nonadenomatous polyps) only; (partial) colonic bowel resections before or at the time of index colonoscopy; acromegaly; uretero-sigmoidostomy; index endoscopy was a sigmoidoscopy; missing pathology or endoscopy report at index colonoscopy; and no surveillance endoscopy.

The study was approved by the Institutional Review Board at the Erasmus MC University Medical Center and confirmed by the local Institutional Review Board of each participating hospital.

Measures and Definitions

Index colonoscopy was defined as the colonoscopy with first adenoma diagnosis. Repeat endoscopy examinations performed within 6 months were considered as one examination and histological findings were combined. In case of combining results from endoscopies, date of last colonoscopy was used.

The adenoma characteristics collected at index and surveillance endoscopies were number of adenomas, and per adenoma found: size (measured by endoscopist and pathologist), presence of HGD and villous histology, and location. For the analysis, we coded the number of adenomas as 1 to 5+, and used endoscopic size of the largest adenoma categorized as <10mm or ≥10mm. Histological characteristics (HGD and villous histology) in any adenoma were coded as present or absent. Adenoma location was considered proximal if at least 1

adenoma was located proximal to the splenic flexure or if location was not specified when located at an endoscope insertion of ≥60cm. The colonoscopy-related characteristics collected at index colonoscopy were colonoscopy reach (coded as full [to cecum], proximal colon, or distal colon), and index bowel preparation (coded as good, moderate, or insufficient).

The 2 outcomes of interest were presence of at least 1 AA and presence of non-advanced adenoma (NAA) only at surveillance endoscopy. We defined an AA as an adenoma with at least1 of the following characteristics: size ≥10mm (either on endoscopic description or pathology), villous histology (≥75% villous architecture), or HGD (including intramucosal carcinoma or carcinoma in situ), or CRC. In contrast, we defined NAA as size <10mm, with tubular or tubulovillous histology, and with low-grade dysplasia. In cases where more than1 adenoma was found, patients were categorized according to most advanced features. We present absolute numbers and percent with AA and NAA at surveillance colonoscopy.

Statistical analysis

Missing values

We coded missing values as negative for presence of HGD, villous histology, and a proximal location. We assumed "a good bowel preparation" and "a full colonoscopy," respectively, when bowel preparation and completeness of colonoscopy were not explicitly documented (n = 2141 and n = 58, respectively). For missing values concerning endoscopic adenoma size at index colonoscopy (n = 584) and sex (n = 2) we used a statistical imputation technique.[20] Imputations were based on correlations with patient characteristics at index colonoscopy: age and gender; adenoma characteristics at index colonoscopy: number of adenomas (1-5+), presence of HGD, (tubulo)villous histology (villous, tubulovillous, tubular), proximal location, and adenoma size (pathology); year of index colonoscopy; outcome (AA, NAA, or no adenoma during surveillance); and surveillance interval, using the aregImpute function in R v2.11 software (R foundation for statistical computing, Vienna, Austria). It is good methodological practice to include the outcome variable in the imputation of predictor variables to avoid biased imputations.[21] The outcome is related to the predictor values; by omitting the outcome in the imputation, the association between the predictor and outcome will falsely be weakened. Imputing missing outcomes was not considered.[21] For adenoma size at surveillance colonoscopy, we used either endoscopic size or size at pathology (size ≥10mm) if available and otherwise we assumed that the adenoma size was < 10mm.

Strength of the association

Multinomial logistic regression analysis was used to assess odds ratios (OR) of predictors of AA and NAA during surveillance. We used a modulated renewal method[22] to make full use of the available follow-up data. For this purpose, we included further surveillance data when available, in those patients with a (consecutive) negative surveillance endoscopy (no AA or NAA) until AA or NAA was observed, or until the last negative surveillance endoscopy, with a maximum of the fifth surveillance period. For these patients, multiple records were included in the dataset, one for each included surveillance event. For each record, the time of surveillance was calculated from the index date (date of colonoscopy with first adenoma diagnosis) to the date of the surveillance endoscopy and the end point was the finding at that particular surveillance endoscopy (AA/CRC, NAA, no adenoma). For example, if a patient had 2 negative surveillance endoscopies and at the third surveillance examination a NAA detected, this patient was included 3 times in our database. This modulated renewal method leads to analysis of all first NAAs and AA/CRCs that occur during follow-up. It enhances the efficiency of the estimation with smaller standard errors of the estimated parameters.

Both univariable and multivariable analyses were performed, in the latter with adjustment for age at index colonoscopy, sex, surveillance interval (coded in years), and number of surveillance endoscopies (coded as 1 - 5) besides the adenoma and colonoscopy characteristics of the index colonoscopy (baseline examination). Analyses were performed using SPSS v17.0 (SPSS Inc, Chicago, IL).

Results

In total, 7086 patients were eligible for inclusion based on a colonoscopy with adenoma removal in one of the participating centers in the study period. Of these, 1674 patients were excluded for reasons of missing pathology (n = 25) or endoscopy reports (n = 1582), or both (n = 67). Another 2422 patients were excluded because of absence of surveillance endoscopy in the study period. The remaining 2990 patients were included in further analysis *(Figure 1)*. The excluded patients were older compared with the included patients (67 vs. 61 years, *Table 1)*, which was in line with expectations, as age is a determinant for the indication of surveillance. There were no differences with respect to sex (56% vs. 55%) and median year of index colonoscopy (2000 for both, *Table 1*). Patients included in our analysis had a higher proportion of AA at index colonoscopy as compared with those without surveillance (38% vs 30%, based on nonimputed variables; P <.001).

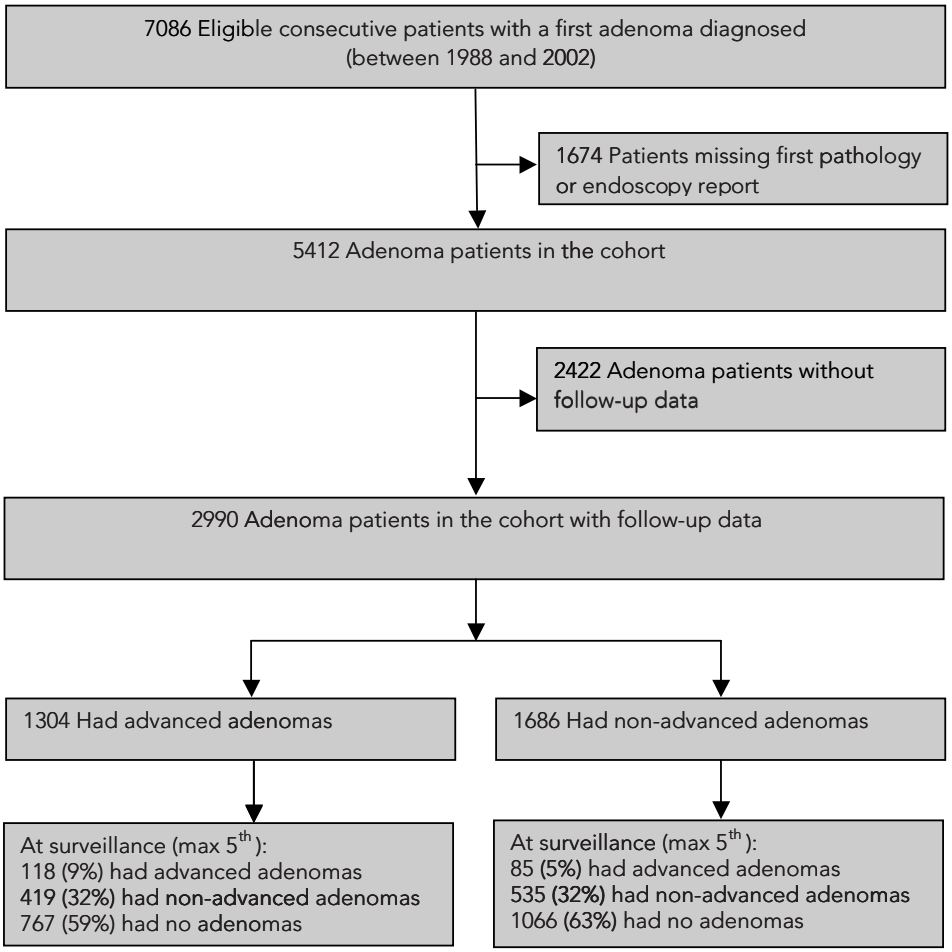

Figure 1 . The study cohort.
Percentages should be interpreted cautiously because they are not based on a formal Kaplan-Meier analysis.

Table 1. Characteristics of Included Patients (With Surveillance) and Excluded Patients (Without Surveillance Endoscopy or Missing Reports)

	Included patients (N = 2990)	Excluded patients (n = 4096)
Male sex n, (%)	1647 (55)	2284 (56)
Age, y, mean	61.3	66.5 [a]
Median year of index endoscopy	2000	2000

[a] *Significant P <.05.*

Mean number of adenomas at index colonoscopy was 1.6 (range, 1 - 15). Only 2.6% had ≥5 adenomas at index colonoscopy. One third of the patients had an adenoma ≥10mm and a similar proportion had one with proximal location *(Table 2)*. Correlations between the different adenoma characteristics at index colonoscopy were modest. The strongest correlation was found between adenoma number and proximal location (Pearson r = .33).

Median interval until first surveillance endoscopy was 24 months (interquartile range [IQR], 12 – 40 months). At first surveillance, 171 patients were diagnosed with at least one AA (median interval, 27 months; IQR, 12 – 57 months), including 26 CRCs (median interval, 40 months; IQR, 20 – 79 months), 655 patients were diagnosed with NAA only (median interval, 25 months; IQR, 13 – 40 months), and 2164 patient had no adenoma or cancer (median interval, 23 months; IQR, 12 – 39 months). Of the 2164 patients with a negative first surveillance endoscopy, 1026 had more than 1 surveillance endoscopy *(Figure 2)*. Median interval between first and second surveillance was 36 months (IQR, 20 – 49 months) in these patients, 200 patients were diagnosed with NAA and 23 with AA. In patients with NAA at first surveillance, the next surveillance was after a median interval of 27 months (IQR, 14 – 39; n = 373), and in patients with AA this was 15 months (IQR, 11 – 28; n = 83). In these last 2 groups at second surveillance, 129 NAA and 8 AA and 31 NAA and 2 AA, respectively, were found *(Table 3)*. When including subsequent surveillance events after a (first) negative surveillance colonoscopy (until a first event or last negative), the mean number of surveillance endoscopies included for those with a negative first surveillance was 1.7. Adding these surveillance examinations increased the number of patients with AA at surveillance to 203 (including 38 CRCs) and with NAA to 954, after a median follow-up period of 35 months (IQR, 13 – 64 months) and 36 months (IQR, 15 – 64 months), respectively. Median follow-up for 1833 patients without any adenoma or cancer was 48 months.

Table 2. Characteristics of the Study Population at Index Colonoscopy (N = 2990)

Characteristic at index colonoscopy	All patients (N = 2990)	Stratified by highest findings at surveillance endoscopy			
		No adenoma (n = 1833)	NAA[a] (n = 954)	AA(-CRC)[b] (n = 165)	CRC (n = 38)
Demographics					
Male sex, n (%)	1647 (55.1)	940 (51.3)	578 (60.6)	106 (64.2)	23 (60.5)
Age groups, n (%)					
40-49	439 (14.7)	285 (15.5)	135 (14.2)	18 (10.9)	1 (2.6)
50-59	865 (28.9)	528 (28.8)	289 (30.3)	38 (23.0)	10 (26.3)
60-69	982 (32.8)	582 (31.8)	331 (34.7)	58 (35.2)	11 (28.9)
70-79	593 (19.8)	368 (20.1)	173 (18.1)	38 (23.0)	14 (36.8)
80-89	111 (3.7)	70 (3.8)	26 (2.7)	13 (7.9)	2 (5.3)
Adenoma characteristics at index					
No. of adenomas, n (%)					
1	2043 (68.3)	1373 (74.9)	562 (58.9)	83 (50.3)	25 (65.8)
2	559 (18.7)	299 (16.3)	212 (22.2)	39 (23.6)	9 (23.7)
3	241 (8.1)	104 (5.7)	112 (11.7)	21 (12.7)	4 (10.5)
4	68 (2.3)	29 (1.6)	31 (3.2)	8 (4.8)	-
5+	79 (2.6)	28 (1.5)	37 (3.9)	14 (8.5)	-
Patients with any adenoma with:					
Size ≥10mm, n (%)[c]	1171 (39.2)	684 (37.3)	379 (39.7)	88 (53.3)	20 (52.6)
Villous histology, n (%)	155 (5.2)	90 (4.9)	39 (4.1)	20 (12.1)	6 (15.8)
HGD, n (%)	419 (14.0)	241 (13.1)	131 (13.7)	34 (20.6)	13 (34.2)
Proximal location, n (%)	950 (31.8)	519 (28.3)	341 (35.7)	77 (46.7)	13 (34.2)
Any advanced adenoma, n (%)[d]	1304 (43.6)	767 (41.8)	419 (43.9)	94 (57.0)	24 (63.2)
Colonoscopy characteristics at index					
Reach colonoscopy, n (%)					
Full, to cecum[e]	2780 (93.0)	1705 (93.0)	884 (92.7)	156 (94.5)	35 (92.1)
Proximal colon	177 (5.9)	109 (5.9)	61 (6.4)	5 (3.0)	2 (5.3)
Distal colon	33 (1.1)	19 (1.0)	9 (0.9)	4 (2.4)	1 (2.6)
Bowel preparation, n (%)					
Good[f]	2718 (90.9)	1665 (90.8)	870 (91.2)	152 (92.1)	31 (81.6)
Moderate	227 (7.6)	141 (7.7)	75 (7.9)	5 (3.0)	6 (15.8)
Insufficient	45 (1.5)	27 (1.5)	9 (0.9)	8 (4.8)	1 (2.6)

AA, advanced adenoma; CRC, colorectal cancer; NAA, nonadvanced adenoma; HGD, high-grade dysplasia.

[a] Includes adenomas <10mm, with tubular or tubulovillous histology and low-grade dysplasia.

[b] Includes adenomas with one or more of the following characteristics; villous histology, HGD, and size ≥10mm.

[c] Based on the imputed size variable, 584 missing values were imputed.

[d] Advanced adenoma includes adenomas with one or more of the following characteristics; villous histology, HGD, and size ≥10mm. Size is based on the imputed size variable.

[e] These were missing in 58 cases and assumed to be full colonoscopies.

[f] These were missing in 2141 cases and assumed to have good bowel preparation.

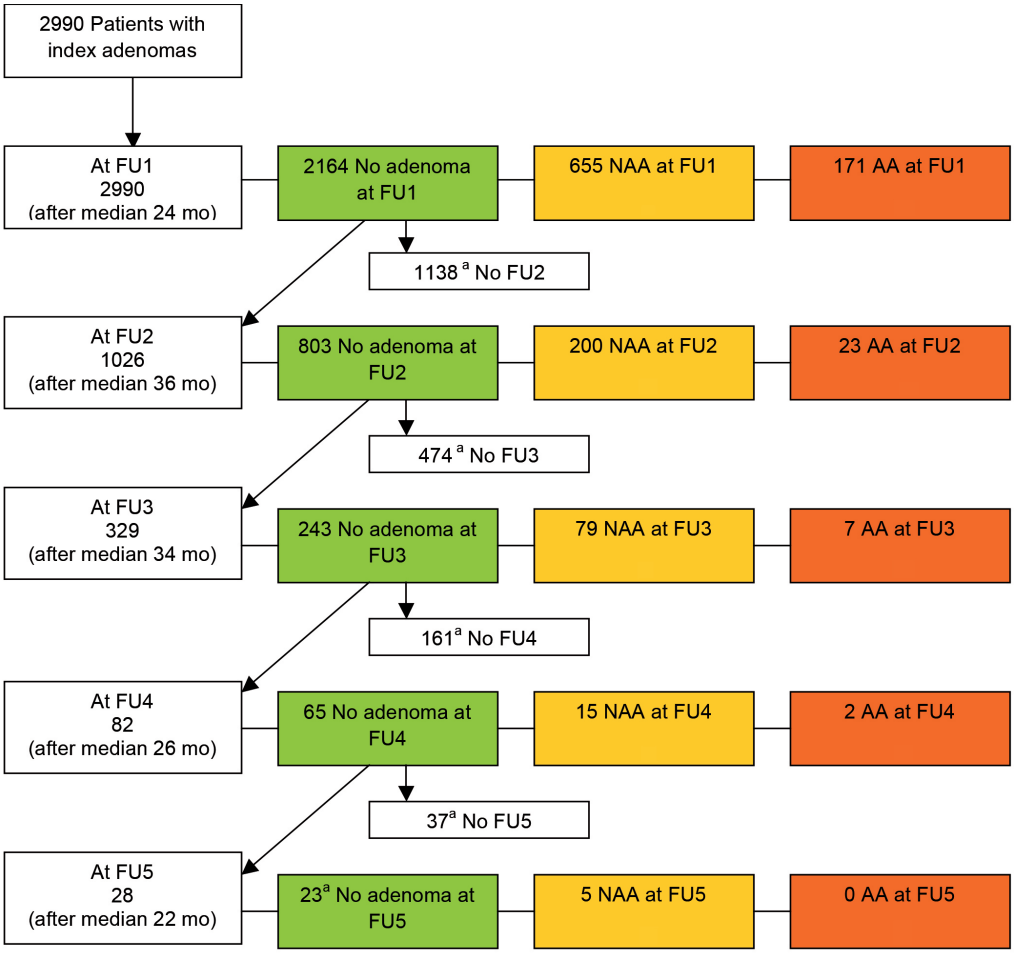

Figure 2. *Flow chart of findings (and median interval) of first and subsequent (for patients without adenomas at previous examinations) surveillance examinations.*

AA includes adenomas with one or more of the following characteristics; villous histology, HGD, and size ≥10mm, including CRC. NAA includes adenomas <10mm, with tubular or tubulovillous histology and low-grade dysplasia. Red blocks add up to 203 patient records with AA at surveillance (in 203 patients). Orange blocks add up to 954 patient records with NAA at surveillance (in 954 patients). Green blocks add up to 3298 patient records with no adenoma at surveillance (in 1833 patients).

[a] Adds up to the number of patients with no adenoma detected at surveillance

FU, Follow-up examination/endoscopy

Table 3. Adenoma Type at First vs Second Surveillance Endoscopies According to Index Findings in (n = 1482) With at Least 2 Surveillance Endoscopies.

Most advanced finding at index colonoscopy	Most advanced finding at first surveillance	Individuals with second surveillance, n (%)	Most advanced finding at second surveillance, n (%)			Median time interval between index to first / first to second examination *(mos)*
			Advanced adenoma	Nonadvanced adenoma	No adenoma	
Advanced adenoma	AA	50 (53)	2 (4)	17 (34)	31 (62)	14 / 15
	NAA	173 (61)	6 (3)	54 (31)	113 (65)	13 / 27
	No	473 (51)	17 (4)	87 (18)	369 (78)	13 / 30
Nonadvanced adenoma	AA	33 (43)	0 (0)	14 (42)	19 (58)	20 / 19
	NAA	200 (54)	2 (1)	75 (38)	123 (62)	19 / 27
	No	553 (45)	6 (1)	113 (20)	434 (78)	17 / 37

NOTE. All values in table concern subjects with at least 2 surveillance colonoscopies.
AA, advanced adenoma; NAA, non-advanced adenoma; No, no adenoma.

Adenoma-related characteristics at index colonoscopy predictive for AA were the number of adenomas (multivariable ORs ranging from 1.6; 95% confidence interval [CI]:1.1 – 2.4 for 2 adenomas to 3.3; 95% CI:1.7 – 6.6 for patients with ≥5 adenomas); any adenoma with a large size (≥10mm; OR = 1.7; 95% CI:1.2 – 2.3), a villous histology (OR = 2.0; 95% CI:1.2 – 3.2); and proximal location (OR = 1.6; 95% CI: 1.2 – 2.3); *Table 4)*. HGD was not predictive in the multivariable analysis. Colonoscopy-related characteristics predictive for AA were insufficient bowel preparation (OR = 3.4; 95% CI:1.6 – 7.4) and reach of the colonoscopy no further than the distal colon (OR = 3.2; 95% CI:1.2 – 8.5). For NAA, the number of adenomas at index colonoscopy was a predictor, in both univariable and multivariable analyses. In the multivariable analysis, ORs for multiplicity ranged from 1.5 (95% CI: 1.3 – 1.9) for patients with 2 adenomas, to 2.8 (95% CI:1.8 – 4.5) for patients with ≥5 adenomas. Colonoscopy-related characteristics were not predictive.

Table 4. OR (95% CI) of Nonadvanced Adenoma and Advanced Adenoma at Surveillance Endoscopy for Index Adenoma and Colonoscopy Characteristics.

Index characteristics	Univariable OR (95% CI)		Multivariable OR [a] (95% CI)	
	NAA [b]	AA [c]	NAA [b]	AA [c]
Adenoma characteristics				
Adenoma number				
1	1.0	1.0	1.0	1.0
2	1.6 (1.3 – 1.9)	1.8 (1.3 – 2.6)	1.5 (1.3 – 1.9)	1.6 (1.1 – 2.4)
3	2.3 (1.8 – 3.0)	2.7 (1.7 – 4.3)	2.3 (1.8 – 3.0)	2.1 (1.3 – 3.4)
4	2.6 (1.6 – 4.0)	3.4 (1.6 – 7.4)	2.5 (1.6 – 4.0)	2.0 (0.9 – 4.6)
5+	2.7 (1.8 – 4.1)	5.3 (2.9 – 9.8)	2.8 (1.8 – 4.5)	3.3 (1.7 – 6.6)
Any adenoma size ≥10mm	1.0 (0.8 – 1.1)	1.7 (1.3 – 2.2)	1.1 (0.9 – 1.3)	1.7 (1.2 – 2.3)
Any adenoma with HGD	0.9 (0.8 – 1.2)	1.8 (1.3 – 2.5)	0.9 (0.7 – 1.1)	1.2 (0.8 – 1.8)
Any villous adenoma	0.7 (0.5 – 0.9)	2.3 (1.5 – 3.5)	0.7 (0.5 – 1.0)	2.0 (1.2 – 3.2)
Any proximal adenoma	1.5 (1.3 – 1.7)	2.1 (1.6– 2.8)	1.2 (1.0 – 1.4)	1.6 (1.2 – 2.3)
Colonoscopy characteristics				
Bowel preparation				
Good	1.0	1.0	1.0	1.0
Moderate	1.0 (0.8 – 1.3)	0.7 (0.4 – 1.3)	1.1 (0.8 – 1.4)	0.8 (0.4 – 1.5)
Insufficient	0.7 (0.3 – 1.5)	3.4 (1.6 – 7.0)	0.7 (0.3 – 1.4)	3.4 (1.6 – 7.4)
Reach colonoscopy				
Full colonoscopy [d]	1.0	1.0	1.0	1.0
Proximal colon	1.1 (0.8 – 1.4)	0.6 (0.3– 1.2)	1.1(0.8 – 1.5)	0.6 (0.3 – 1.3)
Distal colon	0.9 (0.5 – 2.0)	2.4 (0.9 – 6.3)	1.0 (0.5 – 2.2)	3.2 (1.2 – 8.5)

NOTE. The multinomial logistic regression analyses included 2990 patients with 954 NAA and 203 AA detected during follow-up (see Figure 2).
AA, advanced adenoma; NAA, nonadvanced adenoma; HGD, high-grade dysplasia.
[a] Adjusted for the adenoma characteristics at colonoscopy mentioned in the table (adenoma number, any adenoma size ≥10mm, any adenoma with HGD, any villous adenoma, and any proximal adenoma, bowel preparation, reach of the index colonoscopy), and age at index colonoscopy, sex, surveillance interval, and number of surveillance colonoscopies.
[b] Includes adenomas <10mm with tubular or tubulovillous histology and low-grade dysplasia.
[c] Includes adenomas with one or more of the following characteristics: villous histology, HGD, and size ≥10mm, including CRC.
[d] Reach of the colonoscope to the cecum.

Discussion

Our study shows that higher adenoma number, any adenoma with size ≥10mm, any adenoma with a villous histology, and any adenoma with proximal location at index colonoscopy together with insufficient bowel preparation and colonoscopy reach no further than the distal colon are the most important predictors for detecting advanced colorectal neoplasia (AA or CRC) at surveillance endoscopy. These factors were independent predictors for subsequent advanced colorectal neoplasia, meaning that having multiple of these factors at the same time further increases a patient's risk. HGD was not found to be an independent predictor of advanced colorectal neoplasia recurrence.

Examining predictors for both advanced and nonadvanced colorectal neoplasia simultaneously gave us the possibility to discriminate between predictors for advanced and nonadvanced neoplasia. The ORs of adenoma number were very similar for both AA and NAA. It makes sense that adenoma number would be an important predictor for subsequent adenomas because individuals with multiple adenomas have proven to be susceptible to developing adenomas and can be expected to continue to do so in the future[4, 23 24] Furthermore, multiple adenomas at baseline may be associated with a higher probability of missing lesions.[25] In contrast, size ≥10mm and villous histology were only found to be predictors for AA and not for NAA. Again, this can be explained from a susceptibility viewpoint: patients who have already been proven to have AAs develop might be more susceptible to this type of adenoma and not so much for adenomas in general. HGD forms the exception to this rule: this characteristic was not found to be predictive for AA or NAA. This contrasts with some other studies.[24, 26-30] However, these studies were generally small and/or did not adjust for other adenoma characteristics. The study by Toll et al, for example, could not demonstrate the independent predictive effect of HGD, but only an effect of HGD combined with size ≥10mm.[29] Whether HGD is predictive in patients with 1-2 small, nonvillous adenomas may warrant further investigation because this group was quite small in our study. However, when considering statistical interactions of HGD with adenoma number, villous histology or size, HGD was still not a significant predictor. The one other large study of predictors for adenoma recurrence, a pooled analysis that included individual-level data from 8 clinical trials,[9] corroborates our finding on HGD. Together, these findings support the notion that HGD may be dropped as a predictor in surveillance guidelines.

We note that all estimated ORs for adenoma-related predictors were very similar to the earlier pooled analysis of 8 clinical trials[9], indicating that the ORs for AA recurrence from clinical trials apparently also hold for average community-based clinical practice. Clinical trial results might not be generalizable to community-based practice because of higher-quality colonoscopies in trials, which are associated with lower adenoma miss rates and higher rates of complete adenoma removal. If removed incompletely, large, villous and HGD adenomas may pose higher risks of adenoma recurrence than observed from clinical trials. The absolute risk of developing advanced colorectal neoplasia were, however, lower in our study (7% during a median follow-up period of 48 months) than in the pooled analysis of clinical trials by Martinez et al (12% during a median follow-up period of 47 months). In the latter, tubulovillous adenomas were also included in the outcome definition of AA. Including tubulovillous histology in our definition of AA would have increased the recurrence rate of AA to 10% in our study. For any adenoma recurrence, recurrence rates were 39% vs 47%, in our study vs the Martinez study, respectively. These recurrence rates should be interpreted cautiously because they are not based on a formal Kaplan-Meier analysis. However Pinsky et al reported that time to surveillance was not associated with a higher AA recurrence rate.[16]

In addition to adenoma characteristics, our study also investigated the impact of quality of the index examination on (advanced) adenoma recurrence rates. Insufficient bowel preparation and visualization of the colon no further then the distal part of the colon were both strong predictors for AA, but not for NAA. Likely, the missed (advanced) lesions had time to progress and are found at subsequent surveillance (and mainly in AA type). Our finding corroborates the findings of a small population-based case-control study, showing that colonoscopy-related factors (albeit different factors than the once studied here) are more important predictors than adenoma characteristics for AA recurrence.[31]

The major strengths of this study are its large size and its community-based design. The study size provided us with enough power to reliably estimate odds ratios for adenoma recurrence. An observational study also has limitations. First, there may be misclassification of adenoma characteristics. Pathology report protocols differed over time and between pathology centers. Histology reports were generated by local pathologists with the inherent risk of inter-observer variability in characterization of the histological types and degree of dysplasia.[32, 33] This shows from the percentage of patients with HGD at index colonoscopy in our study which varied from 5% to 39% between hospitals, and the range was

2% - 17% for villous histology. We tried to diminish bias due to misclassification of histological type by examining villous histology instead of (tubulo)villous histology, which might be less prone to classification error.[32] Measurement of adenoma size is also prone to error.[34, 35] We used size measured by the endoscopist as a predictor in our analysis, because this is most frequently reported in the literature and adenomas are known to shrink after excision.[34] To avoid misclassification of size to some extent, the arbitrary cutoff value of 10 mm was used to discriminate between small and large adenomas. The misclassification of adenoma histology, size, and location, might have resulted in diluting its predictive effects.

Second, some polyps (potential adenomas) might not have been sent in for pathology. As a result the actual number of adenomas might have been underestimated, which in turn might have led to an overestimation in the effect of adenoma number. Third, the length of the surveillance interval was generally shorter for patients with AA characteristics at index colonoscopy, which could have let to bias. However, the risk ratios of the predictors were very consistent when we compared results from different estimation techniques, including Cox and logistic regression (data not shown). Especially the latter technique without adjustment for surveillance interval would have led to lower risk ratios of the predictors if the results were confounded by the length of surveillance interval. However, this was not the case. Finally, we did not include shape of the adenoma and method of adenoma removal in our analysis, because these were not well documented for the years under investigation. We tried to diminish bias due to incomplete adenoma removal by combining endoscopy results within 6 months.

Because risk of CRC relates to AA in particular, surveillance recommendations should incorporate predictors of advanced colorectal neoplasia. Internationally, surveillance guidelines are based on the presence of characteristics of the advanced adenoma (ie, size ≥10mm, HGD, and [tubulo]villous histology) and adenoma number.[10-14] Historically, the international surveillance guidelines distinguish only 2 patient categories: those with ≥3 and/or AAs and those without. The UK, Scottish, and newer European guidelines distinguish three categories, recommending a 1-year surveillance interval for patients with ≥5 adenomas or very large (≥20 mm) adenomas.[10, 11, 14] That people with ≥5 adenomas are a higher risk-group is corroborated by our results; the OR of patients with ≥5 adenomas was 3.3 compared with an OR of 2.0 for those with 3 or 4 adenomas. However, all these guidelines generally lack recommendations in relation to adenoma location and for patients having multiple risk factors at the

same time, despite their evidence as independent predictors for AA. These aspects should therefore be considered at the next iteration of the surveillance guidelines. Our results imply that further risk stratification in surveillance guidelines is justified because 4 different adenoma characteristics were independently found to be predictive for AA recurrence. For example, an individual with all 4 risk factors has a considerably higher risk and should therefore receive a shorter surveillance interval than a person with just 1 risk factor. Adenoma patients should be grouped based on the risk factors present and their associated risk level, for example, by use of a scoring system or nomogram, such scoring systems are common practice in cardiovascular disease and for some cancers.[36, 37] Then, formal cost-effectiveness analysis is needed to determine what the optimal surveillance interval per risk group should be. Our results form an excellent starting point for setting up such a score chart and determining the optimal surveillance intervals in further research. Further research should also evaluate if the presented adenoma-related predictors and their relative risks hold for an (asymptomatic) adenoma patient population in a situation of mass screening for CRC.

In conclusion, a higher adenoma number, larger adenoma size, villous histology and proximal location are important independent adenoma-related predictors for AA during surveillance in community-based practice. These adenoma-related predictors should be considered in combination with the quality of the index colonoscopy for better patient risk stratification for surveillance aiming for a more personalized surveillance scheme.

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Conflicts of interest
This authors disclose the following: Clemens J.M. Bolwerk is a member of an MSD Medical Advisory Board. The remaining authors disclose no conflicts.

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Chapter 4

Developing a score chart to improve risk stratification of patients with colorectal adenoma

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Abstract

Background and study aims: Current surveillance guidelines risk stratify patients with adenoma by using only one or two factors: adenoma multiplicity or presence of an advanced adenoma characteristic. Combinations of adenoma characteristics are not considered, which limits the predictive value of these guidelines. The aim of the study was to develop a scoring system for more refined risk stratification of patients with adenoma.

Patients and methods: The Dutch Pathology Registry (PALGA) was used to identify newly diagnosed patients with adenoma in 10 Dutch hospitals between 1988 and 2002. Medical records were reviewed until 1 December 2008 for follow-up. Logistic regression analysis was used to assess patient- and adenoma-related predictors of metachronous advanced neoplasia. The prediction model was validated by bootstrapping and cross-validation. A score chart was developed based on identified adenoma-related predictors. The discriminative ability of the prediction model was compared with currently used risk stratifications in surveillance guidelines.

Results: A total of 2914 patients with adenoma were included (mean age 61 years; 55% male). The score chart consisted of characteristics that contributed 1 point (size ≥10 mm, villous histology, proximal location, having 2–4 adenomas) or 2 points (having ≥5 adenomas). A patient's adenoma risk score could range from 0 to 5 points. A score of 5 for a 75-year-old man implied a 5-year risk of advanced neoplasia of 46%. The discriminative ability of the model was moderate (c-statistic 0.712) but better than risk stratifications in current international guidelines, which had c-statistics of 0.642–0.674.

Conclusion: A score chart that combines adenoma-related predictors of advanced colorectal neoplasia optimized the risk stratification of patients with adenoma for appropriate surveillance colonoscopy intervals.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the Western world[1–3]. Detecting and removing (early stage) cancers and precursor lesions (adenomas) reduces CRC incidence and mortality[4–7]. Individuals in whom adenomas are detected have an increased risk of developing CRC compared with the average population, even after adenomas have been removed[6,8–11]. Patients with adenoma are therefore recommended to undergo regular surveillance colonoscopy after polypectomy[12–17].

Surveillance colonoscopy presents a considerable burden for individuals as well as demand on endoscopy units. Surveillance colonoscopies are estimated to constitute 13%–40% of all colonoscopies performed[18–21]. Improved risk stratification of patients with adenoma can increase efficiency because it would target surveillance colonoscopy more accurately to those patients who are most likely to benefit from the procedure. Currently, risk stratification of patients in post-polypectomy surveillance guidelines are predominately based on adenoma multiplicity and categorization of an adenoma as advanced or nonadvanced[12–17]. The definition of an advanced adenoma is an adenoma with at least one of the following characteristics: size ≥10 mm, high grade dysplasia (HGD), or villous histology. Generally, guidelines do not incorporate a higher risk level for patients in whom multiple risk factors (e.g. large adenoma size and villous histology) are present, despite studies showing that each factor is an independent predictor of advanced adenoma recurrence[11,22]. Furthermore, several additional predictors for recurrent advanced colorectal neoplasia, such as older age, male sex, and proximal location of the adenoma(s) are generally not considered at all[11,22]. Including predictors into a scoring system could result in a more accurate risk stratification of patients with adenoma, and may improve efficiency of post-polypectomy surveillance.

The aims of the current large community-based study were: 1) to develop a valid scoring system for risk stratification of patients with adenomas, based on independent predictors of advanced colorectal neoplasia (ACN); and 2) to compare the score model to risk stratifications used in current post-polypectomy guidelines.

Patients and methods

Study population

In a nationwide histopathology registry (PALGA)[23], patients aged 40 years and above who had been newly diagnosed with at least one colorectal adenoma

between 1988 and 2002 in one of 10 hospitals (3 academic and 7 nonacademic) were identified. Local hospital medical records of these patients were reviewed until December 1st 2008 to collect information on patient and adenoma characteristics at index and surveillance colonoscopies. Patients were excluded if they had: an increased risk of CRC (due to inflammatory bowel disease, hereditary CRC syndromes, or a personal history of CRC), (partial) bowel resection, missing pathology or colonoscopy report, poor bowel preparation, and those with a colonoscopy reach no further than intubation of the distal colon (splenic flexure)[22].

The study was approved by the Institutional Review Board of the Erasmus MC University Medical Centre. This approval was endorsed by the local Institutional Review Board of each participating hospital.

Measures and definitions

The outcome of interest at follow-up colonoscopy was presence of ACN (CRC or advanced adenoma). Advanced adenoma was defined as an adenoma with at least one of the following characteristics: size ≥10 mm (either on endoscopic description or pathology), villous histology (≥75% villous architecture), or HGD (including intramucosal carcinoma or carcinoma in situ).

The adenoma characteristics collected at index and follow-up colonoscopies were number of adenomas, and per adenoma removed: size (measured by endoscopist and pathologist), presence of HGD, villous histology, and proximal location. Adenoma location was considered proximal if located proximal to the splenic flexure or if the colonic segment was not specified but colonoscope insertion was ≥60 cm.

Index colonoscopy was defined as the colonoscopy at which a patient's first adenoma diagnosis was made. In line with the literature, repeat colonoscopy examinations performed within 6 months were considered as one examination and findings were combined[24,25]. In these cases, the date of the last colonoscopy (with polypectomy) was used.

Statistical analysis

Missing values

Because endoscopists commonly only reported on bowel preparation and reach if these factors were inadequate, it was assumed that bowel preparation was "good" and that "a full colonoscopy" was conducted when these factors were not explicitly documented (n = 2116 and n = 58, respectively). Similarly, it was assumed that pathologists only reported the presence of villous histology or

HGD and not the absence of these features, and therefore missing values were coded as negative for presence of HGD (n = 351), villous histology (n = 549), and a proximal location (n = 41). For missing values relating to endoscopic adenoma size category at index colonoscopy (n = 568), and sex (n = 2), a statistical multiple imputation technique was used, based on the correlation structure with other covariates[26,27].

Regression analysis

Univariable and multivariable logistic regression analyses were performed to estimate odds ratios (OR) of potential predictors of ACN during surveillance as opposed to nonadvanced adenoma or no adenoma. In the analysis, a modulated renewal method was used to make full use of the available follow-up data, as described previously[22]. Data from follow-up colonoscopies were included, when available, until an adenoma (nonadvanced adenoma or ACN) was detected or until the last negative examination, to a maximum of the fifth follow-up. As the focus of the study was on prediction of risk, a parametric model (i.e. logistic regression) was considered to be more attractive than a model with a nonparametric baseline hazard such as the Cox model, which might be preferred if the focus was on the effect of prognostic factors.

Age, sex, and adenoma characteristics at index colonoscopy were considered as predictors for metachronous ACN. The number of adenomas was coded as 1 to 5+, and the endoscopic size categories of <10 mm or ≥10 mm were used. Histological characteristics (HGD and villous histology) in any adenoma, and proximal location were coded as present or absent. Besides patient characteristics and adenoma characteristics at index colonoscopy, multivariable analyses were adjusted for surveillance interval (coded in years), and number of negative surveillance colonoscopies (coded as 1 to 5).

In the univariable analysis, continuous variables (age, number of adenomas, and the surveillance interval) were considered both continuously (as linear, with polynomial transformations, and with a restricted cubic spline function including 2–4 knots) and categorically. The variant with best model fit in terms of Akaike's Information Criterion (AIC) was chosen to be included in the multivariable model. A lower AIC indicates a better predictive performance.

Model validation

For internal validation, a bootstrapping procedure was performed[28]. First, discriminative ability was assessed according to the concordance (c)-statistic, which is equivalent to the area under the receiver operating characteristic curve. The

c-statistic indicates how well the model discriminates between those patients with and without ACN. A model was developed in the bootstrap sample ("bootstrap model"), and then applied to both the bootstrap sample and the original sample. The difference in model performance (difference in c-statistics) was averaged over 1000 bootstraps to indicate optimism. The c-statistic of the original prediction model was corrected with this optimism. A regular bootstrap scheme was performed, which involved resampling each record rather than records related to one patient (selection of all patient records if a patient had multiple records). Consequently, each record had the same chance to be selected in the bootstrap analysis. This approach, although slightly less accurate than resampling at the patient level, was chosen as it is less complicated and any differences in estimation of optimism are expected to be minor[29].

Discrimination (c-statistic) and calibration characteristics (predicted and observed ACN risk) were further evaluated in a cross-validation procedure where patients from certain hospitals were omitted from the model-fitting procedure one by one. First, the largest hospital was excluded, followed by the second-largest hospital, then the three academic hospitals; finally, the remaining centers were omitted. Each analysis omitted about 700 patients (validation sample) and left about 2200 patients for model development (development sample).

Score chart

A scoring system was developed (score chart), based on the adenoma characteristics that were significant predictors of ACN in the multivariable analysis. Points for each predictor were allocated on the basis of its estimated regression coefficient. The coefficients were scaled by a factor and rounded to whole points. The base category for each predictor was assigned 0 points in the scoring system. Per patient, a total score can be calculated by adding up the points of the adenoma characteristics present. The total score is referred to as the adenoma risk score. The odds ratio was also assessed for a 1-point increase in adenoma risk score in the multivariable score model. Patient-related predictors were not included in the score chart as these impact life expectancy.

Discriminative ability of various risk stratification models

The optimism-corrected discriminative ability of various risk stratifications was compared. First, the discriminative ability (c-statistic) of the null model was assessed, including only surveillance interval and number of consecutive negative (no adenoma detected and removed) surveillance colonoscopies. Then five different models were compared, each extending the null model: 1) a full model

(including all predictors considered); 2) a simplified score model; 3) a model according to the US surveillance recommendation: advanced adenoma or 3+ adenomas vs. 1–2 nonadvanced adenomas; 4) a model according to the UK guideline: 5 or more adenomas or 3 or more with at least one large vs. 3–4 adenomas or at least one large vs. 1–2 small adenomas; and 5) a model according to the Dutch 2002 surveillance guideline: 3 or more adenomas vs. 1–2 adenomas.

The c-statistics of models were compared, with percentage improvement in c-statistic calculated as $([c_{new} - 0.5] - [c_{null} - 0.5]) / (c_{null} - 0.5)$, where the c_{null} refers to the null model and c_{new} refers to a comparator model. The AIC, which penalizes a better model fit for model complexity (degrees of freedom used), was also considered. A lower AIC indicates a better predictive performance.

Absolute risk prediction

A table for 3- and 5-year ACN risk was designed as a guide for clinicians, similar to the risk charts used for cardiovascular disease risk[30]. The multivariable logistic regression score model was used to predict 3-year and 5-year absolute ACN risk according to adenoma risk score, sex (male or female), and age (45–80 years old). ACN risk is presented, stratified by age and sex, as both not only influence ACN risk, but also life expectancy. Microsoft Excel 2010 was used for automated coloring of the cells presenting absolute ACN risk in the table to visualize differences in point estimates. Color differences do not indicate significant differences.

Regression analyses and cross validation were performed using SPSS v21.0 (IBM Corp., Armonk, New York, USA). R v2.11 software (R foundation for statistical computing, Vienna, Austria) was used for imputation (which was done by the aregImpute function), checks of nonlinearity in continuous predictors, bootstrapping, and calculation of absolute ACN risk.

Results

Data were analyzed from 2914 patients with adenoma who had undergone a colonoscopy with adenoma removal followed by at least one surveillance colonoscopy. The mean age (±SD) was 61 ± 10 years, and 54.9% of patients were male *(Table 1)*. Only 2.7% of patients had five or more adenomas at index colonoscopy. At surveillance colonoscopy, 189 patients had ACN.

Table 1 Characteristics of the study population and odds ratios for advanced colorectal neoplasia at surveillance colonoscopy (logistic regression analysis).

Characteristic at index colonoscopy	All patients (n = 2914), n (%)	Stratified by highest findings at surveillance colonoscopy, n (%)		ACN, OR (95%CI), Logistic regression	
		No/nonadvanced adenoma[1] (n = 2725)	ACN (n = 189)	Univariable	Multivariable[2]
Patient characteristics					
Sex Female	1315 (45.1)	1242 (45.6)	71 (37.6)	1.0	1.0
Male	1601 (54.9)	1483 (54.4)	118 (62.4)	1.4 (1.1–1.9)	1.4 (1.0–1.9)
Age (per 20 year)				2.1 (1.6–2.9)	1.8 (1.3–2.4)
40–59 years	1275 (43.8)	1213 (44.5)	62 (32.8)		
60–79 years	1530 (52.5)	1417 (52.0)	113 (59.8)		
80+ years	109 (3.7)	95 (3.5)	14 (7.4)		
Adenoma characteristics					
No. of adenomas					
1	1986 (68.2)	1887 (69.2)	99 (52.4)	1.0	1.0
2	544 (18.7)	500 (18.3)	44 (23.3)	1.7 (1.2–2.4)	1.5 (1.0–2.1)
3	239 (8.2)	215 (7.9)	24 (12.7)	2.2 (1.4–3.5)	1.6 (1.0–2.7)
4	67 (2.3)	59 (2.2)	8 (4.2)	2.9 (1.3–6.1)	1.6 (0.7–3.6)
5+	78 (2.7)	64 (2.3)	14 (7.4)	4.3 (2.4–7.8)	2.5 (1.3–4.9)
Any adenoma with:					
Size ≥10 mm	934 (32.1)	840 (30.8)	94 (49.7)	1.8 (1.3–2.4)[3]	1.7 (1.2–2.3)[3]
Villous histology[4]	153 (5.3)	127 (4.7)	26 (13.8)	2.7 (1.7–4.1)	2.3 (1.4–3.6)
HGD	413 (14.2)	367 (13.5)	46 (24.3)	1.9 (1.3–2.7)	1.3 (0.9–1.9)
Proximal location	946 (32.5)	862 (31.6)	84 (44.4)	1.9 (1.4–2.5)	1.5 (1.1–2.1)
Surveillance characteristics					
Surveillance interval (per 2 year)				0.9 (0.8–1.1)	1.3 (1.2–1.5)
1 year	651 (22.3)	587 (21.5)	64 (33.9)		
2–3 years	826 (28.3)	774 (28.4)	52 (27.5)		
4–5 years	635 (21.8)	599 (22.0)	36 (19.0)		
6+ years	802 (27.5)	765 (28.1)	37 (19.6)		
A negative subsequent surveillance colonoscopy[5]				0.5 (0.4–0.7)	0.4 (0.3–0.5)
0	1914 (65.7)	1755 (64.4)	159 (84.1)		
1	675 (23.2)	653 (24.0)	22 (11.6)		
2	244 (8.4)	237 (8.7)	7 (3.7)		
3+	81 (2.8)	80 (2.9)	1 (0.5)		

ACN, advanced adenoma (includes adenomas with one or more of the following characteristics; villous histology, high grade dysplasia [HGD], and size ≥10 mm), and colorectal cancer.
[1]Includes adenomas <10 mm, with tubular or tubulovillous histology and low grade dysplasia.
[2]Multivariable model: adjusted for the all characteristics at index colonoscopy mentioned in the table (adenoma number, any adenoma size ≥10mm, any adenoma with HGD, any villous adenoma, and any proximal adenoma, age at index colonoscopy [per 20 years], sex, surveillance interval [in years]), and number of surveillance colonoscopies.
[3]OR based on the imputed size variable, 568 missing values were imputed.
[4]≥75% villous component.
[5]Negative means no adenoma detected and removed.

Adenoma number was included as a categorical variable, whereas patient age and surveillance interval were modeled as linear continuous variables. Adenoma-related characteristics at index colonoscopy predictive for detecting ACN at surveillance in the multivariable analysis were: the number of adenomas (ORs ranging from 1.5, 95% confidence interval [CI] 1.1–2.1 for 2 adenomas to 2.5, 95%CI 1.3–4.9 for patients with ≥5 adenomas); any adenoma with size ≥10 mm (OR 1.7, 95%CI 1.2–2.3), villous histology (OR 2.3, 95%CI 1.4–3.6), and proximal location (OR 1.5, 95%CI 1.1–2.1). HGD was not predictive in the multivariable analysis. Patient-related characteristics predictive for ACN were age (per 20 years; OR 1.8, 95%CI 1.3–2.4) and male sex (OR 1.4, 95%CI 1.0–1.9) *(Table 1)*. Adjustment was made for the length of the surveillance interval and the number of negative (no adenoma) follow-up endoscopies, which were associated and inversely associated with a higher ACN risk, respectively.

Performing analysis without imputation did not alter the results; only the point estimate for adenoma size was slightly higher and the point estimate for villous histology was slightly lower.

Table 2 *Validation of the full prediction model (n = 2914).*

Validation sample	Number of patients, n	Discrimination	Calibration characteristics	
		c-statistic (95%CI)	Predicted ACN (%)	Observed ACN, % (95%CI)
Overall[1]	2914	0.707 (0.669–0.744)	–	–
Cross validation[2]				
Academic centers	802	0.675 (0.608–0.743)	7.6	6.9 (5.0–8.7)
Largest hospital	699	0.763 (0.680–0.846)	6.8	5.2 (3.5–6.8)
2nd-largest hospital	687	0.702 (0.612–0.793)	6.0	5.2 (3.5–7.0)
Other centers	726	0.650 (0.574–0.726)	5.9	8.3 (6.4–10.7)

Full model: sex, age, adenoma number, presence of adenomas ≥10 mm, presence of adenomas with a villous histology, presence of proximal adenomas, presence of adenomas with high grade dysplasia, surveillance interval, and number of surveillance colonoscopies.
[1] c-statistic in overall sample corrected for optimism by bootstrapping (1000 replications).
[2] Cross-validation of prediction models developed without the validation sample, validation sample being 3 academic centers (development sample n = 2112, validation sample n = 802); the largest hospital (development sample n = 2215, validation sample n = 699); the 2nd-largest hospital (development sample n = 2227, validation sample n = 687); and other centers (development sample n = 2188, validation sample n = 726).

Model performance – validation

The c-statistic of the full model on the original sample was 0.723 (95%CI 0.685–0.761); following correction for model optimism the c-statistic was 0.707 (95%CI 0.669–0.744) *(Table 2)*. Regarding cross validation on the basis of selecting certain hospitals for model development and validation by the other hospital(s), the model c-statistic varied from 0.650 to 0.763. The discriminative ability of the model was highest in the two largest participating hospitals. The predicted values for ACN risk were all within range of the 95%CIs of the observed values in the validation samples, with the exception of the predicted value in "other centers," which was lower than observed.

Score chart: the adenoma risk score

Regression coefficients of adenoma-related predictors were scaled by a factor of 1.7, such that the estimated regression coefficients of the individual predictors described above resulted in adenoma size ≥10 mm, villous histology, proximal location, and having 2–4 adenomas each contributing 1 point to the adenoma risk score, whereas having ≥5 adenomas contributed 2 points *(Table 3)*. Depending on the number of risk factors present, patients could have an adenoma risk score

Table 3 Score chart based on adenoma characteristics.

Adenoma characteristics	Points*
No. of adenomas	
1	0
2–4	1
≥5	2
Presence of at least one adenoma with:	
Large size (≥10 mm)	
No	0
Yes	1
Villous histology (≥75% villous component)	
No	0
Yes	1
Proximal location	
No	0
Yes	1
Total adenoma risk score (range)	**(0–5)**

**Allocation of points is based on logistic regression coefficients (see paragraph Results: 'score chart: the adenoma risk score').*

within the range of 0–5. One point increase in adenoma risk score corresponded to an odds ratio of 1.69 (95%CI 1.46–1.92). More than 90% of patients had an adenoma risk score of 0–2. Less than 2.5% of patients had a score of 4 or 5.

Discriminative ability of risk stratification used in current guidelines

The discriminative ability of the full model and the score model were both moderate (c-statistic corrected for optimism: 0.707 and 0.712). For the other risk stratifications used in current guidelines these were: c = 0.664 for the US 2012 guideline, c = 0.674 for the UK 2010 guideline, and c = 0.642 for the Dutch 2002 guideline *(Table 4)*. The AIC for the full model and score model were lower than those of the other guidelines, indicating a statistically better fit.

Table 4 Discriminative ability of different risk stratification models (n = 2914).

Model	c-statistic (95%CI)[1]	Relative improvement in c-statistic, %[2]	AIC[3]
Null model[4]	0.614 (0.573–0.655)		1526
NL 2002 model[5]	0.642 (0.600–0.683)	+24	1506
US model[6]	0.664 (0.625–0.703)	+44	1495
UK model[7]	0.674 (0.634–0.713)	+52	1491
Full model[8]	0.707 (0.669–0.744)	+81	1456
Score model[9]	0.712 (0.675–0.750)	+86	1469

[1]c-statistic corrected for optimism by bootstrapping (1000 replications).
[2]Percentage improvement in c-statistic calculated as $((c_{new} - 0.5) - (c_{null} - 0.5) / (c_{null} - 0.5)$, where the c_{null} refers to the null model and c_{new} refers to a comparator model.
*[3]AIC: Akaike's Information Criterion (-2LogLikelyhood +2*degrees of freedom); lower value indicates better fit of the model. For the score model the degrees of freedom from the full model have been used, as it has been derived from that model.*
[4]Null model: includes only surveillance interval and number of surveillance colonoscopies.
[5]NL 2002 model: risk stratification according to the 2002 Dutch guidelines[15]: presence of ≥3 adenomas, surveillance interval, and number of surveillance colonoscopies.
[6]US model: risk stratification according to the 2012 US guidelines[14]: presence of ≥3 adenomas or at least 1 advanced adenoma (size ≥10 mm, high grade dysplasia [HGD], 25% villous histology) surveillance interval, and number of surveillance colonoscopies.
[7]UK model: risk stratification according to the 2010 UK guidelines[13]: adenoma risk category: 5 or more adenomas or 3 or more with at least one large vs. 3-4 adenomas or at least one large vs.1–2 small adenomas, surveillance interval, and number of surveillance colonoscopies.
[8]Full model: sex, age, adenoma number, presence of adenomas ≥10 mm, presence of adenomas with a villous histology, presence of proximal adenomas, presence of adenomas with HGD, surveillance interval, and number of surveillance colonoscopies.
[9]Score model: sex, age, adenoma risk score, surveillance interval, and number of surveillance colonoscopies.

Absolute ACN risk prediction

Absolute ACN risk at surveillance colonoscopy according to adenoma risk score, age, and sex after 3 years ranged from 1.4% in a 45-year-old woman with an adenoma risk score of 0, to 43% in an 80-year-old man with an adenoma risk score of 5 *(Fig. 1)*. The 5-year risk in these patients ranged from 1.9% to 50%. Female patients had an ACN risk at surveillance colonoscopy similar to that of male patients who were 10 years younger with the same adenoma risk score. To calculate ACN risk according to the full prediction model, we refer the reader to the web-based calculator (http://shiny.mgz-intranet.nl/advancedadenomarisk/) or the formula given in Appendix e1 (available online).

Adenoma risk score	Female 3 yr	Female 5 yr	Age	Male 3 yr	Male 5 yr
0	1,4	1,9	45	1,9	2,5
1	2,4	3,1		3,2	4,2
2	3,9	5,1		5,3	6,9
3	6,4	8,3		9	11
4	10	13		14	17
5	16	21		21	26
0	1,6	2,1	50	2,2	2,9
1	2,7	3,6		3,7	4,8
2	4,5	5,9		6,1	7,9
3	7,4	9,5		10	13
4	12	15		16	20
5	19	23		24	29
0	1,9	2,5	55	2,6	3,4
1	3,1	4,1		4,3	5,6
2	5,2	6,7		7	9
3	8,4	11		11	14
4	13	17		18	22
5	21	26		27	32
0	2,2	2,8	60	3	3,9
1	3,6	4,7		4,9	6,4
2	5,9	7,7		8	10
3	9,6	12		13	16
4	15	19		20	25
5	23	29		29	36

Adenoma risk score	Female 3 yr	Female 5 yr	Age	Male 3 yr	Male 5 yr
0	2,5	3,3	65	3,4	4,5
1	4,1	5,4		5,6	7,3
2	6,8	8,8		9,1	12
3	11	14		15	18
4	17	22		22	28
5	26	32		33	39
0	2,9	3,8	70	3,9	5,1
1	4,8	6,2		6,4	8,3
2	7,8	10		10	13
3	13	16		16	21
4	19	24		25	31
5	29	35		36	43
0	3,3	4,3	75	4,5	5,9
1	5,5	7,1		7,4	9,5
2	8,9	12		12	15
3	14	18		19	23
4	22	27		28	34
5	32	38		39	46
0	3,8	5	80	5,2	6,7
1	6,3	8,2		8,4	11
2	10	13		14	17
3	16	20		21	26
4	24	30		31	37
5	35	42		43	50

Fig. 1 Absolute risk of advanced colorectal neoplasia (%) at 3 or 5 years after index colonoscopy according to adenoma risk score (0–5), age (45–80 years), and sex. Color differences visualize differences in point estimates, but do not indicate significant differences.

Discussion

The study shows that older age, male sex, adenoma number, size ≥10 mm, villous histology, and proximal location at index colonoscopy are all independent predictors for detecting ACN at surveillance endoscopy. A model incorporating all of these independent predictors had moderate performance for predicting ACN (c-statistic = 0.707). The discriminatory performance (c-statistic) of risk stratifications used in current surveillance guidelines (US 2012, UK 2010, and the Dutch 2002 surveillance guidelines) ranged from 0.642 to 0.674. The full model had a statistically better model fit (AIC) than the risk stratifications in current surveillance guidelines. A score chart was developed based on the adenoma-related predictors consisting of six risk groups, referred to as the adenoma risk score. The score model, in which the adenoma risk score replaced the separate adenoma-related predictors, had a similar performance as the full model (c = 0.712). The score chart based on adenoma-related predictors can be used as a tool to stratify patients with adenoma more accurately for the risk of detecting ACN at surveillance.

Better risk prediction by the adenoma risk score can be explained from the following example patients: patient A with 3 small distal tubular adenomas (adenoma risk score 1), and patient B with 3 large proximal villous adenomas (adenoma risk score 4). Existing guidelines categorize both patients in the same risk category (i.e. high risk)[14,15]. However, both the current data and previous studies have shown that the risk for patient B is several times higher than that for patient A, because of the presence of multiple risk factors at the same time. The adenoma risk score takes all these factors into account, resulting in better differentiation between these patients.

The need for more detailed risk stratification of patients with adenoma as suggested by the current findings is also supported by a pooled analysis of four prospective US studies comparing 1-year risk of ACN according to risk stratification on the basis of the UK and US guidelines[31]. The analysis also observed a higher discriminative ability for the risk stratification from the UK compared with the US guideline[31]. In addition, the US guideline appeared to be superior in discriminating between low- and intermediate-risk patients, whereas the UK guideline was superior in discriminating between intermediate- and high-risk patients. These findings suggest that combining both risk stratification schemes might result in even better discrimination than either guideline alone. It has spurred calls from gastroenterologists for a more detailed risk stratification method[32]. The adenoma risk score proposed in the current study fulfills these calls.

The current study is the first study to develop and validate a score chart that incorporates all independent adenoma-related predictors in order to determine the risk for metachronous ACN in patients with adenoma. In addition to some data limitations[22], three limitations are noteworthy. First, the length of the surveillance interval was generally shorter for patients with advanced adenoma at index colonoscopy than for those with nonadvanced adenoma (26 vs. 33 months), which could have led to bias in the risk estimates. However, this bias is expected to be small, as there was substantial overlap in the length of the first surveillance interval between patients with advanced adenoma and those with nonadvanced adenoma, and the analysis was adjusted for interval length. Second, up to 20% of cases had missing information for some of the predictors. Missing values were coded as negative for presence of HGD and villous histology in the current study, because pathologists generally report the presence of such features and not absence. This assumption on missing values is supported by the larger proportion of patients with adenomas with HGD or tubulovillous histology in the current study compared with the study of Martinez et al.[11] Finally, the model was not validated externally; instead internal validation by cross validation and bootstrapping was conducted. Although the c-statistics were corrected for optimism, the discriminative ability of the full model and score model might still have been overestimated.

The study was performed in a clinical setting without an organized population screening program. The score chart may therefore not necessarily apply to patients in whom adenomas are detected through CRC screening. In addition, the predicted absolute risk for metachronous ACN in patients with adenoma may not hold for other adenoma patient populations with other background ACN risk. However, the odds ratios for predictors of metachronous ACN in the current study are very consistent with those from other studies[11,33], suggesting that the need for further risk stratification also holds for patients in other settings. Unfortunately, endoscopist quality indicators (such as the adenoma detection rate [ADR]), lifestyle factors or family history were not considered because these data were not available. Future studies should focus on generalizability aspects, such as external validation in distinct cohorts and settings, and consideration of additional predictors.

The ADR is currently an important point of discussion in surveillance of adenoma patients. The controversy arises because adenoma patients of an endoscopist with a high ADR will have more (advanced) adenomas detected, possibly resulting in a higher adenoma risk score than patients of endoscopists with a low ADR. Consequently, the former group of patients, while having a better

clearing examination, would be recommended a shorter surveillance interval than the latter patients, who potentially have more missed adenomas. This contradiction emphasizes the importance of initiatives to improve ADR. Because of the increased attention to colonoscopy quality indicators, such as ADR, and because of improved endoscopy techniques, ADR has increased over time[34]. This increase has led to a second controversy, namely that the number of patients detected with (advanced) adenomas increases and a migration of patients from lower to higher adenoma risk scores occurs. Hence, absolute risk estimates by adenoma risk score from the current study (adenoma patients up to 2002) may not hold in contemporary adenoma patients. Although the absolute risk of advanced adenoma recurrence in contemporary patients may be lower, possibly justifying longer surveillance intervals for these patients, this stage migration is not expected to impact on predictors and the adenoma risk score. Hence, also in the (near) future, surveillance needs to be stratified based on adenoma risk score to ensure efficient use of resources.

Risk stratification that is more closely tailored to individual patients is in line with the current trend toward more personalized health care. By identifying patients at high likelihood of detecting ACN, the adenoma risk score may help to target surveillance colonoscopy. Depending on which ACN risk value is accepted as the cutoff for surveillance colonoscopy, one can determine appropriate surveillance intervals for each adenoma patient. For example, if a 10% yield of ACN is considered high enough to warrant colonoscopy, a 60-year-old female adenoma patient with an adenoma risk score of 3 should receive surveillance after 3 years, whereas a woman of the same age with a lower score can wait for more than 5 years for the next surveillance colonoscopy. The 10% yield chosen here is arbitrary. From an equity perspective, the yield of colonoscopy in screening for the general population could be used as a threshold. In the Rotterdam fecal immunochemical test trial, people are referred for colonoscopy if the concentration of blood in stool exceeds 10 μg per gram feces. At this concentration in the 3rd screening round, 24% of colonoscopies yield advanced adenoma[35]. Using this percentage as a cutoff, only 60-year-old female adenoma patients with a risk score of 5 would receive surveillance after 3 years, whereas all other 60-year-old female adenoma patients would undergo surveillance after 5 years or more.

Although the above example is appealing as a rule-of-thumb, formal cost-effectiveness analysis is needed to determine the optimal surveillance interval. This type of analysis can take life expectancy, as well as costs of surveillance colonoscopy, complications, CRC treatment, and death into account to estimate

costs and life–years gained for different surveillance strategies. This information can then be used to determine optimal surveillance intervals for adenoma patients, based on adenoma risk score, age, and sex, and will provide clinicians with the necessary information on how to efficiently target care to the individual adenoma patients. The use of simulation models to inform post-polypectomy guideline development has been recommended previously[32].

Despite its obvious benefit, a drawback of more sophisticated risk stratification may be its complexity. Current guidelines require a simple assessment – presence or absence of a list of risk factors, with presence indicating a 3-year surveillance interval, otherwise 5–10 years. However, simple guidelines do not necessarily lead to better adherence, if simplicity interferes with clinical judgement[36]. Improved risk stratification together with a better uptake can improve surveillance effectiveness. The adenoma risk score is somewhat more complicated, but this should be surmountable in the current technology era. Score charts are successfully applied in several fields of medicine, such as the SCORE chart used in the prevention of (fatal) cardiovascular risk[30]. The adenoma risk score proposed in the current study has been incorporated into the latest Dutch colonoscopy surveillance guideline in May 2013 (http://www.mdl.nl/uploads/240/1308/Richtlijn_Coloscopie_Surveillance_definitief_2013.pdf). To facilitate the use of the Dutch 2013 guideline, including the score chart, a wallet sized card for clinicians, as well as an App for mobile devices (NLcolosurvRL), have been developed.

In conclusion, a score chart was developed that incorporates combinations of various adenoma-related predictors of metachronous ACN, which improved the risk stratification of patients compared with current guidelines. Clinicians can use the score chart (adenoma risk score) together with age, sex, life expectancy, risk of complications, and patient preferences in their recommendations for the interval for surveillance colonoscopy.

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Appendix e1

Formulas of the multivariable logistic regression analyses

Formula logistic regression analysis, the full model
P(Advanced colorectal neoplasia) = 1 / (1+ exp(–L))
L = –4.238 + 0.571 * ((age – 60)/20) + 0.333 * (male sex) + 0.373 * (2 adenomas) + 0.490 * (3 adenomas) + 0.476 * (4 adenomas) + 0.925 * (5+ adenomas) + 0.270 * (HGD present) + 0.505 * (adenoma ≥10 mm) + 0.822 * (villous histology present) + 0.421 * (adenoma with proximal location present) + 0.147 * (surveillance interval in years)

Fill in a 1 if the sex or adenoma characteristic is present and 0 otherwise. For surveillance interval fill in the number of years.

Formula logistic regression analysis, the score model
P(Advanced colorectal neoplasia) = 1 / (1+ exp(–L))
L = –4.232 + 0.583 * ((age – 60)/20) + 0.318 * (male sex) + 0.523 * (adenoma risk score) + 0.141 *(surveillance interval in years)

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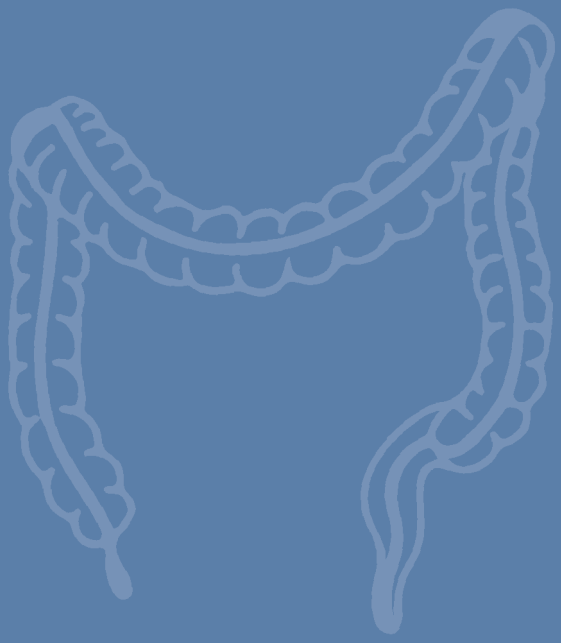

Chapter 5

Personalizing colonoscopy surveillance in adenoma patients - a cost-effectiveness analysis

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Submitted

Abstract

Background: Colonoscopy surveillance guidelines do not consider the combined effect of having multiple predictors of advanced adenoma recurrence and may therefore be suboptimal. We aimed to determine the optimal interval for surveillance given a patient's adenoma risk score (i.e., risk according to a previously developed score chart), sex and age.

Methods: We used microsimulation modelling to estimate quality-adjusted life-years gained and costs of colonoscopy surveillance intervals of 1-10 years, return to FIT screening, and no surveillance, for cohorts of adenoma patients varying by sex, age (40-80 years) and adenoma risk score (0-5). We used incremental cost-effectiveness analysis to determine the optimal interval for each cohort. Analysis were performed for the Netherlands and various other countries (scenario analyses).

Results: The appropriate interval for colonoscopy surveillance depended heavily on adenoma risk score and to a lesser extent on sex and age. Patients with risk score 0 would receive surveillance colonoscopy after 10 years, patients with risk scores 4 and 5 after only 2 or 3 years. Surveillance would no longer be recommended in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older and higher risk patients aged 80 years or older. Results were robust to variations in the overall level of health care costs in a country.

Conclusions: The appropriate interval for colonoscopy surveillance depends heavily on adenoma risk score. Personalizing surveillance using this score targets colonoscopies at those patients most likely to benefit and will increase its efficiency.

Introduction

Colorectal cancer (CRC) is one of the most common cancers and one of the leading causes of cancer-related death in the Western world.[1] Screening for CRC is effective and cost-effective in reducing the morbidity and mortality caused by this disease and is therefore widely recommended.[2-6] Individuals in whom precursor lesions for CRC, so-called adenomas, are detected and removed are at increased risk for CRC compared with the general population. They are therefore recommended to undergo more intensive testing by means of colonoscopy surveillance.[7 8]

Recent studies have identified several important predictors of advanced adenoma recurrence in newly diagnosed adenoma patients.[9 10] These predictors include characteristics of the adenomas removed during colonoscopy: the presence of multiple, large (≥10mm), villous and proximal adenomas, as well as patient characteristics: male sex and older age. The identification of these predictors may allow for extensive risk stratification of adenoma patients followed by careful tailoring of surveillance recommendations. However, most surveillance guidelines do not consider all relevant predictors and are thus restricted in providing tailored recommendations. The 2002 Dutch guidelines, for example, risk stratified adenoma patients based on adenoma multiplicity only.[11] Other guidelines, that do consider multiple predictors, only consider these predictors in simple combinations. The recently published European guidelines, for example, classify patients as high-risk if either 3 or more adenomas or at least one high-risk adenoma is removed (i.e., a large adenoma or an adenoma with (tubulo)villous histology or high grade dysplasia).[7] However, since the number of adenomas removed, large size and villous histology are independent predictors of advanced adenoma recurrence, a patient with 3 large, villous adenomas is at substantially higher risk for CRC than a patient with 3 small, non-villous adenomas, likely justifying a shorter surveillance interval in the former than in the latter patient.

In prior work, we analysed data from the Dutch Surveillance After Polypectomy (SAP) study to develop a score chart to risk-stratify newly diagnosed adenoma patients. This score chart uses information on relevant characteristics of adenomas removed during colonoscopy and integrates this information into one measure: the adenoma risk score (range: 0-5)[12]. The objective of our current study was to determine the appropriate interval for a first surveillance colonoscopy in adenoma patients given their adenoma risk score, sex and age. We performed analyses for the Netherlands (base-case analysis) and various

other countries (scenario analyses). Through this work we hope to facilitate a more personalized approach to surveillance in adenoma patients, ultimately resulting in more efficient surveillance. Since several Western countries recently adopted a population based CRC screening programme,[13] and many screening participants will eventually enter surveillance, a more personalized approach for surveillance will become increasingly important.

Material And Methods

SAP Score Chart

In the SAP study, we gathered data on adenoma findings during index colonoscopy (i.e., the first colonoscopy during which adenomas were detected and removed) and at least one surveillance colonoscopy for almost 3,000 Dutch adenoma patients.[10] Based on these data, we developed a score chart that can be used to stratify newly diagnosed adenoma patients by their risk for advanced adenoma recurrence based on all relevant characteristics of adenomas removed during colonoscopy *(Figure 1)*.[12] The score resulting from this chart, the 'adenoma risk score', ranges between 0 and 5. Compared with the average age- and sex-specific risks for advanced adenoma recurrence in adenoma patients, the relative risks associated with scores 0 up to 5 were 0.58, 0.95, 1.53, 2.42, 3.69 and 5.35, respectively *(Appendix 1)*.

SAP SCORE CHART		
Adenoma Characteristic	**Values**	**Points**
Number of adenomas	1	0
	2 - 4	1
	≥ 5	2
Presence of at least one large adenoma (≥10mm)	No	0
	Yes	1
Presence of at least one villous adenoma*	No	0
	Yes	1
Presence of at least one proximal adenoma	No	0
	Yes	1
Adenoma risk score †		
*An adenoma with at least 75% villous histology. †The adenoma risk score ranges between 0 and 5.		

Figure 1. The SAP Score Chart: Calculating the Adenoma Risk Score.

Cost-Effectiveness Analyses

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Centre (Rotterdam, the Netherlands). The model's structure, underlying assumptions and calibration are described in *Appendix 2*. In brief, MISCAN-Colon simulates the life histories of a large population of persons from birth to death. As each simulated person ages, one or more adenomas may develop. These adenomas can progress from small (≤5mm in diameter), to medium (6-9mm), to large size (≥10mm). Some adenomas can develop into preclinical cancer, which may progress through stages I to IV. However, during each stage, CRC may also be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage of the cancer at diagnosis, the localization of the cancer and the person's age and is based on CRC survival data observed in the South of the Netherlands, as national data were not available.[14]

Surveillance in adenoma patients will alter some of the simulated life histories. Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favourable survival. However, surveillance can also result in serious complications and overdiagnosis and overtreatment of CRC (i.e., the detection and treatment of cancers that would never have been diagnosed without surveillance). By comparing all life histories with surveillance with the corresponding life histories without surveillance, MISCAN-Colon quantifies the effectiveness of surveillance as well as the associated costs.

MISCAN-Colon was calibrated to the age-, stage- and localization-specific incidence of CRC as observed in the Netherlands before the introduction of screening (i.e., between 1999 and 2003) and the age-specific prevalence and multiplicity distribution of adenomas as observed in autopsy and colonoscopy studies.[15-26] The preclinical duration of CRC and the adenoma dwell-time were calibrated to the rates of screen-detected and interval cancers observed in randomized controlled trials evaluating screening using guaiac faecal occult blood tests and a once-only sigmoidoscopy.[27-31] We validated MISCAN-Colon against the long-term outcomes of the National Polyp Study (i.e., a study on the effectiveness of colonoscopic polypectomy).[32] The model showed good concordance with the mortality outcomes observed *(Appendix 2)*. Model parameters as test characteristics of colonoscopy and FIT, complications of colonoscopy, utility loss and costs are described in *Appendix 3*.

Populations simulated

We used MISCAN-Colon to simulate the SAP population after index colonoscopy by age (40, 45, (…), 80 years) and assumed that the model correctly predicted the average risk for CRC over time for all ages *(Appendix 4)*. We used these populations and the relative risks associated with adenoma risk score (score 0: 0.58, score 1: 0.95, score 2: 1.53, score 3: 2.42, score 4: 3.69 and score 5: 5.35) and sex (males: 1.14, females: 0.85) obtained from the SAP-study to simulate cohorts of 10 million adenoma patients for each combination of adenoma risk score, sex and age. Life-expectancy was based on sex-specific life-tables from 2011 obtained from Statistics Netherlands.[33]

Surveillance strategies

Within each cohort, we simulated colonoscopy surveillance with intervals ranging from every 1 up to 10 years. To increase model flexibility in simulating surveillance strategies, we allowed three stopping ages: 75, 80 and 85 years. As alternative 'surveillance' strategies, we simulated referral to the Dutch national CRC screening programme (biennial faecal immunochemical test (FIT) screening from age 55 up to age 75 years) from the first subsequent screen eligible age onwards as well as after a minimum of 10 years.[34] In all cohorts, we also simulated a comparator scenario without further testing: the 'no surveillance' scenario.

Outcomes

For each cohort, we quantified the lifetime effectiveness of each surveillance strategy (i.e., CRC cases prevented, CRC deaths prevented, LYs gained and QALYs gained) as well as the lifetime costs, applying the internationally conventional 3% annual discount rate to both. We expressed the cost-effectiveness of surveillance in terms of the costs per QALY gained.

Analysis

For each cohort, we ruled out all surveillance strategies that were more costly and less effective than other strategies (i.e., simple dominance) or combinations of other strategies (i.e., extended dominance). For each remaining (i.e., efficient) strategy, we calculated the incremental cost-effectiveness ratio by comparing its costs and QALYs gained with those of the next less costly and less effective efficient strategy. We selected the appropriate surveillance strategies by applying a threshold for the willingness-to-pay per QALY gained equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme

(i.e., €2,600 per QALY gained given our base case assumptions) *(Appendix 5)*. The surveillance intervals applied in the selected surveillance strategies are the appropriate intervals for a first surveillance colonoscopy in adenoma patients. In the results section, we present detailed results for 60-year-old females followed by an overview of the appropriate surveillance intervals for all other patients.

Sensitivity Analyses

To explore the uncertainty in the results of our base-case analysis, we repeated our analysis assuming: 1) a weaker and a stronger association between adenoma risk score and the risk for advanced adenoma recurrence (using the lower and upper boundary of the 95% confidence interval of the relative risk associated with a one point increase in adenoma risk score obtained from the SAP study, respectively (Appendix 1)); 2) a lower and higher average risk for advanced adenoma recurrence in adenoma patients (using the lower and upper boundary of the 95% confidence interval of the average risk for advanced adenoma recurrence in adenoma patients obtained from the SAP study, respectively) (Appendix 1); 3) a less favourable average life-expectancy for adenoma patients compared with the general population (78.3 instead of 83.3 years for females and 74.7 instead of 79.7 years for males); 4) twice the base-case colonoscopy miss rates for adenomas and CRC; 5) half and twice the base-case utility losses for colonoscopies and complications; 6) half and twice the base-case costs for colonoscopies; 7) half and twice the base-case costs for CRC care; and 8) differential discounting of costs and effects as recommended by the Dutch National Health Care Institute (using a 4% and 1.5% annual discount rate, respectively). Since the cost-effectiveness of the Dutch national CRC screening programme depends on the assumptions made in the various sensitivity analyses, we adjusted the willingness-to-pay threshold that was applied accordingly *(Appendix 5)*.

Scenario Analyses

To explore the generalizability of our results to other economic settings, we performed scenario analyses in which we assumed a lower and a higher overall level of health care costs (using half and twice the base case costs estimates for colonoscopies and CRC care, respectively). For all levels of health care costs (i.e., Dutch, low and high) we determined the appropriate surveillance intervals applying cost-effectiveness thresholds of €2,600, €5,000, €10,000, €20,000 and €40,000 per QALY gained.

Results

The Impact of Adenoma Risk Score on the Effects and Costs of Surveillance

Surveillance was substantially more effective in patients with a high rather than a low adenoma risk score. For example, 3-yearly colonoscopy surveillance up to age 80 prevented more CRC cases (140 vs. 20 per 1,000 patients) and CRC deaths (93 vs. 13 per 1,000 patients) in 60-year-old females with risk score 5 than in 60-year-old females with risk score 0 *(Table 1)*. It also resulted in more LYs gained (764 vs. 98 per 1,000 patients) and QALYs gained (858 vs. 92 per 1,000 patients). As a result of the larger savings made on CRC care, the net costs of surveillance were substantially lower in patients with a higher adenoma risk score. Among 1,000 60-year-old females, 3-yearly colonoscopy surveillance up to age 80 was associated with a net cost of €823,250 in those with risk score 0 and a net saving of €2,625,092 in those with risk score 5. Hence, each particular surveillance strategy was substantially more cost-effective in patients with a high, rather than a low adenoma risk score.

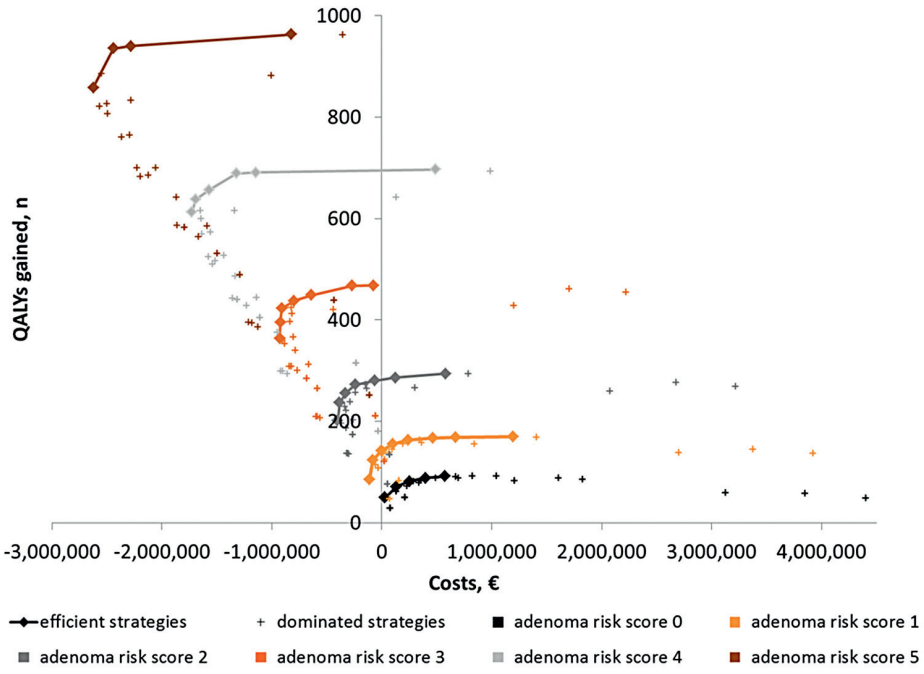
*Table 1. The Effectiveness and Costs of 3-Yearly Colonoscopy Surveillance Up To Age 80 in 60-year-old Females with Adenoma Risk Scores 0 up to 5.**

	EFFECTIVENESS, n							COSTS, €			
	CRC cases prevented	CRC Deaths Prevented	LYs Gained	Impact on Quality of Life (QALYs gained)			QALYs gained	Colono-scopies (E)	Compli-cations (F)	LYs with CRC Care (G)	Total (E+F+G)
Adenoma Risk Score			(A)	Colonos-copies (B)	Compli-cations (C)	LYs with CRC Care (D)	(A+B+ C+D)				
0	20	13	98	-22	0	16	**92**	1,396,215	18,017	-590,982	**823,250**
1	34	21	163	-22	-1	26	**167**	1,422,033	23,701	-981,073	**464,661**
2	53	34	261	-22	-1	42	**280**	1,455,743	31,561	-1,553,521	**-66,217**
3	79	51	397	-21	-1	63	**437**	1,492,334	41,274	-2,332,845	**-799,237**
4	110	72	571	-21	-1	89	**638**	1,521,001	51,304	-3,265,673	**-1,693,368**
5	140	93	764	-20	-1	116	**858**	1,528,846	59,531	-4,213,468	**-2,625,092**

CRC = colorectal cancer; LY = life-year; QALY = quality-adjusted life-year
**Results are based on a comparison with the 'no surveillance' scenario (i.e., no further testing), reported per 1,000 females and discounted by 3% per year.*

Appropriate Surveillance Intervals for 60-Year-Old Females

Figure 2 shows the costs and effects of all surveillance strategies in 60-year-old females with risk scores 0 up to 5. Among the efficient surveillance strategies, more intensive surveillance resulted in only small increases in the effectiveness



**Results are based on a comparison with the 'no surveillance' scenario (i.e., no further testing), reported per 1,000 females and discounted by 3% per year*

Figure 2. *The Effectiveness and Costs of All Surveillance Strategies in 60-year-old Females with Adenoma Risk Scores 0 up to 5.**

of surveillance compared with the increases in costs. In 60-year-old females with risk score 0, for example, the least effective, efficient surveillance strategy (i.e., 10-yearly colonoscopy surveillance up to age 75) resulted in 49 QALYs gained per 1,000 females *(Table 2)*. The most effective, efficient surveillance strategy (i.e., 4-yearly colonoscopy surveillance up to age 80), on the other hand, resulted in 92 QALYs gained per 1,000 females: a 2-fold increase. Simultaneously, the costs of surveillance increased from €538 to €46,488 per 1,000 females: a 22-fold increase.

Based on a willingness-to-pay threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme, the appropriate surveillance strategy in 60-year-old females with adenoma risk score 0 was 10-yearly colonoscopy surveillance up to age 75 *(Table 2)*. In 60-year-old females with a higher adenoma risk score more intensive surveillance strategies remained cost-effective. As a result, the appropriate interval for colonoscopy surveillance decreased from 10 years in females with risk score 0 to 7 years, 5 years, 4 years, 3 years and 2 years in those with risk scores 1 up to 5.

*Table 2. The Incremental Cost-Effectiveness of All Efficient Surveillance Strategies in 60-year-old Females with Adenoma Risk Scores 0 up to 5.**

Adenoma Risk Score	Surveillance Strategy (interval, yrs (stopping age, yrs))	QALYs Gained, n	Costs, €†	Incremental Costs per QALY Gained, €
0	**10 (75)**	**49**	**26,513**	**538‡**
	9 (75)	50	28,231	4,357
	7 (75)	71	131,732	4,739
	6 (80)	82	251,780	11,337
	5 (80)	88	395,541	23,866
	4 (80)	92	573,362	46,488
1	9 (75)	85	-113,302	cost saving
	7 (75)	**123**	**-83,687**	**776‡**
	6 (80)	143	-5,379	3,996
	5 (80)	155	102,341	8,738
	4 (80)	164	242,769	16,099
	3 (80)	167	464,661	77,368
	3 (85)	169	671,107	84,041
	2 (80)	170	1,193,016	492,047
2	6(75)	201	-401,168	cost saving
	5(75)	**237**	**-384,384**	**472‡**
	5(80)	256	-328,588	2,870
	4(80)	272	-240,439	5,451
	3(80)	280	-66,217	22,122
	3(85)	286	122,246	29,822
	2(80)	294	581,276	57,199
3	5(75)	364	-927,511	cost saving
	5(80)	395	-922,363	168
	4(80)	**422**	**-910,897**	**417‡**
	3(80)	437	-799,237	7,378
	3(85)	449	-638,431	13,644
	2(80)	468	-271,927	19,955
	2(85)	468	-75,378	694,588
4	4(80)	612	-1,727,635	cost saving
	3(80)	**638**	**-1,693,368**	**1,341‡**
	3(85)	657	-1,570,667	6,502
	2(80)	689	-1,324,835	7,576
	2(85)	691	-1,143,723	84,042
	1(80)	697	487,378	281,496
5	3(80)	858	-2,625,092	cost saving
	2(80)	**936**	**-2,443,321**	**2,356‡**
	2(85)	940	-2,280,636	36,843
	1(80)	963	-826,352	62,305

QALY = quality-adjusted life-year
**Results are based on a comparison with the 'no surveillance' scenario (i.e., no further testing), reported per 1,000 females and discounted by 3% per year.*
†The costs of colonoscopies, complications and LYs with CRC care with surveillance minus the costs of LYs with CRC care without surveillance.
‡The appropriate strategies are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (i.e., €2,600 per QALY gained) (Appendix 5).

*Table 3. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	5	6	5	5	5	5	4	NS
3	4	5	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	8	7	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	2	2	2	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (i.e., €2,600 per QALY gained) (Appendix 5).*

Appropriate Surveillance Intervals for Other Adenoma Patients

In general, surveillance was more cost-effective in patients with a high, rather than a low adenoma risk score; in males compared with females; and in older compared with younger. As a result, the appropriate surveillance intervals in these groups were shorter *(Table 3)*. The appropriate interval ranged from 10 years in some patients with adenoma risk score 0 to 2 years in some patients with adenoma risk scores 4 and 5. Referral to FIT screening was dominated by colonoscopy surveillance in all cohorts.

Surveillance was no longer cost-effective in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older and females with risk score 2 and patients with risk scores 3-5 aged 80 years or older *(Table 3)*.

Table 4. Appropriate Surveillance in Females with Adenoma Risk Scores 0 up to 5: Results of Sensitivity Analyses and Scenario Analyses for Generalizability to Other Economic Settings.^*

	APPROPRIATE SURVEILLANCE INTERVAL IN 60-YEAR-OLD FEMALES, yrs						AGE AT WHICH SURVEILLANCE WOULD NO LONGER BE RECOMMENDED, yrs					
	Adenoma Risk Score						Adenoma Risk Score					
Analysis	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Base case	**10**	**7**	**5**	**4**	**3**	**2**	**70**	**75**	**80**	**80**	**80**	**80**
Sensitivity analysis												
1a. Weaker association adenoma risk score and risk†	9	7	5	4	4	3	70	75	80	80	80	80
1b. Stronger association adenoma risk score and risk†	10	7	5	4	3	2	65	75	80	80	80	>80
2a. Lower average risk for advanced adenoma recurrence†	10	7	6	4	4	3	65	70	80	80	80	80
2b. Higher average risk for advanced adenoma recurrence†	9	7	5	4	3	2	70	75	80	80	80	80
3. Less favourable life-expectancy for adenoma patients (-5 yrs)	9	6	5	4	3	3	65	70	75	80	80	80
4. Colonoscopy miss rates x 2	10	7	5	4	3	2	65	70	75	80	80	80
5a. Utility losses colonoscopies and complications x 0.5	10	7	5	4	3	2	70	75	80	80	80	80
5b. Utility losses colonoscopies and complications x 2	10	7	5	4	3	3	70	75	80	80	80	80
6a. Colonoscopy costs x 0.5	7	5	4	3	2	2	75	80	80	80	>80	>80
6b. Colonoscopy costs x 2	FIT10	10	7	6	4	4	65	70	75	80	80	80
7a. CRC care costs x 0.5	10	7	6	5	4	3	70	70	75	80	80	80
7b. CRC care costs x 2	7	5	4	3	2	2	70	75	80	80	80	80
8.Differential discounting of costs and effects	8	6	4	4	3	2	70	75	80	80	80	>80
Scenario analyses **Economic context† and Cost-Effectiveness Threshold Used**												
1. Country with low health care costs												
a. €2,600 per QALY gained	7	6	5	4	3	2	70	75	80	80	80	>80
b. €5,000 per QALY gained	7	5	4	3	2	2	75	80	80	80	>80	>80
c. €10,000 per QALY gained	6	4	4	3	2	2	80	80	>80	>80	>80	>80
d. €20,000 per QALY gained	5	4	3	2	2	2	80	>80	>80	>80	>80	>80
e. €40,000 per QALY gained	4	3	2	2	2	1	80	>80	>80	>80	>80	>80
2. Country with Dutch health care costs												
a. €2,600 per QALY gained (base case)	**10**	**7**	**5**	**4**	**3**	**2**	**70**	**75**	**80**	**80**	**80**	**80**
b. €5,000 per QALY gained	7	6	5	4	3	2	70	75	80	80	80	>80
c. €10,000 per QALY gained	7	5	4	3	2	2	75	80	80	>80	>80	>80
d. €20,000 per QALY gained	6	4	4	2	2	2	80	80	>80	>80	>80	>80
e. €40,000 per QALY gained	5	4	3	2	2	2	80	>80	>80	>80	>80	>80
3. Country with high health care costs												
a. €2,600 per QALY gained	10	7	5	4	4	3	65	70	75	80	80	80
b. €5,000 per QALY gained	10	7	5	4	3	2	70	75	80	80	80	80
c. €10,000 per QALY gained	7	6	5	4	3	2	70	75	80	80	80	>80
d. €20,000 per QALY gained	7	5	4	3	2	2	75	80	80	>80	>80	>80
e. €40,000 per QALY gained	6	4	4	2	2	2	80	80	>80	>80	>80	>80

** The appropriate surveillance intervals and ages at which surveillance would no longer be recommended were determined by applying a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening program. For the sensitivity analyses 1a, 1b, 2a and 2b the cost-effectiveness threshold was identical to that used in the base-case analysis: €2,600 per QALY gained, for sensitivity analyses 3, 4, 5a, 5b, 6a, 6b, 7a, 7b and 8 the incremental cost-effectiveness ratios were €5,100, €3,400, €2,600, €2,700, €1,800, €4,600, €4,100, €0 and €4,100 per QALY gained, respectively (Appendix 5).*

^ Orange cells indicate a surveillance interval differing more than 1 year from the interval found in the base-case analysis or a stop age differing from the stop age found in the base-case analysis. For all sensitivity analyses and all scenario analyses, tables similar to Table 3 are given in Appendix 6 and Appendix 7.

†In countries with low and high health care costs, the costs of colonoscopies and CRC care were assumed to be 0.5 and 2 times the base case costs, respectively.
FIT 10 = (biennial) FIT screening after 10 years

Sensitivity and Scenario Analyses

The appropriate surveillance intervals were most sensitive to varying the costs of colonoscopies and the costs of CRC care *(Table 4)*. Higher colonoscopy costs resulted in longer surveillance intervals (patients with risk score 0 would even be referred to FIT screening). Conversely, higher CRC care costs resulted in shorter surveillance intervals, particularly in those with a low adenoma risk score. The ages at which surveillance was no longer cost-effective were also sensitive to the average risk for advanced adenoma recurrence in adenoma patients, the average life expectancy of adenoma patients and the sensitivity of colonoscopy for the detection of adenomas and CRC *(Table 4)*.

While results were sensitive to varying the costs of either colonoscopies or CRC care, they were relatively robust to varying both costs simultaneously (i.e. the overall level of health care costs in a country) *(Table 4)*. Applying higher cost-effectiveness thresholds resulted in substantially more intensive surveillance recommendations, again particularly in those with a low adenoma risk score.

Discussion

Our study demonstrates that the appropriate interval for a first surveillance colonoscopy in adenoma patients depends heavily on adenoma risk score and to a lesser extent on sex and age. While some patients with risk score 0 (i.e., with 1 small (<10mm), non-villous, distal adenoma) would be recommended a surveillance colonoscopy after 10 years, some patients with risk scores 4 and 5 would be recommended a surveillance colonoscopy after only 2 years. Surveillance would no longer be recommended in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older and patients at higher risk aged 80 years or older. Results were relatively robust to the overall level of health care costs in a country. However, applying less stringent cost-effectiveness thresholds resulted in substantially more intensive surveillance recommendations, particularly in those with a low adenoma risk score.

The most important strength of our study is that it provides surveillance recommendations that are tailored to the individual adenoma patient. This ensures that surveillance colonoscopies are targeted at those patients most likely to benefit. The two factors that determine the benefit of surveillance are the patient's risk for CRC and life expectancy. By stratifying patients using the adenoma risk score, we assure that all adenoma findings that predict CRC risk are considered in an appropriate way. Meanwhile, MISCAN-Colon incorporates the impact of sex and age on both CRC risk and life expectancy. Another strength of our study is that we based our recommendations on a formal cost-utility analysis. Within this type of analysis all short and long term costs and health effects (both on quantity and quality of life) of an intervention are explicitly identified, measured, valued and weighed.

Two limitations are of note. First, this study only focuses on the appropriate interval for a first surveillance colonoscopy. Although this is often considered as the most important clinical decision to be made in adenoma patients, most patients will have to undergo multiple surveillance colonoscopies over the course of their lives. In our study we modelled strategies with a fixed surveillance interval to a certain stop age. However, findings at surveillance colonoscopy may alter subsequent advanced adenoma risk. To determine appropriate intervals for subsequent surveillance colonoscopies more evidence is needed. So far, only few, small studies have been conducted in this area with a maximum of two surveillance rounds. These studies suggested that findings at both the baseline

and the most recent colonoscopy impact subsequent advanced adenoma risk, especially presence of high risk lesions at any examination.[35-37] Second, we did not include (sessile) serrated lesions in the our analysis since there was no data available from the SAP study. Surveillance for (sessile) serrated lesions is being recommended, but evidence to support these recommendations is limited.[7 8 38]

The SAP score chart is based on data collected in Dutch adenoma patients. However, since the risk factors for advanced adenoma recurrence observed in the SAP study (as well as the magnitude of risk associated with each risk factor) were very comparable to those in literature,[9] we believe that the score chart is a reliable instrument to risk-stratify adenoma patients in other settings. Moreover, sensitivity analyses show that the appropriate surveillance intervals, as well as the ages to stop surveillance are relatively robust to varying the average risk for advanced adenoma recurrence, while life-expectancy and CRC survival rates do not differ substantially between Western countries. We therefore feel that using the results of the scenario-analyses for different economic contexts *(Table 4)*, can be generalized to other Western countries. Results were sensitive to varying the costs of either colonoscopies or CRC care, but they were relatively robust to varying the overall level of health care costs. Applying higher cost-effectiveness thresholds resulted in more intensive surveillance recommendations.

Our study demonstrates that existing surveillance guidelines do not consistently target colonoscopies at those patients most likely to benefit. According to the current European guidelines, for example, both a 60-year-old female with 3 small, non-villous, distal adenomas and a 60-year-old female with 5 large, villous, proximal adenomas are recommended colonoscopy surveillance after 3 years.[7] However, according to the SAP score chart, the former patient has an adenoma risk score of 1, whereas the latter patient has an adenoma risk score of 5, corresponding to an almost 6-fold higher risk for CRC. Therefore, according to our study, the former patient can be recommended a substantially longer surveillance interval (i.e. 7 instead of 3 years), whereas the latter patient would be recommended a shorter interval (i.e. 2 instead of 3 years).

Although our study demonstrates that more extensive risk stratification of colonoscopy surveillance is indicated, we realize that it might not be feasible to stratify adenoma patients to the level we have done in this study. Since the appropriate surveillance intervals and stop ages are primarily affected by adenoma risk score and to a lesser extent by sex and age, one way to simplify would

be to base surveillance recommendations on adenoma risk score only. This approach was chosen by the Dutch Association of Gastroenterologists when they revisited the guideline for colonoscopy surveillance based on the results of this study in May 2013.[38] The guideline incorporates the score chart and recommends a 3-year interval for patients with risk scores 3-5, a 5-year interval for those with risk scores 1-2 and no surveillance or returning to biennial FIT screening after 10 years for those with risk score 0 (depending on age).

To our knowledge our study is the first to demonstrate that colonoscopy surveillance should no longer be recommended in very old patients. However, the benefits of surveillance in elderly adenoma patients depend heavily on a patient's life expectancy. While surveillance may no longer be cost-effective in patients with an average life expectancy, it may still be relevant in patients with a better-than-average life expectancy. Conversely, surveillance that is cost-effective in patients with an average life expectancy may not be cost-effective or even harmful, in patients with a worse-than-average life expectancy. Hence, studies are required that investigate the appropriate age to stop surveillance based on a patient's life expectancy.

In conclusion, our study demonstrates that existing guidelines for colonoscopy surveillance in adenoma patients do not consistently target colonoscopies at those patients most likely to benefit. A more personalized approach, by using the adenoma risk score, targets colonoscopies at those patients most likely to benefit and has great potential to increase the efficiency of surveillance. Since several European countries recently adopted a population based CRC screening program and many of those participating in screening will eventually enter colonoscopy surveillance, a more personalized surveillance approach will become increasingly important.

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Appendix 1 Relative Risks Associated with Adenoma Risk Scores 0 up to 5

In the SAP study, a one-point increase in adenoma risk score corresponded with an increase in the odds for advanced adenoma recurrence of 1.688 (95% CI: 1.475 - 1.932).[12] Within the SAP study, there were 886 patients with risk score 0, 1,153 patients with risk score 1, 607 patients with risk score 2, 206 patients with risk score 3, 57 patients with risk score 4, and 5 patients with risk score 5. Hence, the average adenoma risk score in the SAP study was 1.111. This score corresponds with an odds ratio (OR) for advanced adenoma recurrence of 1. Hence, in the base case analysis, the OR corresponding with risk score x was 1.688 ^ (x - 1.111), which corresponds to 0.559, 0.943, 1.593, 2.688, 4.538, and 7.660 for risk scores 0 up to 5, respectively. To use these ORs in MISCAN-Colon, we translated them to relative risks (RRs) using the formula: RR = OR / (1 – r + (OR*r)).[39] In this formula r is the average risk for advanced adenoma recurrence observed in the SAP study, which was 0.065 (95% CI: 0.056 – 0.074). The resulting, rounded RRs for risk scores 0 up to 5 were 0.58, 0.95, 1.53, 2.42, 3.69, and 5.35, respectively. For sensitivity analyses 1a ('Weaker association adenoma risk score and risk') and 1b ('Stronger association adenoma risk score and risk'), we repeated the exercise described above using odds ratios for a one-point increase in adenoma risk score of 1.475 and 1.932, respectively. This resulted in RRs for risk scores 0 up to 5 of 0.66, 0.96, 1.38, 1.95, 2.71, and 3.69 and 0.50, 0.93, 1.71, 2.99, 4.89, and 7.30, respectively. For sensitivity analyses 2a ('Lower average risk for advanced adenoma recurrence') and 2b ('Higher average risk for advanced adenoma recurrence') we used the 95% CI boundaries for average risk, as mentioned above, and multiplied the base case RRs with 0.056 / 0.065 = 0.86 and 0.074 / 0.065 = 1.14. This resulted in RRs for risk scores 0 up to 5 of 0.50, 0.82, 1.32, 2.09, 3.18, and 4.61 and 0.66, 1.08, 1.74, 2.75, 4.20, and 6.09, respectively.

Appendix 2 MISCAN-Colon Model Appendix

General Model Structure

MISCAN-Colon is a stochastic microsimulation model for colorectal cancer (CRC) programmed in Delphi (Borland Software Corporation, Scotts Valley, California, United States). It can be used to explain and predict trends in CRC incidence and mortality and to quantify the effects and costs of primary prevention of CRC, screening for CRC, and surveillance after polypectomy.

The term 'microsimulation' implies that individuals are moved through the model one at a time, rather than as proportions of a cohort. This allows future state transitions to depend on past transitions, giving the model a 'memory'. Furthermore, unlike most traditional Markov models, MISCAN-Colon does not use yearly transition probabilities; instead it generates durations in states, thereby increasing model flexibility and computational performance. The term 'stochastic' implies that the model simulates sequences of events by drawing from distributions of probabilities/ durations, rather than using fixed values. Hence, the results of the model are subject to random variation.

MISCAN-Colon consists of 3 modules: a demography module, natural history module, and screening and surveillance module.

The Demography Module

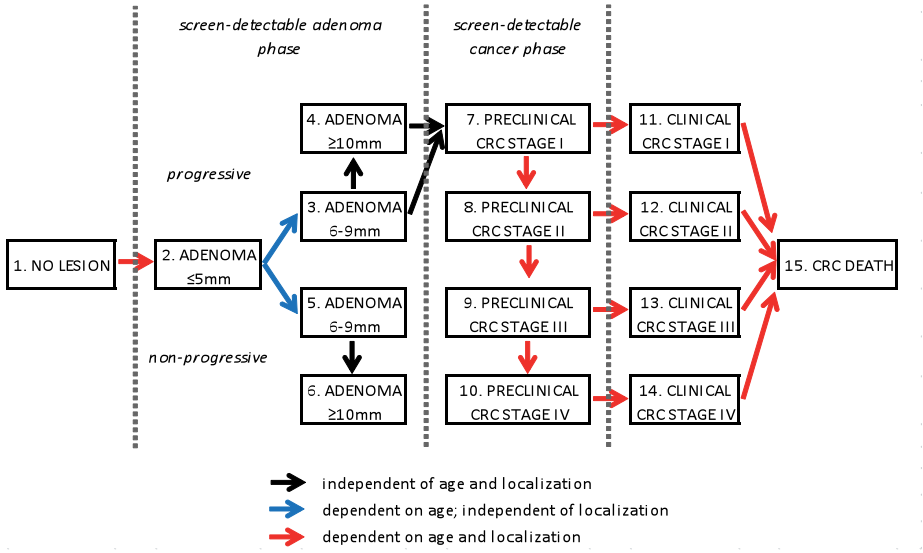
Using birth- and life-tables representative for the population under consideration, MISCAN-Colon draws a date of birth and a date of non-CRC death for each individual simulated. In MISCAN-Colon the maximum age an individual can achieve is exactly 100 years.

The Natural History Module

Transitions

As each simulated person ages, one or more adenomas may develop *(Appendix 2, Figure 1)*. These adenomas can either be progressive or non-progressive. Both progressive and non-progressive adenomas can grow in size from small (≤5mm), to medium (6-9mm), to large (≥10mm). However, only progressive adenomas can develop into preclinical cancer. A preclinical cancer may progress through stages I to IV. However, during each stage CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage of the cancer at diagnosis, the localization of the cancer, and the person's age and is based on CRC survival data observed in the South of the Netherlands, as national data were not available.[14] For individuals with synchronous CRCs at

Appendix 2, Figure 1. An Overview of the Natural History Module of MISCAN-Colon.



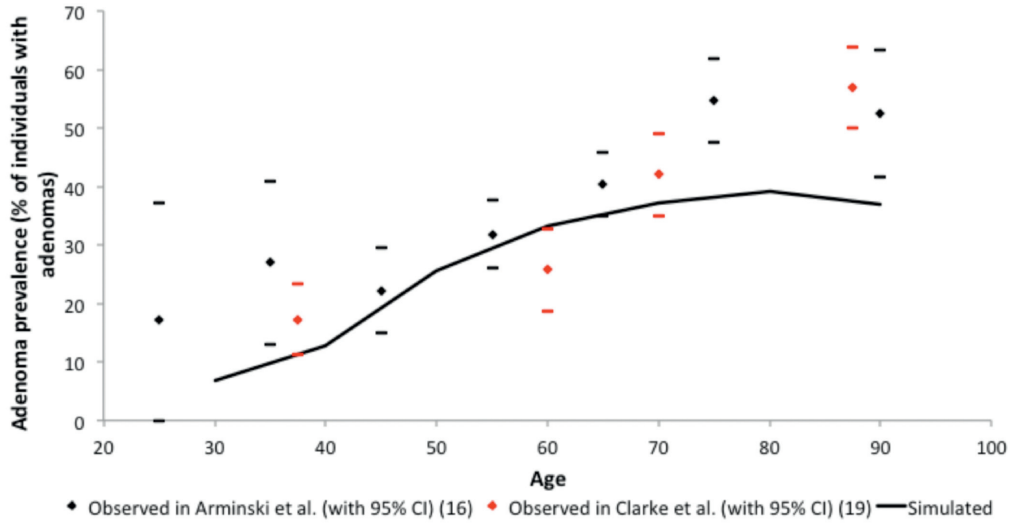
time of diagnosis, the survival of the most advanced cancer is used. The date of death for individuals with CRC is set to the earliest simulated death (either due to CRC or due to another cause (see: 'The demography module').

Transition Probabilities and Durations in States

An individual's risk of developing adenomas depends on the individual's age and a personal risk index. As a result of the latter most individuals develop no adenomas, whilst some develop many. We assumed that the distribution of adenomas over the colon and rectum equalled the distribution of cancers as observed in the Netherlands before the introduction of screening (i.e., between 1999 and 2003).[15] The age-specific onset of adenomas and the dispersion of the personal risk index were calibrated to data on the prevalence and multiplicity distribution of adenomas as observed in autopsy and colonoscopy studies *(Appendix 2, Figure 2)*.[15-26] The age-specific probability of adenoma-progressivity and the age- and localization-specific transition probabilities between preclinical cancer stages and between preclinical and clinical cancer stages were simultaneously calibrated to the age-, stage-, and localization-specific incidence of CRC as observed in the Netherlands, again as observed before the introduction of screening *(Appendix 2, Figure 3)*.[15]

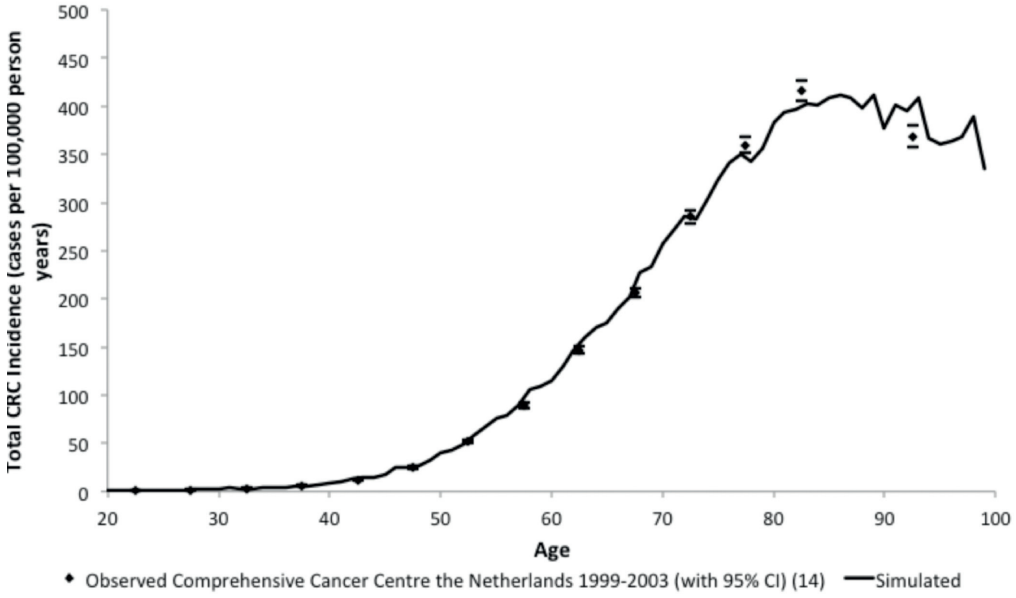
The average durations of the preclinical cancer stages were calibrated to the

Appendix 2, Figure 2. *Adenomas Prevalence Observed in Selected Autopsy Studies Versus Simulated by MISCAN-Colon.**



Observed results are only shown for the two largest studies to which the model has been calibrated. MISCAN-Colon has additionally been calibrated to 8 other autopsy studies.

Appendix 2, Figure 3. *CRC Incidence Observed Before the Introduction of Screening Versus Simulated by MISCAN-Colon.*



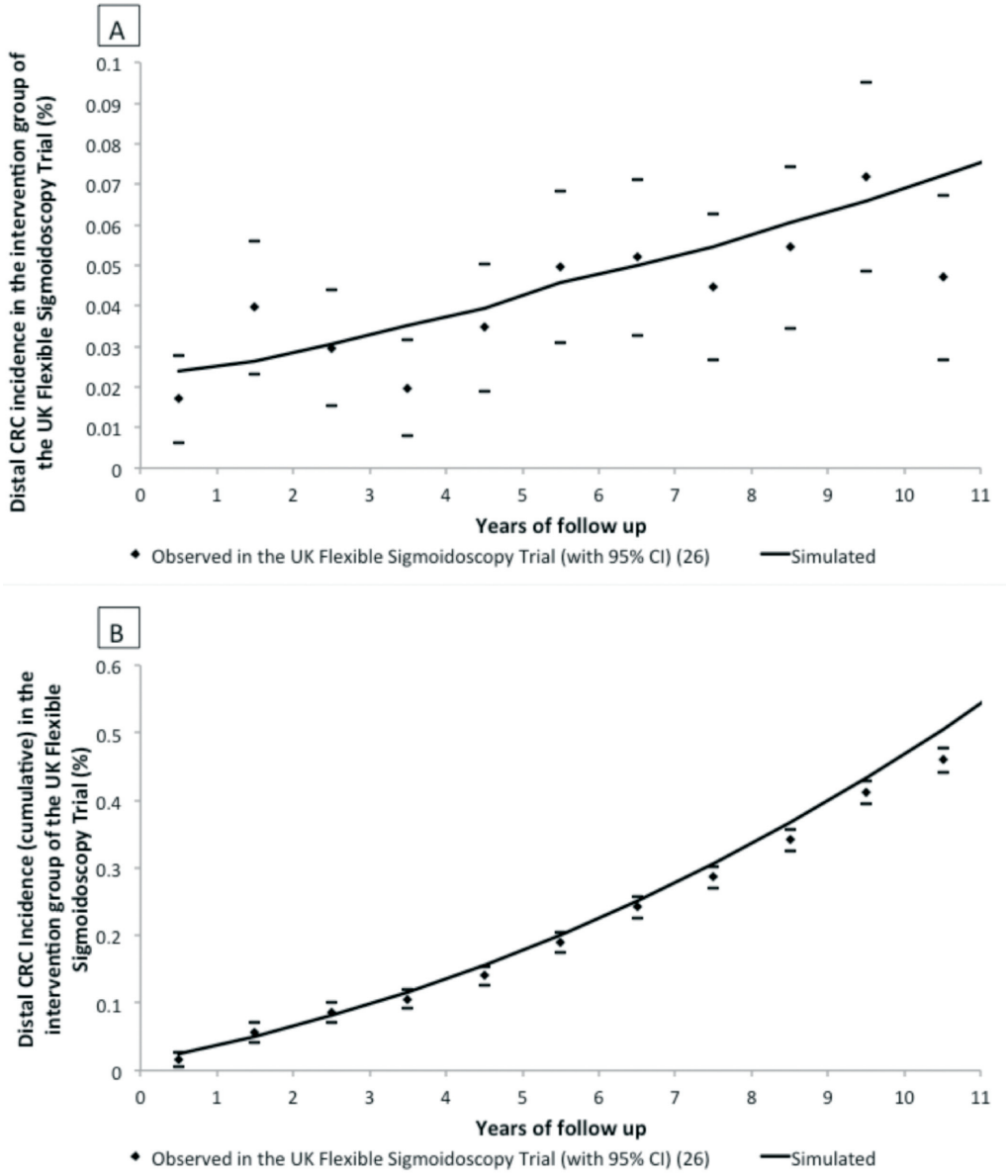
rates of screen-detected and interval cancers observed in randomized controlled trials evaluating screening using guaiac faecal occult blood tests.[28 29 31] This exercise is described extensively in a publication by Lansdorp-Vogelaar and colleagues.[30] The average duration from the emergence of an adenoma (state 2) until progression into preclinical cancer (state 7) (i.e. the adenoma dwell-time) was calibrated to the interval cancer rates observed in a randomized controlled trial evaluating once-only sigmoidoscopy screening *(Appendix 2, Figure 4)*.[27] We assumed an equal overall dwell-time for adenomas developing into CRC from a medium size (30% of all CRCs) and from a large size (70% of all CRCs). All durations in the adenoma and preclinical cancer phase are drawn from exponential distributions. Durations within the adenoma phase and within the preclinical cancer phase are assumed to be perfectly correlated (i.e. if a small adenoma grows into a medium-sized adenoma rapidly, it will also grow into a large adenoma or develop into CRC rapidly); however, durations in the adenoma phase are assumed to be uncorrelated with durations in the preclinical cancer phase (i.e. a rapidly growing adenoma does not necessarily develop into a rapidly progressing cancer). The proportion of medium sized, non-progressive adenomas growing large and the average duration in the medium size, non-progressive adenoma state (state 5) were calibrated to size-specific adenoma detection rates observed in a Dutch randomized controlled trial on colonoscopy screening *(data not shown)*.

The Screening and Surveillance Module

Screening and surveillance will alter some of the simulated life histories: Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favourable survival. The stage-specific survival of screen-detected CRC as observed in randomized controlled trials on guaiac faecal occult blood testing was substantially more favourable than that of clinically detected CRC, even after correcting for lead-time bias.[30] We therefore assigned screen-detected and surveillance-detected cancers that would have been clinically detected in the same stage a survival corresponding to a one stage less progressive cancer. Hence, a cancer detected in stage II, that would also have been clinically diagnosed in stage II, is assigned the survival of a clinically diagnosed stage I cancer. The only exceptions are stage IV cancers. These cancers are always assigned the survival of a clinically diagnosed stage IV cancer.

Besides modeling positive health effects of screening and surveillance, we also model colonoscopy-related complications and over-diagnosis and over-

Appendix 2, Figure 4. Distal CRC Incidence Observed in the Intervention Group of the UK Flexible Sigmoidoscopy Trial Versus Simulated by MISCAN-Colon (per year of follow-up (A), cumulative (B)).

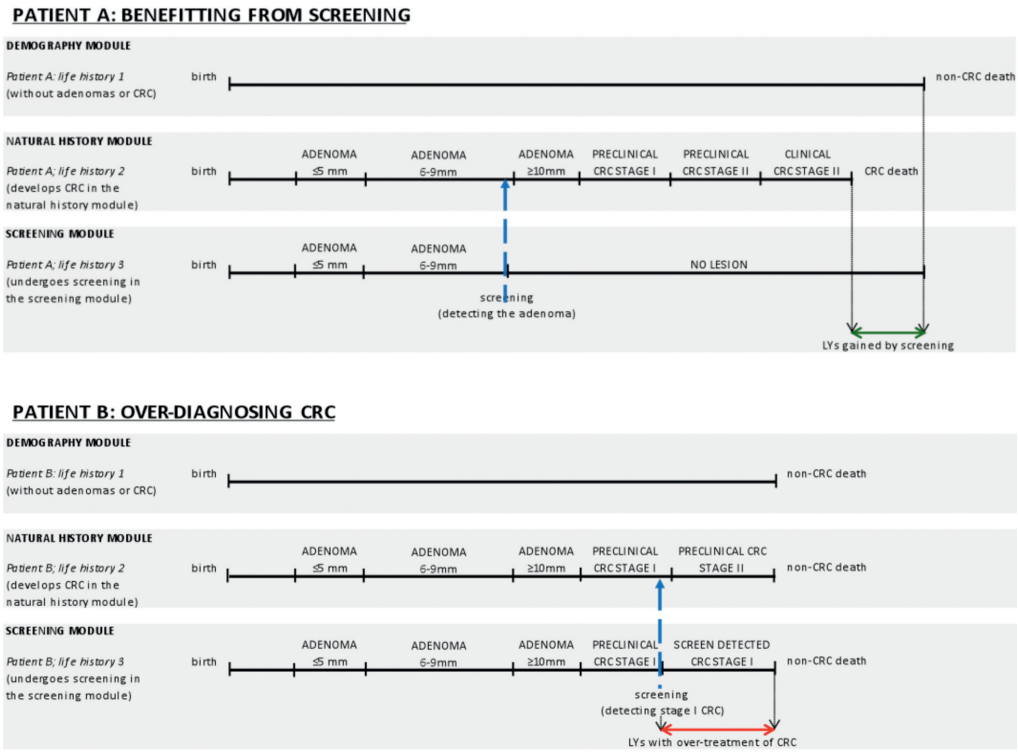


treatment of CRC (i.e. the detection and treatment of cancers that would not have been diagnosed without screening/ surveillance).[40 41]

Integrating Modules

The demography module generates a date of birth and a date of non-CRC death for each individual simulated, creating a life-history without adenomas or CRC. In Patient A in *Appendix 2, Figure 5*, the natural history module generates an adenoma. This adenoma progresses into preclinical cancer, which is diagnosed because of symptoms in stage II and results in CRC death before non-CRC death would have occurred. In the screening module a screening examination is simulated, indicated by the blue arrow. During this examination the adenoma is detected, and as a result both CRC and CRC death are prevented. Hence, in Patient A, screening prolongs life by the amount indicated by the green arrow. Patient B also develops an adenoma, and although this adenoma does progress into preclinical cancer, Patient B would never have been diagnosed with CRC in a scenario without screening *(see life history 2)*. However, during the screening examination simulated in the screening module, again indicated by the blue arrow, CRC is screen-detected in stage I. Hence, in this patient, screening results in over-diagnosis of CRC: it detects a cancer that would

Appendix 2, Figure 5. Integrating Modules: Two example Patients.

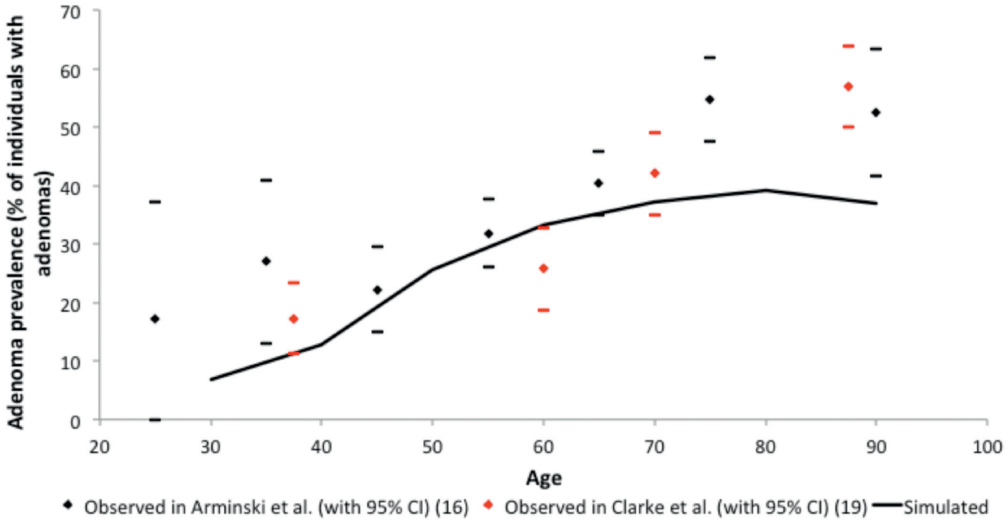


never have been diagnosed in a scenario without screening. Hence, screening does not prolong life, but it does result in additional LYs with CRC care (over-treatment) as indicated by the red arrow.

The Risk for Colorectal Cancer Mortality in Adenoma Patients

We validated MISCAN-Colon against the long-term mortality outcomes of the National Polyp Study: a study assessing the effectiveness of colonoscopic polypectomy.[32] The model showed good concordance with the mortality rates observed *(Appendix 2, Figure 6)*.

Appendix 2, Figure 6. Cumulative CRC Mortality Observed in the National Polyp Study Versus Simulated by MISCAN-Colon.



Appendix 3 Model Parameters

Test characteristics

The sensitivity of colonoscopy for the detection of adenomas and CRC was obtained from a systematic review on miss-rates observed in tandem colonoscopy studies and was 75% for small adenomas (≤5mm), 85% for medium-sized adenomas (6-9mm) and 95% for large adenomas (≥10mm) and CRC.[42] We assumed that 95% of all colonoscopies reached the cecum; for the remaining 5%, the reach of the procedure was assumed to be distributed uniformly over colon and rectum. We assumed that in 10% of all negative colonoscopies a hyperplastic polyp was detected and removed.

The sensitivity of FIT for the detection of adenomas and CRC was calibrated to positivity and detection rates observed in the Dutch trials on FIT screening and was 0% for small adenomas (≤5mm), 6.5% for medium-sized adenomas (6-9mm), 29.2% for large adenomas (≥10mm), 46.7% for cancers that would not have been clinically detected in their current stage and 80.3% for cancers that would have been clinically detected in their current stage.[30] The specificity of FIT was calibrated to the same data and was 97.0%.

Complications of colonoscopy

Age-specific risks for gastrointestinal and cardiovascular complications of colonoscopy requiring a hospital admission or emergency department visit were derived from a study by Warren and colleagues.[40 41] The overall risk associated with colonoscopies with polypectomy increased exponentially with age: from 2 complications per 1,000 colonoscopies at age 40 to 38 complications per 1,000 colonoscopies at age 85. Colonoscopies without polypectomy were not associated with an increased risk for complications.[40 41] We assumed that one out of every 30,000 colonoscopies involving polypectomy resulted in death.[41 43]

Utility losses

We assumed a utility loss (i.e., a loss of quality of life) equivalent to two full days of life per colonoscopy (0.0055 quality-adjusted life-years [QALYs]) and two weeks of life per complication (0.0384 QALYs). We also assigned a utility loss to each life-year (LY) with CRC care *(Appendix 3, Table 1)*.[44]

Costs

The cost-effectiveness analyses were conducted from a societal perspective. The costs of FIT include the costs of the test kit, analysis and organization of the screening programme *(Appendix 3, Table 1)*.[45] Colonoscopy costs were obtained from a Dutch trial comparing colonoscopy with CT colonography screening.[24] The costs of complications and initial and continuing care for CRC were based on reimbursement rates obtained from the Dutch Health Care Authority.[46] The costs of terminal care for CRC were based on the average costs of CRC death obtained from a Dutch study on the disease-specific costs of the last year of life and the relationship between these costs and stage as observed in the US. [47 48] As the costs of terminal care for CRC death in the Netherlands were approximately 40% of the corresponding US costs, we assumed that the costs of terminal care for non-CRC death in CRC patients were also 40% of the corresponding US costs.[48] We adjusted all costs to reflect the 2012 level using the Dutch consumer price index and added patient time costs to all cost estimates.

Appendix 3, Table 1. The Utility Losses and Costs Associated with Surveillance in Adenoma Patients.

UTILITY LOSS, QALYs*				
Per FIT	0			
Per colonoscopy				
Without polypectomy/ biopsy	0.0055			
With polypectomy/ biopsy	0.0055			
Per complication of colonoscopy	0.038			
Per LY with CRC care†‡	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	0.12	0.05	0.70	0.05
Stage II CRC	0.18	0.05	0.70	0.05
Stage III CRC	0.24	0.24	0.70	0.24
Stage IV CRC	0.70	0.70	0.70	0.70

COSTS, 2012 €§				
Per FIT	38			
Per colonoscopy				
Without polypectomy/ biopsy	319			
With polypectomy/ biopsy	456			
Per complication of colonoscopy	1,627			
Per LY with CRC care†‡	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	17,219	686	23,787	9,353
Stage II CRC	22,177	686	23,787	8,912
Stage III CRC	26,584	686	24,889	10,235
Stage IV CRC	30,992	686	32,051	19,931

QALY = quality-adjusted life-year; FIT = fecal immunochemical test; LY = life-year; CRC = colorectal cancer

**The loss of quality of life associated with a particular event.*

†Care for CRC was divided in three clinically relevant phases: the initial, continuing and terminal care phase. The initial care phase was defined as the first 12 months after diagnosis; the terminal care phase was defined as the final 12 months of life; the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between CRC patients dying from CRC and CRC patients dying from another cause. For patients surviving less than 24 months, the final 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.

‡Utility losses for LYs with initial care were derived from a study by Ness and colleagues.[44] For LYs with continuing care for stage I and II CRC, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV CRC, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for CRC, we assumed the utility loss for LYs with initial care for stage IV CRC. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.

§Costs include co-payments and patient time costs (i.e. the opportunity costs of spending time on surveillance or being treated for a complication of colonoscopy or CRC), but do not include travel costs, costs of lost productivity and unrelated health care and non-health care costs in added years of life. We assumed that the value of patient time was equal to the mean wage rate in 2012: €15.93 per hour. We assumed that FITs, colonoscopies and complications used up 1, 8 and 16 hours of patient time, respectively. Patient times for CRC care were obtained from a study by Yabroff and colleagues.[48]

Appendix 4 Simulation of the SAP Population at Baseline

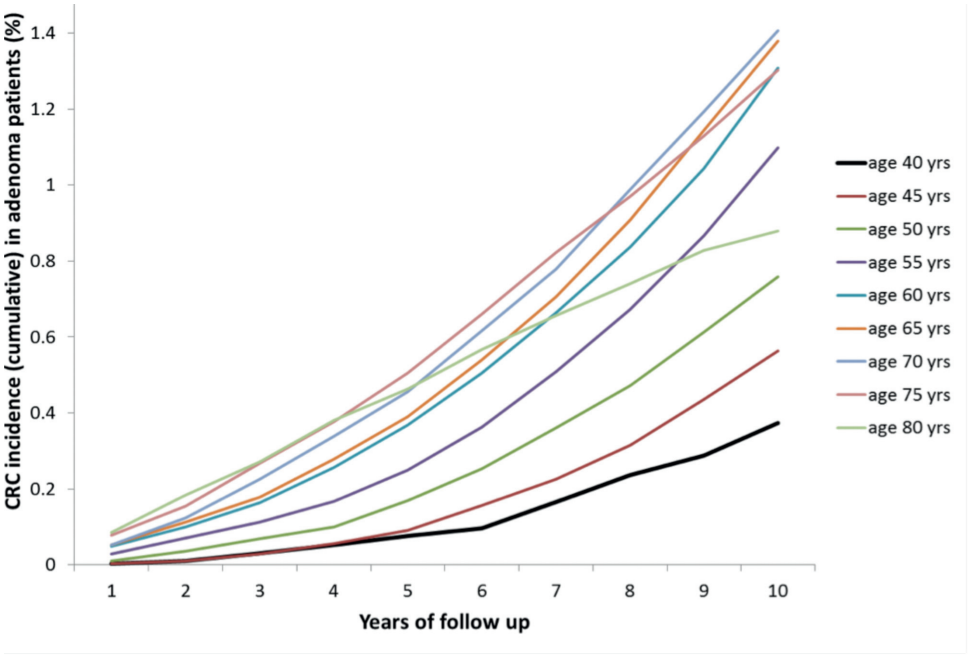
To estimate the average age-specific risks for CRC in adenoma patients, we simulated the SAP population after index colonoscopy by age (40, 45, (…), 80 years). We were able to closely mimic the observed characteristics of the SAP population *(Appendix 4, Table 1)*. The 10-year cumulative risk for CRC ranged from 0.37% in patients aged 40 years to 1.41% in patients aged 70 years *(Appendix 4, Figure 1)*.

Appendix 4, Table 1. The Observed and Simulated Characteristics of the SAP Population at Baseline by Age.

Age (yrs)	Characteristics		Observed (%)	Simulated (%)	Simulated (%)/Observed (%)
40	**Number of adenomas**	1	76.6	76.6	1.00
		2	16.2	16.2	1.00
		3	4.5	4.5	1.00
		4	0.6	0.6	1.00
		5+	1.9	1.9	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	35.1	35.7	1.02
		No	64.9	64.3	0.99
	Presence of at least one proximal adenoma	Yes	21.4	21.8	1.02
		No	78.6	78.2	1.00
45	**Number of adenomas**	1	76.6	76.6	1.00
		2	16.5	16.5	1.00
		3	4.6	4.6	1.00
		4	0.9	0.9	1.00
		5+	1.4	1.4	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	31.6	33.1	1.05
		No	68.4	66.9	0.98
	Presence of at least one proximal adenoma	Yes	22.7	28.8	1.27
		No	77.3	71.2	0.92
50	**Number of adenomas**	1	73.1	73.1	1.00
		2	17.6	17.6	1.00
		3	6.7	6.7	1.00
		4	1.8	1.8	1.00
		5+	0.9	0.9	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	32.4	34.9	1.08
		No	67.6	65.1	0.96
	Presence of at least one proximal adenoma	Yes	25.3	37.5	1.48
		No	74.7	62.5	0.84
55	**Number of adenomas**	1	69.3	69.3	1.00
		2	19.8	19.8	1.00
		3	6.9	6.9	1.00
		4	1.9	1.9	1.00
		5+	2.1	2.1	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	36.3	39.8	1.10
		No	63.7	60.2	0.94
	Presence of at least one proximal adenoma	Yes	29.3	41.9	1.43
		No	70.7	58.1	0.82

Age (yrs)	Characteristics		Observed (%)	Simulated (%)	Simulated (%)/Observed (%)
60	**Number of adenomas**	1	66.5	66.5	1.00
		2	19.9	19.9	1.00
		3	8.2	8.2	1.00
		4	2.0	2.0	1.00
		5+	3.3	3.3	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	39.8	43.2	1.08
		No	60.2	56.8	0.94
	Presence of at least one proximal adenoma	Yes	33.0	47.7	1.44
		No	67.0	52.3	0.78
65	**Number of adenomas**	1	66.3	66.3	1.00
		2	17.9	17.9	1.00
		3	10.1	10.1	1.00
		4	2.4	2.4	1.00
		5+	3.2	3.2	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	40.4	45.0	1.12
		No	59.6	55.0	0.92
	Presence of at least one proximal adenoma	Yes	34.2	49.5	1.45
		No	65.8	50.5	0.77
70	**Number of adenomas**	1	65.9	65.9	1.00
		2	18.3	18.3	1.00
		3	9.3	9.3	1.00
		4	3.1	3.1	1.00
		5+	3.4	3.4	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	41.9	46.9	1.12
		No	58.1	53.1	0.91
	Presence of at least one proximal adenoma	Yes	34.8	51.5	1.48
		No	65.2	48.5	0.74
75	**Number of adenomas**	1	64.3	64.3	1.00
		2	19.6	19.6	1.00
		3	9.5	9.5	1.00
		4	3.5	3.5	1.00
		5+	3.2	3.2	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	45.9	51.3	1.12
		No	54.1	48.7	0.90
	Presence of at least one proximal adenoma	Yes	36.8	55.0	1.49
		No	63.2	45.0	0.71
80	**Number of adenomas**	1	64.1	64.1	1.00
		2	20.0	20.0	1.00
		3	9.8	9.8	1.00
		4	3.1	3.1	1.00
		5+	3.1	3.1	1.00
	Presence of at least one large adenoma (≥10mm)	Yes	47.8	55.3	1.16
		No	52.2	44.7	0.86
	Presence of at least one proximal adenoma	Yes	40.3	56.8	1.41
		No	59.7	43.2	0.72

*Appendix 4, Figure 1. The Cumulative Risk for CRC in Adenoma Patients by Age After Polypectomy According to MISCAN-Colon.**



**The decrease in the 10-year cumulative risk for CRC at the most advanced aged is explained by the increase in the risk for other cause mortality.*

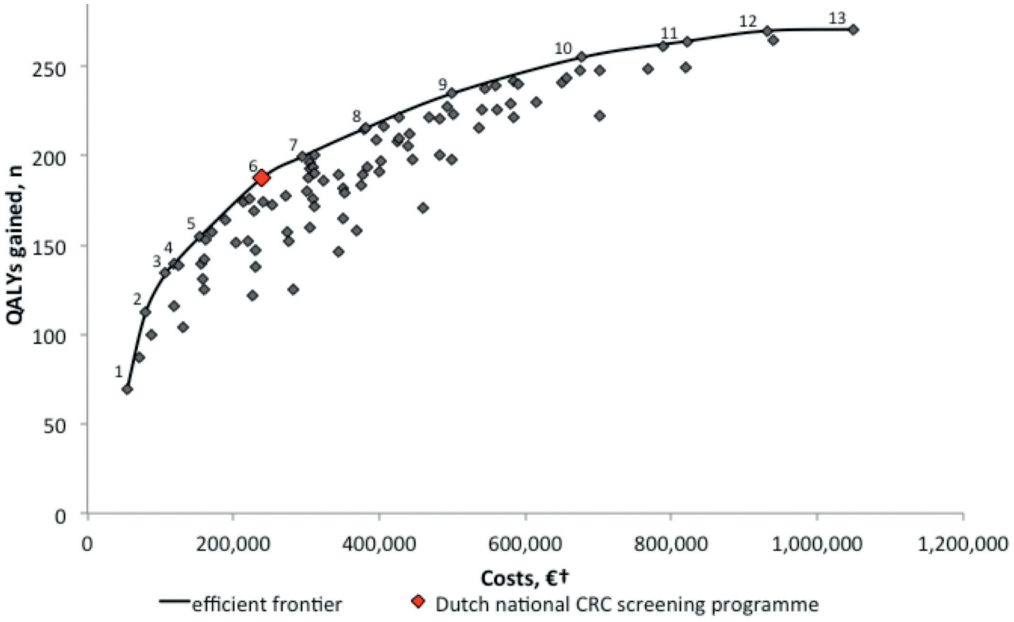
Appendix 5 Cost-Effectiveness of the Dutch National Colorectal Cancer Screening Programme

Within the Dutch national CRC screening programme, individuals are invited for biennial faecal immunochemical test (FIT) screening from age 55 up to age 75 years. The test that is used is the FOB-Gold (Sentinel, Italy) with a cut-off for referral to colonoscopy of 275ng Hb/mL buffer (47µg/g faeces). At this cut-off the test characteristics of the FOB-Gold are broadly equivalent to those observed in the Dutch pilot studies executed prior to the implementation of the national screening programme.[49]

To determine the incremental cost-effectiveness ratio of the national screening programme, the costs and the QALYs gained associated with all possible screening strategies with starting ages 40, 45, 50, 55, 60 and 65 years, stopping ages 70, 75, 80 and 85 years and screening intervals 1, 1.5, 2 and 3 years (96 combinations) were determined. Test characteristics for the FOB-Gold had to be estimated based on data from the Dutch pilot studies, since data from the national screening programme were still very sparse.

Appendix 5, Figure 1 shows the costs and QALYs gained for all screening strategies given the assumptions used in the base-case analysis of the paper. As can be seen in the figure, the national screening programme is on the efficient frontier. Its incremental cost-effectiveness ratio is €2,600 *(Appendix 5, Table 1)*. Appendix 5, Table 2 shows the incremental cost-effectiveness ratios of the Dutch national screening programme given the assumptions used in the various sensitivity analyses performed *(Table 4 of the paper)*.

*Appendix 5, Figure 1. The Costs and QALYs Gained for All Screening Strategies Given the Assumptions Used in the Base-Case Analysis of the Paper.**



*Results are based on a comparison with no screening, reported per 1,000 individuals aged between 55 and 75 years in 2015 and discounted by 3% per year.
†The costs of FITs, colonoscopies, complications, and LYs with CRC care with screening minus the costs of LYs with CRC care without screening.

*Appendix 5, Table 1. The Incremental Cost-Effectiveness of All Efficient Screening Strategies Given the Assumptions Used in the Base-Case Analysis of the Paper (see also Appendix 5, Figure 1).**

Number	Screening Strategy (starting age-stopping age (screening interval))	QALYs Gained, n	Costs, €†	Incremental Costs per QALY Gained, €
1	65-70 (3)	69	53,915	Reference
2	60-70 (3)	112	79,644	603
3	60-70 (2)	134	107,200	1,250
4	60-70 (1.5)	140	118,959	2,125
5	55-70 (2)	154	153,505	2,339
6‡	**55-75 (2)**	**188**	**239,606**	**2,593**
7	55-75 (1.5)	199	294,367	4,649
8	50-75 (1.5)	215	378,642	5,431
9	50-80 (1.5)	235	498,777	6,075
10	50-80 (1)	255	677,983	8,816
11	45-80 (1)	264	820,917	15,853
12	45-85 (1)	270	930,802	18,841
13	40-85 (1)	271	1,048,845	138,845

QALY = quality-adjusted life-year
**QALYs gained and costs are based on a comparison with no screening, reported per 1,000 individuals aged between 55 and 75 years in 2015 and discounted by 3% per year.*
†The costs of FITs, colonoscopies, complications, and LYs with CRC care with screening minus the costs of LYs with CRC care without screening.
‡The Dutch national CRC screening programme.

Appendix 5, Table 2. The Incremental Cost-Effectiveness of the Dutch National CRC Screening Programme given the assumptions made in the various sensitivity analyses performed.

Analysis	Incremental Costs per QALY Gained, €
Base case	2,600
1a. Weaker association adenoma risk score and risk*	2,600
1b. Stronger association adenoma risk score and risk*	2,600
2a. Lower average risk for advanced adenoma recurrence*	2,600
2b. Average risk for advanced adenoma recurrence*	2,600
3. Less favorable life-expectancy for adenoma patients (-5 yrs)†	5,100
4. Colonoscopy miss rates x 2	3,400
5a. Utility losses colonoscopies and complications x 0.5	2,600
5b. Utility losses colonoscopies and complications x 2	2,700
6a. Colonoscopy costs x 0.5	1,800
6b. Colonoscopy costs x 2	4,600
7a. CRC care costs x 0.5	4,100
7b. CRC care costs x 2†	0
8.Differential discounting of costs and effects†	2,800

**We assumed that the assumptions made in these analyses did not change the incremental cost-effectiveness of the Dutch National CRC screening programme. †The Dutch national CRC screening programme was dominated by other strategies in these analyses. We used the incremental cost-effectiveness ratio of the most similar strategy (in terms of the life-time number of screens) that was on the efficient frontier instead.*

Appendix 6 Sensitivity Analyses – Detailed Results

*Appendix 6, Table 1. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 1a. Weaker Association Adenoma Risk Score and Risk.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	10	10	8	9	7	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	6	6	6	5	6	5	3	NS
3	5	5	5	5	4	4	4	3	NS
4	4	4	4	4	4	4	3	3	NS
5	4	4	3	3	3	3	3	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	9	9	8	8	6	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	6	5	5	5	5	5	4	NS	NS
3	5	4	4	4	4	4	4	3	NS
4	4	4	4	3	3	3	3	3	NS
5	3	3	3	3	3	3	3	2	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 2. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 1b. Stronger Association Adenoma Risk Score and Risk.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	10	10	FIT10	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	2	NS
4	3	3	3	3	3	3	2	2	NS
5	3	3	2	2	2	2	2	2	3

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	9	NS	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	4	4	4	4	3	NS
3	4	4	3	3	3	3	3	3	NS
4	3	3	3	3	2	3	2	2	NS
5	2	2	2	2	2	2	2	2	NS

NS = no surveillance, FIT10 = FIT screening after 10 years
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 3. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 2a. Lower Average Risk for Advanced Adenoma Recurrence.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	10	10	NS	NS	NS	NS
1	9	10	8	8	7	7	NS	NS	NS
2	6	6	6	6	6	5	5	4	NS
3	5	5	5	4	4	4	4	3	NS
4	4	4	4	4	4	3	3	2	NS
5	3	3	3	3	3	3	3	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	9	NS	NS	NS	NS
1	8	7	7	6	6	6	NS	NS	NS
2	6	6	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	3	3	2	2	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 4. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 2b. Higher Average Risk for Advanced Adenoma Recurrence.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	10	10	9	9	7	NS	NS	NS
1	8	8	7	7	7	6	5	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	8	6	NS	NS	NS
1	7	6	6	6	6	5	5	NS	NS
2	5	5	4	4	4	4	4	3	NS
3	4	4	4	3	3	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	2	2	2	2	2	2	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 5. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 3. Less Favourable Life-Expectancy for Adenoma Patients (-5yrs)**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	9	NS	NS	NS	NS
1	7	7	7	6	6	6	NS	NS	NS
2	5	5	5	5	5	5	5	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	3	NS
5	3	3	3	3	3	3	3	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	8	9	7	8	NS	NS	NS	NS
1	6	7	7	7	6	6	NS	NS	NS
2	5	5	5	5	4	4	4	NS	NS
3	4	4	4	4	3	3	3	NS	NS
4	3	3	3	3	3	3	3	3	NS
5	3	3	3	2	2	2	3	2	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 6. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 4. Colonoscopy Miss Rates x 2.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	10	10	NS	NS	NS	NS
1	7	8	7	7	7	7	NS	NS	NS
2	5	5	5	5	5	4	5	NS	NS
3	4	4	4	4	4	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	2	2	2	2	2	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	9	NS	NS	NS	NS
1	6	6	6	6	6	7	NS	NS	NS
2	5	4	4	4	4	4	5	NS	NS
3	4	3	3	3	3	3	3	3	NS
4	3	3	3	3	2	3	3	2	NS
5	2	2	2	2	2	2	2	2	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 7. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 5a. Utility Losses Colonoscopies and Complications x 0.5.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	7	7	7	7	6	NS	NS
2	6	5	5	5	5	5	5	4	NS
3	4	5	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	8	6	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	4	4	3	NS
3	4	4	4	4	4	4	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	2	2	2	2	2	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 8. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 5b. Utility Losses Colonoscopies and Complications x 2.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	6	6	6	5	5	5	4	NS
3	5	5	4	4	4	4	4	3	NS
4	4	4	3	3	3	3	3	2	NS
5	3	3	3	3	3	3	2	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	8	7	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	2	2	2	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 9. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 6a. Colonoscopy Costs x 0.5.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	7	7	7	7	7	7	5	NS	NS
1	5	5	5	5	5	4	4	3	NS
2	4	4	4	4	4	3	3	3	NS
3	3	3	3	3	3	3	3	2	NS
4	3	3	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	1	2

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	6	6	6	6	6	6	4	NS	NS
1	5	4	4	4	4	4	4	3	NS
2	4	3	3	3	3	3	3	3	NS
3	3	3	3	3	2	3	2	2	NS
4	2	2	2	2	2	2	2	2	NS
5	2	2	2	2	2	2	2	1	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 10. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 6b. Colonoscopy Costs x 2.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	FIT10	FIT10	FIT10	FIT10	FIT10	NS	NS	NS	NS
1	10	10	10	9	10	8	NS	NS	NS
2	9	8	8	7	7	7	6	NS	NS
3	6	7	6	6	6	6	5	4	NS
4	5	5	5	4	4	4	4	4	NS
5	4	4	4	4	4	3	3	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	FIT10	FIT10	FIT10	FIT10	NS	NS	NS	NS	NS
1	10	9	10	8	8	7	NS	NS	NS
2	7	7	7	6	6	6	5	NS	NS
3	6	6	5	5	5	5	5	NS	NS
4	5	5	4	4	4	4	4	3	NS
5	4	4	4	3	3	3	3	3	NS

NS = no surveillance, FIT10 = FIT screening after 10 years
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 11. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 7a. CRC Care Costs x 0.5.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	10	10	FIT10	NS	NS	NS
1	9	10	8	9	7	8	NS	NS	NS
2	7	7	7	6	6	6	6	NS	NS
3	5	5	5	5	5	5	4	4	NS
4	4	4	4	4	4	3	3	4	NS
5	4	4	3	3	3	3	3	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	9	9	NS	NS	NS	NS
1	9	8	8	8	7	7	NS	NS	NS
2	6	6	6	5	5	5	5	NS	NS
3	5	5	5	4	4	4	4	3	NS
4	4	4	4	4	4	3	3	3	NS
5	3	3	3	3	3	3	3	2	NS

NS = no surveillance, FIT10 = FIT screening after 10 years
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 12. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 7b. CRC Care Costs x 2.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	9	8	8	7	7	NS	NS	NS
1	6	6	6	5	5	5	5	NS	NS
2	4	5	4	4	4	4	4	3	NS
3	4	3	3	3	3	3	3	2	NS
4	3	3	3	3	2	2	2	2	NS
5	2	2	2	2	2	2	2	1	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	7	7	7	6	6	6	NS	NS	NS
1	5	5	5	5	5	4	4	NS	NS
2	4	4	4	4	3	4	3	3	NS
3	3	3	3	3	3	3	3	2	NS
4	2	2	2	2	2	2	2	2	NS
5	2	2	2	2	2	2	2	1	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

*Appendix 6, Table 13. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Sensitivity Analysis 8. Differential Discounting of Costs and Effects.**

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	8	8	9	7	8	8	NS	NS	NS
1	6	6	6	6	6	6	6	NS	NS
2	5	5	5	5	4	4	5	4	NS
3	4	4	3	4	4	4	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	2	2	2	3	2	2	3

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	8	8	8	7	7	7	NS	NS	NS
1	5	5	6	5	5	5	5	NS	NS
2	4	4	4	4	4	4	4	3	NS
3	3	3	3	3	3	3	3	3	NS
4	3	3	3	3	2	3	3	2	NS
5	2	2	2	2	2	2	2	1	NS

NS = no surveillance
**The appropriate intervals are selected using a cost-effectiveness threshold equal to the incremental cost-effectiveness ratio of the Dutch national CRC screening programme (Appendix 5).*

Appendix 7 Scenario Analyses – Detailed Results

Appendix 7, Table 1. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1a. Low Health Care Costs, Cost-Effectiveness Threshold: €2,600/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	10	8	9	7	8	NS	NS	NS
1	7	7	7	6	6	6	6	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	2	2	3	2	2	3

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	8	9	8	8	7	6	NS	NS	NS
1	6	6	6	5	5	5	5	NS	NS
2	5	4	4	4	4	4	4	3	NS
3	4	3	3	3	3	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	2	2	2	2	2	2	2	NS

NS = no surveillance

Appendix 7, Table 2. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1b. Low Health Care Costs, Cost-Effectiveness Threshold: €5,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	7	7	7	7	7	7	6	NS	NS
1	5	5	5	5	5	5	5	4	NS
2	4	5	3	4	4	4	4	4	NS
3	4	3	3	3	3	3	3	2	NS
4	3	3	3	3	2	3	2	2	3
5	2	2	2	2	2	2	2	2	2

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	7	6	6	6	6	6	6	NS	NS
1	5	5	5	5	5	4	5	4	NS
2	4	4	4	4	4	4	4	3	NS
3	3	3	3	3	3	3	3	2	NS
4	3	3	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	2	3

NS = no surveillance

Appendix 7, Table 3. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1c. Low Health Care Costs, Cost-Effectiveness Threshold: €10,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	6	6	6	6	6	6	6	4	NS
1	5	5	5	4	4	5	3	4	NS
2	4	4	3	3	4	3	3	2	3
3	3	3	3	3	3	3	2	2	3
4	2	2	2	2	2	2	2	2	2
5	2	2	2	2	2	2	2	1	2

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	4	4	4	NS
2	3	3	3	3	3	3	3	2	NS
3	3	3	3	3	2	3	2	2	3
4	2	2	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	1	2

NS = no surveillance

Appendix 7, Table 4. *The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1d. Low Health Care Costs, Cost-Effectiveness Threshold: €20,000/QALY gained.*

	FEMALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	3	3	4	3
2	3	3	3	3	3	3	3	2	3
3	2	2	2	2	2	2	2	2	2
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	2	2	1	2

	MALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	4	5	4	4	4	4	4	4	NS
1	4	3	3	3	3	3	3	4	NS
2	3	3	3	3	3	3	3	2	3
3	2	2	2	2	2	2	2	2	3
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	1	1	1	2

NS = no surveillance

Appendix 7, Table 5. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 1e. Low Health Care Costs, Cost-Effectiveness Threshold: €40,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	4	4	4	4	4	5	5	4	NS
1	3	3	3	3	3	3	3	2	3
2	3	3	3	3	2	3	2	2	3
3	2	2	2	2	2	2	2	1	2
4	2	2	2	2	2	2	2	1	2
5	2	2	2	1	1	1	1	1	1

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	4	4	4	4	4	4	4	4	NS
1	3	3	3	3	3	3	3	2	3
2	2	2	2	2	2	2	2	2	3
3	2	2	2	2	2	2	2	1	2
4	2	2	2	2	2	2	2	1	2
5	1	1	1	1	1	1	1	1	1

NS = no surveillance

Appendix 7, Table 6. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2a. Dutch Health Care Costs, Cost-Effectiveness Threshold: €2,600/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	5	6	5	5	5	5	4	NS
3	4	5	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	10	9	10	8	8	7	NS	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	2	2	2	NS

NS = no surveillance

Appendix 7, Table 7. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2b. Dutch Health Care Costs, Cost-Effectiveness Threshold: €5,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	10	8	9	7	8	NS	NS	NS
1	7	7	7	6	6	6	6	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	2	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	2	2	3	2	2	3

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	9	8	8	7	6	NS	NS	NS
1	6	6	6	5	5	5	5	NS	NS
2	5	5	4	4	4	4	4	3	NS
3	4	3	3	3	3	3	3	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	2	2	2	2	2	2	2	NS

NS = no surveillance

Appendix 7, Table 8. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2c. Dutch Health Care Costs, Cost-Effectiveness Threshold: €10,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	7	7	7	7	7	6	6	NS	NS
1	5	5	5	5	5	5	5	4	NS
2	4	5	4	4	4	4	4	4	NS
3	3	3	3	3	3	3	3	2	3
4	3	3	3	3	2	3	2	2	3
5	2	2	2	2	2	2	2	1	2

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	7	6	6	6	6	6	6	NS	NS
1	5	5	5	5	5	4	4	4	NS
2	4	4	4	4	4	4	4	3	NS
3	3	3	3	3	3	3	3	2	NS
4	3	3	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	1	3

NS = no surveillance

Appendix 7, Table 9. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2d. Dutch Health Care Costs, Cost-Effectiveness Threshold: €20,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	6	6	6	6	6	6	6	4	NS
1	4	5	5	4	4	5	5	4	NS
2	4	3	3	3	4	3	3	2	3
3	3	3	3	3	2	3	2	2	3
4	2	2	2	2	2	2	2	2	2
5	2	2	2	2	2	2	2	1	2

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	4	4	4	NS
2	3	3	3	3	3	3	3	2	NS
3	3	3	3	2	2	3	2	2	3
4	2	2	2	2	2	2	2	2	2
5	2	2	2	2	2	2	2	1	2

NS = no surveillance

Appendix 7, Table 10. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 2e. Dutch Health Care Costs, Cost-Effectiveness Threshold: €40,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	3	3	2	3
2	3	3	3	3	3	3	3	2	3
3	2	2	2	2	2	2	2	2	2
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	2	2	1	2

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	4	5	4	4	4	4	4	4	NS
1	4	3	3	3	3	3	3	2	NS
2	3	3	3	3	3	3	2	2	3
3	2	2	2	2	2	2	2	2	3
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	1	1	1	2

NS = no surveillance

Appendix 7, Table 11. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3a. High Health Care Costs, Cost-Effectiveness Threshold: €2,600/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	9	10	FIT10	NS	NS	NS
1	9	9	8	8	7	7	6	NS	NS
2	6	6	6	6	5	5	5	NS	NS
3	5	5	5	4	4	4	4	3	NS
4	4	4	4	3	4	3	3	2	NS
5	3	3	3	3	3	3	3	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	8	FIT10	NS	NS	NS
1	8	7	7	6	6	6	6	NS	NS
2	6	6	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	4	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS

NS = no surveillance, FIT10 = FIT screening after 10 years

Appendix 7, Table 12. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3b. High Health Care Costs, Cost-Effectiveness Threshold: €5,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	10	10	9	10	8	NS	NS	NS
1	9	8	8	7	7	7	6	NS	NS
2	6	5	6	5	5	5	5	4	NS
3	4	5	4	4	4	4	4	3	NS
4	4	4	3	3	3	3	3	2	NS
5	3	3	3	3	2	3	2	2	NS

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	10	9	10	8	8	7	6	NS	NS
1	7	7	6	6	6	6	5	NS	NS
2	5	5	5	5	5	5	4	NS	NS
3	4	4	4	4	4	4	4	3	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	3	2	2	2	2	NS

NS = no surveillance

Appendix 7, Table 13. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3c. High Health Care Costs, Cost-Effectiveness Threshold: €10,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	10	8	9	7	8	NS	NS	NS
1	7	7	7	6	6	6	6	NS	NS
2	5	5	5	5	5	4	4	4	NS
3	4	4	4	4	4	3	3	2	NS
4	3	3	3	3	3	3	3	2	NS
5	3	3	3	2	2	2	2	2	3

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	9	9	9	8	7	6	6	NS	NS
1	6	6	6	5	5	5	5	NS	NS
2	5	5	4	4	4	4	4	3	NS
3	4	3	3	3	3	3	3	3	NS
4	3	3	3	3	3	3	2	2	NS
5	3	2	2	2	2	2	2	2	NS

NS = no surveillance

Appendix 7, Table 14. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3d. High Health Care Costs, Cost-Effectiveness Threshold: €20,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	8	7	7	7	7	6	6	NS	NS
1	5	5	5	5	5	5	5	4	NS
2	4	5	4	4	4	4	4	4	NS
3	3	3	3	3	3	3	3	2	3
4	3	3	3	3	2	3	2	2	3
5	2	2	2	2	2	2	2	1	2

	MALE								
	Age, yrs								
Adenoma Risk Score	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**
0	7	6	6	6	6	6	6	NS	NS
1	5	5	5	5	5	4	4	4	NS
2	4	4	4	4	4	3	4	3	NS
3	3	3	3	3	3	3	3	2	NS
4	3	3	2	2	2	2	2	2	3
5	2	2	2	2	2	2	2	1	2

NS = no surveillance

Appendix 7, Table 15. The Appropriate Intervals For Colonoscopy Surveillance by Adenoma Risk Score, Sex and Age: Results of Scenario Analysis 3e. High Health Care Costs, Cost-Effectiveness Threshold: €40,000/QALY gained.

	FEMALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	6	6	6	6	6	6	6	4	NS
1	4	5	5	4	4	5	5	4	NS
2	4	3	3	3	4	3	3	2	3
3	3	3	3	3	2	3	2	2	3
4	2	2	2	2	2	2	2	1	2
5	2	2	2	2	2	2	2	1	2

	MALE								
	Age, yrs								
Adenoma Risk Score	40	45	50	55	60	65	70	75	80
0	5	5	5	5	5	5	5	4	NS
1	4	4	4	4	4	4	4	4	NS
2	3	3	3	3	3	3	3	2	NS
3	3	3	3	2	2	3	2	2	3
4	2	2	2	2	2	2	2	2	2
5	2	2	2	2	2	2	2	1	2

NS = no surveillance

Part III

Adherence to and acceptance of guidelines for surveillance of adenoma patients

Chapter 6

Adherence to surveillance guidelines after removal of colorectal adenomas: a large, community-based study

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Abstract

Objective: To determine adherence to recommended surveillance intervals in clinical practice.

Design: 2997 successive patients with a first adenoma diagnosis (57% male, mean age 59 years) from 10 hospitals, who underwent colonoscopy between 1998 and 2002, were identified via Pathologisch Anatomisch Landelijk Geautomatiseerd Archief: Dutch Pathology Registry. Their medical records were reviewed until 1 December 2008. Time to and findings at first surveillance colonoscopy were assessed. A surveillance colonoscopy occurring within ±3 months of a 1-year recommended interval and ±6 months of a recommended interval of 2 years or longer was considered appropriate. The analysis was stratified by period per change in guideline (before 2002: 2-3 years for patients with 1 adenoma, annually otherwise; in 2002: 6 years for 1-2 adenomas, 3 years otherwise). We also assessed differences in adenoma and colorectal cancer recurrence rates by surveillance timing.

Results: Surveillance was inappropriate in 76% and 89% of patients diagnosed before 2002 and in 2002, respectively. Patients eligible under the pre-2002 guideline mainly received surveillance too late or were absent (57% of cases). For patients eligible under the 2002 guideline surveillance occurred mainly too early (48%). The rate of advanced neoplasia at surveillance was higher in patients with delayed surveillance compared with those with too early or appropriate timed surveillance (8% vs 4-5%, $p<0.01$).

Conclusions: There is much room for improving surveillance practice. Less than 25% of patients with adenoma receive appropriate surveillance. Such practice seriously hampers the effectiveness and efficiency of surveillance, as too early surveillance poses a considerable burden on available resources while delayed surveillance is associated with an increased rate of advanced adenoma and especially colorectal cancer.

Significance of this study

What is already known on this subject?

- A considerable proportion of colonoscopy use concerns procedures for surveillance purposes. This proportion will further increase with the introduction of mass screening for colorectal cancer (CRC).
- For optimal effectiveness of CRC prevention and limitation of resource depletion, adherence to postpolypectomy surveillance guidelines is mandatory.
- Surveys show that gastroenterologists often advise shorter surveillance intervals than recommended by guidelines.
- No large studies have assessed adherence to surveillance guidelines in clinical practice.

What are the new findings?

- In clinical practice, only a minority of patients (11-24%) receives appropriate surveillance according to guidelines. This is considerably lower than previously estimated from surveys.
- Over 45% of patients receive too intense surveillance compared with the 2002 guidelines.
- Compared with appropriate or too early surveillance, delayed surveillance was associated with a higher rate of advanced and non-advanced neoplasia at surveillance colonoscopy.
- Poor penetration of the 2002 surveillance guidelines within 1 year following implementation illustrates the importance of convincing evidence to support endorsement of new guidelines by physicians.

How might it impact on clinical practice in the foreseeable future?

- Physicians should realise that current adherence to guidelines is inappropriate and that that can seriously hamper effectiveness and efficiency of surveillance.
- Specific interventions should be compared for their effectiveness to improve guideline adherence.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the Western world.[1, 2] Individuals with adenomas are at increased risk to develop CRC compared with the average population, even after the adenoma has been removed.[3-6] Patients with adenoma are therefore recommended to undergo regular colonoscopy surveillance.[7-10]. Currently in the USA about 15-25% of all colonoscopy procedures are being performed for surveillance purposes,[11, 12] while in the Netherlands estimates range from 13% to 40%.[13, 14] Previous research indicated that adherence to postpolypectomy surveillance guidelines is insufficient.[15-23] While too little surveillance threatens the effectiveness of CRC prevention, too intensive surveillance may lead to unnecessary harms and makes inefficient use of colonoscopy resources.

The introduction of mass screening for CRC combined with aging of the population in many Western countries will considerably increase the number of patients with adenoma in the coming years, and thus the number of surveillance colonoscopies required. The number of colonoscopies in the Netherlands has increased significantly from 117 000 in 2004 to 191 000 in 2009.[24] An additional 66 000 to 99 000 colonoscopies each year are expected with full implementation of CRC screening (after a positive faecal immunochemical blood test plus subsequent surveillance).[13, 25, 26] The associated increase in colonoscopy demand together with the limited colonoscopy capacity in many countries[27-30] emphasise the importance of efficiency in surveillance practice and therefore adherence to surveillance guidelines.

Previous studies regarding adherence to postpolypectomy surveillance guidelines mainly consisted of surveys among gastroenterologists, in which the follow-up decision of the gastroenterologist was compared with the guidelines' recommendation.[16, 18, 20, 31] However the gastroenterologists intention immediately after the index colonoscopy is only one factor on whether and when surveillance colonoscopy will take place. Moreover these studies may be prone to bias because of medically desirable answers. Few studies assessed actual adherence to postpolypectomy surveillance guidelines.[19, 23, 32] These were either relatively small single-centre studies[19, 32, 33] or based on a self-reported patient survey.[23] In addition, the proportion of patients not having surveillance at all was not always assessed.

We aimed to determine the extent of adherence to postpolypectomy surveillance guidelines in community-based clinical practice, in which we were also in the position to assess the influence of a change in guideline on adherence rates.

Methods

Patient selection

We used the nationwide registry of histopathology and cytopathology in the Netherlands (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief, PALGA)[34] to identify patients with a first adenoma diagnosis in the period from 1 June 1998 to 31 December 2002 in 10 hospitals (3 academic and 7 non-academic) throughout the Netherlands. This registry includes a résumé of findings of all tissue materials (eg, polyps, biopsies) that have been submitted at any pathology centre in the Netherlands since 1991. Years of inclusion of patients with adenoma per hospital depended on the availability of electronic medical records. Patients with a first adenoma diagnosis aged 40 to 74 years were eligible for inclusion. Patients with any of the following criteria were excluded: (1) (suspected) hereditary CRC syndromes, in particular Lynch syndrome (hereditary non-polyposis colorectal carcinoma), familial adenomatous polyposis, Peutz-Jeghers syndrome, juvenile polyposis, or polyposis associated with mutations in the MUTYH-gene; (2) personal history of CRC or CRC at index colonoscopy; (3) (previous) bowel resections; (4) IBD; (5) acromegaly; (6) ureterosigmoidostomy; and (7) recommended age of next surveillance exceeded the recommended age to stop surveillance. Exclusion criteria 4 to 6 are associated with an increased CRC risk, and we have therefore excluded patients with these conditions.

Data collection

After identification of patients with a first adenoma diagnosis via the PALGA database, patients' medical records, in particular endoscopy and pathology reports, were reviewed in 10 hospitals to collect information on patient characteristics, index and surveillance colonoscopy (colonoscopy or sigmoidoscopy) including corresponding adenoma characteristics, until 1 December 2008, the end of the study. Index colonoscopy was defined as colonoscopy or sigmoidoscopy with first adenoma diagnosis. We considered repeat colonoscopy examinations performed either within 6 months after index colonoscopy, or after surveillance colonoscopy as one examination. In case of combining results from colonoscopies, the date of last colonoscopy with the fullest reach including polypectomy was used. For all patients, date of index colonoscopy, age and sex were collected. In patients without a surveillance colonoscopy before 1 December 2008, we only collected data on index colonoscopy characteristics and adenoma findings in a randomly picked sample of 40% (433/1093) of patients. In all patients with surveillance after adenoma detection we collected data on colonoscopy characteristics and ade-

noma findings, at index and surveillance colonoscopy.

This study was approved by the Institutional Review Board of Erasmus MC University Medical Centre and all participating centres.

Outcomes

We evaluated the time interval to first surveillance colonoscopy as our main outcome measure. Absence of surveillance was defined as not having received surveillance within 90 months or before the end of the study period, whichever came first. The definition of appropriate surveillance was based on the active guideline. In the Netherlands, from June 1998 to October 2001, patients with one adenoma were recommended a 2-3 year surveillance interval; patients with more than one adenoma a 1-year interval.[35, 36] In October 2001, a revised guideline was published and implemented from January 2002 onwards. It was communicated at a national conference and through a report including a wallet sized card with the summary of the guideline by Dutch Institute for Healthcare Improvement.[37] The revised guideline recommended patients with three or more adenomas to have surveillance after 3 years, and patients with fewer than three adenomas to return for surveillance after 6 years. Surveillance colonoscopy could be ceased after age 65 years for patients with cumulative one adenoma at that age, and after age 75 years for patients with cumulative two adenomas.[10] The timing of surveillance colonoscopy was arbitrarily considered appropriate if surveillance has been performed within the range of ±3 months for the 1-year recommendation, and ±6 months for the 2-6 year recommendations. The corresponding appropriate surveillance intervals are given in *table 1*. We also assessed the yield of advanced adenoma (AA) and non-AA at surveillance colonoscopy and relate this to the number of adenomas at index colonoscopy and surveillance interval.

Table 1. Recommended surveillance intervals and intervals considered appropriate in the presented analysis

	Adenoma findings at index colonoscopy		Surveillance interval recommendation		Interval considered appropriate*
June 1998 - 2001	≥2	adenomas	12 months	(1 year)	9 - 15 months
	1	adenoma	24–36 months	(2-3 year)	18 - 42 months
Since 2002	≥3	adenomas	36 months	(3 years)	30 - 42 months
	1 or 2	adenomas	72 months	(6 years)	66 - 78 months

** Appropriate interval is ±3 months for a 1-year interval recommendation and ±6 months for longer interval recommendations.*

Statistical analysis

We used Kaplan-Meier (KM) analysis to estimate the probability over time since polypectomy that a patient would have surveillance colonoscopy. The analysis was stratified by two different periods corresponding to the active guideline (June 1998 to 2002, and from 2002 onwards), and by adenoma number at index colonoscopy: one, two and three+ adenomas. Each patient in the study cohort was followed from index colonoscopy until the first surveillance colonoscopy, or until censored. Patients were censored (A) at reported time of death, (B) on 1 December 2008, or (C) 90 months after index colonoscopy, whichever came first. We assumed no loss to follow-up.

Differences in characteristics between groups were assessed by the Mann-Whitney U test, Kruskal-Wallis test, or χ^2 test. The log-rank test (Mantel-Cox) was used to compare KM curves. All statistical analyses were conducted using the Statistical Package for Social Sciences for Windows v. 17.0 (SPSS, Chicago, Illinois, USA). Two-sided p values <0.05 were considered statistically significant.

Missing values

To perform the KM analysis stratified by active guideline and adenoma number at index colonoscopy, we needed data on adenoma number for all subjects. However, we only collected data on adenoma findings for a subgroup of patients without surveillance (n=433/1093). For missing values for adenoma number (n=660) and gender (n=1) we used a statistical imputation technique.[38] Imputations were based on correlations with patient characteristics (age and sex); hospital type (academic or non-academic); year of index colonoscopy, reach and preparation of index colonoscopy; adenoma characteristics (number of adenomas; presence of villous adenoma; presence of adenomas sized ≥10mm (as measured by the endoscopist or pathologist); adenomas with high-grade dysplasia; and proximal adenomas); and presence of a surveillance colonoscopy, using the aregImpute function in R V.2.11 software (R foundation for statistical computing, Vienna, Austria).

Subanalyses

To assess the influence of having hospitals in the data set without observations over the whole index period (June 1998 – 2002), we compared the KM-curves of surveillance timing from five hospitals with data over the whole period to the other hospitals.

Also, two sub analyses were performed regarding implementation issues. A change in guideline usually involves a transitional phase in which anticipation

(before) and implementation issues (after) influence actual practice. Regarding the former issue, endoscopists possibly anticipated the lengthening of the surveillance intervals in upcoming guidelines. Also, because of the change in the guideline in 2002, clinicians may have prolonged surveillance intervals for patients with a first adenoma diagnosis in 2001 retroactively. We therefore considered the period from October 2000 (1 year before guideline publication) until December 2001 as the transitional phase between the two guidelines. We compared the median surveillance intervals and results of the KM-analysis between the periods June 1998 – October 2000 and October 2000 – December 2001.

Second, because it might take time to familiarise and comply with a new guideline, we also compared median surveillance intervals and the results of the KM analysis for the first half of 2002 versus the second half of 2002.

Additionally, we compared KM curves of time to surveillance colonoscopy between academic and non-academic hospitals and between hospitals with or without an active follow-up system. In general, gastroenterologists gave surveillance recommendations to their patients and informed the patients' general practitioner. In hospitals with an active follow-up system patients were actively reminded to have surveillance colonoscopy by the endoscopy centre. For all subanalyses we looked at patients with one, two or three+ adenomas separately.

Results

A total of 2997 patients with a first adenoma diagnosis were included in our study *(figure 1)*. Their mean age was 58.6 (SD 9.0) years and 57.2% were male *(table 2)*. Of all index endoscopies, 2691 (89.8%) were intended colonoscopies and 306 (10.2%) were sigmoidoscopies. In total, 2303 patients had a first adenoma diagnosis before 2002 and 694 patients in 2002. Most patients with adenoma (70%) were seen in non-academic hospitals. Of all patients with adenoma 11.6% had three or more adenomas. The contribution to this study the in number of patients per hospital varied from 84 to 565.

The study follow-up period considered in our analysis for patients diagnosed before 2002 ranged between 83 months to 90 months. For the patients diagnosed in 2002 it was between 71 months and 82 months. Of the patients with surveillance colonoscopy, the median (25th-75th centile) intervals to first surveillance colonoscopy were 25 (13-40) months for patients with their index colonoscopy before 2002 and 35 (14-48) months for those with their index colonoscopy in 2002 ($p< 0.001$). Before 2002, median surveillance intervals were

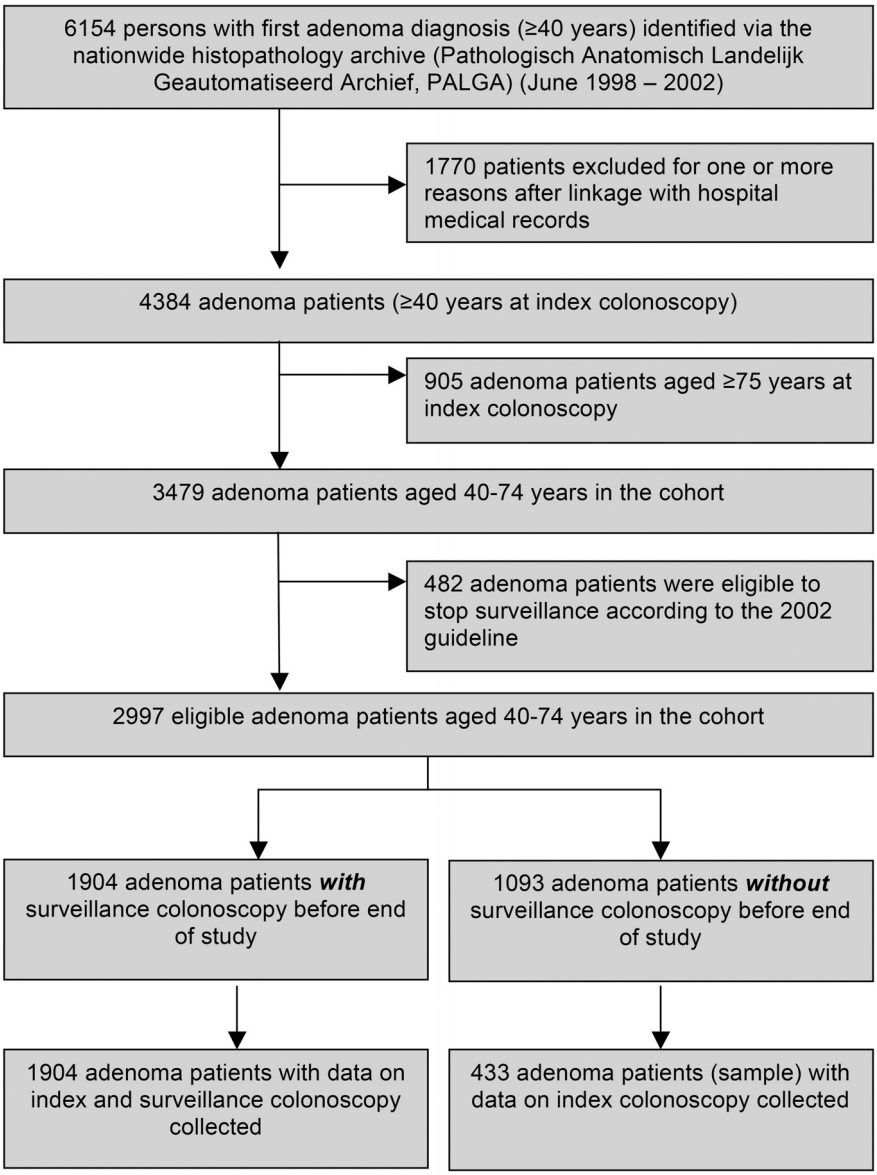

Figure 1. Identification of the study cohort and the subgroups.

27 (13-45) months for those with one adenoma, 22 (12-37) months for those with two adenomas, and 16 (12-35) months for patients with three+ adenomas ($p < 0.001$). In 2002, these intervals were 37 (20-50) months those with one adenoma, 35 (13-45) months those with two adenomas, and 24 (12-37) months for patients with three+ adenomas ($p < 0.001$).

Table 2. Characteristics of the study population at index colonoscopy (n = 2997)

	All patients (n = 2997)
Characteristics of patients with adenoma	
Male (n, %)	1713 (57.2)
Age (mean, SD)	58.6 (9.0)
Active guideline (n, %)	
June 1998 - 2001	2303 (76.8)
2002	694 (23.2)
Hospital type (n, %)	
Non-academic	2097 (70.0)
Academic	900 (30.0)
Geographical area (n, %)	
High density population area	1641 (54.8)
Low density population area	1356 (45.2)
Active follow-up system (n, %)	
No	1975 (65.9)
Yes	1022 (34.1)
Adenoma characteristics	
No. of adenomas (mean, SD)*	1.5 (0.9)
No. patients with (n, %)	
Multiple (≥3) adenomas*	347 (11.6)
Any adenoma with size ≥10mm †‡	1127 (37.6)
Any adenoma with high-grade dysplasia †	368 (12.3)
Any villous adenoma †	150 (5.0)
Any proximal adenoma †	900 (30.0)
Index endoscopy characteristics	
Intended sigmoidoscopy (n, %)	306 (10.2)
Reach endoscope (n, %) †	
Complete colonoscopy §	2538 (84.7)
Proximal colon	293 (9.8)
Distal colon	166 (5.5)
Bowel preparation (n, %) †	
Good ¶	2723 (90.9)
Moderate	221 (7.4)
Insufficient	52 (1.7)

** Variable truncated to 5+ adenomas, and imputed for missing values*
† weighted average (data from 433 patients without surveillance weighted to the 1093 patients without surveillance)
‡ Size ≥10 mm either as reported by endoscopist or pathologist
§ 58 missings assumed to have a complete colonoscopy (in 2337 (1904 + 433) patients with data)
¶ 1598 missings assumed to have a good bowel preparation (in 2337 (1904 + 433) patients with data)

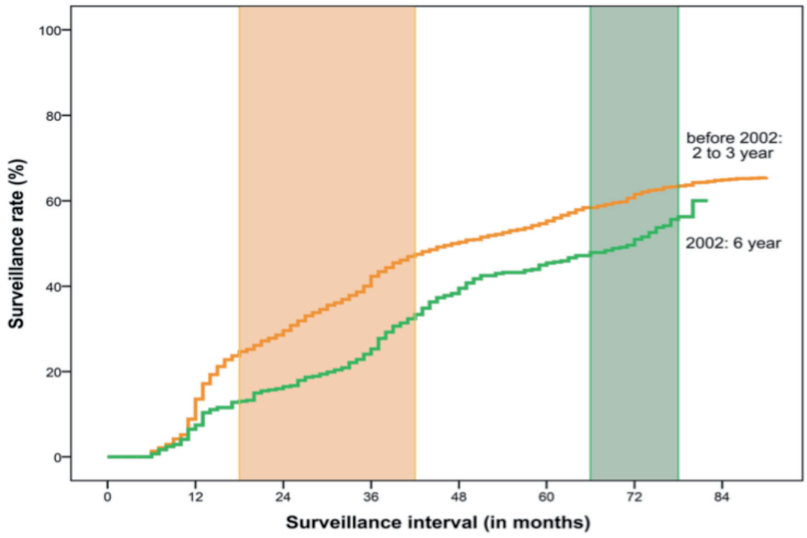

Figure 2 (A). Kaplan-Meier probability curve for surveillance colonoscopy use by month from index colonoscopy for patients with one adenoma, stratified by active guideline. The shaded areas indicate appropriate intervals around 2-3 years (<2002, n = 1676), and 6 years (2002, n = 417).

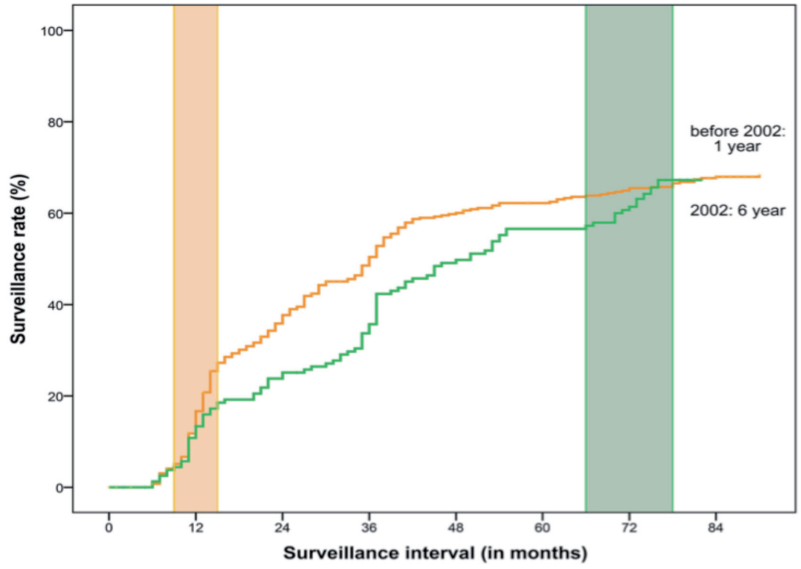

Figure 2 (B). Kaplan-Meier probability curve for surveillance colonoscopy use by month from index colonoscopy for patients with two adenomas, stratified by active guideline. The shaded areas indicate appropriate intervals around 1 year (< 2002, n = 397) and 6 years (2002, n = 160).

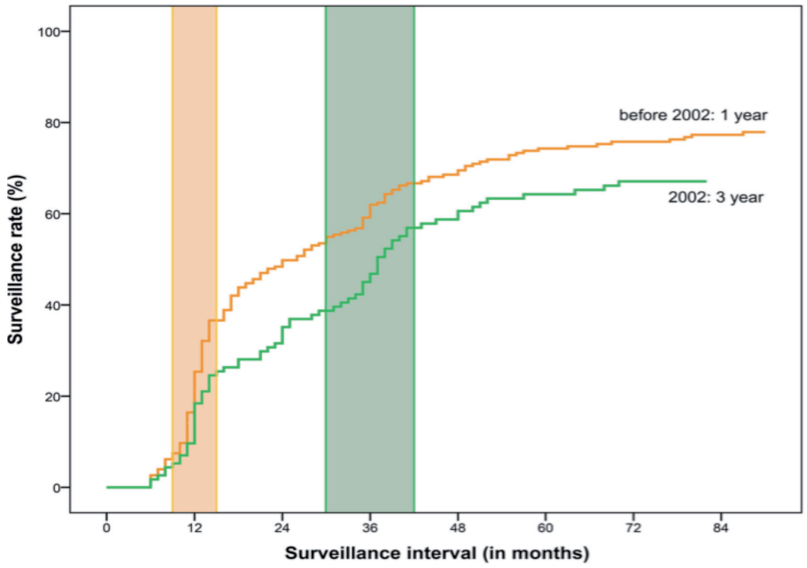

Figure 2 (C). Kaplan-Meier probability curve for surveillance colonoscopy use by month from index colonoscopy for patients with three or more adenomas, stratified by active guideline. The shaded areas indicate appropriate intervals around 1 year (< 2002, n = 230) and 3 years (2002, n = 117).

Table 3. Timing of surveillance colonoscopy relative to recommended intervals according to guideline in effect (by period) and adenoma patient group, Kaplan-Meier analysis

Period of index colonoscopy	Recommended interval (year)	Too early (%)	Appropriate* (%)	Delayed or no surveillance (%)	No surveillance † (%)
June 1998 - 2001					
1 adenoma (n = 1676)	2-3	24	24	53	35
2 adenomas (n = 397)	1	4	23	73	32
3+ adenomas (n = 230)	1	6	30	63	22
Overall (n = 2303)		**19**	**24**	**57**	**33**
In 2002					
1 adenoma (n = 417)	6	47	9	44	40
2 adenomas (n = 160)	6	57	11	33	33
3+ adenomas (n = 117)	3	39	18	43	33
Overall (n = 694)		**48**	**11**	**41**	**37**
Overall, all patients (n = 2997)		**25**	**21**	**53**	**34**

Due to rounding row percentages may not add up to 100%.
** Appropriate interval, before 2002: 1-year plus or minus 3 months, 2-3 years plus or minus 6 months; and in 2002: 3- or 6-years plus or minus 6 months*
† *by the end of the study (1 December 2008) or within 90 months, whichever came first.*

Table 4. Yield of advanced adenoma (AA) at surveillance endoscopy according to number of adenomas at index colonoscopy and timing of surveillance according to the guidelines (n = 1904)

Period of index colonoscopy	Recommended interval (year)	AA (n/ n total)			
		Too early	Appropriate †	Delayed	Total
June 1998 - 2001					
1 adenoma	2-3	3% (12/389)	3% (13/384)	7% (21/298)*	4% (46/1071)
2 adenomas	1	6% (1/16)	3% (3/90)	6% (10/159)	5% (14/265)
3+ adenomas	1	7% (1/14)	9% (6/68)	17% (15/89)	13% (22/171)
Overall		**3% (14/419)**	**4% (22/542)**	**8% (46/546)****	**5% (82/1507)**
In 2002					
1 adenoma	6	5% (9/193)	7% (2/28)	0% (0/3)	5% (11/224)
2 adenomas	6	9% (8/86)	8% (1/12)	-	9% (9/98)
3+ adenomas	3	16% (7/44)	0% (0/20)	9% (1/11)	11% (8/75)
Overall		**7% (24/323)**	**5% (3/60)**	**7% (1/14)**	**7% (28/397)**
Total		**5% (38/742)**	**4% (25/602)**	**8% (47/560)****	**6% (110/1904)**

AA includes adenomas with size of 10 mm or larger at pathology or endoscopy, villous histology or high-grade dysplasia, including CRC.
In total 14 CRCs were found at first surveillance colonoscopy (Before 2002: 1 CRC in those with too early surveillance, 1 CRC in those with appropriate timed surveillance and 10 CRCs in those with delayed surveillance. In 2002: 2 CRCs in those with too early surveillance).
** Significant at level p< 0.05; ** Significant at level p< 0.01.*
† *Appropriate interval, before 2002: 1-year ±3 months, 2-3 years ±6 months; and in 2002: 3- or 6-years ±6 months*
CRC, colorectal cancer

Patients with an index colonoscopy in 2002 were seen after a longer interval than those with an index colonoscopy before 2002 *(figure 2A-C)*. Overall, 21% of patients with adenoma received appropriate surveillance *(table 3)*. The pre-2002 surveillance guideline was better adhered to than the 2002 guideline (24% vs 11% appropriateness). In both periods, a higher proportion of patients with three+ adenomas received appropriate surveillance than patients with one and two adenomas (before 2002: 30% vs 24% and 23%, and in 2002: 18% vs 9% and 11%, respectively).

The overall yield of AA at surveillance was 5% and 7% for patients in both index periods respectively *(table 4)*. The yield of non-AA was 22% for both periods *(see appendix 1)*. The yield of AA at surveillance was, in particular in the index period before 2002, higher in patients with delayed surveillance compared to those with too early or appropriate timed surveillance (8% vs 3% and 4%, p< 0.01). This also pertained to the yield of CRC (1.8% vs 0.2% and 0.4%, p< 0.01).

Subanalyses

Results of all subanalyses are presented in *appendix 2*. No differences were observed in surveillance pattern when comparing five hospitals with data over the whole index period (1998 – 2002) with those without.

Patients with an index colonoscopy in the phase immediately preceding the change in guideline (October 2000 – December 2001) had a significantly longer median (25th-75th centile) surveillance interval than patients with an index colonoscopy between June 1998 and October 2000: 29 (14-44) months versus 21 (12-39) months ($p< 0.001$). However, KM curves for these two periods were only significantly different for patients with one adenoma ($p< 0.001$).

Median surveillance interval were similar between patients with an index colonoscopy in the first half of 2002 versus those in the second half of 2002 for patients with one, two or three+ adenomas (data not shown). Also, KM curves did not differ significantly, indicating no significant implementation issues concerning the new guideline, although the period might have been too short.

When comparing surveillance pattern from academic versus non-academic hospitals, a difference was observed for patients with one or two adenomas with their index colonoscopy before 2002, with longer intervals and less follow-up in academic centres. For hospitals with an active versus passive follow-up system, a different surveillance pattern was observed in patients with two or more adenomas in 2002, with longer intervals and less follow-up in centres with an active follow-up system.

Discussion

This study shows high proportions of inappropriate adherence to the post-polypectomy surveillance guidelines that are in effect in the Netherlands. This finding holds for both guideline periods considered: before 2002, only 24% of patients received appropriately timed adenoma-surveillance; in 2002 only 11% did. Overall, a third of the patients did not receive surveillance at all by the end of the study period. The absence of surveillance in such a large fraction of the patients is alarming, because advanced neoplasia was found in 8% (of which a fifth were CRCs) of those with delayed surveillance, and in particular up to 17% in those with three or more adenomas at index colonoscopy.

Before 2002, inappropriate surveillance was predominantly too late or absent (together, 57% of patients), while in 2002, when the recommended surveillance

intervals were lengthened, 48% of the patients received surveillance too early. Appropriate adherence to surveillance guidelines was somewhat higher for patients with three or more adenomas than for patients with fewer than three adenomas (overall, 26% vs 21%).

The fact that surveillance was mostly delayed before 2002 can be expected when the recommended intervals are relatively short (1 year and 2-3 years). This finding coincides with the findings of two previous small single-centre studies from the Netherlands and the UK.[19, 39] The 2002 change in recommendations to 3 years for patients with three+ adenomas and 6 years for patients with one to two adenomas was associated with a change in average practice towards longer surveillance intervals. However, the increase in interval in actual practice was smaller than the increase in the guideline-recommended interval. As a result, the proportion of patients that received too early surveillance increased from 19% before 2002 to 48% in 2002. This proportion was higher for patients with one to two adenomas compared to those with three+ adenomas (50% vs 39% in 2002). The impact of too early surveillance on colonoscopy demand will be largest in patients with one to two adenomas, since this group represents more than 80% of the current patient population with adenoma.

The poor penetration of the 2002 guideline within 1 year following the implementation illustrates the importance of convincing evidence to support endorsement of new guidelines by community practice. The 2002 guideline was formulated when only limited data were available and showed differences with other international guidelines. It has also been shown that gastroenterologist experienced dilemmas with the guideline,[18] which may explain non-compliance. Patients assumed to be at higher risk for other reasons than adenoma number may have received earlier surveillance colonoscopy than recommended by the guideline. This latter can also be an explanation why the yield of AA was similar for patients with too early surveillance compared with those having appropriately timed surveillance (7% and 5%, respectively). Last year the Dutch guideline has been updated and includes additional adenoma characteristics (http://www.mdl.nl/uploads/240/1308/Richtlijn_Coloscopie_Surveillance_definitief_2013.pdf). Although we combined index colonoscopies within 6 months, some patients still did not have sufficient bowel preparation (165 of those with surveillance), however it turned out not to be a reason for earlier surveillance. Intervals were not different from patients with sufficient bowel preparation (data not shown).

Our findings that surveillance was too frequent in patients whose recommended surveillance intervals were longer (ie, 3 and 6 years) are in line with self-

reported surveillance intervals in US and European surveys among gastroenterologists and/or surgeons,[16-18, 20, 22] and also with the few smaller studies that assessed the appropriate timing of postpolypectomy surveillance colonoscopy in clinical practice.[32, 40] In the latter, 46-54% of the patients with surveillance received it too early.[32, 40] In our study, the corresponding percentage was even higher: 76% (ie, 48% of 63% of the patients with surveillance).

Schoen *et al*[23] reported that surveillance colonoscopy was too early in 34% of patients with a low-risk adenoma profile (patients with one or two non-AAs).The larger proportion of overuse among the low-risk group in our study (48%) may be explained by the discrepancy in risk stratification between the guidelines in effect: whereas patients with one or two adenomas and high-grade dysplasia, a (tubulo)villous aspect, or a size ≥10 mm are classified as high-risk patients according to the US guideline and advised a 3-year surveillance interval,[9] the Dutch 2002 guidelines classified these patients as 'low-risk' and recommended a 6-year interval.[10] Physicians in the Netherlands may have shortened the intervals for these patients, considering them to be at higher risk.[18] On the other hand, we also found a considerably greater overuse of surveillance among patients with a high-risk adenoma profile (39% in patients with ≥three adenomas) than Schoen *et al*[23] did (14-20% patients with ≥three non-AAs or ≥1 AA). In the USA, high-risk patients have been recommended a 3-year interval since 1993. As a consequence, US physicians may be more familiar with the 3-year recommendation than the Dutch physicians were in 2002. Generally, the proportion of patients with too early surveillance tends to be higher among low-risk patients than among higher-risk patients,[23, 32, 39, 41] which may again be inherent to the relatively longer recommended surveillance interval itself or be related to a perceived need for shorter surveillance by patients or their physicians.

An important finding in our study is that an estimated third of patients do not receive surveillance colonoscopy after adenoma detection in community practice. Schoen *et al*[23] reported that approximately half of patients had not (yet) received surveillance colonoscopy after 5 years. These data were based on patient questionnaires and lacked actual assessment of hospital records. Cooper *et al*[42] found a similar proportion using Medicare claims data. However, this population only included subjects aged 70 years and above. Furthermore, as this study was based on Medicare claims data, it implied that it used endoscopy billing codes, in particular polypectomy, instead of histological evaluation. As such, there was no verification of adenoma removal, and also lacked information on advanced versus non-advanced histology. Appropriateness of adherence to guidelines could thus not be assessed. Insight into the absence of surveillance is important in the light of the 8% advanced neoplasia (1.8% CRC, 6.6% AA) re-

currence rate and 25% non-AA recurrence rate in patients with delayed surveillance. This shows that the observed delays are long enough for neoplasia to reoccur and/or progress, and corroborates the expectation that there is a loss in effectiveness when patients do not have timely or not at all have surveillance colonoscopies.

Our study is one of the few studies to have assessed the actual use of postpolypectomy surveillance colonoscopy in clinical practice in a multicentre setting; and it is of considerable size. But two limitations are noteworthy. First, we assumed no loss to follow-up. We feel this is a reasonable assumption, because patient deaths were well-reported in hospital databases (the observed death rate closely matched the expected rate based on age and gender of the population, data not shown) and we did not find correspondence in medical records on colonoscopies performed elsewhere. Finally, the close link between patient, referring family physician, and hospital in the Netherlands induce that the vast majority of patients in the Netherlands regularly attend the same hospital for surveillance and other purposes. Most importantly, we found our results to be robust for this assumption: even if all patients without surveillance would have died or had their surveillance colonoscopy in another hospital with a similar timing as observed for the other patients, still only 32% (21%/66%) would have received appropriate surveillance.

Second, because of time constraints we collected information on index adenoma number in a random sample of 40% (433/1093) of the patients without surveillance colonoscopy after adenoma detection. We assume that this sample is representative. We statistically imputed adenoma number for 660 patients. We expect any bias due to misclassification of patients according to number of adenomas (one, two or three+ adenomas) as a result of imputation to be very small, and that it will not have affected adherence rates.

Our results show that postpolypectomy surveillance guidelines are not being applied appropriately - a much larger proportion than one would expect deviates from the recommendations. Some non-compliance, especially delayed or absent surveillance, should be expected for good reasons, notably comorbidity issues. As far as we know there is no literature on comorbidity rates in patients with adenoma, but it is unlikely that the presence of comorbidity fully explains the observed lack of surveillance in our study. Patients who receive adenoma-surveillance too early represent unnecessary endoscopic procedures, harms and costs. As the implementation of mass screening for CRC is expected to (further) increase the demand for colonoscopies considerably, it will become even more

important to avoid unnecessary use of resources, especially for low-risk patients. On the other side of the spectrum of non-adherence, delayed or absent surveillance represents loss of health benefits.

Which interventions could improve adherence to surveillance guidelines? Several interventions have been previously suggested. One was to update the Dutch 2002 postpolypectomy surveillance guideline towards less discrepancy with the endoscopist's judgment, and thereby improving physicians' compliance. Other suggestions include an active approach policy directed towards patients and general practitioners to invite patients for a surveillance colonoscopy,[19, 43] to disseminate summarised guidelines among professionals through the distribution of wallet-sized cards (which nowadays can also be applications for mobile devices), to place guideline charts near workstations, to reinforce guidelines in regular continuous quality-improvement meetings[44] and to supervise application of guidelines by a nurse coordinator.[45, 46] It is also necessary to increase patients' awareness in terms of their adenoma findings and the need for surveillance, including recommended surveillance interval.[47]Implementation studies are required to determine which of the interventions work best. Monitoring postpolypectomy surveillance intervals combined with efforts to encourage timely adherence should be a mainstay in continuous quality improvement.

In conclusion, the vast majority of patients with adenoma in community-based clinical practice (76-89%) did not receive surveillance timed according to Dutch postpolypectomy surveillance guidelines. The poor penetration of the 2002 guideline within 1 year following the implementation, illustrates the importance of convincing evidence to support endorsement of new guidelines by community practice. Our results suggest that there is considerable room for improving the effectiveness and the efficiency of surveillance practice, because too early surveillance poses a considerable burden on available resources while delayed surveillance is associated with an increased rate of AA and especially CRC. Since adherence to guidelines is mandatory for the effectiveness and cost-effectiveness of CRC prevention (including CRC screening programs), measures should be taken to improve adherence. Implementation studies are needed to determine which of the potential interventions work best.

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Conflicts of interest
Clemens J.M. Bolwerk is a member of an MSD medical advisory board

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Ethics approval
This study was approved by the Institutional Review Board of Erasmus MC University Medical Centre and all participating centres.

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Appendix 1

Yield of non-advanced adenoma (NAA) at surveillance endoscopy according to number of adenomas at index colonoscopy and timing of surveillance according to the guidelines (n = 1904)

Period of index colonoscopy	Recommended interval (year)	NAA, % (n/ n total)			
		Too early	Appropriate[a]	Delayed	Total
June 1998 - 2001					
1 adenoma	2-3 year	17% (68/389)	21% (81/384)	21% (63/298)	20% (212/1071)
2 adenomas	1 year	25% (4/16)	23% (21/90)	28% (45/159)	26% (70/265)
3+ adenomas	1 year	29% (4/14)	31% (21/68)	28% (25/89)	29% (50/171)
Overall		**18% (76/419)**	**23% (123/542)**	**24% (133/546)**	**22% (332/1507)**
In 2002					
1 adenoma	6 year	16% (31/193)	18% (5/28)	0% (0/3)	16% (36/224)
2 adenomas	6 year	27% (23/86)	17% (2/12)	-	26% (25/98)
3+ adenomas	3 year	27% (12/44)	45% (9/20)	36% (5/11)	35% (26/75)
Overall		**20% (66/323)**	**27% (16/60)**	**36% (5/14)**	**22% (87/397)**
Total		**19% (142/742)**	**23% (139/602)**	**25% (138/560)***	**22% (419/1904)**

NAA includes adenomas with size smaller than 10 mm at pathology or endoscopy, tubular or tubulovillous histology and low-grade dysplasia

[a] *Appropriate interval, before 2002: 1-year plus or minus 3 months, 2-3 years plus or minus 6 months; and in 2002: 3- or 6-years plus or minus 6 months**

** Significant at level P < 0.05*

Appendix 2

Subanalyses: comparison (P values) of Kaplan-Meier probability curves for surveillance colonoscopy use by month from index colonoscopy between various subgroups

Period of index colonoscopy	Five hospitals with data over complete period versus the other hospitals	June 1998 - Oct 2000 vs. transitional phase (Oct 2000 – Dec 2001)	1st half vs. 2nd half of 2002	Academic vs. non-academic hospital	Active vs. passive follow-up system
June 1998 - 2001					
1 adenoma	P = 0.86	P < 0.01	n.a.	P < 0.01	P = 0.77
2 adenomas	P = 0.52	P = 0.17	n.a.	P = 0.03	P = 0.52
3+ adenomas	P = 0.10	P = 0.63	n.a.	P = 0.63	P = 0.03
Overall	**P = 0.55**	**P < 0.01**	**n.a.**	**P < 0.01**	**P = 0.34**
In 2002					
1 adenoma	P = 0.95	n.a.	P = 0.34	P = 0.85	P = 0.46
2 adenomas	P = 0.68	n.a.	P = 0.41	P = 0.54	P = 0.05
3+ adenomas	P = 1.00	n.a.	P = 0.62	P = 0.33	P = 0.04
Overall	**P = 0.67**	**n.a.**	**P = 0.41**	**P = 0.92**	**P < 0.01**

Chapter 7

Interpretation and compliance to the updated risk-stratified guideline for colonoscopy surveillance after polypectomy - a nationwide survey.

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Submitted

Abstract

Background: Low compliance (median 59%) to the Dutch guideline for colonoscopy surveillance after polypectomy led to the release of a new guideline in 2013. This new guideline was risk-stratified at a more detailed level than the previous one to achieve more efficient use of colonoscopy resources. This study assessed the feasibility of the risk-stratified guideline by evaluating the correct interpretation of and compliance to this guideline.

Methods: Based on semi-structured interviews with 10 gastroenterologists, we developed an online survey to evaluate gastroenterologists' recommendations for surveillance in 15 example cases of patients with polyps. If recommended intervals deviated from the new guideline, respondents were asked to indicate their motives for doing so.

Results: Ninety-nine out of 592 (16.7%) invited gastroenterologists responded of whom 84 (14.2%) completed the survey. Median compliance to the guideline for the example cases was 76% (14% to 95% per case). The two cases that addressed management of serrated polyps were least often answered correctly (14% and 28% correct answers, respectively). Deviations were mainly due to misinterpretation of the guideline (48%) or misreading of the questions (30%). For example, 92-95% of incorrect answers to cases involving serrated polyps were caused by gastroenterologists scoring them as if they were dealing with conventional adenomas.

Conclusions: The median compliance to the updated colonoscopy surveillance guideline of 76% seems reasonable, and is higher than the compliance to the previous guideline. This shows that detailed (more complex) risk stratification for designation of a surveillance interval is feasible. Compliance could potentially be improved by clarifying the correct interpretation on serrated polyps.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer mortality in the western world.[1] Individuals with adenomas are at increased risk of developing metachronous adenomas and CRC, even after the adenomas have been completely removed.[2-4] Therefore, colonoscopy surveillance after polypectomy is recommended.[5,6] The frequency of colonoscopy surveillance and the compliance to surveillance recommendations are important, since too little surveillance has the risk of diminishing the preventive effect of colonoscopy for CRC, while too intensive surveillance exposes the patient to unnecessary risks and burden and waste of colonoscopy as well as financial resources.
Colonoscopy is a scarce resource and many countries face waiting lists for these procedures.[7,8] With the implementation and expansion of CRC screening programs throughout the world,[9] the demand for colonoscopies will further increase.

Before the introduction of mass screening, colonoscopies for surveillance after polypectomy encompassed about 13% of all colonoscopies conducted in the Netherlands.[10] The recently started CRC screening program will result in an increase in adenoma diagnoses, eventually resulting in an increasing number of patients that meet the criteria for surveillance colonoscopy. This emphasizes the importance of efficient use of colonoscopy capacity and thus also of efficient surveillance strategies.

However, the colonoscopy capacity is often not used efficiently for surveillance. Current international guidelines only consider presence or absence of risk factors for metachronous advanced neoplasia, but do not take into account combinations of risk factors. Several surveys showed suboptimal compliance to guidelines for surveillance after polypectomy in daily practice, with clinicians often recommending too short surveillance intervals.[11-13] A Dutch study reported that 52% of the responding gastroenterologists used shorter surveillance intervals than prescribed by the national guideline.[12] This was caused by clinicians often incorporating other adenoma characteristics, like histology and size of the adenomas into their recommendation, even though at that time the Dutch surveillance guidelines only differentiated the recommended surveillance interval by adenoma multiplicity. [12]

The updated risk-stratified guideline for colonoscopy surveillance introduced in 2013 incorporated multiplicity, size, location and histology of adenomas as well as presence of large serrated lesions.[14] Through a score chart these polyp characteristics are combined into a risk score (0 - 5) to optimize the risk stratification of patients for designation of a surveillance interval. However, this new

guideline is more complex than the previous guideline and most international guidelines. This may cause gastroenterologists to misunderstand or misinterpret the guideline, or potentially even not use it all, eventually resulting in low compliance to the recommendations. Therefore, the aim of our study was to evaluate gastroenterologists' interpretation and compliance to this new guideline.

Materials and Methods

Design

To assess the correct interpretation of and compliance to the Dutch guideline for colonoscopy surveillance after polypectomy, we developed an online survey consisting of 15 example cases of patients that underwent colonoscopy with polypectomy. The survey was pilot-tested during semi-structured interviews with 10 gastroenterologists. We sent the survey to all gastroenterologists in the Netherlands and asked them to designate their surveillance recommendation for each case. If recommendation(s) deviated from the new guideline, their motives for doing so were asked for a maximum of 2 random example cases.

Dutch guideline for colonoscopy surveillance after polypectomy

The new Dutch guideline for surveillance after polypectomy was introduced in 2013.[14] The surveillance interval is based on the number of adenomas and the presence of at least one large adenoma (≥10mm), at least one villous adenoma (>75% villous component) and/or at least one proximal adenoma. Serrated polyps (including hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenoma) are incorporated in the guideline only if at least one serrated polyp measures ≥10mm. Other characteristics (total number, localisation) of the serrated polyps are not taken into account. High-grade dysplasia (HGD) in adenomas is not incorporated as a risk factor in the guideline as it is not confirmed to be an independent risk factor, probably because HGD is highly associated with other factors such as size. Using a score chart, the polyp characteristics are combined into a risk score (0 - 5), see *Figure 1*. The total risk score indicates a recommended surveillance interval of 3 or 5 years, or no surveillance at all.

Survey

The survey consisted of three parts. The first part contained 7 questions on (demographic) characteristics of the gastroenterologist: gender; age; type of hospital; specialisation; number of colonoscopy procedures per year; years of experience

SCORE TABLE FOR PRESENCE OF ADENOMA CHARACTERISTICS AND SERRATED POLYPS*		
Polyp Characteristics	Values	Points
Number of adenomas	1	0
	2-4	1
	≥5	2
Presence of at least one adenoma ≥10mm and/or one large serrated polyp ≥10mm**	No	0
	Yes	1
Presence of at least one villous adenoma***	No	0
	Yes	1
Presence of at least one proximal adenoma****	No	0
	Yes	1
Total risk score		

* A patient with 5 proximal serrated polyps of which 2 ≥ 10 mm fulfil the WHO criteria of the serrated polyposis syndrom; see the guideline of hereditary colorectal cancer.

**A serrated polyp encompasses: hyperplastic polyps, sessile serrated polyps/adenomas and traditional serrated adenomas

***An adenoma with at least 75% villous histology.

****Proximal is defined as cecum, colon ascendens, colon transversum and flexura lienalis

SURVEILLANCE INTERVAL BASED ON THE ADENOMA RISK SCORE	
Score during index colonoscopy	Interval after index colonoscopy
0	No surveillance*
1-2	5 years
3-5	3 years
Score during subsequent colonoscopy	Interval after subsequent colonoscopy
0	5 years**
1-2	5 years
3-5	3 years

*Patients with a score of 0 during index colonoscopy are advised to not undergo surveillance colonoscopy. These patient are sent back to the national screening programme in 10 years if aged 55-75 years at that moment.

**For patients in which a high-risk adenoma (score ≥3) was never detected, surveillance can be ended after two subsequent negative colonoscopies. These patient are sent back to the national screening programme in 10 years if aged 55-75 years at that moment.

Stopping age of surveillance: 75 years, unless the wish and condition of the patient justify a different stopping age

Figure 1: score chart of the Dutch guideline for colonoscopy surveillance after polypectomy.[14]

and if they perform colonoscopies for the national screening programme.

The second part consisted of 15 example cases of patients that underwent colonoscopy with polypectomy. To avoid bias and disadvantages for the later example cases if respondents would not finish the complete survey, there were two versions of the survey that only differed regarding the order of the example cases. The example cases varied in age, gender, adenoma/polyp number, size

and location of adenomas, grade of dysplasia and presence of (tubulo)villous histology, see *Table 3* and *Appendix 2*. Respondents were informed that unless noted otherwise, all patients were in good health; had no familial risk for colorectal cancer; had undergone their first colonoscopy; bowel preparation was good; the cecum was reached; and the polyp was removed in one piece and endoscopically complete.

In each case, the gastroenterologist was asked to recommend the surveillance interval. Response options were: an interval of <1 to 10 years; no surveillance; surveillance only if the patient would be in good condition (at a 3 or 5-year interval); and referral to the clinical geneticist *(Appendix 2)*.

In the third part of the survey respondents were given feedback on the recommendations they had given in part 2. For each case in which the recommendation did not meet the guideline, the respondent was shown a table with the interval they recommended versus the guideline-recommendation. Subsequently, the motives for deviation were asked for a maximum of two random example cases. Response options were: thinking the answer was in agreement with the guideline; not having read the question correctly; not familiar with the new guideline; based on scientific evidence or clinical experience; or an answer in the free text field *(Appendix 2)*.

Pilot-tests

Interviews

10 gastroenterologists were interviewed between May and July 2014 *(Appendix 1)*. The selected gastroenterologists differed in age, gender, setting (regional or academic hospital) and region. One of the authors (MvdM) conducted all interviews, which were audio-recorded. The interviews were semi-structured, starting with open questions on what gastroenterologists considered advantages and bottlenecks of the guideline. Then, they were presented 5 cases and were asked what interval they would recommend and why. Based on the response of the interviewed gastroenterologists the cases were improved and several answering options on why people would potentially deviate from the current guideline were added.

Online pilot

After enhancement of the survey due to the findings of the interviews, the survey was additionally validated by five medical researchers in gastroenterology of the Academic Medical Center (AMC) and the Netherlands Cancer Institute.

Distribution of the survey

The online survey was send by email to all 594 registered gastroenterologists of the Dutch Gastroenterology association in December 2014. A reminder of the survey was sent 6 weeks later in January 2015. The survey was anonymous and written in Dutch.

Statistical analyses

Statistical analyses were conducted with SPSS version 22.0 (IBM corporation, USA). To be considered as a respondent at least 4 baseline questions had to be answered. Descriptive statistics were used to analyze the data; medians and interquartile range (IQR)a were calculated for non-normally distributed data. Outcomes were the number of respondents, the median number of correct recommendations per respondent – for those who responded to all cases -, and the number of correct recommendations per case. Differences between subgroups in correct recommendations per respondent were tested with the Mann-Whitney U test.

Results

Of 592 invitees, 99 (16.7%) responded. One respondent was excluded as he or she did not actively perform colonoscopies. Of the 98 responders, 91 gastroenterologists responded to at least one case, 84 (14.2%) gastroenterologists responded to all cases.

Sixty-five percent of the respondents were male, the median age was 43 years old *(Table 1)*. Most respondents worked in a hospital without gastroenterology trainees (43%), most had 0-10 years of experience (51%), performed more than 300 colonoscopies per year (70%) and performed colonoscopies for the national bowel cancer screening program (63%). Thirty-six percent of the respondents indicated that they did not consult the guideline during the questionnaire, while 48% used the pocket card of the guideline and 10% the app.

The 84 respondents that indicated recommendations for all cases were correct in a median of 10 (out of 15) cases (IQR 3.5) *(Table 2 and Figure 2)*. The number of correct recommendations did not differ by gender, age, type of hospital and participation in the screening program, but consulting the guideline during the questionnaire was associated with an increase in compliance (p=0.015).

Table 1: Baseline characteristics of the respondents (N = 99).

Variable	N	
Age (median)	99	43 (IQR 35-52)
Gender		
Males	64	65%
Females	35	35%
Type of hospital		
Academic	19	19%
Non-academical teaching hospital	37	38%
Peripheral hospital	42	43%
Missing	*1*	
Specialisation		
Gastroenterologist	92	95%
Fellow	5	5%
Missing	*2*	
Years of experience		
None	2	2%
0 to 10	50	51%
10 to 20	21	21%
20 to 30	18	18%
30 to 40	6	6%
>40	2	2%
Colonoscopies per year		
< 150	10	10%
150-300	19	20%
>300	68	70%
Missing	*2*	
Performing colonoscopies for the screening programme		
Yes	61	63%
No	36	37%
Missing	*2*	
Use of source during questionnaire		
None	29	36%
App	8	10%
Pocket card	39	48%
Website	2	2%
2 sources	3	4%
Missing	*18*	

Table 2: Score (median correct recommendations according to the guideline) out of 15 example cases of respondents to all example cases (n=84).

		N	Score out of 15 cases	P-value
Gender	Men	51	10	
	Women	33	10	0.81
Age	<40	37	11	
	>40	47	10	0.62
Academic hospital	Yes	16	11	
	No	67	10	0.44
Performing colonoscopies for the CRC screening programme*	Yes	51	11	
	No	31	10	0.71
Use of source*	Yes	29	11	
	No	52	9	0.02
Total			10	

* *Either use of no source at all, or use of the app, pocket card and/or website.*

Figure 2: Distribution of the score out of 15 example cases (number of correct answers according to the guideline) of the respondents to all example cases (n=84).

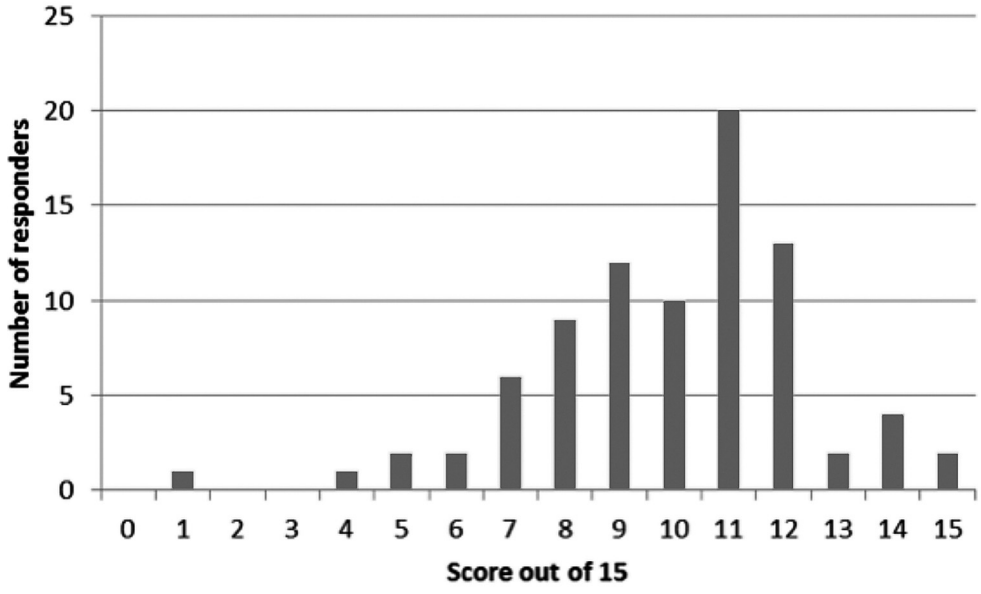

Table 3: Short description of the 15 example cases with the recommended interval and the results per example case.

DESCRIPTION CASE									RESULTS PER CASE					
Common cases														
	Age	**G**	**# AD**	**Size (mm)**	**Vill.**	**HGD**	**# prox**	**Recommended interval**	**N**	**% corr**	**% early**	**% late**	**% no surv**	**% other**
1	60	M	1	8	T	no	0	No surveillance	86	84%	16%	0%	na	0%
2	69	M	1	12	T	no	0	5y	89	91%	1%	1%	3%	3%
3	54	M	1	20*	TV	no	1	5y	85	52%	47%	1%	0%	0%
4	62	F	2	22*	V	no	0	3y	84	79%	6%	15%	0%	0%
5	63	F	4	9	V	no	2	3y	84	90%	0%	7%	0%	2%
6	60	F	5	12	T	no	4	3y	84	95%	2%	1%	0%	1%
7	79	M	5	8	T	no	3	Only if healthy, then 3y‡	84	52%	1%	8%	11%	27%
8	75	M	4	12	T	yes	0	Only if healthy, then 5y‡	84	31%	40%	0%	4%	25%
9	65	M	1	11	TV	yes	0	5y	88	76%	17%§	1%	2%	3%
Serrated adenomas/polyps														
	Age	**G**	**# SP**	**Size (mm)**			**# prox**		**N**	**% corr**	**% early**	**% late**	**% no surv**	**% other**
10	58	F	1	8			1	No surveillance	85	14%	86%	0%	na	0%
11	54	F	2	12			2	5y	86	28%	72%	0%	0%	0%
Family history														
	Age	**G**	**Score**	**FM**	**Age FM**	**Previous examination**			**N**	**% corr**	**% early**	**% late**	**% no surv**	**% other**
12	51	M	2	Brother	<50	Yes, no hereditary CRC		5y	84	83%	14%	0%	0%	2%
13	53	M	1	Sister	<50	no		Refer to geneticist	88	58%	0%	0%	0%	42%
Negative colonoscopies														
	Age	**G**	**Initial Score**	**# neg. colo**					**N**	**% corr**	**% early**	**% late**	**% no surv**	**% other**
14	69	M	4‡	1				5y	86	88%	5%	2%	3%	1%
15	63	F	2‡	2				No surveillance	86	73%	23%	0%	na	3%
TOTAL									1283	66%	22%	3%	2%	7%

G = gender; # AD = the number of adenomas; Size = size of the largest lesion Vill. = presence of villousness, with T = tubular adenoma, TV = tubulovillous adenoma, V = villous adenoma; HGD = presence of high-grade dysplasia; # prox = the number of proximal adenomas; #SP = number of serrated polyps; FM = family member with CRC diagnoses; # neg. colo = number of previous negative colonoscopies; %corr = % of answers correct, according to the guideline (red ≤50% correct, orange ≤ 70% correct) %early = % of answers with a shorter interval than recommended; %late = % of answers with a longer interval than recommended; % no surv = % of answers with no surveillance while this is not recommended; %other = % of answers with another answer (red ≥40% of respondents, orange ≥15% of respondents)

** In the cases with adenomas ≥ 20 mm we describe that patients had had another colonoscopy after 6 months at which no residual tissue was found.*

‡ If surveillance should only take place if healthy due to older age, we defined all answers containing a shorter interval then recommend if healthy as "early", all answers containing a longer interval then recommend if healthy as "late" and an answer with the same interval but without

the addition that the patient should only be screened if healthy as "other".
‡ Full findings at the initial colonoscopy were: 69 year old male: 2 adenomas: Polyp A was a distal villous adenoma of 12 mm. Polyp B was a proximal tubular adenoma of 8 mm with low-grade dysplasia; 63 year old female: 2 adenomas: Polyp A was a distal tubular adenoma of 5 mm with low-grade dysplasia. Polyp B was a distal tubular adenoma of 12 mm with low-grade dysplasia.
§ 10 out of 15 of the respondents with an answer with a too short interval, answered they would offer a surveillance colonoscopy within a year.

Overall, a median of 76% recommendations was correct *(Table 3)*, ranging from 14% to 95% per case. For all cases combined, 22% of the recommended intervals were shorter than the guideline, 3% of the given recommended intervals were longer than the guideline, 7% gave no surveillance interval, but an alternative recommendation while a surveillance interval was recommended (such as referral to a clinical geneticist, or only referral if the patients was in good condition) and 2% recommended no surveillance at all while the guideline did recommend surveillance. In 48% of the deviant cases, gastroenterologists were convinced they had recommended the correct interval, while in 30% of the deviant cases, gastroenterologists had not read the question correctly *(Table 4)*.

The recommendation for surveillance was least often correct for the cases on serrated lesions (case 10, 14% correct, and case 11, 28% correct) *(Table 3)*. All deviant answers recommended a shorter interval (86% and 72%) of which 92% and 95% recommended the interval that would be correct if serrated polyps would be scored the same as conventional adenomas. In 78% and 65%, respectively, of these deviant cases, gastroenterologists had the impression they had recommended the correct interval. 13% and 26% respectively answered that they had not read the question correctly *(Table 4)*.

Next, cases with a patient with older age (≥75 years) were least often answered correctly, at 31% for case 8 and 52% for case 7 *(Table 3)*. In the case of a 75-year old male with four adenomas and one adenoma with HGD (case 8), 40% of the respondents recommended a shorter interval than the guideline and 25% of the respondents recommended surveillance after five years. Responders deviated from the guideline for these cases because they were convinced their answer was in accordance with the guideline or they had not read the question correctly *(Table 4)*. Of those who provided an answer for case 7 and 8 in the free text field, 12 out of 14 mentioned they did not incorporate age or the condition of the patient at older age in their answer. In the case of a 79-year old male with five adenomas (case 7), the correct answer would be to recommend no surveillance, unless the patient remains in good condition, then in 3 years. Eleven percent of the respondents would

Table 4: Short description of the 15 example cases with the recommended interval and the results per example case.

	DESCRIPTION CASE								MOTIVATION TO DEVIATE FROM GUIDELINE				
	Common cases												
	Age	G	# AD	Size (mm)	Vill.	HGD	# prox	Recommended interval	N	% expected to be correct	% based on clinical experience	% did not read correctly	% other
1	60	M	1	8	T	no	0	No surveillance	6	0%	17%	83%	0%
2	69	M	1	12	T	no	0	5y	0				
3	54	M	1	20	TV	no	1	5y	21	62%	10%	10%	19%*
4	62	F	2	22	V	no	0	3y	6	50%	17%	33%	0%
5	63	F	4	9	V	no	2	3y	4	50%	0%	50%	0%
6	60	F	5	12	T	no	4	3y	1	0%	0%	100%	0%
7	79	M	5	8	T	no	3	Only if healthy, then 3y	16	25%	0%	31%	44%ǂ
8	75	M	4	12	T	yes	0	Only if healthy, then 5y	25	32%	0%	44%	24%ǂ
9	65	M	1	11	TV	yes	0	5y	6	50%	0%	17%	33%ǂ
	Serrated adenomas/polyps												
	Age	G	# SP	Size (mm)			# prox		N				
10	58	F	1	8			1	No surveillance	23	78%	0%	13%	9%
11	54	F	2	12			2	5y	23	65%	4%	26%	4%
	Family history												
	Age	G	Score	FM	Age FM	Previous examination			N				
						Yes, no here-			6	17%	17%	50%	17%
12	51	M	2	Brother	<50	ditary CRC		5y	11	18%	9%	36%	36%
13	53	M	1	Sister	<50	no		Refer to geneticist					
	Negative colonoscopies												
	Age	G	Initial Score	# neg. colo					N				
14	69	M	4	1				5y	3	67%	0%	33%	0%
15	63	F	2	2				No surveillance	6	83%	0%	17%	0%
	TOTAL								157	48%	4%	30%	17%

G = gender; # AD = the number of adenomas; Size = size of the largest lesion Vill. = presence of villousness, with T = tubular adenoma, TV = tubulovillous adenoma, V = villous adenoma; HGD = presence of high-grade dysplasia; # prox = the number of proximal adenomas; #SP = number of serrated polyps; FM = family member with CRC diagnoses; # neg. colo = number of previous negative colonoscopies; N = number of answers per case.

** 3 out of 4 respondents answered that they scored the tubulovillous adenoma as a villous adenoma.*

ǂ *12 out of 14 other answers incorporated the age of the patient in their answer.*

‡ *Both (2) respondents mentioned they saw HGD as high risk.*

not recommend any surveillance regardless of physical condition, and 26% of the respondents recommended surveillance after three years. If you assume that after these 3 years everyone would examine these older patients if they are still in good condition, 78% of cases would be answered correctly.

The case with a large tubulovillous adenoma (case 3) was correctly answered by only half (52%) of the gastroenterologists. If incorrect, recommended intervals were

almost always too short, see *Table 3*. Deviations were again mainly due to misinterpretation of the guideline (62%). Three out of four answers in the free text field explained that they scored the tubulovillous adenoma equal to villous adenoma.

Remarkable about the case of the 65-years old male with one adenoma with HGD (case 9) was that even though 76% of the respondents answered correctly, the incorrect answers had a large discrepancy with the interval recommended by the guideline. Eleven percent of the respondents recommended a surveillance colonoscopy within one year, whereas a five-year interval is recommended by the guideline. Two out of six gastroenterologists that answered why they deviated from the guideline for this case responded that they consider lesions with HGD as high risk.

A new aspect in the guideline is that no surveillance is indicated if patients have only one distal non-advanced adenoma (case 1). This was correctly recommended by 84% of the respondents.

The remaining 8 cases were correctly answered by a median of 86% (58% to 95% per case) of the respondents.

Discussion

Using a survey with 15 example cases, we showed that 76% of gastroenterologists recommend surveillance intervals that are in agreement with the current guideline. Cases involving serrated polyps or elderly patients were most often answered incorrectly.

In cases of patients with serrated polyps, the most often quoted reason for deviation from the guideline was that gastroenterologists were convinced their recommendation was in accordance with the guideline. As large inter- and intra-observer variation exists in pathologists for diagnosis various types of serrated polyps, serrated polyps are treated as one histological entity in the guideline. To prevent that patients with only small hyperplastic polyps will receive a surveillance recommendation, number and location of serrated polyps does not impact the length of the surveillance interval in the guideline.[14] In our survey almost all deviant recommendations would have been correct if serrated polyps would be scored the same way as conventional adenomas. For instance, in the case with 2 sessile serrated adenomas/polyps of which the largest was 12 mm and had a proximal location, the risk score should be 1 point (for having large serrated polyps) with a recommended interval of 5 years. However, for conventional adenomas, the size and location would have scored another 2 points, leading to a three year in-

terval: the answer given by most respondents. We therefore recommend to provide further clarification of the guideline on how to deal with serrated polyps. This could potentially be accompanied by further teaching sessions, for example an e-learning course for gastroenterologists is already implemented. With respect to patients older than 75 years, many gastroenterologists did not consider that surveillance recommendations should provide the statement that the vital status of the patient at the time of surveillance should be taken into account (as the "stopping age" is 75). This deviation may have been caused by gastroenterologists overlooking the specific answering option 'unless in good condition'.

Prior to developing the survey, we hypothesized three other instances where gastroenterologists might deviate from the guideline: in cases with adenomas with high-grade dysplasia, in cases with tubulovillous adenomas, and in cases where the guideline recommends returning to the national CRC screening program with FIT. Although cases involving HGD and tubulovillous adenomas were answered according to the guideline by a majority of respondents, some interesting deviations were seen. In the two cases with high-grade dysplasia, 6 and 11% of respondents recommended an interval <1 year while the Dutch guideline recommends 5 years. In the surveillance guideline of the US and in the guideline of the European Society of Gastrointestinal Endoscopy, HGD is considered a high-risk feature.[6,15] However, in the Dutch guideline HGD is not incorporated as a separate risk factor, because a meta-analysis and the study on which the guideline was based on did not confirm HGD as an independent risk factor in addition to the other factors.[4,16] This is mainly explained by the fact that HGD is rarely seen in small (<10mm) tubular or tubulovillous adenoma. Furthermore, there is a large interobserver variation between pathologists making this feature an unreliable risk factor. In the interviews, half of the gastroenterologists mentioned that they were not entirely convinced that HGD should not be incorporated, while one gastroenterologist in the interview specifically mentioned that HGD was not incorporated in this score chart, but should be considered as high-risk assigning a surveillance interval within one year.

Deviations for cases with a (tubulo)villous adenoma seem to be caused by gastroenterologists scoring tubulovillous adenomas as villous adenomas: almost all deviant recommendations would have been correct if the tubulovillous adenoma would be considered equal to a villous adenoma. However, in previous studies a tubulovillous adenoma (>25% and < 75% villous component) was not a risk factor for metachronous disease in a multivariable model,[4,17] Only villous adenoma (>75% villous component) was found to be a risk factor,[16] and therefore assigned an extra point to the risk score chart in the guideline. This might,

however, be confusing because internationally an advanced adenoma is defined as an adenoma ≥10 mm, HGD, or a tubulovillous component (>25%). Also, during the interviews, 6 out of 10 gastroenterologists mentioned that adhering to the guideline was difficult considering the difference between tubulovillous and villous adenomas, because pathology reports in their hospital do not include percentages nor whether adenomas were villous or tubulovillous *(Appendix 1)*.

In contrast to the cases discussed before, the case in which a person with only one distal non-advanced adenoma should return to the screening program was answered correctly by a large majority without striking deviations. Previously these patients would be recommended surveillance after six years, but apparently the change to recommend no surveillance is well accepted.

Compliance to our colonoscopy surveillance guideline is at the high end of that reported in other studies. Ranges of median recommended surveillance intervals in accordance with guidelines lie between 40-69% of cases,[11-13,18-20] compared with a median of 76% found in our study. More specifically, when we compare our estimate of compliance with the reported compliance to the simple 2002 guideline, there is a clear increase in compliance.[12] According to that survey, a median of only 59% (range: 22-80%) of gastroenterologists' recommendations met the guideline. This comparison clearly indicates that more complex guidelines do not necessarily lead to confusion and lower compliance, but that they might actually increase compliance. The reasons are not explored in our study, but possibly it is because they better align with physician's clinical experience.

An important strength of our study is that we based the survey on a pilot which consisted of interviews with 10 gastroenterologists, and that the pilot provided insight into which situations led to deviation of the guideline and the reasoning for deviation. However, our study also has two limitations. First, the response rate to the survey was low. This may have led to non-respondent bias: gastroenterologists with a strong opinion (either positive or negative) might have been more prone to participate. We did however not see any differences in age and gender between respondents and the complete group. Also, the number of responders was higher than in the previous study in the Netherlands,[12] and there was a good spread in types of hospitals, implicating results might be representative. Second, our findings are based on a survey, while compliance in daily practice may be different for various reasons. Preferably actual adherence rates are measured. In a survey, gastroenterologists might give desirable answers although they deviate from guidelines in daily practice. Also, the patient is sometimes referred for surveillance by a surgeon or general practitioner, who has less experience and knowledge of the surveillance guideline

than the gastroenterologists, and finally, if a recommendation is given to a patient, the patient does not always show up after the correct interval.

Our study has four important practical implications. First, the fact that the most often quoted reason for deviation of the guideline is misinterpretation for cases with serrated polyps clearly indicates that the information on these polyps on the score chart or app needs to be improved. Second, it should be further highlighted that according to the guideline HGD should not be taken into account when determining the interval. Moreover, gastroenterologists and pathologists need to discuss how to improve the reporting of the villous or tubulovillous nature of an adenoma in the pathology report to facilitate classification of these lesions. At the time of the introduction of the national colorectal cancer screening programme in 2014, protocols for structured endoscopy and pathology reports were also introduced with predefined categories for histology, which may improve the classification of villous or tubulovillous adenoma. Finally, the use of a pocket-sized score chart, app or other source when making surveillance interval recommendations should be encouraged as this improves compliance to the guideline.

The current Dutch guideline differs from other guidelines regarding the level of risk stratification. While other guidelines divide patients in groups based on a simple heuristic using presence of absence of risk factors,[6,21,22] the Dutch guideline combines several risk factors into a score from zero to five. The Dutch guideline is therefore more complex, which may cause misunderstandings and thereby decrease compliance. However, this study shows that more complexity in a guideline did not lower compliance as assessed in a survey, and that this guideline with risk stratification actually seemed to improve compliance. Since better risk-stratification leads to efficient use of sources and less unnecessary colonoscopies, this should encourage other countries to implement a guideline with more detailed risk-stratification.

In conclusion, the median compliance to the updated colonoscopy surveillance guideline of 76% seems reasonable, and is higher than the compliance to the previous guideline. This shows that detailed (more complex) risk stratification for designation of a surveillance interval is feasible. Compliance could potentially be improved by clarifying the correct interpretation on serrated polyps.

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Appendix 1: Interviews

10 gastroenterologists were interviewed between May and July 2014. The selected gastroenterologists differed in types and regions of hospitals, gender and age. All interviews were conducted by the same researcher (MvdM) and were audio-recorded. The interviews were semi-structured, started with open questions on which issues were considered advantages and bottlenecks of the guideline by the gastroenterologists. Then, 5 example cases were presented, and recommended surveillance intervals and reasoning were discussed. The response of the interviewees helped to improve the detail of the example cases for the survey and helped to develop several answering options on motivation for deviation from the current guideline.

All gastroenterologists used the new guideline. All gastroenterologists deviated from the recommended interval at least once, one deviated twice, and four deviated three times. Even though all gastroenterologists had a positive opinion about the serrated adenomas being included in the new guideline, 7 gastroenterologists gave the patient with serrated polyps a shorter interval than recommended by the guideline. Although all had a score chart available during the interview, they used it incorrectly, thereby assuming their answer was in accordance with the guideline. We included this in the reasons to deviate from the guideline with the answering option: I was under the assumption that my answer was in line with the guideline.

7 of the 10 gastroenterologists gave a shorter interval for the case with a tubuluvillous adenoma (case 3), 4 did not only score villous, but also tubulovillous adenomas. Six gastroenterologists mentioned that adhering to the guideline was difficult considering the difference between tubulovillous and villous adenomas, because pathology reports in their hospital do not include percentages nor whether adenomas were villous or tubulovillous. All gastroenterologists instructed a 75-year old patient to come back for surveillance. They mentioned that, at the follow-up appointment itself, they would determine whether the patient was healthy enough to undergo colonoscopy. Gastroenterologists mentioned adenoma >20mm is usually not removed by en-bloc polypectomy but it should always be done by piecemeal endomucosal resection (EMR), requiring a surveillance colonoscopy between 4-6 months. This was added to the case (case 3 and 4) accordingly.

3 of the 10 gastroenterologists gave a shorter interval than recommended for the case with high-grade dysplasia (HGD). 8 gastroenterologists mentioned the necessity for clean margins with HGD and 1 gastroenterologist would always

recommend surveillance within 3-6 months for a patient with an adenoma with HGD. We therefore added the answering option: based on clinical experience, and based on scientific studies: both with the sub-answer that there were specific clinical reasons for choosing a different interval.

Appendix 2: Survey

Unless noted otherwise:
- All patients were in good health;
- Had no familial risk for colorectal cancer;
- Had undergone their first colonoscopy;
- Bowel preparation was good;
- The cecum was reached;
- The polyp was removed in one piece and endoscopically complete.

	Description case
1	A 60 year old male with 1 distal tubular adenoma of 8 mm with low-grade dysplasia
2	A 54 year old male with 1 tubulovillous adenoma of 20mm with low-grade dysplasia in the proximal colon, which was removed by piecemeal. At the subsequent colonoscopy at 6 months no remnant adenomatous tissue was detected.
3	A 69 year old male with 1 distal tubular adenoma of 12 mm with low-grade dysplasia.
4	A 62 year old female with 2 adenomas. Polyp A is a distal tubulovillous adenoma of 10 mm with low-grade dysplasia. Polyp B is a distal villous adenoma of 22 mm with low-grade dysplasia which was removed by piecemeal. At the subsequent colonoscopy at 6 months no remnant adenomatous tissue was detected.
5	A 60 year old female with 5 adenomas. Polyp A is a distal tubular adenoma of 5 mm with low-grade dysplasia. Polyp B is a proximal tubular adenoma of 7 mm with low-grade dysplasia. Polyp C is a proximal tubular adenoma of 4 mm with low-grade dysplasia. Polyp D is a proximal tubular adenoma of 8 mm with low-grade dysplasia. Polyp E is a proximal tubular adenoma of 12 mm with low-grade dysplasia.
6	A 63 year old female with 4 adenomas. Polyp A is a distal tubular adenoma of 6 mm with low-grade dysplasia. Polyp B is a distal tubular adenoma of 5 mm with low-grade dysplasia. Polyp C is a proximal villous adenoma of 9 mm with low-grade dysplasia. Polyp D is a proximal tubular adenoma of 7 mm with low-grade dysplasia.

	Description case
7	A 79 year old male with 5 adenomas. Polyp A is a distal tubular adenoma of 6 mm with low-grade dysplasia. Polyp B is a proximal tubular adenoma of 8 mm with low-grade dysplasia. Polyp C is a proximal tubular adenoma of 6 mm with low-grade dysplasia. Polyp D is a proximal tubular adenoma of 4 mm with low-grade dysplasia. Polyp E is a distal tubular adenoma of 5 mm with low-grade dysplasia.
8	A 75 year old male with 4 adenoma. Polyp A is a distal tubular adenoma of 4 mm with low-grade dysplasia. Polyp B is a distal tubular adenoma of 6 mm with low-grade dysplasia. Polyp C is a distal tubular adenoma of 12 mm with high-grade dysplasia. Polyp D is a distal tubular adenoma of 9 mm with low-grade dysplasia.
9	A 65 year old male with 1 distal tubulovillous adenoma of 11 mm with high-grade dysplasia.
10	A 58 year old female with 1 serrated adenoma of 8 mm in the proximal colon.
11	A 54 year old female with 2 polyps. Polyp A is a proximal sessile serrated adenoma/polyp of 10 mm. Polyp B is a proximal sessile serrated adenoma/polyp of 12 mm.
12	A 51 year old male with 2 adenomas. Polyp A is a distal tubular adenoma of 7 mm with low-grade dysplasia. Polyp B is a distal villous adenoma with low-grade dysplasia. The male has a brother who was diagnosed with colorectal cancer at age 48 and in which no hereditary syndrome was diagnosed by the clinical geneticist.
13	A 53 year old male with 1 distal tubulovillous adenoma of 11 mm with low-grade dysplasia. His sister was diagnosed with colorectal cancer at age 45 years old.
14	A 69 year old male with a negative colonoscopy. However, the male has had one previous colonoscopy where 2 adenomas were detected. Polyp A was a distal villous adenoma of 12 mm with low-grade dysplasia. Polyp B was a proximal tubular adenoma of 8 mm with low-grade dysplasia.
15	A 63 year old female with a negative colonoscopy. Five years ago she also had a negative colonoscopy. She underwent this colonoscopy because she had 2 detected adenomas at a previous colonoscopy. Polyp A was a distal tubular adenoma of 5 mm with low-grade dysplasia. Polyp B was a distal tubular adenoma of 12 mm with low-grade dysplasia.

What surveillance recommendation would you provide?

- interval of <1 year
- 1 year
- 2 years
- 3 years
- 4 years
- 5 years
- 6 years
- 7 years
- 8 years
- 9 years
- 10 years
- no surveillance
- no surveillance, unless in good condition, then in 3 years
- no surveillance, unless in good condition, then in 5 years
- no recommendation yet, but referral to the clinical geneticist.

Part 3: reasons for deviation

Why did you deviate from the guideline in this case?

- I thought that my answer was in agreement with the guideline;
- I did not read the question correctly;
- I am not familiar with the new guideline;
- I based my recommendation on scientific evidence;
- I based my recommendation on clinical experience;
- Other (+ free text field).

Chapter 8

General discussion

Answers to research questions

In this thesis, we have estimated pooled perforation and mortality rates of colonoscopy *(Chapter 2)*, determined colonoscopy-, adenoma-, and patient-related predictors of advanced colorectal neoplasia recurrence *(Chapter 3, 4)*, developed a score chart to optimize risk-stratification for surveillance of adenoma patients *(Chapter 4)*, proposed intervals for surveillance colonoscopy according to this risk-stratification *(Chapter 5)*, assessed actual adherence rates to previous surveillance guidelines for adenoma patients in clinical practice *(Chapter 6)*, and investigated whether adherence may be better with the updated guideline for surveillance colonoscopy *(Chapter 7)*.

In this chapter, we will answer the specific research questions as formulated in *Chapter 1*, discuss the interpretation of our findings (including the main methodological issues and practical implications), suggest directions for future research, and give our main conclusions and recommendations.

1. What are perforation and mortality rates of colonoscopy according to literature over the past 30 years? (Chapter 2)

In many countries the number of (surveillance) colonoscopies is increasing rapidly, mainly due to national screening programmes for colorectal cancer. When exposing relatively healthy people (people without symptoms) to (surveillance) colonoscopy it is important that colonoscopy is a safe, high-quality procedure. Therefore thresholds for quality assurance have been set, incorporating a maximum rate for colonoscopy complications. To better inform screening participants and patients under surveillance, accurate estimates for complication rates in usual clinical practice are necessary.

Current quality thresholds included a maximum rate of 20 perforations in 10,000 colonoscopies and 10 perforations in 10,000 colonoscopies for screening colonoscopies. [1] In our systematic review of literature, we found a pooled mortality rate of 0.13 (95%CI 0.1 – 0.3) per 10,000 colonoscopies and a pooled perforation rate of 5.7 (95%CI 4.7 – 6.8) per 10,000 colonoscopies with a declining trend over the past decades. When we stratified for type of colonoscopy, perforation rates were 9.7 per 10,000 (95%CI 6.8 – 16.8) for therapeutic colonoscopies and 3.4 per 10,000 (95%CI 2.4 – 4.9) for diagnostic colonoscopies. And the pooled perforation rate for primary screening colonoscopies was 1.8 per

10,000 (95%CI 0.9 – 3.4). The pooled perforation rates are therefore below the set maximum quality thresholds.

2. What are adenoma and colonoscopy-related predictors of (advanced) colorectal neoplasia recurrence at surveillance examinations? (Chapter 3)

The sole factor included for risk stratification in the 2002 Dutch surveillance guideline was the number of adenomas. This may have been a reason for gastroenterologists to deviate from the guideline because there was evidence for more predictors of (advanced) colorectal neoplasia recurrence. However, evidence was limited and mainly based on small studies assessing adenoma predictors one at a time or based on meta-analyses including mostly high-quality examinations in healthy individuals in academic institutions that may not be representative for current practice. Therefore, we determined independent predictors of (advanced) colorectal neoplasia recurrence in community surveillance practice.

In our study, called Surveillance After Polypectomy (SAP), we collected data from community-based surveillance practices in the Netherlands and showed that higher adenoma number, large adenoma size (≥10 mm), villous histology, and proximal location of adenoma at index colonoscopy together with insufficient bowel preparation and limited colonoscopy reach are important predictors for detecting advanced colorectal neoplasia (AA or CRC) at surveillance endoscopy. These factors were independent predictors, implying that having multiple of these factors at the same time further increases a patient's risk. High-grade dysplasia was not found to be an independent predictor of future advanced adenoma detection.

3. How can we improve risk stratification of adenoma patients? (Chapter 4)

Current surveillance guidelines risk-stratify adenoma patients by one or two factors only, and combinations of adenoma characteristics are not considered. Given that several adenoma characteristics, as presented in Chapter 3, are independent predictors of advanced colorectal neoplasia (ACN), how can these factors be considered simultaneously for better risk stratification in surveillance guidelines?

A score chart that combines adenoma-related predictors of ACN can be used to improve risk stratification of adenoma patients for surveillance colonoscopy.

We developed a score chart that consisted of characteristics that contributed 1 point (size ≥10 mm, villous histology, proximal location, 2-4 adenomas) or 2 points (having ≥ 5 adenomas). A patient total risk score could range from 0-5 points. In addition to the adenoma-related predictors, independent patient-related predictors were older age, male gender. Based on the risk of the adenoma patient population in our community-based study, the 5-year absolute risk of ACN ranged from 2,5% for 55 year old women with risk score 0 to 46% for 75-year old men with risk score 5. The score chart we developed is included in the current Dutch 2013 guidelines for surveillance colonoscopy. [2]

4. What are cost-effective strategies for surveillance of adenoma patients with different risk profiles? (Chapter 5)

To propose intervals for surveillance guidelines formal cost-effectiveness analysis is needed. We aimed to determine the optimal interval for surveillance given a patient's adenoma risk score (i.e., risk according to the developed and validated score chart), sex and age.

The appropriate interval for colonoscopy surveillance depended heavily on adenoma risk score and to a lesser extent on sex and age. Patients with risk score 0 would receive surveillance colonoscopy after 10 years, patients with risk scores 4 and 5 after only 2 or 3 years. Surveillance would no longer be recommended in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older and higher-risk patients aged 80 years or older. Results were robust to variations in the overall level of health care costs in a country. However, applying less stringent cost-effectiveness thresholds resulted in substantially more intensive surveillance recommendations, particularly in those with a low adenoma risk score. The surveillance intervals recommended in the Dutch 2013 guidelines were based on results of this study. [2]

5. What are actual adherence rates to recommended surveillance intervals in clinical practice? What is the influence of a recent change in the guideline? (Chapter 6)

Most previous studies about adherence to guidelines for surveillance of adenoma patients were surveys among gastroenterologists and showed that shorter

intervals than recommended by guidelines were often recommended. However, the gastroenterologist's recommendation is only one factor in whether and when surveillance colonoscopy will take place. Therefore, we assessed actual guideline adherence rates in clinical practice.

Actual adherence to the Dutch guidelines for surveillance of adenoma patients was inappropriate in 76 – 89% of cases. This finding holds for both guideline periods considered: before 2002, only 24% of patients received appropriately timed adenoma-surveillance; in 2002 only 11% did. Appropriate adherence to surveillance guidelines was somewhat higher for patients with three or more adenomas than for patients with one or two adenomas (26% vs. 21%). Overall, a third of the patients did not receive surveillance at all by the end of the study period. The absence of surveillance in such a large fraction of the patients is alarming, because advanced neoplasia was found in 8% (of which a fifth were CRCs) of those with delayed surveillance, and in particular up to 17% in those with three or more adenomas at index colonoscopy. Before 2002, inappropriate surveillance was predominantly too late or absent (together, 57% of patients), while in 2002, when the recommended surveillance intervals were lengthened, 48% of the patients received surveillance too early. This proportion was higher for patients with one or two adenomas compared with those with three or more adenomas (50% vs. 39%).

6. Is the new risk-stratified surveillance guideline feasible for gastroenterologists? What difficulties do gastroenterologists have regarding guideline interpretation or compliance? (Chapter 7)

Compliance to the 2002 Dutch surveillance guideline was low, only 11% - 59% of adenoma patients received appropriately timed surveillance ([3], Chapter 6). A new surveillance guideline was released in 2013 and risk-stratified patients at a more detailed level than the previous one.[2] Through a score chart polyp characteristics are combined into a risk score (0 - 5) to optimize-risk stratification of patients for designation of a surveillance interval. Since this new guideline is more complex, it may also lead to low compliance. Therefore, we evaluated gastroenterologists' interpretation and compliance to this new risk-stratified guideline using a nationwide survey including 15 questions with example cases of patients with adenoma or polyp findings.

Respondents that finished all 15 example cases indicated the correct surveillance interval in a median of 10 cases. The number of correct recommendations did not differ by the respondents' gender, age, type of hospital and their participation in the national screening program, but consulting the guideline during the questionnaire was associated with an increase in compliance. The median compliance to the guideline for the example cases was 76%. Compliance ranged from 14% to 95% per case. Cases involving serrated polyps, elderly patients, or adenomas with tubulovillous histology were most often answered incorrectly. Deviations were mainly due to misinterpretation of the guideline (48%) or misreading of the questions (30%). For example, 92-95% of incorrect answers to cases on serrated polyps were based on the fact that these polyps were scored the same as conventional adenomas, taking into account location and number of lesions.

Interpretation of our findings

Predictors of (advanced) neoplasia recurrence and more efficient surveillance of adenoma patients

Methodological issues

Chapters 3 and 4 are based on the SAP-study. The major strengths of this study are its large size and its community-based design. The study size provided us with enough power to reliably estimate odds ratios for (advanced) adenoma recurrence. However, an observational study also has limitations. First, the study was initiated prior to time of structured reporting systems for endoscopy and pathology, which may have resulted in lack of (high) quality of such reports, leading to missing values in some cases or misclassification. There may have been inter- and intra-observer variability between pathologists in characterization of the histological types and degree of dysplasia. [4 5] In the SAP-study, the percentage of patients with HGD at index colonoscopy varied from 5% to 39% between hospitals, and the range was 2% -17% for villous histology. The misclassification of adenoma characteristics may have resulted in diluting their predictive effects. Also, some polyps (potential adenomas) might not have been sent in for pathology. As a result, the actual number of adenomas might have been underestimated, which in turn may have led to an overestimation in the effect of adenoma number as predictor of ACN. Second, since serrated polyps were not accurately captured and reported at time of our study, we did not have sufficient informa-

tion on these lesions. Serrated polyps may have been classified as adenoma, not send in for pathology or not reported at all. Therefore, the presence and risk of ACN that these lesions harbor may have interfered with results for adenomas. Third, since our study is based on a clinical patient population, our results may not necessary apply to patients in whom adenomas have been detected through screening. However, our results are consistent to those found in a meta-analysis of 8 North American studies. [6] Therefore, we believe that the score chart is a reliable instrument to risk-stratify adenoma patients, also in other settings.

In *Chapter 5* we provided surveillance recommendations based on a formal cost-utility analysis. Recommendations that are tailored to the individual adenoma patient, ensures that surveillance colonoscopies are targeted at those patients most likely to benefit. A restriction of our analysis is that it focused on the appropriate interval for a first surveillance colonoscopy as we modelled strategies with a fixed surveillance interval to a certain stop age.

In the cost-effectiveness analysis we included complication rates of 1 per every 30,000 colonoscopies with polypectomy for mortality and age-specific rates for other complications requiring a hospital admission or emergency department visit, ranging from 20 per 10,000 colonoscopies with polypectomy in 40 year olds to 380 per 10,000 colonoscopies with polypectomy in 85 year olds. These rates are higher than the results of our meta-analysis in which we solely assessed perforations *(Chapter 2)*. Our results on pooled complications rates in *Chapter 2* could have been underestimated, as underreporting or under registration of post-colonoscopy complications is a known issue. [7] However, this underestimation may be mitigated since we include complications over a longer period of time, with higher rates in earlier years.

Practical implications

We showed that independent predictors of ACN are insufficient bowel preparation, poor colonoscopy reach, age, sex, number of adenomas, large adenoma size (≥10 mm), villous histology, and proximal location *(Chapter 3, 4)*. We have incorporated these adenoma-related predictors into a score chart that may help to better target surveillance colonoscopy *(Chapter 4)*. Based on formal cost-effectiveness analysis - that takes into account age, sex, life-expectancy, costs of surveillance colonoscopy, complications, and CRC treatment – we proposed optimal intervals for surveillance colonoscopy according to combination of age, sex and adenoma risk score *(Chapter 5)*. We realize that it might not be feasible to stratify adenoma

patients to the level we have done in our analysis. Since the appropriate surveillance intervals and stop ages are primarily affected by adenoma risk score and to a lesser extent by sex and age, one way to simplify surveillance recommendations would be to base on adenoma risk score only. This approach was chosen by the Dutch Association of Gastroenterologists when they revisited the guideline for colonoscopy surveillance. [2] The guideline incorporates the score chart and recommends a 3-year interval for patients with risk score 3-5, 5-year for those with risk score 1-2 and no surveillance or returning to the national screening program after 10 years for those with risk score 0 (if their age is within the screening range of 55-75 years) *(Figure 1)*. Clinicians can use the score chart together with the proposed intervals of surveillance colonoscopy, but should also consider patients' preferences, co-morbidity status, lifestyle, and family history of CRC.

The pooled perforation and mortality rates estimated in *Chapter 2* can be used to inform subgroups of individuals (those with colonoscopy for primary screening, as follow-up after a positive screen test, or for symptoms) on potential harms of colonoscopy. These complication rates can also be used to inform decision analysis and can serve as a benchmark. In addition, our results imply that set quality thresholds for perforation rates can be more stringent, since our pooled rates are remarkably lower.

Adherence to and acceptance of guidelines for surveillance of adenoma patients

Methodological issues

In *Chapter 6* we assessed the actual use of surveillance colonoscopy in adenoma patients in clinical practice. Since we were only in the position to assess adherence in the first year after implementation of the 2002 guideline, this could have resulted in higher rates of inappropriate adherence due to the adaptation phase of new guidelines. But the large proportion of inappropriate adherence will not be fully explained by this issue and will therefore not change our conclusions. Guideline adherence may have improved somewhat in the years after, but it is unlikely that it reached more than 59% as reported in 2008 by a survey performed in the Netherlands. [3]

The strength of our study in *Chapter 7* is that the survey was based on a pilot which consisted of interviews with 10 gastroenterologists that also provided us

SCORE TABLE FOR PRESENCE OF ADENOMA CHARACTERISTICS AND SERRATED POLYPS*		
Polyp Characteristics	Values	Points
Number of adenomas	1	0
	2-4	1
	≥5	2
Presence of at least one adenoma ≥10mm and/or one large serrated polyp ≥10mm**	No	0
	Yes	1
Presence of at least one villous adenoma***	No	0
	Yes	1
Presence of at least one proximal adenoma****	No	0
	Yes	1
Total risk score		

* A patient with 5 proximal serrated polyps of which 2 ≥ 10 mm fulfil the WHO criteria of the serrated polyposis syndrom; see the guideline of hereditary colorectal cancer.

**A serrated polyp encompasses: hyperplastic polyps, sessile serrated polyps/adenomas and traditional serrated adenomas

***An adenoma with at least 75% villous histology.

****Proximal is defined as cecum, colon ascendens, colon transversum and flexura lienalis

SURVEILLANCE INTERVAL BASED ON THE ADENOMA RISK SCORE	
Score during index colonoscopy	Interval after index colonoscopy
0	No surveillance*
1-2	5 years
3-5	3 years
Score during subsequent colonoscopy	Interval after subsequent colonoscopy
0	5 years**
1-2	5 years
3-5	3 years

*Patients with a score of 0 during index colonoscopy are advised to not undergo surveillance colonoscopy. These patient are sent back to the national screening programme in 10 years if aged 55-75 years at that moment.

**For patients in which a high-risk adenoma (score ≥3) was never detected, surveillance can be ended after two subsequent negative colonoscopies. These patient are sent back to the national screening programme in 10 years if aged 55-75 years at that moment.

Stopping age of surveillance: 75 years, unless the wish and condition of the patient justify a different stopping age

Figure 1: Score chart and recommended intervals of the Dutch guideline for colonoscopy surveillance after polypectomy. The surveillance interval is based on the risk score. Serrated polyps are incorporated in the guideline only if at least one serrated polyp measures ≥10mm. Other characteristics (total number, localisation) of the serrated polyps are not taken into account. High-grade dysplasia (HGD) in adenomas is not incorporated as a risk factor in the guideline as it is not confirmed to be an independent risk factor, probably because HGD is highly associated with other factors such as size. The length of the surveillance interval is based on the total score. The total score indicates a recommended surveillance interval of 3 or 5 years, or no surveillance at all.

with insight into situations that may led to deviation of the guideline and its reasoning. A limitation of this survey is the low response rate (17%), which may have led to bias. Gastroenterologists with a strong opinion (either positive or negative) might have been more prone to participate. Gastroenterologists that are dealing with these patients in their daily practice may also be more likely to participate than those with other clinical focus. We did not see any differences in age and gender between respondents and the complete group and there was a good spread in types of hospitals among respondents. Since our findings are based on a survey, compliance in daily practice may be different for various reasons.

Practical implications

In *Chapter 6*, we showed poor adherence with the Dutch 2002 guidelines. Over 45% of patients receive too intense surveillance. Poor penetration of the 2002 surveillance guidelines within 1 year following implementation illustrates the importance of convincing evidence to support endorsement of new guidelines. The 2002 guideline was formulated when only limited data were available and differed from other international guidelines, probably causing gastroenterologist to deviate from the guideline. In this guideline only adenoma number was considered to be a risk factor of future CRC risk. Patients with other risk factors than adenoma number may have received earlier surveillance colonoscopy than recommended by this guideline. Given that the yield of AA was similar for patients with too early surveillance compared with those having appropriately timed surveillance (7% and 5%, respectively), it indeed seem to be the higher risk adenoma population that received too early surveillance. In 2013, the Dutch surveillance guideline has been updated including additional adenoma characteristics for risk stratification *(Figure 1)*.

Our survey *(Chapter 7)* suggests that this guideline update will improve adherence to the recommended intervals, especially for surveillance in patients with conventional adenomas. We cannot directly compare the estimates for compliance to the guideline from *Chapter 7* with *Chapter 6*, because of the difference in study design. However, a previous study with a similar design as Chapter 7 showed that 59% of gastroenterologists complied to the appropriate surveillance interval with the simple 2002 guideline. When we compare this to our estimate of compliance of 76% with the 2013 guideline, there is a clear increase. This comparison indicates that more complex guidelines do not necessarily lead to confusion and lower compliance, but that they might actually increase compliance, as long as important risk factors are considered.

According to our survey, adherence to the 2013 guidelines for colonoscopy surveillance can be improved by: 1) informing gastroenterologists on serrated polyps and its perceived risk for CRC and how to use the guideline in case of serrated lesions, 2) provision of more reasoning why high-grade dysplasia is not included in the score chart, and 3) improved reporting and classification of villous or tubulovillous histology, and emphasizing that only villous histology is a predictor of ACN.

Together, these studies demonstrate that it is important that guidelines for surveillance of adenoma patients are up to date and evidence-based. When guidelines include known independent risk factors of ACN recurrence and risk stratify adenoma patients in a way that better aligns with physician's clinical experience and knowledge, physicians are more likely to adhere. Regular review of surveillance guidelines is recommended. With regard to quality assurance, physicians should realize that inappropriate adherence to guidelines seriously hampers the effectiveness and efficiency of surveillance, as too early surveillance poses a considerable burden on available resources, and delayed surveillance is associated with an increased rate of advanced neoplasia with the consequence that cancers will be missed, which in turn may lead to less cases of CRC deaths prevented.

The European Society of Gastrointestinal Endoscopy (ESGE) recommends that 95% of post-polypectomy surveillance recommendations should adhere to guidelines. [8] Monitoring surveillance intervals combined with efforts to encourage timely adherence should be a mainstay in continuous quality improvement, especially too early surveillance should be prevented. Extra attention may be needed for endoscopists with lower ADR (< 20%), since these physicians also show lower adherence to surveillance guidelines. [9]

Future research and directions

Safety of colonoscopy

We observed a decreasing trend in perforation rate over the past 30 years, suggesting that the colonoscopy procedure has become safer over time. This is likely due to increased colonoscopy quality, better trained and experienced endoscopists, and potentially the shift in comorbidity status of the population undergoing colonoscopy (from a patient population with symptoms with a

presumed higher comorbidity status towards a more healthy population undergoing colonoscopy for (primary) colorectal cancer screening and post-polypectomy surveillance). Conversely, perforation rates may rise when the population undergoing colonoscopy shifts towards a population with follow-up colonoscopy after a positive screen test (higher prevalence of (advanced) lesions requiring polypectomy). Especially the increased removal of large polyps or early cancers during colonoscopy instead of during surgery may cause colonoscopy complications rates to rise in the near future when more advanced techniques of polypectomy will be increasingly performed, like endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). It is important that complication rates (especially mortality rates) do not exceed the complication rates of surgery and vice versa. This should be investigated in order to decide the best treatment option.

Monitoring complications of colonoscopy in clinical practice should be a mainstay of quality control. To accurately monitor the safety of colonoscopy, use of complication registries and uniform registration is essential as well as reliable recording of all complications. Methods to collect information on complications are through review of medical reports, patients' self-reported complications in questionnaires or via telephone consultation, and analysis of administrative data claims. [8] Standard registry of complications should include date of complication, type and severity of late or early (immediate) complication (with uniform definitions), date and location of colonoscopy and with preferably a link to colonoscopy data (colonoscopy indication, type of procedure (therapeutic / diagnostic), type of bowel preparation, method of polypectomy). [8] Complication registries may include more complications than those related to the endoscopic procedure itself and it may not always be clear if the complication is a consequence of the endoscopic procedure. Therefore, it would be good to register the likelihood of the complication to be related to the procedure.

Besides these registries, studies that include control populations to correct for risk of certain complications are desired, especially in case of mortality. However, this requires studies with enormous sample sizes. Complication registries with the possibility of linkage of data with other registries on the individual level may be useful for future research, like linkages with a registry with causes of death and registries of colonoscopy reports. Scandinavian countries may have such possibilities. [10]

Linkage with endoscopy databases would facilitate research on characteristics of colonoscopy and polypectomy related to complications, in order to better

inform patients on potential harms of colonoscopy procedures and it can make endoscopists and health professionals more aware of factors associated with a higher risk of complications. Feedback to gastroenterologists on quality- as well as safety-indicators is essential, especially in screening programmes. In the Netherlands, as part of the Dutch Institute for Clinical Auditing (DICA), a national registry for complications; Dutch Registration of Complications in Endoscopy (DRCE) was launched in 2016 and recently an initiative started for a national database for endoscopies; the Dutch Gastrointestinal Endoscopy Audit (DGEA).

Evaluation of risk stratification

The score chart suggested in *Chapter 4* is based on predictors of ACN in an adenoma patient population before the introduction of the national CRC screening programme, a more symptomatic population. Although we do not expect differences in predictors of ACN in an adenoma population following screening, this should be evaluated. Definitions used for low- and high risk groups in various guidelines are not uniform and warrant further investigation.

Future studies should focus on the effectiveness of surveillance colonoscopy according to various risk classifications in terms of yield of ACN at surveillance examinations and post-colonoscopy interval cancers. Studies should also investigate the longest interval that is still effective in various subgroups. Ideally, instead of ACN as surrogate marker, long-term risk of CRC and CRC mortality reduction are measured to assess effectiveness of a surveillance programme. Using ACN as an surrogate marker is (somewhat) arbitrary, aspects like villousness may be related to development of subsequent villous adenomas (thus ACN), but may not necessarily be related to CRC development.

Currently, several European trials (European Polyp Surveillance – EpoS – studies) have started that aim to determine whether recommended surveillance intervals can be extended by randomly assigning participants to different surveillance intervals based on colonoscopy findings (for low-risk adenoma patients at a 5- and 10 year interval, for high-risk patients at 3- and 5 years) and assessing the yield of CRC at surveillance colonoscopy. However, data collection of this study is scheduled to end no earlier than 2028. [11]

Besides yield of CRC at surveillance, studies investigating characteristics of interval cancers and predictors of interval cancers following colonoscopy are of interest. They can inform us on lesions that are more likely to be missed at colonoscopy or lesions that may harbor increased cancer risk and on patient and procedure related predictors. It has been suggested that interval cancers are more likely to arise from missed sessile (serrated) lesions. [12]

The risk of CRC (or ACN) and need for surveillance in patients with serrated polyps is unclear, and should be studied. Some surveillance guidelines give recommendations for this subgroup of patients, but evidence is low. This may lead to uncertainty in usefulness of surveillance and non-adherence to guidelines. Serrated polyps that are large in size (≥ 10 mm), dysplastic or at proximal location have been associated with a higher risk of ACN at follow-up. [13-15] Guidelines recommend a 3-5 years surveillance interval in these patients. [16 17] In the EPoS-study patients with only serrated polyps will also be followed-up with colonoscopy after 5- and 10 years to assess CRC risk. [11]

Risk attenuation after first surveillance colonoscopy needs to be investigated as findings at surveillance colonoscopy may alter subsequent ACN risk. Evidence on appropriate intervals for subsequent surveillance colonoscopies is lacking. So far, only few, small studies have been conducted in this area with a maximum of two surveillance colonoscopy rounds. These studies suggested that findings at both the baseline and the most recent colonoscopy impact subsequent advanced adenoma risk, especially presence of high-risk lesions at any examination. [18-20]

To further optimize and personalize risk stratification for surveillance, future research may include molecular markers/biomarkers (detected in polyps, stool, or blood), ethnic and lifestyle factors. Nowadays, with the technological developments, the possibility of data collection/gathering and data accessibility has improved. Unique patient identifiers create the option of linkages of (individual) data with other databases, like pathology or cancer registries and demographic databases. This supports performance of large sized studies with improved quality (precision) of research outcomes. An Australian initiative describes an example of whole population data linkage to develop risk stratification models for CRC surveillance with the possibility to include colonoscopy history and adenoma burden over time. [21]

Impact of improved colonoscopy quality on surveillance practice

Justification of lengthening of surveillance intervals is expected in the near future in the light of improved quality of (index) colonoscopy examinations with first adenoma diagnosis. The introduction of CRC screening in the Netherlands has improved colonoscopy quality as well as the method of uniform registration in colonoscopy and pathology reports. With the increase in quality, more (small) polyps will be detected and removed at colonoscopy examinations, which will

result in a shift in risk classification of patients towards higher risk groups. As they were earlier assumed to be at low-risk (when lesions were missed), now they will be classified as higher risk since (more lesions detected and removed and less lesions missed). According to current risk stratifications, this leads toward more stringent surveillance intervals in these patients, while in contrary their ACN risk has lowered due to the higher quality of the examination and therefore in fact justifying longer surveillance intervals. The impact of improved colonoscopy quality on ACN yield at surveillance examinations needs to be studied as well as the understanding of clinical importance of smaller lesions (<10 mm).

Burden of surveillance colonoscopy

As the burden of surveillance colonoscopy is expected to increase, it is important to keep control of endoscopic resources and monitor utilization of surveillance procedures. And how it relates to other colonoscopy indications. One may expect that with the introduction of screening many people will enter a colonoscopy surveillance program, which leads to a larger proportion of colonoscopies being indicated for surveillance purposes. When considering improved colonoscopy quality and colonoscopy overuse in low-risk adenoma patients [9], the burden on endoscopy units will further increase, leading to unnecessary examinations, costs and risks.

(Cost)-effectiveness of surveillance colonoscopy and future surveillance practice

Ideally, surveillance colonoscopy is targeted to a small group of patients that is truly at high risk of developing cancer with an interval as long as possible but still effective. [22] Studies have suggested that surveillance in patients at low-risk for ACN may not be necessary, especially in case of the possibility of referral to a national screening programme. [2 23] Atkin et al. suggests that surveillance may even not be necessary in some intermediate risk patients (patients with adenomas without HGD that are smaller than 20 mm and of distal location) as CRC incidence in this group may be similar compared to the general population. [24] Alternative surveillance strategies as referral to FIT screening (< 10 years) warrant investigation in these groups.

The (cost-) effectiveness of colonoscopy surveillance of adenoma patients in a setting of a national screening program is not clear. A recent cost-effectiveness study evaluated the additional benefit and colonoscopy demand associated

with colonoscopy surveillance according to the Dutch 2013 guideline in a screening setting, and assessed how extending the surveillance intervals to 5 or 10 years would affect these. [25] They concluded that surveillance colonoscopy would not be cost-effective compared to FIT screening in 10 years for low-risk patients (risk score 0) and FIT screening in 2 years for medium to high-risk patients (risk score >=1). FIT screening every two years irrespective of colonoscopy findings, thus also for the low-risk group seemed to be the best strategy. [25] However, to support these findings, evidence on the performance of FIT in a surveillance population and in a population with serrated polyps is needed. According to our study in *Chapter 5* we did not found biennial FIT screening to be a cost-effective surveillance strategy.

Greuter et al. estimated that surveillance colonoscopy can reduce the CRC mortality by 2% in addition to FIT screening and that extending surveillance intervals to 5 years in high-risk patients would decrease colonoscopy demand without substantial loss of effectiveness. [25] However, since the high-risk group comprises only a small proportion of the total (screening) population the reduction of use of resources may not be substantial. More effective in terms of reduction of use of endoscopic resources would be if the interval of low- and intermediate-risk patients could be extended or if these patients can be referred to FIT, as these lower risk groups present the main burden of all surveillance colonoscopies. It would be of interest to further explore the use of FIT in surveillance at various intervals and cut-off levels as compared to the FIT cut-off level and frequency used in the national screening programme.

Conclusions and recommendations

Conclusions

- The post-colonoscopy mortality rate within 30-days is estimated to be 0.1 per 10,000 colonoscopies and the pooled perforation rate is estimated to be 10 per 10,000 for therapeutic colonoscopies and 3 per 10,000 for diagnostic colonoscopies. *(Chapter 2)*

- Independent predictors of ACN recurrence are the adenoma characteristics: number of adenoma, large adenoma size (≥10 mm), villous histology, and proximal adenoma locations; and colonoscopy characteristics: insufficient bowel preparation and poor colonoscopy reach *(Chapter 3)*. Independent pa-

tient-related predictors were increasing age and male gender. *(Chapter 4)*

- Adenoma-related predictors of ACN recurrence can be combined into an adenoma risk score to risk stratify adenoma patients taking into account multiple factors simultaneously, resulting in 6 risk groups. *(Chapter 4)*

- Personalizing surveillance using the adenoma risk score targets colonoscopies to those patients most likely to benefit. The appropriate interval for a first surveillance depends mainly on a patients' adenoma risk score, and to a lesser extent on age and sex. *(Chapter 5)*

- Surveillance colonoscopy should be offered after 2-3 years in patients with high adenoma risk scores (4 or 5), after 4-7 years for intermediate scores (1-3) and after 10 years in patients with a low adenoma risk score (0), with shorter intervals for men and those at older age. *(Chapter 5)*

- Surveillance colonoscopy should no longer be recommended in patients of 70 years and older with adenoma risk score 0, in patients of 75 years and older with risk score 1 and males with risk score 2 and in patients of 80 years and older with higher risk scores. *(Chapter 5)*

- Adherence to the Dutch guidelines for surveillance of adenoma patients in community practice was poor. Prior to 2002, colonoscopy surveillance in adenoma patients was either late or absent. After 2002, almost half of patients received too intense colonoscopy surveillance. There was poor penetration of the 2002 surveillance guidelines in the first year after guideline implementation. *(Chapter 6)*

- Advanced neoplasia was found in 8% (of which a fifth were CRCs) of those with delayed surveillance, and in up to 17% in those with three or more adenomas at index colonoscopy. *(Chapter 6)*

- The new Dutch surveillance guideline that incorporates important predictors of ACN recurrence simultaneously was associated with higher compliance than the previous guideline. *(Chapter 7)*

Recommendations

- The observed colonoscopy mortality and perforation rates can be used to inform individuals about the risks of colonoscopy and these rates can serve as benchmark for endoscopy units. *(Chapter 2)*

- The (inter-)national quality thresholds for perforation rates should be more stringent and should relate to procedure and patient characteristics. *(Chapter 2)*

- Independent adenoma related predictors of advanced colorectal neoplasia recurrence should be considered jointly in risk stratification of adenoma patients for surveillance. We recommend the use of a score chart based on adenoma number, size, villousness and location to tailor surveillance recommendations. *(Chapter 3, 4)*

- Surveillance colonoscopy intervals can be lengthened to 10 years for patients at low risk of advanced colorectal neoplasia recurrence. *(Chapter 5)*

- To support endorsement of (new) guidelines for surveillance of adenoma patients convincing evidence is needed, as well as a clear instruction to avoid misinterpretation. *(Chapter 6, 7)*

- To improve adherence to the current guideline for surveillance of adenoma patients, clarification is needed on the use of the score chart in case of serrated polyps (especially with respect to location and number of these lesions) and adenomas with tubulovillous histology. *(Chapter 7)*

- The use of a pocket-sized score chart, app or other source of the guideline when making surveillance recommendations should be encouraged to improve compliance to the guideline. *(Chapter 7)*

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Chapter 9

Summary
Samenvatting
Dankwoord
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Summary

Surveillance of adenoma patients – towards more efficient guidelines

Colorectal cancer (CRC) is the third most common malignancy in the world. In the Netherlands, about 14,000 people are annually diagnosed with CRC and almost 5,000 people die from this disease. Most colorectal cancers develop from benign precursor lesions to cancer, the majority of these precursors (65-95%) are adenomatous polyps (adenomas). Adenomas can vary in shape and size, arise throughout the colon, and may have various microscopic features. An adenoma large in size (≥10 mm), with (tubulo)villous histology, or high-grade dysplasia is assumed to have elevated risk to develop into CRC. An adenoma with at least one of these characteristics is therefore called an advanced adenoma. Individuals in whom adenomas have been detected and removed may have an increased risk for recurrent adenomas and subsequent CRC. These patients are therefore recommended to undergo regular surveillance colonoscopy. The main focus of this thesis is on colonoscopy surveillance of adenoma patients.

This thesis is divided into 3 parts. In part I, we examined literature to estimate the frequency of complications (perforation and mortality) after colonoscopy. In part II we investigated factors that were predictive for advanced neoplasia (advanced adenoma and cancer) at surveillance. We further assessed how these predictors could be used to improve surveillance of adenoma patients. Finally, in part III, we evaluated to what extent guidelines for surveillance of adenoma patients are adhered to.

Part I: Complications of colonoscopy

In *Chapter 2*, we systematically reviewed medical literature on perforation and mortality after colonoscopy. Through a meta-analysis we estimated a mortality rate of 0.1 per 10,000 colonoscopies and a perforation rate of 5.7 per 10,000 colonoscopies. The perforation rate showed a declining trend over the past decades and depended on the type of colonoscopy. The perforation rate for primary screening colonoscopies was 1.8 per 10,000, for follow-up colonoscopies after a positive non-invasive primary screen test it was 8 per 10,000 colonoscopies, and for therapeutic and diagnostic colonoscopies it was 10 and 3 per 10,000, respectively. The perforation rates of colonoscopy and of primary screening colonoscopy are well below the set maximum quality thresholds by the American and European societies for Gastroenterology (20 and 10 per 10,000 colonoscopies, respectively).

Part II: Predictors of (advanced) neoplasia recurrence and more efficient surveillance of adenoma patients

In *Chapter 3*, we determined which characteristics were associated with the presence of advanced neoplasia at surveillance colonoscopy. In our study, called "Surveillance After Polypectomy" (SAP), we collected data of almost 3,000 adenoma patients with surveillance colonoscopy from 10 hospitals in the Netherlands. We showed that higher adenoma number, large adenoma size (≥10 mm), villous histology, and proximal location of adenoma at index colonoscopy together with insufficient bowel preparation and limited colonoscopy reach were important and independent predictors of advanced neoplasia. Having multiple of these risk factors at the same time further increases a patient's risk. High-grade dysplasia was not found to be an independent predictor.

Based on the four adenoma related predictors for advanced neoplasia at surveillance colonoscopy we developed an adenoma score chart in *Chapter 4*. The score chart consists of characteristics that contribute 1 point (size ≥10 mm, villous histology, proximal location, 2-4 adenomas) or 2 points (having ≥ 5 adenomas). A patient total risk score can range from 0-5 points, resulting in 6 risk groups. The score chart can be used to improve risk stratification of adenoma patients for surveillance colonoscopy. In addition to the adenoma-related predictors, independent patient-related predictors were 'older age' and 'male sex'. According to our prediction model based on the adenoma patient population in the SAP-study, the 5-year absolute risk of advanced neoplasia ranged from 2,5% for 55 year old women with risk score 0 to 46% for 75-year old men with risk score 5.

In *Chapter 5* we performed a cost-effectiveness analysis to assess optimal strategies for surveillance by sex, age and adenoma risk score as developed in *Chapter 4*. Our analysis showed that the appropriate interval for colonoscopy surveillance depended mainly on adenoma risk score and to a lesser extent on age and sex. Patients with risk score 0 should receive surveillance colonoscopy after 10 years, patients with risk scores 1 to 3 after 4 to 7 years, and patients with risk scores 4 and 5 after 2 or 3 years. Surveillance would no longer be recommended in patients with risk score 0 aged 70 years or older, patients with risk score 1 and males with risk score 2 aged 75 years or older and higher-risk patients aged 80 years or older.

Part III: Adherence to and acceptance of guidelines for surveillance of adenoma patients

In this part we evaluated the adherence and acceptance of guidelines for surveillance of adenoma patients in the Netherlands. Based on the SAP study, *Chapter 6* showed that historically adherence to the Dutch guidelines for surveillance colonoscopy was inappropriate in 76 – 89% of cases. Before 2002, only 24% of patients received appropriately timed surveillance colonoscopy. This proportion dropped to a mere 11% after a guideline change in 2002. Appropriate adherence to surveillance guidelines was somewhat higher for patients with three or more adenomas than for patients with one or two adenomas (26% vs. 21%). A third of adenoma patients did not receive surveillance at all by the end of the study period. The absence of surveillance in such a large fraction of the patients is alarming, because advanced neoplasia was found in 8% (of which a fifth were CRCs) of patients with delayed surveillance, and in particular in up to 17% in patients with three or more adenomas. Before 2002, when the guidelines recommended shorter intervals, inappropriate surveillance was predominantly too late or absent (together, 57% of patients). In 2002, when the recommended surveillance intervals were lengthened, 48% of the patients received surveillance too early. The proportion of too early surveillance was higher for patients with one or two adenomas compared with those with three or more adenomas (50% vs. 39%).

In *Chapter 7*, we performed an online survey presenting gastroenterologists 15 cases of patients with polyps to evaluate the acceptance and interpretation of the new guideline for colonoscopy surveillance that was launched in 2013. The median compliance to the guideline (i.e. the proportion of physicians that correctly answered the cases) was 76% for the cases. Compliance ranged from 14% to 95% per case. Cases involving serrated polyps, elderly patients, or adenomas with tubulovillous histology were most often answered incorrectly. Gastroenterologists who consulted the guideline during the questionnaire answered more cases correctly than those who did not. Deviations from the guideline were mainly due to misinterpretation of the guideline (48%) or misreading of the cases (30%). For example, 92-95% of incorrect answers to cases on serrated polyps were based on the fact that these polyps were incorrectly scored the same as adenomas, taking into account location and number of lesions.

An important strength of this thesis is that the main results *(Chapters 3-6)* are based on the SAP-study, a large community-based observational study. However, an observational study also has its limitations. First, the study was initiated

before serrated polyps were widely recognized as an alternative pathway to colorectal cancer. Therefore, serrated polyps were not evaluated in this thesis. Second, adenoma characteristics may have been misclassified, because there were no uniform structured reporting systems for endoscopy and pathology. Third, variation in surveillance intervals between patients could have confounded our results. Finally, we lacked (sufficient) documentation on other potentially important risk factors for advanced neoplasia recurrence such as shape of the adenoma or method of adenoma removal. Notwithstanding these limitations, this study led to some important results.

Based on this thesis we have the following recommendations:

- The observed colonoscopy mortality and perforation rates can be used to inform individuals about the risks of colonoscopy and these rates can serve as benchmark for endoscopy units. *(Chapter 2)*
- The (inter-)national quality thresholds for perforation rates should be more stringent and should relate to procedure and patient characteristics. *(Chapter 2)*
- Independent adenoma related predictors of advanced colorectal neoplasia recurrence should be considered jointly in risk stratification of adenoma patients for surveillance. We recommend the use of a score chart based on adenoma number, size, villousness and location to tailor surveillance recommendations. *(Chapter 3, 4)*
- Surveillance colonoscopy intervals can be lengthened to 10 years for patients at low risk of advanced colorectal neoplasia recurrence. *(Chapter 5)*
- To support endorsement of (new) guidelines for surveillance of adenoma patients convincing evidence is needed, as well as a clear instruction to avoid misinterpretation. *(Chapter 6, 7)*
- To improve adherence to the current guideline for surveillance of adenoma patients, clarification is needed on the use of the score chart in case of serrated polyps (especially with respect to location and number of these lesions) and adenomas with tubulovillous histology. *(Chapter 7)*
- The use of a pocket-sized score chart, app or other source of the guideline when making surveillance recommendations should be encouraged to improve compliance to the guideline. *(Chapter 7)*

Based on the results of this thesis, the guideline for surveillance of adenoma patients was updated in 2013, including the score chart as suggested in *Chapter 4* and with recommended surveillance intervals based on the results from *Chapter 5*.

Samenvatting

Surveillance van adenoompatiënten – op weg naar efficiëntere richtlijnen

Darmkanker (DK) is de derde meest voorkomende kankersoort wereldwijd. In Nederland worden jaarlijks ongeveer 14.000 mensen met DK gediagnosticeerd en overlijden er bijna 5.000 mensen aan. De meeste darmkankers ontwikkelen zich vanuit goedaardige voorstadia (poliepen) tot kanker, in de meeste gevallen (65-95%) zijn deze voorstadia 'adenomen'. Adenomen kunnen variëren in vorm en grootte, komen verspreid over de dikke darm voor en kunnen er onder de microscoop verschillend uit zien. Van adenomen met een grootte van ≥10mm, hooggradige dysplasie en/of een villeus aspect wordt aangenomen dat zij een hoger risico hebben op het ontwikkelen van kanker. Deze worden daarom advanced adenomen genoemd. Patiënten bij wie een adenoom is gediagnosticeerd en verwijderd hebben mogelijk een verhoogd risico op het ontwikkelen van adenomen en DK. Hen wordt daarom geadviseerd periodiek terug te komen voor een controle coloscopie. In dit proefschrift staat met name deze periodieke controle oftewel surveillance van adenoompatiënten centraal.

Dit proefschrift bestaat uit drie delen. In deel I onderzochten we de literatuur om de kans op complicaties na coloscopie (darmperforatie en overlijden) te schatten. In deel II onderzochten we voorspellende factoren voor het detecteren van advanced neoplasie (advanced adenomen en kanker) bij surveillance coloscopie. Verder bepaalden we hoe deze factoren gebruikt kunnen worden om de surveillance van adenoompatiënten te verbeteren. Tot slot evalueerden we in deel III in hoeverre de richtlijnen voor surveillance van adenoompatiënten worden opgevolgd.

Deel I: Complicaties na coloscopie

In *hoofdstuk 2* hebben we de medische literatuur systematisch onderzocht op grote studies die perforaties en overlijden na coloscopie hebben gerapporteerd. Met behulp van meta-analyse hebben we de kans op overlijden na een coloscopie geschat op 0,1 per 10.000 coloscopieën en de kans op een perforatie op 5,7 per 10.000 coloscopieën. De kans op een perforatie is in de loop van de jaren afgenomen en was afhankelijk van het type coloscopie. Bij primaire screening coloscopieën was de perforatiekans 1.8 per 10.000, bij follow-up coloscopie na een positieve niet-invasieve screentest is de kans 8 per 10.000 coloscopieën en bij therapeutische en diagnostische coloscopieën respectievelijk 10 en 3 per 10.000. Hiermee is de kans op een perforatie bij coloscopie en bij primaire screening coloscopie beduidend lager dan de maximaal toegestane

drempelwaarde in kwaliteitsrichtlijnen van de Amerikaanse en Europese maag-darm-lever verenigingen (respectievelijk, 20 en 10 per 10.000 coloscopieën).

Deel II: Voorspellers voor ontwikkeling van (advanced) neoplasie en efficiëntere surveillance van adenoompatiënten

In *hoofdstuk 3* hebben we bekeken welke kenmerken van invloed zijn op het detecteren van advanced neoplasie bij surveillance-coloscopie. Dit hebben we onderzocht in onze studie 'Surveillance After Polypectomy' (SAP), waarin we gegevens van bijna 3.000 adenoompatiënten met surveillance coloscopie(ën) verzamelden in 10 ziekenhuizen in Nederland. We hebben laten zien dat het aantal adenomen, adenoom grootte (≥10 mm), villeus aspect, en proximale locatie van het adenoom bij index coloscopie belangrijke onafhankelijke voorspellers waren voor advanced neoplasie, naast onvoldoende darmvoorbereiding en onvolledig bereik van de coloscoop in de darm. Het hebben van meerdere van deze kenmerken tegelijkertijd doet het risico van de patiënt verder toenemen. Hooggradige dysplasie was geen onafhankelijke voorspeller.

Op basis van de vier adenoomkenmerken, die voorspellend waren voor advanced neoplasie bij surveillance-coloscopie, hebben we een adenoomrisicoscorekaart ontwikkeld in *hoofdstuk 4*. In de scorekaart wordt 1 punt toegekend aan de aanwezigheid van een groot adenoom (≥10mm), een proximaal adenoom, een villeus adenoom en het hebben van 2-4 adenomen, en 2 punten indien er 5 of meer adenomen aanwezig zijn. Middels deze scorekaart kunnen patiënten in 6 risicogroepen worden ingedeeld, met een score variërend van 0-5. De scorekaart kan worden gebruikt ter verbetering van de risicostratificatie van adenoompatiënten voor surveillance. Naast de adenoomkenmerken waren ook hogere leeftijd en mannelijk geslacht voorspellers voor advanced neoplasie. Volgens ons predictie model gebaseerd op de onderzochte groep adenoompatiënten in de SAP-studie varieerde het 5-jaars risico op een advanced neoplasie van 2,5% voor 55-jarige vrouwen met adenoomscore 0 tot 46% voor 75-jarige mannen met adenoomscore 5.

In *hoofdstuk 5* hebben we een kosteneffectiviteitsanalyse uitgevoerd om optimale strategieën te bepalen voor surveillance naar geslacht, leeftijd en adenoom-risicoscore zoals bepaald in *hoofdstuk 4*. Deze analyse laat zien dat het optimale surveillance-interval voornamelijk afhankelijk is van de adenoom-risicoscore, en in mindere mate van leeftijd en geslacht. Surveillance-coloscopie kan worden aangeboden na 2-3 jaar voor patiënten met hoge adenoom-risicoscores (4-5), na 4-7 jaar voor de tussenscores (1-3), en na 10 jaar voor patiënten met een lage risicoscore (0). Surveillance-coloscopie wordt niet meer aanbe-

volen voor patiënten van 70 jaar en ouder met een adenoom-risicoscore 0, voor patiënten van 75 jaar of ouder met risicoscore 1 en mannen met risicoscore 2, en voor hoog-risico patiënten van 80 jaar of ouder.

Deel III: Opvolging en acceptatie van richtlijnen voor surveillance van adenoompatiënten

In dit deel hebben we de navolging van de richtlijnen voor surveillance van adenoompatiënten in Nederland onderzocht. Op basis van de SAP-studie, laat *hoofdstuk 6* zien dat opvolging van de Nederlandse richtlijnen voor surveillance-coloscopie in het verleden ontoereikend was in 76-89% van de gevallen. Voor 2002 ontving maar 24% van de patiënten het correcte surveillance-interval. Na verandering van de richtlijn in 2002 was dit zelfs nog maar 11%. Het percentage correcte surveillance-intervallen was iets hoger voor patiënten met 3 of meer adenomen dan voor patiënten met 1-2 adenomen (26% vs. 21%). Aan het eind van de door ons onderzochte periode ontving een derde van de adenoompatiënten in het geheel geen surveillance-coloscopie. De afwezigheid van surveillance in zo'n groot deel van de patiënten is verontrustend aangezien we in 8% van de patiënten met verlate surveillance-coloscopie advanced neoplasie vonden (waarvan 1 op de 5 een kanker was), en zelfs in 17% in de groep patiënten met 3 of meer adenomen. Voor 2002, toen de richtlijn een korter interval adviseerde, was surveillance-coloscopie vooral te laat of afwezig (totaal 57%). In 2002, toen de richtlijn langere intervallen adviseerde, was surveillance-coloscopie bij 48% van de adenoompatiënten te vroeg. Het aandeel te vroege surveillance was groter bij patiënten met 1-2 adenomen vergeleken met patiënten met 3 of meer adenomen (50% vs. 39%).

In *hoofdstuk 7* hebben we MDL-artsen een online vragenlijst met 15 casussen van patiënten met poliepen voorgelegd om acceptatie en interpretatie van de in 2013 nieuw voorgestelde richtlijn voor surveillance-coloscopie te evalueren. De mediane opvolging van de richtlijn (d.w.z. het percentage artsen dat de casus goed beantwoordde) voor de casussen was 76%. Per casus varieerde de opvolging van 14-95%. Casussen over geserreerde poliepen, oudere patiënten, en adenomen met een tubulovilleus aspect werden het vaakst incorrect beantwoord. Artsen die de richtlijn raadpleegden gedurende de vragenlijst beantwoordden gemiddeld een hoger aantal casussen goed dan zij die dat niet deden. Het incorrect antwoorden op de casussen kwam met name door misinterpretatie van de richtlijn (48%) of onvoldoende lezen van de casus (30%). In het voorbeeld van geserreerde poliepen, zouden 92-95% van de incorrect beantwoordde casussen goed zijn geweest als geserreerde poliepen op

dezelfde manier werden gescoord als adenomen, met inachtneming van locatie en aantal laesies.

Een sterk punt van dit proefschrift is dat de resultaten grotendeels *(hoofdstukken 3-6)* gebaseerd zijn op de SAP-studie, een grote observationele studie. Echter, een observationele studie heeft ook zijn beperkingen. In de eerste plaats, is de studie uitgevoerd voordat erkend werd dat geserreerde poliepen ook tot kanker kunnen ontwikkelen. Geserreerde poliepen zijn daarom in dit proefschrift niet onderzocht. Ten tweede kan er sprake zijn van misclassificatie van adenoomkenmerken, aangezien er geen uniforme gestructureerde registratiesystemen waren voor endoscopische en pathologische verslaglegging. Ten derde kan de variatie in surveillance-intervallen tussen patiënten hebben geleid tot verstoring van de resultaten. Tot slot, ontbrak (toereikende) informatie over andere mogelijke risicofactoren voor advanced neoplasie, zoals de vorm van het adenoom en de wijze waarop deze verwijderd was. Ondanks deze beperkingen, heeft deze studie een aantal belangrijke antwoorden opgeleverd.

Op basis van dit proefschrift doen wij de volgende aanbevelingen:

- De geobserveerde mortaliteits- en perforatieschattingen zouden gebruikt kunnen worden om personen te informeren over de risico's van de coloscopie en kunnen dienen als benchmark voor endoscopieafdelingen *(Hoofdstuk 2)*.
- De gehanteerde drempelwaarden in (inter-)nationale kwaliteitsrichtlijnen ten aanzien van de kans op perforaties na coloscopie kunnen stingenter en zouden onderscheid moeten maken naar procedure- en patiëntkenmerken. *(Hoofdstuk 2)*.
- Onafhankelijke adenoom-gerelateerde voorspellers voor toekomstige detectie van advanced neoplasie zouden gezamenlijk moeten worden meegenomen bij de risico-stratificatie van adenoompatiënten voor surveillance. Wij raden aan om een scorekaart te gebruiken gebaseerd op aantal, grootte, villeus aspect en locatie van de adenomen voor het personaliseren van aanbevelingen voor surveillance *(Hoofdstuk 3, 4)*.
- Intervallen voor surveillance-coloscopie voor patiënten met laag risico op het ontwikkelen van advanced neoplasie kunnen worden verlengd naar 10 jaar *(Hoofdstuk 5)*.
- Om de opvolging te bevorderen, is het belangrijk dat (nieuwe) richtlijnen zijn gebaseerd op overtuigend bewijs, en dat er een duidelijke instructie van de richtlijn is ter voorkoming van misinterpretatie *(Hoofdstuk 6, 7)*.
- Om de opvolging van de huidige richtlijn voor surveillance van adenoompatiënten te bevorderen moet het scoren van geserreerde poliepen (met

name met betrekking tot de locatie en het aantal van deze laesies) en tubulovilleuze adenomen beter toegelicht worden *(Hoofdstuk 7)*.
- Het raadplegen van de richtlijn door middel van een zakkaartje, App of een andere bron bij het bepalen van het surveillance-interval moet aangemoedigd worden, om zo naleving van de richtlijn te vergroten *(Hoofdstuk 7)*.

Op basis van de resultaten in dit proefschrift, is in 2013 de Nederlandse richtlijn voor surveillance van adenoompatiënten aangepast, inclusief de scorekaart voor adenoomkenmerken zoals ontwikkeld in *hoofdstuk 4* en met aanbevolen surveillance-intervallen mede gebaseerd op uitkomsten van *hoofdstuk 5*.

Dankwoord

Wat een rijkdom heb ik mogen ervaren aan begeleiding en support tijdens mijn promotietraject, echt fantastisch!! Ik kan terugkijken op een mooie tijd! En dat heb ik aan velen te danken. Dit proefschrift is mede tot stand gekomen door de inzet en steun van velen. Het is mij dan ook een groot genoegen een aantal personen hiervoor te bedanken.

In de eerste plaats wil ik mijn twee promotoren *(prof. dr. H. J. de Koning en prof. dr. E.J. Kuipers)* en co-promotor *(dr. I. Lansdorp- Vogelaar)* bedanken voor het vertrouwen, de ruimte die mij gegeven werd en de prettige samenwerking.

Beste *Harry*, ook al zagen wij elkaar wat minder frequent en was je wat betreft de inhoudelijke kant van de papers misschien iets minder direct betrokken dan de overige leden, ik heb de begeleidingsgesprekken en samenwerking altijd als zinvol en prettig ervaren. Ik vind je een fijn en relaxed persoon. Veel dank voor jouw kritische blik op een aantal essentiële onderdelen van dit proefschrift. Beste *Ernst*, veel dank voor jouw altijd snelle, enthousiaste en positieve commentaar. Daaraan heb ik veel gehad en dat werkte motiverend. Je positieve benadering, support, open houding en toegankelijkheid heb ik enorm gewaardeerd. Daarnaast straal je rust uit en ben je down to earth. Ik denk dat je voor velen een voorbeeld bent, zeker voor mij! Ik ben daarom ook blij dat jij mijn 2e promotor bent! En ik vind het super dat je daar nu nog tijd voor vrij maakt. Dank!! Beste *Iris*, de meeste begeleiding heb ik aan jou te danken, heel veel dank! Ik kon altijd bij je terecht en heb veel van je kunnen leren. Na jouw review stegen mijn papers gelijk in 'waarde'! Ik heb veel respect voor je, ik vind het knap hoe je alle ballen in de lucht weet te houden, scherp blijft en altijd ontspannen overkomt.

Ook wil ik *prof.dr.ir. J.D.F. Habbema* bedanken voor het vertrouwen en de support met name in de beginfase van mijn promotietraject. Daarnaast hebben *prof.dr. E.W. Steyerberg* en *dr. M. van Ballegooijen* een enorm waardevolle bijdrage geleverd aan zowel de inhoud van dit boekje als aan persoonlijke begeleiding! Beste *Ewout*, heel veel dank voor jouw altijd snelle en enthousiaste commentaar en de tijd die hebt gestoken in de begeleiding. Ik vond onze discussies altijd heel interessant en leerzaam en ik kon altijd direct weer verder, super fijn! De samenwerking heeft geleid tot een aantal belangrijke papers, welke een relevante bijdrage hebben geleverd aan de vernieuwde Nederlandse richtlijn voor surveillance coloscopie. Beste *Marjolein*, je was mijn officiële leidinggevende, bedankt voor het vertrouwen, de persoonlijke begeleiding en je

kritische blik op mijn papers. Discussies leidden vaak tot stof om over na te denken. Dank daarvoor.

Leden van de kleine commissie, *prof.dr. J.A. Hazelzet, prof.dr. A.A.M. Masclee* en *prof.dr. I.D. Nagtegaal*, ik wil jullie bedanken voor de bereidwilligheid dit proefschrift te beoordelen.

Leden van de grote commissie bedankt voor jullie tijd en bereidwilligheid om jullie te verdiepen in hetgeen ik heb onderzocht. Ik kijk ernaar uit om met jullie van gedachten te wisselen tijdens mijn verdediging.

Dank aan alle *co–auteurs* voor de zeer waardevolle input waardoor de kwaliteit van de papers enorm is verbeterd!

Een groot deel van de papers in dit proefschrift zijn gebaseerd op de SAP-studie, een studie die niet kon worden uitgevoerd zonder de inzet van vele partijen. *Mariel Caspari* van de Stichting PALGA, hartelijk dank voor het selecteren van nieuw gediagnostiseerde adenoompatiënten in de aan de SAP-studie deelnemende centra. Heel veel dank aan het personeel van de MDL- *en pathologie afdelingen* van deelnemende centra (Reinier de Graaf Group; Isala Klinieken; Albert Schweitzer Ziekenhuis; Deventer Ziekenhuis; AMC; Medisch Centrum Leeuwarden; UMCG; Orbis Medisch en Zorgconcern; St. Antonius ziekenhuis en het Erasmus MC), met name aan de MDL-artsen *Clemens Bolwerk, Frank ter Borg, Evelien Dekker, Leopold Engels, Jan Kleibeuker, Jan Jacob Koornstra, Wilco Lesterhuis, Pieter Spoelstra, Robin Timmer en Juda Vecht*, zonder het beschikbaar stellen van de data, zou er niks te analyseren zijn… Daarnaast hartelijk dank voor de gastvrijheid, het beschikbaar stellen van werkplekken en de verdere support! Echt top! Mede door jullie inzet liep alles op rolletjes.

Omdat gegevens destijds nog niet gestructureerd werden vastgelegd was er veel werk aan het overnemen van de gegevens van de adenoompatiënten in onze SAP-database, vele handen hebben daaraan bijgedragen: *Anke Enneman, Janine de Zeeuw, Isabel Siemelink, Irene van Sloten, Simone van Kessel, Emma Steenbergen en Judith van den Broek*, heel veel dank! Na ca. 1,5 jaar data verzamelen bereikten we de inclusie van de beoogde 3.000 adenoompatiënten met follow-up gegevens. *Frank Santegoeds*, dank voor alle energie die je gestoken hebt in het ontwikkelen van de SAP-database en je hulp bij data management. *Katharina Biermann*, hartelijk dank voor het beantwoorden van de vragen op gebied van pathologie wanneer we tijdens de dataverzameling onduidelijkheden tegenkwamen in de verslaglegging. Ook *Monique van Leer-*

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De collega's van de MDL-afdeling van het Erasmus MC, *Aafke, Margot, Celine, Vincent, Jerome, Renate, Paul, Paul, Arjun, Lieke, Vera, Lauran, Aria, Esther, Florine, Eline, Femme, Edmee, Nicoline, Veerle, Jorie, Marius, Lisanne, Judith, Vivian, Caroline, Leonie en Atija* wil ik bedanken voor de gastvrijheid en gezelligheid op de afdeling, tijdens lunches, de NVGE congressen in Veldhoven en tijdens de DDW in New Orleans en Chicago! Ik heb ervan genoten! In het bijzonder bedank ik *Aafke en Margot* voor de introductie op de afdeling. *Wendy Holleman* wil ik graag bedanken voor de hulp en ondersteuning.

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Al met al heb je dan na veel inspanning en steun van collega's de inhoud van het boekje voor elkaar gekregen, maar dan ben je er nog niet... *Bert Hoogeveen*, ik ben jou heel dankbaar dat jij, onder enige tijdsdruk, het ontwerp van de omslag en de opmaak van dit proefschrift hebt willen verzorgen! Ik ben heel blij met het resultaat!!

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Tot slot, *mijn ouders*, *Anja en Theo* jullie hebben mij altijd de ruimte gegeven mijn eigen keuzes te maken en hebben altijd volledig achter mij gestaan. Ook tijdens moeilijke tijden, kon ik altijd op jullie terugvallen. Bedankt voor jullie onvoorwaardelijke vertrouwen en steun. Dat geldt natuurlijk ook voor mijn super lieve *broertje, Erik-Jan*!! Ik hou van jullie!!!

Feeling blessed and thankfull. Let's move on to the next chapter...

Else-Mariëtte

Curriculum vitae

Else-Mariëtte Beatrice van Heijningen werd geboren op 24 september 1982 te Leiden. In 2001 behaalde zij haar VWO diploma aan het Adelbert College te Wassenaar. Na het behalen van haar HBO-opleiding 'Voeding en Diëtetiek' aan de Haagse Hogeschool, studeerde zij 'Nutrition and Health' aan de Wageningen Universiteit, met als specialisatie 'Public Health and Nutritional Epidemiology'. Haar stages op gebied van Voeding en Diëtetiek liep zij in het Rijnlands Revalidatie Centrum te Leiden en in het Academisch Medisch Centrum te Amsterdam. Haar afstudeerproject, een wetenschappelijke pilotstudie naar de absorptiecapaciteit van de darm: 'Fecaal energie- en vetverlies bij volwassen IC-patiënten met dunne ontlasting: Is er een probleem?', voerde ze uit in het VUmc te Amsterdam, waarvoor zij in 2006 de Novartis Diëtetiek prijs ontving. Wetenschappelijke stages werden verricht aan de Medical Research Council - Human Nutrition Research, Departement of Public Health Nutrition, Cambridge, Verenigd Koninkrijk en aan Queensland Institute for Medical Research, Brisbane, Australië. Tijdens deze stages verrichtte zij onderzoek naar de invloed van voedingsmiddelen en dranken die toegevoegde, niet van melk afkomstige, suikers bevatten op energie- en nutriënt inname en adipositas bij Britse volwassenen en naar vitamine D inname en huidkanker bij een Australische gemeenschap. Haar afstudeerscriptie aan de Wageningen Universiteit ging over visconsumptie en serum meervoudig onverzadigde vetzuren en het risico op colorectale adenomen.

In juli 2008 startte zij als epidemioloog haar promotieonderzoek op het gebied van doelmatigheid betreffende surveillance van adenoompatiënten (ZonMw-project 'Surveillance after polypectomy – towards efficient guidelines', No. 170882801), onder leiding van Marjolein van Ballegooijen en promotoren Prof. dr. H.J. Koning en Prof. dr. E.J. Kuipers, en co-promotor Iris Lansdorp-Vogelaar. Voor deze studie werd data verzameld in 10 Nederlandse ziekenhuizen: Albert Schweitzer Ziekenhuis, AMC, Deventer Ziekenhuis, Erasmus MC, Isala Klinieken, Medisch Centrum Leeuwarden, Orbis Medisch en Zorgconcern, Reinier de Graaf Groep, St. Antonius Ziekenhuis en het UMCG. In november 2011 haalde zij subsidie binnen voor een vervolgstudie (ZonMw-project 'Surveillance after polypectomy - towards successful implementation of guidelines (SAP-Adh)', No. 171203009).

Sinds voorjaar 2014 is zij werkzaam als data-analist bij Facilitaire Samenwerking Bevolkingsonderzoeken te Utrecht.

List of Publications

1. ***Van Heijningen EMB***, Kooyker A, Massl R, Nieboer D, Meester R, de Koning HJ, Kuipers EJ, Lansdorp-Vogelaar I. Perforation and mortality rates of colonoscopy – systematic review and meta-analysis. *Submitted*.

2. Van der Meulen MP, Ida J. Korfage, ***van Heijningen EMB***, de Koning HJ, van Leerdam ME, Dekker E, Lansdorp-Vogelaar I, on behalf of the working group on the guideline for colonoscopy surveillance. Interpretation and compliance to the updated risk-stratified guideline for colonoscopy surveillance after polypectomy - a nationwide survey. *Submitted*.

3. ***Van Heijningen EMB****, van Hees F*, Steyerberg EW, Kuipers EJ, de Koning HJ, van Ballegooijen M, Lansdorp-Vogelaar I. Personalizing colonoscopy surveillance in adenoma patients - A cost-effectiveness analysis. *Submitted*.

4. ***Van Heijningen EM***, Lansdorp-Vogelaar I, van Hees F, Kuipers EJ, Biermann K, de Koning HJ, van Ballegooijen M, Steyerberg EW; SAP Study Group. Developing a score chart to improve risk stratification of patients with colorectal adenoma. *Endoscopy. 2016 Jun;48(6):563-570*.

5. Van der Meulen MP, Lansdorp-Vogelaar I, ***van Heijningen EM***, Kuipers EJ, van Ballegooijen M. Nonbleeding adenomas: Evidence of systematic false-negative fecal immunochemical test results and their implications for screening effectiveness-A modeling study. *Cancer. 2016 Jun 1;122(11):1680-1688*.

6. ***Van Heijningen EM***, Lansdorp-Vogelaar I, Steyerberg EW, Goede SL, Dekker E, Lesterhuis W, ter Borg F, Vecht J, Spoelstra P, Engels L, Bolwerk CJ, Timmer R, Kleibeuker JH, Koornstra JJ, de Koning HJ, Kuipers EJ, van Ballegooijen M. Adherence to surveillance guidelines after removal of colorectal adenomas: a large, community-based study. *Gut. 2015 Oct;64(10):1584-1592*.

7. Kroep S, Lansdorp-Vogelaar I, Rubenstein JH, Lemmens VE, ***van Heijningen EB***, Aragonés N, van Ballegooijen M, Inadomi JM. Comparing trends in esophageal adenocarcinoma incidence and lifestyle factors between the United States, Spain, and the Netherlands. *Am J Gastroenterol. 2014 Mar;109(3):336-343*.

8. ***van Heijningen EM***, Lansdorp-Vogelaar I, Kuipers EJ, Dekker E, Lesterhuis W, Ter Borg F, Vecht J, De Jonge V, Spoelstra P, Engels L, Bolwerk CJ, Timmer R, Kleibeuker JH, Koornstra JJ, van Ballegooijen M, Steyerberg EW. Features of adenoma and colonoscopy associated with recurrent colorectal neoplasia based on a large community-based study. *Gastroenterology. 2013 Jun;144(7):1410-1418.*

9. Pot GK, Geelen A, ***van Heijningen EM***, Siezen CL, van Kranen HJ, Kampman E. Opposing associations of serum n-3 and n-6 polyunsaturated fatty acids with colorectal adenoma risk: an endoscopy-based case-control study. *Int J Cancer. 2008 Oct 15;123(8):1974-1977.*

10. Strack van Schijndel RJ, Wierdsma NJ, ***van Heijningen EM***, Weijs PJ, de Groot SD, Girbes AR. Fecal energy losses in enterally fed intensive care patients: an explorative study using bomb calorimetry. *Clin Nutr. 2006 Oct;25(5):758-764.*

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Supervisors:	Dr. I. Lansdorp-Vogelaar

1. PhD training

	Year	Workload Hrs/ECTS
General academic skills		
Biomedical English Writing and Communication, Erasmus MC, Rotterdam	2010	4 ECTS
Schrijfgroep Maatschappelijke Gezondheidszorg (MGZ), Erasmus MC, Rotterdam	2010, 2011	80 hrs
CPO Minicursus Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen, Erasmus MC, Rotterdam	2010	8 hrs
In-depth courses		
Absolute risk prediction, NKI, Amsterdam	2012	8 hrs
Health Economics (ESP25)	2010	0.7 ECTS
Clinical Decision Analysis (ESP04)	2010	0.7 ECTS
Large-scale and multicenter studies (ESP58)	2009	0.3 ECTS
Cohort studies (ESP39)	2009	0.9 ECTS
Survival Analysis (ESP28)	2009	1.4 ECTS
Topics in Meta-analysis (ESP15)	2009	0.9 ECTS
Planning and Evaluation of Screening (HS05)	2009	1.4 ECTS
Advanced Analysis of Prognosis Studies (EWP13)	2009	0.9 ECTS
Prognosis Research (EWP16)	2009	0.9 ECTS
Oral presentations		
Coloscopie surveillance (NVGE)	2013	20 hrs
Metachronous colorectal neoplasia after adenoma removal. A multivariate analysis of risk factors for non-advanced and advanced neoplasia (NVGE)	2012	20 hrs
Risk factors for metachronous advanced colorectal neoplasia in a cohort of adenoma patients: advanced morphology and multiplicity (DDW, NVGE)	2011	30 hrs
Post-polypectomy surveillance practice of adenoma patients – considerable room for improvement (DDW, NVGE, MGZ)	2010	50 hrs
SAP studie opzet (MGZ)	2008	20 hrs
Poster presentations		
Updating/Personalized post-polypectomy surveillance guidelines incorporating patient and adenoma-related predictors of advanced colorectal neoplasia: A cost-effectiveness analysis (UEGW, DDW)	2012, 2013	30 hrs
Metachronous colorectal neoplasia after adenoma removal. A multivariate analysis of risk factors for non-advanced and advanced neoplasia (DDW)	2011	20 hrs
Perforation and mortality of colonoscopy – a systematic review (DDW)	2010	20 hrs

1. PhD training

	Year	Workload Hrs/ECTS
(International) conferences		
World Endoscopy Organisation (WEO) - Colorectal Cancer Screening Committee, Vienna, Austria	2016, 2018	18 hrs
Voorjaarscongressen - Nederlandse Vereniging voor Gastroenterologie (NVGE), Veldhoven	2011 - 2013	48 hrs
CvB congres Bevolkingsonderzoeken naar kanker, Utrecht	2017	8 hrs
CvB-café, Amersfoort	2014	8 hrs
Nationaal Congres Bevolkingsonderzoek Darmkanker 'De wind in de zeilen: op naar de start!', Utrecht.	2013	8 hrs
Nationaal Symposium 'De invoering van colonscreening; wat betekent dit voor ons in de praktijk? – een scherpe blik vooruit', Zeist	2012	8 hrs
Nationaal symposium 'Colorectaal carcinoom en de toegevoegde waarde van colonscreening', Oegstgeest	2011	8 hrs
20th United European Gastroenterology Week (UEGW), Amsterdam	2012	32 hrs
Symposium 'Successen van preventie', Rotterdam	2011	4 hrs
Digestive Disease Week (DDW), New Orleans, LA & Chicago, IL, USA	2010, 2011	56 hrs
NvVO 68ste Oncologiedag 'Colorectale Kanker', Utrecht	2010	8 hrs
CISNET Mid-Year meeting, Rotterdam	2009	8 hrs
Patient Oriented research (CPO) Symposium: Cost-Effective Interventions in Health Care: From Evaluation to Application, Erasmus MC, Rotterdam	2009	4 hrs
7e & 8e Erasmus MC Endoscopy Day, Rotterdam	2008 - 2009	16 hrs
Seminars and workshops		
MGZ seminars and journal clubs, Erasmus MC, Rotterdam	2008 - 2013	2 ECTS
Basiscursus MS Access database, Erasmus MC, Rotterdam	2008	8 hrs
Other		
Reviewer for international scientific journals	2014, 2015	40 hrs
Cursus Loopbaanoriëntatie voor wetenschappers, Erasmus MC, Rotterdam	2012	1 ECTS
Honoured grand application 'Surveillance after polypectomy - towards successful implementation of guidelines (SAP-Adh)', No. 171203009 (ZonMw)	2010 - 2011	120 hrs
Projectidee 'Efficient surveillance after polypectomy – Incorporating biomarkers (SAP-bm)', Preventieprogramma, Deelprogramma 3 'Screening en preventieve interventies' (ZonMw)	2010	48 hrs
ZonMw eindverslag en voortgangsverslagen SAP-project	2009 - 2012	72 hrs
PhD days, Erasmus MC, Rotterdam	2011 - 2013	18 hrs

2. Teaching activities

	Year	Workload Hrs/ECTS
Supervising practicals and excursions		
Community project, supervising medical students as part of educational theme 3.C 'Arts en volksgezondheid', Erasmus MC, Rotterdam	2012	20 hrs
Other		
Supervision 7 research assistants (SAP data collection)	2008 - 2010	140 hrs