OPTIMIZING COLONOSCOPY OUTCOMES IN DAILY CLINICAL PRACTICE

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OPTIMIZING COLONOSCOPY OUTCOMES IN DAILY CLINICAL PRACTICE

Optimalisatie van colonoscopie-uitkomsten in de dagelijkse praktijk

(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER 1

General introduction and thesis outline

Colonoscopy has been the procedure of choice for the evaluation of the colon for many years. With the introduction of the first fiberoptic colonoscopes in the late 1960s,[1, 2] physicians gained the opportunity to visualize the entire colonic mucosa. This also enabled the removal of polyps and adenomas from the proximal colon, beyond the reach of the (rigid) proctosigmoidoscope, which was widely used until then.[3] A historical timeline on the relevant advancements in colonoscopy is depicted in Figure 1. In 1979, Shinya and Wolff reported their experience of removing 7,000 polyps during colonoscopy, giving insight into the morphology and distribution of adenomas and collecting further evidence for the adenoma-carcinoma sequence. They recommended a vigorous program for the detection and removal of colonic polyps in an effort to potentially reduce the incidence of colorectal cancer (CRC),[4] a strategy that is still being used. In their landmark study from 1993, Winawer et al. reported on the results of the National Polyp Study, showing that colonoscopy with removal of adenomatous polyps indeed reduced the

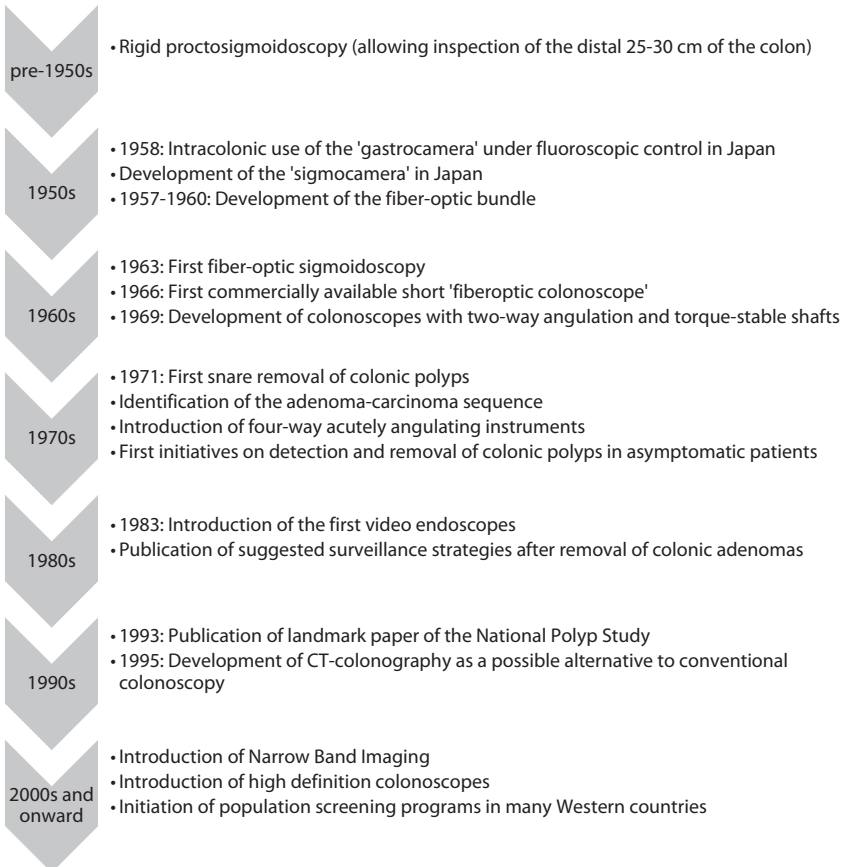

Figure 1. Historical timeline of the advancements in colonoscopy

incidence of subsequent CRC, when compared to the expected CRC incidence in three reference groups.[5]

Around that same time, surveillance strategies for patients in whom one or more adenomas were removed during colonoscopy were formulated in many countries.[6, 7] In the Netherlands, the first consensus guideline was published in 1988,[8] which was amended in 1998 when more data became available.[9] In 2002, a completely new guideline was issued.[10] In the latter, surveillance intervals of 3 or 6 years were advised based on the number of removed adenomas only, irrespective of their size, location and histopathological features. The most recent national guideline is from 2013 and advises a surveillance interval of 3 or 5 years based on a weighted risk score, which incorporates all of the above features [Table 1].[11]

Currently, several Western countries have initiated population screening programs for CRC,[12, 13] either through selection of individuals for colonoscopy with fecal occult blood testing (FOBT) or by offering colonoscopy to average-risk individuals. In the Netherlands, population screening with an immunological FOBT (iFOBT) was initiated in 2014. In the next few years, the program will gradually be introduced, culminating in 2020, when 4.4 million individuals between 55 and 75 years will be invited biennially to perform iFOBT. Based on data from pilot studies in the Nijmegen, Amsterdam and Rotterdam regions,[14, 15] it is estimated that this will result in 72,000 colonoscopies per year performed for positive iFOBTs in the population screening program. Although in due time population screening will probably result in a decrease in colonoscopies performed for symptomatic CRCs, screening colonoscopies are now performed on top of the colonoscopies that are already performed in daily clinical practice for symptoms, inflammatory bowel disease or surveillance after CRC or removal of adenomatous polyps.

At the end of 2014, there are almost 425 practicing gastroenterologists in the Netherlands.[16] Although the number of gastroenterologists in training is allowed to increase modestly by the regulating governmental institution, the implementation of the population screening program for CRC will have substantial impact on colonoscopy capacity. Even before the implementation of the screening program, a steep 64% increase in the number of performed colonoscopies in the Netherlands has been reported between 2004 and 2009, although the number of endoscopists did only increase with 4.6%.[17] Van Turenhout et al. calculated that five years after implementation of an iFOBT-based population screening program, endoscopy capacity needs to be increased with 15%.[17] In 2009 it was reported that up to 11% of colonoscopies in the Netherlands was performed by internists and surgeons.[18] However, new generation internists or surgeons are now no longer trained to perform endoscopy, while the generation internists and surgeons that currently performs endoscopy is rapidly aging. Meanwhile, just like in many parts of the world, the incidence of CRC in the Netherlands is steadily rising.[19, 20]

Table 1. The Dutch consensus guidelines on surveillance after colonoscopic polypectomy

Guideline	1988[8]	1998[9]	2002[10]	2013[11]
Numeric criteria	one vs. more adenomas removed	one vs. more adenomas removed	1-2 adenomas vs. ≥3 adenomas	0-1 adenoma (0 points) vs. 2-4 adenomas (1 point) vs. ≥5 adenomas (2 points)
Histological criteria	None	None	None	≥1 villous adenoma (1 point)
Other criteria	None	None	None	≥1 proximal adenoma (1 point) ≥1 adenoma of serrated polyp with size ≥1 cm (1 point)
Recommended surveillance interval	Confirm removal of all polyps <1 year after indexprocedure If indeed confirmed: Repeat after 5 years in case of 1 adenoma Repeat after 3 years in case of more than one adenoma during indexcolonoscopy No difference between index or follow-up colonoscopies	Surveillance colonoscopy after 1 year no longer necessary, instead confirm removal of all polyps 2-3 year after index procedure Surveillance after confirmation like in the 1988 guideline No difference between index or follow-up colonoscopies	Repeat after 6 years in case of 1-2 adenomas Repeat after 3 years in case of ≥3 adenomas No difference between index or follow-up colonoscopies	Score during index colonoscopy: 0 points: no surveillance, return to population screening program in 10 years 1-2 points: repeat in 5 years 3-5 points: repeat in 3 years Score during follow-up colonoscopy: 0-2 points: repeat in 5 years 3-5 points: repeat in 3 years
Stop criteria	None	None	Patients >65 years with cumulative one adenoma Patients >75 years with cumulative two adenomas	Stop at 75 years (unless wish and vitality of patient justify otherwise) Stop after 2 negative surveillance colonoscopies when patient never had a high risk adenoma (score ≥3). Return to population screening program in 10 years

To adequately handle this increasing number of colonoscopies, it is of utmost importance that patients referred for colonoscopy are adequately triaged. Patients with a high risk of detecting relevant findings should have priority over patients with a very low risk of finding significant pathology. Both the American Society for Gastrointestinal Endoscopy and the European Panel of Appropriateness of Gastrointestinal Endoscopy have

formulated criteria for the appropriateness of indications for colonoscopy,[21, 22] although the sensitivity and specificity of the latter for CRC have been disputed.[23]

Notwithstanding the fact that colonoscopy is increasingly being performed, it is known to be an imperfect procedure. From back-to-back colonoscopy studies, it has been reported that up to 25% of polyps are missed during colonoscopy.[24, 25] Furthermore, the preventive effect of colonoscopy appears to be most prominent for distal CRCs, whereas its performance in preventing proximal CRCs appears less outspoken.[26, 27] Finally, up to 8% of CRCs occur within three years after a previous colonoscopy.[28-32] Recent studies show that these interval CRCs or 'post-colonoscopy CRCs' are most likely due to missed or incompletely resected lesions, rather than being completely new lesions.[33, 34] It is therefore essential that the colonoscopies performed are of the highest possible quality. Several endoscopy societies have issued guidelines on quality indicators for colonoscopy,[35-37] but the exact value of the separate indicators is not undisputed.

The main challenges in the coming years both lie in optimizing quality as well as increasing the quantity of colonoscopies. This means generating and maintaining sufficient colonoscopy capacity to adequately handle the increasing number of both asymptomatic screening subjects and regularly referred patients, while also improving quality of colonoscopies to further diminish the number of post-colonoscopy CRCs.

AIMS OF THIS THESIS

The general objectives of the studies described in this thesis are:

- the identification of ways to improve allocation of the right patient to the appropriate examination at the right time,
- the quantification of the quality of colonoscopy as measured by the occurrence of post-colonoscopy CRC and
- the evaluation of a new colonoscopic steering mechanism to potentially improve the quality of colonoscopy.

OUTLINE OF THIS THESIS

In most cases, the aim of performing colonoscopy is to detect or exclude significant pathology. The increasing demand on colonoscopy capacity in many countries has resulted in waiting lists to undergo the procedure.[38, 39] Symptomatic patients with an increased risk of having CRC should receive priority in undergoing colonoscopy in the light of the knowledge that the 5-year survival rate for early stage CRC is above 90%, while for more advanced stages this drops to less than 10%.[40] Adequately identifying

symptomatic patients with an increased risk of having CRC however remains difficult. In **Chapter 2** we investigate which patient-reported symptoms are associated with an increased likelyhood of detecting CRC during colonoscopy, which may help in prioritizing patients.

Critically appraising colonoscopy capacity also means critically evaluating the use of other endoscopic procedures. In the Dutch health care system, patients are initially seen by general practitioners, who can decide to refer them to a secondary care institution if necessary. In many institutions, general practitioners can refer patients directly for flexible sigmoidoscopy, but not for colonoscopy. This situation promotes a preferential referral pattern towards sigmoidoscopy. In a subset of patients, the findings during flexible sigmoidoscopy result in an indication for full colonoscopy. In **Chapter 3** we evaluate the proportion of patients referred for flexible sigmoidoscopy in which additional colonoscopy was performed, and identify which patients are more likely to undergo additional colonoscopy. Finally, we try to identify a subgroup of patients that are referred because of symptoms but with a low a priori risk of detecting significant findings during flexible sigmoidoscopy.

The American Society of Gastrointestinal Endoscopy was the first society to issue a guideline on quality indicators for colonoscopy in 2006.[35] Since then, several other endoscopy societies have followed.[36, 37] In **Chapter 4** we critically review the available literature on the established quality indicators bowel preparation, cecal intubation rate, withdrawal time, adenoma detection rate, patient comfort and sedation, and complication rate. We evaluate strengths and weaknesses of these quality indicators and identify in which areas additional research is desirable.

Consensus guidelines state that each endoscopist should be able to intubate the cecum in ≥90% of cases.[35, 36] However, the cecal intubation rate may vary between experienced endoscopists. This depends on the skills of the endoscopist, but it is also reported to depend on various other factors, including adequacy of bowel preparation, anatomic variants, fixed colon segment(s), obstructing lesions and pain.[41] In case of incomplete colonoscopy, the physician may choose to schedule a second colonoscopy by a skilled endoscopist with a known high cecal intubation rate, or it can be decided to visualize the remainder of the colon with an alternative modality. In recent years, computed tomography (CT) colonography has emerged as an alternative modality to visualize the colonic lumen, with reported good results for detecting polyps ≥5 mm.[42] It also has been suggested to be a promising screening modality for CRC.[43] In **Chapter 5** we evaluate the diagnostic yield of CT-colonography when routinely performed in patients after incomplete colonoscopy.

As mentioned above, up to 8% of CRCs occur within 3 years of a previous colonoscopy.[28-32] However, it is conceivable that this rate of missed or early CRCs after previous colonoscopy may have decreased over the years, due to increasing professional

awareness of the occurrence of these post-colonoscopy CRCs, increasing attention to quality indicators for colonoscopy and the overall advent of technically more advanced endoscopy equipment. Thus far, studies on the rate of missed or early CRCs have been performed on retrospective cohorts comprised of incident cases of missed or early CRCs from many years, making the evaluation of possible time trends in the rate of post-colonoscopy CRCs difficult if not impossible. In **Chapter 6** we assess the rate of missed or early CRC after a previous colonoscopy with polypectomy in a population-based setting and evaluate its development over a 10-year period. Furthermore, we aim to identify risk factors that are associated with missed or early CRC.

As much as 9-31% of post-colonoscopy CRCs are thought to be due to incompletely resected adenomas.[33, 44] It has been reported that a local recurrence after endoscopic mucosal resection of non-pedunculated colorectal lesions is not uncommon, especially after piecemeal resection of the lesion.[45] The data in the studies on post-colonoscopy CRCs after incomplete adenoma resection were either derived from prevalent CRC cases, used to retrospectively identify post-colonoscopy CRCs, or prospective cohorts of adenoma patients with small numbers of subsequent CRCs. **Chapter 7** focuses on determining the absolute risk of developing CRC after incomplete adenoma resection in a nationwide, population-based study and the identification of risk factors for these post-colonoscopy CRCs.

In **Chapter 8** we describe our first experiences with a new, potentially more intuitive way of controlling the colonoscope: robotic steering with automatic lumen centralization. The principal design of the steering mechanism of flexible endoscopes has not significantly changed in the past 50 years and colonoscopy in its current form is known to have a long learning curve.[46, 47] A radically new, more intuitive way of steering the colonoscope might shorten learning curves, thereby potentially increasing colonoscopy capacity, and improve overall quality of colonoscopy.

In **Chapter 9** the conclusions from this thesis are placed in perspective and recommendations for future research are given, and **Chapter 10** summarizes the results of this thesis.

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CHAPTER 2

Symptoms associated with finding colorectal cancer during colonoscopy

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ABSTRACT

Background

Patients with increased risk of having colorectal carcinoma (CRC) should have priority on the colonoscopy list.

Objective

To investigate whether presenting symptoms of patients referred for colonoscopy could help in identifying patients with increased CRC risk.

Methods

Between February 2007 and November 2010, random outpatients referred for colonoscopy were asked to fill out a questionnaire with regard to symptoms for which the colonoscopy was performed. Informed consent was obtained to review the colonoscopy and histology reports. Multivariate logistic regression was performed to identify predictors for CRC.

Results

In total, 1,458 (21%) patients returned the questionnaire, of whom 925 (63.4%) had undergone prior sigmoidoscopy or colonoscopy. CRC was detected in 41 patients (2.8%). Age over 50 years (adjusted odds ratio (aOR) 3.00 [95% CI 1.30-6.91]) and presenting symptoms rectal blood loss (aOR 4.62 [95% CI 2.31-9.22]) and a change in bowel habits (aOR 3.33 [95% CI 1.50-7.40]) were independently associated with an increased risk of finding CRC. Prior sigmoidoscopy or colonoscopy (aOR 0.24 [95% CI 0.12-0.49]) and fatigue as presenting symptom (aOR 0.22 [95% CI 0.09-0.56]) were associated with a decreased CRC risk. Weight loss, self-reported anemia and abdominal pain were not associated with CRC in this study.

Conclusions

Patients presenting with rectal blood loss, change in bowel habits and those over 50 years have an increased risk of finding CRC during colonoscopy. We recommend that these risk groups should be prioritized on the colonoscopy list over patients that have undergone a previous endoscopy or that are presenting with fatigue.

INTRODUCTION

In recent years, there has been a worldwide increasing demand on colonoscopy capacity resulting in long waiting lists.[1,2] This is at least partly due the increasing incidence of colorectal cancer (CRC).[3] Moreover, with the implementation of CRC screening programs in the Western world, the demand for colonoscopy has grown even more.[4,5] Finally, CRC screening programs also lead to an increasing number of patients undergoing surveillance colonoscopy.[4] Studies have suggested that waiting lists can be shortened by more strictly adhering to the surveillance guidelines after polypectomy.[6,7]

It is imperative that symptomatic patients with an increased risk of having CRC should have priority in undergoing colonoscopy. While early stage CRC has a 5-year survival rate greater than 90%, for more advanced malignancy this drops to less than 10%.[8] However, the correct identification of patients with an increased risk of having CRC based on symptoms remains difficult.

It is not completely clear which of the presenting symptoms most optimally predict the presence of CRC. Studies that have been performed are heterogeneous. This was also noted in recent systematic reviews on this topic.[9-13] Three systematic reviews focused on the diagnostic value of symptoms for CRC in primary care.[9-11] However, these data cannot be extrapolated to the patient population that is seen by hospital-based clinicians and endoscopists on an everyday basis. The remaining two reviews included studies from both primary and secondary care.[12,13]

In the present study, we prospectively investigated presenting symptoms in a random sample of outpatients in a secondary care setting that were referred for colonoscopy to determine which symptoms were most likely able to predict presence of CRC. This could help in prioritizing patients for colonoscopy in daily clinical practice.

METHODS

Study population

Between February 2007 and November 2010, we asked a random sample of consecutive outpatients aged 18 years or older that were referred for colonoscopy to fill out a questionnaire regarding the symptoms for which the procedure was indicated. All patients had been referred for colonoscopy by the outpatient clinics of the departments of Gastroenterology, Internal Medicine or Surgery of the University Medical Center (UMC) Utrecht.

The UMC Utrecht is a mixed secondary and tertiary care center located in the middle of the Netherlands. As such, it serves both as a regional and as a national referral center. The patients included in this study are from all parts of the country.

We excluded hospitalized patients, because in our clinical practice these patients usually undergo emergency colonoscopy, e.g., for acute gastrointestinal bleeding or suspected exacerbation of inflammatory bowel disease (IBD). As such, they do not appear on waiting list for outpatients and fall beyond the aim of this study.

Data collection

One of three nurses regularly occupying the reception desk of the endoscopy suite was instructed to hand out the questionnaire to all outpatients arriving for a colonoscopy, thus providing a random sample of all outpatients. The patients filled out the questionnaires in the waiting room prior to colonoscopy and returned them to the endoscopy nursing staff before the start of the colonoscopy.

Items on the questionnaire included patient's age, gender, whether or not the patient had undergone previous colonoscopy or flexible sigmoidoscopy (FS) and symptoms for which the colonoscopy was indicated. Scored symptoms included rectal blood loss, change in bowel habits, involuntary weight loss, abdominal pain, fatigue and whether to the patient's knowledge anemia had been diagnosed. More detailed information was inquired in case of rectal blood loss (fresh bleeding/mixed through the stools), change in bowel habits (increased/decreased frequency, increased/decreased consistency) and abdominal pain (diffuse or variable, lower or upper hemi-abdomen, left or right hemi-abdomen). We defined a positive response as a 'yes' response to one of the listed symptoms/complaints, while we considered the answers 'no' or 'do not know' negative responses.

All colonoscopies were performed by staff endoscopists or by endoscopists in training under direct supervision of a staff endoscopist. Bowel preparation consisted of 4 l polyethylene glycol (PEG) solution, taken on the day before a scheduled morning colonoscopy or in a split dose regimen for an afternoon colonoscopy. After colonoscopy, we collected the endoscopic and, if applicable, histological findings. Data were then encrypted and further analyzed in an anonymized dataset.

Informed consent

Before the start of the study, the questionnaire and study protocol had been approved by the Medical Ethical Committee of the UMC Utrecht. We obtained informed consent to review the colonoscopy report and, if applicable, the pathology report.

Statistical analysis

Data analysis was performed using Statistical Packages for Social Sciences version 17.0 [SPSS, Chicago, Illinois, USA]. Age, gender and prevalence of CRC were compared between patients that filled out the questionnaire and those who did not. Of the patients who were included in the study, we univariately compared the assessed variables

between patients that were diagosed with CRC and those who were not. We used Pearson chi-squared test for categorical variables. The positive predictive value (PPV) was calculated for each variable of the questionnaire. To identify factors that may be predictive of CRC, we performed univariate and multivariate logistic regression for all main variables related to the outcome CRC. In case of a statistically significant association, we analyzed the variable in more detail if applicable (e.g., for the main variable rectal blood loss, we analyzed wheter flesh bleeding or blood mixed through the stools was mainly responsible for the association). Statistical differences between groups were calculated and reported as odds ratio (OR) and 95% confidence interval (CI).

RESULTS

Study population

A total of 6,909 patients underwent colonoscopy during the study period, of which 1,458 outpatients (21.1% of all patients) filled out the questionnaire. No differences were found in age, gender and prevalence of CRC (2.81% and 2.88%, respectively) between outpatients included in the study and those who did not receive or fill out the questionnaire.

Mean age of the study population was 54.1±14.9 years (range 18-91). In total, 916 (62.6%) patients were 50 years or older and 750 (51.4%) were men [Table 1]. Of all

Table 1. Patient characteristics and reported presenting symptoms

	All patients	No CRC	CRC	
	n (%)	n (%)	n (%)	p-value
n	1458	1417	41	
Male gender	750 (51.4)	721 (50.9)	29 (70.7)	0.012
Age >50 years	912 (62.6)	879 (62.0)	33 (80.5)	0.016
Previous flexible sigmoidoscopy or colonoscopy	925 (63.4)	914 (64.5)	11 (26.8)	<0.001
Presenting symptom*				
Rectal bleeding	397 (27.2)	371 (26.2)	26 (63.4)	<0.001
Change in bowel habits	676 (46.4)	645 (45.5)	31 (75.6)	<0.001
Weight loss	224 (15.4)	214 (15.1)	10 (24.4)	0.104
Abdominal pain	724 (49.7)	707 (49.9)	17 (41.5)	0.287
Anemia (self-reported)	146 (10.0)	139 (9.8)	7 (17.1)	0.127
Fatigue	506 (34.7)	500 (35.3)	6 (14.6)	0.006
No symptoms	261 (17.9)	260 (18.3)	1 (2.4)	0.009

* More than one symptom per patient possible

patients, 925 (63.4%) had undergone a previous FS or colonoscopy. The vast majority of patients (1,197 of 1,458 (82.1%)) underwent colonoscopy for symptoms, 50 (3.4%) asymptomatic patients underwent screening colonoscopy and 211 (14.5%) asymptomatic patients underwent follow-up or surveillance colonoscopy after previous FS or colonoscopy.

CRC was detected during colonoscopy in 41 (2.8%) patients, with 26 cancers localized in the colon and 15 in the rectum [Table 2]. In the group of 533 patients who had not undergone prior FS or colonoscopy, 30 (5.6%) had a CRC. At least one adenoma was detected in 412 (28.3%) patients. IBD was present in 306 (21.0%) patients. In 489 (33.5%) patients, no abnormalities were found during colonoscopy.

Table 2. The frequency of pathology detected during colonoscopy

	Yield of colonoscopy*	
	n=1458	%
Colorectal cancer	41	2.8
Colon cancer	26	1.8
Rectal cancer	15	1.0
At least one adenoma	412	28.3
Advanced adenoma	34	2.3
IBD	306	21.0
Uncomplicated diverticulae	240	16.5
Diverticulitis	7	0.5
Hemorrhoids	81	5.6
Miscellaneous	16	1.1
No abnormalities	489	33.5

Advanced adenoma: adenoma with >25% villous features, ≥1 cm or high grade dysplasia, IBD: Inflammatory Bowel Disease

* More than one finding per patient possible

Colorectal cancer

Results of the univariate analysis are shown in Table 3. Multivariate analysis showed that rectal blood loss (adjusted OR (aOR) 4.62 [95% CI 2.31-9.22]), change in bowel habits (aOR 3.33 [95% CI 1.50-7.40]) and age over 50 years (aOR 3.00 [95% CI 1.30-6.91]) were associated with an increased risk of finding CRC. Previous FS or colonoscopy (aOR 0.24 [95% CI 0.12-0.49]) and the symptom fatigue (aOR 0.22 [95% CI 0.09-0.56]) were inversely associated with the risk of detecting CRC. PPVs for rectal blood loss, self-reported anemia, change in bowel habits and age over 50 years were 6.5, 4.8, 4.6 and 3.6, respectively. Previous FS or colonoscopy and fatigue both had a PPV of 1.2 [Table 4].

When the item rectal blood loss was subdivided into 'fresh bleeding per rectum' and 'blood mixed through stools', repeat multivariate analysis showed that the association

Table 3. Symptoms associated with CRC: results from univariate and multivariate analysis

	Univariate analysis		Multivariate analysis	
	OR	95% CI	aOR	95% CI
Rectal blood loss	4.89	2.56-9.33	4.62	2.31-9.22
Change in bowel habits	3.71	1.81-7.63	3.33	1.50-7.40
Age >50 years	2.52	1.16-5.51	3.00	1.30-6.91
Self-reported anemia	1.89	0.82-4.35	1.95	0.76-5.00
Male gender	2.33	1.18-4.61	1.89	0.91-3.92
Weight loss	1.81	0.88-3.75	1.81	0.77-4.24
Abdominal pain	0.71	0.38-1.34	0.71	0.34-1.47
Previous lower endoscopy	0.20	0.10-0.41	0.24	0.12-0.49
Fatigue	0.31	0.13-0.75	0.22	0.09-0.56

CRC: Colorectal cancer, OR: odds ratio, 95% CI: 95% confidence interval, aOR: adjusted odds ratio

between rectal blood loss and CRC was mainly explained by 'blood mixed through stools' (aOR 3.13 [1.32-7.44]), compared to 'fresh bleeding per rectum' (aOR 1.91 [0.95-3.84]). Furthermore, the association between change in bowel habits and finding CRC was mainly associated with an increased stool frequency (aOR 3.6 [95% CI 1.82-7.03]), compared to a decreased stool frequency (aOR 0.84 [95% CI 0.24-2.98]). In addition, a decreased stool consistency ('loose stools') was found to be associated with finding CRC (aOR 2.53 [1.29-4.97]), while an increased stool consistency ('hard stools') was not (aOR 0.73 [0.27-2.02]). Fatigue was independently inversely associated with CRC.

Because of the large number of patients with a previous colonoscopy or FS, multivariate analysis was repeated for the subgroup of patients without a previous lower GI

Table 4. Symptoms associated with CRC: positive predictive values

	Number of patients	Number of patients with CRC	PPV
Rectal blood loss	397	26	6.5
Change in bowel habits	676	31	4.6
Age >50 years	912	33	3.6
Self-reported anemia	146	7	4.8
Male gender	750	29	3.9
Weight loss	224	10	4.5
Abdominal pain	724	17	2.3
Previous lower endoscopy	925	11	1.2
Fatigue	506	6	1.2

CRC: Colorectal cancer, PPV: positive predictive value

endoscopy [Supplemental Table 1]. Also, multivariate analysis was repeated without the IBD patients included [Supplemental Table 2]. In both cases, the strength and significance of the aforementioned associations did not change.

DISCUSSION

Although screening of the asymptomatic, average-risk population is reported to reduce mortality from CRC,[14-16] the vast majority of CRCs is still being diagnosed in patients undergoing colonoscopy for symptoms.[17] Correctly prioritizing patients that require short-term colonoscopy could ideally help in minimizing a delay until a diagnosis of CRC is made. In this analysis of 1,458 patients referred for colonoscopy, we found that the presenting symptoms rectal bleeding (specifically blood mixed with the stools) and a change in bowel habits (specifically increase in frequency and presence of loose stools) were risk factors for CRC, while fatigue was inversely associated with finding CRC during colonoscopy. In addition, age over 50 years was associated with an increased CRC risk. Having undergone previous FS or colonoscopy was associated with a decreased risk of finding CRC.

In the literature, rectal bleeding appears to be the most consistently reported symptom associated with an increased CRC risk. Similarly to our study, a systematic review and meta-analysis showed that rectal bleeding, and more specifically dark red rectal bleeding, had a high specificity (>95%) for a diagnosis of CRC in a secondary care setting,[12] making this a clinically useful parameter to triage patients for urgent colonoscopy. This was recently confirmed in a large systematic review by Adelstein et al., who analyzed 62 studies and confirmed that rectal bleeding, especially dark red bleeding and blood mixed through the stools, was associated with finding CRC during colonoscopy.[13]

The association between change in bowel habits and presence of CRC is not completely clear. Previous studies have reported varying degrees of associations between this symptom and CRC. A questionnaire-based approach found a positive predictive value (PPV) of 5.0% for any change in bowel habits and finding CRC, with loose motion (PPV 7.7%) and increased stool frequency (PPV 7.2%) being the most important predictors.[18] Bjerregaard et al. also used a questionnaire to investigate the diagnostic value of self-reported symptoms in Danish outpatients. When they analyzed the variable change in bowel habits in more detail, they found that a change in bowel movement frequency was a predictor of CRC (aOR 2.5 [95% CI 1.5-4.1]), but this was not the case for a change in stool consistency (aOR 1.2 [95% CI 0.7-2.0]).[19] An older questionnaire-based study on the diagnostic value of symptoms of CRC in patients undergoing double contrast barium enema[20] and two more recent systematic reviews and meta-analyes,[12,13] did however not find a significant association.

Fatigue is generally thought to be a nonspecific symptom. For that reason, it is probably not included in most studies on presenting symptoms of CRC. We added this item to our questionnaire because it is a frequently heard symptom of patients in daily clinical practice. Interestingly, we found that fatigue was a negative predictor for finding CRC. There have been a few reports on this negative association in the literature, although statistically significant results have not been reported. Steine et al. found fatigue to be a borderline significant negative predictor of CRC (aOR 0.5 [95% CI 0.2-1.0]).[20] Bjerregaard et al. also reported a borderline significant inverse association between fatigue and finding CRC in univariate analysis (OR 0.6 [95% CI 0.4-1.0]), but this symptom was not included in their multivariate analysis.[19] The observed inverse association of the presenting symptom fatigue with the presence of CRC may be a reflection of the presence of a different condition with abdominal symptoms that resulted in the decision to perform colonoscopy, e.g., irritable bowel syndrome (IBS) or another functional abdominal disorder. A recent study showed that fatigue is reported by as much as 61% of IBS patients.[21] The clinical relevance of the found association in our study however is unclear as its usefulness in clinical decision making probably is limited.

We found that patients who had undergone previous FS or colonoscopy had a significantly reduced risk of finding CRC during colonoscopy. The concept that previous colonoscopy with polypectomy protects against CRC is widely accepted and is already known since the publication of the National Polyp Study in 1993.[22] In addition, it has been reported that repeat colonoscopy after previous colonoscopy, even in symptomatic patients, is unlikely to yield significant findings.[23] A case could therefore be made for their suggestion that patients who never had colonoscopy should have priority on the endoscopy lists over those awaiting repeat examinations.

The finding that age over 50 years is associated with an increased risk of CRC is well known; it has clearly been shown in the Western population that the incidence of CRC particularly starts to rise in the sixth decade of life.[24]

A strength of this study is the prospective data collection prior to the diagnostic examination. In contrast to several other reports on symptomatology of CRC, the symptoms and complaints in the current study were directly obtained from the patients by means of a questionnaire. Patient questionnaires have the advantage that the scored symptoms are not biased by the judgment of the referring physician and likely represent a more accurate reflection of the symptoms of patients when they present at or are referred to the outpatient clinic. Questionnaires have been used in other studies evaluating symptoms associated with CRC in patients referred to secondary care.[18-20] These questionnaire-based studies however differ from our study in that Steine et al. investigated the yield of double contrast barium enema,[20] while in the study by Bjerregaard et al. 30% of patients underwent FS alone and complete visualization of the colon was only achieved in 56% of patients.[19] Rather than analyzing individual presenting symptoms,

Selvachandran et al. developed a weighted numerical score based on the combination of both symptoms and a somewhat subjective grading based on clinical experience.[18]

We recognize that our study has some shortcomings. As we primarily focused on patient reported symptoms and signs, we are not informed about other possible indications for colonoscopy which were not or incompletely known by the patients, e.g. the finding of an abdominal mass or abnormal rectal exam at physical examination or abnormalities found at a previous imaging study. A systematic review by Ford et al. concluded that a palpable abdominal mass had a high specificity for finding CRC during subsequent colonoscopy.[12] Similarly, we are not informed about the type of anemia and the corresponding hemoglobin level in patients that reported anemia. As the accuracy of the information given by the patient in this questionnaire was not examined, it may well be that the 10% of patients reporting this symptom are in fact an underestimation of the true prevalence of anemia in the referred patients. This percentage is however in line with the 11% pooled prevalence in a recent systematic review.[12]

This study was performed in a mixed secondary and tertiary referral center. This may have influenced our results. We included a substantial proportion of IBD patients and patients with a previous lower GI endoscopy. This may have caused bias. Performing a subgroup analysis without these patients did however not affect the strength and significance of the associations that we found [Supplemental Tables]. The prevalence of CRC in our study population was relatively low compared to other studies.[12] This is partly due to the large proportion of patients who had previously undergone FS or colonoscopy. The prevalence of CRC in patients who did not have prior FS or colonoscopy (5.6%) was however comparable to that in similar recent studies, i.e., 5.6%[19] and 4.2%.[18] Despite the relatively large proportion of patients with prior FS or colonoscopy, our findings were still statistically significant.

In conclusion, although no single self-reported presenting symptom can identify patients with CRC with high certainty, patients over 50 years of age presenting with rectal blood loss and a change in bowel habits are at increased risk of CRC and should have a priority undergoing colonoscopy over patients presenting with other symptoms. Patients who previously underwent FS or colonoscopy have a lower likelihood of finding CRC.

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Supplemental Table 1. Symptoms associated with CRC: multivariate analysis without the patients with a previous lower GI endoscopy

	Multivariate analysis	
	aOR	**95% CI**
Rectal blood loss	3.46	1.56-7.68
Change in bowel habits	2.51	0.98-6.41
Age >50 years	2.83	1.07-7.46
Self-reported anemia	1.43	0.47-4.38
Male gender	2.46	0.99-6.10
Weight loss	2.47	0.95-6.44
Abdominal pain	0.57	0.24-1.38
Fatigue	0.29	0.10-0.84

CRC: Colorectal cancer, aOR: adjusted odds ratio, 95% CI: 95% confidence interval

Supplemental Table 2. Symptoms associated with CRC: multivariate analysis without the IBD patients

	Multivariate analysis	
	aOR	**95% CI**
Rectal blood loss	4.99	2.49-10.01
Change in bowel habits	3.52	1.57-7.86
Age >50 years	2.54	1.09-5.91
Self-reported anemia	1.93	0.74-5.00
Male gender	1.91	0.92-3.99
Weight loss	1.87	0.79-4.42
Abdominal pain	0.68	0.33-1.42
Previous lower endoscopy	0.33	0.16-0.70
Fatigue	0.23	0.09-0.58

CRC: Colorectal cancer, aOR: adjusted odds ratio, 95% CI: 95% confidence interval

CHAPTER 3

Open-access flexible sigmoidoscopy frequently leads to additional colonoscopy in symptomatic patients over 50 years

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ABSTRACT

Background & Aims

General practitioners (GPs) in the Netherlands have open access to flexible sigmoidoscopy (FS) for patients with lower gastrointestinal symptoms, but not to colonoscopy. This study was performed to investigate the yield of FS in GP-referred patients, to evaluate the proportion of patients in which additional colonoscopy was performed and to investigate whether there was a subgroup of patients referred for symptoms with a low risk of detecting significant findings.

Methods

All patients undergoing FS in 2008 and 2009 who were referred by GPs were analyzed. Indications for additional colonoscopy were the presence of polyps and/or colorectal cancer (CRC), polyp screening or surveillance, incomplete FS or other reasons.

Results

In total, 916 patients underwent FS. A cause for the symptoms was found in 44.2% of patients. In patients aged 50 years or older, additional colonoscopy was more frequently performed than in younger patients (27.5% vs. 9.6%, OR=3.6 [95% CI 2.4-5.4]), mainly due to a higher prevalence of adenomatous polyps (29.9% vs. 10.5%, OR=3.6 [95% CI 2.4-5.4]) and CRC (7.5% vs. 1.3%, OR=6.2 [95% CI 2.2-17.5]) during FS. In 7.8% patients undergoing FS for abdominal pain as the presenting symptom, a probable cause for the symptoms was found, mainly diverticular disease.

Conclusion

Due to the high prevalence of polyps and CRC in symptomatic patients aged 50 years or older undergoing FS, an additional colonoscopy is performed frequently. In patients referred with abdominal pain, FS is unlikely to reveal a relevant cause for the symptoms.

INTRODUCTION

Insufficient capacity of endoscopy units and increasing waiting lists for endoscopy are common in many countries.[1,2] This is mainly due to the fact that the population is aging in the Western world, resulting in a higher prevalence of morbidity. Worldwide, the incidence of colorectal cancer (CRC) is rising.[3-5] This has resulted in the introduction of CRC screening programs in many countries, further increasing the demand on endoscopy units.[6-8]

The mainstay of endoscopic examination of the colon is colonoscopy, which is invasive and requires extensive bowel preparation. Flexible sigmoidoscopy (FS) is an alternative to colonoscopy; however, it has the disadvantage that only the left-sided colon (up to the splenic flexure) can be evaluated. Although this procedure can be experienced as less comfortable for the patient than colonoscopy with sedation,[9] bowel preparation for FS is less burdensome and the endoscopic procedure itself is less time consuming for the endoscopist and patient than colonoscopy. As the incidence of significant findings, i.e. colorectal polyps and CRC, is highest in the left-sided colon,[10] this is a further argument to promote the use of FS.

The health care system in the Netherlands is based on a well developed primary care system. All patients are initially seen by a general practitioner (GP), and only referred to the hospital (second line medical care) if indicated. In general, GPs in the Netherlands have direct access to FS but not to colonoscopy. Although it is already widely accepted that colonoscopy should replace FS for most indications in patients over 50 years of age, the availablity of open access to FS for primary care physicians in the Netherlands still promotes a preferential referral pattern towards FS. This has resulted in a significant number of referrals for FS to Dutch endoscopy units over the years.

In a proportion of patients referred for FS, findings during the examination result in an indication for additional colonoscopy. This procedure needs to be scheduled and the patient should take a repeat and more extensive bowel preparation. These patients thus eventually undergo two endoscopic procedures. To date, the exact burden of open access sigmoidoscopy on our endoscopy capacity is unclear.

Furthermore, a substantial part of GP referrals for FS is for patients presenting with abdominal pain. Based on clinical experience and the literature,[11,12] it may well be that FS in these patients only rarely yields an explanation for the symptoms or clinically relevant findings. Reducing the number of FS procedures in patients with a low a priori risk of detecting relevant findings might help to reduce the high demand on endoscopic capacity.

We conducted a retrospective study to investigate the yield of FS in patients referred by their GP and to evaluate the proportion of patients in which additional colonoscopy was indicated and performed. Furthermore, we investigated whether there was a

subgroup of patients referred for FS for symptoms with a low a priori risk of detecting significant findings during FS.

METHODS

Study population

All patients, 18 years or older, undergoing FS in a large, general hospital and referred by the GP, in the period January 1 2008 through December 31 2009 were identified using the endoscopy reporting system (Endobase [Olympus Medical Systems Europa GMBH, Hamburg, Germany]). All endoscopy reports in the hospital are generated using this reporting system. Patients referred for FS by other (non-GP) physicians were excluded.

All endoscopies were performed using Olympus 160 or 180 series sigmoidoscopes or colonoscopes. Bowel preparation for FS consisted of oral sennosides the day before the procedure and a sodium phosphate enema one to two hours before the procedure. Standard introduction during FS was up to the splenic flexure.

During the study period, there was no mass screening program for CRC in the Netherlands.

Data collection

Age, gender, main indication for and diagnostic yield of FS were collected for all patients. In case of multiple indications, the main indication, as reported by the endoscopist, was used in the analyses. All findings during FS were recorded and used for the analyses. This may have resulted in more than one finding per patient. If applicable, pathology reports and relevant colorectal medical history were reviewed from the patient charts. In our institution, we have strict criteria for additional colonoscopy after FS, i.e.: presence of polyps and/or CRC during FS, polyp screening or surveillance after CRC, incomplete FS or other reasons. If additional colonoscopy had been performed, the indication for the procedure and diagnostic yield were also collected. Patient data were then encrypted and further analyzed.

The interpretation of the findings during FS in relation to the symptoms of the patient was left to the discretion of the phycisian performing the endoscopy.

Data analysis

Patients who underwent FS were divided into two groups: patients younger than 50 years and aged 50 years or older. We investigated whether additional colonoscopy had been performed and to what extent it had been performed more frequently in patients of 50 years or older compared to younger patients and what the main indications for colonoscopy were.

In addition, patients were analyzed according to the indication for FS to investigate in which subsets of patients FS had a higher or lower risk of finding the cause of the symptoms. For this, we analyzed the five most common indications for FS.

Statistical analysis

Data analysis was performed using Statistical Packages for Social Sciences version 15 [SPSS, Chicago, Illinois, USA]. Descriptive statistics were used for continuous variables. The frequencies and percentages were calculated for categorical variables. Statistical differences between groups were calculated using the chi-squared test and expressed in odds ratio (OR) and 95% confidence interval (CI). Means were compared using the Student's t-test. Statistical significance was set at $p<0.05$.

Multivariate analysis was performed to identify indications for FS that were independently associated with finding a cause for the symptom.

Ethical approval

In the Netherlands, no informed consent or institutional approval is required for this type of observational, retrospective research with encrypted patient data.

RESULTS

Patient characteristics

In the study period, a total of 916 patients were referred for FS by the GP, of which 603 (65.8%) were 50 years of age or older. Patient characteristics are summarized in Table 1. The medical history with regard to colorectal disease was not different between patients younger or older than 50 years, except for a higher frequency of a history of colonic

Table 1. Patient characteristics

	All patients	Patients ≥50 years	Patients <50 years	odds ratio [95% confidence interval]
n	916	603 (65.8)	313 (34.2)	
Male	449 (49.0)	284 (47.1)	165 (52.7)	0.80 [0.61-1.05]
Mean age (range)	56.2 (18-93)	65.8 (50-93)	37.8 (18-49)	n/a
History of:				
Colonic polyps	28 (3.1)	25 (4.1)	3 (1.0)	4.47 [1.34-14.92]
Inflammatory bowel disease	8 (0.9)	4 (0.7)	4 (1.3)	0.52 [0.13-2.08]
Colorectal cancer	11 (1.2)	10 (1.7)	1 (0.3)	5.26 [0.67-41.29]

Numbers in parentheses are percentages unless otherwise indicated

polyps in patients of 50 years or older (25/603 (4.1%) vs 3/313 (1.0%), OR 4.47 [95% CI 1.34-14.92]). In patients of 50 years or older, indications for FS were more often a change in bowel habits (93/603 (15.4%) vs. 21/313 (6.7%), OR 2.54 [95% CI 1.55-4.16]), abdominal pain (86/603 (14.3%) vs. 25/313 (8.0%), OR 1.92 [1.20-3.06]) and abnormalities found on previous imaging studies (16/603 (2.7%) vs. 1/313 (0.3%), OR 8.50 [1.12-64.43]) [Table 2].

Endoscopy findings

FS detected a similar rate of patients with hemorrhoids in both age groups; in 155/603 (25.4%) patients of 50 years or older vs. 77/313 (24.6%) patients younger than 50 years. In patients 50 years or older, FS less frequently detected inflammatory bowel disease (IBD) (10/603 (1.7%) vs. 32/313 (10.3%), OR 0.15 [0.07-0.30]) or no abnormalities (153/603 (25.4%) vs. 139/313 (44.4%), OR 0.43 [0.32-0.57]). However, in the older age group more often colorectal polyps (180/603 (29.9%) vs. 33/313 (10.5%), OR 3.61 [2.42-5.39]), CRC (45/603 (7.5%) vs. 4/313 (1.3%), OR 6.23 [2.22-17.49]) and diverticular disease (202/603 (33.5%) vs. 9/313 (2.9%), OR 16.96 [8.56-33.62]) were found [Table 3].

Table 2. Indications for FS per age category*

	All patients	Patients ≥50 years	Patients <50 years	odds ratio [95% confidence interval]
n	916	603	313	
Rectal blood loss	465 (50.8)	273 (45.3)	192 (61.3)	0.52 [0.39-0.69]
Change in bowel habits	114 (12.4)	93 (15.4)	21 (6.7)	2.54 [1.55-4.16]
Abdominal pain	111 (12.1)	86 (14.3)	25 (8.0)	1.92 [1.20-3.06]
Constipation	40 (4.4)	32 (5.3)	8 (2.6)	2.14 [0.97-4.69]
Diarrhea	29 (3.2)	17 (2.8)	12 (3.8)	0.73 [0.34-1.54]
Abnormality on imaging studies	17 (1.9)	16 (2.7)	1 (0.3)	8.50 [1.12-64.43]
Perianal or rectal problems	12 (1.3)	7 (1.2)	5 (1.6)	0.72 [0.23-2.30]
Fecal incontinence	11 (1.2)	8 (1.3)	3 (1.0)	1.39 [0.37-5.27]
Polyp surveillance	9 (1.0)	7 (1.2)	2 (0.6)	1.83 [0.38-8.84]
Familiy history of polyps/CRC	6 (0.7)	2 (0.3)	4 (1.3)	0.26 [0.05-1.41]
Anemia	3 (0.3)	3 (0.5)	0 (0)	n/a
Other indications	28 (3.1)	17 (2.8)	11 (3.5)	0.80 [0.37-1.72]
Not reported	71 (7.8)	42 (7.0)	29 (9.3)	0.73 [0.45-1.20]

Numbers in parentheses are percentages

* Patients categorized according to the most predominant symptom leading to FS

Table 3. Yield of flexible sigmoidoscopy

	All patients	Patients ≥50 years	Patients <50 years	odds ratio [95% confidence interval]
n	916	603	313	
Findings during flexible sigmoidoscopy*				
No abnormalities	298 (32.5)	153 (25.4)	139 (44.4)	0.43 [0.32-0.57]
Hemorrhoids	232 (25.3)	155 (25.7)	77 (24.6)	1.06 [0.77-1.45]
Polyps	213 (23.3)	180 (29.9)	33 (10.5)	3.61 [2.42-5.39]
Diverticular disease	211 (23.0)	202 (33.5)	9 (2.9)	16.96 [8.56-33.62]
CRC	49 (5.3)	45 (7.5)	4 (1.3)	6.23 [2.22-17.49]
IBD	42 (4.6)	10 (1.7)	32 (10.3)	0.15 [0.07-0.30]
Other (unspecified colitis, anal fissure etc)	105 (11.5)	61 (10.1)	44 (14.1)	0.69 [0.46-1.04]
Deemed explanation for indication during FS**				
n***	405 (44.2)	268 (44.4)	137 (43.8)	1.03 [0.78-1.35]
Causes found	471 (51.4)	322 (53.4)	149 (47.6)	1.26 [0.96-1.66]
Hemorrhoids	184 (20.1)	115 (19.5)	69 (22.3)	0.84 [0.60-1.18]
Polyps	112 (12.2)	91 (15.4)	21 (6.7)	2.52 [1.53-4.13]
Diverticular disease	23 (2.5)	23 (3.8)	0 (0)	n/a
CRC	46 (5.0)	43 (7.2)	3 (1.0)	7.98 [2.45-25.93]
IBD	40 (4.4)	9 (1.5)	31 (9.9)	0.14 [0.07-0.29]
Other	66 (7.2)	41 (6.8)	25 (8.0)	0.84 [0.50-1.41]

Numbers in parentheses are percentages. odds ratio comparing patients ≥50 with patients <50 years of age
* Per patient more than one relevant finding possible
** As assessed by performing clinician, percentages represent percentage of total patient group
*** In 66 patients, more than 1 possible cause for the patients' symptoms were found. In 2 patients of these, 3 possible causes were found

In both age groups, a cause for the presenting symptom was found in 44% of patients. Two possible causes for the presenting symptoms were found in 64 patients and three possible explanations for the symptoms were found in 2 patients. Hemorrhoids were thought to be the explanation for the presenting symptoms in 20.1% of all FS procedures. CRC, polyps and diverticular disease were the most common causes of the symptoms in patients of 50 years or older, whereas IBD was more prevalent as a cause in patients younger than 50 years [Table 3].

In patients aged 50 years or older, significantly more frequently an additional colonoscopy was performed compared to the younger patients (166/603 (27.5%) vs 30/313 (9.6%), OR 3.58 [2.36-5.43]) [Table 4]. The predominant indications for additional colonoscopy were polyps or CRC found during FS in both patient groups. In 5.1% of patients

under the age of 40 years, in 14.0% of patients between age 40 and 50 years and in 27.5% of patients of 50 years or older additional colonoscopy was performed (p<0.001).

Diagnostic yield per indication

The five most common indications for FS were rectal blood loss (465/916 (50.8%)), change in bowel habits (114/916 (12.4%)), abdominal pain (111/916 (12.1%)), constipation (40/916 (4.4%)) and diarrhea (29/916 (3.2%)) [Table 2]. The cause for the presenting symptom was found in 324/461 (70.3%) patients with rectal blood loss, in 6/21 (22.2%) patients with diarrhea, in 17/82 (20.7%) patients with a change in bowel habits, in 4/40 (10.0%) patients with constipation and in 8/103 (7.8%) patients with abdominal pain (p<0.001). There was no statistically significant difference in the proportion of additional colonoscopies between these diagnostic groups (range 17.5-24.1%, p=0.33).

Table 5 shows the results of the subset of patients with the lowest yield during FS, i.e. those with abdominal pain as only symptom, compared with patients referred for another indication. Patients referred for abdominal pain were more often 50 years or older (79/103 (76.7%) vs. 524/813 (64.5%), OR 1.82 [1.13-2.93]). Significantly more often no abnormalities were found in this group (49/103 (48.0%) vs. 243/813 (29.9%), OR 2.17

Table 4. Additional full optical colonoscopy after flexible sigmoidoscopy

	All patients	Patients ≥50 years	Patients <50 years	odds ratio [95% confidence interval]
n	916	603	313	
Additional colonoscopy performed	196 (21.4)	166 (27.5)	30 (9.6)	3.58 [2.36-5.43]
Reason for additional colonoscopy				
Polyps during FS	138 (70.4)	116 (69.9)	22 (73.3)	0.84 [0.35-2.02]
CRC during FS	21 (10.7)	18 (10.8)	3 (10.0)	1.09 [0.30-3.97]
Polyps + CRC during FS	7 (3.6)	7 (4.2)	0 (0)	n/a
FS was incomplete	11 (5.6)	11 (6.6)	0 (0)	n/a
Other	19 (2.1)	14 (2.3)	5 (1.6)	1.46 [0.52-4.10]
Yield of additional colonoscopy*				
Polyps	153 (78.1)	132 (79.5)	21 (70.0)	1.66 [0.70-3.96]
Diverticular disease	57 (29.1)	54 (32.5)	3 (10.0)	4.34 [1.26-14.94]
CRC	30 (15.3)	27 (16.3)	3 (10.0)	1.75 [0.49-6.18]
Hemorrhoids	22 (11.2)	17 (10.2)	5 (16.7)	0.57 [0.19-1.69]
IBD	4 (2.0)	1 (0.6)	3 (10.0)	0.06 [0.06-0.55]
Other	3 (1.5)	3 (1.8)	0 (0)	n/a

Numbers in parentheses are percentages

* Percentages represent percentage of all patients in the patient group undergoing additional colonoscopy. Per patient more than one relevant finding possible

Table 5. Yield of flexible sigmoidoscopy in patients solely presenting with abdominal pain

	Abdominal pain	Other	odds ratio [95% confidence interval]
n	103	813	
Male	53 (51.5)	396 (48.7)	1.12 [0.74-1.68]
Mean age (range)	58.8 (24-91)	55.9 (15-93)	p=0.09*
Age over 50 years	79 (76.7)	524 (64.5)	1.82 [1.13-2.93]
History of:			
Colonic polyps	3 (2.9)	25 (3.1)	0.95 [0.28-3.19]
IBD	0 (0)	8 (1.0)	n/a
CRC	1 (1.0)	10 (1.2)	0.79 [0.10-6.21]
Partial colectomy for other reasons	2 (1.9)	1 (0.2)	16.08 [1.44-178.92]
Findings during flexible sigmoidoscopy			
No abnormalities	49 (48.0)	243 (29.9)	2.17 [1.43-3.29]
Hemorrhoids	9 (8.7)	223 (27.4)	0.25 [0.13-0.51]
Polyps	19 (18.4)	194 (23.9)	0.72 [0.43-1.22]
Diverticular disease	37 (35.9)	174 (21.4)	2.06 [1.33-3.18]
CRC	1 (1.0)	48 (5.9)	0.16 [0.02-1.14]
IBD	0 (0)	42 (5.2)	n/a
Other	6 (5.9)	99 (12.2)	0.45 [0.19-1.06]
Found explanation for indication during FS			
n	8 (7.8)**	397 (48.8)	0.09 [0.04-0.18]

Numbers in parentheses are percentages unless otherwise indicated
* t-test
** Being: Diverticular disease in 7 and CRC in 1 patient

[1.43-3.29]). Patients with abdominal pain did not have an increased risk of finding CRC (1/103 (1.0%) vs. 48/813 (5.9%), OR 0.16 [0.02-1.14]). FS was less likely to reveal an explanation for the symptoms in patients with abdominal pain (8/103 (7.8%) vs. 397/813 (48.8%), OR 0.09 [0.04-0.18]). If the cause of the symptoms was found, it was mainly diverticular disease (7/8 patients). The proportion of patients with abdominal pain that underwent additional colonoscopy was the same as in the other patients (15/103 (14.6%) vs. 181/813 (22.3%), OR 0.60 [0.34-1.05]).

In line with these findings, multivariate analysis showed that the indications rectal blood loss (adjusted OR 16.25 [10.30-25.63]), a change in bowel habits (adjusted OR 1.97 [1.16-3.37]) and diarrhea (adjusted OR 2.68 [1.07-6.71]) were independently associated with finding a cause for the symptoms during FS. Constipation (adjusted OR 0.78 [0.26-2.39]) and abdominal pain (adjusted OR 0.70 [0.38-1.30]) were not found to be associated with finding a cause for these symptoms.

DISCUSSION

In this retrospective cohort study of patients referred for FS by their GP, we found that an additional colonoscopy was performed in 27.5% of patients of 50 years or older. This resulted in a significant burden on the capacity of the endoscopy unit. In patients referred for abdominal pain as the only presenting symptom, FS yielded a cause for the symptoms in less than 8% of patients and in these cases mainly diverticular disease was found (7/8).

The observation in our study that findings during FS warranted colonoscopic evaluation in only a minority of patients under the age of 50 years is in line with other reports. Several authors have reported that the incidence of colonic polyps and CRC in patients under the age of 40-45 years presenting with rectal blood loss is low, making FS a valuable tool in this patient group.[13-16] In our study, in only 5.1% of patients under the age of 40 years a full additional colonoscopy was performed, as compared to 14.0% in patients between age 40 and 50 years and 27.5% in patients of 50 years or older. As that the main indication for additional colonoscopy was the finding of polyps and/or CRC during FS, it reflects the increasing incidence of polyps and CRC in the aging population as has been repeatedly reported before.[17,18]

The frequency of isolated proximal adenomas in patients under 40 years of age presenting with rectal bleeding has been reported to be very low[19] and they have been reported in less than 1% of patients aged 41-50 years.[14] These findings combined with the relative low need for additional colonoscopy in our study may still support a role for FS as diagnostic tool in patients under the age of 50 years. However, based on the rising incidence of CRC after the age of 50 years,[18] colonoscopy should be the preferred diagnostic modality in the older age group. We are currently re-considering our open access FS referral policy in patients older than 50 years. As this policy is applied in many institutions in the Netherlands, it means that changing it would definitely decrease the demand on endoscopy capacity, by reducing the substantial number of patients that eventually undergo both FS and colonoscopy. The results of this study could play a role in the discussion whether existing referral protocols in countries with a health care system comparable to that in the Netherlands should be changed.

We also found that FS performed for abdominal pain as only presenting symptom is unlikely to yield an explanation for the symptoms. In contrast, it was associated with a low frequency of finding significant lesions. Although abdominal pain is the third most common indication for FS in our study (12.1% of all referrals), it was unlikely to reveal a cause for the symptoms (in 7.8%). In 7 of these 8 cases, diverticulosis was found to be an explanation for the patients' symptoms. This might however be an overestimation, as it is not always clear whether uncomplicated diverticular disease truly is the cause of abdominal symptoms or in fact a non-significant finding. Interestingly, a recent study

also reported that a colonic investigation was only able to detect an explanation for the symptom abdominal pain in 8% of cases.[20] To prevent unnecessary colonoscopies, these authors have suggested a possible role for CT colonography in this patient group.[20]

As can be expected, the frequency of colonic polyps was not different between patients with and without abdominal pain as indication for FS. This confirms that colonic polyps are asymptomatic in the vast majority of cases.[21] Selinger et al. also reported that colonic evaluation with colonoscopy or CT colonography for patients with abdominal pain found incidental colonic pathology, mainly colonic polyps, in a same proportion of patients compared to those who were referred for other indications,[20] a finding we actually confirmed.

Historically, abdominal pain is often presented as one of the main presenting symptoms of CRC.[22] However, recent publications have concluded that abdominal pain alone has a low predictive value for the presence of CRC.[21,23,24] Our study confirms this and raises the question whether colonoscopic examination should routinely be performed in patients only presenting with abdominal pain as it is unlikely to yield a clinically relevant cause for the pain. Nonetheless, it should be kept in mind that colonoscopy is able to detect asymptomatic colonic polyps in a subgroup of patients, meaning that the indication for colonoscopy changes from a diagnostic to a screening one.

Marderstein et al. proposed that a full colonoscopy is not always indicated in patients presenting with bright red blood after or during defecation, with no family history of colorectal neoplasia or change in bowel habits, as colonoscopy in these patients is unlikely to yield significant findings.[25] The authors defined significant findings as adenomas >1 cm, villous adenoma, cancer in situ or invasive cancer. However, they do not report on the number of patients with 'non significant', other adenomas, which would have been found during FS and would subsequently have led to additional colonoscopy.

A drawback of this study is that we were not informed about the follow-up of patients that did not undergo additional colonoscopy. The frequency of relevant colonic lesions in the more proximal part of the colon in this patient group is therefore unclear. It has been reported that 25-30% of CRCs and 20-25% of adenomatous polyps are located in the proximal colon.[10] Many of these patients, however, are also known to have more distal lesions that will be detected during FS and followed by colonoscopy. A recent meta-analysis showed that more than half of proximal neoplastic colonic lesions occurred isolated, i.e., in patients without concurrent distal polyps or CRC.[26] Thus, based on this finding, it may well be that the need to perform a colonoscopy is even higher than was observed in our study. The absence of information on the follow-up of patients also makes it impossible to report the frequency of other, non-neoplastic diagnoses, e.g. Crohn's disease, in patients who did not undergo additional colonoscopy.

The slightly higher prevalance of a history of colonic polyps in the patients over 50 years might have led to selection bias. However, repeat analysis without these patients

(4.1% and 1.0% of patients older and younger than 50 years, respectively) did not significantly affect our results.

Furthermore, it can be argued that the scoring of the probable cause of the symptoms was rather subjective. This is however a reflection of every day clinical practice in which clinicians make a diagnosis based on the available information.

In conclusion, in patients referred for FS by their GP, in 44.2% the probable cause of the symptoms is found. However, due to the high prevalence of polyps and CRC during FS in patients aged 50 years or older, an additional colonoscopy is performed frequently in this patient group. In patients referred with abdominal pain as the sole presenting symptom, FS is unlikely to reveal a cause of their symptoms with clinical consequences.

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CHAPTER 4

Quality indicators for colonoscopy: current insights and caveats

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ABSTRACT

Colonoscopy is the diagnostic modality of choice for investigation of symptoms suspected to be related to the colon and for the detection of polyps and colorectal cancer (CRC). Colonoscopy with removal of detected polyps has been shown to reduce the incidence and mortality of subsequent CRC. In many countries, population screening programs for CRC have been initiated, either by selection of patients for colonoscopy with fecal occult blood testing or by offering colonoscopy directly to average-risk individuals. Several endoscopy societies have formulated quality indicators for colonoscopy. These quality indicators are almost always incorporated as process indicators, rather than outcome measures. This review focuses on the quality indicators bowel preparation, cecal intubation rate, withdrawal time, adenoma detection rate, patient comfort, sedation and complication rate, and discusses the scientific evidence supporting them, as well as their potential shortcomings and issues that need to be addressed. For instance, there is still no clear and generally accepted definition of adequate bowel preparation, no robust scientific evidence is available supporting a cecal intubation rate ≥90% and the association between withdrawal time and occurrence of interval cancers has not been clarified. Adenoma detection rate is currently the only quality indicator that has been shown to be associated with interval colorectal cancer, but as an indicator it does not differentiate between subjects with one or more adenoma detected.

INTRODUCTION

Colonoscopy is the diagnostic modality of choice for investigation of symptoms suspected to be related to the colon and for the detection of polyps and colorectal cancer (CRC). Colonoscopy with polypectomy has been shown to reduce both the incidence and mortality of subsequent CRC.[1,2]

However, despite being the gold standard, colonoscopy is also known to be not a perfect test. From back-to-back colonoscopy studies, it is estimated that up to 25% of polyps are missed during colonoscopy.[3,4] Furthermore, the preventive effect of colonoscopy is most prominent for distal CRCs, whereas its role in preventing proximal CRCs is less evident.[5,6] Finally, up to 8% of CRCs occur within 3 years after a previous colonoscopy.[7-12] Despite technical advancements and increased professional awareness, this miss rate has not decreased over time.[12] Moreover, recent studies have shown that these so-called post-colonoscopy CRCs are most likely due to missed lesions, rather than being completely new lesions.[13,14]

The incidence of CRC is steadily rising in many parts of the world.[15] Many countries have initiated population screening programs for CRC, either through selection of patients for colonoscopy with fecal occult blood testing (FOBT) or by offering colonoscopy directly to average-risk individuals.[16,17] This has resulted in an increase in the number of colonoscopies performed. For these mass screening programs to be successful, it is of utmost importance that colonoscopies are of high quality and performed according to the latest state of knowledge.

In an effort to optimize general performance of colonoscopy and to decrease inter-individual variation between physicians performing colonoscopy, several quality indicators have been suggested in recent years.[18] These quality indicators however all are process indicators rather than indicators of outcome. Ideally, the quality of colonoscopy should be measured by clinical outcome measures. The goal of colonoscopy in most cases is the detection of neoplastic lesions. After removal of premalignant neoplastic lesions, patients enter a surveillance program. The rate of the occurrence of interval cancers or post-colonoscopy CRCs, defined as CRCs diagnosed in the period between the last colonoscopy and the scheduled surveillance colonoscopy, is a more direct and probably better reflection of the quality of the colonoscopy performed than the main current quality indicators proposed in guidelines.

In this review, we will discuss the main current quality indicators for colonoscopy, the scientific evidence supporting them, as well as their potential shortcomings and issues that still need to be addressed.

BOWEL PREPARATION

A quality indicator issued by several international guidelines is that the endoscopist should report the quality of the bowel preparation for each colonoscopy.[18,19] Several guidelines state that ≥90% of patients undergoing colonoscopy should have had a bowel preparation rated as excellent or at least adequate.[19,20] The quality of bowel cleansing has been shown to impact the ability and time needed to reach the cecum and the detection of polyps, both small and large (≥10 mm).[21,22]

There are several bowel preparation medications available and regimens used for bowel preparation before colonoscopy. These vary from polyethylene glycol (PEG) based solutions, osmotic laxatives (sodium phosphate, magnesium citrate, sodium sulphate) or stimulant laxatives (senna, bisacodyl, sodium picosulphate), either alone or in combination.

In a meta-analysis of randomized controlled trials, split dose bowel preparation before colonoscopy has been demonstrated to significantly improve the number of satisfactory bowel preparations, and is associated with increased patient compliance and decreased nausea compared with full-dose PEG.[23] In a systematic review and meta-analysis, Enestvedt et al. concluded that bowel preparation with 4 liter of split dose PEG-solution is superior than other bowel preparation methods.[24] Several endoscopy societies now recommend 4 liter split dose PEG-solution as the first choice bowel preparation,[25] although 2 liter PEG-solution with ascorbate may be an alternative in the non-constipated patient. Routine use of sodium phosphate preparations is not recommended because of safety concerns, especially in patients with renal insufficiency.[25] In patients using PEG-solutions, the interval between the last ingested dose of PEG-solution and the colonoscopy should be 3-5 hours, as this has been shown to result in significantly better bowel preparation.[26,27]

In the literature, several risk factors for inadequate bowel preparation have been identified. Increasing age[28-31] and male gender[29-32] have repeatedly been reported. A medical history of colorectal surgery,[28,29] diabetes[28,29] and cirrhosis,[29,32] as well as inpatient status[30,32] have also been identified as risk factors for inadequate bowel preparation in several studies. Other risk factors that have been suggested in the literature are a procedural indication of constipation, a reported failure to successfully complete the bowel lavage, the use of tricyclic antidepressants, a history of stroke or dementia,[32] a history of Parkinson's disease, being overweight, having had a positive FOBT,[29] a history of hysterectomy[28] and being of African-American descent.[31] A history of previous polypectomy was a negative predictive factor for inadequate bowel preparation in the study by Ness et al.[32] Furthermore, a later colonoscopy starting time during the day was associated with inadequate bowel preparation in several studies.[30-32] Most of these studies

however were conducted before the wide application of a split-dose bowel preparation regimen. Whether this association currently still is valid remains to be elucidated.

Several scales have been developed to standardize the reporting of bowel preparation quality. Aronchick et al. were the first to propose a validated bowel preparation scale.[33] This is a 5 point categorical scale, rating bowel preparation as excellent (small volume of clear liquid; >95% of surface seen), good (large volume of clear liquid covering 5-25% of surface; >90% of surface see), fair (some semi-solid stool suctioned or washed away; >90% of surface seen), poor (semi-solid stool that could not be suctioned or washed away; <90% of surface seen) or inadequate (repeat bowel preparation necessary). Unfortunately, the reliability of this scale for the distal colon is rather poor.

Rostom and Jolicoeur developed and prospectively validated another bowel preparation scale, the Ottawa scale.[34] In this scale, the colon is divided into three segments: right colon (cecum and ascending colon), mid colon (transverse and descending colon) and rectosigmoid. For each segment, bowel preparation is qualified using a 4 point scale (0: perfectly clear to 4: solid stools and lots of fluid) for each colon segment individually and a 0 to 2 fluid quantity rating as a global value for the entire colon. The scale thus has a range from 0 (perfect bowel preparation) to 14 (completely unprepared).

Finally, in 2009 Lai et al. introduced the Boston Bowel Preparation Scale (BBPS).[35] In this validated bowel preparation scale, the colon is divided into the right colon (cecum and ascending colon), transverse colon (including both the hepatic and splenic flexure) and the left colon (descending colon and rectosigmoid). The BBPS is a ten point scale (0-9) with 0-3 points allocated to each colon segment, i.e. 0 (unprepared colon segment that cannot be cleared), 1 (portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid), 2 (minor residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well) 3 (entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid). In the validation study, a score of ≥5 was considered adequate.The BBPS differs from other preparation scales in that the score is applied after the endoscopist has performed cleansing maneuvers, like suctioning and washing.

All these scales have mainly been used in studies comparing new formulas or different schemes for bowel preparation,[33,36-40] rather than being used to assist in clinical decision making. In a recent retrospective study, Calderwood et al. reported that the BBPS correlated with endoscopist behavior with regard to the advice for follow-up intervals for colonoscopy.[41] A total BBPS score of ≥6 and/or all segment scores ≥2 provided a standardized definition of an 'adequate' bowel preparation, whereas in 96% of examinations with a total score of ≤2 a repeat examination within 1 year was recommended. For scores 3 to 5 however, recommended surveillance intervals varied widely between endoscopists. Future studies should focus on prospectively evaluating these cut-offs

for surveillance interval recommendations and ideally associating them with relevant clinical outcome measures.

The widely adopted quality indicator for bowel preparation has several shortcomings. First of all, there is still no clear and generally accepted definition of adequate bowel preparation. Furthermore, the mere reporting of the quality of bowel preparation in itself is unlikely to significantly affect the quality of the colonoscopies performed, unless it becomes more clear what bowel preparation quality is the absolute minimum to detect relevant findings and to prevent interval cancers. There is also no clear policy on how to proceed when a patient's bowel is inadequately cleansed; the only relevant published studies on this topic had either small patient numbers[42] or a retrospective design.[43]

The rule that ≥90% of patients undergoing colonoscopy should have an excellent or adequate bowel preparation is consensus based and has found its way into several guidelines.[19,20] However, there is no scientific evidence to support this cut-off at 90%. Although inadequate bowel preparation has been shown to negatively affect the rate of detected polyps, this does not appear to be the case for CRCs.[21] It is conceivable that, through the negative effect on the detection of adenomas, an inadequate bowel preparation is associated with a higher rate of interval cancers, but to date, there is no direct evidence to support this.

CECAL INTUBATION RATE

In order to visualize the entire colonic mucosa, intubation of the endoscope to the cecum is mandatory. Cecal intubation is defined as introduction of tip of the colonoscope into the cecal pole, proximal of the ileocecal valve in order to have the entire cecum visualized. Although this sometimes may be challenging, there is consensus that each endoscopist should have a cecal intubation rate of ≥90% of all cases.[18-20,44,45] When not taking into account obstructing CRCs, inadequate bowel preparation or severe colitis, this adjusted cecal intubation rate should be ≥95%.[18] Also, in ≥95% of all screening colonoscopies the cecum should be intubated.[18,19] Furthermore, cecal intubation should be documented by naming and photographing the landmarks of the cecum, i.e. the appendiceal orifice, the ileocecal valve and/or the terminal ileum.

In the literature, several factors have been associated with a higher risk of incomplete colonoscopy or more difficult intubation, with female gender being the most frequently reported predictive factor.[46-50] In addition, patients with advanced age[46,49,50] or a low body mass index,[48-50] or in women with a history of hysterectomy[47] or diverticular disease,[50] colonoscopy is reported to be more difficult and more often incomplete. Finally, poor bowel preparation and lower endoscopist annual case volume have been reported to be associated with a higher risk of incomplete colonoscopy.[49]

Completeness of the colonoscopy is associated with a reduction in mortality from CRC.[6] In a study by Neerincx et al., a secondary colonoscopy after previous incomplete colonoscopy yielded initially missed advanced neoplasia (CRC or advanced adenoma) in 4.3% of patients.[51] In a study on the yield of CT-colonography after incomplete colonoscopy in 136 patients, in 13.9% of patients one or more additional colonic neoplastic lesions (polyp(s) and/or CRC) were found.[52]

These findings suggest that in cases of incomplete colonoscopy the clinician should always perform additional imaging to visualize the remaining colon. Following incomplete colonoscopy, the cecum can usually be intubated in the majority of patients during a repeat colonoscopy with readily available endoscopic instruments, suggesting that a repeat colonoscopy should always be considered.[47,53] CT-colonography might be a useful alternative in these cases, with the additional benefit of detecting potentially relevant extra-colonic findings.[52]

It is important to keep in mind that there is no robust scientific evidence for a cecal intubation rate of ≥90%. Although it is obvious that an endoscopist is not able to adequately inspect colon segments that were not intubated, the accepted minimal cecal intubation rate is based on consensus rather than on a scientific basis.

WITHDRAWAL TIME

In 2006, Barclay et al. were the first to report that colonoscopists with a mean withdrawal time of 6 minutes or more had higher detection rates of any neoplasia and advanced neoplasia.[54] Since then, a recommended mean withdrawal time of at least 6 minutes has been formulated as a quality indicator in several colonoscopy guidelines.[18-20]

However, colonoscopic withdrawal time as a quality indicator is not undisputed. Since the initial publication by Barclay et al.,[54] several observational studies have reported on the association between colonoscopic withdrawal time and the number of detected polyps.[55-59] Other large studies could however not confirm these findings.[60-62] Furthermore, interventions directed at optimizing withdrawal time, in an attempt to improve polyp detection, have yielded conflicting results. Although Barclay et al. did report higher rates of overall and advanced neoplasia detection during screening colonoscopy after implementing a time-dependent colonoscopic withdrawal protocol,[63] other authors were not able to find a difference in overall polyp detection rate after formally implementing such a policy.[64,65]

Gellad et al. were the first to study the association between withdrawal time during an initial, negative colonoscopy and the risk of developing neoplasia in the next five years.[66] They did not detect any significant association. However, mean baseline withdrawal time in the 13 participating centers was rather long (greater than 12 minutes), possibly

explaining the non-confirmatory results. It is possible that withdrawal time no longer is an adequate quality measure for screening colonoscopy above a certain threshold.

The use of the indicator withdrawal time is based on the assumption that endoscopists who take longer to withdraw the colonoscope also use specific techniques to improve visualization of the entire colonic mucosa. A study of two endoscopists with different rates of missed adenomas indeed showed that a better quality colonoscopic withdrawal technique was associated with a longer withdrawal time.[67] Lee et al. reported that the number of detected adenomas was found to be associated with the quality of withdrawal technique, but not necessarily related to withdrawal time.[62] Withdrawal technique may therefore be a more important indicator for colonoscopy quality than withdrawal time. At present, there is however no generally accepted way to quantify an optimal withdrawal technique.

It is conceivable that the derived quality indicator withdrawal time in the future will be replaced by a measure of the proportion of the colonic mucosa that is adequately visualized during colonoscopy. Interestingly, Hong et al. recently reported on a fully automated three-dimensional reconstruction technique from individual colonoscopy images.[68] Such a technique might eventually give real time feedback to the endoscopist on areas of the colonic wall that are not adequately inspected, thus enabling revisiting these areas during the same procedure. The percentage of the colon surface that is visualized by the endoscopist may potentially serve as a new quality indicator for colonoscopy. Furthermore, information on inspected and uninspected areas of the colonic wall may help in training endoscopists, giving insight in possible 'blind spots' during scope withdrawal.

As mentioned above, the association between the quality indicator withdrawal time and the occurrence of interval cancers has not yet been elucidated.

ADENOMA DETECTION RATE

The adenoma detection rate (ADR) is defined as the proportion of screened subjects in whom at least one adenomatous lesion is identified.[18,19,69] In an asymptomatic screening population, an ADR of ≥25% in men and of ≥15% in women over 50 years old has been proposed in the American screening guidelines,[18] whereas the British Quality Assurance Guidelines for Colonoscopy has set the standard ADR, based on their own pilot data, at ≥35% of all screening colonoscopies in patients who had a positive FOBT.[19]

Repeatedly, considerable variations between endoscopists in the rate of detected polyps and adenomas have been shown.[70-74] The ADR is the only current quality indicator that has been demonstrated to be directly associated with interval colorectal cancer. In the landmark study by Kaminski et al., an ADR ≥20% was associated with a reduction

in interval colorectal cancers.[69] A recent study by Corley et al. showed that the ADR was inversely associated with the risk of interval CRC, but also with advanced-stage interval cancers and fatal interval cancers.[75]

In line with these findings, many recent studies have focused on ways to optimize adenoma detection, ranging from inexpensive and easy to implement interventions in daily clinical practice, to minor adaptations of currently used colonoscopy equipment to completely new colonoscopy platforms.

Position changes during colonoscope withdrawal have been reported to increase luminal distension and may reduce the rate of missed lesions.[76] Two small randomized studies have indeed suggested that dynamic patient position changes may improve polyp detection,[77,78] but there was no difference in polyp or adenoma detection rates in another, larger randomized study.[79]

Endoscopy nurse participation as a second observer during colonoscopy has been reported to significantly increase the overall number of detected polyps and adenomas found during colonoscopy,[80] and appears an easy to implement intervention to increase polyp detection rate (PDR) and ADR.[81]

Furthermore, the time of performing the colonoscopy may have an effect on the ADR. Testing the hypothesis that fatigue of the endoscopist, which increases as the day progresses, might affect ADR, Sanaka et al. were the first to report that the ADR of endoscopists was significantly higher in morning colonoscopies than in afternoon colonoscopies.[82] The time of the colonoscopy during the day was an independent predictor for adenoma detection. These findings have been confirmed by almost all other studies on this subject.[83-86] Gurudu et al. proposed that colonoscopies should best be performed in half-day blocks by different physicians. They found no significant difference in ADR between morning and afternoon colonoscopies when endoscopists only perform colonoscopies in half-day blocks.[83]

The use of high definition colonoscopy as compared to standard video colonoscopy has been reported to have only a marginal beneficial effect on the detection of colonic polyps and adenomas in a recent meta-analysis.[87] Due to heterogeneity of the included studies and the fact that no randomized trials were available, these results should be interpreted with some caution.

Virtual chromoendoscopy consists of multiple techniques that use a narrow spectrum of wavelengths with a decreased penetration depth to enhance visualization. Light of short wavelengths increases vascular contrast of the mucosa, potentially improving visualization and the identification of neoplastic lesions. Although there are some conflicting data, most studies and meta-analyses have not been able to demonstrate a substantial increase in ADRs with pan-colonic virtual chromoendoscopy.[88-90]

Cap-assisted colonoscopy is performed by attaching a transparant cap to the tip of the colonoscope. These caps were originally designed to be used during endoscopic

mucosa resection, but they might also aid in depressing colonic folds to improve visualization of the entire colonic mucosa. However, in a meta-analysis of 16 randomized controlled trials including 8,991 subjects, Ng et al. concluded that cap-assisted colonoscopy only had a limited effect on ADR, although a higher proportion of patients with polyp(s) were detected when a cap was attached (relative risk 1.08; 95% confidence interval 1.00-1.17).[91]

It has been reported that retroflexion of the colonoscope might aid in the removal of polyps that are difficult to access endoscopically.[92,93] Conceivably, inspection with a retroflexed colonoscope may also help in increasing visualization of the proximal aspects of colonic folds, especially in the right colon, and thereby increasing ADR. However, although this technique appears safe in experienced hands, both a randomized study and a large prospective observational study failed to demonstrate a relevant increase in the number of detected polyps.[94,95]

In recent years, several new devices have been developed to improve visualization of the proximal sides of colonic folds and inner curvatures. First, the Third-Eye Retroscope® [Avantis Medical Systems], Inc is a through-the-scope catheter with a camera and light source at the tip. After advancement through the working channel of the colonoscope, the catheter is retroflexed 180° (Figure 1). It then provides a 135° retrograde view of the colon. In a randomized, multicenter back-to-back study, the Third-Eye Retroscope yielded a net additional detection rate of 29.8% for polyps and 23.2% for adenomas compared to standard colonoscopy.[96] An advantage of this device is that it can be used with standard colonoscopy equipment. However, use of this device in clinical practice may be hampered by the fact that the Third-Eye Retroscope needs to be removed from

Figure 1. Third-Eye retroscope

the working channel in case a polypectomy snare or biopsy forceps is used. Furthermore, when the device is in place, the colonoscope has reduced suctioning capacity. These factors may increase procedural time and may be experienced as bothersome by the endoscopist.

Recently, Gralnek et al. reported the results of the first international, multicenter, randomized, back-to-back study with the new Full Spectrum Endoscopy™ platform [FUSE; EndoChoice®, Alpharetta, Georgia, United States].[97] The full spectrum colonoscope allows a high resolution 330° view of the colonic lumen, as compared to the 140-170° of standard colonoscopes (Figure 2). In their study including 185 subjects, the adenoma miss rate was significantly lower in patients in whom colonoscopy was performed with the full-spectrum endoscope first: in the latter group five (7%) of 67 adenomas were missed versus 20 (41%) of 49 adenomas in the group that underwent standard colonoscopy first (P <0.0001). Although these results seem promising, further studies are required to determine the potential role for this system in non-expert centers. The obvious disadvantage in the implementation of this new device in daily clinical practice, is that new colonoscopes and main control units are required.

A potential downside of the current definition of ADR is that it does not discriminate between subjects in whom the endoscopist detects one versus more than one adenoma. It has been shown that physicians are more likely to miss additional adenomas during colonoscopy, when they have already detected two or more.[4]

Wang et al. concluded that, despite comparable and adequate ADRs, there can be considerable variability between endoscopists with regard to the total number of adenomas detected per colonoscopy.[98] They introduced a metric called the ADR-plus, the mean number of incremental adenomas after the first, and by coupling this to the ADR the authors were better able to distinguish high- from low-performing endoscopists. Lee et al. introduced two new measures in addition to the ADR that also may provide additional information on the inter-individual variation in the quality of performing colonoscopy: mean adenomas per procedure (MAP) and mean adenomas per positive procedure (MAP+).[99] However, how these new metrics translate to the occurrence of interval cancers is currently not known.

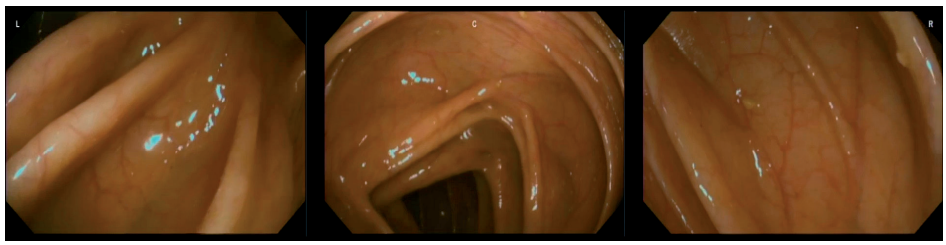

Figure 2. Endoscopic view using the Full Spectrum Endoscopy™ platform (FUSE)

PATIENT COMFORT AND SEDATION

Several guidelines recommend that sedation dosages as well as patient comfort scores should routinely be reported and monitored.[19,20] In their position statement on quality in screening colonoscopy, the European Society of Gastrointestinal Endoscopy (ESGE) proposed that no more than 1% of patients should have a saturation below 85% for more than 30 seconds or should require administration of a reversal agent.[20]

Patient comfort in the screening setting is important, as patients who consider screening colonoscopy as being too uncomfortable, are less likely to participate.[100] It may obviously impact the effect of population screening when a significant proportion of the target population does not participate. Recently, Rostom et al. have prospectively validated a nurse-assisted patient comfort score in a multicenter, international setting,[101] allowing for a uniform registration of patient comfort and comparison of colonoscopy practices. The various endoscopic societies have not yet adopted this validated comfort score. Which scores are considered acceptable and how to avoid drop-outs from the screening program has yet to be determined. Measuring comfort has the obvious caveat that endoscopists, nurses and patients may have different opinions about the level of (dis)comfort during the procedure.

Discomfort during colonoscopy can be reduced by the administration of sedatives. There is worldwide a large variation in the use of sedation for colonoscopy.[102-105] In some countries the majority of patients undergo colonoscopy unsedated, while elsewhere sedation with benzodiazepines combined with opiates is the standard of care. Entonox (nitrous oxide and oxygen) is frequently used in some countries, while elsewhere propofol and general anesthesia are increasingly being used in daily practice. Severe sedation-related complications have been reported to be rare: Behrens et al. reported a rate of 0.01% in their study of 388,404 endoscopies.[106] However, sedation-related adverse events need to be prevented, especially in an otherwise healthy screening population. There is however no validated score to record the level of sedation during colonoscopy, nor is there an accepted gold standard regarding sedation for colonoscopy.

Interestingly, a recent study from the United Kingdom screening program shows that, although there are wide variations in the use of sedation, colonoscopists' individual medication practice does not appear to be related to the occurrence of significant discomfort.[102] Instead, it is suggested that the best endoscopists cause less patient discomfort while using less sedation.[103]

COMPLICATION RATE

Colonoscopy is an invasive procedure that inadvertently will lead to complications in a small subset of patients. The rate of complications obviously is not necessarily associated with the interval CRCs. However, for a population screening program to have an overall beneficial effect, it is crucial that complication rates are low.

Perforation is the most serious complication of colonoscopy. It is defined as the presence of air, luminal contents or instrumentation outside the gastrointestinal tract.[19] It may result from mechanical trauma to the bowel wall, overinsufflation of the colon, or as a result of a therapeutic procedure. In the literature, reported overall rates of perforation range from 0.1-0.6%.[107-109] The perforation rate for diagnostic colonoscopies is lower than that of therapeutic interventions. The British guidelines for screening colonoscopy state a standard of <1:1000 risk of perforation in all colonoscopies,[19,20] and a <1:500 risk of perforation in colonoscopies in which polypectomy is performed.[19] This is largely consistent with the American guidelines,[18] although it is important to keep in mind that there may be a significant variation in perforation risk between a screening population in which each participant undergoes a colonoscopy and a screening population that is pre-selected by means of fecal occult blood testing. Proportionally, it can be expected that more polypectomies will be performed in the latter. Each country should set its own standards according to the local screening strategy.

Historically, surgical closure or resection of the perforated colon segment was the only therapeutic option in case of iatrogenic colonic perforation. Several case series have reported on successful endoscopic closure of small iatrogenic bowel wall defects using metallic endoclips, either with endoclips alone or using a combined technique of endoclips and endoloops.[110,111] In recent years, the over-the-scope clip [Ovesco Endoscopy GmbH, Tuebingen, Germany] has become available, with high rates of successful perforation closure in the first reported case series.[112,113]

Bleeding is the most common complication after polypectomy. Based on the literature, several guidelines set a standard of post-polypectomy bleeding in <1:100 colonoscopies with polypectomy.[18,19] It is known that the risk of bleeding increases with size of the lesion and a more proximal location in the colon.[114] Several endoscopic techniques can be used to prevent bleeding. Cold snaring of small, non-pedunculated polyps may prevent delayed bleeding,[115] even in anticoagulated patients.[116] Submucosal injection with saline and epinephrin prevents immediate bleeding but probably not delayed bleeding.[117] Furthermore, prophylactic placement of a detachable snare around the stalk of a pedunculated polyp may prevent bleeding,[118,119] as well as prophylactic closure of the polypectomy site with metallic clips after removal of large (>2 cm) sessile or flat lesions.[120]

Post-polypectomy coagulation syndrome (PPCS), or transmural burn syndrome, is a known complication of colonoscopic polypectomy. It is defined by the development of abdominal pain, fever, leukocytosis and peritoneal inflammation in the absence of frank perforation that occurs after polypectomy with electrocoagulation.[121] To our knowledge, there is only one study that specifically focused on PPCS. In this large retrospective study, its incidence is reported to be 0.07% of all colonoscopies with polypectomy. Hypertension, a lesion size ≥10 mm and non-polypoid configuration of the lesion were independently associated with PPCS.[121] Correct identification of this entity is important, as this may avoid unnecessary explorative laparotomy. PPCS can usually be treated medically without a need for surgical intervention and without mortality. PPCS is not yet included in the current guidelines.

CONCLUSION

In summary, the main quality indicators for colonoscopy all have their shortcomings [Table 1]. Most of these have been formulated based on consensus. Following the guideline Quality Indicators for Colonoscopy from the American Society of Gastrointestinal Endoscopy from 2006,[18] many other countries have adopted these same quality indicators. The scientific evidence on which they are based is however limited. Potential measures to improve performance on individual quality indicators are summarized in Table 2.

What is not yet clear is how to proceed when a fellow or senior endoscopist does not meet the required standards. Individualized additional training or a binding negative advice to continue the fellowship could be an option for endoscopists in training. However, this could be difficult for senior endoscopists that have practiced for years, especially when the scientific basis for these quality indicators is still not well established. What further needs to be addressed, is how to check that endoscopists indeed perform colonoscopy according to the standard of care set by their peers or national guidelines.

ADR currently is the only quality indicator that has been shown to be directly associated with the outcome measure interval colorectal cancer. As such, it seems reasonable to let this indicator prevail in discussions with endoscopists who fail to meet the set standards.

Ideally, endoscopists should only be evaluated and compared by the most relevant outcome measure in the context of screening colonoscopies, i.e. the occurrence of interval CRCs. Since the incidence of interval CRCs is fortunately rather low, and the duration between colonoscopy and interval CRC is rather long, this may prove to be too slow and rigid a quality indicator in daily practice to timely intervene in case of substandard colonoscopy performance.

Table 1. Quality indicators and their shortcomings

Quality indicator	Proposed standard	Unresolved issues
Bowel preparation	Each endoscopy report should state the quality of the bowel preparation[18,19]	No evidence to support a cut-off of ≥90% No clear and generally accepted definition of adequate bowel preparation
	≥90% of patients undergoing colonoscopy should have had a bowel preparation rated as excellent or at least adequate[19,20]	Unclear what bowel preparation quality is the absolute minimum to detect relevant findings and prevent interval cancers No clear policy on how to proceed in case of inadequate bowel preparation
Cecal intubation rate	Overall cecal intubation rate of ≥90%[18-20] Adjusted cecal intubation rate of ≥95%[18,19] Cecal intubation rate of ≥95% in all screening colonoscopies[18,19]	No robust scientific evidence to support a cut-off of ≥90% No evidence supporting an association between cecal intubation rate and the occurrence of interval CRC
Withdrawal time	≥6 min on withdrawal from cecal pole to anus[18-20]	Conflicting reports on the association between withdrawal time and the number of detected polyps Interventions directed at optimizing withdrawal time have yielded conflicting results No evidence supporting an association between withdrawal time and the occurrence of interval CRC Better endoscopic withdrawal technique is not necessarily associated with withdrawal time An indirect measure to quantify the proportion of the colonic mucosa that is adequately visualized
Adenoma detection rate	≥25% in men and ≥15% in women over 50 yr[18] ≥35% of all screening colonoscopies in patients with a positive FOBT[19]	The only quality indicator that has been shown to be directly associated with interval CRC Does not discriminate between subjects in whom the endoscopist detects one versus more than one adenoma Does not optimally differentiate between high- and low-performing endoscopists
Patient comfort and sedation	Routinely reporting and monitoring of patient comfort scores and sedation dosages[19,20]	Until recently no validated patient comfort score was available Not yet clear what patient comfort scores are considered acceptable The endoscopist, the nurse and the patient may have different opinions about the level of comfort during the procedure No gold standard regarding sedation during colonoscopy No validated score to assess the level of sedation during colonoscopy
Complication rate	Perforation in <1:1000 colonoscopies[18-20] Post-polypectomy bleeding in <1:100 colonoscopies with polypectomy[18,19]	Consensus based Complication rate is mainly dependent on the number of therapeutic colonoscopies, which may vary between screening strategies (colonoscopic screening of the entire population versus selection of high-risk individuals through fecal occult blood testing)

Until we find a better measure to approximate the risk of interval CRCs, the current set of quality indicators will have to suffice. However, they need to be interpreted with caution and continuously adjusted as more information becomes available. For instance, both withdrawal time and ADR are a derivative of the quality with which the entire colonic mucosa is visualized during colonoscopy and in time may be replaced with a more direct measure for the proportion of the colonic mucosa that is inspected.

Table 2. Potential measures to improve performance per quality indicator

Quality indicator	Potential intervention to improve performance	Strength of scientific evidence
Bowel preparation	Split dose bowel preparation	Meta-analysis of randomized controlled trials
	Last ingested dose of PEG-solution 3-5 hours before colonoscopy	Observational, prospective studies
Cecal intubation rate	Additional training and use of auxiliary endoscopic instruments (e.g. pediatric colonoscope)	Expert opinion
Adenoma detection rate	Endoscopy nurse participation as a second observer	Randomized, multicenter studies
	Perform colonoscopy in the morning or in half-day blocks	Retrospective studies
	High definition colonoscopy (compared to standard video colonoscopy, marginal effect)	Meta-analysis
	Cap-assisted colonoscopy (marginal effect)	Meta-analysis of randomized controlled trials
	Third-Eye Retroscope	Randomized, multicenter study
	Full Spectrum Endoscopy (FUSE)	Randomized, multicenter study
Complication rate	Cold snaring of small, non-pedunculated polyps may prevent bleeding	Prospective, multicenter, observational study and small single center randomized controlled study
	Submucosal injection with saline and epinephrin prevents immediate bleeding	Randomized study
	Prophylactic placement of a detachable snare around the stalk of a pedunculated polyp prevents bleeding	Randomized studies
	Prophylactic closure of the polypectomy site with metallic clips after removal of large (>2 cm) sessile or flat lesions may prevent bleeding	Retrospective study

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CHAPTER 5

CT-colonography after incomplete colonoscopy: what is the diagnostic yield?

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ABSTRACT

Background

CT-colonography (CTC) is a diagnostic modality which can be used when the colon is not completely intubated during colonoscopy. It may have the additional advantage that information on extracolonic lesions can be obtained.

Objective

To investigate the yield of CTC of relevant intra- and extracolonic findings in patients after incomplete colonoscopy.

Methods

We reviewed consecutive CTCs performed after incomplete colonoscopy. All intra- and extracolonic findings on CTC were recorded and interpreted for clinical relevance and it was determined whether further diagnostic and/or therapeutic work-up was indicated.

Results

In total, we evaluated 136 consecutive CTCs performed after incomplete colonoscopy. Major indications for colonoscopy included iron-deficiency anemia (25.7%), hematochezia (20.6%), change in bowel habits (18.4%) and colorectal cancer screening or surveillance (11.0%). Major reasons for incomplete colonoscopy were a fixed colon (34.6%) and strong angulation of the sigmoid colon (17.6%). Introduction of the colonoscope was limited to the left-sided colon in 51.5% of cases. Incomplete colonoscopy detected colorectal cancer in 12 (8.8%) patients and adenomatous polyps in 27 (19.9%) patients. CTC after incomplete colonoscopy additionally revealed 19 polyps in 15 (11.0%) and a non-synchronous colorectal cancer in 4 (2.9%) patients. CTC also detected extracolonic findings with clinical consequences in 8 (5.9%) patients, including fistulizing diverticulitis (n=3), gastric tumor (n=2), liver abscess (n=1), osteomyelitis (n=1) and an infected embolus in both renal arteries (n=1).

Conclusions

CTC can be of added value in patients with incomplete colonoscopy as it revealed 27 relevant additional (both intra- and extracolonic) lesions in 19.1% of patients. In cases when CTC detected colorectal cancer after incomplete colonoscopy, it can also be used for staging purposes.

INTRODUCTION

Colonoscopy has been the diagnostic procedure of choice for examining the colon and rectum for many years,[1] although it is well known that detection rates of significant pathology are operator dependent.[2] Cecal intubation rates may vary between experienced endoscopists and depend on various factors, with inadequate bowel preparation, anatomic variants, fixed colon segment(s), obstructing lesions and pain being only a few of the possible reasons for incomplete colonoscopy.[3] A generally accepted rule is however that each endoscopist should be able to intubate the cecum in at least 90% of colonoscopies.[4]

A recent study showed that advanced neoplasia can be missed in up to 4.3% of patients during incomplete colonoscopy, suggesting that further colonic evaluation is mandatory in these cases.[5] One of the suggested options is to refer a patient for a second procedure to a skilled endoscopist with a known high colonoscopic success rate.[6] A repeat colonoscopy on a different occasion, however, has the disadvantage of a repeat, burdensome bowel preparation with the risk of a second procedure failure.

Several radiological modalities are available to visualize the colon. Double contrast barium enema has traditionally been the procedure of choice after incomplete colonoscopy. It has a high success rate (>99%) for visualizing the entire colon.[7] In recent years, computed tomography colonography (CTC) has emerged as an alternative modality to visualize the colonic lumen. Although relatively new, it is a diagnostic modality with proven good results for detecting polyps with a size of 5 mm or larger[8] and has been suggested to be a promising screening modality for colorectal cancer (CRC).[9] In addition, it can be used to investigate the colon in patients in whom colonoscopy is contra-indicated. The fact that both intracolonic and extracolonic lesions can be visualized may make this modality attractive in patients with symptoms, which possibly but not definitely originate from the colon.

To our knowledge, little data are available on the diagnostic yield of CTC in patients after incomplete colonoscopy. In this study, we retrospectively investigated a consecutive cohort of patients who underwent CTC after incomplete colonoscopy, and also focused on additional intra- and extracolonic findings that affected clinical management in these patients.

METHODS

We performed an observational, retrospective study including consecutive patients who underwent CTC after incomplete colonoscopy in our unit in the period January

2007 until April 2011. Incomplete colonoscopy was defined as failure to intubate the cecum. In our institution, CTC has completely replaced double contrast barium enema.

Bowel preparation for colonoscopy consisted of polyethylene glycol (PEG) solution (4 L). Colonoscopies were performed under conscious sedation with midazolam and fentanyl. The decision whether or not the patient should undergo CTC after incomplete colonoscopy was left to the discretion of the endoscopist. In the last few years, in cases when it was decided to perform CTC after incomplete colonoscopy, we had the policy to preferably perform the CTC on the same day as the incomplete colonoscopy.

The CTC protocol consisted of a low-dose CT in the prone position, followed by a full-dose diagnostic CT with intravenous (i.v.) contrast medium in the supine position. Based on prior experience, in our institution we perform the latter as a full-dose CT with i.v. contrast medium to optimize the characterization of extracolonic findings. When CTC was not performed on the same day, patients took a bowel preparation consisting of two doses of magnesium sulphate (30 g) and four doses of bisacodyl (20 mg). Prior to CTC, oral amidotrizoinic acid based contrast medium (20 ml) was administered for fecal tagging. In cases when CTC was performed on the same day, no additional bowel preparation was used. Automated rectal insufflation of carbondioxide was accompanied by i.v. administration of butylscopolamide (20 mg). All CTCs were performed using a 16- or a 64-slice multidetector CT [Philips Medical Systems, Best, the Netherlands] with a detector configuration of 16 x 0.75 mm, 120 kVp (supine)/90 kVp (prone), 200 mAs (supine)/ 100 mAs (prone), a tube rotation time of 0.5 s and a pitch of 1.3. Data were reconstructed using a slice thickness of 1 mm. All radiological data were pre-processed and evaluated using Philips View Forum [Philips Medical Systems, Best, the Netherlands] and reviewed by two expert radiologists.

The results of the colonoscopy and the CTC were separately collected. Findings during colonoscopy, particularly indication for the procedure, most proximally intubated colon segment, reason(s) for failure to intubate the cecum and number and type of intraluminal lesions were obtained from the endoscopy report. All these items are part of a standardized endoscopy report in our unit. For CTC, both intra- and extracolonic findings were recorded. Extracolonic findings were classified in concordance with the CTC Reporting and Data System (C-RADS).[10] Information was collected from the electronic medical record with regard to the follow-up action when CTC revealed specific findings requiring further diagnostic or therapeutic work-up.

In the Netherlands, no informed consent or institutional approval is required for this type of observational, retrospective research with anonymized patient data.

RESULTS

In the study period, a total of 6,931 colonoscopies was performed in our unit. In 506 (7.3%) patients, colonoscopy was incomplete, i.e., the cecum was not intubated. In 136 patients (26.9% of all incomplete colonoscopies, 2.0% of all colonoscopies), CTC was performed after incomplete colonoscopy. Patients in whom colonoscopy was incomplete because of insufficient bowel preparation did not undergo additional CTC but were scheduled for a new colonoscopy after more extensive bowel preparation. Patients with a stricturizing CRC in the ascending colon also did not undergo additional CTC, as the proximal colon will be resected together with the CRC. In the other patients with incomplete colonoscopy, repeat colonoscopy, another type of radiological procedure, such as abdominal CT, or no additional diagnostic procedure was performed, but these were not included in the current evaluation. None of these patients underwent a barium enema.

Mean age of patients undergoing CTC was 63.9 years and 76 (55.9%) patients were female. Indications for colonoscopy are summarized in Table 1. The majority of colonoscopies was performed in symptomatic patients. In 15 (11.0%) asymptomatic patients, colonoscopy was performed for screening or surveillance.

In 70/136 (51.5%) patients, introduction of the colonoscope was limited to the left-sided colon. In 28 (20.6%) patients, the ascending colon was the most proximally intubated colon segment. Reasons for incomplete colonoscopy are summarized in Table 2. Incomplete colonoscopies yielded CRC and adenomatous polyps in 12 (8.8%) and 27 (19.9%) patients, respectively [Figure 1]. All detected polyps were endoscopically removed during the procedure, unless the endoscopist decided otherwise, for example

Table 1. Indications for colonoscopy

	n (%)
Anemia	35 (25.7)
Hematochezia	28 (20.6)
Change in bowel habits	25 (18.4)
Constipation	9 (6.6)
Abdominal pain	8 (5.9)
Familial predisposition for CRC	8 (5.9)
Diarrhea	7 (5.1)
Polyp surveillance	6 (4.4)
Weight loss	2 (1.5)
Screening of asymptomatic patients	1 (0.7)
Suspicion of CRC on abdominal ultrasound	2 (2.2)
Other	5 (3.7)

Table 2. Most proximally intubated part of the colon during incomplete colonoscopy and reasons for incomplete colonoscopy

Most proximally intubated colon part	**n (%)**	
Ascending colon	28 (20.6)	
Hepatic flexure	24 (17.6)	
Transverse colon	14 (10.3)	
Splenic flexure	3 (2.2)	Introduction limited to the left-sided colon in 51.5%
Descending colon	11 (8.1)	
Sigmoid colon	53 (39.0)	
Rectum	3 (2.2)	
Reasons for incomplete colonoscopy		
Fixated sigmoid colon	47 (34.6)	
Angulation of the sigmoid colon	24 (17.6)	
Intractable pain	11 (8.1)	
Obstructing CRC	9 (6.6)	
Dolichocolon (long, abundant colon)	8 (5.9)	
Atonic colon	6 (4.4)	
Inadequate bowel preparation	4 (2.9)	
Abdominal wall herniation	3 (2.2)	
Undetermined colonic stricture	3 (2.2)	
Spastic colon	2 (1.5)	
Systemic problems (bradycardia, chest pain)	2 (1.5)	
Not reported	11 (8.1)	
Other	6 (4.4)	

because the polyp was located in a segment of the colon that was expected to be resected because of a concurrent CRC. In 57 (41.9%) patients, no abnormalities were found during incomplete colonoscopy [Table 3].

Fifty-six (41.2%) patients underwent CTC on the same day as the incomplete colonoscopy [Table 4]. An additional 39.0% of CTCs was performed within 1 month after colonoscopy. CTC after incomplete colonoscopy yielded an additional CRC in 4 patients. These malignancies were all located proximally to a fixed colon segment that could not be passed during colonoscopy. CRC diagnosis was confirmed in all patients during surgical resection and subsequent histopathological examination. None of the CRC patients had a synchronous CRC. In another 15 (11.0%) patients, 19 additional polyps were found, i.e., polyps that were not reported or not removed during the previous colonoscopy [Table 3]. One of these polyps, a flat lesion, was located in a colon segment that had previously been endoscopically inspected. This lesion was later found to contain a focus of adenocarcinoma after endoscopic polypectomy. Six other patients also underwent a second colonoscopy. In 4 of these, CTC findings were reproduced and the adenomatous

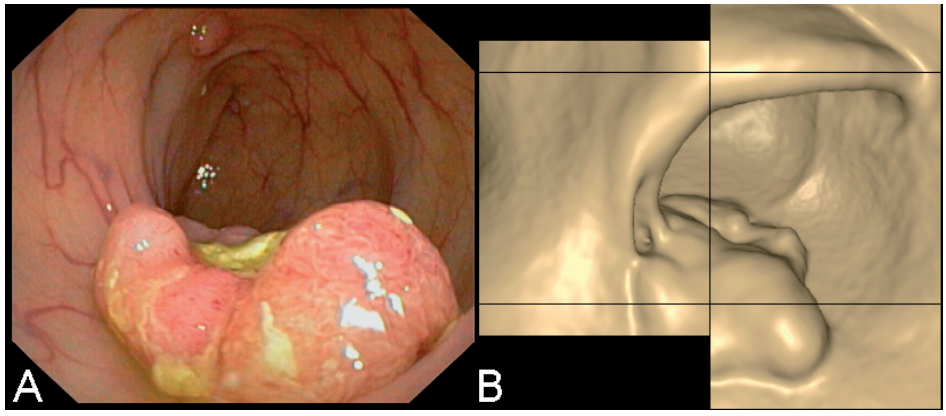

Figure 1. Endoscopic (panel A) and CT colonographic (panel B) appearance of a small, crater shaped colorectal cancer located near the splenic flexure

polyps were endoscopically removed. In two patients, the polyps that were seen in the cecum during CTC were in fact inverted appendix stumps [Figure 2]. The other 8 patients in whom additional polyps were found during CTC (6 of whom had polyps <5 mm) were scheduled for follow-up. There was no significant difference in the additional yield of intracolonic pathology between the patients with and without CRC.

Table 3. Yield of incomplete colonoscopy* and intracolonic findings during CTC

Incomplete colonoscopy	**n (%)**	
CRC	12 (8.8)	
Adenomatous polyp(s)	27 (19.9)	
Diverticular disease	48 (36.8)	
Diverticulitis	7 (5.1)	
Hemorroids	7 (5.1)	
Angiodysplasia	3 (2.2)	
Normal	57 (41.9)	
CTC		**Additional yield compared with colonoscopy**
CRC	16 (11.8)	+4
Polyp(s)	15 (11.0)**	+19**
Diverticular disease	34 (25)	-
Diverticulitis	7 (5.1)	-
Normal	67 (49.3)	-

*>1 relevant finding in 33 patients

** In 15 patients, a total of 19 additional polyps were found that were not previously reported or removed at colonoscopy. One of these polyps was found to harbor CRC at second colonoscopy, two polypoid lesions in the cecum were found to be inverted appendix stumps at second colonoscopy

Table 4. Interval between incomplete colonoscopy and CTC

	n (%)
On the same day as colonoscopy	56 (41.2)
Within 1-7 days after colonoscopy	19 (14.0)
Within 8-14 days after colonoscopy	12 (8.8)
Within 15-31 days after colonoscopy	22 (16.2)
More than 1 month after colonoscopy	27 (19.9)

Extracolonic findings on CTC are summarized in Table 5. The most relevant extracolonic findings were fistulizing diverticulitis (n=3), gastric tumor (lymphoma/GIST) (n=2), liver abscess (n=1), an infected embolus in both renal arteries (n=1) and presacral infiltration caused by chronic osteomyelitis (n=1), all in symptomatic patients. These findings were thought to be an explanation for the patients' presenting symptoms in 6 of 8 patients. None of these patients had a CRC.

Except for staging information, no other relevant extracolonic lesions were detected in the patients with CRC.

CTC could also be used as staging CT in the CRC patients and in the one patient with a missed malignant flat lesion, which was found to be an early adenocarcinoma during second colonoscopy. In all patients, the staging information obtained from the CTC was considered adequate during discussion in our multidisciplinary oncology meeting, i.e. no additional imaging studies of the abdomen were indicated. In 8 of the patients with CRC, locoregional lymphadenopathy and/or distant metastases were found, whereas in the other 9 patients no metastases were detected.

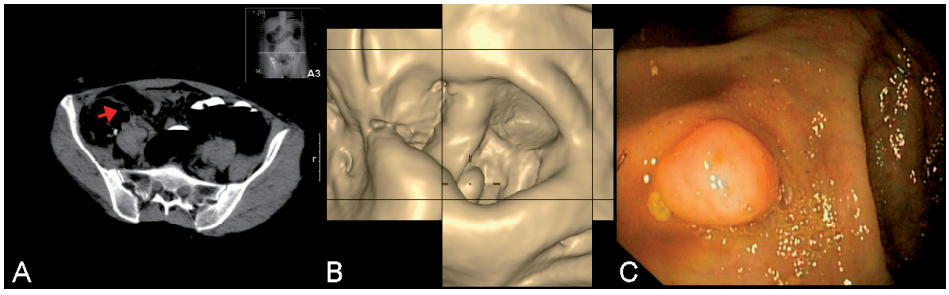

Figure 2. Polypoid lesion at CTC proved to be an inverted appendix stump at repeat colonoscopy
Panel A: regular CT-scan in the prone position (arrow: polypoid lesion), **panel B**: virtual reconstruction, **panel C**: colonoscopic appearance

Table 5. Extracolonic findings classified in concordance with the CTC Reporting and Data System (C-RADS)[10]

C-RADS Category	Category description	Finding	n (%)
E0. Limited examination	Comprised by artifact; evaluation of extracolonic soft tissues severely limited	—	0 (0)
E1. Normal examinatrion or anatomic variant	No extracolonic abnormalities visible	—	56 (41.2)
E2. Clinically unimportant finding	No work-up indicated	Renal cysts / atrophic kidney	11 (8.1)
		Liver cysts / hemangioma / known cirrhosis	11 (8.1)
		Diaphragmatic hernia	7 (5.1)
		Degenerative changes to osseous structures	6 (4.4)
		Inguinal or abdominal wall herniation	6 (4.4)
		Uncomplicated cholecystolithiasis	5 (3.7)
		Atherosclerosis	4 (2.9)
		Asymptomatic urolithiasis	3 (2.2)
		Known lymphadenopathy	3 (2.2)
		Known distant metastases	1 (0.7)
E3. Likely unimportant finding, incompletely characterized	Subject to local practice and patient preference, work-up may be indicated	Small aneurysmatic dilation of aorta or smaller arteries	3 (2.2)
		(Bilateral) benign adrenal gland hypertrophy	3 (2.2)
		Adnexal cysts	1 (0.7)
E4. Potentially important finding	Communicate to referring physician as per accepted practice guidelines	Positive N- or M-stage with newly discovered CRC	8 (5.9)
		Fistulizing diverticulitis	3 (2.2)
		Tumor in the stomach (gastric lymphoma/ GIST)	2 (1.5)
		Liver abscess	1 (0.7)
		Infected embolisms of the renal arteries	1 (0.7)
		Presacral infiltration due to chronic osteomyelitis	1 (0.7)

DISCUSSION

In this retrospective study including 136 consecutive patients with incomplete colonoscopy, we found that CTC yielded additional clinically relevant information on intra- and/or extracolonic lesions in almost a fifth (19.1%) of patients.

Other studies have also reported on the use of CTC after incomplete colonoscopy. These studies were however heterogeneous with regard to patient selection and CTC protocol. Particularly studies on CTC after incomplete colonoscopy from the late 1990s mainly focused on the feasibility of CTC to visualize segments of the colon that were previously not seen during colonoscopy.[11,12] Sali et al. recently reported 42 patients with a positive fecal occult blood test undergoing CTC after incomplete colonoscopy.[13] CTC showed a high per segment and high per lesion positive predictive value (PPV) for colonic masses and polyps larger than 9 mm. Neri et al. performed CTC in patients in whom a CRC was found during incomplete colonoscopy[14] and concluded that CTC provided complete information to adequately address the extent of surgical resection and the presence of liver metastases. Copel et al. performed CTC in 546 patients after incomplete colonoscopy.[15] However, they did not report on the presence of extracolonic findings in these patients. Like in our study, most patients underwent colonoscopy for abdominal symptoms or for reasons that were considered to be associated with an increased risk of having a CRC. Intravenous contrast was only administered in a minority of patients (41.8%), mainly depending on the initial indication for colonoscopy. These authors reported that CTC yielded seven additional CRCs in 6 (1.1%) patients and 76 additional polyps or polypoid lesions (both medium and large, 6-19 mm) in 65 (11.9%) patients. These results are very comparable to our study. The authors also calculated a high per patient PPV for intraluminal lesions. Unfortunately, no information was presented on the presence of extracolonic findings. We clearly demonstrated that relevant pathology can be found outside the colorectum in a significant number of patients.

In our study, we found additional intracolonic lesions on CTC in 19 (14.0%) patients. Two (1.5%) patients had a suspicion of a polyp in the cecum on CTC, but both lesions were found to be inverted appendix stumps at repeat colonoscopy. In both patients, appendectomy had been performed decades before, which was not communicated prior to colonoscopy or CTC. The finding of an inverted appendix stump on CTC has been reported previously and is an important finding that should be considered when a lesion in the cecum is seen on CTC.[16-18] In endoscopic series dating from the 1980s, the prevalence of inverted appendix stumps has been reported to be as high as 1.5% in patients undergoing colonoscopy.[19] However, it should also be kept in mind, that in those years a different technique for performing appendectomy was used.[18]

Interestingly, in our study a significant number of relevant CTC findings was detected outside the colorectum. This is in line with a recent study by Veerappan et al., who also

reported a relatively high yield of relevant extracolonic findings in 11.0% of patients undergoing CTC for colonic screening purposes.[20] This is based on both E3 and E4 lesions according to the C-RADS system [Table 5].[10] The authors concluded that CTC is a valuable alternative for optical colonoscopy for CRC screening. Furthermore, it can be used as a one time procedure to identify significant and treatable intracolonic and extracolonic lesions. However, the screening population in that study did not undergo CTC with i.v. contrast. In our study, we confirmed the findings that 11.0% of patients (n=15) had either an E3 or E4 finding on CTC [Table 5].

The vast majority of patients in this study underwent colonoscopy for abdominal symptoms. For that reason, all patients underwent CTC with i.v. contrast, conceivably adding to the interpretability of the extracolonic tissues. This may also explain our relatively low yield of undetermined incidental findings necessitating further diagnostic evaluation. In case of extracolonic findings, the radiologist was in most cases sufficiently confident with regard to the diagnosis to refrain from advising additional investigations. The use of i.v. contrast medium allows for a better characterization of extracolonic lesions according to the C-RADS system, e.g. downgrading 'incompletely characterized' (E3) extracolonic lesions to 'clinically unimportant findings' (E2) or upgrading them to 'potentially important findings' (E4).[10]

In our study, all relevant extracolonic findings were found in symptomatic patients. We therefore suggest that i.v. contrast should be considered in the population undergoing CTC after incomplete colonoscopy for abdominal symptoms.

The specific composition of our cohort may have influenced our results. Although it is possible that the prevalence of relevant extracolonic pathology is different in symptomatic and asymptomatic patients, the prevalence of relevant extracolonic lesions in our study is in line with previous reports on CTC in the screening population.[20] Furthermore, our findings are in line with the recent literature and with studies that had an alternative cohort composition, suggesting the observations we made are realistic. Caution is however warranted when generalizing our findings to different populations.

Oral contrast medium for fecal tagging prior to the CTC was not used in our patients when it was performed on the same day as the incomplete colonoscopy. Some authors have suggested that fecal tagging has advantages over i.v. contrast in patients without a known colorectal tumor at the time of performing CTC,[21] whereas in patients with a known CRC, i.v. contrast is of added value for staging purposes. The use of fecal tagging has been shown to increase the specificity of findings, i.e., to reduce the risk of false positive findings due to adherent fecal residue in the colon.[22]

A recent study by Chang et al. showed that fecal tagging 2 hours before CTC on the same day as the incomplete colonoscopy results in satisfactory opacification of the colonic lumen in the majority of patients, especially of the more proximal colonic segments that have not been visualized during incomplete colonoscopy.[23] Because we did not

use fecal tagging in the patients referred for same day CTC, it can be argued that there may have been a decreased detection of polyps due to polyps being submerged in an unopacified fluid pool. Although this may have had some effect on our results, patients with incomplete colonoscopy due to inadequate bowel cleansing were not included in the current evaluation. Furthermore, the bowel preparation regimen used in this study for colonoscopy is far more extensive than that for scheduled CTC. The patients who had a same day CTC thus all had an extensive bowel preparation with little or no fecal residue in the colon, conceivably limiting the additional value of added fecal tagging.

Since the last few years, it is our policy to perform CTC on the same day as the incomplete colonoscopy. This was found to be a successful policy, as the overall percentage of same day CTCs in this study was 41.2%, while during the last 2.5 years of the study a total of 54 of 82 (65.8%) CTCs were actually performed on the same day as the incomplete colonoscopy. From a patient's perspective, this has the obvious advantage of avoiding a second bowel preparation.

All CTCs were evaluated by a dedicated CTC radiologist. It has been shown that there is a learning curve for the interpretation of CTCs, with increasing experience and formal training improving specificity.[24,25] It also has been shown that experienced radiologists perform better than inexperienced but trained radiologists in terms of detecting intracolonic lesions and overall accuracy.[26]

A drawback of this study is that second look colonoscopy was not systematically performed when CTC suggested relevant intraluminal findings. This is inherent to the retrospective nature of the study. Furthermore, CTC was performed in only 26.9% of all incomplete colonoscopies. Because we identified our study population through the department of Radiology, we have no precise follow-up information on the other patients that underwent incomplete colonoscopy. We are also not informed about possible clinical factors that may have contributed to the choice for CTC, as the decision to perform additional CTC after incomplete colonoscopy was left to the discretion of the endoscopist. This may have biased our results. However, we believe that our results give a meaningful insight into the value of additional CTC after incomplete colonoscopy in every day clinical practice. Performing CTC raises the issue of radiation exposure. However, in our opinion, one time radiation exposure should not be regarded as a major clinical issue in symptomatic patients.

The final evidence for the added value of CTC after incomplete colonoscopy, if indeed required, should come from a randomized trial in which CTC is compared with repeat colonoscopy performed by another (expert) endoscopist for relevant findings, quality of life and acceptance of patients and cost-effectiveness.

In conclusion, our study shows that CTC is a valuable modality in patients with incomplete colonoscopy. Moreover, the administration of i.v. contrast during CTC can be of added value for detecting and characterizing extracolonic lesions, especially in symptomatic patients.

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CHAPTER 6

No decrease in the rate of early or missed colorectal cancers after colonoscopy with polypectomy over a 10-year period: a population-based analysis

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ABSTRACT

Background & Aims

It is not clear whether the incidence of missed or early colorectal cancers (CRCs) has decreased over time. We compared the rates of missed or early CRC after polypectomy between 1996 and 2006, and aimed to identify risk factors for these.

Methods

We performed a population-based case-control study linking data from the Dutch Pathology Registry with data from the Netherlands Cancer Registry. Of all patients with an incident CRC in 1996 and 2006, we identified whether colonic histology specimens were available in the preceding 3 years. Patients with early or missed CRC were defined as those with previous colonic histology in the 6 to 36 months preceding CRC diagnosis. We performed multivariate logistic regression analysis to identify factors associated with missed or early CRCs.

Results

CRC was diagnosed in 6941 patients in 1996 and 10,963 patients in 2006. The proportions of patients with early or missed CRC were 1.7% of all CRC patients in 1996 and 2.3% in 2006 (P=.012). Early or missed CRCs had a lower tumor, nodal and metastasis stage than regularly diagnosed CRCs (P <.001), but rate of survival, adjusted for TNM stage, did not differ. CRCs of the right colon and transverse colon and splenic flexure were associated with a missed or early CRC (odds ratio [OR]=2.34, 95% confidence interval [CI], 1.80-3.05 and OR=2.14, 95% CI, 1.49-3.08, respectively), as was male sex (OR=1.31, 95% CI, 1.06-1.62).

Conclusion

Based on an analysis of the Dutch population, there has been no decrease in the occurrence of missed or early CRCs over a 10-year period. Location in the right side of the colon was an independent risk factor for missed or early CRCs.

INTRODUCTION

Colonoscopic polypectomy reduces the incidence of subsequent colorectal carcinoma (CRC) and the mortality from CRC in the long term.[1,2] Sometimes CRCs are detected within a few years after previous colonoscopy. Most CRCs diagnosed within the first few years after an index colonoscopy are thought to be due to missed lesions, rather than new lesions.[3] In the last decennia, there have been reports on colonoscopic miss rates, which come almost exclusively from the North-American continent.[4-8] It is however unknown how colonoscopic miss rates have developed over time. Studies on missed or early CRCs have used retrospective cohorts spanning many years, making the evaluation of possible time trends in colonoscopic miss rate difficult if not impossible.[4-8]

It is however conceivable that the rate of missed or early CRCs after previous colonoscopy may have decreased over the years, due to the advent of technically more advanced endoscopy equipment, the increasing interest in quality indicators for colonoscopy[9,10] and ongoing attention to the importance of adequate bowel preparation.

The aim of this study was to assess the rate of missed or early CRC in a population-based setting and to evaluate its development over a 10-year period. The secondary aim was to identify risk factors that were associated with missed or early CRC.

METHODS

Data sources

We obtained data for this nationwide, population-based case-control study from two databases: the Netherlands Cancer Registry and the nationwide network and registry of histopathology and cytopathology diagnoses in the Netherlands (PALGA).

Since 1989, the Netherlands Cancer Registry is a nationwide database that covers over 95% of all incident cancer cases in the Netherlands. PALGA is a national registry, in which summaries of the original pathology reports are centrally archived. It was established in 1971 and accomplished nationwide coverage in 1991, resulting in central archiving of the reports generated by all pathology departments in the Netherlands.[11] Each pathology report is linked to a diagnostic code, in line with the Systemized Nomenclature of Medicine (SNOMED), issued by the college of American Pathologists.[12] The PALGA and the Netherlands Cancer Registry datasets were linked by an independent trusted third party and subsequently encrypted, enabling analysis of the anonymized, merged data.

This study was performed with the approval of and in accordance with the privacy and ethical guidelines of the privacy committee and the research committee of PALGA and the research committee of the Netherlands Cancer Registry.

Study population

We identified all incident cases of adenocarcinoma of the colon and rectum in the Netherlands in the years 1996 and 2006 using the Netherlands Cancer Registry database. Of these, we collected age at diagnosis, gender, incidence year, clinical and pathological tumor, nodal and metastasis (TNM) stage, tumor morphology (using International Classification of Diseases for Oncology (ICD-O)), localization of the tumor (using International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10)), follow-up in days and vital status. We classified the site of the cancer as shown in Table 1.

We preferentially used pathological TNM stage (pTNM). Only if pTNM was not available, we used clinical TNM-staging for the analyses. In the dataset from 1996, TNM version 4 was used, whereas in 2006 TNM version 5 was the standard. We therefore corrected the dataset from 1996 to TNM version 5 to make all data comparable.

From PALGA, we identified all CRC cases from the years 1996 and 2006, in which colonic histology specimens, other than those showing the incident adenocarcinoma at the time of diagnosis, were available in the 36 months prior to a CRC diagnosis. We used the presence of previous colonic histology specimens as a proxy for a previous colonoscopy. We excluded patients with inflammatory bowel disease from the analysis. Age, gender, date of the incident CRC and date and summaries of the previous pathology reports were collected of all patients.

Definition of early or missed CRCs

In line with previous studies on this topic,[5-7,13,14] we defined missed or early CRCs as cancers diagnosed between 6 and 36 months following a histological examination of colonic tissue. This time period is based on the estimated mean sojourn time (the dura-

Table 1. ICD-10 diagnostic codes for CRC site

ICD-10 code	ICD-10 diagnosis	Site
C180	CRC cecum	Right
C182	CRC ascending colon	Right
C183	CRC hepatic flexure	Right
C184	CRC transverse colon	Transverse colon/splenic flexure
C185	CRC splenic flexure	Transverse colon/splenic flexure
C186	CRC descending colon	Left
C187	CRC sigmoid colon	Left
C188	CRC overlapping sites colon	Other
C189	CRC unspecified	Other
C199	CRC rectosigmoid junction	Rectum
C209	CRC rectum	Rectum

ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision, CRC: colorectal cancer

tion of the preclinical screen-detectable period) for CRCs[15,16] and the assumption that CRCs already suspected or detected during colonoscopy are diagnosed within 6 months of the index procedure. Similarly to Singh et al.,[7] we considered individuals with CRC who had previous colonic histology within 6 to 36 months prior to the CRC diagnosis as well as another colonoscopy from 0 to 6 months prior to the CRC diagnosis to have an early or missed CRC at the initial colonoscopy, which was then detected at the subsequent colonoscopy.

We assumed that patients that only had one or more non-cancerous colonic histology specimens available in the period from 0 to 6 months prior to the CRC diagnosis already had a high clinical suspicion of CRC during the colonoscopy and they were considered to have a regularly diagnosed CRC.

Statistical analysis

We used Statistical Analysis Software version 9.2 (SAS Institute, Cary, NC) for data management. Data analysis was performed using Statistical Packages for Social Sciences version 17.0 (SPSS, Chicago, Illinois, USA). We compared missed or early CRCs with regularly detected CRCs for the years 1996 and 2006.

We used descriptive statistics to calculate frequencies and percentages for categorical variables. We calculated statistical differences between groups using the chi-squared test or Fisher's exact test whenever applicable. Means were compared using the Student's t-test. We considered a p-value <0.05 as statistically significant.

We calculated 5-year survival rates and performed Cox proportional hazard regression analysis with correction for age, gender and tumor stage to compare survival between patients with a missed or early CRC and those with a regularly detected CRC. Results were expressed as hazard ratio (HR) with 95% confidence interval (CI).

We performed multivariate logistic regression for the outcome 'missed or early CRC', adjusted for age, gender and tumor localization to identify parameters associated with missed or early CRC in both 1996 and 2006 separately, as well as in the entire study population. Results were expressed as odds ratio (OR) and 95% CI. CRCs with unspecified localization (1.6% of all CRCs) were not included in the multivariate analysis.

RESULTS

Study population

Between 1996 and 2006, the absolute incidence of CRC in the Netherlands increased from 6,941 to 10,963 patients. We found no clinically relevant differences in age or gender between the years. A total number of 601 (8.7%) patients in 1996 and of 1118 (10.2%)

patients in 2006 had a previous colonic tissue specimen in the 36 months preceding the CRC diagnosis (p=0.001).

A slight increase was observed in the proportion of patients with a missed or early CRC, i.e. 119/6,941 (1.7%) patients in 1996 and 248/10,963 (2.3%) patients in 2006, respectively (p=0.012) [Figure 1]. The preceding available colonic tissue specimens showed adenomas in 102/119 (85.7%) patients in 1996 and 216/248 (87.1%) patients in 2006 (p=0.715), of which 19/119 (16.0%) and 32/248 (12.9%) were villous adenomas in 1996 and 2006, respectively (p=0.427). In 14/119 (11.8%) missed CRCs in 1996 and 77/248 (31.0%) missed CRCs in 2006 at least one of the previous detected adenomas showed high-grade dysplasia (p<0.001).

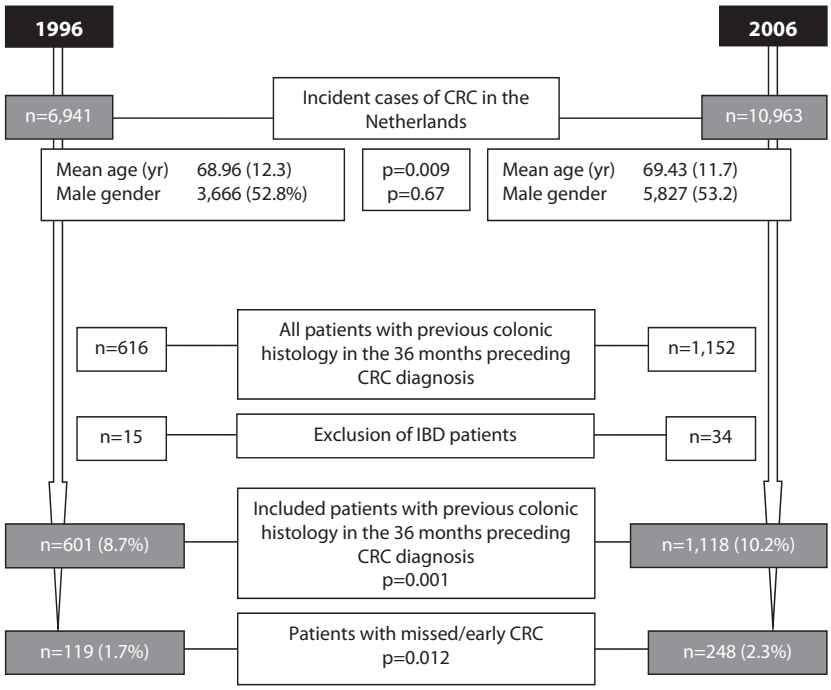

Figure 1. Study population
CRC: colorectal cancer, Mean age (yr) is reported with standard deviation in brackets, missed/early CRC: previous colonic histology in the 6 to 36 months preceding CRC diagnosis

Missed/early versus regularly detected CRCs

In the two studied years, we did not find a consistent significant difference in age and gender between patients with or without missed or early CRCs [Table 2]. Patients with a missed or early CRC were found to have a significantly different distribution in tumor

Table 2. Patient characteristics and tumor localization of CRCs in early or missed and regularly detected CRCs in 1996 and 2006

	1996					2006					Missed CRCs
	Missed		Regular			Missed		Regular			1996 vs 2006
	n	%	n	%	p-value	n	%	n	%	p-value	p-value
Number of patients	119		6822			248		10715			
Mean age (SD)	72.89 (9.6)		68.89 (12.3)		<0.001	70.31 (9.6)		69.41 (11.7)		0.230	0.017
Male gender	65	54.6	3601	52.8	0.691	141	56.9	5686	53.1	0.237	0.687
Tumor localization											
Right	58	48.7	1540	22.8		96	38.7	2877	27.0		
Transverse colon/ splenic flexure	10	8.4	521	7.7		34	13.7	861	8.1		
Left	21	17.6	2031	30.0		47	19.0	3064	28.8		
Rectum	27	22.7	2549	37.7		66	26.6	3676	34.5		
Other	3	2.5	118	1.7	<0.001	5	2.0	169	1.6	<0.001	0.346

SD: standard deviation, CRC: colorectal cancer. Missed: missed/early CRC, previous colonic histology in the 6 to 36 months preceding CRC diagnosis, Regular: Regularly diagnosed CRC

localization compared to regularly detected CRCs, with more tumors located in the right-sided colon, or in the transverse colon/splenic flexure (p<0.001) [Table 2].

Fifty-eight of the 1598 (3.6%) right sided CRCs in 1996 were missed or early CRCs, while 96 of 2973 (3.2%) right-sided CRCs were missed or early CRCs in 2006. Of all CRCs in the transverse colon or splenic flexure, 10/531 (1.9%) and 34/895 (3.8%) were missed or early CRCs comparing 1996 and 2006, respectively. These rates were 21/2052 (1.0%) and 47/3111 (1.5%) for CRCs found in the left colon, and 27/2576 (1.0%) and 66/3742 (1.8%) for CRCs found in the rectum, comparing 1996 and 2006, respectively.

Missed or early CRCs had an earlier and therefore more favorable T-stage, N-stage and M-stage as well as TNM tumor stage, than regularly diagnosed CRCs in both years (p<0.001) [Table 3], whereas no significant difference in T-stage, N-stage and M-stage or TNM tumor stage was seen for missed or early CRCs comparing 1996 and 2006.

In 1996, overall 5-year survival rate in patients with missed or early CRCs was 55.5%. This was 44.8% for regularly detected CRCs (p=0.02). In 2006, overall 5-year survival rates were 56.9% versus 50.2%, respectively (p=0.04). There was however no difference in survival between both groups after adjustment for TNM stage [Table 4].

Table 3. TNM-stage of CRCs in early or missed and regularly detected CRCs in 1996 and 2006

	1996					2006					Missed CRCs
	Missed		Regular			Missed		Regular			1996 vs 2006
	n	%	n	%	p-value	n	%	n	%	p-value	p-value
Number of patients	119		6822			248		10715			
T stage											
T1	20	16.8	566	8.3		47	19.0	812	7.6		
T2	28	23.5	1099	16.1		70	28.2	1636	15.4		
T3	51	42.9	3710	54.4		93	37.5	5575	52.4		
T4	11	9.2	807	11.8		23	9.3	1621	15.2		
Tx	9	7.6	639	9.4	0.001	15	6.0	1003	9.4	<0.001	0.784
N stage											
N0	74	62.2	3398	49.8		150	60.5	5220	48.7		
N1	21	17.6	1582	23.2		51	20.6	2535	23.7		
N2	7	5.9	635	9.3		13	5.2	1576	14.7		
Nx	17	14.3	1207	17.7	0.060	34	13.7	1384	12.9	<0.001	0.926
M stage											
M0	94	79.0	4694	68.8		183	73.8	7595	68.1		
M1	10	8.4	1172	17.2		26	10.5	2284	21.3		
Mx	15	12.6	956	14.0	0.027	39	15.7	1136	10.6	<0.001	0.556
TNM stage											
Stage I	40	37.7	1149	19.1		82	38.0	1711	17.3		
Stage II	31	29.2	2041	33.9		61	28.2	3084	31.2		
Stage III	25	23.6	1651	27.5		47	21.8	2801	28.4		
Stage IV	10	9.4	1171	19.5	<0.001	26	12.0	2275	23.0	<0.001	0.905

CRC: colorectal cancer. Missed: missed/early CRC, previous colonic histology in the 6 to 36 months preceding CRC diagnosis, Regular: Regularly diagnosed CRC

Risk factors for missed or early CRC

Tumors in the right-sided colon were significantly more frequently associated with early or missed CRC, both in 1996 (OR 3.48 [95% CI 2.19-5.55] and in 2006 (OR 1.91 [95% CI 1.38-2.64]). Age, male gender and tumor localization in the transverse colon/splenic flexure were statistically significantly more often associated with a missed or early CRC in one of the years [Table 5].

Multivariate analysis of the entire study population (1996 and 2006) confirmed that early or missed CRC was associated with tumor localization in the right colon (OR 2.34 (95% CI 1.80-3.05]) and in the transverse colon/splenic flexure (OR 2.14 [95% CI 1.49-

3.08]), male gender (OR 1.31 [95% CI 1.06-1.62]) and older age (OR 1.01 [95% CI 1.00-1.02]) [Table 5].

Table 4. Survival: Cox regression analysis

	1996				2006			
			Adjusted for TNM stage				*Adjusted for TNM stage*	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age (per year)	1.05	1.04-1.05	1.05	1.04-1.05	1.04	1.03-1.04	1.05	1.04-1.05
Male gender	0.78	0.74-0.82	0.80	0.76-0.85	0.89	0.85-0.94	0.91	0.86-0.96
Missed or early CRC	0.74	0.60-0.91	0.89	0.71-1.10	0.76	0.63-0.92	0.91	0.74-1.12
TNM stage								
Stage I			1.00	N/A			1.00	N/A
Stage II			1.52	1.39-1.66			1.52	1.36-1.69
Stage III			2.21	2.02-2.43			2.56	2.30-2.85
Stage IV			10.58	9.56-11.71			12.12	10.90-13.49

HR: Hazard ratio, 95% CI: 95% confidence interval

DISCUSSION

This study shows that the rate of missed or early CRCs in the 6 to 36 months after previous colonoscopy, defined by the presence of a previous colonic histopathological examination, in the Netherlands slightly increased from 1.7% in 1996 to 2.3% in 2006. Early or missed CRCs tended to have a more favorable tumor stage than regularly detected CRCs, but had similar survival rates as regularly detected CRCs after adjustment for tumor stage. Localization in the right-sided colon and transverse colon/splenic flexure was an independent risk factor for early or missed CRC.

In the literature, the overall miss rate for CRC has been reported to vary between 2 and 8%.[4-8] The lower rates of missed or early CRCs in our study compared to most previous studies are likely the result of a different study design and other inclusion criteria. In our study, we only included patients of whom previous colonic histology was available, but we were not able to include patients with a previous colonoscopy but without biopsies taken or (adenomatous) polyps removed. In this study we only report the miss rate in patients with an a priori higher risk of recurrent colonic neoplasia, as the previous colonic tissue specimens showed adenomas in the majority of patients. A history of adenoma resection has previously been shown to be a strong risk factor for missed or early CRC in the Canadian province of Manitoba.[7] However, Bressler et al., came to a completely opposite conclusion in another Canadian study.[6]

In previous studies an increased colonoscopic miss rate was reported to be associated with a non-gastroenterology speciality of the performing endoscopist[6,14,17] and the setting in which the endoscopy was performed.[8] In the Netherlands, colonoscopies are not performed in primary care and 86% of the colonoscopies are performed by senior gastroenterologists or gastroenterology fellows under direct supervision.[18]

In contrast to what we expected, the rate of missed or early CRCs did not decrease between 1996 and 2006. Instead, a slight increase was observed in the proportion of patients with a missed or early CRC. To our knowledge, this has not been reported before. Previous reports on colonoscopic miss rates all used retrospective cohorts spanning many years, making the evaluation of possible time trends in colonoscopic miss rate impossible.[4-8] Despite technically more advanced endoscopy equipment over the years, but also the increasing attention to the importance of adequate bowel preparation[19-20] and the growing interest in quality indicators for colonoscopy, such as cecal inubation rate, withdrawal time and adenoma detection rate,[9-10] we did not observe a reduction of the rate of missed or early CRCs over a period of 10 years. Whether this apparent inability to reduce the colonoscopic miss rate is the result of a persistent human inability to detect early lesions, the still imperfect performance of currently used endoscopes due to their 170 degree field of view, a possible rising incidence of difficult to detect flat or depressed lesions or a different biological behavior of new or missed CRCs remains to be established. The fact that we found no difference in survival rates between missed or new CRCs and regularly detected CRCs argues, however, against a different tumor biology. A very recent study from Denmark came to the same conclusion, although the authors used different definitions of early/missed CRCs.[21]

Our study shows that the TNM stage of missed or early CRCs is more favorable than that of regularly diagnosed CRCs. It is conceivable that this is a reflection of the fact that

Table 5. Multivariate analysis: factors associated with missed or early CRC

	1996		2006		Overall	
	Adjusted OR	**95% CI**	**Adjusted OR**	**95% CI**	**Adjusted OR**	**95% CI**
Age (per year)	1.03	1.01-1.04	1.00	0.99-1.01	1.01	1.00-1.02
Male gender	1.34	0.92-1.95	1.29	0.99-1.67	1.31	1.06-1.62
Localization						
Right	3.48	2.19-5.55	1.91	1.38-2.64	2.34	1.80-3.05
Transverse colon/ splenic flexure	1.79	0.86-3.72	2.24	1.47-3.42	2.14	1.49-3.08
Left	0.97	0.54-1.71	0.86	0.59-1.25	0.89	0.65-1.22
Rectum	1.00	N/A	1.00	N/A	1.00	N/A

Overall: Multivariate analysis performed on the 1996 and 2006 cases combined, OR: Odds ratio, 95% CI: 95% confidence interval

early or missed CRCs are smaller and have developed over a shorter period of time than regularly diagnosed CRCs. Robertson et al. also reported that CRCs that are detected in patients that are under close colonoscopic surveillance after previous polypectomy are likely to have a more favorable disease stage compared to CRCs detected in the general population.[22] In this study including 2,915 patients, the authors did not use the term 'early or missed CRC', but all CRCs were diagnosed within a maximum of 4 years after a full colonoscopy with removal of all detected polyps. Interestingly, Singh et al. reported no difference in survival between early/missed CRCs and regularly occurring CRCs in a study on predictive factors for a missed or early CRC after a previous negative colonoscopy.[14] These authors had however no information on disease stage at the time of diagnosis. Our study is one of the first to show that early or missed CRCs have a similar survival as regularly detected CRCs, when adjusting for their more favorable TNM stage.

The finding that CRCs that were located proximal to the splenic flexure were an independent risk factor for missed or early CRCs is in line with previous studies on this topic.[6-7] In recent years, it has been shown that the protective effect of colonoscopy on CRC incidence is highest for left-sided tumors compared to proximal CRCs.[22-26] Likewise, colonoscopy has been shown to reduce the mortality of right-sided tumors to a lesser extent than that of more distally located CRCs.[27-28]

The incidence of CRC in the Netherlands has steadily been rising over the years. In 1996, almost 7,000 patients were registered with a CRC diagnosis, while this had increased to almost 11,000 patients in 2006. In 2011, a further increase was seen with more than 13,000 patients diagnosed with a new CRC.[29] This rising incidence is mainly attributed to the ageing population. At the same time, the total number of endoscopies performed in the Netherlands has also increased: from 325,000 in 1999 to almost 410,000 (of which 116,815 were colonoscopies) in 2004.[30] Since the relative size of this increase corresponds to the rise in CRC incidence, it is unlikely that the lack of decrease of the rate of early or missed CRCs in this study is explained by a change in the use of colonoscopy over time.

A strength of this study is the population-based approach, using two accurate, nationwide data sources with excellent national coverage. It is unlikely that a significant number of patients were missed. A population-based study reduces possible selection bias. Both the PALGA database and the Netherlands Cancer Registry database were developed and initiated in a systematic, structured manner, using internationally accepted standards to report medical descriptions and diagnoses (SNOMEDS and ICD-10, respectively). This allows for uniform identification of CRC cases.

A drawback of this study is that we are not informed about colonoscopies in which no colonic histology was collected or about polyps that have been removed previously, but were not sent in for histopathological examination. Because we used the presence of at least one previous colonic histological specimen as a proxy for a previous colonoscopy,

our results most likely show an underestimation of the true missed or early CRC rate. This makes comparison with previous reports on this topic more difficult. The main finding of this study is that the miss rate did not decrease over a 10-year period. It is unlikely that this finding is limited to patients who previously had a colonoscopy with polypectomy and will be different for patients who had a previous colonoscopy without histology. Due to the design of the study, no information on quality items of colonoscopy, e.g., cecal intubation rates, individual adenoma detection rates and bowel preparation scores was available. Secondly, we are not informed about the indications for the colonoscopies. As there was no mass population screening program for CRC in average risk individuals in the Netherlands during the study period, the colonoscopies were performed for surveillance after previous adenoma and/or CRC, screening of high-risk individuals and diagnostic indications.

The increased awareness for missed CRC and colonoscopy quality is a fairly recent trend. However, increasing overall professionalization of physicians performing colonoscopy, the advent of technically more advanced endoscopy equipment, the search for better bowel preparation schemes and more overall awareness for quality aspects of colonoscopy are all continuous processes, and definitely measurable in 2006. All these aspects have evolved over the years.

We compared the rate of missed or early CRCs between two years, 1996 and 2006. A time trend analysis would possibly have provided a more reliable reflection of the changes over time, but was not possible with the available data. It is important to take this into account when interpreting any trend over time based on the results of this study.

The results of this study highlight the relevance of continuing awareness for missed lesions. Reducing missed lesions, especially in the right colon, remains a challenge. Hopefully, technical innovations of endoscopes will be the solution in reducing the rate of missed or early CRCs. Although new technologies like a retrograde-viewing device or a ultra wide-viewing colonoscope seem promising in improving adenoma detection, data from large, randomized clinical trials in non-referral centers are not yet available.[31-32]

In conclusion, the rate of missed or early CRCs in the Netherlands did not decrease over a 10-year period. Proximal tumors were consistently more likely to be due to missed lesions. Endoscopists should be aware of this caveat, especially in elderly patients and in men. Early or missed CRCs tend to have an earlier and likely more favorable disease stage than regularly diagnosed CRCs.

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CHAPTER 7

Significant risk of post-colonoscopy colorectal cancer due to incomplete adenoma resection: results of a nationwide, population-based cohort study

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Submitted

ABSTRACT

Background & Objectives

Most post-colonoscopy colorectal cancers (PC-CRCs) arise from missed or incompletely resected adenomas and are therefore possibly preventable. The objectives of this study were to assess the overall incidence rate of PC-CRC in patients with one or more adenomas, to determine the risk of PC-CRC due to incomplete adenoma resection, and to identify adenoma characteristics associated with a high risk of PC-CRC due to incomplete adenoma resection.

Methods

We performed a population-based cohort study identifying all patients with a first colorectal adenoma between 2000 and 2010 in the nationwide Dutch Pathology Registry. Outcomes were the incidence rate of PC-CRC overall and PC-CRC due to incomplete adenoma resection, defined as the occurrence of CRC between 6 months and 5 years after adenoma resection in the same colon segment. We performed a multivariable Cox proportional hazard regression analysis to identify adenoma-related risk factors associated with both outcomes.

Results

We included 107,744 patients (mean age 63.4 years (SD 12.8); 53.6% male), with a mean number of 1.23 (SD 0.57) adenomas per patient at baseline. In total, 1,031 patients (0.96%) developed PC-CRC (1.9/1000 person years). PC-CRC due to incomplete adenoma resection occurred in 0.24% (324/ 133,519) of adenomas. Mean follow-up per adenoma was 4.4 years (SD 1.1) and the incidence rate 0.6/1000 years of follow-up. High-grade dysplasia (hazard ratio (HR) 2.54, 95% confidence interval (CI) 1.99-3.25), villous (HR 2.63, 95%-CI 1.79-3.87) and tubulovillous histology (HR 1.80, 95%-CI 1.43-2.27) were risk factors for PC-CRC due to incomplete adenoma resection. Proximal localization was not associated with these PC-CRCs.

Conclusion

PC-CRC due to incomplete endoscopic resection occurred in one in four hundred adenomas and even more frequently in adenomas with villous features or high-grade dysplasia.

INTRODUCTION

Resection of adenomas during colonoscopy effectively reduces the incidence of subsequent colorectal cancer (CRC),[1] but does not preclude its occurrence within the first three to five years after the procedure.[2,3] Rather than developing from rapidly growing new lesions, post-colonoscopy CRC (PC-CRC) is thought to be a consequence of missed or incompletely resected adenomas.[4-6]

There is a considerable risk for colorectal adenomas to be incompletely resected, especially for larger lesions removed in multiple fragments.[7,8] The proportion of PC-CRCs developing from incompletely resected adenomas ranged from 9% to 50% in previous studies,[5,6,9] suggesting that a substantial number of PC-CRCs could have been prevented by increasing awareness, improving quality of endoscopic resection and adhering to surveillance strategies. However, data in these studies were either derived from prevalent CRC cases, used to retrospectively identify PC-CRC, or from prospective cohorts of adenoma patients with small numbers of PC-CRCs. In order to assess the absolute risk of developing PC-CRC after adenoma resection and to identify high-risk adenomas, a large cohort of adenoma patients with a substantial number of PC-CRCs is needed.

We performed a nationwide, population-based cohort study to determine the rate of PC-CRC due to incomplete adenoma resection and to identify adenoma characteristics associated with PC-CRC due to incomplete adenoma resection.

METHODS

Data source and study population

We performed a population-based cohort study using data from the nationwide network and registry of histopathology and cytopathology diagnoses in the Netherlands (PALGA). In this national registry, summaries of the original pathology reports generated by all pathology departments in the Netherlands are centrally archived.[10] PALGA was established in 1971 and has accomplished nationwide coverage since 1991. Each pathology report in PALGA is linked to a diagnostic code, in line with the Systemized Nomenclature of Medicine (SNOMED), issued by the college of American Pathologists.[11]

In PALGA we identified all patients with a first colorectal adenoma between 2000 and 2010. Patients were followed from first adenoma detection and removal (i.e. index adenoma) until September 1, 2013, by scrutinizing all pathology reports of evaluated specimens of colorectal origin. In addition to a summary of the histopathological findings and the respective diagnostic codes, the following parameters were available for each PALGA excerpt: date of examination, gender of the patient and age of the patient at the time of examination.

Data extraction and definitions

Patients were automatically identified in PALGA, based on the diagnostic codes for 'benign tumor' and 'colon' or 'rectum'. We used word recognition to identify adenomas in the pathology report summary texts and diagnostic codes. Subjects in whom no adenoma was detected were excluded. After manually checking and confirming all CRC cases, patients with a prevalent CRC at the time of index procedure (patients in whom a CRC was found before, at the same time, or within 6 months after the first adenoma) were also excluded. We assumed that CRCs diagnosed within 6 months of the index procedure were already detected or suspected during the index colonoscopy.

Histopathological features and location of the adenomas were automatically extracted from the pathology report summary texts and diagnostic codes. Histopathological features consisted of tubular adenoma (TA), tubulovillous adenoma (TVA), villous adenoma (VA), sessile serrated adenoma/polyp (SSA/P), low-grade dysplasia (LGD), high-grade dysplasia (HGD, including carcinoma in situ) and CRC. The colon was subdivided into six segments: cecum, ascending colon (including hepatic flexure), transverse colon (including splenic flexure), descending colon, sigmoid colon and rectum. We identified the locations through word recognition of either the specific colon segment or the type of surgery (for CRC), or the reported distance from the anal verge. The rectum was defined as 0-15 cm from the anal verge, the sigmoid colon as 16-35 cm, the descending colon as 36-50 cm, the transverse colon as 51-70 cm and the ascending colon as >70 cm from the anal verge. Using this approach we assumed that the readily identifiable cecum would be mentioned as such in the pathology report.

Outcome measures

Outcome measures were the incidence rate of PC-CRC, defined as a CRC occurring within 5 years after colonoscopy with adenoma removal, and the risk of PC-CRC due to incomplete resection, defined as PC-CRC after removal of an adenoma from the same colon segment.

Statistical analysis

We used SAS version 9.3 [SAS Institute, Cary, NC, USA] for data management and performed data analysis using Statistical Packages for Social Sciences version 22 [IBM Corp., Armonk, NY, USA].

We performed per adenoma and per patient analyses. In the per adenoma analysis, each new adenoma in a unique colon segment was followed until CRC in the same segment, adenoma in the same segment, end of study (September 1, 2013) or end of five-year follow-up. In case an adenoma occurred in the same colon segment within five years after a previous adenoma, follow-up stopped and was restarted from the time of the second adenoma. Follow-up was set to end at five years or at the end of study,

whichever came first. Adenomas with a follow-up of less than six months (i.e. occurrence of CRC or adenoma, or end of study within six months) were excluded from the per adenoma analysis. Adenomas without a location mentioned in the summary of the pathology report were also excluded.

In the per patient analysis, follow-up was set to end in case of CRC anywhere in the colon, at 5 years after the last adenoma was detected, or at the end of study. Adenomas occurring within six months before CRC were not included.

We performed a multivariable Cox proportional hazard regression analysis to identify risk factors for PC-CRC overall and for PC-CRC due to incomplete adenoma resection. Results are expressed as hazard ratios (HR) with 95% confidence interval (95% CI). We considered a p-value <0.05 to be significant.

Ethical considerations

This study was performed with the approval of and in accordance with the privacy and ethical guidelines of the privacy committee of PALGA.

RESULTS

Study population

In total, 121,378 patients were identified in PALGA. Our search strategy detected one or more adenomas in the pathology reports of 119,233 patients. After exclusion of patients with CRC diagnosed before or at the same time as the first adenoma (n=7,222) and patients with CRC within 6 months of the first adenoma (n=4,267), a total of 107,744 patients were included in the final analysis.

Mean age of the included patients was 63.4 (standard deviation (SD) 12.8) years and 53.6% were male [Table 1]. At the time of first adenoma diagnosis, the mean number of resected adenomas was 1.23 (SD 0.57). The sigmoid colon (39.7%) and rectum (27.6%) were the most frequently reported locations. Villous features, i.e. tubulovillous or villous histology, were found at baseline in 31.4% of patients and high-grade dysplasia was present in 13.8% of patients. The frequency of SSA/Ps was 2.4%. We observed an increase in the incidence of first adenomas from 5,798 in the year 2000 to 19,039 adenomas in 2009.

During follow-up, a mean number of 1.44 (SD 0.94) adenomas were found in the included patients. The cumulative number of adenomas was one in 71.8% of patients, two in 19.4% and three or more in 8.8%. Tubulovillous histology was detected at least once in 29.7% of patients, villous histology in 3.6% of patients and high-grade dysplasia in 14.9% of patients during follow-up.

Table 1. Baseline characteristics, per patient

Total number of patients	**107,744 (%)**
Male gender	57,784 (53.6)
Mean age at first adenoma, years (SD)	63.4 (12.8)
Number of adenomas at baseline	132,974
Mean number of adenomas per patient (SD)	1.23 (0.57)
Location of first adenoma*	
Cecum	9539 (8.9)
Ascending colon	13,049 (12.1)
Transverse colon	10,530 (9.8)
Descending colon	10,424 (9.7)
Sigmoid colon	42,812 (39.7)
Rectum	29,710 (27.6)
Colon not otherwise specified	23,807 (22.1)
Histology of first adenoma*	
Tubular	76,370 (70.9)
Tubulovillous	30,295 (28.1)
Villous	3527 (3.3)
Sessile serrated adenoma/polyp	2619 (2.4)
High-grade dysplasia in first adenoma	14,900 (13.8)
Year of first adenoma diagnosis	
2000	5798 (5.4)
2001	5918 (5.5)
2002	6451 (6.0)
2003	7454 (6.9)
2004	9086 (8.4)
2005	10,797 (10.0)
2006	12,368 (11.5)
2007	14,464 (13.4)
2008	16,369 (15.2)
2009	19,039 (17.7)

*Sum can be >100%, as more than one adenoma can be found at index colonoscopy

A total of 133,519 adenomas were included in the per adenoma analysis, of which the majority was located in the sigmoid colon or rectum (59.7%) [Table 2]. Villous features were found in 30.9% and high-grade dysplasia in 13.6% of adenomas.

Table 2. Baseline characteristics, per adenoma

Number of adenomas*	**133,519 (%)**
Adenoma location (%)	
Cecum	11,601 (8.7)
Ascending colon	16,614 (12.4)
Transverse colon	13,308 (10.0)
Descending colon	12,294 (9.2)
Sigmoid colon	46,747 (35.0)
Rectum	32,955 (24.7)
Adenoma histology (%)	
Tubular	82,069 (61.5)
Tubulovillous	26,821 (27.6)
Villous	4439 (3.3)
Sessile serrated adenoma/polyp	4665 (3.5)
Unknown	5525 (4.1)
High-grade dysplasia	18,138 (13.6)
Year of adenoma diagnosis (%)	
2000	5199 (3.9)
2001	5587 (4.2)
2002	6438 (4.8)
2003	7322 (4.5)
2004	9329 (7.0)
2005	11,633 (8.7)
2006	13,433 (10.1)
2007	16,248 (12.2)
2008	19,083 (14.3)
2009	22,826 (17.1)
2010**	5015 (3.8)
2011**	4907 (3.7)
2012**	5491 (4.1)
2013**	1008 (0.8)

*In the per adenoma analysis, only adenomas with a known location were included
**In the per adenoma analysis, adenomas removed during follow-up of the patients with a first adenoma in 2000-2009 were also included

PC-CRC

In per patient analysis, the risk of developing PC-CRC anywhere in the colon was 0.96% (1031 of 107,744 patients). Mean follow-up per patient was 5.1 years (SD 1.2) and the incidence rate of PC-CRC was 1.88 per 1000 person years [Table 3].

High-grade dysplasia (HR 1.60, 95% CI 1.37-1.86), villous adenoma (HR 1.82, 95% CI 1.42-2.32) and tubulovillous adenoma (HR 1.31, 95% CI 1.14-1.49) were independently

Table 3. Rates of post-colonoscopy CRC

Per patient analysis	
Total number of patients	107,744
PC-CRC (%)	1031 (0.96%)
Mean follow-up per patient, years (SD)	5.08 (1.19)
Incidence rate of PC-CRC	1.88 per 1000 person years
Per adenoma analysis	
Total number of adenomas	133,519
PC-CRC due to incomplete adenoma resection (%)	324 (0.24%)
Mean follow-up per adenoma, years (± SD)	4.35 (1.11)
Incidence rate of PC-CRC due to incomplete resection	0.56 per 1000 years of follow-up

associated with PC-CRC [Table 4]. Higher age at the time of the first adenoma diagnosis was also associated with PC-CRC (HR for each 10 year increase in age 1.39, 95% CI 1.32-1.46).

In contrast, patients in whom 3 or more adenomas were resected during follow-up had a reduced risk of developing PC-CRC (HR 0.69, 95% CI 0.54-0.90).

We did not find an association between proximal location of the resected adenoma and the risk of PC-CRC.

PC-CRC due to incomplete adenoma resection

PC-CRC due to incomplete adenoma resection occurred in 324 (0.24%) of 133,519 adenomas. Mean follow-up per adenoma was 4.4 years (SD 1.1), and the incidence rate of PC-CRC due to incomplete adenoma resection was 0.56 per 1000 years of follow-up [Table 3].

PC-CRC due to incomplete adenoma resection occurred in 123 (0.58%) of 21,134 resected advanced adenomas, defined as villous adenoma and/or adenoma with high-grade dysplasia. In the per adenoma multivariable analysis, high-grade dysplasia (HR 2.54, 95% CI 1.99-3.25), villous adenoma (HR 2.63, 95% CI 1.79-3.87) and tubulovillous adenoma (HR 1.80, 95% CI 1.43-2.27) were independently associated with PC-CRC due to incomplete adenoma resection [Table 5]. We found no association with PC-CRC due to incomplete resection for sessile serrated histology, proximal location, the year of adenoma resection or the number of synchronous adenomas in the same colon segment.

Eighty-eight PC-CRCs (0.07%) were possibly, but not definitely, attributable to incomplete adenoma resection, as these occurred in a segment adjacent to the previously resected adenoma.

Furthermore, during follow-up after 5 years, 111 CRCs (0.08%) were found in the same colon segment as a previously resected adenoma. Both categories of (PC-)CRC were not included in the further analyses.

Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) for PC-CRC anywhere in the colon after adenoma resection

	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
Male gender	0.96	0.85-1.09	1.01	1.32-1.46
Age at diagnosis of first adenoma (per 10 year increase)	1.41	1.33-1.48	1.39	1.32-1.46
Histology, one or more				
Tubulovillous adenomas	1.40	1.23-1.59	1.31	1.14-1.49
Villous adenomas	2.11	1.66-2.67	1.82	1.42-2.32
Sessile serrated adenomas / polyps	0.91	0.62-1.31	1.07	0.73-1.56
One or more adenomas with high-grade dysplasia	1.80	1.55-2.07	1.60	1.37-1.86
Location, one or more adenomas in				
Rectum	1.07	0.93-1.23	1.07	0.93-1.23
Sigmoid	1.01	0.90-1.15	1.02	0.90-1.16
Descending colon	1.09	0.90-1.31	1.15	0.95-1.39
Transverse colon	1.01	0.84-1.21	1.05	0.86-1.19
Ascending colon	1.03	0.86-1.22	0.99	0.83-1.19
Cecum	1.24	1.03-1.49	1.20	0.99-1.45
Incidence year of first adenoma				
2000-2003	1.06	0.91-1.23	0.92	0.79-1.07
2004-2006	0.99	0.85-0.91	0.89	0.77-1.03
2007-2009	Reference		Reference	
Cumulative number of adenomas				
1	Reference		Reference	
2	1.19	1.03-1.39	0.92	0.78-1.08
3 or more	1.14	0.93-1.41	0.69	0.54-0.90

DISCUSSION

In this nationwide, population-based cohort study, we found that the overall incidence rate of PC-CRC within 5 years after adenoma resection was 1.88 per 1000 person years. PC-CRC due to incomplete adenoma resection occurred in 0.24% of adenomas with an incidence rate of 0.56 per 1000 years of follow-up. Villous features and high-grade dysplasia were associated with both overall PC-CRC and PC-CRC due to incomplete adenoma resection.

In recent years, there is accumulating evidence that PC-CRCs are not due to new, rapidly growing and biologically more aggressive tumors,[12-14] but rather due to missed or incompletely resected lesions.[6] Pabby et al. identified all PC-CRCs occurring in 2079 patients participating in the dietary Polyp Prevention Trial and classified these according to probable etiology.[5] During follow-up, they detected 13 PC-CRCs, i.e. 2.2 cases per 1000

Table 5. Hazard ratios (HR) and 95% confidence intervals (CI) for PC-CRC due to incomplete adenoma resection

Variable	Unadjusted		Adjusted	
	HR	95% CI	HR	95% CI
Histology				
Tubulovillous adenoma	1.94	1.55-2.41	1.80	1.43-2.27
Villous adenoma	3.15	2.18-4.54	2.63	1.79-3.87
Sessile serrated adenoma / polyp	0.88	0.47-1.66	1.27	0.68-2.40
High-grade dysplasia	3.12	2.47-3.94	2.54	1.99-3.25
Location				
Rectum	Reference		Reference	
Sigmoid	0.81	0.61-1.07	0.84	0.63-1.11
Descending colon	0.46	0.27-0.77	0.54	0.32-0.92
Transverse colon	0.74	0.48-1.13	0.95	0.62-1.47
Ascending colon	0.97	0.68-1.38	1.14	0.79-1.65
Cecum	0.94	0.52-1.41	1.08	0.71-1.64
Year of adenoma diagnosis				
2000-2003	0.95	0.70-1.29	0.86	0.64-1.17
2004-2006	1.51	0.94-1.55	1.12	0.87-1.44
2007-2009	Reference		Reference	
Number of adenomas in the same colon segment				
1	Reference		Reference	
2	1.23	0.83-1.81	1.10	0.73-1.66
3 or more	2.02	0.83-4.91	1.15	0.67-3.59

person years of observation. Four of these PC-CRCs could be attributed to incomplete adenoma resection (incidence rate 0.68 per 1000 person years). As all included patients participated in a trial, these results are potentially biased, limiting the generalizability to daily clinical practice. Huang et al. retrospectively identified PC-CRCs within 5 years after polypectomy in two Chinese hospitals.[4] Fourteen PC-CRCs were detected in 1794 patients, with an incidence of PC-CRC of 2.9 cases per 1000 person years. The authors attributed seven cases (50%) to incomplete adenoma resection (incidence rate 1.45 per 1000 person years). The small number of PC-CRCs in both studies, in which the same definition of PC-CRC due to incomplete adenoma resection was used as in our study, precludes identification of potential risk factors. The overall incidence rate of PC-CRC in our study of 1.88 cases per 1000 person years is slightly lower than in the abovementioned studies, probably because the data in our study are derived from daily clinical practice, in which follow-up has been less strict than in controlled studies.

Le Clercq et al. performed a population-based study on all CRCs occurring in the South-Limburg region of the Netherlands from 2001 through 2010.[6] They found that

2.9% of all CRCs were PC-CRCs, defined as CRCs diagnosed within 5 years after index colonoscopy. Nine percent of these PC-CRCs were attributed to incomplete adenoma resection. However, identification of PC-CRCs from prevalent CRC cases precludes calculating the absolute risk of developing PC-CRC after (incomplete) adenoma resection. Our study is the first to assess the absolute risk of PC-CRC due to incomplete adenoma resection in a large and unselected cohort of adenoma patients.

It is not surprising that adenomas with villous features and high-grade dysplasia were associated with an increased risk of PC-CRC due to incomplete adenoma resection. These advanced histopathologic features have already previously been associated with an increased risk of adenoma recurrence and subsequent development of advanced adenomas or CRC.[15,16] Advanced adenomas are often large and resected using the piecemeal technique, which has been associated with an increased risk of local recurrence.[7]

Proximal location is repeatedly reported to be a risk factor for PC-CRC,[2,3,14] presumably because lesions in the proximal colon are more prone to be missed during colonoscopy. In our study, proximal location was not associated with PC-CRC due to incomplete adenoma resection. As we chose to only include patients in whom one or more adenoma was detected, we do not have data on patients with negative colonoscopies and or have information on neoplastic lesions that may have been missed during colonoscopy. This may explain why we did not find an association between proximal location and PC-CRC due to incomplete adenoma resection. This hypothesis is supported by the fact that both Pabby et al. and Le Clercq et al. reported that the majority of the PC-CRCs due to incomplete adenoma resection were located in the left-sided colon.[5,6]

Although SSA/Ps have been reported to be more likely to be incompletely resected than conventional adenomas,[8] we did not detect an association between SSA/Ps and the occurrence of PC-CRC.

The major strength of this study is its population-based approach, which reduces possible selection bias. Furthermore, we used a data source with national coverage and excellent accuracy, which allows to pseudo-prospectively follow patients over time. It is therefore unlikely that any incident CRC cases were missed.

A limitation of our study is that we do not have information on resected adenomas that were not retrieved for histopathological examination. Although there was no broadly accepted 'resect and discard' policy in the Netherlands during the study period, an unknown proportion of endoscopically resected adenomas might have been discarded after resection. Our results may overestimate the incidence rate of PC-CRC, as all incident CRCs were detected, but probably not all adenomas. On the other hand, as we do not have information on individual surveillance strategies, it may be true that CRC was detected only after five years because no prior surveillance was performed.

Secondly, we cannot be certain that PC-CRC occurring in the same colon segment is indeed a direct consequence of incomplete adenoma resection. In other studies

however, the same definition is used, as it is practically impossible to relocate the exact polypectomy site, unless marking techniques are routinely applied.

Finally, we had no endoscopic data that might have affected the risk of PC-CRC. The endoscopic morphology of the removed adenomas (size, sessile versus pedunculated polyps), resection technique (cold snaring, snare coagulation or (piecemeal) endoscopic mucosal resection) and quality indicators of the colonoscopy, such as cecal intubation and bowel preparation quality, were not available. During the study period, the population-based screening program for CRC in the Netherlands had not yet started.

The implications of our findings for daily clinical practice are clear. A PC-CRC due to incomplete adenoma resection is likely to happen to each colonoscopist. With the worldwide implementation of CRC screening programs, the total number of polypectomies will increase. Acknowledging that incomplete polypectomies may lead to CRC within only a few years, should keep colonoscopists focused on achieving a radical endoscopic resection. Current guidelines recommend that patients in whom adenomas with villous features and/or high-grade dysplasia have been removed should undergo surveillance at a reduced interval.[17,18] Furthermore, after piecemeal resection of sessile polyps, verification of complete removal is advised within six months, because of the substantial risk of incomplete resection in these cases.[7] The results of our study strongly support the recommended intensified follow-up in case of advanced adenomas, as they carry a substantially higher risk of CRC development.

In conclusion, the absolute risk of PC-CRC due to incomplete adenoma resection was one in four hundred (0.24%) for all adenomas and one in one hundred seventy (0.58%) for advanced adenomas. As we found that the risk of PC-CRC overall and PC-CRC due to incomplete adenoma resection was substantially higher in adenomas with high-grade dysplasia or villous features, our results suggest enhanced surveillance for patients with advanced adenomas.

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CHAPTER 8

Colonoscopy with robotic steering and automated lumen centralization compared with conventional colonoscopy: a randomized in vitro pilot study

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ABSTRACT

Background & Aims

The steering mechanism of flexible endoscopes is considered non-intuitive, non-ergonomic and has a considerable learning curve. We introduced a new platform for performing colonoscopy with robotic steering and automated lumen centralization (ALC) and investigated the performance of this platform by both expert endoscopists and endoscopy naive novices.

Methods

We performed a randomized controlled cross-over trial. Expert endoscopists (n=8) and novices (n=10) performed conventional colonoscopy and colonoscopy with robotic steering and ALC in a validated colon model with simulated polyps (n=21). Endpoints were cecal insertion time, number of detected polyps and subjective evaluation of the platform.

Results

Novices were able to intubate the cecum faster using robotic steering with ALC (median 8'56", interquartile range (IQR) 6'46"-16'34" vs. 11'47", IQR 8'19"-15'33", p=0.65), while experts were faster with conventional colonoscopy (2'9", IQR 1'13"-7'28" vs. 13'1", IQR 5'9"-16'54", p=0.12). Novices detected more polyps with robotic steering and ALC (88.1%, IQR 79.8-95.2% vs. 78.6%, IQR 75.0-91.7%, p=0.17), while experts detected more polyps with conventional colonoscopy (80.9%, IQR 76.2-85.7% vs. 69.0%, IQR 61.0-75.0%, p=0.03). All but one participant thought robotic steering with ALC could make performing colonoscopy easier for novices. Novices were more positive about the new platform (p=0.02) than experts, experiencing an easier and faster introduction of the colonoscope compared with conventional colonoscopy.

Conclusions

Robotic steering with ALC allows endoscopy naive novices to intubate the cecum faster and detect more simulated polyps in a colon model than conventional colonoscopy. Robotic steering with ALC is subjectively easier to learn for novices.

INTRODUCTION

For several decades, colonoscopy has been the procedure of choice to investigate the colorectum. Its broad availability and the initiation of population screening for colorectal cancer (CRC) in many countries has led to a steady increase in the demand for colonoscopy.[1,2]

The numerous physicians that enter colonoscopy training programs every year face extensive learning curves, requiring the performance of several hundred colonoscopies before being able to intubate the cecum in the vast majority of patients.[3,4] This can at least partly be attributed to the non-intuitive steering mechanism of flexible endoscopes. Furthermore, musculo-skeletal complaints due to the non-ergonomic design of the colonoscopy setup are relatively common, and have been reported to occur in up to 50% of endoscopists.[5]

Traditionally, colonoscopy has been practiced with an endoscopy nurse assisting the insertion and withdrawal of the colonoscope. In more recent years, colonoscopy is increasingly performed 'single handed'. However, the large steering wheels of conventional endoscopes can be impractical and difficult to control simultaneously in this way. A more intuitive and ergonomic steering mechanism of colonoscopes may well steepen learning curves and improve efficiency of colonoscopic interventions, subsequently leading to a beneficial effect on colonoscopy capacity.

Robotics may have the potential to overcome the challenges in endoscope control. While in recent years the use of robotics has been widely implemented in minimally invasive surgery, technical studies on the use of robotic steering in gastrointestinal endoscopy have yielded diverse results.[6-8] This is mainly the result of variations in the control setup, with regard to maneuverability of the endoscope and a fixed position of the steering mechanism in several designs.

Both during introduction and withdrawal of the colonoscope, it is important that the tip of the colonoscope is oriented in a matter that optimizes overview of the colonic anatomy. Robotic control of flexible endoscopes allows automated visual flexible endoscope navigation. This could help in keeping the tip of the scope oriented to the colonic lumen.

We introduce a robotic platform with the option of automated lumen centralization (ALC) to assist the endoscopist in endoscopic tip steering. We performed a randomized, controlled, cross-over colon model pilot study to evaluate the feasibility of colonoscopy with robotic steering and ALC, and compared cecal insertion times and the rates of detection of simulated polyps with conventional colonoscopy in both expert endoscopists and endoscopy naive novices.

METHODS

Study population

Both expert endoscopists and novices participated in the study. The expert endoscopists were gastroenterologists from two hospitals (Meander Medical Center, Amersfoort and University Medical Center, Utrecht), all with an individual experience of over 2,000 colonoscopies. The novices were students of Technical Medicine at the University of Twente, Enschede, the Netherlands. All had finished the bachelor program on gastrointestinal diseases, had basic knowledge of gastrointestinal anatomy and pathophysiology, and knew the technical principles of gastrointestinal endoscopy. None of the novices had any experience in performing endoscopy.

Study design

All participants performed a colonoscopy on a single case of a physical colon model both with conventional colonoscopy steering and with robotic steering including the option of ALC. We used a cross-over design; participants were randomized to which of the two modalities they were to start with.

Before testing, each participant received both verbal and written instructions on the goals of this study, the colon model and robotic steering with ALC. Novices also received instructions on the conventional colonoscopy steering mechanism.

Expert endoscopists had five minutes to familiarize with the colon model using the conventional steering method and were allowed 20 minutes to practice with the robotic setup before the study started. Novices were granted ten minutes to get used to the colon model and 20 minutes to practice each modality.

Participants were instructed to introduce the endoscope to the cecum as fast as possible. Withdrawal time was set at six minutes. During testing, we allowed no additional instructions. Participants that were not able to reach the cecum with one of the endoscopic modalities were excluded.

After completion of the tests, the participants filled out a questionnaire on their subjective evaluation of robotic steering with ALC compared with the conventional colonoscopy steering mechanism.

The colon model with simulated polyps

All procedures were performed with an Exera II CLV-180 Olympus endoscopy light source, processor and colonoscope [Olympus, Tokyo, Japan]. We used the Kyoto Kagaku Colonoscope Training Model [Kyoto Kagaku Co. Ltd, Kyoto, Japan], which is a physical colon model consisting of a life-size plastic torso with a synthetic colon inside. The colon is threaded through rubber rings that are attached to the torso, either directly or by

springs. The colon was configured into standard cases, using the layout guides provided by the manufacturer.

Expert endoscopists performed the tests using case 2 of the colon model, which is one of the cases that has previously been validated for assessing colonoscope insertion skills.[9] During pre-testing of the platform setup for feasibility, none of the pre-testing novices was able to reach the cecum with either modality using this case. Therefore, novices performed the tests on (the easier) case 1.

We manually applied 21 foam fabric simulated polyps, varying in size, throughout the colon, in a distribution similar to that reported by Gralnek et al.[10] The novices used a shorter part of the synthetic colon for case 1, so the simulated polyps were redistributed to obtain the same distribution per colon segment as in case 2 [Figure 1].

Robotic steering with automated lumen centralization

When using robotic steering with ALC, the angulation wheels of the endoscope were connected to a remote drive unit and placed in a docking station.[11] The user steered the tip by means of a joystick controller [Figure 2]. To compensate for the lack of haptic feedback from the angulation wheels, a feedback circle was shown on screen to show the participant in which direction and to what extent the tip of the colonoscope was bent.[12]

ALC consisted of a software algorithm that identifies the darkest pixels in the image.[13] The darkest region in the image usually corresponds to the middle of the colonic lumen, which is the target area for the colonoscope. On screen, a small circle continuously depicted the target as detected by the ALC algorithm. When the position of the circle corresponded to the actual target, the participant could actively decide to let the platform steer the scope to center this point in the endoscopic image. This was done by pressing and holding button 1 on the joystick controller. Releasing the button immediately stopped the platform from steering the tip. The algorithm continued to determine the darkest region in the image.

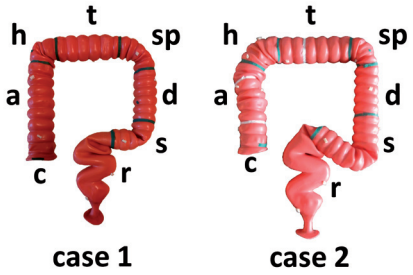

Figure 1. The cases of the colon model with distribution of the simulated polyps
c: cecum, a: ascending colon (3 simulated polyps), h: hepatic flexure (3 polyps), t: transverse colon (2 polyps), sp: splenic flexure (3 polyps), d: descending colon (2 polyps), s: sigmoid colon (4 polyps), r: rectum (4 polyps)

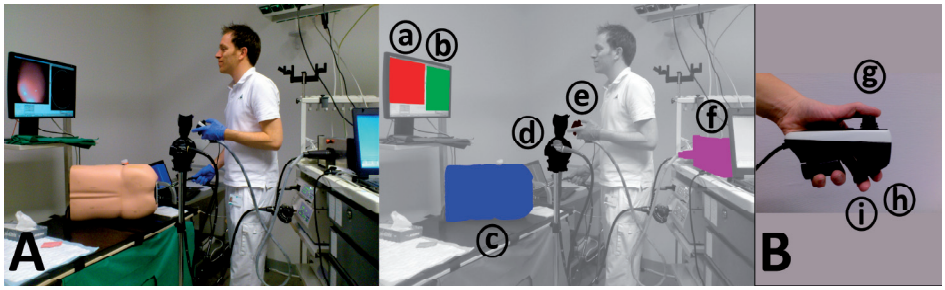

Figure 2. Experimental setup
Panel A: Setup of the experiment. **Panel B:** Detail of the joystick controller.
a: Endoscopic image, b: Visual feedback circle, c: Kyoto Kagaku Colonoscope Training Model, d: Docking station, e: Joystick controller, f: Motor unit, g: Joystick, h: Button 1, i: Button 2

All tests were performed single-handed, with the joystick controller or conventional colonoscope steering mechanism in one hand, and the shaft of the colonoscope in the other hand. With both modalities, the colonoscope could be torqued as usual.

Study endpoints

Primary endpoints of the study were cecal insertion time and the number of detected simulated polyps during endoscope withdrawal. The secondary endpoint was the subjective evaluation of the new platform by the participants.

Statistical analysis

We performed data analysis using Statistical Packages for Social Sciences version 22 [IBM Corp., Armonk, New York, USA]. For both participant groups, we compared median cecal insertion time and number of detected simulated polyps between the robotic and the conventional method using the Wilcoxon signed-rank test. We used Fisher's exact test to compare the median 'on'-time of the ALC option between participant groups. Categorical variables were also compared using Fisher's exact test. All tests were applied two-tailed. We considered $p < 0.05$ to be statistically significant. As this was a pilot study, no power calculation was performed beforehand.

RESULTS

A total of 8 expert endoscopists (7 males, median age 47 [interquartile range (IQR) 42.25-56.25] years) and 12 novices (3 males, median age 21.5 [IQR 20-22] years) participated in the study. We excluded data from two novices from further analyses: one failed to reach the cecum during conventional endoscopy (randomized to robotic steering first) and

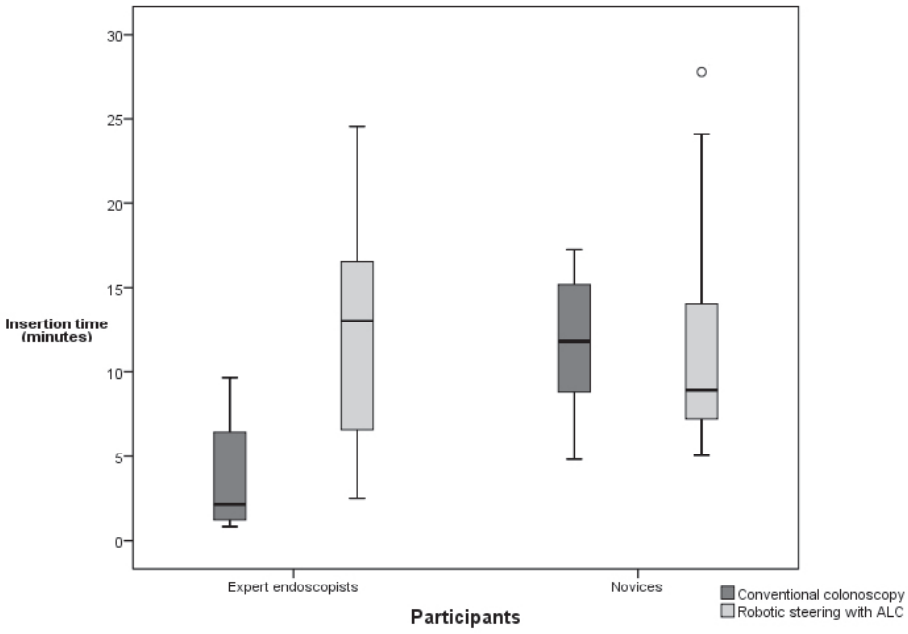

Figure 3. Box-whisker plot with insertion time for expert endoscopists and novices per conventional colonoscopy and robotic steering with ALC

one failed to complete the first procedure without additional instructions (randomized to start with conventional endoscopy).

Novices required a shorter time to intubate the cecum using robotic steering with ALC (8'56", IQR 6'46"-16'34"), compared to conventional colonoscopy (11'47", IQR 8'19"-15'33", p=0.65) [Figure 3]. The insertion time of expert endoscopists was shorter with conventional colonoscopy (median 2'9", IQR 1'13"-7'28"), compared to robotic steering with ALC (13'1", IQR 5'9"-16'54", p=0.12). There was no difference in insertion time between randomization groups in either experts or novices.

During conventional colonoscopy, novices and expert endoscopists detected a median of 78.6% (IQR 75.0-91.7%) and 80.9% (IQR 76.2-85.7%) of all polyps in the studied colon case [Figure 4]. Novices detected more polyps (median 88.1%, IQR 79.8-95.2%, p=0.17) during robotic steering with ALC compared with conventional colonoscopy, whereas expert endoscopists found significantly less polyps (median 69.0%, IQR 61.0-75.0%, p=0.03).

During endoscopy with robotic steering, we found no differences in the median time (of overall time during colonoscopy) that the ALC option was switched on between expert endoscopists (7.3%, IQR 3.3-13.6%) and novices (2.6%, IQR 2.4-4.1%) (p=0.153).

Table 1 shows the results of the post-procedural interviews regarding robotic steering with ALC. All novices and four expert endoscopists were generally positive about robotic

steering with ALC. All participants but one agreed that robotic steering with ALC makes performing colonoscopy easier for novices, but not for experienced endoscopists. All novices thought that introduction of the colonoscope was faster and overall performance was easier with robotic steering with ALC compared to conventional colonoscopy.

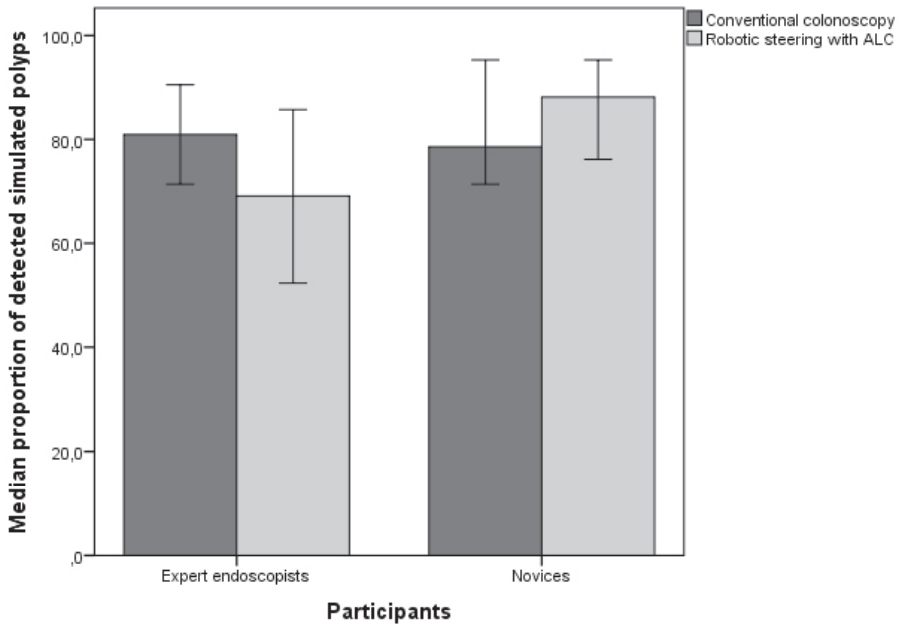

Figure 4. Bar graph with median polyp detection rate for expert endoscopists and novices per conventional colonoscopy and robotic steering with ALC
100% equals 21 simulated polyps. Error bars: 95% confidence interval

DISCUSSION

This randomized cross-over colon model study shows that robotic steering with ALC is feasible. In novices, cecal insertion time was found to be shorter and more polyps were identified using robotic steering with ALC, when compared with conventional colonoscopy. Post-procedure interviews indicated that robotic steering with ALC was appreciated most appropriate for novices.

The median colonoscope insertion time of the novices was almost 9 minutes during colonoscopy using robotic steering wih ALC. This appears an acceptable insertion time for novices performing their first ever colonoscopy, when compared to the 5-9 minutes insertion time expert endoscopists required during conventional colonoscopy in recent prospective studies in humans.[14,15] Overall, the experts and novices in our study detected a larger proportion of simulated polyps during conventional colonoscopy (over 78%),

Table 1. Subjective evaluation of experience and future use of the robotic steering with ALC

Statement	Agrees with statement		p-value*
	Expert endoscopists (n=8)	Novices (n=10)	
Colonoscopy with robotic steering and ALC…			
-Makes introduction of the scope easier	3 (37.5)	10 (100.0)	0.007
-Makes perfoming endoscopy faster	2 (25.0)	10 (100.0)	0.002
-Is more intuitive than conventional colonoscopy	4 (50.0)	9 (90.0)	0.118
-Makes perfoming endoscopy easier for novices	7 (87.5)	10 (100.0)	0.444
-Makes perfoming endoscopy easier for experts	1 (12.5)	1 (10.0)	1.00
I am positive about this platform	4 (50.0)	10 (100.0)	0.023
I see a potential role for this platform in clinical use	5 (62.5)	8 (80.0)	0.608

*Fisher's exact test

compared to the 52.9% of simulated polyps detected by the expert endoscopists in the in vitro colonoscopy study by Gralnek et al.[10] We based the location of the simulated polyps in our colon model on the model used by Gralnek et al., but instead of metallic beads we used foam fabric simulated polyps. These might have been easier to identify.

Allemann et al. and Zhang et al. previously evaluated the performance of a motorized conventional endoscope with a joystick interface.[6,7] Their results were somewhat disappointing, possibly owing to the fixed position of the endoscope in their experimental setup, limiting maneuverability and proprioceptive feedback. Reilink et al. reported no significant difference in cecal insertion time between conventional steering and an intuitive interface when letting novices perform simulated colonoscopy.[8] The design of our platform is different from previous studies as it still allows manual handling of the shaft of the endoscope. Therefore, our platform is more comparable to normal clinical practice.

The strengths of this study are the randomized controlled cross-over design, preventing the influence of a learning effect on the colon model. The novices in our study had no practical experience in performing endoscopy, but had theoretical knowledge on anatomical, pathophysiological and technical aspects of gastrointestinal endoscopy. As such, they are well comparable to fellows starting training in gastrointestinal endoscopy. Furthermore, we used a colon model for which several cases were previously validated.[9]

A potential drawback of this study is that the time to practice on the colon model was only short. Arguably, 20 minutes of practice is too short, especially for the completely endoscopy naive novices. The short practice time is probably also reflected in the fact that the participants had the ALC option turned on during only a small proportion of the total colonoscopy time. Participants were asked to combine many different cognitive

and motoric tasks that were new to them. Pressing and holding an additional button may have been too much to ask. The current experimental setup might therefore not be the optimal way to evaluate the intuitiveness of the ALC option. Considering the fact that this was a feasibility study, and as such not designed and powered to detect significant differences between the different modalities and participant groups, the results of this study are however promising.

Our study shows the potential for robotic steering with ALC, especially in non-experienced endoscopists. As they have been using conventional colonoscopy for many years, it is not surprising that expert endoscopists performed better using the conventional steering mechanism. The potential additional value of the current platform is best indicated by the learning curve of endoscopy naive novices. For endoscopists in training this platform might be attractive, as it can be used as a click-on system on existing and readily available endoscopy equipment. Before introducing this platform in clinical practice, further studies however are required. The next step could be a randomized trial evaluating learning curves of fellows in gastroenterology starting their training using either the conventional steering mechanism or robotic steering with ALC. The primary endpoint in that study should be cecal insertion time.

In conclusion, performing colonoscopy with robotic steering and ALC seems technically feasible. Its main advantages appear to be the intuitiveness for inexperienced endoscopists, who in our study were unequivocally positive about the currently presented platform.

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CHAPTER 9

General discussion

In the current era of a rapidly aging general population, an increasing colorectal cancer (CRC) incidence[1, 2] and the initiation of population-based screening programs for CRC, the main challenges for endoscopists in the coming years lie in increasing the quantity as well as optimizing the quality of colonoscopies. In this thesis, studies are described that aim to improve allocation of a patient with a correct indication to the appropriate examination at the right time, and to quantify colonoscopy quality. In this chapter, the main findings of this thesis, their clinical implications and future perspectives are discussed.

MAIN CONCLUSIONS FROM THIS THESIS

- Patients referred for a change in bowel habits or rectal blood loss are at an increased risk of having CRC and should have priority to undergo colonoscopy.
- Symptomatic patients over 50 years should undergo colonoscopy rather than flexible sigmoidoscopy, because of the high prevalence of polyps and CRC in this patient population.
- In patients with abdominal pain as only symptom, colonoscopy and flexible sigmoidoscopy are unlikely to yield CRC or another relevant cause for their symptoms.
- Of the currently available quality indicators for colonoscopy, only adenoma detection rate (ADR) has been shown to be directly associated with interval CRC.
- CT-colonography (CTC) can effectively be used to visualize the remainder of the colon in case of incomplete colonoscopy.
- The rate of early or missed CRCs in the 3 years following a colonoscopy with polypectomy has not decreased over a 10-year period.
- CRC due to incomplete adenoma resection within a few years after polypectomy occurs in one in four hundred resected adenomas.
- A new colonoscopy platform with robotic steering and automated lumen centralization seems more intuitive and allows faster cecal intubation compared to conventional colonoscopy, at least when performed by endoscopy naive novices.

COLONOSCOPY CAPACITY AND PATIENT ALLOCATION

In the Netherlands, there has been a steep increase in the number of performed colonoscopies in the last decades, although the number of endoscopists has not increased accordingly.[3] While the total number of gastroenterologists steadily increases,[4] the generation of internists and surgeons that perform colonoscopy is rapidly aging and is not replaced by new non-gastroenterologist endoscopists. Based on data from two

large pilot studies,[5, 6] in 2020 the implementation of the fecal occult blood test (FOBT) based population screening program for CRC in the Netherlands is expected to result in an additional 72,000 colonoscopies yearly. Although population screening in due time will probably result in a decrease in colonoscopies performed for symptoms due to CRC, it will also lead to an increasing number of patients undergoing surveillance colonoscopy after adenomas have been removed.[7] As long as endoscopy capacity fails to increase proportionally, the increasing demand for colonoscopy inadvertently will lead to longer waiting lists to undergo the procedure.[8] In this setting, the main challenges are to increase colonoscopy capacity and to allocate patients adequately, allowing timely investigation of patients with a high risk of detecting significant pathology.

Although the regulating governmental institution allows a slight increase in the number of gastroenterologists in training, whether this relatively modest increase in the number of gastroenterologists will indeed increase colonoscopy capacity sufficiently remains to be seen. Fellows that are currently entering their training program in gastroenterology will only contribute to an increase in capacity several years from now. An alternative strategy to increase colonoscopy capacity is to train nurse endoscopists to perform colonoscopy. In a supervised setting, nurse endoscopists are reported to be able to perform colonoscopy with comparable outcomes and adverse event rates to physician endoscopists and with a high patient satisfaction.[9-11] Furthermore, the use of nurse endoscopists has the advantage that it may substantially reduce costs.[9]

Triaging patients that are unlikely to develop significant pathology out of surveillance programs may also increase capacity. Whereas most previous Dutch guidelines for surveillance after polypectomy advised surveillance for each individual in whom at least one adenoma had been removed,[12-14] the most recent guideline from 2013 refers average-risk individuals with no or only one small, left-sided adenoma with low-grade dysplasia to the FOBT-based population screening program.[15] Surveillance is advised to stop at 75 years of age or after two negative colonoscopies when the patient had no high risk adenoma during any of the previous colonoscopies. Furthermore, British studies have shown that strict adherence to the applicable surveillance guidelines reduces waiting lists by reducing overutilization of colonoscopy resources.[16, 17]

Triaging patients to the appropriate examination at the right time remains a challenge. Both the American Society for Gastrointestinal Endoscopy and the European Panel of Appropriateness of Gastrointestinal Endoscopy have formulated criteria for the appropriateness of indications for colonoscopy.[18, 19] However, although the use of an appropriateness evaluation system increased the probability of detecting relevant pathology in a prospective study, the exclusive use of such a system for the selection of patients for colonoscopy resulted in a significant risk of colorectal neoplasms going undetected.[20] In a systematic review and meta-analysis, the appropriateness guidelines were also reported to have a suboptimal sensitivity and a poor specificity for the

detection of CRC.[21] Exclusively relying on the existing appropriateness guidelines for indications of colonoscopy therefore suboptimally differentiates between patients with an increased risk of CRC and patients with an average risk of CRC.

Despite the recent implementation of population screening programs for CRC, a large proportion of colonoscopies is still performed because of symptoms. As a consequence, the vast majority of CRCs is still being diagnosed in patients undergoing colonoscopy for symptoms.[22, 23] Identifying symptoms that are associated with an increased risk of detecting CRC could help in prioritizing patients for colonoscopy. After evaluation of the presenting symptoms in consecutive patients referred for colonoscopy, rectal bleeding and a change in bowel habits were found to be independently associated with an increased risk of detecting CRC. Rectal bleeding, especially dark red bleeding and blood mixed through the stools, appears to be the most consistently reported symptom associated with CRC in the literature,[24-26] warranting prompt further investigation. A change in bowel habits is also repeatedly reported to be associated with CRC,[27, 28] especially loose motion and increased stool frequency. Although abdominal pain traditionally is mentioned as one of the presenting symptoms of CRC,[29] recent studies failed to demonstrate a significant association between abdominal pain and CRC.[25, 26, 30] The work in this thesis confirmed this finding.

It is important that patients with a proper indication for colonic evaluation undergo the appropriate procedure in order to optimize outcome while minimizing the burden on endoscopy capacity. In this thesis, consecutive patients that were referred by the general practitioner for flexible sigmoidoscopy were evaluated. Based on the findings in this study, in symptomatic patients over 50 years of age, full colonoscopy should be the preferred modality, because of the high prevalence of polyps and CRC in these patients. In patients under 50 years, flexible sigmoidoscopy seems a reasonable alternative, since the frequency of isolated proximal colonic neoplasia in patients under 50 years has been reported to be low.[31, 32]

The use of CTC can alleviate the high demand on colonoscopy capactity. In this thesis, the yield of CTC when used in patients with incomplete colonoscopy was investigated. Apart from this indication, CTC can also be used as the primary diagnostic modality in symptomatic patients or for screening for CRC. CTC is known to have a comparable sensitivity as colonoscopy for polyps with a size of 5 mm or more[33, 34] and has the possible advantage of detecting relevant extracolonic pathology.[35] Although probably not as outspoken with newer generation CT technology,[36, 37] a significant disadvantage of CTC is the issue of radiation exposure. This potentially stands in the way of a broad implementation as the preferred modality in (biennial) screening of the entire population at risk. Furthermore, CRC has the obvious disadvantage that intraluminal lesions can be visualized only; no biopsy or polypectomy can be performed.

QUALITY OF COLONOSCOPY AND THE OCCURRENCE OF POST-COLONOSCOPY CRC

Several endoscopy societies have in recent years issued guidelines on quality indicators for colonoscopy.[38-40] These guidelines set targets for indicators such as bowel preparation quality, cecal intubation rate, withdrawal time and ADR. Most of these indicators however are process indicators, rather than indicators of outcome. The quality of colonoscopy should ideally be measured by clinical outcome measures. As a clinical outcome measure, the incidence of interval CRCs or post-colonoscopy CRCs (PC-CRC), defined as CRCs diagnosed within a few years after a colonoscopy where all detected adenomas were removed and before the scheduled surveillance would take place, probably better reflects colonoscopy quality than the current consensus-based process indicators. As a quality indicator, it has however the disadvantage that due to its low incidence and relatively long time between colonoscopy and occurrence of PC-CRC, it may be too slow and rigid in clinical practice.

ADR is the only current quality indicator that has been shown to be directly associated with the occurrence of PC-CRC.[41, 42] It is defined as the proportion of screened subjects in whom at least one adenomatous lesion is identified.[38, 39, 41, 42] ADR however has the disadvantage that it does not optimally differentiate between subjects in whom the endoscopist detects one versus more than one adenoma. Considerable variability has been reported between endoscopists with a similar ADR with regard to the total number of adenomas detected per colonoscopy.[43, 44]

The prevention of PC-CRCs is currently one of the main challenges to endoscopists performing colonoscopy. In the literature, 2 to 8% of all CRCs are reported to be PC-CRCs.[45-51] In this thesis, it was shown that this rate has not decreased over a 10-year period in the Netherlands, despite increasing awareness for these lesions and advancements in endoscopy technology. The survival of patients with PC-CRC, after adjustment for differences in tumor stage, has been reported to be similar for patients with sporadic CRC,[52] suggesting that the majority of these tumors represent missed or incompletely resected lesions, rather than new lesions with a more aggressive tumor biology. As previously reported in the literature,[47, 48, 50, 52] location in the right-sided colon was a risk factor for PC-CRC. Indeed, the protective effect of colonoscopy on CRC incidence has repeatedly been reported to be higher for distal tumors than for proximal CRCs.[53-56] In line with this, colonoscopy has been shown to reduce the mortality of right-sided tumors to a lesser extent than that of more distally located CRCs.[57, 58]

Why are precursor lesions more prone to be missed in the proximal colon? Several possible explanations have been proposed. First, it is accepted that up to 10% of colonoscopies are incomplete.[38, 39] In case of incomplete colonoscopy, obviously not all proximal colon segments are inspected and proximal lesions can be missed. Second,

bowel preparation is more likely to be suboptimal in the proximal colon.[59] Furthermore, several studies have found that right-sided polyps with advanced neoplasia tend to be smaller and more often nonpolypoid (sessile) than left-sided polyps.[60, 61] Finally, sessile serrated lesions are predominantly found in the proximal colon and are most likely more difficult to detect than adenomas.[62-65] Not until recent years, sessile serrated lesions have been recognized as a distinct neoplastic entity with its own distinct biological behavior and pathways through which progression to CRC may occur.[66] They are probably still underdiagnosed in clinical practice in present day.[67]

In previous studies, 9 to 50% of PC-CRCs were thought to develop from incompletely resected colorectal adenomas.[50, 68, 69] In the work described in this thesis, PC-CRC due to incomplete adenoma resection was found to occur in as much as one in 400 resected adenomas overall and in one in 170 resected adenomas with high-grade dysplasia or villous histology. The implication of this finding for clinical practice is clear: PC-CRC due to incomplete adenoma resection will likely happen to each colonoscopist. With the implementation of population screening programs for CRC and the subsequent increase in the number of colonoscopies that will be performed, the total number of polypectomies that is performed will also increase. Conceivably, these PC-CRCs could be prevented by increasing awareness, improving quality of polypectomy and adhering to surveillance guidelines. It is known that there is a considerable risk for colorectal adenomas to be incompletely resected.[70, 71] Specifically piecemeal endoscopic mucosal resection (EMR) of large colorectal lesions is known to carry a significant risk of local recurrence.[71]

Endoscopic submucosal dissection (ESD) has the advantage that the neoplastic colorectal lesion can be resected en bloc, enabling better appreciation of the completeness of the resection by the pathologist. Resection of large colorectal adenomas with ESD has been reported to more frequently result in a radical resection with a consequently lower risk of local recurrence than EMR.[72-74] Up until now, this technically demanding technique has mainly been practiced in Japan. The first experiences in Western institutions were recently published.[75, 76] ESD is known to have a long learning curve and a longer procedure time time than EMR. Furthermore, it is associated with an increased risk of perforation.[72-74] These factors stand in the way of broad implementation of ESD in daily clinical practice, especially because recurrences after EMR can be completely removed by additional endoscopic treatment in the vast majority of cases.[77, 78] For the time being, it seems reasonable to consider (piecemeal) EMR as the standard for resection of larger colonic polyps, while ESD is reserved for highly selected cases in the distal colorectum by specifically trained and experienced endoscopists. As the vast majority of recurrences after EMR are detected at 6 months, this is proposed to be the optimal initial follow-up interval.[71]

FUTURE PERSPECTIVES

The results of this thesis provide several interesting starting points for further studies, aiming at increasing colonoscopy capacity, optimizing patient allocation, increasing overall colonoscopy quality and reducing the number of PC-CRCs.

First of all, it is important to realize that an overwhelming proportion of available colonoscopy resources is used to detect and remove colonic polyps, with the majority of these never developing into CRC during a patient's lifetime. Improved in vivo appreciation of the true risk of malignant progression of individual colonic polyps could significantly impact clinical practice, as polyps with a non-existent or negligible risk of progressing towards malignancy could be left in situ, and colonoscopy resources could be redirected to the resection of high risk polyps. Thus far, attempts at this have been made using narrow band imaging and confocal endomicroscopy, but a broad practical implementation is yet hampered by the suboptimal negative predictive value of these modalities.[79, 80]

With the introduction of nurse endoscopists, the broad availability of CTC and the current evaluation of new, alternative modalities to evaluate the colon, e.g. capsule colonoscopy and magnetic resonance colonography,[81-84] colonoscopists of the future are probably mainly performing therapeutic endoscopy. While natural orifice transluminal endoscopic surgery (NOTES) without laparoscopic assistance is unlikely to be feasible in clinical practice in the near future,[85] colorectal adenomas of increasing size can now be resected safely and effectively endoscopically, thereby avoiding partial colectomy. Therefore, continuous improvement of existing instruments and the development of new practical instrumentation is mandatory.

A more intuitive steering mechanism for colonoscopes can further support these developments. The principal design of the steering mechanism of endoscopes has not significantly changed in the last 50 years.[86] Conventional colonoscopy is by many considered to be non-intuitive and is associated with an extensive learning curve.[87, 88] Moreover, musculo-skeletal complaints due to the non-ergonomic design are common.[89] Novel, more intuitive steering mechanisms could shorten learning curves, thereby indirectly increasing colonoscopy capacity, and could help endoscopists perform more elaborate tasks like difficult polypectomies more efficiently. In this thesis, a new pilot colonoscopy platform that allows robotic steering with automated lumen centralization was evaluated to this extent.

With the increasing endoscopic possibilities to remove large-sized colorectal lesions, and with the implementation of population screening programs resulting in an increased yield of advanced polyps and early CRCs, an increasing number of malignant polyps or early-stage CRCs (T1-stadium) will be endoscopically resected. It is not yet clear which patients should undergo additional surgical resection after a radical endoscopic

resection of a malignant polyp. Several risk factors for the co-presence of lymph node metastasis have been recognized, e.g. the absence of free margins, lymphovascular invasion, poor differentiation grade, deep submucosal invasion, tumor budding and sessile morphology. These are all derived from retrospective cohorts with relatively small case volumes.[90-93] Future research should aim at more clearly identifying patients who are most likely to benefit from additional surgery, especially considering the fact that colon surgery carries its own morbidity and even mortality risk.

The current proposed quality indicators for colonoscopy need further revision as more data becomes available in the literature. Currently, ADR is the only indicator directly associated with the outcome measure PC-CRC, while ADR itself is a derivative of the quality with which the entire colonic mucosa is visualized during colonoscopy. In time it may be replaced by a more direct measure for the proportion of the colonic mucosa that is inspected. A recent publication on a fully automated three-dimensional reconstruction technique from individual colonoscopy images is interesting in this light.[94] A technique like this might eventually give real time feedback to the endoscopist on areas of the colonic mucosa that were not adequately inspected, thus enabling revisiting these areas during the same procedure. The proportion of the colonic mucosa that is visualized by the endoscopist may potentially serve as a new quality indicator for colonoscopy. Furthermore, information on inspected and uninspected areas of the colonic wall may help in training endoscopists, giving insight in possible 'blind spots' during withdrawal of the colonoscope.

Finally, future research on PC-CRCs should aim at definitely establishing that PC-CRCs have similar tumor biology as sporadic CRCs, reducing the number of missed lesions, especially in the proximal colon, and at determining the optimal follow-up interval for confirming radical adenoma resection, particularly after removal of adenomas with advanced histology.

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CHAPTER 10

Summary

Nederlandse samenvatting

Acknowledgements / dankwoord

List of publications

Curriculum vitae

Summary

Since the introduction of the first fiberoptic colonoscopes in the late 1960s, colonoscopy has become the modality of choice for the evaluation of symptoms suspected to originate from the colorectum and for the detection of polyps and colorectal cancer (CRC). CRC is a major cause of morbidity and mortality in the Western world, and in many countries its incidence is still rising. CRCs are known to have a benign precursor lesion, the adenomatous polyp. Removal of adenomas during colonoscopy has been shown to reduce the incidence and mortality of subsequent CRC. Patients in whom one or more adenomas have been resected are offered a surveillance program with colonoscopic examinations at regular intervals dependent on the number and type of the resected adenomas during the previous colonoscopy. Furthermore, in recent years many countries have started population-based screening programs for CRC. In the Netherlands this was started in 2014.

As a result of these developments, there is an increasing demand on colonoscopy capacity. Colonoscopy however is known to be an imperfect test. Up to a quarter of polyps may be missed during colonoscopy, potentially leading to so-called interval or post-colonoscopy CRC. The main challenges in the coming years will be to optimize colonoscopy quality as well as to manage capacity for synchronizing supply and demand for the increasing the number of colonoscopies in the Netherlands. In **Chapter 1** the general aims and outline of this thesis are summarized.

Patients with an increased risk of having CRC should have priority on the colonoscopy waiting list. In **Chapter 2**, it is investigated whether presenting symptoms of patients referred for colonoscopy could help in identifying patients with an increased CRC risk. To this end, 1,458 outpatients filled out a questionnaire in the waiting room of the endoscopy suite prior to their scheduled colonoscopy. The results of the questionnaire were then related to the findings during colonoscopy. After adjustment for confounders, rectal blood loss, a change in bowel habits and age over 50 years were found to be independently associated with the risk of finding CRC. Prior flexible sigmoidoscopy or colonoscopy and fatigue as presenting symptom were inversely associated with the risk of finding CRC. No association was found between weight loss, self-reported anemia or abdominal pain and CRC. These findings suggest that patients over 50 years with rectal blood loss and/or a change in bowel habits should be prioritized on colonoscopy lists.

In many institutions in the Netherlands, general practitioners have open access to flexible sigmoidoscopy for referral of patients with lower gastrointestinal symptoms, but not to colonoscopy. This could stimulate a preferential referral pattern towards flexible sigmoidoscopy, while it is generally accepted that colonoscopy should be the preferred procedure in many of these cases. In **Chapter 3**, 916 consecutive patients that were referred for flexible sigmoidoscopy by general practitioners were evaluated. In 27.5%

of the patients over 50 years, additional colonoscopy was performed, mainly due to the finding of adenomatous polyps and CRC during flexible sigmoidoscopy. Overall, in 44.2% of patients a cause for the presenting symptoms was found. Interestingly, in patients referred for abdominal pain as the only presenting symptom, flexible sigmoidoscopy was unlikely to yield a relevant cause for the symptoms.

In an effort to standardize and optimize the quality of colonoscopy, several endoscopy societies have formulated quality indicators for colonoscopy in the past few years. The main quality indicators bowel preparation, cecal intubation rate, withdrawal time, adenoma detection rate, patient comfort and sedation and complication rate are critically reviewed in **Chapter 4**. The current quality indicators are mostly consensus-based process indicators, rather than outcome measures. The scientific evidence for most indicators is only limited. Adenoma detection rate is currently the only quality indicator that has been shown to be directly associated with interval CRC, but as an indicator it does not optimally differentiate between high and low performing colonoscopists.

Chapter 5 reports on the use of CT-colonography (CTC) after incomplete colonoscopy. CTC is a relatively new diagnostic modality to visualize the colonic lumen, with good to excellent detection rates of colonic polyps. It may be used as an alternative to conventional colonoscopy or compliment colonoscopy in case the cecum could not be intubated. A potential advantage of CTC is that information on extracolonic lesions can also be obtained. In 136 consecutive patients with incomplete colonoscopy, CTC revealed 27 relevant additional lesions (both intra- and extracolonic) in 19.1% of patients. Furthermore, in the patients with CRC, CTC could also be used for staging purposes.

Colonoscopy with removal of all detected adenomas is the gold standard for screening and surveillance of CRC. However, CRC sometimes occurs within 3 years after a previous colonoscopy. Despite increased professional awareness and technically improved endoscopy equipment, it is not clear whether the incidence of these missed or early CRCs has decreased over time. Therefore, a nationwide, population-based case-control study was peformed in **Chapter 6**, linking data from PALGA, the Dutch Pathology Registry, with data from the Netherlands Cancer Registry. The rates of missed or early CRC after polypectomy were compared between the years 1996 and 2006. No decrease in missed or early CRCs was found. After adjustment for a lower tumor, nodal and metastasis (TNM) stage of missed or early CRCs, survival rates were not different between missed or early CRCs and regularly diagnosed CRCs. Location in the right side of the colon was an independent risk factor for missed or early CRCs.

Some of the CRCs occurring within several years after colonoscopy with removal of all detected adenomas are thought to be due to incompletely resected adenomas. The results of a nationwide, population-based cohort study are reported in **Chapter 7**. All patients with a first colorectal adenoma between the years 2000 and 2010 were identified in PALGA. CRC due to an incompletely resected adenoma was defined as a CRC between 6 months and 5 years after adenoma resection in the same colon segment. In a cohort of 107,744 patients, CRC due to incomplete adenoma resection was found in 324 of 133,519 resected adenomas (0.24%, or 1 in four hundred resected adenomas). The incidence rate was 0.56 per 1,000 years of follow up. High-grade dysplasia and a villous or tubulovillous histology were found to be independent risk factors for CRC due to incomplete adenoma resection.

The steering mechanism of conventional flexible endoscopes has not significantly changed in the last 50 years. It is often considered non-intuitive, non-ergonomical and is known to have an extensive learning curve. In **Chapter 8**, the first experiences with a completely new steering platform for colonoscopes are reported. Expert endoscopists and endoscopy naive novices performed colonoscopy on a validated colon model with simulated polyps both with conventional colonoscopy and with the new platform with robotic steering and automated lumen centralization. Novices intubated the cecum faster and detected more simulated polyps with robotic steering with the option of automated lumen centralization and found the new platform to be more intuitive and easier than conventional colonoscopy. Expert endoscopists intubated the cecum faster and detected more simulated polyps during conventional colonoscopy. The novices were unequivocally positive about the new platform. The results of this study justify further studies, primarily aimed at inexperienced endoscopists.

Finally, in **Chapter 9** the results of the studies in this thesis, their implications for clinical practice and future perspectives are discussed.

Nederlandse samenvatting

Colonoscopie is een onderzoek waarbij de dikke darm van binnen wordt bekeken met een flexibele kijker. Sinds de introductie van de eerste fiberoptische colonoscopen eind jaren '60, is colonoscopie het onderzoek van keuze voor de evaluatie van symptomen die mogelijk van de dikke darm afkomstig zijn en voor de detectie van poliepen en dikke darm- en endeldarmkanker (samen 'colorectaal carcinoom' (CRC) genoemd).

In veel landen komt CRC steeds vaker voor. De aandoening leidt tot veel ziekte en sterfte in de Westerse wereld. CRC's hebben een goedaardige voorloper, de adenomateuze poliep ('adenoom'). Het verwijderen van adenomen tijdens colonoscopie, ook wel 'poliepectomie' genoemd, verlaagt de incidentie van en sterfte aan CRC. Patiënten bij wie een of meerdere adenomen zijn verwijderd tijdens colonoscopie krijgen het advies deel te nemen aan een surveillanceprogramma. Op basis van het aantal en het type verwijderde adenomen bij eerdere colonoscopie, wordt het interval tot de volgende colonoscopie bepaald. Daarnaast zijn de laatste jaren in veel landen programma's voor bevolkingsonderzoek naar CRC opgezet. In Nederland is een dergelijk bevolkingsonderzoek in 2014 gestart.

Als gevolg van bovenstaande ontwikkelingen is er een toenemende vraag naar colonoscopieën. Alhoewel colonoscopie steeds vaker wordt toegepast, is bekend dat het geen perfect onderzoek is: tot een kwart van de poliepen kan worden gemist tijdens colonoscopie. Mede hierdoor kunnen zogenaamde 'post-colonoscopie CRC's' optreden. Het optimaliseren van de kwaliteit van colonoscopie, alsook het verhogen van de totale colonoscopiecapaciteit in Nederland, zijn de voornaamste uitdagingen voor de komende jaren.

In **Hoofdstuk 1** worden de algemene doelstellingen van het onderzoek in dit proefschrift beschreven als inleiding op de studies in de daaropvolgende hoofdstukken.

Patiënten die een verhoogd risico hebben op CRC zouden prioriteit moeten krijgen op de wachtlijst voor het ondergaan van een colonoscopie. In **Hoofdstuk 2** wordt onderzocht of de symptomen waarmee patiënten zich presenteren zouden kunnen helpen bij het identificeren van patiënten met een verhoogd risico op CRC. Hiervoor vulden 1458 patiënten een vragenlijst in terwijl ze in de wachtkamer zaten te wachten voorafgaand aan hun geplande colonoscopie. De resultaten van de vragenlijst werden vervolgens gerelateerd aan de bevindingen tijdens de colonoscopie. Bloed bij de ontlasting, een veranderd ontlastingspatroon en een leeftijd boven 50 jaar bleken een verhoogde kans te geven om CRC te vinden bij colonoscopie. Patiënten die een eerdere sigmoidoscopie (endoscopisch onderzoek tot halverwege de dikke darm) of colonoscopie hadden ondergaan hadden een verlaagd risico. Er werd geen relatie gevonden tussen het vinden van CRC en patiënten die aangaven dat gewichtsverlies, buikpijn of een bloedarmoede de reden was om de colonoscopie te verrichten. Deze resultaten suggereren dat patiën-

ten boven de 50 jaar met bloed bij de ontlasting en/of een veranderd ontlastingspatroon met voorrang een colonoscopie zouden moeten ondergaan.

In veel Nederlandse ziekenhuizen kunnen huisartsen patiënten met darmklachten direct verwijzen voor een sigmoidoscopie, maar niet voor een colonoscopie. Alhoewel de heersende opvatting is dat colonoscopie in de meeste gevallen het onderzoek van keuze zou moeten zijn, kan bovenstaande er toe leiden dat patiënten preferentieel voor sigmoidoscopie worden verwezen. In **Hoofdstuk 3** worden 916 opeenvolgende patiënten geëvalueerd die voor sigmoidoscopie werden verwezen door hun huisarts. Van de patiënten ouder dan 50 jaar werd bij meer dan een kwart van de patiënten (27,5%) na deze sigmoidoscopie alsnog een volledige colonoscopie verricht, vooral vanwege het vinden van een of meer adenomateuze poliepen en/of CRC. Bij 44,2% van de patiënten werd tijdens sigmoidoscopie een oorzaak voor de klachten gevonden. Bij patiënten die verwezen werden vanwege buikpijn zonder andere klachten, was het erg onwaarschijnlijk dat met sigmoidoscopie een verklaring voor de klachten werd gevonden.

In een poging om de kwaliteit van colonoscopie te standaardiseren en optimaliseren hebben verscheidene internationale endoscopieverenigingen de laatste jaren kwaliteitsindicatoren geformuleerd. In **Hoofdstuk 4** worden de belangrijkste kwaliteitsindicatoren darmvoorbereiding, coecumintubatiegraad, colonoscoop terugtrektijd, adenoom detectiegraad ('adenoma detection rate', ADR), patiëntcomfort en sedatie en complicatierisico kritisch beschreven. De huidige kwaliteitsindicatoren zijn vooral tot stand gekomen door consensus en zijn vooral procesindicatoren in plaats van uitkomstmaten. De wetenschappelijke onderbouwing van de meeste indicatoren is beperkt. De ADR is op dit moment de enige kwaliteitsindicator waarvan aangetoond is dat deze direct is geassocieerd met het optreden van post-colonoscopie CRC. Als indicator maakt ADR echter geen optimaal onderscheid tussen beter en slechter presterende endsocopisten.

In **Hoofdstuk 5** wordt gerapporteerd over het gebruik van CT-colonografie (CTC, ofwel 'virtuele colonoscopie') in geval een onvolledige colonoscopie is verricht. CTC is een relatief nieuwe diagnostische modaliteit waarmee met behulp van een speciale CT-scan het slijmvlies van de dikke darm onderzocht kan worden. Poliepen kunnen hiermee goed tot uitstekend gedetecteerd worden. CTC kan gebruikt worden als alternatief voor colonoscopie, maar ook als aanvulling op colonoscopie als het niet gelukt is de colonoscoop tot in het diepste punt van de dikke darm, het 'coecum', te introduceren. Een mogelijk voordeel van CTC is dat ook de rest van de buikholte in beeld gebracht wordt. CTC werd verricht bij 136 achtereenvolgende patiënten bij wie de colonoscopie niet volledig was. Er werden 27 relevante, aanvullende bevindingen gedaan (zowel in de dikke darm als ook daarbuiten) bij 19.1% van de patiënten. Bij de patiënten waarbij een

CRC werd gevonden, kon CTC daarnaast direct gebruikt worden om te stadiëren, d.w.z. te beoordelen of er uitzaaiingen zijn.

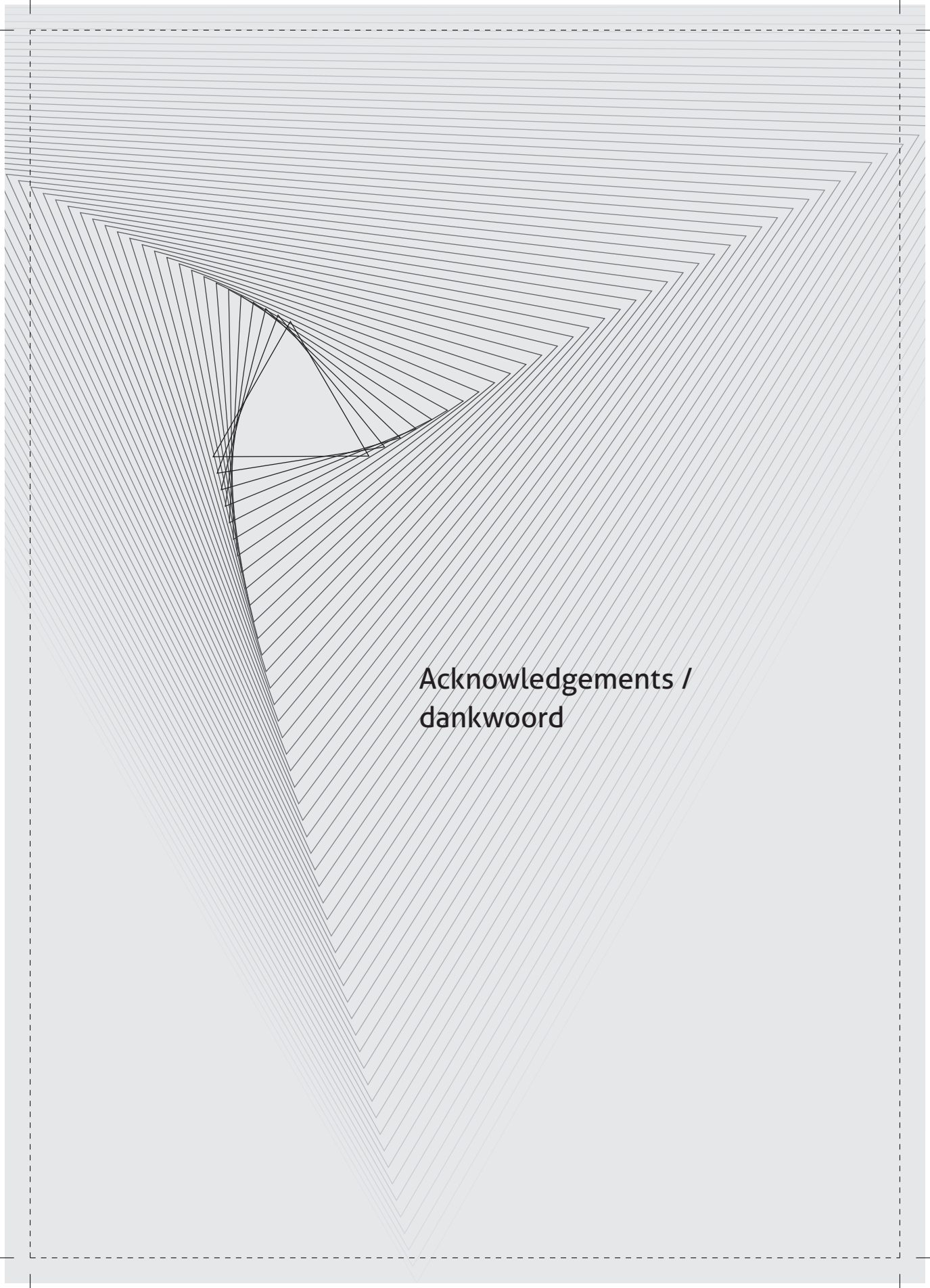
Ondanks het feit dat bij een colonoscopie alle gevonden adenomen worden verwijderd, ontstaan er soms toch CRC's binnen 3 jaar na een colonoscopie. Ondanks toegenomen professionele aandacht hiervoor en betere endoscopie-apparatuur, is het niet duidelijk of de incidentie van gemiste of vroege CRC's afgenomen is in de loop van de tijd. Om dit te onderzoeken werd in **Hoofdstuk 6** een landelijk, bevolkingsbreed 'case-control' onderzoek verricht. Hierin werden de gegevens van het Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA) gecombineerd met die van de Nederlandse Kankerregistratie. Het percentage van gemiste of vroege CRC's na poliepectomie in 1996 werd vergeleken met dat van 2006. Er werd echter geen afname gevonden. Na correctie voor eventuele verschillen in tumorstadium, werd geen verschil gevonden in overleving tussen patiënten met een gemist of vroeg CRC en patiënten met een regulier gevonden CRC. Lokalisatie in het rechter deel van de dikke darm was een onafhankelijke risicofactor voor een gemist of vroeg CRC.

Het wordt aangenomen dat een deel van de CRC's die binnen een aantal jaren na colonoscopie met poliepectomie optreden het gevolg is van incompleet verwijderde adenomen. In **Hoofdstuk 7** worden de resultaten beschreven van een landelijke cohortstudie. Hierin werden alle patiënten die een eerste adenoom hadden in de periode 2000 tot en met 2009 geïdentificeerd via PALGA. CRC ten gevolge van incomplete adenoomresectie werd gedefinieerd als het optreden van CRC tussen 6 maanden en 5 jaar na verwijdering van een adenoom uit hetzelfde deel van de dikke darm. In een cohort van 107.744 patiënten trad CRC ten gevolge van incomplete adenoomresectie op in 324 van de 133.519 verwijderde adenomen (0,24%, ofwel een op de vierhonderd verwijderde adenomen). Dit kwam overeen met een incidentie van 0,56 per 1000 jaren follow-up. De aanwezigheid van ernstig onrustige cellen ('hooggradige dysplasie') in het adenoom en bepaalde andere microscopische kenmerken ('villeuze' en 'tubulo-villeuze adenomen') waren onafhankelijke risicofactoren voor een CRC ten gevolge van een incomplete adenoomresectie.

Het besturingsmechanisme van conventionele flexibele endoscopen is de laatste 50 jaar niet noemenswaardig veranderd. Het wordt vaak gezien als niet intuïtief, niet ergonomisch en het gaat gepaard met een vrij lange leercurve. In **Hoofdstuk 8** wordt gerapporteerd over de eerste ervaringen met een volledig nieuw besturingsmechanisme voor colonoscopen. Ervaren endoscopisten en beginners verrichtten colonoscopieën op een gevalideerd colonmodel met gesimuleerde poliepen, zowel met conventionele besturing als met robotische besturing die bovendien automatisch het midden van de

darm kan vinden ('automatische lumencentralisatie'). Met het nieuwe systeem kwamen beginners sneller tot in het coecum en vonden zij meer poliepen. Zij vonden het nieuwe systeem bovendien ook intuïtiever en gemakkelijker dan de conventionele besturing. Ervaren endoscopisten waren sneller met de conventionele besturing en detecteerden daarmee ook de meeste poliepen. De beginners waren unaniem positief over het nieuwe besturingssyteem. De resultaten van deze studie geven aanleiding tot verder onderzoek, in eerste instantie vooral gericht op onervaren endoscopisten.

Tenslotte worden in **Hoofdstuk 9** de resultaten van dit proefschrift bediscussieerd, net als hun implicaties voor de dagelijkse praktijk en perspectieven voor de toekomst.



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List of publications

H.J.M. Pullens[*], T.D.G. Belderbos[*], M. Leenders, M.E.I. Schipper, P.D. Siersema, M.G.H. van Oijen.
Significant risk of post-colonoscopy colorectal cancer due to incomplete adenoma resection: results of a nationwide population-based cohort study.
Submitted
*authors contributed equally

H.J.M. Pullens, N. van der Stap, E.D. Rozeboom, M.P. Schwartz, F. van der Heijden, M.G.H. van Oijen, P.D. Siersema, I.A.M.J. Broeders.
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Curriculum vitae

Hendrikus Johannes Maria (Paul) Pullens was born on the 19th of September 1980 in Waalwijk. He grew up in Kaatsheuvel. After graduating cum laude from high school (gymnasium, dr. Mollercollege, Waalwijk), he started his medical training at the Radboud University in Nijmegen in 1998.

He worked as a resident in Internal Medicine in Ziekenhuis Gelderse Vallei in Ede in 2004 and 2005 after obtaining his medical degree. Between January 2006 and May 2011 he did his training in Gastroenterology and Hepatology in the University Medical Center Utrecht (supervisor: prof. dr. P.D. Siersema) and the Meander Medical Center in Amersfoort (supervisor: J.R. Vermeijden). After finishing his residency, Paul worked as a gastroenterologist in the UMC Utrecht. Since May 2012, he has been working as a gastroenterologist in the Meander Medical Center.

The work described in this thesis was performed between 2007 and 2015.

Paul lives in Amersfoort with his partner Judith van der Valk and their daughter Hanna (2013). They are expecting another baby in the summer of 2015.