Pitfalls & Opportunities

in Colorectal Cancer Screening

Paul G. van Putten

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Pitfalls and Opportunities in Colorectal Cancer Screening, Thesis, Erasmus MC, Rotterdam, The Netherlands

ISBN: 978-94-6169-387-7
Cover design: Lisa Keijzer (Optima Grafische Communicatie)
Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

Financial support for printing this thesis was financially supported by Roche Nederland, Zambon, Bayer HealthCare, Dr Falk Pharma Benelux B.V., department of gastroenterology and hepatology Erasmus University Medical Center Rotterdam, Erasmus University Rotterdam, and J.E. Jurriaanse Stichting.

Pitfalls and Opportunities in Colorectal Cancer Screening

Valkuilen en kansen in darmkanker screening

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. H.G. Schmidt
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
Woensdag 5 juni 2013 om 13.30 uur

door

Paul Gerard van Putten

geboren te
Noordoostpolder

ERASMUS UNIVERSITEIT ROTTERDAM

PROMOTIECOMMISSIE

Promotoren:	Prof.dr. E.J. Kuipers
	Prof.dr. E.W. Steyerberg
Overige leden:	Prof.dr. M.J. Bruno
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Copromotor:	Dr. M.E. van Leerdam

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Chapter 1

General introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of death from cancer in the Western world [1,2]. Screening has been shown to reduce CRC incidence and mortality [3-6]. The first evidence that colorectal cancer screening could effectively reduce mortality dates back 20 years [7]. Despite this fact, population screening has long been halted at the level of individual testing and discussions of the differences between screening tests. With a wealth of new evidence from various community-based studies looking at test uptake, screening-program organization and the importance of quality assurance, population screening for CRC has come of age. That is, opportunistic individual testing is now shifting towards organized population screening with comprehensive monitoring and full-program quality assurance. Health councils encourage and support member states to implement CRC screening with an organized population-based approach and appropriate quality assurance at all levels. In this process, the focus turns from the test alone to the combination of a range of factors including the target population, test characteristics, uptake, screenee autonomy, capacity, diagnosis and management of the disease, and costs [8]. This thesis aims to explore methods to improve and optimize population screening for CRC.

It is generally recognized that endoscopic capacity is insufficient for the increased demand that results from CRC screening programs [9-14]. Growing health care demands and costs ask for unprecedented solutions, including selective use of resources, and rescheduling of tasks. This includes rescheduling of tasks from physicians to specialized nurses. Introducing nurse endoscopists into gastrointestinal endoscopy service may provide a solution for the insufficient endoscopic capacity. There are several important issues to the establishment of nurse endoscopy. As gastroenterologists are to train and supervise nurse endoscopists, it is important that they support nurse endoscopy. Therefore, we evaluated the views of gastroenterologists towards nurse performed endoscopy in **Chapter 2**.

The decision to introduce NE should be based upon their competence in performing the endoscopy. Data on CRC screening emphasize the need of performing the endoscopy according to the international recognized quality standards with high patient acceptance [15]. Furthermore, costs must be considered. In **Chapter 3** we evaluated the endoscopic quality and patient experiences of nurse endoscopist performed colonoscopy. In **Chapter 4** we compared the endoscopic quality between nurse and physician performed colonoscopy, and evaluated cost differences.

The pathology service also plays an important role in CRC screening since the management of participants in the program depends on the quality and accuracy of the histopathologic diagnosis. Pathology affects the decision to undergo further local or

major resection, as well as surveillance after screening. In addition, it guides strategies for identifying hereditary CRC syndromes such as Lynch syndrome. Accurate pathological assessment is of paramount importance [16]. In **Chapter 5** we evaluated the inter-observer variation in the histological diagnosis of colorectal polyps. In **Chapter 6** we focused on the accuracy of identifying CRC pathology features known to be associated high microsatellite instability (MSI-H). These features are incorporated in various strategies to select cases for germline mutation analysis, in order to identify persons with Lynch syndrome. We described the diagnostic test characteristics and inter-observer variation of MSI-H associated pathology features for identifying MSI-H CRC.

The last issue addressed in this thesis concerns the field of colon imaging. Colon imaging is rapidly evolving and aims to improve CRC screening by lowering patient burden, enhancing neoplasia detection or by providing real-time histology. These methods include techniques with conventional endoscopes. Others make use of modified endoscopes to optimize diagnostic tissue characterization [17]. One such alternative is autofluorescence endoscopy. In **Chapter 7** we compared autofluorescence endoscopy and white light video endoscopy for the differentiation between adenomatous and hyperplastic colorectal polyps at the time of a colonoscopy.

In the final **chapter 8** the main findings of this thesis are summarized and discussed.

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Chapter 2

The views of gastroenterologists about the role of nurse endoscopists, especially in colorectal cancer screening

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ABSTRACT

Background: Nurse endoscopists (NE) may provide a solution for the insufficient endoscopic capacity in colorectal cancer (CRC) screening.
Aim: To determine the views of gastroenterologists about the potential role of NE in gastrointestinal endoscopy.
Methods: A postal questionnaire was sent to all registered gastroenterologists (n=301) and gastroenterology residents (n=79) in the Netherlands.
Results: 235 of 380 (62%) gastroenterologists and residents completed the questionnaire. Overall, 48% were positive towards introduction of NE, whereas 18% were neutral and 34% negative. Respondents expected no major differences in endoscopic quality between physicians and NE. Nevertheless, 69% expected that patient experiences would be better met by physicians. Multivariate analysis showed that actual experience with NE and beliefs that NE are able to provide adequate endoscopic quality and good patient experiences, were independent predictors for a positive attitude towards introduction of NE (OR 6.6 [2.3–18.4], OR 1.9 [1.2–3.5] and OR 2.1 [1.2–2.9], respectively). Respectively 89% and 66% of the respondents considered sigmoidoscopy and colonoscopy for CRC screening, as appropriate procedures to be performed by NE. Diagnostic and therapeutic endoscopies were considered less appropriate.

Conclusion: The majority of gastroenterologists has a positive attitude towards introduction of NE, especially for CRC screening endoscopies.

INTRODUCTION

There is increasing interest and growing demand for nurses to perform gastrointestinal endoscopy. This is, among other factors, driven by the increased endoscopic demand resulting from colorectal cancer screening programs.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death in the Western world [1,2]. Screening has been shown to reduce CRC incidence and mortality [3,4]. Various countries have therefore implemented national CRC screening programs, while many others are about to follow. However, to date, more than half of the eligible population of the European Union is not being offered any form of screening for CRC [5].

CRC screening can be performed with a variety of methods, in particular; stool tests, flexible sigmoidoscopy, colonoscopy and computed tomographic colonography [3]. Irrespective of the chosen method for primary screening, any CRC screening program considerably increases endoscopic demand either for primary screening or for secondary evaluation of patients with a positive primary screening test, and finally for surveillance of patients who were identified with a neoplastic lesion. The endoscopic demand in many countries outweighs the current supply. This is a major hurdle for the introduction as well as continuation of CRC screening in many Western countries [6-11].

Nurse endoscopists (NE) may provide a solution for these capacity problems. NE have been shown to be competent endoscopists [12,13]. In the UK, they form an integral part of the national gastrointestinal service and, among others, contribute significantly to the CRC screening program. The British Society of Gastroenterology (BSG) has approved the role of NE for various endoscopic procedures provided they are adequately trained [14]. In 2005 over 200 NE were practicing in the UK. Their number had significantly increased in only five years [14-16]. The American Society for Gastrointestinal Endoscopy (ASGE) supports the use of NE for screening sigmoidoscopy [17]. In 2002 6.1% of all screening sigmoidoscopies in the USA were performed by non-physician endoscopists [18]. While the role of NE in the UK and USA is expected to further expand, other countries are considering the introduction of NE.

The speed and success of such a process will likely depend on the opinions, expectations and experiences of physician endoscopists who are to train and supervise NE. However to date little is known about the attitude of gastroenterologists towards nurse endoscopy. The aim of the present study was to determine the views of gastroenterologists with respect to the role of NE in gastrointestinal endoscopy in a Western European community.

METHODS

A postal questionnaire was sent to all registered gastroenterologists (n=301) and gastroenterology residents (n=79) in the Netherlands in November 2007. The questionnaire consisted of four sections. The questionnaire first asked for background information, including actual experience of the respondent with NE, or the plan to start with nurse endoscopy. The second part of the questionnaire focused on the expectations of the respondent regarding the quality of, and patient experiences with endoscopic services provided by NE compared to physician endoscopists. With respect to endoscopic quality, the following items had to be scored; cecal intubation rates, the number of detected lesions, and complications. With respect to patient experiences, the items were; pain, stress, satisfaction, and patient preferences. Responses had to be given in a closed format with scores of 1 to 5, representing substantially or moderately better performance by NE, no difference between NE and physician endoscopists, or a moderately or substantially better performance by physician endoscopists, respectively. The total scores for endoscopic quality and for patient experiences were combined. A mean score less than 3 meant expectations of better performance by NE, a score of 3 meant an expected similar performance, and a score >3 meant expectations of better performance by physicians. In addition, the questionnaire asked for the expected effect of NE on costs of endoscopic services, to be scored as; a decrease, no effect or an expected increase of costs. The third section of the questionnaire determined the attitude of the respondent towards the introduction of NE. Respondents could express a positive, neutral or negative attitude. The last section of the questionnaire focused on respondents' opinions regarding appropriate screening, diagnostic and therapeutic endoscopic procedures for NE.

Statistical analysis was performed using the SPSS 15.0 program (SPSS Inc. Chicago, IL). Descriptive statistics were used to analyze and report the data. Chi-square tests were used where appropriate. Multivariate logistic regression analyses were performed to determine which factors predicted a positive response towards nurse endoscopy. A two-sided p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 235 questionnaires were returned, corresponding with a response rate of 62%. Gastroenterologists had a higher response rate than gastroenterology residents (64% vs. 53%). Of all respondents, 82% was gastroenterologist and 18% was resident. The distribution of academic versus general hospital employees was 30 vs. 70%. The mean age of the respondents was 46 years (SD ± 10 years) and 77% was male. This reflects the distribution

of age, sex and work setting of registered gastroenterologists and residents in our country. The responses covered all 94 hospitals in the Netherlands. Eleven (12%) hospitals already employed a total of 17 NE. Twenty-two percent of all respondents worked in a hospital with NE. Eight additional hospitals were considering introduction of nurse endoscopy.

Endoscopic quality, patient experiences and costs of NE

Forty-three percent of the respondents expected no difference in endoscopic quality between physicians and NE, 37% expected physicians to perform better, and 20% expected nurses to perform better. With regard to patient experiences, 69% of the respondents expected physicians to perform better, 19% expected no difference, and 12% expected that patients would be more satisfied with NE than with physician-endoscopists. The individual responses for each of the quality and patient experience parameters are listed in Table 1. Of note, the majority of respondents expected no difference in the number of detected lesions and number of complications between nurse and physician endoscopists. However, 43% of the respondents expected that physicians would have higher cecal intubation rates. With regard to pain, stress and satisfaction experienced by patients, the majority of the respondents expected no difference between nurse and physician endoscopists. Nevertheless, 84% of the respondents expected that patients would prefer a physician over a nurse endoscopist. Forty-nine percent of respondents expected that NE would reduce costs, whereas 41% expected no effect on costs. Respondents' age, gender, type of hospital (academic or general), or position (resident or gastroenterologist) were not related with the expected overall performances of NE, except that female gastroenterologists more often than their male colleagues, expected better patient experiences for physicians (84% vs. 65%, $p = 0.016$). The expectations with respect to endoscopic quality, patient experiences and costs did not differ between respondents from hospitals that already employed NE and respondents with no nurse endoscopy experience ($p = 0.22$, $p = 0.34$, and $p = 0.17$, respectively).

Table 1. Individual responses for each of the expected quality and patient experience parameters

	Nurse better	No difference	Physician better
Endoscopic quality			
- Lesions detection rates	21%	61%	18%
- Complications rates	21%	64%	15%
- Cecal intubation rates	4%	53%	43%
Patient experiences			
- Pain	20%	69%	11%
- Stress	15%	67%	18%
- Satisfaction	11%	63%	26%
- Preference	2%	14%	84%

Attitude towards nurse endoscopy

Figure 1 illustrates the attitude of gastroenterologists towards the introduction of NE. Overall, 48.5% had a positive attitude towards such an introduction. Multivariate analysis showed that respondents who actually (had) worked with NE were significantly more often positive towards introduction of NE than those who lacked such experience (OR 6.6 [2.3 – 18.4]). In addition, beliefs that NE are able to provide adequate endoscopic quality accompanied by optimal patient experiences were independent predictors for a positive attitude towards introduction of NE (OR 1.9 [1.2 – 3.5] and OR 2.1 [1.2 – 2.9], respectively). Respondents' age, gender, type of hospital, position, and expectation about costs were not related with the attitude towards nurse endoscopy.

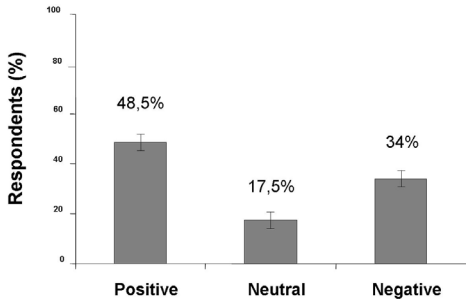

Figure 1. Attitude towards introduction of nurse endoscopists

Potential appropriate procedures for NE

The responses regarding potential appropriate procedures to be performed by NE are listed in Table 2. Of note, screening sigmoidoscopy and colonoscopy were considered appropriate procedures for NE, by respectively 89% and 66% of the respondents. In contrast, only 47% and 45% of the respondents judged diagnostic gastroscopy and colonoscopy appropriate for NE, respectively. Furthermore, only 42% considered removal of polypoid lesions smaller than 10mm an appropriate intervention for NE. Other therapeutic procedures were considered not to be appropriate at all for NE.

DISCUSSION

This study reports the views of gastroenterologists and gastroenterology fellows with respect to the potential role of NE in gastrointestinal endoscopy in a Western country. Despite the limitations of a postal questionnaire, a representative and reliable overview was obtained. The response rate among all Dutch gastroenterologists and residents was, with 62%, acceptable.

Table 2. Potential appropriate procedures for nurse endoscopists.

Procedure	Appropriate	Maybe	Not Appropriate
Screening			
- Sigmoidoscopy	89%	4%	7%
- Colonoscopy	66%	14%	20%
Diagnostic			
- Gastroscopy	47%	18%	35%
- Colonoscopy	45%	17%	38%
Therapeutic			
- Polyp < 10mm	42%	15%	43%
- Polyp >= 10mm	9%	12%	79%
- Other therapeutic procedures*	4%	5%	91%

* Other therapeutic procedures including: injection of ulcers, banding and injection of varices, dilatation of strictures, stent insertion and hot biopsy.

Our results show that the majority of gastroenterologists has a positive attitude towards introduction of NE for sigmoidoscopy and colonoscopy within a CRC population screening program (89% and 66% of the respondents, respectively). In contrast, diagnostic endoscopies were considered less appropriate and therapeutic procedures were considered not to be appropriate for NE. Actual experience with NE and beliefs that NE are able to provide adequate endoscopic quality or good patient experiences were independent predictors for a positive attitude towards introduction of NE.

These results are in agreement with those of a survey in the UK, which predicted an important albeit restricted role for NE. Clinicians from the UK considered diagnostic gastroscopy and sigmoidoscopy appropriate, and diagnostic colonoscopy and therapeutic endoscopies inappropriate for NE. The UK audit however did not specifically investigate the attitude towards screening endoscopies [16].

We obtained our results in the setting of a Western European country with a considerable shortage in trained endoscopists. This shortage is expected to further increase in the next few years, with the pending decision to introduce a nationwide colorectal cancer screening program. In the Netherlands, the Individual Health Care Professionals Act authorizes nurses to perform endoscopies, provided they do so according to the standards of a competent endoscopist as laid down in the regulations of the Dutch Society of Gastroenterology. These regulations are endorsed and the adherence to it is regularly checked in all Dutch centers by the Dutch Society of Gastroenterologists.

Endoscopic capacity studies performed to date have shown that the currently available capacity is not sufficient for the increased demand resulting from CRC screening

programs. The magnitude of the capacity problem depends on the chosen modality of primary screening, the target population, population adherence with the screening program, and finally the surveillance protocol [6-10]. For the Netherlands, recent calculations have shown that even with the most restrictive screening approach, the number of required colonoscopies is likely to double from the current 120.000 to 240.000 per annum on a population of 16 million, including 4.4 million inhabitants in the age range of 50 – 75 years (data not published). The shortage in endoscopic capacity also varies between different regions [10,19]. Together, this asks for more accurate data regarding the insufficient endoscopic capacity and the impact of locally chosen solutions.

There are several ways to close the gap between the required and available endoscopy resources, respectively focusing on strategies that reduce demand or increase supply. Studies have shown that at present 23% to 39% of all gastrointestinal endoscopies are being performed for inappropriate indications or at inappropriate surveillance intervals when compared to guidelines [20-22]. Reduction of these unneeded procedures would free capacity for other purposes. On the other hand, endoscopic capacity can be increased by training of additional endoscopists. However, training of physicians is expensive and fellowship programs in gastroenterology are sparse, and slow to respond to changes in the need for gastroenterologists [23]. In addition, it has been suggested that the need for additional gastroenterologists for endoscopy should be balanced with the need for other aspects of gastroenterology care [7]. A more effective way to increase endoscopic capacity would be to increase productivity and efficiency of currently available gastroenterologists [6,23]. This could be accomplished in a strategy where multiple adequately trained and productive NE are supervised by an experienced gastroenterologist.

Studies that have investigated the endoscopic skills of NE, concluded that NE are effective and can safely perform procedures such as diagnostic gastroscopy and sigmoidoscopy. However, most of these studies were criticized for methodological flaws [12,24]. Only four randomized controlled trials comparing physicians and NE have been performed to date[13,25-27]. In most studies, the methods of training of NE was either not specified, or considered inadequate according to current endoscopic training guidelines. Apart from gastroscopy and sigmoidoscopy, nurse endoscopy studies have so far not elucidated the possibilities and limitations of NE performing colonoscopy. Such information is urgently required in view of the widespread introduction of CRC screening.

With all these developments, guidelines for NE training and criteria to maintain procedural competence after training should be defined. These guidelines should rely on available and future studies regarding the endoscopic skills of NE, and should be well

defined for specific procedures. In the UK the Joint Advisory Group on Gastrointestinal Endoscopy already developed such guidelines [28]. If competence has been demonstrated, individual endoscopists should be credentialed by local institutions to perform the respective endoscopic procedures. In addition, clear job descriptions must define the scope of practice and specific responsibilities for NE and their supervisors. This will also clarify the legal implications and effectiveness for the proposed strategy where gastroenterologists supervise multiple NE. Furthermore, reimbursement policies should be adapted to facilitate a cost-effective and adequate reimbursement. Overcoming these issues will allow introduction of NE in the gastrointestinal endoscopic service.

We conclude that the majority of gastroenterologists has a positive attitude towards introduction of NE, especially for CRC screening endoscopies. In order to define the exact role of NE, precise assessment of endoscopic quality, patient experiences and cost-effectiveness is needed. There is especially a need for studies evaluating NE performing colonoscopy.

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Chapter 3

Nurse endoscopists perform colonoscopy according to the international standard with high patient satisfaction

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Endoscopy

3

ABSTRACT

Background and study aims: To assess endoscopic quality and patient experiences of nurse endoscopists (NE) performing full colonoscopy.

Patients and methods: Ten trained NE were enrolled in this multicenter prospective study. One-hundred consecutive colonoscopies of each NE were evaluated for endoscopic quality and patient experiences. Colonoscopies were performed under supervision of a gastroenterologist, using techniques and protocols of the participating hospitals. Patient experiences were measured using a questionnaire.

Results: Nine out of ten NE were female and median age was 43 years (range 35-49). Before the start of the study, the NE had performed a median number of 528 colonoscopies (range 208-2103). In total 1000 colonoscopies were evaluated; mean patient age 56 years (SD±15), 55% women, 96% class I or II according to the American Society of Anesthesiologists physical status classification system. Colonoscopies were performed for screening or surveillance in 42%, and for symptomatic indications in 58% of patients. The un-assisted cecal intubation rate was 94%, and mean withdrawal time was 10 minutes (SD±5). Adenoma detection rate was 26.7%. In 229 out of 1000 colonoscopies (23%), the NE required assistance from the supervising gastroenterologist. Complication rate was 0.2%; one perforation and one cardiopulmonary complication. 734/1000 patients (73%) completed the questionnaire. 694/734 respondents (95%) were satisfied with the endoscopic procedure. 530/734 respondents (72%) had no specific preference for a physician or nurse endoscopist, whereas 113/734 (15%) preferred a physician endoscopist, and 91/734 (13%) preferred a nurse endoscopist.

Conclusions: Nurse endoscopists perform colonoscopies according to the international recognized quality standards, with high patient satisfaction.

INTRODUCTION

There is increasing interest and growing demand within gastroenterology for nurses to perform colonoscopy. This is, among other factors, driven by the increased endoscopic demand resulting from colorectal cancer screening programs that are widely being introduced.

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of death from cancer in the Western world [1,2]. Screening has been shown to reduce CRC incidence and mortality [3-5]. CRC screening has therefore been implemented in various countries, while being considered by many others [6].

Colonoscopy is the predominant tool for diagnosis and prevention of CRC. Either for primary screening, or as next step for any other positive screening test, and finally for surveillance of patients who were identified with a neoplastic lesion. Colonoscopies account for more than 50% of all current endoscopic efforts in gastroenterology and are performed for screening or surveillance in approximately 50% of all colonoscopic examinations [7]. Modeling data suggest that the demand for colonoscopy will continue to increase [8]. However, in many Western countries endoscopic capacity is insufficient to cope with an increased demand [8-13].

Nurse endoscopists (NE) may provide a solution for the inadequate endoscopic capacity. NE have been shown to be competent in performing gastroscopy and sigmoidoscopy [14,15]. However, to date nurse endoscopy studies have so far not elucidated performances of NE performing colonoscopy. Up to now only three studies evaluated nurse performed colonoscopy. These small single center reports suggest that NE can become competent colonoscopists [16-18]. The aim of the present multicenter study was to assess endoscopic quality and patient experiences of NE performing full colonoscopy.

METHODS

All hospitals in the Netherlands with NE undertaking colonoscopies in 2009, were invited to participate in this multicenter prospective study. In the Netherlands, rules for health care professionals are set by the Individual Health Care Professionals Act (Wet BIG). This act authorizes nurses to perform specific delegated tasks, provided they are competent in performing the task as determined by training and accreditation, and perform the task under a pre-specified level of supervision. All NE had completed their colonoscopic training including a minimum of 200 performed colonoscopies, in accordance with the

standards for endoscopists in gastroenterology, as laid down in the regulations of the Dutch Society of Gastroenterology. All NE were trained to pre-medicate and sedate according to the standards set in the Dutch guideline for non-anesthesiologists on sedation and/or analgesia at remote locations. Enrolled NE performed 100 consecutive colonoscopies per endoscopist, which were evaluated for endoscopic quality and patient experiences. Colonoscopies were performed in patients referred for diagnostic colonoscopy including asymptomatic patient referred for screening or surveillance, and symptomatic patients. Patients under 18 and referred for therapeutic procedures were excluded. All patients had a pre-procedural assessment by a physician familiar with the patient and the procedure. The physical status of patients was assessed via the ASA classification system. Patients were informed about the endoscopy and administration of sedation including its benefits, risks and limitations, as well as possible alternatives. After informed consent was obtained, a physicians order was administered to perform the endoscopy with or without conscious sedation. Colonoscopies were performed using the preparation and techniques according to the protocols of the participating hospitals. Immediately prior to the procedure, the NE conducted a brief re-assessment of changes in the patient`s history, ASA risk score, medication use, and consent for the endoscopy and sedation. NE were allowed to administer and control the sedative/analgesic medications with a physician's order. All endoscopies were performed under indirect supervision of a gastroenterologist. The supervisor was not present in the room, but was present in the endoscopy unit, and on-demand immediately available for technical or diagnostic advice or in case of complications. The study was approved by the ethics committee review board.

Nurse, patient and procedure characteristics

At baseline NE age, gender, and endoscopic experience was obtained. Endoscopic experience was defined as the total number of colonoscopies performed before the start of the study. In addition, the scope of practice with respect to the use of sedative premedication, and performing polypectomies was obtained. The following patient and procedure characteristics were assessed; patient demographics, ASA-risk score according to the American Society of Anesthesiologists physical status classification system, referrer, indication, premedication, bowel preparation, whether cecal intubation was successful or not, cecal intubation time, withdrawal time, detected lesions, needed supervision, and complications. Data were obtained from a standardized portfolio, and from endoscopy procedure reports and electronic medical records.

Patient experiences

Patient experiences were measured by using a questionnaire that was filled in after the colonoscopy, at time of discharge from the recovery room. Patients were asked to score

the perceived pain and discomfort on a three point scale. Secondly, patients had to rate their overall satisfaction with the endoscopic procedure on a 5-point Likert scale. In addition, the questionnaire focused on patients` opinion regarding the communicative and technical skills of the NE. The last section of the questionnaire determined whether patients had a preference for a physician or nurse endoscopist. In addition, patients were asked to rate their preference considering waiting time for a NE and hereafter for a physician endoscopist to be 2 weeks shorter. Responses had to be given on a 5-point Likert scale representing a substantial or moderate preference for a physician endoscopist, no preference for a physician or nurse endoscopist, and a moderate or substantial preference for a NE, respectively.

Statistical analysis

Descriptive statistics were used to analyze and report the data. The unadjusted cecal intubation rate in unassisted and assisted colonoscopies was calculated. Unassisted cecal intubation was defined as having completed the cecal intubation, without assistance from the supervising gastroenterologist. Cecal intubation time was defined as the time from insertion of the colonoscope into the rectum until identification of the cecum. Withdrawal time was the time taken from cecal identification to the time when the scope was withdrawn across the anus, including time taken for manoeuvres such as polypectomies. Mean withdrawal times were calculated in colonoscopies in which no polyps were removed [19]. Adenoma detection rate was defined as the proportion of colonoscopies with adenomas. An unassisted colonoscopy was defined as having completed the procedure (including all aspects such as cecal intubation, polypectomy) without assistance from the supervising gastroenterologist. Binary logistic regression was performed to identify variables associated unassistent colonoscopy. Statistical analysis was performed using the SPSS 17.0 program (SPSS Inc. Chicago, IL).

RESULTS

Nurse endoscopistst

Ten out of 94 hospitals in the Netherlands (11%) employed in total 15 nurses performing colonoscopies. Six hospitals with 10 trained NE were willing to participate in this multicenter prospective study. Four hospitals did not participate for reasons of time restraints. Baseline NE characteristics are shown in Table 1. Nine out of ten NE were female and median age was 43 years (range 35-49). Before the start of the study, NE had performed a median number of 528 colonoscopies (range 208-2103). All NE were trained to premedicate and sedate (midazolam with or without pethidine/fentanyl). However, in one participating hospital with two NE, local prescription stated that the

Table 1 Baseline characteristics of the Nurse Endoscopists

	Nurse Endoscopists (n=10)
Age (median, range)	43 years (35-49)
Female gender	9 (90%)
Colonoscopic experience (median, range)	528 (range 208-2103)
Administration of conscious sedation	10 (100%)
Performing polypectomy	
• Polyp size	
1-5mm	10 (100%)
6-9mm	6 (60%)
≥10mm	0 (0%)
• Method	
Without coagulation	10 (100%)
With Coagulation	6 (60%)

supervising gastroenterologist administered these medications. All were trained to remove diminutive polyps (1-5mm). Six NE (60%) were allowed to remove small polyps (6-9mm) and to remove polyps with coagulation. None of the NE removed large polyps (≥10mm). In addition, none of the NE performed polypectomies in case lifting of the polyp with submucosal injection was necessary. NE trained for a specific procedure (including to premedicate and sedate, and to remove polyps), performed the procedure under indirect supervision of a gastroenterologist.

Patients and procedure characteristics

In total 1000 colonoscopies, 100 consecutive colonoscopies per endoscopist, were evaluated in 1000 patients. Patient and procedure characteristics are shown in table 2. Mean patient age was 56 years (SD±15), 55% of the patients were women, and 96% of colonoscopies were performed in patients with ASA risk score I or II. 91% of patients received conscious sedation with midazolam, with or without pethidine/fentanyl. Bowel preparation was excellent or good in 74% of patients. Colonoscopies were performed for screening or surveillance in 42%, and for symptomatic indications in 58% of patients.

Endoscopic performances

Table 3 summarizes NE endoscopic performances. The un-assisted cecal intubation rate was 94% (median 95%, range between NE 88-97%). Overall, cecal intubation rate was 97%. Mean cecal intubation time was 13 minutes (SD±8), and mean withdrawal time was 10 minutes (SD±5). Adenoma detection rate was high with 26.7% (Median 26%, range between NE 20-41%). In 229 out of 1000 colonoscopies (23%) (range between NE 10-36%) the NE required assistance from the supervising gastroenterologist. More

Table 2. Patient and procedure characteristics

	Patients (n=1000)
Age (mean, SD)	56 years (SD 15)
Female gender	549 (55%)
ASA risk score	
- 1 or 2	959 (96%)
- 3 or more	9 (1%)
- Missing	32 (3%)
Referral	
- General practitioner	601 (60%)
- Gastroenterology	226 (23%)
- Surgery	100 (10%)
- Internal medicine	43 (4%)
- Other	1 (0%)
- missing	29 (3%)
Indication	
- Screening or surveillance	416 (42%)
- Symptomatic	581 (58%)
- missing	3 (0%)
Sedative / analgesic premedication	
- Yes	914 (91%)
- No	71 (7%)
- Missing	15 (2%)
Bowel preparation	
- Excellent / good	743 (74%)
- Fair	36 (4%)
- Poor / very poor	107 (11%)
- Missing	114 (11%)

specifically, assistance was required for not reaching the cecum in 60 cases (6%), for polypectomy assistence in 72 cases (8%), and for interpretation of the endoscopy findings in 97 cases (12%). There were two serious complications in the 1000 colonoscopies (0.2%). One perforation occurred in a patient with polypectomy of a 10 mm large polyp that was removed by the supervising gastroenterologist. The patient was successfully managed conservatively and recovered uneventful. The other complication involved onset of atrial fibrillation at the time of the colonoscopy.

Logistic regression analysis showed that assistance from the supervising gastroenterologist was significantly more often needed in elderly patients (OR 1.03 [1.02 – 1.05]), and in patients with higher ASA risk score (OR 2.71 [1.52 – 4.83]). Patients` gender, the use of

Table 3 Endoscopic performances

	Patients (n=1000)	Performance per endoscopist (median, range)
Cecal intubation rate (unadjusted)		
- Un-assisted	940 (94%)	95% (88 – 97)
- Total	971 (97%)	98% (95 – 100)
Cecal intubation time (Mean)	13.1 min, SD 8.3	11.3 min (8.3 – 19.9)
Withdrawal time (Mean)*	10.2 min, SD 5.1	10.1 min (6.6 – 15.2)
Adenoma detection rate, % (95%CI)	26.7% (23.3 – 29.1)	26% (20 – 41)
Assistance supervisor required		
- Yes	229 (23%)	22% (10 – 36)
- No	712 (71%)	
- Missing	59 (6%)	
Complications		
- Perforation	1 (0.1%)	
- Cardiorespiratory complication	1 (0.1%)	

* only colonoscopies without intervention

sedative premedication, bowel preparation, the indication for the colonoscopy, and NEs' age, gender, and endoscopic experience were not related with unassisted colonoscopy.

Patient experiences

In total, 734 out of 1000 questionnaires were completed, corresponding with a response rate of 73%. 694 out of 734 respondents (95%) were satisfied with the endoscopic procedure. 420/734 (57%) experienced no pain during the colonoscopy, whereas 236/734 (32%) experienced moderate and 77/734 (11%) experienced substantial pain. 722 out of 734 respondents (98%) were satisfied with the communicative skills, and 698 out of 734 respondents (95%) were satisfied with the technical skills of the NE. Furthermore, 530 out of 734 respondents (72%) had no specific preference for a physician or nurse endoscopist. However, considering colonoscopy waiting time for a NE and hereafter for a physician endoscopist to be 2 weeks shorter, respectively 467/734 (64%) and 454/734 (62%) of respondent preferred the colonoscopy at a shorter time interval.

DISCUSSION

To date nurse endoscopy studies have so far not elucidated performances of NE performing full colonoscopy. We performed a multicenter prospective study with ten trained NE performing in total 1000 colonoscopies. Our results demonstrated that trained NE perform colonoscopies according to the international recognized quality standards,

with high patient satisfaction. Cecal intubation rate was over 90%, and adenoma detection rate was high, 26.8%. Two complications occurred in 1000 colonoscopies (0.2%). In only about a quarter of colonoscopies, NE required assistance from the supervising gastroenterologist for an advice, or assistant with introduction of the endoscope or the polypectomy. Assistance was significantly more frequently needed in older patients, and in patients with higher ASA risk score. Patients` gender, the use of sedative premedication, bowel preparation, the indication for the colonoscopy, and NEs' age, gender, and endoscopic experience were not related with requiring assistance. Focusing on patient experiences, the vast majority of patients (95%) were satisfied with the endoscopic procedure. In addition, the majority of patients (72%) had no specific preference for a physician or nurse endoscopist. Of note, patients generally preferred the colonoscopy at a shorter time interval. These data support the use of NE.

Our results are in agreement with previous studies which showed that NE are competent in performing gastroscopy and sigmoidoscopy [14,15,20]. In addition they are in line with findings of previous studies towards nurse performed colonoscopy. To date, three small single center reports were identified. Koornstra et al suggested that nurses can effectively be trained to become competent colonoscopists. Two nurses and one first year fellow were compared through a colonoscopy training protocol with 150 colonoscopies per trainee. Their results showed that nurse and fellow achieved similar cecal intubation rates, cecal intubation times, complication rates, and patient satisfaction during training. Withdrawal times and adenoma detection rates were not measured. More importantly, performance was not formally assessed as end points were only measured during training under direct supervision [16]. Maslekar et al suggested that there are no differences in patient satisfaction in lower gastrointestinal endoscopy between non-physician and physician endoscopists. In total, 503 procedures, including 332 colonoscopies were evaluated. Examinations were performed by one of two non-physician endoscopists or by a physician endoscopist. Results showed that there were no differences in terms of patient satisfaction, In addition, there were no differences in completion rates and complications. However, other established quality indicators for technical performance were not measured [18]. Finally, Limoges-Gonzalez et al suggested that properly trained NE perform screening colonoscopies as safely, accurately and satisfactory as physician endoscopists. 150 subjects referred for screening colonoscopy were randomized to a colonoscopy performed by either a NE (n=1) or by one of two physician endoscopists. Results of this small single center study showed that NE had significantly higher adenoma detection rates, and greater patient satisfaction [17].

In some Western countries, NE already contribute significantly to the gastrointestinal endoscopy services. In the Netherlands, ten out of 94 hospitals (11%) employed in

total 15 nurses performing colonoscopies. The Individual Health Care Professionals Act authorizes these nurses to perform gastrointestinal endoscopies, provided they achieve the standards of a competent endoscopist, as laid down in the regulations of the Dutch Society of Gastroenterology. These regulations are endorsed and the adherence to it is regularly checked in all Dutch centers by means of on-site quality assurance assessments by the Dutch Society of Gastroenterologists. Nurse endoscopy is also widely practiced in the United Kingdom. The British Society of Gastroenterology (BSG) supports the role of NE for various endoscopic procedures. In 2005 over 200 NE were practicing in the UK. Their number had significantly increased in only five years [21-23]. Furthermore, the American Society for Gastrointestinal Endoscopy (ASGE) allows nurses to perform screening sigmoidoscopies [24]. In 2002 6.1% of all screening sigmoidoscopies in the USA were performed by non-physician endoscopists [25].

It is generally recognized that endoscopic capacity is insufficient for the increased demand resulting from CRC screening programs. However, the shortage in endoscopic capacity depends on the chosen modality of primary screening, the target population, population adherence with the screening program, and finally the surveillance protocol [8-12]. In addition, the magnitude of the problem varies between different regions [7,12].

There are several potential solutions to gain endoscopic capacity. Appropriate utilization of endoscopy services would free capacity. Studies have shown that 23% to 39% of all gastrointestinal endoscopies are being performed for inappropriate indications or at inappropriate surveillance intervals when compared to guidelines [26-28]. On the other hand, endoscopic capacity can be increased by training of additional gastroenterologists. However, GI fellowship positions are expensive. In addition, it has been suggested that the need for additional gastroenterologists should be balanced with the need for other aspects of gastroenterology care [8]. A more effective way to increase endoscopic capacity would be to increase productivity and efficiency of currently available gastroenterologists [9,29]. This could be accomplished in a strategy where multiple NE perform endoscopies in a properly supervised setting.

There are several important issues to the establishment of nurse endoscopy. Guidelines for NE training and criteria to maintain procedural competence after training should be defined. These guidelines should rely on available studies regarding the endoscopic skills of NE and be comparable with that of fellows. This in recognition of the educational differences between nurse and physician. Several professional groups already developed such guidelines [30]. If competence has been demonstrated, individual endoscopists should be credentialed by local institutions to perform the respective endoscopic procedures. In addition, clear job descriptions must define the scope of practice and

specific responsibilities for NE and their supervisors. In the Netherlands for example, rules for health care professionals are set by the Individual Health Care Professionals Act (Wet BIG). This act authorizes nurses to perform specific delegated tasks, provided they are competent in performing the task as determined by training and accreditation, and perform the task under a pre-specified level of supervision. In the specific case of prescribing sedation, nurses were not allowed to prescribe these medications. However, NE were allowed to administer and control the sedative/analgesic medications with a physician's order, under indirect supervision, provided they do so according to the standards set in the Dutch guideline for non-anesthesiologists on sedation and/or analgesia at remote locations. Nurses trained and judged competent for performing a specific procedure, will be judged accordingly, and are personally responsible for the procedure. However, it is the responsibility for local institutions to define these responsibilities. These will also clarify the medico-legal implications and effectiveness for the proposed strategy where gastroenterologists supervise NE. Furthermore, reimbursement policies should be adapted to facilitate a cost-effective and adequate reimbursement. Overcoming these issues will allow introduction of NE in the gastrointestinal endoscopic service.

As gastroenterologists are to train and supervise NE, it is important that they support nurse endoscopy. We previously noted that gastroenterologists are in general positive towards an important albeit restricted role for NE [23]. Potential benefits are recognized but concerns are expressed, including adequacy of training, quality, patient acceptance, and interference with training for gastroenterology fellows. Dealing with these concerns is a prerequisite for institutions considering to introduce NE. Recognizing these issues and concerns, the decision to introduce NE should be based mainly upon competence in endoscopy and endoscopic demand as dictated by local conditions.

A limitation of our study was that the performances of NE were not compared with the performances of physician endoscopists. However, we recently performed a representative and comprehensive survey on performance of Dutch gastroenterologists performing colonoscopy. In 12 Dutch endoscopy departments, a total of 4800 consecutive colonoscopies performed by 116 endoscopists were assessed for endoscopic quality. Overall, cecal intubation rate was 92%, and adenoma detection rate was 24% [31]. These results are according to the international recognized quality standards and comparable with the findings in our study. At the moment a prospective observational study is being performed to evaluate differences between nurse and physician endoscopists in quality of colonoscopies and patient experiences. Results are expected at the end of 2012.

In conclusion, our results demonstrated that NE perform colonoscopies according to the international recognized quality standards, with high patient satisfaction. These findings advocate the involvement of NE in colonoscopy.

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Chapter 4

Comparing quality, safety and costs between nurse and physician performed colonoscopy

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ABSTRACT

Background and Aims: To compare endoscopic quality and safety between nurse and physician performed colonoscopy and to evaluate cost differences.

Methods: 7 nurses and 8 physicians without endoscopic experience were enrolled in this multicenter prospective comparative cohort study. Each endoscopist obtained endoscopic training, including a minimum of 100 performed colonoscopies. Next, each endoscopist performed 135 consecutive colonoscopies, which were evaluated for endoscopic quality and safety. Colonoscopies were performed under supervision of a gastroenterologist. Descriptive statistics, multilevel and cost minimization analysis were performed.

Results: All endoscopists completed the training and then performed 1946 of 2025 colonoscopies (96%), which were assessed for quality and safety; 866 were performed by NE and 1080 by PE. Mean patient age was 57yrs in both groups (p=0.69), and about half were women (p=0.76). Endoscopic quality and safety were comparable between NE and PE. Overall cecal intubation rates were 95% and 93% (p=0.38, including procedures where assistance from a supervisor was necessary) and mean withdrawal times were 10.4 and 9.8min (p=0.44), respectively. Adenoma detection rates were 27%, and complication rates 0.5% for both. In both groups, unassisted cecal intubation rates gradually increased with the amount of colonoscopies performed, from 70% for NE and 74% for PE in the beginning until 89% and 86% at the end of the assessment period. Considering a strategy where one gastroenterologist supervised three NE, personnel costs declined from €58.60 to €41.22 per colonoscopy (-€17.38).

Conclusions: In a supervised setting, NE perform colonoscopies according to quality and safety standards, and comparable to PE. However, NE require more supervision, but may substantially reduce costs.

INTRODUCTION

In the Western world colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death [1]. Screening for CRC with removal of adenomatous polyps has been shown to reduce the incidence of and mortality due to CRC [2,3]. This has led to the introduction of CRC screening programs in many countries over the past years [4,5].

Irrespective of the chosen strategy, any CRC screening program considerably increases the demand for colonoscopy [6-8]. However, in many countries colonoscopy capacity is insufficient to meet this projected increase in demand, which serves as a barrier to CRC screening [7-11].

Training of nurse endoscopists (NE) may expand colonoscopy capacity. The introduction of NE training and performance in gastrointestinal endoscopy was first reported in 1977 by the Mayo clinic, USA [12]. Subsequent studies showed that NE were competent in performing upper gastrointestinal endoscopy as well as sigmoidoscopy. These results formed the basis to advocate the involvement of NE in gastrointestinal endoscopy services in several Western countries [13-16]. Their involvement in endoscopy subsequently expanded to colonoscopy [17].

To date, however, only four studies have investigated the quality of colonoscopies performed by NE [17-20]. These studies suggested that NE could become competent colonoscopists, but they were mostly small, single center studies, and did not compare the performance of NE with physician endoscopists (PE). Therefore, the aim of the present study was to compare endoscopic quality, safety and costs of nurse- and physician-performed colonoscopy in a large multicenter prospective cohort study.

METHODS

Hospitals in the Netherlands, interested in introducing NE, were invited to participate in this multicenter prospective cohort study. In the Netherlands, the health care professionals law authorizes nurses to be trained in and perform specific delegated tasks, provided that the tasks are performed according to quality standards and under prespecified supervision [21]. Each participating hospital recruited at least one NE from the pool of nurses working at their GI endoscopy unit. In addition, consecutive PE were enrolled from the group of GI fellows who after two-year training in internal medicine entered the four-year course of gastroenterology training under the auspices of the

Departments of Gastroenterology and Hepatology of the Erasmus University Medical Center Rotterdam, and the Maastricht University Medical Center. The study took place between September 2008 and April 2012.

At baseline, NE and PE included in the study were without any endoscopic experience. All enrolled endoscopists obtained formal training in gastrointestinal endoscopy, according to the standards as laid down in the regulations of the Dutch Society of Gastroenterology [22]. The trainees were trained in and assessed for theoretical knowledge and technical skills. Basic hand skills were trained with use of computer simulators (Olympus and Symbionix) [23,24]. Further technical skills were acquired by hands-on teaching from acknowledged gastrointestinal endoscopy trainers. Initially trainees only observed procedures, followed by attempting the less demanding aspects of gastrointestinal endoscopy, and gradually progressing to performing the entire procedure including specific interventions. The trainees performed upper and lower GI endoscopies, including a minimum of 100 colonoscopies each. All training endoscopies were performed under direct supervision of a gastroenterologist, meaning that the gastroenterologist was present in the endoscopy room during the whole procedure. Instructions were given and interference and assistance took place when necessary.

Colonoscopies were performed with or without moderate sedation (using midazolam and/or an opioid) at discretion of the patient and endoscopist, using the preparation and techniques according to the protocols of the participating hospitals as endorsed by the Dutch Society of Gastroenterology. In case of NE, the sedative medication was administered by the supervising gastroenterologist. In addition, all endoscopists were trained to remove diminutive (1-5mm) and small polyps (6-9mm). Large polyps (≥10mm) were removed by the supervising gastroenterologist.

After completion of the basic training, including at least 100 colonoscopies, each endoscopist next performed 135 consecutive colonoscopies, which were assessed for endoscopic quality and safety. These 135 colonoscopies per endoscopist were used to compare the performance of NE and PE. At this stage, the endoscopists were expected to progress through stages of decreasing supervision, extending from the initial complete direct supervision to a phase of partial indirect supervision. In the latter phase, the supervising gastroenterologist was not necessarily constantly present in the room, but was present at the endoscopy unit and on-demand immediately available for technical or diagnostic advice and assistance.

Colonoscopies were performed in patients referred for diagnostic colonoscopy and included asymptomatic and symptomatic patients. Patients were in order of appearance allocated to colonoscopy lists by secretarial staff of the endoscopy units, and the NE

and PE were randomly assigned to a program without any prior insight in the details of the program and the patients on the list. Patients under 18 years of age or specifically referred for therapeutic procedures were allocated to expert endoscopist programs. All patients underwent a pre-procedural assessment by a physician who was familiar with the patient and the procedure. The physical status of each patient was assessed using the American Society of Anesthesiologists' (ASA) classification system. Patients were informed about the indication, preparation, the endoscopy itself and possible interventions, including its benefits, risks and limitations, as well as possible alternatives. Informed consent was obtained, including consent for performing the colonoscopy with or without sedative/analgesic medication. Immediately prior to the procedure, the endoscopist performed a brief reassessment of the referred patient.

Endoscopist, patient and procedure characteristics

At baseline, endoscopists' demographics were obtained, including age, gender and education. All endoscopists were required to maintain an accurate portfolio of their experience. All performed procedures were recorded on standardized data collection forms, supplemented by validated evaluation sheets and endoscopic skill assessment forms that have been recently validated in a similar form [25]. Furthermore, data were obtained from endoscopy procedure reports and electronic medical records. The following patient and procedure characteristics were assessed: patient demographics, referrer, indication for the procedure, premedication, bowel preparation, reach of the procedure, whether cecal intubation was successful or not, cecal intubation time, withdrawal time, number of detected lesions, need for supervision with cecal intubation or any intervention such as polypectomy, and complications. Information on histology of lesions that were removed during endoscopy was obtained from pathology reports.

Statistical analysis

Descriptive statistics were used to analyze and report the data. The unadjusted cecal intubation rates for unassisted and overall colonoscopies were calculated. Unassisted cecal intubation was defined as having reached the cecum without assistance from the supervising gastroenterologist. Cecal intubation time was defined as the time from insertion of the colonoscope into the rectum until identification of the cecum. Withdrawal time was the time needed from cecal identification to withdrawal of the endoscope from the anus. Mean withdrawal times were calculated with exception for the time needed for removal of polyps [26]. Polyp and adenoma detection rates were defined as the percentage of colonoscopies with polyps and adenomas, respectively. Generalized estimating equations were used for a 2-level analysis to compare outcome parameters in two groups while correcting for the individual endoscopists nested within the groups. In a generalized linear mixed model (specifically a form of logistic regression

for longitudinal data) we compared cecal intubation rates between the two groups over the course of the assessment period. In this model, the variables Group and 'Number of Endoscopies' were used as independent variables and the interaction between these two was also included. The variable 'Number of Endoscopies' was modeled by a 3-degree spline with 2 knots. Correlations between the repeated measurements of endoscopists were accounted for by including a random intercept term for the endoscopists. In addition, cost minimization analyses were performed to compare personnel costs between PE colonoscopy and a scenario where one gastroenterologist supervises multiple NE. Cost calculations were based on 234 workable days per year, 8 working hours per day, 30 minutes examination time per colonoscopy, 3744 performed colonoscopies per unit per year, using the salary schemes of university hospitals in the Netherlands. Since we focused on cost differences, we ignored any non-personnel costs (material, investments, maintenance expense and overhead costs), which we assumed similar in both scenarios. The primary outcome measurement of the study was adenoma detection rate. The sample size was chosen based on a presumed adenoma detection rate of 25%. In order to yield 80% power to detect a 5% decrease in adenoma detection (1-sided Type I error of 5%), we aimed to recruit 6 NE and 6 PE performing 862 colonoscopies per group. Statistical analysis was performed using the SPSS 20 program (SPSS Inc. Chicago, IL). The Institutional Review Boards of the participating centers approved the study.

RESULTS

Endoscopist, patient and procedure characteristics

A total of 7 NE and 8 PE from eight Dutch hospitals participated in this study. Most NE were female (M/F 1/6), whereas PE had an even sex ratio (M/F 4/4). Median age was 32 years for both NE and PE (range 27.4-49.2 for NE, and 29.7-34.6 for PE, p=0.87). All endoscopists completed the training including a minimum of 100 performed colonoscopies each. The number of upper and lower GI endoscopies that were performed during the training period by NE and PE are shown in Table 1.

Table 1. Upper and lower GI endoscopies performed by nurse (NE) and physician endoscopists (PE) during the training period

	NE (n=7)	PE (n=8)	p-value*
Endoscopies during training period, median (range)			
- gastro/sigmoidoscopies	0 (0-203)	358 (211-559)	<0.01
- colonoscopies	100 (100-200)	114 (100-200)	0.54

* Mann-Whitney-U test

Table 2. Patient and procedure characteristics

	NE (n=7) (866 colonoscopies)	PE (n=8) (1080 colonoscopies)	p-Value
Mean age (years, SD)	57.4 (15.0)	57.1 (16.3)	0.69
Female gender, n (%)	431 (50%)	545 (51%)	0.76
ASA risk score	n= 521	n=727	<0.01
- ASA 1 or 2	510 (98%)	664 (91%)	
- ASA 3 or more	11 (2%)	63 (9%)	
Referral	n=704	n=975	<0.01
- Gastroenterology	368 (52%)	594 (61%)	
- Internal medicine	27 (4%)	117 (12%)	
- Surgery	20 (3%)	44 (5%)	
- General practitioner	130 (19%)	92 (9%)	
- Other	159 (23%)	128 (13%)	
Indication	n=843	n=1050	<0.01
- Surveillance	200 (24%)	358 (34%)	
- Symptomatic	643 (76%)	692 (66%)	
Sedative premedication	99%	92%	<0.01
- Midazolam, mean dose (mg, SD)	5.0 (±2.1)	5.3 (±1.8)	<0.01
- Fentanyl, mean dose (mg, SD)	0.057 (±0.0.34)	0.074 (±0.028)	<0.01
- Pethidine, mean dose (mg, SD)	43.7 (±11.5)	42.5 (±12.3)	0.31
Bowel preparation	n=710	n=905	0.29
- Excellent/good/fair	558 (79%)	731 (81%)	
- Poor/very poor	152 (21%)	174 (19%)	

After having finished the training part of the study, each endoscopist performed 135 colonoscopies in consecutive patients who were planned for colonoscopy. In total, 1946 out of the planned 2025 colonoscopies (135 consecutive colonoscopies per endoscopist) (96%) were performed and assessed for competency, the remaining 79 (4%) colonoscopies were not performed as one NE dropped out. Of the 1946 colonoscopies, 866 (45%) were performed by NE and 1080 (55%) by PE. Patient and procedure characteristics of the colonoscopies are shown in Table 2. Patients' age and sex were similar in both groups with a mean patient age of 57 years and an approximate 50/50 male/female distribution. However, NE patients had more often ASA risk scores I or II (respectively 98% vs. 91% ($p<0.01$)), and were more often referred for symptomatic indications (respectively 76% vs. 66% ($p<0.01$). Moderate sedation with midazolam, with or without pethidine/fentanyl, was administered to 99% of the NE patients and to 92% of the PE patients ($p<0.01$). Bowel preparation was excellent or good in approximately 80% of the NE and PE patients ($p=0.29$).

Endoscopic performances

Table 3 summarizes the endoscopic performance of the endoscopists in both groups. Endoscopic quality and safety were comparable between NE and PE. Overall cecal intubation rates (including those procedures where assistance from a supervisor was necessary) were 95% and 93% (p=0.38), mean cecal intubation times were 12.2 and 11.5 minutes (p=0.52), and mean withdrawal times were 10.4 and 9.8 minutes, respectively (p=0.44). During the assessment period, in both groups unassisted cecal intubation rates gradually increased with the amount of colonoscopies performed (Fig.1). In both NE and PE, the spline significantly increased from the beginning of the assessment period towards the end (p<0.01). Compared to PE, NE had lower unassisted cecal intubation rates in the beginning of the assessment period (70% vs. 74% resp.) and also during the assessment they lay below those of the physicians. Towards the end, the two splines converged (89% for NE and 86% for PE respectively), while the differences between the two groups were at no point in time statistically significant. A total of 1597 lesions were detected during the assessment period. Polyp detection rates were 45% for colonoscopies performed by NE and 44% for colonoscopies performed by PE (p=0.82). Adenoma detection rates were 27% for both NE and PE (p=0.93). Mean adenoma number per positive procedure was 2.2 and 1.8 for NE and PE, respectively (p=0.14). Details on histology of all removed polyps are shown in Table 4. Complication rates were 0.5% (4/866) and 0.5% (5/1080) (p=0.99), respectively. There were four complications (0.5%) in 859 colonoscopies performed by NE; three patients suffered from rectal bleeding fol-

Table 3. Endoscopic quality parameters of 1946 procedures performed during the assessment period.

	NE (n=7) (866 colonoscopies)	PE (n=8) (1080 colonoscopies)	p-Value
Cecal intubation rate	n=804	n=1023	
- unassisted	77%	88%	0.04
	n=849	n=1058	
- overall	95%	93%	0.38
Mean cecal intubation time, min (SD)	12.2 (5.8)	11.5 (6.0)	0.52
Mean withdrawal time, min (SD)*	10.4 (4.2)	9.8 (4.3)	0.44
Polyp detection rate, %	45%	44%	0.82
Adenoma detection rate, %	27%	27%	0.93
Carcinoma detection rate, %	3%	4%	0.68
Complications	n=859	n=1079	
- No complications	855 (99.5%)	1074 (99.5%)	0.99
- Bleeding	3 (0.3%)	1 (0.1%)	
- Perforation	0 (0.0%)	0 (0.0%)	
- Cardiorespiratory	1 (0.1%)	4 (0.4%)	

*Only colonoscopies without intervention and without needed supervision included in calculation

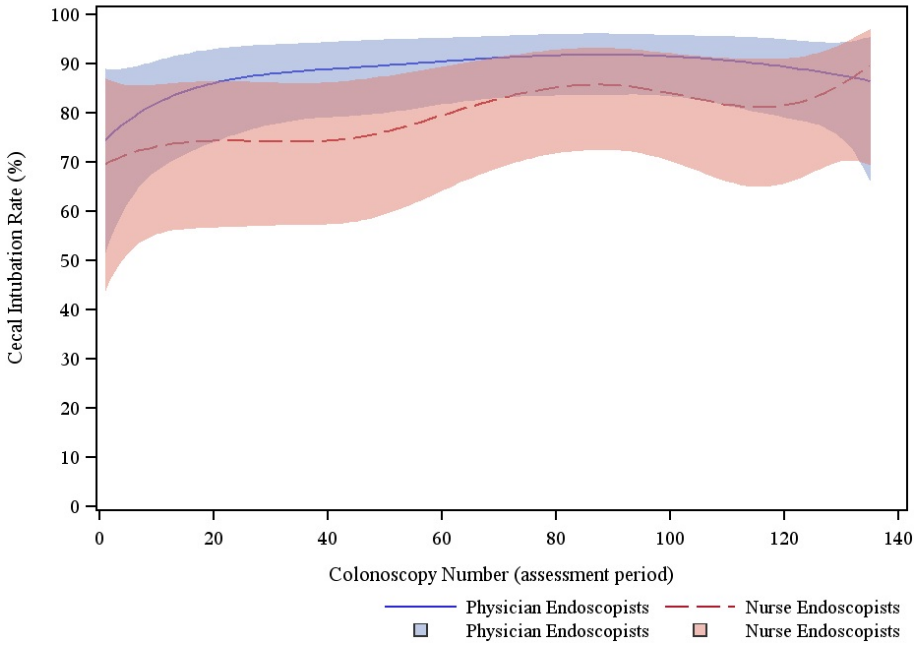

Figure 1. Learning curves (incl. 95% confidence intervals) of NE (red) and PE (blue). The graphs represent the unassisted cecal-intubation rates in the course of the assessment period.

Table 4. Polyps detected during colonoscopy.

	NE (n=7) (866 colonoscopies)	PE (n=8) (1080 colonoscopies)	p-Value
No polyp detected	55%	56%	0.82
Polyp detected	45%	44%	
Total number of polyps detected	660	937	
Not removed, n (%)	38 (6)	45 (5)	0.40
Removed, n (%)	622 (94)	892 (95)	0.43
Histology of removed polyps			
Normal tissue, n (%)	44 (7)	67 (8)	
Pseudopolyp, n (%)	14 (2)	20 (2)	
Hyperplastic polyp, n (%)	176 (28)	254 (28)	
Adenoma, n (%)	343 (55)	466 (52)	
Carcinoma, n (%)	4 (1)	2 (0)	
Other, n (%)	10 (2)	10 (1)	
Missing, n (%)	31 (5)	73 (8)	

lowing polypectomy and one patient developed bradycardia and hypotension during colonoscopy. Five complications (0.5%) occurred in the group of PE; one patient had a postpolypectomy bleeding and four patients developed cardiorespiratory symptoms during colonoscopy resulting in two admissions (one patient developed atrial fibrillation with heart failure and another patient severe tachycardia >170/min).

Costs

Costs were compared in a cost-minimization analysis comparing colonoscopy performed by either a gastroenterologist or by a NE (in a scenario where 1 gastroenterologist supervises 3 NE). Calculations were based on a mean duration of 30 minutes per colonoscopy and accounted for salary costs of the endoscopist and of one assisting endoscopy nurse. Mean personnel costs (€) declined from €58.60 to 41.22€ per procedure (-€17.38) in the NE scenario (Table 5).

Table 5. Cost minimization scenario to compare personnel costs between colonoscopy performed by a gastroenterologist and a scenario where one gastroenterologist supervises three NE. Cost calculations were based on 234 workable days per year, 8 working hours per day, 30 minutes examination time per colonoscopy, and 3744 performed colonoscopies per unit per year.

	Gastroenterologist	Nurse endoscopist
Gastroenterologist	(9614*12*1.08*1.37)/ 3744 = €45.59	(45.59/3 NE)= €15.20
Nurse endoscopist	n.a.	(2744*12*1.08*1.37)/ 3744 = €13.01
Nurse	(2744*12*1.08*1.37)/ 3744 = €13.01	€13.01
Sum	**€58.60**	**41.22€**

DISCUSSION

This is the first prospective comparative study evaluating the quality of colonoscopies performed by NE and PE in a large setting. We found that NE perform colonoscopy with similar quality and safety as PE in terms of generally accepted quality measures such as unadjusted cecal intubation rates, adenoma detection rates, withdrawal times, and complication rates. Unadjusted cecal intubation rates were 95% in NE and 93% in PE, mean withdrawal times were 10.4 and 9.8 minutes, adenoma detection rates were 27% for both, and complication rates were 0.5% and 0.5%, respectively. However, during the assessment period, unassisted cecal intubation rates of the NE lay slightly below those of the PE most of the time, but in both groups they gradually increased with the amount of colonoscopies performed and reached 89% (NE) and 86% (PE) at the end of the assessment. Furthermore, we found that in a scenario of one gastroenterologist supervising three NE, personnel costs in NE performed colonoscopies were lower compared to colonoscopies performed by a gastroenterologist.

So far, only a few studies have compared endoscopic quality of NE performing full colonoscopy with those of PE [18-20]. These small, single center studies showed that adequate training of NE to perform full colonoscopy yielded similar quality and similar low complication rates when compared with colonoscopies performed by PE. Prior data from our group evaluating quality and safety of NE performed colonoscopy in 10 NE performing 1000 colonoscopies in a multicenter cohort study showed that NE performed colonoscopies according to the international recognized quality standards, including unassisted cecal intubation rate over 90% and an adenoma detection rate of about 27% [17]. These studies however did not assess the progress and performance of NE and PE in the same setting and with the same formal endoscopy training. The present study therefore directly compared colonoscopy performed by NE and PE with similar training and performance in the same patient categories and same setting.

The results obtained in the current study are mostly in agreement with those of the previous studies and show that NE are competent in performing colonoscopy, although a regular training program does not yet bring them at a level that fully meets international guideline recommendations and standards. In the Netherlands, a minimum number of 200 colonoscopies are requested for certification for colonoscopy (Dutch Society of Gastroenterology). At the end of the assessment period (thus after having finished at least 235 colonoscopies), unassisted cecal intubation rates of both NE and PE were still slightly below the required 90%. However, overall (unassisted and assisted) cecal intubation met the international standards [27] rates in both groups. These results support that NE can similar to PE and with the same training learn to perform diagnostic colonoscopy at a high quality and safety level.

It is generally recognized that capacity of physician endoscopists will be insufficient for the increased demand for endoscopic procedures, resulting from the introduction of CRC screening programs. In the Netherlands, a nationwide CRC screening program will be implemented in 2013 - 2018, to cover the age group from 55 to 75 years. Screening will be performed by means of biennial fecal immunochemical testing (FIT) and it is estimated that this will lead to a yearly demand for an approximate 80.000 extra colonoscopies. It is important to consider the impact of a nationwide CRC screening program on endoscopic capacity and manpower to avoid unacceptable waiting times. There are several possibilities to approach this problem. First, indications to perform endoscopy should be appropriate. Studies have shown that 23% to 39% of all gastrointestinal endoscopies are being performed for inappropriate indications or at inappropriate surveillance intervals when compared to guidelines [28-30]. Then, training additional PE can increase capacity. However, fellowship positions are expensive and time-consuming and thus do not yield sufficient endoscopic capacity within short time. The training of

NE to perform colonoscopies in a supervised setting may be an effective and cost-saving alternative. A recent survey performed among Dutch gastroenterologists showed that gastroenterologists are positive towards a significant role for NE, with restriction to diagnostic and minimally invasive therapeutic procedures [31].

There are several important issues to the establishment of nurse endoscopy. Guidelines for NE training and criteria to maintain procedural competence after training need to be defined. These guidelines should rely on available studies regarding the endoscopic skills of NE and be comparable with that of fellows. For that purpose, the Dutch Society of Gastroenterologists has developed such guidelines together with a one-year training program, among others based on the results of the current study. Once competence has been demonstrated, national institutions should credential individual endoscopists to perform the respective endoscopic procedures. In addition, clear job descriptions must define the scope of practice and specific responsibilities for NE and their supervisors. This will also clarify the legal implications and effectiveness for the proposed strategy where gastroenterologists supervise multiple NE. Furthermore, reimbursement policies should be adapted to facilitate a cost-effective and adequate reimbursement. Overcoming these issues will allow introduction of NE in the gastrointestinal endoscopic service.

The main limitation of this study is that patients were not randomized between NE and PE, but on a consecutive basis assigned to the next endoscopy list. Furthermore, during training, PE simultaneously performed a fair number of gastroscopies, while most NE did not, which probably led to differences in training. On the other hand, the main advantage of this study is the large size of our cohort of endoscopists and the large number of colonoscopies that were performed and evaluated.

In summary, this study provides support that with the same training and supervision, NE perform colonoscopy with similar quality and safety as PE. However, NE have slightly lower unassisted intubation rates, and during training need more assistance by a supervisor. Our results demonstrate that NE can perform colonoscopies with high quality standard but might require longer training periods or a broad training including both upper and lower GI endoscopies. Our data are generilisable to all patients with ASA I and II who are undergoing diagnostic colonoscopy. They advocate the involvement of NE in colonoscopy. The introduction of nurse endoscopy is relevant in many countries in terms of colonoscopy demand and health care costs.

ACKNOWLEDGEMENTS

The study was funded by The Netherlands Organisation for Health Research and Development of the Dutch Ministry of Health (ZonMW 94507728).

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Chapter 5

Inter-observer variation in the histological diagnosis of polyps in colorectal cancer screening

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Histopathology

ABSTRACT

Aim: To determine the inter-observer variation in the histological diagnosis of colorectal polyps.

Methods and results: 440 polyps were randomly selected from a colorectal cancer (CRC) screening program. Polyps were first evaluated by a general (324 polyps) or expert (116 polyps) pathologist, and subsequently re-evaluated by an expert pathologist. Conditional agreement was reported and inter-observer agreement was determined by using Kappa statistics. In 421/440 polyps (96%) agreement for the non-adenomatous or adenomatous nature was obtained, corresponding with a very good kappa of 0.88. Differentiating adenomas as non-advanced and advanced obtained consensus in 266/322 adenomas (83%), with a moderate kappa of 0.58. For the non-adenomatous or adenomatous nature, both general and expert pathologists, and expert pathologists among each other, showed very good agreement (kappa-values (95%CI); 0.89(0.83-0.95) and 0.86(0.73-0.98), respectively). Categorizing adenomas as non-advanced and advanced showed moderate agreement between general and expert pathologists, and between expert pathologists (kappa-values (95%CI); 0.56(0.44-0.67) and 0.64(0.43-0.85), respectively).

Conclusions: General and expert pathologists demonstrate very good inter-observer agreement for differentiating non-adenomas from adenomas, but only moderate agreement for non-advanced and advanced adenomas. The considerable variation in the interpretation of advanced histology suggests that more objective criteria are required for risk stratification in screening and surveillance guidelines.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death in the Western world [1,2]. The detection and removal of adenomatous colorectal lesions reduces CRC incidence and mortality [3,4]. Advanced adenomas have a greater likelihood of malignant transformation and development of metachronous adenomas than non-advanced adenomas [5]. Conversely, hyperplastic lesions carry minimal risk of adenoma occurrence [6,7].

Histopathological diagnosis of colorectal lesions plays a crucial role in patient management and surveillance after polypectomy. Postpolypectomy surveillance guidelines stratify patients in high and low risk according to their risk of an advanced neoplasia at subsequent colonoscopy. Current guidelines recommend a surveillance colonoscopy 3 years after removal of an advanced adenoma or 3 or more non-advanced adenomas, and 5 to 10 years after removal of 1 or 2 non-advanced adenomas [8]. Histopathologic assessment of colorectal polyps is also vital in screening for CRC. Advanced adenomas are considered the surrogate marker for CRC risk and are a primary end-point of screening [9]. As many countries have implemented or are preparing nation-wide CRC screening [10,11], accurate pathologic assessment of colorectal lesions is of paramount importance.

Concern has been raised about the reproducibility of the histological interpretation, between general and between expert gastrointestinal pathologists [12,13]. The aim of the present study was to evaluate inter-observer variation in histological diagnosis of colorectal polyps detected in a CRC screening program. Furthermore, inter-observer variation was assessed between general and expert gastrointestinal pathologists, and between expert gastrointestinal pathologists.

METHODS

Study setting

As part of a Dutch population-based randomized screening trial (CORERO I trial) we randomly selected 440 polyps. The CORERO I study has been described in detail elsewhere [14]. In brief, this randomized population-based trial compared uptake and diagnostic yield of guaiac based fecal occult blood test (g-FOBT), fecal immunochemical test (FIT) and flexible sigmoidoscopy (FS) screening for CRC. Recruitment took place between November 2006 and November 2007. In total 15,011 individuals aged 50-74 years old were 1:1:1 randomized to be invited for gFOBT, FIT or FS screening. Participants with a positive

gFOBT (Hemoccult II) or FIT (OC-Hemodia Latex; ≥50 nanogram haemoglobin/ml) were referred for colonoscopy. Participants to FS screening were referred for colonoscopy when one of the following criteria was met: presence of a polyp with a diameter ≥10 mm; an adenoma with villous histology (≥25% villous) or high-grade dysplasia; three or more adenomas; ≥20 hyperplastic polyps; or invasive CRC.

Sampling procedure and organization

All polyps detected at FS or colonoscopy were removed. The inter-observer evaluation was conducted on 440 randomly selected polyps; 324 polyps were detected at colonoscopy in participants with a positive gFOBT or FIT (FOBT polyps), and 116 polyps were detected during FS (FS polyps). For initial pathological evaluation, the 324 FOBT polyps were evaluated by a general pathologist (n=23) and the 116 FS polyps were evaluated by an expert gastrointestinal pathologist (n=1). Subsequently, all 440 samples were blindly re-evaluated by an (one of two) expert gastrointestinal pathologist.

Criteria for pathologic classification

The WHO classification was adopted to classify the selected polyps as non-adenomatous or adenomatous [15]. Adenomatous lesions were further categorized according to histologic type, degree of dysplasia, and absence or presence of infiltrating carcinoma. In agreement with the National Polyp study and other studies on CRC screening, we defined a tubular adenoma as an adenoma with less than 25% villous component. Adenomas having a 25% - 75% or more than 75% villous component, were defined as tubulo-villous and villous adenoma, respectively[16-21]. The degree of dysplasia was classified as low or high grade dysplasia. According to the revised Vienna criteria, patients with intramucosal carcinoma or carcinoma in situ were classified as having high-grade dysplasia [22]. Advanced adenomas were defined as adenomas of at least 10mm, or as adenomas with villous histology (≥25%villous) or with high-grade dysplasia. CRC was defined as invasion of malignant cells beyond the muscularis mucosa and was classified according to the TNM classification [23-25].

Statistical analysis

Descriptive statistics were used to analyze and report the data. Conditional agreement was reported using percentages. Inter-observer agreement was determined by using Cohen κ statistics, which are widely used mathematical coefficients adjusting for agreement by chance alone. A value of 0 indicates no agreement better than what would be expected by chance alone. Values of < 0.21, 0.21–0.40, 0.41–0.60, 0.61–0.80 and >0.80 correspond to poor, fair, moderate, substantial and very good inter-observer agreement, respectively. In addition, as the kappa coefficient is influenced by the prevalence and bias of ratings, the prevalence-index and bias-index was calculated. A prevalence effect

exists when the proportion of agreements on the positive classification differs from that of the negative classification. If the prevalence index is high (prevalence of a positive rating is very high or very low), chance agreement is also high and kappa is reduced. A bias effect exists if each observer rates a differing proportion of cases as positive. If the disagreement is asymmetrical, bias is large and kappa is higher than when bias is low or absent [26]. The histological diagnoses were categorized as non-adenomatous or adenomatous. Adenomatous lesions were further categorized as non-advanced or advanced based on histology only. For further categorization, the degree of dysplasia was classified as low or high grade dysplasia. Adenomas were categorized as tubular adenoma or adenoma with ≥25% villous component. In addition, inter-observer agreement was calculated for polyps that were represented by diminutive (1-5mm), small (6-9mm), and large (≥10mm) polyps. The size of each polyp was measured during the endoscopy using an open biopsy forceps with 7mm span. Furthermore, inter-observer agreement between a general and expert pathologist, and between expert pathologists was assessed. Statistical analysis was performed using the SPSS 15.0 program (SPSS Inc. Chicago, IL). A two-sided p-value of < 0.05 was considered statistically significant.

RESULTS

Polyp characteristics

In total, 440 colorectal polyps were evaluated. The polyp characteristics as described by the initial pathologist are shown in Table 1. The initial pathologists identified 106 non-adenomas (24%) and 334 adenomas (76%). Ninety-five of the 440 polyps (22%) were classified as advanced adenomas. The FOBT polyps were, as compared to the FS polyps, significantly larger and more often of advanced histology.

Inter-observer variation

Table 2 shows the agreement among pathologists on histological diagnosis of colorectal polyps. In 421 out of 440 polyps (96%) agreement for the non-adenomatous or adenomatous nature of polyps was obtained. More specifically, pathologists agreed on 99 non-adenomas and 322 adenomas, corresponding with a very good kappa-value of 0.88 (95% CI; 0.83 - 0.94) (prevalence-index 0.51, bias-index 0.01). Categorizing the 322 adenomatous lesions as non-advanced and advanced obtained consensus in 266 adenomas (83%). There was consensus for 198 non-advanced adenomas and 68 advanced adenomas. Inter-observer agreement for classifying adenomas as non-advanced or advanced was moderate with kappa 0.58 (95% CI; 0.48 – 0.68) (prevalence-index 0.40, bias-index 0.01).

Table 1. Polyp characteristics as defined by the initial pathologist

	Total (n=440) n (%)	FOBT polyps (n=324) n (%)	FS polyps (n=116) n (%)	p-value
Polyp				
- Non-adenomatous	106 (24%)	84 (26%)	22 (19%)	0.13
- Adenomatous	334 (76%)	240 (74%)	94 (81%)	
Adenoma				
Non-advanced/advanced*				
- non-advanced	239 (54%)	161(50%)	78 (67%)	0.004
- advanced	95 (22%)	79 (24%)	16 (14%)	
Dysplasia				
- Low-grade dysplasia	307 (70%)	219 (68%)	88 (76%)	0.48
- High-grade dysplasia	27 (6%)	21 (6%)	6 (5%)	
Histologic type				
- Tubular	245 (56%)	166 (51%)	79 (68%)	
- Tubulovillous/villous	82 (19%)	70 (21%)	12 (10%)	0.002
- Carcinoma in situ or intramucosal	7 (2%)	4 (1%)	3 (3%)	
Polyp size**				
- Diminutive (1-5mm)	224 (51%)	135 (42%)	89 (77%)	
- Small (6-9mm)	87 (20%)	68 (21%)	19 (16%)	<0.001
- Large (≥10mm)	129 (29%)	121 (37%)	8 (7%)	

*based on histology only.

**The size of each polyp was measured during the endoscopy

Table 2. Inter-observer agreement between pathologists

	n	Agreement, n (%)	K-values (95% CI)
Non-adenomatous / Adenomatous polyps	440	421 (96%)	0.88 (0.83 - 0.94)
- ≤5mm	224	212 (95%)	0.89 (0.82 - 0.95)
- >5mm	216	209 (97%)	0.84 (0.72 - 0.96)
- <10mm	311	295 (95%)	0.88 (0.82 - 0.94)
- ≥10mm	129	126 (98%)	0.85 (0.67 - 1,02)
Non-advanced / Advanced adenoma	322	266 (83%)	0.58 (0.48 – 0.68)
- ≤5mm	134	123 (92%)	0.48 (0.22 - 0.74)
- >5mm	188	143 (76%)	0.52 (0.39 - 0.64)
- <10mm	205	179 (87%)	0.53 (0.37 - 0.69)
- ≥10mm	117	87 (74%)	0.48 (0.33 - 0.64)
Low grade / High grade dysplasia*	322	304 (94%)	0.62 (0.46 – 0.79)
Tubular / Tubulo-villous and villous adenoma	315	259 (82%)	0.55 (0.44 – 0.66)

* including carcinoma in situ and intramucosal carcinoma.

Among the 322 adenomatous polyps, agreement for low or high grade dysplasia was obtained in 304 polyps (94%). There was consensus for 287 low grade and 17 high-grade dysplastic lesions. Due to the large prevalence-index, inter-observer agreement was only moderate with kappa 0.62 (95% CI; 0.46 – 0.79) (prevalence-index 0.86, bias-index 0.01). Focussing on the high grade dysplastic lesions; pathologists agreed that five lesions had intramucosal carcinoma or carcinoma in situ. On another two lesions there was disagreement in the classification; high grade dysplastic adenoma vs. intramucosal carcinoma/carcinoma in situ. No carcinoma invading the submucosa was observed in any of the samples. Categorizing the 315 adenomas (without intramucosal carcinoma or carcinoma in situ) as tubular adenoma or as adenoma with ≥25% villous component, obtained consensus in 259 polyps (82%). Pathologists agreed on 203 tubular adenomas and 56 adenomas with ≥25% villous histolology. Inter-observer reproducibility for grading villousness was moderate with a kappa-value of 0.55 (95% CI; 0.44 – 0.66) (prevalence-index 0.47, bias-index 0.01). Overall consensus for the non-adenomatous / adenomatous nature, and histological type and grade of dysplasia of adenomas was obtained in 336/440 polyps (76%).

Influence of polyp size on inter-observer variation

The level of agreement between pathologists was not affected by polyp size (Table 2). Within each size category (1-5mm, 5-9mm and ≥10mm), reproducibility was very good for differentiating between non-adenomas and adenomas (with a kappa-value ranging from 0.84 and 0.89), and reproducibility was moderate for categorizing adenomas as non-advanced and advanced (with a kappa-value ranging from 0.48 and 0.53).

Inter-observer variation between general and expert pathologists, and between expert pathologists

Inter-observer agreement in the classification of colorectal polyps was similar between general and expert pathologists on the one hand, and between two expert pathologists on the other hand (Table 3). Both groups showed very good agreement in categorizing polyps as non-adenomatous and adenomatous. The general and expert pathologists agreed on 310/324 polyps (96%), including 80 non-adenomatous and 230 adenomatous polyps. The two expert pathologists agreed on 111/116 polyps (96%); 19 non-adenomatous and 92 adenomatous polyps. Kappa-values were 0.89 (95% CI; 0.83 - 0.95) and 0.86 (95% CI; 0.73 – 0.98), respectively. Of note, the polyps evaluated by the general and expert pathologist had, as compared to the polyps evaluated by the two expert pathologists, a lower prevalence-index. The bias-index was low for both groups.

Furthermore, both groups showed moderate agreement for categorizing adenomas as non-advanced or advanced. The general and expert pathologist agreed on 184/230

Table 3. Inter-observer agreement between general (GP) and expert pathologists (EP), and between expert pathologists (EP`s).

	Combined	GP and EP	EP and EP
Non-adenomatous / Adenomatous			
- K-value (95% CI)	0.88 (0.83 - 0.94)	0.89 (0.83 - 0.95)	0.86 (0.73 - 0.98)
- Prevalence-index	0.51	0.46	0.62
- Bias-index	0.01	0.02	0.01
Non-advanced/Advanced adenoma			
- K-value (95% CI)	0.58 (0.48 - 0.68)	0.56 (0.44 - 0.67)	0.64 (0.43 - 0.85)
- Prevalence-index	0.40	0.31	0.63
- Bias-index	0.01	0	0.02

adenomas (80%), including 128 non-advanced and 56 advanced adenomas. The expert pathologists agreed on 82/92 adenomas (89%); 70 non-advanced and 12 advanced adenomas. Kappa-values were 0.56 (95% CI; 0.44 - 0.67) and 0.64 (95% CI; 0.43 – 0.85), respectively. Of note, the adenomas evaluated by the general and expert pathologist had a lower prevalence-index as compared to the adenomas evaluated by the two expert pathologists. The bias-index was low for both groups.

DISCUSSION

This study describes the inter-observer variation in the histological diagnosis of colorectal polyps detected in a CRC screening program. Our data demonstrated very good inter-observer agreement in categorizing polyps as non-adenomatous or adenomatous (kappa-value 0.88). This level of concordance was better than observed by Yoon et al [13], but consistent with other studies [12,27-30]. Our results showed that inter-observer agreement was only moderate for differentiating between non-advanced and advanced adenomas (kappa-value 0.58). The inconsistency of pathologists in differentiating between non-advanced and advanced adenomas was more frequently based on grading and assessing villousness than on grading of dysplasia. Of note however, kappa-values were moderate for both; grading villous histology (kappa-value 0.55), and due to a large prevalence index also moderate for grading dysplasia (kappa-value 0.62). Our results are in line with other studies also showing a poor to moderate level of agreement for classifying the proportion of villous component and the grade of dysplasia. These studies however did not specifically investigate agreement after stratifying adenomas as non-advanced and advanced [12,13,27-32]. Furthermore, we found that the level of agreement between pathologists was not affected by polyp size.

Our results showed that the inter-observer agreement in categorizing of colorectal polyps was similar between general and expert pathologists one the one hand, and between expert pathologists on the other hand. This is in agreement with previous studies on the histopathological interpretation of colorectal polyps [12,13,27-32]. In addition, in other fields of pathology it was also found that expert pathologists are just as likely to disagree as general pathologists [33-35].

Our data confirm that the classification of advanced adenoma is subject to inter-observer variation [12,13,27-32]. This has major clinical implications for patients with diminutive (1-5mm) and/or small (6-9mm) adenomas, as large adenomas (≥10mm) are already classified as advanced adenomas. A recent systematic review reported that diminutive and/or small adenomas were found to contain advanced histology in 12.5% of screened subjects in an average risk population [36]. Possible misclassification might therefore occur in a large proportion of patients. This has major implications for the decision on surveillance interval, as current guidelines also base the time interval for a surveillance colonoscopy on the presence of advanced adenoma [8]. Misclassification of low risk patients may therefore lead to inadequate colonoscopic surveillance, whereas misclassification of high risk patients may result in unnecessary invasive and costly colonoscopies with some associated morbidity. Furthermore, postpolypectomy surveillance represents 22% of all colonoscopies [37]. In an era of limited endoscopy resources, it is of paramount importance to have objective criteria for risk stratification of subjects with adenoma for recommendations on surveillance interval [38-43].

Furthermore, it has been suggested that the current postpolypectomy surveillance guidelines have limited predictability for advanced adenoma recurrence [44]. A risk profile based on cumulative findings from multiple previous colonoscopies might better stratify patients in high and low risk than the adenoma findings from the most recent examination [45]. In addition, recent evidence indicates that other factors than histological diagnosis, are stronger associated with the development of metachronous advanced adenomas. A pooled multivariate analysis of postpolypectomy patients showed that after four years of follow-up, the risk of metachronous advanced colorectal neoplasia was strongly associated with the number, size, and location of prior adenomas, as well as patient age. In the multivariate analysis, the presence of villous histology was only modestly associated, and the grade of dysplasia was not associated with metachronous advanced neoplasia [46]. In agreement with our findings, some postpolypectomy surveillance guidelines (e.g. the Dutch revised adenoma surveillance guideline and the United Kingdom NHS Bowel Cancer Screening Program) do not use histological subtyping as indicator for surveillance interval, and only use size and number of adenomas [47,48]. Guidelines that do use the presence of advanced adenoma for risk stratification

may reconsider these criteria given the subjectivity, the poor reproducibility, and the uncertainty on the role as a predictor of future risk.

In addition, the level of inter-observer variability needs to be considered in the context of the outcome of current studies and colorectal cancer screening programs. Colorectal cancer screening programs rely on advanced adenoma as intermediate endpoint.

Our study has some limitations. First, in total twenty-three general and two expert pathologists reviewed the pathology specimens. This was done with the deliberate purpose to resemble a situation as seen in a nation-wide colorectal cancer screening program. In such a setting many general pathologists review the biopsy specimens, whereas only a few expert pathologists will review selected specimens, either for quality assurance or because of uncertain diagnosis. Our results will therefore closely reflect outcomes of a population-based nation-wide screening program.

Second, we should emphasize that the level of agreement between the two expert pathologists might be underestimated. The two expert pathologists had, as compared to the general and expert pathologist, higher prevalence-indexes for the differentiation between non-adenomas and adenomas, and between non-advanced and advanced adenomas (table 3). These higher prevalence-indexes predisposed to diagnose or not to diagnose adenomas and advanced adenomas. This increased the chance of agreement, and subsequently suppressed the kappa-values.

In conclusion, this study demonstrated that pathologists have a very good inter-observer agreement for differentiating between non-adenomatous and adenomatous polyps, while the agreement is only moderate for non-advanced and advanced adenomas. Agreement is comparable between general and expert pathologists on the one hand, and between expert pathologists on the other hand. The considerable variation in the interpretation of advanced histology suggests that more objective criteria are required for risk stratification in screening and surveillance guidelines.

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Chapter 6

Limited diagnostic value of microsatellite instability associated pathology features in colorectal cancer

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ABSTRACT

Aim: To determine the diagnostic test characteristics and inter-observer variation of pathology features for identifying MSI-H colorectal cancer (CRC).

Methods and Results: Six pathologists blindly evaluated 177 CRC for the presence of MSI-H associated pathology features. Inter-observer agreement was determined by using Kappa-statistics. In the first random 88/177 cases, mucinous carcinoma, tumor-infiltrating lymphocytes (TIL) and Crohns-like infiltrate (CLI) were the best discriminators between MSI-H and microsatellite stable CRC (OR 5.6 (95%CI 1.7-19), 5.4 (1.8-17) and 3.5 (1.1-11), respectively), with high specificity (89%-91%). The sensitivities for MSI-H, however, were low (31-41%). In addition, inter-observer agreement was moderate for TIL and CLI (kappa 0.38 and 0.48, respectively), but very good for mucinous carcinoma (kappa 0.86). Interpretation of overall histopathology as suggestive for MSI-H performed better than any individual feature; OR 15 (5.2-44), and AUC 0.79. However, inter-observer agreement was moderate (kappa 0.53). In the second set, TIL and CLI were scored according to updated scoring systems. Although both remained the best individual discriminators, test characteristics and inter-observer agreement did not improve.

Conclusions: MSI-H pathology features have moderate accuracy for identifying MSI-H CRC, and are identified with moderate inter-observer agreement. These findings highlight the limitations of clinical strategies, such as the revised Bethesda guidelines, which incorporate the MSI-H associated pathology features in their strategy to identify persons with LS.

INTRODUCTION

Lynch syndrome (LS) is an autosomal dominant inherited disorder caused by mutations in mismatch repair (MMR) genes. LS is the commonest form of hereditary colorectal carcinoma (CRC) and is responsible for approximately 3% of all CRC cases [1,2]. Additionally, LS is associated with extra-colonic cancers, mostly endometrial carcinoma [3]. Early detection of LS is important since colonoscopic surveillance can reduce overall mortality by about 65% [4].

Diagnosis of LS is complicated by the absence of a pre-morbid phenotype. To improve the efficiency of recognizing LS, various guidelines were published to select cases for germline mutation analysis, including a molecular diagnostic work-up of tumors, guided by clinical and pathological criteria. The combination of the revised Bethesda guidelines and MSI testing and/or IHC analysis is nowadays the most widely applied strategy for the identification LS carriers [5], although other effective approaches have been proposed as well [2,6-11].

The revised Bethesda guidelines for lynch syndrome recommend for molecular testing; all CRC in patients diagnosed before age 50 years, and all CRC diagnosed in patients between ages 50 and 59 years with the presence of one or more pathology features known to be associated with high microsatellite instability (MSI-H), namely; mucinous differentiation, signet ring cell pattern, medullary pattern, presence of tumor-infiltrating lymphocytes (TIL), and presence of Crohn's-like infiltrate (CLI) [5,8]. However, concern has been expressed about the reproducibility of the histological interpretation of these MSI-H related pathology features. The aim of this study was to determine the diagnostic test characteristics of MSI-H associated pathology features for identifying MSI-H CRC, and to evaluate the inter-observer variation in the histological diagnosis of these pathology features.

METHODS

Study setting

In total, 177 CRC cases were selected from a multicenter population based prospective study in CRC patients ≤ 70 years (LIMO-study). The LIMO-study has been described in detail elsewhere [10]. In brief, this study evaluated the yield of routine molecular analysis for LS in consecutive CRC patients ≤ 70 years and patients with advanced colorectal adenoma ≤ 45 years. Recruitment took place between May 2007 and September 2009. In total, 1117 CRC cases were included. All tumor specimens were routinely analyzed

for MSI, and immunohistochemical MMR protein expression (MLH1, MSH2, MSH6 and PMS2). Microsatellite unstable tumors without MLH1 expression were also evaluated for MLH1 promotor methylation and somatic BRAF mutations. Tumors were classified as either: (a) likely caused by LS; (b) sporadic microsatellite-unstable; or (c) microsatellite-stable (MSS). Patients likely to have LS were referred to the department of clinical genetics for counseling, eventually followed by germline mutation analysis. Molecular analyses revealed a MSI-H profile in 121 out of 1117 CRC (10.8%).

Sampling procedure and organization

The evaluation was conducted on 177 CRC cases: all 77 MSI-H cases that were available for the agreement analysis, completed with 100 randomly selected MSS cases. Coded hematoxylin and eosin slides, one representative of each case, were blindly evaluated by six pathologists (four general and two expert gastrointestinal pathologists). Each section was cut from the same routine formalin-fixed and paraffin-embedded (FFPE) tissue block as had been used for molecular testing. None of the pathologists had knowledge of patient cancer family history or any results of MSI or immunohistochemistry tests done on the tumor. First, all pathologists blindly evaluated a random subset of 88 of the 177 CRC. Second, a meeting was organized to review the scoring of the different MSI associated pathology features with a focus on discrepant results. In addition, updated scoring systems were introduced. Third, the pathologists blindly evaluated the remaining 89 CRC. Glass slides were completely digitized to produce whole slide images. Whole slide imaging is a relative new technique that uses computerized technology to scan and convert pathology specimen glass slides into digital images which are then accessible for viewing using a monitor and viewing software. We used the Hamamatsu Nanozoomer Digital Pathology (NDP) slide scanner (Hamamatsu, Japan) at a resolution of 40X which is comparable to 400X magnification on a microscope. The obtained files were uploaded into a secured internet environment to which the pathologists had access. NDP Slideviewer software; NDP server and NDP View, provided by Hamamatsu, were used. Images shown in this paper are sections of the files exported from the digital slides. At the discussion meeting, concern was expressed about the possible influence of the digitized technology on the study outcome. In response, glass slides from 17 randomly selected CRC from the first set of CRC were additionally sent to all pathologists for agreement analysis. Pathologists were unaware that these CRC had been included in the first CRC set.

Criteria for pathologic classification

The WHO classification was adopted to classify the CRC [12]. Adenocarcinomas were assessed for degree of differentiation, histology subtype (mucinous differentiation, signet ring cell pattern and medullary pattern), presence of TIL and presence of CLI. The

grade of differentiation was based on the least differentiated area but excluded dedifferentiation or tumor budding at the invasive margin. Poor differentiation was defined as a tumor with at least some glandular structures but with the glands highly irregular and difficult to discern. Mucinous carcinoma was defined as at least 50% of the tumor area comprising secretory mucin. Signet ring cell carcinoma was defined as at least 50% of the tumor composed of signet ring cells. Medullary carcinoma was defined as a tumor that was poorly differentiated or undifferentiated and composed of masses of cells circumscribed with a well-circumscribed margin and a marked lymphocytic infiltrate that was both peri-tumoral and intra-tumoral. Tumor-infiltrating lymphocytes (TIL) were scored as present, when there were at least five intra-epithelial lymphocytes in at least one high-power field and at least 10 high-power fields had been thoroughly searched. A Crohn's-like lymphocytic (CLI) reaction was scored as present, when at least four nodular lymphoid aggregates were counted in a low power field beyond the advancing edge of the tumor and generally within the subserosa or mesenteric fat. In addition, each pathologist was asked to indicate whether, based on the histopathological features, the specific case should be tested for MSI (yes or no).

In the second CRC set and the glass slides, TIL and CLI were scored according to updated scoring systems. We aimed to simplify and improve the categorization of these features, and thereby to improve the diagnostic test characteristics for differentiating between MSI-H and MSS CRC, and to improve the inter-observer agreement. The presence of TIL were scored as; not assessable/ negative/ low/ moderate or substantial, in at least one high-power field and at least 10 high-power fields had been thoroughly searched. Likewise, the presence of CLI were scored as; not assessable/ negative/ low/ moderate or substantial, in a low-power field. To clarify the different scoring possibilities, wallpapers were made and send to all pathologists (Figure 1 and 2).

MSI analysis

MSI analyses were performed on DNA derived from microdissected FFPE tumor tissue, using a panel of five markers, as previously described [13]. Tumors with more than one unstable marker were categorized as MSI-H. Those with one or no unstable marker were categorized MSS.

Statistical analysis

Descriptive statistics were used to analyze and report the data. Histopathological features were scored as present, when the majority of pathologists agreed on the presence of the feature. Diagnostic test characteristics (i.e. sensitivity, specificity, and diagnostic odds ratio) used MSI-status as the reference. Conditional agreement was reported using percentages. Inter-observer agreement was determined by using Cohen's kappa (κ), which is a widely used statistical measure that adjusts for agreement by chance alone.

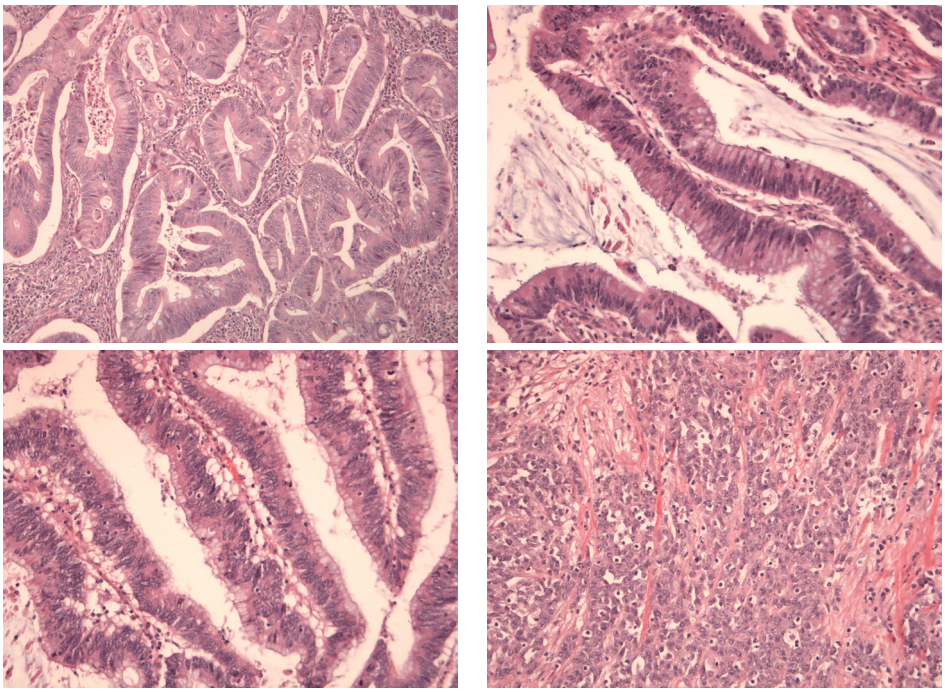

Figure 1. Updated scoring system for tumor-infiltrating lymphocytes. The presence was scored as; negative/low/moderate or substantial

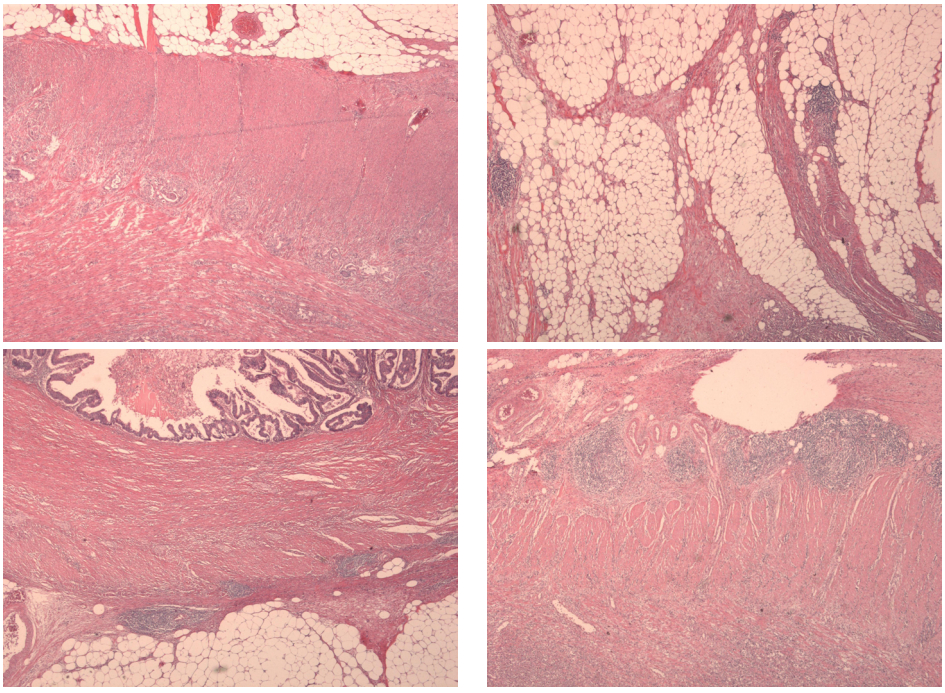

Figure 2. Updated scoring system for Crohn's-like lymphocytic reaction. The presence was scored as; negative/low/moderate or substantial

A κ value of 0 indicates no agreement better than what would be expected by chance alone. Values of < 0.21, 0.21–0.40, 0.41–0.60, 0.61–0.80 and >0.80 correspond to poor, fair, moderate, substantial and very good inter-observer agreement, respectively [14]. The updated scoring systems developed for TIL and CLI were further categorized. The features were scored as present, when their presence was classified as moderate or substantial. Comparisons between expert and general pathologists and the first and second round were evaluated by using receiver operating characteristic (ROC) curves analysis, and calculation of the area under the curve (AUC). Statistical analysis was performed using the SPSS 20.0 program (SPSS Inc. Chicago, IL). A two-sided p-value of < 0.05 was considered statistically significant.

RESULTS

CRC characteristics

In total, 170 out of 177 cases (96%) were evaluable for the agreement analysis: 83 in the first and 87 in the second round. Seven patients (4%) were excluded due to low quality hematoxylin and eosin slides. In the first and second set, 39 out of 83 (47%), and 33 out of 87 (38%) were MSI-H CRC (p=0.23, Table 1). Table 2 shows the inter-observer agreement between pathologists on evaluating the pathology features. Diagnostic test characteristics for predicting MSI-H status and inter-observer agreement in evaluating the MSI-H related pathology features are summarized in Table 3.

Table 1. CRC characteristics as described by the majority of pathologists

	Total (n=170) n (%)	Round 1 (n=83) n (%)	Round 2* (n=87) n (%)
Poor differentiation	46 (27%)	23 (28%)	23 (26%)
Mucinous carcinoma	30 (18%)	18 (22%)	12 (14%)
Signet ring cell carcinoma	4 (2%)	3 (4%)	1 (1%)
Medullary carcinoma	4 (2%)	2 (3%)	2 (2.3%)
Tumor-infiltrating lymphocytes present	31(18%)	21 (25%)	10 (12%)
Crohns like lymphocytic reaction present	37(22%)	17 (21%)	20 (23%)
One or more features suggestive for MSI present	95 (56%)	48 (58%)	47 (54%)
MSI test request	52 (31%)	38 (46%)	14 (16%)
MSI status			
- MSI-H	72 (42%)	39 (47%)	33 (38%)
- MSS	98 (58%)	44 (53%)	54 (62%)

* Updated scoring systems for tumor-infiltrating lymphocytes and Crohns-like infiltrate in second round

Table 2. Paired inter-observer agreement between pathologists on the histological diagnosis of MSI-H related pathology features

	Round 1 (n=83) n (%)	Round 2* (n=87) n (%)
Differentiation (poor/other)		
- Agreement; median, range	60 (73%), 43-68 (51-82%)	60 (69%), 50-71 (57-82%)
- Kappa-value; median, range	0.42 (0.05-0.63)	0.38 (0.15-0.57)
Mucinous carcinoma (yes/no)		
- Agreement; median, range	79 (95%), 77-83 (93-100%)	81 (93%), 77-85 (89-98%)
- Kappa-value; median, range	0.86 (0.78-1.00)	0.73 (0.63-0.90)
Signet ring cel carcinoma (yes/no)		
- Agreement; median, range	80 (96%), 78-83 (94-100%)	87(100%), 85-87 (98-100%)
- Kappa-value; median, range	0.65 (0.26-1.00)	1.00 (0.49-1.00)
Medullary carcinoma (yes/no)		
- Agreement; median, range	75 (90%), 73-82 (88-99%)	85 (98%), 83-87 (95-100%)
- Kappa-value; median, range	0.39 (0.11-0.70)	0.66 (0.32-1.00)
Tumor infiltrating lymfocytes (yes/no)		
- Agreement; median, range	59 (71%), 48-68 (58-82%)	73 (84%), 66-78 (76-90%)
- Kappa-value; median, range	0.38 (0.22-0.48)	0.42 (0.18-0.68)
Crohns like infiltrate (yes/no)		
- Agreement; median, range	66 (80%), 60-71 (72-86%)	72 (83%), 63-79 (72-91%)
- Kappa-value; median, range	0.48 (0.33-0.63)	0.53 (0.30-0.71)
MSI suspected (yes/no)		
- Agreement; median, range	64 (77%), 56-69 (67-83%)	67 (77%), 58-74 (67-85%)
- Kappa-value; median, range	0.53 (0.37-0.65)	0.37 (0.20-0.50)

* Updated scoring systems for tumor-infiltrating lymphocytes and Crohns-like infiltrate in second round

First set

Twenty-three out of 83 cases (28%) were categorized as poorly differentiated by the majority of observers. Poor differentiation was found in 36% of MSI-H (14 of 39) and 20% of MSS (9 of 44) tumors (Odds ratio 2.2, p=0.12). Inter-observer agreement for classifying differentiation was moderate (median kappa 0.42 (range 0.05-0.63). Signet ring cell carcinoma and medullary carcinoma were identified in only 5 out of 83 CRC (7%), without a significant difference between molecular subtypes, and with respectively substantial and fair inter-observer agreement. Mucinous carcinoma was diagnosed in 18 out of 83 CRC (22%). TIL and CLI were present in 21 (25%) and 17 (21%) out of 83 CRC, respectively. Mucinous carcinoma, TIL and CLI were the best individual discriminators for distinguishing MSI-H and MSS cancers (Odds ratio 5.6 (95% CI 1.7-19), 5.4 (95% CI 1.8-17) and 3.5 (95% CI 1.1-11), respectively), with high specificity (91%, 89% and 89%, respectively). The sensitivities for MSI-H, however, were low (36%, 41% and 31% respectively). In addition, inter-observer agreement was only fair to moderate for TIL and CLI (median kappa 0.38

(range 0.22-0.48) and 0.48 (range 0.33-0.63), respectively), but very good for mucinous carcinoma (median kappa 0.86 (range 0.78-1.00)). Lesions with at least one histologic feature present were about 6 times more likely to be MSI-H than those with none of the predictive features (p<0.001). Subjective interpretation of overall histopathology as suggestive for MSI-H, performed better than any individual feature; the odds ratio was 15.0 (95% CI 5.2-44), with sensitivity of 77%, specificity of 82%, and an area under the curve (AUC) of 0.79. However, inter-observer agreement was moderate (median kappa 0.53 (range 0.37-0.65)).

When only considering the two expert pathologists, the diagnostic value of the MSI-H associated pathology features did not improve. The histopathological features were found in comparable proportions, and with comparable predictive values and inter-observer agreement. Of note, the predictive value of TIL for identifying MSI-H CRC improved but inter-observer agreement was moderate and the diagnostic value of overall histopathology for predicting MSI-status remained unchanged (Table 3).

Second set

After the consensus meeting, the diagnostic test characteristics for predicting MSI-H status, and inter-observer agreement in evaluating MSI-H associated pathology features, did not improve. Comparable with the first set, 23 out of 87 cases (26%) were classified as poorly differentiated, poor differentiation did not differentiate between MSI-H and MSS CRC (Odds ratio 1.8, p=0.25), and inter-observer agreement was fair (median kappa 0.38 (range 0.15-0.57)). In addition, the small numbers of signet ring cell and medullary carcinoma were without a significant difference between molecular subtypes, and were scored with very good and substantial inter-observer agreement, respectively. As compared with the first round, the histologic value of mucinous carcinoma decreased. Mucinous carcinoma was identified in 12 out of 87 CRC (14%), without a significant predictive value (Odds ratio 1.8, p=0.35), and with moderate inter-observer agreement (median kappa 0.73 (range 0.63-0.90)). Furthermore, the updated scoring method for TIL and CLI did not improve the test characteristics and the inter-observer agreement. TIL and CLI were scored as present, in 10 (12%) and 20 (23%) out of 87 CRC, respectively. Although both features remained the best individual discriminators (Odds ratio 8.3 (95% CI 1.6-42.1) and 3.3 (95% CI 1.2-9.2), respectively), the test characteristics and agreement did not improve. For CLI, the AUC remained 0.61, and inter-observer agreement stayed moderate (median kappa 0.53 (range 0.30-0.71)). The inter-observer agreement in classifying TIL also remained moderate (median kappa 0.42 (range 0.18-0.68)) but the AUC decreased from 0.65 to 0.60. Lowering the cut-off for scoring TIL present, did increase the proportion of CRC with TIL, and increase sensitivity for MSI-H to 94%, however, specificity dropped till 32%. The AUC of TIL with a lower cut-off was 0.63. As the diagnostic value of TIL decreased, the AUC of at least one or more features suggestive for MSI-H present,

Table 3. Histopathological association with MSI status

Set1, all pathologists (n=6)

	Round1 CRC (n=83) n(%)	MSI-H (n=39) n	MSS (n=44) n	p-value	Odds ratio for MSI-H (95% CI)	Sensitivity for MSI-H %	Specificity for MSI-H %	AUC	Kappa-value Median (range)
Poor differentiation	23(28%)	14	9	0.12	2.2(0.8-5.8)	36%	80%	0.58	0.42 (0.05-0.63)
Mucinous carcinoma	18(22%)	14	4	0.003	5.6(1.7-18.9)	36%	91%	0.63	0.86 (0.78-1.00)
Signet ring cell carcinoma	3(4%)	2	1	0.49	2.3(0.2-26.7)	5%	98%	0.51	0.65 (0.26-1.00)
Medullary carcinoma	2(3%)	2	0	0.13	-	5%	100%	0.53	0.39 (0.11-0.70)
Tumor-infiltrating lymphocytes present	21(25%)	16	5	0.002	5.4(1.8-16.8)	41%	89%	0.65	0.38 (0.22-0.48)
Crohns like lymphocytic reaction present	17(21%)	12	5	0.03	3.5(1.1-11.0)	31%	89%	0.60	0.48 (0.33-0.63)
One or more features suggestive for MSI present	48(58%)	31	17	0.000	6.2(2.3-16.5)	80%	61%	0.70	-
MSI test request	38(46%)	30	8	0.000	15.0(5.2-44)	77%	82%	0.79	0.53 (0.37-0.65)

Set1, expert pathologists only (n=2)

	Round1 CRC (n=83) n(%)	MSI-H (n=39) n	MSS (n=44) n	p-value	Odds ratio for MSI-H (95% CI)	Sensitivity for MSI-H %	Specificity for MSI-H %	AUC	Kappa-value
Poor differentiation	22(27%)	12	10	0.41	1.5(0.6-4.0)	31%	77%	0.54	0.40
Mucinous carcinoma	17(21%)	14	3	0.001	7.7(2.0-29.3)	36%	93%	0.65	0.90
Signet ring cell carcinoma	2(2%)	1	1	0.93	1.1(0.1-18.7)	3%	98%	0.50	0.66
Medullary carcinoma	4(5%)	4	0	0.03	-	10%	100%	0.55	0.39

Tumor-infiltrating lymphocytes present	23(28%)	20	3	0.000	14.4(3.8-55)	51%	93%	0.72	0.45
Crohns like lymphocytic reaction present	18(22%)	12	6	0.06	2.8(0.9-8.4)	31%	89%	0.59	0.53
One or more features suggestive for MSI present	48(58%)	31	17	0.000	6.2(2.3-16.5)	80%	61%	0.70	-
MSI test request	32(46%)	27	5	0.000	17.6(5.5-56)	69%	89%	0.79	0.58

Set2, all pathologist (n=6)

	Round 2 CRC (n=87) n(%)	**MSI-H (n=33) n**	**MSS (n=54) n**	**p-value**	**Odds ratio for MSI-H (95%CI)**	**Sensitivity for MSI-H %**	**Specificity for MSI-H %**	**AUC**	**Paired kappa Median (range)**
Poor differentiation	23(26%)	11	12	0.25	1.8(0.7-4.6)	33%	78%	0.56	0.38 (0.15-0.57)
Mucinous carcinoma	12(14%)	6	6	0.35	1.8(0.5-6.1)	18%	89%	0.54	0.73 (0.63-0.90)
Signet ring cell carcinoma	1(1%)	0	1	0.43	-	0%	98%	0.49	1.00 (0.49-1.00)
Medullary carcinoma	2(2.3%)	2	0	0.07	-	6%	100%	0.53	0.66 (0.32-1.00)
Tumor-infiltrating lymphocytes present	10(12%)	8	2	0.004	8.3(1.6-42.1)	24%	96%	0.60	0.42 (0.18-0.68)
Crohns like lymphocytic reaction present	20(23%)	12	8	0.02	3.3(1.2-9.2)	36%	85%	0.61	0.53 (0.30-0.71)
One or more features suggestive for MSI present	47(54%)	24	23	0.006	3.6(1.4-9.2)	73%	57%	0.65	-
MSI test request	14(16%)	11	3	0.001	8.5(2.2-33.5)	33%	94%	0.64	0.37 (0.20-0.50)

also decreased from 0.70 to 0.65. Furthermore, the value of the subjective interpretation of overall histopathology decreased; the AUC decreased from 0.79 to 0.64, sensitivity dropped from 77% to 33% ($p<0.01$), and the inter-observer agreement was only fair (median kappa 0.37 (range 0.20-0.50)).

Glass slides

Exploring the 17 randomly selected CRC with a light microscope did not influence the level of agreement. Comparable to the digitized CRC, histopathological features were found in comparable proportions, and with comparable inter-observer agreement (Table 4 and Table 5). Numbers were too small to detect a significant diagnostic value of overall histopathology for predicting MSI-status (Odds ratio 7.33, p=0.12, respectively).

Table 4. CRC characteristics as described by the majority of the pathologists on digital and glass slides

	Digital slides round 1 (n=17) n (%)	Glass slides* (n=17) n (%)
Poor differentiation	4 (24%)	6 (35%)
Mucinous carcinoma	1 (6%)	2 (12%)
Signet ring cell carcinoma	0	1 (6%)
Medullary carcinoma	0	0
Tumor-infiltrating lymphocytes present	5 (29%)	2 (12%)
Crohns like lymphocytic reaction present	4 (24%)	5 (29%)
One or more features suggestive for MSI present	9 (53%)	11 (65%)
MSI test request	4 (24%)	3 (18%)
MSI status		
- MSI-H	5 (29%)	5 (29%)
- MSS	12 (71%)	12 (71%)

* Updated scoring systems for tumor-infiltrating lymphocytes and Crohns-like infiltrate on glass slides

DISCUSSION

This paper describes the diagnostic test characteristics and the inter-observer variation of MSI-H associated pathology features for identifying MSI-H CRC. Our data demonstrated that mucinous carcinoma, TIL and CLI were the best individual discriminators for distinguishing between MSI-H and MSS CRC. However, each of these characteristics had a moderate predictive performance (AUC of 0.63, 0.65 and 0.60, respectively). In addition, inter-observer agreement was only moderate for TIL and CLI (median kappa 0.38 and 0.48, respectively), but very good for mucinous carcinoma (median kappa 0.86). CRC with at least one histologic feature were about six times more likely to be MSI-H than those with none of the predictive features ($p<0.001$). In addition, subjec-

Table 5. Paired inter-observer agreement between pathologists on the histological diagnosis of MSI-H related pathology features on digitized and glass slides

	Digitized slides round 1 (n=17) n (%)	Glass slides* (n=17) n (%)
Differentiation (poor/other)		
- Agreement; median, range	14(82%), 10-16 (59-94%)	13(76%), 11-16/(65-94%)
- Kappa-value; median, range	0.49 (0.05-0.85)	0.49 (0.20-0.88)
Mucinous carcinoma (yes/no)		
- Agreement; median, range	16(94%),15-17(88-100%)	16(94%),16-17(94-100%)
- Kappa-value; median, range	0.43 (0.43-1.00)	0.64 (0.64-1.00)
Signet ring cel carcinoma (yes/no)		
- Agreement; median, range	16(94%),16-17(94-100%)	17(100%),16-17(94-100%)
- Kappa-value; median, range	-	-
Medullary carcinoma (yes/no)		
- Agreement; median, range	16(94%), 16-17(94-100%)	16(94%),16-17(94-100%)
- Kappa-value; median, range	-	-
TIL (yes/no)		
- Agreement; median, range	12(71%), 7-14(58-82%)	15/(88%),14-17/(82-100%)
- Kappa-value; median, range	0.35 (-0.21-0.47)	0.43 (0.30-1.00)
Crohns like infiltrate (yes/no)		
- Agreement; median, range	12(71%), 10-15(59-88%)	13(76%), 10-15/(59-88%)
- Kappa-value; median, range	0.47 (0.05-0.63)	0.55 (0.29-0.76)
MSI suspected (yes/no)		
- Agreement; median, range	12 (71%), 7-15(41-88%)	12/(71%),8-16(47-94%)
- Kappa-value; median, range	0.32 (-0.20-0.60)	0.39 (-0.10-0.82)

* Updated scoring systems for tumor-infiltrating lymphocytes and Crohns-like infiltrate on glass slides

tive interpretation of the overall histopathological appearance as suggestive for MSI-H performed even better (Odds ratio 15 (95% CI 5.2-44), AUC 0.79). Although combining the MSI-H associated histology features improved the diagnostic test characteristics, it identified only 80% of MSI-H tumors, and only with moderate inter-observer agreement (median kappa 0.53). In addition, evaluation by expert pathologists did not improve diagnostic test characteristics and inter-observer agreement. Our results are in line with other studies that also showed a low sensitivity and inconsistency between pathologists in evaluating the histopathological features [15-17]. One study suggested even lower sensitivity as well as poorer reproducibility of the MSI-associated pathology features [15]. Others found a somewhat better performance of TIL for identifying MSI-H (sensitivity 81% and 93%, respectively) but at the cost of losing specificity (60% and 62%, respectively) and without performing an agreement analysis [16,17].

A consensus meeting was organized to discuss and review the findings, with a focus on discrepant results. In addition, updated scoring systems were introduced aiming to simplify and improve the categorization of TIL and CLI. Unfortunately, diagnostic test characteristics and inter-observer agreement did not improve. TIL and CLI remained the best individual discriminators, but the diagnostic value was similar (AUC 0.60 and 0.61, respectively), and inter-observer agreement remained moderate (median kappa 0.42 and 0.53, respectively). In addition, the diagnostic value of mucinous carcinoma decreased (OR 1.8, p=0.35, and median kappa 0.73). Therefore, the diagnostic value of overall histopathology for identifying MSI-H also decreased.

Our data confirmed that the MSI-H associated pathology features are subject to limited diagnostic performance in the classification of CRC according to their molecular status, and that they are identified with moderate inter-observer agreement. These results highlight the limitations of clinical strategies, such as the revised Bethesda guidelines, which incorporate the MSI-H associated pathology features in their strategy to identify persons with LS. More specifically, this concerns CRC patients diagnosed between ages 50 and 59 years, because patients diagnosed before age 50 years are already recommended for molecular testing [5]. Possible misclassification might therefore occur in a large proportion of patients if the revised Bethesda criteria are followed, especially because only about 45% of LS patients are diagnosed with CRC before age 50 years [2].

Besides the poor diagnostic performance and subjectivity in evaluating the MSI-H associated pathology features, the revised Bethesda guidelines have been criticized for being too complex [9,18]. In addition, the Bethesda guidelines are poorly implemented in clinical practice [19]. Together, this leads to a significant number of patients with LS who will remain undiagnosed. There is active debate about the optimal and standard approach to screening for MMR deficiency. A variety of strategies have been advocated, including mathematical algorithms to predict MMR gene mutation carriers based on personal and family history [11]. Other approaches rely heavily on routine tumor molecular testing of CRC in patients before age 50 years, before age 70 years or advice universal molecular testing [2,7,9,10].

We used an enriched high-risk sample to efficiently study diagnostic performance. In addition, we used whole slide imaging instead of conventional light microscopes. However, as this could have introduced bias, the study was extended with an additional agreement analysis on 17 glass slides. Results suggested that the level of agreement between a conventional light microscopes and whole slide imaging, was high. These results are consistent with other studies [20,21].

In conclusion, our results demonstrated that the MSI-H associated pathology features are subject to limited diagnostic performance in the classification of colorectal tumors according to their molecular status, and that they are identified with moderate inter-observer agreement. These findings highlight the limitations of clinical strategies, such as the revised Bethesda guidelines, which incorporate the MSI-H associated pathology features in their strategy to identify persons with LS.

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Chapter 7

Autofluorescence colonoscopy allows better differentiation of adenomatous and hyperplastic colorectal polyps than white video colonoscopy

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ABSTRACT

Objective: to compare autofluorescence endoscopy (AFE) and white light video endoscopy (WLE) for the differentiation between adenomatous and hyperplastic colorectal polyps.

Methods: 79 polyps were evaluated with both WLE and AFE. The polyps were detected in a back to back comparative study of WLE with a video colonoscope (CF160, Olympus Optical) and AFE using Xillix OncoLife (CF40, Olympus Optical) in patients from Lynch syndrome or familial CRC families. Back to back colonoscopy was performed by two blinded endoscopists. Lesions were graded as adenomatous or hyperplastic based on the macroscopic appearance. During AFE, autofluorescence ratio (AFR) was calculated for each polyp. Diagnostic test statistics were calculated by using histopathology as the reference value.

Results: Histopathology identified 60 adenomatous and 19 hyperplastic polyps. There was no difference in size of adenomas and hyperplastic polyps (mean of 4.9 mm and 5.6 mm, respectively ($p=0.20$)). The sensitivity of WLE for identifying adenomas was 75% with a specificity of 32%. Adenomas had significantly higher AFR compared to hyperplastic polyps; mean 0.85 and 0.46, respectively ($p<0.001$). When using an ROC determined AFR cut-off value of 0.45, diagnostic test statistics improved considerably as compared to WLE; sensitivity increased from 75% to 93% ($p=0.007$) and specificity from 32% to 63% ($p=0.10$).

Conclusions: AFE has better diagnostic test characteristics than WLE for differentiating between adenomatous and hyperplastic colorectal polyps in Lynch syndrome or familial CRC patients.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death in the Western world [1,2]. The detection and removal of adenomatous colorectal lesions reduces CRC incidence and mortality [3,4]. This effect has not been documented for hyperplastic polyps. With the exception of large right-sided hyperplastic polyps, small hyperplastic polyps do not seem to harbor the risk to develop into adenocarcinoma [5,6].

Conventional white light endoscopy has been limited to detecting and categorization colorectal lesions on the basis of gross morphological changes. Polypectomy and additional histological evaluation are essential and the standard approach to differentiate between adenomatous and hyperplastic lesions. The removal of hyperplastic polyps incurs additional risks, costs and time. Therefore, it would be useful to differentiate between adenomatous and hyperplastic polyps at the time of a colonoscopy. Given the fact that around 50% of polypectomies are performed on non-adenomatous polyps [7], the benefits of real-time histology will be far reaching.

New endoscopic technologies attempt to optimize diagnostic tissue characterization. Autofluorescence endoscopy (AFE) has been considered useful for detecting colorectal neoplasms. It has been suggested that autofluorescence endoscopy has the potential to differentiate between adenomatous and hyperplastic polyps. Autofluorescence is an imaging technique in which the mucosa is illuminated by a short wavelength (blue) light. This light stimulates endogenous tissue molecules, to emit longer wavelength fluorescence light which can be captured by sensitive cameras and displayed as fluorescence image. Because of differences in endogenous composition among various tissues, autofluorescence can potentially distinguish adenomatous from hyperplastic lesions [8,9].

The aim of the present study was to compare autofluorescence endoscopy (AFE) and white light video endoscopy (WLE) for the differentiation between adenomatous and hyperplastic colorectal polyps.

METHODS

Study setting

In a back to back comparative study of WLE and AFE, 79 polyps were evaluated with WLE and AFE. The study has been described in detail elsewhere [10]. In brief, this study compared WLE and AFE for the detection of adenomas in patients with Lynch syndrome

or familial CRC. In total, 75 patients underwent two colonoscopic examinations in one session (figure 1). In the original study design AFE was routinely performed after WLE. However, as this could have introduced bias, the study was extended with additional

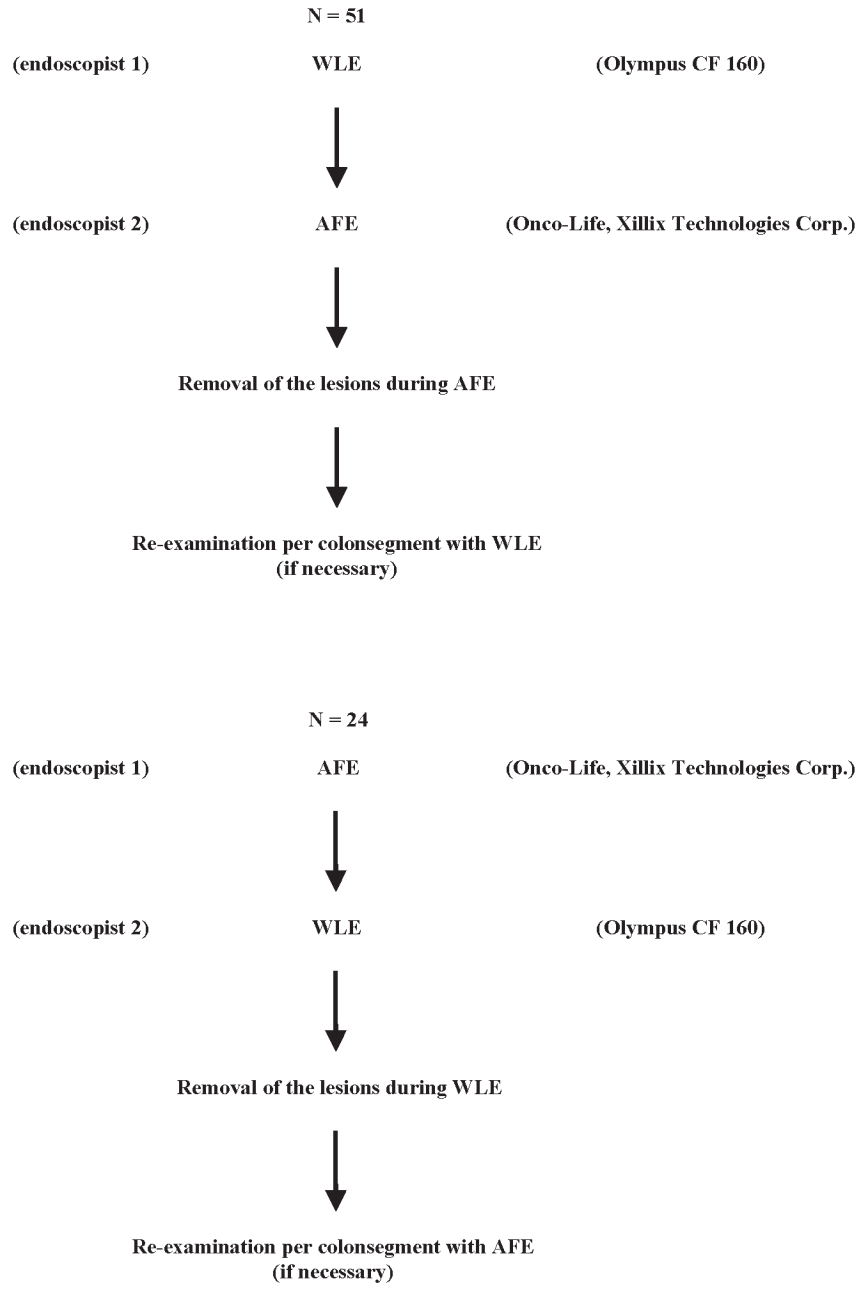

Figure 1. Study setting

patients. These patients underwent back to back endoscopy in a reverse order; AFE followed by WLE. The first colonoscopy was performed with either WLE or AFE by an experienced endoscopist. During the first colonoscopy, all lesions were left in situ. Immediately after the first endoscopic procedure, the first endoscopist left the endoscopy room and a second experienced endoscopist, who was unaware of the results of the first endoscopic procedure, performed the second endoscopic procedure with the alternative endoscopic method. The involved endoscopists; were experienced, had similar adenoma detection rates over the past years as identified from our endoscopy database, and alternated with respect to the type of endoscopy performed in this study (WLE or AFE). In case lesions had been detected during the first endoscopy but missed during the second, the colon was re-examined on a third pass to remove lesions left in situ. In total, 173 lesions were detected. Seventy-nine of the 173 lesions were detected by both WLE and AFE. The remaining 94 lesions were only seen with one of the two light techniques. Standard WLE was performed with a flexible video colonoscope (CF160, Olympus Optical Co, Tokyo, Japan) connected to a xenon light source. AFE was performed using the Onco-Life system (Xillix Technologies Corporation, Richmond, BC, Canada), attached to a standard fiberoptic colonoscope (CF40, Olympus Optical Co, Tokyo, Japan). The Onco-Life system operates in two modes providing both autofluorescence and conventional white light imaging. Pressing a lever on the camera head allows the system to switch modes instantly. In the fluorescence mode, the tissue is exposed to blue and red light and simultaneously captures images in the green and red parts of the visible spectrum, which are combined to provide the fluorescence image. Blue light excites the tissue within the endoscopic field of view. The emitted green tissue autofluorescence passes via a dichroic mirror and a 490-560nm filter to an intensified charge coupled device. The red reflected light passes through a 650-750nm filter to a second charge coupled device. In general, the intensity of green autofluorescence is less in neoplastic than in normal tissue. The intensity of the red reflected light is less influenced by tissue changes. The two acquired images are combined by the digital signal processor to produce a single fluorescence image that can be displayed on a standard Red, Green, Blue monitor. The Onco-Life system also quantifies the fluorescence by providing a numeric representation of the red-to-green autofluorescence ratio (AFR).

Colorectal polyps

All lesions were graded by the endoscopist as either hyperplastic or adenomatous based on the macroscopic appearance. During AFE, AFR of each lesion was calculated. The size of each polyp was measured during the endoscopy using an open biopsy forceps with 7mm span. The polyp size as judged during WLE was used for analysis. Lesions found during AFE and WLE were matched based on the location in the colon and comparison of the photographs taken during both procedures. All identified lesions were removed

during second or third pass (figure 1) and sent in for histology. Resected specimens were stained with haematoxylin and eosin. An expert gastrointestinal pathologist, who was blinded for the endoscopical judgment, evaluated all lesions. The WHO classification was adopted to classify the selected polyps as adenomatous or hyperplastic. Adenomatous lesions were further categorized according to histologic type, degree of dysplasia, and absence or presence of infiltrating carcinoma [11,12].

Statistical analysis

Descriptive statistics were used to analyze and report the data. Sensitivity, specificity and predictive values for predicting neoplasia with WLE and AFE were calculated by using histopathology as the reference value. The performance of AFR itself for differentiating between hyperplastic and adenomatous polyps was analyzed by using receiver operating characteristic (ROC) curves analysis. In addition, diagnostic test statistics were calculated for polyps <6mm and ≥6mm. Differences between WLE and AFE were assessed by using receiver operating characteristic (ROC) curves analysis and McNemar`s test. Statistical analysis was performed using the SPSS 18.0 program (SPSS Inc. Chicago, IL). A two-sided p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Polyp characteristics

In total, 79 colorectal polyps were observed in 31 patients and were evaluated with both WLE and AFE. The polyp characteristics are summarized in Table 1. Bowel preparation was excellent or good in 24 out of 31 patients (77%), and moderate in the remaining 7 patients (23%). In case of a moderate bowel preparation, adequate lavage ensured adequate macroscopic visualization of polyps and ensured that the AFR was not altered by the resembling stool particles. Histopathology identified 19 hyperplastic and 60

Table 1. Polyp characteristics

	Histopathological diagnosis		
	Hyperplastic polyps	**Adenomatous polyps**	**p-value**
Number (n)	19	60	
Size			
- Mean, in mm (95% CI)	5.6 (4.7 – 6.4)	4.9 (4.3 – 5.5)	0.20
- Categorized			
<6mm	9	42	
≥6mm	10	18	
AFR, mean (95% CI)	0.46 (0.34 – 0.58)	0.85 (0.75 - 0.95)	<0.001

adenomatous polyps; 54 tubular adenomas with low grade dysplasia, 2 tubulovillous adenomas with low grade dysplasia, 1 traditional serrated adenoma, and 3 adenocarcinomas. There was no difference in size of hyperplastic polyps and adenomas (mean of 5.6 mm and 4.9 mm, respectively (p=0.20)). Fifty-one polyps were <6mm and 28 polyps ≥6mm. Adenomas had significantly higher AFR compared to hyperplastic polyps; mean 0.85 and 0.46, respectively (p<0.001).

Macroscopic differentiation

The diagnostic performance of WLE and AFE to macroscopically differentiate adenomatous and hyperplastic polyps is shown in Table 2. Sensitivity of WLE for identifying adenomas was 75% with a specificity of 32%. The area under the curve (AUC) was 0.53. Subdividing polyps in <6mm and ≥6mm, WLE had a sensitivity for identifying adenomas of 69% and 89%, respectively. During AFE, polyps were graded based on the autofluorescence image and the numeric representation of the red-to-green AFR. Sensitivity of AFE for identifying adenomatous lesions was 87%, with a specificity of 47%. The AUC was 0.67. After subdividing polyps in <6mm and ≥6mm, AFE had a sensitivity for identifying adenomas of 83% and 94%, respectively. Sensitivity and specificity, of WLE and AFE were not significantly different (p=0.09 and p=0.45, respectively).

Table 2. Diagnostic test characteristics WLE, AFE and AFR for predicting histology

	AUC	Sensitivity	Specificity
WLE	0.53	75%	32%
AFE	0.67	87%	47%
AFR, cut-off			
0.40	0.72	95%	50%
0.45	0.78	93%	63%
0.50	0.78	84%	72%
0.55	0.74	75%	72%

AFR

The performance of AFR itself for differentiating between hyperplastic and adenomatous polyps was analyzed by using ROC curves analysis. The area under the curve was 0.83. Diagnostic test characteristics were calculated for several AFR cut-off values (Table 2). Focusing on a cut-off value of 0.45, sensitivity of AFR for identifying adenomas was 93% with a specificity of 63%. The AUC was 0.78. After subdividing polyps in <6mm and ≥6mm, AFR had a sensitivity for identifying adenomas of 90% and 100%, respectively. Sensitivity of AFR as compared to WLE for identifying adenomas was significantly higher (p=0.007). AFR had no significant higher specificity than WLE (p=0.10).

DISCUSSION

This back to back comparative study provides evidence that AFE has better diagnostic test characteristics than conventional WLE for differentiating between hyperplastic and adenomatous colorectal polyps. Furthermore, we found that AFR performed better than when histology was predicted by the endoscopist based on the fluorescence image and AFR. $AFR^{(0,45)}$ improved diagnostic test statistics considerably as compared to WLE; sensitivity increased from 75% to 93% (p=0.007) and specificity from 32% to 63% (p=0.10). Sensitivity of AFR was especially good in polyps ≥6mm.

Similar to our observations, previous studies demonstrated promising results for AFE as compared to WLE for differentiating between hyperplastic and adenomatous polyps [9,13,14]. However, to date no true comparison between both techniques could be made. To our knowledge, we performed the first back to back comparative study in which polyps were directly evaluated with both WLE and AFE prior to removal. Endoscopies were performed by two independent endoscopists who were unaware of the results of the other endoscopy. Another strength was that WLE was performed with high quality white light video colonoscopes which have the advantage over fiber-optic colonoscopes to provide high quality images. During AFE, on the other hand, a fiberoptic AFE system was used. This system does have a lower resolution than video AFE systems, however, it is unknown whether this is relevant for the fluorescence technique as data comparing these two systems are lacking. Furthermore, contrary to current video AFE systems, the Onco-Life system allows real-time and on-site calculation of the red-to-green AFR [14]. This makes the Onco-Life system suitable for differentiating between adenomatous and non-adenomatous polyps at the time of a colonoscopy.

Chromoendoscopy and narrow band imaging (NBI) are other techniques clinically applied for optical diagnosis of intestinal disorders. Chromoendoscopy involves the application of stains or dyes during endoscopy to improve tissue visualization, characterization and diagnosis of mucosal lesions. Chromoendoscopy has been shown to facilitate the differentiation of polyps [15]. However, chromoendoscopy is time consuming, operator dependent, and it is impossible to switch back to conventional colonoscopy which may influence adequate visualization of other mucosal lesions. These limitations have prevented the wide spread use of chromoendoscopy beyond few specified conditions. NBI on the other hand, is more widely used. Primarily because of the ease of usage and availability at the switch of a button. NBI involves the use of narrow band pass filters in front of a conventional white light source to obtain tissue illumination at selected narrow wavelength bands. This provides optical enhancement of the vascular network and texture of the mucosa thereby assisting tissue characterization. NBI does not improve

adenoma detection but is a promising method for the prediction of colorectal polyp pathology [16,17]. However, the various described NBI classification systems, need to be further standardized and validated for use in routine clinical practice. Combining NBI and video AFE further improved diagnostic accuracy in the differential diagnosis of colorectal polyps [18]. Further development of the new endoscopic techniques are needed for reducing the number of unneeded polypectomies. Potentially it is useful to develop a video system that combines the benefits of WLE, NBI, and AFE, and allows real-time and on-site calculation of the red-to-green AFR.

The benefits of real-time histology would be far reaching. The capability to correctly differentiate hyperplastic and adenomatous lesions at the time of a colonoscopy would allow small distal hyperplastic polyps to be left in situ, or to "resect and discard" polyps without pathological assessment. Anecdotically, it could even be an option to resect diminutive and small adenomas without a further need for histopathology. The histopathological diagnosis might not be needed as it is known that these diminutive and small adenomas have minimal risk of carrying advanced neoplasia. Second, a recent pooled multivariate analysis of postpolypectomy patients showed that the risk of metachronous advanced colorectal neoplasia was strongly associated with the number, size, and location of prior adenomas, as well as patient age, but not with advanced histology [19]. Third, it is known that pathologists have only moderate agreement for differentiating non-advanced and advanced adenomas. In agreement with these findings, some postpolypectomy surveillance guidelines (e.g. the Dutch revised adenoma surveillance guideline and the United Kingdom NHS Bowel Cancer Screening Program) do not use advanced histology as indicator for surveillance interval, and only use size and number of adenomas [20,21]. Reducing the number of unneeded polypectomies would reduce the endoscopic and histopathologic workload, and the number of complications.

A limitation of our study was that this study was performed in a selected high-risk population which influenced the predictive values. In addition, in the original study design AFE was routinely performed after WLE. However, as this could have introduced bias, the study was extended with additional patients. These patients underwent back to back endoscopy in a reverse order; AFE followed by WLE. The current study design enabled a true comparison of WLE and AFE for differentiating between hyperplastic and adenomatous polyps. All endoscopies were performed by two independent endoscopists who were unaware of the results of the prior endoscopy.

In conclusion, this study demonstrates that AFE has better diagnostic test characteristics than conventional White Light video Endoscopy for differentiating between hyperplastic and adenomatous polyps at the time of a colonoscopy. Furthermore, AFR with

a ROC determined cut-off value performed better than when histology was predicted by the endoscopist based on the fluorescence image and AFR. Further development of the new endoscopic technologies are needed for reducing the number of unnecessary polypectomies.

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Chapter 8

Summary and general discussion

The potential of CRC screening has been recognized. It is recommended to implement CRC screening with an organized population-based approach and appropriate quality assurance at all levels. The success of screening depends on the performance of individual components in the screening process. This thesis focused on individual components to improve and optimize population screening for CRC.

First we focused on the insufficient endoscopic capacity that serves as a barrier to CRC screening [1-6]. Introducing nurse endoscopists into gastrointestinal endoscopy service may provide a solution for the insufficient endoscopic capacity. In **Chapter 2** we evaluated the views of gastroenterologists towards nurse performed endoscopy. Results showed that gastroenterologists are in general positive towards an important albeit restricted role for nurse endoscopists. Potential benefits are recognized but concerns are expressed, including adequacy of training, quality, patient acceptance, and interference with training for gastroenterology fellows.

Previous studies already showed that nurse endoscopists are competent in performing gastroscopy and sigmoidoscopy [7,8]. However, the performance in colonoscopy remained to be elucidated. Only three small single center studies evaluated nurse performed colonoscopy. These reports suggested that nurse endoscopists could become competent colonoscopists [9-11]. In **Chapter 3**, we described a large multicenter prospective study with ten trained nurse endoscopists who undertook in total 1000 colonoscopies. Our results demonstrated that trained nurse endoscopists performed colonoscopies according to the international recognized quality standards, with high patient satisfaction. The cecal intubation rate was over 90%, adenoma detection rate was high at 26.8%, and only two complications occurred in 1000 colonoscopies (0.2%). In about a quarter of colonoscopies only, nurse endoscopists required assistance from the supervising gastroenterologist. Focusing on patient experiences, the vast majority of patients (95%) were satisfied with the endoscopic procedure. In addition, the majority of patients (72%) had no specific preference for a physician or nurse endoscopist.

In **Chapter 4** we compared the endoscopic quality between nurse and physician performed colonoscopy. Seven nurses and eight physicians with no endoscopic experience at baseline were enrolled in this large multicenter prospective study. Each endoscopist obtained endoscopic training, including a minimum of 100 colonoscopies. Next, each endoscopist performed 135 consecutive colonoscopies which were evaluated for endoscopic quality. Results demonstrated comparable endoscopic quality for nurse and physician endoscopists; the cecal intubation rates were over 90% (p=0.38), adenoma detection rates were over 25% (p=0.93), and complication rates were low; 0.5% (p=0.99). In both groups, the unassisted cecal intubation rates were just below 90% but gradually increased with the amount of colonoscopies performed, and were nowhere significantly different between nurse and physician endoscopists. Furthermore, we showed that in a

scenario where one gastroenterologist supervises three nurse endoscopists, personnel costs decline with 17 euro per colonoscopy compared to a gastroenterologist performed colonoscopy.

Our findings advocate the involvement of nurse endoscopists in colonoscopy, and should encourage decision-makers to support the development of nurse`s role in endoscopy. However, there are several important issues to the establishment of nurse endoscopy. Guidelines for nurse endoscopy training and criteria to maintain procedural competence after training should be defined. These guidelines should rely on available studies regarding the endoscopic skills of nurse endoscopists and be comparable with that of fellows. This in recognition of the educational differences between nurse and physician. Several professional groups already developed such guidelines [12]. If competence has been demonstrated, individual endoscopists should be credentialed by local institutions to perform the respective endoscopic procedures. In addition, clear job descriptions must define the scope of practice and specific responsibilities for nurse endoscopists and their supervisors. In the Netherlands for example, rules for health care professionals are set by the Individual Health Care Professionals Act (Wet BIG). This act authorizes nurses to perform specific delegated tasks, provided they are competent in performing the task as determined by training and accreditation, and perform the task under a pre-specified level of supervision. Nurses trained and judged competent for performing a specific procedure, will be judged accordingly, and are personally responsible for the procedure. However, it is the responsibility for local institutions to define these responsibilities. These will also clarify the medico-legal implications and effectiveness for the proposed strategy where gastroenterologists supervise nurse endoscopists. Furthermore, reimbursement policies should be adapted to facilitate a cost-effective and adequate reimbursement. Overcoming these issues will allow introduction of nurse endoscopists in the gastrointestinal endoscopic service. It`s time to come to action.

The pathology service also plays an important role in CRC screening. Accurate histopathological assessment is of paramount importance since the management of participants in the program depend on the quality and accuracy of the histopathologic diagnosis [13]. However, concern was raised about the reproducibility of the histological interpretation of colorectal lesions [14,15]. In **Chapter 5**, we evaluated the inter-observer variation in histological diagnosis of colorectal polyps detected in a CRC screening program. Results demonstrated very good inter-observer agreement in categorizing polyps as non-adenomatous or adenomatous (kappa-value 0.88). However, inter-observer agreement was only moderate for differentiating between non-advanced and advanced adenomas (kappa-value 0.58). Furthermore, agreement was similar between general and expert pathologists one the one hand, and between expert pathologists on the other hand.

Our data confirmed that the classification of advanced adenoma is subject to substantial inter-observer variation [14-21]. This has major clinical implications for patients with diminutive (1-5mm) and/or small (6-9mm) adenomas, as large adenomas (≥10mm) are already classified as advanced adenomas. A recent systematic review reported that diminutive and/or small adenomas were found to contain advanced histology in 12.5% of screened subjects in an average risk population [22]. Possible misclassification might therefore occur in a large proportion of patients. This has consequences on the surveillance interval, as current guidelines also base the time interval for a surveillance colonoscopy on the presence of advanced adenoma [23]. Furthermore, postpolypectomy surveillance represents 22% of all colonoscopies [24]. In an era of limited endoscopy resources, it is of paramount importance to have objective criteria for risk stratification of subjects with adenoma for recommendations on surveillance interval [1-6].

Furthermore, it has been suggested that current postpolypectomy surveillance guidelines have limited predictability for advanced adenoma recurrence [25]. A risk profile based on cumulative findings from multiple previous colonoscopies might better stratify patients in high and low risk than the adenoma findings from the most recent examination [26]. In addition, recent evidence indicates that other factors than histological diagnosis, are stronger associated with the development of metachronous advanced adenomas. A pooled multivariate analysis of postpolypectomy patients showed that after four years of follow-up, the risk of metachronous advanced colorectal neoplasia was strongly associated with the number, size, and location of prior adenomas, as well as patient age. In the multivariate analysis, the presence of villous histology was only modestly associated, and the grade of dysplasia was not associated with metachronous advanced neoplasia [27]. Guidelines that do use the presence of advanced adenoma for risk stratification may reconsider these criteria given the subjectivity, the poor reproducibility, and the uncertainty on the role as a predictor of future risk.

In **Chapter 6** we focused on the accuracy of identifying CRC pathology features known to be associated high microsatellite instability (MSI-H). These features are incorporated in various strategies to select cases for germline mutation analysis, in order to identify persons with Lynch syndrome. We evaluated the diagnostic test characteristics and inter-observer variation of MSI-H associated pathology features for identifying MSI-H CRC. Our data demonstrated that mucinous carcinoma, tumor-infiltrating lymphocytes and Crohns-like infiltrate were the best individual discriminators for distinguishing between MSI-H and microsatellite stable CRC. However, each of these characteristics had a moderate predictive performance (AUC of 0.63, 0.65 and 0.60, respectively). In addition, inter-observer agreement was only moderate for tumor-infiltrating lymphocytes and Crohns-like infiltrate (median kappa 0.38 and 0.48, respectively), but very good for mucinous carcinoma (median kappa 0.86). Interpretation of the overall histopathological

appearance as suggestive for MSI-H performed better than any individual feature (Odds ratio 15.0 (95% CI 5.2-43.7), AUC 0.79). Although combining the MSI-H associated histology features improved the diagnostic test characteristics, it identified only 80% of MSI-H tumors, and only with moderate inter-observer agreement (median kappa 0.53). In addition, diagnostic test characteristics and inter-observer agreement did not improve when only considering expert pathologists or adapting the histopathological scoring system.

Our data confirmed that the MSI-H associated pathology features are subject to limited diagnostic performance in the classification of CRC according to their molecular status, and that they are identified with moderate inter-observer agreement [28-30]. These results highlight the limitations of clinical strategies, like the revised Bethesda guidelines, which incorporate the MSI-H associated pathology features in their strategy to identify persons with Lynch syndrome. This has major implications as the revised Bethesda guidelines are considered the mainstay for selecting patients for molecular testing [31].

Besides the poor diagnostic performance and subjectivity in evaluating the MSI-H associated pathology features, the revised Bethesda guidelines have been criticized for being too complex [32,33]. In addition, the Bethesda guidelines are poorly implemented in clinical practice [34]. Together, this leads to a significant number of patients with LS who will remain undiagnosed. There is active debate about the optimal and standard approach to screening for MMR deficiency. A variety of strategies have been advocated, including mathematical algorithms to predict MMR gene mutation carriers based on personal and family history [35]. Other approaches rely heavily on routine tumor molecular testing of CRC in patients before age 50 years, before age 70 years or advice universal molecular testing [32,36-38].

The last issue addressed in this thesis affects the field of colon imaging. New endoscopic technologies like autofluorescence endoscopy attempt to optimize optical diagnostic tissue characterization. In **Chapter 7** we compared autofluorescence endoscopy and white light video endoscopy for the differentiation between adenomatous and hyperplastic colorectal polyps at the time of a colonoscopy. This back to back comparative study provided evidence that autofluorescence endoscopy has better diagnostic test characteristics than conventional white light video endoscopy for differentiating between hyperplastic and adenomatous polyps; the sensitivity for identifying adenomas increased from 75% to 93% (p=0.007) and specificity increased from 32% to 63% (p=0.10).

Similar to our observations, previous studies demonstrated promising results for autofluorescence endoscopy for differentiating between hyperplastic and adenomatous polyps [39-41]. The benefits of real-time histology would be far reaching. The capability to correctly differentiate hyperplastic and adenomatous lesions at the time

of a colonoscopy would allow small distal hyperplastic polyps to be left in situ, or to "resect and discard" polyps without pathological assessment. It could even be an option to resect diminutive and small adenomas without a further need for histopathology. The histopathological diagnosis might not be needed as it is known that these diminutive and small adenomas have minimal risk of carrying advanced neoplasia [22]. In addition, results in chapter 5 demonstrated substantial inter-observer variation in the diagnosis of advanced adenoma. In agreement with these findings, some postpolypectomy surveillance guidelines do not use advanced histology as indicator for surveillance interval, and only use size and number of adenomas [42,43]. Although the results of autofluorescence endoscopy are promising, further development of new endoscopic technologies are needed to reduce the number of unnecessary polypectomies.

In conclusion, we aimed to explore methods to improve and optimize population CRC screening. Pitfalls and opportunities were identified. Focusing on all individual components in the screening process will further improve population screening for CRC.

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Addendum

Samenvatting

Het promotieonderzoek dat nu voorligt omvat diverse aspecten in het bevolkingsonderzoek naar darmkanker. Darmkanker is een van de meest voorkomende vormen van kanker. Een bevolkingsonderzoek kan veel sterfgevallen voorkomen en is kosteneffectief. Daarom wordt het bevolkingsonderzoek in diverse landen al uitgevoerd. In Nederland starten we vanaf september 2013. Het lifetime-risico op darmkanker bedraagt voor een willekeurige Nederlander 4-5%. Mensen tussen de 55 en 75 jaar worden iedere twee jaar uitgenodigd om deel te nemen, en ontvangen daarvoor een ontlastingstest (iFOBT). Bij een afwijkende uitslag volgt een uitnodiging voor een inwendig kijkonderzoek van de dikkedarm (colonoscopie). De schatting is dat met het bevolkingsonderzoek op termijn ongeveer 2400 sterfgevallen per jaar kunnen worden voorkomen. Het doel van dit proefschrift is de kwaliteit en haalbaarheid van het bevolkingsonderzoek naar darmkanker te verbeteren.

Momenteel is er onvoldoende capaciteit om het bevolkingsonderzoek uit te voeren. Het capaciteitsprobleem centreert zich rond de colonoscopie-capaciteit. Een colonoscopie is een inwendig kijkonderzoek van de gehele dikkedarm. Met dit kijkonderzoek kunnen we de voorstadia van darmkanker vinden én behandelen. Colonoscopieën worden verricht door artsen, voornamelijk MDL-artsen. Door de groeiende zorgkosten en het tekort aan MDL-artsen moeten alternatieven onderzocht worden. Daarom is er toenemende belangstelling voor de inzet van verpleegkundig endoscopisten. In **hoofdstuk 2** evalueren wij de mening van MDL-artsen over verpleegkundig endoscopisten. De resultaten laten zien dat MDL-artsen in het algemeen positief zijn over het inzetten van verpleegkundig endoscopisten voor het bevolkingsonderzoek naar darmkanker. Echter, er zijn wel zorgen over de opleiding, kwaliteit, en patiënt tevredenheid.

Eerdere studies lieten al zien dat verpleegkundig endoscopisten competent zijn in het verrichten van andere en relatief eenvoudigere kijkonderzoeken. Verpleegkundig endoscopisten zijn bijvoorbeeld competent in het verrichten van maagonderzoeken (gastroscopieën). Echter, er was nog weinig bekend over de competentie van verpleegkundigen in het verrichten van colonoscopieën. Daarom hebben wij een groot onderzoek uitgevoerd met tien verpleegkundig endoscopisten die in totaal 1000 colonoscopieën hebben verricht. Dit onderzoek staat beschreven in **hoofdstuk 3**. Onze resultaten tonen aan dat verpleegkundig endoscopisten de colonoscopieën verrichten volgens de internationaal geldende kwaliteitscriteria, en met grote patiënt tevredenheid. Slechts in een kwart van de colonoscopieën hadden verpleegkundig endoscopisten hulp nodig van een superviserende MDL-arts.

In **hoofdstuk 4** vergelijken wij de kwaliteit en kosten van colonoscopieën verricht door verpleegkundigen en door artsen. Zeven verpleegkundigen en acht MDL-artsen in opleiding participeerden aan deze studie. Zij hadden bij aanvang van de studie geen colonoscopie ervaring. Elke deelnemer kreeg een colonoscopie-opleiding. Vervolgens verrichtte elke deelnemer 135 colonoscopieën. De resultaten tonen een goede en vergelijkbare kwaliteit tussen verpleegkundigen en artsen. Bovendien suggereren de resultaten dat met de introductie van verpleegkundig endoscopisten kosten bespaard kunnen worden.

Onze bevindingen tonen aan dat verpleegkundig endoscopisten een goede en waardevolle bijdrage kunnen leveren, en een oplossing bieden voor het capaciteitsprobleem in het bevolkingsonderzoek naar darmkanker. Beleidsmakers zouden de ontwikkeling van verpleegkundig endoscopisten moeten stimuleren.

De afdeling pathologie speelt ook een belangrijke rol in het bevolkingsonderzoek naar darmkanker. Een patholoog beoordeelt de gevonden darmafwijkingen op weefsel- en celniveau om te komen tot een diagnose. De behandeling en follow-up van deelnemers aan het bevolkingsonderzoek hangt sterk af van de kwaliteit en betrouwbaarheid van de diagnose. Een juiste diagnose is van levensbelang.

In het algemeen wordt aangenomen dat darmkanker zich ontwikkelt uit een bepaald type zwellingen van de darm, zogenaamde adenomen. Aanvullend wordt er onderscheid gemaakt tussen laag- en hoogrisico adenomen. In **hoofdstuk 5** beschrijven wij de mate van overeenstemming tussen pathologen in de beoordeling van deze darmafwijkingen. De resultaten laten zien dat pathologen niet-adenomen en adenomen goed van elkaar kunnen onderscheiden, maar laag- en hoogrisico adenomen slechts matig. Bovendien was de mate van overeenstemming vergelijkbaar tussen algemeen pathologen en pathologen met maag-, darm-, en leverziekten als aandachtsgebied. Daarom zou de behandeling en follow-up van deelnemers aan het bevolkingsonderzoek, niet afhankelijk moeten zijn van een onderscheid tussen laag- en hoogrisico adenomen.

In het bevolkingsonderzoek naar darmkanker is het ook belangrijk om personen met erfelijke vormen van darmkanker te herkennen. Zij behoeven veelal een andere behandeling en follow-up dan mensen zonder erfelijke vorm van darmkanker (sporadische darmkanker). Ongeveer 5% van de darmkanker is erfelijk. Het Lynch syndroom is de meest voorkomende vorm van erfelijke darmkanker. **Hoofdstuk 6** beschrijft de waarde van pathologiekenmerken voor het herkennen van Lynch syndroom. De pathologiekenmerken zijn opgenomen in diverse strategieën om Lynch syndroom te identificeren. Echter, er was onzekerheid over de diagnostische waarde van deze kenmerken. Onze resultaten laten zien, dat de pathologiekenmerken weinig diagnostische waarde hebben in het identificeren van Lynch syndroom. Daarom zouden de betreffende patholo-

giekenmerken geen onderdeel moeten uitmaken van strategieën voor Lynch syndroom identificatie.

Het laatste onderwerp van het proefschrift betreft nieuwe beeldvormende technieken. Nieuwe beeldvormende technieken kunnen mogelijk ook een bijdrage leveren in het bevolkingsonderzoek naar darmkanker. We hebben ons gericht op de autofluorescentie endoscopie. Dit inwendig kijkonderzoek van de dikkedarm maakt gebruik van een alternatieve lichtbron. Er werd gesuggereerd dat autofluorescentie endoscopie onderscheid zou kunnen maken tussen niet-adenomen en adenomen. Daarmee zou het mogelijk zijn om niet-adenomen in de darm te laten zitten met als gevolg een efficiënter onderzoek en minder risico op complicaties. In **hoofdstuk 7** vergelijken we de autofluorescentie endoscopie met een standaard witlicht colonoscopie voor het onderscheid tussen niet-adenomen en adenomen. De resultaten laten zien dat de autofluorescentie endoscopie beter onderscheid kan maken tussen niet-adenomen en adenomen, dan standaard witlicht colonoscopie. Echter, de betrouwbaarheid van de autofluorescentie diagnose is niet voldoende om de niet-adenomen in de darm achter te laten. Het verdient aanbeveling om de nieuwe beeldvormende technieken verder te ontwikkelen en zo een real-time diagnose mogelijk te maken.

Concluderend hebben wij in het proefschrift diverse methoden onderzocht om de kwaliteit en haalbaarheid van het bevolkingsonderzoek naar darmkanker te verbeteren. Valkuilen en kansen werden ontdekt. Met een verdere verbetering van alle afzonderlijke stappen in het bevolkingsonderzoek, zal het succes en de waarde van het bevolkingsonderzoek verder toenemen.

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Dankwoord

Dit proefschrift is het product van velen. Een aantal mensen wil ik in het bijzonder bedanken.

Allereerst gaat mijn dank uit naar Professor Kuipers. Veel dank voor de geboden kansen en uitdagingen. Af en toe een sprong in het diepe, maar mede dankzij uw positieve houding en uitgezette lijnen altijd blijven drijven. Een zeer waardevolle en leerzame periode. Dank daarvoor.

Professor Steyerberg; altijd een verfrissende en verhelderende blik. Bedankt voor de kritische vragen en de verdieping die u bracht.

Veel dank gaat ook uit naar dr. Monique van Leerdam. Monique ik wil je bedanken voor de subtiele en kundige wijze waarmee je mij door het onderzoekslandschap hebt geleid.

Graag wil ik alle leden van de promotiecommissie bedanken voor hun bereidheid zitting te nemen in de commissie.

Dr. de Man wil ik bedanken voor het in mij gestelde vertrouwen mij op te leiden tot MDL-arts.

Alle verpleegkundigen, verpleegkundig endoscopisten, secretaresses, ondersteunend personeel, arts-assistenten en medisch specialisten van het Erasmus MC; bedankt voor de hulp, interesse en prettige samenwerking.

Ik wil ook alle deelnemende ziekenhuizen en auteurs die hebben bijgedragen aan de hoofdstukken van dit proefschrift hartelijk bedanken.

In mijn onderzoekstijd heb ik het voorrecht gehad samen te werken met een aantal fantastische collega`s. Ieder op een eigen project met andere uitdagingen, maar toch samen in hetzelfde schuitje. Samen werden de tegenvallers verwerkt en de hoogtepunten gevierd. Een kop koffie, een cynische grap, even uitwaaien op de fiets, en hier en daar een feestje. Het was mooi.

Familie en vrienden, hierbij het product van een paar jaar toeven in de academie. Een kaft, een inhoudsopgave, en een aantal hoofdstukken. Het traject was voor de meesten onbegrijpelijk, of inhoudelijk oninteressant. Toch waren jullie altijd erg geïnteresseerd

en ondersteunend. Dank! Met het afronden van het proefschrift is het nu tijd voor nieuwe uitdagingen en andere belangrijke zaken in het leven. Zie jullie snel!

Tot slot, lieve pap, mam, Susan en Carlien, bedankt voor het warme thuis, de onvoorwaardelijke steun, en de mensen die jullie zijn. Jullie zijn top.

Paul
Rotterdam, april 2013

Curriculum Vitae

Paul Gerard van Putten werd geboren op 17 januari 1982 te Noordoostpolder. In 2000 behaalde hij zijn V.W.O diploma aan het Emelwerda College te Emmeloord. Vervolgens studeerde hij Geneeskunde aan de Rijksuniversiteit Groningen. De co-schappen werden doorlopen in het Deventer Ziekenhuis. In augustus 2006 behaalde hij zijn artsexamen. Hierna werkte hij gedurende 8 maanden als arts-assistent interne geneeskunde in Gelre Ziekenhuizen Zutphen. Vanaf mei 2007 verricht hij promotieonderzoek onder begeleiding van prof. dr. E.J. Kuipers, prof. dr. E.W. Steyerberg, en dr. M.E. van Leerdam. In december 2010 startte hij met de opleiding tot MDL-arts vanuit het Erasmus MC Rotterdam (opleider dr. R.A. de Man). De vooropleiding interne geneeskunde heeft hij inmiddels afgerond (opleider prof. dr. J.L.C.M. van Saase).

ISBN: 978-94-6169-387-7