Improving the quality of colonoscopy, detection and resection of colorectal polyps

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Maxime Bronzwaer

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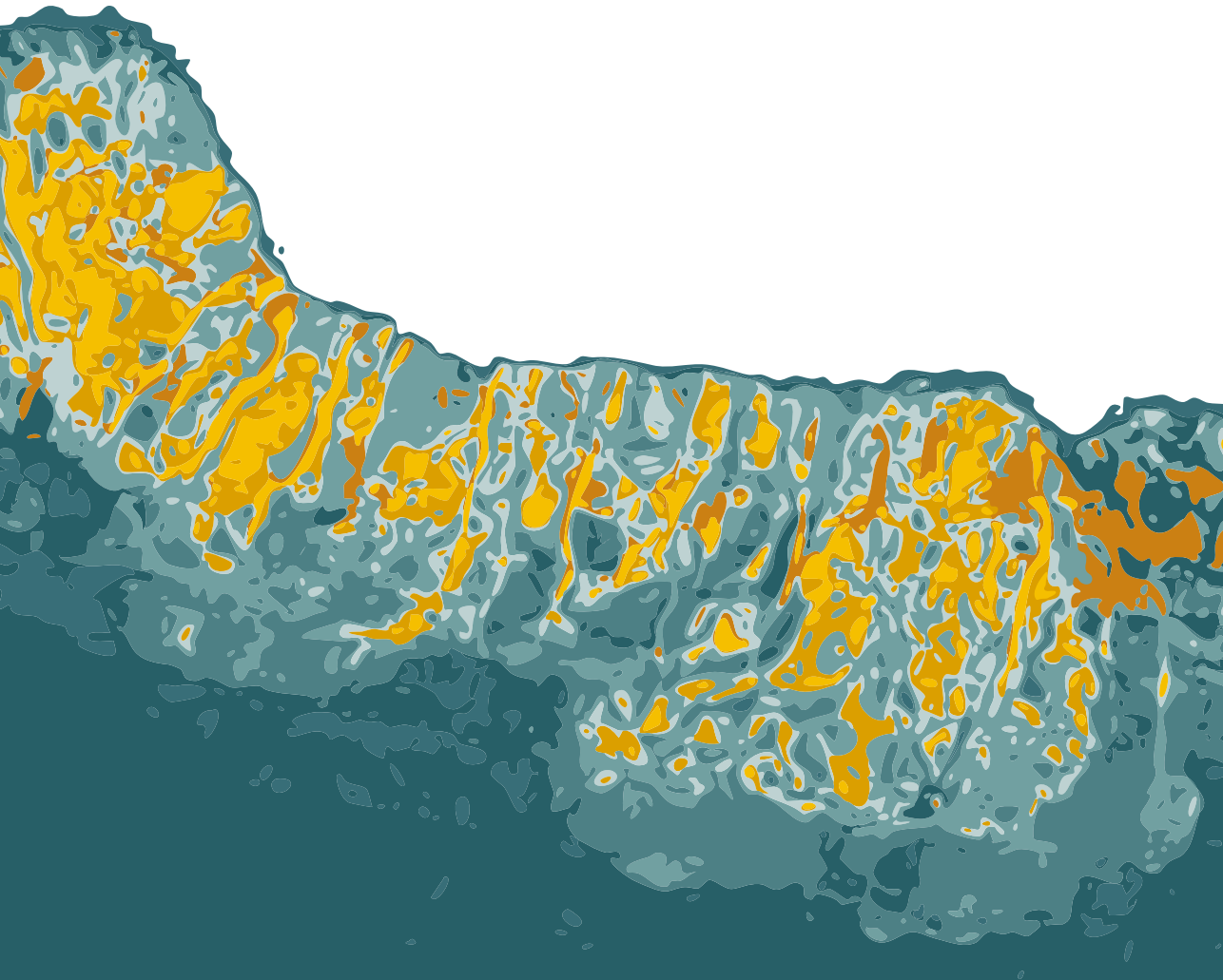
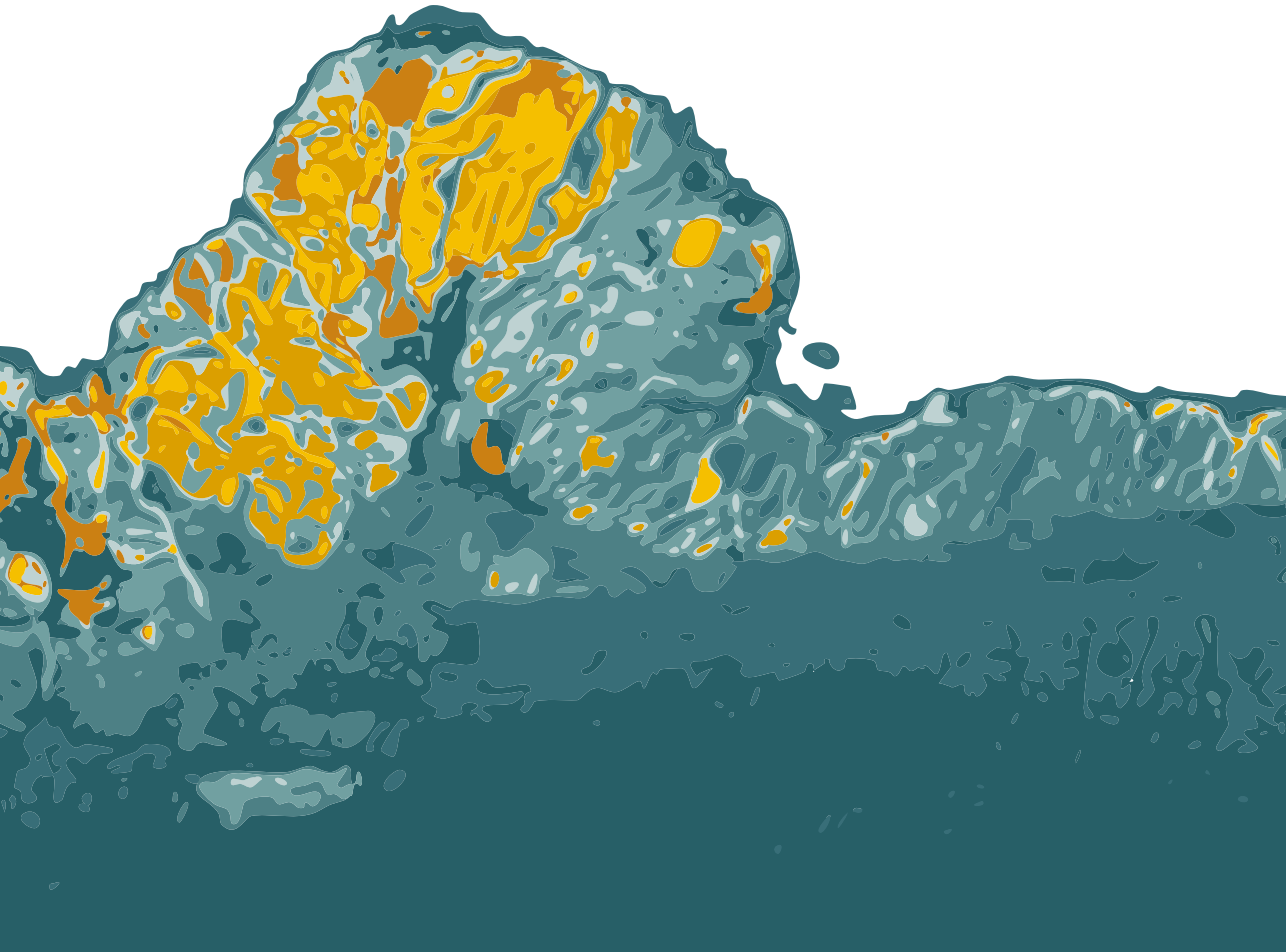


GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS



Colorectal cancer (CRC) is among one of the most common types of cancer and is the second leading cause of cancer related mortality in Western countries. Among these Western populations, the life-time risk of developing CRC is approximately 5%.[1] As CRC gradually develops from premalignant adenomas and serrated polyps (SP), CRC incidence and mortality can be reduced by the detection of cancers at curable stages and by preventing its development through the resection of the neoplastic precursor lesions.[2, 3]

Colonoscopy is the reference standard to halt the progression of CRC and to CRC, because it creates the opportunity to detect CRC and detect and resect its precursor lesions.[2, 3] However it is not perfect, as it does not fully protect against the later development of post-colonoscopy CRCs (PCCRCs).[4-7] PCCRCs are CRCs detected within the proposed surveillance-interval after colonoscopy and PCCRC incidence rates have been reported between 2% and 8%.[4-7] Causes of PCCRCs can be categorized in two major groups: biology-related and colonoscopy-related.[8-14] It is estimated that around 15% of all PCCRCs are actually newly developed cancers with an aggressive biologic behavior and/or an accelerated adenoma-carcinoma pathway.[15, 16] The rest, i.e. the vast majority of PCCRCs, are the result of the imperfection of colonoscopy consisting of premalignant polyps that were either missed or recurred after their incomplete removal.[4-7, 17]

A systematic review of tandem colonoscopy studies has reported a strikingly high pooled polyp miss rate of 22% and especially polyps with a diminutive size (1-5 mm), a flat morphology or lesions located in the proximal colon are prone to be missed.[18] This might furthermore explain the predominant proximal location of PCCRCs.[10, 16, 18, 19] Also inadequately performed colonoscopies, such as incomplete colonoscopies without cecal intubation or colonoscopies with an insufficient bowel preparation, contribute to an increased risk of missing premalignant polyps.[10, 20] Besides, an increasing amount of evidence suggests that 9-27% of PCCRCs are the result of incomplete resected premalignant polyps, resulting in cancers occurring at the previous polypectomy site.[10, 21-23] From the CARE study we learnt that approximately 10% of all polyps is resected incompletely, which varied widely among endoscopists.[17] This furthermore underlines that besides the adequate detection of all premalignant polyps, the complete endoscopic resection of these lesions is essential to assure effective prevention of PCCRCs.

The content of this thesis focuses on a wide range of colonoscopy-related issues related to the assurance, impact and improvement of the quality of colonoscopy, as well as the detection and resection of large non-pedunculated and complex colorectal polyps.

Colonoscopy quality indicators and the detection of colorectal polyps

As the majority of PCCRCs are the result of colonoscopy-related factors, this subgroup of PCCRCs should be preventable by the performance of high quality colonoscopy. Over the recent years the awareness of the importance of high quality colonoscopy has grown and several colonoscopy quality indicators have been proposed.[24] To assess the quality of colonoscopy, the PCCRC detection rate would be the ultimate indicator. However, PCCRC rates are difficult to compare, measure and interpret between individual endoscopists due to their relative rarity, long interval before their development, delay in the time to diagnosis, differences in the used definitions and difficulties with

adequate data collection.[7, 14, 25] Consequently, surrogate colonoscopy quality indicators are needed to measure the quality of colonoscopy in daily clinical practice and to target colonoscopy quality assurance programs and quality improvement initiatives.

The adenoma detection rate (ADR), the proportion of colonoscopies in which at least one histologically confirmed adenoma is detected, is nowadays considered as the most important surrogate quality indicator of colonoscopy. The ADR has been shown to be inversely correlated to PCCRC incidence and CRC mortality in two landmark papers.[26, 27] The first landmark paper from Poland showed that the risk of PCCRC was a tenfold higher in participants who underwent a screening colonoscopy by endoscopists with an ADR less than 20% compared to participants who were examined by endoscopists with a detection rate of 20% or more.[26] The subsequent American study showed that each 1% increase in ADR was associated with a 3% decrease in the PCCRC risk and a 5% reduction in the risk of CRC mortality.[27] However, an important limitation of the ADR is that the indicator can be considered imprecise, due to the fact that it includes any adenoma and not the exact number of the detected adenomas. This potentially results in the so-called 'one and done phenomenon', whereby the detection of one adenoma might diminish enthusiasm of the endoscopist to detect more.[28] It might therefore be relevant to combine the ADR with a quality indicator reporting on the total number of detected adenomas in the population, such as the mean number of adenomas detected per colonoscopy (MAP). However, the exact relevance of the MAP currently remains unknown, as this parameter has not yet been associated with the occurrence of PCCRCs.[28, 29]

An increasing body of evidence underlines that serrated polyps (SPs) also contribute in 15-20% to the development of CRC.[30-32] Additionally, indirect evidence suggest that a significant proportion of PCCRCs seems to arise from proximal located SPs. PCCRCs are likely to demonstrate a CpG island methylator phenotype (CIMP) status and microsatellite instability in accordance with SPs, which also frequently harbor these molecular characteristics.[16, 19, 33-35] Besides, the endoscopic characteristics of these premalignant polyps might also contribute to the development of PCCRCs, as their predominant proximal location, flat appearance and pale color presumably results in higher miss rates.[36, 37] Therefore the proximal serrated polyp detection rate (PSDPR) has been proposed as a quality indicator for colonoscopy.[38-41] However, the PSPDR is not an established quality indicator yet, as the association between the PSDPR and the occurrence of PCCRCs remains to be established.

Poor bowel preparation has been associated with more frequent incomplete colonoscopies, prolonged procedural time and a reduced colonoscopy yield.[42-45] Therefore, adequate bowel preparation is crucial to ensure safe intubation of the cecum and optimal mucosal inspection. Large prospective multicenter studies showed that the detection of polyps of any size was associated with the quality of the bowel preparation; especially the detection of smaller and flat polyps was impaired when bowel preparation was insufficient.[46, 47] Insufficient visualization of the mucosa therefore leads to an increased risk of missing premalignant polyps, which increases the risk for the later development of PCCRCs.[42]

It is self-evident that a complete colonoscopy, defined as the intubation and complete visualization of the cecum, is essential to detect all abnormalities. A key paper demonstrated that a significant number of right-sided CRCs occurred in patients who underwent a previous

incomplete colonoscopy.[4] Hereafter a subsequent study showed that the cecal intubation rate (CIR) was inversely correlated with the occurrence of PCCRCs, as higher PCCRC rates were found in endoscopists having a lower CIR, as well as having incomplete colonoscopies more frequently.[48]

These colonoscopy quality indicators related to detection of premalignant polyps were gradually developed as new evidence became available. Due to the increased awareness of the importance of high quality colonoscopy more and more evidence on colonoscopy quality indicators will become available in the upcoming years. In this regard it is of utmost importance to critically assess the added value of each newly proposed indicator, which should preferably be evidence-based and have an impact on clinical outcomes or quality of life.[49]

Colonoscopy and the resection of (large non-pedunculated and complex) colorectal polyps

Once a premalignant polyp is detected, it is usually resected, as it is known from literature that polypectomy reduces both incidence and mortality of CRC. Data from the National Polyp Study demonstrated that polypectomy of adenomas resulted in a 76-90% prevention of subsequent CRC, and a 53% reduction in CRC mortality.[2, 3] However, these studies also underline that polypectomy is not completely protective against the development of PCCRCs, which is in this regard might be caused by resections that were incomplete.[2, 3, 10, 21-23] Risk factors for an incomplete polypectomy are an increasing lesion size, flat morphology or polyps located at difficult anatomical locations, such as the ileocecal valve, appendiceal orifice, dentate line, involving a diverticulum, or within a segment of inflammation.[50] Also SPs are more difficult to be resected completely, as these lesions might be challenging to delineate.[51]

Besides the complete resection of all adenomatous or serrated polypoid tissue, it is also important to have all resected polyps examined for histopathology to exclude malignant submucosal invasive disease. Before embarking on endoscopic resection the lesion surface should be carefully inspected to assess the potential presence of deep submucosal invasive disease. Deep submucosal invasion is associated with a significant risk of lymph node metastases and therefore endoscopic resection of these lesions should be avoided.[52] Endoscopic risk factors for submucosal invasion are depressed morphology, mucosal friability, absence of a pit pattern (Kudo pit pattern type V or NICE classification type 3) on assessment with advanced imaging techniques, or the presence of nodules larger than 10 mm occurring in laterally spreading polyps.[50, 53-55] If the non-lifting sign is present in treatment-naive lesions, this feature could also be suggestive for submucosal invasion.[50, 53-55] Besides, the size of a polyp is directly related to the risk of submucosal invasive disease. Diminutive lesions harbor a very low risk of submucosal invasion, whereas small (6-9 mm) polyps have a slightly increased risk of 0% to 0.4%, which gradually increases to 2.4% for 10-20 mm lesions and to 19.4% for lesions with a diameter of 20 mm or more.[56, 57] However, a recent study by Burgess et al. showed that a substantial proportion of submucosal invasion might be covert, meaning that it is impossible to recognize the submucosal invasion during endoscopy in a subset of patients. Especially non-granular lesions with a combined Paris Classification (0-Is and 0-IIa+Is) located in the rectosigmoid were at risk to contain covert malignancy.[55]

Diminutive and small polyps comprise 70% to 90% of the detected lesions during colonoscopy and simple snare polypectomy is suitable to completely resect these polyps in an en bloc (single piece) fashion (*Figure 1)*.[58] The use of cold snare polypectomy instead of hot snare coagulation is increasingly performed, as it is associated with a reduced risk of post-polypectomy bleeding.[54] To enhance the safety of hot snare polypectomy, submucosal lifting might be used aiming to reduce the risk of deep thermal injury.[54] However, in large (≥ 20 mm) non-pedunculated polyps or in polyps located at difficult anatomical locations, simple snare polypectomy cannot be performed due to the increased risk of incomplete resection. These large non-pedunculated or complex polyps were therefore traditionally managed by surgical resection.[59, 60] However, over the past decade advanced endoscopic resection techniques, such as piecemeal endoscopic mucosal resection (pEMR) and endoscopic submucosal dissection (ESD), have progressed with great success and are now used in many endoscopy centers around the world.[61]

pEMR is the most commonly performed endoscopic resection technique for large non-pedunculated polyps in Western countries. For pEMR, the polyp is lifted preferably with a blue-colored viscous submucosal injectate, before the polyp is resected in a piecemeal fashion using hot snare coagulation.[54] It is an effective technique, requiring limited training.[54, 62] However, an important limitation of pEMR is the relatively high recurrence rate of around 16.0%, requiring surveillance colonoscopies and re-treatments.[54, 61, 63] However, recurrences after pEMR are usually unifocal, diminutive and benign, and can be managed endoscopically with high success rates.[64]

An alternative endoscopic resection technique is ESD, originally developed in Japan.[65] By using endoscopic knives for the dissection of the submucosal tissue, high en bloc resection rates can be achieved, resulting in low local recurrence rates.[65] An en bloc resection has the additional benefit of facilitating adequate histopathological evaluation of the specimen and if submucosal invasive disease is present the depth of invasion, other high risk features and the resection margins can adequately be assessed. However, ESD is technically demanding and has a relatively long learning curve.[65] When performed by unexperienced endoscopists, ESD is associated with high complication rates and prolonged procedural times.[54, 65] Due to differences in health-care systems, medical education and knowledge between Eastern and Western endoscopy centers, only a limited number of Western endoscopists have sufficient experience to perform colorectal ESD safely and effectively.[66-68] Therefore, in Western countries ESD only seems appropriate for colorectal polyps with a high endoscopic suspicion of superficial submucosal invasion.[65, 69, 70]

In order to avoid the disadvantages of ESD and increase the number of endoscopic en bloc resections of large non-pedunculated and complex colorectal polyps in the West, several advanced endoscopic resection techniques have been proposed and investigated. Transanal endoscopic microsurgery (TEM) can be performed for large non-pedunculated polyps that are located in the rectum.[71] This procedure is performed by a gastrointestinal surgeon using a dedicated TEM platform under general or spinal anesthesia, and facilitates en bloc polyp resection by either full-thickness or submucosal rectal wall excision.[72]

Another recent key development is the introduction of endoscopic full-thickness resection devices, which enable endoscopic full-thickness resections (eFTR) throughout the entire colon. One of these devices is the novel Full-Thickness Resection Device (FTRD, Ovesco Endoscopy, Tübingen,

Germany). It allows definite diagnosis and treatment with immediate secure defect closure of non-lifting polyps, polyps located at difficult anatomic locations, early colorectal cancer and submucosal tumors with a maximum diameter of 20 mm. The device and associated eFTR technique showed a reasonable technical efficacy in the first prospective multicenter studies performed in Germany.[73,74] However, before the FTRD can be routinely applied as a minimally invasive alternative to surgical resection, further larger multicenter studies involving safety and long-term follow-up data are warranted.

As colorectal surgery is associated with significant morbidity and mortality rates, prevention of surgical resection could be considered as one of the primary aims of the performance of advanced endoscopic resection attempts with pEMR, ESD, TEM or eFTR.[62] As more and more knowledge on the performance, including effectivity and safety, of these advanced techniques becomes available, it seems plausible that colonoscopy can safely replace surgery for most patients with large non-pedunculated or complex colorectal polyps.

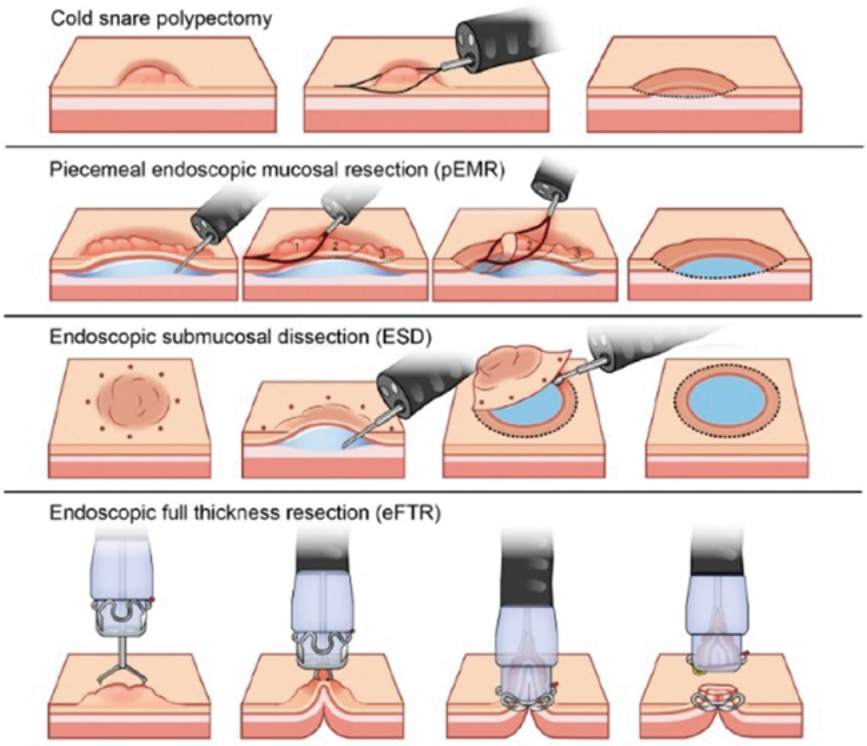


Figure 1. Different polypectomy techniques. Figure 1 is adapted from Dekker et al.[49]

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OUTLINE OF THIS THESIS

The content of this thesis focuses on a wide range of colonoscopy-related issues and is divided in two parts. The first part focuses on quality assurance of colonoscopy, the impact of colonoscopy quality indicators, as well as the improvement of the endoscopic detection of premalignant colorectal polyps. The second part focuses on the endoscopic risk factors of unexpected submucosal invasion present in large rectal polyps, as well as surgical and endoscopic resections for the treatment of large non-pedunculated and complex colorectal polyps.

Part I – Quality of colonoscopy and the detection of colorectal polyps

In the Netherlands, a nationwide screening program for CRC was gradually implemented in 2014. From 2019 onwards, all individuals aged 55-75 will be invited for biennial fecal immunochemical test (FIT)-based screening. Participants with a positive FIT (positivity cut off ≥ 275 ng/ml, FOB gold, Sentinel, Milan, Italy) are subsequently invited to undergo colonoscopy.[75] As high quality of colonoscopy is essential to assure the effectiveness of the screening program, quality requirements were set for endoscopists performing colonoscopies within the Dutch Bowel Cancer Screening Program (BCSP). In **chapter 2** we describe this quality assurance process, including a detailed description of the evidence-based quality indicators that were applied for endoscopist accreditation in the Dutch BCSP.

Both ADR and PSPDR vary between endoscopists.[26, 27, 37, 38, 41, 76-80] Nonetheless, little is known about the long-term effect of variations in ADR and PSPDR on the effectiveness of a nationwide screening program using FIT as a triage modality. Therefore, in **chapter 3** we evaluate the effect of variations in ADR and PSPDR on the long-term CRC incidence and mortality reduction of the Dutch BCSP by using the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) microsimulation model.

Variations in ADR and PSPDR may suggest considerable lesion miss rates of low detecting endoscopists. As endoscopists with a high ADR and PSPDR are able to detect adenomas and proximal SPs more frequently, it can be hypothesized that this is caused by a better recognition of the endoscopic features of these polyps resulting in improved detection. If this correlation is present, it may implicate that by improving the accuracy of optical diagnosis, also the detection of premalignant polyps could increase. Training programs aiming to increase the optical diagnosis are shown to be successful, so improving the optical diagnosis by training might also increase the polyp detection rates as a secondary training benefit.[81] However, little is known about the association between these endoscopy skills and therefore in **chapter 4** we evaluate the correlation between the ADR, PSPDR and the accuracy of optical diagnosis of adenomas and SPs.

From tandem colonoscopy studies, it is known that colonoscopy has a substantial adenoma miss rate (20-26%), which is an important reason for PCCRCs.[6, 18] To improve colonic surface visualisation and thereby aiming to increase ADR, several surface exposing technologies have been developed.[82] Recently the Extra Wide Angle View (EWAVE) colonoscope was developed, which offers a 235° view obtained from a forward-viewing as well as two lateral backward-viewing lenses incorporated into one image. In **chapter 5** we describe a prospective multicentre cohort study assessing the feasibility, safety and diagnostic yield of the EWAVE colonoscope for the detection of colorectal adenomas.

Part II – Resection of large non-pedunculated and complex colorectal polyps

Large non-pedunculated colorectal polyps may demonstrate endoscopic risk factors of submucosal invasion, such as depressed morphology, mucosal friability, the lack of a pit pattern as seen with Kudo pit pattern type V or NICE classification type 3, the presence of nodules larger than 10 mm occurring in laterally spreading polyps or the non-lifting sign present in treatment-naive lesions.[50, 53-55] Despite the endoscopic assessment for the presence of these risk factors in large non-pedunculated colorectal polyps, unexpected cancers are incidentally diagnosed after local endoscopic resection.[53, 83-85] However, little is known about the endoscopic and procedural characteristics of these unexpected cancers occurring in the rectum. Therefore, we compare the endoscopic and procedural characteristics between unexpected rectal cancers and histologically proven rectal adenomas in **chapter 6**.

Traditionally large non-pedunculated colorectal polyps were managed by surgical resection.[59, 60] Although over the past decade endoscopic resection techniques have developed significantly, it remains largely unknown to what extent endoscopic resection has replaced surgical resection of large non-pedunculated colorectal polyps. In **chapter 7** we assess the total volume of colorectal surgery for benign colorectal polyps and the absolute and relative volume changes of this type of surgery over the past decade in the Netherlands.

Replacing surgical resection by endoscopic resection is likely to reduce surgical morbidity, mortality and costs.[50, 60, 61, 86-90] When considering endoscopic removal or surgical resection, knowledge about the risks and benefits of both procedures is essential. Therefore, in **chapter 8** we perform a systematic review to give a comprehensive overview of the literature on post-operative outcomes (morbidity and mortality) of colon surgery for benign colorectal polyps.

Finally, complex colorectal polyps also consist of polyps located at the appendiceal orifice, which are difficult to resect with conventional polypectomy techniques, including pEMR.[50] The FTRD has been developed to perform eFTR with immediate secure defect closure.[73, 74] In **chapter 9** we describe the feasibility, technical success and safety of eFTR procedures with the FTRD for complex colonic polyps involving the appendiceal orifice.

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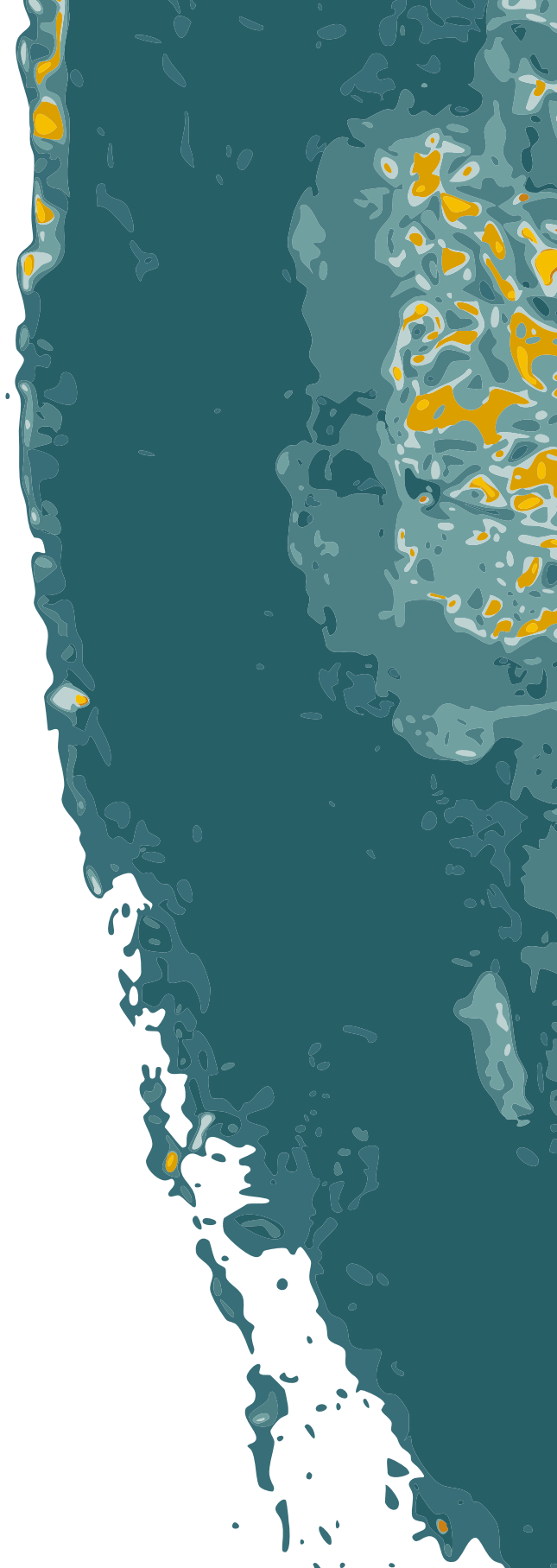

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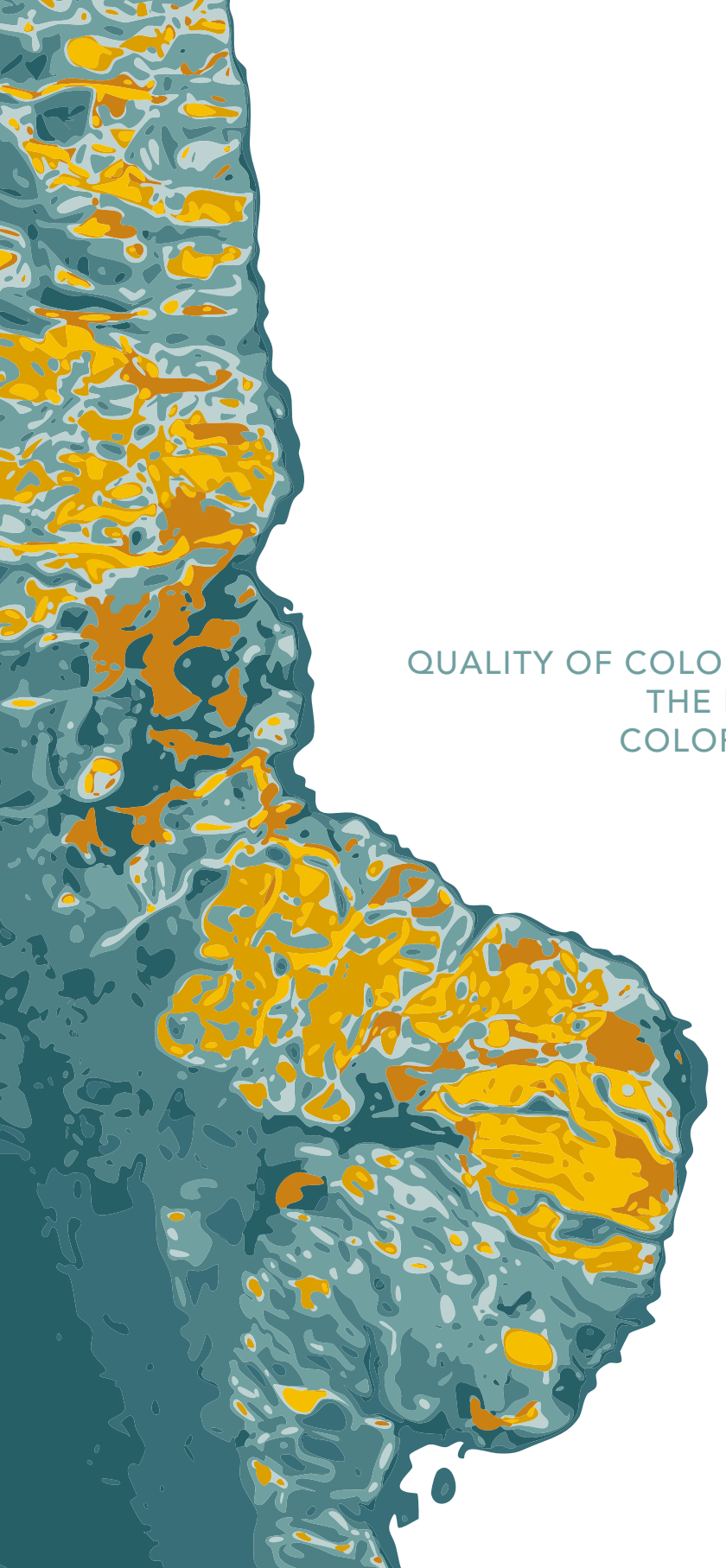

QUALITY OF COLONOSCOPY AND THE DETECTION OF COLORECTAL POLYPS

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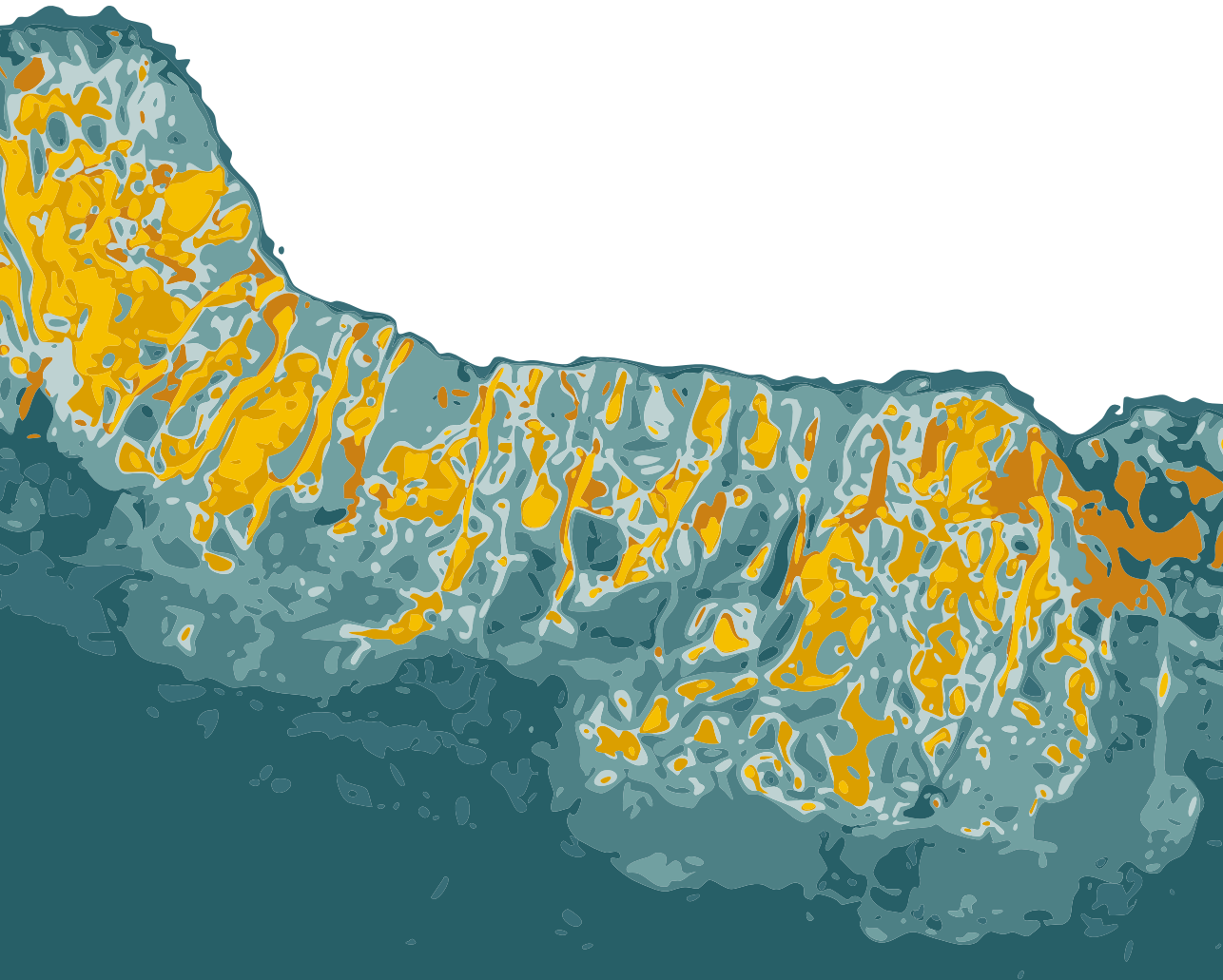

QUALITY ASSURANCE OF COLONOSCOPY WITHIN THE DUTCH NATIONAL COLORECTAL CANCER SCREENING PROGRAM

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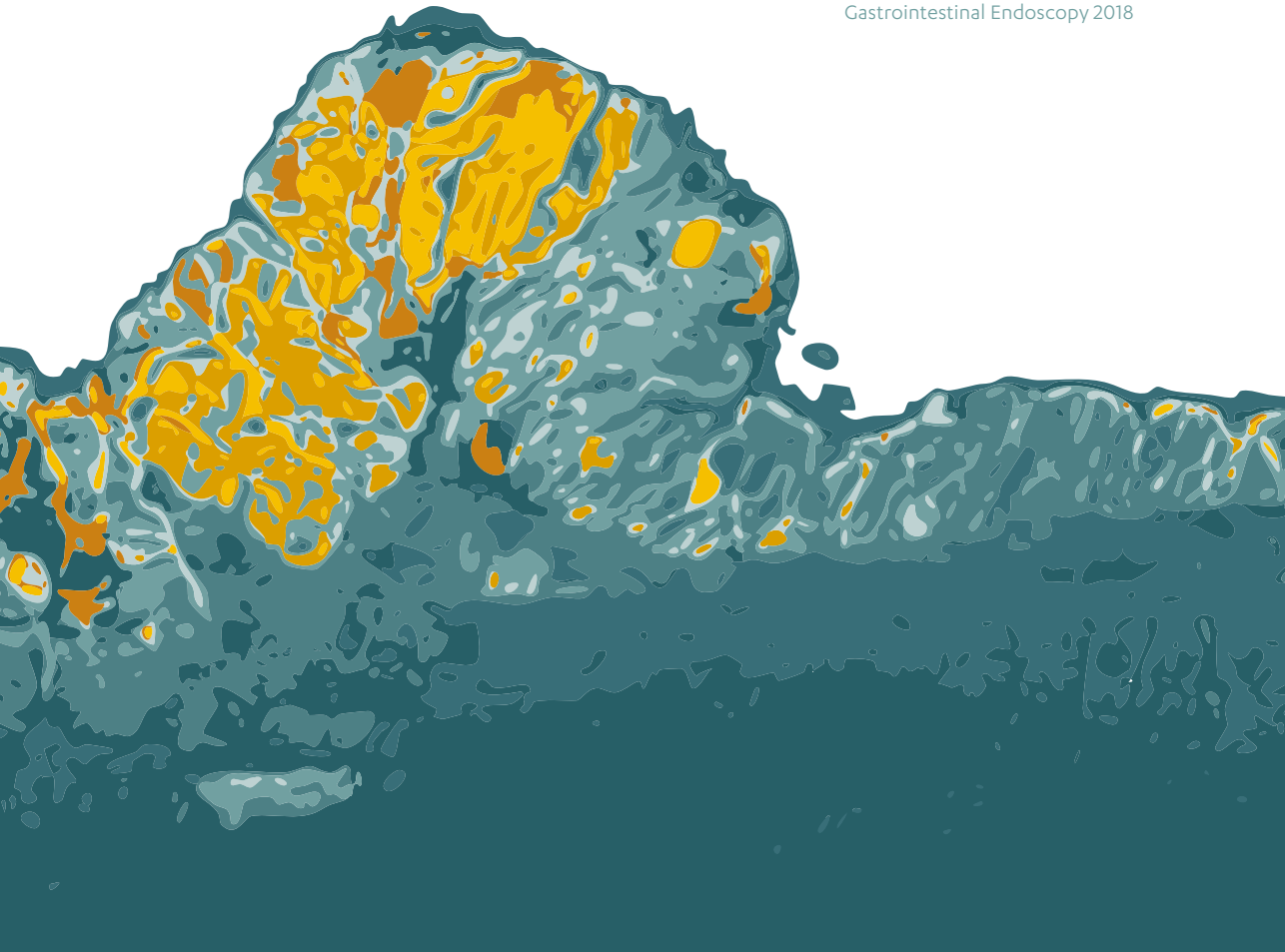
on behalf of the Dutch Colonoscopy Quality Assurance working group

Gastrointestinal Endoscopy 2018



ABSTRACT

Colorectal cancer (CRC) screening is capable of reducing CRC-related morbidity and mortality. Colonoscopy is the reference standard to detect CRC, also providing the opportunity to detect and resect its precursor lesions; colorectal polyps. Therefore colonoscopy is either used as a primary screening tool or as a subsequent procedure after a positive triage test in screening programs based on non-invasive stool testing or sigmoidoscopy. However, in both settings, colonoscopy is not fully protective for the occurrence of post-colonoscopy CRCs (PCCRCs). As the majority of PCCRCs are the result of colonoscopy related factors, a high-quality procedure is of paramount importance to assure optimal effectiveness of CRC screening programs. For this reason, at the start of the Dutch fecal immunochemical test (FIT)-based screening program, quality criteria for endoscopists performing colonoscopies in FIT-positive screenees, as well as for endoscopy centers, were defined. In conjunction, an accreditation and auditing system was designed and implemented. In this report we describe the quality assurance process for endoscopists participating in the Dutch national CRC Screening Program, including a detailed description of the evidence-based quality criteria.

INTRODUCTION AND RATIONALE

Colorectal cancer (CRC) is one of the most frequently diagnosed cancers in the Western world.[1] CRC-related mortality can be reduced by detecting cancers at an early stage as well as by preventing its development by detecting and resecting colorectal adenomas, the most important CRC precursor lesions.[2, 3] The progression from neoplastic polyps, such as adenomas to CRC is very slow (estimated 10-15 years) leaving a long window of opportunity for timely detection and removal. These specific issues make CRC a suitable target for population-based screening.[4]

CRC screening programs can be primary colonoscopy screening programs, in which all participants undergo a screening colonoscopy or can be based on other modalities such as a non-invasive stool test or sigmoidoscopy, which are followed up by colonoscopy in case of a positive test.[5] After a period of careful piloting, the Dutch ministry of Health decided to implement a nationwide screening program based on fecal immunochemical testing (FIT). In pilot-studies, FIT appeared the most accepted screening modality in the Netherlands and outperformed other screening modalities in the detection of CRC per 1000 invitees.[6-10] Gradual implementation of this program is taking place since 2014. From 2019 onwards, all individuals aged 55-75 years will be invited for biennial FIT-screening. Through information leaflets and information provided on the website of the Dutch CRCSP invitees are requested not to participate in FIT screening when they are currently undergoing CRC-related treatments. In addition invitees are advised to discuss participation with their general physician or gastroenterologist if they are experiencing potential relevant GI-symptoms, when being diagnosed with a gastroenterological disease or when they underwent colonoscopy in the preceding 5 years. Only invitees with a positive FIT-result will receive an invitation for a consultation to discuss and schedule a colonoscopy. Reasons not to schedule a colonoscopy during this consultation are a life expectancy of less than five years, screenees who are not willing to undergo colonoscopy or who underwent a proctocolectomy.[11]

Although colonoscopy is the reference standard for the detection of CRC, as well as for detecting and resecting premalignant colorectal polyps, it is not fully protective for the development of post-colonoscopy CRCs (PCCRCs).[2, 3, 12-16] PCCRC rates have been reported between 1 in 130 to 1 in 1000 colonoscopies and comprise between 2% and 8% of all CRCs diagnosed in a population.[17-23] The majority of PCCRCs are the result of colonoscopy-related factors, such as cancers and neoplastic polyps that were missed or recurred after incomplete removal.[12-15, 24] Therefore, to assure the effectiveness of all CRC screening programs, high quality of the colonoscopy procedure is crucial.

Right at the start of the Dutch national Colorectal Cancer Screening Program (CRCSP), quality requirements were set for all stakeholders participating within the Dutch CRCSP such as the laboratories analyzing the FITs, pathology laboratories and also the endoscopy centers and endoscopists performing colonoscopies in FIT-positives. For quality assurance, an accreditation and auditing system was designed and implemented. The design of this quality assurance process for endoscopists was partly based on the Quality Assurance Guidelines for Colonoscopy of the British NHS Bowel Cancer Screening Programme, but we aimed to simplify the different steps in the process.[25]

The aim of this report is to describe the design of the quality assurance process, including a description of the evidence-based quality criteria for endoscopists participating in the Dutch CRCSP. We believe that our experience could serve as an example for quality assurance for colonoscopy services.

DESIGN OF THE QUALITY ASSURANCE PROCESS FOR ENDOSCOPISTS

The first version of the quality assurance process, which included an accreditation program as well as a monitoring plan for endoscopists, was drawn in 2012. Criteria for accreditation and auditing were chosen based on current knowledge and literature. At that time, we were only aware of one other international quality assurance program for screening colonoscopies. The UK had designed the Quality Assurance Guidelines for Colonoscopy for the British NHS Bowel Cancer Screening Programme.[25] Implementation of these British Quality Assurance Guidelines for Colonoscopies resulted in significant improvements of the quality of the colonoscopies performed, as an audit in 2012 demonstrated an increase in the cecal intubation rate of 39% (from 56% to 95%) compared to 2004.[26, 27] This British guideline has served as a basis for the Dutch quality assurance process, but we aimed to simplify the different steps in the process.

The Dutch protocol was written under authority of the National Institute for Public Health and Environment (RIVM), advised by the National Committee for implementation of the national CRCSP and the members of the "Working group for quality requirements of colonoscopy" (*Figure 1*).[28] The working group advised about the design of the program and quality criteria, which were supported by published evidence and were used for accreditation as well as quality assurance of colonoscopies performed within the Dutch CRCSP. Selection of quality criteria was predominantly based on the available evidence in the literature, both to increase support and understanding from the endoscopy community, as well as to create the opportunity to readily adjust the selected quality criteria when new data would become available. Since the implementation of the quality assurance process, quality criteria and target numbers were regularly updated. This report describes the currently used quality criteria and target numbers for endoscopists.[29]

Endoscopist accreditation program

Within the Netherlands, five regional screening organizations are responsible for the implementation and execution of the CRCSP, including accreditation of endoscopists within the program. The accreditation program is led by a group of three to five assessors, whom are gastroenterologists trained and appointed for this task by the screening organization (Test Coordinating Gastroenterologists (TCG)). All endoscopists intending to perform colonoscopies within the Dutch CRCSP can apply for accreditation, and only accredited endoscopists are allowed to perform colonoscopies within the context of the national screening program. Endoscopists are registered in the Dutch Registry of Medical Specialists as a gastroenterologist, internist or surgeon and have a life-time experience of at least 500 colonoscopies, of which at least 200 colonoscopies and 50 polypectomies have been performed in the year prior to the start of the accreditation program. Senior fellows in their final year of residency fulfilling these criteria can also apply.

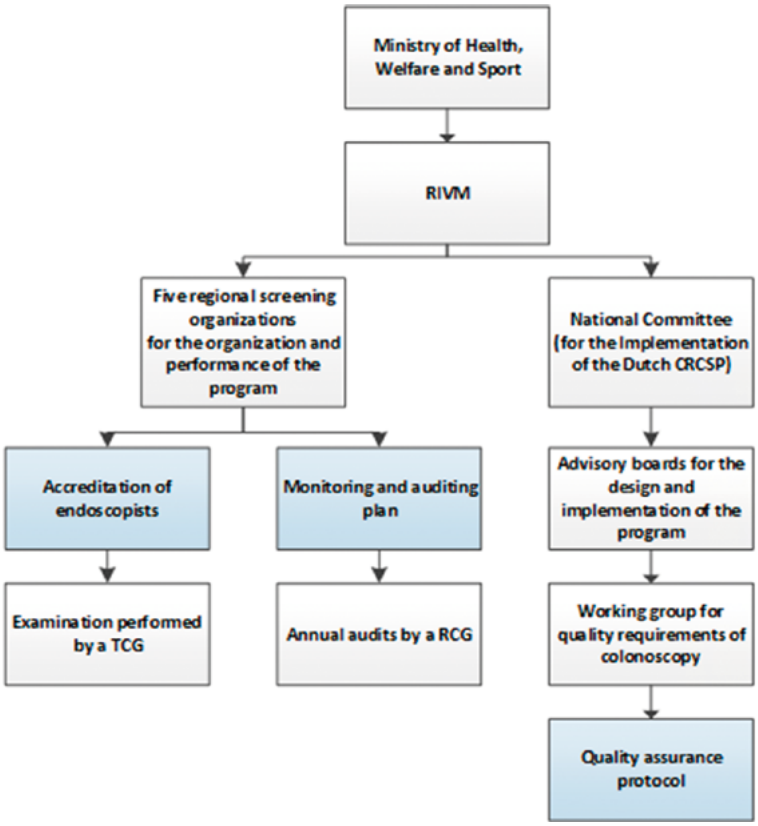


Figure 1. Organizational structure of the quality assurance program of the Dutch CRCSP. RIVM: the National Institute for Public Health and the Environment; TCG: Test Coordinating Gastroenterologist; RCG: Regional Coordination Gastroenterologist.

The endoscopist accreditation program consists of three modules: 1) a colonoscopy registration module, 2) a theoretical e-learning module combined with online assessment of the acquired knowledge, and 3) a practical evaluation of colonoscopy and polypectomy skills (details in *Figure 2*).[30]

For the first module, endoscopists submit quality data of their last 100 consecutive colonoscopies to the website of the regional screening organization. The quality of those 100 colonoscopies, performed in their own practice, is evaluated by a TCG. The predefined criteria for this assessment are described in further detail below.

The e-learning program consists of substantive information about the Dutch CRCSP, epidemiology of CRC, polyp characteristics, colonoscope handling, sedation practice, management of anticoagulants during colonoscopy, surveillance strategies and hereditary and familial CRC syndromes. At the end, in a final online test at least 80% of the questions should be answered correctly. The average duration of this e-learning program is five hours.

After having passed the first two modules, endoscopists are invited for the practical evaluation module. In this module the endoscopist performs two live colonoscopies and uploads three

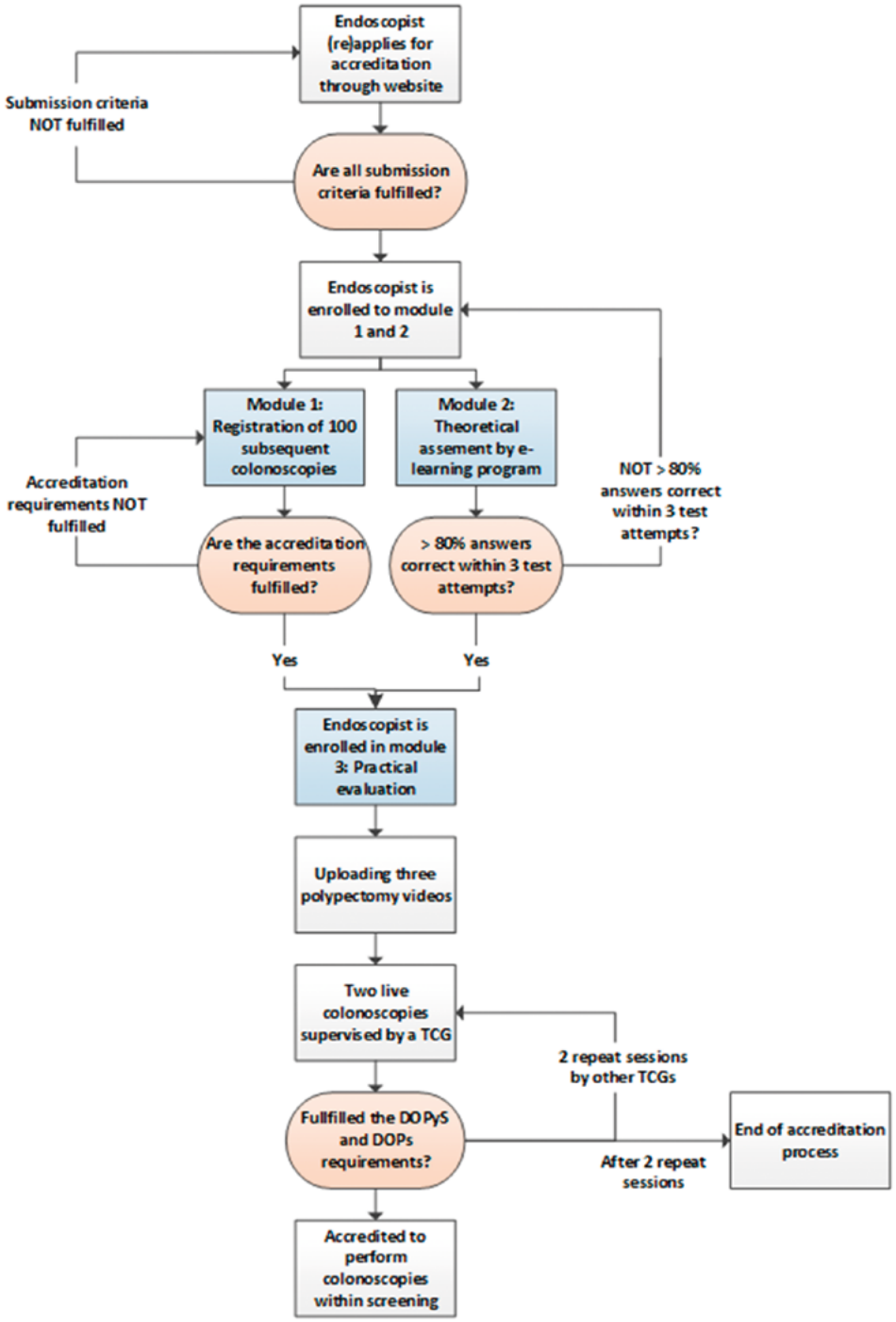


Figure 2. Subsequent steps in the accreditation process for endoscopists. TCG: Test Coordinating Gastroenterologist; DOPyS: Direct Observation of Polypctomy Skills (DOPyS); DOPs: Direct Observation of Procedure or Skills (DOPS)

polypectomy videos and the accompanying endoscopy reports, which are all evaluated by a TCG. The videos should contain endoscopic polyp assessment and procedures of polypectomy and retrieval of a pedunculated polyp of 10-20 mm, endoscopic mucosal resection of a sessile polyp of 10-20 mm and a cold snare polypectomy. The practical skills of the live colonoscopies and the polypectomy videos are assessed according to slightly adjusted version of the validated Direct Observation of Procedure or Skills (DOPS) and Direct Observation of Polypectomy Skills (DOPyS), both developed in the UK.[31] In this slightly adjusted version of the DOPS fourteen domains, such as communication skills with the patient and endoscopy personnel, adequate provision of sedatives and evaluation of patient comfort during the procedure, adequate recognition of cecal landmarks, appropriate mucosal visualization, adequate identification and treatment of detected lesions and endoscopic complications, are considered of major importance. In addition seven other domains, e.g. the performance of positional changes during colonoscopy, adequate use of insufflation and lens cleaning are considered of minor importance. Endoscopists have passed the practical evaluation module if all domains of major importance were rated as 'the used approach exemplifies great endoscopic skills' or 'a competent and safe approach was used, wherein all endoscopic errors were corrected' by the TCG and if none of the domains of minor importance were rated as 'the approach does not satisfy current colonoscopy standards, wherein none of the endoscopic errors was corrected'. After the performance of the live colonoscopies, all endoscopists will receive oral and written feedback from the TCG considering their practical endoscopy skills. If the practical skills of the endoscopist were considered insufficient, two repeat live colonoscopy sessions and polypectomy videos, assessed by another TCG, can be attempted. When the practical skills during these subsequent colonoscopy sessions are also considered insufficient, the endoscopist is advised to acquire additional training and experience. If he or she wishes, the accreditation process can be initiated again.

Number of accredited endoscopists

Between January 2014 and January 2018, a total of 389 endoscopists have been accredited to perform colonoscopies within the Dutch CRCSP. This group comprised of 346 gastroenterologists, 42 internists and 1 surgeon. In January 2018, a total of 527 gastroenterologists were registered in the Netherlands, resulting in a 65.7% (346/527) accreditation-rate. This is a considerably higher coverage than in the British NHS Bowel Cancer Screening Programme, where the rate is approximately 10-20% (Matt Rutter, personal communication).

Detailed information regarding the success-rate of the accreditation program was only available from September 2015 until January 2018. In this period, 93 endoscopists started the accreditation process of which 83 endoscopists (89.2%) were accredited. For 7 endoscopists, the quality of the registered colonoscopies was insufficient. The remaining 86 endoscopists all successfully completed the e-learning module. In the third module, the practical endoscopy skills of 3 of those 86 endoscopists were considered insufficient during two live endoscopy attempts. After this decision, these 3 endoscopists decided to end their accreditation process.

Quality assurance monitoring plan

To assess and ensure the quality of colonoscopies performed within the Dutch CRCSP, a cyclic monitoring plan was developed aiming to support continuous quality improvement. In the Netherlands, daily gastroenterology practice is regularly audited by the Dutch Society of Gastroenterology and Hepatology. In addition to this, a specific annual audit for the Dutch CRCSP is performed by the Regional Coordinating Gastroenterologists (RCGs). During this CRCSP audit, all aspects of the screening process performed by endoscopists and the endoscopy center as a whole are monitored and benchmarked, followed by a discussion on possibilities for quality improvement. These audits might result in a revision of the quality criteria and target numbers.

To facilitate real-time quality assurance and monitoring of the CRC program, a national central database system (ScreenIT, Topicus, Deventer, The Netherlands) was developed.[11] By using the central ScreenIT database the screening process is automatically structured and information from different sources such as personal data from the Municipal Personal Records database, colonoscopy results, and pathology results of the Dutch Pathological Anatomy National Automated Archive (PALGA-database) are integrated (details *Figure 3*).[11, 32] All data within the central ScreenIT database is directly derived from its original data source by automated data connections. Hereby only the original data, as it is registered within the original data source (the Municipal Personal Records database, the colonoscopy reporting program and the PALGA-database), is incorporated in the central database. All the required data within the original data sources is registered systematically and uniformly in order to guarantee the correctness of all incorporated information and to facilitate the automated data connection to the central database. Both the direct automated data connections and the systematic and uniform data entry automatically secure the data integrity of the central database, most importantly because hereby double data entry is avoided, which potentially could result in data-entry mistakes.

In addition to its data integration function, ScreenIT plays an essential role in the automatic delivery of the quality data of all colonoscopies performed within the Dutch CRCSP. It facilitates regular production of standard analyses and reports of all quality criteria for quality assurance, monitoring and benchmarking.[33] These quality data can be analyzed at the level of the individual endoscopist, the endoscopy unit and the Dutch CRCSP as a whole. These automated colonoscopy quality rapports are used during the annual CRCSP audits of the endoscopy centers and endoscopists participating within the Dutch CRCSP.

During the annual CRCSP audit the RCG visits the endoscopy center to discuss the quality of the colonoscopies performed in the preceding year and to discuss the possibilities for quality improvement of the endoscopy center as a whole and of the individual participating endoscopists. Before the actual audit visit, colonoscopy quality reports of the entire endoscopy unit as well as individual endoscopists are automatically generated from the central ScreenIT database by the RCG. These colonoscopy quality reports are provided by email to the endoscopy center before the actual audit visit. At the same time, also the quality criteria of the preceding year and the cumulative data of all quality criteria are provided. All endoscopists participating in that center will receive written feedback on their own colonoscopy quality criteria, comparison with the quality criteria of their

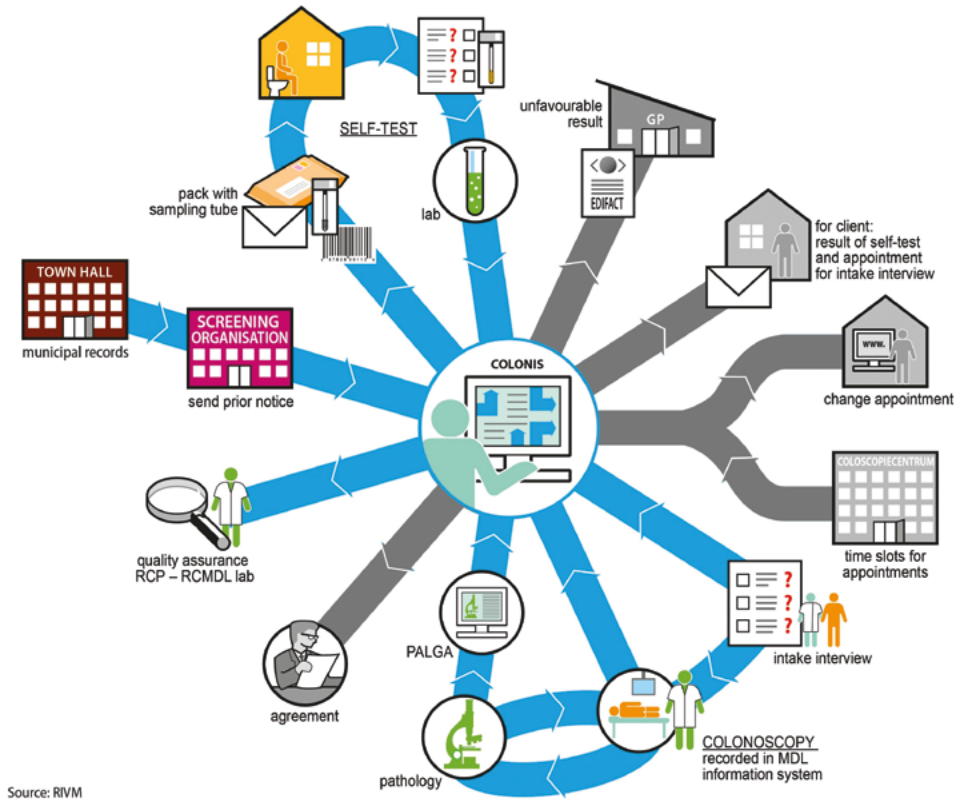


Figure 3. Incorporation of ScreenIT within the Dutch CRCSP[11]

colleagues working in the same endoscopy center and of the colonoscopy center as a whole in comparison with the quality criteria of the entire Dutch CRCSP.

If the parameters of an endoscopist do not meet the audit quality criteria, which are described in further detail below, this will be discussed during the CRCSP audit visit by the RCG. The endoscopist has three to six months after this visit, depending on the severity of the deviation and the importance of the quality indicator, to improve. When the quality criteria at stake have not improved over that period, the endoscopist will be excluded from further participation in the Dutch CRCSP. If the endoscopist wishes, he/she can restart the accreditation process after at least one year of additional training and learning.

QUALITY CRITERIA FOR ENDOSCOPISTS

The pre-defined quality criteria for endoscopists performing colonoscopies within the Dutch CRCSP are used during the accreditation as well as the monitoring process. Most criteria are quantitative and can therefore be calculated directly from data entered in the endoscopy reports. However, these data can only be used if colonoscopy reports include all key quality criteria and its registration is performed systematically and uniformly.[34] One such an example of a completely

structured colonoscopy reporting system was already available, i.e. EndoALPHA.[33] To acquire this aim, a minimal data-set was described. Representatives of all endoscopy-reporting systems were provided with this data-set and had the option to adjust their system to facilitate automatic delivery of the data of the standardized endoscopy report to the ScreenIT-database.

An overview of all currently used quality criteria is provided in *Table 1*. The evidence-based quality criteria are described in further detail below.

Table 1. Overview of all quality criteria for endoscopists performing colonoscopy within the Dutch CRCSP, defined by the national "Working group for quality requirements of colonoscopy"[28, 29]

Quality criteria	Description	Accreditation criterion	Audit criterion
Qualifications and experience			
Professional registration	Endoscopists are responsible for professional and re-registration according to the Individual Health Care Occupations Act	Demonstrable	Demonstrable
Accreditation	Accreditation based on the final attainment levels for an endoscopists according to the Dutch society of Gastroenterologists (NVMDL)	Demonstrable	Demonstrable
Number of colonoscopies	Total number of colonoscopies performed	≥ 500 lifetime	≥ 200 per year
Number of polypectomies	Number of polypectomies performed	≥ 50 lifetime	≥ 50 per year
Completeness of exam			
(Unadjusted) cecal intubation rate	The percentage of colonoscopies with cecal intubation	≥ 90% (unadjusted)	≥ 95% (unadjusted)
Bowel preparation	The percentage of colonoscopies in which the colon is sufficiently clean to inspect the mucosa (BBPS ≥ 6)	-	≥ 90%
Withdrawal time	The percentage of negative colonoscopies* with a withdrawal time of at least 6 minutes	-	≥ 90%
Detection rates			
Cancer detection rate	The percentage of colonoscopies in which (more than) one cancer is detected	-	Monitoring
Adenoma detection rate	The percentage of colonoscopies in which (more than) one adenoma is detected	≥ 20%	≥ 30%
MAP	The mean number of adenomas per procedure (colonoscopy)	-	Monitoring
MAP +	The mean number of adenomas per positive procedure (colonoscopy)	-	Monitoring

Table 1. (continued)

Quality criteria	Description	Accreditation criterion	Audit criterion
Removal rates			
Polyp removal rate	The percentage of polyps removed relative to the total number of polyps detected at colonoscopy	≥ 90%	≥ 90%
Polyp retrieval rate	The percentage of polyps retrieved for histological evaluation relative to the total number of polyps detected at colonoscopy	Monitoring	≥ 90%
Tattooing			
Tattooing	The percentage of cancers that were tattooed, except from those cancers located in the cecum and up to 4 cm from the dentate line	-	Monitoring
Wellbeing of patients			
Complication record	Keeping a complete complication record	Demonstrable	Demonstrable
Complications during colonoscopy	The percentage of colonoscopies in which a complication occurred (up to 30 days after the procedure)	-	Monitoring
Perforation rate colonoscopy	The perforation rate of all colonoscopies (up to 30 days after the procedure)	-	Monitoring
Perforation rate polypectomy	The perforation rate for colonoscopies with polypectomy (up to 30 days after the procedure)		Monitoring
Polypectomy bleeding	The rate of bleeding for colonoscopies with polypectomy (up to 30 days after the procedure)	-	Monitoring
Patient satisfaction			
Comfort Score	The percentage of colonoscopies in which the patient experiences moderate or severe discomfort (according to the GCS)	-	Monitoring

* Negative colonoscopies are colonoscopies in which no colorectal polyps or CRC has been detected.

Qualifications and colonoscopy experience

Competency of colonoscopy may be affected by a learning curve, ongoing number of procedures performed and lifetime colonoscopy experience.[35] The occurrence of adverse events is also dependent on the experience of the endoscopist, as three population-based studies from the USA and Canada demonstrated that colonoscopy-related perforations and bleedings significantly increased if endoscopists performed less than 200 to 300 colonoscopies on an annual basis.[36-38] In conjunction, we decided to set the bar at a minimum life-time experience of 500 colonoscopies, of which at least 200 colonoscopies and 50 polypectomies should be performed in the year prior

to the start of the accreditation program, as well as on an annual basis after accreditation for the Dutch CRCSP.

2

Completeness of the colonoscopy

It is self-evident that completeness of colonoscopy is essential to detect all lesions. A complete inspection of the colon, described as the cecal intubation rate (CIR), is furthermore inversely correlated with the occurrence of PCCRCs, as higher PCCRC rates were found in endoscopists having a lower CIR and having incomplete colonoscopies more frequently.[13, 39] The CIR can be presented in a non-adjusted form based upon the CIR in all patients where the intention was to reach the cecum, and can also be adjusted for factors such as impassable strictures, poor bowel preparation or severe colitis.[40] Since adjusted CIRs are open to gaming and diverse interpretation, it was advised to use the unadjusted CIR for the Dutch CRCSP.[41] During the accreditation program, endoscopists should reach an unadjusted CIR of at least 90%. Visualization of the ileocecal valve, ileal mucosa and appendiceal orifice should be confirmed and photo-documented by at least two endoscopic images of these cecal landmarks. Both the CIR cut-off and the necessity of photo-documentation are in accordance with the European CRC screening guideline.[40, 41]

Adequate bowel preparation

To ensure safe intubation of the cecum and optimize mucosal inspection for lesion detection, adequate bowel preparation is essential. Poor bowel preparation has been associated with incomplete colonoscopies, prolonged procedural time and reduced colonoscopy yield.[42-45] The insufficient visualization of the mucosa can lead to missed neoplastic polyps, which therefore contributes to an increased risk of PCCRCs.[42] An abundant body of evidence showed that an adequately clean colon assessed was associated with increased adenoma and serrated polyp detection.[42, 46-52]

Different scoring systems for bowel preparation exist, however no direct comparisons of performance between the bowel preparation scales are present.[35, 41] The thoroughly validated Boston Bowel Preparation Scale (BBPS) is the most widely used scoring system.[49, 51, 53] Therefore for the Dutch CRCSP, the BBPS is used and because there are no significant differences between moderate, good and excellent bowel preparation in terms of adenoma detection, a BBPS of 6 or higher in at least 90% of colonoscopies is required.[46, 47, 50, 52, 54]

The type and timing of a specific bowel cleansing agent are important contributors to the quality of the bowel preparation.[55] Polyethylene glycol (PEG) split dose bowel preparations are recommended by the European Society of Gastrointestinal Endoscopy (ESGE) as the preferred bowel preparation regimen and therefore these regimens might also be the most commonly used in the Netherlands.[55] However, no specific requirements for any specific bowel preparation solution or regimen were set for the Dutch CRCSP; endoscopists were advised to select their preferred agent and regimen based on their local experience.

Colonoscope withdrawal time

Colonoscope withdrawal time can be used as a surrogate measure for the time taken to carefully inspect the colorectal mucosa to detect all lesions. Endoscopists having a withdrawal time of at

least 6 minutes for negative colonoscopies were shown to have a higher detection rate of neoplasia, with a significant difference for detection of advanced neoplasia compared to endoscopists with a shorter withdrawal time.[56] During the quality assurance program for the Dutch CRCSP, colonoscope withdrawal time should be at least 6 minutes in at least 90% of negative colonoscopies. However, the association between adenoma detection and withdrawal time is complex, since both are influenced by technique. Additional time taken to withdraw the colonoscope could for example also be used to fully clean the colon, to suction pools of liquid and carefully inspect all folds and flexures.[57] It seems likely that the cleaning effort and technique of withdrawal are of more importance than solely the duration of the colonoscope withdrawal. Therefore the withdrawal time should preferably be linked to the detection of neoplastic polyps, as a short withdrawal time accompanied with a low polyp or adenoma detection could be suggestive for an inadequate colonoscopy technique.[35, 58]

Adenoma detection rate and the mean number of adenomas detected per (positive) colonoscopy

The adenoma detection rate (ADR) is the most widely accepted and implemented quality indicator of colonoscopy, as it has been inversely correlated to PCCRC incidence and CRC mortality in two landmark papers.[59, 60] Both studies resulted in the use of ADR benchmarks of at least 20% within CRC screening programs endorsed by European and American CRC screening guidelines.[40, 59-62] These well-established ADR benchmarks of 20% are solely based on cohorts that underwent primary screening colonoscopy. It is of importance to realize that both the colonoscopy indication, as well as patient factors such as age and gender, have an important impact on ADR. All these factors are known to correlate with the adenoma prevalence among the investigated population.[63-65] However, ADRs for specific colonoscopy indications or patient populations currently remain unknown, since in each specific group the relationship with PCCRCs and CRC mortality have to be established. Therefore it was decided to stay conservative with the determination of ADR benchmarks for the Dutch CRCSP and to use the ADR threshold of 20% until evidence regarding indication and patient population specific ADR benchmarks becomes available.

During the accreditation process, ADRs of the accrediting endoscopist are calculated based on 100 colonoscopies submitted through the colonoscopy registration module. Due to daily practice, these 100 colonoscopies might be very heterogeneous in terms of colonoscopy indications and patient characteristics. They usually comprise, e.g. surveillance colonoscopies, colonoscopies performed in symptomatic patients, patients diagnosed with IBD and patients with a positive family history for CRC. Besides, the colonoscopies of the Dutch CRCSP are all performed after a positive FIT, therefore enriched for adenomas and thus ADR should be significantly higher than that in primary colonoscopy screening.[66, 67] Establishing ADR benchmarks in a FIT-positive population is additionally challenged by the fact that the prevalence of adenomas in FIT-positive patients is also affected by the screening history of the participants and, if screened by FIT, the used cut-off of FIT.[66] With the data gathered during the course of the screening program we aim to determine optimal ADR accreditation and audit benchmarks for the Dutch CRCSP.

The ADR can be considered imprecise as the detection of one adenoma might diminish enthusiasm to detect more, also referred to as the 'one and done phenomenon'.[68] Ideally, reporting

of the ADR is combined with a quality indicator reporting on the total number of detected adenomas in the population, such as the mean number of adenomas per colonoscopy (MAP) and the mean number of adenomas per positive colonoscopy (MAP+).[26, 68] In the guaiac-based British NHS Bowel Cancer Screening Programme it was shown that these measures might be a better representation of the performance of an individual endoscopist in detecting adenomas, however a clear correlation with PCCRC rates remains to be established.[26] This is the reason why the MAP and MAP+ were not yet a prerequisite during the accreditation program of the Dutch CRCSP, but both indicators will be monitored during the course of the screening program in order to define accreditation and audit benchmarks in the future.

Polyp removal and retrieval rates

Data from the National Polyp Study pointed out a 76-90% prevention of PCCRCs by colonoscopy with polypectomy of at least one adenoma.[3, 22] To ensure optimal protection of colonoscopy and to reduce patient burden, all resectable lesions should be removed during the initial colonoscopy. However, some colorectal polyps may be too large and/or complex to be removed directly in the same session and in such cases a second colonoscopy is needed for advanced polypectomy techniques.[69] Therefore we decided that during the accreditation program of the Dutch CRCSP, endoscopists should have at least a 90% polyp removal rate during the initial colonoscopy.

As histopathology is the gold standard for diagnosis and is also used to assess subsequent surveillance intervals, it is of importance that all removed lesions are retrieved for histological evaluation. In the UK and USA, polyp retrieval rates of at least 90% and 95% are recommended.[58, 61, 62] For the Dutch CRCSP, the polyp retrieval rate was not a prerequisite during the accreditation program, but during the course of the program this rate will be monitored.

Tattooing

Placing tattoos, allows for optimal localization of polyps and CRCs during additional endoscopic assessment or surgical resection.[70] For the Dutch CRCSP, we decided it should be avoided that patients would have a second colonoscopy for tattoo-placement. All cancers, except for those detected in the cecum or within the most distal four centimeters of the rectum, should be tattooed in at least three quadrants. The rate of tattoo-placement upon detection of CRC will be monitored during the course of the Dutch CRCSP.

Colonoscopy related adverse events

Colonoscopy is an invasive procedure and adverse events may occur during the bowel preparation phase, the procedure itself and in the weeks after colonoscopy. Adverse events occur in about 2 out of every 1000 colonoscopies and adverse event rates increase when a biopsy is taken or polypectomy is performed.[71] Notwithstanding the fact that colonoscopic adverse events are unusual, they can be life-threatening and even result in colonoscopy related mortality with a reported pooled colonoscopy mortality of 2.9 per 100,000 colonoscopies.[71]

The two most frequent occurring colonoscopy associated adverse events are perforation and post-colonoscopy bleeding. Wide variances in perforation rates and post-colonoscopy bleeding

have been reported, ranging from 0.07 to 0.4 per 1000 colonoscopies for perforations and between 0.8 and 2.4 per 1000 colonoscopies for post-colonoscopy bleeding.[71-73] As the screening population after FIT is enriched due to positivity of the test, it seems most likely that the prevalence of neoplastic polyps and therefore the number of polypectomies performed are higher, potentially resulting in higher adverse event rates.

Accurate recording and continuous monitoring of adverse events is an integral part of the Dutch CRCSP. To monitor the safety of the program, each endoscopy center was obliged to use a systematic complication registry, recording the occurrence of colonoscopy related adverse events and mortality after screening colonoscopy. To assure uniform and complete registration of all 30-day and in hospital endoscopic related adverse events, including unplanned hospitalizations occurring up to 30 days after colonoscopy, a nationwide endoscopic complication registry was implemented in January 2016.[74] As from January 2018, continuous registration of all colonoscopy related adverse events in this registry is obligatory.

Patient sedation and satisfaction

Colonoscopy is considered as a burdensome procedure. For all colonoscopies, but especially for those performed within the scope of a screening program it is essential that patients experience as little discomfort as possible. For the Dutch CRCSP, it is required that during the consultation prior to colonoscopy sedation options are discussed in line with the Dutch sedation guideline.[75]

In a study performed within the British NHS Bowel Cancer Screening Programme, sedation practice appeared to be unrelated to comfort scores. Patients receiving no sedation were the least likely to have significant discomfort, whereas patients receiving a combination of intravenous sedation and opiate analgesics were most likely to have significant discomfort.[76] The authors suggest that this might be due to ascertainment bias, as patients who previously developed discomfort during sedation-free colonoscopy will be offered an alternative strategy and patients who prefer no medication reliably anticipate less discomfort.[76] Patient comfort levels are furthermore affected by other patient-related factors and by the endoscopist. It has been suggested that endoscopists performing better on other quality criteria provide higher patient comfort with less sedation.[76, 77]

Important discrepancies between patient-reported and clinician-reported levels of patient comfort during colonoscopy have led to the development of nurse-reported comfort scales, such as the adjusted Gloucester Comfort Scale.[77] The GCS is used within the Dutch CRCSP, as to date, no validated patient-derived measures of patient comfort and endoscopist benchmarks exist.[78] During the accreditation phase reporting on patient comfort was not a prerequisite, but this parameter will be monitored during the course of the program in order to establish accreditation and audit benchmarks in the future.

Future prospects for colonoscopy quality assurance in the Netherlands

During the development and implementation phase of the quality assurance process of the Dutch CRCSP, endoscopists were reluctant to enter the accreditation program. However, the importance and feasibility of the quality assurance program could be emphasized and by time, the program received increasing support by the endoscopy community. We believe that consequently addressing

the evidence-based substantiation of the quality criteria was an important basis for this acceptance. Actually, the awareness of high-quality colonoscopy spread from FIT-positive colonoscopies to all colonoscopy indications, resulting in the recent development of a prospective nationwide registry of *all* colonoscopies in the Netherlands. This prospective registry was initiated by the Dutch Society of Gastroenterology and Hepatology, and incorporates a small minimal data-set of evidence based quality criteria of colonoscopy.[79] Its implementation is ongoing and aims to provide insights in the quality of all colonoscopies performed in Dutch practice, and to further stimulate the development of colonoscopy quality improvement initiatives throughout the country.[79]

The data on colonoscopy quality gathered during the course of the Dutch CRCSP can also be used to assess, benchmark and implement new quality criteria for colonoscopy. Examples of potential new criteria are the PCCRC rate, the detection rate of proximally located serrated polyps (SP) and the Performance Indicator of Colonic Intubation (PICI).

A low rate of PCCRCs is essential for any CRC screening program. PCCRCs may reflect a missed cancer, a cancer arising in a missed or incompletely resected premalignant polyp, or a newly developed cancer after colonoscopy with an aggressive biologic behavior and/or accelerated carcinoma-pathway.[12-15, 24, 80, 81] Furthermore, a recent study on interval CRCs in individuals undergoing multiple rounds of FIT screening showed that patients with a PCCRC had a reduced survival when compared to those with a screen-detected CRC or FIT interval cancer.[82] The latter group consists of CRCs detected after a negative FIT before the invitation of a subsequent FIT screening round.[12, 82] Therefore, the PCCRC rate within each CRC screening program should be carefully monitored.[12, 82] However, due to their relative rarity, long intervals before their development and delay in the time to diagnosis, PCCRC rates are difficult to use as a direct quality measure for individual endoscopists.[12, 40]

An increasing body of evidence suggests that SPs also contribute to the development of CRC.[83-85] Additionally, a significant proportion of PCCRCs seems to arise from proximal located SPs, presumably because these lesions might be more easily missed because of their proximal location, flat appearance and pale color.[86-88] Therefore the proximal SP detection rate (PSDPR) has been proposed as a quality indicator for screening colonoscopy.[89-92] As the histopathological subtyping of SPs tends to be difficult, resulting in a broad diagnostic variability between pathologists, the total group of SP is evaluated instead of its sub-categories sessile serrated lesions, hyperplastic polyps and traditional serrated adenomas.[93] However, the association between the PSPDR and rate of PCCRC has not been assessed yet.[89, 92] Hopefully, the data of the Dutch CRCSP will help to provide relevant data on the PSPDR, and if an established quality parameter, PSPDR might be introduced as an accreditation and audit criterion of the Dutch CRCSP.

An important component of high quality colonoscopy is the comfortable and safe intubation of the cecum. A suboptimal colonoscopy technique might result in pushing harder to reach the cecum, making the colonoscopy more uncomfortable and less safe due to potential endoscope-induced perforations. However, because the CIR is unable to reflect on colonoscopy safety, patient comfort and used sedation, a new composite quality indicator has been proposed recently.[94] The Performance Indicator of Colonic Intubation (PICI) combines these three parameters and was defined as the proportion of colonoscopies in which cecal intubation was achieved with a median midazolam dose of 2 mg or less and a GCS of 1-3 (comfortable to mild discomfort).[94] In an audit of

the British colonoscopy practice a PICI of 54.1% was achieved. PICI identified factors that affected colonoscopy performance more frequently than the CIR or the CIR combined with sedation.[94] Therefore, PICI provides a more complete picture of the performance of colonic intubation than the separate measures of CIR, patient comfort and sedation. As proposed by Valori et al., the PICI might be sufficient to identify, support and monitor individuals that require quality improvement and therefore, it is of interest to evaluate the PICI as a new quality indicator in the Dutch CRCSP.[94]

In this report, the design, the process and the details of the quality assurance process for colonoscopies in the Dutch CRCSP was described, focusing mainly on the accreditation program and quality assurance monitoring plan for endoscopists. The selection of the colonoscopy quality indicators was predominantly evidence-based, both to increase support and understanding from the endoscopy community as well as to create the opportunity to readily adjust these quality criteria when new insights would become available.[29] We believe that our experience might serve as an example for colonoscopy quality assurance programs in other CRC screening programs.

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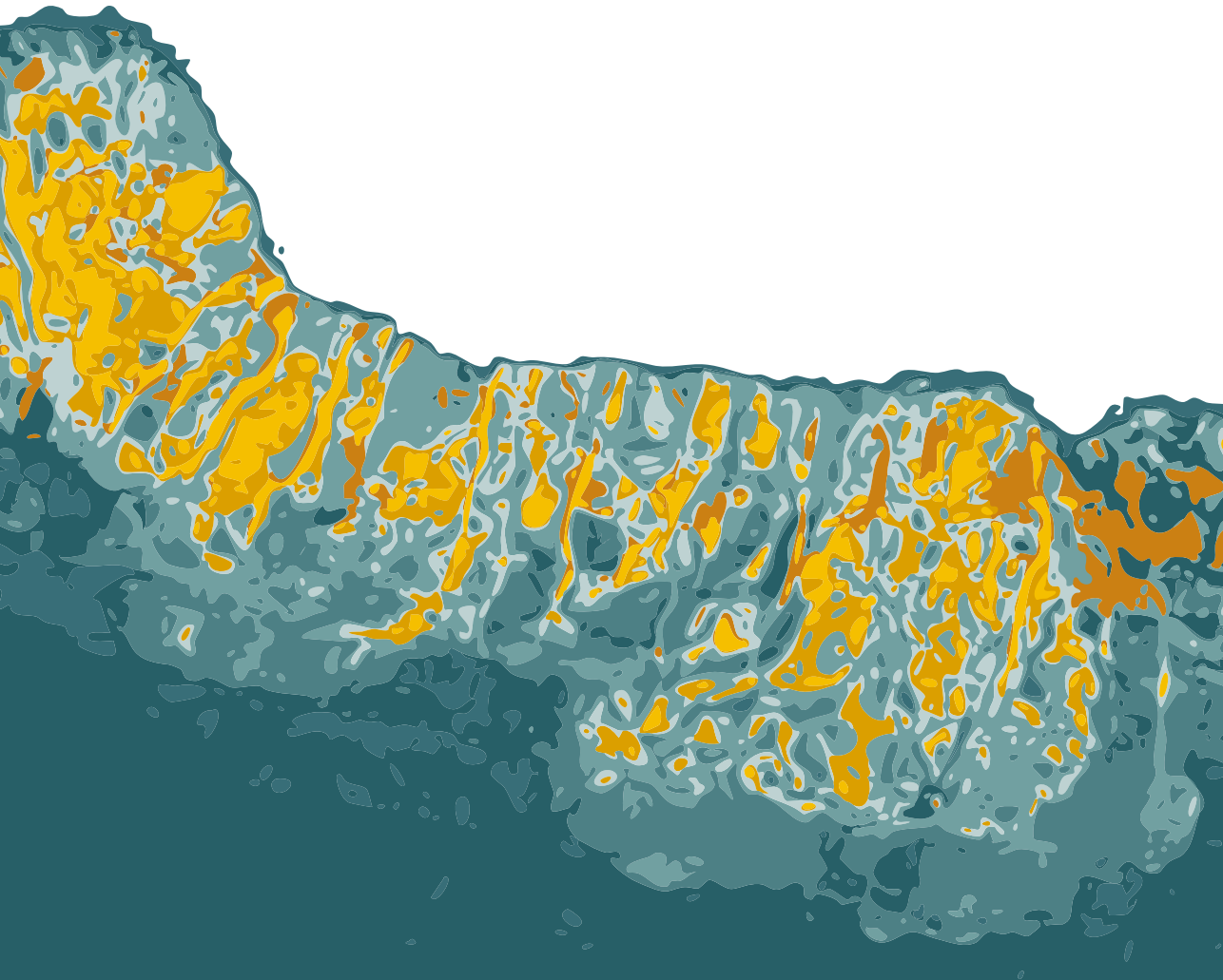

IMPACT OF DIFFERENCES IN ADENOMA AND PROXIMAL SERRATED POLYP DETECTION RATE ON THE LONG-TERM EFFECTIVENESS OF FIT-BASED COLORECTAL CANCER SCREENING

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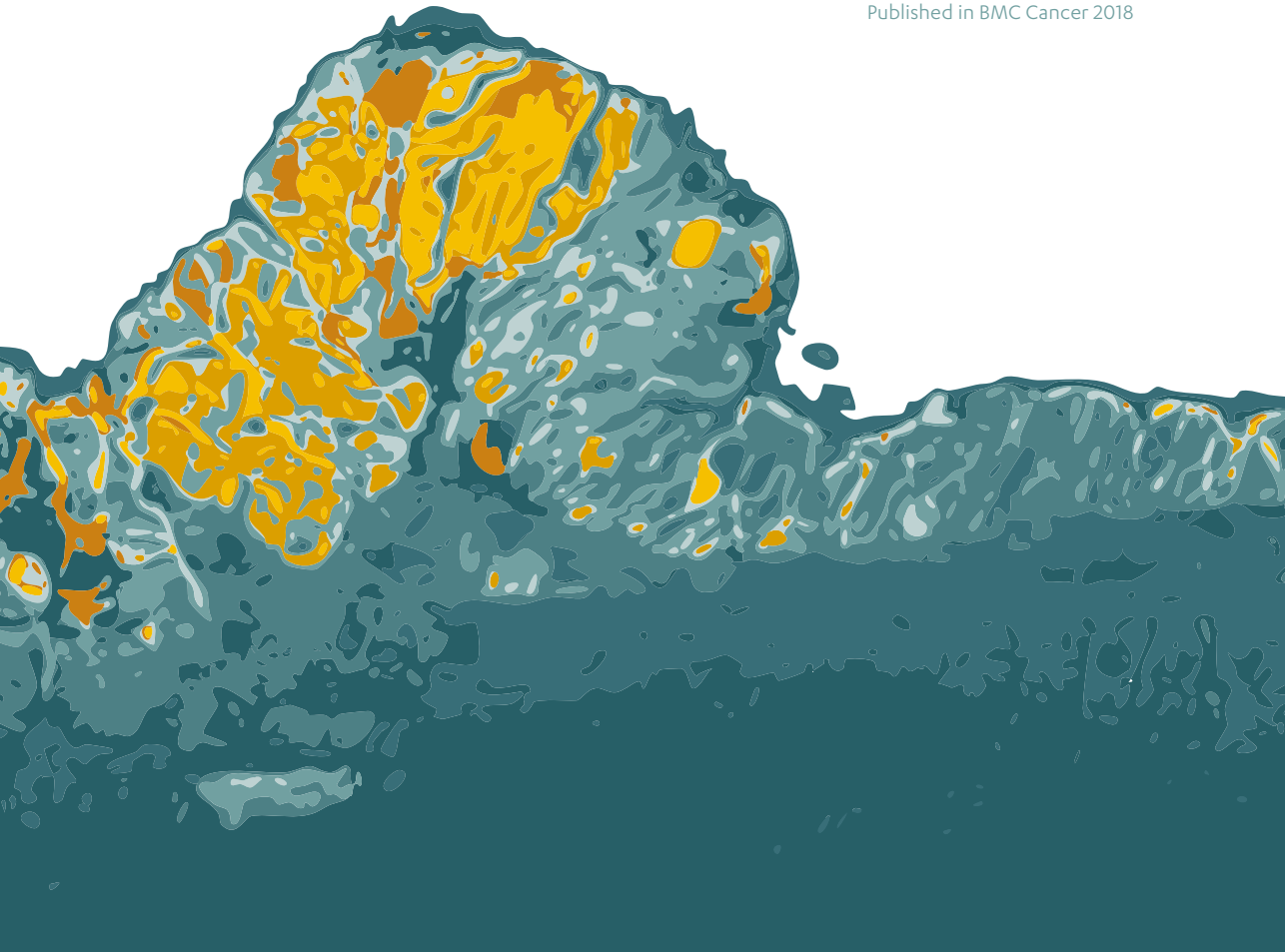

ABSTRACT

Background

Both the adenoma detection rate (ADR) and proximal serrated polyp detection rate (PSPDR) vary among endoscopists. It is unclear how these variations influence colorectal cancer (CRC) screening effectiveness. We evaluated the effect of variation in these detection rates on the long-term impact of fecal immunochemical test (FIT) based screening.

Methods

The Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model was set up to simulate the Dutch national biennial FIT-based CRC screening program between 2014 and 2044. Adherence to FIT and colonoscopy was 73% and 92%. Besides a 'no screening scenario', several screening scenarios varying in ADR and PSPDR were evaluated. Using the available literature on colonoscopy miss rates led to a base-case ADR of 59% and PSPDR of 11%, which were varied with intervals of 3% and 2%.

Results

Compared to no screening, FIT-screening in the base-case scenario reduced long-term mortality with 51.8%. At a fixed PSPDR of 11%, an increase in ADR from 44% to 62% would result in a 10.7% difference in mortality reduction. Using a fixed ADR of 59%, changing the PSPDR from 3% to 15% did not substantially influence long-term mortality (51.0% to 52.3%).

Conclusions

An increase in ADR gradually reduces CRC burden in a FIT-based screening program, whereas an increase in PSPDR only minimally influences long-term outcomes at a population-level. The limited effect of the PSPDR can be explained by the limited sensitivity of FIT for serrated polyps (SPs). Other triage modalities aiming to detect relevant SPs should be explored.

BACKGROUND

Colorectal cancer (CRC) is one of the most prevalent causes of cancer-related morbidity and mortality in Western countries.[1] Both can be reduced by the detection of cancers at early, curable stages and by the detection and removal of colorectal adenomas, the most important CRC precursor lesions.[2, 3] Colonoscopy is the reference standard for the detection and removal of adenomas and its associated CRC mortality reduction is why CRC screening is implemented in many Western countries.[2-4] CRC screening programs can be divided in primary colonoscopy screening programs in which all participants undergo a screening colonoscopy, and screening programs in which the screening colonoscopy is preceded by a triage modality, such as non-invasive stool tests.[4] Only test-positives will undergo colonoscopy. The effectiveness of all CRC screening programs therefore relies on the quality of the colonoscopy, of which the adenoma detection rate (ADR) is the most established quality indicator.[5-8] In primary screening colonoscopy cohorts lower ADRs were associated with higher post-colonoscopy interval cancer and CRC mortality risks.[5, 6]

An increasing body of evidence suggests that serrated polyps (SPs) also contribute to CRC oncogenesis.[9-11] Of all post-colonoscopy CRCs, a significant proportion seems to arise from proximal located SPs, presumably because of high lesion miss rates.[12, 13] As such, the detection of proximal SPs is of importance and the proximal serrated polyp detection rate (PSDPR) has been proposed as a screening colonoscopy quality indicator as well.[14-17] However, the PSPDR is not an established quality indicator, as the association between the PSDPR and the occurrence of post-colonoscopy CRCs has not been established yet.[14, 17]

Both the ADR and the PSPDR are known to vary among endoscopists.[5, 6, 14, 17-23] Nonetheless, little is known about the effect of these variations in ADR and PSPDR on the effectiveness of a screening program using biennial fecal immunochemical testing (FIT) as a triage modality. Therefore, this study aimed to evaluate the effect of variation in ADR and PSPDR on the long-term impact of a biennial FIT-based CRC screening program using the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model.

METHODS

ASCCA model

The ASCCA model, which is extensively described elsewhere, was used for all analyses.[24] In brief, the natural history model incorporates two pathways to CRC: the adenoma-carcinoma pathway and the serrated pathway. The serrated pathway is assumed to contribute to 15% of CRC cases.[25] Individual health trajectories are simulated from age 20 to age 90 or death, whichever comes first. During their life, individuals can develop up to 10 adenomas and 10 SPs. In the model only hyperplastic polyps (HPs) and sessile serrated lesions (SSLs) were included, as traditional serrated adenomas are very rare.[26] The development of each lesion in terms of growth in size is modelled independently. For adenomas, also the development of high-grade dysplasia and villosity is taken into account. Only advanced adenomas and SSLs can progress to CRC. Once an asymptomatic tumor has developed, there is an annual chance that the tumor becomes detected by symptoms or progresses to a more advanced stage. *Appendix table A1* provides an overview of the natural history

parameters. The model satisfactorily replicates Dutch colorectal lesion prevalence, CRC incidence and CRC mortality in the absence of screening.[27, 28] The natural history model is supplemented with a flexible screening and surveillance component, which can be set up to evaluate a range of screening and surveillance strategies. Parameters of the screening and surveillance component are updated regularly using the results of the national monitor of the Dutch CRC screening program.[29]

Dutch screening program and surveillance guidelines

The ASCCA model was set up to simulate the Dutch national CRC screening program; model parameters are shown in *Table 1*. The Dutch screening program was implemented in 2014 and involves biennial FIT-screening.[30] The implementation is phased; each year new birth cohorts are invited until the program is fully implemented in 2019. From 2019 onwards, all individuals aged 55 to 75 will be invited biennially. Individuals with a positive test outcome (cut-off 75 ng/ml) are referred for colonoscopy. FIT characteristics for detecting adenomas were obtained following a previously described calibration procedure.[24] We calibrated against the positivity rate, detection rates and positive predictive values of a Dutch screening pilot study.[31] For SPs, the positivity rate was assumed to be equal to one minus the specificity.[32] We assumed that during colonoscopy, all detected lesions are completely removed, with the exception of small HPs (<5 mm) located in the rectosigmoid.[33] Adherence rates to FIT and FIT-positive colonoscopy were set at 73% and 92% based on the national monitor of the Dutch CRC screening program.[29, 34]

Colonoscopy surveillance is modelled in accordance with Dutch guidelines, which is guided by a risk score based on the number, size and location of the encountered colorectal polyps.[33] This risk score determines the surveillance interval, i.e. 3 or 5 years. If during FIT-positive colonoscopy no adenomas or only one small (≤ 1 cm) tubular adenoma is detected, the individual returns to screening after 10 years. Adherence to surveillance colonoscopy was assumed to be equal to that of FIT-positive colonoscopy, i.e. 92%, and surveillance ends at age 75.

Detection settings

Besides the no screening comparator, we considered FIT-screening with different detection settings (varying both ADR and PSPDR). To estimate the ADR and PSPDR, the model was set up to simulate one round of FIT-screening (cut-off 75 ng/ml) in previously unscreened, asymptomatic individuals aged 55-75 years. First, we assumed size-specific detection rates per adenoma during FIT-positive colonoscopy as reported in a systematic review on adenoma miss rates to calculate the base-case ADR.[7] For SPs, lesion miss rates are not described in the literature. Since the flat appearance, proximal location and pale color of SPs hampers detection, a 10% lower detection rate per SP than per adenoma was assumed to calculate the base-case PSPDR.[35] Subsequently, the detection rate per adenoma was calibrated, such that the ADR increased and decreased with steps of 3% with a minimal ADR of 44%. As the prevalence of proximal SPs is lower than the adenoma prevalence, the PSPDR was increased and decreased with steps of 2% when calibrating the SP detection rate. A minimal PSPDR of 3% was assumed. The maximum ADR and PSPDR were reached under the assumption that all adenomas or SPs were detected. To achieve a specific ADR or PSPDR, the detection rates for

the different size categories per lesion were varied jointly rather than individually. More specifically, we assumed that the absolute difference in detection rates between the different size categories per lesion type remained equal to those reported by Van Rijn et al.[7]

Analyses and study outcomes

Screening was modelled from the introduction of the program in 2014 to 2044, while accounting for the phased rollout. We started with a population based on the 2013 Dutch population age-composition and assumed that this population will age in accordance with the predictions of the Dutch Central Bureau of Statistics.[36]

For each FIT-screening scenario with different detection settings, yearly CRC incidence and mortality rates per 100,000 individuals and colonoscopy demand were evaluated. The FIT-screening scenario assuming the base-case ADR and PSPDR was compared to no screening. Subsequently, we assessed the impact of increasing the PSPDR with the ADR fixed at the base-case value as well as the impact of increasing the ADR with the PSPDR fixed at the base-case value.

Sensitivity analyses

To assess the robustness of our results, we conducted one-way sensitivity analyses, i.e. varying only one parameter at the time. As there is much debate regarding the contribution of the serrated pathway to the CRC incidence, all FIT-screening scenarios with different detection settings were repeated assuming that 30% of CRCs arise from SPs instead of 15% used in the base-case analyses.[9-11] Furthermore, we assumed that FIT detects adenomas and SPs equally well (*Table 1*).

In order to evaluate the impact of surveillance colonoscopy on the study outcomes, we repeated all analyses assuming an alternative strategy of FIT screening without surveillance, in which individuals considered at intermediate or high risk for metachronous lesions at FIT-positive colonoscopy return to FIT-screening after two years. Those at low risk return to the screening program after ten years.[37] To allow for comparability of model results with other studies on ADR variances, all analyses were repeated assuming a fully implemented primary colonoscopy screening program. In this program, individuals aged 55 to 75 are invited every ten years to undergo screening colonoscopy and dependent on the findings, may enter colonoscopy surveillance. Adherence rates for screening and surveillance colonoscopy were set at 22% and 92%.[27, 29] To evaluate the maximal impact of changes in ADR and PSPDR, also primary colonoscopy screening assuming perfect compliance was simulated.

RESULTS

Adenoma and proximal SP detection rates

Table 2 shows the results of calibrating the ADR and PSPDR in one round of FIT-screening in previously unscreened individuals. Assuming detection rates per adenoma based on Van Rijn et al. led to an ADR of 59%.[7] This was considered the base-case ADR. The maximal ADR of 62% was reached when assuming that all adenomas were detected during FIT-positive colonoscopy. A minimal ADR of 44%

Table 1. Overview of important model parameters.

Variable	Base-case analysis		Sensitivity analysis		Reference
FIT-screening					National monitor of the Dutch CRC screening program [29, 34]
Participation FIT	0.73				
Adherence to FIT-positive colonoscopy	0.92				
Adherence to surveillance colonoscopy	0.92				
Primary colonoscopy screening					27, 29
Adherence to screening colonoscopy			0.22		
Adherence to surveillance colonoscopy			0.92		
FIT positivity rate per lesion	Men	Women	Men	Women	31
Healthy	0.96[a]	0.97[a]			
Diminutive adenoma	0.004	0.003			
Small adenoma	0.12	0.10			
Large adenoma	0.30	0.28			
Small SP	0.004	0.003	0.06	0.05	
Large SP	0.004	0.003	0.30	0.28	
Early stage CRC	0.50	0.50			
Late stage CRC	0.85	0.85			
Contribution of serrated pathway to CRC incidence	15%		30%		11
Complications after colonoscopy	0.0028				54-56
Fatal complications after colonoscopy	0.0001				54-56

FIT, fecal immunochemical test. [a]Specificity per individual.

was assumed for which the detection rates of diminutive, small and large adenomas were 36%, 49% and 60%. Thus, the plausible ADR range is between 44% and 62%.

For SPs, 10% lower detection rates per SP compared to the detection rates per adenoma were assumed, leading to a base-case PSPDR of 11%.[7] Assuming that all SPs are detected during FIT-positive colonoscopy led to a maximal PSPDR of 15%. We assumed a minimal PSPDR of 3% for which the detection rates were 15% and 33% for small and large SPs. Therefore, the plausible range for the PSPDR is between 3% and 15%. Table 2 also reports ADRs and PSPDRs for one round of primary colonoscopy screening.

CRC burden and colonoscopy demand

In 2013, CRC incidence and mortality rates were 74.0 cases and 29.3 deaths per 100,000 individuals. In the absence of screening, CRC incidence and mortality are predicted to increase to 104.3 and 42.3 per 100,000 individuals in 2044 due to aging of the population. In the base-case detection setting, thirty years of FIT-screening led to a 36.7% reduction in CRC incidence and a 51.8% reduction in CRC mortality compared to no screening. When the ADR was fixed at 59% and a PSPDR of 3% was assumed, CRC mortality reduction was 51.0% compared to no screening (*Figure 1*). This reduction increased with 1.3% to 52.3% when the PSPDR was increased to 15%. At a fixed PSPDR of 11% and

Table 2. ADR and PSPDR in one round of screening in previously unscreened individuals aged 55-75 years[#].

Calibrated detection rate per adenoma		ADR in previously unscreened individuals aged 55-75 years undergoing one round of		Calibrated detection rate per SP	PSPDR in previously unscreened individuals aged 55-75 years undergoing one round of	
		FIT- screening	Primary colonoscopy screening		FIT- screening	Primary colonoscopy screening
< 6 mm:	36% 49%	44%	21%		3%	3%
6-9 mm:	60%			< 10 mm: 15%		
≥ 10 mm:				≥ 10 mm: 33%		
< 6 mm:	42%	47%	23%		5%	5%
6-9 mm:	55%			< 10 mm: 27%		
≥ 10 mm:	66%			≥ 10 mm: 45%		
< 6 mm:	49% 62%	50%	26%		7%	8%
6-9 mm:	73%			< 10 mm: 40%		
≥ 10 mm:				≥ 10 mm: 58%		
< 6 mm:	56%	53%	28%		9%	10%
6-9 mm:	69%			< 10 mm: 54%		
≥ 10 mm:	80%			≥ 10 mm: 72%		
< 6 mm:	65%	56%	30%		11%*[7]	12%
6-9 mm:	78%			< 10 mm: 68%		
≥ 10 mm:	89%			≥ 10 mm: 86%		
< 6 mm:	74%	59%*[7]	33%		13%	14%
6-9 mm:	87%			< 10 mm: 85%		
≥ 10 mm:	98%			≥ 10 mm: 100%		
< 6 mm:	100%	62%	37%		15%	15%
6-9 mm:	100%			< 10 mm: 100%		
≥ 10 mm:	100%			≥ 10 mm: 100%		

[#] 27% of individuals aged 55-59, 25% of individuals aged 60-64, 24% of individuals aged 65-69 and 25% of individuals aged 70-75.

* an ADR of 59% and a PSPDR of 11% were considered as the base-case detection setting.

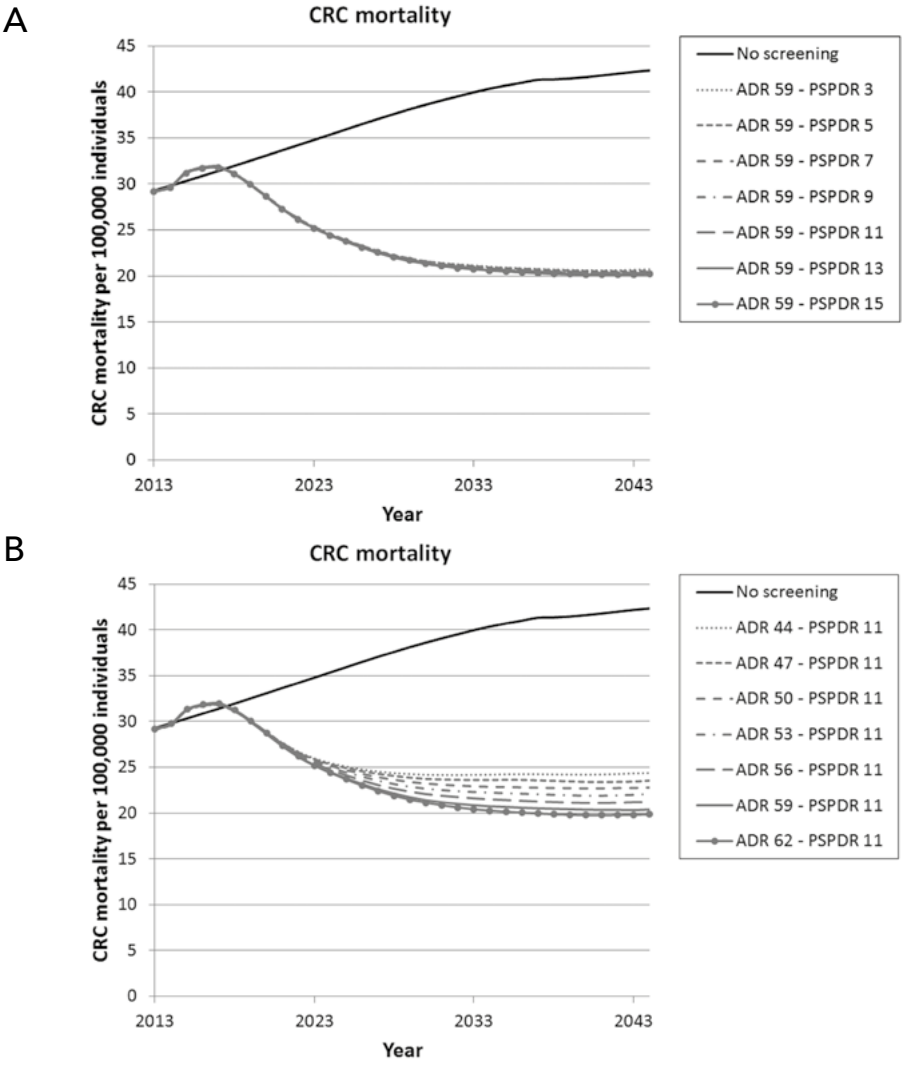

Figure 1. Long-term reduction in CRC mortality due to FIT-screening for different PSPDRs at a fixed ADR of 59% (A) and different ADRs at a fixed PSPDR of 11% (B).

when an ADR of 44% was assumed, CRC mortality reduction was 42.4% compared to no screening. Increasing the ADR to 62% led to a model-predicted mortality reduction of 53.1%, i.e. an increase of 10.7%. Similar patterns were observed for the CRC incidence reduction as shown in the *Appendix, Figure A1*.

In the base-case detection setting 120,862 colonoscopies are required in 2044. Changes in the PSPDR at a fixed ADR of 59% did not influence colonoscopy demand. On the other hand, when the ADR was increased from 44% to 62% at a fixed PSPDR of 11%, colonoscopy demand was predicted to differ with 21,726 colonoscopies per year in 2044.

Sensitivity analyses

Under the assumption that 30% of all CRCs develop according to the serrated pathway, the difference in mortality reduction when increasing the PSPDR over its plausible range (from 3% to 15%) at a fixed ADR of 59% was slightly larger than in the base-case analysis, with an increase of 2.1% from 48.5% to 50.6% (*Figure 2*). The impact of increasing the PSPDR became more pronounced under the assumption that FIT has comparable sensitivity for adenomas and SPs; the difference in mortality reduction when increasing the PSPDR over its plausible range was 3.9% (from 53.2% to 57.2%). When considering a fixed PSPDR and variable ADR (plausible range from 44% to 62%),

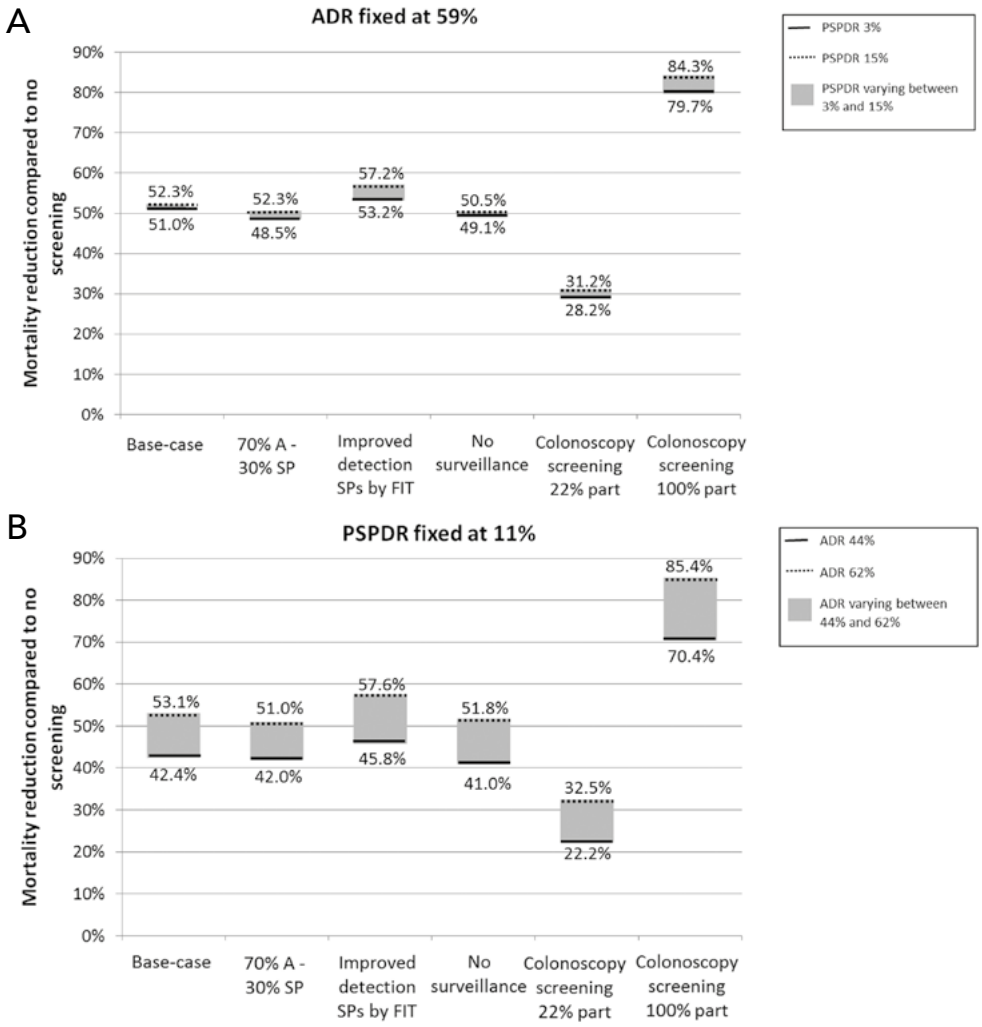

Figure 2. CRC mortality reduction compared to no screening for the base-case analysis and sensitivity analyses with the PSPDR varying between 3% and 15% at a fixed ADR of 59% (A) and with the ADR varying between 44% and 62% at a fixed PSPDR of 11% (B).

changes in contribution of the serrated pathway and detection of SPs by FIT led to a slightly smaller and a slightly greater difference in mortality reduction compared to the base-case analysis.

Evaluating the alternative strategy of FIT screening without surveillance, in which all individuals who were considered at intermediate or high risk at FIT-positive colonoscopy returned to screening after 2 years, we found comparable patterns with the base-case analysis. The difference in mortality reduction was 1.4% (increased from 49.1% to 50.5%) when the PSPDR was increased over its plausible range at a fixed ADR of 59%. When the PSPDR was fixed and the ADR was increased over its plausible range, the difference in mortality reduction increased with 10.8% (from 41.0% to 51.8%).

Also when the analyses were repeated assuming a fully implemented primary colonoscopy screening program with 22% colonoscopy adherence, similar patterns were observed.[27] An increase in the PSPDR over the plausible range only slightly increased the mortality reduction (from 28.2% to 31.2%), whereas an increase in ADR over its plausible range led to a considerable higher mortality reduction (from 22.2% to 32.5%). The maximal impact of an increase in detection rates was evaluated by assuming colonoscopy screening with perfect compliance. When the ADR was fixed, the difference in mortality reduction when increasing the PSPDR over its plausible range was 4.6% (from 79.7% to 84.3%). When the PSPDR was fixed, an increase in ADR over the plausible range led to a 15% difference in mortality reduction (from 70.4% to 85.4%). Results for CRC incidence were similar as shown in the *Appendix, Figure A2*.

DISCUSSION

Based on the ASCCA model, an increase in ADR will gradually reduce CRC incidence and mortality in a biennial FIT-based CRC screening program, whereas an increase of the PSPDR does only minimally impact CRC burden at a population-level. Similar results were found when an alternative strategy of FIT screening without surveillance was evaluated. The impact of an increased PSPDR on long term-outcomes only slightly increased when assuming a 30% instead of 15% contribution of the serrated pathway and under the assumption that FIT would have a comparable sensitivity for adenomas and SPs. The maximum impact of changing either the PSPDR (from 3% to 15%) or ADR (from 44% to 62%) on mortality reduction due to screening was observed when a colonoscopy screening programme with perfect compliance was modelled. In that case, mortality reductions varied with 4.6% and 15% when varying the PSPDR and ADR over its plausible range.

There are two explanations for the limited influence of an increased PSPDR on the model-predicted effectiveness of FIT-based screening. Firstly, only 15-30% of all CRCs originate from the serrated pathway.[11] When assuming a 30% contribution of the serrated pathway to CRC incidence, CRC mortality reduction due to screening varied with 3.8% when increasing the PSPDR over its plausible range compared to 1.3% in the base-case scenario wherein a 15% contribution was assumed. Secondly, under the assumption that FIT has a comparable sensitivity for both adenomas and SPs, a 4.0% difference in mortality reduction by increasing the PSPDR over its plausible range was found. FIT is known to be ineffective to detect clinically relevant SPs, such as larger and/or proximally located HPs and SSLs, since these lesions seldom bleed.[9, 11, 38, 39] This is also supported by our calibration analysis in which equal detection rates per SP led to similar PSPDRs for FIT-

screening and colonoscopy screening. In other words, FIT-screening does not lead to a subgroup of individuals referred for colonoscopy that has an increased SP prevalence. Contrastingly, the ADR was considerably higher after preselection with FIT compared to colonoscopy screening when assuming equal detection rates per adenoma. Positivity of FIT in individuals having relevant SPs is most likely due to the frequent co-occurrence of synchronous advanced adenomas or CRC.[40]

The majority of individuals harbouring relevant SPs without concurrent adenomas will therefore not benefit from FIT-based screening. Particularly these individuals are at risk of developing a FIT interval cancer, as it is suggested that SPs, once dysplastic may evolve relatively quickly into malignancy.[41] Improved detection of proximal SPs during colonoscopy is only effective for improving the effectiveness of a CRC screening program, if colonoscopy is used as a primary screening modality or when a triage test would preselect individuals at increased risk for relevant SPs as well as for advanced adenomas and CRC. Molecular stool testing has shown promising results. However, costs, test specificity, and ease to perform should improve to become a realistic alternative to FIT.[32] Currently, whole stool samples are needed to enable molecular testing. This could be burdensome for screenees and will influence adherence rates, which is crucial for population-based screening programs.[32]

Irrespective of the used triage modality, colonoscopy will remain the reference standard to detect and resect adenomas, SPs and cancer. To ensure the effectiveness of a screening program, quality assurance and monitoring the quality of colonoscopy is of paramount importance. To obtain and assure high quality within the Dutch national CRC screening program, national requirements were set for professionals performing screening colonoscopies. Only endoscopists satisfying pre-defined quality requirements are accredited to perform screening colonoscopies. During the accreditation process, the knowledge and skills of endoscopists are tested by an e-learning, by measuring evidence-based quality indicators and by evaluating the practical skills during colonoscopy.[42]

The ADR is endorsed as the most important (screening) colonoscopy quality indicator, since it is inversely correlated with the occurrence of post-colonoscopy interval cancers and CRC mortality in large primary screening colonoscopy cohorts.[5, 6] However, ADR is criticized as being slightly imprecise, as it does not provide information about incremental adenomas detected besides the first, resulting in the 'one and done phenomenon'.[43] Ideally, reporting of the ADR would be combined with a quality indicator reporting on the total number of detected adenomas.[43] In contrast to these data on ADR, no prospective studies evaluating the association between the PSPDR and the risk of interval cancers have been performed and recommendations for PSPDR thresholds are yet to be determined.[14, 17] As a consequence it can be hypothesized that the 'one and done phenomenon' currently does not apply to the PSPDR. Furthermore, both ADR and PSPDR do not select for neoplastic lesions having a higher neoplastic potential. The histopathological subtyping of SPs tends to be difficult, resulting in a broad diagnostic variability between pathologists.[44] However, by choosing the total group of SP located in the proximal colon, this interobserver variability among pathologists should not influence the results.

Both ADR and PSPDR vary widely, suggesting important lesion miss rates in low detecting endoscopists.[5, 6, 14, 17-23] Up to date, no studies have assessed interventions to improve the PSPDR.

In contrast, several strategies aimed to improve ADR, including simple feedback, involvement of endoscopy nurses and mandating longer colonoscope withdrawal times, as well as multifaceted strategies involving education, audit and feedback. However, all methods had limited effect on ADR.[45-49] The minor impact and poor performance of most interventions may be caused by the paucity of evidence on appropriate factors to target for modification.[50]

The interpretation of detection rates is difficult. This is due to the fact that besides endoscopy skills, detection rates are also influenced by the primary screening test and by the characteristics of the screening population, such as age, gender, screening history and prevalence of neoplastic lesions.[18] Thus, detection rates can only be interpreted in the context of the same screening setting. The calibrated detection rates in this study are based on one round of FIT-screening in previously unscreened, asymptomatic individuals aged 55-75 years. It should be noted that this differs from the Dutch CRC screening program which includes a phased implementation. During the implementation phase, selective cohorts are invited for screening starting with primarily older cohorts.

To the best of our knowledge this is the first microsimulation study investigating the influence of both the ADR and the PSPDR on the effectiveness of a biennially FIT-based as well as a primary colonoscopy screening program. Three other microsimulation studies estimated the effectiveness of primary colonoscopy screening at different levels of adenoma detection, also showing that higher ADRs were associated with important CRC incidence and mortality reductions.[51-53] The study by Meester et al. also investigated the effectiveness of annual FIT-based screening, showing a higher CRC related mortality in lower ADR settings.[53] An important difference between these models and the ASCCA model is the fact that both the adenoma-carcinoma pathway and the serrated pathway are included in the ASCCA model, whereas the other models only incorporate the adenoma-carcinoma pathway. This enabled us to also evaluate the impact of improvements in the PSPDR on CRC incidence and mortality reductions.

However, important limitations have to be acknowledged as well. First, we assumed a 10% lower detection rates rated for SPs than for adenomas to estimate the base-case PSPDR. Currently, the exact miss rates of SPs remain to be determined. However it is possible that the actual miss rates of SPs are higher than assumed in our base-case analysis, caused by the flat appearance, proximal location and pale color of SPs hampering detection.[35] On the other hand, the adenoma miss rates of colonoscopies performed nowadays may potentially be lower than miss rates reported by Van Rijn et al.[7] Since the publication of this study, the awareness of high quality colonoscopy has increased, accompanied by important improvements in the colonoscopy equipment, such as the application of high-definition colonoscopes and advanced imaging techniques. However, recently no new back-to-back studies have been published. To account for the uncertainty regarding this parameter however, we have evaluated a range of miss rates for both adenomas and SPs.

CONCLUSIONS

In conclusion, an increase in ADR gradually will reduce CRC incidence and mortality in a biennial FIT-based screening program after 30-years of follow-up, whereas an increase of the PSPDR does only minimally influence long-term outcomes on a population-level. This limited effect of

the PSPDR is partly explained by our assumption of a 15% contribution of the serrated pathway to the development of CRC, but more importantly by the limited diagnostic accuracy of FIT for SPs. Other triage modalities aiming to detect advanced SPs should be further explored.

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APPENDIX

Table A1. Natural history parameters of the ASCCA model.

Natural history parameters	One-year transition probabilities		References
Adenoma-carcinoma pathway			
Adenoma incidence men			(A1-A3)
(No adenoma to diminutive adenoma)			
Age 20-39	0.003		
Age 40-49	0.007		
Age 50-54	0.019		
Age 55-59	0.022		
Age 60-64	0.024		
Age 65-69	0.028		
Age 70-74	0.033		
Age 75-90	0.035		
Adenoma incidence women			(A1-A3)
Incidence factor	0.6*		
Personal risk index adenoma-carcinoma pathway			(A2,A3)
Standard deviation	1.6*		
Progression in size			(A1,A3-A5)
Diminutive to small adenoma	0.07		
Small to large adenoma	0.10		
Regression in size			(A1,A3)
Small to diminutive adenoma	0.25		
Large to small adenoma	0.15		
Dysplasia			(A1,A3)
(Low grade to high grade)			
Diminutive adenoma	0.004		
Small adenoma	0.009		
Large adenoma	0.010		
Villosity			(A1,A3)
(Tubular to tubulovillous/villous)			
Diminutive adenoma	0.004		
Small adenoma	0.025		
Large adenoma	0.085		
Progression from AA to CRC^	Shape	Scale	(A6)
Men	2*	29*	
Women	2*	27*	
Serrated pathway			
Serrated lesion incidence men	SSA	HP	(A1,A3)
(No serrated lesion to small serrated lesion)			
Age 20-25	0.0001	0.001	
Age 25-29	0.0001	0.001	

Table A1. (continued)

Natural history parameters	One-year transition probabilities		References
Age 30-34	0.0001	0.002	
Age 35-39	0.0001	0.004	
Age 40-44	0.0006	0.007	
Age 45-49	0.0015	0.010	
Age 50-54	0.0016	0.010	
Age 55-59	0.0014	0.006	
Age 60-64	0.0008	0.004	
Age 65-69	0.0008	0.004	
Age 70-74	0.0007	0.002	
Age 75-79	0.0006	0.002	
Age 80-84	0.0005	0.002	
Age 85-90	0.0004	0.002	
Serrated lesion incidence women			(A1,A3)
Incidence factor SSA	0.7*		
Incidence factor HP	0.7*		
Personal risk index serrated pathway			(A1,A3)
Standard deviation	1.7*		
Progression in size			(A1,A3)
Small to large serrated lesion	0.028		
Regression in size			(A1,A3)
Small HP to no serrated lesion	0.0		
Large HP to small HP	0.4		
Progression to CRC	0.006		(A6)
CRC			
CRC	Dwell time in years	Stage distribution detected CRC	(A7,A8)
Stage 1	2.5*	0.19*	
Stage 2	2.0*	0.31*	
Stage 3	1.5*	0.49*	
Stage 4	1.0*	0.01*	

* Parameter value instead of yearly transition probability.
^ Weibull distribution.

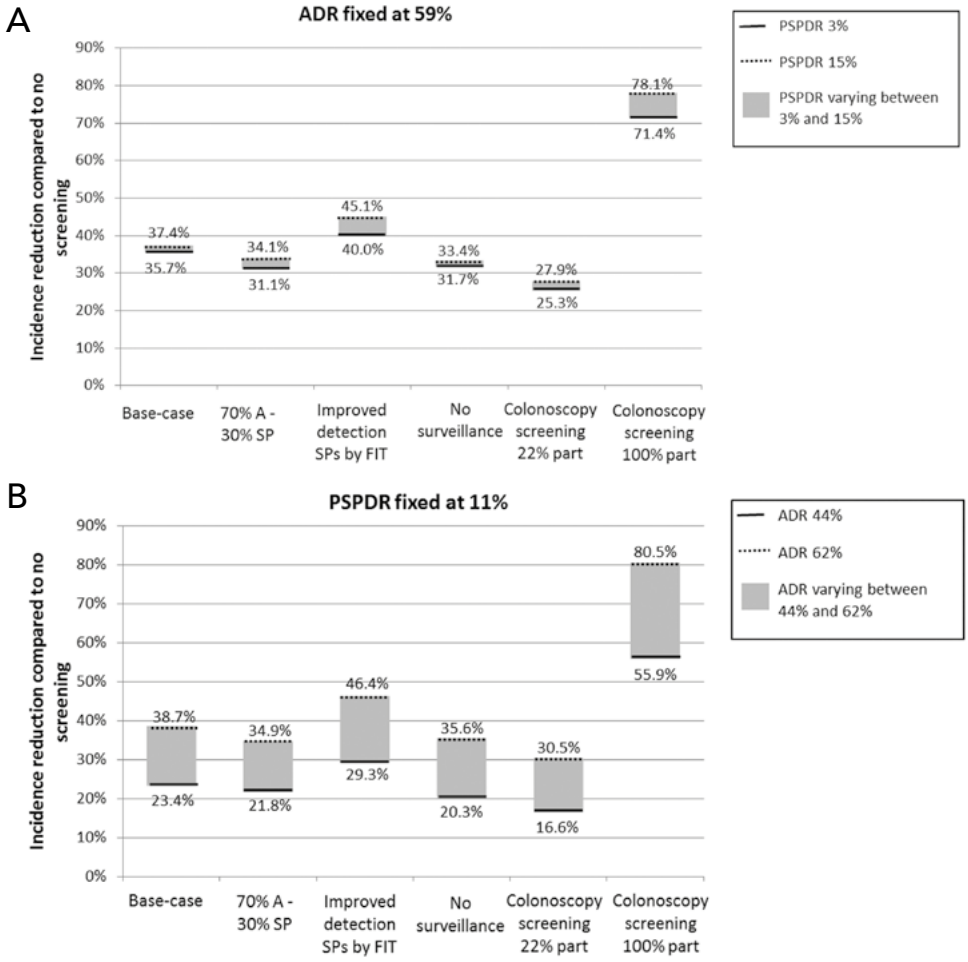

Figure A1. Long-term reduction in CRC incidence due to FIT-screening for different PSPDRs at a fixed ADR of 59% (A) and different ADRs at a fixed PSPDR of 11% (B).

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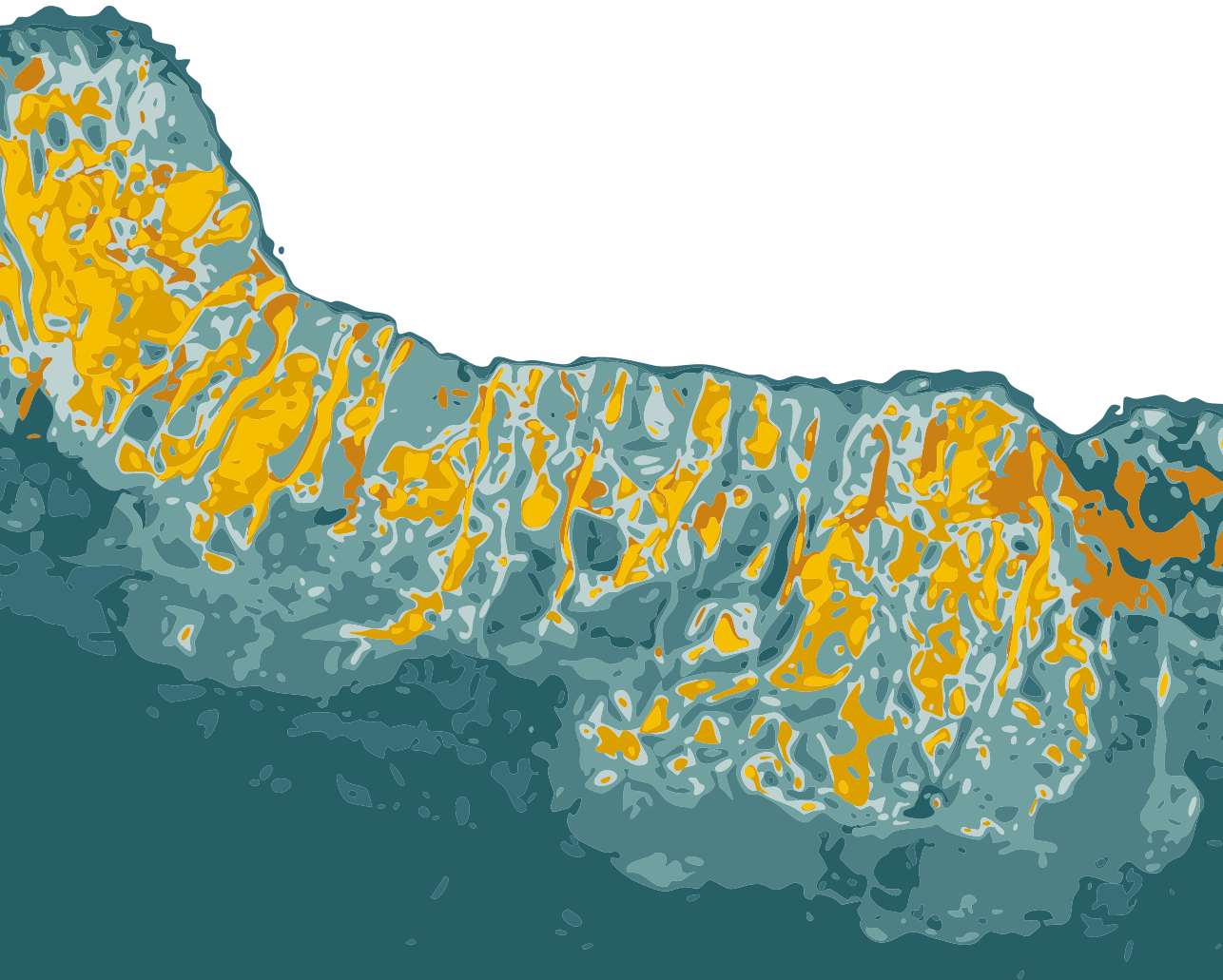

ARE ADENOMA AND SERRATED POLYP DETECTION RATES CORRELATED WITH THE ENDOSCOPISTS' SENSITIVITY OF OPTICAL DIAGNOSIS?

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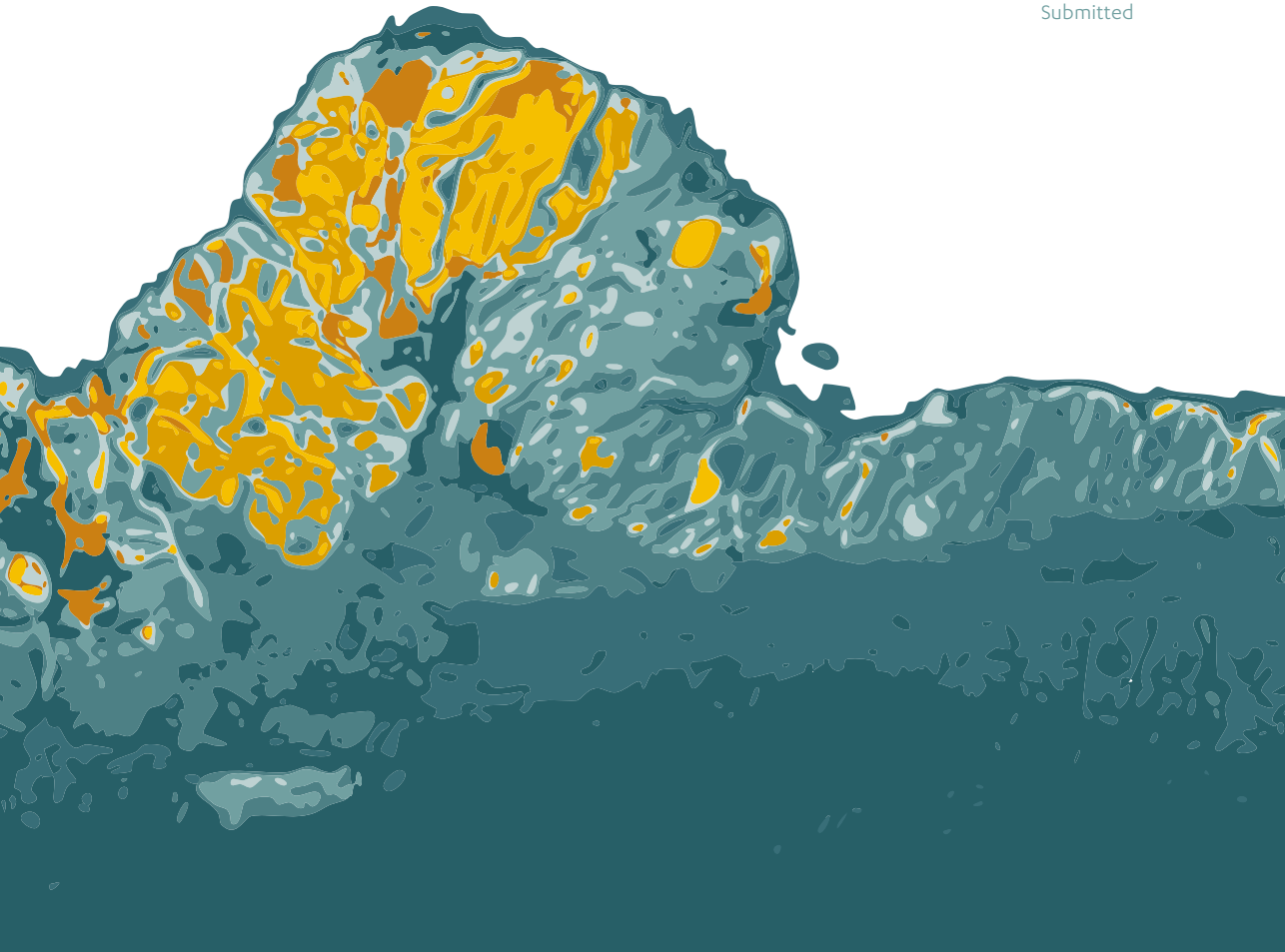


ABSTRACT

Introduction

As endoscopists with a high adenoma detection rate (ADR) and proximal serrated polyp (SP) detection rate (PSPDR) more frequently detect adenomas and proximal SPs, this may be attributed to a better recognition of the endoscopic features of these polyps. However, little is known about the association between endoscopic lesion detection and differentiation skills. Therefore we aimed to evaluate the correlation between the ADR, PSPDR and the sensitivity of optical diagnosis of adenomas and SPs.

Methods

We performed an exploratory post-hoc analysis on data of the DISCOUNT-2 study and included only complete colonoscopies after a positive FIT of endoscopists who performed ≥ 50 colonoscopies within the study. The correlation between the ADR, PSPDR and sensitivity of optical diagnosis of adenomas and SPs was calculated using the Pearson's rho correlation coefficient.

Results

A total of 24 endoscopists performed at least 50 colonoscopies, resulting in a total of 2889 complete colonoscopies. The overall ADR in this FIT-positive population was 84.5% (range 71.4-95.3%), and the overall PSPDR was 32.4% (range 12.3%-42.5%). Sensitivity of optical diagnosis assessed with high confidence of adenomas and SPs was 94.5% (range 83.3-100%) and 74.0% (range 37.5-94.1%), respectively. No correlations could be demonstrated between the ADR and sensitivity of optical diagnosis of adenomas (-0.20, p-value 0.35) and between the PSPDR and its associated diagnostic test sensitivity (PSPDR and SP sensitivity -0.12, p-value 0.57).

Conclusions

In this homogeneous FIT-positive population, no correlation between the ADR and PSPDR and the sensitivity of optical diagnosis of these polyps could be demonstrated. Our exploratory results suggest that lesion detection and differentiation require different endoscopic skills. However, studies with this topic as a primary aim should enable definite conclusions. Until then, accurate monitoring and assurance of both performance indicators is important to secure optimal efficacy of a FIT-based CRC screening program.

INTRODUCTION

Colonoscopy is the reference standard for the detection of colorectal cancer (CRC) and for detecting and resecting its precursor lesions.[1-4] The National Polyp Study demonstrated that after removal of at least one colorectal adenoma, both CRC incidence and mortality were lower than when compared to a reference population.[1, 2] However, colonoscopy is not fully protective for the development of post-colonoscopy CRCs (PCCRCs), which may occur in 2-8% of the patients.[5-10] The majority of PCCRCs seem to result from colonoscopy related factors, such as missed polyps and incomplete polypectomies, and therefore high quality of colonoscopy procedures is crucial.[7, 11-17]

The adenoma detection rate (ADR) is considered one of the most important colonoscopy quality indicators, as the ADR proved to be inversely correlated with the occurrence of PCCRCs and CRC-related mortality.[18, 19] However, ADR monitoring does not fully capture endoscopists' performance and can be flawed by the one-and-done phenomenon.[20, 21] Other colonoscopy quality indicators, such as the mean number of adenomas detected per colonoscopy (MAP), are therefore needed to further obtain insights in the quality of the performed procedures.[20, 21] Moreover, an increasing body of evidence has indicated that 15-20% of all CRCs are derived from serrated polyps (SPs). Additionally, a significant proportion of PCCRCs seem to arise from SPs located in the proximal colon. High miss rates of these polyps might be a major cause of PCCRCs, presumably resulting from their pale color and flat appearance.[22-24] Therefore, the detection rate of proximal serrated polyps (PSPDR) has also been proposed as a colonoscopy quality indicator.

Before embarking on endoscopic resection of a colorectal polyp, endoscopists should make an accurate optical diagnosis and predict histopathology. In case of an accurate optical diagnosis of diminutive polyps, neoplastic polyps could be removed without requesting histopathological evaluation and non-neoplastic polyps could be left in situ. Virtual chromoendoscopy techniques enable real-time optical diagnosis and could thereby guide this decision-making process.[25-27] However, before optical diagnosis strategies are ready for implementation, assurance of adequate differentiation between neoplastic and non-neoplastic lesions is warranted.[28, 29]

Both the ADR and the PSPDR are known to vary among endoscopists.[18, 19, 30-37] As endoscopists with a high ADR and PSPDR are able to detect adenomas and proximal SPs more frequently, it can be hypothesized that this is caused by a better recognition of the endoscopic features of these polyps resulting in improved detection. If this correlation is present, this may implicate that by improving the accuracy of optical diagnosis, the detection of premalignant polyps could increase. Training programs aiming to increase the accuracy of optical diagnosis have shown to be successful, so improving the optical diagnosis by training might also increase the premalignant polyp detection rates.[38] However, little is known about the association between these endoscopy skills and therefore we aimed to evaluate the correlation between the ADR, PSPDR and the sensitivity of optical diagnosis of adenomas and SPs.

METHODS

Study design and ethical approval

This is an exploratory post-hoc analysis from a prospective, randomized observational multicenter (DISCOUNT-2) study evaluating the duration of establishing and maintaining a clinical acceptable accuracy for the endoscopic optical diagnosis of diminutive (≤5 mm) neoplastic colorectal polyps.[38] This study was performed between January 2015 and January 2017 in 12 regional hospitals and 1 academic center in the Netherlands.

Colonoscopy setting and participating endoscopists

All colonoscopies were performed in individuals undergoing colonoscopy after a positive FIT within the Dutch Bowel Cancer Screening Program (BCSP).[39] The Dutch BCSP was implemented in 2014 and its complete rollout is phased; each year new birth cohorts are invited until full implementation in 2019. The program involves biennial FIT-screening in individuals aged 55 to 75 years followed by colonoscopy for all participants with a positive FIT (positivity cut off ≥ 275 ng/ml, FOB gold, Sentinel, Milan, Italy).

Participating endoscopists were accredited to perform colonoscopies within the Dutch BCSP and had performed colonoscopies within the program for at least one year prior to the start of the study. During the accreditation process, the knowledge and skills of endoscopists were tested by e-learning, by measuring evidence-based quality indicators of colonoscopy and by evaluating practical skills during colonoscopy.[40]

For the sake of the DISCOUNT-2 study, all participating endoscopists were trained in optical diagnosis with the validated Workgroup SerrAted polypS and Polyposis (WASP) module. [41] This training phase consisted of an image-based and a real-time training phase. Endoscopists were required to meet predefined thresholds in the training phase before entering the continuation phase of the DISCOUNT-2 study. Further details of the training and the predefined thresholds are described elsewhere.[38]

According to the study protocol of the DISCOUNT-2 study, all detected colorectal lesions were removed, with the exception of multiple (≥ 3) diminutive hyperplastic polyps (HP) detected in the rectosigmoid. These lesions were left in situ and the endoscopist was instructed to biopsy at least one polyp that represented the sample. The endoscopists recorded their optical diagnosis of all polyps during white light endoscopy (WLE) and Narrow Band Imaging (NBI) including their confidence levels.[38]

Colonoscopy features and polyp data collection

During the continuation phase of the DISCOUNT-2 study, all details on colonoscopy were recorded by a structured colonoscopy reporting system with an obligatory choice of fixed text-blocks. Data on evidence-based quality indicators of colonoscopy, such as depth of insertion of the colonoscope, cleanliness of the bowel as assessed with the validated Boston Bowel Preparation Scale (BBPS) and the type of bowel preparation solution were incorporated in the reporting system as well.[42-45]

For this study we collected data based on patient demographics (e.g. age, gender and American Society of Anesthesiologists (ASA) Classification) and polyp characteristics (e.g. location, lesion size assessed by the endoscopist during colonoscopy, morphology, applied treatment and histology diagnosis). Results of the BBPS and maximum insertion depth of the colonoscope by segment were collected as well. All data were entered into an online CastorEDC database.[46]

Histopathologic assessment

All resected colorectal lesions were collected in separate numbered containers for histopathological assessment, which is part of the Dutch BCSP. All lesions were assessed by accredited pathologists with expertise in gastrointestinal pathology in the local hospital. The histopathologic assessment was performed according to the World Health Organisation (WHO) 2010 Classification.[47]

Inclusion and exclusion criteria

For this exploratory post-hoc analysis we only included the complete colonoscopies performed by endoscopists who performed at least 50 complete colonoscopies within the continuation phase of the DISCOUNT-2 study. Colonoscopies performed in patients with the endoscopic suspicion of polyposis syndrome and inflammatory bowel disease, were excluded.

Study outcomes and statistical analysis

For each endoscopist who performed at least 50 complete colonoscopies during the continuation phase of the DISCOUNT-2 study individual premalignant polyp detection rates were calculated. The calculated detection rates consisted of the ADR (the proportion of colonoscopies in which at least one histopathologically confirmed adenoma was detected), the MAP (the mean number of histopathologically proven adenomas detected per colonoscopy), the PSPDR (the proportion of colonoscopies in which at least one histopathologically confirmed proximal SP defined as an HP, sessile serrated lesion (SSL) or traditional serrated adenoma (TSA) was detected) and the mean number of histopathologically proven proximal located SPs detected per colonoscopy. The proximal colon was defined as proximal to the descending colon (splenic flexure, transverse colon, ascending colon and cecum), in accordance with the Dutch guideline for colonoscopy surveillance.[48] All SPs detected in the proximal colon were included to measure the PSPDR, regardless of polyp size and histopathology.

The diagnostic test sensitivities of optical diagnosis were calculated for all adenomas and proximal SPs with a diameter of 1-5 mm considering the histopathological diagnosis as the reference standard. Only endoscopic histology predictions of polyps with a diameter of 1-5 mm with high confidence were used to calculate the sensitivity of optical diagnosis of adenomas and SPs. Due to the limited number of detected SSLs and high-confidence histopathology predictions of SSLs per individual endoscopist within the DISCOUNT-2 study, we decided not to separately analyze the SSL detection rate and the sensitivity of optical diagnosis of SSLs.

Count variables as well as categorical variables were reported as percentages. The MAP and the mean number of proximal SPs were considered as Poisson distributed data and were therefore

reported as mean ± standard deviation (SD). Generalized estimating equations modeling using binary logistic regression adjusted for clustering of polyps and patients per endoscopist was used to compare the categorical ADR, PSPDR and sensitivity of optical diagnosis of adenomas and SPs. Generalized estimating equations using Poisson logistic modeling adjusted for clustering of polyps and patients per endoscopist was used to compare the Poisson distributed data, such as the MAP and mean number of proximal SPs detected per colonoscopy, between endoscopists.

Funnel plots were created to further investigate the potential variation in the ADR and PSPDR. Funnel plots were created to evaluate ADR and PSPDR of each individual endoscopist with respect to the overall mean ADR and PSPDR of the study by using approximate upper and lower 95% confidence limits. To further investigate potential intra-endoscopist variability in these premalignant polyp detection rates, ADR and PSPDR were compared between the first 50 complete colonoscopies and the last 50 complete colonoscopies of endoscopists who performed more than 100 complete colonoscopies in this study.

The correlation between the ADR, PSPDR, MAP, mean number of proximal SPs and sensitivity of optical diagnosis of adenomas and SPs was calculated using the Pearson's rho (ρ) correlation coefficient for all endoscopists who performed at least 50 complete colonoscopies. A p-value < 0.05 was regarded statistically significant. All statistical analyses were performed by using SPSS Statistics version 24 (SPSS, Chicago, Illinois, USA).

RESULTS

Colonoscopy characteristics

In total, 27 endoscopists performed 3144 colonoscopies in the DISCOUNT-2 study, of which 24 endoscopists performed at least 50 complete colonoscopies. These 24 endoscopists performed a total of 2955 colonoscopies, of which 2889 were complete and were therefore eligible for inclusion in the analyses (*Figure 1*). The overall cecal intubation rate was 97.8% (2889/2995), which was not significantly different between the participating endoscopists (*Supplementary table A1*). Median age of the patients was 66 years (IQR 63-69) and 60.4% was male. Other patient demographics and colonoscopy quality indicators of these 2889 complete colonoscopies are described in *Table 1*.

Endoscopist performance in adenoma and SP detection

In this cohort of 2889 complete colonoscopies, a total of 6828 adenomas and 1644 SPs (1.308 HPs and 336 SSLs) were detected (*Table 2*). For all endoscopists, overall ADR was 84.5% (range 71.4-95.3%), MAP was 2.33 ± 2.2 (range 1.52 ± 1.84 - 3.64 ± 3.06), PSPDR was 13.7% (range 4.3-29.0%) and mean number of proximal SPs detected per colonoscopy was 0.19 ± 0.55 (range 0.04 ± 0.20 - 0.43 ± 0.81). Among endoscopists, all detection rates were significantly different (p < 0.001). For details per endoscopist see *Table 2* and *3*.

Funnel plots showing each individual endoscopist's ADR and PSPDR with respect to the overall mean of the study are shown in *Figure 2a* and *2b*, respectively. With the exception of one endoscopist, all endoscopists achieved an ADR above the lower 95% confidence limit. One endoscopist had an ADR above the upper 95% confidence limit. All endoscopists had a PSPDR above the lower 95% limit and one endoscopist was an outlier with a PSPDR above the upper 95% confidence limit.

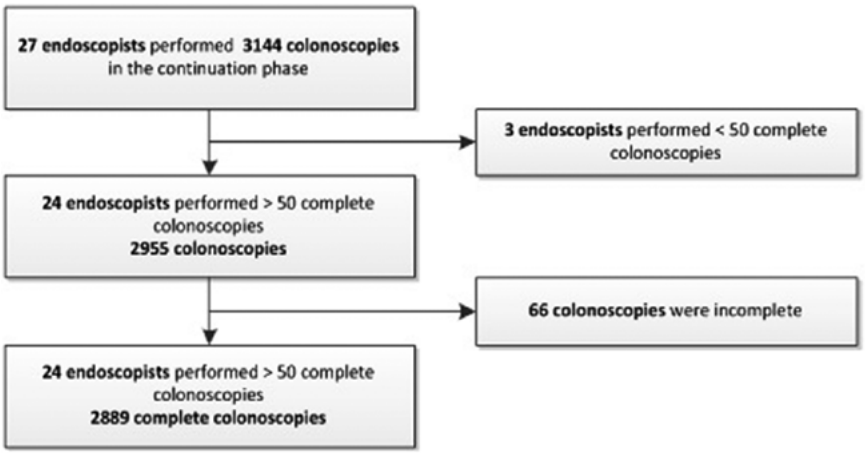


Figure 1. Flowchart of in and excluded colonoscopies in the study

Table 1. Patient demographics and colonoscopy quality indicators of all complete colonoscopies performed among endoscopists whom performed > 50 complete colonoscopies

	Complete colonoscopy (n = 2889)
Patient demographics	
Male – no patients (%)	1774 (60.4%)
Median age – years (IQR)	66 (63-69)
ASA classification – no patients (%)	
I : Healthy	699 (24.2%)
II: Mild systemic disease	2034 (70.4%)
III: Severe systemic disease	51 (1.8%)
Missing	105 (3.6%)
Colonoscopy quality indicators	
Unadjusted cecum intubation rate – no patients (%)	2889 (100%)
BBPS ≥ 6 – no patients (%)	2796 (96.8%)
Median BBPS (IQR)	9.00 (8.00-9.00)
Median withdrawal time (negative colonoscopies) – minutes:seconds	8:00 (6:00-10:00)

The differences in ADR and PSPDR between the first 50 complete colonoscopies and the last 50 complete colonoscopies of endoscopists who performed more than 100 complete colonoscopies within the study are presented in *Table 4* and *5*. No significant differences were found when assessing the overall ADR (83.7% vs 83.9%, p-value 0.94) and PSPDR (12.1% vs 14.3%, p-value 0.24) between the first 50 and last 50 performed complete colonoscopies. When assessing individual endoscopists, the ADR of endoscopist 17 significantly increased from 66.0% to 86.0% and of endoscopist 8 the PSPDR significantly increased from 4.0% to 16.0%.

Table 2. Overall detection rates and diagnostic test sensitivites of all complete colonoscopies performed

	Complete colonoscopies (n = 2889)
Total number of detected lesions – No (%)	9415
Adenomas	6828 (72.5%)
Hyperplastic polyps	1308 (13.9%)
SSLs	336 (3.5%)
SSLs with dysplasia	37 (0.39%)
Carcinoma	126 (1.3%)
Other non-neoplastic	524 (5.6%)
Lesion not retrieved for histopathology	293 (3.1%)
Detection rates	
ADR – No (%)	2441 (84.5%)
MAP ± SD	2.33 ± 2.2
PSPDR – No (%)	396 (13.7%)
Mean number of proximal SPs per patient ± SD	0.19 ± 0.55
Diagnostic test sensitivities	
Sensitivity for adequate endoscopic prediction of adenomas (diameter 1-5mm)*– No (%)	2233 (94.5%)
Sensitivity for adequate endoscopic prediction of SPs (diameter 1-5mm)*– No (%)	526 (74.0%)

* Only endoscopic histology predictions with high confidence were used to calculate the sensitivity of adenomas and SPs

Endoscopists' diagnostic test sensitivities

Adenomas and SPs with a diameter of 1-5 mm were correctly optically diagnosed with high confidence in 93.5% (range 83.3-100%) and 74.0% (range 37.5-94.1%), respectively. All diagnostic test sensitivities were significantly different among endoscopists ($p < 0.001$), details per endoscopist are listed in *Table 6*.

Correlation between the diagnostic test sensitivities and the adenoma and SP detection

The correlation between the ADR, MAP, PSPDR, the mean number of proximal SPs and the diagnostic test sensitivities is presented in *Table 7* and *Supplementary figures A1a* and *A1b*. No significant correlations between the detection of adenomas and the sensitivity of optical diagnosis of adenomas could be demonstrated (ADR and adenoma sensitivity ρ -0.20, p-value 0.35, MAP and adenoma sensitivity ρ 0.14, p-value 0.50). Also no correlation could be demonstrated between the detection of proximal SPs and its associated diagnostic test sensitivities (PSPDR and SP sensitivity ρ -0.12, p-value 0.57 and mean number of proximal SPs detected per colonoscopy and SP sensitivity ρ -0.08, p-value 0.70).

Table 3. Detection rates of the complete colonoscopies performed per endoscopist

Endoscopist	No of procedures	ADR* (%)	MAP* (%)	PSPDR* (%)	Mean no proximal SP* (%)
1	82	86.6%	3.05 ± 2.64	22.0%	0.27 ± 0.57
2	113	77.9%	2.04 ± 1.76	10.6%	0.13 ± 0.41
3	222	86.5%	2.45 ± 2.34	13.5%	0.18 ± 0.50
4	155	85.8%	2.76 ± 2.44	**29.0%**	**0.43 ± 0.81**
5	146	74.0%	1.81 ± 2.21	8.2%	0.09 ± 0.31
6	94	91.5%	2.54 ± 1.89	10.6%	0.24 ± 0.86
7	168	81.0%	2.16 ± 1.9	13.1%	0.16 ± 0.47
8	188	82.4%	2.23 ± 2.06	10.6%	0.13 ± 0.45
9	134	88.1%	2.26 ± 1.81	11.9%	0.14 ± 0.41
10	124	92.7%	2.84 ± 2.12	16.1%	0.18 ± 0.44
11	122	76.2%	1.73 ± 1.81	4.9%	0.06 ± 0.27
12	116	87.1%	1.64 ± 1.23	**4.3%**	**0.04 ± 0.20**
13	110	84.5%	1.96 ± 1.70	10.0%	0.13 ± 0.41
14	57	89.5%	2.19 ± 1.62	22.8%	0.30 ± 0.63
15	129	**95.3%**	2.99 ± 2.41	17.8%	0.20 ± 0.47
16	92	84.8%	2.25 ± 2.11	20.7%	0.30 ± 0.71
17	184	79.3%	2.18 ± 2.28	14.1%	0.20 ± 0.60
18	95	84.2%	2.20 ± 1.95	14.7%	0.18 ± 0.46
19	160	90.0%	**3.64 ± 3.06**	16.9%	0.26 ± 0.72
20	74	83.8%	2.97 ± 3.21	18.9%	0.27 ± 0.73
21	90	78.9%	1.69 ± 1.61	7.8%	0.13 ± 0.56
22	70	**71.4%**	**1.52 ± 1.84**	8.6%	0.10 ± 0.35
23	65	93.8%	2.39 ± 1.82	13.8%	0.20 ± 0.62
24	99	86.9%	1.96 ± 1.74	11.1%	0.19 ± 0.67
Overall	**2889**	**84.5%**	**2.33 ± 2.2**	**13.7%**	**0.19 ± 0.55**

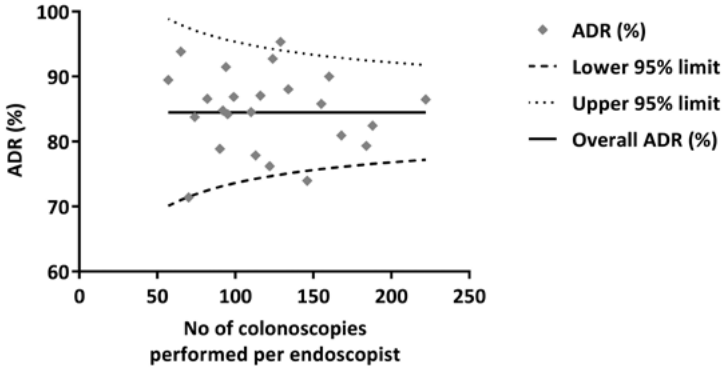
* p-value < 0.001 The highest and lowest detector are presented in bold

DISCUSSION

In this exploratory post-hoc analysis of a prospective, randomized observational multicenter study of colonoscopies performed in a FIT positive population, no correlations could be demonstrated between the ADR, MAP, PSPDR, the mean number of proximal SPs and the sensitivity of optical diagnosis of these polyps.

We hypothesized that as endoscopists with a high ADR and PSPDR might be better at recognizing the endoscopic features of these polyps and thus be better in making a correct optical diagnosis of these polyps. In other words, those endoscopists could perform better in recognizing specific endoscopic features of adenomas and SPs, resulting in their high polyp detection rates. To our surprise however, this correlation could not be demonstrated and based on our exploratory data, training programs primarily focusing on optical diagnosis of polyps resulting in high accuracies in optical diagnosis, do therefore not might seem to help to improve polyp detection rates of the endoscopist as a secondary training benefit.[38] There is, however, very limited evidence on other factors that would help to improve individual polyp detection rates, and therefore more studies are needed to target new colonoscopy improvement initiatives.[49]

A. Funnel plot showing each endoscopists's ADR relative to the global mean



B. Funnel plot showing each endoscopists's PSPDR relative to the global mean

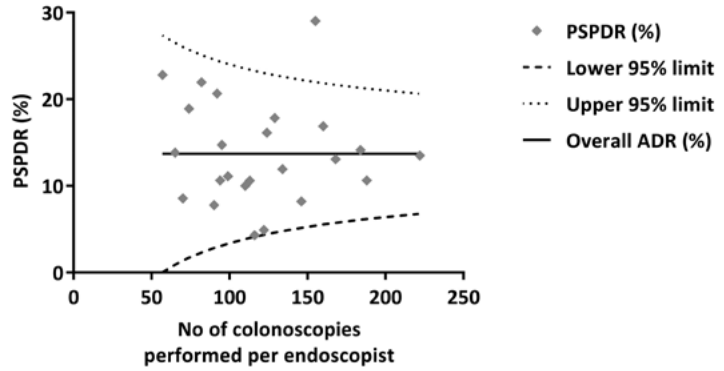


Figure 2. Funnel plot showing each endoscopist's detection rate with respect to the global mean

Our study was performed in a unique study situation where data of both the optical diagnosis, including confidence levels, as well as detection rates of adenomas and proximal SPs were collected in FIT-positive colonoscopies. These procedures were performed according to the current daily practice in the Netherlands and all data was prospectively collected in an era of awareness of the malignant potential of SPs, as well as of the importance of high quality colonoscopy. However, the reason that we were not able to demonstrate a correlation between endoscopic lesion detection and optical diagnosis skills could potentially be explained by the composition of the participating endoscopists of the DISCOUNT-2 study. The participating endoscopists consisted of a homogeneous group of high performing endoscopists, as they were all accredited to perform colonoscopies within the Dutch BCSP. Furthermore they were trained in optical diagnosis by the validated WASP classification and were only enrolled in this study if they met predefined thresholds in the training phase of the DISCOUNT-2 study.[40, 41] In addition, the endoscopists had to perform structured reporting of all polyps in their daily clinical practice, including their optical diagnosis using NBI. Possibly, these requirements resulted in a selected group of endoscopists with a special interest in the subject as well as in clinical research. Besides, all colonoscopies were performed after a positive FIT-result, and this enriched population could have accelerated the learning curve of optical

Table 4. Differences in ADR between the first 50 complete colonoscopies and the last 50 complete colonoscopies performed per endoscopist who performed > 100 complete colonoscopies

Endoscopist	No of procedures	ADR first 50 colonoscopies	ADR last 50 colonoscopies	p-value
2	113	76.0%	76.0%	1.00
3	222	90.0%	92.0%	0.73
4	155	86.0%	82.0%	0.59
5	146	74.0%	70.0%	0.66
7	168	72.0%	86.0%	0.09
8	188	84.0%	84.0%	1.00
9	134	96.0%	88.0%	0.14
10	124	96.0%	86.0%	0.08
11	122	80.0%	70.0%	0.25
12	116	84.0%	86.0%	0.78
13	110	84.0%	82.0%	0.79
15	129	96.0%	98.0%	0.56
17	184	66.0%	86.0%	0.02
19	160	88.0%	88.0%	1.00
Overall	**2889**	**83.7%**	**83.9%**	**0.94**

Table 5. Differences in PSPDR between the first 50 complete colonoscopies and the last 50 complete colonoscopies performed per endoscopist who performed > 100 complete colonoscopies

Endoscopist	No of procedures	PSPDR first 50 colonoscopies	PSPDR last 50 colonoscopies	p-value
2	113	10.0%	10.0%	0.75
3	222	14.0%	14.0%	0.34
4	155	30.0%	30.0%	0.66
5	146	8.0%	8.0%	0.73
7	168	10.0%	20.0%	0.16
8	188	4.0%	16.0%	0.05
9	134	10.0%	14.0%	0.54
10	124	14.0%	14.0%	1.00
11	122	6.0%	4.0%	0.65
12	116	4.0%	6.0%	0.65
13	110	12.0%	8.0%	0.51
15	129	14.0%	18.0%	1.00
17	184	10.0%	20.0%	0.16
19	160	20.0%	24.0%	0.63
Overall	**2889**	**12.1%**	**14.3%**	**0.24**

diagnosis of these endoscopists. Possibly, having a more heterogeneous group of endoscopists could have influenced the results of our study. However, Pohl et al published a study with similar findings and found no difference between low and high adenoma detectors in achieving optical

Table 6. Diagnostic test sensitivities of the complete colonoscopies performed per endoscopist

Endoscopist	No of procedures	Sensitivity adenomas (%)*	Sensitivity SPs (%)*
1	82	99.0%	73.9%
2	113	86.9%	72.7%
3	222	97.5%	81.3%
4	155	98.4%	77.4%
5	146	95.0%	83.3%
6	94	97.6%	84.0%
7	168	92.5%	85.3%
8	188	97.2%	**56.0%**
9	134	88.9%	83.3%
10	124	98.5%	**94.1%**
11	122	97.3%	71.4%
12	116	91.2%	85.7%
13	110	**100%**	37.5%
14	57	87.5%	53.8%
15	129	83.9%	66.7%
16	92	88.0%	65.4%
17	184	88.7%	73.9%
18	95	90.6%	82.4%
19	160	**100%**	70.8%
20	74	96.0%	63.6%
21	90	94.0%	73.3%
22	70	97.3%	63.2%
23	65	**83.3%**	76.5%
24	99	97.1%	90.9%
Overall	**2889**	**94.5%**	**74.0%**

* p-value < 0.001. Only endoscopic histology predictions with high confidence of polyps 1-5 millimeters were used to calculate the sensitivity. The highest and lowest detector are presented in bold

Table 7. Pearson coefficient for detection rates and diagnostic test sensitivities

Comparison	Pearson rho (ρ)	p-value
ADR - sensitivity for adenomas	-0.20	0.35
MAP - sensitivity for adenomas	0.14	0.50
PSPDR - sensitivity for SPs	-0.12	0.57
Mean no prox SPs - sensitivity for SPs	-0.08	0.70

diagnosis quality benchmarks according to the PIVI statements.[50] Both our studies might underline that lesion detection and accurate histology prediction require different endoscopic skills and both should be monitored to assure a high quality, but also effective colonoscopy practice. However, both our studies consisted of post-hoc analyses of multicenter randomized trials, and therefore inherit the important limitation that they were not powered to demonstrate a correlation between

endoscopic lesion detection and differentiation skills. A prospective study would therefore provide more definite evidence for a potential correlation.

Furthermore, another limitation of our study has to be acknowledged as well. A relatively small number of colonoscopies per endoscopist and thus, for the assessment of individual performance only a limited number of individual observations for diagnostic test accuracy with high confidence were available for the separate assessment of SP subtypes. This was the reason why we were not able to analyze the correlation between the SSL detection rate and the sensitivity of optical diagnosis of SSLs for individual endoscopists. Therefore, it was decided to analyze the correlation between the PSPDR and the optical diagnosis of SPs, even though endoscopists were trained in optical diagnosis with the validated WASP, which differentiates between adenomas, HPs and SSLs.

Among participating endoscopists, both ADR and PSPDR were highly variable. Only two endoscopists had an ADR below or above the 95% confidence limit with respect to the overall mean ADR and one endoscopist achieved a PSPDR above the 95% confidence limit. The large variation in ADR and PSPDR does not seem to be caused by a high intra-individual variability or learning curve per endoscopist, as only two endoscopists significantly increased their ADR or PSPDR during the course of the study. The variations in adenoma and proximal SP detection rates may suggest considerable lesion miss rates for low detecting endoscopists.[18, 19, 30-37] However, although ADR has been inversely correlated with the occurrence of PCCRCs and CRC-related mortality in large primary colonoscopy screening cohorts, the long-term consequences of variances in ADR in FIT-screening are not yet known.[18, 19] The consequence of low proximal SP detection rates for any colonoscopy indication remains unknown as well, as the PSPDR has not yet been associated with PCCRCs and CRC-related mortality. Previous research demonstrated that the wide variation in ADR among endoscopists might be caused mainly by variations in detection of small and flat adenomas. However, the clinical relevance of these small adenomas can be questioned, as it is unknown whether the improved detection of these adenomas will also result in a reduction of PCCRCs on the long run. These small adenomas harbor a low risk of harboring CRC, and if they would ever progress to cancer this would take many years (estimated 10-15 years).[51] Besides, most patients who underwent a colonoscopy where adenomas were detected will receive subsequent surveillance colonoscopies. So if small low-risk adenomas are missed during the initial colonoscopy, these lesions might still only harbor low risk features when detected during the subsequent surveillance colonoscopy.[48, 51]

Based on these data, it can be concluded that ADR and PSPDR vary widely among accredited endoscopists performing colonoscopies in a FIT-positive population. No correlation between adenoma and proximal SP detection and the sensitivity of the optical diagnosis of these polyps could be demonstrated. Our exploratory results indicate that achieving quality in these parameters requires different endoscopic skills, however further prospective studies primarily addressing the aim are needed to draw definitive conclusions. Until then, accurate training, monitoring and auditing of both performance indicators is important to secure optimal efficacy of a FIT-based CRC screening program.

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APPENDIX

Table A1. Cecal intubation rate (CIR) of all colonoscopies performed per endoscopist

Endoscopist	No of procedures	CIR (%)	P-value
1	84	97.6%	0.73
2	117	96.6%	
3	227	97.8%	
4	158	98.1%	
5	148	98.6%	
6	96	97.9%	
7	170	98.8%	
8	191	98.4%	
9	136	98.5%	
10	124	100%	
11	125	97.6%	
12	118	98.3%	
13	112	98.2%	
14	60	96.6%	
15	129	100%	
16	93	98.9%	
17	189	97.4%	
18	99	96.0%	
19	162	98.8%	
20	80	92.5%	
21	93	96.8%	
22	73	95.9%	
23	68	95.6%	
24	103	96.1%	
Overall	**2955**	**97.8%**	

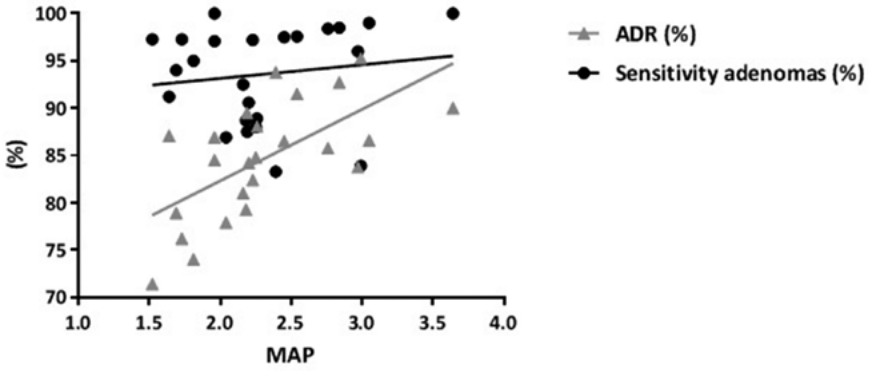

Figure A1a. Correlation between the ADR and sensitivity to predict adenomas
* Correlation ADR-MAP ρ 0.64, p-value 0.001; ADR-sens adenomas ρ -0.20, p-value 0.35; MAP-sens adenomas ρ 0.14, p-value 0.50. Each data point represents the ADR and sensitivity of optical diagnosis of adenomas with high confidence of an individual endoscopist, which are superimposed in the figure. The 95% CI of the ADR slope is: 3.50-11.62. The 95% CI of the sensitivity of adenomas slope is: -2.95 to 5.83.

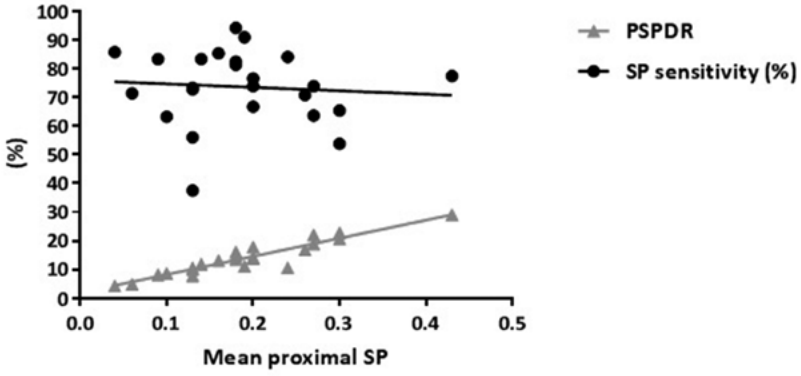

Figure A1b. Association between the PSPDR and sensitivity to predict SPs
* Correlation PSPDR-mean no proximal SP ρ 0.94, p-value < 0.001; PSPDR-SP sensitivity ρ -0.12, p-value 0.57; mean no proximal SPs-SP sensitivity ρ -0.08, p-value 0.70. Each data point represents the PSPDR and sensitivity of optical diagnosis of SPs with high confidence of an individual endoscopist, which are superimposed in the figure. The 95% CI of the PSPDR slope is: 52.92-73.43. The 95% CI of the sensitivity of SPs slope is: -76.42 to 52.44.

Table A2. Pearson coefficient for detection rates and diagnostic test sensitivities of all colonoscopies performed

Comparison	Pearson rho (ρ)	p-value
ADR - sensitivity for adenomas	-0.21	0.33
MAP - sensitivity for adenomas	0.13	0.54
PSPDR - sensitivity for SPs	-0.12	0.58
Mean no prox SPs - sensitivity for SPs	-0.08	0.70

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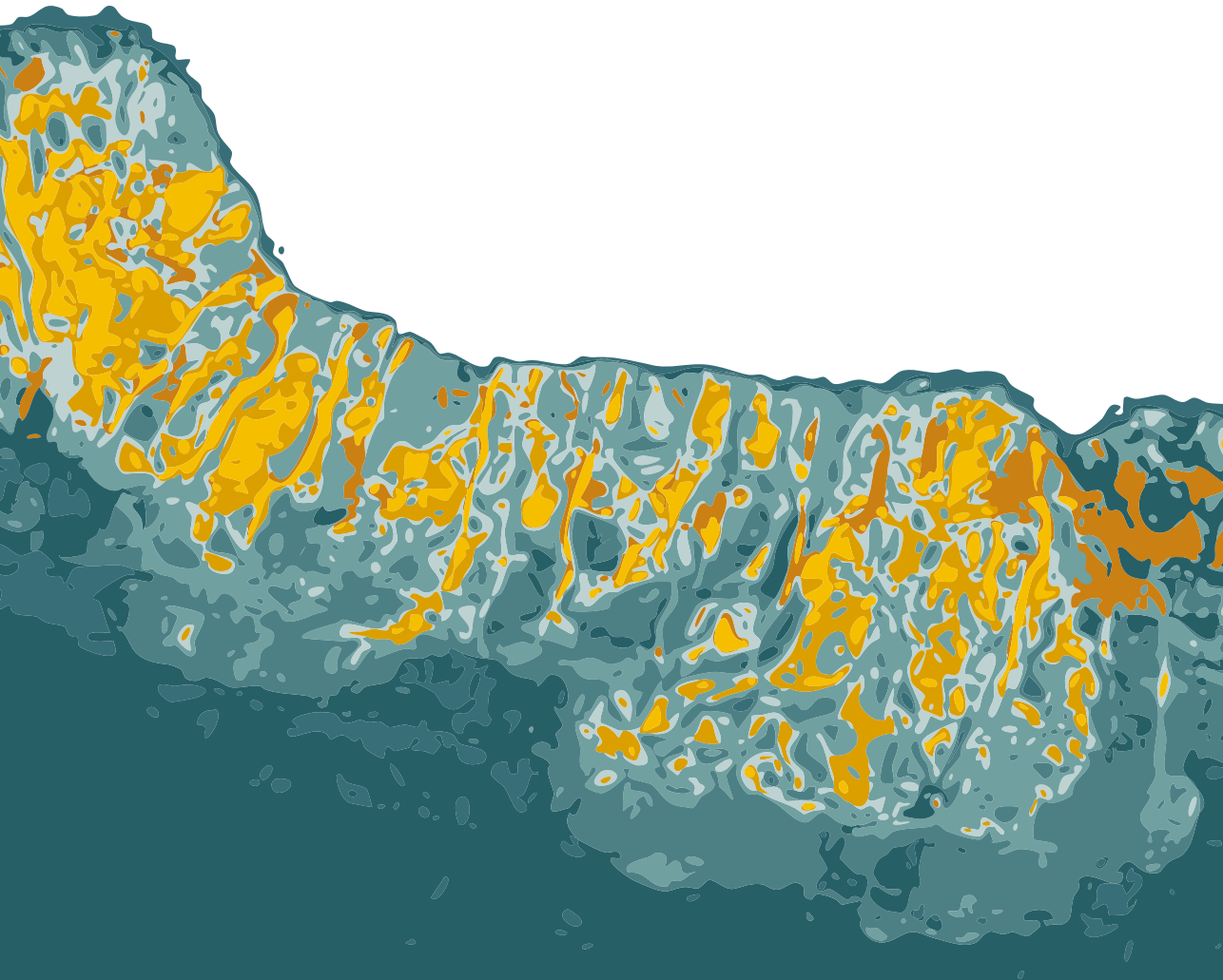

FEASIBILITY, SAFETY AND DIAGNOSTIC YIELD OF THE EXTRA WIDE ANGLE VIEW (EWAVE) COLONOSCOPE FOR THE DETECTION OF COLRECTAL LESIONS

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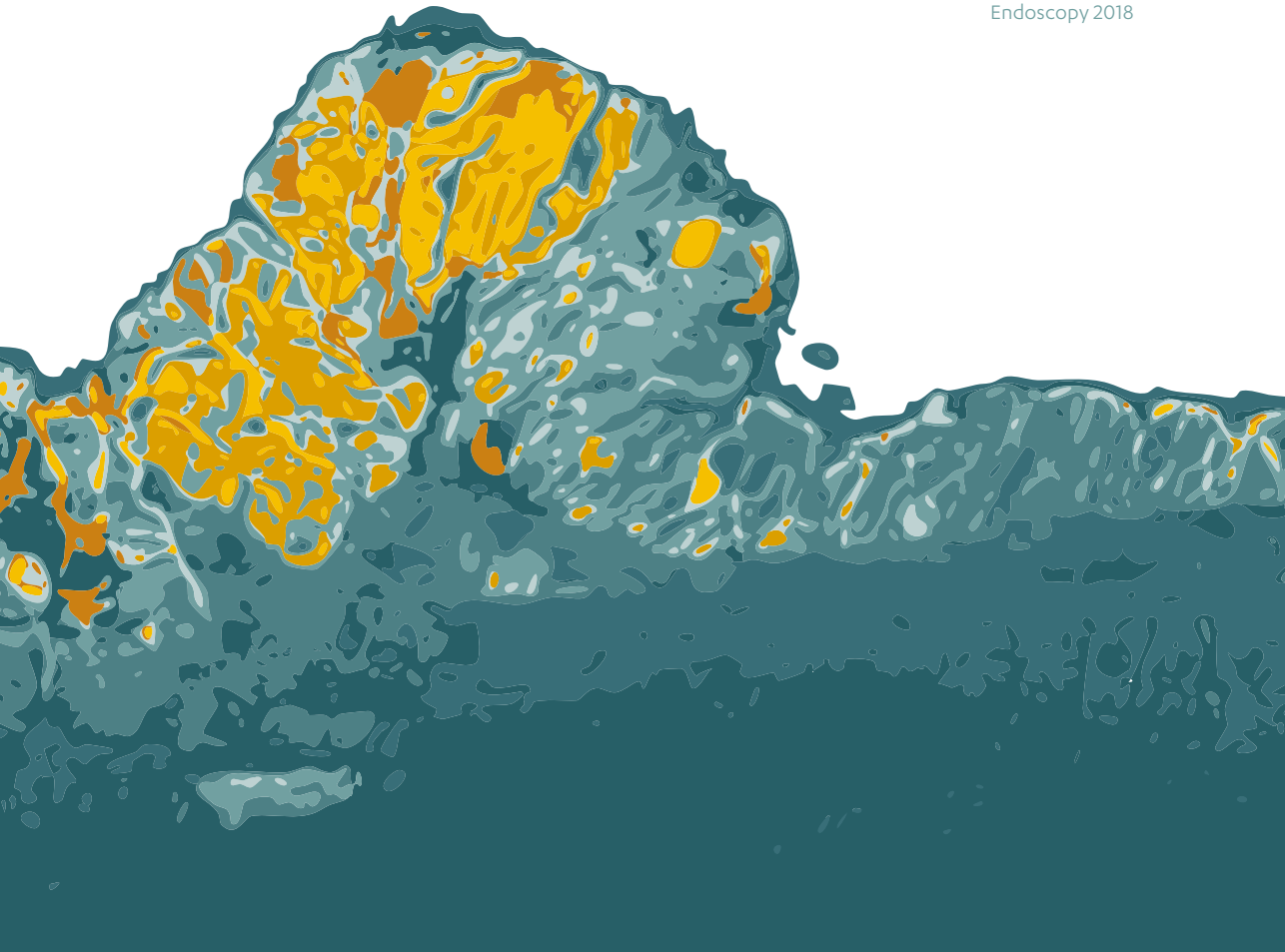
Endoscopy 2018



ABSTRACT

Background and study aims

The adenoma detection rate (ADR) of conventional colonoscopy can still be improved. We conducted a prospective multicentre cohort study assessing the feasibility, safety and diagnostic yield of the Extra Wide Angle View (EWAVE) colonoscope offering a 235° view obtained from a forward-viewing and two lateral backward-viewing lenses incorporated into one image.

Patients and methods

The study was performed between November 2015 and June 2016. EWAVE-colonoscopy was performed in patients with an increased risk of colorectal cancer by experienced and EWAVE-trained endoscopists (≥500 colonoscopies, ≥10 with the EWAVE system).

Results

A total of 193 patients underwent EWAVE colonoscopy. The cecal intubation rate was 97.4%. EWAVE colonoscopy had a polyp detection rate (PDR) of 61.1% (118/193), ADR of 39.9% (77/193) and advanced ADR of 13.5% (26/193). No adverse events occurred.

Conclusions

EWAVE colonoscopy is feasible and safe. The ADR appears comparable to those achieved with conventional colonoscopes in similar patient populations. To further elucidate the additional benefits of wide-angle view colonoscopes randomized trials would be required.

INTRODUCTION

Colonoscopy is the reference standard for the detection and removal of colorectal adenomas, the well-known precursor lesions of colorectal cancer (CRC).[1] Colonoscopy is associated with a significant adenoma miss rate of 22%, which might result in post-colonoscopy interval cancers.[2, 3] In order to improve colonic surface visualisation and thereby aiming to increase adenoma detection rates, several surface exposing technologies have been proposed. However, results on adenoma detection rates (ADR) and adenoma miss rates have been variable between studies.[4]

Recently the Extra Wide Angle View (EWAVE) colonoscope was developed (Olympus Medical Systems), which offers a 235° view obtained from a forward-viewing as well as two lateral backward-viewing lenses incorporated into one image. We conducted a prospective multicentre cohort study assessing the feasibility, safety and diagnostic yield of the EWAVE colonoscope for the detection of colorectal adenomas.

PATIENTS AND METHODS

This prospective multicenter cohort study was performed between November 2015 and June 2016 in five endoscopy centers (University Hospital Hamburg-Eppendorf, Hamburg; Klinikum Garmisch-Partenkirchen, Garmisch-Partenkirchen; Evangelischen Krankenhaus Düsseldorf, Düsseldorf; Academic Hospital Edouard Herriot, Lyon and Bergman Inwendige Zorg Amsterdam (IZA) at the Academic Medical Centre, Amsterdam). The study (NTR4536, www.trialregister.nl) was approved by all ethical committees. Written informed consent was obtained from all patients.

Patients

Patients with an increased risk of colorectal cancer scheduled for conventional colonoscopy were invited to participate. An increased risk of colorectal cancer was defined as a positive fecal occult blood test (FOBT), a personal history of colorectal cancer or colorectal adenomas, positive family history of colorectal cancer or symptoms suggestive for colorectal neoplasms. Exclusion criteria were patients known with polyposis syndromes, polyps with a polypectomy indication, inflammatory bowel disease (IBD), complications of colonic diverticulosis, prior abdominal surgery, coagulation abnormalities, anticoagulant use, American Society of Anesthesiologists (ASA) score greater than 2 and pregnant or lactating patients.

EWAVE colonoscopy

Patients received sedation and bowel preparation in accordance with local practice in the endoscopy clinics. A total Boston Bowel Preparation Score (BBPS) of ≥ 6 was considered adequate. All EWAVE colonoscopies were performed by experienced and EWAVE-trained endoscopists (≥500 colonoscopies, ≥10 with the EWAVE system).

The EWAVE colonoscope is a prototype and consists of two lateral-backward viewing lenses with a side view of 42.5° in addition to a 147° forward viewing lens (*Figure 1a*). A death angle of 3° is present between the lenses, resulting in a total view of 235°. Views obtained from both lenses are simultaneously constructed and displayed as one image (*Figure 1b*). The colonoscope is equipped

with a variable-stiffness function and Narrow Band Imaging (NBI), but no High Definition (HD) is incorporated.[5]

Endoscopists intubated the cecum without performing polypectomies during introduction; intubation of the terminal ileum was not intended systematically. If polyps were detected endoscopic removal of these lesions was attempted according to the polypectomy technique selected by the endoscopist. Hyperplastic polyps smaller than 10 mm located in the lower rectosigmoid were considered for detection analysis, but were not endoscopically removed. Polyp features including polyp size, location and morphology (Paris Classification) were reported. Each polyp was numbered in the sequence of discovery and sent to histopathology in a separate specimen container. Cecal intubation and colonoscope withdrawal time were recorded with a system clock. No recommendations were given about the minimum or maximum duration of colonoscope withdrawal.

Histopathology and adverse events:

Histopathology was processed using the standard methods and evaluated by local dedicated GI pathologists according to the Vienna criteria.[6] All procedural and post-procedural adverse events (14 days after the procedure) were recorded.

Outcome measures and statistical analysis

The primary endpoint was the ADR; the proportion of colonoscopies in which at least one histologically confirmed adenoma was detected. Secondary endpoints included: overall detection of polyps, the polyp detection rate (PDR), the advanced ADR, sessile serrated lesion (SSL) detection rate, cecal insertion time and the occurrence of adverse events.

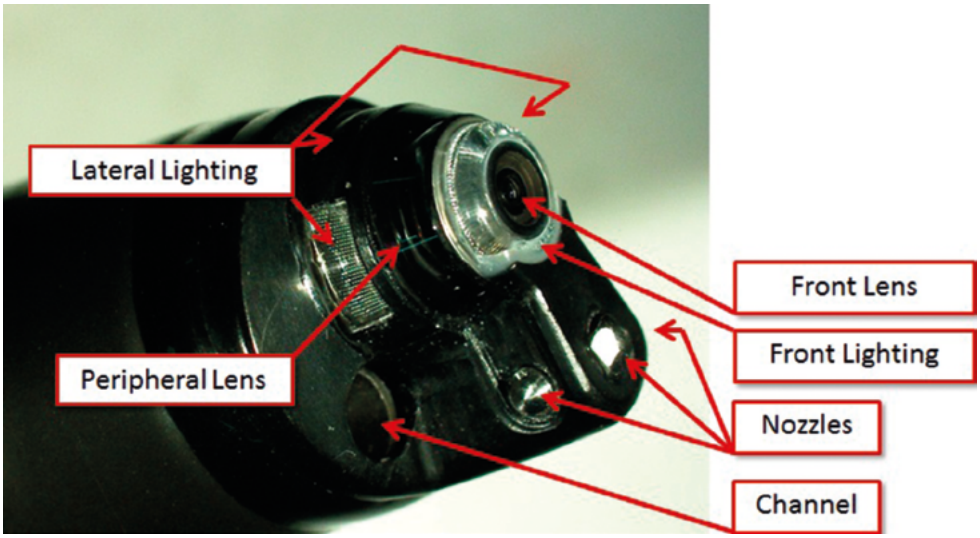


Figure 1a. Picture of the EWAVE colonoscope prototype

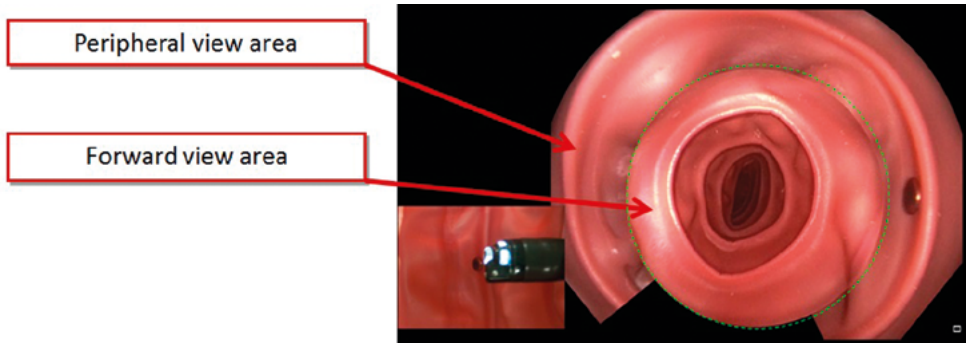


Figure 1b. Animation of the endoscopic image of the EWAVE colonoscope with a polyp detected in the lateral backward-viewing lense

The descriptive data are reported as median with interquartile range (IQR) or mean ± standard deviation where appropriate. Numerical data were analysed using the student β t-test or Mann-Whitney U test according to the distribution. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 23 (SPSS, Chicago, IL, USA).

RESULTS

Patients

Between November 2015 and June 2016 200 patients consented to participate and 193 underwent EWAVE colonoscopy (*Figure 2*). Patient demographics are shown in *Table 1*. During the study, technical problems involving the durability of the lens system occurred and replacement colonoscopes of the same EWAVE prototype were not available. Therefore patient inclusion was ceased and it was decided to report on the performed procedures until that moment.

EWAVE colonoscopy characteristics

Five patients had an incomplete EWAVE colonoscopy caused by colonic obstruction, poor bowel preparation, colonoscope looping or technical problems. The cecal intubation rate was 97.4% (*Table 2*). The median cecal intubation time was 4:00 minutes (IQR 02:00-07:00) and mean net withdrawal time was 16:00 ± 06:49 minutes. There was no significant decrease in the mean net withdrawal time during the second half of the study (16:55 ± 07:06 vs 15:03 ± 06:25, p = 0.06) as shown in *Table 3*. No adverse events were reported.

Lesion characteristics and lesion detection rates

During EWAVE colonoscopy, a total of 260 polyps and 4 colorectal cancers were detected in 118 patients. Endoscopic as well as histopathological characteristics of the polyps are shown in *Table 4*. During EWAVE colonoscopy 99.2% (n = 258) of the polyps were removed endoscopically. The remaining two polyps were removed during an additional colonoscopy.

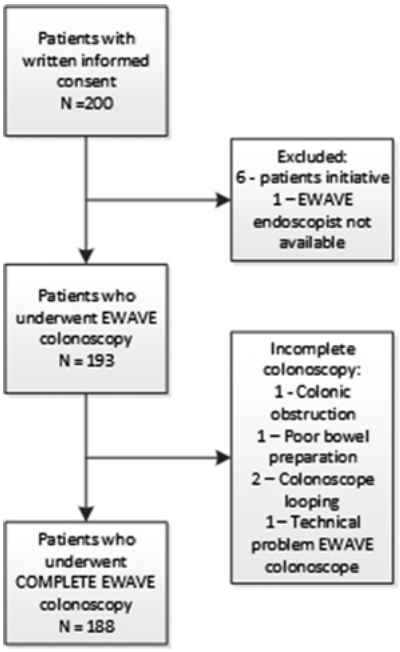


Figure 2. Flow-chart patient inclusion

Table 1. Patient characteristics

Patient characteristics	N=200
Gender (%)	
Male	97 (48.5%)
Female	103 (51.5%)
Mean age - years (SD)	60.8 (13.2)
ASA classification (%)	
I: Healthy	114 (57.0%)
II: Mild systemic disease	86 (43.0%)
Median BMI (kg/m2) (IQR)	25.9 (23.0-29.6)
Patients with ≥ 1 indication (%)	26 (13.0%)
Colonoscopy indication (%)	
Symptoms*	99 (49.5%)
Personal history of CRC or adenoma	66 (33.0%)
Familial history of CRC or adenoma	47 (23.5%)
FOBT positive	10 (5.0%)
No of scheduled colonoscopies per center (%)	
1	16 (8.0%)
2	20 (10.0%)
3	21 (10.5%)
4	38 (19.0%)
5	105 (52.5%)

* Symptoms: rectal blood loss, change in bowel habits or abdominal pain

Table 2. Colonoscopy characteristics

Colonoscopy characteristics	N=193
Bowel Cleansing procedure given (%)	
PEG	189 (98.0%)
Picosulfate	2 (1.0%)
PhosphoSoda	1 (0.5%)
Cleanprep	1 (0.5%)
Bisacodyl	19 (9.8%)
Adequate total BBPS (≥ 6) - no of patients (%)	177 (91.7%)
Sedation used (%)	188 (97.9%)
Hypnotics (propofol)	79 (42.0%)
Opioides (fentanyl/remifentanyl)	35 (18.6%)
Benzodiazepines (diazepam/midazolam)	18 (9.6%)
Sedation given by anesthesiologist? (%)	22 (11.4%)
Complete colonoscopy - no of patients (%)	188 (97.4%)
Total duration of Colonoscopy - mean minutes:seconds (SD)*	23:42 (09:28)
Cecal intubation time - median minutes:seconds (IQR)*	04:00 (02:00-07:00)
Withdrawal time – mean minutes:seconds (SD)*	18:31 (08:48)
Net Withdrawal time - mean minutes:seconds (SD)*/**	16:00 (06:50)

* Only complete colonoscopies were analyzed
** Net withdrawal time is the withdrawal time recorded without the time taken to remove the detected lesions

Table 3. Differences in net withdrawal time

	First half of the included patients per endoscopy center	Second half of the included patients per endoscopy center	p-value
Overall net withdrawal time mean (SD)*	16:55 (07:06)	15:03 (06:25)	0.06
Net withdrawal per participating center – mean (SD)*			
Center 1 (n=8 vs n=7)	21:15 (05:07)	16:48 (06:27)	0.16
Center 2 (n=8 vs n=8)	13:08 (05:40)	12:31 (03:46)	0.80
Center 3 (n=11 vs n=10)	17:01 (03:44)	16:10 (07:02)	0.73
Center 4 (n=19 vs n=19)	12:17 (07:22)	08:18 (02:14)	0.03
Center 5 (n=49 vs n=49)	18:47 (07:01)	17:25 (05:53)	0.30

* Only complete colonoscopies were analyzed
** Net withdrawal time is the withdrawal time recorded without the time taken to remove the detected lesions

Table 4. Polyp characteristics

Polyp characteristics	N=264
Median lesion size in mm (IQR)	4.0 (3.0-5.75)
Polyp location (%)	
Cecum/Ascending	81 (30.7%)
Transverse	47 (17.8%)
Descending	45 (17.0%)
Sigmoid	48 (18.2%)
Rectum	43 (16.3%)
Lesion morphology (%)	
0-Ip	41 (15.8%)
0-Is	159 (61.2%)
0-IIa	57 (21.9%)
0-IIb	3 (1.2%)
Lesion removed (%)	258 (99.2%)
Cold biopsy	164 (63.6%)
Cold Snare	26 (7.7%)
Polypectomy (snare coagulation)	41 (15.9%)
EMR (lift and snare)	26 (10.1%)
Diagnostic biopsy	3 (1.1%)
Histopathology	
Tubular adenoma	126 (48.8%)
Tubulovillous adenoma	14 (5.4%)
Sessile serrated lesion negative for dysplasia	6 (2.3%)
Hyperplastic	98 (38.0%)
Invasive cancer	4 (1.6%)
Non hyperplastic/non adenoma	5 (1.9%)
Not submitted to histopathology/inadequate sample	11 (4.3%)
Dysplasia in adenomas (%)	
Low-grade dysplasia	135 (96.4%)
High-grade dysplasia	5 (3.4%)

The ADR for EWAVE colonoscopy was 39.9% (n = 77) and the PDR was 61.1 % (n = 118) (*Table 5*). In 13.5% (n = 26) and 2.1% (n = 4) of patients at least one advanced adenoma or at least one SSL was detected.

DISCUSSION

This prospective multicenter cohort study shows that EWAVE colonoscopy is feasible and safe. The cecal intubation rate was 97.4% with a median cecal intubation time of 4:00 minutes (IQR 2:00–7:00). An ADR of 39.9% was achieved and no adverse events occurred during the course of the study.

Wide-angle view colonoscopy has the theoretical advantage to detect lesions located behind folds or at the inner curve of the flexures more effectively. However, conflicting results in the context of adenoma miss rates and ADR were found in studies examining wide-angle colonoscopes.[5, 7-10] Insertion and withdrawal of a wide-angle colonoscope could be more efficient due to improved

Table 5. Colonoscopy findings

Colonoscopy findings	N=193
Patients with one or more adenomas detected / ADR (%)	77 (39.9%)
Mean no of adenomas resected or biopsied ± SD	0.73 ± 1.2
Patients with one or more polyps detected / PDR (%)	118 (61.1%)
Mean no of polyps resected or biopsied ± SD	1.37 ± 1.57
Patients with one or more advanced adenomas (%)*	26 (13.5%)
Mean number of advanced adenomas resected or biopsied ± SD*	0.35 ± 0.85
Patients with one or more non-pedunculated adenomas (Is-IIa-IIb-IIc)	67 (34.7%)
Patient with one or more right sided adenomas (including transverse)	51 (26.4%)
Patients with one or more SSL detected (%)	4 (2.1%)
Mean number of SSL resected or biopsied ± SD	0.05 ± 0.29
Other lesions found (%)	69 (35.8%)
Diverticulitis	2 (2.9%)
Diverticulosis	60 (87.0%)
Unspecific colitis	1 (1.4%)
Other	6 (8.7%)
Colonoscopies without polyps or abnormalities detected	75 (38.9%)

* an adenoma with at least one of the following characteristics; ≥ 75% villous component, high grade dysplasia or lesion size ≥ 10 mm.

visual guidance during insertion and obviating the need for repeated intubation to inspect behind folds.[7] Nevertheless, the mean net withdrawal time of our study was significantly longer when compared to recent randomized trials.[9, 10] The prolonged withdrawal time could be caused by an extended learning effect of the endoscopists to get accustomed to the constructed image of the EWAVE colonoscope and the time needed to switch between the forward view and convex image of the lateral-backward viewing lenses. When comparing the first and the second half of the performed EWAVE colonoscopies there was a trend of decreasing net withdrawal time, however this did not reach statistical significance.

Additionally, all participating endoscopists were aware of the study aims and therefore the Hawthorne effect on withdrawal time, as well as the ADR could not be excluded. An average withdrawal time of ≥ 6 minutes is associated with an increased ADR, which seems to stabilize after an 8 to 11 minute withdrawal.[11, 12] However, the association is complex, since both the ADR and withdrawal time are additionally influenced by withdrawal technique in order to improve mucosal visualization.[12] Therefore it remains difficult to establish to what extent the prolonged net withdrawal time of the EWAVE colonoscopy has contributed to the ADR.

The strength of the study is the prospective data collection of a large number of high quality procedures performed in both tertiary and regional endoscopy centers. A number of limitations have to be acknowledged as well. First, there is no direct comparison with conventional colonoscopy data. When considering similar patient populations, results suggest that ADR with EWAVE could be superior to ADR for conventional colonoscopy (25.8-31.8%).[13, 14] However, a randomized trial comparing the most recent colonoscope generation (Olympus CF-HQ190) with the previous one

(Olympus CF-H180), performed by the same investigators, showed an ADR slightly above 40% for the most recent instrument [manuscript in preparation]. Thus, it appears unlikely that this EWAVE colonoscope without HD result in the detection of more adenomas than the latest generation HD conventional colonoscopies. Therefore, we do not think a randomized trial using the present prototype instrument will show a benefit in a similar patient population, whereas for screening populations this can only be speculated. Secondly, patients with an increased risk of colorectal cancer were included which limits the generalizability to average-risk screening patients. Thirdly, the net withdrawal time was 16 minutes, which is significantly longer than the minimum withdrawal time recommended and reported by recent randomized trials.[9, 10] Finally, the detection rate of SSL was relatively low, when compared to similar patient populations.

The study was terminated early due to technical limitations of the investigated EWAVE prototype. Therefore the above mentioned findings apply to a prototype that will probably not become available in daily clinical practice. Currently a new EWAVE prototype is developed, which has improved in optical lens durability, brightness of the illumination, lens cleaning, resolving power and a slightly widened maximum field of view. To test these improvements and to homogenize withdrawal times, a randomized comparison with conventional colonoscopy is needed to firstly elucidate the additional benefit of the improved EWAVE colonoscope. At present, it seems that mechanical devices, like Endocuff or Endorings fare better than wide angle colonoscopes, which would be an interesting topic of further randomized trials.[5, 15]

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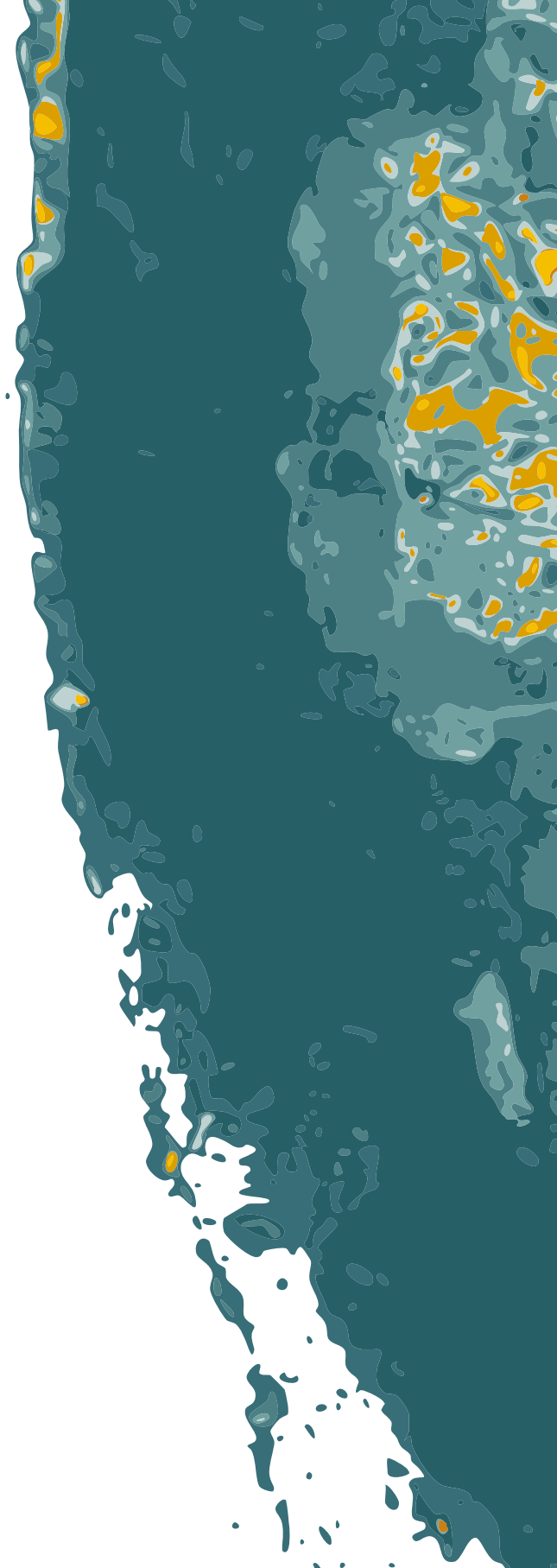

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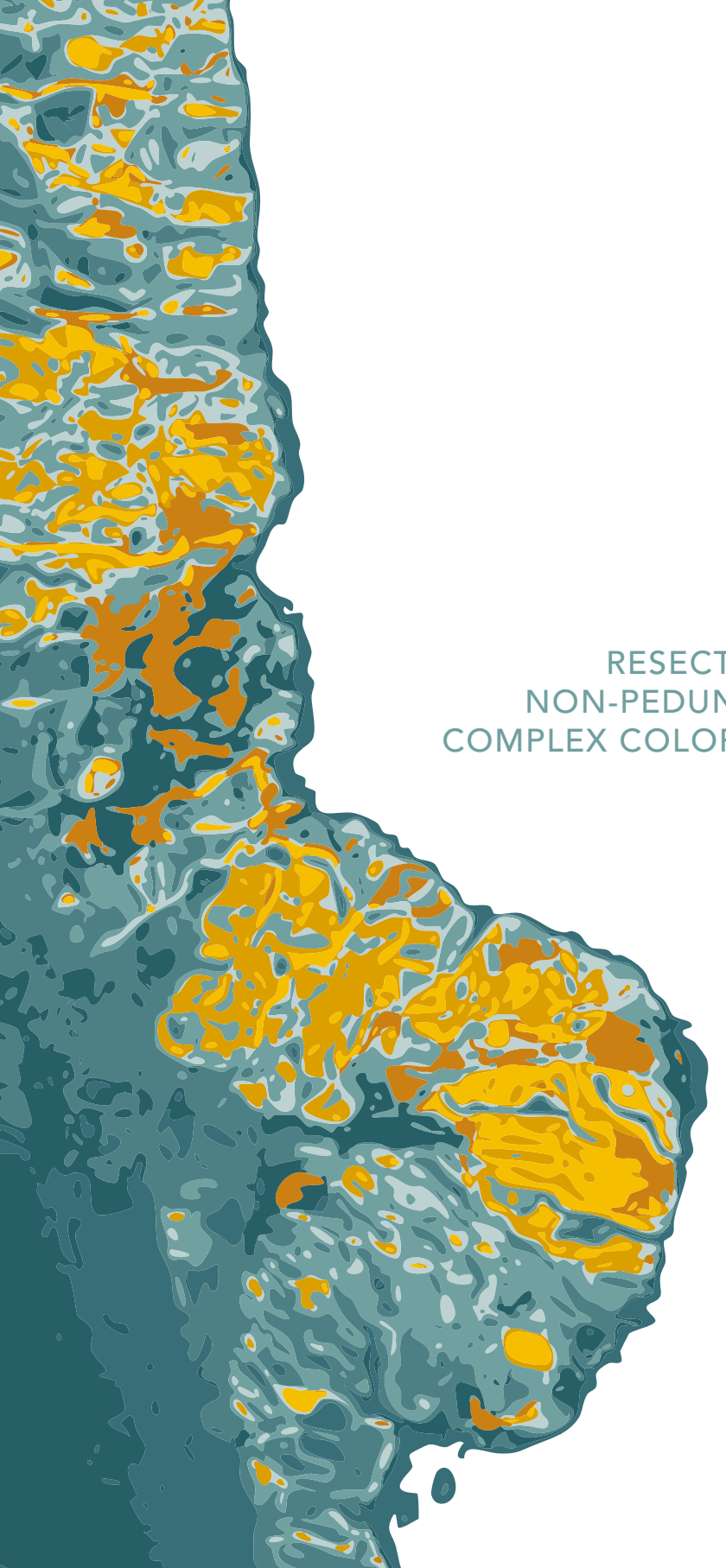

RESECTION OF LARGE NON-PEDUNCULATED AND COMPLEX COLORECTAL POLYPS

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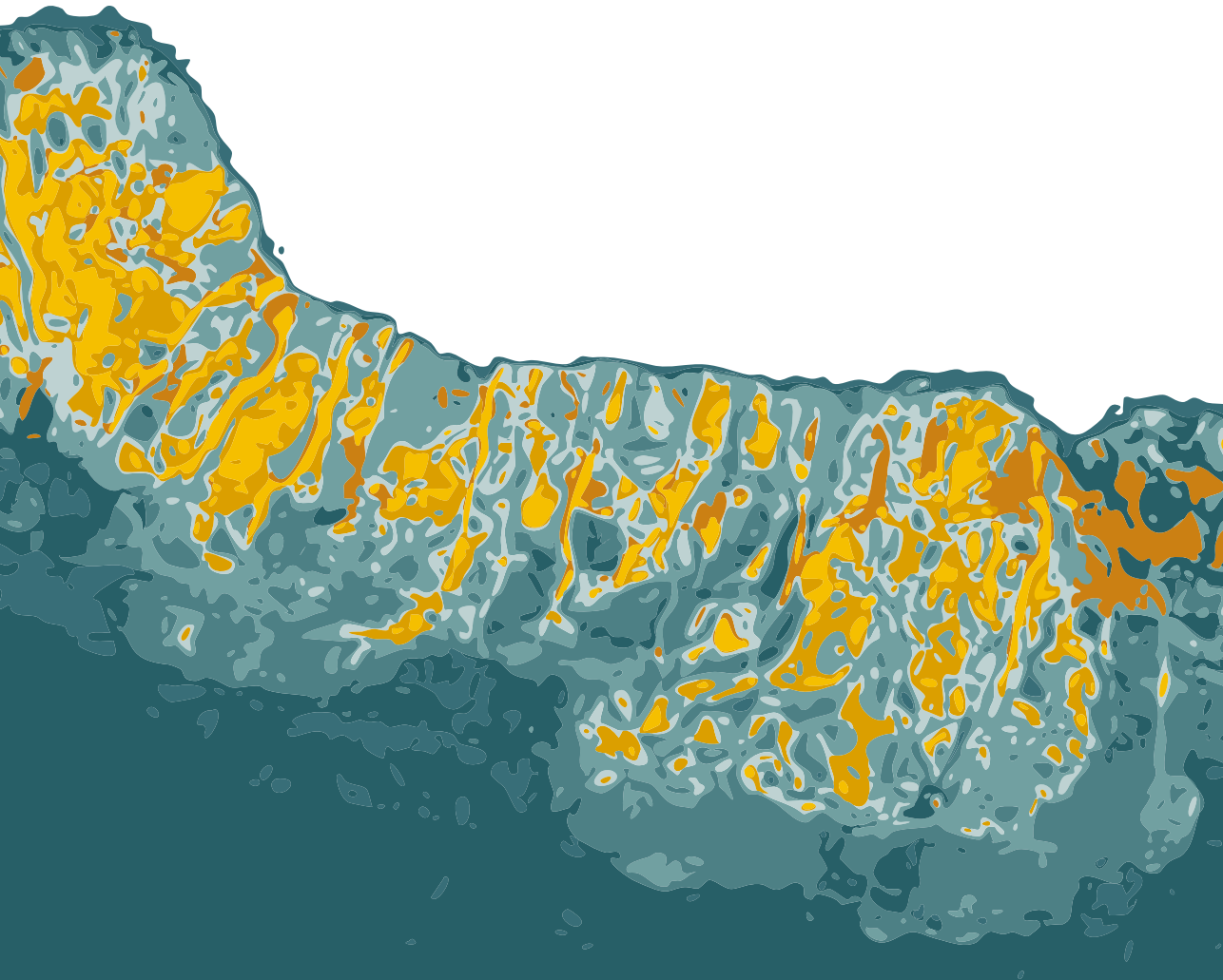
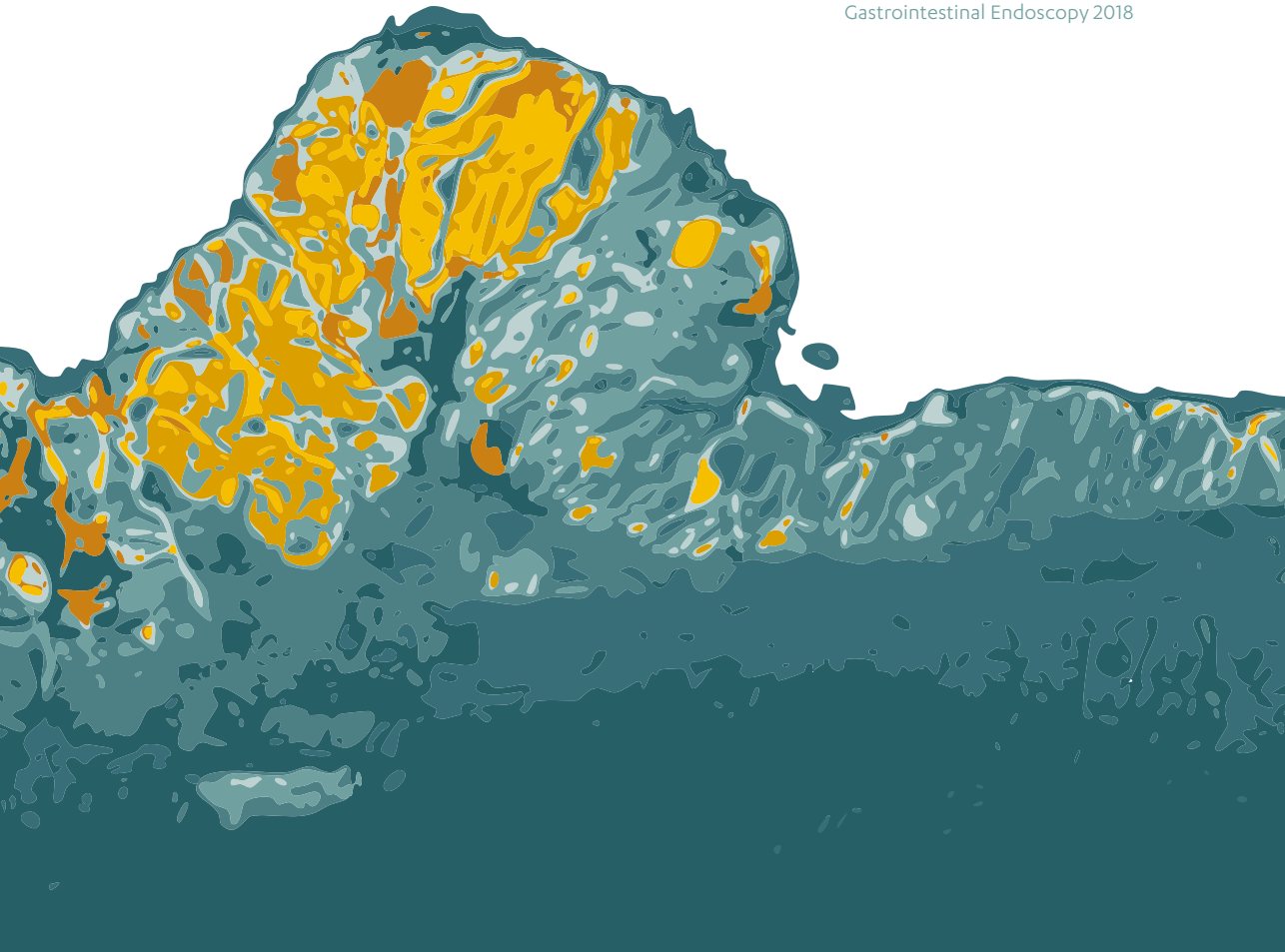


THE OCCURRENCE AND CHARACTERISTICS OF ENDOSCOPICALLY UNEXPECTED MALIGNANT DEGENERATION IN LARGE RECTAL ADENOMAS

M.E.S. Bronzwaer, G.D. Musters, R.M. Barendse, L. Koens, E.J.R. de Graaf, P.G. Doornebosch, M.P. Schwartz, E.C.J. Consten, E.J. Schoon, I.H.J.T. de Hingh, P.J. Tanis, E. Dekker, P. Fockens
on behalf of the TREND study group

Gastrointestinal Endoscopy 2018



ABSTRACT

Introduction

Large non-pedunculated rectal polyps are most commonly resected by endoscopic mucosal resection (EMR) or transanal endoscopic microsurgery (TEM). Despite pre-procedural diagnostics, unexpected rectal cancer is incidentally encountered within the resected specimen. This study aimed to compare the diagnostic assessment and procedural characteristics of lesions with and without unexpected submucosal invasion.

Methods

A post-hoc analysis of a multicenter randomized trial (TREND study) was performed, in which patients with a non-pedunculated rectal polyp of ≥ 3 cm without endoscopic suspicion of invasive growth were randomized between EMR and TEM.

Results

Unexpected rectal cancer was detected in 13% (27/203) of patients; 15 after EMR and 12 after TEM. The majority consisted of low risk T1 cancers (78%, n=18). There were no differences in the diagnostic assessment between lesions with and without unexpected submucosal invasion. Diagnostic biopsies revealed similar rates of high grade dysplasia (28% (7/25) vs 18% (26/144)). If compared to EMR of adenomas, EMR procedures of unexpected cancers had a lower success-rate of submucosal lifting (60% vs 93%, $p<0.001$), were more often assessed as endoscopically incomplete (33% vs 10%, $p=0.01$) and were more frequently terminated prematurely (60% vs 8%, $p=0.001$).

Discussion

Diagnostic assessment of large non-pedunculated rectal polyps revealed similar characteristics between unexpected cancers and adenomas. Unexpected cancers during EMR were non-lifting in 40%, endoscopically assessed as incomplete in 33%, and terminated prematurely in 60%. In treatment naïve patients, these factors should raise suspicion of malignancy and need discussion in a multidisciplinary team meeting for deciding on further treatment strategies.

INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent causes of cancer related deaths in the Western world.[1] Early endoscopic detection and removal of colorectal adenomas, a precursor lesion of CRC, is known to reduce CRC incidence and mortality.[2, 3] In the Western world, large (≥ 3 cm) non-pedunculated colorectal polyps are most commonly resected by piecemeal endoscopic mucosal resection (EMR). This technique is safe and effective.[4, 5] However, it is associated with significant local recurrence rates requiring surveillance colonoscopies and additional endoscopic treatment attempts.[6] When large non-pedunculated polyps are located in the rectum, transanal endoscopic microsurgery (TEM) can also be performed.[7] TEM enables en bloc polyp resection by either full-thickness or submucosal rectal wall excision.[8]

Large non-pedunculated colorectal polyps may demonstrate endoscopic risk factors of submucosal invasion, such as a depressed morphology (Paris classification type 0-IIc), mucosal friability, Kudo pit pattern type V, NICE classification type 3, non-granularity or the presence of nodules larger than 10 mm occurring in laterally spreading lesions and the non-lifting sign present in treatment-naive lesions.[4, 5, 9] Despite endoscopic investigation of the known endoscopic risk factors, unexpected cancers are incidentally diagnosed after local endoscopic resection of large non-pedunculated rectal polyps.[9-12] Little is known about the endoscopic characteristics of these unexpected cancers diagnosed in large rectal adenomas appearing benign during colonoscopy. Therefore, the aim of this study was to compare the diagnostic assessment of unexpected rectal cancers and histologically proven rectal adenomas based on a post-hoc analysis of a multicenter randomized trial.[13] Furthermore, procedural characteristics of piecemeal EMR and transmural TEM were compared between lesions with and without unexpected submucosal invasive disease.

METHODS

Patients

Patients included in this post-hoc analysis were selected from a randomized trial (TREND study) comparing recurrence rates of large rectal adenomas within 24 months after either piecemeal EMR or transmural TEM.[13, 14] Patient recruitment took place between 2009 and 2013 in 17 Dutch hospitals, of which four academic centers, and one Belgian academic center. The study protocol was approved by the Institutional Review Board of each participating center and written informed consent was obtained from all patients.

Patients were eligible when diagnosed with a large (≥ 3 cm) non-pedunculated rectal adenoma without endoscopic characteristics of submucosal invasion, and if at least 50% of the adenoma was situated within 15 cm from the dentate line. Endoscopists were requested to use the Paris classification to describe lesion morphology and the Kudo pit pattern to classify the mucosal pattern. The Kudo pitt pattern was evaluated with white light endoscopy and virtual chromoendoscopy, such as Narrow Band Imaging (NBI), FICE or I-scan. Virtual chromoendoscopy was only used at the discretion of the endoscopist and was dependent of the availability of virtual chromoendoscopy equipment in the endoscopy centers.[15, 16]

Exclusion criteria were endoscopic features of malignant progression defined as a Kudo pit pattern V, clear excavation or depression of the lesion and, if conducted, histology showing

submucosal invasion. A pre-procedural rectal endoscopic ultrasound (EUS) was allowed but not a prerequisite for inclusion in the study. An EUS was advised when submucosal invasion could not be completely excluded endoscopically. If the EUS showed the suspicion of invasive growth patients were discussed in the participating hospital and it was at the discretion of the gastroenterologist or gastrointestinal surgeon in which endoscopic findings were leading in this decision making process. Suspicion of invasive growth by EUS was not an absolute exclusion criterion for inclusion in the TREND study, as EUS is known to be associated with significant interobserver variability for assessing submucosal invasion as well as a limited diagnostic accuracy in daily clinical practice.[14, 17]

Once histopathologic evaluation of the resection specimen revealed malignant degeneration despite adherence to the inclusion criteria, the patient was included in this post-hoc analysis. Patients underwent additional surgical treatment or surveillance according to the national rectal cancer guideline.[18] All patients were discussed during multidisciplinary team meetings in the participating centres where the final treatment was agreed upon. Surveillance involved chest X-rays, ultrasound or computed tomography (CT) of the abdomen and pelvis and/or magnetic resonance imaging (MRI) or CT of the pelvis.

Intervention strategies

Piecemeal EMR was performed as described by Karita and Hurlstone.[19, 20] Argon Plasma Coagulation (APC) was used to treat potential remnants within the resection plane and was appointed to be used prophylactically on the edges of the mucosal defect according to the study protocol. Procedures were performed by experienced endoscopists and an expert panel evaluated a video-recorded procedure of each participating endoscopist prior to inclusion of patients. TEM was performed as described by Buess et al. and was performed by experienced surgeons whom followed a formal training program for TEM.[7] Both intervention strategies are described in more detail elsewhere.[13, 14]

Histopathological evaluation

After EMR, all the resected pieces were collected for histopathological evaluation and were directly immersed into formalin. Resection specimens after TEM were stretched and pinned on cork or paraffin before immersion into formalin.[14] If malignant progression was present, additional characteristics including tumor size, differentiation grade, infiltration depth according to the TNM staging system and Sm-stage in case of a T1 cancer, venous invasion, lymphatic invasion and resection margins were evaluated.[21] These additional characteristics were also collected of the surgical resection specimen when completion surgery was performed. When rectal cancer was diagnosed, the histopathology slides of the EMR or TEM specimen as well as the specimen of additional surgical procedure were centrally revised by a dedicated gastrointestinal pathologist (LK). The reported histopathological characteristics were based on the surgical resection specimen when additional surgical resection was performed. If not, the characteristics of the EMR or TEM specimen were described.

Outcome parameters

The diagnostic work-up of unexpected rectal cancers and histopathologically proven rectal adenomas was compared based on diameter, Paris classification, Kudo pit pattern, biopsy results

if diagnostic biopsies were taken, and for those who underwent EUS, suspicion of invasive growth and clinical lymph node status. EMR procedures of unexpected cancers and adenomas were evaluated regarding the percentage of successful lifting, endoscopic judgement of completeness and early termination of the procedure. TEM procedures were evaluated regarding en bloc as well as full-thickness resection rates. Finally, the additional surveillance strategy or surgical treatment of the unexpected rectal cancers and the occurrence of local recurrences and distant metastasis were evaluated. Data concerning the long-term follow-up data, such as the occurrence of local recurrences and distant metastasis, were collected retrospectively.

Statistical analysis and ethical considerations

The descriptive data are reported as median with interquartile range (IQR) or mean ± standard deviation according to the distribution of the data. Categorical data were analysed with Chi-square-test or Fisher's exact test, where appropriate. Numerical data were analysed using the student's t-test or Mann-Whitney U test according to the distribution. A p-value < 0.05 is considered statistically significant. The Bonferroni correction was used when multiple comparisons are performed in order to decrease the chance of incorrect rejection of the null hypothesis due to multiplicity. Statistical analysis was performed using SPSS 24 (SPSS, Chicago, IL, USA).

RESULTS

Patients

A total of 203 patients were included in the analysis of the TREND study.[13] Of these patients, 27 (13%) were diagnosed with an unexpected rectal cancer; fifteen initially treated with EMR and twelve with TEM. There were no differences in baseline patient characteristics between the unexpected rectal cancers and the histologically proven rectal adenomas included in the TREND study (*Table 1*). Rectal blood loss was more frequently reported by patients with cancer than those with a benign lesion (82% vs 52%, p = 0.004). Unexpected rectal cancers were equally distributed among participating centers (data not shown).

Lesion characteristics

The mean size of the unexpected rectal cancers was 47.0 ± 11.8 millimeters as shown in *Table 2*. The majority (75%, n = 21) had a sessile (Is) morphology and a Kudo pit pattern III-L or IV was seen in 15% or 30%. The Paris classification and Kudo pit patterns were not described in 15% and 56% of the patients, respectively. *Figures 1* and *2* show the endoscopic images of one case of an unexpected cancer and one case not found to have malignant degeneration after resection.

Fourteen of the 27 (52%) patients with unexpected rectal cancer underwent EUS prior to treatment, which showed benign features of a T0-lesion in nine patients (64%). In the five remaining cases, the ultrasonographist did not draw a definitive conclusion on the invasion depth. These patients were not excluded from the study, since suspicion of invasive growth on EUS was not an absolute exclusion criterion. Eligibility for the TREND study was determined on the discretion of the gastroenterologist or gastrointestinal surgeon. In these patients endoscopic findings were

Table 1. Patient demographics of the patients with an unexpected rectal cancer when compared to the histologically proven benign adenomas

	Total study cohort (n=203)		
	Rectal cancers (n=27)	Benign adenomas (n=176)	p-value
Gender – No (%)			0.57
Male	16 (59)	94 (53)	
Female	11 (41)	82 (47)	
Age – Yr ± SD	67.4 ± 8.6	66.8 ± 10.5	0.78
American Society of Anesthesiologists classification – No (%)			0.20
I: Healthy	11 (41)	89 (51)	
II: Mild systemic disease	16 (59)	77 (44)	
III: severe systemic disease	-	10 (5.0)	
Body Mass Index ± SD	26.2 ± 4.2	25.8 ± 3.7	0.57
Anticoagulant use – No (%)	9 (33)	41 (23)	0.26
Antiplatelet agents	1 (4)	22 (13)	0.32
Vitamin K antagonists	8 (30)	24 (14)	0.05*
Symptoms – No (%)	27 (100)	160 (91)	0.10
Rectal blood loss	22 (82)	92 (52)	0.004
Fecal incontinence	-	9 (5)	0.23
Changed bowel habits	22 (82)	111 (63)	0.06
Fecal urgency	11 (41)	60 (34)	0.50
Prolaps	1 (6)	21 (16)	0.28
Hospital type – No (%)			0.36
Academic	5 (19)	47 (27)	
Regional	22 (82)	129 (73)	

* Remained not significant after performing the Bonferoni correction.

leading. In 25 (93%) patients diagnostic biopsies were taken prior to the resection, showing low-grade dysplasia in eighteen patients (72%) and high-grade dysplasia in seven patients (28%). Results of diagnostic assessment of the unexpected rectal cancers were not significantly different from the histologically proven adenomas.

Procedural characteristics

For piecemeal EMR, the success rate of submucosal lifting was significantly lower in the unexpected cancers compared to the benign adenomas (60% vs 93%, $p < 0.001$, further details in *Table 3*). Endoscopic resections, including per protocol APC treatment of the edges of the mucosal defect and potential remnants within the resection defect, were significantly more often judged as macroscopically incomplete in malignant lesions than in benign adenomas (60% vs 85%, $p = 0.01$). Early termination of the procedure occurred more often during treatment of unexpected malignant lesions (60% vs 8%, $p = 0.001$). No significant differences were found in other procedural characteristics, including the procedural or post-procedural complication rates.

Table 2. Results of diagnostic assessment of the unexpected rectal cancers when compared to the histologically proven benign adenomas.

	Total study cohort (n=203)		
	Rectal cancers (n=27)	Benign adenomas (n=176)	p-value
Diameter (mm) ± SD	47.0 ± 11.8	46.5 ± 16.0	0.88
Distance from anal verge (cm) ± SD	6.2 ± 3.6	5.2 ± 4.1	0.21
Paris classification – No (%)			0.33
Ip	-	1 (1)	
Is	20 (74)	93 (53)	
IIa	3 (11)	39 (22)	
Unknown	4 (15)	43 (24)	
Kudo classification – No (%)			0.52
III-S	-	5 (3)	
III-L	4 (15)	43 (24)	
IV	8 (30)	48 (27)	
Unknown	15 (56)	80 (46)	
EUS – No (%)			0.09
Yes	14 (52)	54 (31)	
No	13 (48)	120 (68)	
Missing	-	2 (1)	
EUS stage – No (%)			0.14
T0	9 (64)	38 (70)	
T1-T3	4 (29)	16 (30)	
Missing	1 (7)	-	
EUS lymph nodes – No (%)			0.10
No	11 (79)	51 (94)	
Missing	3 (21)	3 (6)	
Pre procedure biopsies – No (%)			0.16
No	2 (7)	32 (18)	
Yes	25 (93)	144 (82)	
Adenoma subtype			0.19
Tubular	1 (4)	17 (12)	
Tubulovillous	12 (48)	82 (57)	
Villous	12 (48)	41 (29)	
Missing	-	4 (3)	
Grade of dysplasia			0.38
Low grade dysplasia	18 (72)	114(79)	
High grade dysplasia	7 (28)	26 (18)	
Missing	-	4 (3)	

Histopathological evaluation of unexpected cancers

The majority of the unexpected cancers consisted of T1 cancers (n = 22, 82%); three T2 (11%) and two T3 cancers (7%) were identified. Eighteen cancers (78%) were well to moderately differentiated and

had no lymphatic or venous invasion. None of the retrieved lymph nodes after radical completion surgery were positive for metastasis (*Table 4*).

Additional surgical treatment of unexpected cancers

After diagnosis of rectal cancer, 12 of 15 (80%) patients who were primarily treated with EMR and 5 of 12 (42%) patients with initial TEM underwent completion surgery (OR 5.6 (95%CI 1.02-30.90), p = 0.04). After EMR, six patients underwent TEM, two underwent abdomino-perineal resection (APR) and four low anterior resection (LAR). After TEM, one patient underwent LAR and

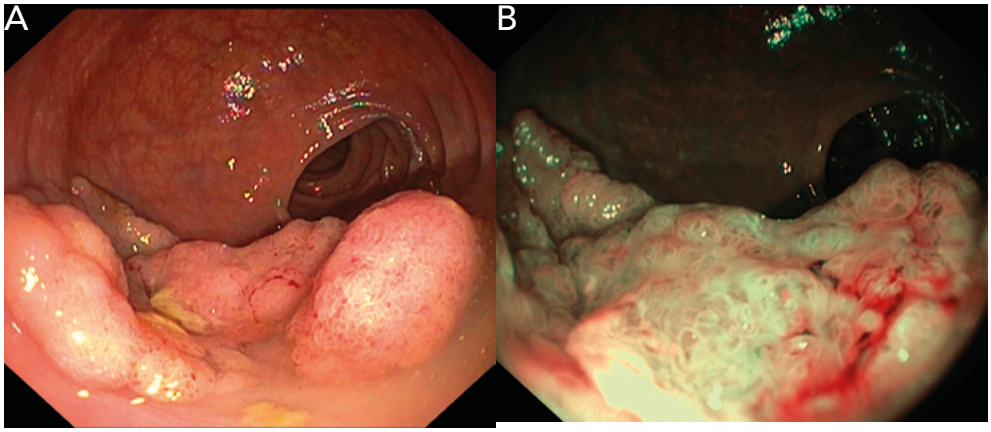


Figure 1. Endoscopic pictures of a case of an unexpected rectal cancer included in the post-hoc analysis of the TREND study. A: White light endoscopy image of an unexpected rectal cancer; B: Virtual chromoendoscopy image of an unexpected rectal cancer

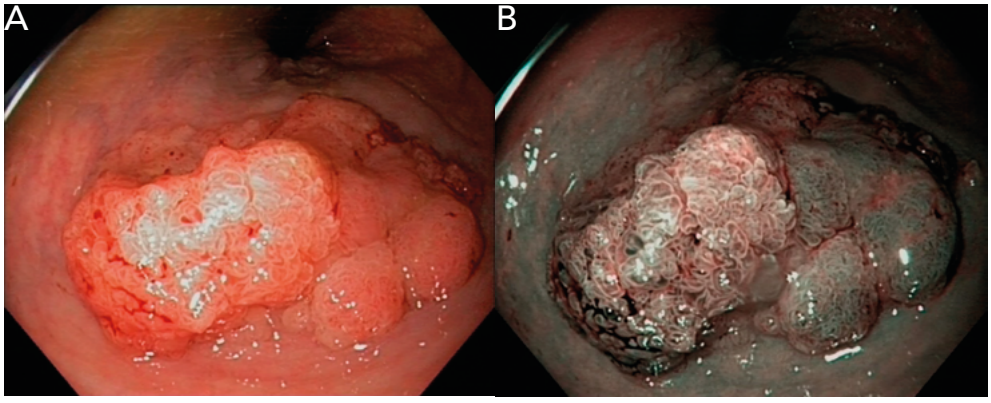


Figure 2. Endoscopic pictures of a case of a benign adenoma without malignant degeneration included in the TREND study. A: White light endoscopy image of a rectal tublovillous adenoma with low grade dysplasia; B: Virtual chromoendoscopy image of a rectal tublovillous adenoma with low grade dysplasia

Table 3. Procedural characteristics of the unexpected rectal cancers when compared to the included benign adenomas

	Total study cohort (n=203)			
	Malignant lesions (n=27)	Benign adenomas (n=176)	p-value	OR (95% CI)
Endoscopic radical resection overall – No (%) (EMR procedures only)			0.01	0.22 (0.06-0.80)
No	5 (33)	9 (10)		
Yes	9 (60)	74 (85)		
Missing	1 (7)	4 (5)		
Early termination of the procedure – No (%) (EMR procedures only)			0.001	0.13 (0.04-0.48)
No	6 (40)	80 (98)		
Yes	9 (60)	7 (8)		
Submucosal lifting – No (%) (EMR procedures only)			<0.001	10.8 (2.74-42.59)
No	6 (40)	5 (6)		
Yes	9 (60)	81 (93)		
Missing		1 (1)		
Median procedural time – Min (IQR)	67 (42-87)	60 (40-86)	0.95	
Median admission duration – days (IQR)	1.0 (0-1)	1.0 (0-2)	0.37	
Full Thickness Resection – No (%) (TEM procedures only)			0.45	
No	1 (8)	14 (16)		
Yes	11 (92)	76 (84)		
En bloc resection – No (%) (TEM procedures only)			0.21	
No	-	10 (11)		
Yes	12 (100)	80 (89)		
Median resection margin – mm (IQR) (TEM procedures only)	3.0 (3.0-5.0)	4.0 (2.0-5.0)	0.50	
Procedural complication per patient – No (%)			0.44	
No	25 (93)	155 (92)		
Bleeding	2 (7)	7 (4)		
Peritoneal breach	-	7 (4)		
Missing	-	7 (4)		
Post procedural complications per patient	4 (15)	39 (22)	0.38	
Clavien-Dindo –– No (%)			0.35	
I	-	11 (22)		
II	3 (50)	9 (18)		
IIIa	2 (33)	21 (42)		
IIIb	-	5 (10)		
IV	1 (17)	3 (6)		
V	-	1 (2)		

the remaining four patients APR. All additional surgery was performed within 6 months (median 2 months (IQR 1.0-4.75)) after the diagnosis of unexpected rectal cancer. The type of surgery and surgery related complications were not significantly different after EMR or TEM (*Table 5*). *Supplementary table A1* shows that no cancers were downgraded, but that 3 cancers primarily treated with EMR were upgraded in tumor stage after completion surgery. In contrast, no cancers were upgraded or downgraded after completion surgery following TEM. In a total of 9 patients (4 after initial TEM and 5 after initial EMR), no residual cancers was detected in the completion resection specimen.

Follow-up/survival data

After a mean follow up of 4.4 ± 1.2 years, overall survival was 100%. One locally recurrent rectal cancer (4%) was detected after 22 months during a planned surveillance colonoscopy. This recurrence

Table 4. Staging of the unexpected rectal cancers[++/*]

	EMR (n=15)	TEM (n=12)	Total (n=27)	p-value
pT-stage – No (%)				0.33
T1	12 (80)	10 (83)	22 (82)	
T2	1 (7)	2 (17)	3 (11)	
T3	2 (13)	-	2 (7)	
Sm-stage – No (%)				0.58
Sm1	3 (25)	2 (20)	5 (23)	
Sm2	2 (17)	2 (20)	4 (18)	
Sm3	2 (17)	4 (40)	6 (27)	
Not assessable	5 (42)	2 (20)	7 (32)	
pN-stage – No (%)				0.66
N0	5 (33)	5 (42)	10 (37)	
Nx	10 (67)	7 (58)	17 (63)	
Differentation grade – No (%)				0.59
Good-moderate	10 (67)	8 (67)	18 (78)	
Moderate	2 (13)	2 (17)	4 (17)	
Mucinous	0 (0)	1 (8)	1 (4)	
Missing	3 (20)	1 (8)	4 (15)	
Venous invasion – No (%)	0 (0)	0 (0)	0 (0)	-
Lymphatic invasion– No (%)	0 (0)	0 (0)	0 (0)	-
Histopathological completeness of resection – No (%)				0.04[*****]
Deep margin negative[**]	8 (53)	N/A	19 (70)[****]	
R0[***]	N/A	11 (92)	N/A	
Rx	7 (47)	1 (8)	8 (30)	

[++] Previously published data[13]

[*] If patients underwent completion surgery the resection specimen was used for tumor staging. If no completion surgery was performed the tumor stage based on the EMR or TEM specimen was used.

[**] EMR procedures only

[***] TEM: R0 when the basal and lateral margins were free of malignancy

[****] The total histopathological completeness resection are the deep margin negative EMR procedures and R0 TEM procedures taken together

[*****] Remained not significant after performing the Bonferoni correction.

Table 5. Additional treatment strategy of the unexpected rectal cancers

	EMR (n=15)	TEM (n=12)	Total (n=27)	p-value
Additional therapy – No (%)[++]				0.04
Surveillance	3 (20)	7 (58)	10 (37)	
Surgery	12 (80)	5 (41)	17 (63)	
Type of completion surgery – No (%)[++]				0.04*
APR	2 (17)	4 (80)	6 (35)	
LAR	4 (33)	1 (20)	5 (29)	
TEM	6 (50)	0 (0)	6 (35)	
Neo-adjuvant radiotherapy – No (%)				0.19
Yes	6 (40)	2 (17)	8 (30)	
No	9 (60)	10 (83)	19 (70)	
Adjuvant Chemotherapy – No (%)				0.36
Yes	1 (7)	-	1 (4)	
No	14 (93)	12 (100)	26 (96)	
Post procedural complications – No (%)	3 (25)	1 (17)	4 (22)	0.69
Clavien Dindo– No (%)				0.51
I	1 (33)	1 (100)	2 (50)	
II	1 (33)	-	1 (25)	
III-a	-	-	-	
III-b	-	-	-	
IV	1 (33)	-	1 (25)	
V	-	-	-	

* Remained not significant after performing the Bonferoni correction.
[++] Previously published data[13]

occurred after TEM of a well-differentiated T1Sm1 cancer without lymphatic or venous invasion and with complete margins. The recurrence turned out to be a well-differentiated T3N1M0 rectal cancer, which was additionally treated by LAR after neo-adjuvant chemoradiotherapy.

Distant metastases were found in three patients (11%), whom all underwent surveillance after TEM of moderately to well-differentiated T1Sm3 rectal cancers without lymphatic or venous invasion and with complete margins after 34, 63 and 72 months, respectively. One of those patients underwent completion TEM, because of the inability to assess the resection margins after EMR. Metastases consisted of pulmonary metastases in two patients and a solitary liver metastasis in one. One patient with pulmonary metastases underwent palliative treatment; the other received intentionally curative radiotherapy. The patient with liver metastasis was treated surgically.

DISCUSSION

Despite pre-procedural diagnostics, unexpected rectal cancers were encountered in 13% of large non-pedunculated rectal polyps which appeared benign. This seems comparable to reported incidences of malignant degeneration in these lesions (6.9%-14%).[9-12] This post-hoc analysis did not reveal any significant differences in diagnostic findings between the unexpected cancers and the histologically proven adenomas. Unexpected cancers during EMR were non-lifting in 40%, endoscopically assessed as incomplete in 33%, and procedures were terminated prematurely

in 60%, all these proportions were significantly higher compared to EMR of ultimately proven adenomas. The majority of the unexpected cancers were low risk T1, and none were found to be lymph node positive in case of radical completion surgery, resulting in excellent long-term oncological outcomes.

There are several techniques to increase overall diagnostic accuracy of submucosally invasive disease, but further improvement is required. Advanced imaging techniques such as virtual chromoendoscopy and magnifying endoscopy have been acknowledged to improve the identification of morphological features suggestive of submucosal invasion, such as irregular or absent surface vascular patterns (Kudo V pit-pattern or NICE classification type 3).[5, 22-24] Both classification systems are associated with a learning curve and interobserver variability. Several training modules are described to improve optical diagnosis with advanced imaging techniques, but none focus primarily on endoscopic recognition of submucosal invasion in large non-pedunculated colorectal lesions. Besides that, all published data are derived from expert endoscopy centers.[5, 22, 24, 25] Therefore, applicability of these classification systems for the identification of suggestive features of submucosal invasion remains unknown in daily practice.

To determine the presence of an invasive component in large non-pedunculated rectal lesions, random diagnostic mucosal biopsies can be included in the diagnostic work-up. As usually both benign and malignant parts are present in these unexpected cancers, biopsies are associated with an inherent sampling error.[26] This implies a chance of underdiagnosis and therefore random diagnostic biopsies should not be used for a reliable diagnosis and determination of additional treatment strategies; unless targeted biopsies are taken from highly suspicious areas in order to prove malignancy.[5] Accordingly, in our series, almost all lesions were biopsied and the distribution of low-grade and high-grade dysplasia did not differ between the unexpected cancers and proven benign adenomas.

Also, EUS can be used as a diagnostic modality for clinical staging of rectal lesions. A 97.3% sensitivity and 96.3% specificity for large benign rectal adenomas was found in EUS expert centers.[27] Within these expert centers, EUS is the most accurate imaging modality to discriminate between T1 and T2 rectal cancer. However, it is associated with a low accuracy in discriminating T1 substages, such as sm1, sm2 and sm3. The quality of EUS is highly dependent upon the experience of the diagnosing physician, which is underlined by a clearly lower accuracy of EUS in daily clinical practice.[17]

In addition to the pre-procedural endoscopic risk features of colorectal lesions, the procedural non-lifting sign is also associated with an increased risk of submucosal invasion, as confirmed in the present study.[28] However, non-lifting can also be caused by fibrosis, which may be the result of prior treatment attempts, taking diagnostic biopsies or as a reaction to submucosal injection.[5, 9, 29] When non-lifting occurs in flat or sessile treatment naïve lesions during EMR, a suspicion of malignancy should rise and it should be considered to abandon the procedure.

This post-hoc analysis showed that the need of completion surgery was significantly higher after EMR, but the proportion of radical total mesorectal excision (TME) was comparable between EMR and TEM.[13] In contrast to TEM, after piecemeal EMR, endoscopists and pathologists are unable to assess invasion depth and resection margins, which commonly necessitates additional surgery, even in the absence of other risk factors.[18] Therefore in patients with endoscopic suspicion of

submucosal invasion a piecemeal resection should be avoided.[4, 5] Patients with a low-risk T1 cancer (well to moderately differentiated, no lymphatic or venous invasion and clear resection margins) initially treated with piecemeal EMR can thereafter be treated with full-thickness TEM. After this local resection without additional radical completion surgery or chemo-radiotherapy, these patients have acceptable oncological outcomes with local recurrence rates of less than five percent and a limited risk of lymph node metastasis.[30, 31]

It is generally advised that high-risk T1 cancers (poorly differentiated, lymphatic or venous invasion) and higher T-stages should be treated with radical completion surgery. This is because of higher local recurrence rates (up to 25%) and a more than 10% risk of lymph node metastasis.[10, 30, 31] This strategy is also endorsed by Dutch and European guidelines.[18, 32] Good oncological outcomes are achieved after this completion surgical resection with a five-year disease free survival of approximately 95%, local recurrence rates of about 5% and distant recurrence rates of less than 10%.[33-38] Comparable and adequate oncological outcomes are found in the present study with a lymph node metastasis rate of 4%, a subsequent local rectal cancer recurrence rate of 4% and distance metastases rate of 11%. However due to the limited follow-up period and the small number of patients in this analysis, caution is required when interpreting these results.

Our study has certain limitations. First, advanced imaging techniques were only used at the discretion of the endoscopist and the availability and experience of these techniques in the endoscopy centers, reflecting daily practice during the study period (2009-2013). Therefore in only half of the patients the Kudo pit pattern was described, which could have been one of the causes of misclassification of the unexpected rectal cancers. Secondly, the histopathological handling of the EMR and TEM specimen is inherently different. A pinned down TEM specimen allows a more precise determination for the presence of invasive cancer as well as the resection margins, whereas incomplete margins and invasive cancer could be missed on the multiple EMR specimen which were just immersed in formalin. In addition, due to the fragmentation of the EMR specimen it is difficult to reliable assess tumor invasion depth, which was also shown in our study as 3 unexpected cancers primarily treated with EMR were upgraded in tumor stage after the performed completion surgery. Contrastingly, no cancers were upgraded or downgraded after completion surgery following TEM. Caution is required when interpreting these results as only a limited number of patients underwent completion surgery after EMR and TEM. Another limitation of the study is the retrospective collection of long-term follow-up data, such as the occurrence of local recurrences and distant metastasis. Lastly, the absolute number of patients that appeared to have an unexpected cancer is relatively small.

To the best of our knowledge, this is the first study describing the occurrence as well as procedural characteristics of unexpected rectal cancers after endoscopic and ultrasonographic preoperative lesion assessment in daily practice. In conclusion, there were no differences in pre-procedural diagnostics that could already have indicated the presence of invasive growth. During EMR, non-lifting, endoscopically assessed irradical resection, or early termination were associated with unexpected cancers. This should raise suspicion of malignancy in treatment naïve patients, where after the patient should be discussed in a multidisciplinary team meeting, in which additional tailored en bloc full-thickness resection with TEM or completion surgery should be considered.

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APPENDIX

Supplementary Table A1. Pre-surgical and post-surgical tumor staging of the patients whom underwent completion surgery

Patient	Primary treatment	Pre surgical tumor staging	Type of performed completion surgery	Histopathological findings of the completion surgery	Post surgical staging
1	TEM	T2NxMx	APR	T2N0[+]	T2N0
2	TEM	T2NxMx	APR	No residual cancer[+]	T2N0
3	TEM	T1Sm1NxMx	LAR	No residual cancer	T1sm1N0
4	TEM	T1Sm2NxMx	APR	No residual cancer	T1Sm2N0
5	TEM	T1Sm3NxMx	APR	No residual cancer	T1Sm3N0
6	EMR	T1NxMx	APR	T3N0[+]	T3N0
7	EMR	T2NxMx	APR	T3N0[+]	T3N0
8	EMR	T1NxMx	LAR	T2N0[+]	T2N0
9	EMR	T1NxMx	TEM	T1Sm1Nx	T1Sm1Nx
10	EMR	T1NxMx	TEM	T1Sm2Nx	T1Sm1Nx
11	EMR	T1NxMx	TEM	T1Sm3Nx	T1Sm3Nx
12	EMR	T1NxMx	LAR	No residual cancer[+]	T1Sm*N0
13	EMR	T1NxMx	TEM	No residual cancer	T1Sm*Nx
14	EMR	T1NxMx	LAR	No residual cancer[+]	T1Sm*N0
15	EMR	T1NxMx	TEM	No residual cancer	T1Sm*Nx
16	EMR	T1NxMx	TEM	T1Sm3Nx	T1Sm3Nx
17	EMR	T1NxMx	LAR	No residual cancer[+]	T1Sm*N0

*Sm depth was not assessable [+] received neo-adjuvant radiotherapy

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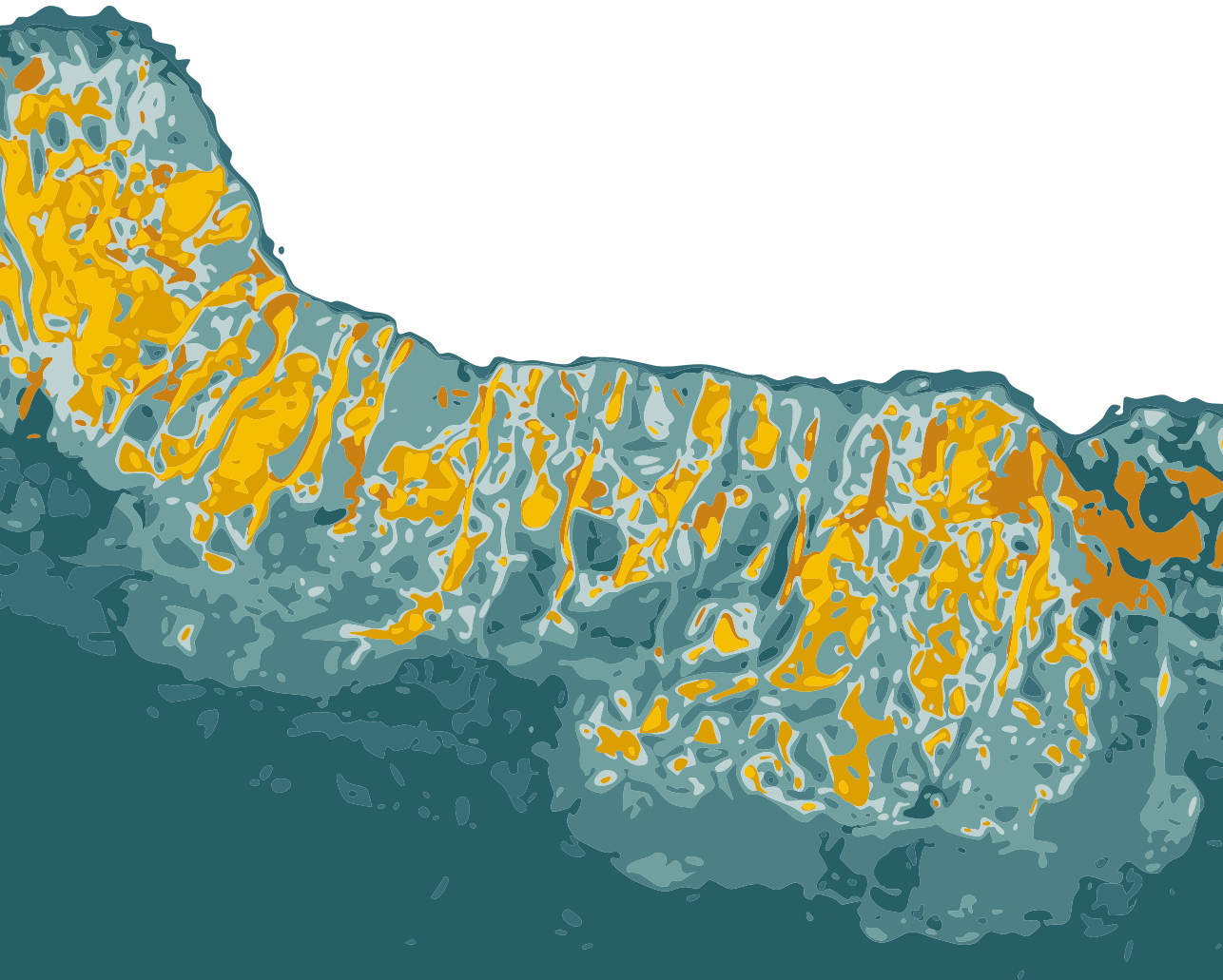

SURGERY FOR BENIGN COLORECTAL POLYPS IN THE LAST 11 YEARS: IS THE VOLUME DECREASING?

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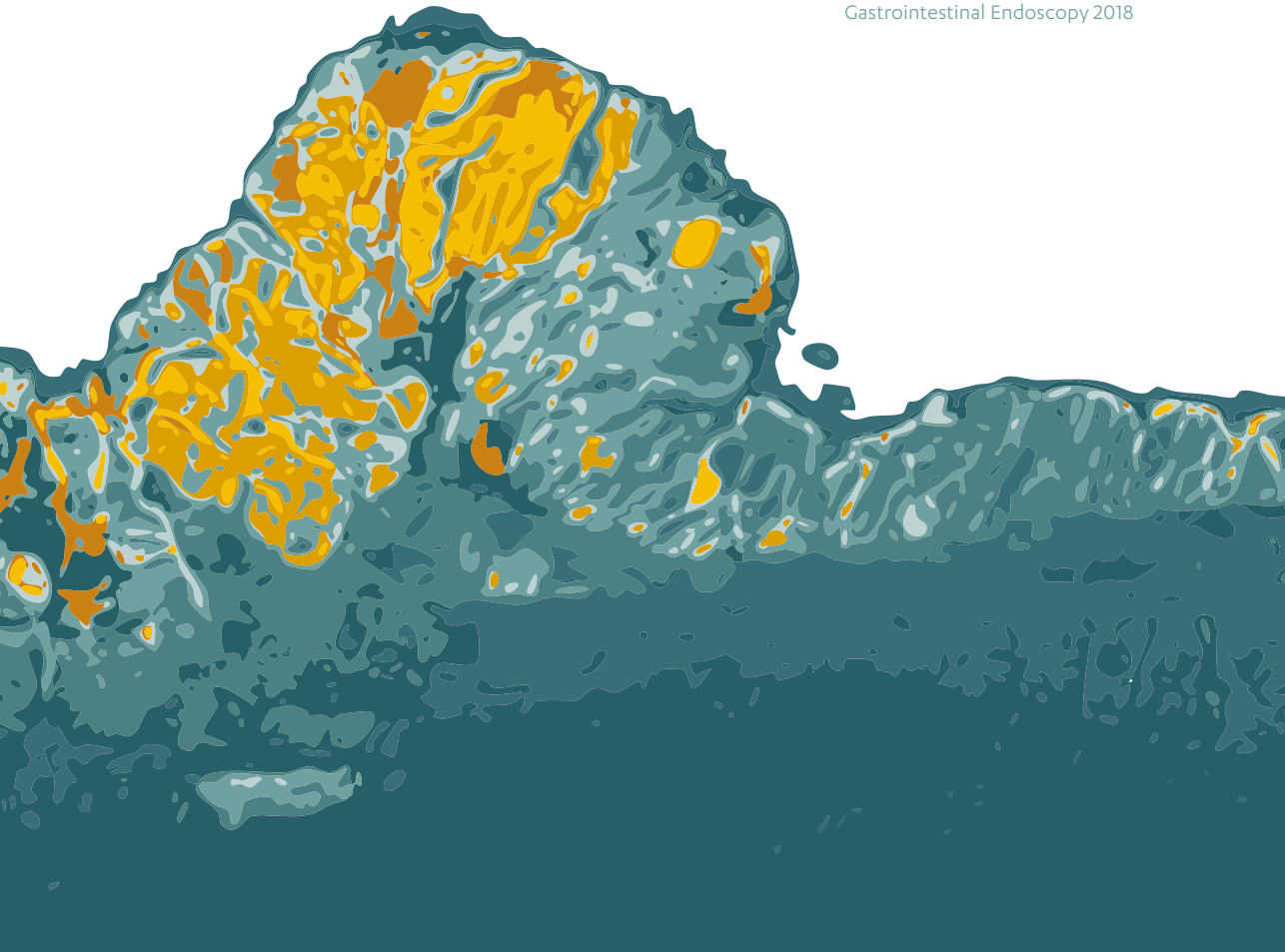
Gastrointestinal Endoscopy 2018



ABSTRACT

Introduction

Traditionally large complex colorectal polyps were managed by surgical resection (SR) and in recent years endoscopic resection (ER) has progressed significantly. However, to what extent ER has replaced SR remains largely unknown. We performed a multicenter retrospective cohort study to assess the volume and volume changes of SR for benign colorectal polyps over the past decade.

Methods

Patients who underwent SR for a benign colorectal polyp in the Netherlands between 2005 and 2015 were selected from the prospective nationwide Dutch Pathology Registry. Clinical characteristics were obtained from patient charts of patients who underwent SR in the province of Noord-Holland.

Results

A total of 5937 patients was treated with SR for a colorectal polyp and the absolute (454-739 per year) and relative volumes (0.20%-0.37% per colonoscopy per year) of SR remained stable. In the province of Noord-Holland, 928 (15.6%) underwent SR. In these patients submucosal lifting and ER were attempted in 19.9% (n = 175) and 15.0% (n = 134). After 2010 patients were more likely to undergo lifting (27.7 vs 11.4% p-value < 0.001) and ER attempts (18.8% vs 10.9% p-value = 0.001) before definitive SR. Twenty-two patients (2.4%) had been referred to another endoscopy clinic.

Conclusion

Surgical resection for large complex colorectal polyps was still frequently performed and remained stable. A small percentage of patients underwent ER attempts before SR and referral for an additional ER attempt only occurred in a minority of cases. To increase ER attempts, implementation of a regional multidisciplinary referral network should be considered.

INTRODUCTION

Colorectal adenomas and sessile serrated lesions (SSL) are the well-known precursors of colorectal cancer (CRC).[1, 2] Colonoscopic polypectomy reduces CRC incidence and mortality and is therefore widely accepted and implemented.[3, 4] However, there are limitations in the technical ability to completely resect so-called complex colorectal polyps. Risk factors for incomplete endoscopic resection are a lesion size larger than 40 mm, flat morphology or lesions located at the ileocecal valve, appendiceal orifice, dentate line, involving a diverticulum or within a segment of inflammation.[5] Other factors associated with incomplete endoscopic resection (ER) are the so called non-lifting sign and prior failed ER attempts.[5-7]

Traditionally large and complex non-pedunculated colorectal polyps were managed by surgical resection (SR).[8, 9] However over the past decade ER techniques, such as piecemeal endoscopic mucosal resection (pEMR) and endoscopic submucosal dissection (ESD), have progressed significantly and are now applied in many endoscopy centers around the World to treat complex colorectal polyps.[10] Replacing SR by ER will reduce surgical morbidity, mortality and costs.[5, 9-15] It remains largely unknown to what extent ER has replaced SR. We therefore performed a multicenter retrospective cohort study in the Netherlands to assess the total volume of colorectal surgery for benign colorectal polyps and the absolute and relative volume changes over the past decade. Secondly, we assessed endoscopic characteristics of the resected lesions, surgical characteristics as well as surgical related morbidity and mortality.

METHODS

Study design and patient identification

This is a multicenter retrospective cohort study (NTR6294, www.trialregister.nl) consisting of patients who underwent SR for the treatment of benign colorectal polyps in the Netherlands. Patients were selected based on histopathology excerpts of SR specimen using the Pathological Anatomy National Automated Archive (PALGA-database). The PALGA-database is a nationwide network and registry of histopathology and cytopathology. This database contains pathology reports generated in the Netherlands since 1971 and has complete national coverage since 1991, encompassing data from all pathology laboratories from all academic and nonacademic hospitals in the Netherlands.[16]

The PALGA-database was searched with the following search terms: 'Colon', 'Rectum', 'Resection', 'Polyp', 'Adenoma, 'Lesion' or a (Dutch) synonym. The search included SR specimens between 1th January 2005 and 31th December 2015. Thereafter cases were further confirmed or excluded after careful evaluation of individual pathology excerpts. Secondly, patient charts from all cases whom underwent SR in the province of Noord-Holland (15 regional and 2 academic hospitals, 1.7 million inhabitants between 30 and 90 years of age, which is in accordance with the age distribution of our cohort) were evaluated in further detail to assess the endoscopic characteristics of the resected lesions, surgical characteristics as well surgical related morbidity and mortality.

The study protocol was presented to the Medical Ethics Review Committee of the Academic Medical Center. They decided that formal ethics agreement was not required according to

the Medical Research Involving Human Subjects Act (WMO), as patient data was retrieved during standard care and no interventions were performed for the sake of this study. Separate approval of the study in the participating centers was obtained. The study was carried out in accordance with the declaration of Helsinki.[17]

Study population

All patients who underwent SR for a benign colorectal polyp were included. A benign colorectal polyp was defined as an adenomatous lesion (tubular, tubulovillous or villous), hyperplastic polyp, SSL or traditional serrated adenoma with or without low or high-grade dysplasia according to the Vienna criteria.[18] The following exclusion criteria where applied: malignant submucosal invasion present in preoperative biopsies, (partial) endoscopic polypectomy specimen or SR specimen; SR performed for synchronous CRC or emergency SR such as bowel perforation, bowel obstruction, ischemia, diverticulitis, appendicitis or ileus. Patients known with hereditary polyposis syndromes or inflammatory bowel disease (IBD) were excluded as well. For the secondary analysis of the clinical characteristics of the resected lesions, surgical characteristics as well as surgical related morbidity and mortality, only patients were included who underwent a colonoscopy prior to SR in the province of Noord Holland.

Patient characteristics

One investigator (MB) manually abstracted all clinical characteristics of all patients whom underwent SR in the province of Noord Holland from patient charts. The patients' age; gender; American Society of Anesthesiology (ASA) Physical Status Classification System; Body Mass Index (BMI) were recorded.

Lesion and colonoscopy characteristics

Data from all colonoscopy reports prior to SR were collected consisting of the following colonoscopy characteristics; date of colonoscopy; endoscopy center; performing endoscopist; colonoscopy indication; depth of intubation and cleanliness of the bowel assessed by the endoscopist. The following data concerning lesion characteristics were collected; lesion size as assessed by the endoscopist during colonoscopy; lesion location (ileocecal valve, appendiceal orifice, cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid or rectum); endoscopic lesion morphology divided in pedunculated, sessile, laterally spreading, depressed or stenosing and endoscopic appearance distinguished as adenomatous, serrated, hyperplastic or malignant.

Additionally the number of colonoscopies performed to assess the lesion(s); endoscopic treatment(s) performed divided in diagnostic biopsies, submucosal lifting, ER attempts and tattoo placement; other colorectal lesions or abnormalities found; follow-up advice for further treatment given, divided in direct referral for SR or additional ER attempt and the final reason for referral for SR were recorded.

Surgical characteristics

Collected data concerning surgical characteristics were the hospital where the SR was performed; type of surgery subdivided in open or laparoscopic surgery; post-operative admission at the Intensive Care Unit (ICU); total length of hospital stay; post procedural adverse events up to 30 days after the procedure and overall mortality related to the performed SR. Post-operative adverse events were classified according to the Clavien-Dindo Classification.[19, 20]

Outcome measures and statistical analysis

The primary outcome measure was the volume of patients referred for colorectal SR performed to treat benign colorectal polyps in the Netherlands between 2005 and 2015. Secondary outcome measures were the absolute and relative volume changes of SR over the same time period. As the exact incidence of colorectal polyps was unknown, the relative volume changes of SR per year were calculated by dividing the annual nationwide volumes of the performed SR for benign polyps by the annual nationwide colonoscopy volumes.[21-24] This analysis was adapted from a recent study assessing the magnitude of radical rectal surgery performed in the Netherlands.[24] Other secondary outcome measures were a description of the endoscopic lesion characteristics, colonoscopy characteristics including performed endoscopic treatment attempts, surgical characteristics and surgery related morbidity and mortality of all SR performed in the province of Noord-Holland.

These descriptive quantitative data were described according to their distribution. Normal distributed data were described with the mean and the standard deviation and data with a skewed distribution were described using the median and the interquartile range. Pearson's Chi Square or Fisher's exact test were used to compare categorical variables. A p-value < 0.05 was considered as statistically significant. Statistical analysis was performed using SPSS 23 (SPSS, Chicago, IL, USA).

RESULTS

Between January 1th 2005 and December 31th 2015 a total of 5937 patients underwent SR for a benign colorectal polyp in the Netherlands, of which 928 patients (15.6%) were treated in the province of Noord-Holland (*Figure 1*). All seventeen hospitals in the province of Noord-Holland were invited to participate in the clinical data collection of the study. One smaller regional hospital declined participation. Therefore, this cohort consists of the clinical data collected in the remaining 14 regional and two academic hospitals in the province of Noord-Holland. From these 928 patients, eight patients were immediately referred for SR without undergoing a colonoscopy, as invasive growth was suspected on radiologic imaging. From five patients endoscopy reports could not be retrieved and it was therefore unclear whether or not these patients had undergone colonoscopy before SR. These thirteen patients were excluded from the analysis. The remaining 915 patients who did undergo a colonoscopy prior to SR were included and the clinical characteristics of these patients are described in further detail.

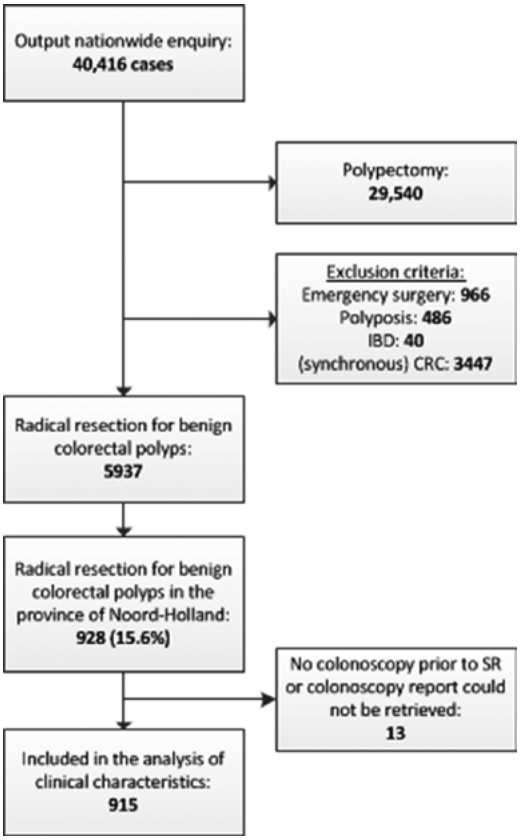


Figure 1. Flowchart of included excerpts from the PALGA database

Annual volumes of SR and demographic patient characteristics

The absolute and relative volumes of SR ranged between 454 and 739 or 0.20% and 0.37% per colonoscopy per year, which remained stable over the past decade (*Supplementary table 1*, *Figure 2a* and *2b*).

The volume of SR per hospital in the province of Noord-Holland ranged between 14 and 127 and the highest SR volumes per hospital were achieved in two large teaching hospitals (hospital 7 and 10). The two most reported indications for SR were endoscopic irresectability or inaccessibility of the polyp in 60.8% (n = 556) and suspicion of malignancy in 25.9% (n = 237) (details in *Table 1*). In three patients the indication for referral towards SR were scored as other; two of these patients had multiple polyps without signs of a hereditary polyposis syndrome and one patient specifically preferred SR over ER because of a traumatic experience with colonoscopy. Demographic patient characteristics are shown in *Table 2*.

Lesion characteristics

The lesion characteristics of the polyps detected during colonoscopy are shown in *Table 3*. The polyps were located in the proximal colon in 67.3% (n = 616), had a median diameter of 35 mm (IQR 25-50)

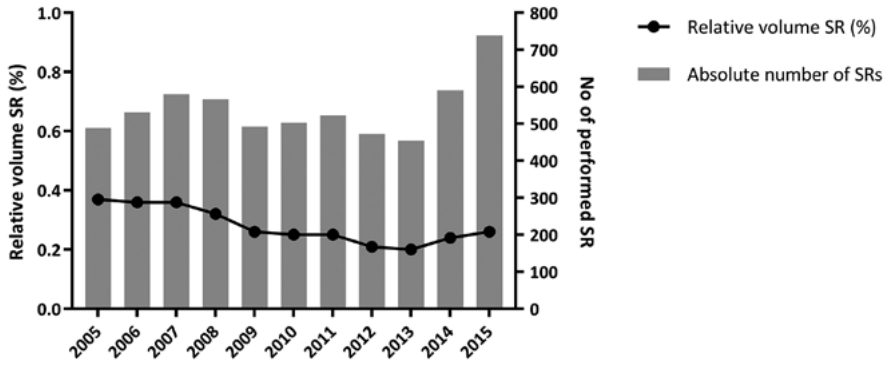


Figure 2a. Relative changes in SR plotted against the annual number of performed colonoscopies

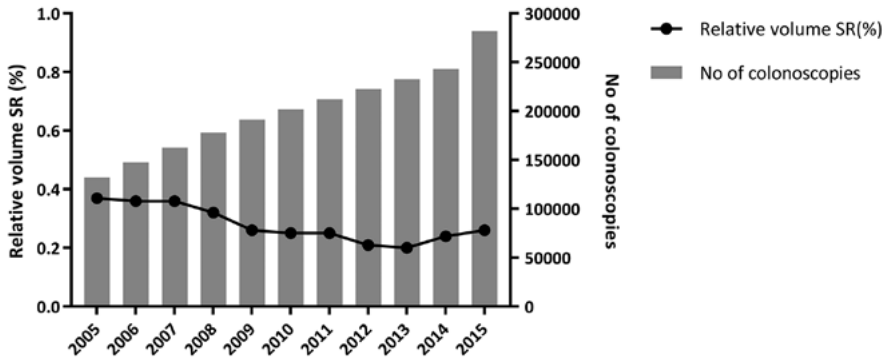


Figure 2b. Relative changes in SR plotted against the annual number of performed SRs

and a non-pedunculated morphology (Paris classification 0-Is, 0-IIa, 0-IIb, 0-IIc) in 90.6% (n = 829). The majority was endoscopically assessed as adenomatous (76.2%, n = 697). Histopathology revealed either tubular, tubulovillous or villous adenomas in 94.4% (n = 864) of which 64.7% (n = 559) and 34.4% (n = 297) contained low-grade dysplasia and high-grade dysplasia.

Colonoscopy characteristics and referral patterns after the first colonoscopy

Most colonoscopies (51.1%, n = 468) were executed because of symptoms suspicious for CRC (*Table 4*). Colonoscopies were complete in 91.6% (n = 788) and the cleanliness of the colon was assessed as adequate by the performing endoscopist in 91.0% (n = 742). Diagnostic biopsies had been taken in 88.7% (n = 798) and submucosal lifting was attempted in 19.9% (n = 175), showing non-lifting in 70.1% (n = 122). ER was initiated in 15.0% (n = 134) and was incomplete in 80.6% (n = 108). After 2010, patients were more likely to undergo endoscopic removal attempts before referral towards SR, including submucosal lifting (27.7% vs 11.4%, $p < 0.001$) and ER attempts (18.8% vs 10.9%, $p < 0.001$) (*Table 5*).

Table 1. Volumes of performed SR and indication for referral towards SR

	N = 915
Reason surgical resection – No (%)	
Endoscopic irresectable or inaccessable	556 (60.8%)
Too large diameter	169 (30.4%)
Inaccessable	66 (11.9%)
Not specified	321 (57.7%)
Endoscopic suspicion of malignancy	237 (25.9%)
Incomplete polypectomy	117 (12.8%)
Other	3 (0.3%)
Not described	2 (0.2%)
Hospital type – No (%)	
Academic	107 (11.7%)
Peripheral	808 (88.3%)
Volume SR per hospital – No (%)	
1	73 (8.0%)
2	37 (4.0%)
3	14 (1.5%)
4	68 (7.4%)
5	41 (4.5%)
6	64 (7.0%)
7	127 (13.9%)
8	57 (6.2%)
9	85 (9.3%)
10	91 (9.9%)
11	45 (4.9%)
12	30 (3.3%)
13	88 (9.6%)
14	34 (3.7%)
15	32 (3.5%)
16	29 (3.2%)

Table 2. Patient demographics

	N = 915
Gender – No (%)	
Male	465 (50.8%)
Female	450 (49.2%)
Mean age (yr ± SD (Range)	67.4 ± 10.0 (33-90)
ASA-score – No (%)	
I: Healthy	204 (22.3%)
II: Mild systemic disease	469 (51.3%)
III: severe systemic disease	226 (24.7%)
IV: Severe systemic disease that is a constant threat to life	15 (1.6%)
Missing	1 (0.1%)
Median BMI (kg/m2) (IQR)	25.2 (22.8-28.0)

Table 3. Lesion characteristics

	N = 915
Median lesion diameter (mm) (IQR)	35 (25.0-50.0)
Polyp location – No (%)	
Proximal	616 (67.3%)
Cecum	256 (28.0%)
Ileocecal valve	62 (6.8%)
Appendiceal orifice	32 (3.5%)
Ascending colon	156 (17.0%)
Hepatic flexure	41 (4.5%)
Transverse colon	61 (6.7%)
Splenic flexure	8 (0.9%)
Distal	292 (31.9%)
Descending colon	54 (5.9%)
Sigmoid	175 (19.3%)
Rectum	63 (6.9%)
Not described	7 (0.8%)
Lesion morphology – No (%)	
Sessile (Is)	536 (58.6%)
Flat (II-a)	167 (18.3%)
Excavated (II-c)	41 (4.5%)
Depressed (II-b)	85 (9.3%)
Pedunculated (I-p)	64 (7.0%)
Not described	22 (2.4%)
Macroscopic aspect – No (%)	
Adenomatous	697 (76.2%)
SSL	4 (0.4%)
Hyperplastic polyp	1 (0.1%)
Adenocarcinoma	199 (21.7%)
Other	5 (0.5%)
Not described	9 (1.0%)
Histology – No (%)	
Adenomatous	
Tubular adenoma	178 (19.5%)
Tubulovillous adenoma	603 (65.9%)
Villous adenoma	83 (9.1%)
SSL	20 (2.2%)
Traditional serrated adenoma	3 (0.3%)
Hyperplastic polyp	10 (1.1%)
Non-hyperplastic/non-adenoma	
Lipoma	12 (1.3%)
Cystadenoma appendix	1 (0.1%)
Not described	6 (0.7%)
Dysplasia – No (%)	
Low-grade dysplasia	570 (62.3%)
High-grade dysplasia	305 (33.3%)
Negative for neoplasia	26 (2.8%)
Not described	14 (1.5%)

Table 4. Colonoscopy characteristics

	N = 915
Indication first colonoscopy – No (%)	
Symptoms*	468 (51.1%)
Surveillance	142 (15.5%)
Positive family history for CRC	46 (5.0%)
Asymptomatic colonoscopy after positive FIT	106 (11.6%)
Abnormalities on radiologic exams	98 (10.7%)
Other	29 (3.2%)
Not described	26 (2.8%)
Complete colonoscopy – No (%)	788 (91.6%)
Not described	55 (6.0%)
Depth of intubation – No (%)	
Cecum	788 (91.6%)
Ascending colon	11 (1.3%)
Hepatic flexure	9 (1.0%)
Transverse colon	5 (0.6%)
Splenic flexure	3 (0.3%)
Descending colon	9 (1.0%)
Sigmoid	33 (3.8%)
Rectum	2 (0.2%)
Clean colon – No (%)	742 (91.0%)
Not described	100 (10.9%)
Treatments performed – No (%) overall**	866 (96.1%)
Diagnostic biopsies	798 (88.7%)
Lifting	175 (19.9%)
Non-lifting	122 (70.1%)
Complete lifting	52 (29.9%)
ER attempt	134 (15.0%)
Complete ER	26 (19.4%)
Incomplete ER	108 (80.6%)
Tattoo	414 (48.6%)
Other lesions found – No (%)	617 (69.2%)
Polyps	523 (58.6%)
Median number (IQR)	2.0 (1.0-3.0)
Diverticulosis	150 (16.8%)
Hemorroids	14 (1.6%)
Other	10 (1.1%)
Angiodysplasia	4 (40.0%)
Microscopic colitis	2 (20.0%)
Post-radiotherapy angiectasia	1 (10.0%)
Stenosing diverticulits	1 (10.0%)
Lipoma	2 (20.0%)

* Symptoms: macroscopic rectal blood loss, abdominal discomfort, changed bowel habits, anemia

** Both the first colonoscopy and additional follow-up colonoscopies

Table 5. Changes of performed endoscopic treatment between 2005-2010 and 2011-2015

	2005-2010	2011-2015	P-value
Lifting attempt – No (%)			< 0.001
Yes	48 (11.4%)	127 (27.7%)	
No	373 (88.6%)	332 (72.3%)	
Lifting complete – No (%)			0.90
Yes	14 (29.2%)	38 (30.2%)	
No – non lifting	34 (70.8%)	88 (69.8%)	
ER attempt – No (%)			0.001
Yes	47 (10.9%)	87 (18.8%)	
No	383 (89.1%)	376 (81.2%)	
ER complete – No (%)			0.96
Yes	9 (19.1%)	17 (19.5%)	
No	38 (80.9%)	70 (80.5%)	
Biopsies – No (%)			0.17
Yes	394 (90.2%)	404 (87.3%)	
No	43 (9.8%)	59 (12.7%)	

A total of 714 (78.0%) patients were immediately referred for SR after their first colonoscopy. The remaining 201 (22.0%) patients underwent additional colonoscopies for either (additional) ER attempts or endoscopic surveillance before the definite referral for SR (*Table 6*). Twenty-two patients (2.4% of all surgically treated patients) were referred to another endoscopy center for an additional ER attempt before SR.

Surgical characteristics and complications

The most commonly performed type of SR was a right-sided hemicolectomy (45.0%, n = 412) (*Table 7*). Other types of SR performed in the proximal colon were ileocecal resection in 155 patients (16.9%), transversectomy in 17 patients (2.0%) and appendectomy in 1 patient (0.1%). The surgical procedures were performed laparoscopically in 66.8%. The median hospital stay was 6.0 days (IQR 4.0-10.0). Sixty patients (7.5%) were admitted at the ICU after SR with a median duration of 3.5 days (IQR 1.25-7.75). A total of 526 post-operative adverse events occurred in 318 (34.8%) patients, which are further specified in *Table 7*. The mortality related to the performed SR was 1.4% (n = 13).

DISCUSSION

Over the past decade, colorectal surgery for the resection of benign colorectal polyps detected during colonoscopy was still frequently performed in the Netherlands. The absolute and relative volumes of SR remained stable over the study period. This is similar to other studies investigating SR and ER for benign colorectal polyps, showing that SR remains widely applied.[10, 25-27] Over the past decade nationwide volumes of colonoscopy have increased, which suggests that also a higher number of complex colorectal polyps will have been found endoscopically. Keeping in mind a stable volume of SR over the past decade, potentially more successful ER procedures have been

Table 6. Referral patterns after first colonoscopy

	N = 915
Referral after first colonoscopy – No (%)	
SR	714 (78.0%)
Additional colonoscopy for surveillance after radical ER or an additional ER attempt	201 (22.0%)
Median number of additional colonoscopies (IQR)	1.0 (1.0-2.0)
Indication first additional colonoscopy – No (%)	
Surveillance after radical ER	11 (5.5%)
ER attempt	190 (94.5%)
Patients whom underwent ≥ 2 follow-up colonoscopies – No (%)	33 (3,6%)
Indication ≥ 2 follow-up colonoscopies – No (%)	
Surveillance after radical ER	13 (39.4%)
ER attempt	20 (60.6%)
Location where additional colonoscopy is performed – No (%)	
Own endoscopy center	179 (89.1%)
Other endoscopy center	22 (10.9%)
Tertiary	18 (81.8%)
Other regional	4 (18.2%)

performed nationwide and regionally. Regrettably, no comparative data were available on the overall nationwide volumes of successful ER procedures performed as well as in the participating centers of the province of Noord-Holland in order to confirm this causality.

Prevention of SR could be considered as one of the primary aims of ER of large complex non-pedunculated colorectal polyps.[28] This is essential since colorectal surgery is known to be associated with significant morbidity and mortality, which are significantly higher when compared to ER.[26, 29-31] Surgical adverse event rates (morbidity and mortality) in patients whom underwent SR for non-malignant polyps range between 9.9% and 24.0% and between 0.7% and 1.1%.[25-27, 32, 33] The adverse event and mortality rates found in our cohort seem slightly higher than previously reported in the literature. This could potentially be explained by the fact that only 66.8% of the patients in our cohort underwent laparoscopic SR, which is associated with lower morbidity and mortality rates when compared to open SR.[34] However, caution is required when interpreting these results as different definitions of morbidity and mortality have been used throughout the literature.[25-27, 32, 33]

In recent years the knowledge of the efficacy and safety of ER techniques, as well as the experience with performing ER for large complex non-pedunculated colorectal polyps has progressed tremendously.[28, 35] An increasing body of evidence suggests that many lesions currently referred for SR are amenable to endoscopic treatment when performed in experienced hands. When performed by experienced endoscopists over 90% of all large complex colorectal polyps can be removed by ER.[10, 13, 36, 37] In the study by Friedland et al., 71% of advanced colonic lesions without biopsy-proven CRC, already referred for SR, could be treated by ER during a repeat colonoscopy performed in a tertiary center performed by an experienced endoscopist. In these patients SR could thereby directly be avoided.[13] Therefore we would like to make a plea that all patients having a complex benign colorectal polyp assessed unamenable for ER should be referred for repeat

Table 7. Surgical characteristics and complications

	N = 915
Type of Surgery – No (%)	
Ileocecal resection	155 (16.9%)
Appendectomy	1 (0.1%)
Right sided hemicolectomy	412 (45.0%)
Transversectomy	18 (2.0%)
Left sided hemicolectomy	68 (7.4%)
Sigmoid resection	115 (12.6%)
Rectal sigmoid resection	13 (1.4%)
Rectal surgery	92 (9.9%)
APR	5 (5.4%)
TME	6 (6.5%)
LAR	81 (88.0%)
Completing colectomy	1 (0.1%)
Subtotal colectomy	13 (1.4%)
Wig exision polyp	27 (3.0%)
Type of surgery – No (%)	
Laparoscopic resection	611 (66.8%)
Open resection	303 (33.1%)
Not described	1 (0.1%)
Median hospital stay - days (IQR)	6.0 (4.0-10.0)
Patients admitted at the ICU – No (%)	60 (7.5%)
Median duration of ICU admission - days (IQR)	3.5 (1.25-7.75)
Not described	112 (12.2%)
Patients with post-operative adverse events – No (%)	318 (34.8%)
Not described	42 (4.6%)
Median number of post-operative adverse events per patient (IQR)	1.0 (1.0-2.0)
Post-operative adverse events – No (%)	526
Clavien Dindo I	156 (29.7%)
Clavien Dindo II	180 (34.2%)
Clavien Dindo IIIa	27 (5.1%)
Clavien Dindo IIIb	76 (14.4%)
Clavien Dindo IVa	68 (12.9%)
Clavien Dindo IVb	6 (1.1%)
Clavien Dindo V	13 (2.5%)
Post-operative adverse events type – No (%)*	
Ileus	70 (13.3%)
Pneumonia	57 (10.8%)
Anastomotic leakage	51 (9.7%)
Wound infection	47 (8.9%)
Post-procedural bleeding	25 (4.8%)
UWI	20 (3.8%)
Intra-abdominal abces	18 (3.4%)
Sepsis	17 (3.2%)
Mortality of SR – No (%)	13 (1.4%)

* Only complications which occurred ≥ 15 times

colonoscopy performed by an endoscopist having extensive experience in performing ER before definitive referral for SR.

In our study cohort ER attempts had been performed before the definitive referral towards SR in a minority (15.5%) of patients, which significantly increased over the last five years of the study period. The exact reason why ER attempts were not performed remains unknown and could not be extracted from the collected data from patient charts. It is likely that ER was not frequently attempted because 60.8% of the lesions was assessed as being endoscopic irresectable or inaccessible and 25.9% as having a high probability of being malignant. It can be speculated that there was a limited awareness of the endoscopic risk factors for submucosal invasion, the potential indications, efficacy, and safety of ER techniques and a limited personal or local ER expertise, which evidently improved over the recent years.

Additionally, an even smaller proportion (2.4%) of patients had been referred to another hospital for an additional ER attempt before SR. A similar pattern was shown in the study of Le Roy et al. in which only 1.3% of the patients were referred towards a tertiary interventional endoscopy center.[25] The decision whether or not to refer a patient to a different endoscopy center for an additional ER attempt versus immediate referral towards SR may depend on the certainty of the endoscopist that all available ER techniques have been explored. Also, the unawareness of the expertise and experience of colleagues in performing ER in a nearby endoscopy center and possibly also the reluctance to refer a patient for a potential unnecessary second colonoscopy could contribute to this decision.

In order to increase the number of ERs before the definitive referral for SR, implementation of regional multidisciplinary referral networks could be considered. More treatment options and ER experience will become more widely accessible and therefore SR can potentially be avoided in a subgroup of patients.[5, 11, 36] One could speculate that in accordance with the study of Friedland et al. SR and its associated morbidity and mortality could have been prevented in approximately 70% of the patients, when all patients underwent a repeat colonoscopy by an experienced endoscopist due to the implementation of a regional referral network. Gastroenterologists are in our opinion primarily responsible for the adequate indication to refer a patient with a complex colorectal polyp for SR, but also to refer for an additional ER attempt. Surgeons should also be aware of previously performed ER attempts by either the endoscopist in a local hospital or an interventional endoscopy center. Therefore also surgeons should critically assess the indication for SR and should consider referring patients without an opinion of an experienced colonoscopist, to such interventional centers before embarking on SR.

Our study has important limitations. First, all clinical data was collected retrospectively from patient charts, which may have let to omission of data, although the national pathology database is considered an accurate prospective database. For example it remains unclear how the shared decision process went regarding to either perform ER or SR and what the exact patient preferences were in this regard. Second, the patient selection in our study could have led to selection bias, since patients were identified according to their resection specimen and there is no comparative data available on the volumes of successful ER procedures performed in the participating centers. Third, there was no systematic follow-up after colonoscopy making a comparison of adverse events between the colonoscopies with ER attempts and the adverse events related to SR not entirely

reliable. Fourth, the generalizability of the results to other countries with other health care systems remains unknown.

To the best of our knowledge, this is the first study investigating the volume changes over time as well as the previous ER attempts before definitive referral towards SR of benign colorectal polyps. This is an unique cohort of patients, since resection specimen are derived from a histopathology database with national coverage, which is singular for the Netherlands.[16] This is also one of the largest multicenter cohort studies investigating the volume of SR for benign colorectal polyps in in both academic and regional hospitals. Other studies included smaller numbers of patients or selected patients solely from a tertiary interventional endoscopy center.[25, 26] Remarkably all performed studies investigating SR for benign colorectal polyps are retrospective and regional. Therefore nationwide prospective registries for SR for benign colorectal polyps could be indicative to further elucidate the current volume of SR and its associated morbidity and mortality.

In conclusion, colorectal surgery is still frequently applied for the resection of benign complex colorectal polyps and the absolute and relative volume of SR remained stable over the past decade. In a relatively small number of patients ER attempts were performed before SR and referral to a tertiary colonoscopy center for ER was rarely done. Therefore implementation of a regional multidisciplinary referral network with access to endoscopy centers with ER experience should be considered to increase the number ER attempts and potentially avoid SR and its related morbidity and mortality in a subset of patients. Gastroenterologists and gastrointestinal surgeons should be aware of these data and apply this knowledge before referring and accepting patients for SR.

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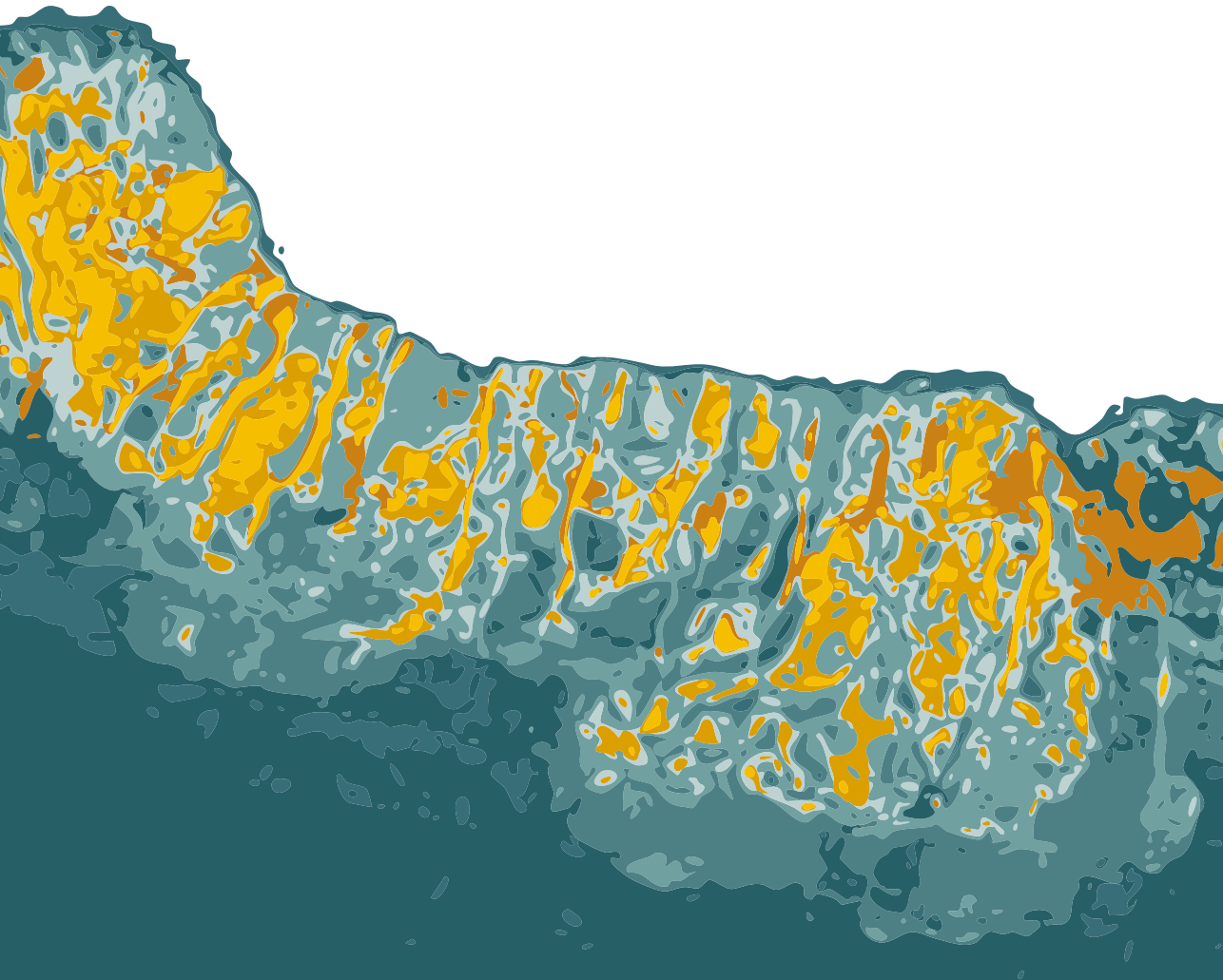

OUTCOMES OF SURGICAL RESECTION FOR BENIGN COLON POLYPS: A SYSTEMATIC REVIEW

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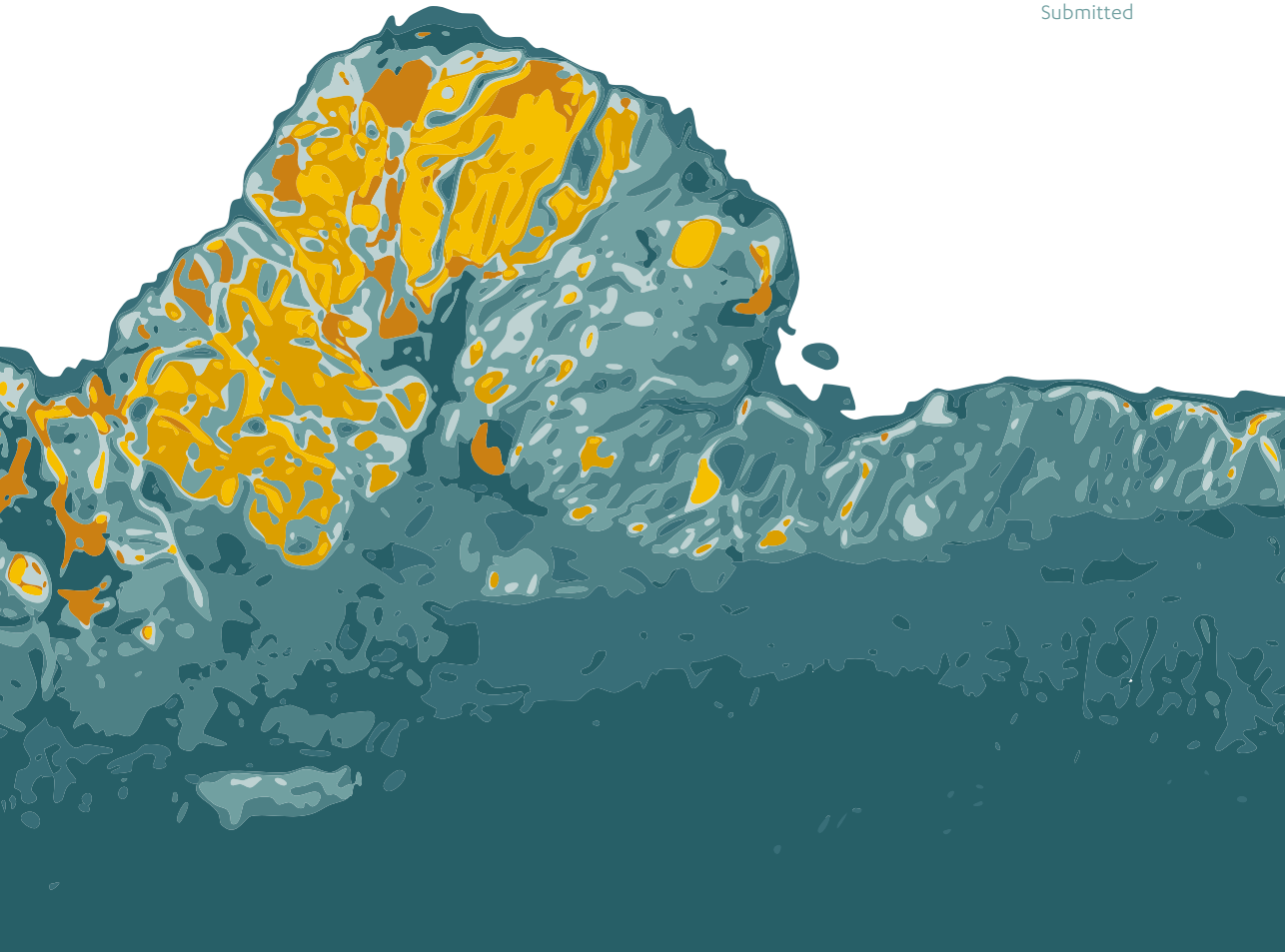
Submitted



ABSTRACT

Background and aim

Not all benign colon polyps are suitable for endoscopic resection, although criteria for endoscopic non-resectability vary worldwide. Clinical decision-making largely depends on endoscopic treatment options, as well as postoperative risks after surgical resection. This systematic review aimed to determine postoperative outcomes and the characteristics of surgically resected benign colon polyps.

Methods

MEDLINE, EMBASE and the Cochrane Library were searched for studies investigating the outcomes of surgical resections for benign colon polyps. Studies were considered eligible when at least one postoperative outcome (morbidity and/or mortality) was reported. Studies primarily reporting on rectal polyps were excluded, because this can be appreciated as a different clinical entity compared to the colon.

Results

Of the 4210 studies retrieved, 26 studies describing 139,897 patients were included. Most common indications for surgical resection were polyp location in the right-sided colon, a non-pedunculated morphology and a large polyp size. Unexpected malignancy varied between 1.5% and 33.3%. Short-term (28- or 30-day) complication rates ranged from 9.9% to 56.5%, of which surgical complication rates ranged between 8.5% and 43.5% and non-surgical complication rates ranged between 0% and 13.5%. Severe complications (Clavien Dindo 3+) ranged from 0% to 10.1%. Short-term mortality rates ranged from 0% to 2.5%.

Conclusion

Postoperative morbidity and mortality after colon resection for benign polyps are substantial. This pleads for referral to an advanced interventional endoscopist to evaluate possibilities for endoscopic treatment of large, non-pedunculated and/or difficult located colon polyps without suspicion of submucosal malignant invasion before referral for surgery.

INTRODUCTION

Colorectal cancer (CRC) develops from benign precursor lesions, and malignant transformation takes multiple years, if occurring at all.[1] This makes CRC very suitable for population-based screening. Detecting early stage CRC or its benign precursor lesions (colorectal polyps) by Fecal Occult Blood Testing (FOBT) with subsequent endoscopic resection reduces the incidence and mortality of CRC.[2, 3] Polyps might also be found as part of primary colonoscopy screening programs, surveillance programs in high-risk patients or accidentally during colonoscopy for other indications.

The majority of benign colon polyps can be resected endoscopically with low complication rates.[4, 5] However, a subset of benign appearing polyps may be judged as being not eligible for endoscopic treatment, although this assessment might substantially vary depending on available advanced endoscopic skills, endoscopy equipment, scheduled procedural time and experience of supporting nursing staff. Polyp size, morphology, location and suspicion of malignancy are important contributors to this judgement.[6, 7] For these patients, surgical resection can be considered varying from local excision of the bowel wall to formal segmental resections or even subtotal colectomy. However, surgical resection of benign polyps is expected to come with higher rates of treatment-associated morbidity and mortality when compared to endoscopic resection based on the extensive data published on CRC surgery.[8-11]

When considering endoscopic or surgical resection, knowledge about the benefits and risks of both procedures is essential to enable a comprehensive shared decision-making process. Also, the estimated prognostic impact of a certain polyp in the individual patient within the context of comorbidities has to be taken into account. For CRC screening programs, which target asymptomatic populations, the potential benefits and harms of the program should be well balanced. Analysis of surgical procedures for benign polyps with its associated risks should be part of this evaluation.

It should be emphasized that decision making and clinical implications can be different for colon and rectal polyps. This is related to the possibilities to apply surgical transanal techniques for local resection of rectal polyps and to different postoperative risks related to the extraperitoneal localization of suture lines.

The purpose of this systematic review was to give a comprehensive overview of the literature on postoperative outcomes (morbidity and mortality) of colon surgery for benign polyps, thereby excluding studies that primarily report on surgery for rectal polyps. Other outcomes of interest included indications for a surgical resection, the type of surgical procedures performed, polyp characteristics, malignancies found at histopathology of the resected polyps and length of stay (LOS).

METHODS

Literature search

This systematic review was conducted in accordance to the PRISMA guidelines.[12] A literature search was performed of the following electronic databases: PubMed, EMBASE and the Cochrane Library. The search strategy was devised with the assistance of a research librarian. A combination of MESH and all-field search terms were used for ''benign'', ''polyp'', ''colon'', ''colorectal'', ''surgery'' and

''adverse events'' and their most common synonyms. The detailed search strategy is provided in the *Appendix A1*. Reference lists from the included articles were hand searched for other eligible articles.

In- and exclusion criteria

Only complete studies published in English or Dutch between January 1st, 1980 and July 1st, 2017 were considered eligible for this systematic review. The following study designs were included: randomized controlled trials, prospective cohort studies, retrospective cohort studies, case-controlled studies and cross-sectional studies. Furthermore, only studies reporting on at least one primary postoperative outcome (morbidity or mortality) of surgical resections of benign colon polyps were included.

Studies were excluded if (1) the analysis included outcomes of other indications for surgery (e.g. suspicion of invasive growth, other benign gastrointestinal diseases like inflammatory bowel diseases or diverticulitis and hereditary intestinal polyposis syndromes like familial adenomatous polyposis) and the authors did not report on postoperative outcomes (morbidity and mortality) separately, (2) the majority (> 50%) of benign colorectal polyps was located in the rectum instead of the colon and the authors did not report on outcomes of the resection of benign colon polyps separately, (3) studies in which resections were performed in an emergency setting (e.g. volvulus, ileus, appendicitis, perforation or colorectal bleeding).

Study selection

Studies were independently evaluated by three authors (MN, MB, JA) by screening title, abstract, and then full body text, with articles being removed at each step according to the exclusion criteria. To ensure that all potentially relevant studies were considered for inclusion, each study with uncertain eligibility at review of title and abstract was further examined by two authors reading the full text independently. Any disagreements were resolved by consensus.

Assessment of Risk of Bias

The risk of bias was assessed using the Newcastle-Ottawa Scale.[13] The included studies were reviewed on the selection of the study group, comparability of the groups, and the ascertainment of outcome of interest. Per item, studies were ranked with stars.

Outcome measures and data extraction

Primary outcome measures included postoperative morbidity and mortality. Morbidity comprised all complications described in the study and their severity was classified according to Clavien Dindo if relevant data were available.[14] If the type of complications were described in the studies, the complications were further classified as surgical or non-surgical complications. Surgical complications were defined as complications directly related to the surgical procedure itself, such as surgical site infections, wound infections, wound dehiscences, anastomotic complications, post-operative ileus, abdominal abscesses, post-operative hemorrhage, hernias, fistulas and

iatrogenic damage to the surrounding organ systems. Non-surgical complications included all other complications not directly related to the surgical technique itself, such as cardiovascular, pulmonary, thrombo-embolic, urinary tract, neurologic and infectious complications not located at the surgical site.

Secondary outcome measures included the surgical re-intervention rate after complications, referral rates for surgery of benign polyps, indications for surgery and polyp characteristics (size, location and morphology). Furthermore, surgical procedures were assessed for approach and type of procedure, final histopathology, and LOS. To enable a comprehensive overview of the literature, no strict definitions were used.

Data were systematically extracted using a predefined data extraction form. Descriptive statistics were used to summarize study findings. Because of the expected heterogeneity of the methodology of the included studies and expected differences of observed patients and polyps, pooled analysis was not considered to be methodologically sound.

RESULTS

Included studies

The literature search and study selection process are shown in *Figure 1*. After removing duplicates, the search strategy retrieved 4210 articles. A total of 26 studies met the inclusion criteria, with a total number of patients per study ranging from 9 to 124,036. Nineteen studies reported exclusively on colon polyps, while seven included a minority of rectal polyps. Of all 26 studies, 25 (96.2%) were cohort studies, 6 (23.1%) were multicenter studies, and 18 studies (69.2%) originated from the US. Study periods ranged between 1980 and 2016. Study baseline characteristics and patient demographics are summarized in *Table 1*. The independent ratings according to the Newcastle-Ottawa Scale are shown in *Table 2*.

Referral rate and indications for surgery

The rate of surgical referrals was reported by three of the included studies. Church et al. reported that 49 (9.5%) of 513 adenomas larger than 2 cm were referred for surgery.[15] Le Roy et al. reported a surgical resection in 175 out of 4251 (4.1%) patients with a benign polyp identified through the French CRC screening program.[16] Finally, in the British Bowel Cancer Screening Program, 121 (21.7%) of 557 polyps larger than 2 cm with sessile or flat morphology were referred for surgical resection.[17]

Explicit reasons of referral for surgical resection of the polyp were reported in five studies (*Table 3*). Polyp location was the most common reason for referral in three studies, all reporting the right-sided colon as the most common location for referral.[18-20] In the other two studies, polyp size was the main reason for referral.[17, 21] In those respective studies, median size of the polyp was 4.0 cm (IQR 2.5-5.4)[21] and mean 3.8 ± 1.9 cm.[17] Overall, polyp size was reported in 21 of the 26 studies as median, mean, ranges or categories. In studies that used a categorization for polyp size, the majority of the polyps that were referred for surgery were > 2 cm[16, 21-23], and in the studies that reported on median polyp sizes, sizes ranged from 1.8 cm to 4.0 cm.[18, 19, 21, 24]

Another commonly reported reason of referral for surgery consisted of a sessile morphology.[18, 19, 21] Overall, the majority of the polyps that were surgically resected were sessile,

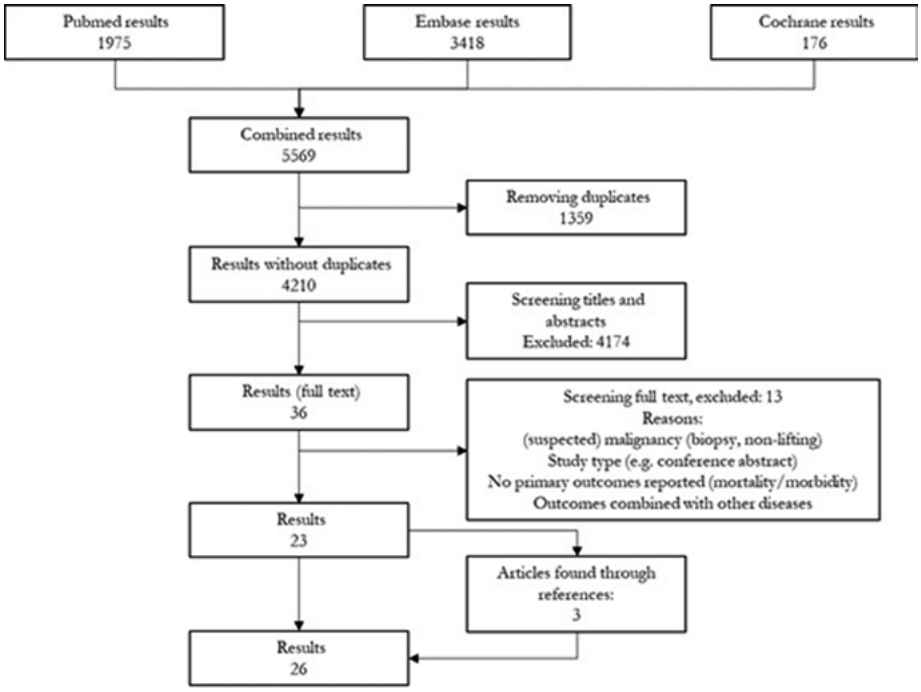


Figure 1. Flowchart of systematic search and included studies in review

ranging from 46.3% to 100%.[16-19, 21, 22, 24, 25] Details of the reported morphology varied greatly, with four studies only differentiating between sessile or pedunculated.[18, 21, 22, 25] Three studies also differentiated between sessile and flat, in which flat morphology ranged from 6.9% to 33.3%.[16, 19, 24]

Approach and type of surgical procedure

In eight studies, laparoscopic surgery was the initial approach for all included patients (*Table 3*).[18, 20, 26-31] Overall rate of laparoscopic surgery among the included studies ranged from 8.7% to 100%. In total, 21 of the 26 studies reported on the type of surgery, mainly consisting of oncologic resections. Five of these 21 studies also described other procedures like colotomy, laparoscopy assisted endoscopic polypectomy or local resections or excisions (e.g. wedge resection, full-thickness excision, and segmental resection), ranging from 6.3% to 32.7%.[16, 20, 30, 32, 33]

Postoperative outcomes

All 26 studies reported on complication rates (*Table 4*). However, the definition of complications varied widely between studies. For example, Alder et al.[33] and Lee et al.[17] only described postoperative surgical complications (e.g. as minor, moderate severe, or as type of surgical complication such as postsurgical bleeding, anastomotic problems, wound infections or postoperative ileus), whereas Keswani et al. only reported procedural and post-procedural complications that led to a delay in discharge or to a readmission.[34] The overall complication rate, with varying definitions, ranged

Table 1. Overview of baseline characteristics of studies included

Publication	Country	Time period	Study type	Patient number	Reported Age as category, mean or median with ±SD or (range)	ASA III and higher
Peery et al. (2017)[36]	USA	2011-2014	Multi center Cohort (Prospective)	12,732	≤49 yrs: 878 (7%) 50-59 yrs: 3243 (25%) 60-69 yrs: 4191 (33%) 70-79 yrs: 3395 (27%) ≥80 yrs: 1018 (8%)	6234/12,732 (49%)
Dulskas et al. (2017)[32]	Lithuania	2006-2016	Single center Cohort (Prospective)	58	Mean: 65.9±8.9 yrs	NR
Gorgun et al. (2016)[24]	USA	1997-2012	Single Center Cohort (Retrospective)	439	67 years (range 27-97)	NR
Lascarides et al. (2016)[18]	USA	2010-2013	Single center Randomized controlled trial	17	Median: 61 yrs (49–85)	9/17 (53%)
Keswani et al. (2016)[34]	USA	2003-2013	Single center Cohort (Retrospective)	359	Mean: 64±11 yrs	87/359 (27%)
Church and Erkan (2016)[15]	USA	1980-2008	Single center Cohort (Retrospective matched)	78	Mean: 66.8±10.2 yrs	NR
Hernandez-Boussard et al. (2016)[35]	USA	2008-2012	Multi center Cohort (Retrospective)	124,036	Mean: 65.4 yrs (SD NR)	NR
Le Roy et al. (2015)[16]	France	2003-2012	Multi center Cohort (Retrospective)	175	Mean: 62.8±6.8 yrs	NR
Brigic et al. (2014)[21]	UK	2006-2012	Multi center Cohort (Prospective matched)	46	Mean: 67.3±8.9 yrs	5/46 (11%)
Lee TJ et al. (2013)[17]	UK	2006-2009	Multi center Cohort (Retrospective)	121	Mean: 66.7±3.6 yrs	NR
Ikard et al. (2013)[22]	USA	2001-2010	Single center Cohort (Retrospective)	126	Mean: 65.1±7.9 yrs	108/126 (86%)
Lee MK et al. (2013)[39]	USA	2008-2012	Single center Cohort (Retrospective)	9	Mean: 68.3 yrs (30-82)	NR
Jang et al. (2012)[37]	USA	1991-2009	Multi center Cohort (Retrospective)	386	Mean: 66.8±12.3 yrs	53/386 (14%)
Cruz et al. (2011)[26]	USA	2006-2010	Single center Cohort (Prospective)	68	Mean: 63.8 ± 9.6 yrs	NR
Loungnarath et al. (2010)[23]	USA and Canada	1991-2003	Single center Cohort (Retrospective)	165	Mean: 69.1 yrs (SD NR)	25/165 (16%)
Itah et al. (2009)[27]	Israel	2003-2009	Single center Cohort (Prospective)	64	Mean: 71 yrs (SD NR)	NR
Blumberg et al. (2009)[28]	USA	2004-2007	Single center Cohort (Retrospective)	44	Mean: 67±12 yrs	13/44 (30%)
Hauenschild et al. (2009)[29]	Germany	1993-2004	Single center Cohort (Retrospective)	54	Mean: 63.2 yrs (34-81)	NR

Table 1. (continued)

Publication	Country	Time period	Study type	Patient number	Reported Age as category, mean or median with ±SD or (range)	ASA III and higher
Benedix et al. (2008)[30]	Germany	1995-2005	Multi center Cohort (Prospective)	525	Males: median 64.8 yrs (21–91) Females: median 65.6 yrs (16–92)	NR
Pokala et al. (2006)[31]	USA	1999-2003	Single center Cohort (Prospective)	51	Males: mean: 68.9 ± 11.7 yrs Females: mean: 67.6 ± 11.3 yrs	30/51 (59%)
Alder et al. (2006)[33]	USA	1997-2006	Single center Cohort (Retrospective)	79	Median: 66 yrs (38- 85)	48/79 (60%)
Lipof et al. (2005)[25]	USA	1999-2003	Single center Cohort (Retrospective)	48	Mean: 68.6 ± 9.1 yrs	NR
Church, J. M. (2003)[19]	USA	1989-2002	Single center Cohort (Retrospective)	15	Mean: 68.8±6.1 yrs	9/15 (60%)
Young-Fadok et al. (2000)[38]	USA	1992-1997	Single center Cohort (Retrospective case-matched)	76	Laparoscopic: mean: 72.3 (range 45-86) Open mean: 70.6 (range 45-82)	NR
Eijsbouts et al. (1999)[20]	Netherlands	1991-1997	Single center Cohort (Retrospective)	20	Mean: 63.2 yrs (range 45-83)	NR
Joo et al. (1998)[40]	USA	1992-1996	Single center Cohort (Prospective)	45	Mean: 71.2 yrs (SD NR)	NR

Table 2. Quality assessment of studies included

Publication	Selection	Comparability	Outcome/exposure
Peery et al. (2017)[36]	**	N/A	***
Dulskas et al. (2017)[32]	**	N/A	**
Gorgun et al (2016)[24]	**	0	***
Lascarides et al. (2016)[18]	**	*	*
Keswani et al. (2016)[34]	***	0	***
Church and Erkan (2016)[15]	**	*	0
Hernandez-Boussard et al. (2016) [35]			
Le Roy et al. (2015)[16]	***	*	**
Brigic et al. (2014)[21]	***	*	**
Lee TJ et al. (2013)[17]	***	0	***
Ikard et al. (2013)[22]	**	N/A	***
Lee MK et al. (2013)[39]	***	0	**
Jang et al. (2012)[37]	**	N/A	*
Cruz et al. (2011)[26]	***	0	***
Loungnarath et al. (2010)[23]	**	0	**
Itah et al. (2009)[27]	**	N/A	**
Blumberg et al. (2009)[28]	**	N/A	**
Hauenschild et al. (2009)[29]	**	N/A	**
Benedix et al. (2008)[30]	**	N/A	***
Pokala et al. (2006)[31]	**	N/A	**
Alder et al. (2006)[33]	**	N/A	*
Lipof et al. (2005)[25]	**	N/A	***
Church et al. (2003)[19]	**	N/A	**
Young-Fadok et al. (2000)[38]	***	0	**
Eijsbouts et al. (1999)[20]	**	N/A	**
Joo et al. (1998)[40]	***	0	0

Selection (maximum 4 stars): Case definition adequacy, selection of the non-exposed cohort, ascertainment of exposure, outcome of interest was not present at start of study. Comparability on the basis of the design or analysis (maximum 2 stars): Age, other controlled factors. Outcome/exposure (maximum 4 stars): Assessment of outcome, follow-up long enough (defined as ≥3 years), adequacy of follow-up of cohorts. N/A: not applicable. 0: zero stars

between 1.7% and 57.7%. Studies reporting on peri-operative or in-hospital complications showed a complication rate between 1.7% and 35.4%.[23, 30, 33, 35] Short-term (28- or 30-day) complication rates varied between 9.9% and 56.5%. The, short-term surgical complication rates ranged between 8.5% and 43.5% and short-term non-surgical complication rates between 0% and 13.5%.[16, 17, 21, 22, 24, 28, 29, 36] Severe complications (Clavien Dindo 3+) were reported in six studies and ranged from 0% to 10.1%.[15, 16, 21, 30, 32, 37] Surgical reinterventions ranged from 0% to 8.9%.[16, 18, 19, 21, 22, 25-27, 29-32, 34, 36-38]

When looking at the five studies that included relatively larger patient populations (> 100 patients) and were performed since the year 2000, surgical complication rates ranged from 8.5% to 19.4% and the non-surgical complication rate from 4.6% to 13.5%.[16, 17, 22, 34, 36] Four of these studies reported on a surgical re-intervention rate, ranging from 3.1% to 5.6%.[16, 22, 34, 36] Eleven studies reported specifically on anastomotic leakage as a complication (excluding complications reported

Table 3. Indications of referral for surgery of a benign polyp, polyp characteristics and surgical procedure

Publication	Indication for referral to surgeon N (%)	Location of polyp N (%)	Polyp Size (cm) Mean, Median or Category (cm: N (%))
Peery et al. (2017)[36]	NR	Colon: 12,223/12,732 (96%) Rectum: 509/12,732 (4%)	NR
Dulskas et al. (2017)[32]	NR	Cecum: 1/42 (2.4%) Ascending colon: 3/42 (7.1%) Hepatic flexure: 1/42 (2.4%) Transverse: 3/42 (7.1%) Splenic flexure: 2/42 (4.8%) Descending colon: 2/42 (4.8%) Sigmoid: 8/42 (42.9%) Rectum: 12/42 (28.6%)	Mean: 3.5 ± 1.9 (?)
Gorgun et al. (2016)[24]	NR	Cecum: 199/439 (45.3%) Ileocecal valve: 30/439 (6.8%) Ascending colon: 91/439 (20.7%) Hepatic flexure: 33/439(7.5%) Transverse colon: 34/439 (7.7%) Splenic flexure: 7/439 (1.6%) Descending colon: 7/439 (1.6%) Sigmoid colon: 38/439 (8.7%)	Median: 2.7 (range 0 - 11) (P)
Lascarides et al. (2016)[18]	Location: 7/17 (41.2%) Size and location: 4/17 (23.5%)	Caecum: 9/17 (52.9%) Ascending colon: 5/17 (39.4%)	Median: 1.8 (P)

Morphology N (%)	Laparoscopic surgery N (%)	Surgical procedure N (%)
NR	9717/12,732 (76.3%) Conversion rate: NR	NR
NR	41/58 (70.7%) Conversion rate: 0/41 (0%)	Colotomy: 17/58 (29.3%) Laparoscopy assisted endoscopic polypectomy: 2/58 (3.4%) Right hemicolectomy: 2/58 (3.4%) Ileo-cecal resection: 2/58 (3.4%) Left hemicolectomy: 7/58 (12%) Sigmoid resection: 10/58 (17.2%) Anterior resection: 18/58 (31.0%)
Sessile: 252/439 (57.4%) Pedunculated: 109/439 (24.8%) Flat: 78/439 (17.8%)	293/438 (54%) Conversion rate: 35/293 (12%)	Right hemicolectomy: 378/439 (86.1%) Left hemicolectomy: 52/439 (11.8%) Total colectomy: 9/439 (2.1%)
Sessile: 17/17 (100%) Pedunculated: 0/17 (0%)	17/17 (100%) Conversion rate: 3/17 (17.6%)	Right hemicolectomy: 17/17 (100%)

Table 3. (continued)

Publication	Indication for referral to surgeon N (%)	Location of polyp N (%)	Polyp Size (cm) Mean, Median or Category (cm: N (%))
	Morphology: 4/17 (23.5%) Size: 2/17 (11.8%)	Hepatic flexure: 3/17 (17.6%)	
Keswani et al. (2016)[34]	Complex colorectal polyps because of their size, morphology or location (not further specified)	NR	Mean: 3.0 ± 1.9 (S)
Church and Erkan (2016)[15]	NR	Cecum: 29/78 (37.2%) Ileocecal valve: 4/78 (5.1%) Ascending colon: 24/78 (31%) Hepatic flexure: 7/78 (9.0%) Transverse colon: 3/78 (3.8%) Descending colon: 5/78 (6.4%) Sigmoid: 3/78 (3.8%) Rectum: 3/78 (3.8%)	Mean: 2.7 (P)
Hernandez-Boussard et al. (2016) [35]	NR	NR	NR
Le Roy et al. (2015) [16]	NR	Right colon: 36/175 (20.6%) Transverse colon: 5/175 (2.9%) Left colon: 22/175 (12.6%) Sigmoid/rectum: 112/175 (64%)	<1.0: 12 (6.9%) 1.0-2.0: 21 (12.0%) ≥2.0: 142 (81.1%) ≥3.0: 113 (64.6%) ≥4.0: 65 (37.1%)

Morphology N (%)	Laparoscopic surgery N (%)	Surgical procedure N (%)
NR	209/359 (58.2%) Conversion rate: NR	Right/extended right hemicolectomy 261/359 (72.7%) Transverse/left hemicolectomy: 49/359 (13.6%) Transverse/left hemicolectomy: 49/359 (13.6%)
NR	35/78 (44.9%) Conversion rate: NR	NR
NR	NR	NR
Sessile: 81/175 (46.3%) Pedunculated: 77/175 (44%) Flat: 12/175 (6.9%) Tumor-like: 1/175 (0.6%) Unknown: 4/175 (2.3%)	104/175 (59%) Conversion rate: 14/104 (13%)	Abdominal surgery: 153/175 (87.4%) Transanal excision: 22/175 (12.6%)

Table 3. (continued)

Publication	Indication for referral to surgeon N (%)	Location of polyp N (%)	Polyp Size (cm) Mean, Median or Category (cm: N (%))
			≥5.0: 34 (19.4%) (S)
Brigic et al. (2014) [21]	Size: 14/46 (30.4%) Location: 12/46 (26.1%) Morphology: 12/46 (26.1%) Incomplete removal: 4/46 (8.7%) Recurrent polyp: 2/46 (4.3%) Unknown: 2/46 (4.3%)	Caecum: 19/46 (41.3%) Ascending colon: 6/46 (13%) Hepatic flexure: 1/46 (2.2%) Transverse colon: 3/46 (6.5%) Splenic flexure: 3/46 (6.5%) Descending colon: 4/46 (8.7%) Sigmoid: 10/46 (21.7%)	Median: 4.0 (IQR 2.5-5.4) <2.5: 7 (15%) 2.5-3.4: 13 (28%) 3.5-4.4: 5 (11%) 4.5-5.4: 8 (17%) >5.5: 11 (24%) Unknown: 2 (5%) (P)
Lee TJ et al. (2013) [17]	Size: 42/121 (34.7%) Location : 13/121 (10.7%) Unknown: 66/121 (54.5%)	Right-sided: 57/121 (47.1%) Left-sided: 64/121 (52.9%)	Mean: 3.8±1.9 (P)
Ikard et al. (2013) [22]	NR	Ascending colon: 76/126 (60.3%) Transverse colon: 14/126 (11.1%) Descending colon: 4/126 (3.2%) Sigmoid: 15/126 (11.9%) Rectum: 11/126 (8.7%) Multiple sites: 6/126 (4.8%)	<3.0: 58 (46.0%) 3.0-5.0: 39 (30.9%) ≥5.0: 20 (15.9%) Unknown: 8 (6.4%) (S)
Lee MK et al. (2013) [39]	NR	NR	Mean: 2.9 (range 1.5–5.2) (S)

Morphology N (%)	Laparoscopic surgery N (%)	Surgical procedure N (%)
Sessile: 34/46 (73.9%) Pedunculated: 8/46 (17.4%) Not recorded: 4/46 (8.7%)	44/46 (96%) Conversion rate: 2/44 (4.5%)	Right hemicolectomy: 29/46 (63%) Left hemicolectomy: 6/46 (13%) Sigmoid colectomy: 11/46 (23.9%)
Sessile or flat: 121/121 (100%)	NR	NR
Sessile: 105/126 (83.3%) Pedunculated: 8/126 (6.4%) Not recorded: 3/126 (10.3%)	11/126 (8.7%) Conversion rate: 8/11 (72%)	Partial colectomy: 108/126 (85.7%) Total colectomy: 2/126 (1.6%) Low anterior resection: 9/126 (7.1%) Transanal resection: 7/126 (5.6%)
NR	NR	NR

Table 3. (continued)

Publication	Indication for referral to surgeon N (%)	Location of polyp N (%)	Polyp Size (cm) Mean, Median or Category (cm: N (%))
Jang et al. (2012) [37]	NR	Right colon: 263/386 (68.1%) Transverse colon: 33/386 (8.6%) Left colon: 16/386 (4.2%) Sigmoid: 38/386 (9.8%) Rectum: 23/386 (6.0%) Multiple sites: 13/386 (3.4%)	Mean: 3.0±1.9 (P)
Cruz et al. (2011) [26]	NR	Cecum: 22/68 (32.4%) Ascending colon: 21/68 (30.9%) Hepatic flexure: 12/68 (17.6%) Transverse colon: 2/68 (2.9%) Splenic flexure: 2/68 (2.9%) Descending colon: 1/68 (1.5%) Sigmoid: 8/68 (11.8%)	Mean: 2.9 ± 1.2 (range 1.0-8.0) (S)
Loungnarath et al. (2010) [23]	NR	NR	≤1.0: 3 (1.8%) 1.0-2.0: 33 (20.1%) >2.0: 123 (75%) Unknown: 5 (3.0%) (P)
Itah et al. (2009) [27]	NR	NR	Mean: 2.63 ± 1.11 (S)

Morphology N (%)	Laparoscopic surgery N (%)	Surgical procedure N (%)
NR	264/386 (72%) Conversion rate: 13/264 (4.9%)	(Sub)Total colectomy: 14/386 (3.6%) Right hemicolectomy: 273/386 (70.7%) Transverse colectomy: 6/386 (4.2%) Left hemicolectomy: 27/386 (7.0%) Sigmoidectomy: 35/386 (9.1%) LAR/APR: 21/386 (5.4%)
NR	68/68 (100%) Conversion rate: 0/68 (0%)	Total colectomy: 2/68 (2.9%) Right hemicolectomy: 57/68 (83.8%) Left hemicolectomy: 2/68 (2.9%) Anterior resection: 7/68 (10.3%)
NR	104/165 (63%) Conversion rate: 5/104 (4.8%)	Right hemicolectomy: 130/165 (78.8%) Extended right Hemicolectomy: 9/165 (5.5%) Left hemicolectomy: 7/165 (4.2%) Sigmoid resection: 19/165 (11.5%)
NR	64/64 (100%) Conversion rate: 3/64 (4.7%)	Subtotal colectomy: 3/64 (4.6%) Right colectomy: 42/64 (65.6%) Transverse colectomy: 2/64 (3.1%)

Table 3. (continued)

Publication	Indication for referral to surgeon N (%)	Location of polyp N (%)	Polyp Size (cm) Mean, Median or Category (cm: N (%))
Blumberg et al. (2009) [28]	NR	Prox. splenic flexure: 37/44 (84.1%) Distal splenic flexure: 7/44 (15.9%)	Mean: 2.9±1.8 (P)
Hauenschild et al. (2009) [29]	NR	NR	NR
Benedix et al. (2008) [30]		Cecum: 92/525 (17.5%) Ascending colon: 56/525 (10.7%) Flexure(hepatic/spleen): 35/525 (6.8%) Transverse colon: 23/525 (4.4%) Sigmoid: 187/525 (3.6%) Rectum: 132/525 (25.1%)	NR
Pokala et al. (2006) [31]	NR	NR	Mean: 3.1 (IQR 2-4.4) (P)

Morphology N (%)	Laparoscopic surgery N (%)	Surgical procedure N (%)
		Sigmoidectomy: 6/64 (9.3%) Anterior resection: 7/64 (10.9%)
NR	44/44 (100%) Conversion rate: 2/44 (4.5%)	Right hemicolectomy: 36/44 (81.8%) Transverse colectomy: 1/44 (2.3%) Left hemicolectomy: 5/44 (11%) Sigmoid resection: 2/44 (4.5%)
NR	58/58 (100%) Conversion rate: 4/58 (6.9%)	Ileocolic resection: 20/54 (37.0%) Right colectomy 12/54 (22.2%) Transverse colectomy: 1/54 (1.9%) Left colectomy: 1/54 (1.9%) Sigmoid resection: 6/54 (11.1%) Anterior rectal resection: 14/54 (25.9%)
NR	525/525 (100%) Conversion rate: 17/525 (3.2%)	Local resection/excision: 61/525 (11.6%) Ileocecal resection: 74/525 (14.1%) Right hemicolectomy: 88/525 (16.8%) Left hemicolectomy: 7/525 (1.3%) Sigmoid resection: 169/525 (32.2%) Anterior rectum resection: 126/525 (24%)
NR	51/51 (100%) Conversion rate: 5/51 (9.8%)	Right Hemicolectomy: 39/51 (76.4%) Left Hemicolectomy/sigmoid resection: 12/51 (23.5%)

Table 3. (continued)

Publication	Indication for referral to surgeon N (%)	Location of polyp N (%)	Polyp Size (cm) Mean, Median or Category (cm: N (%))
Alder et al. (2006) [33]	NR	Cecum: 35/79 (44.3%) Ascending colon: 11/79 (13.9%) Hepatic flexure: 4/79 (5.1%) Transverse colon: 5/79 (6.3%) Splenic flexure: 1/79 (1.3%) Descending colon: 4/79 (5.1%) Sigmoid: 9/79 (11.4%) Rectum: 7/79 (8.9%)	Mean: 3.3 ± 1.64 (P)
Lipof et al. (2005) [25]	NR	NR	Mean: 2.6 ± 1.2 (S)
Church, J. M. (2003) [19]	Location: 6/15 (40%) Morphology: 3/15 (20%) Recurrent polyp: 1/15 (6.6%) Size: 1/15 (6.6%) Unknown: 4/15 (6.6%)	Cecum: 2/15 (13.3%) Ileocecal valve: 1/15 (6.6%) Ascending colon: 3/15 (20%) Hepatic flexure: 2/15 (13.3%) Transverse colon: 3/15 (20%) Sigmoid: 4/15 (26.7%)	Median: 3.0 (range 1.5–4.8) (P)
Young-Fadok et al. (2000) [38]	NR	NR	Median: Lap: 3.0 (range 1-7) Open: 3.7 (range 0.3-10.5)
Eijsbouts et al. (1999) [20]	Location: 11/20 (55%) Size: 7/20 (35%)	Cecum: 6/20 (30%) Hepatic flexure: 4/20 (20%)	Malignant polyps range: 3-6cm Benign polyps range: 1.7-5.5 (P)

Morphology N (%)	Laparoscopic surgery N (%)	Surgical procedure N (%)
NR	12/80 (15%) Conversion rate: NR	Polypectomy or sleeve resection : 5/79 (6.3%) Right hemicolectomy: 56/79 (70.9%) Left hemicolectomy: 11/79 (13.9%) Rectal resection: 8/79 (10.1%)
Sessile: 37/48 (77.1%) Pedunculated: 2/48 (4.2%) Not recorded: 9/48 (18.8%)	45/48 (94%) Conversion rate: 0/45 (0%)	NR
Sessile: 7/15 (46.7%) Flat: 5/15 (33.3%) Pedunculated: 3/15 (20%)	NR	NR
NR	38/76 (50%) Conversion rate: 7/38 (18%)	Right hemicolectomy: 76/76 (100%)
NR	20/20 (100%) Conversion rate: 1/20 (5%)	Colotomy: 6/20 (30%) Ileocecal resection: 2/20 (10%)

Table 3. (continued)

Publication	Indication for referral to surgeon N (%)	Location of polyp N (%)	Polyp Size (cm) Mean, Median or Category (cm: N (%))
	Other: 2/20 (10%)	Transverse colon: 1/20 (5.0%) Descending colon: 1/20 (5.0%) Sigmoid: 6/20 (30%) Rectum: 2/20 (10%)	
Joo et al. (1998) [40]	NR	NR	Mean Lap: 2.6±1.7 Open: 2.7±1.5 (?)

NR: Not Reported. (P): size of the polyp assessed by Pathology. (S): size of polyps assessed endoscopic. (?) unknown how the size of the polyp was assessed. Lap: laparoscopic procedure. Open: Open procedure. LAR: Low Anterior Resection. APR: AbdominoPerineal Resection

Table 4. Overview per study of complications, unexpected malignancy and LOS

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
Peery et al. (2017)[36]	30-day adverse events	1830/12,732 (14.4%)	**Surgical complication: 1,087/12,732 (8.5%)** Superficial surgical site infection: 600/12,732 (4.7%) Anastomotic leak or abscess: 325/12,732 (2.6%) Deep surgical site infection: 87/12,732 (0.7%) Wound dehiscence: 75/12,732 (0.6%) **Non-surgical complication: 1,048/12,732 (8.2%)** Urinary tract infection: 179/12,732 (1.4%) Pneumonia: 174/12,732 (1.4%)

Morphology N (%)	Laparoscopic surgery N (%)	Surgical procedure N (%)
		Right hemicolectomy: 4/20 (20%) Left hemicolectomy: 1/20 (5.0%) Sigmoid resection: 5/20 (25%) Anterior resection: 2/20 (10%)
NR	23/45 (51%) Conversion rate: 4/23 (17%)	Right hemicolectomy: 26/45 (57.8%) Transverse colectomy: 1/45 (2.2%) Left hemicolectomy: 4/45 (8.9%) Sigmoid colectomy: 11/45 (24.4%)

Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
NR	459/12,732 (3.6%)	NR	Mean: 5 days Lap: 4.8 ± 5.9 days Open: 6.4 ± 5.7 days

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Acute renal failure: 93/12,732 (0.7%) Deep venous thrombosis: 83/12,732 (0.7%) Pulmonary embolism: 42/12,732 (0.3%) Stroke/CVA: 21/12,732 (0.2%) Myocardial infarction: 60/12,732 (0.5%) Cardiac arrest: 53/12,732 (0.4%) Sepsis: 234/12,732 (1.8%) Septic shock: 109/12,732 (0.9%)
Dulskas et al. (2017)[32]	post-operative 12-month	4/58 (6.9%) 0/58 (0%)	**Surgical complication: 1/58 (1.7%)** Partial ileus: 1/58 (1.7%) **Non-surgical complication: 3/58 (5.2%)** Urinary tract infection: 2/58 (3.4%) Urinary retention: 1/58 (1.7%)
Gorgun et al. (2016)[24]	Post-operative 30-day	83/439 (18.9%)	**Surgical complication: 63/439 (14.3%)** Ileus: 29/439 (6.6%) Wound infection: 21/439 (4.8%) Intra-abdominal abscess: 7/439 (1.6%) Anastomotic leak: 5/439 (1.1%) Wound dehiscence: 4/439 (0.9%) Enter-cutaneous fistula: 3/439 (0.7%) Bleeding (reoperation): 3/439 (0.7%)

	Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
	II: 4/58 (6.9%)	0/58 (0%)	4/58 (6.9%) (B) pT1: 3 /58 (5.2%) pT2: (NET) 1/58 (1.7%)	Mean: 5.2 ± 2.4 days (range 1-14)
	NR	NR	Overall: 37/439 (8.4%) (B) Stage I: 23/439 (5.2%) Stage IIA: 11/439 (2.5%) Stage IIIA: 2/439 (0.5%) Stage IIIB: 1/439 (0.2%)	NR

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Non-surgical complication: 11/439 (2.5%) Urinary tract infection: 8/439 (1.8%) Pulmonary embolism: 2/439 (0.5%) Superior mesenteric vein thrombosis: 1/439 (0.2%)
Lascarides et al. (2016)[18]	postoperative	4/17 (23.5%)	**Surgical complication: 3/17 (17.6%)** Superficial surgical site infection: 1/17 (5.8%) Ileus: 1/17 (5.8%) Bleeding per rectum: 1/17(5.8%) **Non-surgical complication: 1/17 (5.8%)** Urinary tract infection: 1/17 (5.8%)
Keswani et al. (2016)[34]	12-month Adverse events delaying the initial hospitalization discharge or requiring hospital readmission	62/359 (17.3%)	**Surgical complication: 50/359 (13.9%)** Bowel obstruction or ileus: 12/359 (3.3%) Anastomotic leak: 11/359 (3.1%) Wound infection: 4/359 (1.1%) GI bleeding: 9/359 (2.5%) Ileostomy takedown: 6/359 (1.7%) Hernia repair: 4/359 (1.1%) Acute kidney injury: 4/359 (1.1%) **Non-surgical complication: 33/359 (9.2%)** Cardiac: 8/359 (2.2%) Deep venous thrombosis: 6/359 (1.7%)

	Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
	NR	1/17 (5.9%)	4/17 (23.5%) (B)	Median: 4.94 days (range 1–13)
	NR	11/359 (3.1%)	excluded	Mean: 5 days (IQR 4-7)

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			CVA: 1/359 (0.3%) Infection: 8/359 (2.2%) Dehydration 2/359 (0.6%) Urinary retention: 2/359 (0.6%) Other: 6/359 (1.7%)
Church and Erkan (2016)[15]	postoperative	45/78 (57.7%)	**Surgical complication:** **33/78 (42.3%)** Prolonged ileus: 22/78 (28.2%) Hemorrhage: 6/78 (7.7%) Wound infection: 3/78 (3.8%) Pelvic abscess, peritonitis: 1/78 (1.3%) Wound dehiscence: 1/78 (1.3%) **Non-surgical complication:** **11/78 (14.1%)** Heartburn, oxygen Requirement: 2/78 (2.6%) Diarrhea: 2/78 (2.6%) Left ventricular failure: 2/78 (2.6%) Pulmonary embolism: 1/78 (1.3%) Atelectasis: 1/78 (1.3%) Bronchospasm: 1/78 (1.3%) Confusion: 1/78 (1.3%) Atrial fibrillation: 1/78 (1.3%)

Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
I:32/78 (41%) II: 5/78 (6.4%) III: 5/78 (6.4%) IV: 3/78 (3.8%)	NR	excluded	Mean 7.3 ± 4.7 days

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Dysuria, urinary retention: 1/78 (1.3%)
Hernandez-Boussard et al. (2016) [35]	PSI* event (in hospital)	2047/124,036 (1.7%)	N/A
Le Roy et al. (2015) [16]	28-day	42/175 (24%)	**Surgical complication: 34/175 (19.4%)** Postoperative transit dysfunction: 10/175 (5.7%) Postoperative pain: 5/175 (2.9%) Delayed healing: 1/175 (0.6%) Scar abscess: 5/175 (2.9%) Disunified scar: 1/175 (0.6%) Abdominal abscess: 3/175 (1.7%) Evaluate colonic stenosis: 1/175 (0.6%) Anastomotic fistula: 2/175 (1.1%) Hemoperitoneum bleeding: 1/175 (0.6%) Pneumoperitoneum: 1/175 (0.6%) Peritonitis: 2/175 (1.1%) Hemorrhagic shock: 1/175 (0.6%) Occlusive syndrome: 1/175 (0.6%) **Non-surgical complication: 8/175 (4.6%)** Heparin-ind. Thrombocytopenia: 1/175 (0.6%) Urinary infection: 2/175 (1.1%) Thromboembolic event: 2/175 (1.1%) Duodenal ulcer: 1/175 (0.6%)

Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
NR	NR	NR	Mean 5.81 days (SD/Range NR)
I: 17/175 (9.7%) II: 11/175 (6.3%) III: 9/175 (5.1%) IV: 4/175 (2.3%) V: 1/175 (0.6%)	10/175 (5.7%)	excluded	Median: 8 days (IQR 6-9 days)

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Septic shock: 2/175 (1.1%)
Brigic et al. (2014) [21]	30-day	26/46 (56.5%)	**Surgical complication: 20/46 (43.5%)** Ileus: 9/46 (19.6%) Wound infection: 5/46 (10.9%) Anastomotic leak (grade C): 4/46 (8.7%) Adhesive small bowel obstruction: 1/46 (2.2%) Bleeding per rectum: 1/46 (2.2%) **Non-surgical complication: 6/46 (13.0%)** Pneumonia: 2/46 (3.4%) Unexplained fever/raised I nflammatory markers: 1/46 (2.2%) Atrial fibrillation: 1/46 (2.2%) Acute coronary syndrome: 1/46 (2.2%)
Lee TJ et al. (2013) [17]	30-day surgical complications	12/121 (10.7%)	**Surgical complication: 13/121 (10.7%)** Wound infections: 6/121 (5.0%) Postoperative ileus: 3/121 (2.5%) Anastomotic complications: 2/121 (1.7%) Postsurgical bleed: 1/121 (0.8%) Intra-abdominal sepsis: 1/121 (0.8%) **Non-surgical complication 0/121 (0.0%)**
Ikard et al. (2013) [22]	30-day 12-month	40/126 (31.7%) 11/126 (8.7%)	**Surgical complication: 19/126 (15.1%)**

Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
I: 1/46 (2.2%) II: 21/46 (4.6%) III: 4/46 (8.7%)	4/46 (8.9%)	excluded	Median 5.5 days (IQR 4-8)
NR	NR	25/121 (20.7%) (B or V)	Mean: 7 days (range 1-27 days)
NR	7/126 (5.6%)	Overall 32/126 (25.4%)* (?) *5 patients were noted to have microscopic foci of malignancy in their polyp biopsies	Patients without 30 day mortality and morbidity: Median: 3 (IQR 1-5)

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Deep surgical site infection: 13/126 (10.3%) Dehiscence: 4/126 (3.2%) Organ space infection: 2/126 (1.6%) **Non-surgical complication*: 17/126 (13.5%)** Multiple systems affected: 5 (4.0%) Pulmonary: 4 (3.2%) Central nervous system: 4 (3.2%) Urinary tract/renal: 3 (2.4%) Cutaneous: 1 (0.8%)
Lee MK et al. (2013) [39]	postoperative	3/9 (33.3%)	**Surgical complication: 3/9 (33.3%)** Wound infection: 2/9 (22.2%) Postoperative ileus: 1/9 (11.1%) **Non-surgical complication 0/9(0.0%)**
Jang et al. (2012) [37]	Postoperative (surgical?)	106/386 (27.5%)	**Surgical complication: 86/386 (22.3%)** Ileus: 42/386 (9.8%) Transfusions: 28/386 (7.3%) Wound infections: 12/386 (3.1%) Wound dehiscence: 2/386 (0.5%) Anastomotic leak: 1/386 (0.3%) Intra-abdominal abscess: 1/386 (0.3%)

Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
		Stage I: 11/126 (8.7%) Stage II: 10/126 (7.9%) Stage III: 10/126 (7.9%) Stage IV: 1/126 (0.8%)	Patients with 30 day mortality and morbidity: Median:5 (IQR 2-7)
NR	NR	Overall 3/9 (33.3%) (V) PT1N0: 3/9 (33.3%)	Median: 5 (range 3-8)
I/II: 92/386 (24%) III: 14/386 (3.6%)	5/386 (1.3%)	Overall 62/386 (16.1%) (B&V) I: 46/386 (11.9%) II: 5/386 (1.3%) III: 10/386 (2.6%) IV: 1/386 (0.3%)	Mean: 6.5 days ± 3.7

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Non-surgical complication 0/386 (0.0%)
Cruz et al. (2011) [26]	30-day	7/68 (10.3%)	**Surgical complication: 7/68 (10.3%)** Postoperative ileus: 3/68 (4.4%) Wound infection: 2/68 (2.9%) Anastomotic leak: 2/68 (2.9%) **Non-surgical complication 0/68 (0.0%)**
Loungnarath et al. (2010) [23]	perioperative	30/165 (18.2%)	**Surgical complication: 31/165 (18.8%)** Hernia: 16/165 (9.7%) Wound infection: 5/165 (3.0%) Small bowel obstruction: 6/165 (3.6%) Anastomotic leakage: 2/165 (1.2%) Ileus: 1/165 (0.6%) Peritonitis: 1/165 (0.6%) **Non-surgical complication: 2/165 (1.2%)** Myocardial infarction: 1/165 (0.6%) Pulmonary embolism: 1/165 (0.6%)
Itah et al. (2009) [27]	Postoperative major complication (reintervention)	3/64 (4.6%)	**Surgical complication: 3/64 (4.6%)** Non-functioning anastomosis: 1/64 (1.6%) Small bowel injury: 1/64 (1.6%) Anastomotic leakage: 1/64 (1.6%):

Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
NR	2/68 (2.9%)	1/68 (1.5%) (B) T1N1M0: 1/68 (1.5%)	Mean: 3.5 days ± 1.6
NR	NR	Overall 22/165 (13.3%) (B) I 13/22 (7.9%) II 7/22 (4.2%) III 2/22 (1.2%)	Laparoscopic: Median: 4 days (IQR/range NR) Converted to open: Median: 6 days (IQR/range NR)
NR	3/68 (4.6%)	Overall 9/64 (14.1%) (B&V) T1N0 = 2/64 (3.1%) T2N0 = 2/64 (3.1%) T2N1 = 1/64 (1.6%)	NR

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Non-surgical complication: 0/64 (0.0%)
Blumberg et al. (2009) [28]	30-day	9/44 (20.5%)	**Surgical complication: 9/44 (20.5%)** Anastomotic bleed: 4/44 (9.1%) Wound infection: 3/44 (6.8%) Rectus sheath hematoma: 1/44 (2.3%) Port site hernia: 1/44 (2.3%) **Non-surgical complication: 0/44 (0.0%)**
Hauenschild et al. (2009) [29]	intra- and postoperative	5/54 (9.3%)	**Surgical complication:** 4/54 (7.4%) Trocar site infection: 1/54 (1.9%) Major bleeding: 1/54 (1.9%) Leakage of a rectal stump: 1/54 (1.9%) Intraoperative bleeding of a trocar channel: 1/54 (1.9%) **Non-surgical complication: 1/54 (1.9%)** Shoulder arm syndrome with temporary peroneal nerve paresis due to surgical positioning: 1/54 (1.9%)
Benedix et al. (2008) [30]	perioperative	109/525 (20.8%)	**Surgical complication: 96/525 (18.3%)** Wound healing problems: 33/525 (6.3%) Postoperative ileus: 20/525 (3.8%) Anastomotic leak: 19/525 (3.6%)

Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
		T3N0 = 2/64 (3.1%) T3N1 = 2/64 (3.1%)	
NR	NR	Overall 6/44 (13.6%) (B) I 3/44 (6.8%) II 2/44 (4.5%) III 1/44 (2.3%)	Median: 4 days (IQR/range NR) Mean: 4.5 ± 1.3 days
NR	1/54 (1.9%)	Excluded	Mean: 9.1 days (range 4-33)
I/II: 84/525 (16%) III: 25/525 (4.8%)	16/525 (3.0%)	Overall 95/525 (18.1%) (B) I 66/95 (12.6%) II 15/95 (2.9%) III 14/95 (2.7%)	Median: 11 days (range 3-107 days)

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Hematoma/abscess: 16/525 (3.0%) Bleeding requiring surgery: 8/525 (1.5%) **Non-surgical complication: 46/525 (8.8%)** Cardiopulmonary complications: 23/525 (4.4%) Urinary tract infection: 15/525 (2.9%) Sepsis: 5/525 (1.0%) Neurological complications: 3/525 (0.6%)
Pokala et al. (2006) [31]	undefined	6/51 (11.7%)	**Surgical complication: 4/51 (7.8%)** Small-bowel obstruction: 2/51 (3.9%) Anastomotic leakage: 1/51 (2.0%) Abscess: 1/51 (2.0%) **Non-surgical complication: 2/51 (3.9%)** Exacerb. of angina and CHF*: 2/51 (3.9%)
Alder et al. (2006) [33]	in hospital surgical complications:	28/79 (35.4%)	NR
Lipof et al. (2005) [25]	postoperative	2/48 (4.2%)	**Surgical complication: 2/48 (4.2%)** Anastomotic leakage: 1/48 (2.1%) Wound infection: 1/48 (2.1%) **Non-surgical complication: 0/48 (0.0%)**
Church, J. M. (2003) [19]	undefined	2/15 (13.3%)	**Surgical complication: 2/15 (13.3%)**

	Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
	NR	2/51 (3.9%)	11/51 (21.6%) (B)	Mean 3.1 ± 1.9 days
	NR	NR	13/79 (16.5%) (B)	NR
	NR	1/48 (2.1%)	6/48 (12.5%) (B)	NR
	NR	1/15 (6.6%)	3/15 (20%) (V or B)	Median: 7 days (range 5-10)

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Incisional hernia: 1/15 (6.7%) Splenic trauma (splenectomy): 1/15 (6.7%) **Non-surgical complication: ?**
Young-Fadok et al. (2000) [38]	postoperative	11/76 (14.5%)	**Surgical complication: 4/76 (5.3%)** Postoperative hemorrhage: 2/76 (2.6%) Small bowel obstruction symptoms: 1/76 (1.3%) Ecchymosis around a port site: 1/76 (1.3%) **Non-surgical complication: 5/76 (6.6%)** Cardiac arrhythmias: 3/76 (3.9%) Benign abdominal wall crepitus: 1/76 (1.3%) Urinary retention: 1/76 (1.3%)
Eijsbouts et al. (1999) [20]	undefined	2/20 (10%)	**Surgical complication: 1/20 (5.0%)** Wound infection: 1/20 (5.0%) **Non-surgical complication: 1/20 (5.0%)** Urinary infection: 1/20 (5%)
Joo et al. (1998) [40]	postoperative	11/45 (24.4%)	**Surgical complication: 7/45 (15.6%)** Nasogastric tube required: 7/45 (15.6%) **Non-surgical complication: 4/45 (8.9%)** Atrial fibrillation: 1/45 (2.2%) Pneumonia: 1/45 (2.2%)

	Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)
	NR	2/76 (2.6%)	15/76 (19.7%) (?)	Laparoscopic, median: 4.0 days (range 3-10) Open controls, median: 7.0 days (range 4-19)
	NR	NR	4/20 (20%) (B or V) Dukes stage B1 3/20 (1.5%) Dukes stage B2 1/20 (0.5%)	Median: 5 days (range 3-16)
	NR	NR	7/45 (15.6%) (B)	Lap, mean: 6.5 ±2.0 days Open, Mean 9.4 ± 2.7 days

Table 4. (continued)

Publication	Follow up/definition of complication	Complication rate N (%)	Clustered complications N (%)
			Hyperhydration: 1/45 (2.2%) Dehydration: 1/45 (2.2%)

* PSI : patient safety indicators: PSI event are inpatient adverse events identified by Agency for Healthcare Research and Quality. NR: Not Reported. (B): histology of the polyp assessed by Biopsy. (V): histology assessed Visually. CI: Confidence Interval. CHF: Congestive Heart Failure. Supp: Support. LOS: Length of Stay. SBO: Small Bowel Obstruction.

as anastomotic bleeding, anastomotic complication and abdominal abscess), ranging between 0.3% - 8.7% of the patients.[21, 23-27, 30, 31, 34, 36, 37] (*Supplementary table S1*)

Mortality rates were reported in 21 (80.8%) studies, using different definitions (*Table 5*). Within these studies, overall mortality ranged from 0% to 3.2%. In four studies that used the definition 'peri-operative' or 'in-hospital mortality', mortality ranged from 0.7% to 2.5%.[23, 30, 33, 35] Six studies reported short-term (28- or 30-day) mortality, ranging from 0% to 1.6%.[16, 17, 22, 28, 29, 36] Twelve month mortality was reported in 3 studies, ranging from 0% to 3.2%.[22, 32, 34] In nine studies, mortality was reported with phrases such as 'no mortality', 'number of deaths in the postoperative period' or reported mortality rates without a clear timeframe. In these studies, mortality rates ranged from 0% to 1.8%.[15, 19, 21, 24, 27, 37-40]. When looking at the five studies that included a relatively larger patient population (> 100 patients) since the year 2000, the mortality ranged from 0.57%% to 1.6%.[16, 17, 22, 34, 36]

Histopathology of resection specimens

Eighteen studies reported on the rate of malignancy at histopathology in polyps that were preoperatively judged as benign (*Table 3*). In those studies, an unexpected malignancy was detected in 1.5% to 23.5% of the polyps that were preoperatively assessed as benign by biopsy, and up to 33.3% of the polyps that were preoperatively assessed as benign by optical diagnosis at endoscopy. In eight of those 18 studies, a post-surgical malignancy rate of ≥ 20% was reported.[17-20, 22, 31, 38, 39] Eleven of those 18 studies also reported on the stages of the unexpected cancers found; proportion of stage I among all patients initially treated for a benign polyp ranged between 1.5% and 33.3%.[17, 20, 22-24, 26-28, 30, 32, 37] The percentage of patients reported to have stage III disease ranged from 0.7% to 7.9% in eight studies.[22-24, 26-28, 30, 37] Incidental diagnosis of stage IV was reported in two studies, with a rate of 0.3% and 0.8%, respectively.[22, 37]

LOS was reported in 22 studies, either as a mean (11 studies) ranging from 3.1 to 9.4 days, or median (11 studies) ranging from 4 to 11 days (*Table 4*).

Clavien dindo Grade N (%)	Surgical reintervention N (%)	Pathology: Overall Malignant and Tumor stage (if available) N(%)	LOS Mean/median Days (±SD or range)

DISCUSSION

This systematic review reveals that surgery for benign colon polyps was associated with a substantial risk of postoperative morbidity, with reported mortality rates up to 3.2%. Indications for surgery were mainly based on right-sided location, large size and non-pedunculated (sessile or flat) morphology. It should be mentioned that heterogeneity among the included studies was substantial, regarding patient populations, indications, and surgical characteristics. Also, patients from different parts of the world were included during almost four decades. Nevertheless, the results of the present systematic review provide valuable data on a group of patients with benign colon polyps exposed to potentially high-risk surgical procedures. This information is essential for shared decision-making in patients with polyps deemed unsuitable for a less invasive endoscopic resection.

Reasons for referral to the surgeon for resection of a benign polyp remains largely subjective to what physicians believe is a 'difficult' polyp to remove endoscopically.[41] In our review, only five studies explicitly reported on reasons for surgical referral. The most commonly mentioned reasons were large size, location in the right colon and non-pedunculated morphology. These three features are well known risk factors for incomplete endoscopic resection and adverse events.[17, 42]

Until recently, the preferred treatment of benign polyps deemed unsuitable for conventional endoscopic removal consisted primarily of a surgical resection. However, nowadays, (piecemeal) Endoscopic Mucosal Resection (EMR) can be considered as an effective alternative treatment for most of these benign polyps, achieving technical success rates of > 90% when (piecemeal) EMR is performed in experienced hands.[7, 43, 44] Because of the risk of potential recurrence of the polyps after using the piecemeal EMR technique in up to 16%-20% of the cases, surveillance colonoscopies are necessary.[43, 45, 46] However, recurrences are usually unifocal, diminutive, and benign, making them suitable to be successfully managed by endoscopic re-resections in up to 93% of the cases.[43] In addition to piecemeal EMR, emerging relatively new techniques, such as endoscopic submucosal dissection (ESD), endoscopic full-thickness resection (eFTR) and laparoscopic-assisted endoscopic

Table 5. Mortality rates

Publication	Follow up of mortality	Mortality rate N (%)
Peery et al. (2017)[36]	30-day	85/12,732 (0.66%)
Dulskas et al. (2017)[32]	12-month	0/58 (0%)
Gorgun et al. (2016)[24]	Undefined	1/439 (0.2%)
Lascarides et al. (2016)[18]	NR	NR
Keswani et al. (2016)[34]	12-month	4/359 (1.1%)
Church and Erkan (2016)[15]	undefined 'no mortality'	0/78 (0%)
Hernandez-Boussard et al. (2016)[35]	In hospital	806/124,036 (0.65%)
Le Roy et al. (2015)[16]	28-day	1/175 (0.57%)
Brigic et al. (2014)[21]	undefined 'no mortality'	0/46 (0%)
Lee TJ et al. (2013)[17]	30-day	1/121 (0.82%)
Ikard et al. (2013)[22]	30-day	2/126 (1.6%)
	12-month	4/126 (3.2%)
Lee MK et al. (2013)[39]	undefined	0/9 (0%)
Jang et al. (2012)[37]	postoperative	1/386 (0.26%)
Cruz et al. (2011)[26]	NR	NR
Loungnarath et al. (2010)[23]	perioperative	3/165 (1.8%)
Itah et al. (2009)[27]	undefined	0/64 (0%)
Blumberg et al. (2009)[28]	30-day	0/44 (0%)
Hauenschild et al. (2009)[29]	30-day	0/54 (0%)
Benedix et al. (2008)[30]	perioperative	5/525 (0.95%)
Pokala et al. (2006)[31]	NR	NR
Alder et al. (2006)[33]	in hospital	2/79 (2.5%)
Lipof et al. (2005)[25]	NR	NR
Church, J. M. (2003)[19]	undefined 'no mortality'	0/15 (0%)
Young-Fadok et al. (2000)[38]	undefined	0/76 (0%)
Eijsbouts et al. (1999)[20]	NR	NR
Joo et al. (1998)[40]	undefined 'no mortality'	0/45 (0%)

polypectomy (LAEP) increasingly expands the possibilities of endoscopic removal of benign polyps previously not amendable for endoscopic treatment.[47]

In the present review, three studies reported specifically on the prevention of surgery through a second assessment of the patient/polyp by an advanced interventional endoscopist.[25, 48, 49] In these studies, surgery was avoided in 32%[25] to 74%[19] of the patients by repeating the endoscopy by an experienced surgeon or gastroenterologist. A study by Friedland et al. specifically looked at repeat colonoscopy including (piecemeal) EMR attempts by an experienced endoscopist (>1000 EMRs) of patients referred for surgical resection of a polyp without biopsy-proven cancer.[50] They found that 71% (27/38) of the noncancerous polyps could be successfully treated endoscopically.

When considering the best treatment modality for benign polyps deemed unsuitable for conventional endoscopic removal, safety of the procedure is one of the aspects that plays an essential role. Our review demonstrated substantial surgical complication rates. In piecemeal EMR, being the most commonly used endoscopic alternative in the Western world for the resection of large benign polyps, the main complications consist of post-polypectomy bleeding, occurring in

5-7%[45, 51] of the patients following resections of ≥ 20mm polyps, and of perforations, occurring in 1.4%-1.5%.[45, 52] In addition, it is important to notice that most of the complications associated with piecemeal EMR can be managed endoscopically, as shown by the systematic reviews of Hassan et al., in which post-EMR complication-related surgery was limited to 1%.[45] Besides having less treatment-associated mortality and morbidity, endoscopic resection is also significant cheaper when compared to surgery. Costs savings of $6990[53] and $7602[54] per patient have been demonstrated, mainly related to lower procedural costs and shorter LOS. Moreover, because of the less invasive nature of an endoscopic procedure, patients are likely to have a fast recovery and early return to their normal daily activities.

Although (advanced) endoscopic resections seem to have multiple advantages for the patient compared to a surgical resection, reliable endoscopic criteria with their appropriate use for the identification of possible malignant histology in a polyp are crucial in deciding on the optimal treatment. In our review, studies reported unexpected malignancy rates between 1.5% and 33.3%. However, description of detailed polyp surface characteristics and whether or not polyps were assessed with advanced imaging techniques, such as magnifying endoscopy and virtual chromoendoscopy, was largely unavailable in these studies. The availability of high definition and advanced imaging techniques, together with the use of the Paris morphology classification system and the use of pit pattern and surface classification systems (NICE NBI classification and Kudo pit pattern classification system) are likely to improve diagnostic accuracy nowadays.[55-58] Using these classification systems, Burgess et al. recently investigated factors associated for covert malignancy in large non-pedunculated colorectal polyps or laterally spreading lesions (≥20 mm) in patients referred for piecemeal EMR to academic hospitals in Australia.[59] They found a Kudo pit pattern V, a depressed component (Paris classification 0-IIc), rectosigmoid location, sessile (Paris Classification 0-Is) or slightly elevated sessile polyps (0-IIa+Is Paris classification), non-granular surface morphology, and increasing size to be associated with submucosal invasive cancer. This information could support decisions on whether endoscopic or surgical resection is most appropriate for a polyp deemed unsuitable for conventional endoscopic removal. If limited submucosal invasion is suspected, an en bloc resection should always be performed to enable histopathological assessment of the resection margins. It is important to notice that when a benign histology of the polyp is suspected by optical evaluation, confirmation of the benign histology by random biopsies does not contribute to a more reliable diagnosis due to an inevitable sampling error.[37]

When considering that the variability in judgement regarding potential endoscopic treatment of patients with 'difficult' polyps is largely physician and resource dependent, referring them to an advanced interventional endoscopist first to evaluate the possibilities for endoscopic treatment could potentially result in a significant reduction of excess surgical procedures for these 'difficult' colon polyps. In concordance with the recent ESGE guidelines and UK guideline, our results plead for the installation of regional referral networks and expert centres, as this might result in more endoscopic resection options and endoscopic resection experience becoming more widely accessible.[6, 7, 47]

This is the first study that provides a comprehensive overview of the literature on outcomes of surgery for benign polyps in the colon. However, important limitations should be acknowledged as

well. Many of the studies included in our review were of moderate to poor methodological quality and consisted of small sample sizes. Furthermore, when interpreting our results, it is of importance to keep in mind that the (efficacy and safety of the) surgical techniques, as well as histological assessment, are developing in a rapid pace, challenging extrapolation to present day. However, in an effort to make or results valuable for the present time, we decided to make a sub-analysis of our primary outcome measures for studies that were performed since the year 2000 and included more than 100 patients. Another limitation is the presentation of our results in ranges, sometimes resulting in quite extreme values. For example, when leaving out one study with extremely high complication rates[21], short-term complication rates ranged up to 31.7% instead of 56.6%, with a short-term surgical complication rate up to 20.5% (instead of 43.5%) and an equal upper limit of short-term non-surgical complication rates, namely up to 13.5%.[16, 17, 22, 24, 28, 29, 36] Furthermore, it is important to realize that for the studies included in our review, the decision to refer a patient for surgery had already been made (it is a pre-selected group of patients), and therefore we were not informed about the original patient cohorts and their characteristics (i.e. of the patients not referred for surgical resection). In addition, study populations were not always representative for current practice with population-based CRC screening programs. For example, Ikard et al. reported on a population of elderly males with high comorbidity in a Veterans Health setting.[22] In other studies, endoscopic management was first attempted by an expert endoscopist before patients ultimately underwent surgery[25, 48, 49] or only surgical outcomes of patients not considered candidates for endoscopic procedures were reported.[60] Besides, indications for surgery varied widely between studies. For example, Lee et al only included polyps larger than 20 mm with non-pedunculated morphology and excluded all pedunculated polyps.[61] Alder et al. excluded polyps with a biopsy revealing high grade dysplasia and carcinoma in situ.[62] In addition, patients in whom the final resection specimen revealed cancer were excluded in five studies, possibly leading to underestimation. Lastly, outcomes were reported heterogeneously across studies, using different definitions and timeframes.

In conclusion, our review demonstrated that surgical resection of benign colon polyps is associated with substantial morbidity and mortality. This underlines the importance of thriving for less invasive endoscopic treatment. Deemed difficulties, such as the right-sided location, large polyp size and sessile morphology, might be relative contraindications for endoscopic resection. Such patients might benefit from referral to an expert endoscopic center for the comprehensive assessment of the optimal treatment strategy.

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APPENDIX

Table A1. Complication rates categorized of studies with at least 1 event reported in that category

	Number of studies	Range
Surgical complications		
Anastomotic leakage/abscess	11	0.3%-8.7%
Bleeding	12	0.6%-11.4%
Ileus	13	0.6%-28.2%
Infections (including abscess)	19	1.1%-22.2%
Wound dehiscence/hernia	10	0.5%-9.7%
Organ injury	3	1.1%-6.7%
Other	11	0.7%-15.6%
Non-surgical complications		
Cardiac	8	0.6% - 6.5%
Pulmonary	5	1.4% - 3.4%
Cardiopulmonary	1	4.4%
Thrombo-embolic	6	0.6% - 2.0%
Urinary tract	11	0.6% - 5.8%
Neurologic	3	0.6% - 3.2%
Sepsis	3	1.0% - 2.9%
Other	9	0.7% - 4.8%

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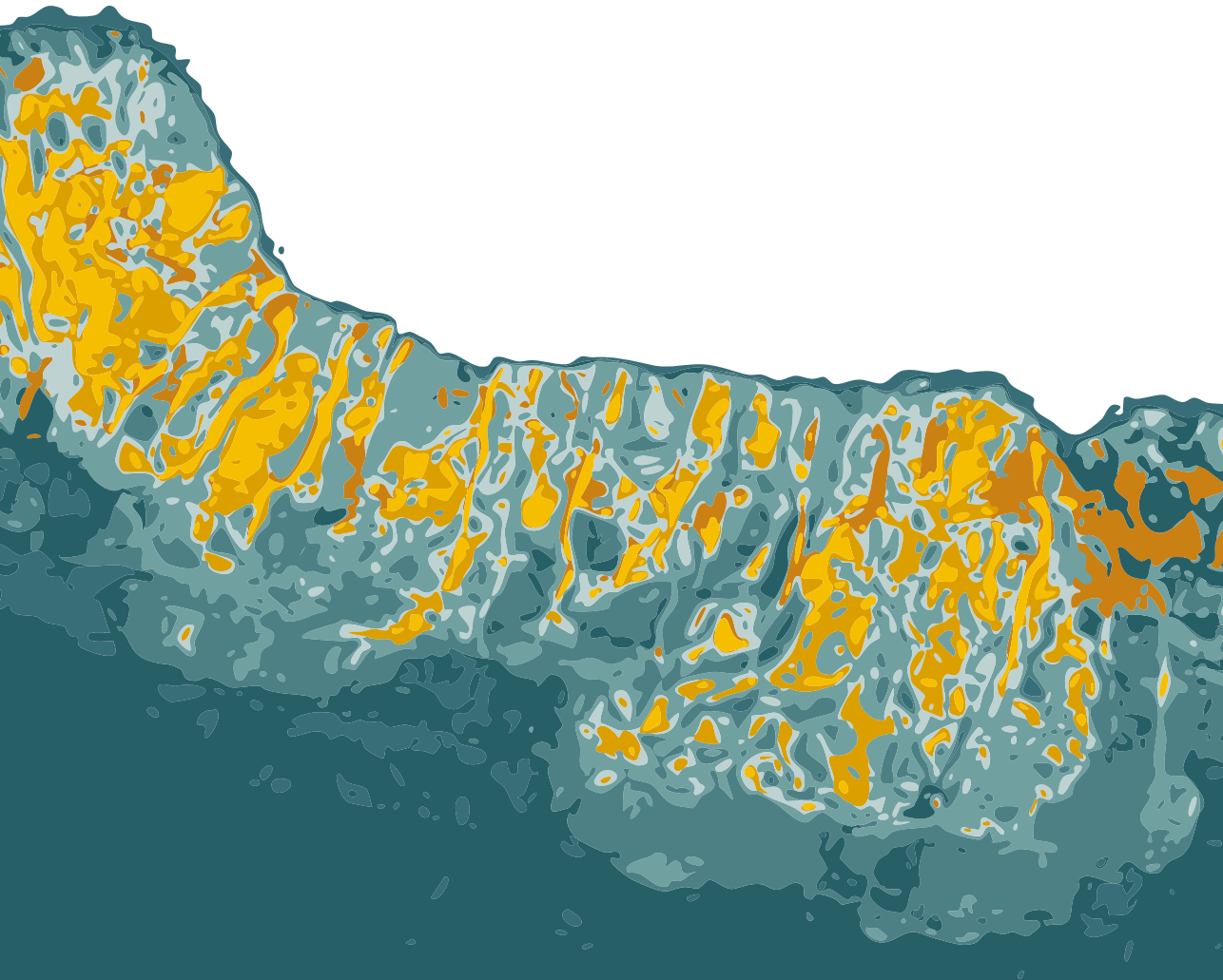

ENDOSCOPIC FULL-THICKNESS RESECTION OF POLYPS INVOLVING THE APPENDICEAL ORIFICE – A PROSPECTIVE OBSERVATIONAL CASE STUDY

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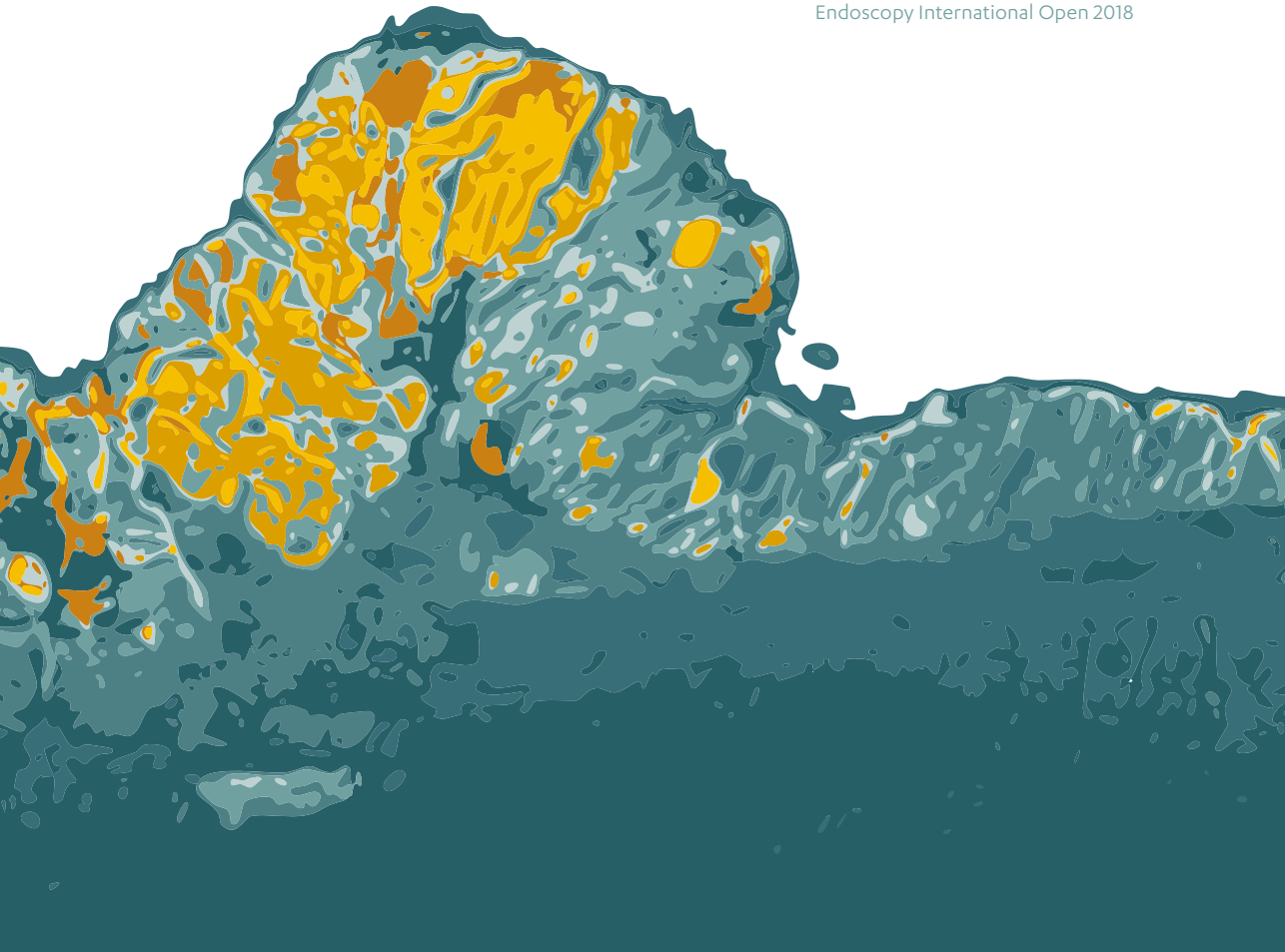

ABSTRACT

Background and study aim

Colorectal polyps involving the appendiceal orifice (AO) are difficult to resect with conventional polypectomy techniques and therefore often require surgical intervention. These appendiceal polyps could potentially be removed with endoscopic full-thickness resection (eFTR) performed with a full-thickness resection device (FTRD). The aim of this prospective observational case study was to evaluate feasibility, technical success and safety of eFTR procedures involving the AO.

Methods

This study was performed between November 2016 and December 2017 in a tertiary referral center by two experienced endoscopists. All patients referred for eFTR with a polyp involving the AO, which could not be resected by EMR due to a more than 50% circumferential involvement of the AO or deep extension into the AO were included. The only exclusion criterion was a lesion diameter > 20 mm.

Results

Seven patients underwent eFTR for a polyp involving the AO. All target lesions could be reached with the FTRD and retracted into the device. Technical success with an endoscopic radical en bloc and full-thickness resection was achieved in all cases. Histopathological R0 resection was achieved in 85.7% (6/7). One patient who previously underwent an appendectomy developed a small abscess adjacent to the resection site, which was treated conservatively. Another patient developed secondary appendicitis followed by a laparoscopic appendectomy.

Conclusion

This small exploratory study suggests that eFTR of appendiceal polyps is feasible and can offer a minimally invasive approach for radical resection of these lesions. However, more safety and long term follow-up data is needed to evaluate this evolving technique.

INTRODUCTION

Endoscopic removal with conventional polypectomy techniques is suitable for most benign colorectal polyps.[1] However, occasionally conventional snare polypectomy cannot be performed due to an increased risk of incomplete resection or perforation, for example in cases of submucosal tumors, non-lifting polyps or polyps located at difficult anatomic locations, such as the appendiceal orifice (AO).[2-4] In order to allow definite diagnosis and treatment of these lesions, a novel endoscopic full-thickness resection device (FTRD, Ovesco Endoscopy, Tübingen, Germany) has been developed to perform endoscopic full-thickness resection (eFTR) with immediate secure defect closure.[5-10] Except from general case series describing eFTR procedures throughout the colon, little is known on the detailed technical outcomes and effectivity of eFTR procedures performed to treat polyps involving the AO.[5, 11, 12] Therefore, the aim of this prospective observational case study was to evaluate feasibility, technical success and safety of eFTR procedures for colonic polyps involving the AO.

Methods

This prospective observational case study was performed in a referral center for eFTR procedures (Academic Medical Center, Amsterdam, the Netherlands). Two certified endoscopists having extensive colonoscopy (≥ 1000 procedures) and complex polypectomy (≥ 500 procedures) experience performed all procedures after being trained in an ex-vivo porcine model.

Patients

All patients referred for eFTR in our endoscopy center with a polyp involving the AO, which could not be resected by endoscopic mucosal resection (EMR), due to a more than 50% circumferential involvement of the AO or deep extension into the AO, between November 2016 and December 2017 were included. Extension into the AO was defined as deep, when the distal margin of the target lesion in the AO could not be overseen by the endoscopist. The only exclusion criterion applied was a lesion diameter larger than 20 mm.

Description of the FTRD

The FTRD is a pre-assembled over-the-scope device consisting of a transparent cap with a modified over-the-scope-clip (OTSC; compression width 12.3 mm). The transparent cap has an inner diameter of 13 mm and a length of 23 mm. A monofilament polypectomy snare is preloaded into the tip of the cap. The snare is not advanced through the working channel, but runs along the outer shaft of the colonoscope underneath a plastic sheet. The device has a Conformité Européene (CE) mark and is commercially available throughout Europe.[5]

eFTR procedure

All patients received standard split dose PEG bowel preparation. All procedures were performed under propofol sedation. Prophylactic antibiotic therapy consisting of a single dose of intravenous metronidazole and cefazolin was given at the start of the procedure. Patients without a previous appendectomy received a five day post-procedural oral antibiotics regimen in order to prevent

secondary appendicitis. Prior to the eFTR procedure, the target lesion was identified with a conventional colonoscope using both HD white light endoscopy (WLE) and narrow band imaging (NBI). The diameter of the lesion and extinction of the polyp into the AO was estimated by the discretion of the endoscopist. Hereafter the colonoscope was withdrawn and the FTRD was mounted onto the colonoscope, which was advanced to the target lesion. After identification of the target lesion, a specialized grasping forceps (Ovesco Endoscopy, Tübingen, Germany) was advanced through the working channel to grasp the lesion. The lesion was slowly pulled into the cap and with the lateral margins of the lesion pulled into the cap, the OTSC was deployed. Immediately thereafter the created pseudopolyp was resected by the pre-loaded snare, while the OTSC secured the integrity of the cecal wall (*Figure 1*).[5] The resection specimen was entrapped into the cap and withdrawn. The colonoscope without the FTRD was introduced once again to inspect the position of the OTSC.

Patients were hospitalized for 24 hours to closely monitor clinical signs of discomfort, bleeding, perforation or infection. The advised dietary regimen was a clear fluid diet for 24 hours, where after a normal diet was started.

Histopathology handling and follow-up of adverse events

The resection specimen was stretched and pinned down on paraffin before immersion into formalin, which was analyzed by an experienced gastrointestinal pathologist. The length of the appendiceal resection was systematically assessed by measuring the length from the cecal lumen to the horizontal resection margin. Patients were contacted 14 days after the procedure to follow up on delayed adverse events.

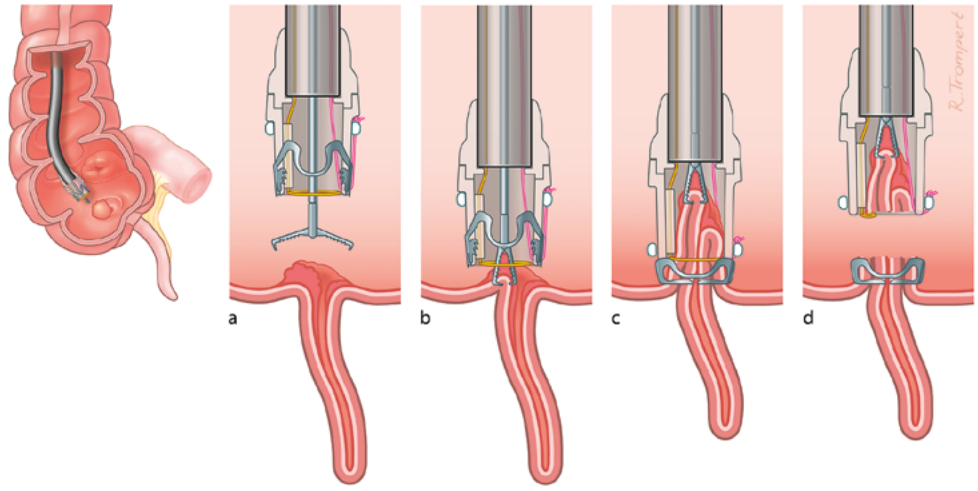

Figure 1. Schematic illustration of the eFTR procedure of a polyp involving the AO

Outcome measures

The primary outcome measure was to describe the technical success of eFTR procedures involving the AO, defined as an endoscopic radical en bloc resection of the target lesion. Secondary outcome measures included; full-thickness (muscularis propria present in the resection specimen) and histopathological proven R0 resection (vertical and horizontal margins free of polypoid tissue), the occurrence of device malfunctions and procedure related adverse events.

Ethics and statistics

The study protocol was presented to the institutional review board. As eFTR procedures were considered part of standard health care, additional approval or informed consent was not required according to Dutch law. The study was carried out in accordance with the Declaration of Helsinki.[13] No sample size calculation was conducted for this study. For descriptive statistics, the median with interquartile range (IQR) was used for variables with a skewed distribution by using SPSS 24 (SPSS, Chicago IL, USA).

RESULTS

Between November 2016 and December 2017, eight patients were referred for eFTR of a polyp involving the AO. One patient was excluded and did not undergo eFTR, because the diameter of the target lesion was 35 millimeters. Three of the remaining seven patients underwent an appendectomy in the past. Other demographic patient characteristics are shown in *Table 1*.

Polyp characteristics

All lesion characteristics were shown in *Table 2*. Six out of seven polyps were previously biopsied or treated by a lifting and/or snare polypectomy attempt. The median polyp size estimated by the discretion of the endoscopist during colonoscopy was 12 millimeters (10-15), all polyps were non-pedunculated and five endoscopically appeared as a sessile serrated lesion (*Figure 2*).

Table 1. Patient demographics

Patient characteristics	**N = 7**
Female – no (%)	6 (85.7%)
Median age - years (IQR)	64 (55-67)
ASA classification – no (%)	
II: Mild systemic disease	7 (100%)
Anticoagulant use – no (%)	0 (0%)
Appendectomy in the medical history – no (%)	2 (28.6%)
Primary indication of the first colonoscopy – no indications (%)	
FIT positive national screening program	2 (28.6%)
Symptoms*	2 (28.6%)
Surveillance	2 (28.6%)
Familial history of CRC or adenoma	1 (14.3%)

* Symptoms: rectal blood loss, change in bowel habits or abdominal pain

Table 2. Endoscopic target lesion characteristics

	Preceding appendectomy	Previously treated*	Type of performed treatment	Lesion diameter (mm)	Appendiceal involvement (%)	Paris Classification	Macroscopic aspect (KUDO)
1	No	No		10	50%	Is	Serrated
2	Yes	Yes	Diagnostic biopsies	20	100%	IIa	Serrated
3	No	Yes	Successful lifting Incomplete polypectomy attempt	12	75%	IIa	Adenomatous (III-V)
4	No	Yes	Successful lifting	5	50%	Is	Serrated
5	Yes	Yes	Diagnostic biopsies	12	75%	Is	Serrated
6	Yes	Yes	Successful lifting Incomplete polypectomy attempt	10	100%	Is	Adenomatous (III-V)
7	No	Yes	Endoscopic lifting, non-lifting sign	15	50%	Is	Serrated
Overall	3/7 (42.9%)	6/7 (85.7%)		12 (10-15)⁺	75% (50-100)⁺	Is 5/7 (71.4%) IIa 2/7 (28.6%)	Adenomatous 2/7 (28.6%) Serrated 5/7 (71.4%)

* A preceding treatment attempt could consist of diagnostic biopsies, a submucosal lifting attempt or a polypectomy attempt with snare coagulation

⁺Median (IQR)

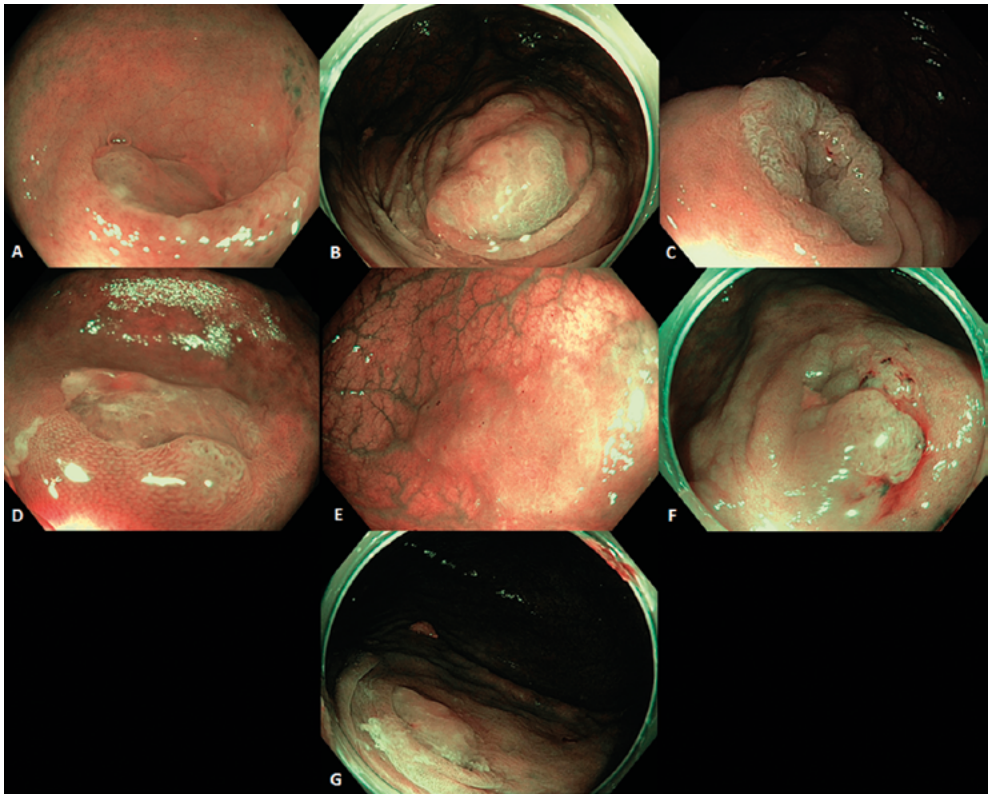

Figure 2. Endoscopic pictures of the seven colorectal polyps involving the AO prior to the eFTR procedure. A| NBI picture of a sessile serrated lesion without dysplasia of the first case; B | NBI picture of a sessile serrated lesion without dysplasia of the second case; C |NBI picture of an adenomatous lesion, which appeared to be a sessile serrated lesion with low-grade dysplasia during histopathology of the third case; D | NBI picture of a sessile serrated lesion without dysplasia of the fourth case; E |NBI picture of the sessile serrated lesion without dysplasia of the fifth case; F | NBI picture of a tubulovillous adenoma with low-grade dysplasia of the sixth case; G |NBI picture of the sessile serrated lesion without dysplasia of the seventh case

eFTR characteristics, histopathology and adverse events

All lesions could be reached and retracted into the FTRD and all procedures resulted in an endoscopic radical en bloc resection (*Table 3, Figure 3-5*). No device malfunctions and immediate adverse events or discomfort occurred. All resections were full-thickness with histopathological radical vertical resection margins, as shown in *Table 3* and *Figure 6*. The horizontal margin of the third case was positive for serrated tissue, resulting in a R0 resection rate of 85.7% (6/7). It was decided to perform a surveillance colonoscopy six months later, showing a clear and histopathological proven recurrence (*Figure 7*). Subsequently, this patient underwent a laparoscopic cecectomy.

Two patients developed fever and abdominal discomfort in the lower right-sided quadrant of the abdomen two days after the eFTR. The abdominal computed tomography (CT) scan of one patient revealed a small abscess adjacent to the OTSC after a preceding appendectomy (sixth case)

Table 3. Procedural and histopathological characteristics

Procedural characteristics	N = 7
Target lesion reached – no (%)	7 (100%)
Target lesion retracted into the FTRD – no (%)	7 (100%)
Endoscopic macroscopic en bloc resection – no (%)	7 (100%)
Device malfunction – no (%)	0 (0%)
Median total duration of the procedure including colonoscopy without FTRD – minutes (IQR)	38 (33-57)
Median total duration of the eFTR procedure – minutes (IQR)	20 (19-37)
Intra procedural complications – no (%)	0 (0%)
Post procedural complications – no (%)	2 (28.6%)
Secondary appendictis	1 (14.3%)
Appendicular abscess	1 (14.3%)
Post procedural admission – no (%)	7 (100%)
Median duration of admission – days (IQR)	1 (1-1)
Profylactic antibiotic treatment given per procedural – no (%)	7 (100%)
Post procedural antibiotic treatment given – no (%)	5 (71.4%)
Histology – no (%)	
Sessile serrated lesion	6 (85.7%)
Tubular adenoma	1 (14.3%)
Dysplasia – no (%)	
Low-grade dysplasia	2 (28.6%)
Negative for dysplasia	5 (71.4%)
R0 resection – no (%)	6 (85.7%)
Vertical margins free of polyp	7 (100%)
Horizontal margins free of polyp	6 (85.7%)
Full thickness resection – no (%)	7 (100%)
Median size of total resection preparation – mm (IQR)	34 (29-35)
Mean/median size of total resection preparation – mm (IQR)	15 (7-17)
Median length from the cecal lumen to the horizontal resection margin – mm (IQR)	8.25 (8.00-9.25)

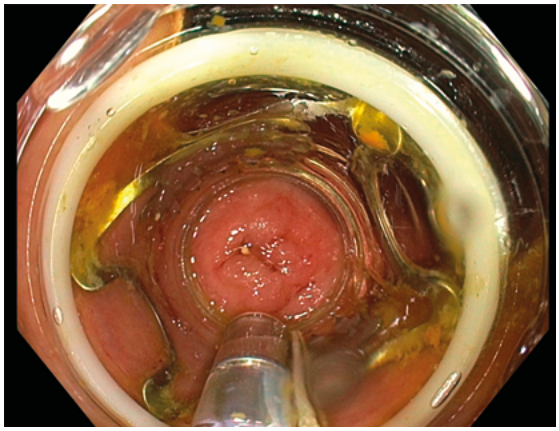

Figure 3. Endoscopic picture when the OTSC is mounted onto the colonoscope

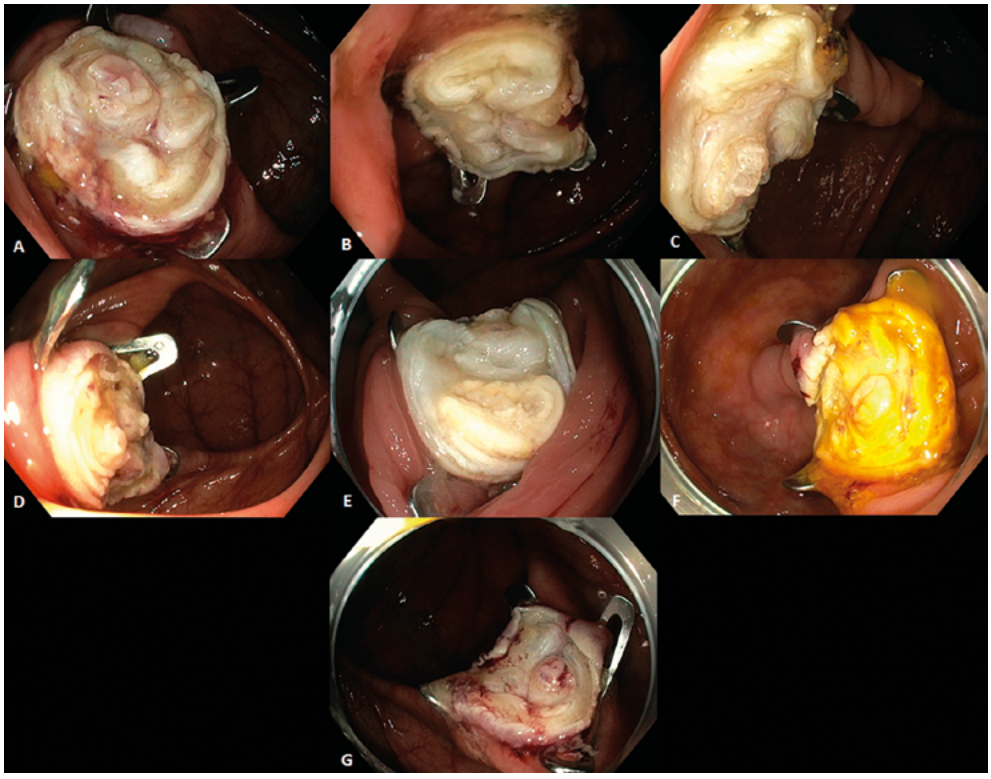

Figure 4. Endoscopic pictures of the OTSC after the eFTR procedure. A| HD WLE picture of the OTSC of the first case; B | HD WLE picture of the OTSC of the second case; C | HD WLE picture of the OTSC of the third case; D | HD WLE picture of the OTSC of the fourth case; E | HD WLE picture of the OTSC of the fifth case; F | HD WLE picture of the OTSC of the sixth case; G | HD WLE picture of the OTSC of the seventh case

and the CT-scan of the other patient (seventh case) showed secondary appendicitis. The abscess was treated by an ultrasound guided puncture and aspiration of the abscess content and the patient with the secondary appendicitis underwent a subsequent laparoscopic appendectomy. Both procedures were followed by intravenous and oral antibiotic regimens for seven days.

DISCUSSION

This small prospective observational case study shows that the relatively new eFTR technique to resect polyps involving the AO is feasible with good technical success. All lesions could be reached and retracted, although advancing the colonoscope with the mounted FTRD to the AO can be challenging due to the length of the device, especially through angulated or fixated diverticular segments. Furthermore, all procedures resulted in endoscopic radical en bloc and histopathological proven full-thickness resections.

In our study the horizontal margin was positive in one case, resulting in a R0 resection rate of 85.7%. The median resection length of the appendix was 8.25 millimeters (IQR 8.00-9.25). It is of

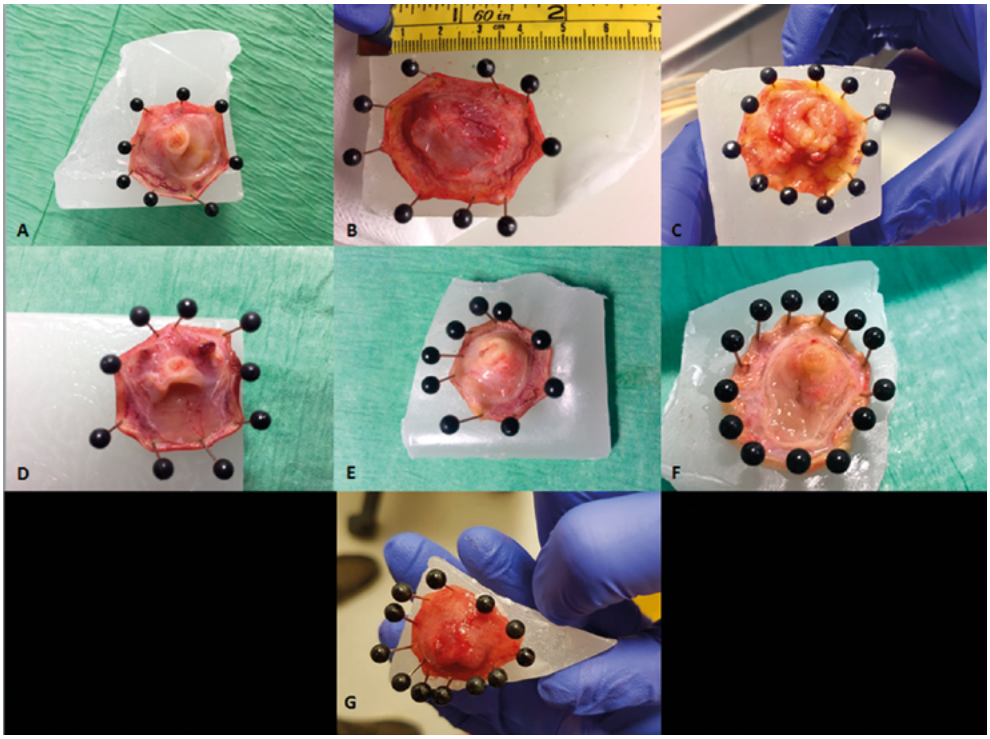

Figure 5. Macroscopic pictures of the resection specimens after eFTR. A| The serosal site of the sessile serrated lesion without dysplasia of the first case; B | The serosal site of the sessile serrated lesion without dysplasia of the second case; C | The mucosal site of the sessile serrated lesion with low grade dysplasia of the third case; D | The serosal site of the sessile serrated lesion without dysplasia of the fourth case; E | The serosal site of the sessile serrated lesion without dysplasia of the fifth case; F | The serosal site of the tubulovillous adenoma with low-grade dysplasia of the sixth case; G | The mucosal site of the sessile serrated lesion without dysplasia of the seventh case.

importance to explicate that the appendix is only partially resected during eFTR, due to a partial inversion of the appendix into the cecum before OTSC placement and the subsequent resection (*Figure 1*). This creates the chance of irradical resection of target lesions that extend deeper into the AO, especially as during colonoscopy it is difficult to oversee the exact depth of extension into the appendix. Therefore in cases with positive horizontal resection margins it is of importance to perform a follow up colonoscopy to evaluate the presence of recurring polypoid tissue and if so additional surgical resection may be warranted. As the lateral margins of the target lesion are more easily to oversee endoscopically with eFTR than the deep horizontal margin in the AO, the chance of irradical resection of the lateral margin will probably be less likely and in this small study lateral margins were all negative. However, if this would be the case follow up endoscopy will be indicated. If macroscopic recurrence is present either endoscopic resection attempts with conventional resection techniques or additional surgery could both be treatment options depending on the size and location of the recurrence. Although in the majority of patients the OTSC will spontaneously

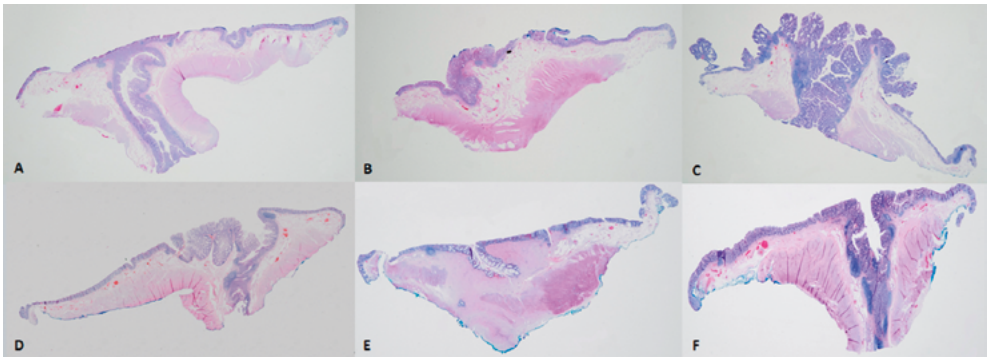

Figure 6. Microscopic histopathology pictures of the resection specimens after eFTR. A| The sessile serrated lesion without dysplasia of the first case; B | The sessile serrated lesion without dysplasia of the second case; C | The sessile serrated lesion with low-grade dysplasia of the third case; D | The sessile serrated lesion without dysplasia of the fourth case; D | The sessile serrated lesion without dysplasia of the fourth case; E | The sessile serrated lesion without dysplasia of the fifth case; F | The tubulovillous adenoma with low-grade dysplasia of the sixth case.

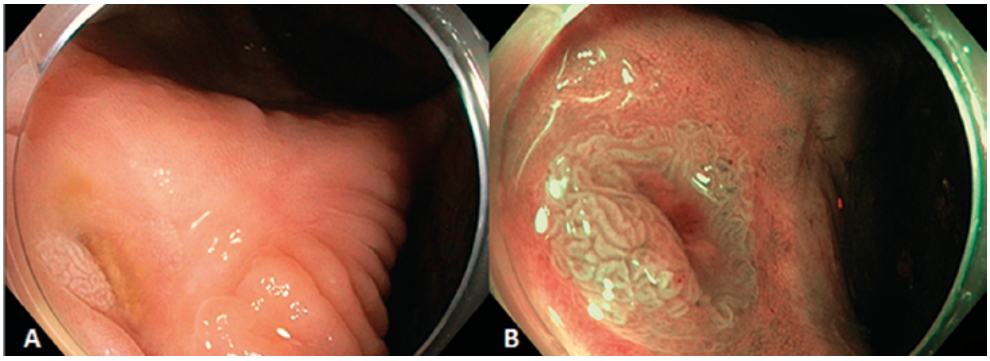

Figure 7. Endoscopic visible recurrence 6 months after the eFTR procedure of the sessile serrated lesion with low-grade dysplasia of the third case. A | HD WLE picture of the endoscopic visible recurrence; B | NBI picture of the endoscopic visible recurrence.

be detached from the cecal wall, it could be possible that the OTSC is still in position. If so a bipolar cutting device (remOVE System, Ovesco Endscopy) is available through the manufacturer to remove the OTSC.[12]

Although all patients received prophylactic antibiotic treatment, one patient developed secondary appendicitis. This is most likely caused by retained mucus within the remaining appendix, which is occluded by the OTSC. Furthermore another patient developed a small abscess adjacent to the OTSC, which could be treated conservatively. In a recent prospective multicenter study three out of the 34 (8.8%) patients undergoing eFTR for a polyp involving the AO developed secondary appendicitis and one patient required additional laparoscopic appendectomy.[12] This risk seems

lower when compared with the findings of our study, however caution is required in comparing results in these limited number of cases.

Endoscopic resection of polyps involving the AO is often regarded as controversial due to a high risk for incomplete resection and perforation. For this reason patients are commonly referred for surgical resection. Recently successful endoscopic resections of polyps involving the AO with EMR or ESD have been described in expert tertiary endoscopy centers. However, these procedures mainly involved lesions without deep extension into the AO or when less than 50% of the circumference of the AO was involved.[14-17] For lesions with a lesion diameter less than 20 millimeters combined with a more than 50% circumferential involvement of the AO or deep extension into the AO, eFTR could be an important alternative endoscopic strategy. Especially when considering that eFTR is less demanding to perform and it is relatively easy to learn.[11, 12]

In conclusion, eFTR of AO polyps is feasible and appears to be effective in this small prospective case study performed in a single tertiary referral center. However, before eFTR of appendiceal polyps can routinely be applied as a minimally invasive and cost-effective alternative to surgical resection, further larger multicenter studies involving safety and long term follow–up data are warranted.

ACKNOWLEDGMENT

Figure 1 is made by Rogier Trompert Medical Art, Maastricht, The Netherlands.

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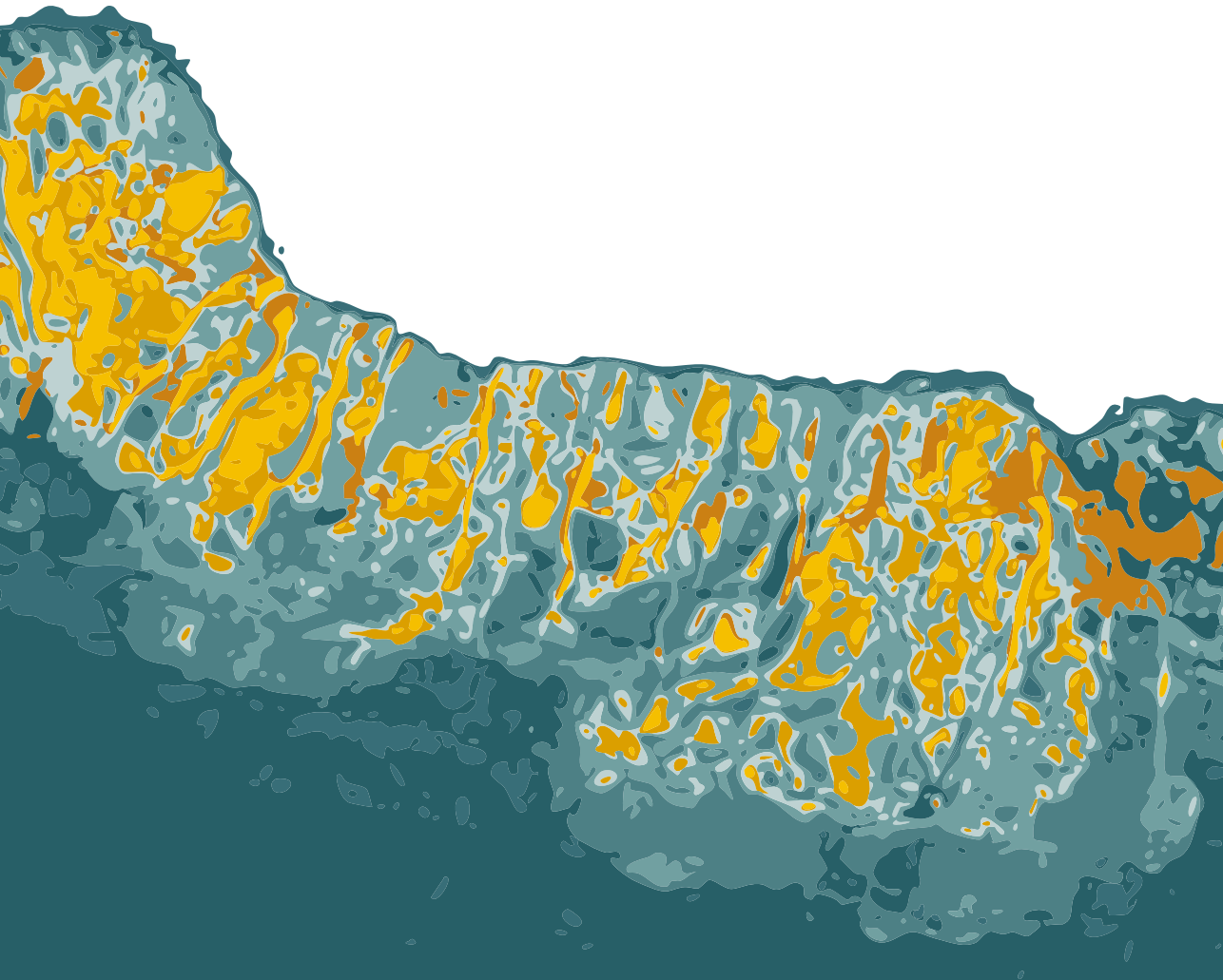
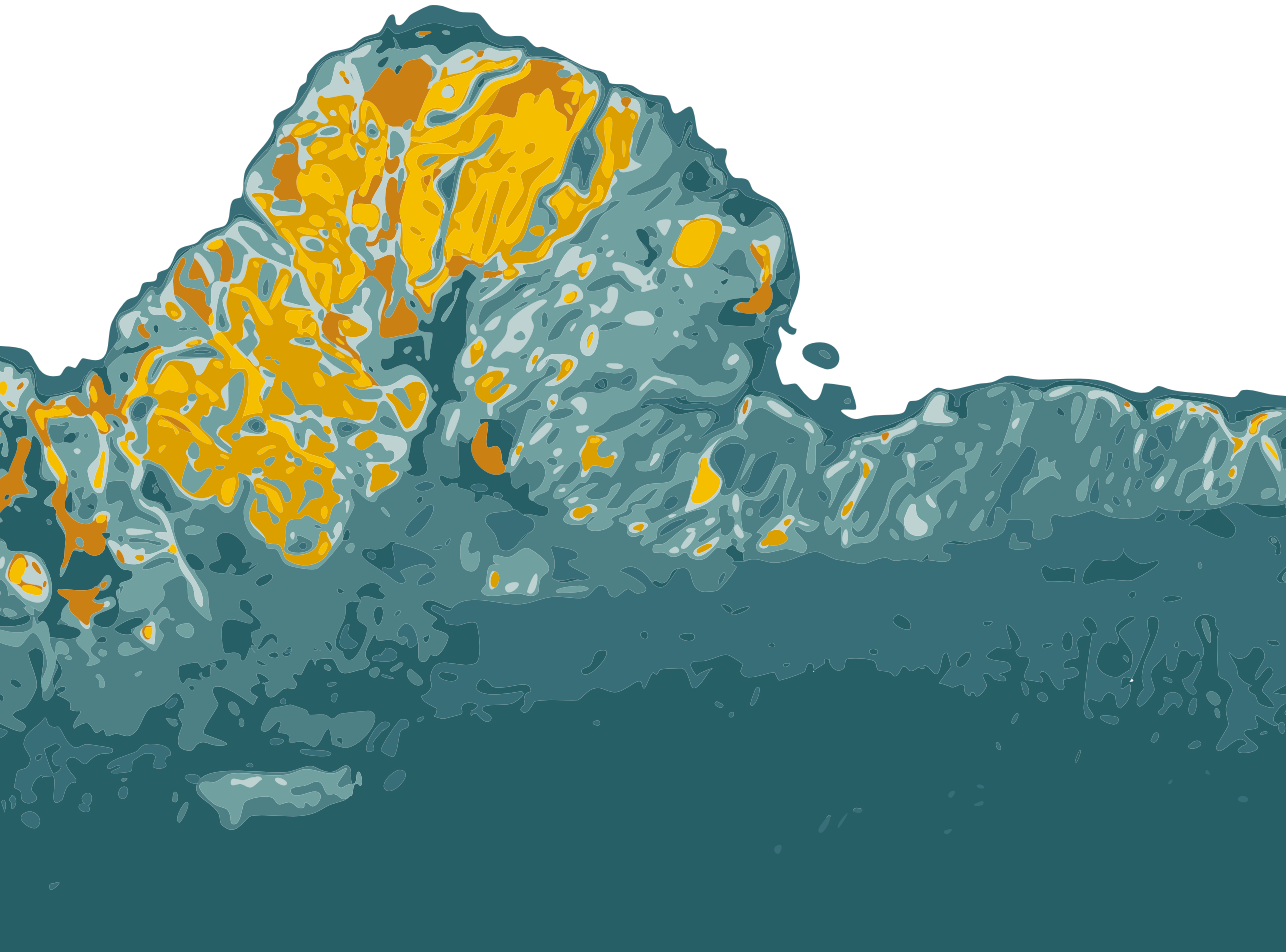


THESIS SUMMARY AND FUTURE PERSPECTIVES



THESIS SUMMARY

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in the Western world. Early and adequate endoscopic detection of CRC combined with the complete endoscopic resection of premalignant colorectal polyps during colonoscopy has the potential to reduce CRC incidence, as well as CRC-related mortality. The progression from premalignant polyps to CRC is slow, leaving a long window of opportunity for timely detection and removal of the benign precursor lesions of CRC. This makes CRC a suitable target for population-based screening programs, which consist of the performance of colonoscopy whether or not preceded by a triage modality, such as non-invasive stool tests.

Unfortunately, in its current form colonoscopy does not completely protect against CRC, as post-colonoscopy CRCs (PCCRC) do occur at a rate of 2% to 8%. In order to optimize the quality of colonoscopy and reduce the incidence of PCCRCs, several quality indicators have been established. These key performance indicators target quality improvement initiatives and seem to be useful to improve the detection and resection of premalignant polyps, including large non-pedunculated and complex ones. The research reported in this thesis covers a wide range of colonoscopy-related issues, all related to the assurance, impact and improvement of the quality of colonoscopy in the first part, and the detection and resection of large non-pedunculated and complex colorectal polyps in the second part.

Part I – Quality of colonoscopy and the detection of colorectal polyps

In **chapter 2** we described the quality assurance process, including a detailed description of the evidence-based quality criteria for endoscopists participating in the biennial fecal immunochemical test (FIT)-based Dutch Bowel Cancer Screening Program (BCSP). Because the program targets healthy individuals that are actively recruited from the general population, it was decided that quality assurance and safety of colonoscopy would be of key importance. Therefore, right at the start of the Dutch BCSP, quality requirements were set for endoscopy centers, as well as for endoscopists performing colonoscopies in FIT-positives. The described experience of the Dutch BCSP might serve as an example for quality assurance in other CRC screening programs.

Although both the adenoma detection rate (ADR) and proximal serrated polyp (SP) detection rate (PSPDR) are known to vary among endoscopists, little was known about the impact of these variations on the effectiveness of a nationwide CRC screening program using FIT as a triage modality. In **chapter 3** the effect of variation in ADR and PSPDR on the long-term impact of the Dutch BCSP was evaluated by using the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) microsimulation model. Based on this model, an increase in ADR will gradually result in a reduction of CRC incidence and mortality, whereas an increase of the PSPDR only has a minimal impact on CRC burden at a population-level. The limited effect of the PSPDR on a population level could be partly explained by our assumption of a 15% contribution of the serrated pathway to the development of CRC, but more importantly by the limited diagnostic accuracy of FIT for SPs. Other triage modalities aiming to detect advanced SPs should therefore be further explored.

The variations in the ADR and PSPDR suggest that some endoscopists have considerable lesion miss rates. As endoscopists with a high ADR and PSPDR are able to detect adenomas and proximal SPs

more frequently, it was hypothesized in **chapter 4** that this could be caused by a better recognition of the endoscopic features of these polyps resulting in improved detection. To our surprise, in the exploratory post-hoc analysis of a prospective, randomized observational multicenter study of FIT-positive colonoscopies, no correlation between the sensitivity of the optical diagnosis of adenomas and SPs with the detection of these polyps could have been demonstrated. Our exploratory results might indicate that lesion detection and accurate histology prediction require different skills. However, studies with this topic as a primary aim should enable definite conclusions. Until then, accurate monitoring and assurance of both performance indicators is important to secure optimal efficacy of a FIT-based CRC screening program.

In **chapter 5** we conducted a prospective multicenter cohort study assessing the feasibility, safety and diagnostic yield of the Extra Wide Angle View (EWAVE) colonoscope for the detection of colorectal adenomas. The EWAVE colonoscope offers a 235° view obtained from a forward-viewing, as well as two lateral backward-viewing lenses incorporated into one image. We demonstrated that EWAVE colonoscopy is feasible and safe. The cecal intubation rate was 97.4% with a median cecal intubation time of 4:00 minutes (IQR 2:00–7:00) and no adverse events occurred in our study. To our disappointment, in this study the ADR of 39.9% appears comparable to the ADRs achieved with conventional colonoscopes in similar patient populations. Due to technical limitations of the investigated EWAVE prototype the study had to be terminated early. Currently an improved EWAVE prototype has been developed and to elucidate the potential additional benefits of this improved EWAVE colonoscope, a randomized comparison with conventional colonoscopy is eagerly awaited.

Part II – Resection of large non-pedunculated and complex colorectal polyps

Little is known in literature about the endoscopic characteristics of unexpected cancers diagnosed in large non-pedunculated rectal adenomas. We therefore compared the diagnostic assessment between unexpected rectal cancers and histologically proven benign rectal adenomas in **chapter 6**. Despite pre-procedural diagnostics, which could consist of the use of advanced imaging techniques, diagnostic biopsies and a rectal endoscopic ultrasound, unexpected rectal cancers were encountered in 13% of large non-pedunculated rectal polyps that were judged by the endoscopist to be benign. During attempted piecemeal endoscopic mucosal resections (pEMR), the non-lifting sign, the resection endoscopically assessed as irradical and early termination of the procedure were factors associated with unexpected cancers. As these factors should raise suspicion of malignancy in treatment naïve patients, these patients should be discussed in a multidisciplinary team meeting. Tailored en bloc full-thickness resection, transanal endoscopic microsurgery (TEM) or completion surgery are additional treatment options that should be discussed.

Traditionally large non-pedunculated colorectal polyps were managed by surgical resection. Over the past decade advanced endoscopic resection techniques, such as pEMR and endoscopic submucosal dissection (ESD), have progressed significantly. However, the extent in which endoscopic resection has replaced surgical resection for complex non-pedunculated colorectal polyps is largely

unknown. In **chapter 7** we assessed the total volume of colorectal surgery for benign colorectal polyps and the absolute and relative volume changes over the past decade in the Netherlands. Between January 1th 2005 and December 31th 2015, a total of 5937 patients underwent surgical resection for a benign colorectal polyp and the absolute (454-739 per year) and relative volumes (0.20%-0.37% per colonoscopy per year) remained stable. In a relatively small number (19.9%) of patients, endoscopic resection attempts were performed before surgical resection and patients were rarely referred (in 2.4%) to a tertiary colonoscopy center for endoscopic resection. Therefore, we concluded that implementation of a regional multidisciplinary referral network with easy access and referral to dedicated endoscopy centers should be implemented. An increase in the number of endoscopic resections will result in the avoidance of unnecessary surgical resection in the majority of patients, leading to a reduction of morbidity, mortality and costs.

In **chapter 8,** the existing literature on post-operative outcomes (morbidity and mortality) of colon surgery for benign colorectal polyps was systematically reviewed. Of the 4210 studies retrieved, 26 studies describing 139,897 patients were included. Surgery for benign colon polyps was associated with a considerable risk of postoperative morbidity (surgical complication rates range 8.5-43.5% and non-surgical complication rates range 0-13.5%), and mortality rates up to 3.2% were reported. The substantial morbidity and mortality of surgical resections combined with the fact that advanced endoscopic resection techniques have improved significantly underline the importance of striving for non-surgical treatment in these patients. As more endoscopists develop experience in advanced endoscopic resection techniques, patients will benefit from referral to an experienced interventional endoscopist before referral towards surgery.

Among the complex colorectal polyps some of these involve the appendiceal orifice (AO). In order to allow endoscopic treatment of complex colorectal polyps, early colorectal cancer and submucosal tumors, a novel endoscopic full-thickness resection device (FTRD) to perform endoscopic full-thickness resection (eFTR) has been developed. **Chapter 9** described the feasibility, technical success and safety of seven eFTR procedures for polyps involving the AO. This small prospective observational case study showed that eFTR of AO polyps is feasible with good technical success. All procedures resulted in an endoscopically radical en bloc resection. The lateral margins were histopathologically negative in all resections and the horizontal margin was positive in one case, resulting in a R0 resection rate of 85.7% (6/7). One patient developed a small abscess adjacent to the resection site, which was treated with an ultrasound guided puncture and aspiration. Another patient developed secondary appendicitis, which was treated with a subsequent laparoscopic appendectomy. These results suggests that eFTR of AO polyps might be applied as a minimally invasive alternative to surgical resection, however further safety and long term follow–up data are warranted.

FUTURE PERSPECTIVES

Quality of colonoscopy and improvement of detection of colorectal polyps

In the past decade, awareness of the importance of high quality colonoscopy has increased, supported by an increasing body of evidence suggesting that high quality colonoscopy will minimize the risk of post-colonoscopy colorectal cancers (PCCRCs).[1] This has led to the development of many initiatives to monitor and to improve the quality of colonoscopy. In the Netherlands, this started with the implementation of specific quality requirements for endoscopists performing colonoscopies within the Dutch Bowel Cancer Screening Program (BCSP).[2] This quality assurance program was subsequently followed by the development of a prospective nationwide quality registry for all colonoscopies performed in the Netherlands.[3] Its implementation is currently ongoing and the aim is to provide insight in the quality of every colonoscopy performed within the Dutch healthcare system.[3]

Most colonoscopy quality improvement initiatives that are described in literature aim to increase the adenoma detection rate (ADR) during colonoscopy.[4-11] This parameter is widely considered as the most important and well-established key performance indicator. In fact, the ADR is currently the only performance indicator that was shown to be inversely correlated with the occurrence of PCCRCs and CRC mortality.[12, 13] To increase the ADR, several strategies have been proposed, including mandating minimal colonoscope withdrawal times, standardized positional changes, use of hyoscine-N-butylbromide, provision of simple feedback by report cards, as well as implementing multifaceted strategies involving education, audit and feedback.[4-11] However, all single faceted strategies only had a limited effect on the ADR.[4-11]

The most effective colonoscopy quality improvement initiatives to increase the ADR were the multifaceted strategies, consisting of educational interventions followed by audit and feedback. These interventions consisted of colonoscopy skills improvement courses, educational videos or multimedia presentations focusing on the endoscopic features of adenomas and the importance of colonoscopy key performance indicators, such as the completeness of the colonoscopy and an adequately cleaned colon.[5-11]

Therefore, this type of multifaceted strategies should form the basis of newly developed colonoscopy quality improvement initiatives. For the design of an effective audit- and feedback-based quality improvement initiative, several factors should be taken into account. First of all it is crucial that the endoscopists trust the provided feedback data. Therefore it is important that these data are obtained from a valid data source; ideally directly from colonoscopy reporting systems and histopathology databases. To further increase the acceptability of the feedback, case-mix adjustments should be performed for individual endoscopists.[14] Furthermore, it is important that feedback is provided regularly and individually in both a verbal and written format, and is delivered by a colleague or supervisor.[14] A second important factor for success of a quality assurance system is to minimize the administrative burden for the audit and feedback process. This can be done e.g. by using an audit and feedback reporting system that automatically generates audit and feedback reports from its original data source.[15] Although this requires systematic and uniform

data registration, double data entry is avoided thereby preventing data-entry mistakes and also increasing the integrity of the provided feedback. Lastly, it is essential to support endoscopists with inadequate performance to improve their quality of colonoscopy. It is important that a negative quality report is followed by individual feedback, including suggested actions and explicit targets to improve their colonoscopy quality.[14]

Another target for quality improvement of colonoscopy is to improve the mucosal surface visualization, aiming to increase the detection of adenomas. These surface exposing technologies include cap-fitted colonoscopy, Endocuff or EndoRings assisted colonoscopy, through-the-scope optical devices, G-Eye colonoscopy, full-spectrum endoscopy (FUSE) and (prototype) extra wide angle view colonoscopies.[16-26] Most surface exposing technologies showed conflicting results on ADR and adenoma miss rates.[16-25] The first feasibility studies, consisting of back-to-back study designs performed by expert endoscopists, showed significant improvements in ADR and adenoma miss rates, but most positive findings could not be confirmed in subsequent comparative randomized trials.[17, 18, 24, 25]

Endocuff assisted colonoscopy is the only technique that results in a significant increase in ADR, as assessed in a recently published meta-analysis solely consisting of randomized controlled trials.[26] This increase in ADR was the most clearly present in endoscopists with low (< 25%) to moderate ADRs (< 35%), but Endocuff was not able to improve ADR in endoscopists with high adenoma detection rates (ADR > 45%).[26] It could therefore be considered to routinely implement the use of Endocuff among these low to moderately detecting endoscopists. However, it is of importance to realize that two versions of the Endocuff exist and have been studied; the original Endocuff device consisting of two horizontal circular rows of short projections ("arms") and the modified Endocuff Vision, which has one row of longer and more flexible arms.[27, 28] The authors of the meta-analysis did not include a comparison of the two different devices.[26] One of the largest studies included in the meta-analysis, however, was the multicenter randomized controlled trial performed by Ngu et al. which was performed in the setting of the British Bowel Cancer Screening Program.[26] This study showed a significant increase in ADR with the use of Endocuff Vision, and because of the large size of this study it might greatly have influenced the overall pooled positive effect of Endocuff-assisted colonoscopy.[26] Therefore, it would be of interest to further investigate the use of newer Endocuff Vision in other cohorts.[26-28]

An important limitation of all studies with new endoscopic techniques and devices, including those on Endocuff, is that it is not possible to blind endoscopists for the use of the new device. As a consequence, the attitude of endoscopist towards the new technique, either positive or negative, could subconsciously have influenced the detection of adenomas; with a new technique they might be more motivated to perform a thorough examination. Therefore, when designing a study with new endoscopic techniques and devices, it is essential to create a setting in which the tested device and conventional colonoscopy are optimally comparable in terms of patient population, motivation of endoscopists, their experience with the new technique and all key performance indicators, such as cecal intubation rate and colonoscope withdrawal time.

Those studies on colonoscopy quality improvement initiatives or surface exposing technologies that showed an increase in ADR, were often positive based on an increased detection of diminutive

and flat adenomas. It is however unknown whether the improved detection of these tiny adenomas will also result in a reduction of PCCRCs on the long run. Diminutive adenomas incur a very low risk of harboring CRC, and if they would ever progress to cancer this would take many years (estimated dwell time 10-15 years).[29] Besides, most patients who underwent a colonoscopy where adenomas were detected will receive subsequent surveillance colonoscopies.[29, 30] So when tiny, diminutive adenomas are missed during an initial colonoscopy, these lesions will have a new chance to be detected during a planned surveillance procedure, and will probably still harbor only low-risk features when being detected.[31] Another result of the increased adenoma detection rates is that this will also result in more patients being advised to undergo surveillance colonoscopies. This will increase the demand for surveillance colonoscopies and will evidently put pressure on the available colonoscopy capacity.[32] Ideally, we would therefore only offer surveillance colonoscopies to those who will indeed benefit from this on the long term. The prospective randomized European Polyp Surveillance (EPoS) study aims to investigate optimal surveillance intervals after removal of low- and high-risk adenomas. The results of this study are eagerly awaited to enable effective and tailored surveillance strategies after high quality colonoscopy in the future, however the first results of this study cannot be expected before 2023.

Improving endoscopic characterization of colorectal polyps harboring submucosal invasion

After the detection of premalignant polyps it is of importance that endoscopists carefully inspect the lesion to assess the potential presence of cancer. If submucosal invasion is present, but it is only superficial, there is a small risk of lymph node metastasis and the lesion can still be resected endoscopically. It is however of importance that the endoscopic resection is performed in an en bloc method to assure appropriate histopathological assessment of the radicality of the procedure, as well the presence of other risk factors for lymph node metastasis. As deep submucosal invasion (sm2/3 or invasion depth ≥ 1000 µm) is associated with a significant risk of lymph node metastases, it is essential that this is ruled out by the endoscopist and endoscopic resection are avoided in these cases.[33] Careful inspection is especially important in large polyps, as the risk of submucosal invasive disease gradually increases with increasing lesion size.[34] Lesions of 10-20 mm harbor a 2.4% risk of submucosal invasion, which gradually increases to 19.4% for lesions with a diameter of 20 mm or more.[34]

High-definition white light endoscopy combined with advanced imaging techniques, which use filtered light to enhance the vascularity of the mucosal surface, are useful to differentiate between benign colorectal polyps and polyps harboring deep submucosal invasion.[35] Most studies evaluating endoscopic differentiation between benign polyps and polyps with submucosal invasion (T1 CRCs) have been performed in expert centers in Asia. These studies reported a pooled sensitivity of 85.0% for differentiating between benign colorectal polyps and T1 CRCs when using advanced imaging techniques with specialized magnifying endoscopes.[36] A recent prospective multicenter study performed by Backes et al. demonstrated that experienced and trained Dutch endoscopists achieved a slightly lower sensitivity of 78.7% for the optical diagnosis of T1 CRCs and a sensitivity of 63.3% for

the optical diagnosis of submucosal invasion depth.[37] Sensitivities of both Asian and Western expert endoscopists could still improve, but a 100% sensitivity of the real-time optical diagnosis for T1 CRCs does not seem realistic, as a recent study by Burgess et al. showed that a substantial proportion of lesions with submucosal invasion are covert and thus not visible as such for the endoscopist.[38]

Moreover, it seems logical to expect non-expert Western endoscopists to have a lower sensitivity and accuracy for T1 CRCs and its submucosal invasion depth, as specialized magnifying endoscopes with advanced imaging techniques are less widely spread in Western endoscopy centers. Another possible barrier is the low prevalence of T1 CRCs in the daily endoscopy practice of non-expert endoscopists, hindering sufficient training and possibilities to acquire or maintain experience with those lesions.[39] These factors underline the importance of implementing training programs in this field, especially for endoscopists performing colonoscopies in the patients that participate in FIT-screening, as they have a high incidence of T1 CRCs.[39]

Several training modules, consisting of still images or video-based training programs whether or not followed by audit and feedback, have shown to improve optical diagnosis with advanced imaging techniques.[35, 40] However, the current available training modules do not focus on the endoscopic recognition of submucosal invasion, but on the optical differentiation between neoplastic and non-neoplastic polyps. Therefore, new training programs focusing on accurate recognition of T1 CRCs in daily practice should be developed, evaluated and implemented. Ideally, these training programs consist of an educational intervention followed by audit and feedback. Endoscopists should be trained to perform structured lesion assessment including size, morphology, location and mucosal surface patterns using high-definition virtual chromoendoscopy.[38] For this purpose the score chart by Backes et al. could be used, which was validated among expert endoscopists and demonstrated good performance in the endoscopic differentiation between large non-pedunculated adenomas and T1 CRCs.[37] The score chart itself consists of the location of the lesion, the surface structure, the presence of a depressed area, spontaneous bleeding and the Hiroshima classification.[37] However, before its widespread implementation in daily practice it is essential that this score chart is also validated among unexperienced endoscopists, who will be trained in its use, followed by audit and feedback. After this second validation study the score chart could potentially be added as an educational intervention to the accreditation process and quality assurance program for endoscopists participating in the Dutch BCSP.

Another potential solution to improve the endoscopic differentiation between non-invasive colorectal polyps and T1 CRCs might be the use of computer-aided diagnosis systems.[41] Recently, deep learning has opened the field of artificial intelligence by enabling a more detailed image analysis and an almost real-time polyp characterization by automatically analyzing relevant endoscopic characteristics from endoscopic video images. A recent study of unaltered endoscopy videos with a frame processing time of 50 milliseconds showed a high overall accuracy of 94% in sorting diminutive colorectal polyps into conventional adenomas versus hyperplastic polyps.[42] However, data for differentiation between non-invasive colorectal polyps and T1 CRCs and real-time endoscopic data in prospective trials are not yet available. If these high accuracies would indeed be verified in prospective clinical trials, colonoscopy practice will be revolutionized. If so, the most likely scenario seems that artificial intelligence will then be used to support the endoscopist's optical

diagnosis, with the endoscopist making the final decision or only making a definite decision when the endoscopist and the computer-aided diagnosis system agree.[41]

While the results of new training programs and computer-aided diagnosis studies are awaited, a pragmatic first step would be the implementation of a standardized approach of photographing and filming lesions that the endoscopist suspects to contain submucosal invasion. This footage would allow consultation of an expert endoscopist. A web-based portal, where standardized endoscopic photos and/or videos are uploaded and assessed by experts might facilitate this process of consultation. The images could then be assessed before definite referral of the patient, limiting unnecessary referrals.

Improving endoscopic resection of large non-pedunculated colorectal polyps and T1 CRCs

After endoscopic differentiation between non-invasive colorectal polyps and T1 CRCs, the most appropriate treatment strategy should be selected. Most benign colorectal polyps can be safely resected by conventional polypectomy techniques. However, large non-pedunculated polyps or complex polyps located at a difficult anatomical location are difficult or even impossible to remove by these techniques.[43]

In Western countries, piecemeal endoscopic mucosal resection (pEMR) is the most commonly performed technique to resect benign large non-pedunculated polyps or complex polyps located at difficult anatomical locations. When pEMR is performed in experienced hands, over 90% of all large non-pedunculated and complex colorectal polyps can be resected endoscopically.[44, 45] Therefore, pEMR is a valuable (cost-)effective and safe alternative to surgical resection of these lesions.[46, 47] However, if there is a suspicion of submucosal invasive growth, piecemeal resection methods should be avoided. The most important reason is that the polyp is cut in several pieces, which impedes a reliable histopathological diagnosis on the presence of submucosal invasion, and if this is present it also limits the histopathological assessment of high-risk features for lymph node metastasis.[43, 47-49] Thus, accurate histopathological diagnosis requires en bloc resection of the lesion.[49] Accurate assessment of these high-risk features is crucial, because according to the guidelines, patients with a T1 CRC are advised to undergo adjuvant oncological surgical resections when at least one high-risk feature is present.[50-53]

Moreover, in those lesions with submucosal invasion, it is important to try to accurately predict submucosal invasion depth aiming to select patients who could benefit of an endoscopic en bloc resection. As deep submucosal invasion is a known risk factor for lymph node metastases, those patients should be referred to surgery as primary treatment modality.[33, 36] Patients with superficial submucosal invasion are ideal candidates for endoscopic en bloc resection, which in lesions smaller than 20 mm could consist of simple snare polypectomy technique and for lesions exceeding 20 mm could be performed by endoscopic submucosal dissection (ESD).

ESD is a technically demanding resection technique and therefore associated with long learning curves and longer procedural times compared to pEMR.[47, 54] Currently, a relatively small but increasing number of endoscopists is adequately trained to safely perform ESD in Europe.[54] In

Japan, where this technique was developed, ESD training typically involves an extensive period of mentorship. During this extensive training period a senior trainee subsequently observes ESD cases, assists an expert, and commences resections under direct supervision. These training programs start with ESD in the distal stomach, which is considered relatively simple compared to ESD in the colon. As the prevalence of early gastric cancer is much lower in Western countries, it is not feasible to start training in those easier anatomical locations.[55-59] From literature it appears that ex vivo porcine models could be used as a surrogate for the performance of gastric ESD and these models could therefore be used as a first step in Western ESD training programs.[54] After this start, Western endoscopists might potentially be able to safely start performing colorectal ESD under direct supervision. It would be of great interest to assess the effectivity of training in ex vivo porcine models in Europe on a larger scale, because when successful this might help to increase the number of endoscopists experienced in the performance of ESD.

Recently, two new en bloc resection techniques have been introduced in clinical practice. These techniques consist of hybrid resection techniques and endoscopic full-thickness resection (eFTR).[60-62] In hybrid resection techniques the ESD technique is used to make a circumferential incision around the lesion, followed by a snare resection. A recent meta-analysis showed a pooled overall en bloc resection rate of 68.4% for large non-pedunculated colorectal polyps.[60] This suggests that at this stage, hybrid resection techniques are not a good alternative for ESD and should only be applied to resect benign appearing large non-pedunculated colorectal polyps. However, the role of hybrid resection techniques as part of a step-up training process for the standard ESD technique for Western endoscopists could be further investigated.[60]

For eFTR, various devices and techniques have been described. The full-thickness resection device (FTRD, Ovesco Endoscopy, Tübingen, Germany) has the benefit to allow en bloc full thickness resection with immediate defect closure of lesions with a maximum diameter of 20 mm.[61, 62] The largest prospective multicenter trial encompassing 181 patients reported an overall endoscopic radical en bloc resection rate of 89.5% and a R0 resection rate of 76.9%.[61] In the same multicenter trial the endoscopic en bloc resection rate was 82.6% and the R0 resection rate was 72.4%. However, these resections were curative in only 44.8% of the patients.[61] The other patients were advised to undergo subsequent surgical resection, because they had positive lateral and/or deep resection margins whether or not combined with the presence of deep submucosal invasion.[61] Based on this high rate of subsequent surgical resections, it might be concluded that at this stage it is too controversial to perform eFTR for T1 CRCs. These results are however only based on a small cohort of 29 patients and therefore further evidence is needed to draw definitive conclusions of the effectivity and oncological safety of eFTR for this indication.[61]

To increase the percentage of patients with large, complex or potentially invasive polyps that can benefit from the above mentioned resection techniques, these patients should be referred to centers with enough expertise with these techniques; i.e. expert centers. However, based on the literature and data described in this thesis, endoscopists might not always be aware of the different treatment options and/or be hesitant to refer patients to another endoscopy center.[63, 64] To overcome the endoscopists' potential hesitance and improve the infrastructure for referrals to expert endoscopy centers, implementation of regional referral networks might help.

This way more advanced treatment options will become widely accessible, potentially decreasing the number of patients undergoing unnecessary surgery leading to lower morbidity, mortality and costs.

In the quickly emerging field of high quality colonoscopy and advanced endoscopic resection techniques, many improvements have been established in the last decade. However, important challenges to further improve colonoscopy practice remain. Future research should therefore focus on reducing variations in colonoscopy performance. This could be done by the implementation of multifaceted quality improvement initiatives, by improvement of endoscopic differentiation between benign colorectal polyps and T1 CRCs and by further optimization and evaluation of non-invasive endoscopic treatment modalities.

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NEDERLANDSE SAMENVATTING

Dikke darmkanker is een van de meest gediagnosticeerde vormen van kanker in de Westerse wereld. Darmkanker ontstaat geleidelijk uit darmpoliepen. De darmpoliepen waar darmkanker uit kan ontstaan zijn in te delen in twee groepen; de adenomateuze poliepen en de sessiel serrated poliepen. De detectie van vroege, nog behandelbare stadia van darmkanker gecombineerd met de complete verwijdering van deze darmpoliepen tijdens een darmonderzoek, een zogeheten coloscopie, kunnen ervoor zorgen dat zowel het voorkomen van darmkanker en de sterfte aan darmkanker verlaagd kunnen worden. Omdat de progressie van darmpoliepen tot darmkanker langzaam gaat, is er een lange periode waarin deze darmpoliepen nog op tijd gedetecteerd en verwijderd kunnen worden. Dit heeft tot gevolg dat darmkanker een geschikte ziekte is voor het uitvoeren van een bevolkingsonderzoek. Daarom is in 2014 in Nederland een landelijk bevolkingsonderzoek darmkanker gestart met als doel darmkanker en darmpoliepen in een zo vroeg mogelijk stadium op te sporen om zo de sterfte aan darmkanker te verminderen. Personen tussen de 55 en de 75 jaar worden elke twee jaar uitgenodigd om een ontlastingstest, de fecaal immunochemische test (FIT), in te leveren. De FIT meet de aanwezigheid van bloed in de ontlasting, wat veroorzaakt kan worden door de aanwezigheid van darmpoliepen en darmkanker. De FIT wordt gebruikt als een triage test. Alleen mensen met bloed in de ontlasting en dus een positieve FIT worden doorverwezen voor een coloscopie.

Helaas beschermt een coloscopie in zijn huidige vorm niet optimaal tegen het ontstaan van darmkanker. In de periode na een coloscopie tot aan de geadviseerde controle coloscopie treedt soms toch nog darmkanker op: de zogenaamde post-coloscopie darmkankers. Tussen de 2% en de 8% van alle gediagnosticeerde darmkankers blijkt een post-coloscopie darmkanker te zijn. Om de kwaliteit van coloscopie te optimaliseren en daardoor het voorkomen van post-coloscopie kankers te verlagen, zijn er verschillende kwaliteitsindicatoren voor coloscopie vastgesteld. Deze kwaliteitsindicatoren voor coloscopie kunnen gebruikt worden bij het opzetten van initiatieven om de kwaliteit van de coloscopie te verbeteren. Daarnaast kunnen kwaliteitsindicatoren voor een coloscopie ook nuttig zijn om de detectie en verwijdering van darmpoliepen, verder te optimaliseren. Het onderzoek wat beschreven wordt in dit proefschrift omvat veel verschillende coloscopie-gerelateerde onderwerpen. Het eerste deel van het proefschrift richt zich op de kwaliteitsborging, de invloed van de kwaliteit van coloscopie op de effectiviteit van het Nederlandse bevolkingsonderzoek darmkanker en mogelijkheden ter verbetering van de kwaliteit van coloscopie. Het tweede deel beschrijft onderzoek dat gericht is op de detectie en verwijdering van grote niet-gesteelde en complexe darmpoliepen. De grote niet-gesteelde darmpoliepen zijn vlakke darmpoliepen met een diameter groter dan twee centimeter en de complexe darmpoliepen bestaan uit darmpoliepen, die eerder endoscopisch behandeld zijn of gelokaliseerd zijn op moeilijke anatomische lokalisaties.

Deel I – De kwaliteit van coloscopie en de detectie van darmpoliepen

In **hoofdstuk 2** beschreven we het kwaliteitsborgingsproces voor endoscopisten, die coloscopieën uitvoeren voor het Nederlandse bevolkingsonderzoek darmkanker. Ook werd gedetailleerd beschreven aan welke kwaliteitsindicatoren voor coloscopie deze endoscopisten tijdens dit kwaliteitsborgingsproces moeten voldoen. Tijdens de invoering van het Nederlandse bevolkingsonderzoek darmkanker werd besloten dat de kwaliteit en de veiligheid van de coloscopieën uitgevoerd binnen het bevolkingsonderzoek van ultiem belang zijn. Dit werd zelfs gezien als belangrijker dan het kunnen verwerken van het grote aantal extra coloscopieën, die uitgevoerd moeten worden door de invoering van het bevolkingsonderzoek. Dit is zo belangrijk, omdat voor het bevolkingsonderzoek darmkanker merendeels gezonde personen uit de algemene bevolking actief benaderd worden om deel te nemen. Daarom werden er meteen bij de start van het Nederlandse bevolkingsonderzoek darmkanker kwaliteitseisen vastgelegd. Deze eisen gelden zowel voor de endoscopie centra als voor de endoscopisten, die coloscopieën uitvoeren voor het bevolkingsonderzoek darmkanker. De beschreven ervaring van het kwaliteitsborgingsproces van het Nederlandse bevolkingsonderzoek darmkanker zou kunnen dienen als een voorbeeld voor andere darmkanker screeningsprogramma's[3].

De adenoom detectie rate (ADR; het percentage coloscopieën waar tenminste 1 adenoom wordt gevonden) en de proximale serrated poliep detectie rate (PSPDR; het percentage coloscopieën waar tenminste 1 proximaal gelokaliseerde serrated poliep wordt gevonden) zijn twee voorbeelden van kwaliteitsindicatoren voor coloscopie. Hoewel het bekend is dat de hoogte van de ADR en de PSPDR varieert tussen endoscopisten, was er weinig bekend wat de invloed van deze variaties is op de effectiviteit van een landelijk darmkanker screeningsprogramma, dat FIT gebruikt als een triage test. In **hoofdstuk 3** hebben we geëvalueerd wat het lange termijn effect was van variaties in de ADR en PSPDR op de effectiviteit van het Nederlandse bevolkingsonderzoek darmkanker. Dit werd gedaan met behulp van het eerder gevalideerde ASCCA (Adenoma and Serrated pathway to Colorectal Cancer) microsimulatie model. Gebaseerd op resultaten van dit model werd aangetoond dat een stijging in de ADR op den duur zal resulteren in een geleidelijke afname van het voorkomen van darmkanker en de sterfte aan darmkanker, terwijl een stijging van de PSPDR maar een minimale impact hierop zal hebben. Het minimale effect van de PSPDR op het voorkomen van darmkanker en de sterfte aan darmkanker zou gedeeltelijk verklaard kunnen worden door de aanname in het model dat de serrated pathway slechts voor 15% bijdraagt aan het ontstaan van darmkanker. Een andere mogelijk verklaring hiervoor zou de beperkte effectiviteit van FIT om serrated poliepen te detecteren kunnen zijn. Het is daarom belangrijk om verder onderzoek te doen naar andere triage testen, die serrated poliepen beter zouden kunnen detecteren.

De variaties in de ADR en PSPDR suggereren dat sommige endoscopisten tijdens een coloscopie een aanzienlijk aantal adenomen of proximale serrated poliepen over het hoofd zien. Omdat endoscopisten met een hoge ADR en PSPDR vaker in staat zijn om adenomen en proximale serrated poliepen te detecteren, hebben we in **hoofdstuk 4** onderzocht of dit mogelijk veroorzaakt zou kunnen worden door een betere herkenning van de endoscopische kenmerken van deze poliepen.

Tot onze verrassing konden wij geen correlatie aantonen tussen de endoscopische voorspelling van de histopathologische diagnose van adenomen en serrated poliepen en de endoscopische detectie van deze darmpoliepen. Dit zou mogelijk kunnen impliceren dat de detectie van darmpoliepen en het accuraat voorspellen van de histopathologische diagnose van deze darmpoliepen verschillende technische vaardigheden van de endoscopist vereisen. De detectie en endoscopische inschatting, ook wel de optische diagnose genoemd, van adenomen en serrated poliepen zouden daarom beiden goed moeten zijn om een optimale effectiviteit van een darmkankerscreenings programma te garanderen.

In **hoofdstuk 5** hebben we de uitvoerbaarheid, de veiligheid en de diagnostische opbrengst voor de detectie van adenomen van de Extra Wide Angle View (EWAVE) coloscoop onderzocht. Dit werd onderzocht in een prospectieve multicenter cohort studie. De EWAVE-coloscoop creëert een endoscopisch beeld van 235°, wat opgebouwd is uit de samengevoegde beelden van één voorwaarts kijkende en twee opzij- en terugkijkende lenzen. Wij toonden aan dat een coloscopie met de EWAVE-coloscoop haalbaar en veilig is. De caecum intubatie rate (het percentage coloscopieën waarin het caecum, het diepste anatomische punt van de dikke darm, gehaald werd) was 97.4% met een mediane coecum intubatie tijd van 4:00 minuten (IQR 2:00-7:00). Ook kwamen er tijdens ons onderzoek geen complicaties voor. De ADR met de EWAVE-coloscoop was met 39.9%. Dit is echter vergelijkbaar met de ADRs, die gehaald worden in vergelijkbare patiëntpopulaties met het gebruik van een reguliere coloscoop. Door technische beperkingen van het onderzochte prototype van de EWAVE-coloscoop moest het onderzoek voortijdig worden gestaakt. Momenteel is er een verbeterde versie van de EWAVE-coloscoop ontwikkeld en om de mogelijke extra voordelen van dit nieuwe prototype in kaart te brengen zal een gerandomiseerde vergelijking met reguliere coloscopie noodzakelijk zijn.

Deel 2 – Verwijdering van grote niet-gesteelde en complexe darmpoliepen

In de literatuur is er vrij weinig bekend over de endoscopische kenmerken van grote niet-gesteelde darmpoliepen waarin bij de histopathologische evaluatie onverwachts darmkanker gevonden wordt. Daarom hebben we in **hoofdstuk 6** de beoordeling tussen onverwachte kankers ontstaan in de endeldarm (rectum) vergeleken met de beoordeling van histopathologisch bewezen goedaardige rectale adenomen. Ondanks dat de beoordeling van de endeldarmpoliep, die werd uitgevoerd met geavanceerde licht technieken, diagnostische biopten en/of een rectale endo-echografie, resulteerde in de verwachting dat het om een goedaardige poliep ging, werd in 13% van grote niet-gesteelde endeldarmpoliepen onverwacht door de patholoog kanker gevonden. Tijdens de behandeling, die bestond uit een piecemeal endoscopische mucosale resectie (pEMR), bleken het zogenaamde non-lifting sign, een endoscopische behandeling die door de endoscopist werd beoordeeld als irradicaal en een vroegtijdige beëindiging van de pEMR factoren die geassocieerd waren met de aanwezigheid van de onverwachtse diagnose van endeldarmkanker. Als de endoscopist tijdens een pEMR bij patiënten, die nog nooit eerder endoscopisch zijn behandeld één van deze factoren tegenkomt, zou dit in een verdenking op de aanwezigheid van kanker moeten resulteren. Deze patiënten dienen daarna besproken te worden op een multidisciplinair

overleg, waar een en bloc (verwijdering in één stuk) endoscopische full-thickness resectie (eFTR), transanale endoscopische microchirurgie (TEM) of een aanvullende oncologische chirurgische operatie als mogelijke aanvullende behandeloptie overwogen kunnen worden.

Traditioneel werden grote, niet-gesteelde darmpoliepen behandeld door middel van een chirurgische operatie, waarbij een deel van de dikke darm verwijderd word. In het laatste decennium is er veel vooruitgang geboekt in de uitvoering van geavanceerde endoscopische behandeltechnieken, zoals pEMR en endoscopische submucosale dissectie (ESD). Het is echter grotendeels onbekend in welke mate deze endoscopische behandelingen de chirurgische behandeling van grote niet-gesteelde darmpoliepen heeft vervangen. In **hoofdstuk 7** beschrijven we het totale aantal uitgevoerde operaties voor goedaardige darmpoliepen in Nederland en hebben we de absolute en relatieve veranderingen over het afgelopen decennium in kaart gebracht. Tussen 1 januari 2005 en 31 december 2015 hebben in totaal 5937 patiënten een chirurgische operatie ondergaan voor de behandeling van een goedaardige darmpoliep. De absolute (454-739 per jaar) en relatieve (0.20%-0.37% per coloscopie per jaar) aantallen operaties bleven stabiel. In een relatief klein aantal (19.9%) patiënten werd een pogingen tot endoscopische behandeling uitgevoerd voordat de definitieve verwijzing voor een operatie plaatsvond. Opvallend was dat patiënten zelden (in 2.4%) voor een aanvullende endoscopische behandeling naar een ander coloscopie centrum werden verwezen. Daarom kan geconcludeerd worden dat gemakkelijke toegang en verwijzing naar toegewijde endoscopie centra zou moeten worden gefaciliteerd, bijvoorbeeld door middel van het organiseren van regionale multidisciplinaire verwijsnetwerken. Dit zal hopelijk resulteren in een toename van het aantal endoscopische behandelingen en het voorkomen van onnodige operaties, die mogelijk ook leiden tot een afname van morbiditeit, mortaliteit en kosten.

In **hoofdstuk 8** hebben we de complicaties (morbiditeit en mortaliteit) van darmoperaties voor goedaardige darmpoliepen onderzocht door middel van een systematische literatuurstudie. Van de 4210 onderzoeken, die in de medische literatuur werden gevonden werden in totaal 26 studies met 139,897 patiënten in onze analyse geïncludeerd. Een chirurgische operatie voor goedaardige darmpoliepen was geassocieerd met een aanzienlijk risico op postoperatieve morbiditeit (spreiding voor chirurgische complicaties van 8.5% tot 43.5% en spreiding niet-chirurgische complicaties 0% tot 13.5%), en daarnaast werden mortaliteitscijfers tot 3.2% gerapporteerd. De aanzienlijke morbiditeit en mortaliteit van chirurgische operaties in combinatie met het feit dat de geavanceerde endoscopische behandeltechnieken in het afgelopen decennium duidelijk verbeterd zijn, onderstrepen het belang van het streven naar een niet-chirurgische behandeling van deze groep patiënten. Omdat er steeds meer endoscopisten ervaren worden met het verrichten van geavanceerde endoscopische behandeltechnieken, zullen steeds meer patiënten voordeel hebben van een verwijzing naar een ervaren interventie endoscopist voordat een eventuele verwijzing voor een chirurgische operatie plaatsvindt.

Onder de complexe darmpoliepen vallen ook poliepen die gelokaliseerd zijn in de appendix opening. Voor de endoscopische behandeling van complexe darmpoliepen, vroege darmkankers en submucosale tumoren is een nieuw “endoscopische full-thickness resectie device” ontwikkeld om eFTR uit te voeren. Tijdens een eFTR procedure wordt de darmpoliep, vroege darmkanker of submucosale tumor samen met de gehele dikte van de dikke darm tijdens coloscopie verwijderd.

Hoofdstuk 9 beschrijft de haalbaarheid, het technisch succes en de veiligheid van zeven eFTR procedures die werden verricht voor de verwijdering van darmpoliepen met betrokkenheid van de appendix opening. Deze kleine prospectieve observationele case studie toonde aan dat eFTR uitgevoerd om darmpoliepen met betrokkenheid van de appendix opening haalbaar is, en een goede kans op technisch succes heeft. Alle procedures resulteerden in een endoscopisch radicale verwijdering van de poliep in één stuk (en bloc). De snijvlakken aan de zijkant van alle procedures waren histopathologisch negatief voor poliepweefsel en in één patiënt was het diepe snijvlak positief voor poliepweefsel, wat resulteerde in een R0 resectie rate van 85.7% (6/7). Eén patiënt ontwikkelde een klein abces naast de plaats van de eFTR procedure, wat behandeld werd met een echografische geleide punctie met drainage. Een andere patiënt ontwikkelde een secundaire appendicitis, die behandeld werd met een daaropvolgende chirurgische appendectomie. Deze resultaten suggereren dat een eFTR procedure van darmpoliepen met betrokkenheid van de appendix opening een mogelijk minimaal invasief alternatief voor een chirurgische operatie is, maar wel zijn er meer data over de veiligheid van deze procedures nodig.

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LIST OF PUBLICATIONS

Publications in this thesis

Quality assurance of colonoscopy within the Dutch national colorectal cancer screening program
Bronzwaer MES, Depla ACTM, van Lelyveld N, Spanier MBW, Oosterhout YH, van Leerdam ME, Spaander MCW, Dekker E; Dutch Colonoscopy Quality Assurance working group
Gastrointest Endosc. 2018 Sep 18. [Epub ahead of print]

Impact of differences in adenoma and proximal serrated polyp detection rate on the long-term effectiveness of FIT-based colorectal cancer screening
Bronzwaer MES*, Greuter MJE*, Bleijenberg AGC, IJspeert JEG, Dekker E, Coupé VMH
* Both authors contributed equally to this article.
BMC Cancer. 2018 Apr;18(1)

Endoscopic full-thickness resection of polyps involving the appendiceal orifice – a prospective observational case study
Bronzwaer MES, Bastiaansen BAJ, Koens L, Dekker E, Fockens P.
Endosc Int Open. 2018 Sep;6(9)

The occurrence and characteristics of endoscopically unexpected malignant degeneration in large rectal adenomas.
Bronzwaer MES, Musters GD, Barendse RM, Koens L, de Graaf EJR, Doornebosch PG, Schwartz MP, Consten ECJ, Schoon EJ, de Hingh IHJT, Tanis PJ, Dekker E, Fockens P; TREND study group.
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Bronzwaer MES, Koens L, Bemelman WA, Dekker E, Fockens P; COPOS study group.
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Feasibility, safety, and diagnostic yield of the Extra Wide Angle View (EWAVE) colonoscope for the detection of colorectal lesions.
Bronzwaer MES, Dekker E, Weingart V, Groth S, Pioche M, Rivory J, Beyna T, Neuhaus H, Ponchon T, Allescher H, Fockens P, Rösch T.
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Other publications

Effective reporting of key performance indicators is essential for balancing the benefits and drawbacks of colonoscopy.
Dekker E, **Bronzwaer MES**.
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Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline.
Ferlitsch M, Moss A, Hassan C, Bhandari P, Dumonceau JM, Paspatis G, Jover R, Langner C, **Bronzwaer MES**, Nalankilli K, Fockens P, Hazzan R, Gralnek IM, Gschwantler M, Waldmann E, Jeschek P, Penz D, Heresbach D, Moons L, Lemmers A, Paraskeva K, Pohl J, Ponchon T, Regula J, Repici A, Rutter MD, Burgess NG, Bourke MJ.
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Maintenance of optimal vitamin D status in children and adolescents with inflammatory bowel disease: a randomized clinical trial comparing two regimens.
Pappa HM, Mitchell PD, Jiang H, Kassiff S, Filip-Dhima R, DiFabio D, Quinn N, Lawton RC, **Bronzwaer MES**, Koenen M, Gordon CM.
J Clin Endocrinol Metab. 2014 Sep;99(9)

PHD PORTFOLIO

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
Basic course in Legislation and Organisation for Clinical Researchers (BROK)	2015	1.0
Searching for Systemetic Review	2015	0.1
Clinical Data Management	2015	0.3
Practical Biostatistics	2015	1.1
Project management	2016	1.0
Specific courses		
Training Statistics ENDOAPLHA Documentation	2015 & 2017	0.5
Seminars, workshops and master classes		
Biweekly research seminars Gastroenterology	2014-2018	2.0
Biweekly colorectal cancer group meeting	2014-2018	2.0
Biweekly colorectal cancer group journal club	2017-2018	1.0
Gut-club meetings	2014-2018	1.5
AG&M PhD retreat	2016 & 2017	1.0
Medical Business Masterclass	2016	0.5
Value Based Health Care Masterclass	2017	0.5
DOO – Finance in Health Care	2017	0.1
Presentations		
Oral Presentations		
Gut Club Research Meeting (1)	2015	0.1
ESGE Guideline Meeting (1)	2015	0.1
Antonius Research fund (2)	2015, 2016	0.5
WEO CRC screening meeting (1)	2016	0.5
European Society of Coloproctology (1)	2016	0.5
United European Gastroenterology Week (2)	2016, 2017	1.0
Digestive Disease Days (spring and fall) (2)	2016, 2017	1.0
Poster presentations		
United European Gastroenterology Week (1)	2016	0.5
European Society of Coloproctology (1)	2016	0.5
Digestive Disease Week (2)	2017	1.0

Phd Portfolio. (continued)

	Year	Workload (Hours/ECTS)
(Inter)national conferences		
WEO CRC screening meeting; *Barcelona, San Diego, Vienna, Chicago*	2015-2017	1.0
United European Gastoenterology Week; *Barcelona, Vienna, Barcelona*	2015-2017	2.0
European Society of Coloproctology; *Milan*	2016	0.5
Digestive Disease Days - fall *Velthoven*	2016	0.5
Digestive Disease Week; *San Diego, Chicago*	2016, 2017	2.0
Digestive Disease Days – spring *Velthoven*	2017	0.5
2. Teaching		
Lecturing		
Elective gastroenterology science course for 2nd year medical students	2015-2017	1.5
2nd year medical students (research traineeship)	2015	0.5
Accredited lecture on the indications of colonoscopies for assistants of general practitioners	2015	0.2
Lecture for biomedical science master students of the University of Amsterdam	2016	0.2
Supervising		
Extra curricular project Lieve Leijssen	2015	0.5
Extra curricular project Esther Nieuwenhuis	2017	0.5
Bachelorthesis Sofie Eerligh	2016	1.0
Bachelorthesis Jurr Andriessen	2017	1.0
3. Parameters of Esteem		
Grants		
Antonius Research fund - the Pilot study: LumenR ESD for the treatment of rectal adenomas in the Netherlands	2015	
NVGE travel grant	2016	
UEGW travel grant	2016, 2017	
Awards and Prizes		
UEGW Oral Free Paper Prize: Colorectal cancer: Diagnostic and therapeutic aspects. 'Prevalence and characteristics of unexpected rectal cancer in benign appearing large non-pedunculated rectal polyps'.	2016	

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ABOUT THE AUTHOR

Maxime Eline Stephanie Bronzwaer was born on September 21st 1990 in Eindhoven, the Netherlands. At the age of eight she and her family moved to Krommenie (Noord-Holland), where she grew up. In 2008 she graduated from high school at the Bertrand Russell College in Krommenie. That same year she started medical school at the University of Amsterdam. Her enthusiasm for science was founded in 2012, when she finished an eight month scientific internship at Boston Children's Hospital, Boston, Massachusetts, USA. Under the supervision of H.M. Pappa and Prof. R.J. Grand, she studied the maintenance of optimal vitamin D status in children and adolescents with inflammatory bowel disease. During her clinical rotations, she got involved in the colorectal cancer research group of Prof. dr. E. Dekker. After her final rotation in Gastroenterology and Hepatology in the Slotervaart Hospital at the end of 2014, she started her PhD project at the Academic Medical Center in Amsterdam under the supervision of prof. dr. E. Dekker and prof. dr. P. Fockens. During these three and a half years, she worked on several studies regarding the improvement of the quality of colonoscopy, as well as improvement of the detection and resection of colorectal polyps, which resulted in this thesis. In September 2018, she started her training in Gastroenterology and Hepatology at the Department of Internal Medicine at the Onze Lieve Vrouwe Gasthuis (dr. M.C. Weijmer and dr. Y.F.C. Smets) in Amsterdam. Hereafter she will continue her training as a gastroenterologist at the Academic Medical Center (dr. K.M.A.J. Tytgat and prof. dr. U.H.W. Beuers).