No more hide and seek

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Strategies to optimize diagnosis and endoscopic treatment of complex colorectal neoplasms

Roel Bogie

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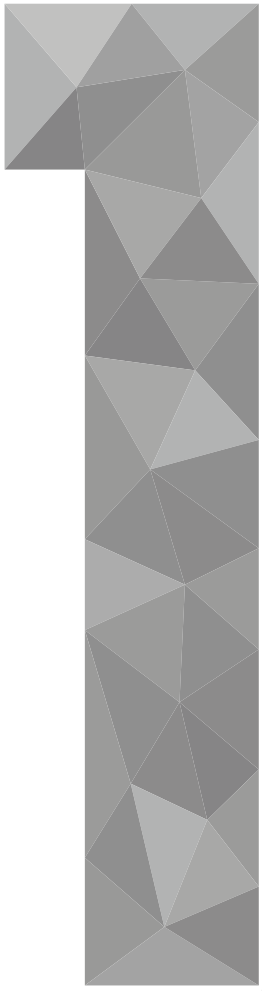

General introduction

Colonoscopy is the gold standard method for the detection and resection of colorectal neoplasms (CRNs). The opportunity for direct radical resection of detected CRNs is a major advantage of colonoscopy. By removing precursor lesions of colorectal cancer (CRC), colonoscopy is an important tool in the prevention of CRC. It is regarded as safe[1] and effective in confirming the diagnosis and removing precursor neoplasms. The number of colonoscopies performed has further increased as a consequence of the introduction of national CRC screening programs.[2] Healthy, symptom free persons are now receiving colonoscopies in order to prevent CRC later on in life, emphasizing the need for safety and efficacy of colonoscopic procedures and interventions. The search for precursor lesions that may develop into CRC is key, reassembling the 'hide and seek game' for the endoscopist. The better the endoscopist performs in this game (higher detection of such precursor lesions), the lower the patients' risk of developing CRC is.[3] This thesis focuses on how to deal with large colorectal neoplasms and how to prevent the occurrence of CRC after colonoscopy, two important topics within colonoscopy safety and efficacy.

Colonoscopy

National colorectal cancer screening program

In the Netherlands, a nationwide CRC screening program started in 2014 with high yields of CRCs, adenomas and serrated lesions. All Dutch citizens between 55 and 75 years old receive biannually an invitation for a fecal occult blood test (FOBT). In case the FOBT is positive (abnormal), the participant will be referred for a colonoscopy. All colonoscopies are performed by experienced, specially trained and monitored colonoscopists to assure high quality standards. After a negative colonoscopy, patients will re-enter the national screening program after 10 years.[4]

The screening program poses a burden on colonoscopy capacity, not only because of a high number of patients referred for colonoscopy, but also because of the treatment of the many CRNs found and the high number of surveillance colonoscopies needed.[5] Small CRNs can be resected during the first colonoscopy in most cases, but large CRNs, especially in the case of multiple large CRNs, often need a second colonoscopy to resect the CRNs completely. Furthermore, large CRNs have higher risk of residual and recurrent neoplastic tissue and need second look colonoscopies. Thus, after complete removal of CRNs, depending on number, size, and histology, surveillance colonoscopies may be necessary.[6]

Safety and efficacy of colonoscopy

Colonoscopy is a safe procedure with overall very low rates of complications[1] such as bleeding, infection and perforation. The risk of complications significantly increases by performing polypectomies especially for large CRNs.[7] Bleeding occurs in 0.06% (95% CI: 0.02-0.11) of all colonoscopies without polypectomy, but when polypectomy is performed, the risk increases to 0.98% (95% CI: 0.77-1.21).[1] The risk of perforations doubles after polypectomy: 0.04% (95% CI: 0.02-0.08) overall in colonoscopies without polypectomy and 0.08% (95% CI: 0.06-0.10) in colonoscopies with polypectomy.[1] Larger CRNs often need more complex procedures like endoscopic mucosal resection or endoscopic submucosal dissection as endoscopic treatment, thereby even further increasing the risk of post-polypectomy bleeding and perforation.[7, 8] In general, resection of large CRNs is associated with higher risk of complication, is more time consuming, and requires often additional colonoscopies and a shorter post-polypectomy surveillance interval.

All in all, colonoscopy remains a safe procedure and is currently the most appropriate examination for the nation-wide CRC screening of the population in addition to fecal occult blood testing. By participating in the national CRC screening program, participants take a small procedure related risk in return for a significant risk reduction with respect to the development of CRC. This can only be achieved by complete visualization of the colonic mucosa and effective resection of premalignant neoplasms. To achieve this, quality benchmarks have been set, e.g.: adequate bowel preparation in ≥90% of all colonoscopies (Boston Bowel Preparation Scale [BBPS] ≥6, minimal 2 for each segment), cecal intubation rate in ≥90% of all colonoscopies, detection of ≥1 adenoma in ≥25% of patients, and withdrawal time of ≥6 minutes.[9] Use of the correct therapeutic intervention is also a benchmark (≥80% correct therapy) and is important for reducing the need of multiple interventions and for decreasing residual tumor and recurrence risk. However, the most effective treatment is dependent of the lesion (size and histological type). Level of difficulty increases with size.[10]

Polyp classification

In order to accurately diagnose CRNs and select the best therapeutic option, lesion characterization is the first step. CRNs can be subdivided based on size, shape, and histology. Size is an important predictor for the risk of submucosal invasion, residual tissue and recurrence and determines (in combination with shape) which endoscopic treatment is indicated.[11] CRNs can be diminutive (≤5 mm), small (6-10 mm) and large (≥10 mm). According to ESGE guidelines, lesions larger than 20 mm are considered as very large and are more difficult to resect en-bloc.[12]

The Paris classification is used to characterize CRN shape (**Figure 1.1**). CRNs can be divided into polypoid and non-polypoid based on the height of the lesion. Non-polypoid CRNs are defined as having a height of maximal half the diameter of the lesion.[13, 14] Polypoid CRNs can have a stalk (pedunculated) or a broad basis (sessile). Non-polypoid CRNs can be flat or depressed.[15]

Histologically, CRNs can be subdivided into hyperplastic polyps, adenomas, sessile serrated lesions, traditional serrated adenomas and CRCs.[16] Adenomas consist of three types: tubular, villous and tubulovillous adenomas. Sessile serrated lesions occur with and without dysplasia. Serration is one of the levels for histological classification; hyperplastic polyps, sessile serrated lesions with and without dysplasia and traditional serrated adenoma belong to the group of serrated lesions, while adenomas are non-serrated. Another level of classification is dysplasia; adenomas, traditional serrated adenomas, sessile serrated lesions with dysplasia and CRCs are considered as dysplastic, while hyperplastic polyps and sessile serrated lesions without dysplasia are considered as non-dysplastic.

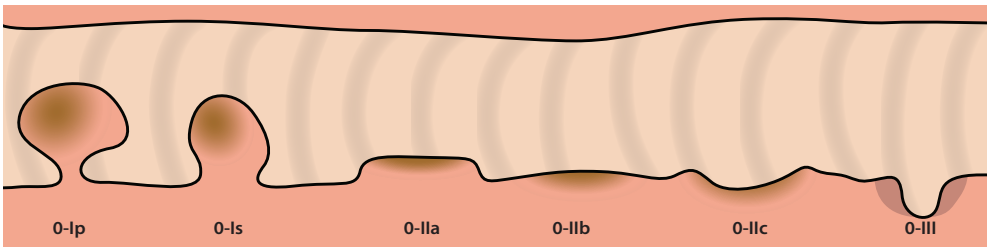

Figure 1.1: Paris classification. | *0-I lesions are polypoid and 0-II and 0-III lesions are non-polypoid. Combinations are possible.*

Laterally Spreading Tumors and Large Non-Polypoid Colorectal Polyps

Laterally Spreading Tumors, further abbreviated as LSTs, are large, flat appearing neoplasms in the colon and rectum. They have firstly been described in Japan by prof. Kudo as lesions challenging to detect while posing a hazard to rapid progression into CRC.[17] LSTs are defined as lesions growing superficially (laterally) along the mucosa instead of growing upwards (luminal) or downwards (submucosal), of minimal 10 mm in diameter.[11] Although polypoid components can be present in LSTs, they are regarded as non-polypoid colorectal neoplasms.[17] LST is a endoscopic, morphological classification, regardless of histology.

LSTs are of special interest because of the occurrence of different surface structures and specific corresponding clinical features. The surface can consist of granules or can be completely flat (**Figure 1.2**). Both LST subtypes can be subclassified into two subtypes; the endoscopic Kudo LST classification. LSTs consisting of evenly sized granules are called LST granular homogenous (LST-G-H). When one or more dominant granules (large, sessile like components) exist in a granular LST, it is called a LST granular nodular-mixed (LST-G-NM). These dominant granules are minimal 10 mm in size. LSTs with flat surface are called non-granular LSTs and can contain a pseudo-depression (subtle dentation) on the surface. Non-granular LSTs without pseudo-depression are called LST non-granular flat elevated (LST-NG-FE) and those with pseudo-depression LST non-granular pseudo-depressed (LST-NG-PD).[11] In contrast to pseudo-depressions, depressions have more abrupt walls and are an indication of deep mucosal invasion. These can occur in all premalignant neoplasms, regardless of morphology.

The risk of containing submucosal invasion (SMI, i.e. colorectal cancer) in LSTs differs per subtype. Overall, LSTs have a lower to similar risk of SMI than pedunculated and sessile neoplasms of equal size.[18, 19] However, some subtypes may have a higher than average risk of SMI.[11, 20] LSTs are more challenging to resect than large polypoid polyps and require additional experience.[21] The combination of large size and a non-polypoid morphology, often with a proximal colonic location, makes endoscopic mucosal resection challenging.[10]

The BSG guidelines proposed the term Large Non-Pedunculated Colorectal Polyps (LNPCPs) for all non-pedunculated colorectal neoplasms of minimal 20 mm in size.[10] Besides LSTs of 20mm or larger, also sessile neoplasms of 20 mm or larger are included.

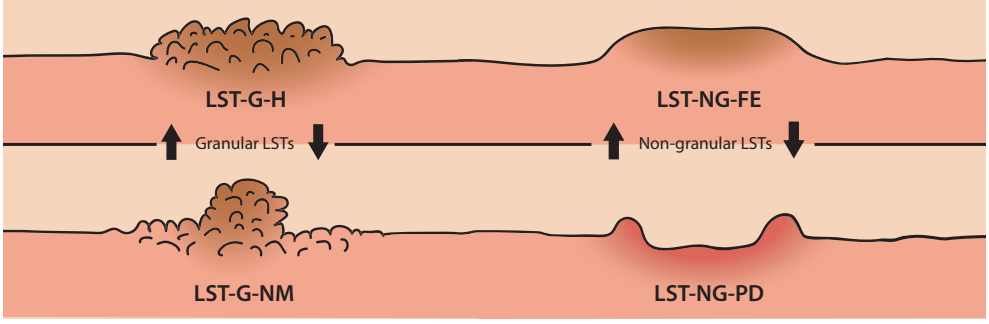

Figure 1.2: Endoscopic Kudo LST classification. | *Illustration of the four known subtypes of LSTs.*

Post-colonoscopy colorectal cancers

Although colonoscopy is effective in CRC prevention, CRC may still occur after a colonoscopy negative for cancer. When a CRC is diagnosed after a previous colonoscopy that was negative for CRC, a so called post-colonoscopy CRC has occurred (PCCRC).[22] The pooled incidence of PCCRCs found within 36 months after a previous colonoscopy in a large meta-analysis was 3.7% of all CRCs (95% CI: 2.8 – 4.9).[23] There is variation in the definition of PCCRCs. Previously, the maximal time between a negative colonoscopy and the CRC diagnosis to be allowed to call it PCCRC is set to 36, 60 and 120 months and even longer in different studies.[23, 24] Currently, all CRCs found between 6 and 120 months after a negative colonoscopy are regarded as PCCRCs.[25] CRCs found within 6 months are regarded as prevalent CRCs, since in most cases a new colonoscopy was planned within 6 months due to an insufficient examination of the first one.

Different causes of PCCRCs have been identified. Patients with multiple, large or more advanced neoplasms during colonoscopy, require a surveillance colonoscopy within a few years.[6] A CRC found after a previous colonoscopy without signs of a CRC is called a PCCRC.[25] Insufficient examinations, i.e. colonoscopies with inadequate bowel preparation or incomplete colonoscopy, contribute to missing lesions that can become PCCRCs. Incomplete endoscopic resections of large CRNs can also cause PCCRCs when residual tissue is able to develop into carcinoma. Some PCCRCs are assumed to develop from CRNs that have been missed by the endoscopist due to unknown reason and some are assumed to develop from new precursor lesions with a fast progression into CRC.[26] This shows that causes of PCCRCs are multifactorial. Some factors are influenced by the patient (performing bowel preparation according to instructions, coming back in time for surveillance colonoscopy), some by the endoscopist (making clear agreements with the patient about surveillance, taking time for complete bowel visualization, arranging a second colonoscopy in case of an insufficient examination or incomplete resection) and some by biology of the neoplasm (subtle appearance, faster progression into carcinoma).

Precursor lesions

Some types of CRNs may contain a higher risk of PCCRCs than others. Non-polypoid neoplasms in general and sessile serrated lesions with dysplasia are considered important contributors to PCCRCs because of their subtle appearance and their predominant location in the proximal colon. PCCRCs are also often located in the proximal colon and have often a non-polypoid appearance, suggesting their origin from flat precursor lesions.[26] Non-polypoid and sessile serrated lesions are easier to overlook, especially in the case of suboptimal bowel preparation[27, 28] and in untrained endoscopists.[29] Some studies showed a high frequency of microsatellite instability, CpG island methylator phenotype and BRAF mutations in PCCRCs;[24, 30-32] molecular features associated with sessile serrated lesions.[33]

LSTs are also hypothesized to be precursor lesions of PCCRCs (**Figure 1.3**). Especially the non-granular LSTs have a subtle appearance, which makes them easier to miss with the potential to develop into a PCCRC. Since LSTs are non-polypoid neoplasms, the same arguments as for non-polypoid CRNs apply. However, some additional arguments should be considered. Resection of large LSTs is difficult with high risk on residue/ recurrence.[10, 12, 34, 35] Without sufficient surveillance this residue/ recurrence could eventually result in a PCCRC. Patients with LSTs are believed to have a higher risk on synchronous and metachronous CRNs[36, 37] which hypothetically increases the risk of (PC-)CRC. PCCRCs occur also more often after previous diagnosis of LST-NG.[38] Another hypothesis is

that LSTs have a typical morphology because of specific molecular alterations that could go hand in hand with an accelerated adenoma-carcinoma sequence. So, LSTs have the potential to become invasive and share features with PCCRCs. However, direct evidence is lacking and it remains unclear to what extent LSTs contribute to development of PCCRCs.

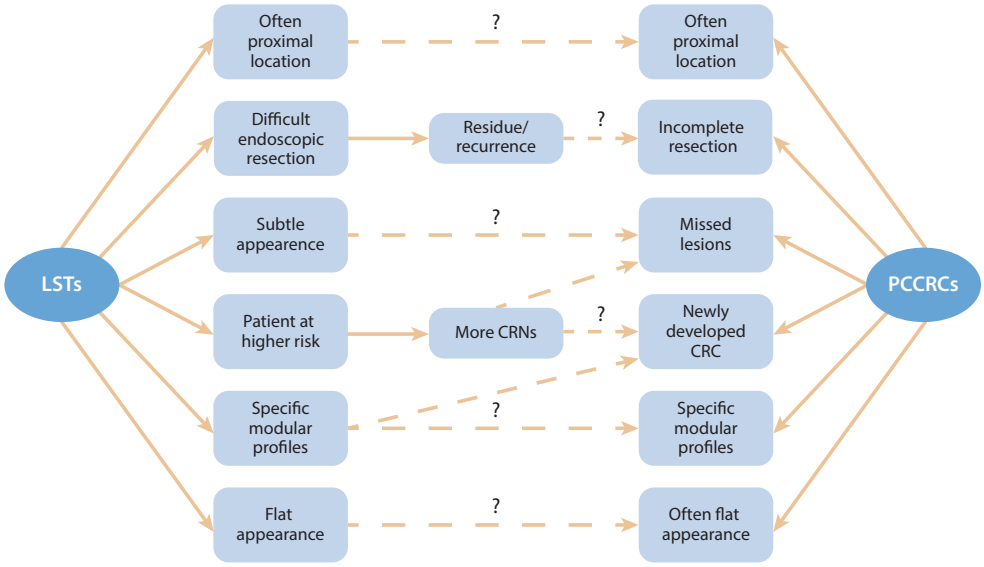

Figure 1.3: Hypothetical links between LSTs and PCCRCs.

Link with inflammatory bowel disease

Patients with inflammatory bowel disease (IBD) have an increased risk of developing CRC.[39] Instead of the classic adenoma-carcinoma sequence, the chronic effect of cytokines an chemokines caused by inflammation leads to dysplasia which could eventually turn into carcinoma. PCCRCs are also more common among IBD patients, reporting 15.1% of all CRCs in Crohn disease patients and 15.8% in ulcerative colitis patients within a hospital population.[40] More recent data on IBD related CRC risk from the general population are lacking. Besides IBD associated CRC, IBD patients are also at risk of common CRC but are excluded from the national screening programs. Patients are therefore dependent on IBD specific surveillance that starts 8 years after onset of IBD.[41] The risk of PCCRCs may be increased by difficult detection of IBD associated dysplasia, higher prevalence of flat lesions and a shortened duration of the carcinogenic process induced by inflammation.[39]

Aims and outline of this thesis

In this thesis, we hypothesized that LSTs are an important contributor to PCCRCs. A number of studies were conducted on both topics, each also individually important for quality of colonoscopy. The aims of this thesis are (I) to investigate the malignant potential, clinical significance, and therapeutic options of LSTs, (II) to examine how to limit the risk of PCCRCs and (III) to study whether non-polypoid and specifically LSTs are major contributors to PCCRCs.

The first part of this thesis is about LSTs (in combination with LNPCPs) and their clinical significance (**Chapters 2-6**). **Chapter 2** focuses on the LST definition and whether it is applicable in clinical practice. In this study the endoscopic Kudo LST classification is validated among international experts and endoscopy trainees. In **Chapter 3** we aimed to investigate worldwide prevalence and malignant potential of LSTs. In **Chapter 4** we focused at the LSTs diagnosed in the Maastricht University Medical Center and we investigated whether patients with LSTs have a different risk of colorectal neoplasia than other patients with colorectal neoplasms. Whether prevalence of LSTs (and the other LNPCPs) increased in national CRC screening setting and the management of these lesions is studied in **Chapter 5**. In **Chapter 6** we performed another meta-analysis to see whether thermal ablation could contribute to a more effective resection of LNPCPs (including LSTs).

PCCRC is the subject of the second part of this thesis (**Chapter 7-11**). PCCRCs are important regarding effectiveness and safety of colonoscopy, especially with the implementation of national colorectal cancer screening programs. In **Chapter 7** we summarized Western post-colonoscopy surveillance guidelines and added practical tips and tricks to optimize surveillance to prevent PCCRCs. Currently surveillance intervals are calculated based on polyp numbers and polyp size and histology. For histology, resection and pathological examination is necessary for each polyp. Whether we are ready for optical diagnosis only in small polyps and calculate surveillance intervals based on this assessment, was studied in **Chapter 8**. As we hypothesize that non-polypoid colorectal neoplasms (NP-CRNs) are important contributors to PCCRC, training in the detection and resection of NP-CRNs may reduce PCCRC incidence. This was studied in **Chapter 9**. Because of the higher prevalence NP-CRNs, the risk of developing a PCCRC may also been increased. Further investigation into the role of NP-CRNs in the development of PCCRCs was done in **Chapter 10**. The biology of PCCRCs development was studied in this chapter by using molecular analysis. A molecular analysis of PCCRCs was performed and the profiles found were compared with the known profile of detected (previously called 'prevalent') CRCs. In **Chapter 11** the incidence of PCCRCs among inflammatory bowel disease (IBD) patients was studied. Patients with IBD have relatively more often NP-CRNs than the general colonoscopy population, i.e. patients referred for screening colonoscopy or patients with symptoms justifying colonoscopic examination. Finally, in **Chapter 12** we summarize these findings and discuss the current insights, implications for clinical practice and remaining questions about LSTs, PCCRCs and their connection.

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Development and validation of an educational web-based system for endoscopic classification of laterally spreading tumors

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Unpublished

Abstract

Objective

Correct endoscopic classification of Laterally Spreading Tumors (LSTs) in the colon and rectum is a prerequisite in order to predict the risk of containing submucosal invasion and to determine the optimal therapeutic plan. We examined the interobserver agreement (IOA) for classification of LSTs among international experts, and among fellows before and after training.

Design

We developed an educational web-based system to classify the aspect of LSTs using the endoscopic Kudo classification of LSTs. We used a case-based collection of LSTs with high-definition white-light endoscopy images and chromoendoscopy images. We calculated the IOA using Fleiss kappa coefficients, Gwet's coefficients and the mean proportion of pairwise agreement.

Results

A total of 72 cases were assessed by 14 experts and 21 fellow raters. Overall, there is substantial IOA (Gwet's AC1) for Kudo classification of LSTs (0.62, 95% CI: 0.55 – 0.69) and their categorization into granular vs non-granular subtype (0.75, 95% CI: 0.66 – 0.83) among experts. The IOA (Fleiss kappa) varies by endoscopic subtype: 0.76 (95% CI: 0.73 – 0.78) for LST-G-NM, 0.56 (95% CI: 0.53 – 0.58) for LST-G-H, 0.55 (95% CI: 0.52 – 0.57) for LST-NG-FE and 0.53 (95% CI: 0.50 – 0.55) for LST-NG-PD. Training significantly improved the IOA for Kudo classification of LSTs among fellows (Gwet's AC1 [95% CI]: 0.43 [0.37-0.50] before vs 0.59 [0.53-0.65] after, $P<0.001$).

Conclusion

Our study validates the Kudo endoscopic classification of LSTs. Substantial IOA was found for classification of LSTs among international experts and training significantly improved the IOA among fellows.

Introduction

Laterally Spreading Tumors (LSTs) are large flat colorectal neoplasms which can be resected with minimally invasive procedures, i.e. endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), thereby avoiding surgery.[1, 2] Four endoscopic subtypes have been described: homogenous granular subtype (LST-G-H) which displays regular and equally sized granules on the surface; nodular mixed granular subtype (LST-G-NM) which displays a granular surface with at least one dominant nodule (sessile component); flat-elevated non-granular subtype (LST-NG-FE) which displays a completely flat and smooth surface; and pseudo-depressed non-granular subtype (LST-NG-PD) which displays a flat and smooth surface with a superficial indentation.[3] Using this endoscopic classification of LSTs is of critical importance since the risk of containing submucosal invasion (SMI) varies between subtypes,[4] guiding the preferred method of resection.[5, 6]

Colorectal neoplasms in general are classified using the Paris classification.[7, 8] This classification is less useful for LSTs because it cannot distinguish between granular and non-granular subtypes. The overall agreement when applying the Paris classification among colonoscopy experts was only fair to moderate in a single study and did not improve after a short training.[9] Practical clinical guidelines propose a lesion-specific approach for treatment of LSTs.[2, 6, 10] To implement these guidelines in clinical practice, the Kudo endoscopic classification of LSTs requires good interobserver agreement (IOA) and at first has to be validated. Few studies addressed the IOA in using the endoscopic Kudo classification,[11, 12] and none tested this among international colonoscopy experts. Training of endoscopists has to be provided on applying this classification.

In the current study we gathered a photo collection of LSTs, validated the endoscopic Kudo LST classification among international colonoscopy experts and developed and validated an e-learning on LST classification. The aims of this study were (I) to examine whether the Kudo LST classification is a useful tool in practice; (II) to test whether an e-learning on LST classification is effective among trainees. Furthermore, we explored the IOA in the application of the Paris classification on LSTs and in selecting the most suitable treatment strategy among colonoscopy experts.

Material and Methods

We employed the Guidelines for Reporting Reliability and Agreement Studies (GRRAS).[13] We conceived the study using a stepwise approach as displayed in **Figure 2.1**.

Definition of LST

LSTs were defined as non-polypoid colorectal neoplasms (NP-CRNs) at least 10mm in diameter which grow mainly laterally along the mucosal wall instead of growing only upward (luminal) or only downward (submucosal).[3, 14] The endoscopic LST Kudo classification has four subtypes: LST-G-H (regular surface, evenly-sized granules), LST-G-NM (granular surface with at least one dominant nodule [sessile component]), LST-NG-FE (completely flat surface) and LST-NG-PD (smooth surface with subtle indentation) (**Figure 2.2**).

Development phase

The core group investigators (HMC and LC, National Taiwan University Hospital [NTUH] and SS and RB, Maastricht University Medical Centre [MUMC+]) selected the LST cases that were diagnosed at the endoscopy units of the academic centers **(Figure 2.1**, step 1). A total of 103

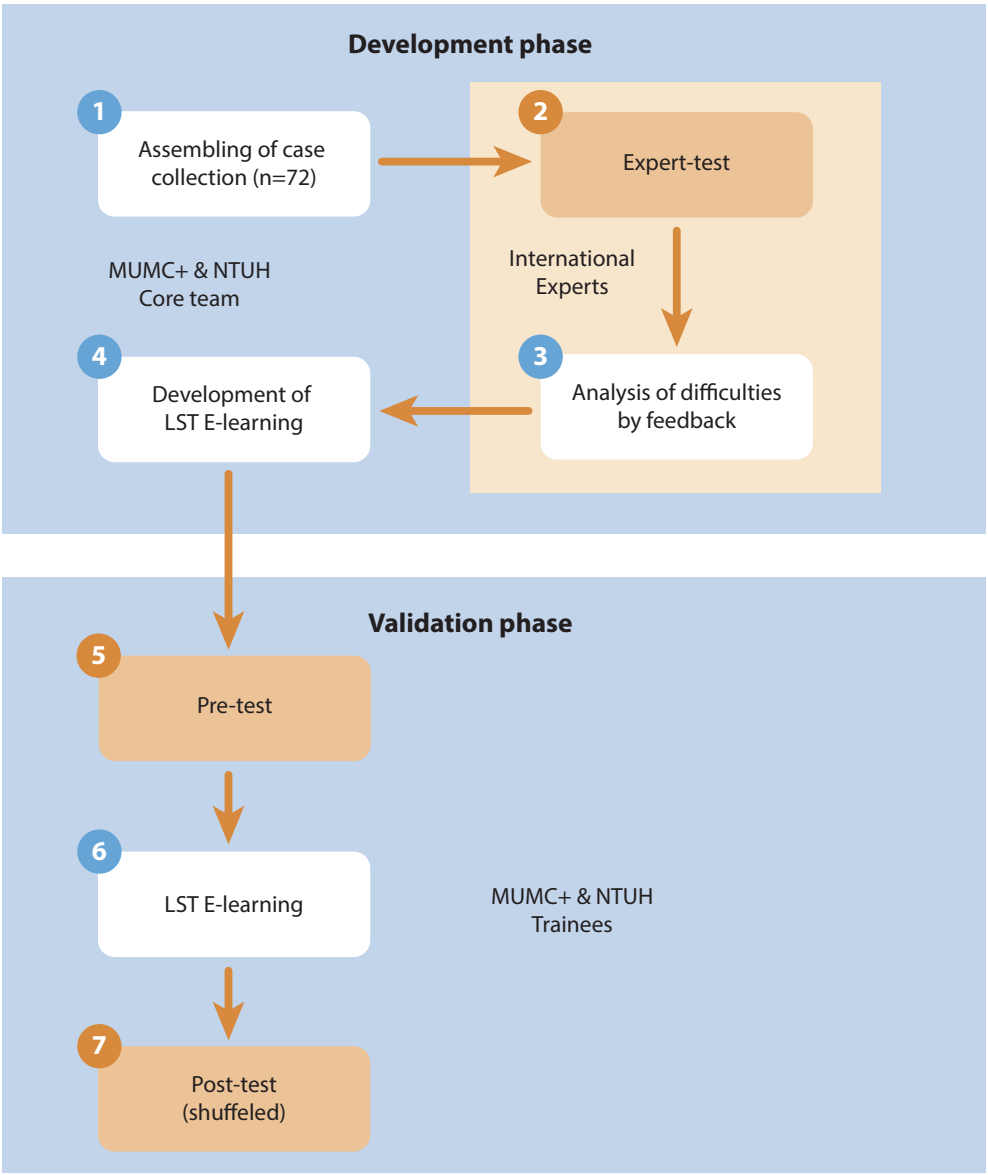

Figure 2.1: Study flow-chart. | *MUMC+: Maastricht University Medical Centre, NTUH: National Taiwan University Hospital.*

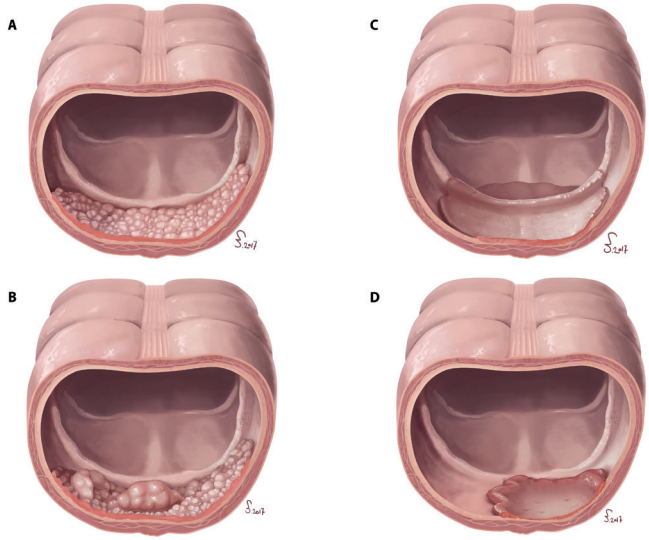

Figure 2.2: Illustration of the endoscopic Kudo classification. | *A: LST-G-H, B: LST-G-NM, C: LST-NG-FE, D: LST-NG-PD. Licensed by Erik Wallert (www.erikwallert.nl).*

cases with anonymized clinical data and endoscopic images were kindly provided by two of the study investigators (HMC, SS). High-definition white-light colonoscopy and chromoendoscopy images were available in all cases. Both Olympus (H260 or H290 series) and Pentax (EC-3890i series) colonoscopes were used. To ensure uniformity in classification of images from the 2 centres, we selected only endoscopic images using dye-based chromoendoscopy (indigo carmine 0.04%). Endoscopic images using digital chromoendoscopy techniques were not used. For each case photo documentation comprised long-view images to assess the location and size of the LST and close-view images to assess the endoscopic shape (at least 2 per case). All images were taken in a clean and well-insufflated colon before starting the resection. Post-resection histopathology assessed by experienced gastroenterology pathologists was available but not presented to raters.

Sample size calculation indicated that minimal 50 cases were needed for a 95% confidence interval of +-0.10 in case of a suspected kappa coefficient of 0.75.[15] We invited colonoscopy experts from Western and Eastern countries and colonoscopy trainees from MUMC+ and NTUH in the study. We included at least 6 raters in each group. The precision of the kappa coefficient does not increase much more when including more than 6 raters.[15] We assumed an equal distribution of the endoscopic Kudo subtypes of LSTs. To facilitate sensitivity analysis, a total number of 72 cases were included. From the 103 cases selected by the study investigators out of their personal selection, eventually 72 were selected to use in the modules. Selection was based on a quality-assessment comprising clarity of the image, the presence of air bubbles, presence of long-view and short-view, level of air insufflation and use of blue dye. As in daily practice, multiple cases had flaws on some of the points. Therefore, the core-team selected the 72 cases with the highest overall quality.

Fourteen international experts in colonoscopy were invited to participate (Step 2). All experts perform research in image-enhanced endoscopy-assisted diagnosis and endoscopic resection of

colorectal neoplasms, with special attention for NP-CRNs. A case-based discussion was induced to find out how experts assessed the LSTs. These key principles were later on used in the LST training module. Each rater received a personal account to access an online web-system (**Figure 2.3**). The observers were familiar with the study goals, but were not informed about the suspected proportion of Kudo subtypes of LSTs, the resection method used, and the lesion histopathology. Raters were blinded from the entries of their peers.

Clinical records (e.g. patient's age, gender, medical history, indication for colonoscopy, lesion size and the location of the lesion) were presented in the upper right corner (**Figure 2.3**, Area A). We attempted to mimic the real life situation in which the same information is available to the endoscopist. Lesion size as measured at the time of colonoscopy was shown since this feature is more difficult to estimate on still images.

At least 3 endoscopic images were presented for each LST, using HD white light colonoscopy (one image) and dye-based chromoendoscopy (one long-view image and one short-view image). Dye-based chromoendoscopy was employed in all cases to clarify the lesion border and to assess the endoscopic shape (**Figure 2.3**, Area B). Raters could deliberately navigate back and forth through the images using the arrows.

Then the raters were asked to complete a survey, comprising the following questions: (I) What is the endoscopic Kudo LST classification subtype of the lesion? (4 options; LST-G-H, LST-G-NM, LST-NG-FE and LST-NG-PD); (II) What is the Paris classification subtype of the lesion? (9 options; 0-Ip, 0-Is, 0-Ips, 0-IIa, 0-IIb, 0-IIc, 0-IIa+IIc, 0-IIa+Is and other [specified by rater by using comments]); (III) What is the best therapeutic plan? (4 options; EMR, ESD, surgery and other [specified by using comments]); and (IV) How was the image quality? (3 options; excellent, good and sufficient) (**Figure 2.3**, Area C).

The raters were encouraged to provide specific comments where applicable. After completing all questions, the case could be submitted and transition was made to a new case. The raters were not allowed to navigate back to the previous case. Raters were able to pause the survey and continue at a later moment. After completing the last case, the module was locked.

After completion of the test by all experts, IOA and specifically difficulties in the classification were discussed within the core-group (Step 3).

We developed a LST training module (Step 4) in the detection of LSTs, in applying the endoscopic Kudo classification and Paris classification of LSTs, and selecting the therapy of choice. This comprised scientific information and case-based photo documentation, videos and illustrations. All experts provided input to the development of the training module. The original case-based discussion and the feedback on the expert test were incorporated.

The training module consisted of a video with two times five LST cases with feedback for practicing the endoscopic Kudo LST classification in between (5 after short introduction, 5 at end before summary). The video contained scientific information about LSTs, including the classification, the risk of submucosal invasion and recurrence risk. A stepwise approach for diagnosing LSTs was applied, including tips and tricks of experts. Special attention was payed to the use of chromoendoscopy, submucosal injection and air insufflation.

Cases provided during the training module were different cases than in the tests. Trainees were allowed to do the training module multiple times when desired.

Validation phase

We invited endoscopy fellows from the MUMC+ and NTUH in the study to test whether the endoscopic LST classification can be taught to novices using an e-learning. The trainees all had at least some endoscopy experience. All fellows completed a test before (pre-test) and after (post-test) the LST training. Age, year of traineeship, number of colonoscopies performed (attended and unattended) and number of endoscopic resections performed were collected at the start of the pre-test (Step 5). The pre-test was identical with the test accomplished by the experts. The LST e-learning (Step 6) became available at least a week after completion of the pre-test and was available till the end of the study. The post-test (Step 7) became available at least one week after the completion of

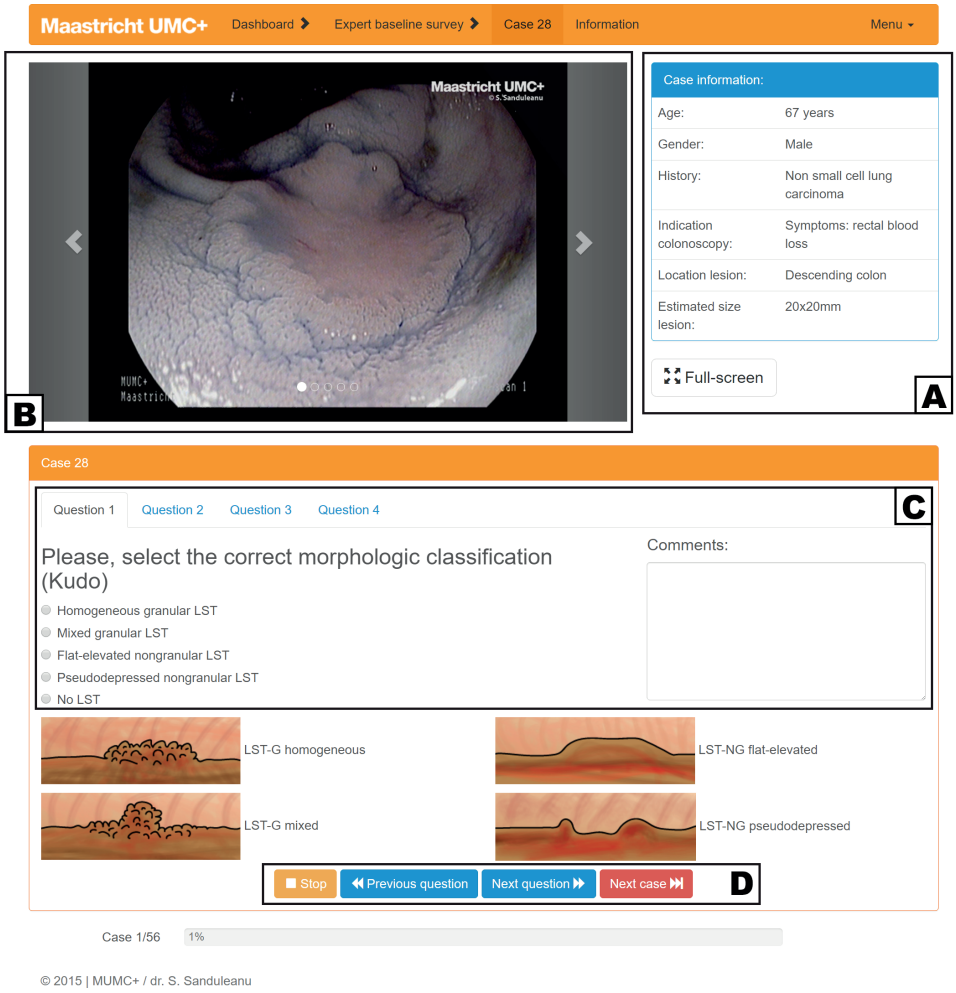

Figure 2.3: Screenshot of the web-based system. | *Area A displays information about patient and lesion. Area B displays multiple pictures. Area C presents four questions per case. Area D can be used to navigate through the questions, to stop the module (and continue at a later moment) and to proceed with the next case (only possible when all four questions are answered).*

the e-learning and contained the same cases as the pre-test, in a different order to limit recall bias.

Statistical analysis

We calculated the IOA among raters for endoscopic Kudo classification and Paris classification of LSTs using Fleiss kappa coefficients with 95% confidence intervals and Gwet's first order coefficients where appropriate.[16-18] In case of an unequal proportion of endoscopic subtypes, the Gwet's first-order agreement coefficient (AC1) is a more robust tool than the Fleiss kappa coefficient.[18] We examined difficulties in differentiation between subtypes by calculating the proportion of pairwise agreement.[9] To examine the spread of the agreement, Cohen's kappa coefficients between all possible pairs of expert raters were calculated. To compare performance between endoscopy fellows and experts, an overall expert opinion was calculated by using the most common answer. Concordance was calculated between endoscopy fellows and this extracted answer by presenting the proportion of matching answers.

We categorized the level of IOA according to Landis and Koch:[19] perfect agreement, almost perfect agreement, substantial agreement, moderate agreement, fair agreement, slight agreement and less than chance agreement (kappa coefficient: 1, 0.81-0.99, 0.61-0.80, 0.41-0.60, 0.21-0.40, 0.01-0.20 and <0 respectively). We performed sensitivity analysis to adjust for high impact of single raters. We used an adapted paired t-test to compare the agreement coefficients before and after training.[20] A Z-test was used to test differences in agreement between groups. *P* values ≤0.05 were considered significant. Statistics were performed using R statistics 3.2.2 for Microsoft Windows[21] with the 'kappaSize' module for sample size calculations[15, 22] and the R scripts of Advanced Analytics, LLC.[18, 20,23]

Table 2.1: Overview of the inter-observer agreement results among experts. | **Fleiss kappa coefficients which do not match with mean pairwise agreement and Gwet's AC1 score because of unequal proportion of categories.*

Feature	Gwet's AC1 [95% CI]	Fleiss kappa [95% CI]	Mean pairwise agreement
Kudo endoscopic classification	0.62 [0.55-0.69]	0.59 [0.58-0.61]	71.0%
Granular vs non-granular	0.75 [0.66-0.83]	0.74 [0.71-0.76]	87.1%
Per Kudo subtype:			
LST-G-H	-	0.56 [0.53-0.58]	-
LST-G-NM	-	0.76 [0.73-0.78]	-
LST-NG-FE	-	0.55 [0.52-0.57]	-
LST-NG-PD		0.53 [0.50-0.55]	

Table 2.1 *(continuation)*

Feature	Gwet's AC1 [95% CI]	Fleiss kappa [95% CI]	Mean pairwise agreement
Sensitivity analysis			
After exclusion of most influential rater:			
Kudo endoscopic classification	0.63 [0.57-0.70]	0.61 [0.60-0.63]	72.1%
Granular vs non-granular	0.77 [0.69-0.85]	0.76 [0.74-0.79]	88.3%
Per Kudo subtype:			
LST-G-H	-	0.58 [0.55-0.61]	-
LST-G-NM	-	0.76 [0.73-0.78]	-
LST-NG-FE	-	0.58 [0.55-0.60]	-
LST-NG-PD	-	0.55 [0.52-0.58]	-
High vs lower case image quality:			
High quality	0.67 [0.51-0.70]	0.66 [0.63-0.68]	74.9%
Lower quality	0.59 [0.50-0.68]	0.48 [0.46-0.50]	67.6%
First vs second half of cases:			
First half	0.61 [0.51-0.70]	0.56 [0.54-0.58]	69.7%
Second half	0.64 [0.55-0.73]	0.62 [0.60-0.64]	72.4%
After exclusion of SSA/Ps	0.59 [0.51-0.67]	0.60 [0.58-0.61]	69.0%
Influence of lesion size:			
10-19 mm	0.72 [0.61-0.82]	0.56 [0.53-0.59]	76.6%
20-29 mm	0.49 [0.38-0.59]	0.46 [0.43-0.49]	61.0%
≥30 mm	0.66 [0.55-0.77]	0.64 [0.62-0.67]	74.3%
West vs East:			
Kudo endoscopic classification: West	0.63 [0.55-0.71]	0.61 [0.58-0.64]	71.8%
Kudo endoscopic classification: East	0.71 [0.64-0.78]	0.61 [0.58-0.64]	73.5%
Paris Classification			
Paris complete	0.71 [0.65-0.78]	0.51 [0.49-0.52]*	73.8%
Paris 4 groups (IIa, IIa+c, IIa+Is and other)	0.71 [0.65-0.78]	0.52 [0.51-0.54]*	75.8%
Treatment			
Endoscopic resection vs surgery	0.94 [0.91-0.97]	0.11 [0.08-0.13]*	94.2%
All treatment options	0.63 [0.55-0.70]	0.32 [0.30-0.34]*	68.5%

Results

A total of 14 experts (7 Asian, 5 European, 1 American and 1 Australian) and 21 endoscopy fellows (10 MUMC+, 11 NTUH) participated. The LST cases comprised 50 adenomas, 18 sessile serrated adenomas/polyps and 4 early cancers.

Endoscopic classification of LSTs among experts

The overall IOA among experts for the endoscopic Kudo LST classification was moderate to substantial (Gwet's AC1 coefficient: 0.62, 95% CI: 0.55 – 0.69, **Table 2.1**). Full IOA was found in 16 cases (22.2%). In 15 cases only one rater disagreed (20.8%). After recoding the endoscopic Kudo classification into 2 categories (granular vs non-granular subtype), the IOA was substantial (Gwet's AC1 coefficient: 0.75, 95% CI: 0.66 – 0.83). Full IOA was found in 38 cases (52.8%). In 18 cases only one rater disagreed (25.0%).

Agreement differed by Kudo subtypes (**Table 2.1**). The overall mean pairwise agreement was 71.0% with the highest proportion of agreement pairs in the LST-NG-FE group (**Table 2.2**). Notably, of all possible pairs, 10.7% were discordant pairs between LST-NG-FE and LST-NG-PD and 9.6% were discordant pairs between LST-G-H and LST-NG-FE. The highest Cohen's kappa coefficient for the Kudo subtypes between expert raters was 0.81, while the lowest was 0.31 (median 0.61).

The overall IOA for the Paris classification was substantial (Gwet's AC1: 0.71, 95% CI: 0.65 – 0.78, mean pairwise agreement 73.8%). Full IOA was present in 20 cases (27.8%). In 15 cases only one rater disagreed (20.8%). After recoding the full Paris classification into 4 categories (0-IIa, 0-IIa+IIc, 0-IIa+Is and other), the IOA was consistent (Gwet's AC1: 0.71, 95% CI: 0.64 – 0.78) with a mean pairwise agreement of 75.8%. None of the LSTs were categorized as Paris 0-Ip or 0-Ips subtype of lesions. The free option was used only four times (2x 0-Is and 2x 0-Is+IIa).

Therapeutic plan

Almost perfect agreement was found between expert raters in selecting either endoscopic treatment (EMR or ESD) or surgery as most suitable treatment (Gwet's AC1 score: 0.94, 95% CI: 0.91 – 0.97; mean pairwise agreement: 94.2%). IOA when specifying endoscopic treatment into EMR and ESD as the most suitable treatment was moderate to substantial (Gwet's AC1 score: 0.63, 95% CI: 0.55 – 0.70; mean pairwise agreement: 68.5%). Most discordant pairs were found between the choices EMR vs ESD as most suitable treatment (25.6%). Rater's origin (West vs East) did not influence the agreement for endoscopic treatment vs surgery and EMR vs ESD (Gwet's AC1 0.64 vs 0.66).

Table 2.2: Overview of all observed answer pairs between all expert raters for all cases. | *A total of 6552 pairs of answer were given (14 raters can make 91 unique pairs [14 x 13 x ½] for each of the 72 cases [91 x 72 = 6552]). Pairs of agreement are marked in grey. For example: a random rater classified a case as LST-G-H while another random rater agreed 1042 times. The situation that a randomly chosen rater classified a LST as LST-G-H while another randomly chosen rater classified the LST as LST-G-NM happened 350 times, 5.3% of all 6552 observations.*

LST-G-H	1042	(15.9%)						
LST-G-NM	350	(5.3%)	999	(15.2%)				
LST-NG-FE	632	(9.6%)	107	(1.6%)	2010	(30.7%)		
LST-NG-PD	80	(1.2%)	28	(0.4%)	701	(10.7%)	603	(9.2%)
	LST-G-H		LST-G-NM		LST-NG-FE		LST-NG-PD	

Table 2.3: Overview of the inter-observer agreement results among fellows. | **Fleiss kappa coefficients which do not match with mean pairwise agreement and Gwet's AC1 score because of unequal proportion of categories.*

Feature	Gwet's AC1 [95% CI]			Fleiss kappa [95% CI]			Mean pairwise agreement	
	Pre-test	Post-test	*P* value	Pre-test	Post-test	*P* value	Pre-test	Post-test
Kudo endoscopic classification	0.43 [0.37-0.50]	0.59 [0.53-0.65]	<0.001	0.42 [0.42-0.44]	0.57 [0.56-0.59]	<0.001	57.4%	68.9%
Granular vs non-granular	0.63 [0.55-0.71]	0.81 [0.75-0.88]	<0.001	0.63 [0.62-0.65]	0.81 [0.79-0.82]	<0.001	81.5%	90.6%
Per Kudo subtype:								
LST-G-H	-	-	-	0.35 [0.33-0.37]	0.54 [0.52-0.55]	-	-	-
LST-G-NM	-	-	-	0.53 [0.51-0.55]	0.69 [0.68-0.71]	-	-	-
LST-NG-FE	-	-	-	0.43 [0.42-0.45]	0.59 [0.57-0.60]	-	-	-
LST-NG-PD	-	-	-	0.36 [0.35-0.38]	0.44 [0.42-0.45]	-	-	-
MUMC+ vs NTUH:								
MUMC+	0.41 [0.34-0.48]	0.58 [0.51-0.65]	<0.001	0.39 [0.37-0.41]	0.56 [0.53-0.59]	<0.001		
NTUH	0.47 [0.40-0.54]	0.60 [0.53-0.66]	<0.001	0.46 [0.43-0.48]	0.58 [0.55-0.60]	<0.001		
P value	0.233	0.754		<0.001	0.420			
Paris classification	0.33 [0.29-0.36]	0.45 [0.41-0.49]	<0.001	0.20 [0.20-0.21]*	0.30 [0.29-0.31]*	<0.001	39.3%	49.7%
Paris 4 groups (IIa, IIa+IIc, IIa+Is and other)	0.35 [0.31-0.39]	0.44 [0.39-0.49]	<0.001	0.23 [0.22-0.24]*	0.33 [0.32-0.34]*	<0.001	49.2%	56.3%

Factors influencing variation in classification among experts

A sensitivity analysis where the most influencing expert rater was excluded (statistically identified), showed comparable results (**Table 2.1**). Gwet's AC1 for the endoscopic Kudo classification was 0.63 (95% CI: 0.57 – 0.70).

The IOA for the endoscopic Kudo classification was similar for experts from East (SK, HMC, RS, HY, ST, TM, LCC) compared to those from West (AO, AS, MR, RK, TK, RS, SS) (*P*=0.520, **Table 2.1**). Overall, IOA on image quality was fair to moderate (Gwet's AC1: 0.35, 95% CI: 0.28 – 0.42; mean pairwise agreement: 51.8%). After recoding excellent and good quality as one category the IOA was almost perfect (Gwet's AC1: 0.85, 95% CI: 0.80 – 0.89; mean pairwise agreement: 86.8%). In 34 cases (47.2%) all observers agreed on the sufficient quality for analysis of that case.

The influence of the case order was also tested (first 36 vs second 36 cases) showing a Gwet's AC1 coefficient of 0.61 (95% CI: 0.51 – 0.70) and 0.64 (95% CI: 0.55 – 0.73) respectively. Excluding the 18 cases of SSA/Ps (14 predominantly scored as LST-NG-FE) resulted in a Gwet's AC1 coefficient of 0.59 (95% CI: 0.51 – 0.67); mean pairwise agreement: 69.0%. We examine the influence of lesion size on the assessment of the LSTs: Gwet's AC1 coefficients were 0.72 (95% CI: 0.61 – 0.82), 0.49 (95% CI: 0.38 – 0.59) and 0.66 (95% CI: 0.55 – 0.77) for LSTs of 10-19mm, 20-29mm and ≥30mm, respectively.

Table 2.4: Overview of all observed answer pairs, before and after training, between all fellow raters for all cases. **|** *A total of 15,120 pairs of answer were given (21 raters can make 210 unique pairs [21 x 20 x ½] for each of the 72 cases [210 x 72 = 15,120]). Pairs of agreement are marked in grey. For example: before training, a random rater classified a case as LST-G-H while another random rater agreed 1875 times. The situation that a randomly chosen rater classified an LST as LST-G-H while another randomly chosen rater classified the LST as LST-G-NM happened 1764 times before training, 11.7% of all 15,120 observations.*

A) Pre-test

LST-G-H	1875	(12.4%)						
LST-G-NM	1764	(11.7%)	2485	(16.4%)				
LST-NG-FE	1398	(9.2%)	516	(3.4%)	3070	(20.3%)		
LST-NG-PD	468	(3.1%)	410	(2.7%)	1886	(12.5%)	1248	(8.3%)
	LST-G-H		LST-G-NM		LST-NG-FE		LST-NG-PD	

B) Post-test

LST-G-H	1998	(13.2%)						
LST-G-NM	1255	(8.3%)	2604	(17.2%)				
LST-NG-FE	774	(5.1%)	157	(1.0%)	4332	(28.7%)		
LST-NG-PD	275	(1.8%)	220	(1.5%)	2025	(13.4%)	1480	(9.8%)
	LST-G-H		LST-G-NM		LST-NG-FE		LST-NG-PD	

Endoscopic classification of LSTs before and after training in fellows

Before training, the IOA for the endoscopic Kudo LST classification among endoscopy fellows was fair to moderate (Gwet's AC1 coefficient: 0.43, 95% CI: 0.37 – 0.50, **Table 2.3**). Full agreement was present in 4 cases, while in 4 cases only 1 rater disagreed. The overall mean pairwise agreement was 57.4%, with the highest proportion discordant pairs between LST-NG-FE and LST-NG-PD (12.5%) and between LST-G-H and LST-G-NM (11.7%, **Table 2.4a**). After recoding the endoscopic Kudo classification into 2 categories (granular vs non-granular subtype), the IOA was also moderate to substantial (Gwet's AC1 coefficient: 0.63, 95% CI: 0.55 – 0.71; Fleiss kappa: 0.63, 95% CI: 0.62 – 0.65) with a pairwise agreement of 81.5%.

After training, the IOA for the endoscopic Kudo LST classification among endoscopy fellows significantly increased (Gwet's AC1 coefficient: 0.59, 95% CI: 0.53 – 0.65, $P<0.001$). Full agreement was now present in 6 cases, while in 14 cases only 1 rater disagreed. The Fleiss kappa of all four LST subtypes increased after training (**Table 2.3**). The overall mean pairwise agreement increased to 68.9%, with the highest proportion discordant pairs between LST-NG-FE and LST-NG-PD (13.4%) (**Table 2.4b**). After recoding endoscopic Kudo classification into granular vs non-granular, the IOA increased to substantial/almost perfect agreement (Gwet's AC1 coefficient: 0.81, 95% CI: 0.75 – 0.88) with a pairwise agreement of 90.6%. IOA for the Paris classification also statistically improved after training ($P<0.001$).

Before training, a small, non-significant difference in agreement between fellows of the MUMC+ and NTUH existed: Gwet's AC1 0.41 (95% CI: 0.34 – 0.48) vs 0.47 (95% CI: 0.40 – 0.54) respectively ($P=0.223$). After training, the Gwet's AC1 value was similar: 0.58 for the MUMC+ (95% CI: 0.51 – 0.65) vs 0.60 for the NTUH (95% CI: 0.53 – 0.66) ($P=0.754$). Mean age was slightly higher among the NTUH fellows: 31.4 years (MUMC+, SD: 1.5) vs 33.3 years (NTUH, SD: 1.8) ($P=0.019$). Furthermore, the fellows in the NTUH had performed more colonoscopies under supervision (Modus 1-500 in MUMC+ and >2000 in NTUH, $P=0.004$) and unattended (Modus 0-500 in MUMC+ and 501-1000 in NTUH, $P<0.001$) than the fellows of the MUMC+. Finally, NTUH fellows were also more experienced with endoscopic resections (Modus 0 in MUMC+ and 1-20 in NTUH, $P=0.004$).

Initially, endoscopy fellows had 68.1% concordance with the overall expert opinion in the endoscopic Kudo classification (see **Table 2.5**). For determining granularity vs non-granularity, the concordance was 87.3%. After the training, the concordance with the experts on endoscopic Kudo classification became 76.5% and for granular vs non-granular status 93.1%. Both before and after training, the endoscopy fellows had most concordant pairs with the cases that the experts classified as LST-G-NM. The largest improvement after training was for the LST-NG-FE cases: from 64.4% to 77.3% accordance. Regarding endoscopy fellows, the concordance with experts increased for 17 raters, remained stable for one rater and decreased for three raters after training (see **Figure 2.4**).

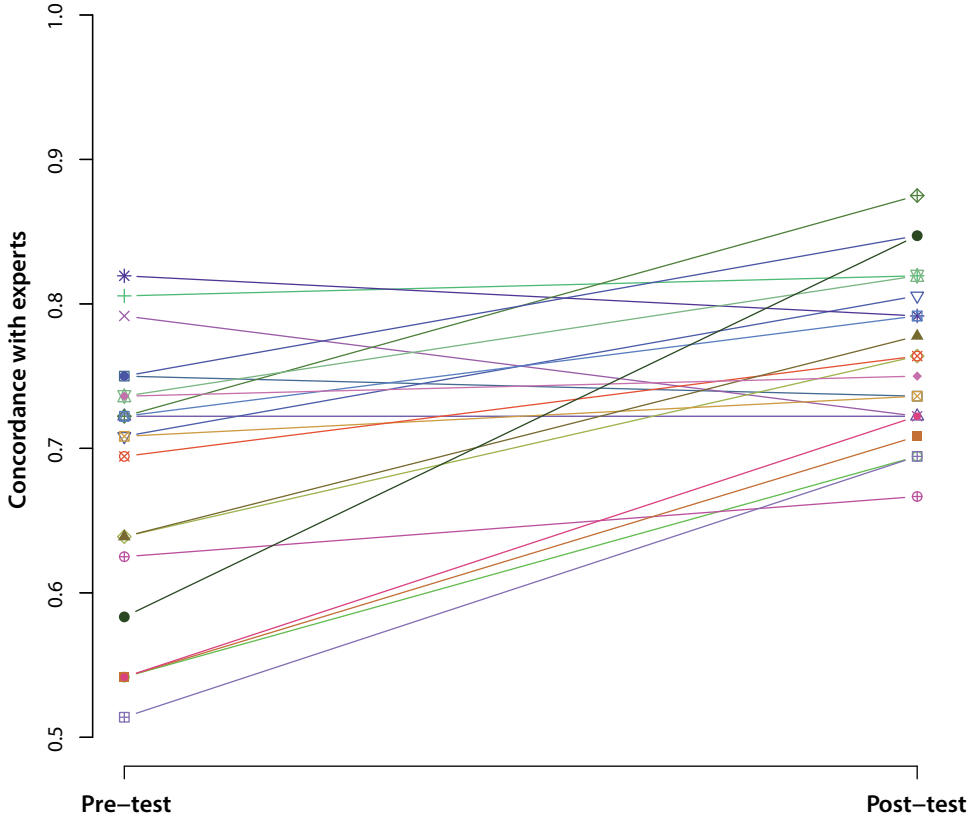

Figure 2.4: Plot showing the concordance rates for the endoscopic LST Kudo classification of all trainees before and after the LST e-learning. | *Each trainee is displayed with a different symbol (color).*

Table 2.5: Concordance of endoscopy trainees compared to overall experts' opinion on the endoscopic Kudo classification.

Feature	Pre-test	Post-test
Endoscopic Kudo LST classification	68.1%	76.5%
Granular / non-granular	87.3%	93.1%
LST-G-H	67.2%	71.1%
LST-G-NM	80.3%	87.6%
LST-NG-FE	64.4%	77.3%
LST-NG-PD	62.3%	67.1%

Discussion

This is the first study to test the validity of the endoscopic Kudo classification of LSTs in a group of colonoscopy experts and endoscopy fellows. There is moderate to substantial IOA in applying the endoscopic Kudo classification and in classifying LSTs as granular vs non-granular subtype among international experts. Because the risk of containing SMI in endoscopic subtypes of LST varies considerably, correct classification of LSTs is an essential step in selecting the preferred therapy to optimize the patient outcome.

Moderate to substantial agreement was found between experts on both full endoscopic Kudo classification and on classifying LSTs into granular and non-granular. However, the Gwet's AC1 value was higher for the granular/non-granular classification than for the endoscopic Kudo classification (0.75, 95% CI: 0.66 – 0.83 vs 0.62, 95% CI: 0.55 – 0.69). This may indicate that it is easier to distinguish granular LSTs from non-granular LSTs than recognizing the presence/absence of a dominant nodule or depression within granular and non-granular LSTs. The highest proportion of discordant pairs was observed between flat and pseudo-depressed non-granular LSTs (10.7%). Thus, experts had most disagreement in recognizing pseudo-depressions within non-granular LSTs.

Endoscopy trainees pursued the specifically designed e-learning on endoscopic Kudo classification. Their IOA improved significantly with kappa values approaching those of the experts. Such training helps to implement the Kudo classification into clinical practice. Although training significantly improved the Gwet's AC1, it remained in the moderate range. As with the experts, classifying LSTs into granular and non-granular resulted in higher IOA: substantial agreement before training with almost perfect agreement after training. In a significant proportion of cases, discordant pairs between LST-G-H and LST-NG-FE were found (9.6% for experts and 9.2% for fellows [before training]). Training effectively improved granular recognition, since only 5.2% of all observations were discordant pairs between LST-G-H and LST-NG-FE after training. The highest rate of discordant pairs was seen between flat elevated and pseudo-depressed non-granular LSTs, both before and after training, confirming the observation in the expert group. Furthermore, the proportion of discordant pairs between LST-G-H and LST-G-NM decreased after training, indicating that training made the recognition of a dominant nodule easier.

For each individual case concordance of answers between endoscopy fellows and experts as group could be interpreted as diagnostic accuracy, assuming that the opinion of the majority of experts is the reference. Initially, 68.1% of the cases scored by endoscopy fellows were correctly classified according to the overall expert's decision. This increased to 76.5% after training, but still almost a quarter of all trainee ratings were misclassified according to the experts' rating. Again, after recoding into only granular/non-granular LSTs, the concordance increased (87.3% pre-training and 93.1% post-training). It is obvious that not only within but also between the rater groups (experts and endoscopy fellows), the largest disagreement exists in determining whether pseudo-depression is present.

A Korean multicenter study examined the IOA of the full endoscopic Kudo classification of LSTs in experts and trainees.[11] Without special LST training, the Fleiss kappa coefficient for IOA was 0.73, comparable to the present study, with the highest agreement in the LST-G-NM category. The untrained fellows had a significantly lower IOA than experts (kappa coefficient: 0.55 vs 0.73). In the present study we showed that training increased the level of IOA among trainees almost reaching that of the experts. The higher overall Fleiss kappa coefficient in the Korean study could have been the result of including raters from the same academic center or centers from the same geographic region. Previous exchanges and communication between centers could have improved the IOA in

classifying LSTs in the Korean study.

In a Japanese study the ability to differentiate between three granular LST subtypes was tested in highly experienced endoscopists, less experienced endoscopists and students.[12] While the experts showed an almost excellent agreement (kappa coefficient: 0.84) when using chromoendoscopy images, the endoscopists often disagreed whether LST-G had small or large nodules.[12] White light images showed lower IOA (kappa: 0.78). The overall high IOA in this Japanese study could be partially explained by the fact that only LST-G cases were included.

A Dutch study of the IOA of the Paris classification in 7 expert raters showed a pre-training Fleiss kappa coefficient of 0.42 (95% CI: 0.38 – 0.46) with a pairwise agreement of 67%.[9] After a short training, the Fleiss kappa coefficient was 0.38 (95% CI: 0.35 – 0.41). A large proportion of the neoplasms were smaller than 10mm, which makes differentiation more difficult. Recoding the answers to polypoid and non-polypoid neoplasms did not improve the agreement (Fleiss kappa: 0.43). In contrast to our study, that study included video clips of all Paris subtypes of colorectal neoplasms. The distribution of categories was unequal, though. In the present study, only LSTs were included, which limited the number of relevant Paris categories by definition rendering the distribution of answers again unequal. To mitigate this factor, in our study we used the Gwet's AC1 estimation in calculating the kappa coefficients for IOA since it is a more appropriate estimator than the Fleiss kappa coefficient in case of unequal proportions.[18] This could explain the higher IOA coefficient in the present study (0.71 vs 0.42). It should be taken into account that the Paris classification has no category for LSTs, and valuable information about surface structure of LSTs (granular vs non-granular) cannot be retrieved, which hinders the colonoscopist to predict the risk of submucosal invasion (SMI). In contrast to the Kudo classification, the Paris classification has been widely implemented in endoscopy practice. We suggest considering amendment of the Paris classification with granularity status for large NP-CRNs.

An important finding of the present study is the almost perfect agreement (Gwet's AC1: 0.94) between experts on primary treatment of LSTs by either endoscopy or surgery. The agreement on type of endoscopic resection (i.e. EMR, ESD, or 'other endoscopic treatment') was moderate (Gwet's AC1: 0.63). Even among experts in Japan, selection of endoscopic treatment by either EMR or ESD on the same neoplasm may differ significantly and is still under debate.[5] The LST Kudo subtypes are increasingly applied in practice to determine the optimal treatment strategy.[6] Treatment strategy depends on biological factors (risk of SMI and lymphovascular invasion) and technical factors (lesion location and size, patient's comorbidity and preference and endoscopist's expertise). Patients with low risk early CRCs (well or moderate differentiated adenocarcinoma with absence of lymphovascular invasion, invasion depth of less than 1000μm and with negative vertical margins) can be safely treated endoscopically with low risk of recurrences (0.8%).[24] The prevalence of SMI differs among the subtypes with low risk for the LST-G-H and high risk for the LST-NG-PD.[3, 4, 15] Non-granular LSTs, and in particular the LST-NG-PD, have often multifocal invasion and fibrosis.[25] When LST-G-NM contains SMI, this is mostly at the basis of a dominant nodule.[25] So the endoscopic Kudo classification of LSTs can provide important information for endoscopic resection and is the first step in diagnosis. A high IOA for LST classification will help standardizing the treatment. In addition, detailed inspection of pit pattern using chromoendoscopy and magnifying colonoscopes helps to identify invasive areas and predict histology with high accuracy.[26, 27] Combined use of endoscopic Kudo classification and the Kudo pit pattern of the epithelial surface improves the prediction of SMI in LSTs which in turn will improve the agreement in selection of the best therapy.

Some methodological aspects should be acknowledged. To our knowledge, this is the first

international study on IOA of endoscopic classification of LSTs in the colon and rectum. To simulate the real-life practice, we assembled a systematic case-collection of LSTs. For didactic purpose, only high-quality images were used. We developed a case-based system for LST classification with e-learning and validated it among endoscopy fellows at two different centers. This educational program had significantly improved the performance of endoscopy trainees and can now be used worldwide. It should be taken into account that the durability of the learning effect has not been assessed in the present study.

The effect of not using chromoendoscopy on the IOA of the endoscopic Kudo classification remains unknown, although we expect the IOA to be lower. Chromoendoscopy is not commonly used in all centers worldwide, but is advised by experts for lesion characterization.[28] In the present study, only images of chromoendoscopy with contrast dye were used. The effect of using digital chromoendoscopy instead of dye chromoendoscopy on the IOA of the endoscopic Kudo classification remains to be clarified. Because the availability of ESD differs among centers, both experts' and trainees' views on most suitable resection technique could have been biased.

In this study, we compared the IOA of the fellows for LST classification with that of experts, who were considered to be the reference. Because of the lack of a gold standard, diagnostic accuracy could not be calculated. The IOA of the endoscopic Kudo LST classification was examined instead. Intraobserver agreement (the consistency in scoring of individual raters in a single case) could not be assessed because of single measurements. The use of short endoscopy movies showing the LST instead of still images could further improve the classification. Of note, IOA was lower in the cases scored as 'of insufficient quality' by at least one rater. Future studies should use high-definition endoscopy movies that mimic real life better.

A more objective assessment method to identify pseudo-depressions, dominant nodules, and subtle granules may help to improve the IOA of the endoscopic Kudo LST classification. Identification of a dominant nodule may become more straightforward when using 5mm as cut off for a dominant nodule, as suggested by the study of Shigita et al.[12] The risk of SMI is leading in the treatment strategies[1] and is higher for LST-G with dominant nodules of at least 5mm. Small granules may be difficult to distinguish with standard colonoscopy while dye-based chromoendoscopy provides more detail. Notably, recognition of pseudo-depression remains a challenge for both experts and (trained) endoscopy fellows.

Conclusion

In summary, our study confirms that the Kudo endoscopic classification of LSTs is a practical tool. Substantial IOA was found for classification of LSTs among international experts. A specific designed e-learning significantly improved the IOA among fellows. Training of endoscopists in applying the endoscopic Kudo classification is a meaningful first step in improving endoscopic treatment of LSTs.

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Endoscopic subtypes of colorectal laterally spreading tumors and risk of submucosal invasion: A meta-analysis

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Abstract

Background and study aims

Many studies have reported on laterally spreading tumors (LSTs), but systematic reviews of the data to determine their risk of containing submucosal invasion (SMI) are lacking. We systematically screened and analyzed the available literature to provide a more solid basis for evidence-based treatment.

Methods

We conducted a systematic search in PubMed, Embase, the Cochrane Library, and Scopus for published articles until July 2017. We estimated pooled prevalence or odds ratios (ORs) with 95% confidence intervals (CIs), using random effects models. We classified endoscopic subtypes into LST-*granular* (LST-G), which comprises the homogeneous (LST-G-H) and nodular mixed (LST-G-NM) subtypes and LST-*non-granular* (LST-NG), which comprises the flat elevated (LST-NG-FE) and pseudo-depressed (LST-NG-PD) subtypes.

Results

We identified 2949 studies, of which 48 were included. Overall, 8.5% (95% CI: 6.5 – 10.5%) of LSTs contained SMI. The risk of SMI differed among LST subtypes: 31.6% in LST-NG-PD (95% CI: 19.8 – 43.4%), 10.5% in LST-G-NM (95% CI: 5.9 – 15.1%), 4.9% in LST-NG-FE (95% CI: 2.1 – 7.8%) and 0.5% in LST-G-H (95% CI: 0.1 – 1.0%). SMI was more common in distally rather than in proximally located LSTs (OR 2.50, 95% CI: 1.24 – 5.02). The proportion of SMI increased with lesion size (10-19mm: 4.6%; 20-29mm: 9.2%, ≥30mm: 16.5%). The pooled prevalence of patients with one or more LSTs in the general colonoscopy population was 0.8% (95% CI: 0.6 – 1.1%).

Conclusion

The majority of LSTs are non-invasive at the time of colonoscopic detection and can be treated with (piecemeal) endoscopic mucosal resection. Pretreatment diagnosis of endoscopic subtype, specifying areas of concern (nodule or depression) determines those LSTs at highest risk of containing SMI, where en-bloc resection is the preferred therapy.

Introduction

Large flat-appearing neoplasms, also known as laterally spreading tumors (LSTs)[1] constitute an important contributor to post-colonoscopy colorectal cancer.[2] Endoscopic diagnosis and resection of LSTs is known to be technically difficult.[3, 4] The European Society of Gastrointestinal Endoscopy (ESGE) guidelines on colorectal polypectomy and the British Society of Gastroenterology guidelines for the management of large non-pedunculated colorectal neoplasms state that most colorectal neoplasms can be treated with (piecemeal) endoscopic mucosal resection (EMR).[5, 6] Endoscopic resection should be safe and performed with a minimum number of pieces. If superficial submucosal invasion (SMI) is suspected, en-bloc resection should be the therapy of choice. En-bloc resection for superficial neoplasms larger than 20mm can be achieved by endoscopic submucosal dissection (ESD).[7]

The most effective LST treatment strategy is still under debate. An Australian multicenter study showed that piecemeal EMR is an effective treatment in most cases of flat and sessile neoplasms ≥20mm.[8] After initially successful EMR, 98.1% of the patients were free of adenoma and did not require surgery. A Japanese study from a centre experienced in ESD showed that granular LSTs with a dominant nodule and non-granular LSTs with a pseudo-depression are associated with a substantial risk of SMI (19 and 39% respectively) which was multifocal in 16 and 45%, respectively. This group suggested that en-bloc endoscopic resection is the preferred therapy in such cases.[9]

Although clinical practice guidelines acknowledge substantial differences in the risk of SMI between different LST subtypes, the therapeutic implications are unclear. A large number of studies have examined the risk of LSTs containing SMI, but no meta-analysis of the data is currently available. We performed a systematic review with meta-analysis to determine endoscopic predictors of increased risk of SMI in LSTs in order to provide a more solid basis for evidence-based therapy.

Methods

We conducted and reported this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[10] We employed an a priori established protocol[11] which is available on request.

Definitions

The term 'laterally spreading tumor' defines a laterally growing superficial neoplasm (instead of upward or downward growth) of at least 10mm in size.[1] The term 'superficial neoplasm' relies on macroscopic assessment and refers to lesions that are non-invasive in appearance.[12] Superficial neoplasms can contain low grade dysplasia, high grade dysplasia (HGD) or submucosal invasion (SMI) which are amenable to endoscopic resection. The term 'non-polypoid' is defined as a lesion with a height less than half of its diameter[13] or as a lesion with protrusion <2.5mm above the mucosa.[14, 15] We used the WHO classification for histopathology.[16] Intramucosal carcinoma was coded as adenomatous HGD.

LSTs were subclassified using the endoscopic Kudo classification (which should not be confused with the Kudo pit-pattern classification) into LST-granular (LST-G), which comprises the homogeneous (LST-G-H) and nodular mixed (LST-G-NM) subtypes, and LST-non-granular (LST-NG), which comprises the flat elevated (LST-NG-FE) and pseudo-depressed (LST-NG-PD) subtypes

(**Figure 3.1**).[1] The homogenous granular and flat elevated non-granular LST subtypes correspond with the Paris 0-IIa subtype, the nodular mixed granular LST subtype consists of a combination of the Paris 0-IIa and 0-Is subtypes, and the pseudodepressed non-granular LST subtype consists of a combination of the Paris 0-IIa and 0-IIc subtypes.[15]

Information sources

Before starting the study, the reviewers (RB, MV, LS) were trained in designing search queries by an experienced medical research librarian. We included all original publications (English language) reporting on LSTs up to 1 July 2017. We searched PubMed, Embase, Scopus, and Cochrane Library with MeSH (colorectal neoplasms) and non-MeSH terms: (lateral* spreading tumor OR LST OR non polypoid OR ((nonpolypoid OR non-polypoid OR flat) AND (tumor OR lesion OR neoplas* OR adenoma OR cancer OR carcinoma*))) AND (colorectal OR colon OR colonic). Given the heterogeneity in the definition of an LST, the search terms and the hierarchy were selected to capture all relevant studies (highest sensitivity with lower specificity). Because of the detailed information needed for

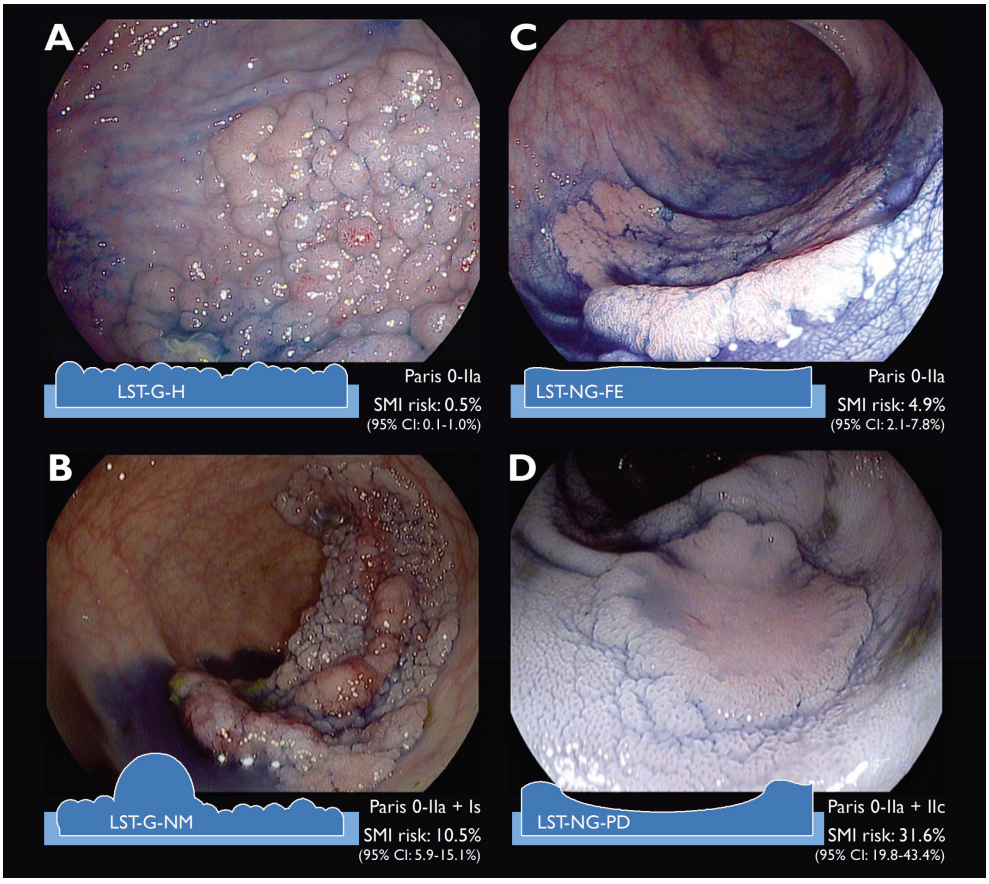

Figure 3.1: Endoscopic images of the four endoscopic Kudo LST subtypes. | *Together with a schematic overview of these lesions showing: A, granular homogenous LST (Paris IIa); B, granular nodular mixed LST (Paris IIa+Is); C, non-granular flat elevated LST (Paris IIa); D, non-granular pseudo-depressed LST (Paris IIa+IIc).*

this systematic review, we did not include abstracts and conference proceedings. A cross-reference check of the retrieved articles was performed to identify additional publications. When further information from original studies was needed, the authors were contacted.

Study selection

Selection of articles based on title and abstract was performed by one reviewer (RB) and checked by a second reviewer (MV or LS). The full text articles were then reviewed. Eligible studies to calculate pooled prevalence of LSTs were those reporting the population size, number of patients with at least one LST, and total number of patients with at least one colorectal neoplasm; studies to calculate the risk of SMI were those reporting the total number of consecutively diagnosed LSTs and their histopathology. Population-based studies reporting histopathological outcomes were included in both analyses. We excluded studies in selected populations (e.g. patients with inflammatory bowel disease or hereditary CRC syndromes), studies including only consecutive cases referred for surgery or ESD, and those primarily designed as reviews or editorials. For studies where there was any suspicion of cohort overlap between publications, the publication with the most extensive data was used. In particular, this applied to the Australian Colonic Endoscopic Mucosal Resection (ACE) study[17, 18] and the Flat Lesions Italian Network (FLIN) study.[19] Disagreements were resolved through discussion with the study coordinator (SS).

Data extraction

The reviewers independently extracted the following information onto standardized paper forms: author; country; publication year; enrollment period; duration of enrollment; setting (primary or referral center); study design (retrospective vs. prospective study); definitions of a laterally spreading tumor (LST); eligibility of the study for analyses (prevalence estimates vs malignancy risk); mean/median age of the patients with LSTs; sex distribution; total number of patients examined; number of patients with at least one LST; number of patients with at least one colorectal neoplasm; number of LSTs; endoscopic features of each LST (location, size, endoscopic subtype) and their histopathology.

Assessment of methodological quality

To assess study quality and the potential risk of bias in individual studies, we used criteria derived from the Loney scale for prevalence studies,[20] in conjunction with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[21] The studies included in this meta-analysis have features of both population-based and diagnostic accuracy studies, rendering the Loney scale and QUADAS-2 criteria as the most suitable for quality assessment. Risk of bias comprises the risk of population bias and risk of outcome bias. For population bias, we assessed whether the study used a general colonoscopy population, whether the sampling frame was unbiased and whether adequate exclusion criteria had been used. An overall assessment of the risk of bias was provided (high vs low). For outcome bias we assessed whether the study examined LSTs as a primary outcome, whether complete colonoscopy was used for diagnosis, whether the endoscopists and pathologists were unbiased and whether the majority of the lesions found had been histopathologically analyzed (>90% of all lesions). Again, an overall assessment of the risk of bias in the outcome measurements was provided (high vs low).

Statistical analysis

All pooled prevalence rates and odds ratios (ORs) along with a 95% confidence interval (CI) were

calculated using random effect models. We used the R statistical program version 3.2.2 to process all the collected data.[22] Using raw numbers from the included articles and a binomial distribution, the prevalences and their 95% CIs were calculated per study. A random-effects model with DerSimonian-Laird estimator, which takes into consideration both within and between study heterogeneity, was applied to the raw proportions and odds ratios using the Metafor package version 1.9.[23] For the pooled prevalence of LSTs, a double arc-sinus correction was applied (Freeman-Tukey). [24] This method adjusts for variance instability in situations of low prevalence. After correction, the results were converted to the original proportion scale for interpretation. Heterogeneity was tested with the Q test for significance and with the inconsistency index (I^2), where a value of >50% was considered as substantial heterogeneity between studies. Funnel plots with Egger's test for asymmetry were constructed to test the possible effect of publication bias.[25] Additionally, sensitivity analyses were performed after exclusion of studies with a high risk of bias. Potential effect modification of

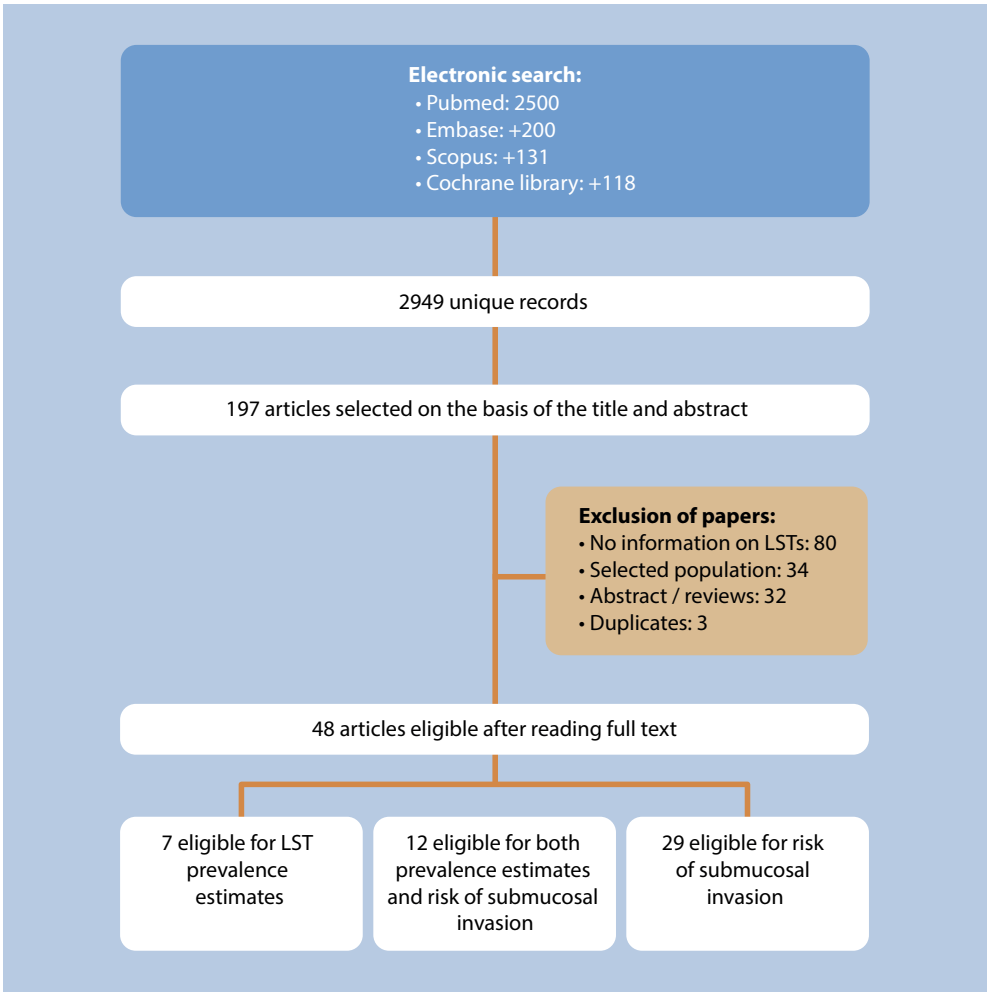

Figure 3.2: Flow-chart of the search, and inclusion and exclusion of articles on prevalence and submucosal invasion in LSTs.

geographical region (studies from East Asian countries and Western studies) and starting year of inclusion was tested by adding these variables to the models mentioned before. A two-sided *P* value ≤0.05 was considered statistically significant.

Results

A total of 2949 unique articles were identified (**Figure 3.2**). Based on title and abstract, we selected 197 articles for full text examination and included 48 studies in this meta-analysis. Of these, 19 were population based studies[19, 26-43] (1398 LST patients with 2663 LSTs) and 29 were lesion-based (**Figure 3.3**).[1, 9, 17, 44-69] Twelve studies qualified as both population- and lesion-based studies.[19, 26, 30, 32-34, 36, 37, 39-41, 43] **Table 3.1** shows an overview of the eligible studies used to calculate the pooled prevalence of LSTs and pooled risk of SMI. Two studies reported only the largest lesion per patient[26, 29]. Among the population-based studies, eight were Asian,[26, 27, 30, 32-34, 36, 38] eight were European[19, 29, 35, 37, 39, 41-43] and three were American studies.[28, 31, 40] In all studies, LST subtypes were classified using conventional chromoendoscopy (where specified). Five studies additionally used digital chromoendoscopy.[19, 31, 49, 50, 70]

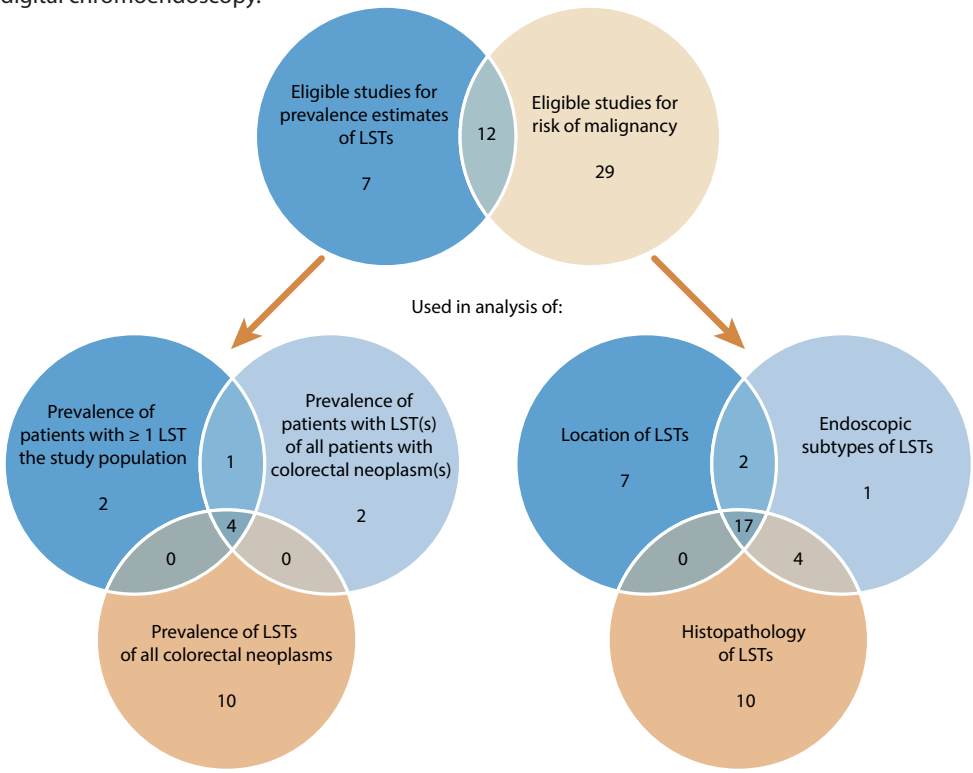

Figure 3.3: Overview of the studies used for the various calculations. | *Note: 31 studies (10+17+4) provided information about LST histology. Of these 31 studies, 26 were used for SMI rate (**Figure 3.8a**), one study was only used for HGD rate (**Figure 3.8b**) and four studies were only used for SMI rate of LSTs ≥20mm (**Figure 3.12**). Of the 31 studies, 21 (17+4) reported histopathology data and endoscopic LST subtypes. Of these 21 studies, 15 provided the SMI rate in LST-G vs LST-NG (**Figure 3.9**), and seven of these provided the SMI rate for the endoscopic Kudo subtype.*

Table 3.1: Overview of all included studies.

Study		Prevalence estimates			LST features			LST definition							
		Prevalence of LSTs	Prevalence of patients with LSTs in neoplasm(s)	Prevalence of LSTs of all neoplasms	Location	Endoscopic subtype	Histology	LST term used	Serrated lesions excluded	Study design	Inclusion criteria	Exclusion criteria	Duration of study (years)	Age of the study population (years)	Males (%)
Katano	**2017**				•			•	o	R	Therapy (ESD)	NA	3	NA	NA
Burgess	**2017**						•	•	o	P	Therapy (EMR), LSTs ≥20mm	NA	8	Mean 67.7*	53.2% *
Yamada	**2016**				•			•	•	R	Therapy (ESD, surgery)	FAP, IBD	11	Mean 66	55.8%
Kudo	**2015**				•	•	•	•	•	R	Therapy (all)	IBD	8	Mean 66.2	65.0%
Zhao	**2014**	•			•	•	•	•	o	P	All indications	FAP,IBD,SPS	10½	Median 62	56.0%
Xiang	**2014**			•				o	•	R	Therapy (EMR, ESD)	FAP, IBD, SPS, Lynch syndrome, colonic resection	2	?	65.4%
Togashi	**2014**						•	•	•/o	P	All indications, LSTs ≥20mm	NA	2	Mean 66.6	68.2%
Miyamoto	**2014**					•	•	•	•	R	Therapy (all)	FAP, IBD	5	Median 68	63.1%
Konda	**2014**				•	•		•	•	P	Therapy (all)	FAP, IBD, Lynch syndrome	NA	Mean 68.1	62.7%

Table 3.1: (continuation)

Dos Santos	**2014**			•				•	•	P	All indications	IBD, SPS, previous resections, incomplete colonoscopy, inappropriate bowel prep.	5	NA	NA
Yoon	**2013**				•			•	•	R	Therapy (ESD)	NA	3½	Mean 63.8	60.4%
Urban	**2013**				•	•	•	•	o	P	Therapy (EMR)	Previous treatment, polyposis syndromes	1	Mean 66.1	64.6%
Reinhart	**2013**	•	•					o	o	R	Screening	Symptoms, surveillance	4	Median 60.6	49.0%
Kim	**2013**		•		•	•	•	•	o	R	Therapy (all)	NA	6½	Mean 65.0	60.1%
Kakugawa	**2013**				•			•	•	R	NA	NA	4½	Median 64	54.8%
Terasaki	**2012**						•	•	o	R	Therapy (EMR, ESD) ≥20mm	NA	3¾	Mean 67.5	57.7%
Nakae	**2012**				•	•	•	•	•	R	Therapy (all)	FAP, IBD, Lynch syndrome, multiple CRC	NA	Mean 68.7	55.7%
Martínez	**2012**		•					•	o	P	All indications	Incomplete colonoscopy, inappropriate bowel prep.	5	NA	NA
Kim	**2012**				•	•	•	•	•/o	R	Therapy (EMR)	NA	7	Mean 61.8	74.0%
Rotondano	**2011**	•	•	•	•	•	•	•	o	P	All indications	Incomplete colonoscopy, inappropriate bowel prep., known polyp	¼	Mean 61.2 (SD 14.4)	52.2%
Kim	**2011**		•		•	•	•	•	•/o	R	Therapy (all)	NA	3	Mean 62.5	58.2%

Table 3.1: *(continuation)*

Study		Prevalence estimates			LST features			LST definition							
		Prevalence of LSTs	Prevalence of patients with LSTs in neoplasm(s)	Prevalence of LSTs of all neoplasms	Location	Endoscopic subtype	Histology	LST term used	Serrated lesions excluded	Study design	Inclusion criteria	Exclusion criteria	Duration of study (years)	Age of the study population (years)	Males (%)
Kaku	**2011**			•	•	•	•	•	•	P	Screening	FIT+ patients	5¾	Mean 58.1	43.1%
Kaji	**2011**				•	•	•	•	•	P	Therapy (EMR, ESD)	FAP, IBD, Lynch syndrome	4½	Mean 68.9	65.3%
Sugimoto	**2010**				•			•	o	P	Therapy (ESD)	FAP, IBD, Lynch syndrome	1	Mean 65.8	59.3%
Matsuda	**2010**			•			•	•	•	R	Therapy (all)	NA	5 ¼	Mean 63.4 (SD 9.9)	70.9%
Bustamante-Balén	**2010**			•				•	o	P	All indications	FAP, IBD, SPS, history of CRC, previous resection	1 ½	Mean 62	47%
Oka	**2009**					•	•	•	•/o	R	Therapy (?)	NA	17½	NA	NA
Huang	**2009**				•	•	•	•	•	R	Therapy (all)	FAP, IBD	7	Mean 59	61.5%
Chiu	**2009**	•	•	•	•	•	•	•	•	P	Screening	NA	2	Mean 51.2	55.8%
Urban	**2008**				•	•	•	•	o	R	Therapy (EMR)	NA	4	NA	NA
Tantau	**2008**	•	•	•	•	•	•	•	•	P	All indications	FAP, IBD, Lynch syndrome	1	Mean 62.5	58.3%

Table 3.1: *(continuation)*

Nosho	**2008**				•	•		•	•	R	Therapy (all)	FAP, Lynch syndrome	NA	Mean 67	57.9%
Kudo	**2008**					•	•	•	•	P	Therapy (?)	NA	22	NA	NA
Kil Lee	**2008**			•				o	•	P	All indications	NA	7	Mean 58.7 (SD 10.4)	70.1%
Kaltenbach	**2007**				•			o	•	R	Therapy (EMR)	NA	5	NA	NA
Uraoka	**2006**				•	•	•	•	•	R	Therapy (all)	FAP, IBD, precious history of CRC	4	NA	NA
Parra-Blanco	**2006**	•	•	•			•	o	•	R	All indications	FAP, IBD, Lynch syndrome	2½	Mean 62.5 (SD 13.3)	61.1%
Katsinelos	**2006**				•	•	•	•	•	R	Therapy (EMR, surgery)	NA	8	Mean 66.5	38.1%
Hiraoka	**2006**					•		•	•	P	Therapy (EMR, surgery	FAP, IBD, Lynch Syndrome	1½	Median 66*	67.9%
Su	**2005**						•	•	•	R	Therapy (EMR)	NA	3	Mean 54.5*	61.7%
O'Brien	**2004**			•			•	o	•	R	Therapy (all)	FAP, IBD, history or CRC or previous polypectomy	9½	Mean 62	73.0%
Kim	**2003**				•	•	•	o	•	R	All indications	NA	5½	Mean 60.6*	72.4%
Tsuda	**2002**			•			•	o	•	P	All indications	FAP, IBD, Lynch syndrome	2	Mean 67.5*	50.7%
Tanaka	**2001**						•	•	•/o	P	Therapy (all), LSTs ≥20mm	NA	NA	NA	NA
Saito	**2001**				•			•	•	R	Therapy (all)	NA	10½	Mean 65	59.9%
Rembacken	**2000**			•				o	•	P	All indications	Incomplete colonoscopies	3¾	Mean 59	41.2%

Table 3.1: *(continuation)*

Study		Prevalence estimates			LST features			LST definition								
		Prevalence of LSTs	Prevalence of patients with LSTs in neoplasm(s)	Prevalence of LSTs of all neoplasms	Location	Endoscopic subtype	Histology	LST term used	Serrated lesions excluded	Study design	Inclusion criteria	Exclusion criteria	Duration of study (years)	Age of the study population (years)	Males (%)
Teixeira	**1996**					•	•	•	•	P	Therapy (all)	NA	2	NA	NA
Jaramillo	**1995**			•			•	○	○	P	All indications	FAP, IBD, Lynch syndrome	1	Mean 62	43.1%

*P: Prospective; R: Retrospective; All indications: screening, surveillance and symptoms; Therapy (all): EMR, ESD and surgery; IBD: inflammatory bowel disease; FAP: familial adenomatous coli syndrome; SPS: serrated polyposis syndrome; NA: not available; •: yes; ○: no; *: Patients with polyps in general instead of LSTs.*

Table 3.2: Risk of bias in the included studies. | *A mix of criteria (Loney scale and QUADAS-2 tool) were used.*

Study		Population				Outcome assessment				
		General colonoscopy Population	Unbiased sampling frame	Adequate exclusion criteria	Selection of patients introduced bias	LST was primary outcome measure	Complete colonoscopy was used	Assessors were unbiased	Majority lesions histopathological assessed	Risk of bias by outcome measurement
Katano	**2017**	N	N	N	H	N	U	U	U	L
Burgess	**2017**	N	N	N	H	N	U	U	Y	L
Yamada	**2016**	N	N	Y	H	Y	U	U	Y	L
Kudo	**2015**	Y	Y	Y	L	Y	U	U	Y	L
Zhao	**2014**	Y	Y	Y	L	Y	Y	U	Y	L
Xiang	**2014**	Y	N	Y	H	N	Y	Y	Y	L
Togashi	**2014**	Y	Y	N	L	Y	Y	U	Y	L
Miyamoto	**2014**	Y	Y	Y	L	Y	U	U	Y	L
Konda	**2014**	Y	N	Y	H	Y	U	U	Y	L
Dos Santos	**2014**	Y	Y	Y	L	N	Y	U	Y	L
Yoon	**2013**	U	N	N	H	Y	U	U	Y	L
Urban	**2013**	U	N	N	H	Y	U	U	Y	L
Reinhart	**2013**	N	Y	Y	L	N	Y	U	Y	L
Kim	**2013**	Y	Y	U	L	Y	U	N	Y	L
Kakugawa	**2013**	N	N	N	H	Y	U	U	Y	L
Terasaki	**2012**	N	N	N	H	Y	U	U	Y	L
Nakae	**2012**	U	U	Y	H	Y	U	U	Y	L
Martínez	**2012**	Y	Y	N	L	Y	Y	U	Y	L
Kim	**2012**	N	N	N	H	Y	U	U	Y	L
Rotondano	**2011**	Y	Y	Y	L	Y	Y	Y	Y	L
Kim	**2011**	Y	Y	U	L	Y	Y	U	Y	L
Kaku	**2011**	N	Y	U	L	Y	Y	U	Y	L
Kaji	**2011**	Y	Y	Y	L	Y	U	U	Y	L
Sugimoto	**2010**	Y	N	Y	H	Y	U	U	Y	L
Matsuda	**2010**	Y	N	U	H	Y	Y	U	Y	L

Table 3.2: *(continuation)*

Study		Population				Outcome assessment				
		General colonoscopy Population	Unbiased sampling frame	Adequate exclusion criteria	Selection of patients introduced bias	LST was primary outcome measure	Complete colonoscopy was used	Assessors were unbiased	Majority lesions histopathological assessed	Risk of bias by outcome measurement
Bustamante-Balén	**2010**	Y	Y	Y	L	N	Y	U	Y	L
Oka	**2009**	Y	U	U	H	Y	U	U	Y	L
Huang	**2009**	Y	Y	Y	L	Y	U	U	Y	L
Chiu	**2009**	N	Y	Y	L	Y	Y	Y	Y	L
Urban	**2008**	N	Y	N	H	Y	U	U	Y	L
Tantau	**2008**	Y	Y	Y	L	Y	Y	U	Y	L
Nosho	**2008**	U	N	U	H	Y	U	U	Y	L
Kudo	**2008**	U	U	U	L	Y	U	U	U	L
Kil Lee	**2008**	Y	N	N	H	N	Y	U	Y	L
Kaltenbach	**2007**	Y	N	N	H	N	Y	U	Y	L
Uraoka	**2006**	U	Y	Y	L	Y	U	U	Y	L
Para-Blanco	**2006**	Y	N	Y	L	N	U	U	Y	L
Katsinelos	**2006**	Y	U	Y	L	Y	U	U	Y	L
Hiraoka	**2006**	N	Y	Y	L	Y	U	U	Y	L
Su	**2005**	Y	N	N	H	Y	U	U	Y	L
O'Brien	**2004**	Y	Y	Y	L	N	Y	Y	Y	L
Kim	**2003**	Y	U	N	H	N	Y	U	Y	L
Tsuda	**2002**	Y	Y	Y	L	N	Y	U	Y	L
Tanaka	**2001**	N	N	N	H	Y	U	U	Y	L
Saito	**2001**	Y	U	N	H	Y	U	U	Y	L
Rembacken	**2000**	Y	N	N	H	N	Y	N	Y	L
Teixeira	**1996**	U	U	N	H	Y	U	U	Y	L
Jaramillo	**1995**	Y	Y	Y	L	N	Y	U	Y	L

H = high risk on bias, L = low risk on bias, U = unknown, Y = Yes, N = No.

Study quality

The risk of outcome bias was low in all included studies. The risk of population bias was high in four population based studies and in 20 lesion-based studies (**Table 3.2**). **Table 3.3** summarizes the definition of LSTs in the included studies.

Prevalence

Seven studies reported the total number of patients included (136,896 patients) and the number of patients with one or more LSTs. Five of these included all consecutive patients undergoing colonoscopy,[19, 26, 31, 37, 39] while two studies included only patients undergoing screening colonoscopy.[29, 36] The pooled prevalence of patients with one ore more LSTs of all patients was 0.8% (95% CI: 0.6 – 1.1%, I^2: 92.4%, **Figure 3.4a**). The pooled prevalence of patients with one or more LSTs among patients with neoplasms was 3.0% (95% CI: 2.3 – 3.7, I^2: 93.9%, **Figure 3.4b**). The pooled prevalence of LSTs among all neoplasms was 3.6% (95% CI: 2.5 – 4.9, I^2: 96.9, **Figure 3.4c**). Geographic region and starting year of inclusion had no significant effect on LST prevalence. The funnel plots of these analyses are shown in **Figure 3.5**. Heterogeneity and Funnel plot asymmetry were significant (P<0.001) in all three analyses.

Table 3.3: Laterally spreading tumor definition used in the included studies.

#	Definition	Based on (publication)	Studies
1	"A neoplasm with predominantly lateral growth of at least 10 mm in diameter; this is in opposition to polypoid (upward growth) or flat and depressed lesions (downward growth)."	Kudo 2008[1] / Kudo 1993[81]	Katano 2017,[44] Burgess 2017,[17] Yamada 2016,[9] Kudo 2015,[45] Zhao 2014,[26] Togashi 2014,[46] Miyamoto 2014,[47] Konda 2014,[48] Yoon 2013,[49] Urban 2013,[50] Kim 2013,[30] Kakugawa 2013,[51] Nakae 2012,[53] Kim 2012,[54] Kim 2011,[32] Kaku 2011,[33] Kaji 2011,[55] Sugimoto 2010,[56] Matsuda 2010,[34] Oka 2009,[57] Huang 2009,[58] Chiu 2009,[36] Urban 2008,[59] Nosho 2008,[60] Kudo 2008,[1] Uraoka 2006,[62] Katsinelos 2006,[63] Hiraoka 2006,[64] Su 2005,[65] Tanaka 2001,[67] Saito 2001,[68] Teixeira 1996[69]
2	"Large non-polypoid lesion <2.5mm in height (height:width ratio <1:3 for LST-G-NM)"	Paris classification 2003[82]	Dos Santos 2014,[28] Rotondano 2011,[19] Tantau 2008[37]
3	"Non-polypoid lesion ≥10mm in size"	-	Xiang 2014,[27] Reinhart 2013,[29] Kaltenbach 2007,[61] Parra-Blanco 2006,[39] O'Brien 2004,[40] Kim 2003,[66] Tsuda 2002,[41] Rembacken 2000,[42] Jaramillo 1995[43]
4	"Non-polypoid lesions >10mm with height:width ratio <1:2"	Sawada 1989[83]	Bustamente-Balen 2010[35]
5	No definition	-	Terasaki 2012,[52] Martinez 2012[31]

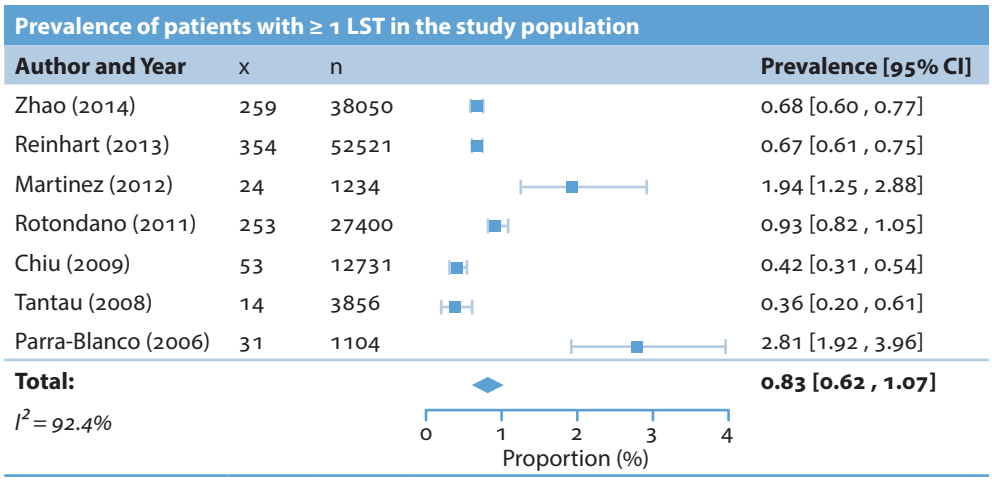

Figure 3.4a: Forest plots showing prevalence estimates with 95% confidence intervals (Cis). | *patients with one or more LSTs in the study population (x, number of LST patients; n, number of patients).*

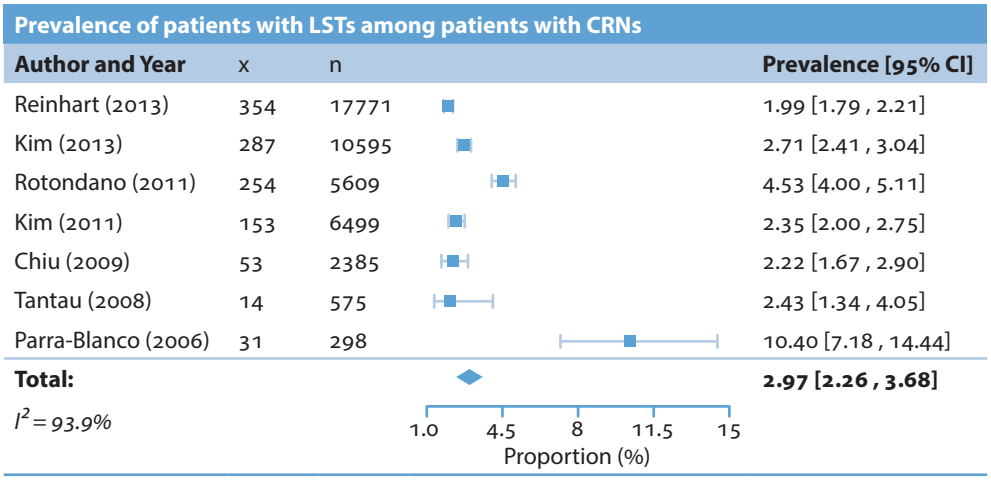

Figure 3.4b: Forest plots showing prevalence estimates with 95% confidence intervals (Cis). | *patients with one or more LSTs among patients with colorectal neoplasms (x, number of LST patients; n, number of patients with neoplasms).*

Prevalence of LSTs among all CRNs			
Author and Year	x	n	**Prevalence [95% CI]**
Xiang (2014)	172	4632	3.7 [3.2 , 4.3]
Dos Santos (2014)	66	2067	3.2 [2.5 , 4.0]
Rotondano (2011)	254	6553	3.9 [3.4 , 4.4]
Kaku (2011)	62	3269	1.9 [1.5 , 2.4]
Matsuda (2010)	453	6638	6.8 [6.2 , 7.5]
Bustamente (2010)	14	613	2.3 [1.3 , 3.8]
Ciu (2009)	53	3494	1.5 [1.1 , 2.0]
Tantau (2008)	14	802	1.7 [1.0 , 2.9]
Kil Lee (2008)	107	3263	3.3 [2.7 , 3.9]
Parra-Blanco (2006)	43	490	8.8 [6.4 , 11.6]
O'Brien (2004)	16	1504	1.1 [0.6 , 1.7]
Tsuda (2002)	11	973	1.1 [0.6 , 2.0]
Rembacken (2000)	49	327	15.0 [11.3 , 19.3]
Jaramillo (1995)	18	300	6.0 [3.6 , 9.3]
Total:			**3.6 [2.5 , 4.9]**
$I^2 = 96.9\%$			

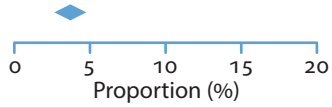

Figure 3.4c: Forest plots showing prevalence estimates with 95% confidence intervals (Cis). | *LSTs among all colorectal neoplasms (x, number of LSTs; n, number of colorectal neoplasms).*

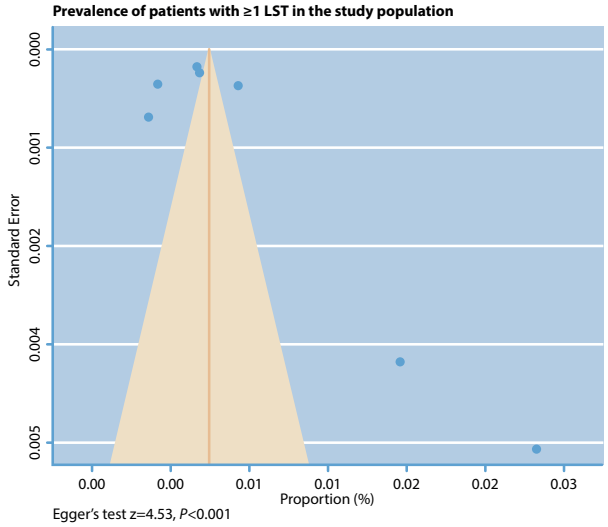

Figure 3.5a: Funnel plot showing prevalence estimates of patients with one or more LSTs in the study population.

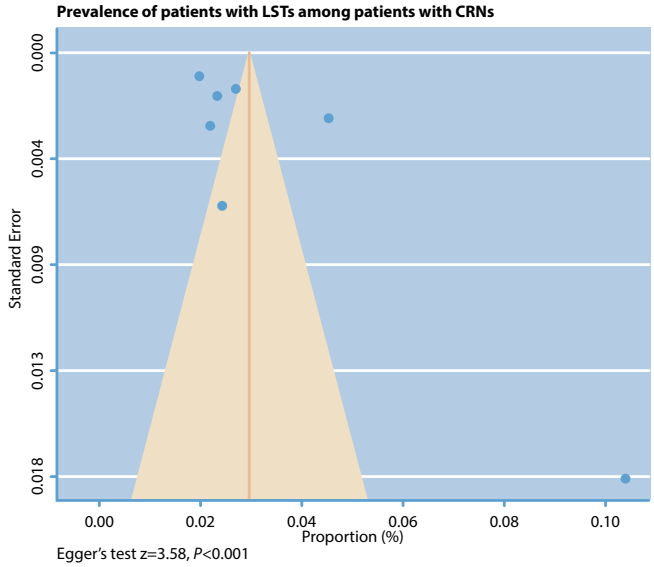

Figure 3.5b: Funnel plot showing prevalence estimates of patients with LSTs among patients with colorectal neoplasms.

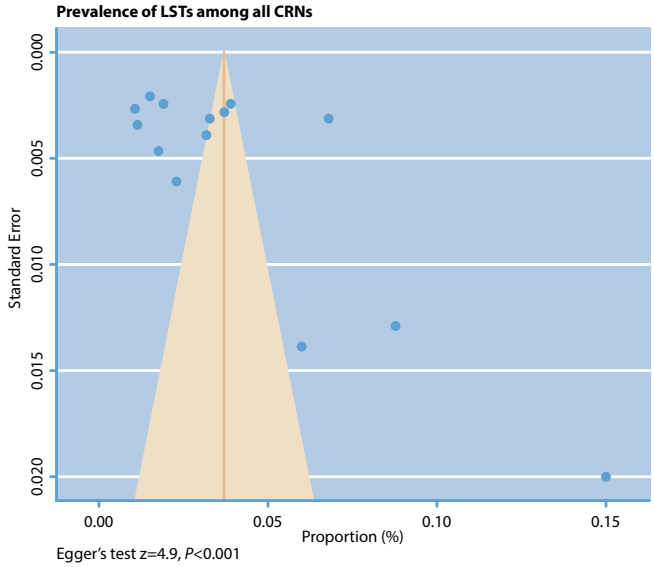

Figure 3.5c: Funnel plot showing prevalence estimates of LSTs among all colorectal neoplasms.

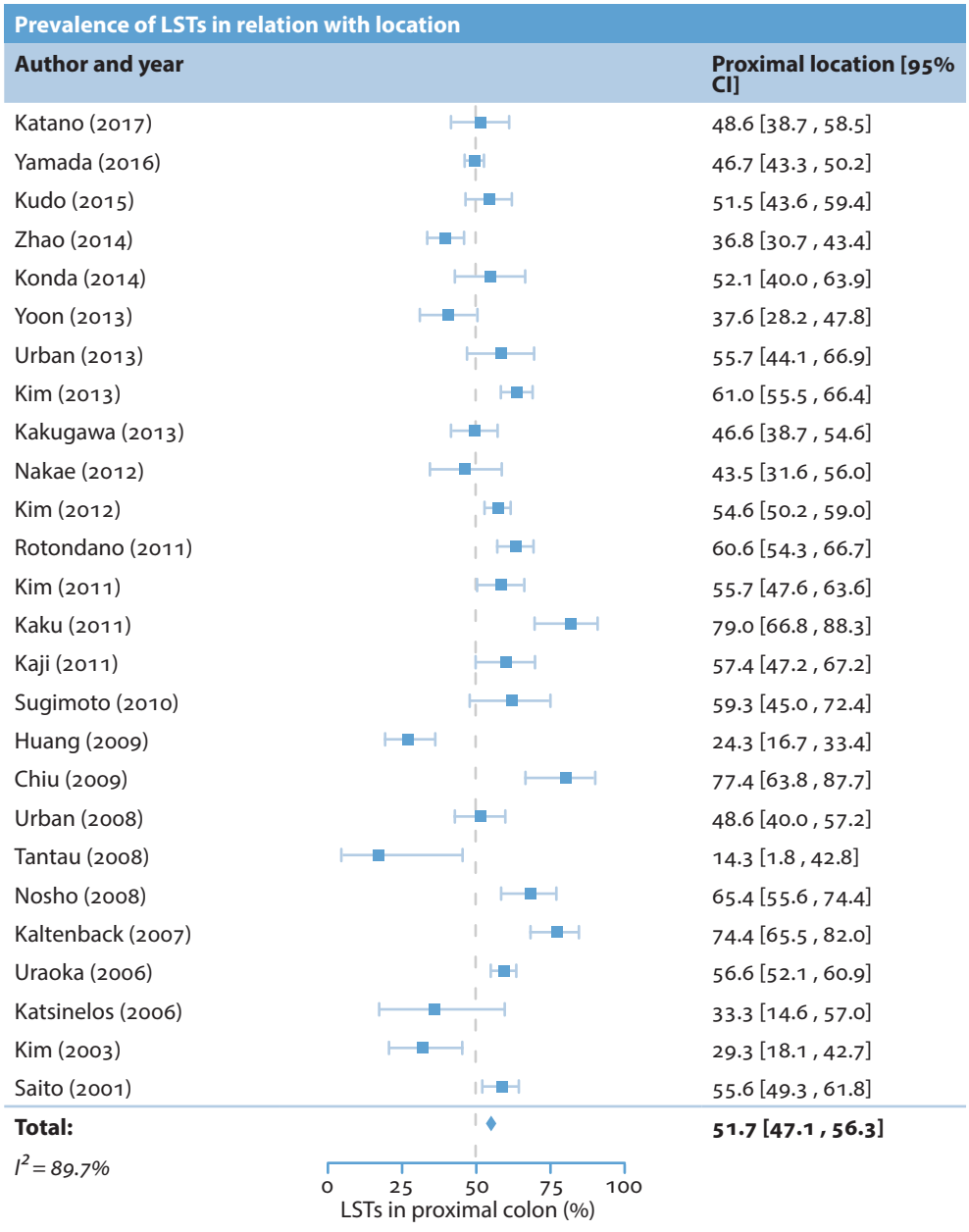

Figure 3.6a: Comparison of LSTs located in the proximal and distal colon. | *Forest plot showing prevalence estimates for LSTs located in the proximal colon.*

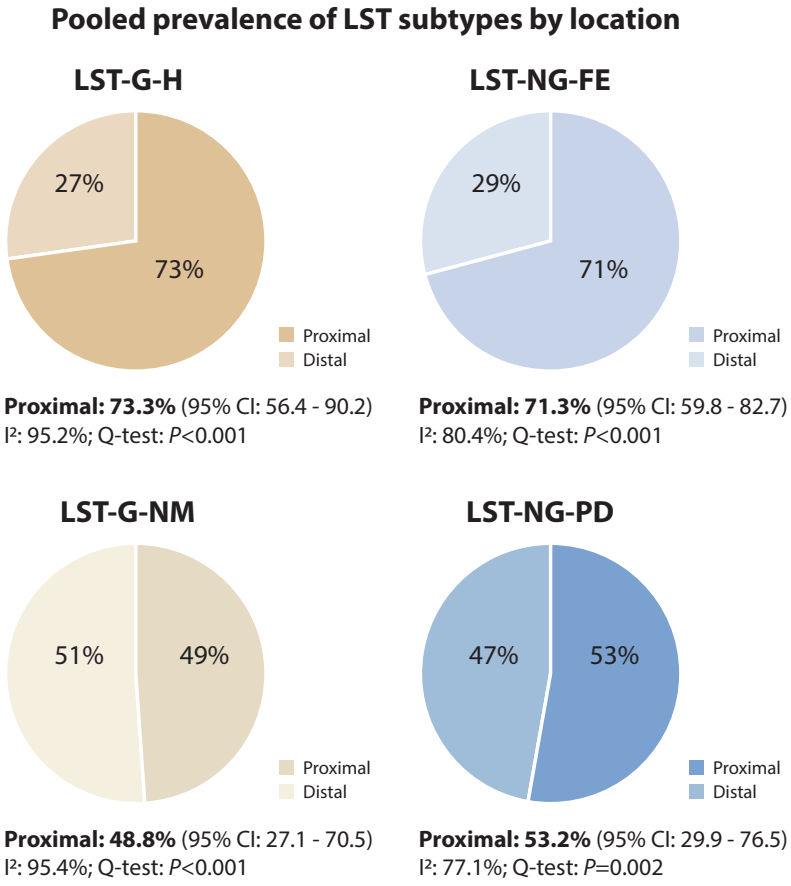

Figure 3.6b: Comparison of LSTs located in the proximal and distal colon. | *Distribution of endoscopic LST subtypes throughout the colon. The Q test for heterogeneity was significant for all four analyses.*

Location and endoscopic subtype

There were 26 studies that examined the prevalence of LSTs by colonic location. Pooled prevalence of proximally located LSTs was 51.7% (95% CI: 47.1 – 56.3, I^2: 89.7%, **Figure 3.6a**). Granular LSTs were found significantly less often in the proximal colon than non-granular LSTs (OR 0.68, 95% CI: 0.48 – 0.97, I^2: 77.1%, 17 studies).[9, 19, 26, 30, 32, 33, 36, 44, 45, 48, 51, 53, 54, 56, 58, 60, 62] The majority of homogenous granular and flat elevated non-granular LSTs were located in the proximal colon (73% and 71% respectively), while nodular mixed granular and pseudo-depressed non-granular LSTs were more evenly distributed over the colon (49% and 53% respectively in the proximal colon, **Figure 3.6b**, data from five studies).[19, 26, 30, 32, 54]

Prevalence of LST-G among all LSTs

Author and year	LST G	LST NG	Prevalence [95% CI]
Kudo (2015)	47	116	0.29 [0.22 , 0.36]
Zhao (2014)	161	128	0.56 [0.50 , 0.62]
Miyamoto (2014)	267	229	0.54 [0.49 , 0.58]
Konda (2014)	25	48	0.34 [0.24 , 0.46]
Urban (2013)	46	33	0.58 [0.47 , 0.69]
Kim (2013)	201	125	0.62 [0.56 , 0.67]
Nakae (2012)	36	33	0.52 [0.40 , 0.64]
Kim (2012)	324	169	0.66 [0.61 , 0.70]
Rotondano (2011)	211	43	0.83 [0.78 , 0.87]
Kim (2011)	96	62	0.61 [0.53 , 0.68]
Kaku (2011)	25	37	0.40 [0.28 , 0.54]
Kaji (2011)	68	33	0.67 [0.57 , 0.76]
Oka (2009)	622	741	0.46 [0.43 , 0.48]
Huang (2009)	89	22	0.80 [0.72 , 0.87]
Chiu (2009)	29	24	0.55 [0.40 , 0.68]
Urban (2008)	128	10	0.93 [0.87 , 0.96]
Tantau (2008)	14	0	1.00 [0.77 , 1.00]
Nosho (2008)	72	35	0.67 [0.58 , 0.76]
Kudo (2008)	332	367	0.47 [0.44 , 0.51]
Uraoka (2006)	287	224	0.56 [0.52 , 0.61]
Katsinelos (2006)	15	6	0.71 [0.48 , 0.89]
Hiraoka (2006)	23	12	0.66 [0.48 , 0.81]
Kim (2003)	43	15	0.74 [0.61 , 0.85]
Teixeira (1996)	26	22	0.54 [0.39 , 0.69]
Total:			**0.61 [0.54 , 0.68]**

$I^2 = 96.8\%$

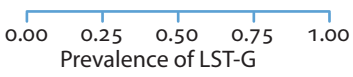

Figure 3.7: Forest plot showing prevalence estimates of granular LSTs among all LSTs. | *G: granular LSTs, NG: non-granular LSTs.*

Prevalence of SMI in LSTs			
Author and year	x	n	**Prevalence [95% CI]**
Kudo (2015)	35	149	23.5 [16.9 , 31.1]
Zhao (2014)	24	211	11.4 [7.4 , 16.5]
Miyamoto (2014)	76	496	15.3 [12.3 , 18.8]
Urban (2013)	2	74	2.7 [0.3 , 9.4]
Kim (2013)	14	282	5.0 [2.7 , 8.2]
Nakae (2012)	16	69	23.2 [13.9 , 34.9]
Kim (2012)	9	493	1.8 [0.8 , 3.4]
Rotondano (2011)	6	225	2.7 [1.0 , 5.7]
Kim (2011)	11	141	7.8 [4.0 , 13.5]
Kaku (2011)	5	62	8.1 [2.7 , 17.8]
Kaji (2011)	9	101	8.9 [4.2 , 16.2]
Matsuda (2010)	30	332	9.0 [6.2 , 12.6]
Oka (2009)	98	1363	7.2 [5.9 , 8.7]
Huang (2009)	11	111	9.9 [5.1 , 17.0]
Chiu (2009)	5	53	9.4 [3.1 , 20.7]
Urban (2008)	5	136	3.7 [1.2 , 8.4]
Tantau (2008)	4	14	28.6 [8.4 , 58.1]
Kudo (2008)	74	699	10.6 [8.4 , 13.1]
Uraoka (2006)	51	511	10.0 [7.5 , 12.9]
Parra-Blanco (2006)	1	43	2.3 [0.1 , 12.3]
Katsinelos (2006)	2	21	9.5 [1.2 , 30.4]
Su (2005)	4	106	3.8 [1.0 , 9.4]
Kim (2003)	7	58	12.1 [5.0 , 23.3]
Tsuda (2002)	3	11	27.3 [6.0 , 61.0]
Teixeira (1996)	4	48	8.3 [2.3 , 20.0]
Jaramillo (1995)	2	9	22.2 [2.8 , 60.0]
Total:			**8.5 [6.5 , 10.5]**
$I^2 = 86.8\%$			

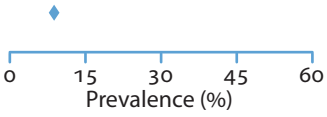

Figure 3.8a: Forest plots showing prevalence estimates. Submucosal invasion in LSTs. | *x, number of LSTs with submucosal invasion; n, total number of LSTs.*

Prevalance of HGD in LSTs			
Author and year	x	n	**Prevalence [95% CI]**
Kudo (2015)	51	149	34.2 [26.7 , 42.4]
Zhao (2014)	86	211	40.8 [34.1 , 47.7]
Miyamoto (2014)	263	496	53.0 [48.5 , 57.5]
Urban (2013)	43	74	58.1 [46.1 , 69.5]
Kim (2013)	67	282	23.8 [18.9 , 29.2]
Nakae (2012)	26	69	37.7 [26.3 , 50.2]
Rotondano (2011)	76	225	33.8 [27.6 , 40.4]
Kim (2011)	33	141	23.4 [16.7 , 31.3]
Kaku (2011)	17	62	27.4 [16.9 , 40.2]
Kaji (2011)	34	101	33.7 [24.6 , 43.8]
Matsuda (2010)	164	332	49.4 [43.9 , 54.9]
Huang (2009)	33	111	29.7 [21.4 , 39.1]
Chiu (2009)	11	53	20.8 [10.8 , 34.1]
Urban (2008)	70	136	51.5 [42.8 , 60.1]
Tantau (2008)	5	14	35.7 [12.8 , 64.9]
Parra-Blanco (2006)	6	43	14.0 [5.3 , 27.9]
Katsinelos (2006)	9	21	42.9 [21.8 , 66.0]
Su (2005)	53	106	50.0 [40.1 , 59.9]
O'Brian (2004)	1	16	6.2 [0.2 , 30.2]
Kim (2003)	19	58	32.8 [21.0 , 46.3]
Tsuda (2002)	2	11	18.2 [2.3 , 51.8]
Teixeira (1996)	39	48	81.2 [67.4 , 91.1]
Jaramillo (1995)	4	9	44.4 [13.7 , 78.8]
Total:			**36.7 [30.3 , 43.2]**
$I^2 = 91.9\%$			

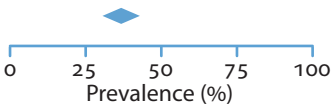

Figure 3.8b: Forest plots showing prevalence estimates. High grade dysplasia in LSTs. | *x, number of LSTs with high grade dysplasia; n, total number of LSTs.*

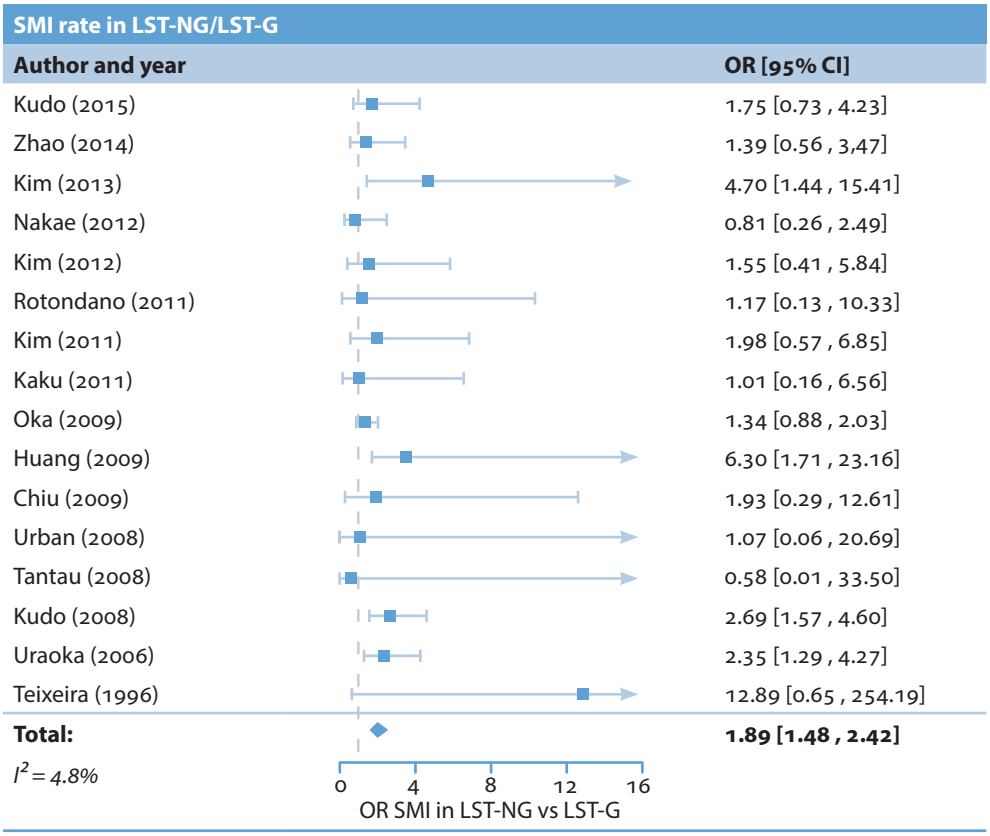

Figure 3.9: Forest plots showing pooled odds ratio (OR) of a LST containing submucosal invasion in the non-granular vs granular subtype.

A total of 24 studies examined the prevalence of LSTs by granular vs non-granular endoscopic subtype. Pooled prevalence of granular LSTs was 61% (95% CI: 54 – 68, I^2: 96.8%, **Figure 3.7**). Eight studies examined the distribution of the four endoscopic LST subtypes.[1, 19, 26, 30, 32, 50, 54, 57] The pooled prevalences of homogenous granular, nodular mixed granular, flat elevated non-granular and pseudo-depressed non-granular LST subtypes were 35.4% (95% CI 27.2 – 43.6, I^2: 96.0%), 26.1% (95% CI 18.5 – 33.8, I^2: 97.0%), 33.0% (95% CI: 22.8 – 43.2, I^2: 97.5%) and 5.5% (95% CI: 3.2 – 7.8, I^2: 91.8%), respectively.

Risk of submucosal invasion

Overall, LSTs were found to contain SMI in 8.5% of the cases (95% CI: 6.5 – 10.5%, I^2: 86.8%, 26 studies, **Figure 3.8a**) and HGD in 36.7% of the cases (95% CI: 30.3 – 43.2%, I^2: 91.9%, 23 studies, **Figure 3.8b**). Geographic region did not influence the SMI risk.

Non-granular LSTs more often contained SMI than granular LSTs: 11.7% versus 5.9% (OR 1.89, 95% CI: 1.48 – 2.42, **Figure 3.9**). The prevalence of SMI in LSTs stratified by endoscopic LST subtype was examined in seven studies.[1, 19, 26, 30, 32, 54, 57] The pooled prevalences of SMI by endoscopic LST subtype were: 31.6% in pseudo-depressed non-granular LSTs (95% CI: 19.8 – 43.4%, I^2: 61.6%), 10.5% in nodular mixed granular LSTs (95% CI: 5.9 – 15.1%, I^2 : 77.8%), 4.9% in flat elevated non-granular LSTs (95% CI: 2.1 – 7.8%, I^2 : 80.0%), and 0.5% in homogenous granular LSTs (95% CI: 0.1 – 1.0%, I^2: 0.0%, **Figure 3.10**). Funnel plot asymmetry for the SMI analysis was significant (P<0.001), but was not significant for the HGD analysis (**Figure 3.11**).

The pooled prevalence of SMI increased by lesion size from 4.6% (95% CI: 3.1 – 6.0%) to 9.2% (95% CI: 6.6 – 11.8%) and 16.5% (95% CI: 9.8 – 23.3%) for LSTs 10-19mm, 20-29mm and ≥30mm (**Table 3.4**). Ten studies reported the SMI rate in LSTs ≥20mm, which resulted in a pooled SMI rate of 11.3% (95% CI: 8.2 – 14.4%, I^2: 85.1%) (**Figure 3.12**).

LSTs containing SMI were more often located in the distal colon than in the proximal colon: pooled odds ratio 2.50 (95% CI: 1.24 – 5.02, I^2: 0%, three studies, **Figure 3.13**). One study examined the proportion of LSTs with SMI stratified by colonic segment, which was 4.5%, 3.4% and 14.6% for the proximal colon, descending colon, and rectum, respectively.[32] Another study compared SMI risk for rectal versus colonic LSTs (30% versus 13%).[47]

Sensitivity analysis

A sensitivity analysis excluding the studies with a high risk of population bias (**Table 3.2**) resulted in an SMI rate of 9.9% (95% CI: 7.1 – 12.8, I^2: 83.8%, 16 studies were left), compared with 8.5% in the original analysis (26 studies). Four studies used for the prevalence of LSTs among all neoplasms had a high risk of population bias.[27, 34, 38, 42] A sensitivity analysis excluding these four studies resulted in a pooled prevalence of 2.7% (95% CI: 1.8 – 3.8%, I^2: 93.8%) for LSTs among all neoplasms (compared with 3.6% when these four studies were included).

The SMI rate was 8.6% (95% CI: 6.6 – 10.7%, I^2: 87.9%, 23 studies) when three studies that used the term 'large (≥10mm) non-polypoid colorectal neoplasms' (instead of LST)[39, 41, 66] were excluded. The prevalence of patients with one or more LSTs did not change when two studies that used the same term[29, 39] were excluded and the precalence of LSTs among all neoplasms was 2.9% (95% CI: 1.6 – 4.5%, I^2: 97.7%) when seven studies that used this term[27, 38-43] were excluded.

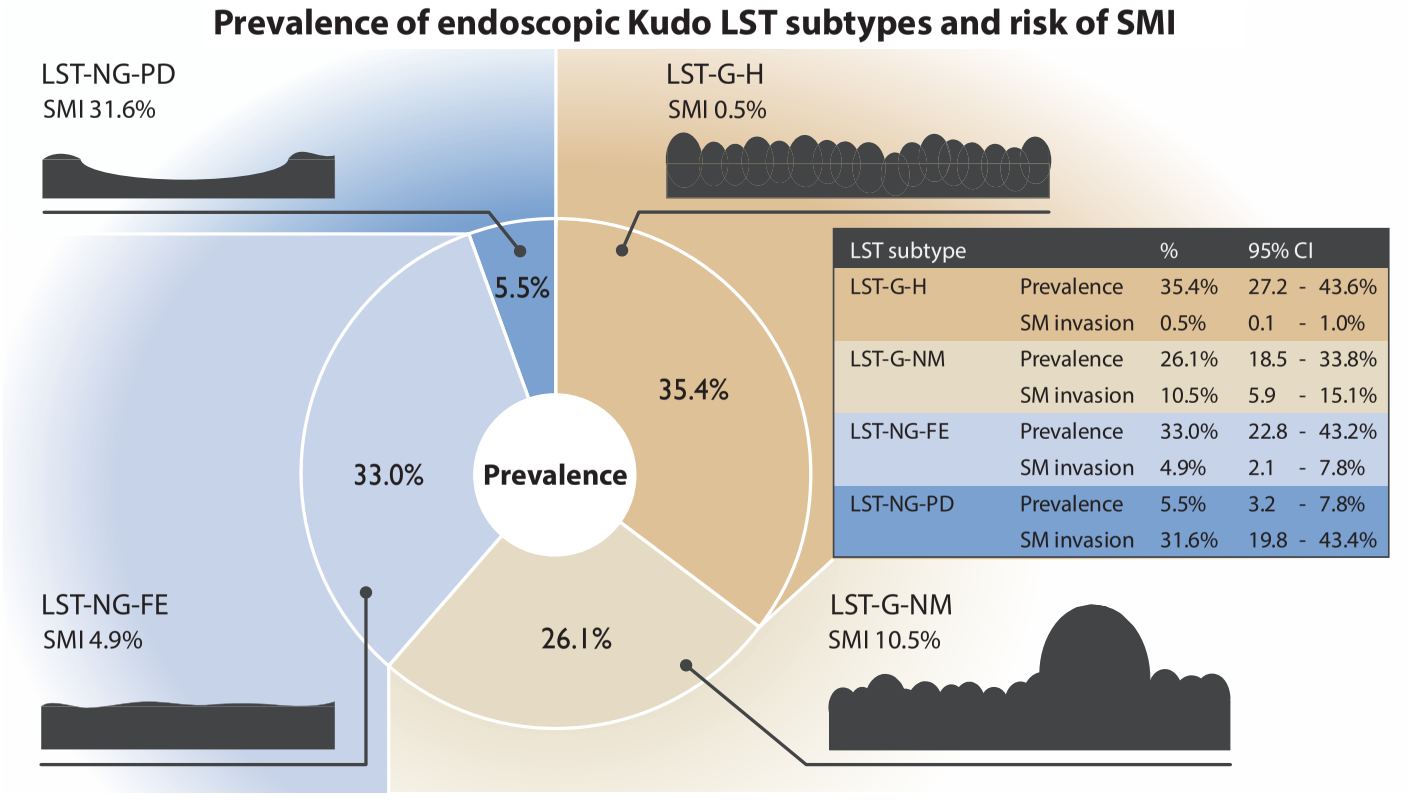

Figure 3.10: Overview of the prevalence of LST endoscopic subtypes and rates of submucosal invasion (SMI). | *LST-NG-PD, non-granular pseudo-depressed LST; LST-G-H, granular homogenous LST; LST-NG-FE, non-granular flat elevated LST; LST-G-NM, granular nodular mixed LST.*

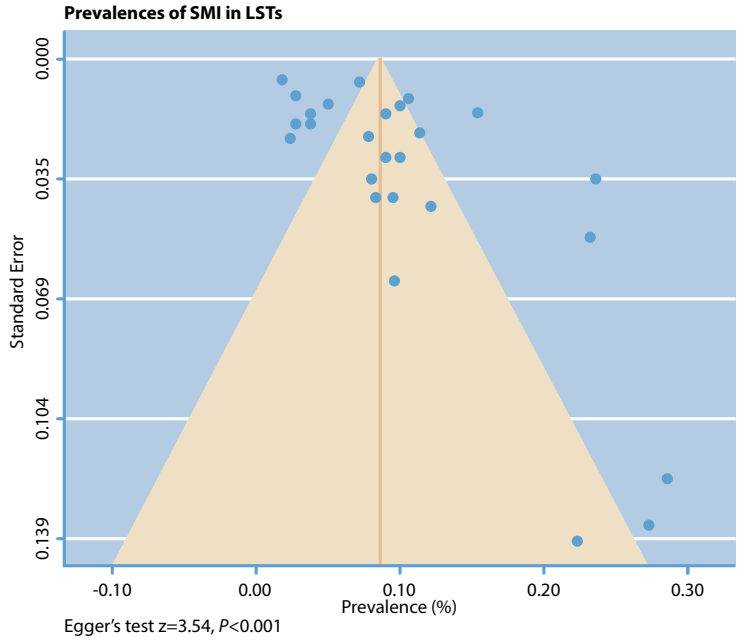

Figure 3.11a: Funnel plots showing prevalence estimates of submucosal invasion in LSTs.

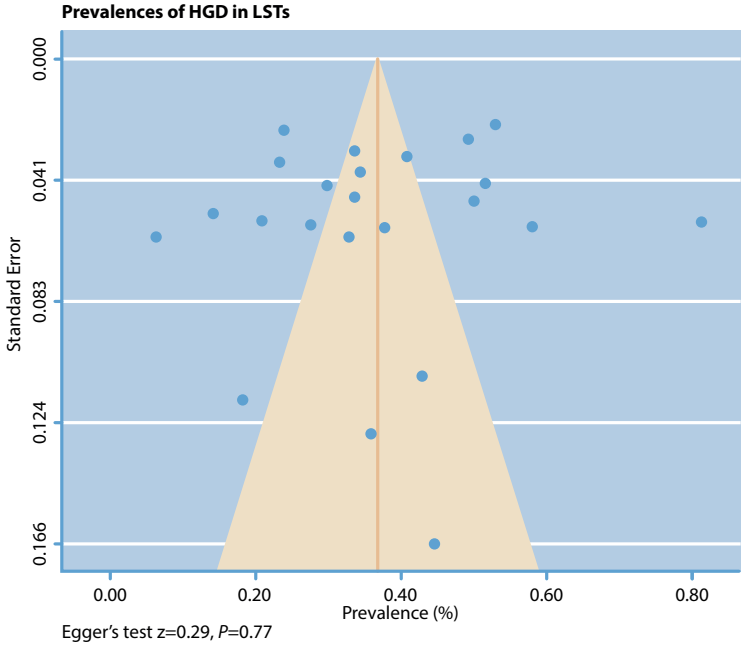

Figure 3.11b: Funnel plots showing prevalence estimates of high grade dysplasia in LSTs.

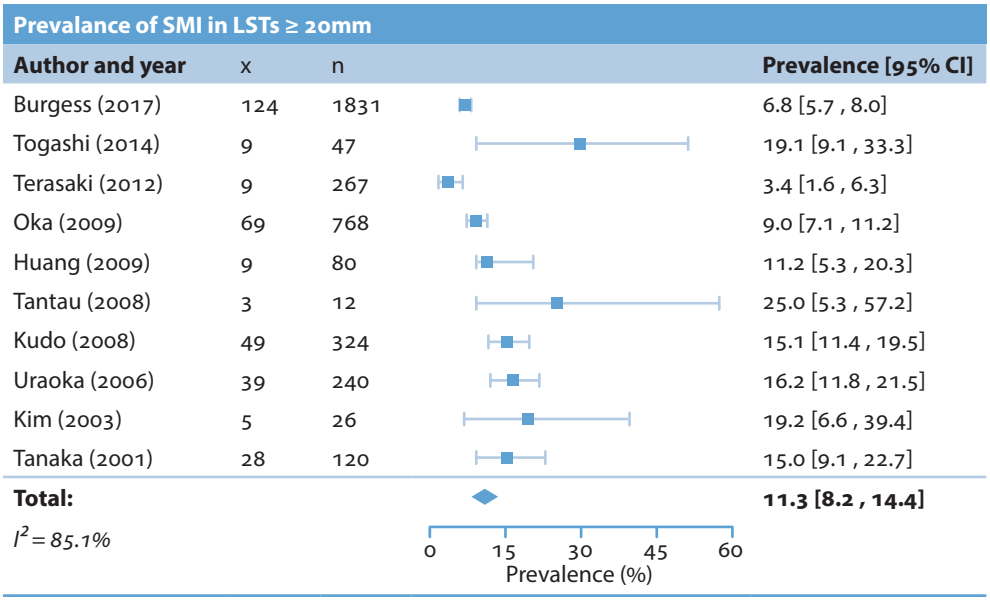

Figure 3.12: Forest plot showing prevalence estimates of submucosal invasion in LSTs ≥20mm.

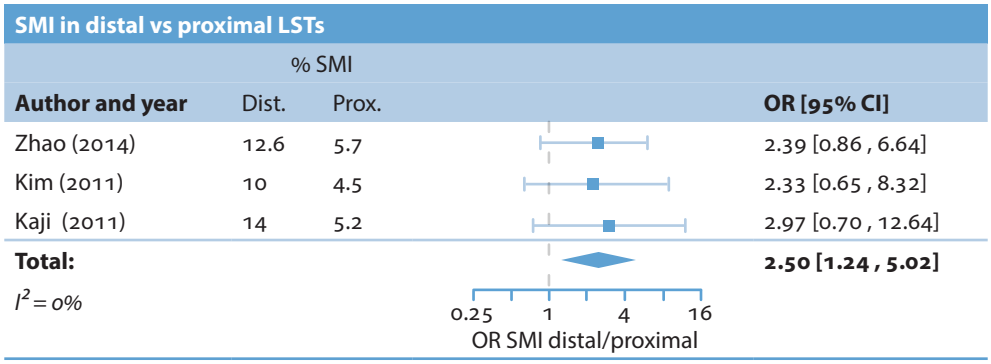

Figure 3.13: Forest plot of the pooled odds ratio (OR) of submucosal invasion (SMI) in distally vs proximally located LSTs.

Table 3.4: Risk of submucosal invasion in laterally spreading tumors, stratified by size.

Size	10-19 mm	20-29 mm	≥ 30 mm
Risk to contain submucosal invasion	4.6% (95% CI: 3.1 - 6.0%)	9.2% (95% CI: 6.6 - 11.8%)	16.5% (95% CI: 9.8 - 23.3%)
Heterogeneity index (I^2)	31.6%	14.1%	69.5%
References	*1, 37, 38, 57, 58, 62, 66, 68*	*1, 37, 57, 58, 68*	*1, 37, 57, 58, 68*

Discussion

This systematic review and meta-analysis shows that the majority of LSTs (91.5%) are non-invasive and thereby can be treated by (piecemeal) EMR. The risk of SMI is associated with the endoscopic Kudo subtype, and the lesion size and location. SMI is most common in pseudo-depressed non-granular LSTs (31.6% SMI, prevalence 5.5%) and nodular mixed granular LSTs (10.5% SMI, prevalence 26.1%). Optical diagnosis with close inspection of the areas of concern (depression, nodule) can determine LSTs at high risk of containing SMI, where en-bloc resection is the preferred therapy.

There is ongoing discussion about the optimal treatment strategy of LSTs. For a long time, EMR techniques and surgery were considered to be the first-line therapy options.[71] Colorectal adenoma with superficial SMI (maximal 1000µm invasion below the muscularis mucosae at all foci) have a very low risk of lymph node metastasis and it is oncologically safe for them to be resected by EMR.[8, 12] However, EMR is not technically suitable for en-bloc resections of neoplasms larger than 20mm in diameter.[6, 62, 72] Applying EMR in such cases leads to piecemeal resection, which is associated with a higher risk of local residue / recurrence. A meta-analysis that evaluated recurrence risk in non-pedunculated neoplasms showed a local residue / recurrence rate of 20% after piecemeal resection vs 3% after en-bloc resection.[73] The multicenter ACE study, which included large flat and sessile lesions (≥20mm) resected by EMR, showed a recurrence rate of 16% after 4 months and 6.7% after 16 months.[8] Most cases of recurrence (93%) could however still be managed endoscopically and only 1.9% of patients with an initially successful (piecemeal) EMR required surgery because of recurrence or SMI after 16 months.[8]

Endoscopic submucosal dissection (ESD) has emerged as a minimally invasive endoscopic technique to resect large LSTs en-bloc.[68] The advantages of en-bloc resection by ESD compared with piecemeal EMR are higher rates of complete resection with lower recurrence rates. A large cohort study with 5-year follow-up in a Japanese centre with expertise in performing ESD, demonstrated low recurrence rates (2.4% recurrence, 0.4% cancerous recurrence) in neoplasms that were initially curatively resected (e.g. free resection margins and no signs of deep SMI).[74] ESD enables a precise histopathological diagnosis to be made as there is reduced fragmentation and less cauterization artifact.[7] In terms of its potential disadvantages, ESD is technically more challenging, the procedure duration is increased and it has a higher risk of perforation.[75] The ESGE polypectomy guidelines recommend en-bloc resection of lesions that are suspected to contain superficial SMI. [5] ESD, instead of EMR, may be the therapy of choice in LSTs >20mm with a high risk of (multifocal) SMI and local fibrosis.[7, 62] In a large cohort study of LSTs that were resected en-bloc, multifocal invasion was present in 45% of pseudo-depressed non-granular LSTs and in 16% of the nodular mixed granular LSTs with SMI, indicating that en-bloc resection is the preferred therapy in such cases.[9] It is uncertain whether application of ESD prevents surgery. A European cohort study on the resection of large rectal non- pedunculated neoplasms showed high rates of en-bloc and R0 resections by ESD (81.4% and 65.1%, respectively), but with a curative resection rate of only 30.2% because of deep SMI;[76] 83.3% of the non-curative cases had deep SMI. Only two of the studies included in the present meta-analysis explicitly reported the deep SMI rates: 71.4%[45] and 54.5%.[32] This indicates that surgery is still necessary in a large subset of cases after performing ESD with the aim of curative resection. RCTs looking at long-term cancerous recurrences after endoscopic resection will be necessary to clarify whether the application of ESD for LSTs with superficial SMI can increase curative endoscopic resection rates.

The findings of this meta-analysis show that the majority of LSTs are non-invasive at the time of colonoscopic detection, allowing for removal by (piecemeal) EMR. However, detailed characterization with prediction of the risk of containing SMI is necessary to distinguish LSTs that can be resected piecemeal from those in which en-bloc resection would be more favorable. Chromoendoscopy is a useful tool in determining the endoscopic LST subtype as it better delineates nodules and granules. Because of the pooling effect of the dye, pseudo-depressions will also be better visualized. A prediction of SMI in LSTs can be made with higher accuracy by detailed inspection of the pit pattern. Among a highly-experienced group of endoscopists, the accuracy in prediction of deep SMI was 91.7%.[9] The recognition of a large nodule or a depressed area is not complicated, but prediction with high confidence of the depth of SMI using pit patterns is challenging, and magnifying colonoscopes and additional training are required.[71] Application of the endoscopic LST classification is therefore a simple first step to determine the a priori risk of SMI. In general, homogenous granular and flat elevated non-granular LSTs have a low a priori risk of containing SMI (0.5% and 4.9%, respectively). Where en-bloc resection is not feasible or safe, the endoscopist can choose to apply oligo-piecemeal EMR. Nodular mixed granular and pseudo-depressed non-granular LSTs have a higher a priori risk of containing SMI and applying advanced imaging techniques to the areas of interest (dominant nodules, pseudo-depressions) could inform treatment decisions. Training in EMR of large neoplasms remains a critical first step, because most LSTs can be efficiently treated this way.[6, 71] In the absence of experience with diagnosis by advanced imaging, the endoscopist should refer the patient to a centre with experience. As shown in this meta-analysis, the prevalence of pseudo-depressed non-granular LSTs is fairly low (5.5% of all LSTs). The additional workload for performing ESDs is not significant, but the oncologic outcome of resection is potentially better. Once the decision is made that an LST has an increased risk of SMI, the treatment modality will vary widely based on local experience, patient preference, endoscopist training, costs, and logistics.

In this meta-analysis, we found a higher risk of SMI in LSTs located in the distal colon compared with those in a proximal location (OR 2.50, 95% CI: 1.24 – 5.02). This is supported by the finding that pseudo-depressed non-granular and nodular mixed granular LSTs, which have a higher risk of SMI, are more often located in the distal colon. Endoscopic resection of neoplasms located in the distal colon, especially in the rectum, is technically easier to perform and has a lower risk of perforation than when performed in the proximal colon.[77]

Another finding of this meta-analysis was that the pooled rate of LSTs did not appear to change by geographic region or starting year of the study. Most included studies used general colonoscopy populations and there were only a few studies in screening settings. LST prevalence may be higher in screening populations selected with fecal occult blood tests and future studies will be required to investigate the prevalence of LSTs in such high risk populations.

In this meta-analysis, the endoscopic Kudo LST classification, instead of the Paris classification, was used to subdivide LSTs. The majority of the papers used the endoscopic Kudo classification. As displayed in **Figure 3.1**, homogenous granular and flat elevated non-granular LSTs are often considered as Paris 0-IIa lesions, while nodular mixed granular LSTs are considered as Paris 0-IIa+Is and pseudo-depressed non-granular LSTs as Paris 0-IIa+IIc, although other combinations are possible.[1] The multicentre ACE study into risk factors for SMI in large (≥20mm) non-pedunculated neoplasms that were resected by EMR used the Paris classification. Along with rectosigmoid location and lesion size, the Paris classification in combination with granularity status was shown to be predictive of SMI.[17] Granularity is not included in the Paris classification and should be mentioned separately.

From a clinical, oncologic, and biologic point of view, simply referring to both homogenous granular and flat elevated non-granular LSTs as LST 0-IIa lesions would be a non-differential

categorization. Valuable information regarding the risk of SMI would be missing as the risks of SMI are different (0.5 vs 4.9%). Furthermore, the Paris classification does not distinguish between real depression (sharply demarcated and deep based, deeper than the healthy mucosa) and pseudo-depression (less clear demarcation and shallow).[15] The distinction between 'depression' and 'pseudo-depression' could aid in the differentiation between deep and superficial SMI, which has therapeutic consequences. Studies will be required to compare the interobserver agreement in both endoscopic Kudo LST classification and Paris classification of LSTs.

The strengths of this systematic review reside in the inclusion of a substantial number of studies, reflecting the worldwide experience over approximately two decades. Our study is the first to present the global experience on the risk of SMI in LSTs stratified by endoscopic subtype, and lesion size and location to provide a more solid basis for the treatment strategy. Several limitations to our study should be acknowledged. First, there is variation in the definition of LSTs among studies. In order to capture all relevant studies, we expanded the definition to include 'non-polypoid lesion ≥10mm', as a surrogate for LST. Some studies included serrated polyps, while others did not. Furthermore, there is wide variation among studies with respect to study design, inclusion criteria and endoscopists' experience in the diagnosis and treatment of LSTs, which is reflected in the high heterogeneity index in some analyses. To mitigate any potential bias, we performed sensitivity analyses, which showed similar results.

For prevalence estimates, only data from population-based studies were used. However, the design and goals of these studies were different. There were two outliers in the prevalence analysis that involved smaller studies from experienced centers.[31, 39] For estimates of the risk of containing SMI in LSTs, both population-based and consecutive lesion studies were included, with even higher heterogeneity. Because the a priori risk of superficial SMI is an indication for en-bloc resection, studies using only specimens that were en-bloc resected could bias the outcomes and were excluded from the analysis. Bias among the studies that reported SMI rates could also be caused by differences in tissue processing.[9, 56] Resected specimens were sectioned with different sampling intervals[47, 48, 62] and the use of specific stains for the muscularis mucosae[78] varied among studies. Piecemeal resection may lead to the underestimation of SMI.[30] Outliers in the SMI analyses were all studies in small-sized populations, which limited their effect on the pooled outcome. Publication bias could lead to an overestimation of the prevalence of LSTs and of the proportion of LSTs with SMI. The statistically significant outcome of the Egger's test could also be the effect of smaller studies and/or less solid methodology.[79]

Furthermore, the location analysis also showed multiple outliers. In the study by Yamada et al.,[9] only one proximally located granular LST was included; in the study by Chiu et al., [36] granular LSTs were predominantly located in the proximal colon. A number of studies examined consecutive LSTs resected in endoscopy centers with expertise in ESD, while others were performed in screening colonoscopy practice. Within fecal immunochemical test (FIT) positive populations, the sensitivity for detection of proximal and non-polypoid neoplasms is relatively low. [80] Because of differences in the total area of the epithelial mucosal surface, nodular mixed granular LSTs and non-granular LSTs may differ in their bleeding risk, which could affect the sensitivity of the FIT-test. It remains to be determined whether these factors underlie the large differences in results between studies.

In conclusion, this meta-analysis summarizes worldwide data on the risk of SMI in LSTs. Although the vast majority of LSTs are non-invasive and can be treated with (piecemeal) EMR, non-granular LSTs are at higher risk of SMI. Optical diagnosis of LSTs with accurate image interpretation highlights areas of concern (dominant nodule, depression) where en-bloc resection is the preferred therapy.

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Metachronous neoplasms in patients with laterally spreading tumors during surveillance

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Abstract

Background

Laterally spreading tumors represent a major challenge for endoscopic detection and resection.

Objective

To examine synchronous and metachronous neoplasms in patients with laterally spreading tumors.

Methods

We prospectively collected colonoscopy and histopathology data from patients who underwent colonoscopy in our centre at up to 6 years' follow-up. Post-resection surveillance outcomes between laterally spreading tumors, flat colorectal neoplasms 10mm or greater, and large polypoid colorectal neoplasms (10mm or greater), were compared.

Results

Between 2008 and 2012, 8120 patients underwent colonoscopy for symptoms (84.6%), screening (6.7%) or surveillance (8.7%). At baseline, 151 patients had adenomatous laterally spreading tumors and 566 patients had adenomatous large polypoid colorectal neoplasms. Laterally spreading tumor patients had more synchronous colorectal neoplasms than large polypoid colorectal neoplasm patients (mean 3.34 vs 2.34, $P<0.001$). Laterally spreading tumor patients significantly more often developed metachronous colorectal neoplasms (71.6% vs 54.2%, $P=0.0498$) and colorectal neoplasms with high grade dysplasia / submucosal invasion than large polypoid colorectal neoplasm patients (36.4% vs 15.8%, $P<0.001$). After correction for age and gender, laterally spreading tumor patients were more likely than large polypoid colorectal neoplasm patients to develop a colorectal neoplasm with high grade dysplasia or submucosal invasion (hazard ratio 2.9, 95% confidence interval 1.8-4.6). The risk of metachronous colorectal cancer was not significantly different in laterally spreading tumors compared to large polypoid colorectal neoplasm patients.

Conclusion

Patients with laterally spreading tumors developed more metachronous colorectal neoplasms with high grade dysplasia / submucosal invasion than large polypoid colorectal neoplasm patients. Based on these findings, endoscopic treatment and surveillance recommendations for patients with laterally spreading tumors should be optimized.

Introduction

Non-polypoid (flat and depressed) colorectal neoplasms (NP-CRNs) are common precursors of colorectal cancer (CRC).[1-4] Up to 15% of patients undergoing elective colonoscopy have NP-CRNs.[1, 3] A significant subset of NP-CRNs are the laterally spreading tumors (LSTs), which are lesions minimally 10mm in size, growing laterally along the mucosa, rather than luminal or submucosal growth.[5] LSTs have a high risk of containing submucosal invasion (SMI)[6] and risk of local recurrence after endoscopic resection,[7, 8] emphasizing the need for an effective treatment. Endoscopic resection of LSTs is challenging and requires additional expertise.[9] Endoscopic mucosal resection (EMR) frequently results in piecemeal resection with LST residue and high local recurrence rates[7, 10] leading to superfluous colonoscopies, resection procedures, and surgery referrals.[11]

Previous studies have shown that patients with LSTs have a higher risk of synchronous neoplasms.[12, 13] This finding could affect the surveillance strategy for LST patients. At our academic endoscopy unit, we examined the prevalence of LSTs, endoscopic subtypes and histology in our prospective colonoscopy database. We aimed to explore whether LST patients more frequently develop synchronous and metachronous neoplasms, compared to patients with large polypoid colorectal neoplasms (LP-CRNs).

Methods

From 2007 onwards, all endoscopists (faculty and trainees) receive regular extensive training in the detection, diagnosis and resection of NP-CRNs.[14] The training curriculum consists of lectures, video-training using accredited programs and personal feedback during colonoscopy.[14] Special attention is given to the application of selective chromo-endoscopy and endoscopic mucosal resection (EMR). The present study was approved by the Medical Ethical Review Committee of the Maastricht University Medical Centre (MEC 14-4-046), Dutch trial register (NTR4844). The need for individual informed consent was waived.

Cohort

Between February 2008 and February 2012, all patients who underwent colonoscopy for screening, surveillance or symptoms, were included. This was before the start of the national CRC screening program. Patients aged less than 18 years, with hereditary polyposis syndrome, inflammatory bowel disease or prior colectomy were excluded. All findings within the first 6 months after the first colonoscopy were regarded as baseline findings. The majority of colonoscopies were performed by endoscopy trainees under direct supervision of 11 senior endoscopists, who ensured quality and helped with resections. All patients received split-dose bowel cleansing. High-definition Pentax endoscopes were used.

Post-polypectomy surveillance colonoscopy was performed according to national[15] and international guidelines.[16, 17] Three- and 5-year surveillance intervals were recommended after resection of LSTs or LP-CRNs. Piecemeal resection was additionally followed by surveillance colonoscopies within 6 months to ensure radicality of resection. Clinical and surgical follow-up data were collected for each patient with large (≥10mm) colorectal neoplasms (CRNs) at index colonoscopy up until 6 years after inclusion or until death occurred.

Definitions

LSTs are colonic lesions growing laterally along the mucosa rather than upward (luminal) or downward (submucosal), with a minimal diameter of 10mm (Paris 0-IIa, 0-IIb, 0-IIa+IIc or 0-IIa+Is).[5] Serrated lesions were included for descriptive purposes, but excluded in the risk analyses. LP- CRNs are defined as polypoid neoplasms (Paris 0-Ip, 0-Is or 0-Isp) of at least 10mm in size. The colonic location was referred to as either proximal or distal from the splenic flexure. Lesion size was measured using a biopsy forceps/minisnare. Patients with both LSTs and LP-CRNs were considered as LST patients.

LSTs were classified based on their endoscopic appearance using the Kudo classification into granular and non-granular.[5] Granular LSTs are classified into granular homogeneous subtype (LST-G-H) and granular nodular mixed subtype (LST-G-NM). Non-granular LSTs are classified into non-granular flat elevated subtype (LST-NG-FE) and non-granular pseudo-depressed subtype (LST-NG-PD).

Detection of LSTs

Colonoscopy records including photo-documentation were independently reviewed by two study investigators (RMMB and LCC). In case of uncertainty, data were reviewed by the study supervisor (SSD) and discussed to achieve consensus. The location of neoplasms, size, shape (Paris classification,[18] Kudo classification of LSTs[5]), histopathology, and resection modality (i.e., endoscopic resection [en-bloc versus piecemeal] or surgery) were recorded.

The histopathology of all CRNs was addressed by GE pathologists according to the World Health Organization classification.[19] CRNs comprised adenomas, serrated lesions and early cancers. Large flat lesions that turned out to be advanced carcinoma (T2-4) after biopsy or resection were not classified as LSTs. Suspected CRNs with normal or inflammatory histology, were excluded from analysis. Adenomas were subdivided into tubular, tubulovillous, and villous adenomas. Submucosal invasion (SMI) was defined as carcinogenic cells invading the muscularis mucosae. Serrated lesions were subdivided into hyperplastic polyps, sessile serrated lesions (SSL) with and without dysplasia, and traditional serrated adenomas (TSA).

Endoscopic resection was considered complete when careful visual inspection showed no residual neoplastic tissue. All reports of follow-up colonoscopy were reviewed for the presence/absence of neoplastic tissue at the previous location of the LST. The presence of visually and/or histologically confirmed neoplastic tissue after successful resection was considered as residue/recurrence. Surgery reports and referral letters were reviewed and surgery was categorized into primary surgery (without endoscopic resection attempt) and additional surgery (after endoscopic resection attempt).

Statistical analysis

Numerical variables were presented with means (standard deviation; SD), while numbers (%) were used for categorical variables. Time trends in LST prevalence were tested using a chi-square or Fisher's exact test and time trends in treatment were tested using a binary logistic regression model for surgical referral (yes/no) and endoscopic en-bloc resection (yes/no) correcting for year of study, LST size, and the presence of SMI. Colonoscopic findings at index colonoscopy between LST patients and LP-CRN patients were compared using chi-square tests for binary variables and independent-samples t-tests for numeric variables. We compared findings during follow-up colonoscopy between both groups using a multivariable logistic regression model for binary variables. Because

of the excessive zero count in some numerical variables, Poisson regression analysis with zero-inflation correction was used to compare the means between groups. In addition, the number of CRNs at index colonoscopy and the number of follow-up colonoscopies were accounted for in both models. In a subanalysis, the same aforementioned models were applied in LST patients to compare subtypes and size (LSTs <20mm and ≥20mm). In the case of small groups (n<20), an additional Fisher's exact test was performed. The death-censored event-free rate was compared between LST and LP-CRN patients using a Cox regression model correcting for age and sex, in which event is the detection of CRNs with high grade dysplasia (HGD) or SMI. Two-sided *P* values of 0.05 or less were considered statistically significant. IBM SPSS version 23 was used for all analysis, except for the zero-inflation corrected model, which was analyzed using R statistics version 3.1.2 by using the Political Science Computational Laboratory package (PSCL).[20]

Results

Figure 4.1 shows the study flowchart. Between February 2008 and February 2012, 8120 patients were examined (mean age: 58.9 years [SD 16.0], 46.0% men). Indications for colonoscopy were symptoms (84.6%), screening (6.7%) or surveillance (8.7%). At the index colonoscopy, 223 LSTs in 188 patients were found (2.3% of all patients). Furthermore, 810 LP-CRNs were found in 610 patients at index colonoscopy (7.5% of all patients). The mean LP-CRN size was 19.0mm (SD 14.4, range 10-130 mm) and did not significantly differ from that of LSTs, namely 19.4mm (SD 10.3, range 10-70mm, *P*=0.686).

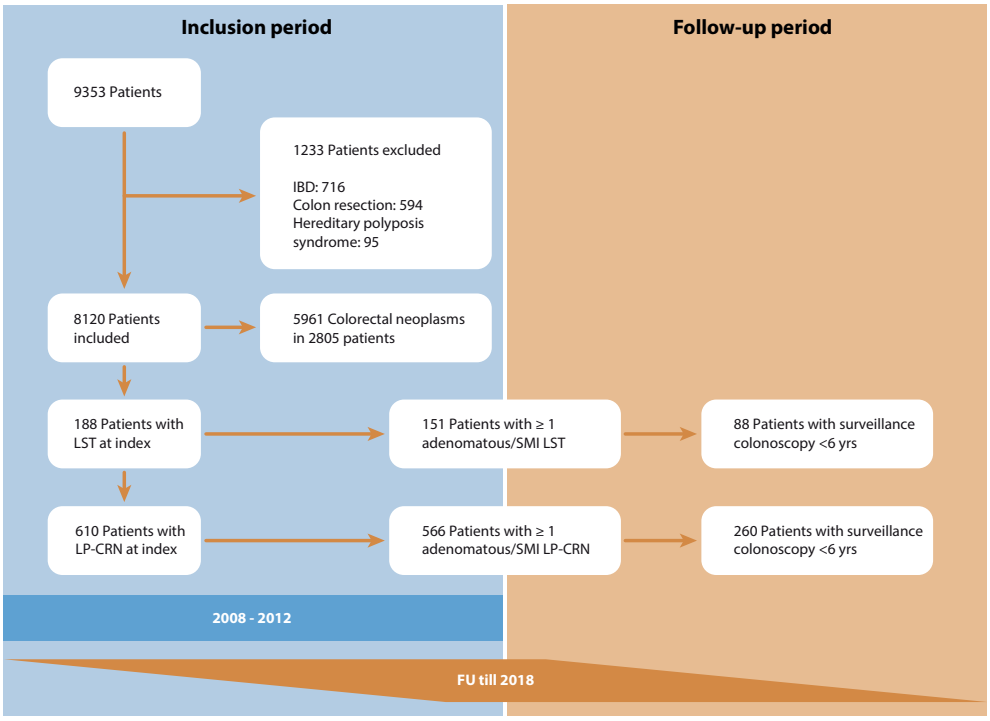


Figure 4.1: Flowchart explaining the data collection. | *Some excluded patients presented with not one but two exclusion criteria. SMI: submucosal invasion, FU: follow-up.*

Photo documentation was available in 96.4% of LST cases. The proportion of LST-G-H, LST-G-NM, LST-NG-FE and LST-NG-PD LSTs was 18.6%, 8.8%, 62.8% and 9.8%, respectively. **Table 4.1** shows the patient characteristics and histopathology, by LST subtype at baseline. The LST detection rate and rate of HGD or SMI within LSTs did not significantly change over time (*P*=0.935, *P*=0.760 and *P*=0.277 respectively; **Table 4.2**).

Table 4.1: Endoscopic and histologic characteristics of LSTs. | *LST-G-H: homogenous granular LSTs; LST- G-NM: nodular mixed granular LSTs; LST-NG-FE: flat elevated non-granular LSTs; LST-NG-PD: pseudo-depressed non-granular LSTs.*

	LST-G-H (n=40)	LST-G-NM (n=19)	LST-NG-FE (n=135)	LST-NG-PD (n=21)	Unknown (n=8)	**Total (n=223)**
Mean size in mm (SD)	22.2 (9.7)	26.8 (9.3)	16.9 (9.0)	21.9 (10.3)	27.6 (20.1)	**19.4 (10.3)**
Location, n (%)						
Cecum	18 (45.0)	7 (36.8)	31 (23.0)	6 (28.6)	3 (37.5)	**65 (29.1)**
Ascending colon – splenic flexure	17 (42.5)	5 (26.4)	78 (57.7)	9 (42.9)	2 (25.0)	**111 (49.3)**
Descending colon – sigmoid	3 (7.5)	2 (10.6)	18 (13.3)	2 (9.6)	2 (25.0)	**26 (11.6)**
Rectum	2 (5.0)	6 (31.6)	8 (5.9)	4 (19.0)	1 (12.5)	**21 (9.4)**
Histopathology, n (%)						
Submucosal invasion	1 (2.5)	3 (15.8)	4 (2.9)	5 (23.8)	1 (12.5)	**14 (6.2)**
Adenoma HGD	8 (20.0)	9 (47.4)	18 (13.3)	7 (33.3)	2 (25.0)	**44 (19.7)**
Adenoma LGD	24 (60.0)	4 (21.1)	68 (50.4)	7 (33.3)	3 (37.5)	**106 (47.5)**
SSL	3 (7.5)	1 (5.3)	24 (17.7)	1 (4.8)	0 (0)	**29 (13.0)**
TSA	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	**1 (0.4)**
Hyperplastic polyp	4 (10.0)	2 (10.5)	20 (14.8)	1 (4.8)	2 (25.0)	**29 (13.0)**
Resection, n (%)						
En-bloc resection	13 (32.5)	2 (10.5)	63 (46.7)	5 (23.8)	2 (25.0)	**85 (38.1)**
Piecemeal resection	13 (32.5)	7 (36.8)	37 (27.4)	8 (38.1)	2 (25.0)	**67 (30.0)**
Surgery	6 (15.0)	8 (42.1)	10 (7.4)	5 (23.8)	4 (50.0)	**33 (14.8)**
No resection	8 (20.0)	2 (10.6)	25 (18.5)	3 (14.3)	0 (0)	**38 (17.1)**

Table 4.2: Time-trends in LST diagnosis. | *CRN: colorectal neoplasm. *Surveillance indicated before the start of the study.*

Findings	Year 1	Year 2	Year 3	Year 4
Number of colonoscopies	1941	2098	2074	2007
Number of CRNs (mean per colo)	1521 (0.8)	1856 (0.9)	1718 (0.8)	2150 (1.1)
Number of LSTs (% of lesions)	54 (3.6)	55 (3.0)	54 (3.1)	60 (2.8)
Indication of colonoscopy (% of colonoscopies):				
Screening	161 (8.3)	145 (6.9)	130 (6.3)	108 (5.4)
Surveillance*	204 (10.5)	162 (7.7)	181 (8.7)	155 (7.7)
Symptoms	1576 (81.2)	1791 (85.4)	1763 (85.0)	1744 (86.9)
Submucosal invasion (% of LSTs)	1 (1.9)	5 (9.1)	5 (9.3)	3 (5.0)
High grade dysplasia (% of LSTs)	9 (16.7)	13 (23.6)	9 (16.7)	11 (18.3)
Proximal location (% of LSTs)	45 (83.3)	36 (65.5)	46 (85.2)	50 (83.3)
10-19 mm (% of LSTs)	27 (50.0)	30 (54.5)	27 (50.0)	36 (60.0)
20-29 mm (% of LSTs)	15 (27.8)	7 (12.7)	15 (27.8)	16 (26.7)
≥30 mm (% of LSTs)	12 (22.2)	18 (32.7)	12 (22.2)	8 (13.3)

Resection

Of the 223 LSTs found, 152 were resected endoscopically; 38 LSTs were left in place (older age, comorbidities, frailty, patient's preference). Twenty-two LSTs were primarily referred for surgical resection (suspected malignancy, technical difficulty for endoscopic resection). In 11 cases additional surgery was performed after attempted endoscopic resection. Logistic regression after correction for lesion size and the presence of SMI showed that the proportion of surgical referrals remained stable over time (odds ratio [OR] per year: 0.8, 95% confidence interval [CI]: 0.5-1.2, *P*=0.220) while the proportion of endoscopic en-bloc resections increased (OR per year: 1.5, 95% CI: 1.1 – 1.9, *P*=0.007) (**Figure 4.2**). Among LST patients who underwent surveillance, 15 (14.2%) showed residue/recurrence.

Synchronous neoplasms

We compared 151 patients with one or more adenomatous or SMI LSTs at index colonoscopy, with 566 patients with one or more adenomatous or SMI LP-CRN at index colonoscopy (**Table 4.3**). At index colonoscopy, the mean number of synchronous CRNs, adenomas and CRNs with HGD or SMI were significantly higher (*P*<0.001, *P*<0.001 and *P*=0.001 respectively) in LST patients than in LP-CRN patients. The mean number of synchronous CRCs was significantly lower in LST patients versus LP-CRN patients (0.17 vs 0.28, *P*=0.003). LST patients had significantly more NP-CRNs versus LP-CRN patients (mean of 1.52 vs 0.09, *P*<0.001).

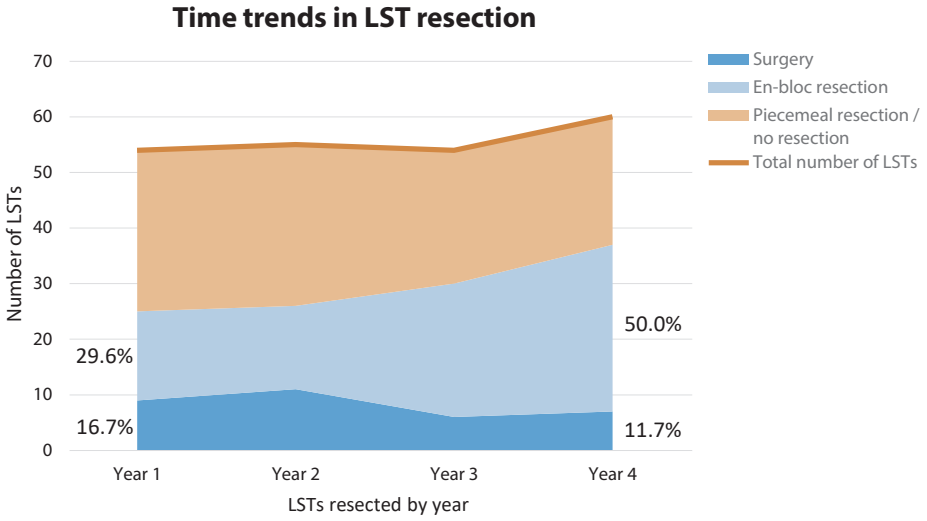


Figure 4.2: Time trends in resection of LSTs after training at our institution.

Table 4.3: Synchronous findings in patients with ≥1 LST at index colonoscopy with patients with ≥1 large polypoid colorectal neoplasm (LP-CRN) at index colonoscopy. | *CRN: colorectal neoplasm, HGD: high grade dysplasia, SMI: submucosal invasion, yrs: years.*

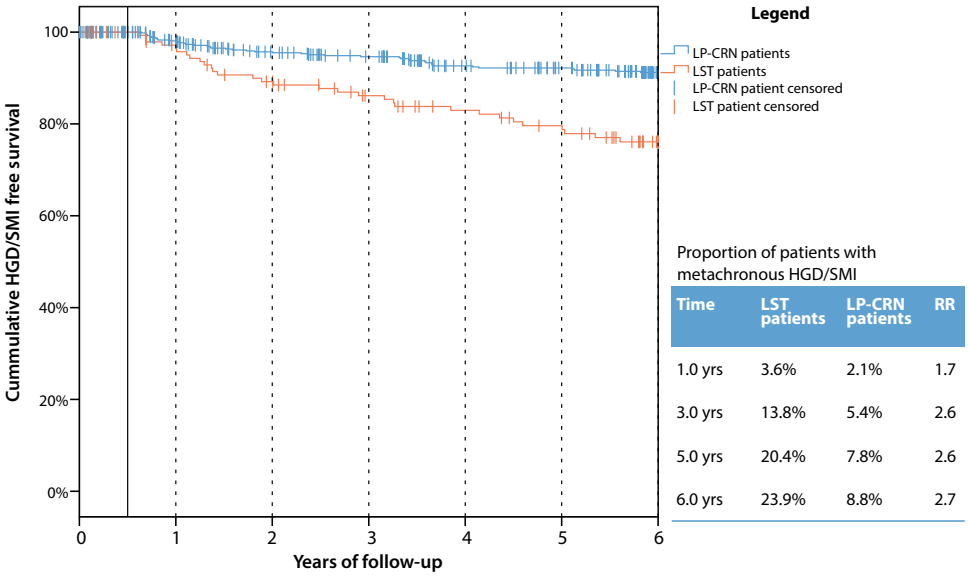
Clinical features	Patients with ≥1 neoplastic LST (n=151)	Patients with ≥1 LP-CRN (no LSTs) (n=566)	*P* value
Mean age, yrs (SD)	67.6 (10.7)	67.9 (11.5)	0.800
Male (%)	83 (55.0)	313 (55.3)	0.942
Mean FU time, yrs (SD)	5.11 (1.76)	4.90 (1.92)	0.189
Mean time till last FU scopy, yrs (SD)	3.59 (1.65)	3.55 (1.70)	0.881
Mean number of FU scopies (SD)	2.15 (1.36)	1.51 (0.79)	<0.001
Mean number of CRNs at index (SD)	3.34 (2.61)	2.34 (2.38)	<0.001
Mean number of non-polypoid CRNs at index (SD)	1.52 (1.00)	0.09 (0.37)	<0.001
Mean number of CRNs with HGD/ SMI at index (SD)	1.96 (1.56)	1.51 (1.17)	0.001
Mean number of adenomas at index (SD)	2.71 (2.33)	1.90 (2.04)	<0.001
Mean number of CRCs at index (SD)	0.17 (0.42)	0.28 (0.47)	0.003
Mean number of serrated neoplasms at index (SD)	0.50 (1.14)	0.37 (0.88)	0.221

Metachronous neoplasms

LST patients more often had a surveillance colonoscopy within 6 years than LP-CRN patients (58.3% vs 45.9%, *P*=0.007) and the interval between index and surveillance was significantly shorter (1.85 vs 2.55 years, *P*<0.001). During the first surveillance colonoscopy, LST patients more often had an advanced adenoma than LP-CRN patients (22.7% vs 12.7%, *P*=0.024). Five CRCs were found at first surveillance colonoscopy, all in LP-CRN patients and none in LST patients (*P*=0.336).

During follow-up, LST patients more often underwent surveillance colonoscopies than LP-CRN patients (58.3% vs 45.9%). Overall, 36.4% of all patients with adenomatous LSTs at baseline developed one or more CRNs with HGD or SMI during follow-up compared with 15.8% of patients with LP-CRNs at baseline. After correction for the number of CRNs at index and the number of follow-up colonoscopies, HGD or SMI was significantly more often found during follow-up in LST patients than LP-CRN patients (36.4% vs 15.8%, *P*<0.001). A Cox regression model correcting for age and gender showed a hazard ratio of 2.9 (95% CI: 1.8 – 4.6) for LST patients to develop a CRN with HGD or SMI within 6 years (**Figure 4.3**). This association was not materially influenced by the initial indication for colonoscopy. The mean number of adenomas found during follow-up was significantly higher for LST patients versus LP-CRN patients (1.82 vs 1.24, *P*=0.032; **Table 4.4**). During follow-up, LST patients more often had metachronous NP-CRNs than LP-CRN patients (44.3% vs 20.0%, *P*<0.001).

Within LST patients, patients with LST-NG-PD developed fewer adenomas during follow-up than patients with other subtypes (mean 0.82 vs 2.08, *P*=0.018). LST patients with LSTs of 20 mm or greater developed only slightly more neoplasms (mean 2.00 vs 1.89, *P*=0.045) than patients with smaller LSTs (<20 mm). There was no significant effect of LST size on the number of adenomas.



Proportion of patients with metachronous HGD/SMI

Time	LST patients	LP-CRN patients	RR
1.0 yrs	3.6%	2.1%	1.7
3.0 yrs	13.8%	5.4%	2.6
5.0 yrs	20.4%	7.8%	2.6
6.0 yrs	23.9%	8.8%	2.7

Figure 4.3: Colorectal neoplasm (CRN) with HGD or SMI free survival of six years of follow-up in patients with large CRNs at index (Kaplan-Meier). | *Follow-up started after 0.5 years (vertical line) since all CRNs found within 6 months were counted as index CRNs.*

Table 4.4: Metachronous lesions in patients with LSTs and patients with LP-CRNs at index. | *Patients without any follow-up were excluded. P values after correction for number of follow-up colonoscopies and number of neoplasms at index.*

Clinical features during follow up	Patients with ≥1 neoplastic LST(n=88)	Patients with ≥1 LP-CRN (no LSTs) (n=260)	*P* value
Patients with ≥1 CRN (%)	63 (71.6)	141 (54.2)	0.050†
Mean number of CRNs (SD)	2.80 (4.99)	1.45 (2.36)	0.002‡
Patients with ≥ 1 adenoma (%)	63 (71.6)	134 (51.5)	0.015†
Mean number of adenomas (SD)	1.82 (2.09)	1.24 (1.93)	0.032‡
Patients with ≥ 1 CRN with SMI (%)	1 (1.1)	5 (1.9)	0.824†
Mean number of CRNs with SMI (SD)	0.01 (0.11)	0.02 (0.14)	0.411‡
Patients with ≥ 1 CRN with HGD/SMI (%)	32 (36.4)	41 (15.8)	<0.001†
Mean number of CRNs with HGD/SMI (SD)	0.51 (1.03)	0.22 (0.57)	0.002‡
Patients with ≥ 1 non-polypoid CRN (%)	39 (44.3)	52 (20.0)	<0.001†
Mean number of non-polypoid CRNs (SD)	1.16 (2.73)	0.34 (0.90)	<0.001‡

†Logistic regression model ‡Poisson regression corrected for zero-inflation. CRN: colorectal neoplasm, HGD: high grade dysplasia, SMI: submucosal invasion.

Discussion

In this population-based colonoscopy cohort, the prevalence of LSTs was low and remained stable over time. After training, endoscopic resection of LSTs became more efficient, along with increasing endoscopists' experience.

An important finding of our study is that LST patients not only have more synchronous but also more metachronous neoplasms (including more HGD/SMI) compared to LP-CRN patients. The number of surveillance colonoscopies performed was also higher in LST patients. This may have been the result of technical difficulties with endoscopic resection of LSTs and of more synchronous CRNs found in such patients. Therefore, more intensive surveillance could detect additional small CRNs. After correction for the number of surveillance colonoscopies, however, the number of metachronous CRNs with HGD or SMI remained significantly higher in LST patients. Hypothetically, longer surveillance intervals facilitate adenomas to progress and become more advanced. LP-CRN patients had longer intervals between the index and first surveillance colonoscopy than LST patients, but fewer metachronous CRNs with HGD or SMI were found. Of note is that all five cases of CRC detected at first surveillance colonoscopy were diagnosed in LP-CRN patients, while we previously found a low rate of post-colonoscopy CRCs in our region (0.8 per 1000 colonoscopies, 0.34 per 1000 person-years of follow-up).[21]

Little is known about the influence of neoplasm shape on the rate of metachronous CRNs. A previous study in a US-based population compared findings of the first surveillance colonoscopy in patients with NP-CRNs at index with those of patients with polypoid CRNs at index.[22] Patients with NP-CRNs more often had advanced neoplasms at baseline (63% vs 25%) and were more often diagnosed with advanced neoplasms (relative risk 1.6, 95% CI: 1.05 – 2.6) during the first surveillance colonoscopy than patients with polypoid CRNs. Cohorts of LSTs show high numbers of synchronous CRNs in patients with NP-CRNs and LSTs.[12, 13, 22, 23] Our findings confirm and expand on these data in comparison with polypoid neoplasms of comparable size. In a cohort of LST patients, synchronous CRNs were common among patients with large LSTs.[13] Most patients in that study were referred for endoscopic resection of LSTs. Unfortunately, a control group was lacking. One may speculate that endoscopists stop looking for additional CRNs after the detection of a large LST.[13] In our population, the number of synchronous CRNs was much lower and the average size of LSTs was smaller than in the US study. We cannot exclude the possibility that some of the metachronous CRNs in our cohort may actually have been missed synchronous CRNs. Nevertheless, strict surveillance is required in LST patients to diagnose CRNs and prevent development into advanced CRNs. According to current international post-polypectomy surveillance guidelines, a 3-year surveillance interval is recommended after complete removal of advanced adenomas.[24, 25] No specific advice has been provided regarding LST patients. In our study, the number of CRCs found during surveillance was low and did not differ significantly between LST and the LP-CRN patients. On the other hand, we more frequently found advanced neoplasia in LST patients. Most recent surveillance guidelines have become more conservative than before, based on a lower than previously estimated absolute risk of CRC.[25, 26] The guidelines state that further improvements in the quality of index colonoscopy would be more effective. Perhaps new detection and determination techniques such as artificial intelligence could result in an even lower risk of CRC.[27] Until then, data investigating the long-term CRC risk in the LST subgroup are necessary to reveal whether this subgroup may benefit from stricter surveillance.

An explanation for the increased risk of metachronous CRNs in LST patients remains unknown. Underlying genetic predisposition and yet undiscovered environmental factors[22] may play a role.

Different molecular pathways may be involved in LSTs.[28] Of note is that patients with LST-NG-PD, the subtype with the highest risk of SMI, have the lowest number of metachronous neoplasms. In the present study, special attention was given to distinguish suspected residue/recurrence from metachronous CRNs. Hence, residue/recurrence does not explain our findings. The detection of NP-CRNs is strongly dependent on high-quality bowel preparation.[29, 30] In our study, only patients with adequate bowel preparation and complete visualization of the colonic mucosa were included.

The 2.3% LST prevalence in our population was higher than the pooled prevalence of 0.8% found in a meta-analysis.[31] A possible explanation is that our endoscopists were trained in the detection and resection (EMR) of NP-CRNs.[14] The detection rate of LSTs was stable over time. Of note, our university hospital functions as a secondary care referral center for colonoscopies. Between 2008 and 2012, the number of referred LST cases was low.

Large flat serrated lesions were considered to be LSTs, but were excluded in the risk analysis. The discussion as to whether serrated lesions should be included or not as LSTs is ongoing. Some LST studies have excluded serrated lesions[32] while others did not.[33]

Resection skills seemed to improve at group level over time, as shown by an increase in en-bloc resection rates. In our study we found a relatively high (14.2%) residue/recurrence rate after endoscopic resection of LSTs, which is in line with previous data.[10] Endoscopic submucosal dissection (ESD) was not available in our center between 2008 and 2012. The use of ESD may increase en-bloc resection rates and thereby reduce recurrence rates.[34]

The strengths and limitations of the current study should be acknowledged. To our knowledge, this is the first study examining time-trends in LST diagnosis and treatment, and studying the metachronous findings of LSTs compared to a control group of comparable sized neoplasms. Furthermore, individual quality measures for colonoscopy (e.g., cecal intubation and adenoma detection rate) were recorded. Given the trained environment in which the study was performed, our data cannot be extrapolated to general clinical practice. In addition, most colonoscopies were performed by trainee endoscopists, arguably leading to lower adenoma detection rates. In a recent study the adenoma detection rates in trainees were not much different from their supervisors, and was dependent on the performance of their supervisor.[35] Furthermore, neoplasm prevalence may be different in other patient populations, for instance in screening colonoscopy populations.

An important limitation of our study is that surveillance colonoscopies were not performed in all patients. Older patients, patients with comorbidities and patients who declined surveillance were lost to follow-up. Although this reflects the real-life situation, we recognize that this might have biased the results. To mitigate bias, we adjusted the logistic regression model by baseline neoplasms and the number of follow-up colonoscopies performed. In addition, at the time of data-collection the endoscopic Kudo classification was not widely used. To identify potentially misclassified lesions, photo documentation of all large sessile CRNs was systematically reviewed. Another limitation is that complete resection rates were primarily estimated based on endoscopic findings without the routine use of dye, possibly resulting in an underestimation of residues.[36]

Conclusion

In this population-based cohort, LSTs have a low and stable prevalence over time. Patients with LSTs had a higher risk of developing metachronous CRNs with HGD or SMI than patients with LP-CRNs, suggesting that these patients may benefit from stricter surveillance. Based on these findings, endoscopic treatment and surveillance recommendations for LST patients should be optimized.

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Evaluation of polypectomy quality indicators of large, nonpedunculated colorectal polyps in a nonexpert, bowel cancer screening cohort

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Abstract

Background & aims

With the introduction of the national bowel cancer screening program, the detection of sessile and flat colonic lesions ≥20mm in size, defined as large non-pedunculated colorectal polyps (LNPCPs), has increased. The aim of this study was to examine the quality of endoscopic treatment of LNPCPs in the Dutch screening program.

Methods

This investigation comprised two related, but separate, sub-studies (one with a cross-sectional design and one with a longitudinal design). The first examined prevalence and characteristics of LNPCPs in data from the national Dutch screening cohort, from February 2014 until January 2017. The second, with screening data from five endoscopy units in the Southern part of the Netherlands from February 2014 until August 2015, examined performance on important quality indicators (technical and clinical successes, recurrence rate, adverse event rate, and surgery referral rate). All patients were part of the national Dutch screening cohort.

Results

In the national cohort, a LNPCP was detected in 8% of participants. Technical and clinical success decreased with increasing LNPCP size, from 93% and 96% in 20 to 29mm lesions to 85% and 86% in 30 to 39mm lesions and to 74% and 81% in ≥40mm lesions (P<0.001; P=0.034). The cumulative recurrence rate at 12 months increased with LNPCP size, from 9% to 22% and 26% in the respective size groups (P=0.095). The adverse event rate was 5%. The overall surgical referral rate for non-invasive LNPCPs was 7%.

Conclusions

In this performance of two sub-studies it was shown that quality parameters for endoscopic resection of large polyps in the Dutch screening cohort are not reached, especially in ≥30mm polyps. Endoscopic resection of large polyps could benefit from additional training, quality monitoring, and centralization either within or between centers.

Introduction

One of the goals of the fecal immunochemical test (FIT) based bowel cancer screening program (BCSP) is to prevent cancer by removing high-risk advanced colorectal neoplasia.[1] Large non-pedunculated colorectal polyps (LNPCPs), defined as sessile and flat colonic lesions ≥20mm in size, are believed to be especially at risk of progression to cancer and bear the risk of submucosal invasion, which increases with size. In addition, endoscopic resection is technically more challenging and associated with a higher risk of adverse events and recurrence.[2] With LNPCPs expected to account for a significant amount of care within screening programs, quality of care for these lesions is of great importance.

The Dutch BCSP is controlled on quality indicators such as the cecal intubation rate (CIR), Gloucester comfort scale, and adenoma detection rate (ADR) to optimize the outcome of colonoscopy.[1, 3] Until now, no performance indicators exist for the quality of polypectomy, whereas the need for such measures has been recognized in the field.[4, 5] Quality of endoscopic care for LNPCPs can be described by two pillars: effectiveness of endoscopic resection, displayed by technical and clinical success rate, recurrence rate, performing surveillance colonoscopy, and referral to surgery, and safety of endoscopic care for LNPCPs, displayed by adverse event rate. Current evidence suggests there is still room for improvement regarding quality of endoscopic care for LNPCPs, because recurrence after endoscopic mucosal resection (EMR) is significant,[6] compliance with surveillance guidelines is suboptimal[7] and non-invasive LNPCPs are frequently referred for surgery.[8, 9] Although expert centers have reported their outcomes of EMRs performed on LNPCPs, little is known regarding these outcomes in a screening setting. In this performance of two sub-studies, we evaluated the quality of endoscopic care for LNPCPs in the Dutch BCSP. Main outcomes were technical and clinical success, recurrence rate, surveillance compliance, adverse event rate of endoscopic therapy and surgery referral rate for LNPCPs.

Methods

For this study, cross-sectional data of the Dutch screening registry were used to determine the LNPCP prevalence, supplemented by longitudinal, regional screening data for in-depth analysis. Within the Dutch BCSP, citizens aged 55 to 75 years are invited to perform a FIT once every two years. Participants with positive FIT results are invited for a screening colonoscopy. We included all screening colonoscopies performed from the onset of the screening program in February 2014 up to January 2017. Non-screening colonoscopies were excluded.

National registry

Within the national BCSP, endoscopists have to be certified for quality assurance purposes. Certification involves a minimum number of colonoscopies and polypectomies per year, achievement of predefined quality levels for colonoscopy (CIR ≥90% and ADR ≥20%), a mandatory e-learning module (including Paris classification practicing), and evaluation of polypectomy skills by live practice and videos.[3, 11] Formal training in advanced polypectomy was non-existent at that time. Registration of specific parameters is obligatory within the screening program. These parameters include colonoscopy characteristics (i.e., Boston Bowel Preparation Score, CIR, cecal withdrawal time and inspection time) and endoscopic aspects of colorectal lesions (i.e., size, location [proximal location was defined as proximal to the splenic flexure], Paris classification, predicted histology, and resection technique). These data are stored in a national information system, called ScreenIT.[10]

The national screening organization provided national screening data, consisting of the total number of index colonoscopies and the number of index colonoscopies with one or more LNPCP detected between February 2014 and January 2017. Of the latter, colonoscopy characteristics and endoscopic aspects were described. Conclusions regarding histology, as evaluated by accredited pathologists, were not available for individual polyps, because of a lack of coupling of endoscopy reports and pathology data. Furthermore, because only index colonoscopies were collected within the national screening organization, endoscopic or surgical follow-up data were also not available.

Regional cohort

For evaluation of polypectomy quality indicators, follow-up data were needed of which the national cohort did not provide. Therefore, a prospective regional cohort of screening colonoscopies (part of the national registry) was used, containing the same parameters as the ScreenIT database. Patients were included if they had a screening colonoscopy between February 2014 and August 2015 in one of five endoscopy units in the Southern part of the Netherlands: Maastricht University Medical Centre+, Zuyderland Medical Centre [two locations], Maxima Medical Centre Veldhoven and Diagnostic Centre Maastricht. None of these centres was a referral centre. In addition to the colonoscopy parameters and polyp characteristics registered in the national cohort, data concerning patient characteristics (medical history and lifestyle factors), more detailed lesion characteristics (endoscopic, histopathological), endoscopic or surgical therapy, and 3-year follow-up including surveillance endoscopies were collected. In contrast to the ScreenIT data, coupling of endoscopic to histopathological findings at the patient and individual polyp level was warranted, providing the possibility of in-depth analysis.

The Medical Ethical Review Committee of the Maastricht University Medical Center (MEC 14-4-046) approved the study and waived the need for informed consent. The study is registered at the Dutch Trial Register (NTR4844).

Outcome

The main outcomes were technical and clinical success, recurrence rate, surveillance compliance, adverse event rate, and surgery referral rate of LNPCPs. We calculated the size, morphology, site and access (SMSA) score for every LNPCP, with both easy and difficult accessibility, because this feature was not reported in our data. Hence, LNPCPs were categorized into SMSA-score 3 (both calculated scores <12), SMSA-scores 3 to 4 (lower score <12 and upper score ≥12) and SMSA-score 4 lesions (both calculated scores ≥12). Technical success was defined as a macroscopically complete resection during the first attempt, as judged by the endoscopist. Clinical success was defined as the absence of neoplasia 12 months after primary treatment. Clinical success included cases that never showed recurrence in these 12 months, but also cases that showed recurrence after 6 months, were treated successfully and showed no signs of neoplasia at the 12 month follow-up colonoscopy. Because of variation in surveillance intervals used in our regional cohort, we determined the recurrence rate after 6 and 12 months, and after 3 years. Recurrence was defined as all visible neoplastic tissue (size ≥1mm) in and around (within 5mm) the scar. The recurrence rate was calculated for all macroscopically complete, endoscopically resected LNPCPs and was cumulative (cumulative recurrence at 12 months included the lesions that showed recurrence at 12 months, but also the lesions that showed recurrence at 6 months). In addition, recurrence rates after piecemeal and en-bloc EMR were determined after 12 months. Initial (macroscopically) complete resection was defined as complete resection of neoplastic tissue at the index colonoscopy, without residual neoplastic tissue being present at the resection site. Surveillance compliance was determined by comparing advised surveillance intervals with the recommended intervals in the applicable guidelines, namely the

Dutch guidelines of colonoscopy surveillance (2013) and the European Society of Gastrointestinal Endoscopy (ESGE) post-polypectomy colonoscopy surveillance guidelines (2013).[12, 13] Surveillance intervals according to these guidelines were 4-6 months for piecemeal resection and 3 years for en-bloc R0-resection and serrated lesions.

Adverse events were divided into post-polypectomy syndrome (abdominal pain), direct post-polypectomy bleeding (identification of bleeding within 24 hours), delayed bleeding (symptoms of bleeding >24 hours after endoscopic therapy), and deep mural injury (DMI). Surgery referral rate was defined as the proportion of LNPCPs referred for surgery and was divided into primary and secondary surgery. Primary surgery was defined as surgical treatment without prior attempt at endoscopic resection. Secondary surgery was defined as surgery after prior endoscopic resection. Referral for surgery was performed without consultation of expert endoscopists. Finally, experience and dedication of endoscopists was determined and association with technical success, and direct surgery referral was explored. Experienced endoscopists were defined as endoscopists with more than 10 years of experience, conforming to the definition used by Oka et al.[14] Dedicated endoscopists were defined as endoscopists who were executing advanced polypectomy programs in their centre. Endoscopists were stratified according to their experience and dedication into three groups: non-experienced, non-dedicated endoscopists; an intermediate group, consisting of experienced, non-dedicated endoscopists and non-experienced, dedicated endoscopists; and experienced, dedicated endoscopists.

The performance on the different quality indicators within the Dutch screening program cohort was compared with benchmarks. These benchmarks were based on current evidence, including a systematic review evaluating endoscopic resection of large colorectal polyps, a systematic review evaluating local recurrence rates in large colorectal polyps and the experience in the English BCSP.[2, 6, 15] Furthermore, the prevalence, endoscopic appearance, and location of LNPCPs was evaluated. The prevalence of LNPCPs was calculated at the patient level and was defined as the proportion of patients presenting with one or more LNPCPs during index colonoscopy.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics, recurrence rates, and surgical referral percentages were analyzed with descriptive statistics and are reported as proportions (%) for categorical variables and mean with standard deviation (SD) or median with interquartile range (IQR) for numerical variables. To verify whether the regional cohort was a representative sample of the national cohort, the one sample *t*-test was used for continuous measures and the Chi-Square test for goodness of fit for categorical measures. One-way ANOVA, Kruskal-Wallis, Chi Square or the Fisher's exact tests was used to compare groups within one cohort. *P* values ≤0.05 were considered statistically significant. Although there was multiple testing of outcome data arising from individual patients, no corrections to *P* values were made because the purpose of the research was not to test any specific hypotheses about quality, but to describe important measures of quality and to highlight any potential differences. Therefore, all *P* values are presented uncorrected for multiple testing and should be taken as descriptive, only. Notwithstanding, it should be noted that with any nominally significant *P* value in this report, except for where $P<0.001$, correction for multiple testing by the method of Bonferroni would have removed the significance from that finding.

In case of missing data, complete case analysis was performed. To assess performance differences between various centres in the regional cohort, leave-one-out cross-validation analyses were performed for main outcome measures.

Results

Prevalence of LNPCPs in the screening cohort

Patient and polyp characteristics of both the national and regional screening cohort are provided in **Tables 5.1** and **5.2**. In the national screening cohort, 124,155 patients underwent a colonoscopy after a positive FIT, and the prevalence of LNPCP patients was 8%. A total of 11,130 LNPCPs were found, of which 5788 (52%) were located in the proximal colon. The median size of LNPCPs was 25.0 mm (20-35), and 2053 (18%) were ≥40mm in size. This subgroup of LNPCPs (≥40mm) was evenly distributed over the proximal and distal colon (1039 vs. 1014, 51% vs. 49%), but mainly located in the rectosigmoid (882/2053, 43%) and right-sided colon segments (873/2053, 43%).

Comparison of the national and regional cohort on patient, polyp, and colonoscopy characteristics confirmed that the regional cohort was a representative sample of the national cohort (**Tables 5.1** and **5.2**). Although there were statistically significant differences in LNPCP prevalence, size, and morphology, these small differences were not considered clinically relevant.

Table 5.1: Patient characteristics in the national and regional cohort. | *P value corresponds to the comparison of national cohort (2014-2017) versus regional cohort (2014-2015), unless stated otherwise (*).*

	National cohort		Regional cohort	
	2014-2017	2014-2015	2014-2015	
Overall patient characteristics	**n = 124 155**	**n = 68 471**	**n = 3085**	***P* value**
Age in years, mean (SD)	67.4 (5.0)	68.0 (4.8)	68.2 (5.4)	0.001 *0.098
Gender, female n (%)	49,502 (40)	27 328 (40)	1229 (40)	0.944
LNPCP patients, n (%)	9772 (8)	5513 (8)	282 (9)	0.011 *0.034
2014	1910 (8)	1910 (8)	156 (10)	
2015	3603 (8)	3603 (8)	123 (8)	
2016	3964 (8)			
2017 (until February)	295 (7)			
LNPCP patient characteristics	**n = 9772**	**n = 5624**	**n = 282**	
Age in years, mean (SD)	67.8 (5.0)	68.1 (4.7)	68.5 (5.1)	0.006 *0.149
Gender, female n (%)	3520 (36)	1976 (35)	99 (35)	0.755
ASA Classification, n (%)				
I			129 (46)	
II			141 (50)	
III			12 (4)	
IV			0	

**statistical comparison between national cohort 2014-2015 and regional cohort 2014-2015*

Table 5.2: LNPCP lesion and colonoscopy characteristics in the national and regional cohort.

	National cohort n = 11 130#	Regional cohort n = 332#	
LNPCP lesion characteristics			***P* value**
Median size, mm (IQR)	25.0 (20-35)	30.0 (20-40)	0.012
Proximal location, n (%)	5788 (52)	175 (53)	0.811
Location			0.067
Colon	8297 (75)	262 (79)	
Cecum/ascending colon	4016 (36)	117 (35)	
Rectum	2833 (25)	70 (21)	
Morphology, n (%)			0.004
Sessile	8107 (73)	267 (80)	
Flat	2904 (26)	65 (20)	
Unknown	83 (1)	0	
Paris classification, n (%)			
Is		267 (80)	
IIa		45 (14)	
IIa+c		7 (2)	
IIb		7 (2)	
IIc		5 (2)	
IIc+a		1 (0.3)	
SMSA-score^, n (%)			
SMSA-3		139 (42)	
SMSA-3/4		96 (29)	
SMSA-4		97 (29)	
Index colonoscopy characteristics			
BBPS ≥6, n (%)	10 696 (96)	275/282 (98)	0.235
Cecal intubation rate, n (%)	10 903 (98)	274/282 (97)	0.315
Mean cecal withdrawal time, minutes (SD)*	29.7 (18.0)	28.4 (14.8)	0.160
Treatment strategy index colonoscopy, n (%)			0.661
Snare resection (with coagulation)	7746 (70)	226 (68)	
Biopsy/not removed	3347 (30)	94 (31)	
Other**	37 (0.3)	2 (1)	

Table 5.2: *(continuation)*

	National cohort n = 11 130#	Regional cohort n = 332#
Histopathologic outcome***, n (%)		
Serrated polyps****		29 (9)
Adenoma, low-grade dysplasia		187 (59)
Adenoma, high-grade dysplasia		48 (15)
Submucosal invasion		55 (17)
Histology of adenomas, n (%)		
Tubular histology		113 (48)
Tubulovillous histology		112 (48)
Villous histology		10 (4)

 # These numbers indicate the total amount of LNPCP lesions found. This differs from the number of LNPCP patients as shown in Table 5.1, due to multiple LNPCP lesions per patient in some cases.
^SMSA stands for size, morphology, site and access of a lesion and reflects the complexity for endoscopic treatment.
** The cecal withdrawal time includes the procedure time.*
*** Other treatment strategies include cold snaring, endoloop or resection by biopsy.*
**** In the national cohort, histopathology cannot be linked to specific lesions. In the regional cohort, 319 of 332 LNPCP lesions were evaluated by the pathologist (the remainder were lost during colonoscopy).*
***** Serrated polyps include hyperplastic lesions (n=11), sessile serrated adenomas (n=15) and traditional serrated adenomas (n=3).*

Technical success rate of endoscopic therapy

Both in the national and regional cohort, approximately 30% of the lesions were not resected during index colonoscopy. In the national cohort, 1189 of 6203 (19%) of the 20 to 29mm LNPCPs were not resected during the initial colonoscopy, while this were 1096 of 2873 (38%) and 1047 of 2054 (51%) for 30 to 39mm and ≥40mm LNPCPs respectively (P<0.001).

In the regional cohort, endoscopic therapy was performed in 266 of 332 (80%) of the LNPCPs (**Figure 5.1**). Most LNPCPs (242/266, 91%) were resected by EMR, whereas 21 of 266 (8%) were resected by hot snaring and 3 of 266 (1%) by endoscopic submucosal dissection (ESD). Technical success was achieved in 231 of 266 cases (87%, 95% CI: 82 – 91). Technical success rates were similar across the different centres (mean 87%, range leave-one-out-analysis 83-89%). Technical success decreased with increasing LNPCP size, with 126 of 135 (93%) in 20 to 29mm, 56 of 65 (86%) in 30 to 39mm and 49 of 66 (74%) in ≥40mm LNPCPs (P=0.001). Technical success was higher in LNPCPs that were resected during the first encounter (211/238, 89%), compared with LNPCPs that were resected in a second colonoscopy (20/28, 71%, P=0.018). Reasons for technical failure were non-lifting of the lesion and/or difficult accessibility of the lesion. Technically failed cases were managed by referral to another center (n=6), referral for surgery (n=12), and endoscopic follow-up with resection of the residual neoplastic tissue during one or multiple follow-up colonoscopies (n=17).

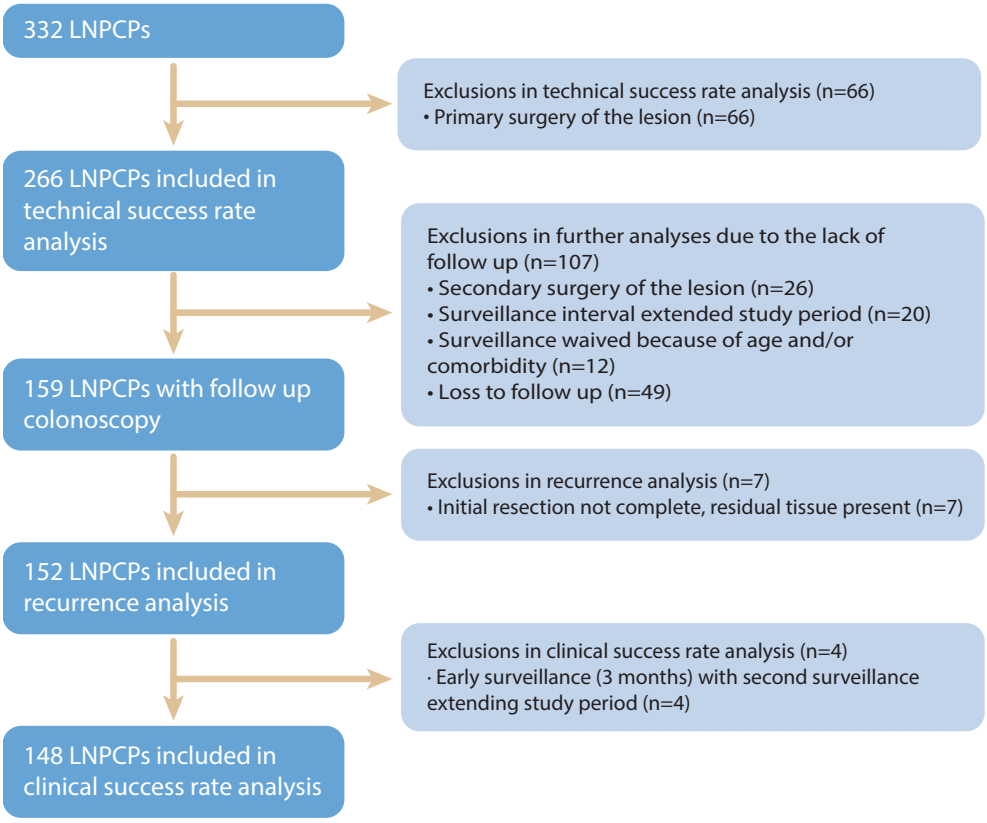

Figure 5.1: Flowchart of LNPCPs included in the quality indicator analyses in the regional BCSP cohort.

Recurrence after endoscopic therapy (regional cohort)

In 152 cases, follow-up colonoscopy was performed after initial macroscopically complete resection (included in recurrence analysis; **Figure 5.1**). The cumulative recurrence rate in the regional cohort was 10% (15/152) after 6 months, 16% (24/152) after 12 months and 19% (29/152) after 3 years (**Figure 5.2**). After 12 months, the recurrence rate was 22% (21/94, 95% CI: 15 – 32) for piecemeal and 8% (3/38, 95% CI: 2 – 22) for en-bloc resection. The overall recurrence rate after 12 months increased with LNPCP size; 5 of 53 (9%) in 20 to 29mm LNPCPs, 8 of 36 (22%) in 30 to 39mm LNPCPs, and 11 of 43 (26%) in ≥40mm LNPCPs (P=0.095). No adjuvant treatment was performed to prevent recurrence.

Most recurrences at 12 months (22/24) were unifocal, smaller than 5mm, and could be treated endoscopically. Six months after treatment of these recurrences, none showed additional recurrence. Two of 24 recurrences were interval carcinomas, treated surgically (**Table 5.3**). Variation was seen between the centres regarding the recurrence rate (leave-one-out-analysis range 4-11% after en-bloc resection and 17-24% after piecemeal resection; **Table 5.4**).

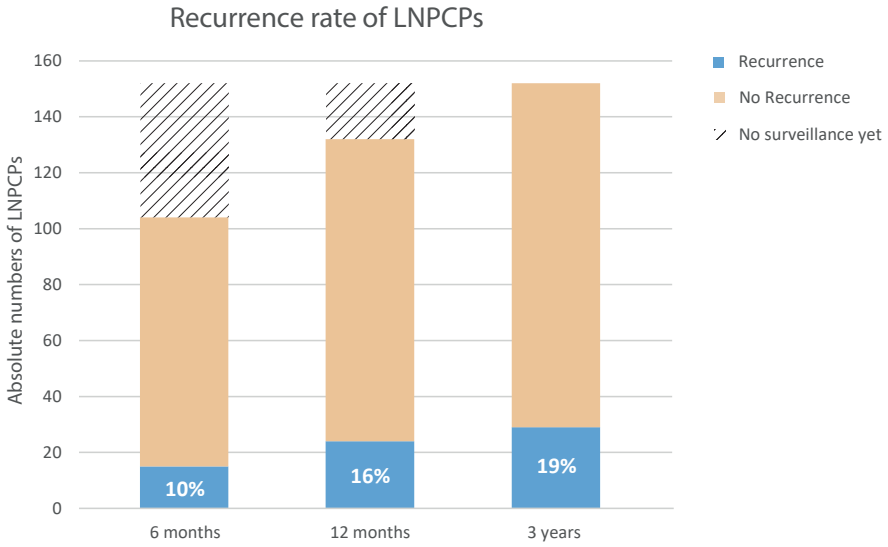

Figure 5.2: Recurrence rate of LNPCPs in the regional screening cohort.

Table 5.3: Characteristics of interval cancers.

		Interval cancer #1	Interval cancer #2
Initial lesion	Size	20 mm	50 mm
	Morphology	Sessile	Sessile
	Location	Rectum	Ascending colon
	Type of resection	En-bloc EMR	Piecemeal EMR
	Pathology	T1NoMo adenocarcinoma Resection margin 0.1mm Kikuchi sm2 No lymphovascular invasion	Tubulovillous adenoma high-grade dysplasia
Interval cancer	Time to diagnosis	6 months	3 years Loss-to-follow-up (surveillance at 6 months has not been performed)
	Diagnosed by	Endoscopy	Endoscopy
	Indication	Surveillance	Symptomatic iron deficiency
	Treatment	Transanal endoscopic microsurgery	Major surgery
	Pathology	T2NoMo adenocarcinoma Ro-resection	T2NoMo No lymphovascular invasion
	Sequel	Wait and see at patient's request 1 year later: metastasized disease	-

Table 5.4: Results of leave-one-out analyses. | *LOO = Leave-one-out analysis.*

Outcome measure	Total (95% CI)	LOO #1	LOO #2	LOO #3	LOO #4	LOO #5
Technical success	86.8% (82.0-90.5)	88.1%	83.2%	86.1%	86.8%	88.6%
Cumulative recurrence at 12 months						
Piecemeal	22.3% (14.7-32.3)	22.8%	16.7%	23.9%	24.4%	21.8%
En-bloc	7.9% (2.1-22.5)	7.9%	4.0%	11.1%	8.6%	8.3%
Clinical success	87.2% (80.4-91.9)	87.0%	89.5%	84.8%	86.3%	88.3%
Primary surgery referral rate	6.9% (4.5-10.4)	6.7%	9.8%	8.6%	7.0%	3.5%
Proximal location of lesions referred due to complexity	51.5% (33.9-68.8)	53.8%	55.2%	55.6%	51.9%	33.3%

Clinical success rate of endoscopic therapy (regional cohort)

For clinical success rate analysis, 148 LNPCPs were included (**Figure 5.1**). Clinical success was achieved in 129 of 148 cases (87%, 95% CI: 80 – 92). Clinical success decreased with increasing LNPCP size, with 61 of 65 (94%) in 20 to 29mm, 33 of39 (85%) in 30 to 39mm, and 35 of 44 (80%) in ≥40mm LNPCPs (*P*=0.078). Clinical success was achieved in 115 of 133 (87%) of the LNPCPs resected during the first encounter, and in 14 of 15 LNPCPs (93%) resected in a second colonoscopy (*P*=0.451). In most cases, the reason for clinical failure was the absence of surveillance endoscopy and therefore no possibility to treat recurrence within the first 12 months.

Again, variation between the centers was seen regarding the clinical success rate (mean 87%, range leave-one-out-analysis 85-90%; **Table 5.4**).

Compliance with surveillance intervals (regional cohort)

In 210 of 332 cases, a surveillance interval was advised after endoscopic resection. The advised surveillance intervals are shown in **Table 5.5**. Compliance with surveillance guidelines was fulfilled in 85 of 115 (74%) piecemeal resected adenomatous LNPCPs and 19 of 47 (40%) en-bloc Rx/R1-resected adenomatous LNPCPs. In the other cases, the advised surveillance interval extended the recommended interval with more than 6 months. Compliance with surveillance intervals was 13 of 26 (50%) and 6 of 22 (27%) in en-bloc R0-resected adenomatous and serrated LNPCPs, respectively. In these groups, a large part of the LNPCPs was scheduled for earlier surveillance than the recommended 3 years.

Adverse events (regional cohort)

Adverse events occurred in 14 of 266 (5%, 95% CI: 3 – 9) endoscopic procedures, all of which were resolved without surgery. Adverse events were post-polypectomy syndrome (1/266, 0.4%), direct post-polypectomy bleeding (3/266, 1%) and delayed bleeding (10/266, 4%). No deep mural injury occurred. An additional colonoscopy was performed in 5 direct and delayed bleeding cases (5/14, 36%), with clipping of the defect in 2 cases. The adverse event rate per size group was 5 of 161

(3%) in 20 to 29mm LNPCPs, 3 of 85 (4%) in 30 to 39mm LNPCPs and 6 to 86 (7%) in ≥40mm LNPCPs (*P*=0.366).

Surgery for LNPCPs (regional cohort)

Of the 332 LNPCPs in the regional cohort, 92 were treated by surgery. Characteristics of these lesions are shown in **Table 5.6**. Nine LNPCPs (3%) were referred for local excision by transanal endoscopic microsurgery (TEM; referral for TEM instead of EMR/ESD was based on local experience and availability) and another 15 LNPCPs were surgically resected because of a synchronous malignant colorectal lesion, which needed major surgical treatment (these 15 lesions were captured within the surgical specimen; the synchronous malignant lesions were not part of the group of 332 LNPCPs). These cases were excluded from the surgery referral rate analysis, leaving 68 LNPCPs (20%) referred for major surgery. Primary surgery was performed in 51 cases (15%), and secondary surgery in 17 cases (5%).

Primary surgery was performed because of suspicion of submucosal invasive cancer (SMIC) in 18 of 51 cases (35%), of which 16 (89%) showed SMIC in the surgical specimen. In 33 of 51 cases (65%, 10% of the total number of LNPCPs) there was no suspicion for SMIC during endoscopy, and the referral reason was "endoscopic unresectable or inaccessible", not further specified (all being SMSA-score 3 or 4 lesions). Most (22/33, 67%) of these non-suspicious, complex lesions were ≥30mm and 17 of 33 (52%) were located proximally. Of the 33 lesions, 12 (36%) showed SMIC in the surgical specimen. Accordingly, the overall primary surgery referral rate for non-invasive LNPCPs was 23 of 332 (7%, 95% CI: 5 – 10).

Secondary surgery was performed because of SMIC in 13 of 17 cases (77%) and because of non-lifting of non-invasive LNPCPs in the other 4 cases (24%).

Leave-one-out analysis showed clear variation between centres in the surgery referral rate for non-invasive LNPCPs (mean 7%, range leave-one-out-analysis 4%-10%), especially for proximal lesions (mean 52%, range leave-one-out-analysis 33%-56%, **Table 5.4**).

Table 5.5: Advised surveillance intervals after endoscopic resection of LNPCPs in the regional BCSP cohort.

	Adenomas (n=188)			Serrated lesions (n=22)
	Piecemeal EMR (n=115)	Rx/R1 en-bloc EMR (n=47)	R0 en-bloc EMR (n=26)	
3-6 months	85 (74%)	19 (40%)	6 (23%)	7 (32%)
1 year	19 (17%)	7 (15%)	5 (19%)	4 (18%)
3 years	11 (10%)	12 (26%)	13 (50%)	6 (27%)
5 years	0 (0%)	9 (19%)	2 (8%)	5 (23%)

Values are n (%). Lesions were included with available pathology assessment and advised surveillance interval. Green indicates too early, red indicates too late and yellow indicates appropriate surveillance interval recommendations (based on Dutch guideline colonoscopy surveillance[12] and ESGE guideline[13]).

Table 5.6: Lesion characteristics of primary surgically, secondary surgically and endoscopically treated LNPCPs.

	Overall (n=332)	Primary surgery (n=66)*	Secondary surgery (n=26)*	Endoscopic treatment (n=240)	*P* value
Median size, mm (IQR)	30 (20-40)	30 (20-40)	28 (20-50)	25 (20-35)	0.171
Proximal location, n (%)	175 (53)	30 (46)	11 (42)	134 (56)	0.117
Location					0.148
Colon	262 (79)	52 (79)	19 (73)	191 (80)	
Cecum/ascending colon	117 (35)	24 (36)	6 (23)	87 (36)	
Rectum	70 (21)	14 (21)	7 (27)	49 (20)	
Morphology, n (%)					0.023
Sessile	267 (80)	46 (70)	24 (92)	197 (82)	
Flat	65 (20)	20 (30)	2 (8)	43 (18)	
SMSA-score**, n (%)					0.079
SMSA-3	139 (42)	22 (33)	13 (50)	106 (44)	
SMSA-3/4	96 (29)	21 (32)	3 (12)	70 (29)	
SMSA-4	97 (29)	23 (35)	10 (38)	64 (27)	
Villous component, n (%)	122 (38)	19 (29)	5 (19)	98 (41)	0.031
Dysplasia, n (%)					<0.001
No dysplasia	30 (9)	2 (3)	2 (8)	20 (8)	
Low-grade dysplasia	199 (60)	20 (30)	6 (23)	179 (75)	
High-grade dysplasia	48 (15)	14 (21)	4 (15)	29 (12)	
Carcinoma	55 (17)	30 (45)	14 (54)	12 (5)	

Values are n (%) inless otherwise defined.
** These groups not only include lesions referred for major surgery, but also include lesions referred for transanal endoscopic microsurgery (TEM) and lesions referred for surgery due to a synchronous lesion.*
*** SMSA stands for size, morphology, site and access of a lesion and reflects the complexity for endoscopic treatment.*

Endoscopist experience in the regional screening cohort

In the regional 332 LNPCP cases, 24 endoscopists were involved. Fifteen (63%) had more than 10 years of experience and 9 (38%) were dedicated to advanced polypectomy programs in their center. The direct surgery referral and technical success rates were, respectively, 51% and 71% for non-experienced, non-dedicated endoscopists, 17% and 88% for intermediate group endoscopists, and 8% and 90% for experienced, dedicated endoscopists ($P<0.001$ and $P=0.064$, respectively).

Direct surgery referral rates and technical success rates for experienced versus non-experienced and dedicated versus non-dedicated endoscopists are shown in **Table 5.7** and **5.8**.

Table 5.7: Direct surgery referral rate according to experience and dedication of endoscopists.

	Non-dedicated	Dedicated	Total
≤10 years experience	25/49 (51%; 95% CI: 37-65)	19/93 (20%; 95% CI: 13-30)	142
>10 years experience	15/106 (14%; 95% CI: 8-23)	7/84 (8%; 95% CI: 4-17)	190
Total	155	177	332

Table 5.8: Technical success rate according to experience and dedication of endoscopists.

	Non-dedicated	Dedicated	Total
≤10 years experience	17/24 (71%; 95% CI: 49-87)	67/74 (91%; 95% CI: 81-96)	98
>10 years experience	78/91 (86%; 95% CI: 76-92)	69/77 (90%; 95% CI: 80-95)	168
Total	115	151	266

Discussion

In this performance of two sub-studies, the prevalence and outcomes of LNPCP polypectomy within the BCSP were analyzed. An LNPCP prevalence of 8% was observed. Technical and clinical success rates for endoscopic resection were 87% (95% CI: 82 – 91) and 87% (95% CI: 80 – 92) respectively. Cumulative recurrence rates after 12 months were 22% (95% CI: 15 – 32) after piecemeal resection and 8% (95% CI: 2 – 22) after en-bloc resection, and adverse events occurred in 5% of cases (95% CI: 3 – 9). The primary surgery referral rate for non-invasive LNPCPs was 7% (95% CI: 5 – 10).

The prevalence of LNPCPs of 8% found in our study is in line with other large cohorts,[16-18] but is higher compared with an English BCSP cohort. It should be taken into account that in the English BCSP cohort, preselection occurred.[15]

Although quality indicators for colonoscopy are widely implemented, increasing awareness has highlighted the need for quality indicators for polypectomy to further optimize screening program.[4, 5, 19] The measured quality outcomes for (large) polypectomy in this study were technical success, recurrence rate, and clinical success, and showed room for improvement. The technical success rate in our regional cohort (87%) is lower than reported in expert centers (95%) and a meta-analysis (96%; 95% CI: 96 – 97).[2, 20] The clinical success rate in our cohort (87%) is also lower than reported in the English BCSP (94%) and expert centers (96%).[15, 21] These differences might be explained by the fact that we observed a decrease in success rates with increasing LNPCP size. *Sidhu et al.* described technical success rates of 99% in SMSA-2 lesions in expert centers, decreasing to 93% in SMSA-4 lesions, in which SMSA refers to the size, morphology, site and access of a lesion and reflects the complexity of a colorectal lesion with regard to endoscopic treatment.[22] In contrast, we showed a decreased technical success rate to 74% in ≥40mm lesions. Although the resection of 20 to 29mm lesions in the Dutch BCSP is of sufficient quality, the gap in quality between expert centers and BCSP endoscopists clearly widens from ≥30mm sized LNPCPs. This emphasizes that the level of experience in endoscopic resection of LNPCPs is important for success.[14, 23] To increase exposure, centralization within or between centers should therefore be considered, and additional training should be implemented in clinical practice. Furthermore, implementation of quality monitoring on endoscopic resection could improve the outcomes on quality parameters and reduce practice variation. The lower clinical success rate in our study can partially be explained by non-compliance with surveillance guidelines. Not performing surveillance after six months influences the clinical success rate because of lack of opportunity to treat possible recurrences early. This stresses the importance of compliance with surveillance guidelines, of which we, in line with current evidence,[7] have shown that there is still substantial non-compliance.

The cumulative recurrence rates of 22% for piecemeal and 8% for en-bloc resection after 12 months are similar to recurrence rates described in large polypectomy cohorts (15%-31% piecemeal, 3%-6% en-bloc) and meta-analyses (20% piecemeal [95% CI: 16 – 25], 3% en-bloc [95% CI: 2 – 5]).[2, 6, 14, 21, 24, 25] However, expert centers recently reported lower recurrence rates of 4.0% to 5.4% after adjustment of endoscopic treatment strategies.[26] This illustrates that recurrence rates in the Dutch BCSP can still be significantly improved by further ameliorating resection techniques. Detailed analysis showed that recurrence rates increased significantly with lesion size in our cohort, with a clear difference between 20 to 29mm and ≥30mm lesions (from 9% to 22%). Here, a clear difference in recurrence rates between the BCSP cohort and expert centers is illustrated, given the fact that reported recurrence rates in expert centers are 7% for SMSA-score 2 lesions, 9% for SMSA-score 3 lesions, and only increased to 24% in SMSA-score 4 lesions.[22] Again, this confirms the need for additional training and monitoring on quality parameters for polypectomy and stresses the item to

consider centralization of treatment of ≥30mm lesions.

Safety of endoscopic resection in the screening program was high, which is in line with current evidence.[2, 15] The adverse event rate was only 5%.

Although the primary surgery referral rate for non-invasive LNPCPs (7%) is lower than previously described,[2, 15] a Dutch study on benign rectal polyps showed significant referral for major surgery, whereas 73% of cases were assessed as "probably feasible" for endoscopic therapy.[9] Furthermore, *Vermeer et al.* showed that a large amount of benign lesions were referred for major surgery because of complexity, without reassessment for endoscopic resection by an advanced endoscopy center.[8] Additionally, *de Neree tot Babberich et al.* showed that predominantly large lesions in the proximal colon were referred for surgery, whereas risk of malignancy in proximal lesions was smaller than in distal lesions.[27] A similar observation was made in our study. Therefore, current evidence suggests that despite emerging endoscopic techniques, the shift from surgical to endoscopic treatment of large colorectal polyps is lingering, and a significant number of non-invasive LNPCPs are still referred for surgery. This may also be an important quality measure because surgery has higher morbidity compared with endoscopic resection.[28]

Furthermore, our data support the assumption that experienced and dedicated endoscopists have higher success rates in advanced polypectomy and are less likely to refer large polyps for surgery than non-experienced and non-dedicated endoscopists. This again stresses the importance of additional training, consultation with dedicated experts and centralization of care for large colorectal polyps.

Several limitations of our study should be acknowledged. First, we assumed the regional cohort to be a representative sample of the national cohort. Given the limited data from the national cohort, this assumption and extrapolation of results should be made with caution. However, we have shown that the two cohorts match on important parameters in this study. Second, recurrence rates may have been underestimated because of the limited compliance with surveillance guidelines. Follow-up colonoscopy was performed in only 67% of cases, of which most were performed within 12 months. In addition, the lesions without follow-up mainly consisted of en-bloc resected 20 to 29mm lesions, influencing the recurrence rate only minimally. Furthermore, determining recurrence rates at 12 months for en-bloc resection may also have led to an under- or overestimation, because not all patients within this group underwent a surveillance colonoscopy within 12 months, because the surveillance guidelines advise follow-up after 3 years for these resections. Variance in surveillance intervals may also have caused bias in clinical success analysis at 12 months. Third, the accessibility portion of the SMSA-score was not described in our cohort. Therefore, SMSA-score was calculated with both easy and difficult accessibility. Although we did not find any associations between SMSA-score and recurrence rate or surgery referral rate, it should be noted that we could not draw any conclusions regarding the value of the SMSA-score based on this cohort because exact accessibility per lesion was unknown. Fourth, the level of training of endoscopists participating in our study is not measured systematically, quality of resection is not retrievable, and it is unknown whether recent insights have already been implemented in clinical practice. However, all endoscopists have followed the national bowel cancer screening training program and have been certified for screening colonoscopies. Finally, our study showed variation between centers that unfortunately could not be further investigated at national level. To gain more insight in the quality of polypectomy and variation between centers at the national level, the national ScreenIT registry should be optimized for evaluation purposes and quality indicators for polypectomy should be included.

In conclusion, in this Dutch screening program cohort it was shown that quality parameters for endoscopic resection of LNPCPs are not reached, especially in ≥30mm polyps. Endoscopic resection of large polyps could benefit from additional training, quality monitoring, and centralization, either within or between centres.

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Thermal ablation of mucosal defect margins to prevent local recurrence of large colorectal polyps: A systematic review and meta-analysis

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Abstract

Background

Endoscopic mucosal resection of large non-pedunculated colorectal polyps is characterized by a high risk of recurrence. Thermal ablation of the mucosal defect margins may reduce recurrence in these lesions, but a systematic overview of the current evidence is lacking.

Materials and methods

We searched PubMed, Embase and Cochrane until July 2021, for studies on thermal ablation of mucosal defect margins of large non-pedunculated colorectal polyps. Main goal of this meta-analysis was to identify pooled risk difference of recurrence between thermal ablation vs no adjuvant treatment. Secondary goal was to identify pooled recurrence rate after snare soft tip coagulation (STSC) and argon plasma coagulation (APC).

Results

Ten studies on thermal ablation of mucosal defect margins were included, with three studies on argon plasma coagulation, six studies on snare tip soft coagulation and one study comparing both treatment modalities, representing a total of 316 APC cases and 1598 STSC cases. Overall pooled risk difference of recurrence was -0.17% (95% CI: -0.22 – -0.12) as compared to no adjuvant treatment. Pooled risk difference was -0.16% (95% CI: -0.19 – -0.14) for STSC and -0.26 (95% CI: -0.80 – 0.28) for APC. Pooled recurrence rate was 4% (95% CI: 2 – 8) for STSC and 9% (95% CI: 4 – 19) for APC.

Conclusions

Thermal ablation of mucosal defect margins significantly reduces recurrence rate in large non-pedunculated colorectal lesions compared to no adjuvant treatment. While no evidence for superiority exists, snare tip soft coagulation may be preferred over argon plasma coagulation, because this method is the most evidence-based, and cost-effective modality.

Introduction

Large (≥20mm) non-pedunculated colorectal polyps are prevalent in current endoscopy practice, and when considered benign, the primary approach for these lesions is endoscopic mucosal resection.[1] Endoscopic mucosal resection (EMR) is associated with fewer complications than more invasive resection techniques such as endoscopic submucosal dissection (ESD) or surgery.[2, 3] However, the pitfall in endoscopic mucosal resection of large colorectal polyps remains the higher risk of recurrence, mostly reported between 15-20% at six months.[1, 4] Risk factors for recurrence after endoscopic resection are widely studied and the most important factors include piecemeal resection, lesion size ≥4cm and intraprocedural bleeding.[5]

In the search for effective measures to lower the recurrence rates after (piecemeal) EMR of large colorectal lesions, experience is gained with regard to adjuvant treatment measures. Adjuvant treatment refers to additional treatment of the mucosal defect after all visible neoplastic tissue has been removed. Argon plasma coagulation (APC) and snare tip soft coagulation (STSC) are techniques that are often used in this setting. Ablation of mucosal defect margins with APC or STSC is increasingly performed in order to prevent local recurrence.[6, 7]

With thermal ablation of mucosal defect margins only recently emerging, not all current guidelines incorporated firm statements regarding this adjuvant measure. The European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline for colorectal polypectomy and endoscopic mucosal resection (2017) stated that the role of adjuvant thermal ablation of the EMR resection margins to prevent recurrence requires further study.[8] However, the American Society for Gastrointestinal Endoscopy (ASGE) recently published a renewed guideline about endoscopic removal of colorectal lesions, in which the use of adjuvant thermal ablation of the post-EMR margin is incorporated as a conditional recommendation with moderate-quality evidence.[7]

To investigate and summarize current evidence on thermal ablation of mucosal defect margins, we set out to perform a systematic review and a meta-analysis assessing the effect of adjuvant thermal ablation, compared to no adjuvant treatment, of mucosal defect margins on recurrence of large colorectal polyps removed by endoscopic mucosal resection.

Materials & methods

This systematic review was conducted according to a predefined protocol that has been registered in the international prospective registry for systematic reviews (PROSPERO): CRD42020189860. Our study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[9]

Search strategy and inclusion criteria

The electronic databases of PubMed, EMBASE and Cochrane were searched for articles published between January 1990 and July 19, 2021. The search terms comprised synonyms for "colon" or "rectum", "colonoscopy", "colorectal polyps" as domain and "adjuvant or additional treatment" or "argon plasma coagulation" or "snare tip soft coagulation" as intervention. The search was performed after consultation of a search expert. Studies for inclusion were selected after removing duplicates. Studies were eligible for inclusion if they were written in English, published in peer-reviewed journals and reported original data from randomized clinical trials or observational studies. Studies were included if thermal ablation was used as an adjuvant treatment, meaning that all neoplastic

tissue was removed during the EMR and no residual tissue was detected during careful inspection of the EMR-defect. Studies were excluded if thermal ablation was used as an adjunctive treatment on residual neoplastic tissue after EMR.

Study selection

Two authors (LWTM and RMMB) independently screened titles and abstracts identified by our search. Subsequently, independent assessment of full-text articles for final inclusion was performed. We cross-checked reference lists of included studies and screened references that cited the included articles. Consensus was reached by discussion and in case of disagreement or uncertainty about eligibility by consultation with senior authors (AAMM and LMGM).

Data collection

A predesigned data extraction form was used to extract relevant data of included studies. Two authors (LWTM and RMMB) independently extracted the data. Disagreement was resolved by discussion between the two authors. If no agreement could be reached, this was discussed with senior authors (AAMM and LMGM). Data were extracted based on the six-month follow-up interval. When a study did not report outcomes at six months, data were extracted based on the 12-month follow-up interval. This follow-up interval of six months is in line with current surveillance guidelines stating that first surveillance colonoscopy should be performed at six months.

We extracted the following data: author, year of publication, country, study design, randomization, blinding, number of participating centers, number of patients, number of included lesions, size in mm, % proximal location, type of ablative therapy, follow-up interval, and outcome.

Local recurrence and risk difference

The main goal was to identify local recurrence (at 6 to 12 months) after endoscopic resection. Local recurrence was assessed for all adjuvant treatment modalities, as well as separately for snare tip soft coagulation (STSC) and argon plasma coagulation (APC). As a secondary goal, pooled recurrence rates for STSC and APC were calculated for comparison.

Sensitivity analysis was performed to evaluate the recurrence and risk difference in studies only including lesions from a size of ≥20mm, thus leaving out two studies that included lesions from a size of ≥10mm or ≥15mm. Furthermore, a second sensitivity analysis was performed to account for potential case overlap in STSC studies from one research group (Australia). For this analysis, pooled estimates were calculated with only one study of this specific research group included.

Assessment of methodological quality

Two authors (LWTM and RMMB) independently evaluated the methodologic quality and potential risk of bias in included studies. We used the Quality in Prognostic Studies (QUIPS) tool for randomized studies, as recommended by the Cochrane Prognosis Methods Group.[10] In addition, the Newcastle-Ottawa Scale (NOS) was used for quality assessment of both non-randomized and randomized studies. We defined the components of the NOS according to our research question. For "representativeness of the exposed cohort" we evaluated whether there was no selection based on location, size or complexity of the lesions. For "selection of the non-exposed cohort" we evaluated whether the controls were derived from the same population as the exposed group, and whether there were reasons to believe that the non-exposed group did not receive adjuvant treatment for a specific reason (e.g., other resection technique used, inexperienced endoscopist).

"Representativeness of the exposed cohort" and "selection of the nonexposed cohort" together composed the evaluation of possible selection bias. For "ascertainment of cohort" we evaluated whether it was clear that adjuvant treatment methods were applied fully and correctly. For "demonstration that outcome of interest was not present at the start of the study" we evaluated whether the study described no visible residue present at the first resection. For "comparability" we evaluated the study controlling for exposure vs non-exposure, baseline characteristics and both cohorts being samples of the same general population. Hence, potential confounding bias was evaluated. For "assessment of outcome" definition of recurrence had to be described and documented in the studies. For "follow-up long enough for outcome to occur" we used a minimal follow-up period of 6 months. Finally, "adequacy of follow-up" was defined by description of loss-to-follow-up by the different studies, where <15% loss-to-follow-up, evenly distributed over groups, was acceptable.[11]

Disagreement was resolved through discussion and consensus was reached by coordination with senior authors (AAMM and LMGM).

Statistical analysis

Pooled risk differences (RDs) along with 95% confidence intervals (CIs) were calculated using random-effect models with Mantel-Haenszel method. R statistical program version 4.0.5 was used to process all collected data.[12] The Metafor package version 3.0.2 was used for calculations and plotting.[13]

Secondary, pooled recurrence rates after STSC and APC treatment were calculated by applying generalized linear mixed models with a logit link to the raw data (recurrence yes/no), where a random intercept on study level was included to account for the study effect.

Heterogeneity was assessed with the Q test for significance and with the inconsistency index (I^2), where a value of >50% was considered as substantial heterogeneity between studies. Funnel plots with Egger's test for asymmetry were constructed to test the possible effect of publication bias.[14]

Crude estimates were used for statistical analysis. A two-sided *P* value of ≤0.05 was considered statistically significant.

Results

Included studies

Our search identified 2979 papers, of which ten met our inclusion and exclusion criteria (**Figure 6.1**). Study characteristics are shown in **Table 6.1**. Argon plasma coagulation (APC) was evaluated as adjuvant treatment modality in 3 studies, while STSC was evaluated in 6 studies. One additional study retrospectively compared both treatment modalities, with 50 patients receiving APC and 51 patients receiving STSC. The ten included studies represented a total of 316 APC cases and 1598 STSC cases.

All studies included large colorectal polyps, but inclusion criteria differed between studies, with the size of lesions suitable for inclusion ranging from ≥10mm to ≥20mm. Mean age and gender distribution between groups in the included studies were comparable. Furthermore, the included studies reported comparable size and location of lesions between intervention and control groups.

Table 6.1: Baseline study characteristics.

Author, year	Country	Study design	Randomization	Blinding	No. of participating centers	No. of patients	No. of lesions
Albuquerque, 2013	Brazil	RCT	Yes	No	1	20	21
Brooker, 2002	UK	RCT	Yes	No	1	21	21
Kandel, 2019	USA	Prospective cohort	No	No	1	120	120
Katsinelos, 2019*	Greece	Retrospective cohort	No	No	1	101	101
Klein, 2019	Australia	RCT	Yes	No	4	416	416
Park, 2019	South Korea	Retrospective cohort	No	No	1	156	176
Raju, 2020	USA	Retrospective cohort, no control group	No	No	1	246	246
Shahidi, 2020	Australia	Prospective cohort	No	No	2	413	413
Shahidi, 2021	Australia	Prospective cohort	No	No	1	817	817
Sidhu, 2021	Australia	Prospective cohort, no control group	No	No	6	1049	1049

**Comparison between APC and STSC. STSC reported as intervention group (IG) and APC as control group (CG)*
 # Estimated mean + SD, calculated from reported size categories with frequencies
APC = argon plasma coagulation; STSC = snare tip soft coagulation; NR = not reported; NA = not applicable

Table 6.1: *(continuation)*

Size in mm (mean±SD or median+IQR)	Proximal location	Type of ablative therapy (settings)	Follow-up interval	Outcome – local recurrence		*P* value
				Intervention group	**Control group**	
34 (±13)	43%	APC 60W Gasflow 2.0L/min	3 and 12 months	2/10 (20%)	2/11 (18.2%)	NR
26 (±10)	62%	APC 45-55W right, 65W left colon Gasflow 2.0L/min	3 and 12 months	1/10 (10%)	7/11 (63.6%)	0.02
28 (±11)	82%	STSC 20-80W Soft coag mode	6 months	7/60 (12%)	18/60 (30%)	0.01
41 (±13)	16%	STSC 20W Soft coag mode APC 50W right, 70W left Gasflow 1.5L/min	3, 6 and 12 months	7/51 (13.7%)	8/50 (16%)	0.34
30 (IQR 25-45)	52%	STSC 80W Soft coag mode Erbe effect 4	6 and 18 months	10/192 (5.2%)	37/176 (21.0%)	<0.001
22 (±10) #	NR	STSC 80W Soft coag mode Erbe effect 4	3-12 months	8/171 (4.8%)	3/5 (60%)	0.002
35 (IQR 30-45)	80%	APC 30-35W Gasflow 0.8L/min	6 and 18 months	11/246 (4.5%)	NA	NA
40 (IQR 30-60)	NA	STSC 80W Soft coag mode Erbe effect 4	6 months	0/30 (0%) 3/51 (5.9%)	12/48 (25%) 28/160 (17.5%)	0.002 0.041
35 (IQR 30-50)	72%	STSC 80W Soft coag mode Erbe effect 4	6 months	2/336 (0.6%)	82/481 (17.0%)	<0.001
35 (IQR 25-45)	54%	STSC 80W Soft coag mode Erbe effect 4	6 months	10/707 (1.4%)	NA	NA

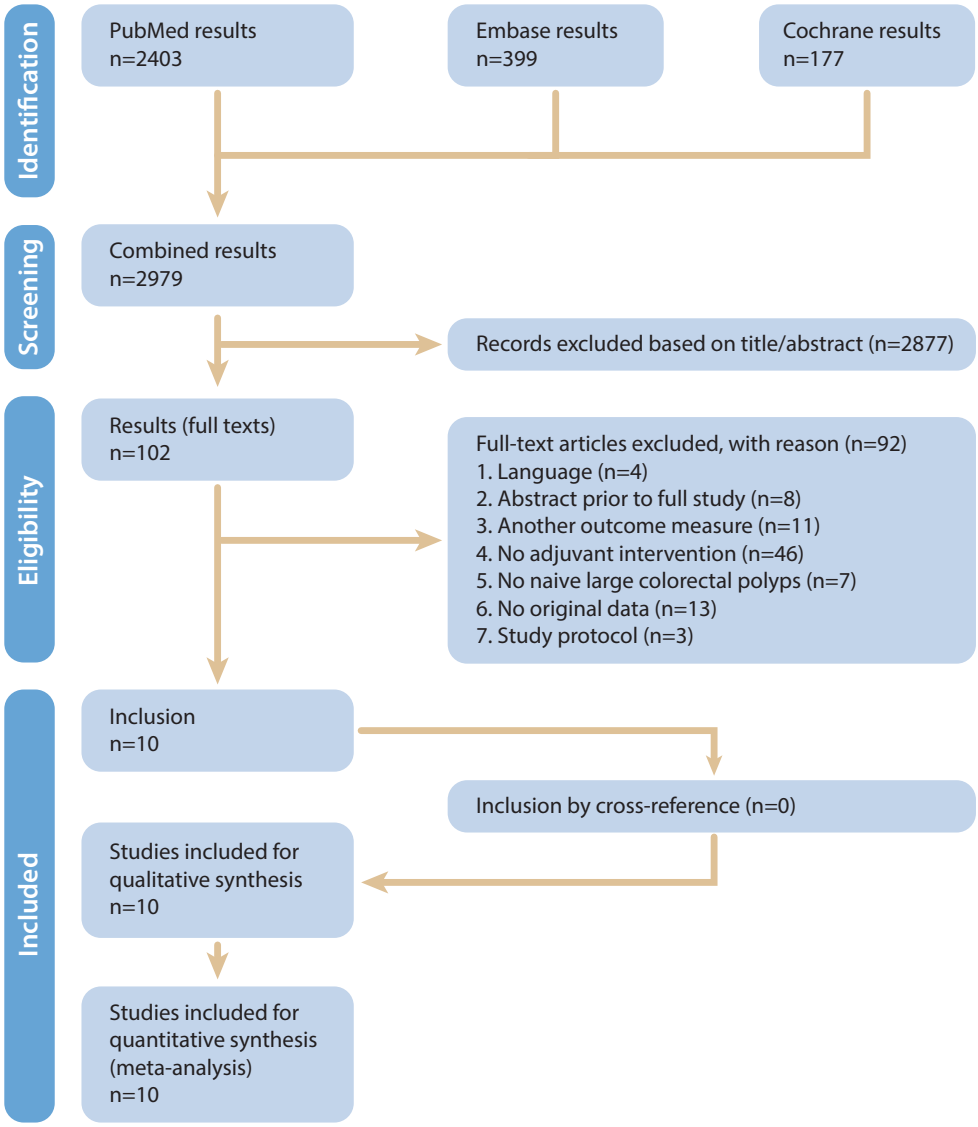

Figure 6.1: Study flowchart.

Quality assessment

Quality and risk of bias assessment according to the QUIPS tool for randomized trials is presented in **Table 6.2**. In addition, quality and risk of bias assessment according to the Newcastle Ottawa Scale for all included studies is presented in **Table 6.3**.

Adjuvant thermal ablative treatment

The main results of the effect of adjuvant STSC and APC on recurrence are presented in **Figure 6.2**. Pooled estimates of the effect of any adjuvant treatment modality on recurrence yielded a statistically significant risk difference of -0.17 (95% CI: -0.22 – -0.12) compared to no adjuvant treatment. Pooled estimates of the effect of STSC on recurrence yielded a statistically significant risk difference of -0.16 (95% CI: -0.19 – -0.14), while the pooled effect of APC on recurrence yielded a non-significant risk difference of -0.26 (95% CI: -0.80 – 0.28).

Risk of publication bias is presented in **Figure 6.3**. The funnel plot shows two studies being outliers, but this was not significant (Egger's test *P*=0.112).

Sensitivity-analysis without the two studies including lesions from a size of ≥10 and ≥15mm showed no difference in outcome, with an overall risk-difference of -0.16 (95% CI: -0.19 – -0.13).

Sensitivity-analysis to account for possible case overlap in studies from the same research group did also not show any significant difference in outcome, with a STSC-specific risk-difference ranging from -0.18 to -0.22 (95% CI lower bound ranging from -0.09 to -0.12 and upper bound ranging from -0.25 to -0.34).

Comparing thermal ablation modalities

Pooled estimates of the recurrence rates after STSC and APC are presented in **Figure 6.4**. Pooling studies reporting on STSC yielded a recurrence rate of 4% (95% CI: 2 – 8), while a recurrence rate of 9% (95% CI: 4 – 19) was seen for APC.

One of 10 included studies directly compared APC (n=50) and STSC (n=51) in a retrospective manner, and showed no significant difference in recurrence after APC vs STSC (16% vs 13.7%; *P*=0.34).

Table 6.2: Quality assessment (QUIPS) for randomized controlled trials.

First author, year of publication	Study participation	Study attrition	Prognostic factor measurements	Outcome measurement	Study confounding	Statistical analysis and reporting
Albuquerque, 2013	M	L	L	L/M	L/M	L/M
Brooker, 2002	M	L	L	L/M	L/M	L
Klein, 2019	L	L	L	L	L	L

Abbreviations: L = low risk of bias; M = moderate risk of bias; H = high risk of bias.

Table 6.3: Quality assessment of included studies *(according to the Newcastle-Ottawa Scale).*

	Selection				Comparability	Outcome			Total score
	Representativeness exposed cohort	Selection of nonexposed cohort	Ascertainment of cohort	Demonstration outcome not present at start		Assessment of outcome	Follow-up long enough	Adequacy of follow-up	
Albuquerque, 2013	/	*	*	*	*	*	*	*	7*
Brooker, 2002	*	*	*	*	*	*	*	*	8*
Kandel, 2019	*	*	*	*	**	*	*	*	9*
Katsinelos, 2019	*	*	*	*	**	*	*	/	8*
Klein, 2019	*	*	*	*	**	*	*	*	9*
Park, 2019	/	*	*	/	*	*	*	/	5*
Raju, 2020	*	NA	*	*	NA	*	*	*	6* (9*)
Shahidi, 2020	/	*	*	*	**	*	*	*	8*
Shahidi, 2021	*	*	*	*	/	*	*	*	7*
Sidhu, 2021	*	NA	*	*	NA	*	*	*	6* (9*)

Representativeness of exposed cohort: no selection based on location, size, or complexity of lesions.
Selection of nonexposed cohort: controls derived from same population as exposed group, no reasons to believe that nonexposed cohort did not receive exposure for specific reasons (e.g. other resection technique, inexperienced endoscopist).
Ascertainment of cohort: adjuvant treatment methods were described and applied fully and correctly.
Demonstration outcome not present at start: description of no visible residue present at first resection.
Comparability: study controls for exposure vs non-exposure and baseline characteristics, and both cohorts are samples of the same general population.
Assessment of outcome: definition of recurrence has to be described and documented.
Follow-up long enough: minimal follow-up period of 6 months.
Adequacy of follow-up: loss-to-follow-up is described and <15% loss-to-follow-up Is acceptable/
Maximum score comparability = 2 stars; maximum total score = 9 stars/
*Abbreviations: * = star / points; / = no point; NA = not applicable/*

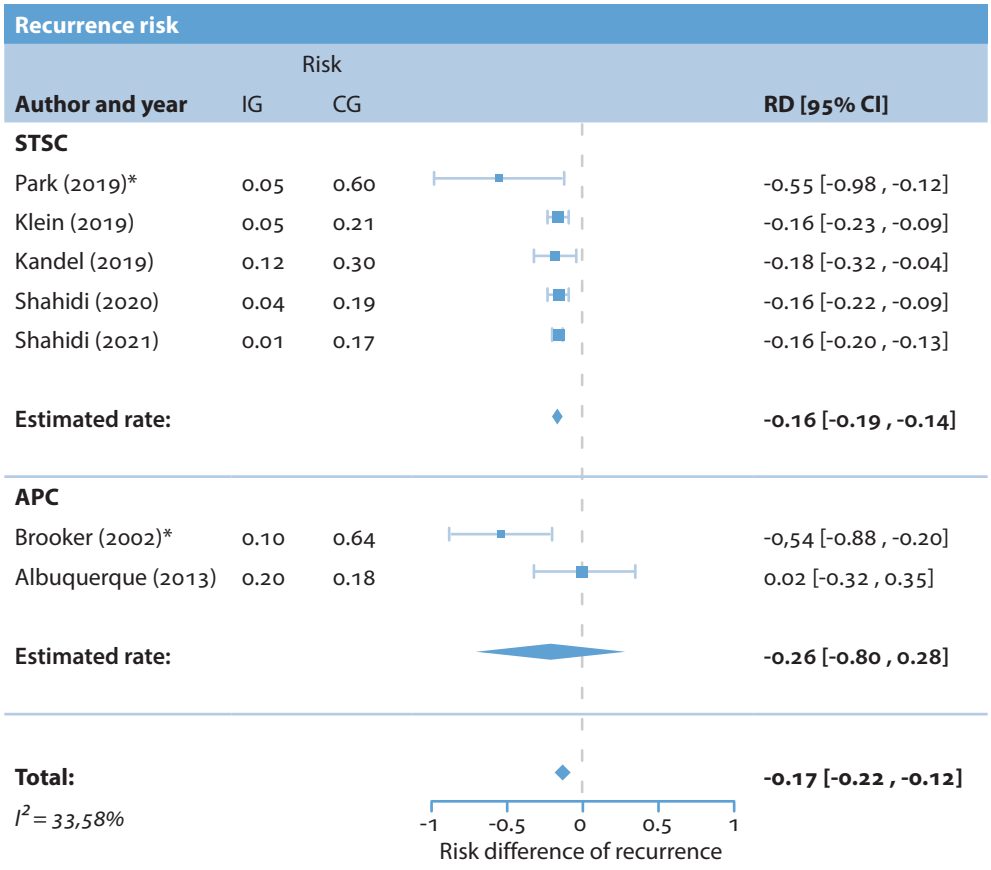

Figure 6.2: Pooled data of included studies. | *IG = intervention group; CG = control group; RD = risk difference; STSC = snare tip soft coagulation; APC = argon plasma coagulation.*
** Not all included lesions in this study are ≥20mm in size.*

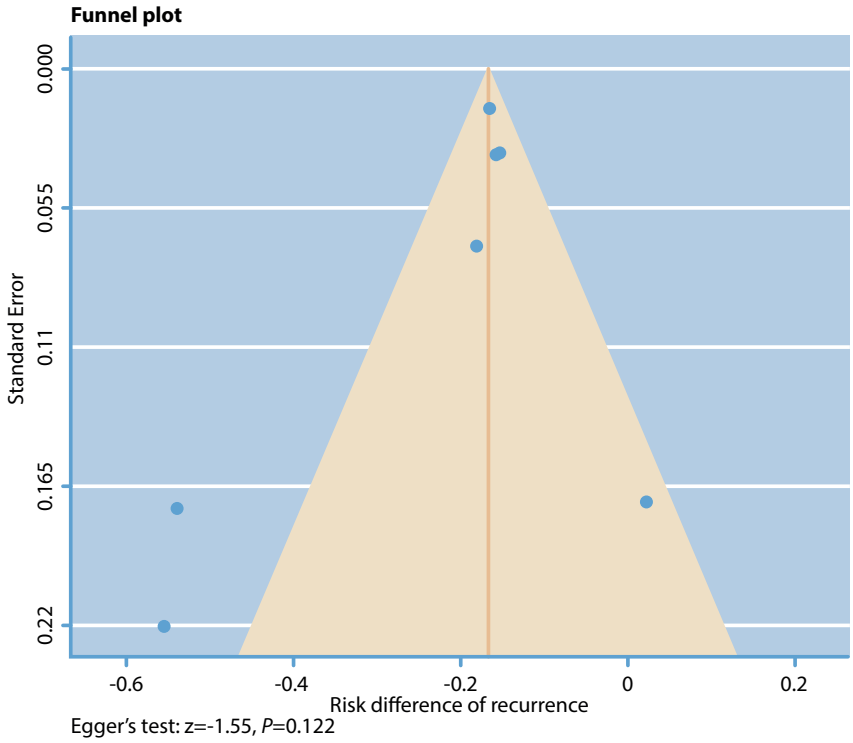

Figure 6.3: Funnel plot of included studies.

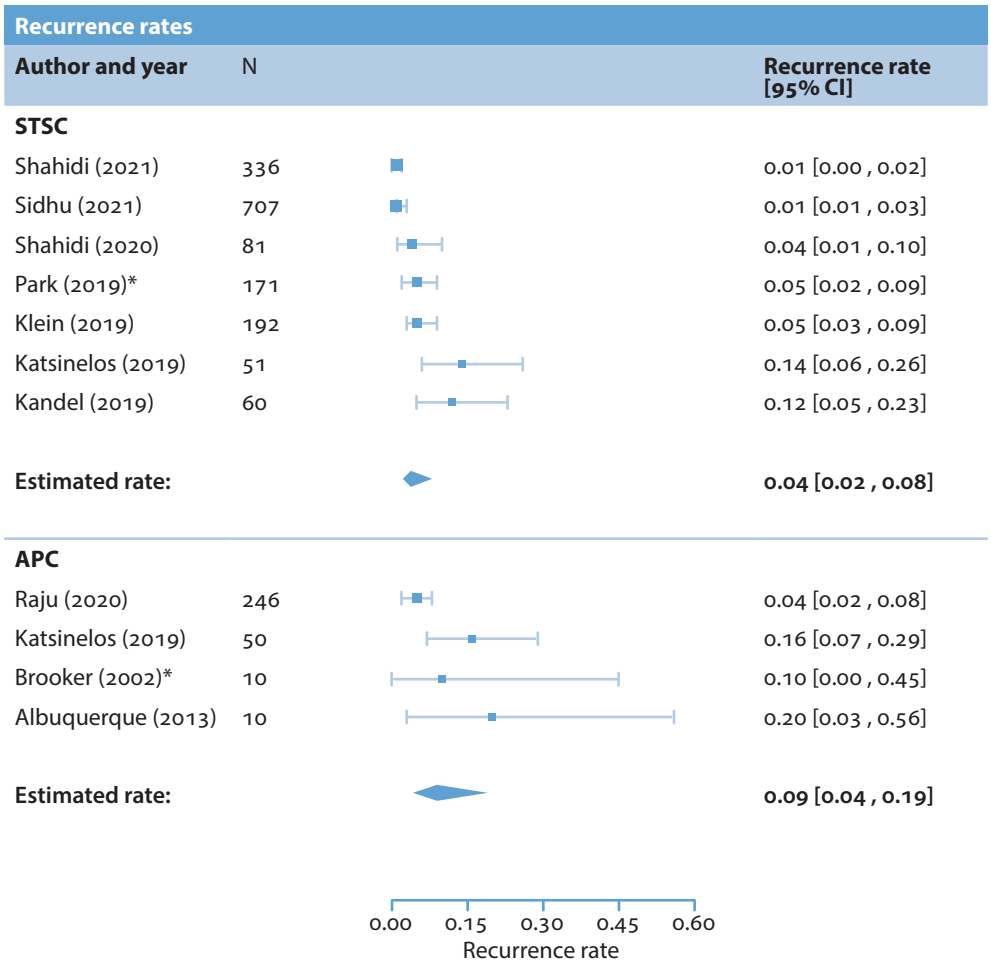

Figure 6.4: Pooled recurrence rates for STSC and APC after 6-12 months.
** Not all included lesions in this study are ≥20mm in size.*

Discussion

This systematic review and meta-analysis of 10 studies shows that adjuvant thermal ablative treatment of mucosal defect margins reduces recurrence rate after endoscopic resection of large colorectal polyps (RD -17%; 95% CI: -22% – -12%). Soft tip snare coagulation showed a significantly reduced recurrence rate, while argon plasma coagulation did not lead to a significant reduction in recurrence. Pooled recurrence rates showed 4% and 9% recurrence after STSC and APC, respectively.

Our findings are in accordance with recent studies on thermal ablation of mucosal defect margins that concluded that thermal ablation after endoscopic resection, also described as EMR-T, is an effective measure to reduce recurrence in large colorectal polyps.[6, 15, 16] In addition, a recent meta-analysis about endoscopic techniques to reduce recurrence rates after colorectal EMR also showed that treatment of the EMR resection margins significantly reduces recurrence.[17] However, this meta-analysis by Kemper et al. harbors some concerns. First, it did not include all currently available evidence regarding thermal ablation of resection margins. Kemper et al. evaluated thermal ablation in only four studies, together accounting for 529 lesions, whereas we evaluated thermal ablation in ten studies, together accounting for 3380 lesions. Second, in the effect analysis, they also included studies in which extended EMR and precutting was performed. This may have influenced the results. Third, they did not perform sensitivity analysis for size and case overlaps. Fourth, using only randomized controlled trials (RCTs) for their comparison between APC and STSC ruled out important observational studies. Especially for APC, the original RCTs are of questionable quality and applicability to current practice. Based on the data of this systematic review and meta-analysis, evaluating all currently available evidence on this subject, it can be concluded that thermal ablation of mucosal defect margins should be incorporated for all large (≥20mm) colorectal polyps removed by piecemeal approach.

Two treatment modalities are available for thermal ablation, which both seem to reduce the risk of recurrence. However, in this meta-analysis, APC did not show a significant reduction when pooling studies, in contrast to STSC, which significantly reduced recurrence risk. While pooled data are presented for STSC and APC separately, this information should be interpreted with caution. A couple of recent high-quality studies have been published on STSC, but the evidence on APC is of moderate quality. The number of lesions included in the APC studies is very small (Brooker et al. n=21; Albuquerque et al. n=21). Furthermore, the study by Brooker et al. showed a recurrence rate of 63.6% in the control group, which raises the question whether these data are representative for current practice.[18, 19] In addition to the studies by Brooker et al. and Albuquerque et al., an abstract by Chattree and Rutter (2015) also reported data on the effect of APC on recurrence. In this abstract, a total of 153 piecemeal EMR procedures were retrospectively analyzed, with 18% vs 31% recurrence in APC group vs non-APC group respectively (P=0.064).[20] Sensitivity analysis, including these abstract data, did not lead to a significant effect of APC. Consequently, at this point, the evidence on the effect of APC to reduce recurrence is of insufficient quantity and quality to make any firm statements.

In addition to risk reduction analysis, all available evidence (including observational studies without control group) was pooled to estimate recurrence rate after APC and STSC. The difference in pooled recurrence rate after APC and STSC was not statistically significant, given the overlapping confidence intervals. Therefore, superiority of one of these modalities remains unknown at this time.

Settings used during thermal ablation of mucosal defect margins sometimes differ between operators. However, our data showed that operators in general agree about the settings for STSC. For STSC, universally, the soft coagulation mode is used with a current of 80 Watts and effect mode

4 on Erbe ENDO CUT Q.[6, 15, 21-23] Settings for APC show more variation between operators, with currents between 30-70 Watts and a gas flow of 0.8-2.0 liters per minute.[18, 19, 24, 25] A recent study in porcine models evaluating the effects of STSC and APC showed that APC applied at 1.0 L/min, 30 W, was associated islands of preserved mucosa.[26] Therefore, it appears that higher power in APC is necessary to achieve deeper thermal ablation. We advise using forced coag 60 Watts when applying APC.

En bloc EMR is associated with lower recurrence rates compared with piecemeal EMR (3% vs 20%).[27] However, en bloc resection by EMR is difficult for lesions ≥20mm. Therefore, most large colorectal polyps are resected piecemeal when there is no suspicion for submucosal invasion. Of the included studies in this meta-analysis, only three made the distinction between en bloc and piecemeal resection,[6, 21, 25] and only one of these three performed post-hoc analysis to evaluate the specific effects of EMR-T after en bloc and piecemeal resection separately.[6] In this study, there was no significant difference in recurrence rate after traditional en bloc EMR (0/23; 0%) compared to en bloc EMR-T (1/25; 4%). Therefore, it appears that the positive effects of EMR-T seen after piecemeal resection, are not seen in en bloc resections. Combining these data with the fact that recurrence rates after en bloc resection are already low, the added value of thermal ablation remains questionable. Prospective studies, with larger numbers are needed to make more firm statements about the value of thermal ablation after en bloc resection.

While large colorectal polyps without suspicion of submucosal invasion could be treated by endoscopic mucosal resection, the discussion remains ongoing whether some of these lesions should be removed en bloc by endoscopic submucosal dissection.[28, 29] The main argument for non-selective ESD on large colorectal polyps, is the fact that it is associated with lower recurrence rates compared to EMR.[27, 30, 31] In a systematic review and meta-analysis by Fuccio et al., recurrence rate after ESD was only 2.0% (95% CI: 1.3 – 3.0).[3] However, with the emergence of EMR-T, recurrence rates after EMR can be significantly reduced to percentages as low as 1.3%,[15] waiving this advantage of ESD over EMR. As thermal ablation of mucosal defect margins is not associated with a higher frequency of adverse events,[15] it should be preferred over ESD for treatment of large colorectal polyps without suspicion for submucosal invasion. However, it is of utmost importance to perform a thorough selection of cases suitable for EMR. When there is any suspicion for submucosal invasion, one needs to perform an en bloc resection to obtain free resection margins (R0 resection), which enables pathologists to perform detailed pathological analysis.[32, 33] Endoscopic mucosal resection on superficially invasive colorectal cancers leads to suboptimal treatment outcomes, with low R0-resection rates.[34] Therefore, in case there is any doubt about potential submucosal invasion being present, an en bloc resection technique such as ESD is preferred.

Alternatives to EMR-T are present, such as (extra-)wide field EMR (also known as extended EMR) or marking of the lesion prior to EMR. In (extra-)wide field EMR, a wider excision is performed to excise at least 5mm of normal-appearing tissue around the edges of the lesion. However, a large cohort study, comparing extended EMR with standard EMR did not show a reduction of recurrence after extended EMR.[35] Furthermore, a recent retrospective observational study by Emmanuel et al. showed that microscopic residual adenoma was detected at the apparently normal defect margins in 19% of cases after wide-field EMR.[36] These studies suggest that wide-field EMR is not the appropriate technique to secure that all microscopic adenomatous tissue is being resected and prevent recurrence.

Another recently evaluated alternative to EMR-T is margin marking before EMR. A single-center historical control study, performed by Yang et al., showed that margin marking before EMR reduced

recurrence rates with 80% when compared with conventional EMR.[37] This technique may therefore provide an alternative to margin ablation. However, larger prospective or randomized studies might be desired to validate these outcomes. In the future, expanding the scope to not only treating defect margins, but also the base of resection, might be important to further reduce recurrence.[36, 38]

Our study has some limitations. First, some studies included in this meta-analysis were performed on a small number of patients. Especially in the studies concerning APC, the numbers of patients were limited, which leads to a higher heterogeneity when pooling studies and wider confidence intervals. Heterogeneity was also caused by different duration of follow-up between studies. Therefore, especially the data concerning APC should be interpreted with caution.

Second, this study does not allow us to perform sub-analyses based on specific risk profiles (e.g., piecemeal vs en bloc; number of pieces; high-grade dysplasia; experience of endoscopist, local access to the lesion). Unfortunately, none of the included studies evaluated the relationship between the number of pieces and the additional value of thermal ablation. In other words, might thermal ablation only be of added value from a specific number of pieces onwards. This question therefore remains unanswered. Consequently, we are unable to make any firm statement about which specific lesions could benefit the most from thermal ablation.

Third, while it was not the primary goal of this systematic review, we could not detect a significant difference in effectivity between APC and STSC to reduce recurrence. However, only one comparative study of both treatment modalities exists, of which reliability and generalizability could be questioned because of the retrospective, single endoscopist design, small numbers and long time period of inclusion.[24] Because of these concerns, a prospective randomized controlled trial should be performed to determine whether there is a difference between APC and STSC in reducing the risk of recurrence. Despite the lack of evidence, one could argue that STSC is preferred over APC because of standard availability with EMR and the fact that for APC an additional APC probe is needed, which leads to additional costs.[15] Therefore, STSC is considered the most cost-effective modality and, consequently, suggested as primary thermal ablative treatment modality in most cases. Furthermore, a recent study in porcine models showed possible superiority of STSC over APC, demonstrated by less incomplete ablation with islands of preserved mucosa after STSC compared to APC.[26]

Conclusion and future perspectives

Thermal ablation of mucosal defect margins significantly reduces the risk of recurrence after resection of large non-pedunculated colorectal polyps and should be used universally for piecemeal-resected LNPCPs. Although evidence for superiority is lacking, STSC is preferred over APC because this is the most evidence-based and probably most cost-effective modality. Further (randomized) studies are needed to investigate the difference between APC and STSC efficacy in reducing recurrence after endoscopic resection of large non-pedunculated colorectal polyps.

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Optimizing post-polypectomy surveillance: A practical guide for the endoscopist

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Abstract

Several gastrointestinal societies strongly recommend colonoscopy surveillance after endoscopic and surgical resection of colorectal neoplasms. Common denominators to these recommendations include: high-quality baseline colonoscopy before inclusion in a surveillance program; risk stratification based on clinicopathologic profiles to guide surveillance intervals; and endoscopist responsibility for providing surveillance advice. Considerable variability also exists between guidelines (i.e. regarding risk classification and surveillance intervals). In this review, we examine key factors for quality of post-polypectomy surveillance practice, in particular bowel preparation, endoscopic findings at baseline examination and adherence to surveillance recommendations. Frequently asked questions by the practicing endoscopist are addressed.

Introduction

The vast majority of gastrointestinal professional societies recommend colonoscopy surveillance after endoscopic and surgical resection of colorectal neoplasms, to diagnose synchronous and metachronous advanced neoplasms and early colorectal cancer (CRC).[1-9] In the West, up to one fourth of the total number of colonoscopies are carried out for surveillance.[10, 11] As population-based screening has been adopted in many European countries, the economic burden of colonoscopy surveillance will expand in the future.[1] It is thus critical to optimize the utilization of colonoscopy resources in practice. Previous post-polypectomy surveillance studies identified risk subgroups, based on endoscopic (number, location, size) and histological (villosity, high-grade dysplasia or CRC) features of colorectal neoplasms at baseline examination.[12-16] Such studies could not provide details on the quality of examination (e.g. bowel preparation, cecal intubation, adenoma detection and resection rates). Joint efforts to optimize quality in colonoscopy performance have now shifted to the forefront of surveillance practice.[1, 2] To establish optimal surveillance intervals, randomized controlled trials are needed using robust endpoints, such as reduction of interval CRC rate and mortality from CRC. In real-life, it is cumbersome to generate such data: large sample sizes and long-term follow-up are required. Using the detection of advanced adenoma and early CRC as alternative is easier and allows immediate intervention. Ongoing randomized controlled trials[17, 18] will inform about evidence-based surveillance intervals. Furthermore, standardizing the nomenclature for an interval CRC will facilitate surveillance-specific benchmarking.[19, 20]

Several preconditions should be met to ensure the quality and effectiveness of colonoscopy surveillance. Foremost of which are optimal bowel preparation, the ability of the endoscopist to detect adenomatous and serrated polyps, and to effectively resect them, the clinician's adherence to surveillance guidelines, and certain patient-related factors (age, comorbidity) affecting participation. Monitoring quality measures at all these levels is critical to identify room for potential improvements.[21] In this review, we outline key principles for improving the quality of post-polypectomy surveillance in routine practice. We briefly summarize evidence of the appropriateness and frequency of surveillance intervals. We specifically address the following questions:

1. How does quality of bowel preparation affect surveillance intervals?
2. How do findings at baseline colonoscopy influence surveillance intervals?
3. How to improve adherence to surveillance recommendations?

A practical guide is proposed to assist the application of surveillance recommendations in clinical practice.

Methods

We conducted a systematic search in Pubmed and the Cochrane Library using questions that are relevant to surveillance practice (**Table 7.1**). We retrieved key original studies, systematic reviews and meta-analyses (whenever available), up to March 1st, 2015. Specifically analyzed were general features and differences in recommended surveillance intervals across guidelines.

Quality of bowel examination

Intuitively, post-polypectomy surveillance can be initiated only after a high quality index colonoscopy.[1] The recent European Society of Gastrointestinal Endoscopy (ESGE) guidelines defines a high-quality colonoscopy as "a complete examination with a meticulous inspection of adequately cleaned colorectal mucosa, and at which all neoplasms detected have been completely removed and retrieved for histological examination."[1]

Table 7.1: Search strategy | *Results through March 2015.*

Question	Search	Results	Outcome
How does quality of bowel preparation affect surveillance intervals?	'colonoscopy' combined with: 'preparation', 'lavage' and 'cleaning'; 'colon', 'bowel' and 'colorectal'; 'efficiency', 'effectiveness', 'result', 'outcome' and 'polyp/adenoma detection rate'	570 results, 46 reviews	18 relevant articles supplemented by 8 articles derived from references
How do findings at baseline colonoscopy influence surveillance intervals?	'colonoscopy', 'colonoscopic' and 'colon endoscopy' combined with: 'surveillance', 'followup' and 'follow-up'; 'risk', 'post-polypectomy' and 'incidence'	7311 results, 77 meta-analyses	3 relevant meta-analyses included
Secondary question: What is the appropriate surveillance interval?	'colonoscopy', 'colonoscopic', 'colon endoscopy' combined with: 'surveillance', 'followup', 'follow-up'; and 'post-polypectomy', 'postpolypectomy'; and 'adenoma', 'carcinoma', 'advanced neoplasia', 'CRC', 'advanced adenoma', 'ADR', 'adenoma detection rate'	85 results	7 relevant articles, 4 articles derived from references and guidelines
Secondary question: What is the recurrence rate after endoscopic resection of colorectal polyps?	'colonoscopy', 'colonoscopic', 'colon endoscopy' combined with: 'EMR', 'endoscopic mucosal resection', 'removal'; and 'adenoma', 'lesion', 'lesions', 'polyp', 'polyps'; and 'follow-up', 'followup', 'surveillance'; and 'recurrence', 'residue'	194 results, 15 reviews	4 recent, relevant articles (2 meta-analyses), 11 key articles derived from references and guidelines
Secondary question: What is the role of serrated lesions in determining surveillance intervals?	'colonoscopy', 'coloscopy' and 'colon endoscopy' combined with: 'serrated polyps', 'serrated lesions', 'serrated adenomas', 'SSAP*', 'SSA/P*', 'SSA*' and 'SSP*'	318 results, 49 reviews	12 relevant articles, 3 key articles derived from references and guidelines
How to improve adherence to surveillance recommendations?	'colonoscopy', 'coloscopy' and 'colon endoscopy' combined with: 'surveillance', 'follow-up', 'followup'; and 'patient compliance', 'adherence', 'underuse', 'utilization'; with limit: 'Humans'	978 results	8 relevant articles, 5 articles derived from references

Quality of bowel preparation is critical for optimizing the diagnostic and therapeutic yield of colonoscopy.[1-4, 7] Of course, cecal intubation is important in visualizing the entire colonic mucosa,[22, 23] albeit it is less modifiable. Insufficient bowel preparation prolongs insertion time and hinders detection and resection of colorectal neoplasms, especially subtle appearing flat and depressed adenomas and sessile serrated polyps.[24-28] It is a risk factor for the detection of advanced adenomas during follow-up.[16, 22, 29] Insufficient bowel preparation requires repeated examination, increasing the cost and risk of complications.[29, 30] Several issues need to be clarified to optimize the colonoscopy surveillance practice: For example: How to define adequate bowel cleansing?; When to stop and when to repeat colonoscopy in case of insufficient bowel preparation?; And how to record information regarding bowel preparation? Many colonoscopy practice guidelines[1, 2, 5, 23, 29] now recommend that bowel preparation should be considered sufficient if lesions ≥5mm in size can be detected. Furthermore, post-polypectomy surveillance guidelines[23, 29, 31-33] recommend a split dose of 2-4 L polyethylene glycol (or a same-day regimen for afternoon colonoscopies). Qualification of the degree of bowel cleansing using a valid and reliable scale is crucial, although not yet widely implemented in routine practice.[29] **Table 7.2** summarizes the most common assessment scales: Aronchick Bowel Preparation Scale, Ottawa Scale and Boston Bowel Preparation Scale (BBPS).[34-37] The Aronchick Scale relies on a qualitative assessment, which seems easier to apply, albeit estimation of the percentage of colonic mucosa visualized can be difficult.[34] Given the lack of reliability data, the Aronchick scale is presently not recommended for clinical practice. The Ottawa scale evaluates cleanliness and quantity of fluid as separate items.[35] In contrast to the Ottawa and Aronchick scales which report the quality of bowel preparation before cleansing (washing and suctioning), the BBPS quantifies the degree of bowel preparation during withdrawal, after maximal cleansing of the mucosa and is preferable.[36] The BBPS correlates with the polyp detection rate (40% for BBPS ≥5 versus 24% for a BBPS <5).[36, 38] Furthermore, endoscopists seem to be more confident of not missing lesions >5mm when BBPS is rated 6 versus 5 (82% versus 33%).[39] To improve uniformity in reporting using the BBPS scale, the designers provided a set of images and a 15-minute web training module.

The next confronting issue is when to stop and when to repeat colonoscopy in cases of insufficient bowel cleansing. Current guidelines recommend to already estimate the degree of bowel preparation in the rectosigmoid.[29] If a surveillance colonoscopy is carried out and the bowel preparation is inadequate to allow detection of polyps ≥5mm, then the procedure should be aborted and rescheduled. Alternatively, bowel cleansing can be continued and the procedure rescheduled later on the same day.[33] Inadequate bowel preparation is a risk factor for insufficient bowel preparation at repeat colonoscopy.[40, 41] A recent meta-analysis showed comparable adenoma detection rates in patients with moderate versus high quality bowel preparation.[37] However, endoscopists tend to schedule patients with 'fair' bowel preparation sooner than those with excellent preparation (65.9% ≤1 year).[42] In case the colonoscopy was complete but the degree of bowel preparation was inadequate, then a repeat colonoscopy should be recommended within 1 year (or earlier in cases of suspected advanced neoplasia), using a more intensive bowel preparation (combination of diet, medication and personalized patient instruction).[2, 27, 29] Of note, rescheduling of the procedure is frequently omitted or unnecessarily postponed in practice. A single-center retrospective study by Lebwohl et al. including 12,787 colonoscopies found that the quality of bowel preparation was poor or fair in 24% of cases.[43] However, only 17% of these patients were rescheduled for repeat examination within 3 years. Among patients receiving re-examination with optimal preparation, the miss rates of adenomas and advanced adenoma were 42% and 27%,

respectively.[43]

Next, it is important to carefully record and document the quality of bowel preparation, especially when insufficient bowel preparation is the reason to stop. Endoscopists may consider reporting the suspected reasons for failure of bowel preparation, e.g. failure to follow split-dose instructions, delay of the procedure or comorbidity. Understanding such factors will provide targeted solutions, such as better communication with patients and logistical improvements.

Table 7.2: Comparison of most frequently applied bowel preparation scales.

	Scale		
Feature	Aronchick	Ottawa	Boston
Splitting in segments	No	Yes (3 parts)	Yes (3 parts)
After cleaning by endoscopist	No	No	Yes (washing, suctioning)
Total score	1-5 (excellent to inadequate)	0-14 (excellent to inadequate)	0-9 (inadequate to excellent)
Scoring system	Excellent: small volume of clear liquid or ≥95% of surface seen; Good: large volume of clear liquid covering 5-25% of the surface but ≥90% of surface seen; Fair: some semi-solid stool that could be suctioned or washed away but ≥90% of surface seen; Poor: semi-solid stool that could not be suctioned or washed away and <90% of surface seen; Inadequate: repreparation needed.	Part A: Splitting colon into: Right colon (R): cecum – ascending colon; Mid colon (M): transverse – descending colon; Rectosigmoid colon (R-S): rectosigmoid. Scoring for each section: - 0 (excellent): perfect - 1 - 2 (fair): necessary to suction liquid stool - 3 (poor): necessary to wash and suction - 4 Part B: Fluid quantity of whole colon: - 0: no fluid - 1: moderate fluid - 2: lots of fluid Total: Score A + score B (sum of scores for each section)	Splitting colon into: Right colon: cecum – ascending colon; Transverse colon: hepatic flexure – sphlenic flexure; Left colon: descending colon – rectum. Scoring for each section: 0: unprepared colon segment with mucosa not seen because of solid stool that cannot be cleared; 1: portion of mucosa of the colon segment seen, but other areas of the colon segment are not well seen because of staining, residual stool, and/or opaque liquid; 2: minor amount of residual staining, small fragments of stool, and/or opaque liquid, but mucosa of colon segment is seen well; 3: entire colonic mucosa, colon segment seen well, with no residual staining, small fragments of stool, or opaque liquid. Total: Sum of scores for each section.

Detection and resection of colorectal neoplasms

Detection

The majority of post-polypectomy surveillance guidelines use risk stratification to determine surveillance intervals (**Figure 7.1**). Patients with multiple, large, proximal adenomas, or adenomas with unfavorable histology (villosity or high-grade dysplasia) at baseline colonoscopy have a greater risk of synchronous and metachronous neoplasms,[44-46] justifying more intensive surveillance. Evidence on the optimal post-polypectomy surveillance intervals is scarce.[12, 47] Lack of conclusive data from randomized controlled trials and uncertainty surrounding many issues partly explain discrepancies in recommendations. For example, there is variation between society guidelines with regard to definition of risk factors and recommended surveillance intervals in some subgroups (**Figure 7.1**).

To ensure a high-quality surveillance program, the diagnostic and therapeutic yield at the index examination should be optimized. A recent large multicenter study from the UK (Quality Improvement in Colonoscopy study), found that implementation of a bundle of measures (e.g. withdrawal time ≥6 minutes; use of butyl scopolamine; position change during colonoscopy to optimize visualization; and rectal retroflexion) improves adenoma detection rates.[48] To improve uniformity in surveillance practice, the post-polypectomy surveillance guideline of the ESGE[1] recommend risk stratification in two groups: (1) low risk group, which consists of patients with 1 or 2 non-advanced adenomas versus (2) high-risk group, which consists of patients with ≥3 adenomas or ≥1 advanced adenoma (≥10mm, villous histology or high-grade dysplasia). The ESGE guideline recommend that the low-risk group further participates in the screening program or return for follow-up colonoscopy after 10 years (whatever option is available). Conversely, patients in the high-risk group are recommended to undergo colonoscopy surveillance 3 years after the baseline colonoscopy (**Figure 7.2**).[1] Both recommendations are strong and based on moderate quality evidence: a meta-analysis found that advanced neoplasia was diagnosed during follow-up in 1.6% of patients without neoplasia and in 3.6% of those with low-risk findings (relative risk of 1.8, 95% CI: 1.3 – 2.6).[49] A prospective Korean study showed that advanced adenoma recurrence at 5 years after a baseline colonoscopy was similar in low-risk patients versus patients without neoplasms, concluding that extending the surveillance interval beyond 5 years for the low-risk patients is safe.[50] Case-control studies confirm the absolute low risk of CRC in the 5 years after polypectomy.[51-53] In a pooled analysis of eight American, prospective studies including 9167 patients, 15.5% of the high-risk group and 6.9% of the low-risk group developed advanced adenoma during follow-up, whereas 0.8% of the high-risk and 0.5% of the low-risk patients developed CRC.[8] Two meta-analyses confirmed that patients with more than two adenomas had a higher risk of developing advanced adenomas in surveillance than patients with one or two adenomas at baseline.[15, 54] Of note, most studies did not specifically examine the quality of index-colonoscopy and relation with metachronous neoplasms. Data from the ongoing randomized controlled Japan Polyp Study indicate that two complete colonoscopies (at baseline and after 1 year) have the potential to lengthen subsequent follow-up intervals.[17]

Several distinct features of current post-polypectomy surveillance guidelines need to be acknowledged. The post-polypectomy surveillance guideline of the British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland (UK guideline) classify three risk subgroups: low, intermediate and high-risk groups recommending surveillance intervals of 5, 3 and 1 year(s), respectively.[3] Martinez et al. compared the outcomes of applying

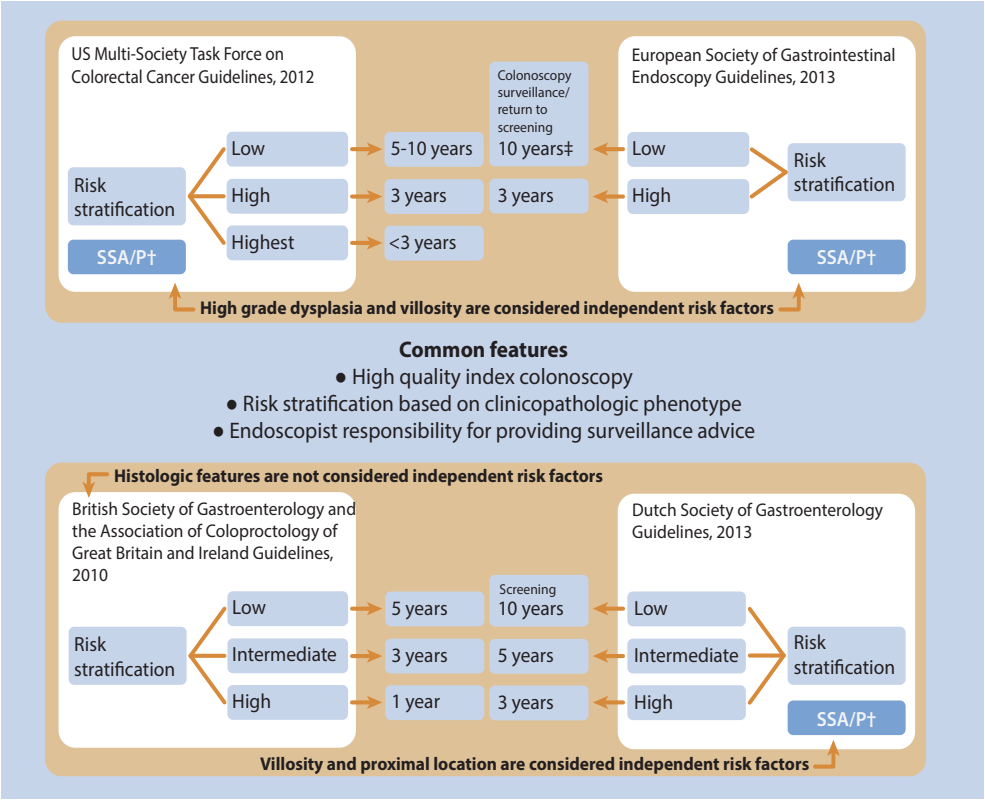

Figure 7.1: Common and specific features of some post-polypectomy surveillance guidelines. |
United States Multi-Society Task Force on Colorectal Cancer post-polypectomy surveillance guidelines:[2] low risk, 1-2 tubular adenomas <10mm; high risk, 3-10 adenomas or ≥1 advanced adenoma; highest risk, >10 adenomas. European Society of Gastrointestinal Endoscopy post-polypectomy surveillance guidelines:[1] low risk, 1-2 tubular adenomas <10mm; high risk, ≥3 adenomas or ≥1 advanced adenoma. British Society of Gastroenterology and the Association Coloproctology of Great Britain and Ireland post-polypectomy surveillance guidelines:[3] low risk, 1-2 adenomas <10mm; intermediate risk, 3-4 adenomas <10mm or ≥1 ≥10mm; high risk, ≥5 small adenomas or ≥3 adenomas with ≥1 ≥10mm. Revised Dutch Society of Gastroenterology post-polypectomy surveillance guidelines:[7] low risk, score 0 (no or 1 non-advanced distal adenoma); intermediate risk, score 1-2; high risk, score 3-5.
†Presence of SSA/P included in determining surveillance intervals, ‡Follow-up colonoscopy or return to screening program (if available) after 10 years.

the UK versus the US guidelines in a pooled American population (four prospective studies) who underwent one year follow-up colonoscopy. The risk for advanced adenoma or CRC at one year after baseline colonoscopy was assessed using both US and UK stratification. The proportions of patients who were diagnosed with advanced adenomas or CRC at one year were 3.8% of the low risk and 11.2% of the high risk patients, when using the US guideline versus 4.4% of low risk, 9.9% of intermediate risk and 18.7% of high risk patients, when using the UK guideline.[55] Thus, surveillance colonoscopy after one year seems to be beneficial for the high-risk group, as defined by the UK criteria (12.1% of all patients) without a substantial increase in the overall rate of surveillance

colonoscopies (only 0.03 colonoscopies per patient per 5 years).[55] Vemulapalli et al. also found that application of the UK guidelines better predicts advanced neoplasms in the high risk group.[56]

The recent post-polypectomy surveillance guidelines of the European guidelines for quality assurance in colorectal cancer screening and diagnosis recommend a similar risk stratification as the UK guidelines.[9] As several organized screening programs are now running in Europe, low-risk patients are recommended to return to such screening after 10 years.

The revised Dutch post-polypectomy surveillance guidelines propose a personal risk score assessment, based on independent risk factors (e.g. number of adenomas, size ≥10mm, villous histology and proximal location).[7] Using such a score, patients can be stratified into three risk groups, with cut-off values derived from a cost-benefit analysis.[8, 15, 16] Patients who score 0, 1-2 or 3-5 are recommended to return to the screening program after 10 years (no surveillance colonoscopy), or to undergo surveillance colonoscopy after 5 years and after 3 years, respectively. Upon validation, such strategy may lead to personalized surveillance advice in practice.[7]

With regard to signs of unfavorable histology, villosity and high-grade dysplasia are considered independent risk factors by some[1, 2, 4-6] but not other post-polypectomy surveillance guidelines.[3, 7] High-grade dysplasia does not seem to be an independent risk factor for advanced colorectal neoplasm diagnosis after polypectomy.[8, 16] Approximately 98% of adenomas with high-grade dysplasia are also large or villous.[16] Integrated risk profiles can be considered to personalize surveillance intervals. As such, Chiu et al.[57] showed that the metabolic syndrome is a risk factor for developing advanced neoplasms in patients at low-risk and those without neoplasms at baseline examination.

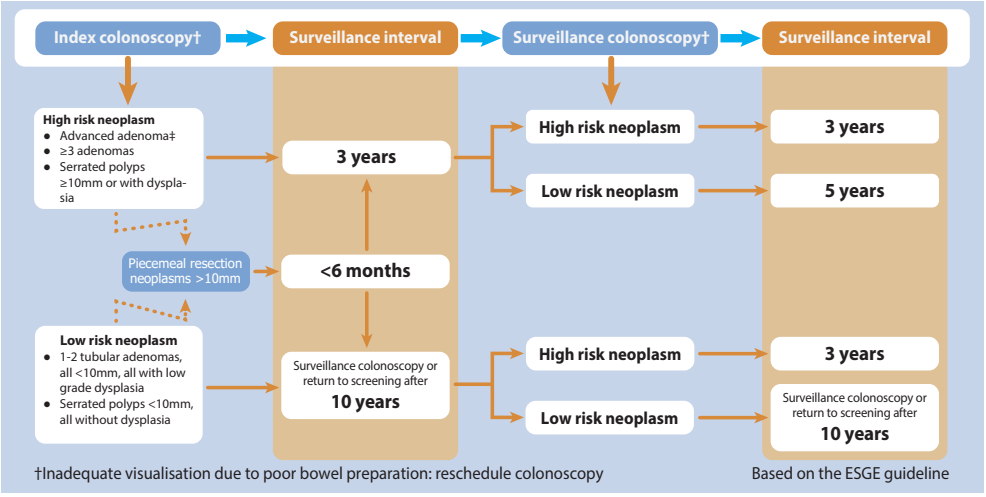

Figure 7.2: Clinical decision algorithm for determining post-polypectomy surveillance intervals in practice | *Based on the post-polypectomy colonoscopy surveillance guidelines of the European Society of Gastrointestinal Endoscopy [ESGE], 2013.*[1]

†The ESGE guidelines define sufficient visualization as allowing reasonable exclusion of the presence of lesions ≥5mm.

‡Advanced adenoma is defined as adenoma with villous histology, high grade dysplasia or a size ≥10mm.

Polyp resection

Next to diagnosis, completeness of polyp resection affects the recommendation on surveillance interval. Incomplete polyp resection contributes to 9-19% of the postcolonoscopy CRCs (PCCRCs).[20, 45, 58-60] A study by Pohl et al. including experienced gastroenterologists found that 10.1% (95% CI: 6.9 – 13.3) of polyps 5-20 mm in size were incompletely resected.[61] In particular, large size (RR 2.1) and sessile serrated adenomas/polyps (SSA/Ps) (RR 3.7) were independent risk factors for incomplete resection. Endoscopists with high polypectomy rates also have a lower risk of PCCRCs in their patients (OR 0.61, 95% CI: 0.42 – 0.89).[62]

A recent meta-analysis assessed the effectiveness of endoscopic resection, using the need for subsequent surgery as primary endpoint. Overall, 8% (95% CI: 7 – 10) of all patients needed surgery, of whom 7% (95% CI: 6 – 9) were for incomplete resection of lesions ≥20mm, highlighting room for potential improvement.[63] In cases of suspected incomplete polyp resection, tattooing of the location is advisable to facilitate identification at next colonoscopy or surgery.[64]

With increasing adoption of endoscopic resection techniques (endoscopic mucosal resection and endoscopic submucosal dissection) in the West, the need for surgical treatment of large colorectal polyps and early CRC will decline.[65-67] Such shift in management may also increase colonoscopy follow-up. Two meta-analyses on post-EMR recurrence rates (mean follow-up: 23 months) showed similar rates: 13.1% versus 15%. Piecemeal resection had a significant higher recurrence rate than en-bloc resection (OR 4.4, 95% CI: 2.1 – 9.4):[68] 20% (95% CI: 16 – 25) for piecemeal versus 3% (95% CI: 2 – 5) for en-bloc resection.[69] Pooling analyses including follow-up data showed that 91 to 96% of all polyp recurrences are detected within six months, confirming the need for follow-up at 6 months to assess radicality.[69] Lesions with high-grade dysplasia or CRC had a greater rate of recurrence than those with low-grade dysplasia.[69] Endoscopic resection of laterally spreading tumors irrespective of size is now safe and the recurrence rates dramatically decreased.[67, 70-73] Whether 1-year follow-up should be recommended after piecemeal resection of laterally spreading tumors is presently unknown and needs clarification. The number of repeat colonoscopies to safeguard radicality of resection will likely decrease with training improvements and sustained practice.

Serrated polyps

A number of revised post-polypectomy guidelines recommend inclusion of serrated polyps to assess surveillance intervals after polypectomy, although evidence is weak.[1, 2, 5-7] Hyperplastic polyps (which are the most common form of serrated polyps) are benign lesions, without any risk of malignant transformation.[74, 75] Several observational studies found that hyperplastic polyps alone are associated with slightly increased risk of adenomas, but not of advanced adenomas.[76, 77] Compared with the presence of adenoma alone, simultaneous presence of hyperplastic polyps and adenomas at baseline colonoscopy is not associated with increased risk of (advanced) adenomas at surveillance.[78] Some studies showed that presence of serrated polyps is associated with synchronous advanced neoplasia.[79-82] In contrast to hyperplastic polyps, the increasingly recognized sessile serrated adenomas/polyps (SSA/Ps) and traditional serrated adenomas are associated with risk of progression to CRC. Several observational studies found that SSA/Ps are risk factors for having synchronous advanced adenomas and CRC, especially when large (≥10mm) or dysplastic.[79-81, 83-87] The presence of large serrated polyps correlated with both synchronous distal and proximal advanced adenomas and CRC, although the correlation was stronger for proximal neoplasms.[79] While awaiting more data, presence of large or dysplastic serrated polyps is now considered a risk

factor for metachronous neoplasms, requiring intensified surveillance.[2, 7]

A recent population-based study from Norway investigated the risk to develop CRC in patients with serrated polyps.[88] A total of 12,955 patients undergoing sigmoidoscopy were followed (mean follow-up period: 10.9 years). Patients with serrated polyps ≥10mm in size (n=81) had a significant higher risk of developing CRC than those without any polyps at baseline (HR 4.2, 95% CI: 1.3 – 13.3). A comparable risk of CRC was found in patients with advanced adenoma (HR 3.3, 95% CI: 2.1 – 5.2). Only one of the three CRCs diagnosed in patients with serrated polyps occurred in the same segment as a previous polypectomy. In 24 patients, a large serrated polyp was identified at baseline examination and not resected (biopsy alone), of whom only one developed CRC in a different colonic segment.[88] The authors concluded that presence of serrated polyps at baseline exam is a risk factor for CRC during follow-up, but is not necessarily a causal factor.

Compliance with surveillance guidelines

Adherence to surveillance recommendations

Adherence to surveillance recommendations includes both physician compliance and patient compliance. Recent guidelines underscore the responsibility of the endoscopist for determining, documenting and communicating the correct surveillance interval, including written recommendations.[1, 89] Lack of compliance with the recommended surveillance intervals is a significant contributor to metachronous CRC.[90] Adherence to surveillance recommendations seems to vary among physicians, with both too short and too long intervals.[91-94] A Dutch retrospective cohort study found a high proportion of inappropriate surveillance intervals: 76% of patients before versus 89% after the implementation of revised guidelines.[94] In the past, patients were more likely to have their surveillance colonoscopy too late or not at all (57% of cases), whereas a substantial proportion of patients now receive their surveillance colonoscopy too early (48% of cases), perhaps reflecting an increased awareness. Data about physicians' compliance with surveillance recommendations are controversial. A study from the USA found that endoscopists who received their education a long time ago were less compliant.[95] Others found that 97% of the recommendations were according to the guidelines.[96]

Patient compliance with recommended post-polypectomy surveillance intervals ranges from 52 to 85%,[12, 92, 97] with as much as 41.6% non-compliance among patients with advanced adenoma at baseline.[92] Such compliance rates are similar to those in participants of CRC screening programs, and may increase with aging, female gender and repeat screening rounds.[98] Most common barriers to surveillance are procedural barriers (discomfort during colonoscopy and the need for bowel preparation) and facilitation barriers (lack of time, difficulty in making an appointment or transportation concerns).[99] Patients who do not attend their surveillance colonoscopies, are more likely to perceive barriers than the attenders. In contrast, patients with a higher degree of cancer worries or perceived benefits from colonoscopy are more likely to participate in surveillance programs.[99] Automatic systems sending reminders to patients and telephone calls may improve patient compliance.[97, 99, 100]

What should be the upper age limit for surveillance?

The majority of post-polypectomy surveillance guidelines acknowledge the benefit of surveillance up to the age of 75 years.[1, 2, 4, 5, 7] For patients aged 85+, it is unlikely that the benefits of

surveillance counterbalance the risks or increase the life-expectancy.[1, 2, 4, 5, 7] It is presently unknown whether surveillance between the ages of 75 and 85 years is beneficial. In a cross-sectional study, Lin and colleagues showed that the extension of life expectancy with screening can be up to 15 times lower in patients aged 80+ versus those aged 50 to 54 years.[101] The number of colonoscopies per life-year saved ranged from 4 to 16 in patients aged 80+ versus 0.5 to 2 in those aged 50-54 years, according to the assumptions made. The risk of detecting adenomas and especially advanced adenomas increases with age.[8, 15, 102] As the progression from adenoma to carcinoma is estimated to take approximately 10 years, it is reasonable to provide surveillance to patients with a life expectancy of 10 years.[7] However, complications in general, including perforations, are more common in the elderly (incidence ratio 1.7, 95% CI: 1.5 – 1.9 for having an adverse event at 80+ vs 65-80 years).[103] We should bear in mind that the risk of developing interval CRC also increases with age, possibly caused by a lower effectiveness of colonoscopy to prevent cancer in older, frail patients. Insufficient bowel preparation and presence of comorbidities, such as diverticular disease and cardiovascular disease, partly explain this.[19, 33, 102] It has been suggested that comorbidity is a better predictor for inadequate bowel preparation than age itself.[41, 104] Using model estimates of harm-benefit ratios, Lansdorp-Vogelaar and colleagues proposed tailoring of the decision to cease screening for breast cancer, prostate cancer and CRC, according to age and comorbidity.[105] For individuals with no, mild, moderate and severe comorbidities, the harm-benefit ratios of screening until the ages of 76, 74, 72 and 66 respectively were comparable with average-health individuals and consistent across cancer types. While awaiting more evidence, the clinical decision of when to stop surveillance needs to consider the severity of comorbidities, life-expectancy and patient preferences.

Conclusion

The present review summarized principles for optimizing the quality of post-polypectomy surveillance in practice. The majority of professional society guidelines now recommend: a high-quality baseline colonoscopy before inclusion in a surveillance program; risk stratification based on clinicopathological profiles to guide surveillance intervals; and endoscopist responsibility for providing surveillance advice. The recommended surveillance intervals will always vary as a result of the level of scientific evidence, economic and logistic factors. Data from randomized controlled trials will form the basis for evidence-based surveillance intervals in the near future. The quality in performance of colonoscopy is a major driver for post-polypectomy surveillance intervals. Continuous monitoring of bowel preparation by using validated scales, adenoma detection, polyp resection and interval CRC rates are important steps. Quality photo-documentation is perhaps the most universally understood communication tool and improves education. Endoscopists should therefore consider providing documentation on bowel preparation, completeness of examination, and diagnosis and therapeutic steps, as illustrated in **Figure 7.3**. Such a structured approach will permit, in turn, strict compliance with the recommended surveillance intervals. Finally, for a successful surveillance program, patient education and full compliance are critical. Patient counseling, taking into consideration individual risk profiles and life expectancy, paves the way towards cost-effective surveillance strategies.

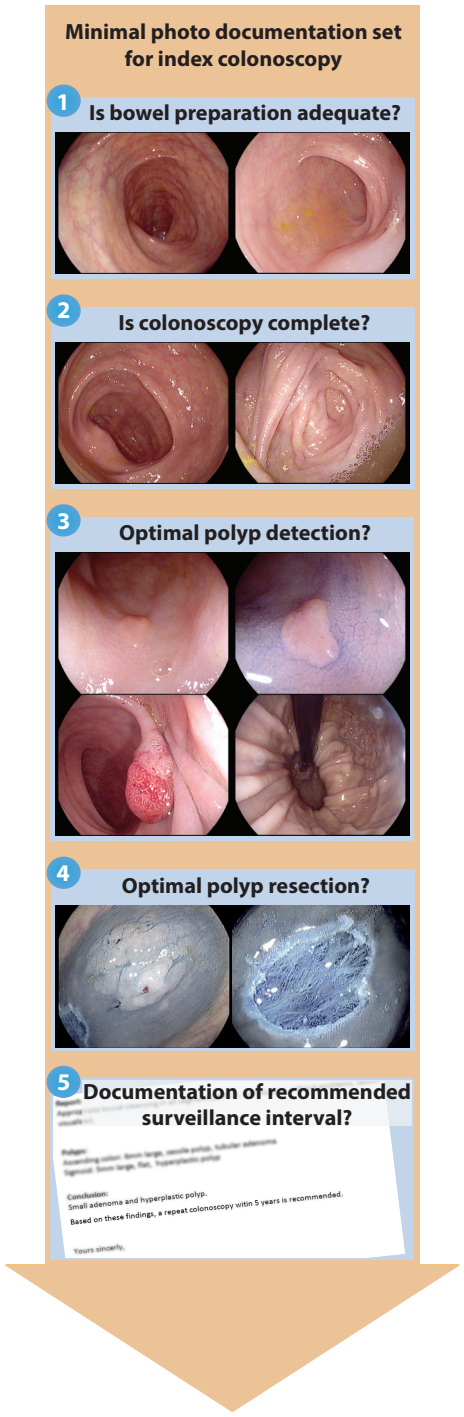

Figure 7.3: Minimal photo-documentation set at baseline and surveillance colonoscopy. | *(1) During withdrawal, the quality of bowel preparation should be evaluated after cleansing of the colonic mucosa. For this, a validated scale should be used (e.g. Boston Bowel Preparation Scale); (2) Completeness of colonoscopy needs to be documented by at least a long view image of the ileo-cecal valve (left) and a close view image of the appendiceal orifice (right); (3) Then, each lesion should be carefully characterized. In this case, two colorectal neoplasms were identified. (Upper images) Nonpolypoid neoplasm long view image (left) permits estimation of the location and size of the lesion, whereas a close view image and selective chromoendoscopy (right) better clarifies the borders and shape. (Lower images) Polypoid colorectal neoplasm (left). Retroflexion eventually rules out rectal pathology (right); (4) The endoscopic technique used (left) and radicality of resection (right) can be documented; (5) The recommended surveillance interval should be included in the final colonoscopy report. The endoscopist has the main responsibility to determine the surveillance interval and provide a written recommendation.*

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Update of post-polypectomy surveillance guidelines since 2015

Since the publication of our paper "Optimizing post-polypectomy surveillance: A practical guide for the endoscopist", most of the described post-surveillance guidelines have been updated with new algorithms. For instance, specific new information about serrated polyps was added. Furthermore, the indications for surveillance colonoscopy have become less extensive. A large retrospective cohort study, investigating findings during follow-up of patients with adenomas, showed that patients with proximal, large (≥10 mm) and high-grade dysplastic adenomas seemed to have more benefit from surveillance than the patients with adenomas without these characteristics. The number of patients with cancer during surveillance were low.[1] A second study with similar methodology, that used the old definition of high risk findings including more than two adenomas and villosity, showed similar results.[2] Therefore, an overview of the updated, currently used post-polypectomy surveillance guidelines with a comparison of their progenitor guidelines is provided in **Table 7.3**.

In the European Society of Gastrointestinal Endoscopy (ESGE) polyp surveillance guidelines update, the most liberal surveillance algorithm was chosen.[3] In comparison to the previous version from 2013, less patients need surveillance. Only patients with at least 5 adenomas, with at least one large (≥10mm) adenoma or sessile serrated lesion, or with high grade dysplasia are in need for surveillance after 3 years.[3] The guidelines of the British Society of Gastroenterology and the Association of Coloproctology of Great Britain and Ireland (BSG/ACGBI/PHE) previously identified three risk groups, but simplified to two groups in its updated formats, in a similar way as in the ESGE guidelines. A large subset of cases previously classified as intermediate risk are now classified as low risk. This means that patients previously receiving surveillance after three years will now return to the default colorectal cancer screening program. Surveillance after one year is now replaced by surveillance after three years.[4]

The currently applicable US Multi-Society Task Force on Colorectal Cancer (US-MSTF CRC) Guidelines are more complex. While the two previously mentioned updates of the guidelines simplified their surveillance advice, these US guidelines have increased in complexity. The intervals differ between 1 and 10 years. In contrast to the other guidelines, adenomas with villous characteristics and a higher number adenomas remain a significant risk factor in these guidelines.[5] Previous studies showed an association between adenoma villosity and recurrent advanced adenoma.[6] However, a meta-analysis pooling 13 studies showed no significant effect on adenoma recurrence (RR 1.21, 95% CI: 0.97 – 1.45).[7] Furthermore, a recent population-based study with colorectal cancer incidence ratios as outcome instead of adenoma recurrence, showed no effect of villous histology.[8] The ESGE guidelines and BSG/ACGBI/PHE guidelines clearly state that surveillance intervals should reduce the risk of metachronous CRC and not metachronous adenomas while allocating higher impact on papers with this outcome. The US-MSTF guidelines in contrast appear to focus more on uncertainties and are more conservative in their recommendations.[3-5]

Recently, also the Japan Gastroenterological Endoscopy Society (JGES) published their updated post-polypectomy surveillance guidelines. In this guideline 3 different surveillance intervals can be distinguished. Noticeable, higher significance is given to the occurrence of high grade dysplasia, or carcinoma in situ as it is called in Japan.[9]

All these updated surveillance guidelines agree that high quality index colonoscopy is a prerequisite for the protective effect of colorectal cancer development.[3-5, 9] Concerning patients

with large numbers of adenomas or serrated polyps, referral for genetic screening to underlying polyposis syndromes is advised.[3] A shorter surveillance interval is also recommended for these patients by some guidelines, because of a larger appearing chance of missing neoplasia.[9]

Although a general consensus on the significance of sessile serrated lesions appears from the surveillance guidelines, the surveillance intervals itself differ. Studies suggesting more metachronous CRCs in patients with sessile serrated adenomas and traditional serrated adenomas are retrospective and based on very few cases.[10, 11] A larger prospective study still had in absolute counts a low number of CRC cases among patients with sessile serrated lesions.[12] However, a large retrospective case-control study showed a strong association between sessile serrated lesions and metachronous CRC occurrence.[13] Additionally, molecular profiling shows that the so-called serrated pathway is found in about a third of all CRCs. The same molecular features, a CpG island methylation phenotype and BRAF gene mutations, occur frequently in sessile serrated lesions.[14]

In conclusion, additional data have provided evidence that the risk of metachronous CRC after a high-quality clearing colonoscopy is lower than previously thought. This additional information has resulted in less intense surveillance regimens by the described guidelines. Data that have become available on sessile serrated lesions have resulted in a more generally accepted consensus about sessile serrated lesions being significant for metachronous CRCs. This led more often to shorter surveillance intervals for patients with these lesions. Evaluation of current surveillance regimens in the upcoming years will reveal whether the current strategies are helpful or not, just as recently published studies have changed the follow-up regimens for patients with conventional adenomas.

Table 7.3: Overview of four of the most relevant post-polypectomy surveillance guidelines, comparing the old and the new advice.

Guideline	Old groups	New groups	Old advice	New advice
ESGE guidelines[3]	**Low risk** ≤2 tubular adenomas, all <10mm	**Low risk** ≤4 adenomas, all <10mm	Back to screening/ colonoscopy after 10 yrs	Back to screening/ colonoscopy after 10 yrs
	High risk ≥3 adenomas / HGD / size ≥10mm	**High risk** ≥5 adenomas / HGD / size ≥10mm / SP ≥10mm or dysplastic	Surveillance after 3 yrs	Surveillance after 3 yrs
BSG/ACGBI/PHE guidelines[4]	**Low risk** 1-2 adenomas <10mm	**Low risk** <5 adenomas/ SPs with no advanced features / ≤1 advanced adenoma/SP	Surveillance after 5 yrs	Back to screening
	Intermediate risk 3-4 adenomas <10mm / ≥1 adenomas ≥10mm in size	-	Surveillance after 3 yrs	-

Table 7.3: *(continuation)*

Guideline	Old groups	New groups	Old advice	New advice
	High risk ≥5 adenomas / ≥3 adenomas with ≥1 adenoma ≥10mm in size	**High risk** ≥2 adenomas/ SPs with ≥1 advanced (SP with dysplasia, size ≥10mm or HGD) / ≥5 adenomas/SPs	Surveillance after 1 yr	Surveillance after 3 yrs
US-MSTF guidelines[5]	**Low risk** 1-2 tubular adenomas	**Low risk** 1-2 tubular adenomas / 1-2 SPs	Surveillance after 5-10 yrs	Surveillance after 7-10 yrs (adenomas) / 5-10 yrs (SPs)
	-	**Intermediate risk** 3-4 adenomas or SPs / hyperplastic polyp ≥10mm	-	Surveillance after 3-5 yrs
	High risk 3-10 adenomas / ≥1 adenoma with villosity, ≥10 mm or HGD	**High risk** 5-10 adenomas or SPs / adenoma or SP ≥10mm / villous histology, HGD or dysplastic SP / TSA	Surveillance after 3 yrs	Surveillance after 3 yrs
	Highest risk >10 adenomas	**Highest risk** >10 adenomas	Surveillance within 3 yrs	Surveillance after 1 yr
JGES guidelines[9]	-	**Low risk** 1-2 adenomas, SPs	-	Surveillance after 3-5 yrs
	-	**Intermediate risk** 3-9 adenomas	-	Surveillance after 3 yrs
	-	**Highest risk** ≥10 adenomas / HGD / size ≥20mm	-	Surveillance after 1 yr

HGD: high grade dysplasia, SP: serrated polyp, yrs: years, yr: year.

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Optical diagnosis of diminutive polyps in the Dutch bowel cancer screening program: Are we ready to start?

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Abstract

Background and study aims

Implementation of optical diagnosis of diminutive polyps may potentially increase the efficacy and cost-effectiveness of colonoscopies. To adopt such strategy in clinical practice, the Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) thresholds provide the basis to be met: ≥90% negative predictive value (NPV) for diagnosis of adenomatous histology and ≥ 90% agreement on surveillance intervals. We evaluated this within the Dutch bowel cancer screening program (BCSP).

Patients and methods

Endoscopic and histological data were collected from participants of the national bowel cancer screening program with an unfavorable fecal immunochemical test referred for colonoscopy between February 2014 and August 2015 at four endoscopy centers. The "resect and discard" scenario was studied, resecting diminutive polyps without histological evaluation. Agreement between optical diagnosis and histological diagnosis was measured for surveillance intervals according to Dutch, European and American post-polypectomy surveillance guideline.

Results

Fifteen certified endoscopists participated in this study and included 3028 diminutive polyps. In 2330 patients both optical and histological diagnosis were available. Optical diagnosis of diminutive polyps showed NPV of 84% (95% CI: 80 – 87) for adenomatous histology in the rectosigmoid. Applying the 'resect and discard' strategy resulted in 90.6%, 91.2%, 90.9% agreement on surveillance intervals for the Dutch, European and American guidelines, respectively.

Conclusion

Our data representing current clinical practice in the Dutch BCSP practice on optical diagnosis of diminutive polyps showed that accuracy of predicting histology remains challenging, and risk of incorrect optical diagnosis is still significant. Therefore, it is too early to safely implement these strategies.

Introduction

Colorectal cancer (CRC) is a major cause of cancer-related mortality and morbidity in the Western world.[1] To reduce CRC incidence and mortality, CRC screening programs have been implemented.[2, 3] Screening via fecal immunochemical testing (FIT) is proven to be effective in reducing CRC-related deaths.[4]

In 2014 the FIT-based Dutch Bowel Cancer Screening Program (BCSP) was implemented for individuals aged 55 to 75 years. After an unfavorable FIT result, patients are invited for a colonoscopy to detect and resect (pre-) cancerous lesions. This has resulted in an increase in number of colonoscopies, polyp detection and resection, and histological assessments, leading to a substantial financial burden on the health care system.[5]

The majority of polyps found during screening colonoscopy are small (≤10mm) and contain non-advanced histologic features, but in current clinical practice all polyps are resected and sent for histological assessment, on which surveillance recommendations are made.

It has been seriously questioned whether histological evaluation of all these small, diminutive lesions is worthwhile and more efficient and cost-effective strategies should be implemented.[6]

Optical diagnosis of colorectal polyps refers to "in vivo" estimation of histology of the polyp by endoscopists using high-definition endoscopy in conjunction with (virtual) chromoendoscopy.[7] Two strategies are proposed for implementation in clinical practice, but only if the Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) thresholds are met.[7] First, the 'resect and discard' strategy applies to diminutive (≤5mm) colorectal adenomatous polyps which are resected, but are not sent out for histological evaluation (PIVI threshold: ≥90% agreement between optical diagnosis and histological diagnosis in determining the post-polypectomy surveillance interval). Second, the 'diagnose and leave' strategy, where diminutive hyperplastic polyps in the rectosigmoid are identified and left in situ (PIVI threshold: ≥90% negative predictive value [NPV] for optical diagnosis of diminutive adenomatous polyps).[8]

Up to now, data on optical diagnosis have been obtained mainly in study settings, i.e. from expert centers with high confidence optical diagnosis, as the PIVI guidelines suggest. However, to actually implement these strategies, data from routine clinical practice are needed. Here, we present the first detailed data from the Dutch BSCP; a real-life but standardized endoscopy practice setting.

The aim of this study was to evaluate whether PIVI thresholds are met regarding: A, the diagnostic accuracy of optical diagnosis for diminutive polyps; and regarding B, the 'resect and discard' and 'diagnose and leave' strategies, within the BCSP in a defined region of the Netherlands, South Limburg, representing our national data.[9, 10]

Methods

Longitudinal data collection was performed in the four endoscopy centers in the South-Limburg region of the Netherlands: one academic center (Maastricht University Medical Center (MUMC+)) and three regional (Diagnostic Center Maastricht and Zuyderland Medical Center Sittard-Geleen and Zuyderland Medical Center Heerlen) endoscopy units. All endoscopic and histological data of FIT-unfavorable participants (55-75 years) who underwent colonoscopy within the contact of the Dutch BCSP from February 2014 to August 2015 were collected.

A threshold of 15µg Hb/g feces was considered FIT unfavorable (FOB gold, Sentinel, Milan, Italy) in the first six months, but was raised to 47µg Hb/g because of limitations in endoscopy capacity.[5] We included all patients with index colonoscopies fulfilling the quality criteria in the screening program (cecal intubation and adequate bowel preparation defined as Boston Bowel Preparation Score [BBPS] ≥6) in this retrospective analysis. This trial is registered in the Netherlands Trial Registry (NTR4844) and the medical ethical committee of the MUMC+ assigned approval for the prospective colonoscopy database (number: 14-4-046). Need for informed consent was waived by the Institutional Review Board.

Endoscopists and equipment

European guidelines for quality assurance in CRC screening have been set.[3] In the Netherlands, endoscopists have to be certified before being allowed to participate in the BCSP.[11, 12] To be admitted to the Dutch BCSP, endoscopists should have performed at least 300 colonoscopies and over 50 polypectomies per year. Furthermore, quality measures have been set and are evaluated.[11] In addition, endoscopists are required to register 100 consecutive colonoscopies with corresponding quality indicators. Then, a theoretical e-learning module should be accomplished and colonoscopy skills are evaluated in live practice setting and via videos.[12] All endoscopists in this study fulfilled the quality measures for the screening program as described above but they received no specific additional training regarding optical diagnosis of colorectal polyps.

Because the data are retrieved from a clinical practice setting, endoscopists performed standard care and were not informed about the study. All parameters currently included in the standardized endoscopy-report for the Dutch BCSP were obtained, assuming that all lesions found have been described in this report, as this is current clinical practice.

Among others, location, size, Paris-classification and predicted histology (optical diagnosis) were reported and the removed polyps were collected and sent in for histological evaluation. The classification options for estimated histology were: adenomatous polyp, hyperplastic polyp, sessile serrated lesion, carcinoma and other. No specific classification system (NICE, WASP) nor the confidence of the estimated histology are included in the standardized endoscopy-report. Therefore, these data were not available for evaluation.

High-definition white light colonoscopy (HD-WLE) was used in all endoscopy units and also (virtual) chromoendoscopy was available and used upon discretion of the endoscopist. All colonoscopies were performed using endoscopic equipment containing virtual chromoendoscopy, either I-scan (Pentax Medical Europe) used in one endoscopy unit or NBI (Olympus, Tokyo, Japan), used in the three other endoscopy units. The use of image-enhancement was not systematically included in the endoscopy report. To obtain an estimation on the use of image-enhancement endoscopy (IEE), we reviewed the photo documentation to see whether image-enhancement was captured in the photos. The use of IEE is scored for every polyp, and in case no photo was available or in case of more polyps in the same region, there had to be at least five (consecutive) photos where IEE was used for a positive score.

Colonoscopy

Standard bowel preparation regimens were used with polyethylene glycol solution containing ascorbic acid or Picosulfate sodium (Moviprep Norgine GmbH, Marburg, Germany or Picoprep, Ferring GmbH, Kiel, Germany). After introduction to the cecum, the quality of bowel preparation was scored using the Boston Bowel Preparation Score (BBPS), where 3 is the maximum score for

each segment (right, transverse, left) resulting in a total maximum score of 9.[13] BBPS score of ≥2 for each segment and ≥6 in total is considered adequate bowel preparation.

Histology

All resected lesions were sent to the local pathology department and processed according to standard protocol. All pathologists had been trained and authorized for participation in the BCSP.[11] The Vienna criteria for gastrointestinal epithelial neoplasia were used for classifying the biopsies, and the diagnosis by histology was used as reference.[14]

Outcome measures and statistical analysis

The outcome was the diagnostic accuracy, i.e. overall accuracy, sensitivity, specificity, NPV and positive predictive value (PPV) between optical diagnosis and histological diagnosis of diminutive polyps, where histological diagnosis was used as reference standard. All polyps ≤5mm with both optical diagnosis and histological evaluation were included in the analysis. To clarify the results, the data were dichotomized into adenomas versus all other polyps and hyperplastic polyps versus all other polyps. Cross tables were made allowing to calculate the overall accuracy (percentage of congruent pairs), sensitivity, specificity, NPV and PPV.

To take into account use of IEE, a sensitivity analysis is performed, using Chi-square test, for the use of IEE and optical diagnosis. To analyze whether diagnostic accuracy differs between the endoscopy units Chi-square test was used. We performed a sensitivity analysis to measure the effect of clustering (i.e. multiple lesions per patient), by calculating the values of the first primary outcome was to determine with and without multilevel correction.

The other outcome parameter was the post-polypectomy surveillance intervals based on optical diagnosis, according to a) Dutch Surveillance Guidelines[15], b) European post-polypectomy colonoscopy surveillance guidelines[16], and c) American Guidelines for surveillance after polypectomy.[2]

Surveillance intervals were determined per patient based on a combination of optical diagnosis (for diminutive polyps) and histology, where histology was used as reference. For each individual patient, all lesions (diminutive but also larger lesions) were taken into account when determining the interval of surveillance.

These outcomes are chosen to evaluate whether two strategies can be implemented in clinical practice. The PIVI threshold for implementing the "resect and discard" strategy is ≥90% agreement between optical diagnosis and histological diagnosis in determining the post-polypectomy surveillance interval. For implementation of the "diagnose and leave" strategy: the PIVI threshold that should be met is ≥90% NPV for optical diagnosis of diminutive adenomatous polyps.

Statistical analyses were performed using IBM SPSS Statistics for Windows Statistical Package for Social Sciences (version 22, IBM Corp, Armonk, New York, United Stated) and R-statistics was used for the sensitivity analysis (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between February 2014 and August 2015, 2470 participants in the Dutch BCSP with an unfavorable FIT result underwent an index colonoscopy with polypectomy in the South-Limburg region. A total of 140 cases were excluded due to insufficient colonoscopy quality (no cecal intubation [n=51], inadequate bowel preparation [n=19] or both [n=70]) (**Figure 8.1**), resulting in 2330 patients eligible for this study. In **Table 8.1** characteristics of the included patients are described.

Fifteen endoscopists participated in this study (n=5 from the academic center, n=10 from the regional endoscopy units). All had extensive colonoscopy experience (endoscopy experience in years: mean 10.9 years, SD 5.7, range 3 to 22 years) and had been certified for the national CRC screening program. The number of BCSP colonoscopies performed per endoscopist in the current study varied (mean 165 colonoscopies, SD 119, range 11 to 363).

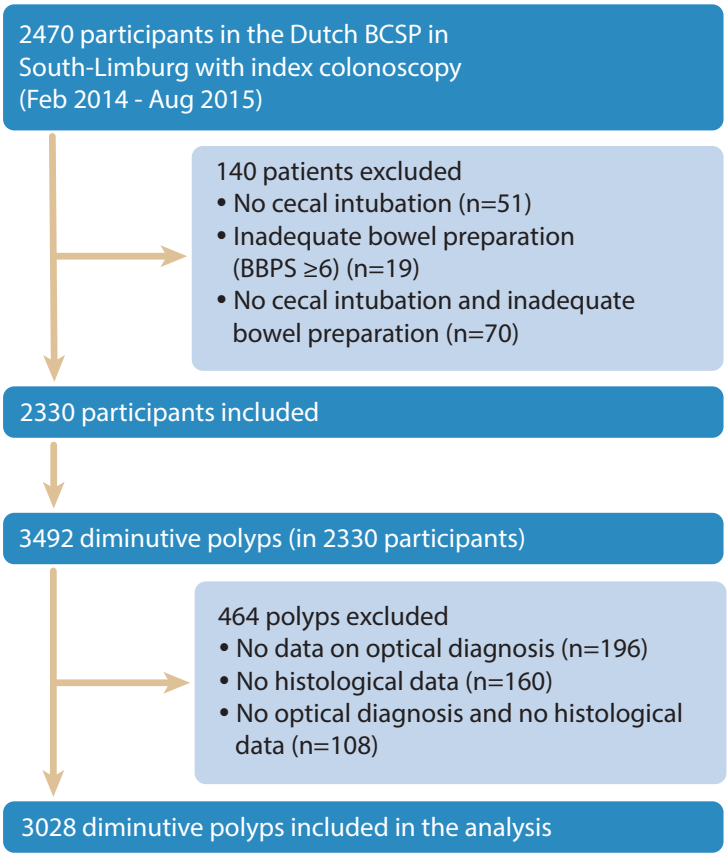

Figure 8.1: Flowchart of the included patients and polyps.

Lesion characteristics

In total, 7369 polyps were found; 1573 were >10mm and 2304 with size 6 to 10mm. From the total of 3492 diminutive polyps, both optical diagnosis (n=196 missing) and histological data (n=160 missing) needed to be available (n=108 both missing), resulting in 3028 diminutive lesions that were included (**Figure 8.1**). Endoscopic characteristics of these polyps are shown in **Table 8.2**. Median size of diminutive polyps was 4mm and 40% of the polyps were located in rectosigmoid (n=1222). Histology showed that 67% were adenomatous and 19% hyperplastic. In the 1 to 5mm group, a total of three carcinomas were detected and 15 adenomas showed high-grade dysplasia (**Table 8.2**).

Table 8.1: Characteristics of the included patients (n=2330). | *ASA: American Society of Anesthesiologists.*

Characteristic	
Age (mean, SD), years	68 (5)
Gender (female, n (%))	889 (39)
ASA classification (n, %)	
1	801 (34)
2	1440 (62)
3	88 (4)
4	1 (0)
Boston Bowel Preparation Score (mean, SD)*	9 (1)
Cecal withdrawal time (mean, SD), minutes	17 (11)

**Only patients with cecal intubation and BBPS ≥6 were included.*

Table 8.2: Endoscopic and histologic characteristics of the diminutive lesions and the accuracy per center.

Characteristic	Lesions in colon and rectum	Lesions in rectosigmoid
Number of diminutive lesions	3028	1222
Polyp size (mean, SD) in mm	4 (1)	4 (1)
Polyp size (n, %)		
1-2mm	544 (18)	192 (16)
3-5mm	2484 (82)	1030 (84)
Paris classification (n, %)*		
Ip	235 (8)	118 (10)
Is	2477 (82)	985 (81)
IIa	264 (9)	95 (8)
IIb	15 (0)	4 (0)
Unclassified	37 (1)	20 (1)

Table 8.2: *(continuation)*

Histology (n, %)		
Adenoma	2038 (67)	602 (49)
Tubular	1964	572
Villous	1	1
Tubulovillous	73	29
Sessile serrated lesion or traditional serrated adenoma	106 (4)	41 (3)
Hyperplastic polyp	563 (19)	439 (36)
Carcinoma	3 (0)	2 (0)
Other finding	99 (3)	48 (4)
No abnormality	222 (7)	92 (8)
Dysplasia (n, %)		
For adenomas		
- Low-grade dysplasia	2022 (99.2)	589 (97.8)
- High-grade dysplasia	15 (0.7)	12 (2.0)
- Unclassified	1 (0.1)	1 (0.2)
For sessile serrated lesions		
- With dysplasia	31 (29.2)	10 (24.4)
- Without dysplasia	71 (67.0)	30 (73.2)
- Unclassified	4 (3.8)	1 (2.4)
Diagnostic accuracy per endoscopy center (n of polyps, % correctly estimated lesions)	**Adenomas in colon and rectum**	**Hyperplastic polyps in rectosigmoid**
Center 1**	839 (77)	339 (72)
Center 2**	1007 (74)	397 (70)
Center 3**	928 (77)	386 (73)
Center 4**	254 (76)	100 (70)

**There were no Paris II-c lesions, since these are not considered amenable to optical diagnosis.*
***No significant difference in overall diagnostic accuracy between the centers for adenomas in colon (P=0.393) or hyperplastic polyps in rectosigmoid (P=0.769).*

Table 8.3: Optical diagnosis versus histological evaluation of diminutive polyps.*

	Lesions in colon and rectum (n=3028)	
	Adenomas (n=2038)**	**Hyperplastic polyps (n=563)****
Overall accuracy (95% CI)	76% (74-77)	79% (77-80)
Sensitivity (95% CI)	90% (88-91)	48% (44-53)
Specificity (95% CI)	47% (44-50)	85% (84-87)
Positive Predictive Value (95% CI)	78% (76-79)	43% (39-47)
Negative Predictive Value (95% CI)	69% (66-73)	88% (86-89)
	Lesions in the rectosigmoid (n=1222)	
	Adenomas (n=602)**	**Hyperplastic polyps (n=439)****
Overall accuracy (95% CI)	72% (69-74)	71% (69-74)
Sensitivity (95% CI)	89% (86-92)	54% (49-59)
Specificity (95% CI)	55% (51-59)	81% (78-84)
Positive Predictive Value (95% CI)	66% (62-69)	61% (56-66)
Negative Predictive Value (95% CI)	84% (80-87)	76% (73-78)

**Diagnostic performance for different polyp subtypes (hyperplastic and adenomatous lesions) were calculated by dichotomizing outcomes, where histological outcome is used as reference.*
***These numbers represent the total number of adenomas and hyperplastic polyps using histological evaluation, i.e. the reference.*

Performance of optical diagnosis

Optical diagnosis for diminutive adenomas in the colon and rectum showed a diagnostic accuracy of 76% (95% CI: 74 – 77) compared to histological diagnosis. The NPV for adenomatous histology was 69% (95% CI: 66 – 73, **Table 8.3**). In the rectosigmoid, a total of 1222 diminutive lesions were found and the NPV for adenomatous histology was 84% (95% CI: 80 – 87). For hyperplastic polyps in the rectosigmoid the NPV was 76% (95% CI: 73 – 78), the PPV was 61% (95% CI: 56 – 66) and the overall accuracy was 71% (95% CI: 69 – 74, **Table 8.3**).

A total of 150 polyps in the rectosigmoid (12.3% of the total) were optically misdiagnosed as hyperplastic. In 5.1% and 1.9% of the cases, an adenoma or sessile serrated lesion, respectively, would have been left in place (5.3% other/no abnormality, **Table 8.4**). For optically misdiagnosed lesions (in 139 of 150 cases photo documentation available), no significant difference was found with regard to use of IEE (P=0.620). Diagnostic accuracy for diminutive adenomas in the colon and rectum ranged from 74 to 78% (P=0.393) between the four endoscopy units and regarding hyperplastic lesions in the rectosigmoid, diagnostic accuracy ranged from 70 to 73% (P=0.769, **Table 8.2**).

Overall diagnostic accuracy between the 15 endoscopists ranged from 69 to 87%. From 2576 polyps photo documentation was available. Image enhancement had been documented by endoscopy photos in 36.9%, where in the majority of the cases I-scan was used. There was no significant difference between the use of IEE and the correct optical diagnosis for both adenomas

in the colon and rectum (*P*=0.612) and for hyperplastic polyps in the rectosigmoid (*P*=0.842). The sensitivity analysis to correct for clustering (i.e. multiple lesions per patient) showed similar results (data not shown).

Table 8.4: Specification of the polyps incorrectly estimated as hyperplastic polyp in the rectosigmoid region.

Pathology evaluation	No	% from incorrectly estimated hyperplastic polyps	% from total polyps in rectosigmoid
Total	150*	100%	12.3%
Adenoma	62	41.3%	5.1%**
Tubular	59		
Villous	0		
Tubulovillous	3		
Serrated lesions	23	15.3%	1.9%**
Sessile serrated lesion	22		
Traditional serrated adenoma	1		
Other	23	15.3%	1.9%
Inflammatory polyp	20		
Leiomyoma	1		
B-cell lymphoma	2		
No abnormality	42	28.0%	3.4%

**A total of 150 polyps in rectosigmoid (12.3% of the total) were optically misdiagnosed as hyperplastic.*
***In 5.1% and 1.9% of the cases, an adenoma or serrated lesion, respectively, would have been left in place.*

***Table 8.5: Surveillance intervals based on optical diagnosis vs histology**, according to different guidelines (NL, EU, USA) and applying the 'resect and discard' scenario.*

	Agreement between optical diagnosis and histology	Surveillance earlier	Surveillance later*
Dutch guideline	90.6% n=2110	6.2% n=144	3.3% n=76
European guideline	91.2% n=2126	5.9% n=137	2.9% n=67
American guideline	90.9% n=2119	6.2% n=145	2.8% n=66

**This includes also the patients who receive no surveillance according to optical diagnosis. The number of patients who would receive no surveillance are for the Dutch guideline 36/76 patients, for the European guideline 36/67 patients and according to the American guideline 4/66.*

Table 8.6: Surveillance intervals based on optical diagnosis vs histology, *according to: A) the Dutch surveillance guideline (2012); B) the ESGE (European) surveillance guideline (2013); C) the AGA (American) surveillance guideline (2012); applying the "resect and discard" strategy. For this strategy optical diagnosis was used for polyps ≤5 mm in the entire colon while for all other polyps, histological evaluation was used to determine surveillance intervals.*

A)

		Surveillance intervals based on histology				
Surveillance intervals based on optical diagnosis		**3-year**	**5-year**	**10-year**	**No surveillance**	**Total**
	3-year	584	38	16	0	638
	5-year	9	612	39	19	679
	10-year	9	22	384	32	447
	No surveillance	0	19	17	530	566
	Total	602	691	456	581	2330

B)

		Surveillance intervals based on histology			
Surveillance intervals based on optical diagnosis		**3-year**	**10-year**	**No surveillance**	**Total**
	3-year	903	81	2	986
	10-year	31	684	54	769
	No surveillance	3	33	539	575
	Total	937	798	595	2330

C)

		Surveillance intervals based on histology					
Surveillance intervals based on optical diagnosis		**3-year**	**5-year**	**5- to 10-year**	**10-year**	**No surveillance**	**Total**
	3-year	1175	35	39	1	0	1250
	5-year	5	27	2	0	0	34
	5- to 10-year	16	3	408	35	17	479
	10-year	5	5	28	65	16	119
	No surveillance	1	0	2	1	444	448
	Total	1202	70	479	102	477	2330

Surveillance intervals

In **Table 8.5** results of the surveillance intervals are given. Surveillance intervals have been calculated at patient level, meaning that if only diminutive polyps were found, the surveillance interval is based on optical diagnosis solely, whereas if additional polyps (>5mm) were found, the histology of these non-diminutive polyps determined the surveillance intervals. For the 'resect and discard' strategy agreement for the Dutch, European, and American guidelines was 90.6%, 91.2% and 90.9%, respectively. Approximately 6.0% would have received a shorter surveillance interval based on optical diagnosis, while in 2.8% to 3.3% of the cases a longer surveillance interval would have been recommended. A detailed overview of the surveillance intervals for the "resect and discard" and "diagnose and leave in place" strategies using different guidelines is presented in **Table 8.6** and **Table 8.7**.

Table 8.7: Surveillance intervals based on optical diagnosis vs histology, *according to: A) the Dutch surveillance guideline (2012); B) the ESGE (European) surveillance guideline (2013), and C) the AGA (American) surveillance guideline (2012); applying the "diagnose and leave in place" strategy. For this strategy optical diagnosis was used for polyps ≤5 mm in the rectosigmoid while for all other polyps, histological evaluation was used to determine surveillance intervals.*

A)

		Surveillance intervals based on histology				
Surveillance intervals based on optical diagnosis		**3-year**	**5-year**	**10-year**	**No surveillance**	**Total**
	3-year	601	13	0	0	614
	5-year	1	669	30	2	702
	10-year	0	7	412	34	453
	No surveillance	0	2	14	545	561
	Total	602	691	456	581	2330

B)

		Surveillance intervals based on histology			
Surveillance intervals based on optical diagnosis		**3-year**	**10-year**	**No surveillance**	**Total**
	3-year	928	40	0	968
	10-year	9	742	38	789
	No surveillance	0	16	557	573
	Total	937	798	595	2330

C)

		Surveillance intervals based on histology					
Surveillance intervals based on optical diagnosis		**3-year**	**5-year**	**5- to 10-year**	**10-year**	**No surveillance**	**Total**
	3-year	1193	15	23	0	0	1231
	5-year	2	53	0	0	0	55
	5- to 10- year	6	0	441	29	9	485
	10-year	0	2	14	72	15	103
	No surveillance	1	0	1	1	453	456
	Total	1202	70	479	102	477	2330

Discussion

We have evaluated the accuracy of optical diagnosis of diminutive polyps, as well as the scenarios for "resect and discard" and "diagnose and leave" in the clinical endoscopy practice setting of the Bowel Cancer Screening Program (BCSP) in the Netherlands. Optical diagnosis of diminutive adenomatous polyps in the rectosigmoid showed 72% diagnostic accuracy and 84% NPV: thus, the PIVI thresholds were not met.

When applying the "resect and discard" scenario, agreement on surveillance intervals between optical and histological diagnosis applying the Dutch, European and American surveillance guidelines was 90.6 %, 91.2% and 90.9%, respectively. Therefore, at group level, the PIVI thresholds (≥90% agreement) concerning surveillance strategies were met.

Given the substantial amount of research focusing on optical diagnosis and the potential cost savings, this is an important and clinically relevant topic.[17, 18] However, results of studies assessing optical diagnosis of small and diminutive polyps vary considerably. So far, data have been obtained predominantly in well controlled study settings, where endoscopists were additionally trained in recognition and characterization of lesions and had been instructed on the systematic use of image-enhancement. Baseline characteristics of the diminutive lesions in our study are within the range of variation reported in recent literature, and are therefore representative for national and global data.[19, 20]

When evaluating published data from additionally trained endoscopists, the NPV for optical diagnosis of adenomas in the rectosigmoid varies from 82.0% to 94.7% in studies where narrow-band imaging (NBI) was used.[21] Ladabaum et al.[22] showed that while only 25% of the trained endoscopists used NBI, polyps were assessed with over 90% accuracy.

Image enhancement for optical diagnosis of diminutive polyps is considered to be beneficial, but remains an item of discussion since several studies have not shown significant differences in accuracy for optical diagnosis with image enhancement compared to HD-WLE.[23-25] In our study, reflecting daily endoscopy practice, use of image-enhancement in addition to HD-WLE was left at the discretion of the endoscopist. In 36.9% use of image-enhancement was photo-documented and no significant differences were found in optical diagnosis with or without use of IEE.

Experience and additional training of endoscopists may substantially add to accuracy of optical diagnosis. Endoscopists working in academic centers obtain better results in optical diagnosis compared to endoscopists working in community practices.[22] Indeed, in a surveillance setting in non-academic centers without additional training, Kuiper et al.[26] noted low sensitivity (77.0%) and specificity (78.8%) for optical diagnosis.

In our study, performance of academic and regional centers with respect to optical diagnosis was in the same range. Concerning surveillance intervals, in previous studies, 19% inaccuracy in determining surveillance intervals based on optical diagnosis has been reported.[26] It should be noted that surveillance intervals were calculated on patient level, therefore, all polyps (diminutive but also larger polyps) were taken into account, noticing that intervals are affected mostly by the larger polyps. Therefore, optical misdiagnosis of smaller polyps can be overruled by the presence of larger polyps. This raises the question whether surveillance interval is the most appropriate criterium when deciding on diminutive polyps. It does however perfectly represent the impact of the guidelines used in current clinical practice.

A recent Dutch study from Vleugels et al. has shown that at group level in a selected population of endoscopists after additional training, optical diagnosis of diminutive polyps (with high-confidence) in the Dutch FIT-based CRC screening setting using NBI met the ASGE PIVI thresholds.[20] However, at individual level, only 59% of the additionally trained endoscopists did meet these PIVI thresholds. The authors showed that selected endoscopists, additionally trained by a validated training module on NICE[27] and WASP[28] were able to diagnose neoplastic lesions (with high confidence) using NBI in the rectosigmoid with pooled NPVs of more than 90%.[20] In addition, they were also able to accurately recommend surveillance intervals based on optical diagnosis.[20] When interpreting these data, it should be noted that these endoscopists represent an expert group, of which endoscopists were only allowed to participate after passing an additional exam (≥90% diagnostic accuracy (same as in PIVI)).[20] Therefore, the results of that study cannot be extrapolated directly to community practice. On the other hand, Vleugels et al.[20] have clearly shown that optical diagnosis may become feasible in a special setting in which endoscopist training and feedback is incorporated.

In a study by Schachschal et al. performed in a screening setting, optical diagnosis had an accuracy of only 71.1% and NPV of 59.3%.[29] Our results compare favorably with that study with NPV for hyperplastic polyps in the rectosigmoid and for adenomas in the colon of respectively 76% and 69%. The agreement on surveillance intervals in our study reached an accuracy of over 90%, while data from the Schachschal et al. study cannot be retrieved from the manuscript.[29]

To implement these strategies in clinical practice, costs should be considered. Using simulation modelling, optical diagnosis in the Dutch BCSP appears to save costs without decreasing program effectiveness when compared with current histology analysis of all diminutive polyps.[30] In line with these modelling data, Hassan et al. have already shown that the "resect and discard" strategy for diminutive polyps detected during screening indeed results in economic benefit without impact on program efficacy.[6] Applying these strategies may not only result in cost savings but also in a reduction of risks of polypectomies and of patient discomfort.

If lesions are left in situ (i.e. "diagnose and leave"' scenario), an incorrect optical diagnosis may have significant impact. In our study 12%of the rectosigmoid lesions was estimated as hyperplastic but contained other histology (i.e. adenomas and serrated polyps). When the lesions are removed (i.e. "resect and discard" scenario), the impact of incorrect optical diagnosis is limited.

High-risk lesions found in our study (3 carcinomas and 15 lesions with high-grade dysplasia) should be considered carefully. Here, evaluation of treatment and resection margins is of importance, and they should receive stricter follow-up. Several strengths of our study need to be acknowledged. First, we evaluated the efficacy of the optical diagnosis strategy within a) the structured setting of the nationwide Bowel Cancer Screening Program, and b) regular endoscopy practices where all participating endoscopists were qualified and accredited for performing colonoscopies for the Dutch FIT-based BCSP,[12] but without additional training or selection for competency in optical diagnosis. We prospectively collected data from four endoscopy units (both academic and regional) in South Limburg (the Netherlands). The results therefore reflect daily clinical practice in the Netherlands in the first years of implementation of the BCSP.

Several limitations need to be acknowledged as well. Since standardized endoscopy reports are used for data collection, some detailed information is lacking. Therefore, the results of this study should be interpreted with caution. First, the level of confidence with which an endoscopist rates his/her optical diagnosis is relevant. A meta-analysis from 2015 showed that estimations with high-confidence are more likely to be correct.[7] In our real-life study endoscopists neither were asked for nor included the level of confidence in the standard endoscopy report and we were therefore

not able to assess the level of confidence for optical diagnosis. Second, image-enhancement was used upon discretion of the endoscopist, but the specific use per polyp was not reported. Based on photo documentation, image-enhancement was used in at least 36.9% of endoscopies.

To improve performance and to allow implementation of optical diagnosis in the setting of a national BCSP, essential steps need to be taken: 1) for equipment, standard use of high-definition white light endoscopy with additional image enhancement; 2) for endoscopists, additional training and monitoring of individual performance; 3) standard use of optical classification systems (e.g. NICE or WASP); 4) inclusion of "the level of confidence in optical diagnosis" of the endoscopist in the optical diagnosis algorithm; and 5) photo documentation and archiving.[31, 32]

Implementation of optical diagnosis strategy in clinical practice remains challenging.[31] A simplified approach has been suggested by Atkinson and East; [33] the DISCARD-lite strategy where all diminutive polyps proximal to rectosigmoid junction are assumed premalignant and therefore "resect and discard" is applied, while hyperplastic polyps in the rectosigmoid can be left in situ. A recent study by Von Renteln et al. indicates that this simplified combined optical and location-based strategy may help to overcome current challenges in the implementation of the 'resect and discard' strategy.[34]

In the near future an important role for artificial intelligence (AI) in optical detection and characterization of diminutive polyps is foreseen, thus reducing or even eliminating endoscopist inter-observer variability. Several computer-aided detection and characterization systems and algorithms are being developed with promising preliminary data such as a NPV for identification and classification of diminutive rectosigmoid adenomas ranging from 91.5% to 97%.[35-38] More extensive research in larger clinical trial settings is necessary to confirm and expand on these results.

Based on our data from regular endoscopy care in the bowel cancer screening program, we cannot recommend leaving diminutive rectosigmoid polyps in place. On the other hand, the thresholds for the "resect and discard" strategy, i.e. agreement on post-polypectomy surveillance intervals were met. Implementation of this strategy can therefore be considered. These results, however, need to be validated, in a setting where the above-mentioned steps have been implemented (i.e. standardized and structural use of level of confidence and use of IEE).

Conclusion

To conclude, our study representing current clinical practice in the Dutch BCSP practice on optical diagnosis of diminutive polyps showed that accuracy of predicting histology remains challenging, and risk of incorrect optical diagnosis is significant. Therefore, it is too early to safely implement these strategies. It remains to be determined whether optical diagnosis will structurally meet the PIVI criteria in routine clinical endoscopy practices.

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Impact of endoscopist training on post-colonoscopy colorectal cancer rate

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Abstract

Introduction

Post-colonoscopy colorectal cancers (PCCRCs) are considered to be a crucial quality outcome measure for colonoscopy. PCCRCs may occur due to various reasons such as non-adherence to surveillance intervals, inadequate bowel examination, incomplete polyp resection, missed lesions or newly developed cancers. Recent studies indicate that non-polypoid colorectal neoplasms (NP-CRNs) and serrated lesions, which are smaller and more easily overlooked during colonoscopy, may be important precursor lesions of PCCRC. The present study was undertaken to investigate whether systematic training in detection and resection of NP-CRN reduces the PCCRC rate.

Methods

In the Maastricht UMC+, all endoscopists were systematically trained in 2008 to optimize detection and resection of NP-CRNs. PCCRCs found after colonoscopy performed 4 years before and 4 years after training were included. For PCCRC identification, we used follow-up data until 2014.

Results

After training the PCCRC rate decreased by more than 50% from 2.0 per 1000 colonoscopies to 0.8 per 1000 colonoscopies. Of the 11 PCCRCs found after training, 45% was associated with missed lesions, 18% due to non-adherence to surveillance intervals, 18% due to newly developed CRC, 18% due to inadequate bowel examination and none due to incomplete polyp resection.

Conclusion

Systematic training in detection and resection of NP-CRNs appears to be able to reduce the PCCRC rate. However, to further minimize the PCCRC rate a multifactorial approach is needed, where training, but also adherence to surveillance intervals and employing quality indicators for colonoscopy are of importance.

Introduction

It has been clearly shown that population-based colorectal cancer screening either by fecal testing and/or colonoscopy significantly reduces CRC incidence and mortality.[1, 2] Although colonoscopy is considered as gold standard method for polyp detection and removal, it should be noted that colonoscopy is not perfect since still some CRCs are detected after a negative colonoscopy.[3] For a CRC screening program to be effective, the occurrence of these so-called post-colonoscopy colorectal cancers (PCCRCs) should be as low as possible. Several factors influence sensitivity of colonoscopy and thus occurrence of PCCRCs; for instance, image quality of the colonoscopes (high definition), bowel cleansing and skills of the endoscopist.[4] This way, the occurrence of PCCRCs is an important quality outcome parameter for CRC screening programs.

It is known that PCCRCs occur due to various reasons (non-adherence to surveillance intervals, inadequate bowel examination, incomplete polyp resection, missed lesions or newly developed cancers),[5] where previous studies showed that a large subset of PCCRCs is due to missed lesions[6, 7] and could thereby be preventable.

It could be hypothesized that precursor lesions of PCCRCs are often non-polypoid colorectal neoplasms (NP-CRNs) or serrated lesions, which are known to be mainly located in the proximal colon and have a flat appearance.[8, 9] This hypothesis is based on previous studies showing PCCRCs harbor these same characteristics; often located in the proximal colon, a flat appearance and smaller in size,[6, 10] making them more difficult to detect and resect.[3, 8] In addition, a subset of NP-CRNs and serrated lesions have different molecular features (compared to polypoid neoplasms), which may be more closely associated with carcinoma.[11, 12]

Taken together, PCCRCs are likely to derive from non-polypoid/serrated lesions, which are more challenging to detect and resect. In order to prevent PCCRCs, training and advanced endoscopic skills are required.

McGill et al. investigated the effect of endoscopy training in a longitudinal assessment (ranging from 200 to 1600 performed colonoscopies).[13] Over time, an increase in the detection of NP-CRNs was seen, indicating that non-polypoid adenoma detection is a skill that can be learned, but does require time and effort.[13] Up to now, no study has explored whether systematic training in detection and resection of NP-CRNs directly leads to reduction in PCCRC rate. Aim of the present study was to examine PCCRC rate and PCCRC etiology before and after implementation of a short systematic training program for the detection and resection of NP-CRNs.

Methods

Data collection

At the Maastricht University Medical Center+, a specific training program for detection and resection of non-polypoid neoplasms was initiated in 2008. A specific aim of that training program was to increase awareness and detection of NP-CRNs. All endoscopists, faculty, and trainees at our university hospital were trained in a systematic training program comprising of lectures to improve awareness and basic knowledge, learning from experts, videos, cases and individual feedback.[14]

From there, a prospective cohort study was initiated, including all colonoscopies performed between February 2008 and February 2012. Patients with hereditary CRC syndromes or history of

CRC were excluded, as well as patients with inflammatory bowel disease or patients younger than 18 years of age.

All newly diagnosed CRC cases from January 2004 to October 2014 were retrieved using the Nationwide Pathology Database (PALGA). We cross-linked detailed patient information from the hospital registries to endoscopic and pathological reports (see **Figure 9.1**). In that way we were able to identify post-colonoscopy colorectal cancers (PCCRCs). In addition, all CRC cases found in the prospective database were also screened for PCCRCs. Year of the last negative colonoscopy was used to compare PCCRC incidence pre- and post-training.

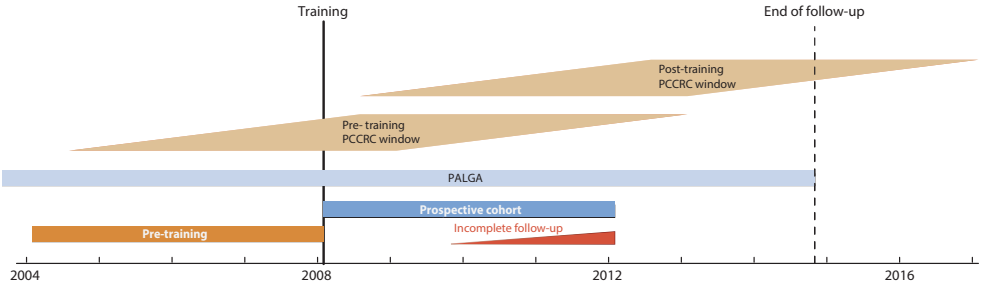


Figure 9.1: Overview of study and the data sources used.

Definition and statistical analysis

PCCRCs were defined as a CRC diagnosed 6 to 60 months after a colonoscopy that was negative for CRC. PCCRC rate after training was determined by the number of PCCRCs divided by the total number of colonoscopies (including surveillance colonoscopies), as described by Morris et al.[15] Patient years of follow-up (PYFU) were calculated using the time between index colonoscopy and end of follow-up (October 2014).

Prior to training, only data on the number of colonoscopies per year were available. To estimate the PYFU we assumed that prior to training, the subset of index colonoscopies and mean follow-up was the same as in 2008 (i.e. both pre- and post-training 48.5 months).

As sensitivity analysis we assumed complete follow-up (i.e. 60 months) for colonoscopies prior to training instead of the estimated 48.5 months. A Z-test was performed to compare PCCRC rates before and after training. A *P* value <0.05 was considered statistically significant.

The other outcome parameter was the etiology of the PCCRCs, together with clinical and pathological characteristics (i.e. size, location, macroscopic appearance and histopathology). Location was subdivided in proximal colon (cecum to splenic flexure) and distal colon (descending colon to rectum).

The PCCRCs were classified using the Pabby algorithm[5] modified by Huang et al.[16] (**Figure 9.2**). Based on findings at the index-examination, time between colonoscopy and CRC diagnosis, location and stage of the tumor at diagnosis, the PCCRCs were categorized on most likely etiology: non-adherence to surveillance intervals, inadequate examination/surveillance, incomplete resection, missed lesions or newly developed CRC.

This study was approved by the Institutional Review Boards of the Maastricht University Medical Center+ and is registered in the Netherlands Trial Registry: NTR4844. Approval for the prospective colonoscopy database is assigned by the MEC of the Maastricht University Medical Center+ (MUMC+) with number 14-4-046. The need for informed consent was waived by the Institutional Review Board.

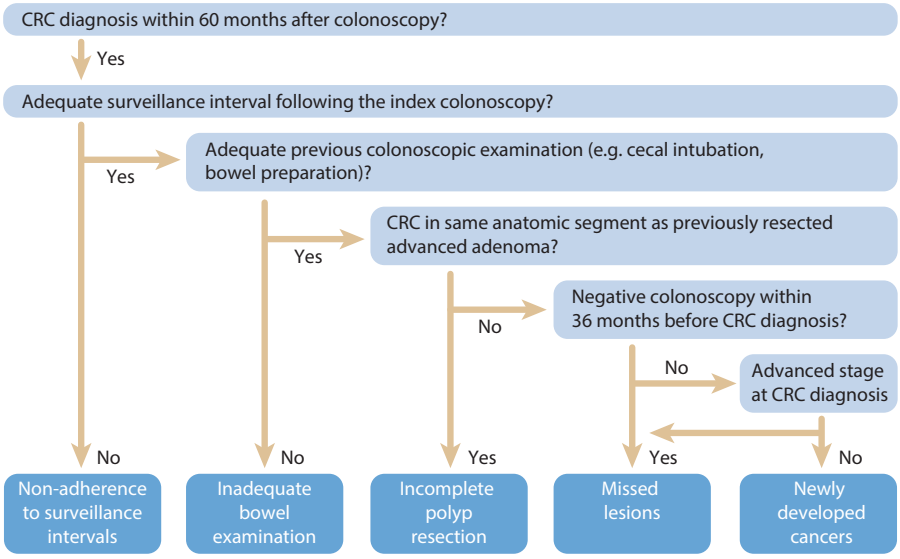


Figure 9.2: Modified algorithm by Pabby et al.[5] evaluating the most likely etiology of post-colonoscopy colorectal cancers (PCCRCs).

Results

The post-training cohort of 9353 patients was enrolled from a total of 13,190 colonoscopies in four years (2008-2012). Patients underwent elective colonoscopy for symptoms, surveillance or screening. Patients with IBD, hereditary CRC or a history of CRC were excluded (n=1136). The analyzed post-training population consisted of 8217 patients with a mean age of 59.1 years (SD 15.8) and of which 54% is female.

Prior to training (2004-2008), 8,468 colonoscopies were performed. Based on the findings of 2008, we estimated that 5275 unique patients would have had one or more colonoscopies during this period of four years. We assumed that all patients of this study period had 48 months of follow-up, since this was the case for the patients included in 2008. With this information, we calculated the total years of follow-up (PYFU) for the pre-training cohort (2004-2008) which was 21,299 person years. The total years of follow-up for patients from the post-training prospective cohort (2008-2012) was measured at 31,993 person years.

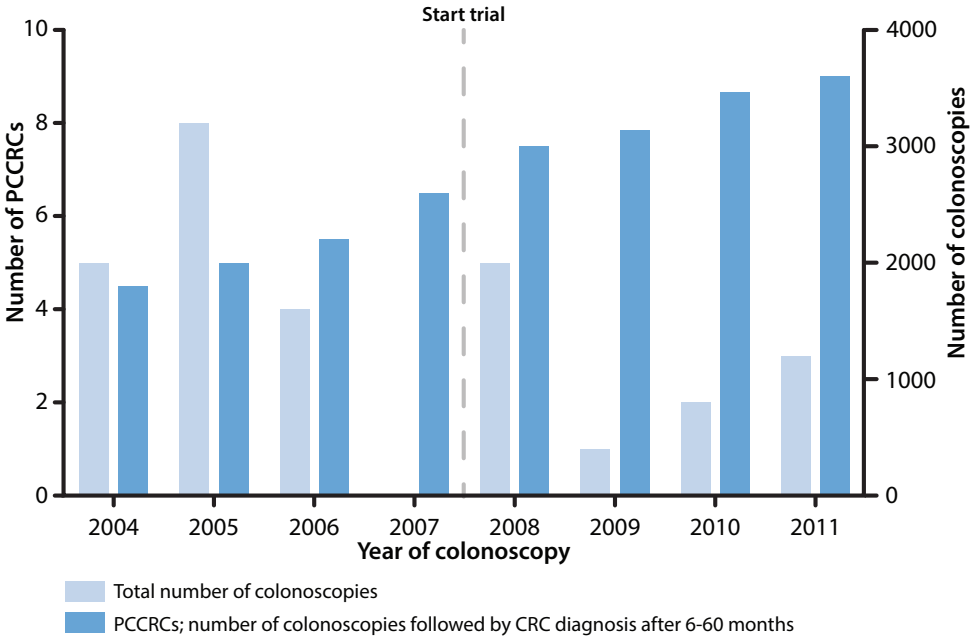
When comparing the PCCRC rates before and after training, this study shows that the PCCRC rate declined after implementation of training by more than 50% from 2.0/1000 colonoscopies before training to 0.8/1000 colonoscopies after training (P=0.031). These rates result in an estimated decrease from 0.79/1000 PYFU before training to 0.34/1000 PYFU after training (P=0.041) (**Figure 9.3**).

A total of 11 patients (mean age [SD] 76.8 years [7.4]; 45% female) were diagnosed with PCCRCs after colonoscopy between February 2008 and February 2012, i.e. in the post-training cohort.

Clinical characteristics of these PCCRC cases are shown in **Figure 9.4**. From the PCCRC patients, ten patients were older than 70 years. The time to CRC diagnosis varied from 14 to 52 months. In contrast with previous data, PCCRCs were more equally distributed over the proximal and distal colon. Nine patients had diverticular disease and two patients had proven metastatic disease at time of diagnosis. Indication for index colonoscopy were symptoms (54.5%) (i.e. rectal blood loss, anemia) or surveillance (45.5%).

Using the Pabby algorithm (**Figure 9.2**), potentially missed lesions remained the main explanation (45.4%) for the occurrence of PCCRC, while no PCCRC case could be attributed to incomplete resection. Non-adherence to surveillance intervals comprised 18.2% of cases, as well as inadequate bowel examination (18.2%) and newly developed cancers (18.2%).

Applying the 60-month follow-up as a sensitivity analysis, the PCCRC rate before training is estimated at 0.64/1000 PYFU. When comparing to the PCCRC rate after training (0.34/1000 PYFU) the difference is less distinctive (*P*=0.144).



Note: Cumulative PCCRC rate decreased from 2.0 per 1000 colonoscopies before training to 0.8 per 1000 colonoscopies after training

Figure 9.3: Number of yearly post-colonoscopy colorectal cancers (PCCRCs) and number of colonoscopies before and after systematic endoscopists training (February 2004-February 2012).

Case	1	2	3	4	5	6	7	8	9	10	11
Age, gender	79, F	74, F	79, M	80, M	85, F	76, F	76, M	84, F	75, M	80, M	57, F
Indication (index exam)	Sympt	Surv	Surv	Surv	Sympt	Surv	Surv	Sympt	Sympt	Surv	Sympt
Time T0-CRC (months)	52	6	56	22	28	51	44	24	15	48	44
Location	Prox	Prox	Dist	Dist	Prox	Prox	Prox	Dist	Dist	Prox	Dist
Comorbidity	DD	C-V	DD	DD	DD	DD	DD	DD / C-V	DD		
Tumor Stage	T3 N0M0	T3 N0M1	T2 N0M0	T3 N0M0	T4 N0M0	T3 N0M0	T4 N0M0	T1 N0M0	T1 N0M0	T3 N0M0	Tx N0M1
Likely etiology	New cancer	Missed lesion	Surveil-lance	Missed lesion	Missed lesion	New cancer	Inadeq. exam.	Inadeq. exam.	Surveil-lance	Missed lesion	Missed lesion

Figure 9.4: Clinical characteristics of the patients with a PCCRC from 2008-2012.
Sympt = symptoms, Surv = surveillance, Prox = proximal colon, Dist = distal colon, DD = diverticular disease, C-V = cardiovascular disease, Surveillance = nonadherence to surveillance interval, Inadeq exam = inadequate bowel examination.

Discussion

We observed a more than 50% decrease in PCCRC rate from 2.0 per 1000 colonoscopies before training to 0.8 per 1000 colonoscopies after systematic endoscopist training. The majority of PCCRCs (82%) appeared to be potentially preventable, as they were attributable to missed lesions, nonadherence to surveillance intervals and inadequate bowel examination.

Nayor et al. have previously shown that non-adherence to surveillance intervals may increase the number of PCCRC cases, especially in cases where bowel preparation at index examination was inadequate.[17] Apart from non-adherence to surveillance intervals and inadequate bowel preparation, several studies have shown that over 50% of PCCRCs can be attributed to missed lesions and up to 20% to incomplete resection.[6, 7]

In line with our results, other studies on education and training in quality of polyp detection and endoscopic resection have shown that colonoscopy quality parameters generally improve after training.[18, 19] Coe et al.[18] have shown that for adenoma detection rate (ADR) and Kaminski et al.[19] for ADR and also for detection of non-polypoid lesions. On the other hand, Shaukat et al.[20] did not observe a significant change in adenoma detection rate of individual endoscopists despite implementation of a training program.

Based on previous research, PCCRCs are more likely to be proximally located, smaller in size and have a flat macroscopic appearance compared to prevalent CRCs. Together with the knowledge that adequate bowel preparation is more difficult to achieve in the proximal colonic area, these findings suggest that PCCRCs could have originated from precursors which have been overlooked more easily during index colonoscopy.[6, 7]

In the current study, the 11 PCCRC cases we analyzed were equally distributed over the colon. This could be the result of fewer missed proximally located lesions after training. In line with previous data, patients with PCCRC are usually older compared to prevalent CRC cases and have substantially more comorbidity, in particular diverticular disease,[21, 22] which makes the performance of a complete colonoscopy far more difficult.

Missed lesions were the most common cause of PCCRC (45%) in our study, a finding that is in line with previous data.[3, 7, 23] In another Dutch population-based study on PCCRCs (total n=147) performed by our group, 13.6% of the PCCRCs were attributable to newly developed cancers,[6] comparable with the results in the present study (18.2%). Another preventable factor is inadequate bowel examination (e.g., no cecal intubation or insufficient bowel preparation). Nowadays quality indicators for colonoscopy have been introduced and implemented to assure the quality of each colonoscopic intervention.[4]

Incomplete resected polyps have been reported as contributor to PCCRCs in up to 19% of cases.[7, 24, 25] In the present study, no PCCRCs could be attributed to incomplete resection. Non-adherence to surveillance interval accounted for 18% of our PCCRCs, a percentage that is higher compared to other studies.[26] It should be noted that adherence to surveillance intervals is a shared responsibility of patients and of physicians and endoscopy staff.[17]

Some strengths and limitations of our study should be mentioned. First, this study is unique because of availability of colonoscopy data and CRC data prior to and after systematic training of endoscopists. Second, a detailed description of all PCCRCs is available. In a study on PCCRC, CRC and number of colonoscopies covering the whole South-Limburg region (including three large hospitals), we found that PCCRC rate in the decade prior to systematic endoscopist training

accounted for approximately 2.0 per 1000 colonoscopies,[6] identical to the rate found prior to training in the present study. Since this PCCRC rate showed no significant decline over time, this observed percentage validates the pre-training cohort estimations and underlines the difference between pre-and post-training PCCRC percentages.

It is however important to acknowledge that bias may have occurred. First, the follow-up ended in October 2014. Therefore, regarding the colonoscopies performed after October 2009, the occurrence of late onset PCCRCs cannot be excluded with certainty. In this way especially 'newly developed' PCCRCs will be missed, which is less influenced by training. To limit this bias, the rate of PCCRCs pre- and post-training were presented as PCCRCs/1000 person years of follow-up.

Second, person years of follow-up prior to training were based on estimation, resulting in bias in case the real follow-up would be longer. To overcome this bias, a sensitivity analysis was performed using 60 months of follow-up in the cohort prior to training.

Finally, data were prospectively collected after training, resulting in validation of the PALGA dataset since additional PCCRCs may be identified. In the retrospectively collected pre-training data this additional check was not available, theoretically leading to a small chance of underreporting PCCRCs.

Taken into account these limitations, our data pointed out that focusing on endoscopist related factors such as systematic short-interval training for the recognition and complete resection of NP-CRN may help to minimize PCCRC rate.

In conclusion, we have shown a decrease in PCCRC rate after implementation of systematic training in NP-CRN detection and resection by more than 50%. The etiology of the PCCRCs lies mostly in missed lesions, and in a lesser extent to non-adherence to surveillance intervals, inadequate bowel examination and newly developed cancers. So, there is room for further improvement.

In order to further minimize the PCCRC rate it should be acknowledged that a multifactorial approach is needed giving attention to training in detection and resection of polyps, especially of NP-CRNs, adherence to colonoscopy surveillance intervals and employing quality indicators for colonoscopy.

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10

Molecular pathways in post-colonoscopy versus detected colorectal cancers: Results from a nested case-control study

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Abstract

Background

Post-colonoscopy colorectal cancers (PCCRCs) pose challenges in clinical practice. PCCRCs occur due to a combination of procedural and biological causes. In a nested case-control study, we compared clinical and molecular features of PCCRCs and detected CRCs (DCRCs).

Methods

Whole-genome chromosomal copy number changes and mutation status of genes commonly affected in CRC were examined by low-coverage whole genome sequencing and targeted sequencing, respectively. Microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) status was also determined.

Results

In total, 122 PCCRCs and 98 DCRCs with high quality DNA were examined. PCCRCs were more often located proximally ($P<0.001$), non-polypoid appearing ($P=0.004$), early stage ($P=0.009$), and poorly differentiated ($P=0.006$). PCCRCs showed significantly less 18q loss (false detection rate <0.2), compared to DCRCs. No significant differences in mutations were observed. PCCRCs were more commonly CIMP-high ($P=0.014$) and MSI ($P=0.029$). After correction for tumor location, only less 18q loss remained significant ($P=0.005$).

Conclusion

Molecular features associated with the sessile serrated lesions (SSLs) and non-polypoid colorectal neoplasms (NP-CRNs) are more commonly seen in PCCRCs than in DCRCs. These together with the clinical features observed support the hypothesis that SSLs and NP-CRNs are contributors to the development of PCCRCs. The future focus should be directed at improving the detection and endoscopic removal of these NP-CRNs and SSLs.

Introduction

Colonoscopy is an effective screening tool for colorectal cancer. However, in 3.7% (95% CI: 2.8 – 4.9) of all colorectal carcinomas, a preceding colonoscopy did not detect the (pre-)malignant lesion.[1] These so-called post-colonoscopy colorectal cancers (PCCRCs) can be subdivided with respect to etiology into biological factors and procedural factors.[2-4] In previous studies, it was noted that more than half of the PCCRCs had missed lesions as most likely etiology.[5, 6]

It is hypothesized that the underlying mechanisms may differ depending on the causes of PCCRCs. Missed lesions could be the result of non-polypoid (flat) colonic lesions which are easily overlooked during endoscopy.[7] Large flat lesions, the so-called laterally spreading tumors, frequently contain high grade dysplasia and early carcinoma.[8, 9] Resection of these lesions is more difficult, leading to higher recurrence rates.[10] Sessile serrated lesions (SSLs) are often flat and have a pale appearance, thereby increasing the risk of being missed.[11] These lesions are thought to develop into CRC via a different molecular pathway.[12, 13] Newly developed cancers may result from a fast growing precursor lesion. Underlying molecular pathological mechanisms, such as microsatellite instability (MSI), could be involved in this more rapid development.[2, 14]

Previous studies have pointed to differences in molecular profiles between PCCRCs and detected CRCs (DCRCs) with more often MSI and CpG island methylator phenotype (CIMP) in PCCRCs.[14-16] Here, detected CRCs are defined as CRCs found in patients without previous colonoscopy or with colonoscopy >10 years ago. Several studies showed that after correcting for tumor location, no differences were found in genetics between PCCRCs and DCRCs.[17, 18] In this study, next to MSI and methylation status, whole genome DNA copy number changes and mutations in CRC-related genes was performed, in order to assess the biological pathways involved in PCCRCs. Based on the World Endoscopy Organization (WEO) classification for PCCRCs, we compared PCCRCs to DCRCs, in a nested case-control study. Second, we compared the subgroup of PCCRCs with probable biological etiology with detected CRCs, so that procedural causes would not confound the biology behind PCCRCs. We hypothesize that PCCRCs have a molecular profile that is different from DCRCs, presumably more similar to non-polypoid and/or sessile serrated precursor lesions.

Materials and methods

Study population

All colorectal cancers detected between January 1, 2001 and December 31, 2010 were collected in three large-volume hospitals (one university and two large general teaching hospitals) in the region of South Limburg, The Netherlands.[5] An electronic pathology database was used to identify all CRCs and this was crosschecked with the Dutch Cancer Registration. Patients with hereditary CRC, inflammatory bowel disease (IBD) or a history of previous CRC were excluded. For each case, data of the last colonoscopy were retrieved from patient files in the three local hospitals. Based on its geography, the South Limburg region is frequently used for population-based studies. It is characterized by a stable population over time, as shown by a low net migration rate (0.8 per 1000 inhabitants per year).[19] The study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre, which waived the need for informed consent because of the retrospective character and absence of possible consequences for individual diagnosis. The study is registered as study NTR3093 in the Dutch trial register (www.trialregister.nl).

Definitions

The WEO consensus statement was published in 2018, after the period of data collection from 2001 to 2010.[20] Since variables as cecal intubation, fecal contamination and whether a CRC was detected in a segment with previous neoplasia were registered in the database, as well as the detailed Pabby classification,[4] retrospective application of the WEO definition to the prospectively collected dataset was possible and has been used.

Post-colonoscopy CRCs (PCCRCs) were defined as colorectal carcinomas that were detected between 6 months and a maximum of 10 years after index colonoscopy that was negative for CRC, according to the WEO guideline for PCCRC.[20] Detected CRCs (DCRCs) were defined as CRCs without prior colonoscopy or colonoscopy >10 years before. The most likely etiology of each PCCRC was determined. Based on this algorithm, all PCCRCs were selected from the population-based database containing all CRCs.

PCCRC cases were identified among the CRCs in the database, based on the calculated interval between diagnosis and last colonoscopy. Then, all PCCRC cases were manually checked for the most probable explanation based on the patient records. The WEO classifies the PCCRCs as arising from a possible missed lesion with prior adequate examination, a possible missed lesion with prior inadequate examination, a detected lesion that is not resected, a likely incomplete resected lesion and a likely newly developed CRC. Since the causes of missed lesions with adequate prior examination and newly developed CRCs were more likely related to biological factors than PCCRCs probably related to incomplete resections of lesions, no resection at all or missed lesions due to inadequate prior examination, we will further divide these categories as biological PCCRCs and procedural PCCRCs, respectively. According to the WEO 2018 classification,[20] probably missed lesions with prior adequate examination PCCRCs (<4 years after colonoscopy) can only be found after a complete (cecum visualization) colonoscopy in a well-prepared colon with no previous resection at the site of the metachronous PCCRC. These features were prospectively collected for each case.

Morphology (protruded vs flat) was based on endoscopists and pathologists' judgement. Distal location was defined as distal from the splenic flexure. Tissues of all PCCRCs and an approximately equal number of randomly selected DCRCs were selected for DNA analysis. To assess and (afterwards) control for the effect of all tumor features on the molecular profile a random control group, instead of a matched one (which would remove the influence of one or two features), was drawn. In addition, a matched sample would result in a smaller effective sample size in case of missing values, since the matched control (case) is then also treated as missing if the case (control) is missing.

Material

Formalin-fixed, paraffin-embedded (FFPE) samples from the CRCs were used for DNA extraction. All data and tissues were coded. Archival material was used in compliance with the institutional ethical regulations and national guidelines.

DNA was isolated as previously described.[21] In brief, DNA from FFPE material was isolated following macro-dissection (>70% cancer cells). A three-day incubation period with proteinase K in lysis buffer (ATL buffer, QIAmp, DNA micro-kit, Qiagen, Venlo, The Netherlands) was performed. Every day, proteinase K (10 µl of 20 ng/µl) was freshly added. DNA was isolated using the QIAmp DNA micro-kit (Qiagen) and concentrations and purity were measured on a Nanodrop ND-1000 spectrophotometer (Isogen, IJsselstein, The Netherlands).

DNA copy number alterations analysis

DNA copy number alterations analysis was performed by low-coverage whole genome sequencing (WGS).[22] Briefly, DNA was fragmented by sonication (Covaris S2, Woburn, MA, USA) and run on the HiSeq 2000 (Illumina, San Diego, CA, USA) on a 50 bp single-read modus using the Illumina Truseq Nano kit. DNA copy number data analysis was done as previously described.[23]

Mutation analysis

For mutation analysis, the TruSeq Amplicon Cancer Panel (TSACP; Illumina Inc, San Diego, CA, USA) comprising 212 amplicons from 48 genes that are simultaneously amplified in a single-tube reaction, was used. Of each FFPE-DNA sample a total of 150 ng DNA (unless otherwise specified) was used as input for amplicon library preparation according to the manufacturer's instructions. Up to 24 differently barcoded, individual sequence libraries were equimolarly pooled prior to sequencing. These multiple-sample sequence library pools were loaded either on a MiSeq Personal Sequencer (Illumina) using a MiSeq Reagent Kit v2 (300 cycles) (Illumina), according to the manufacturer's instructions (first 28 samples), or loaded on a HiSeq2500 and run in rapid run mode, 150 bp paired-end (the rest of the samples).

MSI status analysis

MSI analysis was performed using a multiplex marker panel (MSI Multiplex System Version 1.2, Promega, Madison, WI, USA), as previously described.[24] When two or more markers were instable, the sample was classified as microsatellite instable (MSI), all other samples were classified as microsatellite stable.

CIMP status analysis

CpG island methylator phenotype (CIMP) in the CRC samples was determined using the CIMP panel (*CACNA1G, IGF2, NEUROG1, RUNX3 and SOCS1*) as defined by Weisenberger et al.[25] by nested methylation-specific PCR (MSP) using sodium bisulphite-modified genomic DNA (EZ DNA methylation kit ZYMO research Co., Orange, CA, USA), as described before.[26, 27] CRCs were classified as CIMP-positive when ≥3 of the 5 CIMP markers were methylated.[25]

Statistical analysis

Patient characteristics were analyzed with descriptive statistics. To compare differences between the PCCRCs and DCRCs regarding their clinic-pathologic features, independent-samples t-test for age distribution or Chi-square test (or Fisher's exact test, when applicable) for all categorical features were applied. *P* values <0.05 were considered significant.

To analyze the genomic changes between selected groups of patients CGHtest 1.1 was used.[28] *P* values were calculated by performing a Chi-square test with 10,000 permutations. Separate analyses were run to test for gains and losses. This test procedure includes a permutation-based false discovery rate (FDR) correction for multiple testing. Alterations occurring <5% were a priori excluded and a FDR <0.2 was considered statistically significant.

A logistic regression model correcting for age, gender and location was applied after imputing missing data to assess the associations of several molecular features with PCCRCs compared to DCRCs. Multiple imputation of missing data allows for missingness depending on observed variables (missing at random; MAR), uses all available data (no list-wise deletion), and reduces the risk of bias

from features that coincide with a lesser quantity of tissue available for molecular analysis.

The missingness of molecular features was imputed using the other molecular features and patient characteristics (with correlation ≥0.01) as predictors. The patient characteristics consisted of gender, patient age, tumor location, early stage, mucinous CRC, morphology (polypoid/non-polypoid), size, presence of diverticulosis and whether the CRC was a PCCRC or not. The MICE package version 2.46.0 was used to impute missing data, using 30 sets with 20 iterations.[29] Convergence was checked by inspecting the trace lines.

Unsupervised hierarchical clustering was performed on a binary distribution of molecular features. All molecular features which appeared to be different between groups in univariate analysis of both all PCCRC and biological PCCRC analyses, were included. In addition, all mutations with an observed prevalence of a minimal 9% were included.

The Ward.D algorithm of the hclust() function in R statistics was used for clustering.[30] This is a distance algorithm finding compact and spherical clusters. It is similar to a complete algorithm that takes the lowest sum of squared distances of the average in a cluster.[31, 32] It is a commonly used algorithm when there is no specific hypothesis about the linkage between the observations in advance. This was the case with these data.

Heatmaps were plotted using Gplots.[33] The heatmaps show patterns which are in line with the known subtypes as published previously.[34] So, the use of the Ward algorithm seems legitimate with these data. The clusters were cut based on the same previously published subtypes of CRC and corresponding molecular features.

Based on the dendrogram, the number of primary branches was determined. Differences in the proportion of PCCRCs and genetic alterations between branches were tested using the Chi-square test. All statistical analyses were performed with R statistics version 3.4.0.[30]

Table 10.1: Baseline characteristics of PCCRCs versus DCRCs.

Features	PCCRCs (n=122)	DCRCs (n=98)	*P* value*
Mean age (SD)	71.8 (9.1)	69.4 (11.4)	0.089
Male (%)	70 (57.4)	57 (58.2)	1.000
Current/previous smoking (%)	28 (23.0)	21 (21.9)	0.980
Proximal location (%)	77 (63.6)	31 (31.6)	<0.001
Flat appearance (%)	58 (47.9)	27 (27.8)	0.004
T1 carcinoma (%)	21 (17.6)	5 (5.1)	0.009
Poor differentiation (%)	32 (29.6)	12 (12.8)	0.006
Mucinous histology (%)	17 (13.9)	13 (13.3)	1.000
Diverticulosis (%)	58 (47.5)	20 (20.8)	<0.001
Mean tumour size (SD)	3.6 (1.8)	4.6 (1.9)	<0.001

** P value < 0.05 considered significant.*

Results

During a 10-year period, 5701 patients were diagnosed with CRC within the South Limburg region. Of these patients, 594 were excluded because of hereditary CRC, IBD or a previous history of CRC (**Figure 10.1**). The remaining 5107 patients had a total of 5303 CRCs, of which 151 were PCCRCs according to the WEO classification. From the remaining DCRCs, 143 controls were randomly selected. High quality DNA was available in 122 of 151 PCCRCs and 98 of 143 DCRCs. CIMP status was available for all samples. Good quality DNA copy number profiles were obtained for 105/122 PCCRCs and 88/98 DCRCs. In some cases, DNA was insufficient for analysis of MSI status and mutation data (**Figure 10.1**).

Of the 122 PCCRCs used in molecular analysis, 94 had a probable biological cause (75 cases of possible missed lesions with prior adequate examination, and 19 cases of likely new CRC) and 28 had a probable procedural cause (21 cases of possible missed lesions with prior inadequate examination, 6 cases of likely prior incomplete resection, and 1 case of previous detected lesion without resection).

Clinical characteristics

Clinical characteristics of the two groups of CRC patients are shown in **Table 10.1**. Baseline characteristics of the PCCRCs were significantly different in several aspects from DCRCs with respect to proximal location, flat appearance, and smaller size (**Table 10.1**). PCCRCs were significantly more often stage T1 carcinoma and poorly differentiated compared to DCRCs.

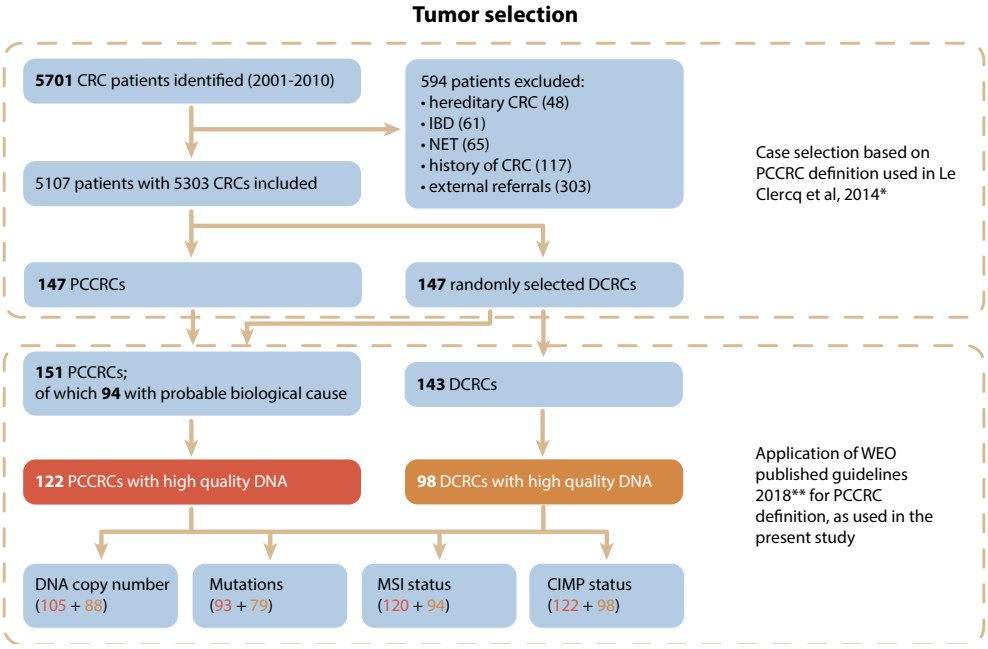

Figure 10.1: Flow-chart of the process of selection of CRC cases for molecular analysis. | *PCCRCs, post-colonoscopy CRCs; DCRCs, detected CRCs. *le Clercq et al.[5] **Rutter et al.[20]*

Molecular features of all PCCRCs versus DCRCs

DNA copy number analysis was complete in 105 PCCRC cases (86.1%) and 88 DCRC cases (89.8%) (**Figure 10.1**). Overall, PCCRCs and DCRCs had comparable patterns of chromosomal alterations (gains and losses), with a high prevalence of gains of 7p, 7q, 8q, 13q, 20q and losses of 8p, 17p, 18p and 18q (**Figure 10.4**). However, PCCRCs showed less frequently loss of 18q in comparison to DCRCs in univariate CGH analysis (FDR<0.2).

Mutation data were complete in 93 PCCRC cases (76.2%) and in 79 DCRC cases (80.6%) (**Figure 10.1**). A panel of 48 cancer-related genes was tested (**Figure 10.5**), of which none of the genes was significantly different between PCCRC and DCRC in univariate testing. The results focus on the nine altered genes with a prevalence of at least 9% in all CRCs analyzed, namely *APC, BRAF, FBXW7, KIT, KRAS, PIK3CA, PTEN, SMAD4 and TP53*, see **Table 10.2**. Gene mutation frequencies were comparable between PCCRCs and DCRCs.

MSI and high CIMP status were significantly more common in PCCRCs vs DCRCs (**Table 10.2**).

To correct for partially missing molecular data, multiple imputation (MI) was used (**Table 10.3**). A logistic regression model analysis was performed after MI, corrected for gender, age at diagnosis and tumor location, and the obtained pooled estimation ORs and 95% CIs were similar to those obtained from complete case analysis (list-wise deletion of cases with missing values). After applying the correction for age, gender, and tumor location, only loss of 18q chromosome remained significantly less common in the PCCRCs (OR 0.4, 95%CI: 0.2 – 0.7; **Figure 10.2a**).

Table 10.2: Molecular characteristics of PCCRCs versus DCRCs.

Features	PCCRCs (n=122)	DCRCs (n=98)	*P* value*	FDR**
APC gene mutation	37/93 (39.8)	39/79 (49.4)	0.268	
BRAF gene mutation	17/93 (18.3)	8/79 (10.1)	0.195	
FBXW7 gene mutation	8/93 (8.6)	9/79 (11.4)	0.723	
KIT gene mutation	19/93 (20.4)	18/79 (22.8)	0.851	
KRAS gene mutation	32/93 (34.4)	24/79 (30.4)	0.690	
PIK3CA gene mutation	16/93 (17.2)	13/79 (16.5)	1.000	
PTEN gene mutation	11/93 (11.8)	6/79 (7.6)	0.502	
SMAD4 gene mutation	8/93 (8.6)	9/79 (11.4)	0.723	
TP53 gene mutation	36/93 (38.7)	38/79 (48.1)	0.278	
Gain of chromosome 13q	52/105 (49.5)	60/88 (68.2)		0.303
Loss of chromosome 17p	45/105 (42.9)	42/88 (47.7)		0.986
Loss of chromosome 18q	49/105 (46.7)	64/88 (72.7)		0.107
MSI	26/120 (21.7)	9/94 (9.6)	0.029	-
CIMP high profile	61/122 (50.0)	32/98 (32.7)	0.014	-

** P value <0.05 considered significant; ** FDR<0.2 considered significant. PCCRC: post-colonoscopy colorectal cancer; DCRC: detected colorectal cancer; FDR: false detection rate; MSI: microsatellite instability; CIMP: CpG island methylator phenotype.*

Table 10.3: Comparison of baseline characteristics between CRC cases with and without missing data. | *CCA: complete case analysis.*

Characteristic	CCA (n=162)	Imputed cases (n=58)	*P* value
PCCRC (%)	89 (54.9)	33 (56.9)	0.918
Mean age in years (SD)	71.0 (10.4)	70.0 (9.7)	0.499
Mean CRC size in cm (SD)*	4.07 (1.88)	4.05 (1.99)	0.959
Gender (% male)	93 (57.4)	34 (58.6)	0.996
Location CRC (% proximal)	85 (52.5)	23 (40.4)	0.156
Morphology (% flat)	66 (41.3)	19 (32.8)	0.328
TNM stage (% T1)	18 (11.1)	8 (14.5)	0.662
CRC differentiation (% good/intermediate)	119 (77.8)	39 (79.6)	0.945
Mucinosity (% >50% present)	19 (11.7)	11 (19.0)	0.248

**Size is missing in 4 cases.*

Molecular feature analysis

All PCCRCs vs DCRCs

Mutation	*P* value	OR [95% CI]
APC	0.97	1.01 [0.52 , 1.98]
BRAF	0.941	1.04 [0.40 , 2.69]
FBXW7	0.905	0.94 [0.36 , 2.47]
KIT	0.767	0.89 [0.41 , 1.92]
KRAS	0.986	0.99 [0.49 , 2.03]
PIC3CA	0.919	0.96 [0.41 , 2.24]
PTEN	0.566	1.34 [0.49 , 3.61]
SMAD4	0.661	0.80 [0.30 , 2.15]
TP53	0.385	0.75 [0.39 , 1.44]
18q loss	0.004	0.39 [0.21 , 0.74]
MSI	0.296	1.59 [0.66 , 3.81]
CIMP high	0.294	1.38 [0.75 , 2.55]

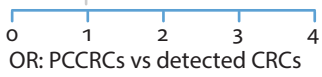

Figure 10.2a: Comparison of molecular features between post-colonoscopy colorectal cancers (PCCRCs) and detected colorectal cancers (DCRCs). | *Forest plots showing the associations of several molecular features of PCCRCs compared to DCRCs.*

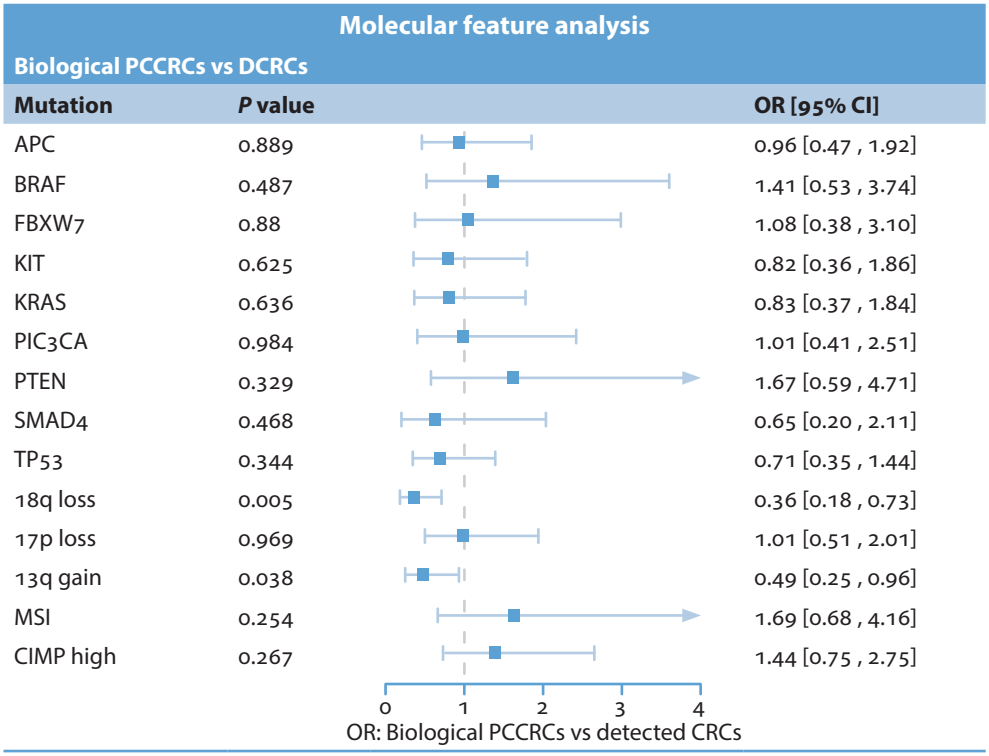

Figure 10.2b: Comparison of molecular features between post-colonoscopy colorectal cancers (PCCRCs) and detected colorectal cancers (DCRCs). | *Forest plots showing the associations of several molecular features of PCCRCs with plausible biological etiology compared to DCRCs, after multiple imputation of missing values and correction for age, gender, and tumor location. OR, Odds Ratio; CI, confidence interval.*

Molecular features of biological PCCRCs only versus DCRCs

When comparing the 94 PCCRCs caused by biological factors to the DCRCs, next to the loss of 18q chromosome, the gain of the 13q chromosome and loss of a small segment of the 17p chromosome (1 MB size), were also significantly less often present in PCCRCs compared to DCRCs in univariate analysis (**Table 10.4**). MSI and high CIMP remained significantly more prevalent in PCCRCs. In the 48 gene panel, significantly more BRAF was present in PCCRCs compared to DCRCs (P=0.049 and P=0.031, respectively). After correction for age, gender and tumor location in a logistic regression model, of the above-mentioned differences, only 18q loss and 13q gain remained significantly different. All other molecular characteristics between PCCRCs and DCRCs were comparable (**Figure 10.2b**).

Clustering analysis considering all molecular features

Interaction between the molecular features was not tested in the logistic regression models because of limited power. Hierarchical clustering was used to show whether certain molecular features correlated. The prevalence of each CRC type within the identified clusters was tested afterwards.

Table 10.4: Molecular characteristics of PCCRCs with likely biological cause versus DCRCs.

Features	Biological PCCRCs (n=94)	DCRCs (n=98)	*P* value*	FDR**
APC gene mutation	24/68 (35.3)	39/79 (49.4)	0.121	
BRAF gene mutation	16/68 (23.5)	8/79 (10.1)	0.049	
FBXW7 gene mutation	7/68 (10.3)	9/79 (11.4)	1.000	
KIT gene mutation	13/68 (19.1)	18/79 (22.8)	0.733	
KRAS gene mutation	19/68 (27.9)	24/79 (30.4)	0.887	
PIK3CA gene mutation	11/68 (16.2)	13/79 (16.5)	1.000	
PTEN gene mutation	10/68 (14.7)	6/79 (7.6)	0.265	
SMAD4 gene mutation	4/68 (5.9)	9/79 (11.4)	0.378	
TP53 gene mutation	23/68 (33.8)	38/79 (48.1)	0.113	
Gain of chromosome 13q	37/78 (47.4)	60/88 (68.2)		0.179
Loss of chromosome 17p	29/78 (37.2)	42/88 (47.7)		0.051
Loss of chromosome 18q	34/78 (43.6)	64/88 (72.7)		0.062
MSI	22/93 (23.7)	9/94 (9.6)	0.017	
CIMP high profile	48/94 (51.1)	32/98 (32.7)	0.015	

** P value <0.05 considered significant; ** FDR<0.2 considered significant; PCCRC: post-colonoscopy colorectal cancer; DCRC: detected colorectal cancer; FDR: false detection rate; MSI: microsatellite instability; CIMP: CpG island methylator phenotype.*

In selecting variables for the clustering analysis, loss of 18q, loss of 17p and gain of 13q were included since these had at least one significant segment difference in univariate analysis. In addition, MSI and CIMP were included because of univariate significance. Finally, we added the nine gene mutations with a prevalence of ≥9% (APC, BRAF, FBXW7, PIK3CA, SMAD4, TP53, KRAS, PTEN and KIT mutations). With hierarchal clustering, three major branches of CRCs were detected (**Figure 10.3a**). Within the branches, the prevalence of PCCRCs was significantly different: 62.0%, 67.9% and 46.5% (*P*=0.018) for branch 1, 2 and 3, respectively. Biological PCCRCs were also observed more frequently in clusters 1 and 2, compared to 3 (48.0% and 53.6% compared to 35.1%; *P*=0.010) (**Figure 10.3a, Table 10.5a**). Branch 1 was characterized by the presence of high CIMP (100%), with only one case of MSI (2.0%) and relatively frequent BRAF mutations (25.6%) (**Figure 10.3b, Table 10.5b**). Branch 2 had frequently MSI (56.4%) and a high frequency of BRAF mutations (31.9%), and very often high CIMP (60.7%). Finally, branch 3 had hardly any MSI (2.7%), a few cases of high CIMP (7.9%) and no BRAF mutations (0.0%), and it was enriched for DNA copy number changes (*P*<0.001). Gain of chromosome 13q (77.9%), loss of chromosome 17p (68.4%) and loss of chromosome 18q (82.1%) were most common in branch 3, but also in branch 1 (63.8%, 44.7% and 70.2%, respectively) (**Figure 10.3**). The combination of high CIMP and MSI appeared to be most associated with PCCRCs (**Figure 10.3b**). PCCRCs had significantly more often both CIMP and MSI than detected CRCs (15.7% vs 4.1%, *P*=0.010). The prevalence of non-polypoid CRCs was not significantly different between

branches (P=0.073). Proximal location clearly differed among the clusters, being more prevalent in branches 1 and 2 compared to branch 3 (P<0.001).

Discussion

We analyzed molecular features of PCCRCs and of DCRCs in a nested case-control series derived from a well-defined population-based cohort, to test the hypothesis whether PCCRCs have a molecular profile that is different from DCRCs. In addition to MSI and CIMP status, which have been frequently analyzed in previous studies, we used extensive profiling including low-coverage whole genome sequencing to determine DNA copy number alterations as well as targeted next-generation sequencing, targeting a panel of 48 cancer-related genes, to test our hypothesis.

PCCRCs were significantly more often located in the proximal colon, had more often a flat appearance, were more often smaller in size and more often contained early CRC. Molecular analysis showed that PCCRCs were more frequently MSI and CIMP-high and showed less frequently losses of chromosome arm 18q, when compared to DCRCs. However, after correction for age, gender, and tumor location, only loss of the 18q chromosome arm remained significant as PCCRCs are strongly correlated with proximal location. Considering only PCCRCs with a possible biological cause in the comparison to DCRCs, we observed that PCCRCs were more MSI, with high CIMP, had more frequently BRAF mutations, had less frequently losses of 18q and 17p as well as less gain of 13q. However, again, after correction for age, gender, and tumor location, only loss of 18q and gain of 13q remained significant. Of interest, no significant differences in any molecular features were found between procedural PCCRCs and DCRCs, as expected (data not shown).

Previous studies, comparing PCCRCs with DCRCs found higher rates of MSI and CIMP among PCCRCs,[14, 15] although in some studies the prevalence of MSI among PCCRCs compared to DCRCs was only moderately increased.[18, 35] This is in line with our findings, where we observed a significant difference in MSI and CIMP status that disappeared when we corrected for tumor location. A study looking at PCCRCs diagnosed within 5 years after negative colonoscopy, showed no difference between BRAF, KRAS and PIK3CA gene mutations.[16] These gene mutations were also in our study not statistically different between PCCRCs and DCRCs.

For the first time, we show that certain DNA copy number alterations are less frequent in PCCRC compared to DCRC, and that is even more clear when considering only biological PCCRCs in the comparison. However, we do observe a similar whole genome DNA copy number pattern in PCCRCs compared to DCRCs, implying that chromosomal instability (CIN) also plays a role in PCCRCs. This is also in agreement with a previous study showing that interval CRCs presented a CIN phenotype, similar to non-interval CRCs, although this analysis was based on FISH data comprising only chromosomes 8, 11 and 17.[36]

Multiple pathways for the development of CRC have been proposed. Chromosomal instability (CIN), microsatellite instability (MSI) and hypermethylation are considered the three main pathways, although these pathways are not fully independent of each other.[37-40] Our cluster analysis, considering all significant variables (univariate analysis) and gene mutations occurring in at least 9% of the cases, showed three major clusters with marked similarity to these pathways. Cluster 1 was characterized by CIMP and DNA copy number changes, with almost no MSI, reflecting the hypermethylation pathway. Cluster 2 was characterized by MSI with frequent CIMP and BRAF gene mutations and reflects the MSI pathway. Cluster 3 was characterized by the absence of high CIMP and MSI and by a high frequency of DNA copy number changes and could be considered as the CIN

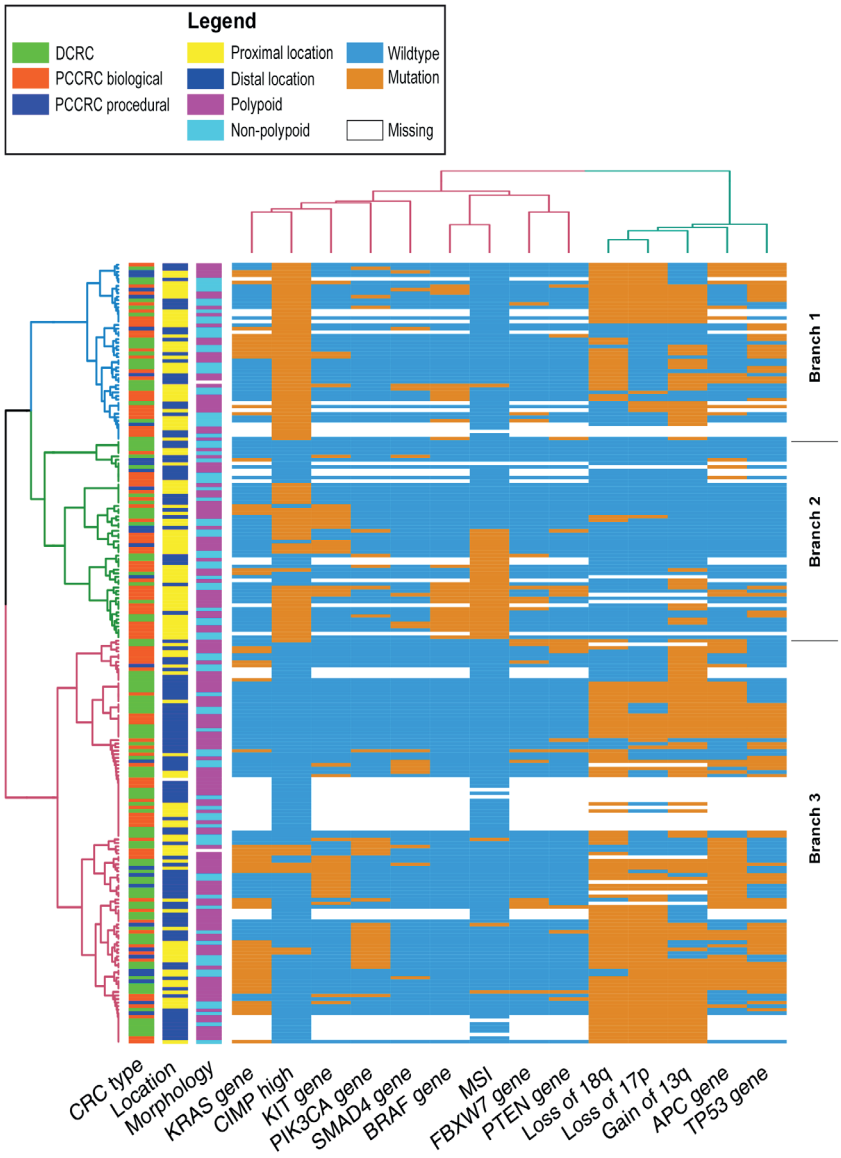

Figure 10.3: Unsupervised hierarchal cluster analysis based on the molecular features of all CRCs analyzed. | *In the cluster analysis results of the nine genes most commonly mutated in this study (APC, TP53, KRAS, KIT, PIK3CA, BRAF, FBXW7, SMAD4 and PTEN), the significant chromosomal alterations (loss of 17p, loss of 18q and gain of 13q), CIMP status and MSI, were included.*

A) Heatmap displaying the distribution of all clinical and molecular features of all CRCs analyzed in this study. *Orange indicates presence (mutation) while blue indicates absence (wildtype) of these features. The first three columns represent CRC type (Biological PCCRCs: red, Procedural PCCRCs: blue, DCRCs: green), CRC location (proximal: yellow, distal: dark blue) and CRC morphology (polypoid: purple, non-polypoid: light blue). After clustering of the CRCs, three large branches can be detected (blue, green, and red).*

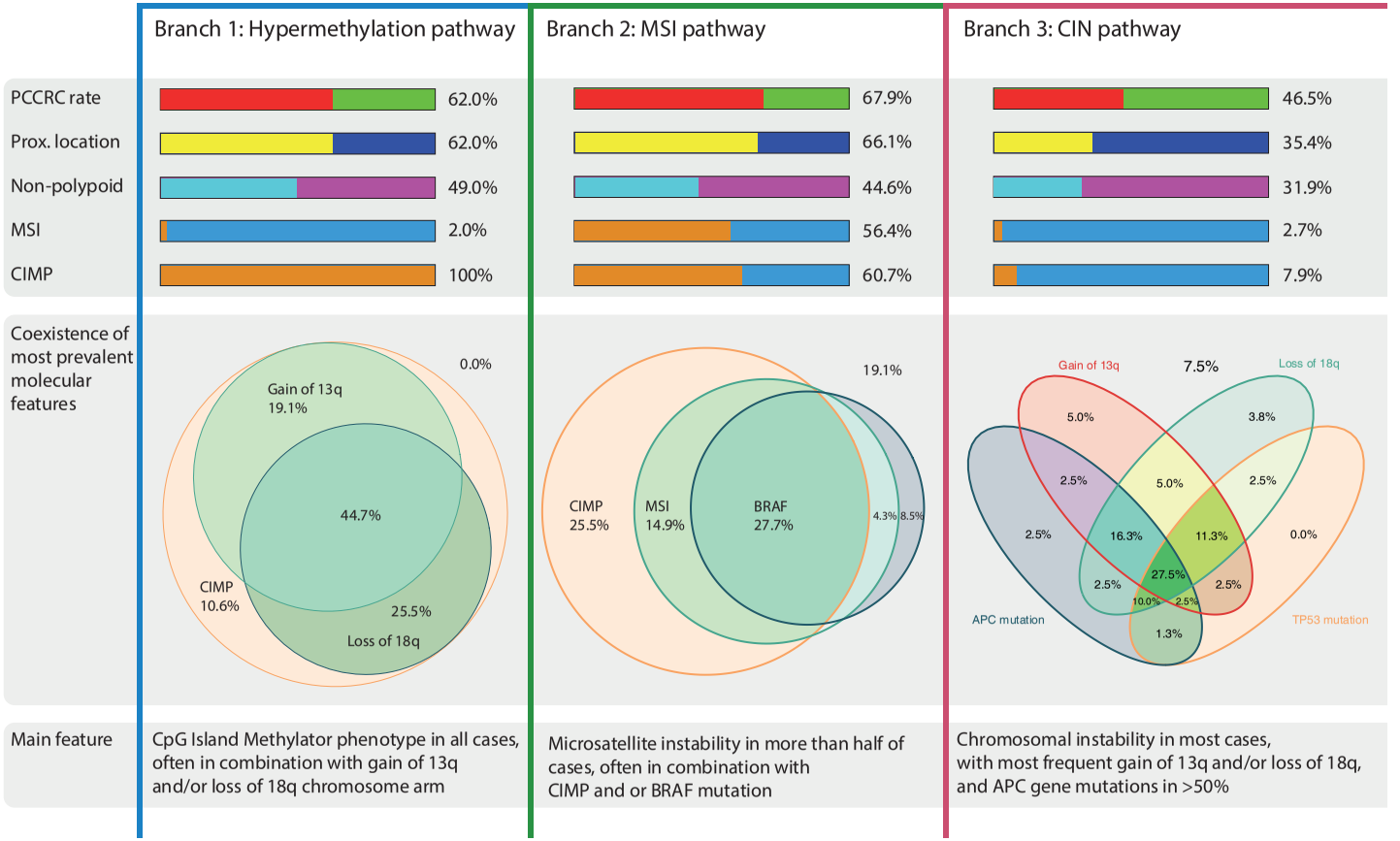

Figure 10.3 B): Overview of hallmark features of each branch from clustering analysis. | *Red: PCCRC, green: DCRC, yellow: proximal location, dark blue: distal location, light blue: non-polypoid, purple: polypoid, orange: MSI / high CIMP present, blue: MSI / high CIMP absent.*

Table 5a+b: Comparison of branches of the hierarchical clustering analysis.

A)

Branch	PCCRC (55.5%)	Biological PCCRC (42.7%)	Procedural PCCRC (12.7%)	Proximal location	Nonpolypoid
1 (n=50)	31 (62.0%)	24 (48.0%)	7 (14.0%)	31 (62.0%)	24 (49.0%)
2 (n=56)	38 (67.9%)	30 (53.6%)	8 (14.3%)	37 (66.1%)	25 (44.6%)
3 (n=114)	53 (46.5%)	40 (35.1%)	13 (14.3%)	40 (35.4%)	36 (31.9%)
	P=0.018*	*P*=0.084**		*P*<0.001*	*P*=0.073*

B)

Branch	MSI	CIMP high	BRAF	KRAS	13q gain	17p loss	18q loss
1 (n=50)	1 (2.0%)	50 (100%)	10 (25.6%)	13 (33.3%)	30 (63.8%)	21 (44.7%)	33 (70.2%)
2 (n=56)	31 (56.4%)	34 (60.7%)	15 (31.9%)	6 (12.8%)	8 (15.7%)	1 (2.0%)	2 (3.9%)
3 (n=114)	3 (2.7%)	9 (7.9%)	0 (0.0%)	37 (43.0%)	74 (77.9%)	65 (68.4%)	78 (82.1%)

** Chi-square test used to compare whether PCCRC rates were different between branches.*
*** Chi-square test used to compare whether the subset biological PCCRC was different among branches.*

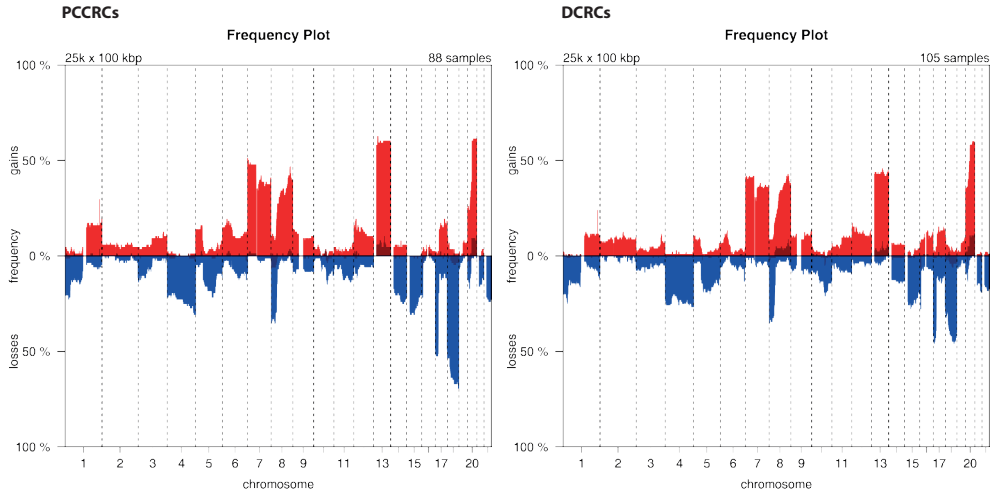

Figure 10.4: PCCRCs and DCRCs frequency plots of DNA copy number gains and losses throughout the whole genome. | *Red: gains, blue: losses.*

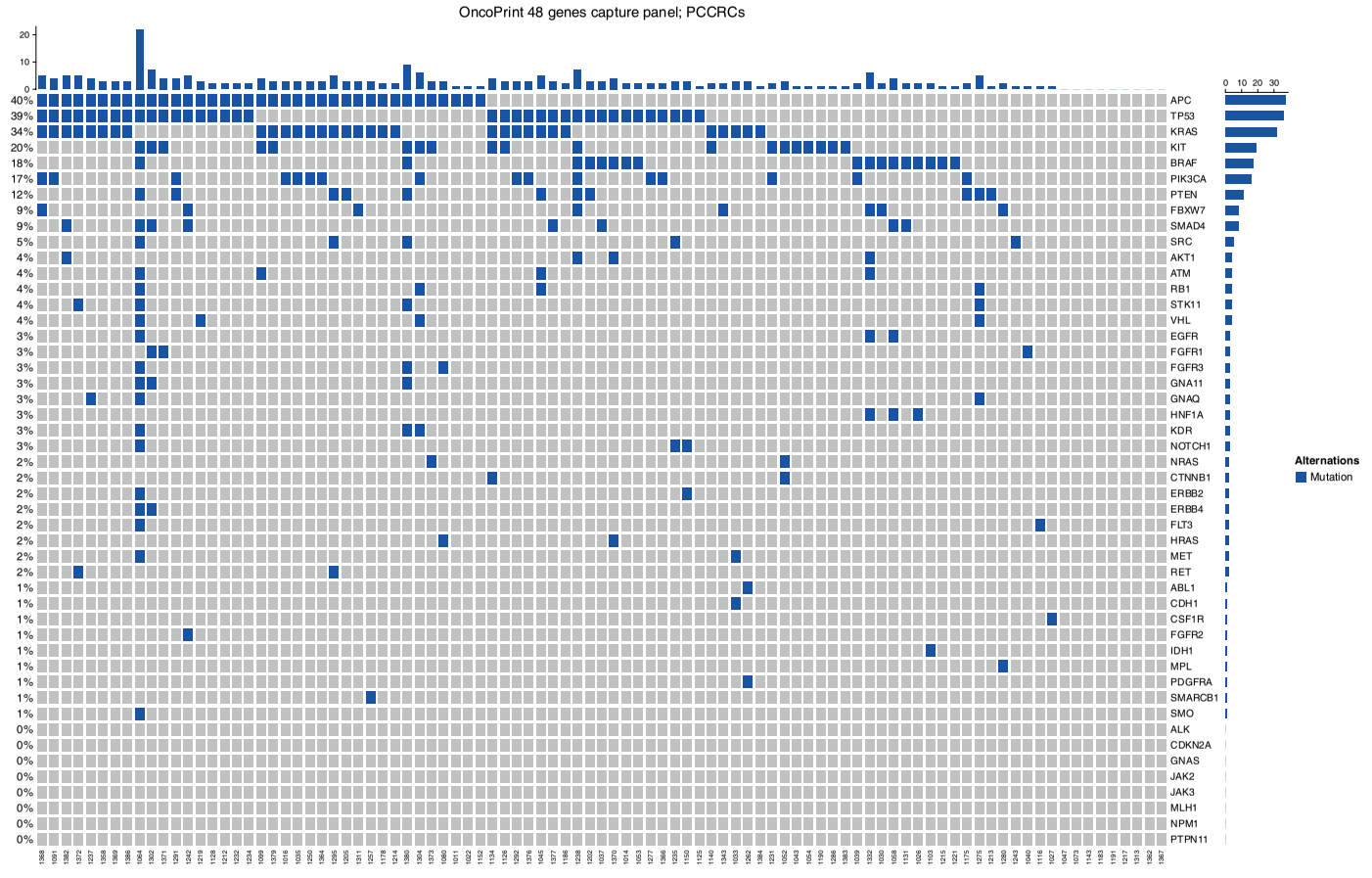

Figure 10.5: Mutation frequencies detected in PCCRCs and DCRCs. | *Oncoprint matrix showing the 48 tested genes (rows) in CRC cases (columns). Blue coloured block: mutations detected; grey coloured block: no mutation detected. Left panel: results of PCCRCs; right panel: results DCRCs.*

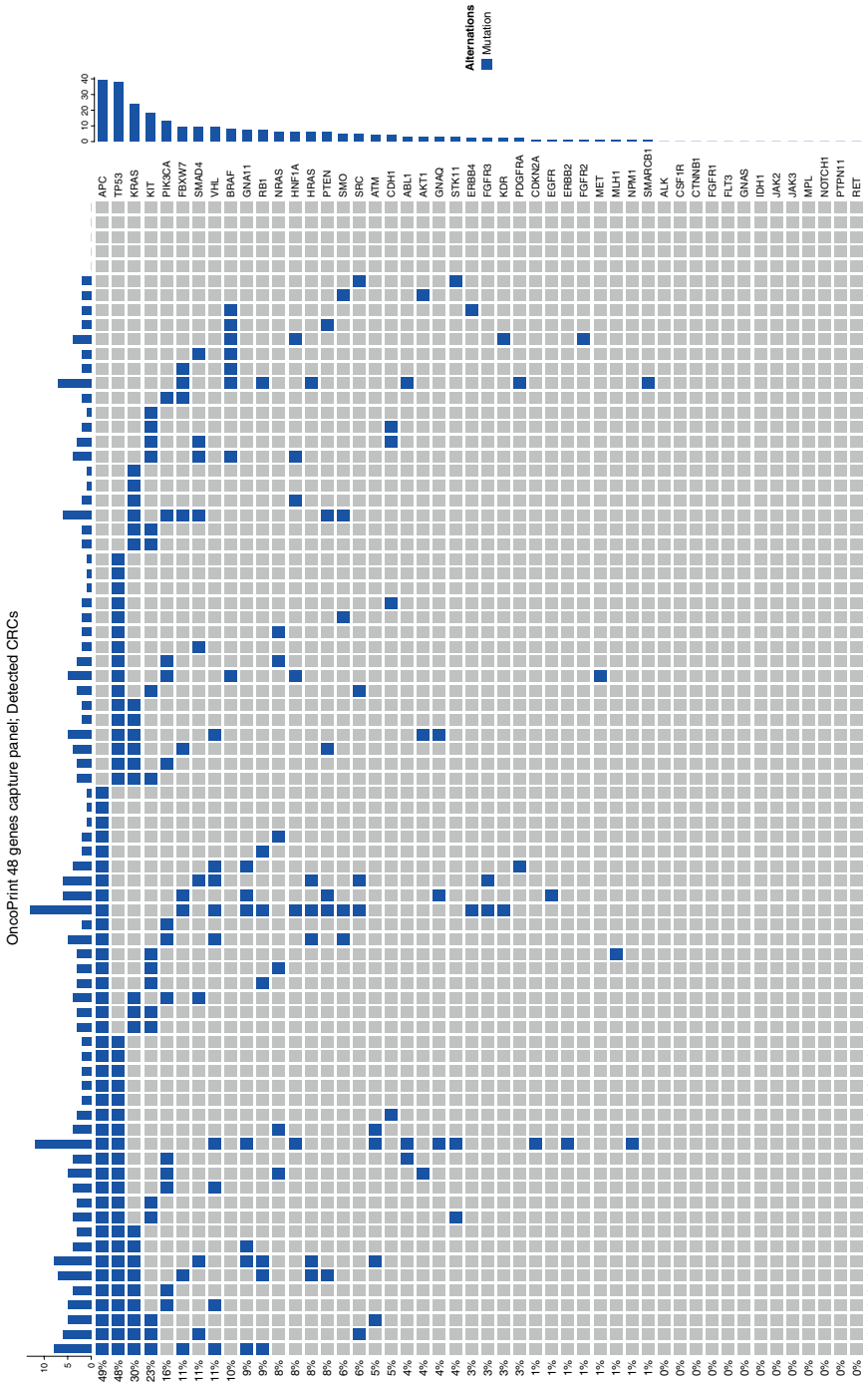

Figure 10.5: *(continuation)*

pathway. While cluster 3 contained most CRCs, in cluster 2 the percentage of PCCRCs was highest (67.9%).

BRAF mutations were not independently associated with PCCRCs, but were shown to have a strong association with MSI in another study.[41] Our clustering analysis indeed shows one cluster with frequent MSI and another with frequent CIMP high cases independent of MSI status. Our data confirm the strong association between PCCRCs and MSI, BRAF gene and CIMP phenotypes, but a specific PCCRC pathway was not found. The association between location and presence of MSI, CIMP and BRAF mutations has been studied before and is hypothesized to explain the lower efficacy of proximal colonoscopy.[42] The majority of the PCCRCs included in this study were considered to result from missed lesions with the previously performed adequate examination (75/122 PCCRCs).

PCCRCs have been associated with non-polypoid and sessile serrated precursor lesions, so their molecular profiles may be more similar. SSLs are considered potential contributors to PCCRCs because of their flat or sessile appearance with pale color, high prevalence in the proximal colon and their subtle lesion borders that make radical resection more difficult.[43, 44] CIMP and BRAF mutations and to a lesser degree MSI are associated with the pathogenesis of SSLs.[45, 46] Our data reveal that in the PCCRC group CIMP high profile, BRAF and CIMP are more prevalent compared to the DCRC group, supporting an association with SSLs. Non-polypoid colorectal neoplasms (CRNs) in general have a molecular profile that is different from polypoid CRNs.[47] DNA copy number losses of chromosome 17p and 18q were observed less frequently in non-polypoid vs polypoid CRN.[24] Mutations in KRAS and APC were less common while BRAF mutations were more common in non-polypoid than in polypoid CRNs.[47, 48] No differences in MSI status were observed[48, 49] and evidence on differences in CIMP status is lacking. Several of these molecular features (KRAS, APC, BRAF mutations, DNA copy number changes) correspond with features that we identified in PCCRCs. Therefore, based on similarities in molecular profiles, our data support the hypothesis that both SSLs and non-polypoid CRNs may contribute to the development of PCCRC.

In order to reduce the occurrence of PCCRC, detection and determination of non-polypoid CRN and SSLs should be improved. Detailed training of endoscopists in recognizing non-polypoid CRN and SSLs is important and has been proven to be successful.[50] The introduction of benchmarks and of training has resulted in increased adenoma detection rates[51-53] and has decreased the risk on PCCRCs.[54, 55] In the near future, technical advances like artificial intelligence, may help to improve detection, determination and adequate endoscopic resection of subtle colorectal neoplasms and thereby help to further reduce the percentage of PCCRCs.[56]

Some limitations of our study should be acknowledged. First, not all CRC samples harbored high-quality DNA, leading to missing data in the molecular analyses. To overcome this, multiple imputation analysis was used for the results, showing no differences with the complete case analysis. Second, clinical data were collected retrospectively, based on patient files and national and regional registries. The reliability of the results depends on completeness of these registries and of the patient records. To limit bias, cross-reference checks have been performed.[5] Migration in and out of the region could lead to undetected PCCRCs. However, the migration rate in the South Limburg region is very low and all three hospitals in the region were included. Third, while patients with known Lynch syndrome were excluded, some yet undiagnosed cases may be present in the included cases. However, only one case with MLH1 mutation occurred among all analyzed CRCs. Lastly, we used a one on one ratio in selecting PCCRCs and DCRCs instead of a larger control group. This could have reduced the power of the study.

Strengths of our study are that to our knowledge it is the first study, a) integrating whole genome DNA copy number sequencing with CRC mutation analysis and MSI and CIMP status, b) with unsupervised hierarchical clustering analysis to form unbiased groups, and c) with cases and controls selected for this study derived from a well characterized population-based cohort with detailed information on probable etiology.

Conclusion

Compared to detected CRCs, PCCRCs are significantly more often proximally located, non-polypoid appearing, early stage and poorly differentiated. PCCRCs showed molecular characteristics common to the canonical CIN, MSI and hypermethylation pathways. After correction for gender, age at diagnosis and tumor location, PCCRCs compared to detected CRCs harbored less often loss of 18q chromosome. Although no PCCRC specific pathway could be defined, pathways associated with sessile serrated and non-polypoid CRNs were more common. In combination with the clinical features observed in PCCRCs, these findings support the hypothesis that SSLs and non-polypoid CRNs are contributors to the development of these cancers. In order to further reduce the occurrence of PCCRC, the focus should be directed at improving the detection, determination and endoscopic removal of these non-polypoid CRNs and SSLs.

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Incidence and classification of post-colonoscopy colorectal cancers in inflammatory bowel disease: A Dutch population-based cohort study

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Abstract

Background

Patients with inflammatory bowel disease (IBD) colitis are at increased risk for colorectal cancer (CRC). We examined the proportion and most likely etiology of potentially preventable post-colonoscopy CRCs (PCCRCs) in a population-based cohort. Furthermore, adherence to IBD surveillance guidelines was evaluated in both PCCRCs and the remainder of prevalent CRCs.

Methods

All IBD patients diagnosed from 1991 to 2011 in the South Limburg region of The Netherlands (i.e. IBDSL cohort) were included. CRC cases were cross-checked with the Dutch pathology database and cancer registry. PCCRCs were defined as cancers diagnosed within 6-60 months after a colonoscopy and were classified as attributable to 'inappropriate surveillance interval', 'inadequate bowel examination', 'incomplete resection', 'missed lesion' or 'newly developed cancer'.

Results

Twenty CRC cases were identified during 25,931 patient years of follow-up in 2,801 patients. The proportion of PCCRCs was 45.0%. Of these, 55.6% could be considered a 'missed lesion', while other possible etiologies occurred only once. Considering both PCCRCs (n=9) and prevalent CRCs (n=11), ten were detected after publication of the surveillance guideline, but only three patients were enrolled. Moreover, six CRCs (30.0%) were detected before the recommended start of surveillance.

Conclusions

In the IBDSL cohort, 45.0% of all CRCs were considered to be PCCRCs, mainly classified as missed lesions. Additionally, a large proportion of CRCs in our cohort were observed before a surveillance endoscopy was performed. Therefore, stringent adherence to IBD surveillance guidelines, improving endoscopy techniques and adjusting the surveillance program may lead to a decrease in CRC incidence.

Introduction

Over the past decades, the incidence of colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD) appears to have decreased in many countries.[1, 2] Recent accurate population-based studies indicating a lower incidence have been published, and this decrease may partly be attributed to improved disease control and the implementation of international surveillance guidelines.[3] However, patients with Crohn's disease (CD) with colonic involvement and patients with ulcerative colitis (UC) patients with left-sided or extensive colitis remain at increased risk of developing CRC.[1, 2, 4-7]

An upcoming area of interest is the incidence of potentially preventable post-colonoscopy CRCs (PCCRCs). These comprise all CRCs arising within 6 to 60 months after a full colonoscopy that was negative for CRC. In the general population PCCRCs constitute 2.9-3.7% of all CRCs.[8, 9] However, in patients with CD and UC, Wang et al. found much higher rates of 15.1% and 15.8%, respectively.[10] Apart from a limited number of studies using hospital-based or selected populations, data on PCCRC incidence from population-based cohorts are lacking.[10-12]

Several studies in the general population found missed lesions to be a major contributor to PCCRCs.[9, 13, 14] In IBD, missed lesions are thought to occur even more frequently.[10] This may be due to the large proportion of flat lesions in IBD and technical difficulties in the detection of dysplasia when mucosal inflammation is present.[15] Besides missed lesions, inappropriate surveillance intervals, incomplete resection of polyps and incomplete colonoscopies are important contributors to PCCRCs.[9, 14]

In this study, we evaluated the proportion of PCCRCs in the population-based IBD South-Limburg (IBDSL) cohort and determined the most likely etiology for their occurrence. In addition, for both PCCRCs and prevalent CRCs, adherence to IBD surveillance guidelines was evaluated.

Methods

Setting and data collection

All IBD patients included in the population-based IBDSL cohort were eligible for this study. This cohort has previously been described in detail.[16] In brief, all patients diagnosed with IBD between January 1991 and June 2011, of at least 18 years of age at diagnosis and living in the region of South Limburg were included. IBD was diagnosed by certified gastroenterologists based on the combination of endoscopic, radiological and/or histological findings. A multifaceted identification strategy involving hospitals, the nationwide Dutch pathology database (PALGA)[17] and general practitioners, resulted in 93% completeness of our cohort. As the remaining patients were unlikely to be biased towards a specific phenotype, an unselected population was assured. The IBDSL study design has been approved by the Ethics Committee of the Maastricht University Medical Centre (NL31636.068.10), is registered in ClinicalTrial.gov (NCT02130349) and meets the ethical standards of the revised version of the Declaration of Helsinki.[18]

Cancer related data were obtained in order to study the overall cancer risk in the IBDSL cohort.[7] In short, cancer data were collected through medical chart review and cross-checked with PALGA as well as the Dutch cancer registry (IKNL).[17, 19] All IBDSL patients were followed until 2013, or until lost-to-follow-up (i.e. death or permanent migration).

In this study, all of the observed CRC cases from the IBDSL cohort were included and additional data were retrieved from patients' medical files. Since both the algorithm for classifying PCCRCs and the IBD surveillance guidelines are not designed for neuro-endocrine tumors (NETs), we excluded these malignancies from the dataset. In addition to the previously collected tumor-node-metastasis stage (TNM), differentiation stage, location of metastases, and IBD to CRC interval, all colonoscopy findings prior to CRC diagnosis were gathered. Each patient's eligibility for the IBD surveillance program according to the then applicable Dutch IBD guidelines, regardless of whether they actually received surveillance, was also assessed. It should be noted that the first guideline on IBD surveillance in the Netherlands was published in the year 2008 and that this Dutch guideline was to a large extent in line with the European Crohn's and Colitis Organisation (ECCO) guidelines. This guideline advised surveillance from 8 years after IBD onset in the case of colonic involvement, except for UC patients with only ulcerative proctitis (Montreal classification E1)[20] and patients with only one inflamed colonic segment in CD. Surveillance endoscopies should have been scheduled once every 3 years during the first decade of surveillance, followed by a surveillance endoscopy once every 2 years in the second decade and once every year in the third decade. A surveillance endoscopy should have been performed by either taking four random biopsies every 10cm of least at nine different locations or by screening using chromoendoscopy. Patients with a concurrent diagnosis of primary sclerosing cholangitis (PSC) should have been enrolled immediately after diagnosis for annual surveillance endoscopies.[21] Enrolment status in the surveillance program of all patients who were diagnosed with CRC was retrieved from patients' medical files and colonoscopy reports. Also, the applied IBD surveillance method (i.e. either multiple random biopsies or the use of chromoendoscopy) was retrieved from the latter.

Definitions

Colorectal cancers were classified according to the time of occurrence with respect to the index colonoscopy (i.e. the last colonoscopy in which no cancer was detected). In line with previous studies, we defined a CRC that occurred between 6 and 60 months after the index colonoscopy as 'PCCRC'.[9, 22-25] When a PCCRC occurred during a surveillance period (i.e. according to the Dutch IBD surveillance guidelines or Dutch post-polypectomy surveillance guidelines)[21, 26-28] and before the date of the next recommended exam, it was considered as 'interval CRC' in agreement with the consensus of the Colorectal Cancer Screening Committee of the World Endoscopy Organization.[29] CRCs that could not be classified as PCCRC were regarded as 'prevalent CRCs'. Sigmoidoscopies were not regarded as full endoscopies and therefore neglected.

For each PCCRC, the most likely etiology (i.e. procedural factors or tumor biology) was determined according to a previously described algorithm (**Figure 11.1**).[9, 24, 30] PCCRCs were classified as (i) 'inappropriate surveillance interval' when detected after the index colonoscopy without receiving adequate follow-up according to previously mentioned surveillance guidelines. It should be noted that these Dutch post-polypectomy surveillance guidelines have not been designed for IBD patients. However, since the IBD guidelines do not specify surveillance intervals after occurrence of dysplasia, we used these regular guidelines for the algorithm. (ii) 'Inadequate bowel examination' was defined as inadequate bowel preparation or incomplete intubation (i.e. cecum not visualized) during the index colonoscopy. (iii) 'Incomplete resection' was defined as the development of a CRC in the same anatomic segment as a previously resected advanced adenoma (i.e. villous component, adenoma >10mm or high-grade dysplasia). (iv) PCCRCs detected between 6-36 months after the index colonoscopy as well as advanced PCCRCs (i.e. >T1N0M0) between 6-60 months were defined as 'missed lesions'. (v) If a non-advanced PCCRC was observed after 36 months, it was considered to be a 'newly developed cancer'.

Statistics

Statistical analyses were performed with SPSS (version 20.0, SPSS Inc., Chicago, IL, USA) to describe cohort characteristics. Incidence rates were calculated per 1000 patient years at risk (PYAR). To correct for overestimation of the PYAR, the years after a colectomy were censored and the year of diagnosis and the year follow-up ended only counted as half patient years as described before.[7] Due to low number of CRCs, further statistical analysis was not performed.

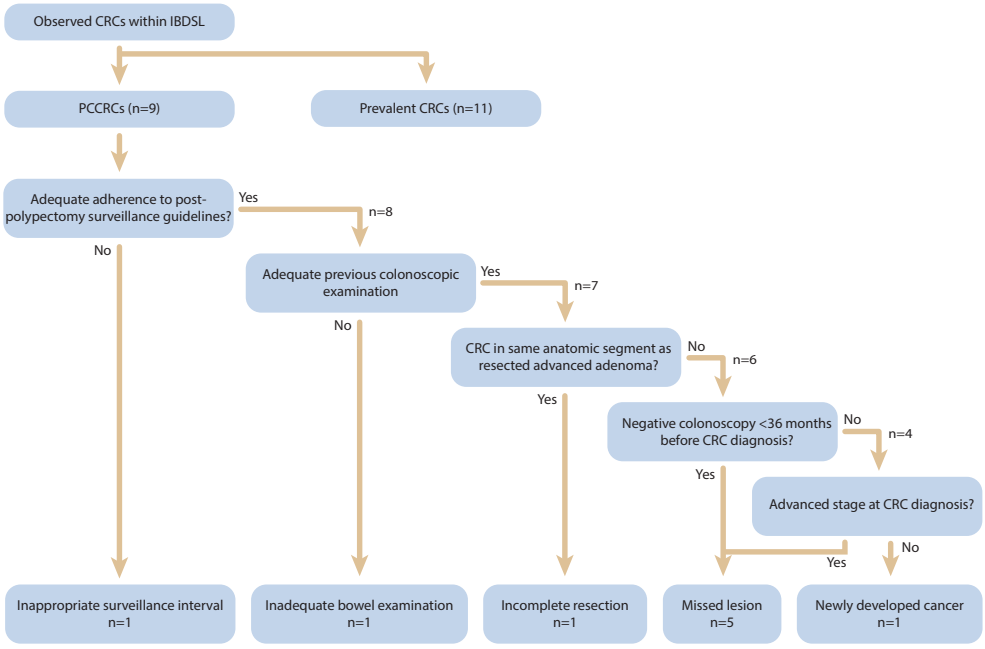

Figure 11.1: Algorithm to classify CRCs according to procedural factors or tumor biology.

Results

In total, 2801 IBD patients were included in the IBDSL cohort of which 1644 had UC and 1157 had CD. Baseline characteristics of the patients are shown in **Table 11.1**. The median follow-up was 8.8 (IQR 4.9 – 14.8) and 8.1 (IQR 4.3 – 13.6) years for UC and CD, respectively. As shown in our previous study, CRC incidence could be evaluated in 25,931 PYAR.[7] After exclusion of NETs, 11 CRCs were observed in UC patients and 9 CRCs were observed in CD patients. The total incidence rate of CRC in our cohort was 0.77/1000 patient years. A general description of all CRCs is published elsewhere.[7]

Of all CRCs, 9 (45.0%) were considered to be PCCRCs. The PCCRC incidence rate was 0.39/1000 PYAR. Characteristics of the observed PCCRCs are provided in **Table 11.2**. Of the PCCRCs, 55.6% was observed in males and the mean age at CRC diagnosis was 71.6 years (range 34-83). Six (54.5%) PCCRCs were observed in UC and 3 (33.3%) in CD patients. All UC patients with a PCCRC had at least a left-sided colitis (Montreal E2) and all CD patients with a PCCRC had colonic or ileocolonic disease

(Montreal L2/3) during follow-up. PCCRCs were diagnosed on average 36.1 months (SD 17.2) after the index colonoscopy. Seven (77.8%) patients had active disease on the index colonoscopy. One PCCRC was discovered during surgery, whereas all other PCCRCs were detected by endoscopy. Four (44.4%) PCCRCs were located in the proximal colon and 3 (33.3%) were detected in an early stage (T1N0M0). Most of the PCCRCs were characterized as regular adenocarcinoma, except for two mucinous adenocarcinomas. TNM-stages and cell differentiation can also be found in **Table 11.2**. None of the patients with a PCCRC was diagnosed with PSC at diagnosis or during follow-up.

Since guideline adherence is applicable to both PCCRCs and prevalent CRCs, we analyzed the adherence in all 20 CRC cases of the IBDSL cohort. All patients with CRC had at least a left-sided colitis (UC) or colonic involvement (CD) during follow-up and were eligible for surveillance. Ten out of the 20 CRCs (50.0%) were found within the recommended surveillance time window and after the Dutch guideline for IBD patients was published (i.e. after 2008). Only three patients received adequate surveillance with chromoendoscopy or random biopsies, and only one of these received the first surveillance endoscopy within 8 years after diagnosis. Notably, 6 (30.0%) CRCs were observed in eligible IBD patients before the recommended start of surveillance according to the current ECCO guidelines.

Discussion

This is the first population-based analysis of PCCRC incidence in IBD, in which we observed that 45.0% of all incident CRCs were considered to be PCCRCs. Regarding their etiology, missed lesions attributed to 55.6% of the PCCRCs. Poor adherence to surveillance intervals, inadequate bowel examination, incomplete resection and newly developed cancer each accounted for one PCCRC. Ten (50.0%) CRCs were found within the recommended surveillance time window, but only three patients had been enrolled at the time of CRC detection. Moreover, according to the current ECCO guidelines, six (30.0%) CRCs in the IBDSL cohort were detected before surveillance was recommended.

Although the overall CRC incidence in our cohort was low (i.e. 0.77/1000 patient years),[7] a relatively large proportion of PCCRCs (45.0% of all CRCs in our cohort) was found. The proportion of PCCRCs in a population-based cohort study in the general population of the same region, using the same definitions, was only 2.9%.[9] The high rate of PCCRCs in our cohort may in part be explained by the frequent use of routine endoscopies to detect disease activity. These endoscopies are inferior in detecting dysplasia compared with chromoendoscopy or a random biopsy procedure (i.e. required methods for adequate IBD surveillance). Furthermore, disease activity may disguise dysplasia and hinder resection. As a consequence, poor dysplasia detection may occur during the performance of colonoscopies for other indications (e.g. follow-up of disease activity) and a false sense of safety can remain. So far, only a few studies have investigated PCCRC incidence in IBD. Wang et al. reported a proportion of PCCRCs of 15.1% and 15.8% in UC and CD, respectively, in an elderly (i.e. >67 years old) IBD population in the USA.[10] These lower proportions of PCCRCs may be due to the more stringent definition (i.e. only CRCs within 36 months after a colonoscopy were considered to be PCCRC); though, 20% of the CRCs in our cohort would still have been classified as PCCRCs using the same definition. However, differences in guidelines, definitions and populations hinder a direct comparison. In surveillance cohorts, although different definitions have been used, the proportion of true interval CRCs, which is a subset of PCCRCs, still ranges from 21 to 29%.[11, 12] Notably, six PCCRCs in this study, and one additional prevalent CRC in the remainder of cases, were diagnosed above the age of 75. The current ECCO guideline does not make any recommendation

Table 11.1: Baseline characteristics of the total study population.

	Ulcerative colitis	Crohn's disease
Patients, n	1644	1157
Male, n (%)	891 (54)	430 (37)
Age at diagnosis, median (IQR)	45.0 (32.2-59.1)	34.3 (24.3-46.9)
Follow-up, median (IQR)	8.8 (4.9-14.8)	8.1 (4.3-13.6)
Total number of PSC cases, n (%)	13 (0.8)	6 (0.5)
Total number of CRC, n	11	9
Total number of PCCRC, n (%)	6 (55)	3 (33)
Phenotype at diagnosis*		
E1, n (%)	556 (34)	
E2, n (%)	777 (48)	
E3, n (%)	296 (18)	
L1, n (%)		496 (43)
L2, n (%)		369 (32)
L3, n (%)		266 (23)
L4, n (%)		123 (11)
B1, n (%)		894 (78)
B2, n (%)		177 (15)
B3, n (%)		84 (7)
P, n (%)		92 (8)

*N: number of patients, IQR: inter quartile range, *: phenotype according to Montreal Classification. Disease extent of UC was defined as ulcerative proctitis (E1), left sided UC (E2) and extensive UC (E3). Disease location of CD was defined as ileal involvement (L1), exclusive colonic involvement (L2), ileocolonic involvement (L3) or isolated upper disease (L4). L4 is a modifier, added to L1-L3 when concomitant upper gastrointestinal disease is present. Disease behavior of CD was defined as non-stricturing/non-penetrating (B1), stricturing (B2), penetrating (B3). Perianal disease (P) is a modifier, added to B1-3 when perianal disease is present.*

Table 11.2: Characteristics of PCCRCs detected in the IBDSL cohort.

Pt		IBD				PCCRC			
	Gender	Type	Age [years]	Montreal^ [diag/max]	Risk factors for CRC [FH/ Sm/P/St]	Age	IBD-CRC interval [months]	Time since last colonoscopy [months]	Disease activity/ dysplasia index colonoscopy
1*	M	UC	60	E2/E2	FH-/Sm-/P-/St-	75	178	20	Moderate/ LGD
2	F	UC	65	E3/E3	FH**/Sm+/P-/St-	69	51	22	Mild/LGD
3	M	UC	76	E2/E2	FH-/Sm+/P-/St-	77	8	8	Mild/No
4	F	UC	68	E1/E2	FH+/Sm+/P-/St-	83	181	29	No/No
5	F	UC	60	E2/E2	FH-/Sm+/P-/St-	69	104	52	Mild/No
6*	M	UC	65	E2/E3	FH**/Sm+/P-/St-	78	155	45	Mild/No
7	M	CD	64	L1/L3	FH-/Sm-/P-/St-	78	178	59	Mild/No
8	F	CD	28	L3/L3	FH**/Sm+/P-/St-	34	69	41	Mild/No
9*	M	CD	71	L2/L2	FH-/Sm+/P-/St-	81	116	49	No/LGD

*Pt: patient number, *: interval CRC, 'M': male, 'F': female, IBD: inflammatory bowel disease, UC: ulcerative colitis, CD: Crohn's disease, FH: first-degree relative with CRC (yes (+), no (-), or unknown (**)), Sm: current or past smoker (yes (+), no (-)), P: presence of PSC (yes (+), no (-)), St: presence of strictures in the past (yes (+), no (-)), LGD: low-grade dysplasia, WLE: white light endoscopy, HD: high definition endoscopy, RB: random biopsy procedure (number of jars obtained), ^: phenotype according to Montreal Classification at diagnosis (diag) and at maximum during follow-up (max). Disease extent of UC was defined as ulcerative proctitis (E1), left sided UC (E2) and extensive UC (E3). Disease location of CD was defined as ileal involvement (L1), exclusive colonic involvement (L2), ileocolonic involvement (L3).*

Table 11.2: *(continuation)*

Endoscopic technique index colonoscopy	IBD surveillance program applicable/ enrolled	Location	Type	TNM-stage	Differentiation
WLE	Y/N	Rectum	Adenocarcinoma	T1NoMo	Moderate
WLE	N/N	Rectum	Adenocarcinoma	T1NoMo	Moderate–Poor
WLE	N/N	Rectum	Adenocarcinoma	T3N1Mo	Unknown
HD	Y/N	Ascending colon	Mucinous adenocarcinoma	T3NoMo	Poor
WLE	Y/N	Ascending colon	Adenocarcinoma	T1NoMo	Well
WLE + RB [×10]	Y/Y	Ascending colon	Mucinous adenocarcinoma	T2N1Mo	Poor
WLE	Y/N	Rectum	Adenocarcinoma	T3NoMo	Moderate
WLE	N/N	Transverse colon	Adenocarcinoma	TxNxM1	Unknown
WLE	Y/N	Rectum	Adenocarcinoma	T3NoMo	Moderate

on when to stop surveillance in IBD patients.[3] Also the Dutch guideline which was available during the follow-up of this study did not include such recommendation.[21] However, as stated in an update of this guideline in 2015 (i.e. after our follow-up ended) clinicians are advised to 'discuss further surveillance strategies with the patient when he/she reaches the age of 75'.[31] Since we observed a lot of PCCRCs in the elderly, we agree that continuation of surveillance, if no contra-indications exist, may be worthwhile and should be discussed by future guideline committees.

Fifty-six percent of the PCCRCs were defined as 'missed lesions' due to their rapid occurrence after an index colonoscopy or an advanced stage at diagnosis. Based on the dwell time between a newly developed neoplasm and an invasive carcinoma, we assume that neoplasia must have been present during the index colonoscopy.[32, 33] However, the turnover time from dysplasia to carcinoma in IBD may be shorter than in the general population given the frequent detection of advanced CRCs in IBD.[34] This may be related to specific molecular pathways and differences in polyp morphology.[35, 36] Taking these factors into account, some PCCRCs classified as missed lesions by the algorithm may actually be newly developed CRCs. The rate of missed lesions in the present study is in line with a large study performed in the general population in the same region as our cohort.[9] However, due to the increased occurrence of easily missed flat lesions in IBD,[13] we expected the percentage of missed lesions in the present study to be even larger. Next to a possible rapid turnover time from dysplasia to carcinoma and the increased occurrence of flat lesions in IBD, the high number of missed lesions may again be a consequence of the increased difficulty of dysplasia detection when mucosal inflammation is present. In addition, almost every index colonoscopy was performed using white light endoscopy (standard definition) which is considered to be inferior to high definition endoscopy and chromoendoscopy. Since procedural explanations for PCCRC incidence has only been scarcely investigated in IBD populations and different definitions are used, direct comparisons cannot be made. Mooiweer et al. studied the incidence of CRCs in a surveillance cohort and found 24% to be related to inadequate colonoscopies, 53% to be related to inadequate surveillance intervals and 12% to be related to inadequate management of dysplasia.[12]

Notably, 30.0% of all CRC cases in our cohort were found in IBD patients with at least left-sided or segmental colitis before the recommended start of IBD surveillance (i.e. 8 years after IBD onset), which is in line with a previous nationwide study.[37] Since current guidelines still advise the first surveillance endoscopy at 8 years after IBD onset, these findings raise the question of whether the surveillance guidelines in IBD are optimal. Since disease activity at diagnosis impairs the chance of CRC/dysplasia detection, inclusion of a first surveillance endoscopy after diagnosis when remission is achieved, should be taken into account and discussed by future guideline committees. Only when absence of dysplasia is guaranteed, can a patient be safely enrolled in the present IBD surveillance program. Since surveillance status was only available for patients with a history of CRC and not for the entire IBDSL cohort, adherence to IBD surveillance guidelines could not be assessed. As the overall incidence of CRC in our cohort was rather low,[7] we assumed that IBD surveillance was not inferior compared with other countries. According to the previous Dutch (applicable during our study period) and current ECCO guidelines, 10 out of the 20 CRCs (50.0%) were found within the recommended surveillance time window and after the Dutch guideline for IBD patients was published (i.e. after 2008). Only three patients received adequate surveillance with chromoendoscopy or random biopsies and only one of these received the first surveillance endoscopy within 8 years after diagnosis. Therefore, nine patients with CRC could potentially have avoided CRC through more stringent adherence to IBD surveillance guidelines by medical practitioners. Although tight surveillance in UC was an international problem in the previous era,[38] van Rijn et al. performed a questionnaire-based study on guideline adherence in the Netherlands in which 95% of all UC

patients and 65% of all CD patients appeared to receive some type of surveillance.[39] However, only 27% of the Dutch gastroenterologists adhered to the international guidelines.[39] Since the Dutch IBD guideline was introduced in 2008 and the study of van Rijn et al. was performed earlier, the current adherence in the Netherlands may have improved. Although the actual guideline adherence cannot be assessed from our dataset, the present study suggests that there is still room for improvement. Closer adherence by gastroenterologists may lead to improvement in this area, and general practitioners should also adhere to the guidelines more closely because patients with longstanding clinical remission might no longer be under the care of gastroenterologists.

The major strength of this study is the assessment of PCCRC incidence in a population-based IBD cohort thereby reflecting the full disease spectrum from mild to severe cases. Moreover, the IBDSL cohort includes detailed medical data from patients with IBD gathered through extensive manual exploration of patient files since 1991. This ensures very accurate data and a real-time estimation of the true incidence of CRC; therefore the proportion of PCCRCs we have determined is reliable. Several limitations should also be addressed. Most importantly, the algorithm used has been developed for sporadic CRCs and makes certain assumptions. For example, rectal cancer that is found 20 months after an index colonoscopy with incomplete cecal intubation is regarded as due to 'inadequate bowel examination' instead of 'missed lesion' due to the algorithm. However, neglecting these assumptions in our study will only lead to more 'missed lesions' and therefore, to the same conclusion. In addition, we did observe a low number of CRCs and therefore a low absolute number of PCCRCs in our cohort. Therefore, minor changes in the number of incident cases would have had a large impact on the percentages of the different etiologies and incidence rates. Furthermore, some of the patients in this cohort had a relatively short follow-up time. As the risk of CRC is higher in patients with longstanding IBD, both CRC and PCCRC rates may be higher after a longer time period of follow-up. Finally, sigmoidoscopies were excluded in the algorithm we used. Since patients with UC are screened frequently for disease activity using a sigmoidoscopy, PCCRC rates may have been even higher if these endoscopies had been taken into account.

Since PCCRC rates were much higher for IBD patients in this population-based study compared with the rates in the general population, it is important that we continue to improve adherence to the IBD surveillance guidelines for patients under the care of gastroenterologists and also for patients being cared for by general practitioners. Also, the guideline could be adapted to prevent CRCs between the diagnosis of IBD and the start of CRC screening. Because most of the PCCRCs were regarded as missed lesion, there is some room for improvement in dysplasia detection during endoscopy. The increasing awareness and appraisal of the IBD surveillance guideline and improvement of endoscopy techniques may lead to better results and hopefully a further decrease in the incidence of CRC, and of PCCRC in particular, in future studies.

In conclusion, this first population-based cohort study on PCCRC incidence in IBD shows that 45.0% of all CRCs were considered to be PCCRCs. Most of the PCCRCs were classified as missed lesions. Additionally, a large proportion of CRCs in our cohort were observed before an IBD surveillance endoscopy was performed, either due to lack of enrollment in the surveillance program or due to development of a CRC before the recommended start of surveillance. Therefore, stringent adherence to IBD surveillance guidelines, improving endoscopy techniques and adjusting the surveillance program may help to decrease both CRC incidence and the proportion of PCCRCs in IBD.

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General discussion

Quality and effectiveness of colonoscopy is more important than ever in the era of population-based screening programs for colorectal cancer (CRC). Asymptomatic people are now receiving colonoscopy as a primary or a confirmatory test to diagnose CRC precursors and CRC at an early stage. Safety and effectiveness of colonoscopy are prerequisites to justify the use of this diagnostic and therapeutic tool in colon cancer screening programs. Studies around the world showed that post-colonoscopy complications, such as colonic perforation or bleeding, have a low occurence.[1] In the Dutch national CRC screening program a fatal complication rate of about two to nine per 100,000 colonoscopies was reported, depending on the estimation method used.[2, 3] However, missed lesions, incomplete procedures, recurrences and preventable additional colonoscopies or surgery should also be considered as an additional risk for patients, as they lead to additional burden and health risks for patients.

A large part of this thesis was focused on CRCs that occur after colonoscopies that are negative for CRC, the so-called post-colonoscopy colorectal cancers (PCCRCs).[4] From the perspective of the endoscopist, the risk of PCCRC occurrence may be modifiable. Better detection of high-risk lesions, better therapeutic strategies and more strict surveillance, may reduce the occurrence of PCCRCs and may improve efficacy of nationwide colon cancer screening programs. Laterally spreading tumors (LSTs) are large flat neoplasms which are potential precursor lesions of PCCRCs.[5] LSTs are harder to detect and resect,[6] which could eventually lead to PCCRCs when managed incorrectly.[7] Furthermore, their treatment can be more challenging, posing a burden on patients and on colonoscopy capacity.[8, 9] In the end, better management strategies for LSTs may result in reduced risk of PCCRC and in increased treatment efficacy with reduced burden for patients.

In this thesis, ways to optimize quality, safety and efficacy of colonoscopy (and eventually also of the CRC screening program) have been studied from the perspective of LSTs and PCCRCs. We searched for evidence to support our hypothesis that LSTs may be precursor lesions of PCCRCs. By studying LSTs we aimed to achieve better diagnosis, better endoscopic treatment, reduced need for surgery and reduced prevalence of (untreated) recurrence. Understanding the biology of PCCRCs could provide clues on how to reduce the PCCRC incidence.

Laterally spreading tumors

LSTs are defined as all non-polypoid colorectal neoplasms of minimal 10mm in size. LSTs can be subtyped into four morphological types; two main types based on surface, LST granular and non-granular (LST-G and LST-NG resp.), with each two subtypes. The granular LSTs can consist of evenly sized granules, called homogeneous granular, or can have a dominant nodule (sessile component), called nodular-mixed granular (LST-G-H and LST-G-NM resp.). The non-granular LSTs can have a complete flat surface, called flat-elevated, or can have a central depression in the elevated tissue, called pseudo-depressed (LST-NG-FE and LST-NG-PD resp.). This classification is called the Kudo LST classification (see **Figure 2.2**).[5] Subtyping of LSTs has therapeutic consequences, as the risk of containing submucosal invasion differs among subtypes. Therefore, not only experts but all colonoscopists should be able to apply the LST classification in daily practice.

In **Chapter 2** the Kudo LST classification was tested on interobserver agreement and practical usefulness. Among experts, moderate to substantial interobserver agreement was found (Gwet's AC1 coefficient: 0.62, 95% CI: 0.55 – 0.69), with overall mean pairwise agreement of 71.0%. Classifying LSTs only into granular versus non-granular resulted in a higher interobserver agreement (Gwet's AC1 coefficient: 0.75, 95% CI: 0.66 – 0.83) and was considered to be more easy to distinguish. To investigate difficulties in the Kudo LST classification, mean pairwise agreement was calculated per

LST subtype. Of the 29.0% possible pairs with discordance, more than 1/3 (10.7%) were between LST-NG-FE and LST-NG-PD and 1/3 (9.6%) between LST-G-H and LST-NG-FE. This indicates that experts disagreed on presence of pseudo-depression in LST-NG and granularity patterns. In another study, the kappa to differentiate LST-NG-PD from LST-NG-FE was much higher among two Japanese experts (0.93).[10]

Next, a group of endoscopy trainees was tested, which had lower interobserver agreement initially. An e-learning for training of the Kudo LST classification has been developed that was completed by all endoscopy trainees before they applied the endoscopic classification again in a post-test. Afterwards the trainees performed better, almost matching the results of the expert group (Gwet's AC1 coefficient: 0.59, 95% CI: 0.53 – 0.65). Analyzing discordant pairs showed that pre-training, the trainees had difficulties with differentiating LST-NG-FE from LST-NG-PD and LST-NG-FE from LST-G-H similar to the experts. However, differentiating LST-G-NM from LST-G-H was also problematic. Post-training, the disagreement in differentiating LST-G-H from LST-NG-FE and LST-G-H from LST-G-NM improved, but differentiating LST-NG-FE from LST-NG-PD was slightly worse (from 12.5% to 13.4% discordant pairs). This means that the recognition of pseudo-depressions remains difficult and additional training and/or clarification of the definition is needed. Using objective measures when to call a granule dominant or not, could help to improve overall agreement.[11]

Morphology of LSTs can also be described using the Paris morphological classification.[12] Among experts, substantial agreement was measured (Gwet's AC1 of 0.71, 95% CI: 0.65 – 0.78, **Chapter 2**). This was much lower among trainees, both pre- and post-test (Gwet's AC1 of 0.33 and 0.45 resp.). In another study among both trainees and gastroenterology staff, applying the Paris classification after training showed substantial agreement in LSTs (Gwet's AC1 0.62, 95% CI: 0.53 – 0.71). No differences between trainees and staff members were found in the agreement coefficients.[13] These results show that as an alternative to the Kudo LST classification, the Paris classification could be used for communication, although information about granularity is missing.

Chapter 2 shows that e-learning is an effective tool to familiarize with and learn endoscopic classifications. The website uses cases with questions about morphology and best treatment, alternated with videos providing tips and tricks for applying endoscopic classifications and assessing the risk of submucosal invasion. It prepares young endoscopists to use the Kudo LST classification in real life setting. The use of cases in an online environment is also in line with new learning tools outside the field of medicine and fits well with the needs of newer generation endoscopists.[14]

LST prevalence

In the last two decades, the number of studies reporting LSTs rapidly increased with multiple definitions used. To study worldwide LST prevalence and the specific features, a pooled analysis of prevalence, morphology, colorectal location, and histological outcomes was performed in **Chapter 3**. The prevalence was quite low, in only 0.83% (95% CI: 0.62 – 1.07) of all patients undergoing colonoscopy LSTs were found. Among all colorectal neoplasms found, 3.6% were LSTs (95% CI: 2.5 – 4.9). Distal location and larger size were associated with an increased submucosal invasion (SMI) risk of LSTs. LST subtype influenced the risk of SMI, with high risk for non-granular pseudo-depressed and granular mixed-nodular LSTs and low risk for granular homogenous LSTs. The conclusion of the study was that assessment of LST morphology is important for SMI risk estimation before endoscopic treatment. Using the pooled data, multivariable analysis to analyze independent risk factors was not possible. In a large study analyzing risk factors for SMI in large non-pedunculated neoplasms (≥20mm) distal location was an independent risk for SMI.[15] Recently, rectal located LSTs were also found to have a greater malignant potential than LSTs located in the colon.[16, 17] LST-G-NM

are frequently found in the rectum and may contain submucosal invasion, even with a completely benign looking surface pattern.[18, 19] However, multivariable analysis in multiple other LST studies showed an independent effect of LST Kudo subtype and size on risk of SMI, but not of location.[20-23] This may indicate that LSTs behave differently from other colorectal neoplasms and that assessment of LST morphology and size are most important to determine risks.

In the Maastricht UMC+ a higher LST prevalence of 2.3% was found as described in **Chapter 4**. This was found among all patients undergoing colonoscopy between 2008 and 2012, before the start of the national CRC screening program. The higher prevalence may be explained by the fact that all staff and endoscopy trainees were trained on the detection of flat neoplasms in 2007, resulting in more skills and awareness.[24] In the national CRC screening setting, the prevalence of LSTs was expected to be even higher. **Chapter 5** shows that in the first years of the screening program, 8% of patients had a large non-pedunculated colorectal polyp (LNPCP) of minimal 20mm in diameter. These consist of sessile lesions (Paris Is) and LSTs. About a quarter of the LNPCPs are LSTs, meaning that the prevalence of larger LSTs (minimal 20 mm) is 2% of all persons receiving colonoscopy in the national screening program.

Optical diagnosis in LNPCPs

In **Chapter 3 and 4** the Kudo LST classification was applied to the large flat lesions. As described earlier, LSTs are nowadays more often studied as a subcategory of the LNPCPs. The features characteristic for the Kudo LST subtypes, such as granularity, dominant nodules and (pseudo) depressions, are now frequently applied to all LNPCPs.[15] A logistic regression model with stratification with maximal fitting showed that a Kudo V pit pattern, increasing size, distal location, non-granular components, sessile components and depressions were all independent risk factors for submucosal invasion. Some neoplasms have overt signs of submucosal invasion, such as depression and Kudo V pitt patterns. When these signs are missing, non-granular LSTs and non-granular sessile adenomas have the highest risk on covert submucosal invasion.[15] An additional study showed that optical diagnosis has a high sensitivity for submucosal invasion in flat and granular LSTs, but this sensitivity is much lower in LNPCPs located in the distal colon or with sessile components. This information is important in selecting the most suitable method of treatment. A new classification system combining the morphological characteristics with other signs of submucosal invasion in colorectal neoplasms, shows promising results in terms of interobserver agreement and sensitivity for submucosal invasion.[25, 26]

LST treatment

The most relevant implication of **Chapter 3** was that the majority of LSTs were non-invasive at the time of colonoscopic detection, so endoscopic treatment by (piecemeal) endoscopic mucosal resection (EMR) is an option. Pretreatment diagnosis of endoscopic subtype, with specific attention for areas of concern (nodule or depression), enables to identify the LSTs with the highest risk of containing SMI. In these cases en-bloc resection would be beneficial.[6] For large colorectal neoplasms (≥20mm), en-bloc resection can only be achieved by surgery or endoscopic submucosal dissection (ESD).

With EMR, mucosal neoplasms are lifted from the submucosa by injection saline beneath the lesion. Then, a snare is placed around the neoplasm and a cut is made with the help of electrocoagulation.[27] Lifting is also the first step of ESD. Here, a knife with electrocoagulation is used to dissect lesions from their margins to the center. Part by part the submucosa is cut apart from the muscularis externa.[28] ESD is more difficult to perform than conventional endoscopic resection,

requiring expertise and time.[29] Furthermore, the risk of perforation and bleeding is higher with ESD than EMR.[30] Finally, ESD only leads to curative resections of superficial neoplasia, and in case of submucosal invasion, only T1a lesions can be curatively treated by ESD.[31] On the other hand, in case en-bloc resection is needed, ESD is less invasive with lesser side effects compared to surgical resection. So, when en-bloc resection is indicated, ESD is an attractive therapeutic option for superficial neoplasms.

Which colorectal neoplasms should be resected en-bloc is still under debate. In Japan, ESD is widely available with high level expertise and facilities.[29] Therefore, in Japan many LSTs are treated by ESD. In the Western world, however, only few centers perform ESD and the need for en-bloc resection is still questioned.[32, 33] En-bloc resection reduces the risk of recurrence,[34-36] but most recurrences can be treated with conventional endoscopic resection afterwards.[37] A meta-analysis on LST treatment reports that 87.7% of all LST recurrences could be effectively treated by colonoscopy.[38] When submucosal invasion is suspected, en-bloc resection facilitates histological diagnosis and is able to provide information about multifocal invasion.[6] With respect to LSTs, the largest risk on submucosal invasion and multifocal invasion exists in LST-NG-PD.[10, 18, 39] LST-G-NM may also contain multifocal invasion,[10, 18] but till now piecemeal EMR with resection of the dominant nodule in one piece and then removal of the granular 'skirt' has been considered as effective treatment.[6, 29, 32, 39] Recently, data of LST-G-NM showed that the risk of submucosal invasion is highly dependent on colonic location. Rectal LST-G-NM have a higher risk on submucosal invasion than LST-G-NM located elsewhere, especially with increasing size, justifying en-bloc instead of piecemeal resection.[17] Compared to completely flat lesions, in colorectal neoplasms with large nodules, endoscopic clues pointing to the presence of submucosal invasion are not present or when present, are often missed.[19] In the near future, ESD procedures will be more widely applied in Western countries. In doing so, evidence will become available on cost-effectiveness of more invasive endoscopic treatments for high risk LSTs.[40, 41]

EMR was used as technique for endoscopic resection of LSTs described in **Chapter 4**. An overall residue/recurrence risk of 14.2% was found. This rate is in line with the 12.6% recurrence rate found in a meta-analysis.[38] ESD was not available in the period when the data were collected. Nonetheless, with increasing skills and experience still more than half of all LSTs were resected en-bloc in the final year of study. The quality of endoscopic resection after the start of the national CRC screening program was studied in **Chapter 5**. In this study, national screening data of the first three years of the program was used, supplemented by detailed outcome data of the first one and a half year collected in a regional cohort. This study showed that even after the start of the national CRC screening program in 2014, most LNPCPs (including large LSTs) were still resected by EMR. Only 1% was resected by ESD. As expected, recurrence rates were higher with piecemeal resection (22% in piecemeal resected and 8% in en-bloc resected LNPCPs) and this percentage increased with larger size. Still, the clinical success rate, defined as no residual or recurrent tissue at 12 months after first encounter, was 87% overall (95% CI: 80 – 92). **Chapter 5** concluded that the resection quality of LNPCPs within the national screening program should improve, perhaps with additional training or centralization. Within piecemeal resected LNPCPs by EMR, factors as size ≥40mm, intraprocedural bleeding, and high-grade dysplasia are predictive for recurrence, stressing the need for well-timed second look colonoscopy.[42]

Options to reduce the high recurrence rates after piecemeal resection were studied in **Chapter 6**. Thermal ablation of resection margins is a technique applied after full macroscopic resection of neoplasms. With the idea that microscopic remnant neoplastic tissue remains in the

border, eradication of the residual tissue may reduce recurrence rates. Whether there is sufficient evidence for application of these techniques in common practice, a meta-analysis was performed. **Chapter 6** showed an overall 18% reduction in recurrence risk with applying thermal ablation after EMR (95% CI: 11 – 26). Two modalities were studied: snare tip soft coagulation (STSC) and argon plasma coagulation (APC). Subgroup analysis for STSC showed a significant reduction, but for APC significance was not reached, probably because of a small number of studies. When all observational studies about STSC were included, a pooled recurrence risk of only 5% was noted (after 6 - 12 months, 95% CI: 2 – 10). STSC requires no additional materials and can be applied directly after EMR using the same snare. This technique is therefore easy to employ in endoscopy practice and could reduce recurrence of piecemeal resected neoplasms. **Chapter 6** concludes that the use of STSC after piecemeal EMR of LNPCPs is recommended. Another simple and apparently effective technique is marking of the lesion prior to EMR. In a study in which soft tip coagulation before lifting is used to mark the borders, EMR was performed in which all mucosa between the markers was removed. This study showed a recurrence risk reduction of 80% (8.1% after marking versus 28.7% without marking, *P*=0.0004).[43]

LST patients at risk

LSTs clearly pose a risk for development into CRCs by difficulties in detection and resection, with recurrences. Adequate, complete LST resection should be effective and result in CRC reduction. In **Chapter 4** we studied synchronous and metachronous neoplasms found during colonoscopies in patients with large neoplasms (≥10mm). Patients with LSTs had more synchronous neoplasms and also had more flat neoplasms in general than patients with a large polypoid neoplasm. This observation is in line with findings in other studies.[44, 45] During 6-year follow-up, the risk of developing a new high-risk neoplasm (with HDG or SMI) was also increased in LST patients compared to patients with large polypoid neoplasms (hazard ratio of 2.9, 95% CI: 1.8 – 4.6). Although LST patients had their surveillance colonoscopy within a shorter interval and more frequently, correction for this in a Cox regression model did not alter the conclusion. During follow-up, LST patients developed more often nonpolypoid neoplasms than patients with large polypoid neoplasms at baseline. The risk of especially LST-NG for developing advanced neoplasia during surveillance, was confirmed in the Japanese Polyp Study. In this study, almost 1500 patients were randomized into surveillance colonoscopy after one and three years and into only after three years, after a double baseline clearing colonoscopy. The presence of LST-NG at baseline was the largest risk factor in univariate analysis for advanced neoplasia within a 3 year colonoscopy surveillance (OR 6.61, 95% CI: 2.11 – 17.61).[46]

For non-polypoid neoplasms in general, more frequent advanced neoplasia are found during surveillance when compared to polypoid neoplasms. In the before-mentioned Japanese Polyp Study, baseline presence of small (<10mm) non-polypoid neoplasms, was the second largest risk factor for advanced neoplasms during surveillance (OR 3.04, 95% CI: 1.01 – 12.11).[46] A study comparing the follow-up findings of patients with non-polypoid and polypoid neoplasms found a risk ratio of 1.6 (95% CI: 1.1 – 2.6).[47] Patients with non-polypoid lesions had also more often new non-polypoid lesions during surveillance, but the risk for developing CRC was similar.[47] So, susceptibility to develop nonpolypoid or polypoid neoplasms is apparently influenced by patient profiles.

Since patients with LSTs are known to have a higher risk of synchronous and metachronous neoplasms, the morphology of colorectal neoplasms can be used for risk stratification in surveillance guidelines. **Chapter 4** concludes that stricter surveillance intervals should be advised to patients with LSTs. It is not yet standard practice to include morphology in decision making (see **Chapter 7**),

but patients with LSTs may benefit from shorter surveillance intervals than patients with polypoid neoplasms.

Post-colonoscopy colorectal cancers

One of the risk factors for the development of PCCRCs is inaccurate post-polypectomy surveillance. As discussed in **Chapter 7**, this can be caused by both endoscopists and patient related factors. In this chapter we reviewed the main components of different post-polypectomy surveillance guidelines and tried to subtract the most important common features. Risk assessment for new colorectal neoplasms varied and different surveillance intervals were advised between guidelines. Currently new guidelines have been published. In the **Addendum** of **Chapter 7** an overview of the current post-polypectomy guidelines is provided, showing that follow-up strategies are still different among the most used surveillance guidelines. However, high quality index colonoscopy is a prerequisite for an adequate surveillance program. It all starts with high quality bowel preparation, high cecal intubation rates and sufficient withdrawal time, to visualize the complete colonic mucosa.[48] The use of intravenous spasmolytics and timing of the colonoscopy (planned at the first half of the program), is associated with higher adenoma detection rates.[49] A large, long-term observational study showed that after single colonoscopy with high quality, the incidence rate of CRC is half of that after a colonoscopy with lesser quality.[50] New endoscopic techniques may help to further improve mucosal visualization by stretching plicae.[51] Systematic training of endoscopists on indirect signs of neoplasia (fold deformation, stool/mucus attachment, disappearing vessels, red rings) may also increase detection rates.[52] A large population-based study investigation PCCRC development within 3 years after colonoscopy, showed that prior polypectomy was a significant risk factor (RR 2.32, 95% CI: 1.97 – 2.72).[53] Risk for recurrence remains after resection of large colorectal neoplasms, especially after piecemeal resection. Therefore, follow-up colonoscopy is necessary within 6 months.[36] **Chapter 7** concludes that it is the responsibility of the endoscopist to convince the patient on the need for surveillance and adhere to the requested interval. By more strict adherence and compliance, the rate of PCCRC caused by procedural errors should decrease.

Optical diagnosis

Recognition of subtle precursor lesions is a next step in prevention of PCCRCs. In **Chapter 9** we showed that training in the detection and resection of flat neoplasms likely reduces the PCCRC prevalence. In Maastricht, systematic training on the detection of non-polypoid colorectal neoplasms had started in 2007 and comprised of lectures, training videos, feedback and supervision during colonoscopy.[24] Formation of the prospective database that has been used in **Chapter 4** was started in 2008 with the aim to study non-polypoid neoplasms in more detail. Information from this database and from the National Pathology database was merged to identify PCCRCs in the period before and after starting the systematic training of endoscopists. Despite the facts that bias is likely to occur because of incomplete follow-up post-training and the assumptions made while correcting for this, the PCCRC rate was markedly lower in the post-training era. Technological improvements in quality of endoscopic imaging and in quality of bowel cleansing may also have helped to reduce PCCRC prevalence.[53]

Improvements in optical diagnosis of polyps may lead to another advantage of colonoscopy. Prediction of polyp histology with high accuracy could reduce the need for histopathological analysis after resection. Diminutive hyperplastic lesions in the distal colon could even be left in situ. Such a strategy will save both time and costs, reducing the burden of screening colonoscopies.

On the other hand, leaving pre-malignant colorectal neoplasms in situ or applying inappropriate surveillance intervals may increase PCCRC risk and should be avoided. Patients' acceptance of relying on the endoscopist's optical diagnosis may also be limited according to an Australian questionary study.[54] In **Chapter 8** the performance of endoscopists who qualified for and were certified to participate in the Dutch national colorectal cancer screening program, was tested. A local database was used, containing the first 2470 national CRC screening colonoscopies in the South Limburg region after implementation in 2014. Suspected histology had to be documented for each polyp as a requirement from the national screening organization. The diagnostic accuracy of diminutive lesions (≤5 mm) was low with 76% (95% CI: 74 – 77) throughout the colon. Selecting only diminutive lesions of the rectum, the diagnostic accuracy was even worse with 71% (95% CI: 69 – 74). The negative predictive value, however, was 84% (95% CI: 80 – 87). **Chapter 8** concludes that with these results, leaving diminutive lesions in the distal colon is not yet a safe option. Resection without histopathological assessment is another strategy. When applying this so-called 'resect and discard' strategy, surveillance interval advices are identical to the advice after histopathological assessment in more than 90% of the cases. The 9% discrepancies led in about 6% of the cases to shorter intervals and in about 3% to longer surveillance intervals. Improvements in tools for optical polyp assessment, such as the BASIC classification, could help to improve the diagnostic accuracy, making these strategies more favorable.[55]

PCCRCs in IBD patients

So far, patients with inflammatory bowel disease (IBD) were excluded in all studies because of a much higher incidence of CRC.[56] Chronic inflammation is thought to stimulate carcinogenesis through specific molecular pathways.[57] The adenoma-carcinoma dwell time may be shorter because of this. Furthermore, neoplasia in IBD patients are predominantly flat, leading to more difficult detection, especially in case of active inflammation. Taken together, these data suggest that IBD patients are at higher risk for developing PCCRCs.

In **Chapter 11**, the frequency and etiology of PCCRCs within all CRCs detected in IBD patients was studied. The IBD South Limburg cohort was used, containing 1644 patients with ulcerative colitis and 1157 patients with Crohn's disease at the time of analysis. This database comprised a total of 25,931 person years at risk for CRC diagnosis, in which 20 CRCs were detected. Nine of these CRCs complied with the definition of PCCRC. The adapted Pabby algorithm was applied, resulting in five probably missed lesions, one inappropriate surveillance interval, one inadequate bowel examination, one incomplete resection, and one newly developed cancer. A similar subdivision of etiology, with the highest proportion of missed lesions, was also seen in the PCCRCs within the general population based cohort of the same region.[58] The conclusion was that the default interval between IBD diagnosis and start of surveillance colonoscopies of eight years, may be too long. The active inflammation at IBD diagnosis impairs neoplasm detection and could reduce adenoma dwell time. In IBD patients, adequate visualization of the mucosa is a key factor for successful surveillance. A repeat colonoscopy after successful treatment of inflammation was suggested to assure a neoplasm free colon as start of surveillance. A large population-based study from Sweden confirmed the higher risk of developing PCCRC among IBD patients. Compared to non-IBD patients, the relative risk of having a CRC diagnosis within 3 years after last colonoscopy was 3.82 (95% CI: 2.94 – 4.96) for Crohn's disease and 5.89 (95% CI: 5.10 – 6.80) for ulcerative colitis.[59]

Molecular features of PCCRCs

As stated above, in IBD patients reduced adenoma dwell time could explain the high incidence of PCCRCs (with respect to all CRCs). In healthy individuals (at risk for sporadic CRC), the precursor lesions of PCCRCs have also been hypothesized to have reduced dwell time. If this is the case, we expect them to have unique molecular features. Otherwise, other features, such as shape and location, may contribute to their occurrence. In **Chapter 10** we examined the molecular profile of all PCCRCs diagnosed between 2001 and 2010 in the South Limburg region. We also studied the molecular profile of randomly selected prevalent CRCs from the same population.

Based on an often flat appearance and proximal colonic location of LSTs (**Chapter 3**), on the fact that non-polypoid neoplasms and serrated lesions have a subtle and more difficult to detect appearance[60, 61] and on a higher recurrence risk of non-polypoid neoplasms,[36] we hypothesized that non-polypoid and serrated lesions may frequently contribute to PCCRCs. Results showed that MSI, CIMP and BRAF gene mutations are associated with PCCRCs. Gain of the 13q chromosome and loss of the 18q chromosome were less frequent in PCCRCs. A PCCRC specific molecular profile was not found. Instead, our findings support the hypothesis that non-polypoid neoplasms and serrated lesions are important precursor lesions. After correction for colonic location, the differences in MSI, CIMP and BRAF gene mutation were no longer present. We already know that non-polypoid and serrated lesions are predominantly located in the proximal colon, so the result that these molecular findings are predominantly found proximally further supports the hypothesis.

A study focusing on molecular profiles, used histology specimens of CRC developed within a serrated neoplasm and confirmed the proposed serrated pathway.[62] In that study, 5 of the 6 studied CRCs contained the same mutations as the surrounding sessile serrated neoplastic tissue; CIMP, MSI and BRAF gene mutations. The remaining CRC had features of the CIN pathway and lacked the BRAF mutation of the surrounding tissue. The authors state that the sessile serrated precursor lesions not always had signs of cytological dysplasia, meaning that serrated lesions should always be considered as precursor lesion. Several other studies also pointed to an increased risk of developing CRC in patients with sessile serrated lesions.[63, 64] Using national databases for a case-control study, it was demonstrated that patients with SSA/Ps had a OR of 3.07 (95% CI: 2.30 – 4.10) for developing CRC when compared to controls.[63] Sessile serrated lesions with cytology markers or a proximal location additionally increased the risk. In that study, hyperplastic polyps were reviewed by pathologists to apply the new definition for serrated lesions. The conclusion of the authors was that patients with sessile serrated adenoma/polyps or traditional serrated adenoma, had a similar to or even higher risk of developing CRC than patients with conventional adenomas.[63] Another study that used data from a randomized controlled study to CRC screening, largely agrees with this conclusion.[64] However, in that study several serrated lesions remained in situ after taking biopsies. Years later some of the patients from that study developed CRC, but not at the location of the previously diagnosed serrated lesion. This led to the conclusion that patients with sessile serrated lesions may have a higher risk profile for CRC, but not directly from malignant growth of the serrated lesions.[64] Furthermore, previous studies showed that high risk serrated lesions coincide with advanced adenomas.[61] Since only 23 serrated lesions were left in situ, data is scarce and definite conclusions cannot be drawn.

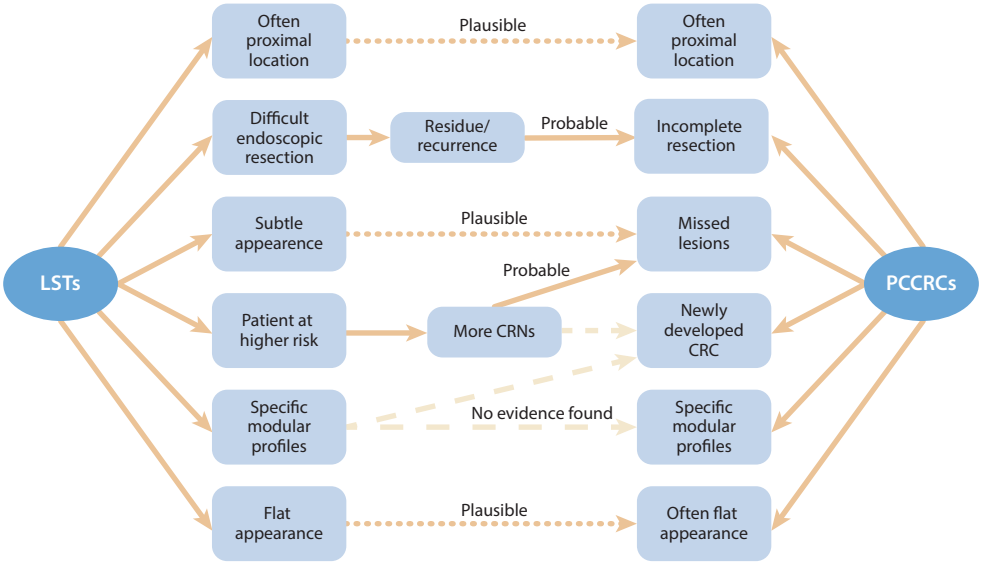

Figure 12.1: Links between LSTs and PCCRCs.

Link between LSTs and PCCRCs

LSTs have already been introduced in **Chapter 1** as potential precursor lesions of PCCRCs. Using the collected data in this thesis, we can now update the links between LSTs and PCCRC with further evidence (**Figure 12.1**). As discussed before, the etiology of PCCRC occurence is thought to be multifactorial, with factors determined by endoscopists, patients, precursor lesions and combinations (**Figure 12.2**).

As discussed in **Chapter 2**, about half of all LSTs are found in the proximal colon. For PCCRCs this is 60%.[58] In general, both polyps[65] and CRCs[58] are more frequently located in the distal colon. In **Chapter 3** we showed that endoscopic resection of LSTs is difficult. When endoscopic resection was considered to be complete, still 14.7% had residue/recurrence. A large meta-analysis provided data of even higher recurrence rates in large non-pedunculated neoplasms.[36] Our results suggest, however, that not only the LSTs themselves pose a risk for PCCRCs. Patients with LSTs have significantly more often advanced metachronous neoplasms than patients with large polypoid neoplasms. So, with currently accepted surveillance intervals applied, LSTs patients may harbor more potential precursor lesions for PCCRC development and thus may have a higher risk of PCCRCs. LSTs of the non-granular subtype, were also the most common advanced neoplasms found during surveillance after two clearing colonoscopies in the Japanese Polyp Study.[46] This indicates that PCCRC may arise from LST-NG.

Some LSTs have a more subtle appearance (LST-NG) than others (LST-G-NM) and the risk of missing a LST will therefore differ by subtype. Because of their size (≥10mm) the risk of missing LSTs in a well-prepared colon will be low, but it is conceivable that a non-granular LST can be missed under a layer of feces. LST-NG-PD pose the highest risk for submucosal invasion (**Chapter 2**) while the ones with submucosal invasion have the smallest size (**Chapter 3**). So it is plausible that a high risk LST-NG-PD may be missed and will develop into PCCRC. Furthermore, LST patients may sooner develop metachronous neoplasm, possibly leading to newly developed CRCs.

The more frequently present flat appearance of PCCRCs in comparison to prevalent CRCs has been discussed above, as this was one of the arguments for the hypothesis that non-polypoid neoplasms contribute to etiology of PCCRCs. The molecular profile of PCCRCs that we have determined, supported this assumption. LSTs also have other specific molecular features. Multiple studies compared molecular features between granular and non-granular LSTs. Non-granular LSTs have less often KRAS gene mutations than granular LSTs.[66-69] In particular KRAS gene mutations may be associated with LST-G in the proximal colon.[70] APC gene mutations were less common in LST-NG,[71] but were overall more often present in LSTs.[72] LST-G and polypoid CRNs appeared to have similar molecular findings in several studies,[66, 71] so perhaps LST-NG have more molecular features in common with non-polypoid neoplasms. Overall, TP53 and BRAF gene mutations and MSI were uncommon in LSTs.[71] High-methylation phenotypes were also uncommon,[73] so LSTs do not match the frequently seen molecular features of PCCRCs as discussed in **Chapter 10**.

Another study combined LST genetics, epigenetics and transcriptomics and showed that LSTs had a number of mutations comparable to microsatellite stable CRC.[74] In that study, APC, KRAS, SOX9 and BRAF were often found to be mutated in LSTs, but these mutations were identified as early clonal events. ANO5, NRXN1 and SLITRK1 genes were also often mutated and methylated, which is a new finding. The axonal guidance system was affected in comparison to normal mucosa, which could be the explanation why LSTs have a lateral instead of luminal growth pattern. All by all, it is very likely that LSTs are precursors of CRCs according to the chromosomal instability pathway. Thus, it is possible that LSTs are precursor lesions of PCCRCs that develop through the chromosomal instability pathway and that sessile serrated lesions may cause PCCRCs through MSI and hypermethylation pathways.

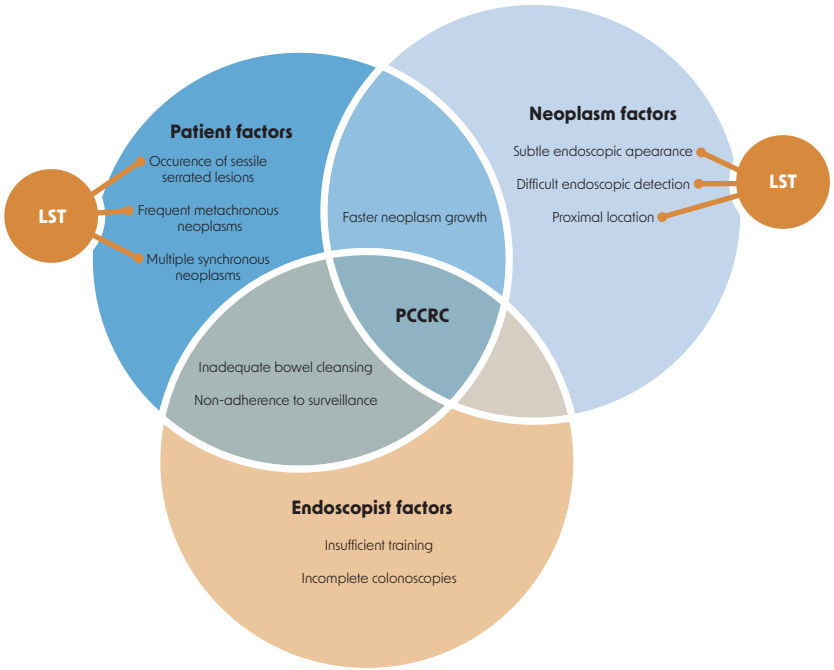

Figure 12.2: Overview of the factors contributing to PCCRC occurence and the factors associated with LSTs.

Implications for clinical practice and future perspectives

Sub-classification of LSTs is a useful first step in assessing risk of submucosal invasion (**Chapter 2**) that can be easily taught to novices using an e-learning (**Chapter 4**). Additional classifications using pit patterns and vascularization in combination with modern visualization tools like (virtual) chromoendoscopy and magnification endoscopy will be used more frequently.[75, 76] These developments may help to improve clinical decision making with early differentiation between endoscopic and surgical treatment strategies. Artificial intelligence (AI) may become the new standard, either as a detection aid pointing to the presence of neoplasia and/or as a determination aid by predicting histology based on endoscopic appearance.[77] Currently, many difficulties and concerns exist with respect to detection and determination of LSTs and sessile serrated lesions by artificial intelligence.[78] Up to now, artificial intelligence used for assessing whether a detected lesion is premalignant or not has a high positive predictive value, but rather low negative predictive value, especially in large and sessile serrated lesions.[79] As outlined in this thesis, these neoplasms are believed to have the highest risk of developing into a PCCRC. Without improvement of the AI algorithms, by training them more specifically for LSTs and sessile serrated lesions,[80] the aim of further reducing PCCRCs will not be achieved. As shown in **Chapter 3** and **Chapter 5**, the efficacy of endoscopic resection should further improve. A prospective study with systematic training of endoscopists in the diagnosis and endoscopic treatment of large non-pedunculated neoplasms is on its way.

The ultimate goal of all colonoscopic interventions is to prevent development of CRCs. Monitoring of PCCRC incidence is an important quality indicator of CRC screening programs. With the introduction of the national CRC screening program in the Netherlands, systematic registration of the occurrence of interval CRC was started.[81] These data will be used to monitor quality at the level of endoscopists, but these data could also been used as prospective database for studies on etiology. In the meantime, the PCCRC definition has changed. Recently a consensus statement of the World Endoscopy Organization resulted in changes in the upper time limit for PCCRCs to 10 years after a negative colonoscopy.[82] Therefore, we used an older definition as used by Pabby and all,[83] in **Chapter 11**, while in **Chapter 10** we applied the WEO definition. The definitions for most likely etiology have also changed. Since the sojourn time (time between occurrence of preclinical cancer and detected cancer) has been estimated between 4.5 to 5.8 years,[84] cutoff time for newly developed CRC became higher (4 instead of 3 years). This new international classification is a prerequisite for further studies and international comparison of data.

As shown in **Chapter 9**, commonly occurring colorectal neoplasms are the presumed precursor lesions of PCCRC. Prevention should therefore focus on detection, determination and resection of colorectal neoplasms. More detailed knowledge about specific molecular profiles of the potentially most malignant precursor lesions is welcomed. This knowledge can not only provide insight in neoplastic growth patterns which could lead to pathway specific treatment strategies, but could also assist in the diagnostic process. Because of capacity problems, costs, discomfort and potential risks of colonoscopies, alternative methods for screening and surveillance are currently being investigated. Molecular stool and blood tests are being developed that may help to detect specific molecular features of CRCs.[85, 86] Such tests could help to reduce the occurrence of interval carcinomas within the screening program since the FIT test has less sensitivity for right sided lesions and for non-polypoid lesions.[87] Within the Dutch CRC screening program fewer proximally located colorectal neoplasms are detected compared to symptomatic patients with a CRC diagnosed outside the screening program, in regular care.[88] It is important that these new molecular stool tests

have a high sensitivity for all neoplasms with malignant potential, also when located in the proximal colon. Detection of molecular profiles frequently seen in PCCRCs in screening patients, could reduce PCCRC occurrence by detection and resection of the precursor lesion with high risk. With a high sensitivity for colorectal neoplasms in non-invasive tests, colonoscopy will become more and more an interventional technique to resect neoplasms in patients with positive screening tests. This may provide the endoscopist with new strategies to win the 'hide and seek' game with premalignant colorectal neoplasms.

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Addendum

Summary
Nederlandstalige samenvatting
Impact paragraph
List of publications
Acknowledgements / dankwoord
Curriculum Vitae
Abbreviations used

Summary

Colorectal cancer is a prevalent cancer which develops from precursor lesions, so called colorectal neoplasms. Because transformation from early neoplasm to colorectal cancer takes years, colorectal cancer is in theory and in practice, a largely preventable disease. Colonoscopy is used for the prevention of colorectal carcinoma by diagnosis and treatment (removal) of colorectal neoplasms. However, not all polyps have the same malignant potential, and some are more difficult to detect or resect. Furthermore, colonoscopy is not able to prevent all colorectal cancers because some neoplasms are missed during colonoscopy or because of incorrect (incomplete) treatment. Large non-pedunculated (flat and sessile) colorectal neoplasms (LNPCPs) are neoplasms which are especially difficult to detect and to treat endoscopically. This thesis consists of two parts. Firstly, LNPCPs were studied in detail focusing on morphology and treatment. Secondly, colorectal cancers occurring after colonoscopy, the so-called post-colonoscopy colorectal cancers (PCCRCs) were studied with the focus on etiology.

An introduction on both topics was provided in **Chapter 1**. The prerequisites for high quality colonoscopy were outlined, including the remaining difficulties and challenges of modern colonoscopy. High quality colonoscopy is essential for preventing PCCRCs. One of the prerequisites is effective, adequate treatment of precursor lesions. This is becoming more difficult with increasing size of a neoplasm. This is especially true for the LNPCPs, large colorectal neoplasms (of minimal 20 mm in size) without a stalk. Large flat (non-polypoid) colorectal neoplasms are a large subset of the LNPCPs. These lesions are also called laterally spreading tumors (LSTs). LSTs are of special interest because their substantial variation in morphology. Four morphological LST subtypes have been defined in the Kudo LST classification. These subtypes are used to assess submucosal invasion risk in the LSTs based on general morphology.

In **Chapter 2**, the agreement of applying the Kudo LST classification was tested among experts and trainees. An educational web-based system was developed and used for this goal. First, well-documented LST cases from the Maastricht University Medical Center (Maastricht UMC+) and from the National Taiwan University Hospital (NTUH) were collected. The 72 cases with the highest quality images were then presented to 14 international experts on the topic of large flat colorectal neoplasms. They were asked to provide the most applicable Kudo LST classification, the applicable Paris morphology classification and the most appropriate treatment modality of each case. The experts showed substantial interobserver agreement in applying the Kudo LST classification (Gwet's AC1 0.62, 95% CI: 0.55 – 0.69), especially in recognition of the nodular-mixed granular LSTs (Fleiss kappa 0.76, 95% CI: 0.73 – 0.78). Based on the input of the experts, an online training module consisting of background information and cases for practicing was developed. The next step was to invite 21 endoscopy fellows from the Maastricht UMC+ and NTUH to answer the same questions as the experts for all 72 cases. After this, each fellow followed the new online training module. Several weeks after this individual e-learning, each fellow answered the same questions for the 72 cases, now hustled in a different order. Initially, the fellows scored a lower interobserver agreement as the experts (Gwet's AC1 0.43, 95% CI: 0.37 – 0.50), but after this single training it improved to a comparable level as the experts (Gwet's AC1 0.59, 95% CI: 0.53 – 0.65). This study showed that the Kudo LST classification is a useful classification since there was substantial agreement among experts, and that it was teachable to novices using an online training module.

To summarize the features of each LST subtype, a meta-analysis was performed in **Chapter 3**. After an extensive search, data of 48 papers were used to study the prevalence of LSTs, the prevalence of each subtype, the submucosal invasion rate of each subtype and the preferred colonic location of LSTs. The results showed an overall prevalence of 0.83% (95% CI: 0.62 – 1.07) among all

colonoscopies, consisting of 3.6% of all colorectal neoplasms detected (95% CI: 2.5 – 4.9). Generally, LSTs are equally prevalent in the proximal and distal colon, but granular LSTs may be more prevalent distally than proximally. The prevalence and the rate of submucosal invasion at diagnosis varies between the LST Kudo subtypes. Homogeneous granular LSTs are most common (35.4%, 95% CI: 27.2 – 43.6) with the lowest rate of submucosal invasion (0.5%, 95% CI: 0.1 – 1.0). Pseudo-depressed non-granular LSTs have the lowest prevalence (5.5%, 95% CI: 3.2 – 7.8) while having the highest risk of submucosal invasion (31.6%, 95% CI: 19.8 – 43.4). The study showed that the classification of LSTs based on macroscopic appearance is helpful in assessing risk on submucosal invasion and should be used to determine the most appropriate treatment strategy.

The high risk of submucosal invasion in some LST subtypes, suggests that inadequate resection could contribute to the risk of developing colorectal cancer. Whether patients with LSTs have a specific risk profile for developing metachronous colorectal neoplasms has not yet been studied. In **Chapter 4**, data from a prospective polyp database was used to study LSTs and to compare them with large polypoid neoplasms. Follow-up data from all patients with larger colorectal neoplasms (of minimal 10 mm in diameter) were additionally collected. The results showed that LST patients had significantly more synchronous colorectal neoplasms than patients with large polypoid colorectal neoplasms (mean 3.34 vs 2.34, $P<0.001$). Patients with LSTs also developed significantly more often metachronous neoplasms within the six year follow-up (71.6% vs 54.2%, $P=0.0498$) and more often colorectal neoplasms with high grade dysplasia or submucosal invasion (36.4% vs 15.8%, $P<0.001$). After correction for age and gender, compared to large polypoid neoplasm patients, LST patients had a higher risk (hazard ratio 2.9) of developing a new colorectal neoplasm with high grade dysplasia or submucosal invasion. These results warrant the need for strict surveillance in LST patients, as they appear to be a population at higher risk.

The importance of this finding for current clinical practice is highlighted in **Chapter 5**. Data on LNPCP prevalence in the first years of the Dutch colorectal cancer screening program showed that LNPCPs occurred in 8% of all participants undergoing colonoscopy. Detailed data of the findings during the first years of screening, including follow-up, were collected in three hospitals in the South-Limburg region of the Netherlands. The local prevalence of LNPCPs was comparable to the national prevalence. Overall, 30% of the LNPCPs that were encountered, were not resected directly. This rate increased with LNPCP size. The overall technical success rate of endoscopic resection was 87% (95% CI: 82 – 91). The clinical success rate was shown also to be 87% (95% CI: 80 – 92) and was defined as no residue after one year. Both rates decreased with increasing LNPCP size. Overall recurrence after a technical successful resection was 22% (95% CI: 15 – 32) for piecemeal and 8% (95% CI: 2 – 22) for en-bloc resection. Most of the recurrences could successfully be treated by repeated endoscopic resection, but two recurrences were carcinomatous and required additional surgery. These data show that in current endoscopy practice, endoscopic treatment of LNPCPs is still difficult with room for further improvement.

To investigate whether simple interventions could reduce LNPCP recurrence risk, a systematic meta-analysis was performed in **Chapter 6**. The goal of this meta-analysis was to study the effectiveness of thermal ablations of the resection borders after endoscopic mucosal resection. A total of 10 studies investigated snare tip soft coagulation (STSC) or argon plasma coagulation (APC) in relation to recurrence after large neoplasm resection. Pooling the risk difference of one of both interventions in comparison with no additional treatment, showed a risk reduction of 18% (95% CI: -26 – -11) after 6 to 12 months. Since STSC does not require use of additional materials during colonoscopy, this technique is probably most cost-effective.

In the next part of the thesis, post-colonoscopy colorectal cancer was the main topic of interest. In **Chapter 7**, a review of colonoscopy surveillance prerequisites was performed. An overview of the

current surveillance guidelines in 2015 was presented with an update of the new guidelines published up to the end of 2021. The intervals of surveillance differ among international guidelines. However, all guidelines stress the importance of high-quality bowel preparation, complete colonoscopy, clear communication about intervals and high adenoma detection rates of endoscopists. Additionally, the intervals are all based on risk stratification using clinicopathological characteristics of the removed neoplasms. Over the last 10 years, new evidence about colorectal cancer risk after polypectomy showed a lower risk than expected after a high-quality index colonoscopy. The risk of developing colorectal cancer after removal of sessile serrated lesions is now estimated to be higher and has led to intensification of colonoscopic surveillance in these patients.

For the determination of post-polypectomy surveillance intervals, histopathology is used. However, using optical diagnosis could reduce histopathology costs. In **Chapter 8**, the accuracy of optical diagnosis during national CRC screening colonoscopies was studied. Data of the first 3028 small polyps detected in the national CRC screening program in the South-Limburg region was used to compare the endoscopist's diagnosis with the pathologist's diagnose. Taking into account the complete colon, a diagnostic accuracy of only 76% (95% CI: 74 – 77) was found, with a negative predictive value for adenomatous histology of 69% (95% CI: 66 – 73). Taking into account only the rectosigmoid region, the diagnostic accuracy was even lower with 71% (95% CI: 69 – 74), but the negative predictive value for adenoma was higher with 84% (95% CI: 80 – 87). Applying the resect and discard strategy (i.e. removing the neoplasms without sending them for histopathology) for lesions up to 5 mm in size, would have led to more than 90% identical surveillance intervals than after pathological assessment of all resected neoplasms. In about 6% the interval was even shorter than based on histopathological outcomes. Based on these results, the accuracy of optical diagnosis is currently too low to omit the histopathological diagnostic process.

Whether training on colonoscopy quality and detection of flat colonic neoplasms can indeed reduce the PCCRC incidence, was studied in **Chapter 9**. This comparison was performed based on estimated PCCRC incidence rates derived from multiple sources. The PCCRCs were obtained and identified from a database containing all CRC diagnoses between 2004 en 2014 in the Maastricht UMC+. Using a prospective colonoscopy database from 2008 to 2012 with follow-up data, the person years of follow-up within this period could be calculated (sum of years between index and end of follow-up or PCCRC occurrence). The training occurred late 2007. The number of colonoscopies between 2004 and 2008 was registered in the hospital. The mean follow-up time per patient for this period was estimated based on the data from 2008. Year of last colonoscopy before PCCRC diagnosis was used for comparison. Because of the lack of full prospective data on PCCRC before training, the results are partly based on extrapolation of person years of follow-up, using this data from the year 2007 for estimates of 2004 till 2006. Before training, in 2.0 per 1000 colonoscopies, a PCCRC occurred afterwards, while after training this was 0.8 per 1000 colonoscopies. Incidence rates expressed per patient years of follow-up (PYFU) showed a rate of 0.79/1000 PYFU before and 0.34/1000 PYFU after training. Despite the bias that may have occurred based on the estimation on surveillance occurrence prior to training we made, a positive effect of training on the detection and resection of flat colonic neoplasms on PCCRC incidence was observed.

Additional evidence for PCCRC occurrence from flat neoplasms was provided in **Chapter 10**. A prospective database containing all detected CRCs and all PCCRCs was used, where all PCCRCs and an equally sized random selection of detected CRCs were sent for molecular analysis. This analysis comprised of whole genome sequencing for comparing copy number changes, detection of mutations in 48 commonly affected genes in CRC, CpG island methylator phenotype determination and presence of microsatellite instability. Loss of chromosome 18q was significantly less common in PCCRCs compared to detected CRCs (46.7 vs 72.7%, false discovery rate 0.11). Microsatellite

instability (21.7 vs 9.6%, *P*=0.029) and a high CpG island methylator phenotype (50.0 vs 32.7%, *P*=0.014) were significantly more common in PCCRCs. An unsupervised clustering model was applied showing three main branches of PCCRCs, corresponding to the hypermethylation pathway, the microsatellite instability pathway and the chromosomal instability pathway. Previous studies showed that sessile serrated lesions were associated with the hypermethylation pathway and in lesser degree with the microsatellite instability pathway. For non-polypoid neoplasms, BRAF gene mutations were more common. PCCRCs were overrepresented in the hypermethylation and microsatellite pathway (62% and 68% PCCRCs resp.), while underrepresented in the chromosomal instability pathway (47% PCCRCs). This study showed no specific separate pathway for PCCRCs. The pathways associated with sessile serrated lesions and flat lesions were more common in PCCRCs however. The hypothesis that both sessile serrated lesions and non-polypoid neoplasms may be precursor lesions of PCCRCs still applies and is supported by our data.

Chronic inflammation of the colon mucosa is a risk factor for developing neoplasms. Therefore, patients with inflammatory bowel disease (IBD) need colonoscopic surveillance. In **Chapter 11**, the occurrence of PCCRCs in patients with IBD was studied. For this study, the population based IBD South-Limburg cohort was used. This cohort contains all adult IBD patients diagnosed between 1991 and 2011. All diagnoses of CRC that we encountered were cross-checked with the national cancer registry. Colonoscopies performed in the 5 years preceding the diagnosis of CRC led to the identification of a PCCRC. In the included group of 2801 IBD patients, 20 CRCs occurred, with a incidence rate of 0.77/1000 patient-years. Nine CRCs were identified as PCCRC (45%, 0.39/1000 patient-years at risk). Of them, five PCCRCs were classified as most likely occurring from missed neoplasms. Another important finding was that six of all CRCs were detected before the start of colonoscopic surveillance (within 8 years after diagnosis recommended). The conclusion of the study is that IBD patients have a higher risk on PCCRC development, but also on developing CRC before start of the surveillance. New endoscopy techniques improving dysplasia detection in IBD patients should be developed. Applying an index colonoscopy earlier after first remission is obtained, could possibly help to prevent CRC development prior to the first surveillance colonoscopy, which is planned based on recommendations in current guidelines.

In the final chapter, **Chapter 12**, the relevance of the endoscopic subclassification of LSTs in clinical practice was discussed. The incorporation of morphological assessment with knowledge on features of submucosal invasion, prior to endoscopic resection was advocated. LST treatment and surveillance recommendations were discussed. The links between LSTs and development of PCCRCs was also discussed. The hypothesis from chapter 1 was tested with the findings from chapter 2 to 11, concluding that LST patients may be at higher risk for PCCRC development due to more metachronous neoplasms and higher chance of incomplete resection. We conclude that attention for high quality detection, determination and resection of colorectal neoplasms is probably still the most effective PCCRC prevention measure.

Nederlandstalige samenvatting

Darmkanker is een veel voorkomende kanker en ontstaat uit voorloper afwijkingen, de zogenaamde colorectale neoplasieën, oftewel darmpoliepen. De transformatie van een vroeg stadium neoplasie tot darmkanker duurt jaren en daarom is darmkanker, zowel in theorie als praktijk, een grotendeels te voorkomen ziekte. Coloscopie wordt gebruikt voor het voorkomen van dikke darmkanker, door vroeg stadium neoplasie op te sporen en te behandelen (verwijderen). Echter niet alle poliepen zijn hetzelfde. Er is een verschil in het risico op het ontstaan van kanker in poliepen en daarbij zijn sommige poliepen lastiger te detecteren of te verwijderen dan andere. Daarnaast kan coloscopie niet alle dikkedarmkanker voorkomen omdat sommige poliepen gemist worden, of doordat ze onvolledig verwijderd worden. Grote niet-gesteelde poliepen (vlakke en sessiele poliepen) oftewel de LNPCPs (*large non-pedunculated colorectal neoplasms*) zijn in het bijzonder moeilijk met endoscopie op te sporen en te behandelen. Deze thesis bestaat uit twee delen. In het eerste deel worden de LNPCPs in detail bestudeerd met de focus op morfologie (vorm) en behandeling. In het tweede deel wordt er gekeken naar darmkanker die ontdekt wordt na een coloscopie, de zogenoemde post-coloscopie colorectale kankers (PCCRCs; *post-colonoscopy colorectal cancers*). Hierbij ligt de focus op oorzaken tot het ontstaan.

Een introductie betreffende beide onderwerpen wordt in hoofdstuk 1 gegeven. De voorwaarden voor kwalitatief hoogwaardige coloscopie worden weergegeven, inclusief de nog steeds aanwezige moeilijkheden en uitdagingen van hedendaagse coloscopie. Hoog-kwalitatieve coloscopie is namelijk essentieel voor het voorkomen van PCCRCs. Een van de voorwaarden hierin is effectieve en adequate behandeling van poliepen. De moeilijkheid hiervan neemt toe met poliepgrootte. Dit geldt vooral voor LNPCPs, de grote darmpoliepen (minimaal 20mm grootte) zonder een steel. Grote vlakke poliepen zijn een grote subgroep van de LNPCPs en worden ook wel de *laterally spreading tumors* (LSTs) genoemd oftewel zijwaarts strekkende tumoren. Deze LSTs zijn extra interessant door een duidelijke variatie in morfologie. Er worden namelijk vier verschillende subtypen onderscheiden, gedefinieerd volgens de Kudo LST classificatie. Deze subtypering wordt gebruikt om met behulp van de vorm het risico op de aanwezigheid van beginnende darmkanker (submucosale invasie) in de poliep te bepalen.

In hoofdstuk 2 werd de overeenstemming in toepassing van de Kudo LST classificatie getest tussen experts en studenten. Om dit te testen werd een educatief online systeem ontwikkeld. Allereerst werden goed gedocumenteerde LST-casussen uit het Maastricht Universitair Medisch Centrum (MUMC+) en uit het Nationaal Taiwanees Universiteitsziekenhuis (NTUH) verzameld. Hieruit werden de 72 casussen met de hoogste kwaliteit foto's geselecteerd en vervolgens aan 14 internationale experts op het gebied van grote vlakke darmpoliepen gepresenteerd. Ze werden gevraagd om de Kudo LST classificatie, de Paris morfologie classificatie en de meest geschikte behandelingsmethode voor elke casus te rapporteren. De experts hadden aanzienlijke overeenstemming bij het toepassen van de Kudo LST classificatie (Gwet's AC1 0,62, 95% CI: 0,55 – 0,69), vooral in het herkennen van de nodulaire-gemengde granulaire LSTs (Fleiss kappa 0,76, 95% CI: 0,73 – 0,78). Op basis van de ervaringen van de experts werd een online trainingsmodule ontwikkeld, bestaande uit achtergrondinformatie en casussen uit de praktijk. Vervolgens werden 21 endoscopie studenten uit het Maastricht UMC+ en het NTUH uitgenodigd om voor alle 72 casussen dezelfde vragen te beantwoorden als de experts. Vervolgens volgde elke student de nieuwe online trainingsmodule. Enkele weken na deze individuele e-learning beantwoordde elke student nogmaals dezelfde vragen voor de 72 casussen, nu gehusseld in een nieuwe volgorde. Aanvankelijk scoorden de fellows een lagere overeenstemming dan de experts (Gwet's AC1 0,43, 95% CI: 0,37 – 0,50), maar na deze eenmalige training verbeterde deze tot een vergelijkbaar niveau als de experts (Gwet's AC1 0,59, 95% CI: 0,53 – 0,65). Deze studie toonde aan dat de Kudo LST classificatie een

bruikbare classificatie is, aangezien er aanzienlijke overeenstemming is gevonden onder experts, en die aan te leren is aan MDL-artsen in opleiding met behulp van een online trainingsmodule.

Om de kenmerken van elk LST subtype samen te vatten, werd een meta-analyse uitgevoerd in hoofdstuk 3. Na uitgebreid zoeken werden de gegevens van 48 artikelen gebruikt om de prevalentie van LSTs, de prevalentie van elk subtype, de submucosale invasiegraad van elk subtype en de voorkeurslokalisatie van LSTs in de dikke darm te bestuderen. De resultaten toonden een algemene LST prevalentie van 0,83% (95% CI: 0,62 − 1,07) in alle colonoscopieën en 3,6% van alle gedetecteerde colorectale neoplasmata (95% CI: 2,5 – 4,9). In het algemeen komen LSTs evenveel voor in het proximale als in het distale colon, maar granulaire LSTs kunnen distaal meer voorkomen dan proximaal. De prevalentie en de mate van submucosale invasie bij diagnose varieert tussen de LST Kudo subtypes. Homogene granulaire LSTs komen het meest voor (35,4%, 95% CI: 27,2 – 43,6) met het laagste percentage submucosale invasie (0,5%, 95% CI: 0,1 – 1,0). Niet-granulaire LSTs met pseudodepressie hebben de laagste prevalentie (5,5%, 95% CI: 3,2 – 7,8) terwijl ze het hoogste risico op submucosale invasie hebben (31,6%, 95% CI: 19,8 – 43,4). De studie toonde aan dat de classificatie van LSTs op basis van macroscopisch voorkomen nuttig is bij het beoordelen van het risico op submucosale invasie en moet worden gebruikt om de meest geschikte behandelingsstrategie te bepalen.

Het hoge risico op submucosale invasie in sommige LST subtypes suggereert dat inadequate resectie zou kunnen bijdragen tot het risico op het ontwikkelen van colorectale kanker. Of patiënten met LSTs een specifiek risicoprofiel hebben voor het ontwikkelen van metachrone (later gedetecteerde) colorectale neoplasmata (latere darmpoliepen) was nog niet onderzocht. In hoofdstuk 4 zijn gegevens uit een prospectieve poliep database gebruikt om LSTs te bestuderen en te vergelijken met grote polypoide neoplasmata (gesteelde en sessiele poliepen). Follow-up gegevens van alle patiënten met grotere colorectale neoplasmata (van minimaal 10mm in diameter) werden aanvullend verzameld. De resultaten toonden aan dat LST patiënten significant meer synchrone colorectale neoplasmata hadden dan patiënten met grote polypoide colorectale neoplasmata (gemiddeld 3,34 versus 2,34, P<0,001). Patiënten met LSTs ontwikkelden ook significant meer metachrone neoplasmata binnen de zes jaar follow-up (71,6% versus 54,2%, P=0,0498) en meer colorectale neoplasmata met hooggradige dysplasie of submucosale invasie (36,4% versus 15,8%, P<0,001). Na correctie voor leeftijd en geslacht hadden LST patiënten, in vergelijking met patiënten met een grote polypoïde poliep, een hazard ratio van 2,9 voor het ontwikkelen van nieuwe colorectale neoplasmata met hooggradige dysplasie of submucosale invasie. Deze resultaten rechtvaardigen de noodzaak van strikte opvolging van LST patiënten, aangezien het een risico populatie lijkt te zijn.

Het belang van deze bevinding voor de huidige klinische praktijk wordt belicht in hoofdstuk 5. Gegevens over de prevalentie van LNPCPs in de eerste jaren van het Nederlandse darmkanker screeningsprogramma lieten zien dat LNPCPs voorkwamen bij 8% van alle deelnemers die een colonoscopie ondergingen. Gedetailleerde gegevens over de bevindingen tijdens de eerste jaren van screening, inclusief follow-up, werden verzameld in drie ziekenhuizen in de regio Zuid-Limburg in Nederland. De lokale prevalentie van LNPCPs was vergelijkbaar met de nationale prevalentie. In totaal werd 30% van de aangetroffen LNPCPs niet direct verwijderd. Dit percentage nam toe met de grootte van het LNPCP. Het totale technische succespercentage van endoscopische verwijdering was 87% (95% CI: 82 – 91). Het klinische succespercentage bleek ook 87% (95% CI: 80 – 92) te zijn en werd gedefinieerd als geen residu na één jaar. Beide percentages namen af met toenemende LNPCP grootte. Het totale recidiefrisico na een technisch succesvolle resectie was 22% (95% CI: 15 – 32) voor gefragmenteerde en 8% (95% CI: 2 – 22) voor in een geheel verwijderde LNPCPs. De meeste recidieven konden succesvol worden behandeld door herhaalde endoscopische resectie,

maar twee recidieven bevatten kanker en vereisten aanvullende chirurgie. Deze gegevens tonen aan dat in de huidige endoscopiepraktijk de endoscopische behandeling van LNPCPs nog steeds moeilijk is, met ruimte voor verdere verbetering.

Om te onderzoeken of eenvoudige interventies het LNPCP recidiefrisico kunnen verminderen, werd in hoofdstuk 6 een systematische meta-analyse uitgevoerd. Het doel van deze meta-analyse was om de effectiviteit van thermische ablatie van de resectiegrenzen na endoscopische mucosale resectie te bestuderen. In totaal 10 studies onderzochten het recidiefrisico bij het toepassen van *snare tip soft coagulation* (STSC) of *argon plasma coagulatie* (APC) na resectie van grote darmpoliepen. Het poolen van het risicoverschil van één van beide interventies in vergelijking met geen extra behandeling, toonde een risicoreductie van 18% (95% CI: -26 – -11) na 6 tot 12 maanden. Aangezien STSC geen gebruik van extra materiaal tijdens de colonoscopie vereist, is deze techniek waarschijnlijk het meest kosteneffectief.

In het volgende deel van het proefschrift waren de PCCRCs het belangrijkste onderwerp. In hoofdstuk 7 werd een overzicht gegeven van de voorwaarden voor surveillance (opvolging) met coloscopie. Een overzicht van de geldende surveillance richtlijnen in 2015 werd gepresenteerd met een update van de nieuwe richtlijnen gepubliceerd tot en met eind 2021. De intervallen van surveillance verschillen tussen de internationale richtlijnen. Alle richtlijnen benadrukken echter het belang van een goede darmvoorbereiding, een volledige coloscopie, duidelijke communicatie over de intervallen en een hoge detectiegraad van adenomen door endoscopisten. Bovendien zijn de intervallen allemaal gebaseerd op risicostratificatie aan de hand van klinische en pathologische kenmerken van de verwijderde neoplasmata. In de afgelopen 10 jaar is uit nieuw bewijsmateriaal over het risico van colorectale kanker na poliepverwijdering gebleken dat het risico lager is dan verwacht na een initiële hoogkwalitatieve coloscopie. Het risico op het ontstaan van colorectale kanker na verwijdering van sessiele geserreerde (gezaagde) laesies (*sessile serrated lesions*) wordt nu hoger ingeschat en heeft geleid tot intensivering van de coloscopische surveillance bij deze patiënten.

Voor de bepaling van de intervallen tussen coloscopie met poliepverwijdering en vervolgscopieën wordt histopathologie gebruikt. Het gebruik van optische diagnostiek zou echter de kosten van histopathologische analyse kunnen verlagen. In hoofdstuk 8 werd de nauwkeurigheid van optische diagnose bij coloscopie uitgevoerd voor het bevolkingsonderzoek darmkanker, bestudeerd. Gegevens van de eerste 3028 kleine poliepen, gedetecteerd in het darmkanker screeningsprogramma in de regio Zuid-Limburg, werden gebruikt om de diagnose van de endoscopist te vergelijken met de diagnose van de patholoog. Kijkend naar poliepen uit het gehele colon, werd een diagnostische nauwkeurigheid van slechts 76% (95% CI: 74 – 77) gevonden, met een negatief voorspellende waarde voor adenomateuze histologie van 69% (95% CI: 66 – 73). Wanneer alleen poliepen uit het rectosigmoïd gebied werden meegenomen, was de diagnostische nauwkeurigheid nog lager met 71% (95% CI: 69 – 74), maar de negatief voorspellende waarde voor adenomen was hoger met 84% (95% CI: 80 – 87). Toepassing van de *resect and discard* strategie (d.w.z. het verwijderen van de poliepen zonder ze op te sturen voor histopathologie) voor laesies tot 5 mm groot, zou hebben geleid tot meer dan 90% identieke intervallen tussen coloscopie ten opzichte van die na pathologische beoordeling van alle verwijderde neoplasmata. In ongeveer 6% was het interval zelfs korter dan op basis van histopathologische uitkomsten. Op basis van deze resultaten is de nauwkeurigheid van de optische diagnose momenteel niet goed genoeg om de histopathologische diagnostiek achterwege te laten.

Of training gericht op coloscopie kwaliteit en de detectie van vlakke colonpoliepen inderdaad de PCCRC incidentie kan verminderen, werd bestudeerd in hoofdstuk 9. Deze vergelijking werd uitgevoerd op basis van geschatte PCCRC incidentiecijfers afgeleid uit meerdere bronnen. De

PCCRCs werden verkregen en geïdentificeerd uit een database met alle CRC diagnoses tussen 2004 en 2014 in het Maastricht UMC+. Met behulp van een prospectieve database bestaande uit alle coloscopieën van 2008 tot 2012 met follow-up gegevens, konden het aantal follow-up persoonsjaren binnen deze periode worden berekend. De training vond eind 2007 plaats. Het aantal coloscopieën tussen 2004 en 2008 werd in het ziekenhuis geregistreerd. De gemiddelde follow-up tijd per patiënt voor deze periode werd geschat op basis van de gegevens uit 2008. Het jaar van de laatste coloscopie vóór de PCCRC diagnose werd gebruikt voor de vergelijking. Wegens het ontbreken van volledige prospectieve gegevens betreffende PCCRCs vóór de training zijn de resultaten gedeeltelijk gebaseerd op een schatting. Vóór de opleiding trad bij 2,0 per 1000 coloscopieën achteraf een PCCRC op, terwijl dit na de training 0,8 per 1000 coloscopieën was. Omgerekend naar aantal persoonsjaren follow-up, trad een PCCRC op bij 0,79 patiënten per 1000 jaren follow-up vóór en bij 0,34 patiënten per 1000 jaren follow-up na de training. Ondanks de bias die kan zijn opgetreden op basis van de door ons gemaakte schattingen, werd een positief effect van training naar opsporing en resectie van vlakke colonneoplasmata op de PCCRC incidentie waargenomen.

Aanvullend bewijs voor het voorkomen van PCCRC uit vlakke neoplasmata werd geleverd in hoofdstuk 10. Op basis van een prospectieve database met alle gedetecteerde CRCs en alle PCCRCs, werden alle PCCRCs en een even grote willekeurige selectie van gedetecteerde CRCs, opgestuurd voor moleculaire analyse. Deze analyse bestond uit *whole genome sequencing* voor het vergelijken van DNA veranderingen, detectie van mutaties in de 48 vaakst aangetaste genen bij CRC, bepaling van het *CpG eiland methylatie fenotype* en aanwezigheid van microsatellietinstabiliteit. Verlies van chromosoom 18q kwam significant minder vaak voor in PCCRCs vergeleken met gedetecteerde CRCs (46,7 versus 72,7%, valse opsporingsratio 0,11). Microsatellietinstabiliteit (21,7 versus 9,6%, *P*=0,029) en een hoog *CpG-eiland-methylatie fenotype* (50,0 versus 32,7%, *P*=0,014) kwamen significant vaker voor in PCCRCs. Er werd een niet-gesuperviseerd clustermodel toegepast dat drie hoofdtakken van PCCRCs liet zien, die overeenkwamen met de eerder beschreven hypermethyleringsroute, de microsatelliet instabiliteitsroute en de chromosomale instabiliteitsroute. Eerdere studies toonden aan dat *sessile serrated lesions* geassocieerd zijn met de hypermethyleringsroute en in mindere mate met de microsatelliet instabiliteitsroute. Bij vlakke poliepen komen BRAF-genmutaties vaker voor. PCCRCs waren oververtegenwoordigd in de hypermethylerings- en microsatellietroute (respectievelijk 62% en 68% PCCRCs), terwijl ze ondervertegenwoordigd waren in de chromosomale instabiliteitroute (47% PCCRCs). Deze studie toonde geen specifieke, afzonderlijke route voor PCCRCs aan. De ontstaansroutes geassocieerd met *sessile serrated lesions* en vlakke laesies kwamen echter vaker voor in PCCRCs. De hypothese dat zowel *sessile serrated lesions* als vlakke poliepen voorgangers van PCCRCs kunnen zijn, geldt nog steeds en wordt door onze gegevens ondersteund.

Chronische ontsteking van het darmslijmvlies is een risicofactor voor het ontwikkelen van neoplasmata. Daarom moeten patiënten met inflammatoire darmziekten (IBD) coloscopisch worden gecontroleerd. In hoofdstuk 11 werd het voorkomen van PCCRCs bij patiënten met IBD bestudeerd. Voor deze studie werd het populatie gebaseerde IBD Zuid-Limburg cohort gebruikt. Dit cohort bevat alle volwassen IBD patiënten gediagnosticeerd tussen 1991 en 2011. Alle diagnoses van CRC die we tegenkwamen werden gekruist met de nationale kankerregistratie. Coloscopieën uitgevoerd in de 5 jaar voorafgaand aan de diagnose van CRC leidden tot de identificatie van een PCCRC. Bij de 2801 geïncludeerde IBD patiënten traden 20 CRCs op, met een incidentie van 0,77/1000 patiëntjaren. Negen CRCs werden geïdentificeerd als PCCRC (45%, 0,39/1000 patiëntjaren met een verhoogd risico). Van hen werden vijf PCCRCs geclassificeerd als zeer waarschijnlijk voorkomend uit gemiste neoplasmata. Een andere belangrijke bevinding was dat zes van alle CRCs werden ontdekt vóór het begin van de coloscopische opvolging (start binnen 8 jaar na IBD diagnose aanbevolen). De conclusie van de studie is dat IBD patiënten een hoger risico hebben op de ontwikkeling van

PCCRCs, maar ook op de ontwikkeling van CRC vóór het begin van de endoscopische opvolging. Nieuwe endoscopietechnieken die de detectie van dysplasie bij IBD patiënten verbeteren, moeten worden ontwikkeld. Het toepassen van een eerdere eerste coloscopie nadat de eerste ziekteremissie is verkregen, zou mogelijk kunnen helpen om CRC ontwikkeling te voorkomen voorafgaand aan de eerste opvolgingscoloscopie, gepland op basis van aanbevelingen in de huidige richtlijnen.

In het laatste hoofdstuk, hoofdstuk 12, werd de relevantie van de endoscopische subclassificatie van LSTs in de klinische praktijk besproken. Er werd gepleit voor de integratie van morfologische beoordeling met kennis over kenmerken van submucosale invasie, voorafgaand aan endoscopische resectie. Aanbevelingen voor behandeling en opvolging van LSTs werden besproken. Het verband tussen LSTs en de ontwikkeling van PCCRCs werd ook besproken. De hypothese uit hoofdstuk 1 werd getoetst aan de bevindingen uit de hoofdstukken 2 tot en met 11, met als conclusie dat LST-patiënten mogelijk een hoger risico lopen op de ontwikkeling van PCCRC door meer metachrone neoplasmata en een hogere kans op onvolledige resectie. Wij concluderen dat aandacht voor kwalitatief goede detectie, classificatie en resectie van colorectale neoplasmata waarschijnlijk nog steeds de meest effectieve maatregel in PCCRC preventie is.

Impact paragraph

Colorectal cancer (CRC) is one of the most prevalent cancers in the Western world with high impact on quality of life.[1] Because of the natural course of CRC development, through precursor lesions, population-based CRCs screening programs can be (cost)effective.[2] CRC screening comprises early detection of CRC precursor lesions. Colonoscopy has a major role in the detection of these precursors lesions (mostly adenomas) and enables immediate treatment by endoscopic resection, with proven reduction of CRC occurrence and mortality.[3] However, colorectal lesions vary in their characteristics and difficulties in being detected and resected. Furthermore, some patients still develop CRC after colonoscopy, meaning that prevention failed.[4] These CRCs are called post-colonoscopy colorectal cancers. This thesis has focused on a) specific large colorectal neoplasms because of their high malignant potential and difficulties in being detected and adequately resected and, b) the etiology of post-colonoscopy cancers in combination with possible associations with specific precursor lesions.

Large non-pedunculated colorectal polyps

Large non-pedunculated colorectal polyps (LNPCPs) comprise of colorectal neoplasms without a stalk, 20 mm or larger in size.[5] Flat neoplasms within this group are called laterally spreading tumors and can be subclassified into four types with each a different surface morphology using the Kudo LST classification.[6] The aims of this thesis were to validate the Kudo LST classification, to study the risk of submucosal invasion (malignancy rate) in each LST subtype and to study whether patients with LSTs have a higher risk of synchronous and metachronous neoplasms. Additionally, we studied the quality of LNPCP resections in current practice and explored ways to optimize these procedures.

Our results show that although agreement among experts in the application of the Kudo LST is not perfect, substantial agreement was achieved. Additionally, the same classification can be taught to endoscopy trainees by using e-learnings. After a relatively short intensified online training program, the trainees reached substantial agreement in scoring when applying the Kudo LST classification. These data indicate that online training is a valuable tool for learning to apply endoscopic classifications and that the Kudo LST classification can be used by all endoscopists after a short training. Studies like these may stimulate e-learnings to become default in endoscopy training of residents in Gastroenterology and Hepatology.

The next step was to study whether the Kudo LST subtypes indeed have a different risk of containing cancer, information that is essential for safe endoscopic treatment. Multiple studies, both case-series and population-based cohorts, already have reported on LST prevalence and histopathological outcomes. A large meta-analysis was performed merging all these data of various studies. This meta-analysis showed that the risk of containing cancer was indeed very different among the Kudo LST subtypes. This knowledge has contributed to new recommendations for treatment of large non-pedunculated polyps, as described in current European, American and Japanese guidelines.[7-9]

Whether patients with large flat colorectal polyps are at higher risk of developing new lesions during follow-up, was studied using a prospective database of alle consecutive colonoscopies performed between 2004 and 2008. All patients with at least a large (10 mm or larger) polyp were included and follow-up data were obtained for at least 5 years after the first colonoscopy. Comparison of patients with non-polypoid (flat) lesions to patients with polypoid lesions showed more synchronous lesions at index colonoscopy and more metachronous lesions during surveillance

colonoscopies in patients with non-polypoid (flat) lesions. These data indicate that in patients with flat colorectal neoplasms, new neoplasms develop at higher speed. Furthermore, these new neoplasms are more often flat, with more risk of being missed by colonoscopy. Current guidelines on surveillance after polyp removal do not stratify for interval of follow-up colonoscopy based on polyp morphology.[10-12] With these results in mind, future guidelines may take into account the number of flat neoplasms found at index colonoscopy. Large prospective studies on the safety of expanding surveillance intervals should take "flat morphology" into account in their analysis.

Post-colonoscopy colorectal cancers

Post-colonoscopy colorectal cancers were studied in detail to find clues for clinical improvements in order to reduce the incidence of PCCRCs. One goal was to study critical factors to further optimize colonoscopy surveillance and whether training may help to reduce PCCRC incidence. A small scale study we performed, focusing on PCCRC incidence before and after implementation of center-wide training on the detection and resection of flat colorectal polyps, pointed to a reduction in PCCRC incidence after training. Although there are several biases and also technical advancements during the years when this study was performed, these results stress the importance of training in endoscopy. It could guide other centers in providing more systematical endoscopy education to endoscopists (in training).

The biology of PCCRCs was also studied. Therefore, molecular profiling was performed, to test whether specific mutations are more prevalent among PCCRCs compared to commonly occurring colorectal cancers. Our comprehensive molecular analysis included not only 48 genes often mutated in CRC but also whole genome sequencing of PCCRCs and commonly occurring CRCs. These samples were all retrieved from a population-based cohort with specific attention for tumor characterization. No PCCRC specific molecular pattern was found, indicating that PCCRCs develop from the same precursor lesions as commonly occurring CRCs. Some molecular features, however, were more common in PCCRCs than in other CRCs. These features are often found in specific colorectal polyps, namely sessile serrated lesions and flat lesions. Both were already hypothesized to be frequent precursors of PCCRCs. Based on our in-depth analysis, it is now clear that PCCRCs are not biologically different from commonly occurring CRCs. It is also clear that more subtle, and therefore more difficult to detect lesions may contribute to PCCRC development. Our data strengthen that further research should focus on improvements in detection and resection of colorectal lesions to prevent them from developing into PCCRC.

Starting from 2014, population-based screening for colorectal cancer was implemented in the Netherlands. This screening is organized by bi-annual fecal occult blood testing as first step. In case of a positive (unfavorable) test outcome, patients are referred for colonoscopy.[13] Despite this stepwise approach, negative (unnecessary) colonoscopies are common (in 30-35%) after an initial positive fecal occult test. In the future, the fecal occult blood tests may be supplemented by molecular stool tests in which mutations will be tested pointing to colorectal neoplasia. In these cases, it is important that there is a high sensitivity for mutations frequently found in PCCRCs. This is also important because the fecal occult blood test is thought to be less sensitive for neoplasms located in the right sided colon.[14] Such strategies may yield a higher detection rate during colonoscopy for subtle lesions with malignant potential. The data on PCCRC etiology indicate that research should focus on techniques to help endoscopists in detecting the more subtle lesions. Reducing or even eliminating miss rates will probably also reduce PCCRC rates. Introducing new endoscopic resection techniques thereby limiting recurrence risks will also contribute to reduce PCCRC rates.

Our data show for the first time that patients with large flat colorectal neoplasms have a higher

risk of developing new neoplasms during follow-up. All data on PCCRCs presented in this thesis show that PCCRCs occur through known CRC pathways and that the key for PCCRC reduction will lie in education of endoscopist and optimizing detection and resection of precursor lesions. This knowledge is useful for programs to reduce the occurrence of PCCRCs and in developing practical endoscopy guidelines. In conclusion, data obtained by the research presented in this thesis will help to develop diagnostic and therapeutic strategies to end the “hide and seek" game of complex colorectal neoplasms.

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Curriculum Vitae

Roel (Maria Michael) Bogie was born on April 25th 1990 in Geleen, the Netherlands. After graduating high school, at the Graaf Huyn College in Geleen, he started studying Medicine at the Faculty of Health, Medicine and Life Sciences of Maastricht University.

During the last year of Medicine, he applied for a scientific internship at the Gastroenterology and Hepatology department of the Maastricht University Medical Center. The foundation of the thesis was made during this internship and let to a PhD-candidate position. After graduating for the Medical Doctor's degree in 2014, he commenced on a full-time PhD project under supervision of dr. S. Sanduleanu-Dascalescu, dr. B. Winkens and prof. dr. A.A.M. Masclee. The PhD-fellowship was affiliated to the department of Internal Medicine, division of Gastroenterology and Hepatology of the Maastricht University Medical Center+, to GROW, School for Oncology and Reproduction, and to CAPRHI, School of Care and Public Health Research Institute, of Maastricht University.

During three and a half years full-time work on the PhD-project, several side projects came on his path. Local coordination of the industry initiated G-EYE study and helping with the initiation of the STAR-LNPCP study are some examples of these side projects. Together with his peers, a local database for follow-up studies in the national bowel cancer screening patients was developed. He performed the statistical analyses of multiple peer-reviewed meta-analyses.

During his PhD-fellowship, he participated in several PhD courses and had the opportunity to present several studies at the United European Gastroenterology Week. He was awarded with the Oral Free Paper Prize for the presentation of genetic profiles in post-colonoscopy colorectal cancers.

In 2018, he started with his residency Gastroenterology and Hepatology at the Maastricht University Medical Center. As of 2022, he temporarily started working in the Catharina Hospital in Eindhoven as part of this residency.

Abbreviations used

95% CI	95% confidence interval
ADR	Adenoma detection rate
AGA	American gastroenterology association
AI	Artificial intelligence
APC	Argon plasma coagulation
ASA	American Society of Anesthesiologists
ASGE	American Society for Gastrointestinal Endoscopy
BBPS	Boston bowel preparation scale
BCSP	Bowel cancer screening program
BSG	British society of gastroenterology
CD	Crohn's disease
CGH	Comparative genomic hybridization
CIMP	CpG island methylator phenotype
CIR	Cecal intubation rate
CRC	Colorectal cancer
CRN	Colorectal neoplasm
DCRC	Detected colorectal carcinoma
ECCO	European Crohn´s and Colitis Organisation
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
ESGE	European Society of Gastrointestinal Endoscopy
FAP	Familial adenomatous coli syndrome
FDR	False discovery rate
FIT	Fecal immunochemical test
FOBT	Fecal occult blood test
FU	Follow-up
HD-WLE	High-definition white light colonoscopy
HGD	High-grade dysplasia
I^2	Inconsistency index
IBD	Inflammatory bowel disease
IEE	Image-enhancementendoscopy
IQR	Interquartile range
IBD	Inflammatory bowel disease
IOA	Interobserver agreement
LNPCP	Large non-pedunculated colorectal polyp
LP-CRN	Large polypoid colorectal neoplasm
LST	Laterally spreading tumor
LST-G-H	Homogenous granular LST
LST-G-NM	Nodular-mixed granular LST
LST-NG-FE	Flat elevated non-granular LST
LST-NG-PD	Pseudo-depressed non-granular LST
MUMC	Maastricht university medical center
MEC	Medical ethical commity
MI	Multiple imputation
MSI	Microsatelite instability
NBI	Narrow band imaging
NET	Neuro-endocrine tumor

NOS	Newcastle-Ottawa scale
NP-CRN	Non-polypoid colorectal neoplasm
NPV	Negative predictive value
NTUH	National Taiwan university hospital
OR	Odds ratio
PCCRC	Post-colonoscopy colorectal cancer
PIVI	Preservation and Incorporation of Valuable endoscopic Innovations
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PYAR	Patient years at risk
PYFU	Patient years of follow-up
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2
QUIPS	Quality in Prognostic Studies
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative risk
PSC	Primary sclerosing cholangitis
SD	Standard deviation
SMI	Submucosal invasion
SMIC	Submucosal invasive cancer
SPS	Serrated polyposis syndrome
SSA/P	Sessile serrated adenoma/polyp
SSL	Sessile serrated lesion
STSC	Snare tip soft coagulation
TEM	Transanal endoscopic microsurgery
TSA	Traditional serrated adenoma
UC	Ulcerative colitis
WGS	Whole genome sequencing
WEO	World endoscopy organisation
WHO	World health organisation
Yrs	Years