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Advancing patient-centered care in the management of large rectal adenomas and T1 colorectal cancer

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Citation
Dekkers, N. (2026, May 26). *Advancing patient-centered care in the management of large rectal adenomas and T1 colorectal cancer*. Retrieved from https://hdl.handle.net/1887/4304910

Version:	Publisher's Version
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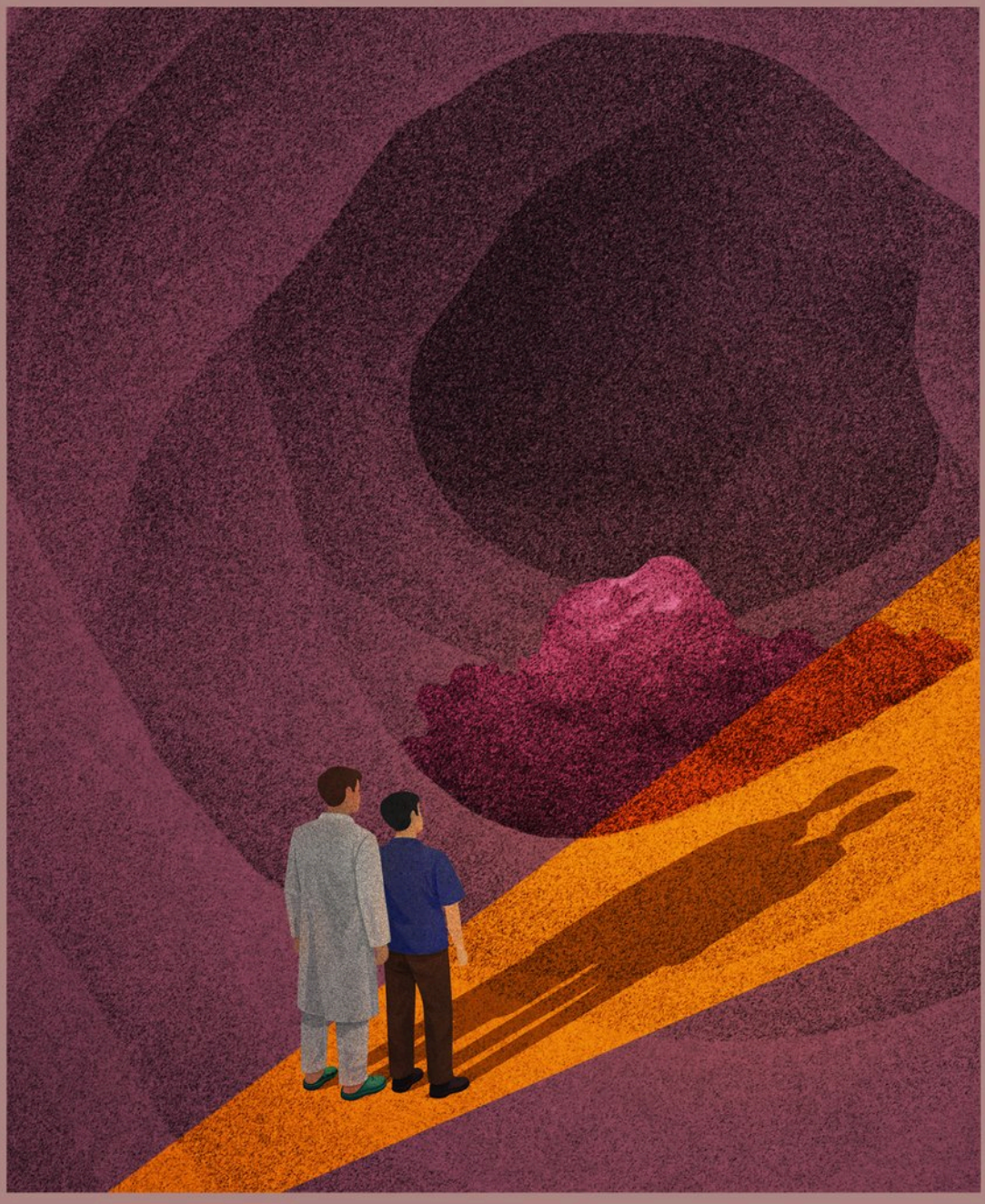
Note: To cite this publication please use the final published version (if applicable).

ADVANCING PATIENT-CENTERED CARE IN THE MANAGEMENT OF LARGE RECTAL ADENOMAS AND T1 COLORECTAL CANCER

NIK DEKKERS



Advancing patient-centered care in the management of large rectal adenomas and T1 colorectal cancer

Nik Dekkers

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Printing of this thesis was financially supported by Nederlandse vereniging voor Gastroenterologie, ChipSoft, MICRO-TECH, Meditec

ISBN: 978-94-6537-357-7

Printing: Ridderprint, ridderprint.nl
Layout and design: Dennis Hendriks, persoonlijkproefschrift.nl
Cover design: Phil van Dulm

Advancing patient-centered care in the management of large rectal adenomas and T1 colorectal cancer

Proefschrift

ter verkrijging van

de graad van doctor aan de Universiteit Leiden,

op gezag van rector magnificus prof. dr. S. de Rijcke,

volgens besluit van het college voor promoties

te verdedigen op dinsdag 26 mei 2026

klokke 16.00 uur

door

Nik Dekkers

geboren te Alkmaar

in 1993

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Prof. dr. J.C.H. Hardwick

Co-promotors
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Journey before destination

— Brandon Sanderson*, The Way of Kings*, 2010

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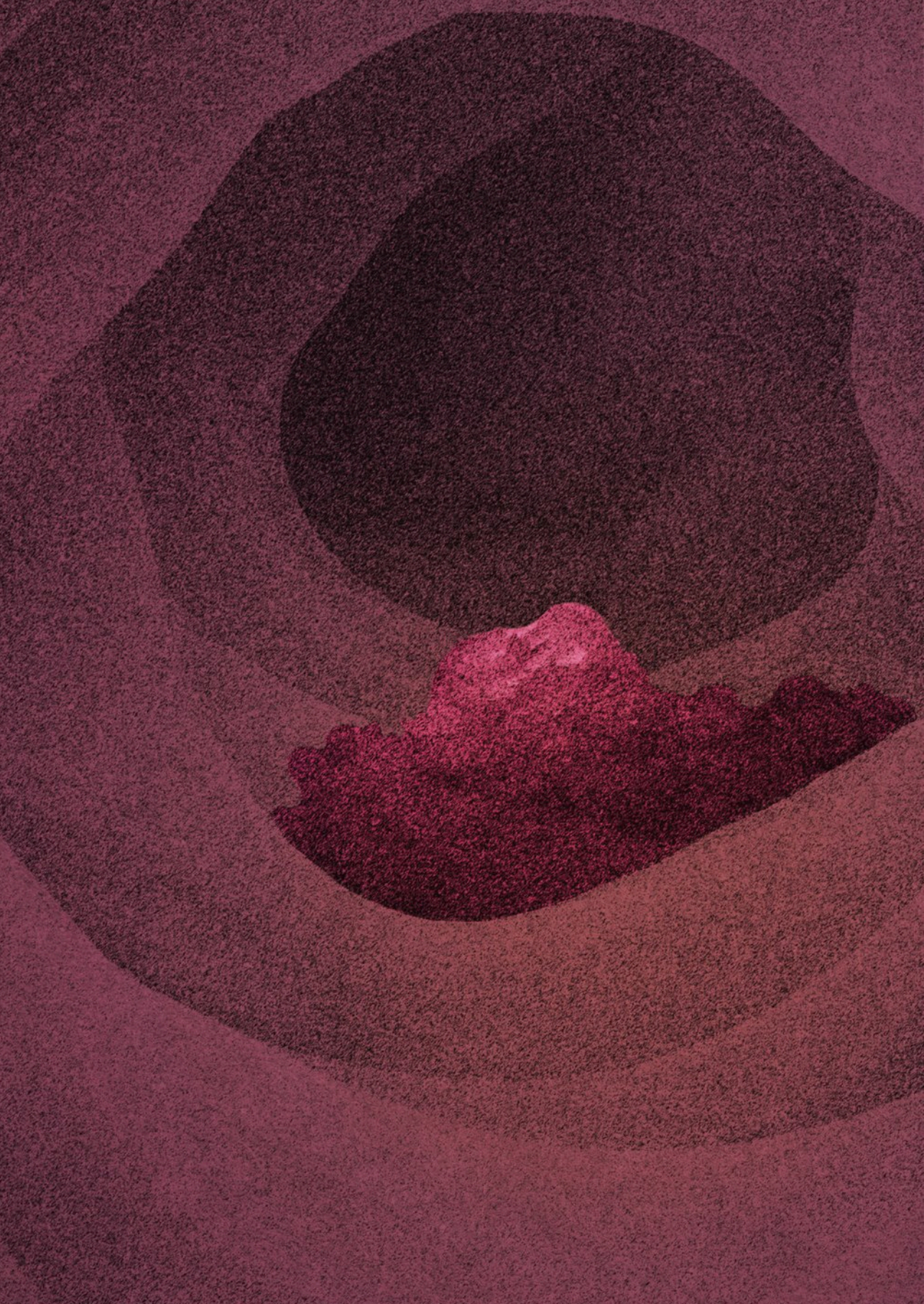

CHAPTER 1

General introduction and thesis outline

General introduction

Colorectal cancer

Colorectal cancer (CRC) is one of the most frequently diagnosed cancers, and the second leading cause of cancer-related mortality worldwide.[1] In 2023, approximately 12,000 patients in the Netherlands were diagnosed with CRC, about 3,000 of whom had rectal cancer.[2] CRC develops from benign precursor lesions, following either the adenomatous or, less commonly, the serrated pathway.[3] While all precursor lesions carry malignant potential, only a subset progress to invasive cancer by invading through the muscularis mucosae, potentially extending into the bowel wall, and eventually even metastasizing to other organs. The progression from normal epithelium to CRC typically takes between 10 and 15 years, providing a valuable window for screening and early treatment.[4]

In recent years, many countries have implemented nationwide screening programs to reduce CRC-related morbidity and mortality by detecting and treating disease at an earlier (pre)malignant stage. The Netherlands introduced such a program in 2014, utilizing fecal immunochemical testing to measure hemoglobin levels in stool samples.[5] If these exceed a set threshold, a colonoscopy is performed. Since the start of the program, colorectal lesions have indeed been diagnosed at earlier benign or premalignant stages in all forms and sizes. When CRC is already present in these asymptomatic patients enrolled in screening, it is found at earlier stages compared to patients referred for colonoscopy due to symptoms.[6] Especially the larger premalignant and early-stage cancers present clinical challenges in terms of diagnosis and management.

Optical diagnosis

The variety of colorectal lesions that can be detected during endoscopy can be categorized in different ways. For example based on their anatomical location (colon or rectum), and based on their size, with lesions larger than 2 cm often defined as large. Another way to categorize colorectal lesions is by shape, for example referring to whether a polyp has a stalk (pedunculated) or not (non-pedunculated). In addition, an assessment can be made of the suspected histology of a lesion, distinguishing between benign, superficial submucosal invasion (so-called superficially invasive T1CRC), and deeper invasion (deep invasive T1CRC or more advanced stages of CRC). This assessment is called optical diagnosis. All these classifications are important, as they help determine the most appropriate way of removing a lesion and thereby preventing progression to (more advanced) CRC.

Optical diagnosis has the greatest treatment implications for larger non-pedunculated lesions, as it guides whether a lesion can be removed in multiple pieces (piecemeal) or requires more elaborate local resection techniques to remove it in one piece (en bloc). When cancer is present, piecemeal resection should be avoided as it impairs accurate histological assessment of resection margins and assessment of the oncological risk, potentially leading to unnecessary major surgery with significant morbidity. This is particularly relevant for rectal cancers, where surgery carries the highest risk of requiring a permanent stoma and sexual dysfunction. This topic will be discussed in more detail later, beginning with an overview of the optical diagnosis of these larger non-pedunculated lesions.

For the optical diagnosis of large non-pedunculated rectal lesions, various modalities are available. The first is conventional white-light endoscopy, which employs standard broad-spectrum light to visualize the mucosal surface, during which the endoscopist should be alert to features that may suggest cancer. This approach enables a structured evaluation of the lesion's size, morphology, and surface characteristics. Size can be estimated using instruments with known dimensions, such as biopsy forceps. Although size alone is a poor predictor, it is independently associated with malignant disease.[7] Morphology is commonly described using the Paris classification. According to this system, non-pedunculated lesions are further categorized as: flat (with less than 2.5 millimeters elevation from the mucosa), sessile (showing more pronounced elevation), containing a depressed or even excavated component. Depressed areas warrant specific attention, as they may indicate the presence of (early invasive) cancer and excavation is suggestive for deeper invasion(8).[8] Non-pedunculated lesions that predominantly spread laterally along the bowel wall are also referred to as lateral spreading tumors (LSTs). In LSTs the surface texture, also called granularity, should also be evaluated. LSTs can be categorized into granular types, which includes homogeneous and nodular mixed subtypes, and non-granular types, which include flat elevated and pseudodepressed subtypes. The risk for submucosal invasion is lowest for granular homogeneous LSTs (0.5%) and highest for granular nodular mixed (10.5%) and non-granular pseudodepressed types (31.6%).[9] Optical diagnosis with white-light endoscopy alone has a limited sensitivity ranging between 21 and 46%,[10] and should therefore not be used as the sole method.

Advanced imaging techniques can be used to allow for a more detailed evaluation of the lesion's surface. These techniques include dye-based chromoendoscopy and virtual modalities that utilize different wavelengths of light or optical filters, such as the commonly used Narrow-Band Imaging. Using these methods, both the vascular pattern and the pit pattern, referring respectively to the network of blood vessels and the microscopic openings of the mucosal glands, can be assessed. The regularity of these patterns can be interpreted using one of the available classification systems, such as the Hiroshima classification.[11-16] Regardless of the specific classification used, regular

patterns are suggestive of benign histology, whereas irregular patterns may indicate superficially invasive T1CRC. The disruption or absence of surface patterns is generally associated with deeper invasive carcinomas. Overall, narrow-band imaging has been reported to achieve a sensitivity of approximately 85%.[10] However, this estimate is derived from studies involving various lesion types and is likely overestimated in the context or large non-pedunculated lesions. While combining white-light endoscopy with advanced imaging can improve diagnostic performance,[17] the accuracy in this subgroup remains limited. To better address these limitations, the OPTICAL risk model was developed in the Netherlands. This model integrates observations from both modalities into a structured assessment, yielding a reported sensitivity of 78.7%.[18] Despite these advances, a considerable degree of uncertainty in the optical diagnosis remains, underscoring the need for further improvements.

Adding other imaging modalities, such as magnetic resonance imaging or endoscopic ultrasound, appears to be of little added value, as these techniques tend to overstage lesions and thereby increase the risk of overtreatment.[19] Improving education and training may contribute to better diagnostic performance of optical diagnosis, particularly given the substantial variability observed between community level endoscopists and experts.[20] However, even studies conducted in expert centers with dedicated endoscopists have demonstrated a significant risk of optically missed cancers, ranging from 11-22%.[18, 21, 22] This observation suggests that education alone will not be sufficient to achieve adequate diagnostic accuracy. Moreover, this suggests some T1CRCs may lack clear visual signs and therefore remain undetected with current techniques, so-called covert cancers.[23] Besides educational initiatives, new technologies are therefore needed to improve optical diagnosis.

In light of the uncertainty surrounding optical diagnosis, caution is warranted when treating large non-pedunculated lesions, particularly in the rectum, where incorrect piecemeal removal of a cancerous lesion has the most serious consequences for the patient. Accordingly, the current Dutch guideline discourages piecemeal resection for all large rectal lesions, except for homogenous granular lesions where it may be considered, as these carry a negligible risk of malignancy.[24] In such benign lesions, piecemeal removal by piecemeal endoscopic mucosal resection may offer advantages such as the lower complication rates and generally shorter procedure times compared to en bloc resections.[25, 26] However, piecemeal resections are associated with higher recurrence rates ranging between 19 and 29%,[27-29] necessitating more stringent surveillance, which can also justify an en bloc resection of these homogeneous granular type lesions, a strategy that may even be the most cost-effective.[30-32] All other large non-pedunculated rectal lesions should in any case be treated with an en bloc resection, effectively managing them as if they were T1CRC.

T1 colorectal cancer

Early-stage CRC, or T1CRC, is defined according to commonly accepted Western criteria as cancer with histologically confirmed invasion through the muscularis mucosae into, but not beyond, the submucosa. Due to their limited invasion, most T1CRCs can still be removed completely by local, organ-preserving, resections. However, T1CRCs still have the potential to metastasize, primarily to locoregional lymph nodes. If lymph node metastases (LNM) are present, a local resection alone is considered non-curative. Instead, current guidelines recommend a more extensive surgical resection, that includes removal of the affected bowel segment along with the draining lymph nodes, followed by adjuvant systemic therapy in case of colon cancer with histologically confirmed LNM.[33] In rectal cancer, LNM similarly requires more extensive treatment, which may involve (chemo)radiotherapy, radical surgery, or both.

Ideally, preoperative staging would allow for accurate detection of LNM. However, current staging techniques, including optical endoscopic imaging, endoscopic ultrasound, computed tomography and magnetic resonance imaging for rectal lesions, are insufficiently accurate, even when used in combination. The most commonly used risk-model is histology based and can only be applied after resection. This has led to a two-step approach in the management of T1CRC. The local resection, aimed at achieving a complete en bloc resection, is the first step and can be considered a "diagnostic resection". Pathological analysis of the locally resected specimen is then used to determine the need for additional oncological resection, based on the risk of residual disease and LNM. This oncological risk must be carefully weighed against the potential risks associated with additional treatment, or completion surgery, on an individual basis. There is an increased oncological risk if resection margins are positive or uncertain, suggesting potential incomplete resection, or if so-called high-risk features for LNM are present. These features include poor tumor differentiation, high-grade tumor budding, lymphovascular invasion, and deep submucosal invasion.[34] Although not yet included in formal guidelines, a recent study suggests that deep submucosal invasion alone may not be a strong predictor, potentially not justifying additional oncological surgery on its own.[35]

By adopting this two-step approach, extensive surgery and its associated morbidity and mortality can be avoided in patients with a radically resected low-risk T1CRC (i.e., absence of all high-risk features), which is the case in approximately 65-85% of patients with superficially invasive carcinomas and 30-50% of those with deep invasion.[36, 37] Multiple studies have shown the long-term safety of this strategy;[38-40] however, the short-term effects of local endoscopic resections, such as their impact on surgical morbidity, have not been thoroughly investigated. For prior local surgical resections, available literature suggests that they might increase complexity of completion surgery and thereby increase procedure times and complication rates.[41]

Since complete risk stratification requires a complete en bloc resection specimen and incomplete resection always necessitates additional treatment, it is crucial to select an advanced local resection technique that enables complete en bloc removal of lesions suspected to have submucosal invasion.

En bloc resection techniques for large non-pedunculated colorectal lesions

Several flexible endoscopic and local surgical resection techniques are available, allowing for the complete en bloc removal of large non-pedunculated lesions, even with submucosal invasion. The selection of the preferred technique depends on factors such as the lesion's location, size, and available local expertise. Additionally, the expected invasion depth plays a crucial role in determining the technique, as the dissection plane varies between methods.

Endoscopic techniques

Endoscopic submucosal dissection (ESD) is a technique that involves injecting fluid into the submucosa to lift the lesion, making a circumferential incision around the target area, and performing dissection within the submucosal layer just above and parallel to the muscularis propria using an electrosurgical knife introduced via a flexible endoscope.[42, 43] ESD enables radical en bloc resections, even for larger lesions, but its effectiveness is limited for deeply invasive T1CRCs due to the constraints of its dissection plane.[44-46] ESD can technically be performed throughout the entire colon, but in the West, it is primarily used in the rectum due to its relatively higher perforation rate of approximately 4%.[47] The thicker submucosa of the rectum and the typically limited clinical consequences of perforations (i.e., unintended full-thickness defects), which are often manageable with conservative treatment alone, make it a safer site than the proximal colon.[48] In Western countries, ESD is mainly performed in expert centers by dedicated endoscopists, as the lack of adequate training, and perhaps financial compensation, has limited its widespread adoption.[48, 49]

Endoscopic full-thickness resection (eFTR) is a technique that uses a full-thickness resection device that allows for transmural resection of the colonic wall, extending as deep as the serosa.[50] Unlike ESD, eFTR has a clear size limitation of 15-20 mm,[51] making it unsuitable for large lesions. Additionally, maneuvering in the rectum is challenging, making other techniques preferable in this location. Consequently, eFTR is primarily used for smaller non-lifting lesions or those in technically challenging locations, such as near the appendix.[52] Furthermore, eFTR can be used in a hybrid approach in combination with a piecemeal resection for larger lesions, enabling complete removal of the most suspicious part of a larger lesion.[53]

Endoscopic intermuscular dissection (EID), is a relatively new endoscopic resection technique that involves dissection at the deeper intermuscular plane, present in the rectum, as performed more frequently in local surgical resections in the rectum, while still using a flexible endoscope. The first three-year follow-up study shows promising results that EID may offer a viable alternative to radical surgery for some patients with deep invasive carcinomas.[22]

Local surgical techniques

The most commonly used local surgical resection technique in the Netherlands is transanal minimally invasive surgery (TAMIS). For this procedure, a transanal single-incision laparoscopic surgery (SILS) port, CO_2 insufflation to create a pneumorectum, and standard laparoscopic instruments are used to lift and dissect the lesion. TAMIS is exclusively intended for treatment of rectal lesions and can be used to remove those located up to 15-20 cm from the anal verge, allowing for complete en bloc resection regardless of the lesion's size.[54, 55] Ideally, the dissection plane is partial thickness, following the intermuscular plane between the circular and longitudinal layers of the muscularis propria, using a diathermic hook. This approach preserves the integrity of the mesorectal fascia and does not compromise surgical resection planes should completion surgery be required. For lesions near the dentate line, the distal margin can be incised without a port using standard transanal retractors. Transanal endoscopic microsurgery (TEM) is a comparable videoscopic transanal excision technique that is used to a lesser extent due to its reliance on specialized, costly instruments including a TEM scope, and angled instruments.[56] In contrast to TEM, TAMIS allows for more distal dissections due to its shorter port, offers a greater working angle, and may be less traumatic to the anal sphincter.[57, 58]

Preferred techniques for large non-pedunculated rectal lesions

For large non-pedunculated rectal lesions in which submucosal invasion cannot be excluded with certainty based on optical diagnosis, or when (superficially invasive) T1CRC is suspected, the preferred technique is either ESD or TAMIS. Both are considered standard of care and have demonstrated satisfactory long-term outcomes.[59, 60] Due to the lack of large-scale head-to-head comparative trials, these techniques are currently used interchangeably in the Netherlands and the choice between ESD and TAMIS is based more on the clinical team's preference and available expertise than on scientific evidence.

Patient involvement in T1 colorectal cancer care

Medical decision-making is often complex, especially in cancer care, as it involves uncertain evidence, the weighing of potential benefits against possible harms and consideration of the likelihood of different outcomes,[61] while also aligning choices

with individual patient values and preferences. Because of this complexity and the heterogeneity in both clinical factors and personal preferences, it is essential for healthcare providers to actively involve patients in the decision-making process.

Shared decision-making is a collaborative process in healthcare that involves both clinicians and patients working together to make informed treatment decisions. It entails healthcare providers sharing relevant medical information, including potential benefits, risks, and uncertainties, while patients contribute their values, preferences and lifestyle factors.[62] A prerequisite is thus that patients receive clear and comprehensible information, which can be challenging in practice for various reasons. Medical information is often complex, involving multiple considerations and nuances that can be difficult for non-experts to grasp. In addition, the information provided by physicians may not always align with patients' preferences,[63, 64] and in cancer care medical details can be emotionally charged, especially when discussing aspects such as survival or the risk of recurrence.[65]

Although the patient journey of T1CRC involves several complex decisions, such as the choice to perform additional treatment or not after local resection, information provision and decision-making has never been evaluated. Evaluating these processes from patients' perspective can help to identify unmet informational needs and guide more patient-centered care in T1CRC.

Thesis outline

The main goal of the various chapters presented in this thesis is to improve the management of patients with non-pedunculated rectal adenomas and T1CRC through a patient-centered approach. To achieve this, various challenges in optical diagnosis, local treatment, completion surgery, follow-up and decision-making were studied and educational resources were developed for healthcare providers and patients. Firstly, in **Chapter 2** we developed an educational module for endoscopists, covering key aspects of a polypectomy, based on the national guideline. The remainder of this thesis is subdivided into three parts.

Part I: Optical diagnosis & Local treatment

In part I, the focus lies on optical diagnosis and local treatment. Regarding optical diagnosis, **Chapter 3** introduces a potential novel technique to enhance optical imaging of T1CRC: tumor-targeted fluorescence-guided endoscopy. This preparatory study investigates the most suitable imaging target for this approach in vitro. **Chapter 4** describes the study protocol of the randomised controlled TRIASSIC trial, which

compares transanal minimally invasive surgery to endoscopic submucosal dissection for the resection of larger rectal adenomas and T1 rectal cancers. **Chapter 5** presents the results of an ancillary study of this trial, comparing the physical recovery of both procedures using wearable accelerometers to assess physical activity.

Part II: Treatment strategies after local treatment

In part II, the focus lies on treatment strategies after local resection. In **Chapter 6** we evaluated the results of completion surgery after ESD, comparing the morbidity and mortality of primary oncological resections with those of completion surgery following ESD in patients with suspected T1 CRC. In **Chapter 7**, a meta-analysis was conducted to evaluate the risk and time patter of cancerous recurrence after local resection of T1 rectal cancer, comparing endoscopic and local surgical resection techniques.

Part III: Patient empowerment

In part III, the focus lies on patient empowerment. **Chapter 8** presents an evaluation of T1CRC patients' perspectives on information provision, including their information needs, and experience on the decision-making process. In **Chapter 9** educational videos on T1CRC for patients are presented. The videos highlight key aspects of the T1CRC patient journey, including the complex decision to either proceed with additional treatment after local resection of refrain from further treatment.

Finally, **Chapter 10** provides a summary of the findings in this thesis, and elaborates on future perspectives.

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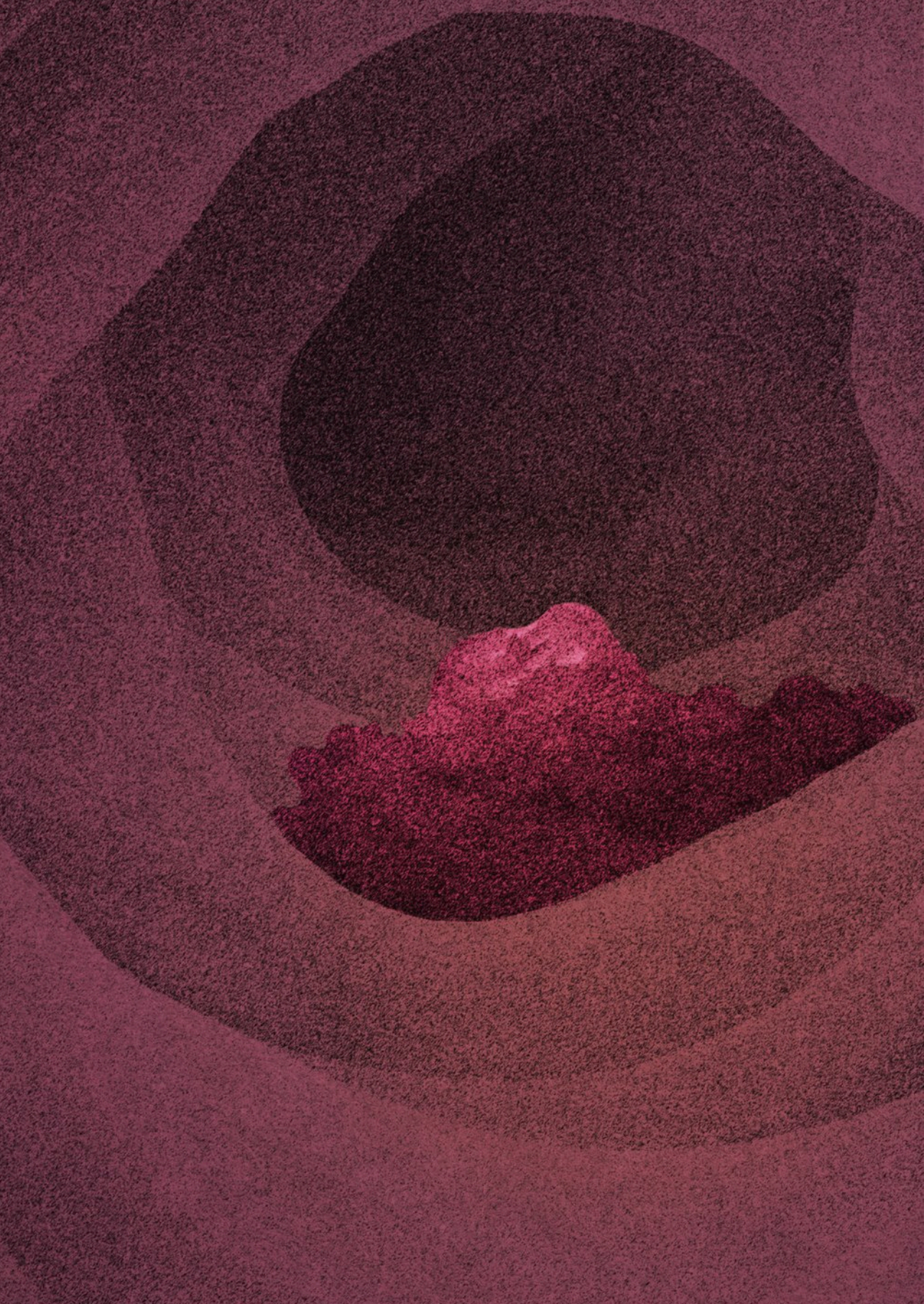


CHAPTER 2

E-learning poliepectomie - Bevolkingsonderzoek Nederland

Nik Dekkers, Alexandra M.J. Langers, Jurjen J. Boonstra

Access via: http://leeromgeving-bevolingsonderzoekdarmkanker.nl

About this course

To be able to perform colonoscopies as part of the national screening program in the Netherlands (i.e., Bevolkingsonderzoek Nederland), endoscopists must meet specific requirements and complete a certification process. This process includes recording quality indicators of 100 subsequently performed colonoscopies, practical observations and assessments, as well as theoretical training and exams. In support of this, several e-learning modules are available. These e-learnings are updated in case of significant changes in the literature or guidelines. Our e-learning is one of four mandatory courses for endoscopists. It covers the most important aspects of polypectomy, including polyp assessment, resection techniques for various types of polyps, managing recurrence, and addressing complications. The content is fully based on the in 2021 revised national guideline for polypectomy.

The course is in Dutch and consists of eight chapters, featuring text, original images, endoscopic images, and concise videos with step-by-step instructions. In addition to questions during the course with immediate feedback, the module includes a final test. This test comprises of 10 multiple-choice questions with a pass mark of 80%. For this test 30 multiple-choice questions were provided by the authors. The estimated time required to complete the course is 90 minutes.

This course was developed in 2022 by Alexandra Langers, Jurjen Boonstra and Nik Dekkers in collaboration with Bevolkingsonderzoek Nederland. The content of the e-learning was reviewed by gastroenterologists associated with Bevolkingsonderzoek Nederland (Marc de Bièvre, Annekatrien Depla, Evelien Dekker) as well as gastroenterologists not affiliated with Bevolkingsonderzoek Nederland (Frank Wolters, Claudia Verveer)

Chapters

1. Beoordeling poliep
2. Randvoorwaarden poliepectomie
3. Behandeling Kleine niet-gesteelde poliepen (<10 mm)
4. Behandeling niet-gesteelde poliepen zonder verdenking invasie
5. Niet-gesteelde poliepen met verdenking op submucosale invasie
6. Behandeling gesteelde poliepen
7. Behandeling lokaal recidief
8. Complicaties
9. Toets

Disclosure of conflict
The authors involved in the development of this course have no potential conflicts of interest to report

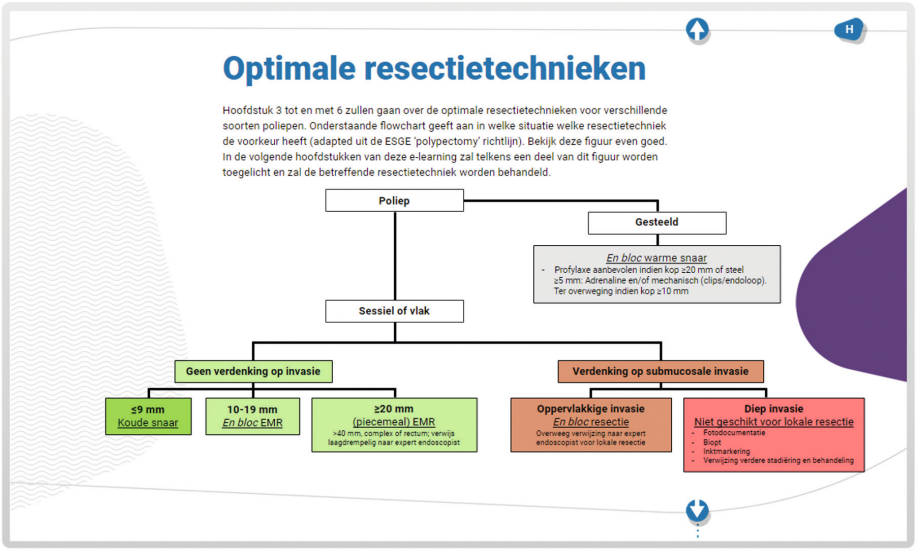
Acknowledgements
The authors extend our gratitude to Hao Dang for his valuable contributions in editing the videos included in this course.

Release date
June 2023

Funding
The development of this course was made possible through a grant awarded by Stichting Kwaliteitsgelden Medisch Specialisten (SKMS), enabling its availability to all gastroenterologists in the Netherlands.

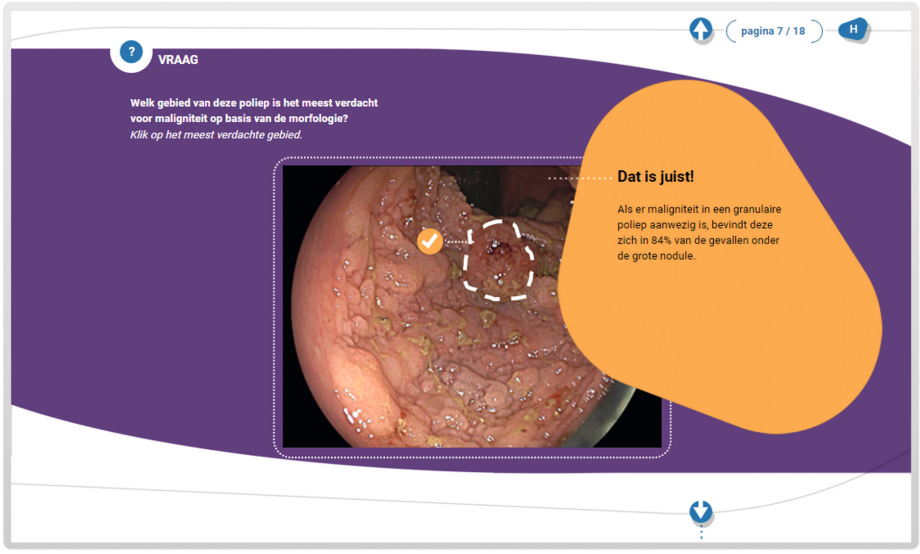
Accreditation
This course has been accredited by the Dutch Society of Gastroenterology (NVMDL). Participants who complete the course are eligible to receive 1.5 accreditation points.

Stills from the course

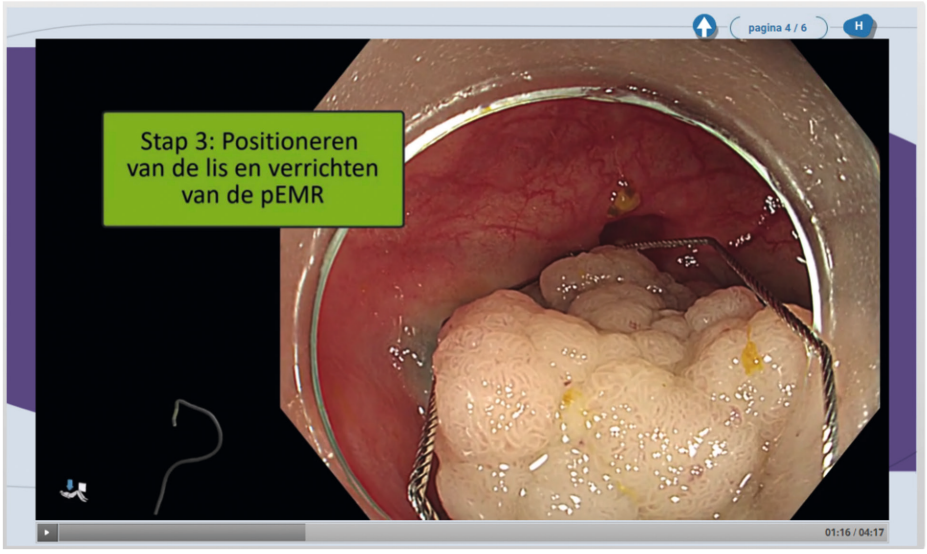


Overview figure including preferred management of various sorts of polyps based on gross morphology, size, and suspicion of (submucosal) invasion

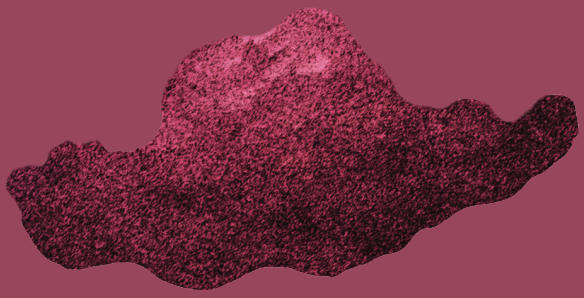
Discussing the association of various morphological features with the presence of submucosal invasion.



Example of a question that appears throughout the course. In this question, participants were asked to click on the area of the polyp that is most suspect for submucosal invasion based on morphological features. After clicking, feedback is directly provided in the orange colored shape.

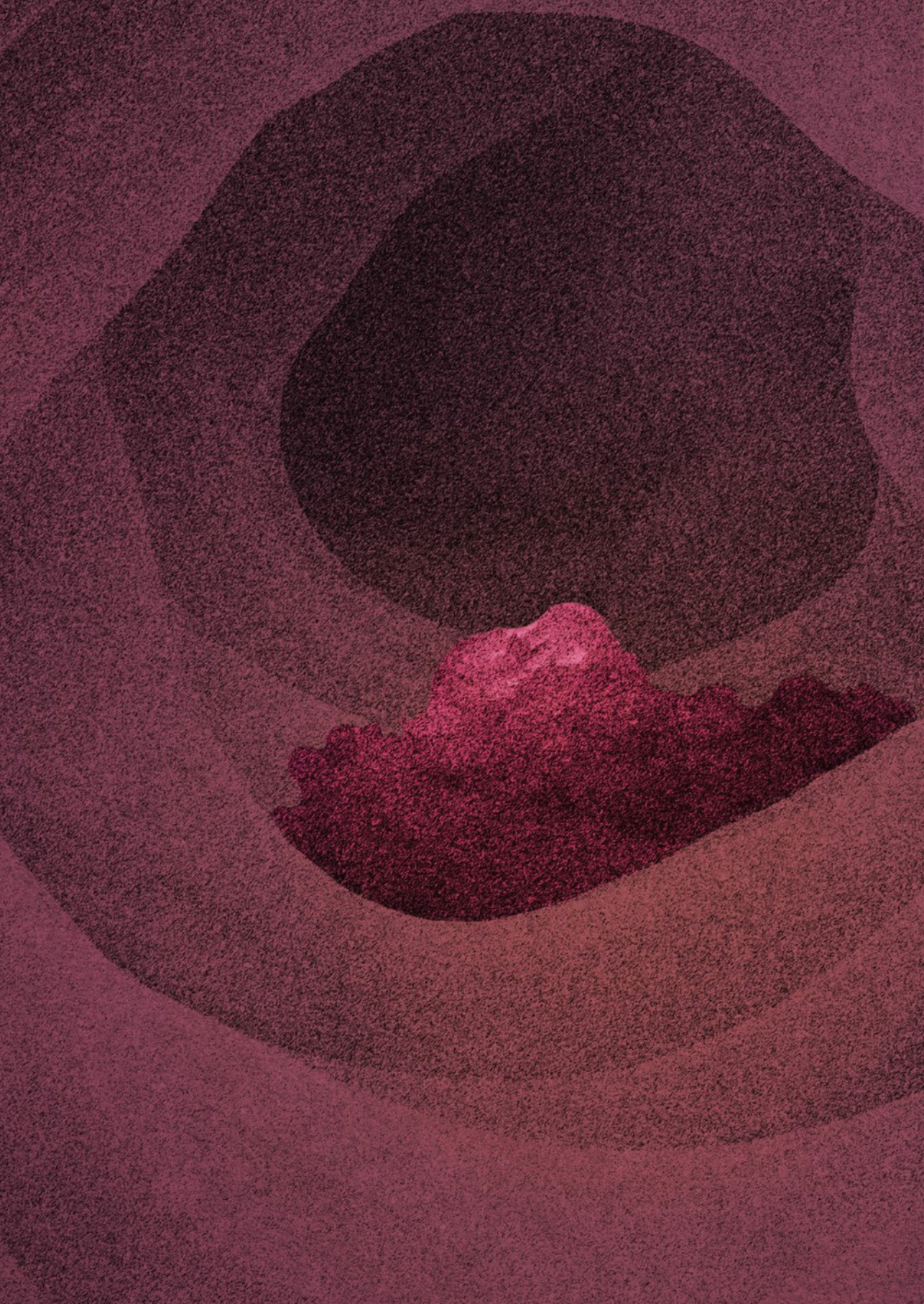


Still from the video showing the execution of a piecemeal endoscopic mucosal resection (pEMR) with step-by-step instructions.



PART I

Optical diagnosis & Local treatment



CHAPTER 3

Colorectal polyps: Targets for fluorescence-guided endoscopy to detect high-grade dysplasia and T1 colorectal cancer

Nik Dekkers*, Elham Zonoobi*, Hao Dang, Mats I. Warmerdam, Stijn Crobach, Alexandra M. J. Langers, Jolein van der Kraan, Denise E. Hilling, Koen C. M. J. Peeters, Fabian A. Holman, Alexander L. Vahrmeijer, Cornelis F. M. Sier, James C. H. Hardwick, Jurjen J. Boonstra
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United European Gastroenterology Journal 2023

Abstract

Background: Differentiating high-grade dysplasia (HGD) and T1 colorectal cancer (T1CRC) from low-grade dysplasia (LGD) in colorectal polyps can be challenging. Incorrect recognition of HGD or T1CRC foci can lead to a need for additional treatment after local resection, which might not have been necessary if it was recognized correctly. Tumor-targeted fluorescence-guided endoscopy might help to improve recognition.

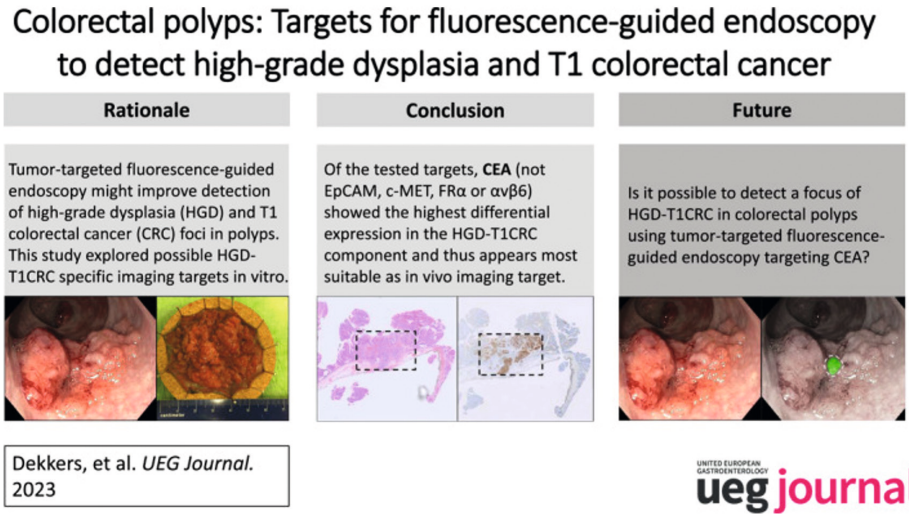
Objective: Selecting the most suitable HGD and T1CRC-specific imaging target from a panel of well-established biomarkers: carcinoembryonic antigen (CEA), c-mesenchymal-epithelial transition factor (c-MET), epithelial cell adhesion molecule (EpCAM), folate receptor alpha (FRα), and integrin alpha-v beta-6 (αvβ6).

Methods: En bloc resection specimens of colorectal polyps harboring HGD or T1CRC were selected. Immunohistochemistry on paraffin sections was used to determine the biomarker expression in normal epithelium, LGD, HGD, and T1CRC (scores of 0–12). The differential expression in HGD-T1CRC components compared to surrounding LGD and normal components was assessed, just as the sensitivity and specificity of each marker.

Results: 60 specimens were included (21 HGD, 39 T1CRC). Positive expression (score >1) of HGD-T1CRC components was found in 73.3%, 78.3%, and 100% of cases for CEA, c-MET, and EpCAM, respectively, and in <40% for FRα and αvβ6. Negative expression (score 0–1) of the LGD component occurred more frequently for CEA (66.1%) than c-MET (31.6%) and EpCAM (0%). The differential expression in the HGD-T1CRC component compared to the surrounding LGD component was found for CEA in 66.7%, for c-MET in 43.1%, for EpCAM in 17.2%, for FRα in 22.4%, and for αvβ6 in 15.5% of the cases. Moreover, CEA showed the highest combined sensitivity (65.0%) and specificity (75.0%) for the detection of an HGD-T1CRC component in colorectal polyps.

Conclusion: Of the tested targets, CEA appears the most suitable to specifically detect HGD and T1 cancer foci in colorectal polyps. An in vivo study using tumor-targeted fluorescence-guided endoscopy should confirm these findings.

Graphical abstract



Key summary

Summarize the established knowledge on this subject

- To determine the preferred local resection technique for colorectal polyps, it is crucial to estimate the risk of high-grade dysplasia (HGD) or early stage colorectal cancer (T1CRC).
- The accuracy of optical diagnosis is not optimal, especially in larger polyps.
- Tumor-targeted fluorescence-guided endoscopy might help to improve the recognition of a focus of HGD or T1CRC in colorectal polyps.
- The most suitable imaging target for specifically detecting a focus of HGD or T1CRC in colorectal polyps is currently unknown.

What are the significant and/or new findings of this study?

- It is feasible to detect HGD and T1CRC foci in colorectal polyps in vitro by staining for tumor-specific targets.
- Of the tested targets, carcinoembryonic antigen (CEA) most frequently showed differential expression in the HGD and T1CRC components compared to surrounding polyp tissue with low-grade dysplasia.
- An in vivo study is needed to confirm CEA as suitable target to specifically detect HGD or T1CRC foci in colorectal polyps by fluorescence-guided endoscopy.

Introduction

Since the introduction of population-based screening programs, a growing number of large colorectal polyps have been detected.[1] These large polyps can often be removed by local resections.[2,3] To determine the preferred local resection technique, it is crucial to estimate the risk of high-grade dysplasia (HGD) or early stage T1 colorectal cancer (T1CRC). Preferably, polyps suspected to harbor a focus of HGD or T1CRC are removed en bloc to facilitate complete histological assessment, after which the need for additional treatment is determined.[4] In contrast, incorrect recognition of a focus of HGD or T1CRC may lead to inappropriate treatment (i.e. piecemeal resection) and the need for oncological surgery, thereby unnecessarily exposing patients to the risk of surgical morbidity and mortality. Although the reported percentages vary greatly, it is clear that there is room for improvement in the optical diagnosis of T1CRCs. Among experts, the rate of unrecognized T1CRCs is still 13%–22%,[5,6] whereas among endoscopists at the community level, the rate of misclassified T1CRCs can increase up to 81%.[7] Unfortunately, the additional value of imaging modalities such as endoscopic ultrasound or magnetic resonance imaging seems limited. Tumor-targeted fluorescence optical imaging (FOI) might help to improve the recognition of a focus of HGD or T1CRC in colorectal polyps during endoscopic assessment, possibly aiding the process of decision-making for the preferred local resection technique.

Near-infrared FOI is a promising technique that combines the administration of a targeted fluorescent contrast agent with the use of Near-infrared light. It allows for real-time optical imaging by selectively highlighting cells that express certain molecular targets.[8] In the surgical field, tumor-targeted FOI has been applied for different aspects of CRC,[8] including intraoperative detection and demarcation,[9] and intraoperative imaging of metastases.[10] In the endoscopic field, FOI has been applied to aid polyp detection[11] and to evaluate neoadjuvant treatment response in locally advanced rectal cancer.[12] Fluorescence-guided endoscopy enables intraluminal visualization of polyps based on specific biomolecular features by using fluorescently labeled molecular probes that bind to specific molecular targets for which a tracer is administered prior to imaging.[13] These fluorescent-targeting tracers can be administered intravenously, orally, or as spray dyes. By adding a layer of information to the conventional endoscopic assessment of polyps, this strategy can potentially improve the accuracy of optical diagnosis and thereby improve real-time clinical decision-making for the preferred local resection techniques of larger polyps. To the best of our knowledge, no study has focused on the ability of tumor-targeted FOI to detect foci of HGD or T1CRC in colorectal polyps. Before embarking on a clinical study, examining which biomarker is most suitable as a FOI tumor target is necessary.

The target selection for imaging purposes depends on different characteristics, including the differential expression in the target tissue compared to normal tissue.[14] Enhanced

protein expression in the target tissue and low or even absent expression in normal tissue are prerequisites. T1CRCs often reside in polyps that consist of several stages of dysplasia. A suitable target should be able to distinguish a focus of HGD or T1CRC from the surrounding LGD component of a polyp. Promising targets in CRC detection, with available fluorescence targeting probes, include carcinoembryonic antigen-related adhesion molecule 5 (CEACAM5, from here on to be referred to as CEA), c-mesenchymal-epithelial transition factor (c-MET), epithelial cell adhesion molecule (EpCAM), folate receptor alpha (FRα) and integrin αvβ6. Carcinoembryonic antigen is a membrane-bound glycoprotein with known expression in the majority of CRCs and little expression in normal mucosa.[15] c-MET is the membrane-bound hepatocyte growth factor receptor involved in proliferation and invasion. C-MET overexpression has been demonstrated in the sequence of colorectal adenoma-carcinoma sequence as an early event.[16,17] EpCAM is a transmembrane glycoprotein involved in cell-cell interactions and cell-stroma adhesions that is generally overexpressed in epithelial malignancies such as colorectal cancer.[18] FRα is a membrane-bound folic acid-binding and transporting protein, with higher expression in CRCs than in normal mucosa or adenoma.[19] αvβ6 is an integrin subtype that is expressed only in epithelial cells, with significantly increased expression in epithelial tumors.[20] Although several studies have reported the enhanced expression of these markers in CRC, neither have studied the differential expression between a component of HGD or T1CRC and the surrounding component of LGD in colorectal polyps.

We aimed to select the most HGD-T1CRC specific fluorescence-guided endoscopy target for an in vivo pilot study.

Materials and methods

Population

Formalin-fixed paraffin-embedded tissue blocks from patients who underwent en bloc endoscopic submucosal dissection (ESD) (between February 2013 and November 2019) in the Leiden University Medical Center for lateral spreading polyps harboring a focus of T1CRCs or HGD located in the rectum or sigmoid were retrieved from the pathology department. To increase the sample size, we also included a random sample of 10 FFPE blocks from patients who underwent en bloc endoscopic mucosal resection (EMR) for non-granular T1CRCs in the rectum or sigmoid (between February 2013 and November 2019). Prior to inclusion, slides were reexamined by a pathologist specialized in gastro-intestinal pathology (S.C.) and re-staged accordingly. Patients with an insufficient amount of tissue were excluded. Ethical approval was obtained from the Medical Ethical Committee of the Leiden University Medical Center, and the requirement for obtaining informed consent was waived (reference: B20.016, 11-06-2020). The study protocol

conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution›s human research committee.

Clinical variables

Demographic patient characteristics (sex, age) and clinical data (polyp morphology, procedure-related parameters, histology parameters) were collected from electronic medical records. En bloc resection was defined as macroscopic removal of the lesion in a single piece. High-grade dysplasia was defined as architectural abnormality and severe cytologic atypia without invasion through the muscularis mucosae. T1 colorectal cancer was defined as tumors with tumor invasion through the muscularis mucosae and into, but not beyond, the submucosa.

Antibodies and immunohistochemistry

Based on hematoxylin-eosin (HE)-stained slides, a pathologist specialized in gastrointestinal pathology (S.C.) selected a representative formalin-fixed paraffin-embedded tissue block for each patient, containing as many stages of dysplasia (normal, LGD, HGD, and T1CRC) as possible. Selected tissue blocks were sectioned (4 µm) and mounted on adhesive slides. Sections were deparaffinized with xylene for 15 min, rehydrated in decreasing ethanol concentrations and then rinsed in demineralized water. Subsequently, endogenous peroxidase was blocked using 0.3% hydrogen peroxide (Merck Millipore, Netherlands) in demineralized water for 20 min. Specifications regarding antigen retrieval and antibodies are provided in supplementary Table 1. Afterward, the slides were rinsed in phosphate-buffered saline (PBS, pH7.4), and stained with the appropriate secondary antibody (EnVision anti-mouse or anti-rabbit horseradish peroxidase) (Dako) for 30 min, followed by another washing step. Immunoreactions were visualized with diaminobenzidine substrate buffer (Dako) after 10 min, counterstained using Mayer's hematoxylin solution (Sigma-Aldrich, USA), and dehydrated at 37°C before being mounted with Pertex (Leica Microsystems, Germany). Negative (PBS) and conjugate control (only secondary antibody) were included to rule out nonspecific staining.

To ensure that the different stages of dysplasia were the same throughout all sectioned slides of one block, the first and last slides from each block were stained with HE and examined by a pathologist specialized in gastrointestinal pathology (S.C.).

Scoring method

All stained slides were digitally scanned (InstelliSite Ultra-Fast Scanner, Philips). HE-slides of each case were utilized to determine one clear region of each present stage of dysplasia (S.C. and N.D.). These regions were then marked on the digitally scanned HE slide. Subsequently, the same regions were marked in the remaining slides of that case that were stained with study markers (N.D.). The marking process for one case is shown in Supplementary Figure 1. The target expression in all stages of dysplasia was

quantified using the immunoreactive score (IRS). The IRS was calculated by multiplying the positive cell proportions (PS) and staining intensity score as previously described.[21] PS represented the percentage of positively stained cells and ranged between 0 and 4 (0 = no positive cells; 1 = <10% positive cells; 2 = 10–50%, 3 = 51–80%, 4 = >80%). Intensity score represented staining intensity and ranged between 0 and 3 (0 = no color reaction; 1 = mild reaction; 2 = moderate reaction; 3 = intense reaction). The total IRS was a range between 0 and 12 and was further subdivided into subgroups (0–1 = negative, 2–3 = mild, 4–8 = moderate, 9–12 = strongly positive). Three observers independently evaluated the marker expression (N.D., J.B., and J.H.). All cases with disagreement regarding the IRS subgroup were discussed until a consensus was reached. The average of the individual scores within the same subgroup resulted in the definitive IRS.

Statistical analyses

Statistical analyses were performed using IBM SPSS version 24.0 (Chicago, USA) and GraphPad Prism 6 (La Jolla, CA, USA). The differential expression of each biomarker was studied by subtracting the expression scores of the LGD or normal colon component from the expression scores of the adjacent HGD-T1CRC component from the same slide. Sensitivities and specificities of HGD-T1CRC detection were calculated from the mean staining scores by receiver operating characteristic (ROC) curves. In the two markers that showed the greatest differential expression, the influence of morphological polyp characteristics on the occurrence of negative expression in the HGD-T1CRC component was explored using the chi-squared test. Mean IRS for different stages of dysplasia were compared using the Wilcoxon rank test. A p-value ≤0.05 was considered statistically significant.

Results

In total, tissue blocks of 39 T1CRC patients and 21 patients with HGD were included (Figure 1). A component of normal colon tissue was present in all cases, but due to the small size of this component, it was deemed insufficient for scoring in 3/60 cases. In two other cases, no distinct LGD component could be identified. For these 5 cases, components of the other stages of dysplasia were included in the results.

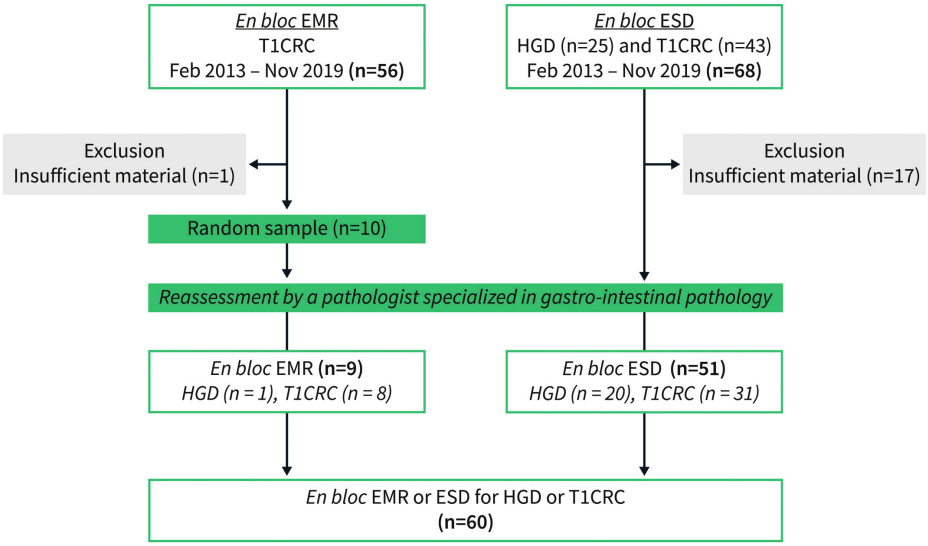
Patient and polyp characteristics are shown in Table 1. The overall median polyp size was 40 mm (range 8–100). The median polyp size was 15 mm (range 8–20) in the en bloc EMR subgroup and 40 mm (range 14–100) in the ESD subgroup. Macroscopic polyp morphology was flat elevated in 24 (40%) and sessile in 36 (60%). Polyps were mainly located in the rectum or rectosigmoid.

Table 1. Clinical-pathological characteristics of the study cohort.

	Number of cases n=60 (%)
Patient characteristics	
Sex, male	44 (73.3)
Age, years, median (range)	65 (35-84)
Treatment	
ESD	51 (85.0)
En bloc EMR	9 (15.0)
Polyp characteristics	
Location	
Sigmoid	11 (18.3)
Rectosigmoid	10 (16.7)
Rectum	39 (65.0)
Diameter polyp, mm, median (range)	40 (8-100)
Gross morphology	
Flat elevated	24 (40.0)
Sessile	36 (60.0)
Paris classification	
Is	29 (48.3)
0-IIa	5 (8.3)
0-IIa + Is	18 (30.0)
0-IIa + c	8 (13.3)
Granularity	
Granular	20 (33.3)
Non-granular	40 (66.7)
Maximal degree of dysplasia	
HGD	21 (35.0)
T1CRC	39 (65.0)
Adenoma component (n=42)	
Tubular	12 (20.0)
Villous	4 (6.7)
Tubulovillous	25 (41.7)
Serrated	1 (1.7)

Values are n (%) unless otherwise defined.
CRC colorectal cancer, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *HGD* high-grade dysplasia, *LST* lateral spreading tumor.

Figure 1. Flowchart of patient selection. *CRC* colorectal cancer, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *HGD* high-grade dysplasia.



Expression of markers in different stages of dysplasia

Positive cell proportions and intensity scores varied widely for all markers throughout the cohort in normal, LGD, HGD and T1CRC tissues. Figure 2 shows all individual staining scores (IRS) in normal, LGD and HGD or T1CRC for each target; these scores are independently arranged in ascending order per target to illustrate the distributions across the cohort. The mean IRS of each target in the different stages of dysplasia is shown in Table 2.

If the HGD or T1CRC component showed positive expression (i.e. staining score >1), CEA and FRα were predominantly expressed on the apical membrane of the HGD-T1CRC component, while c-MET, EpCAM, and αvβ6 showed a more membranous, circumferential staining pattern in the HGD-T1CRC components. Figure 3 shows the positive expression pattern of the different targets; for each target, the most representative case of positive expression in the HGD-T1CRC component was selected. An example of the staining pattern in the entire polyp of all targets in the same case of T1CRC is shown in Figure 4.

Figure 2. Staining scores of CEA, c-MET, EpCAM, FRα, and αvβ6 in normal colorectal tissue, low-grade dysplasia (LGD) and high-grade dysplasia (HGD) or T1 colorectal cancer (T1CRC) were expressed as immunoreactive scores. The total immunoreactive scores were independently arranged in ascending order to demonstrate the distributions across our cohort. *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *CRC* colorectal cancer, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha, *IRS* immunoreactive score.

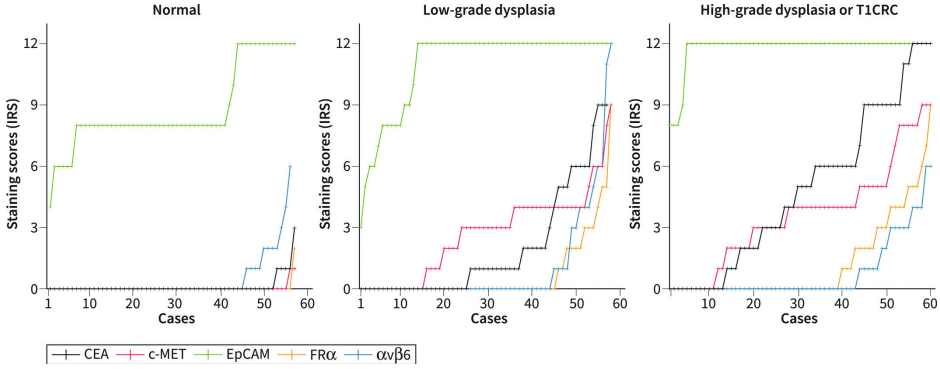


Table 2. The mean immunoreactive score (IRS) for the component of normal tissue, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and T1 colorectal cancer (T1CRC) (minimum 0, maximum 12)

Target	**Normal** mean IRS (n=57)	**LGD** mean IRS (n=58)	**HGD-T1CRC** mean IRS (n=60)	**p-value** Normal vs HGD-T1CRC	**p-value** LGD vs HGD-T1CRC
CEA	0.08	1.83*	4.78	<0.001	<0.001
c-MET	0.02	2.64	3.58	<0.001	0.003
EpCAM	8.79	10.95	11.75	<0.001	0.011
FRα	0.04	0.70	1.23	0.001	0.051
αvβ6	0.42*	1.01	0.76	0.075	0.930

* Data of one case was missing due to a broken slide on which the IRS of that component could not be assessed properly.

CEA carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha, *IRS* immunoreactive score.

Figure 3. Positive staining pattern of all targets in the high-grade dysplasia (HGD) or T1 colorectal cancer (T1CRC) component. For each target, an illustrative case was selected with positive expression in the HGD-T1CRC component (i.e. staining score >1). The region enclosed by the rectangle with dashed line consists of HGD or T1CRC. An overview image (left) and enlargement of the HGD-T1CRC region (right) are provided for each target. (**a**) CEA expression and (**b**) c-MET expression. (**c**) EpCAM expression. (**d**) FRα expression. (**e**) αvβ6 expression. *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor.

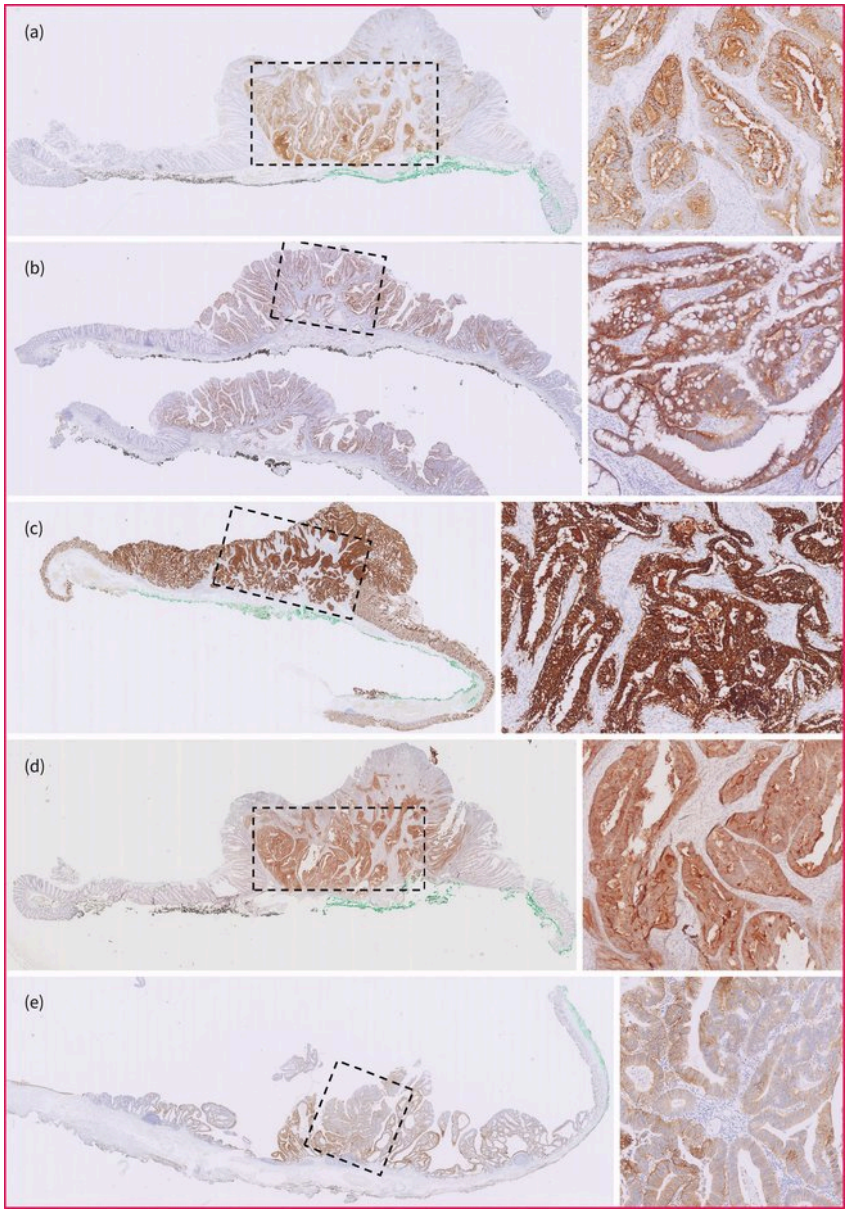
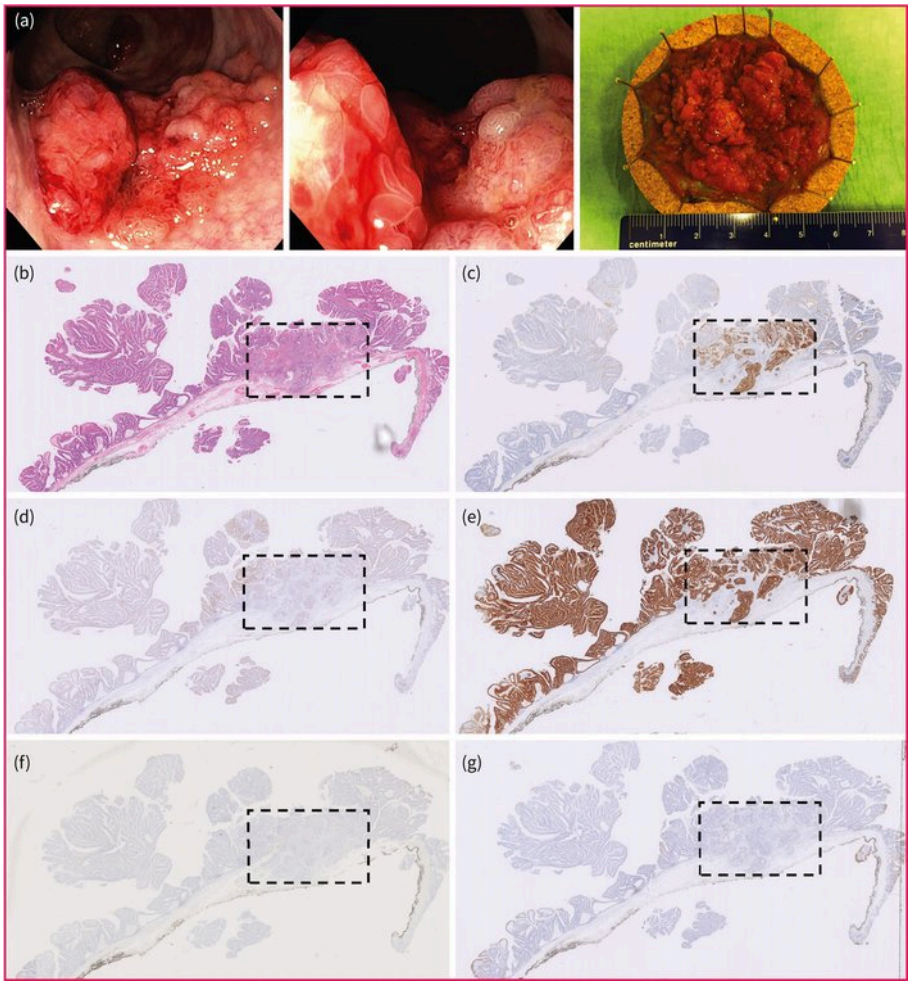


Figure 4. Overall staining pattern of all targets in the same case of T1 colorectal cancer (T1CRC). The region enclosed by the rectangle with dashed line consists of HGD-T1CRC. (**a**) Endoscopic images and resection specimen after endoscopic submucosal dissection. (**b**) HE slide. (**c**) CEA expression. (**d**) c-MET expression. (**e**) EpCAM expression. (**f**) FRα expression. (**g**) αvβ6 expression. *HE* hematoxylin-eosin, *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor.



Expression of markers in normal tissues

Carcinoembryonic antigen expression was negative in 56/57 (98.2%). C-MET expression was negative in all cases. Epithelial cell adhesion molecule expression was positive in all cases, showing moderate (41/57, 71.9%) to strong (16/57, 28.1%) expression. Folate receptor alpha expression was negative in 56/57 (98.2%). αvβ6 expression was negative in 49/56 (87.5%).

Expression of markers in low-grade dysplasia

Carcinoembryonic antigen expression was negative in 37/57 (64.9%). C-MET expression was negative in 19/58 (32.8%), most of cases showed a moderate expression (22/58, 37.9%). Epithelial cell adhesion molecule expression was positive in all cases, showing moderate (10/58, 17.2%) to strong (48/58, 82.8%) expression. Folate receptor alpha expression was negative in 47/58 (81.0%). αvβ6 expression was negative in 48/58 (82.8%).

Expression of markers in high-grade dysplasia or T1 colorectal cancer

Carcinoembryonic antigen expression was positive in 44/60 (73.3%), showing a strong expression in 16/60 (26.7%). C-MET expression was positive in 47/60 (78.3%), showing a strong expression in 3/60 (5%). Epithelial cell adhesion molecule expression was positive in all cases, showing a strong expression in 57/60 (95%). Folate receptor alpha expression was positive in 18/60 (30.0%), strong expression was observed in 1/60 (1.7%). αvβ6 expression was positive in 12/60 (20.0%), but strong expression was not observed.

Differential HGD-T1CRC expression compared to normal

The staining intensity was higher in the HGD-T1CRC component than the adjacent normal component for CEA in 46/57 (80.7%), c-MET in 46/57 (80.7%), EpCAM in 40/57 (70.2%), FRα in 20/57 (35.1%), and αvβ6 in 14/56 (25.0%) (Figure 5). Carcinoembryonic antigen showed the greatest increase in IRS. If there was an increase, the HGD-T1CRC component scored on average 6.0 points higher (95% CI 5.0–7.0) than the adjacent normal component. For c-MET this was 4.4 (95% CI 3.8–5.1) (Table 3).

Table 3. The magnitude of the increase in the immunoreactive score (IRS) between the high-grade dysplasia (HGD) or T1 colorectal cancer (T1CRC) component and the normal or low-grade dysplasia (LGD) component if an increase was present, expressed as mean and 95% confidence interval.

Target	Increase in IRS between the HGD-T1CRC and normal component Mean (95%CI)	Increase in IRS between the HGD-T1CRC and LGD component Mean (95%CI)
CEA	6.0 (5.0-7.0), n=46	4.5 (3.4-5.5), n=38
c-MET	4.4 (3.8-5.1), n=46	3.0 (2.2-3.9), n=25
EpCAM	4.3 (4.0-4.6), n=40	5.0 (3.5-6.5), n=10
FRα	3.6 (2.6-4.5), n=20	2.9 (1.8-4.0), n=13
αvβ6	2.9 (2.0-3.7), n=14	2.3 (1.0-3.7), n=9

CEA carcinoembryonic antigen, *CI* confidence interval, *c-MET* c-mesenchymal-epithelial transition factor, *CRC* colorectal cancer, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha, *HGD* high-grade dysplasia, *IRS* immunoreactive score, *LGD* low-grade dysplasia.

Differential HGD-T1CRC expression compared to low-grade dysplasia

The staining intensity was higher in the HGD-T1CRC component than the surrounding LGD component for CEA in 38/57 (66.7%), c-MET in 25/58 (43.1%), EpCAM in 10/58 (17.2%), FRα in 13/58 (22.4%), and αvβ6 in 9/58 (15.5%) (Figure 5). For CEA, if there was an increase in IRS, HGD-T1CRC components scored on average 4.5 points higher (95% CI 3.4–5.5) than adjacent LGD components. For c-MET, this was 3.0 (95% CI 2.2–3.9) (Table 3).

Separate results for the HGD and T1CRC subgroups can be found in the supplementary results.

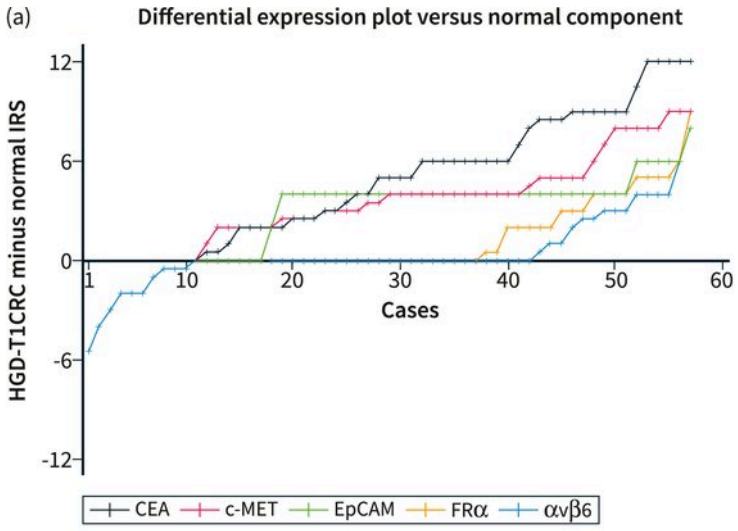
Specificity and sensitivity for HGD-T1CRC detection

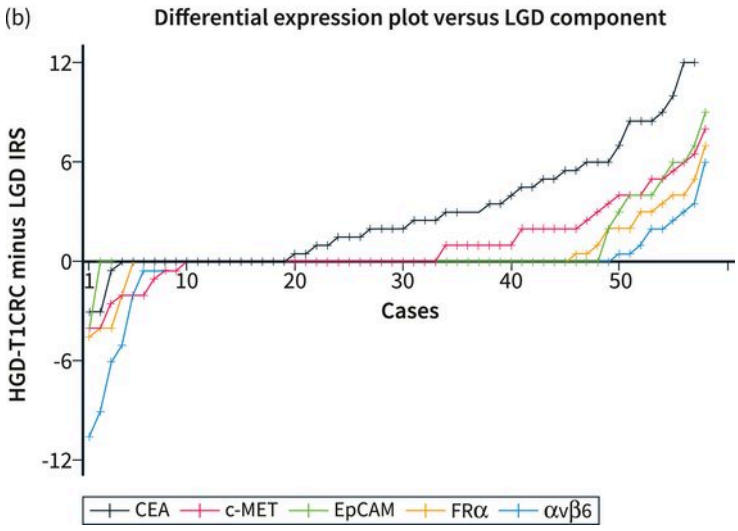
Varying the limit of detection, we examined what proportion of HGD-T1CRC components would be visualized (sensitivity) and what proportion of LGD components would be visualized (specificity). A receiving operating characteristic (ROC) was plotted for each marker to select the optimal cut-off scores (i.e. scores with the greatest combined sensitivity and specificity). Using these optimal cut-off scores, sensitivity and specificity for detection of the HGD-T1CRC component versus surrounding LGD were 65.0% and 75.0% for CEA (cut-off >2.5), 55.0% and 60.3% for c-MET (cut-off >3.5), 93.3% and 22.4% for EpCAM (cut-off >11), 16.7% and 93.1% for FRα (cut-off >3.5), and 28.3% and 75.9% for αvβ6 (cut-off <0.5). Supplementary Figure 2 shows the ROC curves for detection of the HGD-T1 components compared to the normal and LGD components.

Correlation between carcinoembryonic antigen and c-mesenchymal-epithelial transition factor expression and morphological characteristics

For CEA and c-MET, negative staining in the HGD or T1CRC component did not statistically differ between flat elevated and sessile polyps, granular and non-granular polyps, and smaller or larger polyps (dichotomized, using 40 mm as cut-off), all $p > 0.05$ (supplementary Table 2). Additional information regarding the cases with negative CEA staining in the HGD or T1CRC component is provided in supplementary results.

Figure 5. Differential expression plots. Differential expression scores were calculated by subtracting the IRS of the normal or low-grade dysplasia component from the IRS of the HGD-T1CRC component. Differential expression scores were independently arranged and connected in ascending order to demonstrate the distributions across the cohort. (**a**) shows the differential expression plot for HGD-T1CRC components compared to surrounding normal colorectal tissue. (**b**) shows the differential expression plot for HGD-T1CRC components compared to surrounding components of LGD. *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *CRC* colorectal cancer, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha, *IRS* immunoreactive score, *LGD* low-grade dysplasia.





Discussion

This study is the first to evaluate the suitability of CEA, c-MET, EpCAM, FRα, and αvβ6 as possible targets to detect a focus of HGD or T1CRC in large colorectal polyps using tumor-targeted fluorescence-guided endoscopy. Our results indicate that CEA shows the most differential expression for the HGD-T1CRC component of the tested markers. Therefore, CEA appears to be the most promising target for in vivo testing.

Carcinoembryonic antigen outperformed the other markers by showing the greatest differential HGD-T1CRC expression, especially compared to the LGD component. In comparison to CEA, positive expression (i.e. Immunoreactive score >1) in the HGD-T1CRC component was found more frequently for c-MET (47/60, 78.3%). However, c-MET lacked the degree of differential expression with LGD because the expression in the LGD component was also positive in a considerable amount of cases, which was in line with previous studies. C-MET was even successfully used as an in vivo FOI target for polyps.[11] EpCAM showed a positive expression in the HGD-T1CRC component most frequently of all tested biomarkers (60/60, 100%) but hardly showed any differential expression with the LGD components. The number of cases with a positive expression in the HGD-T1CRC component for FRα (18/60, 30.0%) and αvβ6 (12/60, 20.0%) were too low to be considered as suitable targets.

For CEA, positive expression in the HGD-T1CRC component was seen in 44/60 (73.3%) cases. This was slightly lower than the previously reported 87%–99% in studies that mainly included more advanced CRC stages.[15,22] Since not all HGD-T1CRC components show positive expression for CEA, not all patients will benefit from tumor-targeted FOI targeting CEA. It would be preferable to be able to select those patients who would. This study could not identify morphological polyp characteristics that were associated with negative tumor expression. However, it should be kept in mind that the current study may be underpowered to identify relevant factors. Moreover, serum CEA levels do not appear informative for predicting expression levels.[23] Additionally, screening CEA expression on pre-operative biopsies does not appear to be a feasible selection strategy because, in accordance with the motive of this study, recognizing and thus being able to take biopsies from the HGD-T1CRC component in larger polyps can be challenging. CEA›s imperfect tumor expression rate may hamper its clinical implementation as HGD- and T1CRC-specific FOI targets. However, the perfect target has yet to be discovered and CEA appears to be the most promising. Alternatively, a combination of two complementary targets could be considered. Based on our results, c-MET and EpCAM could enhance the detection of HGD-T1CRC versus normal tissue, but this does not contribute to better distinction between HGD-T1CRC foci versus LGD components compared to single target CEA, which was the aim of this study.

Based on the results of this study, we are conducting a clinical pilot study to assess whether it is possible to specifically detect an HGD or T1CRC component in non-pedunculated rectal polyps using SGM-101, a fluorochrome-labeled anti-CEA monoclonal antibody. After intravenous administration of this fluorescent CEA-targeting tracer, imaging will be performed using a fluorescence-endoscope. For this clinical study, it should be taken into account that immunohistochemical studies can only partly mimic the in vivo situation where several other factors can potentially influence the performance. These factors include tissue penetration, background staining, immunological response and sensitivity of the NIR-camera system. However, despite these challenges, the feasibility and safety of fluorescence-labeled contrast agents targeting CEA for in vivo tumor imaging have already been shown. For example, SGM-101 showed enhanced differentiation between normal and cancerous tissues in pancreatic cancer and CRC.[24] Additionally, its application during CRC surgery influenced clinical decision-making.[9] A promising novel clinical application of CEA-targeted fluorescent agents might be during endoscopic assessment of colorectal polyps where it could help to improve the recognition of HGD-T1CRC foci and therefore aid the process of decision-making for the preferred local resection technique.

Although the results are promising, the present study has some limitations. The main drawbacks are the relatively small number of cases and the use of semiquantitative immunohistochemistry to measure protein expression. Even though immunohistochemistry is routinely used, it frequently lacks standardization and therefore interpretation of staining patterns might be heterogeneous. Our study attempted to minimize this by using validated antibodies and a previously published scoring system.[21] Lastly, the biomarker panel only consisted of well-established biomarkers with clinically available tracers to save time-consuming steps in the cascade of developing new imaging tracers, such as safety trials.[25] By using this pragmatic approach, there is a possibility that the most suitable HGD-T1CRC specific target is yet to be discovered and was not included in the panel of this study.

Conclusion

Of the tested targets, CEA appears the most suitable to specifically detect foci of HGD and T1CRC in colorectal polyps. An in vivo study using tumor-targeted fluorescence-guided endoscopy should confirm these findings.

Supplemental materials

Supplemental Table 1. Specifications of antigen retrieval and used antibodies.

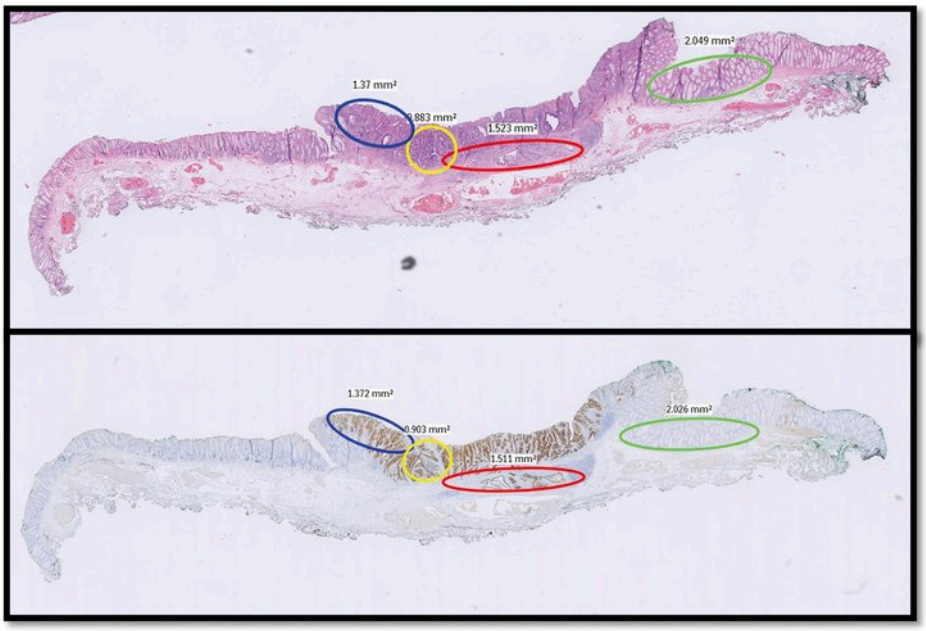
Antibody	Company	Clone	Stock concentration	Dilution	Antigen Retrieval	Fluorescent agents
Anti-CEACAM5	Santa Cruz Biotechnology	CI-P83-1	0.2 µg/mL	1/2500	Dako PT Target Retrieval Solution, pH 6.0	SGM-101
Anti-c-MET	Bio SB	EP1454Y	1 µg/mL	1/50	Dako PT Target Retrieval Solution, pH 6.0	EMI-137
Anti-EpCAM	Acris Antibodies	MOC-31	0.64 mg/mL	1/10000	Dako PT Target Retrieval Solution, pH 6.0	VB5-845D-800CW
Anti-FRα	BioCare Medical	26B3.F2	Ready-to-use	Ready-to-use	Diva Decloaker Solution, pH 6.2	OTL-38
Anti-αvβ6	Biogen Idec	6.2A1	0.5 µg/mL	1/100	0.4% pepsin	cRGD-ZW800-1*

*Also has to ability to bind integrins such as αvβ3 and αvβ5.
CEA (CEACAM5) carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha.

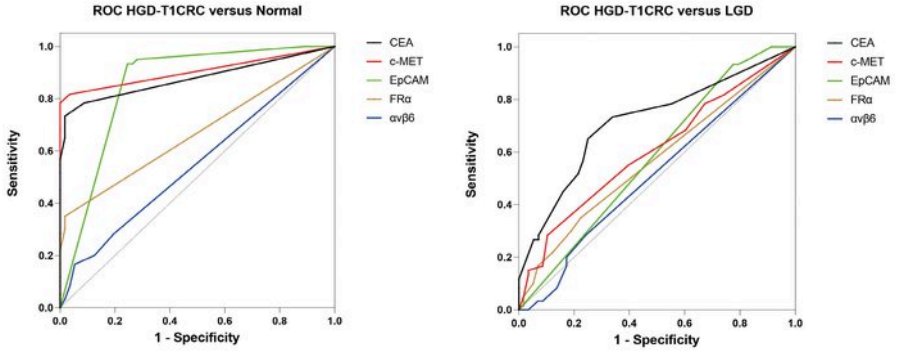
Supplemental Table 2. Morphological polyp characteristics and its relation to positive or negative staining, using Chi-squared test. - negative staining (i.e. score 0-1), *+* positive staining (i.e. score >1). *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor.

	CEA -	CEA +	p-value	c-MET -	c-MET +	p-value
Granularity						
Granular	4	16	0.409	3	17	0.375
Non-granular	12	28		10	30	
Gross morphology						
Sessile	9	27	0.721	8	28	0.898
Flat elevated	7	17		5	19	
Size						
<40mm	6	23	0.311	6	23	0.859
≥40mm	10	21		7	24	

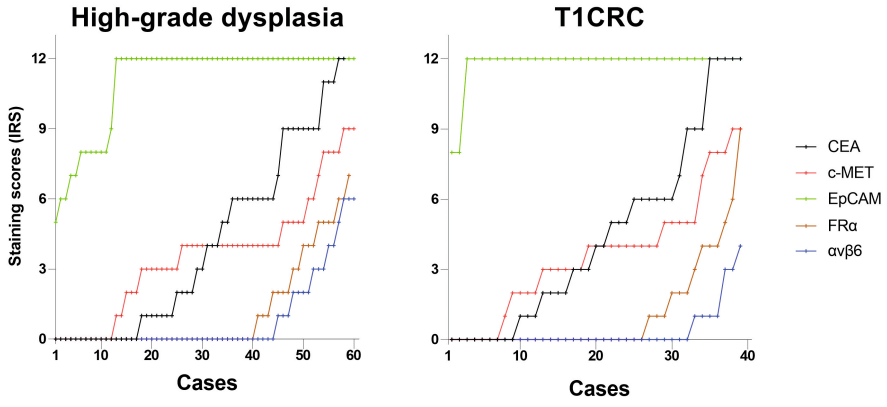
Supplementary Figure 1. Marking of areas in a case of T1CRC. One distinctive region of normal colon tissue (green), low-grade dysplasia (blue), high-grade dysplasia (yellow) and T1 colorectal cancer (red) was assessed by a pathologist specialized in gastro-intestinal pathology (S.C.) and marked by a researcher (N.D). Hematoxylin and eosin slide (upper) and immunohistochemical staining for carcinoembryonic antigen expression (lower).



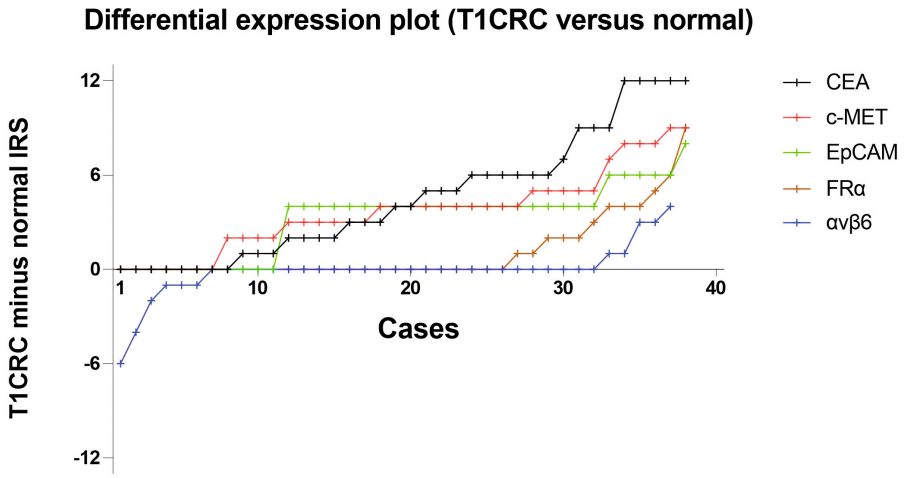
Supplementary Figure 2. Receiver operating characteristic (ROC) curves were plotted for each marker. The left figure shows the ROC curves for HGD-T1CRC and normal tissue: CEA and c-MET follow the left y-axis and top x-asis, identifying it as sensitive and specific discriminator between the HGD-T1CRC component and normal tissue (*left*). FRα and αvβ6 tend to follow the reference line, indicating poor performance. EpCAM follows the top x-as closely, indicating high sensitivity, however lacks the specificity of CEA and c-MET. The right figure shows the ROC curves for the HGD-T1CRC component compared to the component of low-grade dysplasia: all markers but CEA follow the reference line, indicating poor performance. *ROC* Receiver operating characteristic, *CRC* colorectal cancer, *LGD* low-grade dysplasia, *HGD* high-grade dysplasia, *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha.



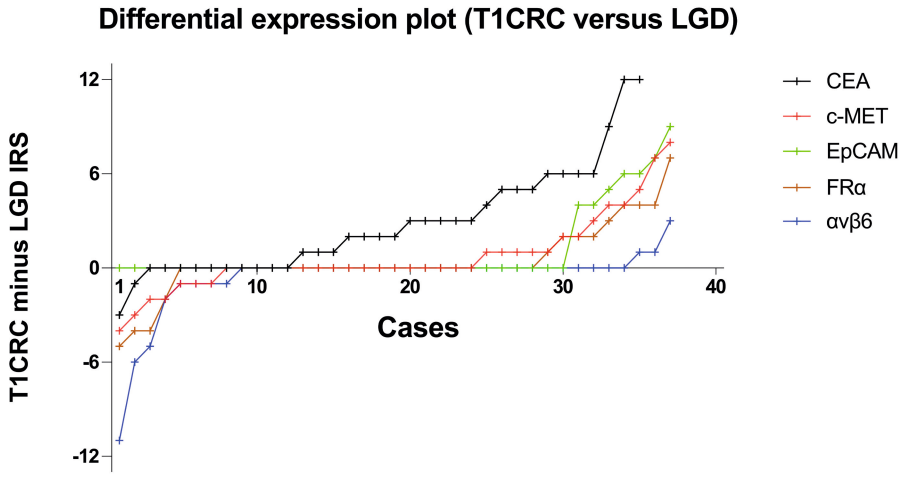
Supplementary Figure 3. Expression levels of CEA, c-MET, EpCAM, FRα and αvβ6 in high-grade dysplasia and T1CRC. The total immunoreactive scores were independently arranged in ascending order to demonstrate the distributions across our cohort. *CRC* colorectal cancer, *HGD* high-grade dysplasia, *IRS* immunoreactive score, *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha.



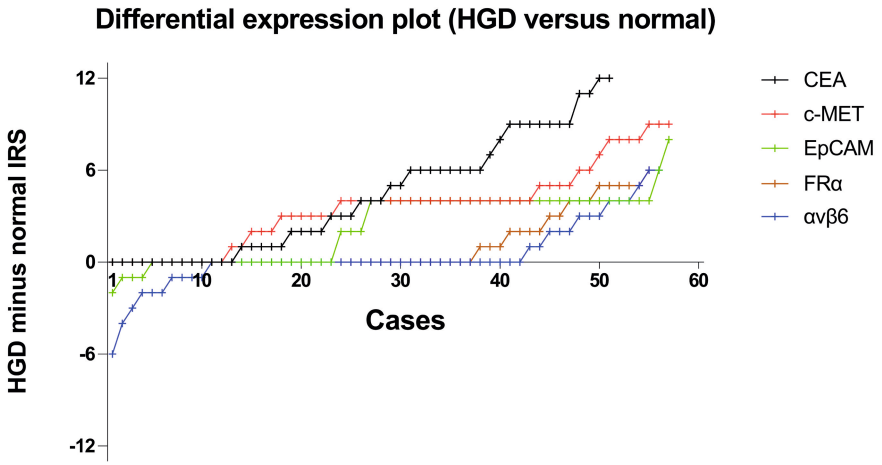
Supplementary Figure 4. Expression scores of normal colon components were subtracted from those of adjacent T1 CRC components to quantify the degree of differential expression for each case. Differential expression scores were independently arranged and connected in ascending order to demonstrate the distributions across our cohort (left). *CRC* colorectal cancer, *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha.



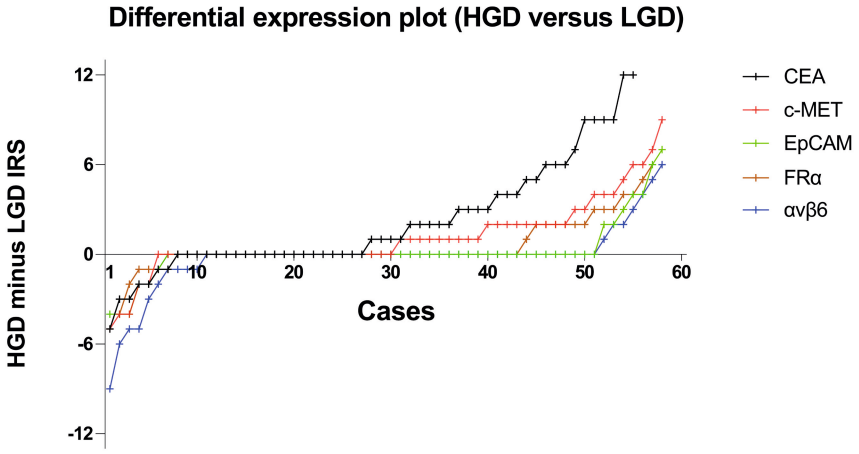
Supplementary Figure 5. Expression scores of low-grade dysplasia components were subtracted from those of adjacent T1CRC components to quantify the degree of differential expression for each case. Differential expression scores were independently arranged, and connected, in ascending order to demonstrate the distributions across our cohort (left). *CRC* colorectal cancer, *LGD* low-grade dysplasia, *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha.



Supplementary Figure 6. Expression scores of normal colon components were subtracted from those of high-grade dysplasia components to quantify the degree of differential expression for each case. Differential expression scores were independently arranged, and connected, in ascending order to demonstrate the distributions across our cohort (left). *CRC* colorectal cancer, *CEA* carcinoembryonic antigen, *HGD* high-grade dysplasia, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha.



Supplementary Figure 7. Expression scores of low-grade dysplasia components were subtracted from those of high-grade dysplasia components to quantify the degree of differential expression for each case. Differential expression scores were independently arranged, and connected, in ascending order to demonstrate the distributions across our cohort (left). *CRC* colorectal cancer, *HGD* high-grade dysplasia, *LGD* low-grade dysplasia, *CEA* carcinoembryonic antigen, *c-MET* c-mesenchymal-epithelial transition factor, *EpCAM* epithelial cell adhesion molecule, *FRα* folate receptor alpha.



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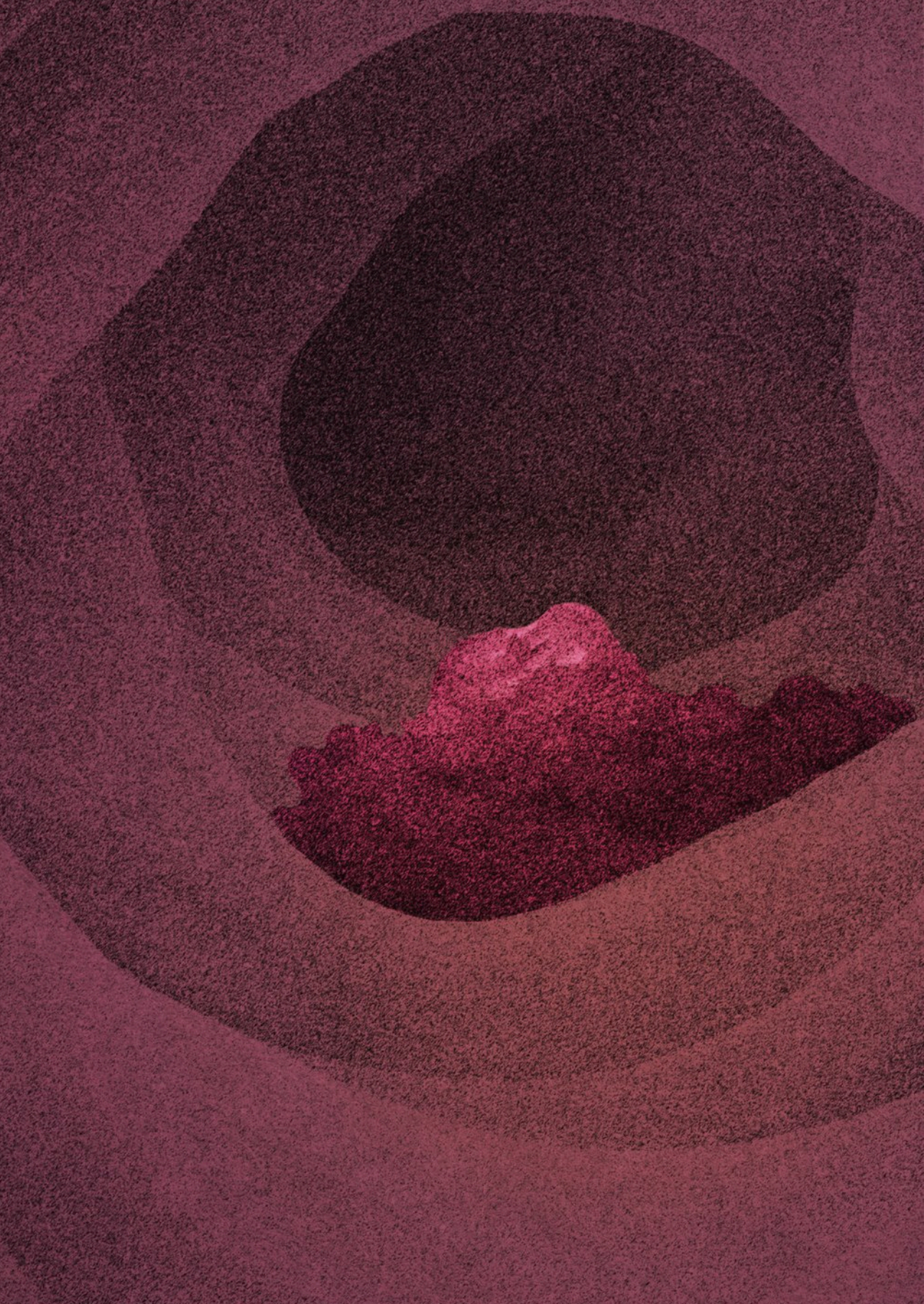

CHAPTER 4

Transanal minimally invasive surgery (TAMIS) versus endoscopic submucosal dissection (ESD) for resection of non-pedunculated rectal lesions (TRIASSIC study): study protocol of a European multicenter randomised controlled trial

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BMC Gastroenterology 2020

Abstract

Background: In the recent years two innovative approaches have become available for minimally invasive en bloc resections of large non-pedunculated rectal lesions (polyps and early cancers). One is Transanal Minimally Invasive Surgery (TAMIS), the other is Endoscopic Submucosal Dissection (ESD). Both techniques are standard of care, but a direct randomised comparison is lacking. The choice between either of these procedures is dependent on local expertise or availability rather than evidence-based. The European Society for Endoscopy has recommended that a comparison between ESD and local surgical resection is needed to guide decision making for the optimal approach for the removal of large rectal lesions in Western countries. The aim of this study is to directly compare both procedures in a randomised setting with regard to effectiveness, safety and perceived patient burden.

Methods: Multicenter randomised trial in 15 hospitals in the Netherlands. Patients with non-pedunculated lesions >2cm, where the bulk of the lesion is below 15cm from the anal verge, will be randomised between either a TAMIS or an ESD procedure. Lesions judged to be deeply invasive by an expert panel will be excluded. The primary endpoint is the cumulative local recurrence rate at follow-up rectoscopy at 12 months. Secondary endpoints are: 1) Radical (R0-) resection rate; 2) Perceived burden and quality of life; 3) Cost effectiveness at 12 months; 4) Surgical referral rate at 12 months; 5) Complication rate; 6) Local recurrence rate at 6 months. For this non-inferiority trial, the total sample size of 198 is based on an expected local recurrence rate of 3% in the ESD group, 6% in the TAMIS group and considering a difference of less than 6% to be non-inferior.

Discussion: This is the first European randomised controlled trial comparing the effectiveness and safety of TAMIS and ESD for the en bloc resection of large non-pedunculated rectal lesions. This is important as the detection rate of these adenomas is expected to further increase with the introduction of colorectal screening programs throughout Europe. This study will therefore support an optimal use of healthcare resources in the future.

Trial registration: Netherlands Trial Register, NL7083, 06 July 2018.

Background

Colorectal cancer (CRC) has the second highest incidence rate of all cancers in Europe with an annual incidence rate of approximately 500.000 of which 175.000 are located in the rectum.[1] Since the introduction of population based screening, CRCs are more often detected at an earlier disease stage than symptom-detected CRCs.[2] Resection of pre-malignant precursors has shown to lower the mortality rate due to CRC by 50%.[3] Along with the clearly benign polyps and clearly invasive cancers, colorectal cancer screening also detects many lesions in the act of progressing from one to the other. These lesions present a diagnostic challenge and complex clinical decision making to avoid overtreatment with unnecessary mortality and morbidity on the one hand but also undertreatment on the other. This dilemma is most acute for rectal lesions where standard surgical resection techniques are associated with higher rates of mortality and serious morbidity, such as a permanent stoma and sexual dysfunction, which can be avoided by organ sparing techniques.[4]

Ideally, preoperative staging would allow for accurate prediction of invasive cancer and the chance of local lymph node metastases. Unfortunately, current pre operative staging is far from perfect. This is true for all available staging modalities (MRI, endoscopic ultra sound, advanced optical endoscopic imaging) both individually and in combination. This has been shown by a previous randomised study of organ sparing treatment of rectal polyps, the TREND study: 13% of the lesions preoperatively staged as benign turned out to be malignant.[5] Currently most lesions that are not overtly cancerous on endoscopic inspection are resected by piecemeal Endoscopic Mucosal Resection (pEMR) in Western countries. However, piecemeal resection has an important disadvantage in that it prevents optimal histological assessment. This can make histological distinction between a benign and a malignant lesion impossible leading to unnecessary surgical resections or to under staging and undertreatment. The safety and feasibility of en bloc resections in the rectum, combined with the limitations of preoperative staging are leading to a shift away from pEMR to en bloc resection of large lesions in the rectum. Furthermore, a recent cost effectiveness analysis suggests that an en bloc resection strategy might also be cheaper than a piecemeal resection strategy for rectal lesions by reducing the numbers of patients requiring additional radical rectal surgery.[6]

Lesions can be removed en bloc with a flexible endoscope by Endoscopic Submucosal Dissection (ESD). ESD results in high en bloc rates and low recurrence rates of around 2%.[7] However, ESD has longer procedure times, is difficult to perform and associated with relatively high rates of perforation (5%).[8] Fortunately, the clinical consequences of perforation in the rectum are usually limited and can almost always be treated conservatively. Several surgical techniques are also available for local en bloc resection of large non-pedunculated rectal lesions. Such as Transanal Endoscopic Micosurgery (TEM) or Transanal Minimally Invasive Surgery (TAMIS). The TAMIS technique has largely

superseded classical TEM since it requires minimal investment in specialised equipment. Here the lesion is removed transanally with the use of a silicon-rubber port and standard laparoscopic instruments. Compared to ESD it also has a relatively short learning curve, short procedure times and is financially well compensated.

No reports have been published comparing TAMIS and ESD directly. Two recently published meta-analysis comparing TAMIS/TEM to ESD concluded a similar rate of adverse events, recurrence rate and en bloc resection rate.[9,10] Regarding the procedure and hospitalization duration both papers came to a different conclusion. The first concluded that ESD was associated with shorter procedure times and duration of hospitalization,[10] the second concluded that there was no difference.[9] However, both meta-analyses largely included ESD procedures that were conducted in Asian countries. As a result the findings may not be representative for the daily practice in the West where the results of ESD tend to be inferior. The aim of the TRIASSIC study is to perform a multicentre, randomised controlled study comparing ESD to TAMIS for the en bloc removal of large non-pedunculated rectal lesions in a Western population. This is important as the detection rate of these lesions has increased greatly with the introduction of screening programs. This study will enable the optimal use of healthcare resources in the future.

Methods/design

Hypothesis

We hypothesise that ESD will lead to non-inferior recurrence rates in lesions that prove to be benign. We hypothesise that TAMIS will have a higher R0 resection rate for lesions that prove to be invasive but that this will not translate to a reduced need for additional surgery. We further hypothesise that ESD will lead to less serious complications than TAMIS and lower societal costs.

Objective

The primary aim of this study is to compare both procedures with regard to local recurrence rates at 12 months. The secondary aims are to compare costs, complication rates and the burden perceived by patients in both the short and long term between the two procedures.

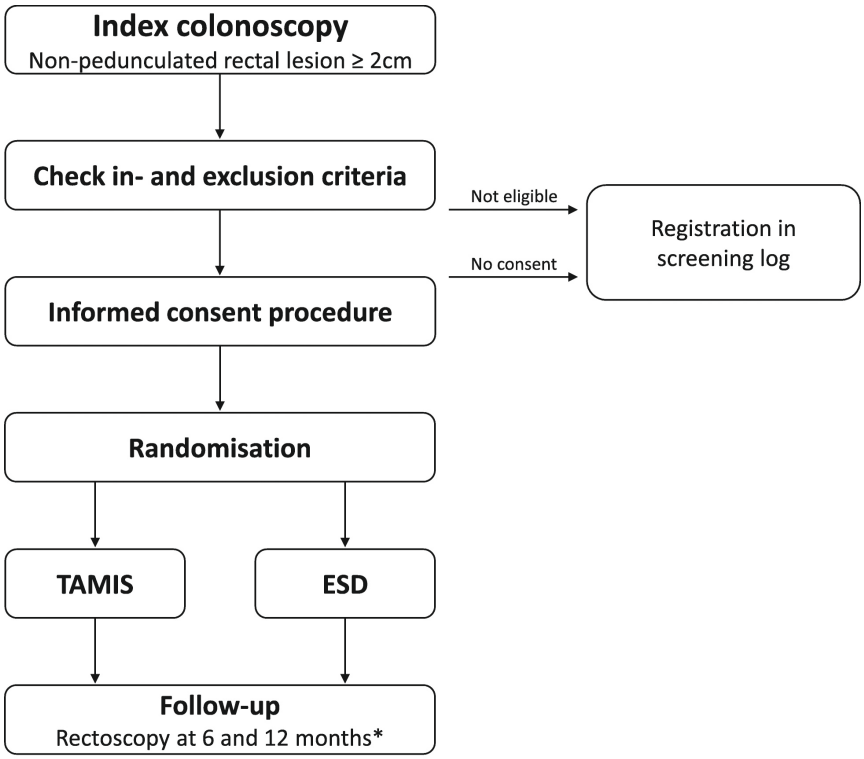
Design

This will be a multicentre randomised non-inferiority trial comparing TAMIS and ESD in patients with large rectal lesions. The flowchart of the design of the TRIASSIC study is shown in Figure 1.

Randomisation

Patient data will be entered into a cloud-based electronic data capture system (Castor). This system will randomise patients to either the TAMIS or the ESD group. Stratification will take place for the distance of the lesion to the dentate line and lesion size.

Figure 1. Flowchart of the TRIASSIC study. *TAMIS* Transanal Minimally Invasive Surgery, *ESD* Endoscopic Submucosal Dissection. *If recurrence is found at 12-month colonoscopy this will be resected and a further surveillance colonoscopy is planned 6 months later.



*If recurrence is found at the 12-month colonoscopy this will be resected and a further surveillance colonoscopy planned 6 months later.

Blinding

Blinding was deemed unfeasible for this trial since both procedures are very different in nature, performed by different specialists and require different associated care facilities within the hospital.

Study population
In order to be eligible to participate in this study, a subject must meet all of the following inclusion criteria:

1. Non-pedunculated lesion > 2cm in the rectum where the bulk of the lesion is below 15cm from the anal verge found at endoscopy
2. ≥18years old
3. Written informed consent

A subject is not eligible for inclusion in case of presence of any of the following exclusion criteria:

1. Features of advanced disease or deep-submucosal invasion at optical endoscopic evaluation*
2. Features of advanced disease on cross-sectional imaging*
3. Prior endoscopic resection attempt
4. The risks of treatment are felt to exceed the benefits.

* *Where there is discordance in the results, the optical endoscopic evaluation will be given the most weight and the case discussed by an expert panel.*

Participating centres
The TRIASSIC study will be performed in the Netherlands in at least 5 academic and 10 non-academic centres. The following hospitals are participating in the trial: Leiden University Medical Center, Amsterdam University Medical Center (Amsterdam Medical Center and Vrije Universiteit University Medical Center), University Medical Center Utrecht, Erasmus medical Center, IJssel land hospital, Alrijne hospital, Haaglanden Medical Center, Diakonessenhuis, Deventer hospital, Meander Medical Center and the St. Antonius hospital. The following hospitals have shown interest in participation: Bravis hospital, Isala hospital, Albert Schweitzer hospital, Maasstad hospital, Netherlands Cancer institute, University Medical Center Groningen, Maastricht University Medical Center, Medical Center Leeuwarden, Elisabeth TweeSteden hospital, Laurentius hospital, Gelre hospital and Hagaziekenhuis.

Intervention strategies
Transanal minimally invasive surgery (TAMIS)
This procedure was first described by Atallah et al.[11] The procedure will be performed under either general or spinal anaesthesia at the discretion of the anaesthetist. For this trial only the GelPOINT® path transanal access platform will be used. This is to ensure the greatest possible uniformity in procedures and was already being used by the vast majority of surgeons prior to the study. After insertion of the instruments the margins of the lesion may be marked with coagulation dots to facilitate the incision at the lesion margins at the discretion of the surgeon. The incision must be placed at a distance of at

least 5 mm around the border of the lesion to prevent thermal damage complicating the histological assessment. If a lesion is very distal (i.e., at or just above the dentate line), the distal margin can be incised using standard transanal retractors and electrocautery. Before the start of the lateral or proximal portion of the dissection, the TAMIS port can be inserted to be used for the remainder of the dissection. Ideally a partial thickness resection of the lesion will be performed following the intramuscular plane of the muscularis propria using a diathermic hook but a full thickness resection may be performed at the discretion of the surgeon. The wound may be closed, if required, with laparoscopic suture material in a transverse direction so as not to narrow the lumen of the rectum. The type of sedation and precise instruments will be noted in the CRF. Pneumorectum will be achieved using CO2 for insufflation. Initial pressure settings should be between 12- and 20-mmHg and can be increased if there is difficulty in maintaining dis tension for visualisation. An anal block with bupivacaine or ropivacaine bilaterally is recommended. All other aspects of the procedure and post-procedural care are at the discretion of the operator.

Endoscopic submucosal dissection (ESD)

After insertion of the endoscope the margins of the lesion may be marked with coagulation dots to facilitate the incision at the lesion margins at the discretion of the endoscopist. The lesion will be 'lifted' by injection of fluid into the submucosa. The choice of injection fluid is at the discretion of the operator. A partial or full circumferential incision will be made around the lesion (at the discretion of the operator) at a distance of at least 5 mm from the border of the lesion to prevent thermal damage complicating the histological assessment. Dis section will take place in the submucosal layer under neath the specimen just above and parallel to the underlying muscularis propria layer. The choice of ESD knife is at the discretion of the operator and must be recorded in the CRF. All procedures will be performed with a high-resolution magnifying video-endoscope. The procedure will be performed under sedation, not general anaesthesia. The choice of sedation technique is at the discretion of the endoscopist but Propofol sedation is recommended. In the case of intraprocedural perforation, this will be treated using clips and desufflation of the peritoneal cavity if required, with an intra venous cannula. In the case of minor bleeding from a small vessel, contact coagulation with the tip of a knife or coagulation with haemostatic forceps will be used for haemostasis. In cases of a severe bleeding from a large vessel or artery, haemostatic forceps will be used for haemostasis. If a pulsating large vessel is exposed within the resection wound, clipping can be performed to pre vent delayed bleeding. All of this is considered standard care and should be mentioned in the CRF. All other aspects of the procedure and post-procedural care are at the discretion of the operator.

Decision-making regarding patient management

Patients will be discussed at the local multidisciplinary meeting (standard care) and decisions regarding the management of the patient including the need for additional

radical surgical resection or other treatment options, will be made there in the normal way in accordance with the current national guidelines.

Follow-up

The follow-up consists of a rectoscopy performed 6 and 12months after the TAMIS/ESD by an endoscopist trained in advanced endoscopic imaging techniques. Three white light pictures, 3 enchanced imaging pictures and preferably a short video should be taken of the scar. In case of no visible recurrence 3 biopsies of the scar should be taken. In case of visible benign recurrence an attempt at an endoscopic resection will be performed, or a re-TAMIS. If recurrence is found at the 12-month rectoscopy this will be resected and further surveillance will be planned for 6months later.

Informed consent procedure

Patients meeting all criteria stated above will be informed about the trial at the outpatient clinic by a member of the research team. After written consent is obtained the patient will be allocated to either the TAMIS or the ESD group by computerised randomisation. Subsequently, the patient will be scheduled for therapy at a participating centre. Intervention failure: cross-over If the primary procedure fails, cross-over to the other treatment is possible, but only if the specialist that has to perform the cross-over treatment, deems it feasible.

Quality assurance

Expert panel

An expert panel was established for this trial consisting of five gastroenterologists (JH, JB, LM, AK, BB) and three surgeons (PD, EG, RH). All are specialized in the assessment and treatment of advanced polyps and (early invasive) rectal cancers and perform either the ESD or the TAMIS procedures within this trial. All lesions should be approved by the expert panel before randomisation by review of the endoscopy pictures and video. A lesion is deemed as suitable for participation if a minimum of 2 gastroenterologists and 1 surgeon think the lesion meets the criteria. The expert panel can also be consulted in difficult cases (for example when advanced cross-sectional imaging and endoscopic assessment disagree).

Experience requirement

Specialists performing ESD or TAMIS in the TRIASSIC study need to have performed at least 25 procedures. The specialists will be asked to send anonymised procedural data including lesion characteristics, procedure time, complications, histology and follow up (if available) of the latest 15 procedures and an unedited video. To be able to perform procedures in the TRIASSIC study at least 10 of these 15 procedures must have resulted in a R0 resection of lesions >2cm in size and must have been performed without complications.

Histopathological evaluation

Appropriate handling of the resected specimens is critical for accurate histological assessment and will be done as follows (identical to standard care). The resected specimen will be pinned onto a paraffin, rubber or cork sheet so that the normal mucosa surrounding the lesion is evenly flattened and the mucosal surface can be observed. The specimen will then be photographed with a millimetre ruler next to it and fixed in formalin. The specimen should, preferably, be examined by a GI pathologist. The specimen should be photographed, measured and macroscopic appearance described including the lesion, mucosal defects, other abnormalities and the resection margins. The specimen should also be inked. A different colour should be used for the resection plane and the edges of defects. A tangent that touches the focus closes to the horizontal margin is assumed. The first cut is carried out in the direction perpendicular to the tangent. Hereafter the specimen is sectioned into slices parallel to the first cut. Lastly all slices should be embedded in cassettes for histological diagnosis. Incomplete (R1) resection is defined as tumour infiltration of the margins and/or if infiltration cannot be determined because of coagulation artefacts. In case of an adenocarcinoma the high-risk factors will be assessed; grade of tumour budding, invasion depth, differentiation grade, presence of lymphovascular invasion and radicality.

Central pathology revision

All resection specimens will be revised centrally by an expert pathologist.

Outcomes

Primary study endpoint (for non-inferiority)

1. Cumulative recurrence rate at follow-up rectoscopy after 12 months, histologically confirmed from resected visible residual disease or, if not present, from biopsies of the scar.

Secondary study endpoints

2. Radical (R0-) resection rate, defined as dysplasia free vertical and lateral resection margins at histology.
3. To compare the perceived burden of the treatment and quality of life among patients using questionnaires ((EORTC) QLQ-C29,[12] EUROQOL EQ-5D-5L,[13] COREFO[14]).
4. Overall complication rate*
5. Surgical referral rate defined as the number of patients that are referred for trans-abdominal surgical management at 12months.
6. Cost effectiveness at 12 months.

* complications are defined as follows:

- *Intraprocedural peritoneal breach: the condition in which the abdominal cavity is visible from the colorectal lumen during the procedure because of mural tissue defects, that requires (1) (prolonged) admission or (2) surgery.*
- *Intraprocedural bleeding: bleeding that occurs during the procedure that cannot be controlled by standard local haemostasis techniques such as electrocoagulation or clips and that requires (1) transfusion or (2) termination of the TAMIS or ESD procedure.*
- *Postprocedural bleeding: bleeding within 30 days after the procedure resulting in (1) new presentation at the hospital, (2) hospital admission, transfusion (3) or (4) repeated intervention to obtain haemostasis.*
- *Postprocedural bowel perforation: a bowel perforation within 30 days after the procedure that is detected after completion of the procedure during which a peritoneal breach did not occur, diagnosed by abdominal pain with focal guarding and a rise in C-reactive protein and/or fever (T > 38.5 C) in combination with free air in the peritoneal cavity at abdominal CT.*
- *Postprocedural serositis: abdominal pain with focal guarding and/or fever (T > 38.5 C) within 30 days after the procedure, but without signs of perforation (free air at abdominal CT) and in the absence of another infection focus (urinary, pulmonary etcetera) that requires (prolonged) admission.*

Sample size calculation

The sample size was calculated for the primary outcome parameter, the cumulative recurrence rate at 12 months. To assess the non-inferiority of the ESD procedure the sample size calculation was based on the assumption that the recurrence rate will be 3% in the ESD group and 6% in the TAMIS group based on a systematic review of the literature specifically for studies performed in the West. If there is a true difference in favour of ESD of 3%, then 166 patients are required to be 80% sure that the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will exclude a difference in favour of the TAMIS of more than 6%. (Software: PASS Version 15– www.ncss.com). We have chosen a non-inferiority margin of 6% because we believe that this difference in risk of benign recurrence between the intervention group and usual care group is clinically acceptable. To allow for patients lost to follow-up (4%) and patients requiring additional surgical resection due to high risk characteristics (12%) in whom the primary outcome cannot be assessed, a total of 198 patients will be included; 99 patients in each arm. The incidence of large rectal non-pedunculated lesions in the Netherlands is estimated to be between 250 and 500 new cases a year. We estimated that the participation of 15 centres will be required to complete the inclusion period within 3 years. To avoid unnecessary delay, we will start this trial with 5 centres and will extend the number of centres during the course of the trial.

Ethics

This clinical investigation will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. This clinical investigation will comply with the practices set out in EN ISO14155:2011. This investigation was approved by the Medical Ethics Committee of the Leiden University Medical Center (NL61603.058.18). The study will be conducted according to the rules on medical research involving human subjects (Medical Research (Human Subjects) Act), in Dutch: Wet Medisch Wetenschappelijk Onderzoek met mensen (WMO). In addition, approval has been obtained from all of the participating hospitals: Amsterdam University Medical Center (Amsterdam Medical Center and Vrije Universiteit University Medical Center), University Medical Center Utrecht, Erasmus medical Center, IJsselland hospital, Alrijne hospital, Haaglanden Medical Center, Diakonessenhuis, Deventer hospital, Meander Medical Center and the St. Antonius hospital.

Data-analysis

To assess the non-inferiority of the ESD procedure, the difference between the cumulative recurrence rates at 12 months in both groups will be compared to the non-inferiority margin of 3% using a one-sided Mantel Haenszel test (with alpha 0.025) to account for stratification factors. For the other variables, normality will firstly be assessed. The secondary endpoints will be compared using the student t-test or Mann-Whitney U test and Chi-square or Fisher's exact test as appropriate. Multivariate regression will be considered for adjustment for possible confounding if necessary. The analysis will primarily be carried out on an intention-to-treat basis.

Economic evaluation

The Health Economic Expert responsible for the study will perform the Economic Evaluation. The economic evaluation will consist of a cost-effectiveness analysis from a healthcare perspective (CEA: costs per prevented recurrence) and a cost-utility analysis from a societal perspective (CUA: costs per QALY, estimated using the Dutch tariff for the EuroQol EQ-5D 5L at 0, 6 and 12months). Both analyses will be trial based, using patient reports, with a one-year time horizon. Costs will include the index interventions with hospitalisation (estimated from patient charts), subsequent hospital and non-hospital healthcare and productivity during the study follow-up (measured using patient questionnaires at 6 and 12 months).

Cost-price analyses will be performed for the TAMIS and ESD procedures, including procedure time, materials and anaesthesia. Other healthcare and societal costs will be valued and discounted according to the Dutch guidelines for economic evaluations.[15,16] Average costs and patient outcome will be compared according to intention-to-treat, using net-benefit analysis, and using multiple imputation to account for missing data.

Discussion

In 2010 The European Union published recommendations that colorectal cancer screening should be performed in all member states.[17] CRC screening reveals more large precursor lesions for which local excision may be the optimal treatment. However, the choice as to whether to perform local excision and with which technique is still unclear, especially in Western countries where Endoscopic Submucosal Dissection is being introduced slowly and remains controversial. As stated in the introduction, most lesions that are not overtly cancerous on endoscopic inspection are resected by pEMR in Western countries. The limitations of this technique which only allows sub optimal histological assessment are illustrated by the TREND study; 3 out of 87 (3%) patients had a carcinoma during follow-up after removal of a pT0 lesion in the piecemeal EMR group, versus none in the en bloc TEM group.[5] Malignant recurrence at the removal site of a benign adenoma occurs in approximately 1–2% of cases.[18,19] A possible explanation is pathological under staging with small areas of invasion being missed in the assessment of the pEMR specimens. A different explanation is remnant adenomatous tissue that progresses into a carcinoma. Surgical resection due to uncertain histology after pEMR of large lesions optically staged as benign occurs in 3.5% of cases.[20] These limitations are encouraging a shift away from pEMR towards en bloc resections of large rectal lesions. However, the en bloc resection method of choice is unclear. In 2017 the European Society for Endoscopy recommended that a comparison between ESD and local surgical resection is needed to guide decision making for the optimal approach for the removal of large rectal lesions in Western countries.[21] The reason ESD is compared to TAMIS, instead of TEM, in the TRIASSIC study is because TAMIS provides the benefits of advanced videoscopic transanal excision at a fraction of the cost of TEM.[11] No additional investment is required and the TAMIS port has a shorter shaft length, allowing an increased working angle and more distal dissection compared to the TEM port.[22] There are also suggestions that TAMIS may be less traumatic to the anal sphincter, compared to TEM.[23]

For this trial it was decided to include all rectal lesions >2cm, both including those clinically staged as benign and early invasive. It could be argued that the advantages of en bloc resection only outweigh the disadvantages in early invasive lesions. This is the basis for the Japanese indications for colorectal ESD where a lesion must have at least one high risk feature for early invasion. However, for reasons that are unclear, Western centres seem to be less good at recognising these high risk features with very high rates of “covert” cancer in lesions clinically staged as benign.[24,25] The likelihood of “covert” cancer is associated with lesion size, site within the colon and lesion morphology. In the rectum all clinically benign lesions >2cm have a >5% chance of harbouring a focus of “covert” cancer, regardless of morphology. Piece meal EMR is therefore an inappropriate treatment in at least 5% of rectal lesions >2cm. We feel that this is unacceptably high and that en bloc resection is justified in all rectal lesions

> 2 cm. Similarly, clinical staging of massive invasion (>T1 sm1) is also only accurate in 50% in expert Western centres.[25] In the other 50% local en bloc resection would have been sufficient. Cross sectional imaging with MRI or Endoscopic Ultrasound does not improve this.[26] Likewise, determination of the N status of rectal lesions is problematic. MRI has been shown to have a sensitivity of 94% and a specificity of only 67%.[27] A systematic review of the performance of Endoscopic Ultrasound (EUS) showed a pooled sensitivity of 73.2% and a pooled specificity of 75.8%.[28] The consequence of the poor performance of the preoperative staging methods is that the staging of early stage cancers is increasingly being performed by the histology sample obtained by diagnostic en bloc resection. This approach has already been formalized for other early GI cancers such as oesophageal cancers[29] but not yet for rectal cancer. Diagnostic resection allows accurate pathological examination but only if performed en bloc and when care is taken to ensure optimal orientation of the specimen.

The TRIASSIC study is the first direct comparison between rectal en bloc resection techniques in a randomised setting in a Western population. The TRIASSIC study will increase the current knowledge as to which is the preferred minimally invasive resection method for rectal en bloc resections. This is important as the detection rate of large rectal lesions (polyps and early cancers) has greatly increased with the introduction of CRC screening. This study will support the optimal use of healthcare resources in the future.

Supplementary materials

The participant information sheet is available online as Additional file 1 at https://bmcgastroenterol.biomedcentral.com/

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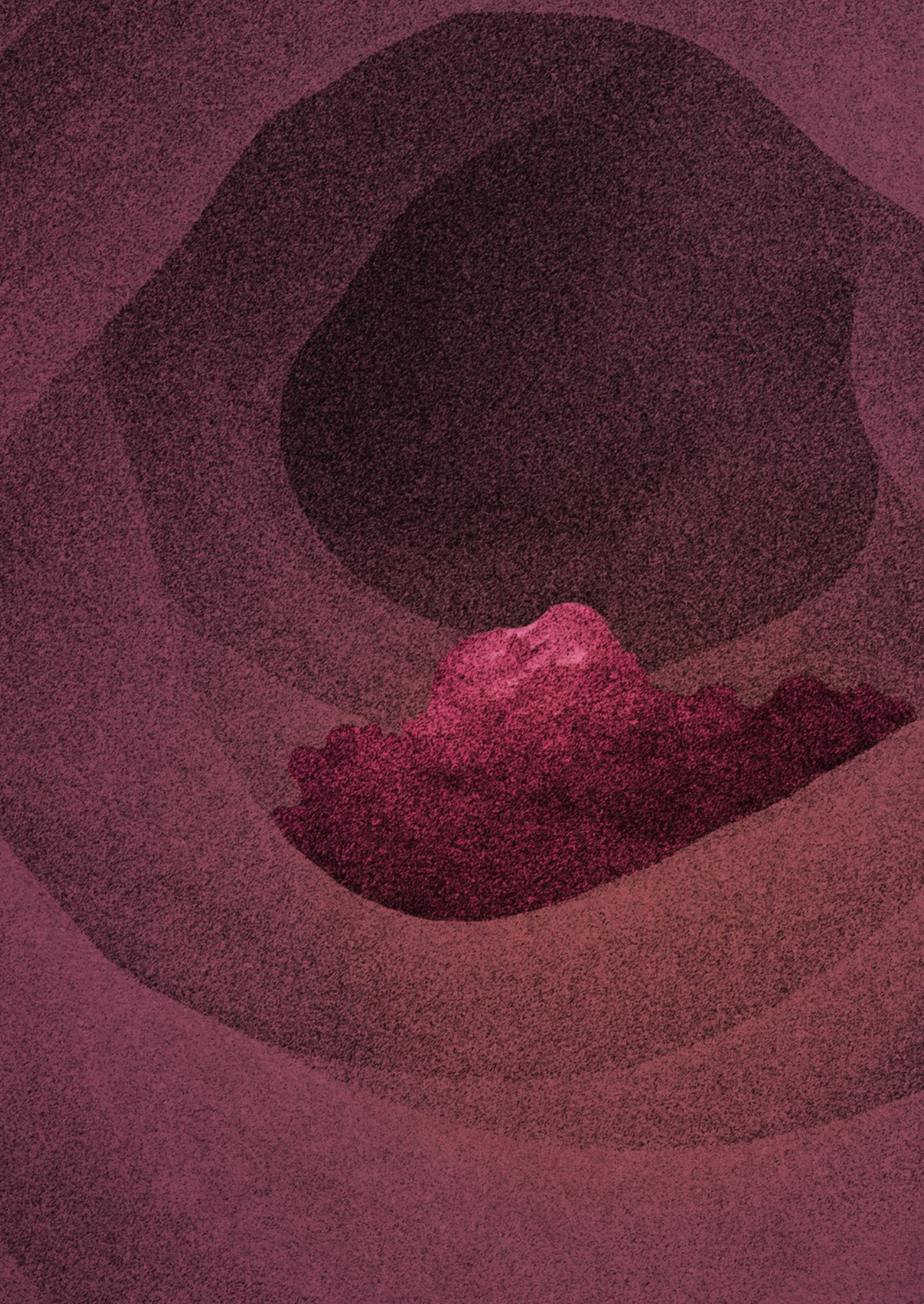

CHAPTER 5

Physical recovery after local resection of nonpedunculated rectal adenomas and T1 carcinomas: endoscopic submucosal dissection versus transanal minimally invasive surgery

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Gastrointestinal Endoscopy 2025

Abstract

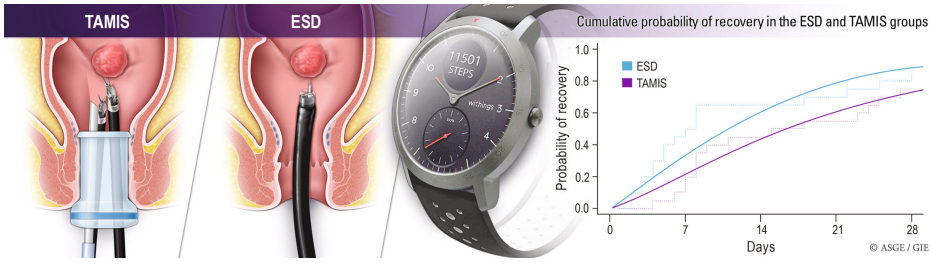
Background and Aims: Rehabilitation of physical activity is an important functional outcome after endoscopic surgery. Our aim was to quantitatively assess recovery after endoscopic submucosal dissection (ESD) and transanal minimally invasive surgery (TAMIS).

Methods: In the TRIASSIC study (Netherlands Trial Registry: NL7083), patients with rectal polyps >20 mm were randomized between ESD and TAMIS. This ancillary study used smartwatches to track activity data for a 14-day preoperative baseline period and a 28-day postoperative recovery period. The primary end point for noninferiority was the mean time to recovery (≥90% of baseline step count for 2 consecutive days), assessed by means of Weibull regression with a 7-day noninferiority margin.

Results: Forty patients were included: 20 ESD and 20 TAMIS procedures. Median lesion size was 42.5 mm (interquartile range [IQR], 25-50), with 17.5% pT1RCs and 82.5% nonmalignant rectal polyps. Compliance with smartwatch measurements was 98.4% (IQR, 94.2-100). Within the 28-day timespan, 17 patients (85%) in the ESD group recovered and 15 (75%) in the TAMIS group (P = .43). Mean recovery times were 13.9 days for ESD and 21.0 days for TAMIS, indicating noninferiority of ESD (95% confidence interval of difference, −3.41 to 20.25). Recovery as measured by smartwatch significantly correlated with self-reported recovery (Spearman rho, 0.644; P < .001). Moderate to severe pain scores (≥4 out of 10) were reported by 15 patients (42.9%): in 27.8% of the ESD group and 58.9% of the TAMIS-group (P = .06). Increased pain scores were significantly associated with decreased physical activity (P < .01).

Conclusions: In terms of mean time to physical recovery, ESD was noninferior to TAMIS. Post-procedural pain was significantly associated with reduced physical activity.

Graphical abstract



Introduction

Nationwide screening programs have increased the detection rate of advanced rectal adenomas and early-stage, T1, rectal cancers.[1] Local en bloc resection techniques are recommended as first-line treatment for these neoplasms and are deemed to be curative if high-risk features for locoregional or distant metastases are absent.[2] In this context, both endoscopic submucosal dissection (ESD) and transanal minimally invasive surgery (TAMIS) have emerged as primary resection techniques for achieving a local en bloc resection. Although ESD and TAMIS are considered standard-of-care approaches, their relative merits remain to be fully elucidated owing to a lack of direct comparative trials. The TRIASSIC trial aims to address this knowledge gap as the first randomized study to directly compare both resection techniques on effectiveness, safety, and cost-effectiveness.[3]

In the context of value-based health care, functional recovery and patient-reported outcomes have become increasingly important outcome parameters.[4,5] After ESD and TAMIS, patients typically undergo a brief in-hospital observation before being discharged to continue their recovery at home. A recent study highlighted considerable unmet information needs among T1 colorectal cancer patients regarding their physical recovery.[6] To date, quantitative data on recovery of ESD and TAMIS are lacking, and only 1 questionnaire-based study assessed how long patients perceived their recovery to take.[7] Therefore, further characterization of this recovery phase could provide valuable insights for preoperative consultations and possibly identify patients who might benefit from prehabilitation or postsurgical physical therapy. Wearable accelerometers present a promising method to quantitatively assess physical activity during this recovery phase, as demonstrated previously in patients undergoing abdominal surgery.[8,9]

The present study aimed to evaluate and compare physical recovery after ESD and TAMIS with the use of a wearable accelerometer as quantitative measure, while also correlating the accelerometer data with self-reported recovery times.

Methods

Design and ethics

This study was an ancillary study of the TRIASSIC trial; a multicenter randomized trial comparing the effectiveness, safety, and cost-effectiveness of ESD and TAMIS for the resection of nonpedunculated rectal lesions. The study protocol for the TRIASSIC study has been described previously.[3] Ethical approval was obtained from the Medical Ethics Committee, Leiden, the Hague, and Delft (NL61603.058.18). All patients provided written informed consent before participation.

Population

This study was conducted from October 2020 to December 2022 in 2 tertiary hospitals (Leiden University Medical Center and Amsterdam University Medical Center) and 3 community hospitals (Haaglanden Medical Center, IJsselland Hospital, and Alrijne Hospital) in collaboration with the Center for Human Drug Research. The study followed the inclusion and exclusion criteria of the TRIASSIC trial with the addition of the fourth and fifth exclusion criteria:

- Inclusion criteria: (1) non-pedunculated lesion >20 mm in the rectum, with the bulk of the lesion below 15 cm from the anal verge found at endoscopy; (2) ≥18 years of age.
- Exclusion criteria: (1) features of advanced disease or deep-submucosal invasion at optical endoscopic evaluation or cross-sectional imaging; (2) previous endoscopic resection attempt; (3) risks of treatment exceed the benefits; (4) wheelchair dependency at baseline; (5) inability to wear or use a smartwatch.

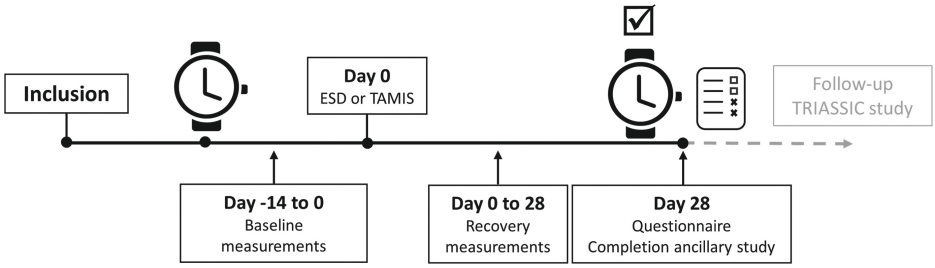
Study procedures

Patient enrollment occurred concurrently with that of the main trial. On inclusion, patients were randomized between ESD and TAMIS in a 1:1 ratio. Randomization was stratified for polyp size (<40 mm or ≥40 mm) and distance to the dentate line (<10 mm, 11-99 mm, or 100-150 mm). ESD and TAMIS procedures were executed at the discretion of an experienced gastroenterologist or surgeon, as previously described.[3] The dissection plane of TAMIS was either intermuscular or full-thickness. Endoluminal suturing was used only in case of a full-thickness resection to close the endoluminal defect. For sedation, ESD was performed with the use of propofol sedation, whereas TAMIS was performed with the patient under general anesthesia. Local analgesics, such as ropivacaine or bupivacaine (eg, via block or tissue infiltration), were recommended for both procedures. In both groups, patients were instructed to take paracetamol (acetaminophen) if pain occurred, and in cases where more pain was expected (eg, involvement of dentate line, pain during hospital observation), opioid analgesics were prescribed to be taken as needed. Regarding recovery instructions, surgical patients were typically advised to avoid lifting heavy objects during the first 2 weeks after surgery, particularly when suturing was involved. Beyond this, no other restrictions were placed on patients in either group, and early resumption of physical activity was emphasized as vital for the recovery process.

Study procedures are outlined in Figure 1. This study spanned 6 weeks, starting 2 weeks before resection. Patients were instructed to wear a Withings Steel heart rate smartwatch (Withings, Issy-les-Molineux, France) continuously throughout this period to monitor step count, heart rate, and sleep duration. Data synchronization occurred daily via a Motorola G6 smartphone (Motorola, Chicago, Ill, USA) using the HealthMate application. Both devices were previously used in a similar home-based setting.[10] The 2

weeks preceding treatment served as the baseline measurement, and the subsequent 4 weeks were considered the recovery period. The 28-day timespan was determined based on a previously reported study,[7] which described an average self-reported recovery time of 20 days after endoscopic resection. Efforts were made to minimize patients' awareness of activity parameters by concealing the total step count visuals. Patients could still view the percentage of daily step goals reached, which was set at the maximum of 20,000 steps to minimize the potential motivational impact it could have. However, patients were not informed that the limit was set at 20,000 steps.

Figure 1. Flow-diagram of study procedures. *ESD* Endoscopic submucosal dissection, *TAMIS* Transanal minimally invasive surgery.



During the initial 2 weeks of the recovery phase, patients were instructed to record pain scores (range, 0-10) twice daily in a numeric pain journal. On study completion, patients were asked to complete a questionnaire regarding their experience with the study devices ("Was it clear how to use the study devices?" "Did you experience wearing the smartwatch as burdensome?" "Did you feel stimulated to be more physically active by wearing the smartwatch?") and time to recovery ("After how many weeks did you feel like your normal self?"). Thereafter, follow-up was carried out in accordance with the TRIASSIC study protocol.[3] Patients were excluded and replaced if local resection was unsuccessful, defined as termination of the procedure without tumor removal, or if baseline measurements were insufficient owing to reasons unrelated to device compliance or tolerability (<7 days with a wear time of ≥50%).

Outcomes

The primary end point of this study was time to physical recovery. Physical recovery was defined as achieving or surpassing 90% of the baseline average step count, as established in previous studies,[11,12] with the additional requirement that this level must be maintained for 2 consecutive days. Secondary end points included smartwatch tolerability, the percentage of patients recovered within 4 weeks, an exploratory analysis of factors influencing physical recovery, the correlation between perceived (i.e. questionnaire) and objective (i.e. smartwatch) recovery, and the description of step count, heart rate, and sleep duration trajectories during the recovery phase.

Tolerability and quality assurance

Tolerability was assessed via the end-of-study questionnaire and device compliance. Compliance was determined by dividing the number of observations in the data set by the expected observations, based on total wear time. Hours lacking registered heart rate and step count were deemed noncompliant, indicating not worn. Compliance also ensured data representativeness; days with <50% wear time during daytime (6 am–10 pm) or nighttime (0 am–5 am) were excluded from respective analyses, as consistent with previous studies.[13,14]

Statistical analyses

For data visualization and analysis, R version 4.1.0 was used (with packages lme4, emmeans, and ggeffects). Data aggregation and tabulation were performed using PySpark version 2.4.6 (Apache Software Foundation, Forest Hill, Md, USA). We aimed to determine if physical recovery after ESD was noninferior to TAMIS, defined by a noninferiority margin of 7 days in mean time to recovery. Owing to right-censoring in both groups, where patients did not meet the recovery criteria within the 28-day timespan of the study, the original analysis plan to assess noninferiority via *t* test was adapted to a Weibull regression analysis. The estimated parameters from the Weibull regression were used to calculate the mean time to recovery in both groups, and percentile bootstrapping was applied to calculate a confidence interval (CI) for the difference in mean time to recovery.[15] This approach ensured that the original scale for the noninferiority definition was respected despite the presence of right-censoring. The Mann-Whitney *U* test was used to compare continuous variables. The Fisher exact test was used to compare categorical data. The Kruskal-Wallis test was used to assess differences between the medians of 3 or more independent groups. The Spearman rank correlation coefficient was used to evaluate the relationship between recovery time as measured by smartwatch and subjective time to recovery reported via questionnaire. Univariate analyses were performed with the use of Cox proportional hazards regression models.

Details on the normalization of baseline physical activity, the mixed-effects models used for analysis, and the exploration of correlations between post-procedural pain and daily physical activity can be found in the supplementary methods.

Sample size calculation

To demonstrate noninferiority of ESD, based on an expected recovery time of 20 days after both ESD and TAMIS,[7] a noninferiority margin of 7 days, a significance level of 5%, and a power of 90%, a total of 18 patients were required in each arm, based on a *t* test. To account for loss to follow-up or device malfunction, a total of 40 patients were included (20 in each arm).

Results

The study population consisted of 40 patients, with 20 patients in the ESD group and 20 patients in the TAMIS group. A flow diagram illustrating the selection process is presented in Figure 2. One patient was replaced in each group: in the ESD group owing to termination of the procedure without tumor removal, prompted by the suspicion of deep muscular invasion, later confirmed by histologic assessment of the surgically resected specimen; and in the TAMIS group because the procedure was executed prematurely, resulting in only 3 days of baseline measurements. Baseline characteristics and activity data recorded at baseline are presented in Table 1. The mean daily step counts at baseline were 3414 steps in the ESD group and 3406 in the TAMIS group. In the ESD group, all but 1 patient received a local injection of either ropivacaine (1 unit, 20 mL, 7.5 mg/mL) or bupivacaine (1 unit, 20 mL, 2.5 mg/mL). In the TAMIS group, all patients received a local anesthetic block with similar dosages of either ropivacaine or bupivacaine.

Figure 2. Flowchart of patient selection. Patients were replaced if local resection was unsuccessful, defined as termination of the procedure without tumor removal, or if baseline measurements were insufficient due to reasons unrelated to device compliance/tolerability (<7 days with a wear time of at least 50%). *ESD*, Endoscopic submucosal dissection, *TAMIS* transanal minimally invasive surgery.

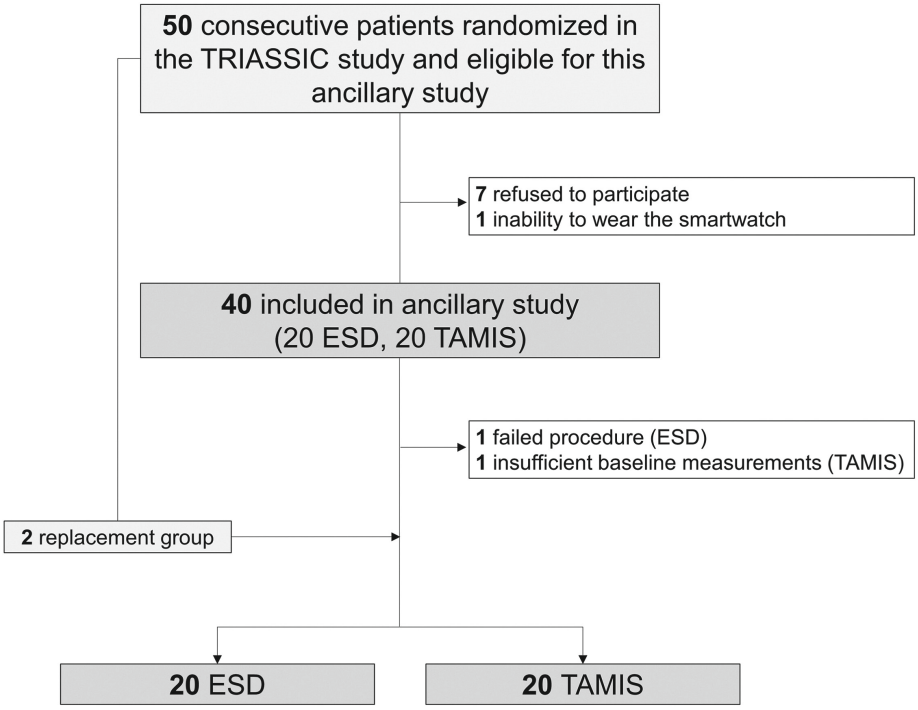


Table 1. Baseline characteristics and activity measurements

	ESD (n=20)	TAMIS (n=20)
Age, years, mean (SD)	66.1 (7.3)	67.2 (7.7)
Sex, male	10 (50)	7 (35)
Body Mass Index, mean (SD)	25.2 (5.3)	26.9 (5.4)
CCI score, median (IQR)	2 (1)	3 (1)
Polyp size, mm, mean (SD)	45.5 (20.4)	46.8 (26.8)
Polyp distance to dentate line		
< 1cm	6 (30)	4 (20)
1-15cm	14 (70)	16 (80)
Polyp orientation in the rectum*		
Involvement of ventral wall	7 (35)	16 (80)
Only dorsal and lateral orientation	13 (65)	4 (20)
Duration procedure, minutes, mean (SD)	101 (38.9)	72.6 (36.2)
Dissection plane		
Submucosa	20 (100)	1 (5)
Inter-muscular	-	13 (65)
Full-thickness	-	6 (30)
Admission time, days, mean (SD)	1.8 (0.8)	2.3 (1.7)
Histology		
Benign	16 (80)	17 (85)
T1	4 (20)	3 (15)
Daily step count at baseline, mean (SD)	3413 (1346)	3406 (1345)
Heart rate at baseline, beats per minute, mean (SD)	73.8 (7.2)	73.2 (7.3)
Sleep duration at baseline, hours, mean (SD)	7.5 (1.4)	7.6 (1.4)

Data are shown as mean ± SD, n (%), or median (interquartile range).
* Based on magnetic resonance imaging.
ESD Endoscopic submucosal dissection, *TAMIS* transanal minimally invasive surgery.

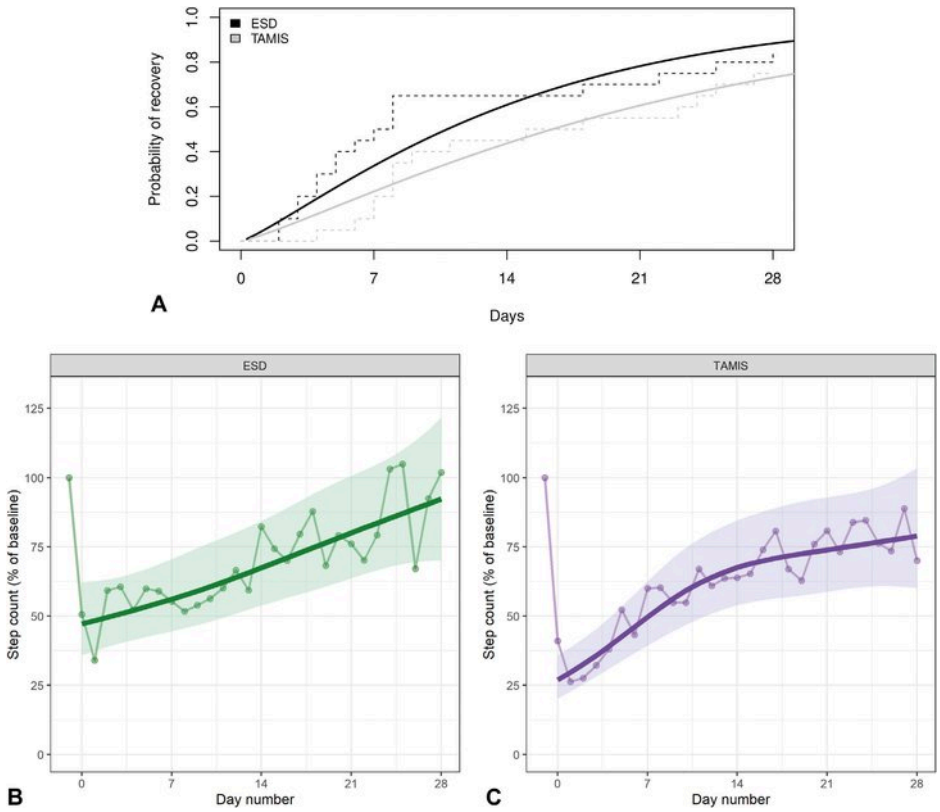
Recovery and physical activity

The mean times to recovery were 13.9 days for patients undergoing ESD and 21.0 days for those undergoing TAMIS (95% CI for the difference, −3.41 to 20.25), proving noninferiority of ESD (Figure 3A). The goodness of fit of the Weibull regression model was graphically assessed and appears reasonable (Figure 3A). Within the 28-day timespan, 17 patients (85%) in the ESD group and 15 (75%) in the TAMIS group met the predefined criteria for physical recovery (P = .43).

Overall estimated physical activity trajectories, categorized by treatment group, are displayed in Figure 3B and C. On average, the daily step count decreased to 30.1% of baseline, with reductions to 34.0% in the ESD group and 26.2% in the TAMIS group.

During the initial 6 days, the estimated step count relative to baseline was consistently higher in the ESD group. The most significant disparity occurred on the second day (59.3% vs 27.6% of baseline step count). On the last 2 days of measurements, the estimated percentages of baseline step count were 92.3% to 101.9% for ESD and 70.0% to 88.9% for TAMIS. The individual patient physical activity trajectories are presented in Supplementary Figure 1 (ESD group) and Supplementary Figure 2 (TAMIS group).

Figure 3. Cumulative probability of recovery in ESD and TAMIS groups (**A**). Dashed lines represent empirical estimates (i.e. Kaplan-Meier) and solid lines represent Weibull-regression model estimates. Estimated recovery trajectories of ESD (**B**) and TAMIS (**C**). The individual dots indicate the estimated population mean of physical activity; shaded areas represent the estimated 95% confidence intervals of the mean. A steeper initial decline in step count is observed in the TAMIS group, whereas the end-of-study step count compared with baseline is greater in the ESD group. *ESD* Endoscopic submucosal dissection, *TAMIS* transanal minimally invasive surgery.



Potential factors influencing physical recovery

Baseline characteristics, activity metrics, and pain scores stratified by recovery within the 28-day time frame are presented in Table 2. In the exploratory univariate analysis, a larger polyp size, greater proximity to the dentate line, and higher pain scores in

the first week after resection were found to be significantly associated with failure to achieve recovery within the 28-day time frame (Table 2). In the nonrecovered group, the median polyp size was 55 mm, the distance to the dentate line was 5 mm, and the pain score in the first postoperative week was 4.3 out of 10. In the recovered group, the corresponding values were 40 mm, 35 mm, and 0.4.

Tables 2. Exploratory univariate analysis using the Cox proportional hazards model to assess factors associated with reaching recovery within 28 days

Study variable	**Recovered within 28 days**		**Hazard ratio (95% CI)**	**p-value**
	Yes (n=32)	**No** (n=8)		
Age, median (IQR)	65.5 (13)	69.5 (7)	0.961 (0.914-1.010)	0.117
Male, n (%)	20 (87.0)	3 (13.0)	-	0.072
Female, n (%)	12 (70.6)	5 (29.4)	0.515 (0.250-1.061)	
BMI, median (IQR)	24.9 (8.1)	28.9 (9.7)	0.973 (0.916-1.033)	0.368
CCI, median (IQR)	3.0 (1)	2.5 (1)	1.002 (0.844-1.189)	0.985
Daily step count at baseline, mean (SD)	5175.5 (3662.9)	4387.3 (3961.3)	1.037 (0.951-1.130)*[1]	0.409
Polyp diameter, mm, median (IQR)	40.0 (25)	55.0 (35)	0.973 (0.953-0.993)	0.007†
Polyp distance to dentate line, cm, median (IQR)	3.5 (40)	0.5 (28)	1.011 (1.002-1.020)	0.014†
Involvement of ventral rectal wall				
No, n (%)	12 (37.5)	5 (62.5)	-	0.495
Yes, n (%)	20 (62.5)	3 (37.5)	1.284 (0.626-2.632)	
Dissection plane				
Submucosa, n (%)	17 (85)	3 (15)	-	0.590
Intermuscular, n (%)	12 (85.7)	2 (14.3)	0.813 (0.382-1.728)	0.366
Full-thickness, n (%)	3 (50)	3 (50)	0.366 (0.107-1.246)	
TAMIS procedure, n (%)	15 (75)	5 (25)	-	0.164
ESD procedure, n (%)	17 (85)	3 (15)	1.640 (0.817-3.291)	
Pain score first week post-op‡, median (IQR)	0.4 (3.4)	4.3 (3.9)	0.743 (0.616-0.895)	0.002†

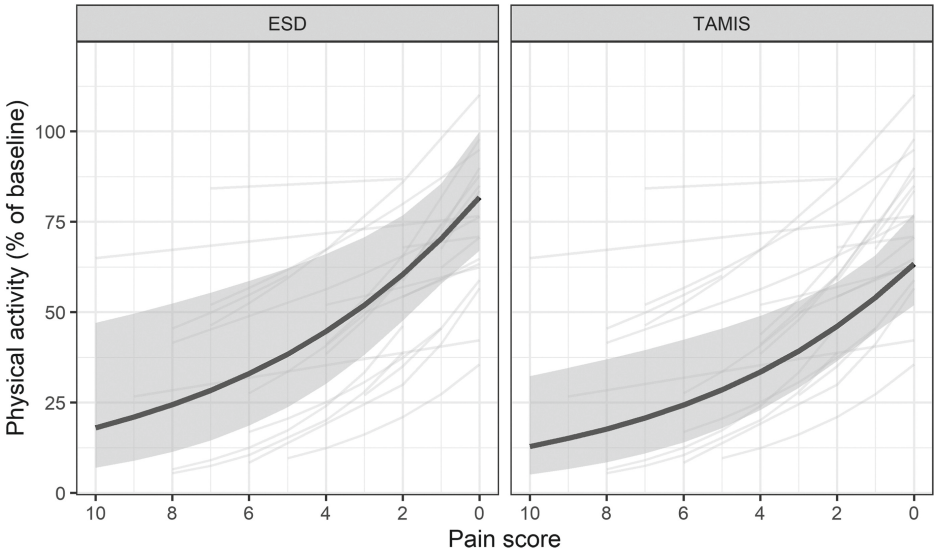
Values are shown as n (%), median (interquartile range), or mean ± SD.
BMI Body mass index, *CCI* Charlson comorbidity index, *CI* confidence interval, *ESD* endoscopic submucosal dissection, *TAMIS* transanal minimally invasive surgery.
* Hazard ratio and 95% CI are reported per 1000 steps.
† P < .05.
‡ Self-reported pain scores (n = 35); 5 patients did not complete the pain diary.

Post-procedural pain and physical activity

The pain journal was completed by 35 patients (87.5%). In the first week, moderate to severe pain scores (ie, ≥4) were reported by 15 patients (42.9%): 5 of 18 (27.8%) in the ESD group and 10 of 17 (58.9%) in the TAMIS group ($P = .06$). In the second week, moderate-severe pain scores were reported by 6 of these patients (17.1%), 3 in each group. No statistical significant difference in pain score was observed on any day.

Pain scores were significantly associated with the level of physical activity compared with baseline (Figure 4). For all patients, for every 1-point increase in pain score, step count compared with baseline decreased by 14% (95% CI, 8%-20%; $P < .001$). In the ESD group, for every 1-point increase in the pain score, step count compared with baseline decreased by 14% (95% CI, 4%-23%; $P = .009$). In the TAMIS group, for every 1-point increase in the pain score, step count compared with baseline decreased by 15% (95% CI, 5%-23%; $P = .005$).

Figure 4. Mixed effects model investigating the relationship between pain score and physical activity. Pain scores were significantly associated with the level of physical activity compared to baseline. *ESD* Endoscopic submucosal dissection, *TAMIS* transanal minimally invasive surgery.



Perceived time to recovery

In the end-of-study questionnaire, 19 patients (47.5%) reported being recovered within 2 weeks, 7 (17.5%) reported recovery in the third or fourth post-procedural week, and 13 (32.5%) did not feel recovered at the end of the study. One patient (2.5%) did not complete the questionnaire. Recovery time as measured by the smartwatch significantly correlated with the self-reported time to recovery in the questionnaire (Spearman correlation coefficient = 0.644; $P < .001$). Supplementary Figure 3 displays

the physical activity trajectories categorized by the times in which patients reported they had recovered in the end-of-study questionnaire.

Compliance and tolerability

The overall median compliance with HR, physical activity and sleep duration measurements combined was 98.4% (interquartile range [IQR], 94.2-100). Median compliance was highest for heart rate measurements (100%; IQR, 97.7-100) and lowest for sleep duration measurements (97.7%; IQR, 90.7-100). Supplementary Figure 4A illustrates the compliance of the smartwatch data, categorized by treatment group. Compliance did not differ between the ESD and TAMIS groups (98.4% vs 98.8%, respectively; *P* = .40).

Thirty-seven patients (94.9%) reported that they found the devices easy to use, and 2 patients needed assistance from a family member. Of the participants, 32 (80%) found the study devices nonburdensome, 5 (15%) were neutral, and 2 patients (5%) found them burdensome. The reported level of burden did not significantly correlate with compliance to activity measurements (*P* = .24 in the ESD group, *P* = .6 in the TAMIS group) (Supplementary Figure 4B). Patients who indicated that they found their use to be burdensome were nonetheless sufficiently compliant with the devices. Four patients (10.3%) stated in the questionnaire that wearing the smartwatch motivated them to be more active, 26 patients (66.7%) reported no change, and 9 patients (23.1%) were neutral on the matter.

Heart rate and sleep duration trajectories

The daily average heart rate during baseline and recovery measurements are shown in Supplementary Figure 5A. The heart rate of patients in the TAMIS group remained roughly stable throughout the study. In the ESD group, there were minor fluctuations around the time of the procedure. On the day before the procedure (ie, day −1), the average heart rate of patients in the ESD group was lower than in the TAMIS group. The day after the procedure, this trend reversed. For the rest of the baseline period, recovery period, and the day of the procedure, the heart rate was similar between the groups.

Average sleep duration trajectories measured by the accelerometer are shown in Supplementary Figure 5B. Apart from the day of the procedure, when the ESD group showed a greater decrease in sleep duration and the TAMIS group had relatively longer sleep duration, no major differences were seen between the groups.

Discussion

This study revealed that the average physical recovery time after ESD (13.9 days) was noninferior to TAMIS (21.0 days); 8 (20%) of the 40 patients overall did not achieve physical recovery within 28 days: 3 in the ESD group and 5 in the TAMIS group. In addition, a significant association was observed between post-procedural pain and reduced physical activity. This is the first study to quantitatively assess physical recovery after ESD and TAMIS, providing empirical evidence on their recovery trajectories and recovery times.

The overall recovery trajectories of ESD and TAMIS identified in this study align with existing literature from studies that also used accelerometers to assess recovery of other procedures, showing stable baseline activity levels, an initial post-procedural decline in step count, and gradual recovery toward baseline levels.[12,16-18] Specific activity metrics of the recovery trajectories also aligned with those of other surgeries. After 4 weeks, the ESD group's step count relative to baseline resembled that for inguinal hernia repair patients (open, laparoscopic, or robotic approach), and the TAMIS group was more similar to patients undergoing minimally invasive abdominal surgery (eg, cholecystectomy, segmental colectomy, abdominal wall hernia repairs, or prostatectomy via laparoscopic or robotic approach).[18] These consistencies across studies validate our methodology and recovery time estimates, and help to contextualize the recovery trajectories of ESD and TAMIS with other types of surgery.

Despite noninferiority in recovery times, ESD showed several favorable differences during the recovery phase, including a less steep decline in step count and a higher proportion of patients recovering within 28 days. Because both groups were balanced in confounders owing to the randomized design and similar post-procedural care (eg, pain management strategy, duration of admission), these differences likely stem from the less invasive character of the ESD procedure. Notably, moderate to severe pain scores, which we have shown to be associated with decreased physical activity, were more common in the TAMIS group during the first post-procedural week. This may be due to greater tissue damage from a deeper dissection plane and the potential need for endoluminal suturing for full-thickness resections in the TAMIS group. In addition, post-procedural pain in the TAMIS group may have been further exacerbated by the insertion of the transanal access platform or the occasional use of anal retractors, which are not used during the ESD procedure. Based on previous literature, it is unlikely that the difference in anesthesia technique (propofol sedation vs general anesthesia) contributed to these findings.[19]

When the current definition of physical recovery was used, which correlated with patient perception of recovery, a substantial number of patients (20%) did not recover within 28 days. Preoperative identification of patients at risk for slower recovery could

enhance patient care by better management of patient expectations and more targeted monitoring. Owing to the study's primary aim and corresponding sample size, we could perform only an exploratory univariate analysis of potential risk factors for nonrecovery. That analysis showed that increased polyp size and proximity to the dentate line were associated with not achieving recovery within 28 days. Interestingly, those factors were significantly correlated with the average pain score in the first week after surgery, which also emerged as a significant postoperative factor associated with nonrecovery in univariate analysis. Future studies with larger sample sizes should further explore these potential risk factors to further improve preoperative planning and patient outcomes. An alternative to preoperative risk identification is to use wearables for postoperative at-home monitoring. By tracking recovery trajectories, wearables can detect slower-than-expected recovery early on, enabling timely intervention.

We found a significant correlation between the objective physical recovery times measured by smartwatch and patient-reported recovery times. Although questionnaires might thus capture a rough estimate of recovery times, continuous at-home monitoring with smartwatches offers the optimal balance of close monitoring coupled with the benefits of early hospital discharge. It might capture fluctuations and trends that intermittent questionnaires more easily miss. Moreover, quantitative wearable data have the potential to provide more reliable and accurate assessments by reducing biases and inaccuracies inherent in self-reported data, such as recall bias or subjective interpretation of questions. Although wearables are more onerous than questionnaires for some, our study demonstrated that, with proper counselling, satisfactory adherence can be achieved, which exceeded that of most previous studies.

Several limitations of this study should be acknowledged. First, the 28-day monitoring period might not capture all recovery trends. Extending this period in future studies could provide more detailed recovery data by allowing more patients to meet the criteria for recovery but may reduce patient compliance. Second, despite patients mostly being unaware of their activity metrics, their awareness of being observed likely influenced their activity levels during both the baseline and recovery period (Hawthorne effect), affecting more than the ±10% of patients who reported increased physical activity due to the study. However, if this awareness was present in the pre- and post-procedural periods, its impact on the primary end point may be limited. Third, the need to adapt the original analysis plan to account for unexpected right-censoring while reporting in the original scale in terms of mean recovery time required the use of a parametric Weibull regression model. This approach implies assumptions regarding the underlying distribution of the time to recovery and the proportional hazard assumption. Although visual inspection suggests that our choice is reasonable, it might introduce bias in the estimated difference in mean time to recovery. Finally, relying on step count as the primary metric for physical activity may not fully capture other important aspects of recovery, such as range of motion or muscle strength. If noninvasive well tolerated

methods become available to measure these additional aspects, future studies should try to incorporate them.

This study has several implications for clinical care. First, these findings provide valuable information to improve information provision in outpatient clinics and address previously reported unmet information needs involving the post-treatment course.[6] In addition, the study emphasizes the occurrence of post-procedural pain and its negative impact on activity levels, highlighting the need for vigilant monitoring and effective pain management during the recovery phase. Moreover, we have identified increased polyp size and proximity to the dentate line as potential preoperative risk factors for slower recovery after ESD and TAMIS that warrant further investigation. Finally, with the understanding of average recovery trajectories, at-home monitoring can aid in early identification of patients not recovering as expected who might be at risk of readmission or adverse events.

Conclusion

In this prospective randomized study, we established through at-home monitoring with smartwatches that physical recovery after ESD is noninferior to TAMIS, with mean recovery times of 13.9 days and 21.0 days, respectively. In addition, a significant association was shown between post-procedural pain and reduced physical activity. These findings can be used to optimize information provision and improve post-procedural care.

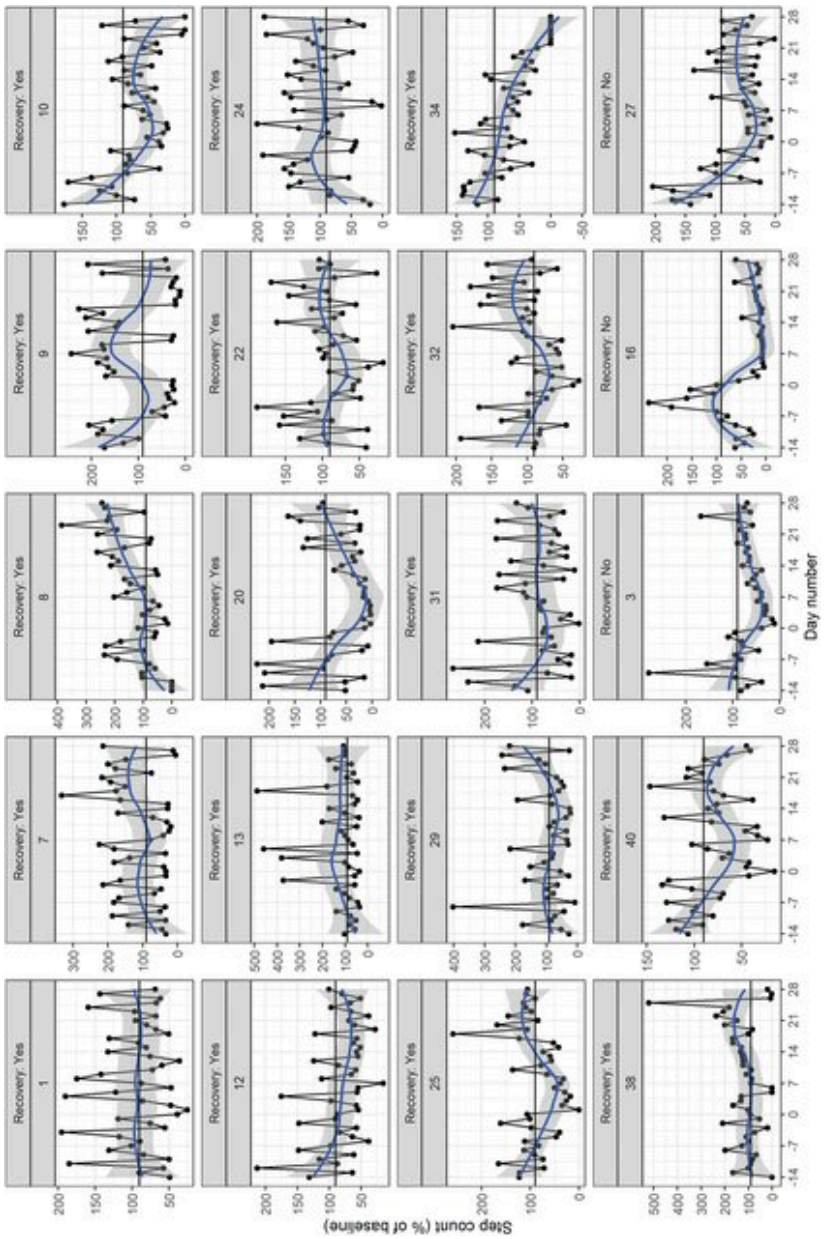
Supplementary materials

Supplementary methods

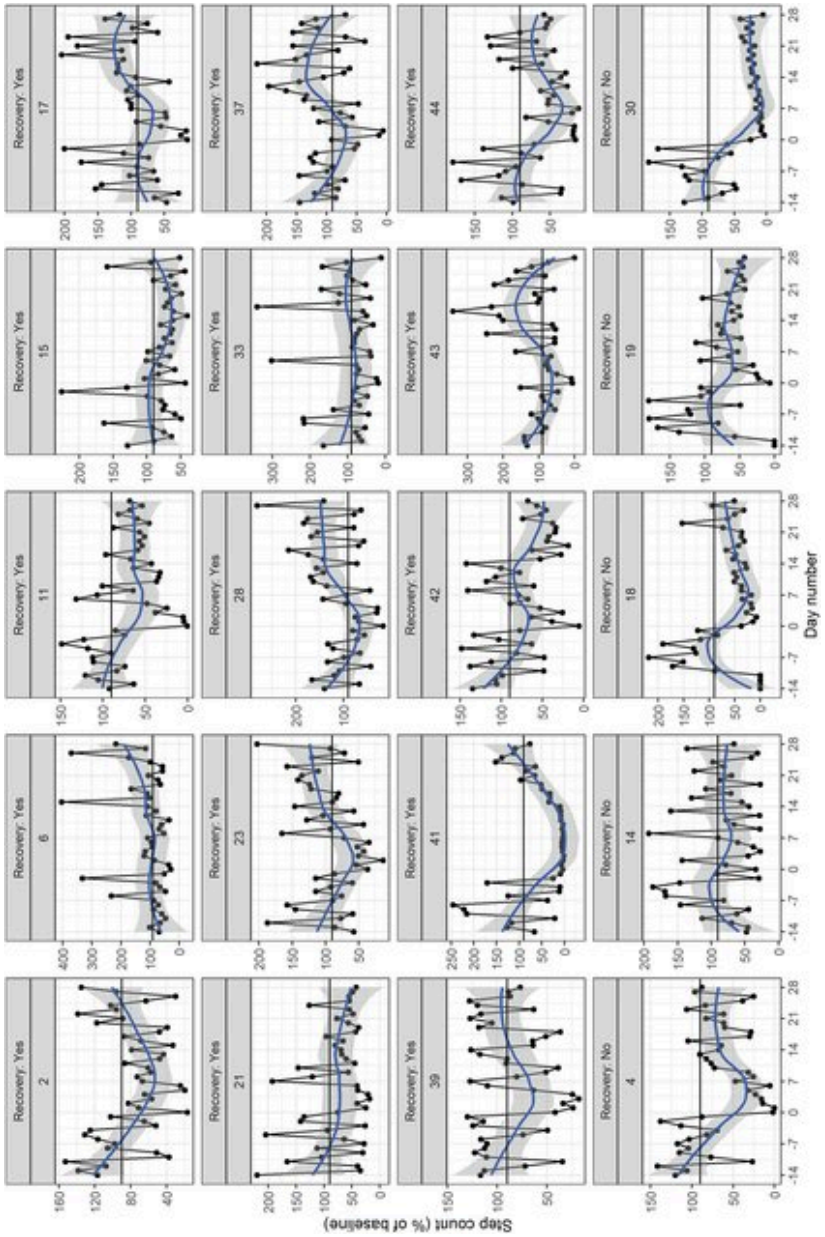
To account for differences in baseline physical activity, step count per day throughout the study period was normalized as a percentage relative to the average step count in the baseline period. Then, a mixed-effects model was fitted with the log-transformed step count percentage as the dependent variable and with time, wear time, day type (weekday, weekend day) and procedure (ESD or TAMIS) as fixed factors, with subjects as random intercepts. Additionally, a smoothed average was visualized via an identical mixed-effects model where time was fitted as a natural spline from the day of the procedure onward.

To study whether post-procedural pain influenced daily physical activity, a correlation between daily pain score and daily physical activity was explored. A mixed-effects model was fitted with the log-transformed step count percentage as the dependent variable and pain score, procedure, wear time and day type as fixed factors, with pain score as a random slope and subjects as random intercepts. The average trend was estimated per procedure.

The average heart rate per day and sleep duration per day were estimated using a mixed-effects model with time and procedure as fixed factors and subject as random intercepts. Additionally, the average heart rate per hour was estimated for each procedure and across separate study phases (baseline period, procedure day -1 day, procedure day, procedure day +1 day, recovery period) via a mixed-effects model with hour of the day, study phase, and procedure as fixed factors and subjects as random intercepts.

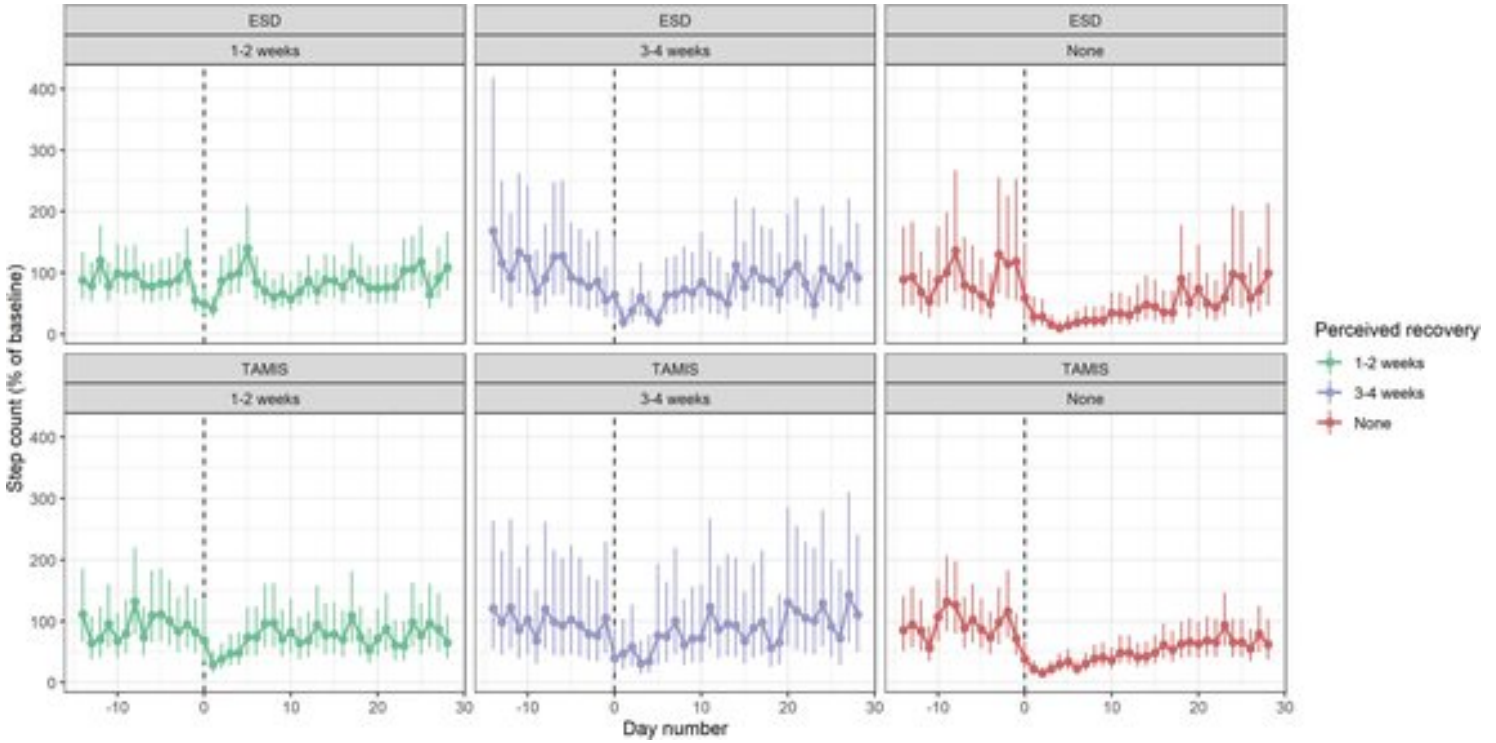


Supplementary Figure 1. Individual recovery plots for the endoscopic submucosal dissection group. The *dots* represent daily step counts relative to baseline. The *horizontal black lines* indicate 90% of baseline activity. The *blue lines* depict the trend in recovery trajectory. For each individual plot, it is indicated whether the criteria for recovery were met within the 28-day time frame.

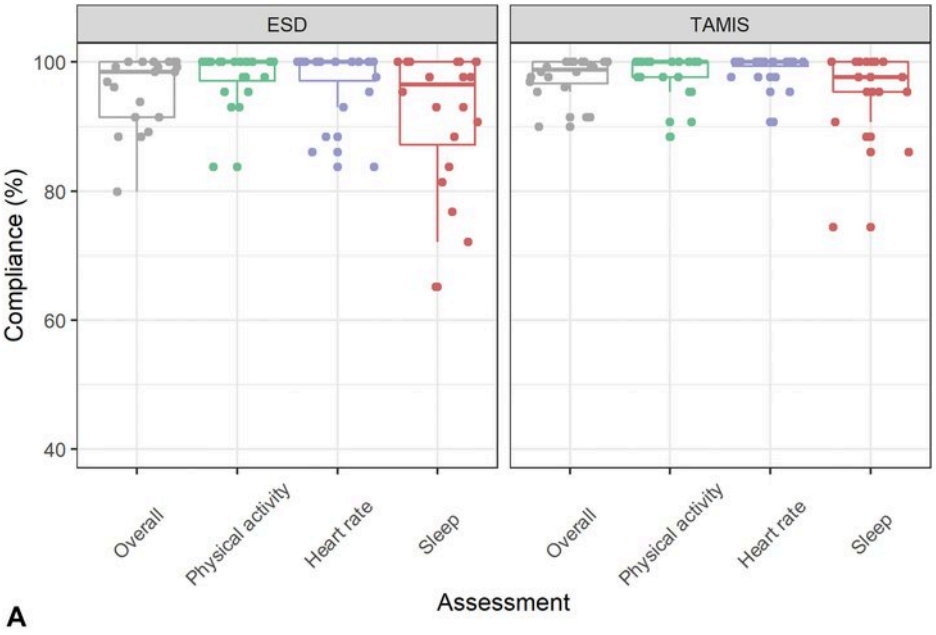


Supplementary Figure 2. Individual recovery plots for the transanal minimally invasive surgery group. The *dots* represent daily step counts relative to baseline. The *horizontal black lines* indicate 90% of baseline activity. The *blue lines* depict the trend in recovery trajectory. For each individual plot, it is indicated whether the criteria for recovery were met within the 28-day time frame.

Supplementary Figure 3. The recovery trajectories organized by perceived time to recovery and resection technique. *Green graphs* depict recovery trajectories of patients who reported recovery within 2 weeks in the end-of-study questionnaire. *Purple graphs* represent trajectories of patients who reported recovery in the third or fourth week. *Red graphs* depict trajectories of patients who reported not being recovered within 4 weeks. *Dots* represent estimated population means, and *vertical lines* indicate the 95% confidence intervals of the means. *ESD* Endoscopic submucosal dissection, *TAMIS* transanal minimally invasive surgery.



Supplementary Figure 4 A. The median and interquartile ranges for compliance with study tasks, including both overall compliance and individual measurements. **B.** The association between perceived burden reported in questionnaire (answer to "Did you experience wearing the smartwatch as burdensome?") and compliance to measurements as measured by Kruskal-Wallis test. *ESD* Endoscopic submucosal dissection, *TAMIS* transanal minimally invasive surgery.



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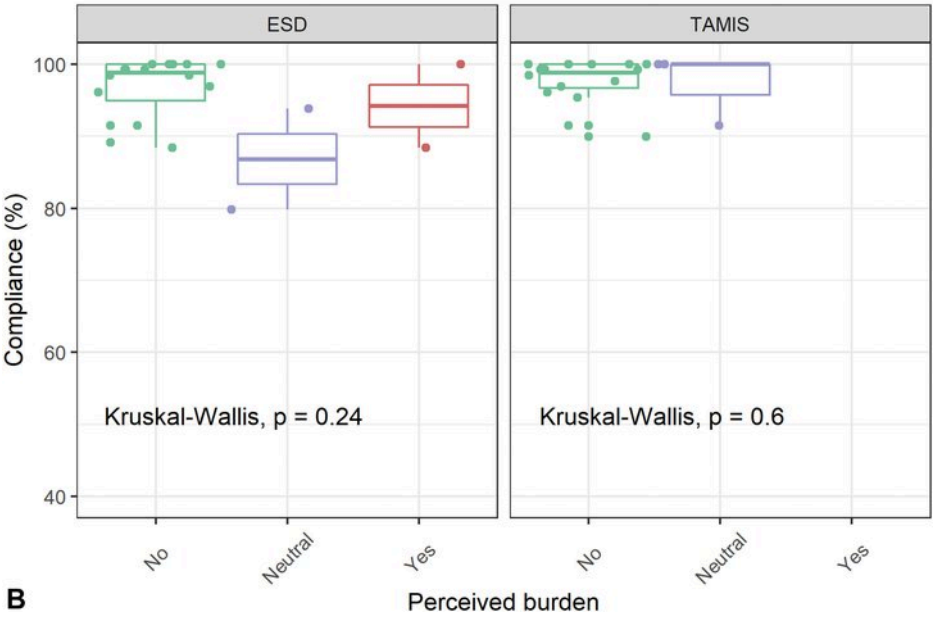
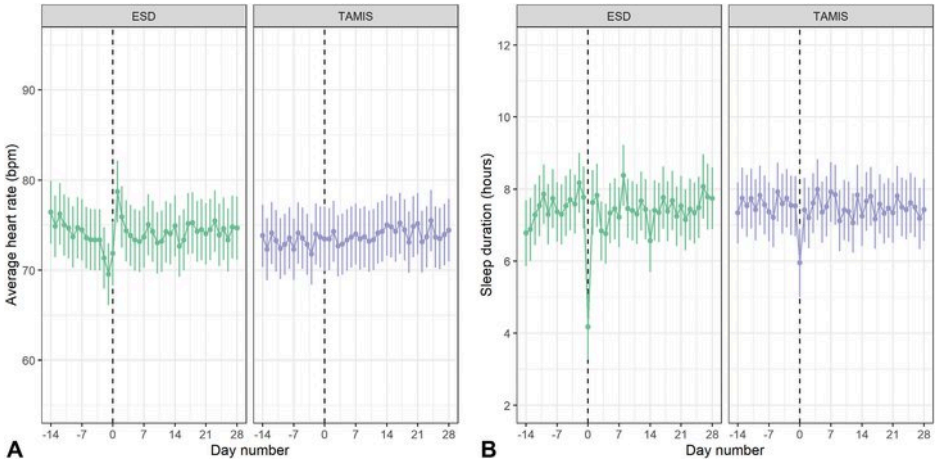


B

Supplementary Figure 5 A. Mean average heart rate with 95% confidence intervals during the baseline and recovery periods. **B.** Average sleep duration with 95% confidence intervals during the baseline and recovery periods. *Bpm* beats per minute, *ESD* endoscopic submucosal dissection, *TAMIS* transanal minimally invasive surgery.



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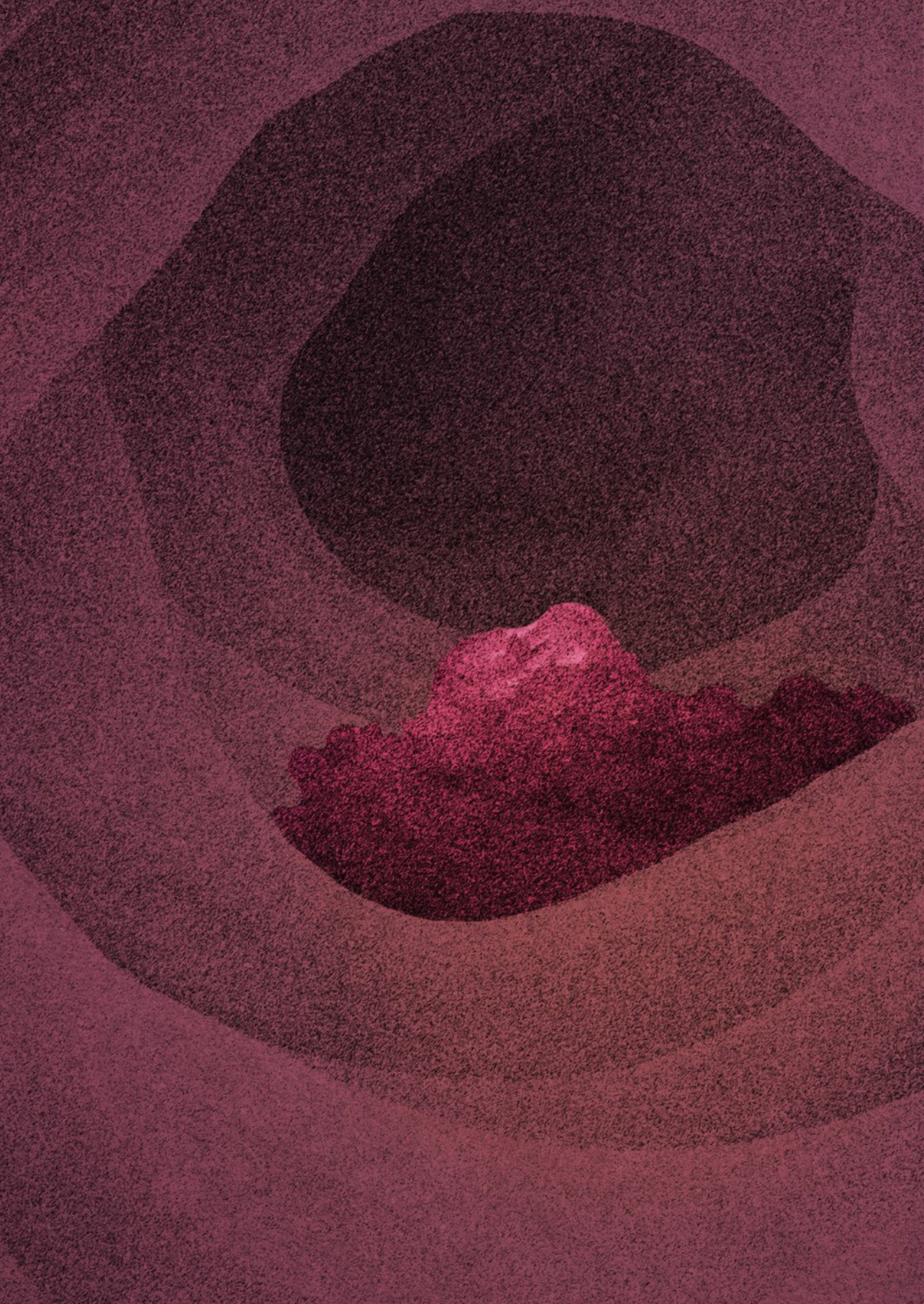
PART II

Treatment strategies after local treatment



CHAPTER 6

Outcome of completion surgery after endoscopic submucosal dissection in early-stage colorectal cancer patients

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Cancers (Basel) 2023

Abstract

T1 colorectal cancers (T1CRC) are increasingly being treated by endoscopic submucosal dissection (ESD). After ESD of a T1CRC, completion surgery is indicated in a subgroup of patients. Currently, the influence of ESD on surgical morbidity and mortality is unknown. The aim of this study was to compare 90-day morbidity and mortality of completion surgery after ESD to primary surgery. The completion surgery group consisted of suspected T1CRC patients from a multicenter prospective ESD database (2014–2020). The primary surgery group consisted of pT1CRC patients from a nationwide surgical registry (2017–2019). Patients with rectal or sigmoidal cancers were selected. Patients receiving neoadjuvant therapy were excluded. Propensity score adjustment was used to correct for confounders. In total, 411 patients were included: 54 in the completion surgery group (39 pT1, 15 pT2) and 357 in the primary surgery group with pT1CRC. Adverse event rate was 24.1% after completion surgery and 21.3% after primary surgery. After completion surgery 90-day mortality did not occur, though one patient died in the primary surgery group. After propensity score adjustment, lymph node yield did not differ significantly between the groups. Among other morbidity-related outcomes, stoma rate (OR 1.298 95%-CI 0.587-2.872, p = 0.519) and adverse event rate (OR 1.162; 95%-CI 0.570-2.370, p = 0.679) also did not differ significantly. A subgroup analysis was performed in patients undergoing rectal surgery. In this subgroup (37 completion and 136 primary surgery), these morbidity outcomes also did not differ significantly. In conclusion, this study suggests that ESD does not compromise morbidity or 90-day mortality of completion surgery.

Introduction

A growing number of early-stage colorectal cancer (CRC) patients are primarily treated with a local resection instead of major surgery.[1] Endoscopic submucosal dissection (ESD) is an increasingly popular local resection technique that can be used to resect suspected T1CRCs en bloc, regardless of their size. These ESDs can be considered as definitive treatment for a portion of these T1CRCs.[2,3] However, if either resection margins are positive, indicating a possibility of an incomplete resection, or if high-risk features for lymph node metastasis (LNM) are present, current guidelines recommend completion surgery.[4,5] These high-risk features include poor differentiation, deep submucosal invasion, high-grade tumor budding and lymphovascular invasion.[5] In current practice, there is an indication for completion surgery in more than half of the T1CRC patients after ESD.[6]

Whether a prior ESD affects the outcome of possible completion surgery has been a topic of discussion. Multiple studies have shown the long-term safety of ESDs,[7-11] but the influence of ESD on surgical morbidity remains unclear. Morbidity rates of completion surgery following local resections have mostly been studied for prior local surgical resections, such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS). A recent meta-analysis on this subject illustrated that prior local surgical resections increase the complexity of completion surgery, leading to increased procedure times and an increased adverse event rate compared to primary oncological resections.[12] It was hypothesized that the preceding local surgical resections caused inflammatory changes that could lead to scarring and fibrotic changes surrounding the previous resection site, resulting in adhesions and challenges for dissection of the correct anatomic planes and performing anastomosis.[13] This raises the question of whether the same applies to a preceding ESD, despite the more superficial dissection plane of the submucosa.

The aim of this study is to compare the morbidity of completion surgery after ESD to primary surgery in a Western population of suspected T1CRC patients, using data from a nationwide database and propensity score adjustment to correct for baseline differences between both groups.

Materials and methods

Population

A retrospective cohort study was performed. Approval for this study was obtained from the institutional review board (IRB) of the Leiden University Medical Center (reference G18.097) and the Dutch ColoRectal Audit (DCRA; reference DCRA202015). The need for informed consent was waived by both IRBs.

Completion Surgery Group

Patients in the completion surgery (CS) group were selected from a prospective database of consecutive ESD procedures from three tertiary hospitals in the Netherlands: Leiden University Medical Center (LUMC), Erasmus Medical Center (EMC) and University Medical Center Utrecht (UMCU) between 2014 and 2020. Patients who underwent completion surgery after ESD for suspected T1CRC, located in the rectum or sigmoid, were selected. Exclusion criteria were neoadjuvant therapy and missing data on ≥5 outcome variables.

Primary Surgery Group

The primary surgery (PS) group consisted of patients from a nationwide database for surgical data, the DCRA database (January 2017 and December 2019). More information regarding the methodology, quality checks and external validation of this nationwide registration has been described previously.[14,15] Patients who underwent primary oncological resection for pT1CRC, located in the rectum or sigmoid, were selected. Exclusion criteria were neoadjuvant therapy, missing data on ≥5 outcome variables and patients were excluded if it was not clearly stated that a prior local resection did not take place.

Clinical variables

Demographic patient characteristics (sex, age, comorbidity, body mass index) and clinical data (staging MRI, procedure-related parameters, histology parameters, adverse events, 90-day mortality) were collected. Adverse events were subdivided into surgical (anastomotic leak, abscess, bleeding, ileus, fascial dehiscence, perforation, urethral or bladder injury, surgical site infection) and non-surgical (e.g., pulmonary, cardiac, thrombotic, infectious, neurological). If applicable, multiple adverse events were recorded for one patient. Furthermore, data regarding reinterventions and outcomes of sustained injuries, as a result of an adverse event, were collected. For the CS group, additional clinical data was collected (ESD procedure-related parameters, tumor morphology, additional histology parameters, indication for completion surgery).

Surgical resections (primary and completion) were grouped according to anatomic location. Surgical segmental resections of the sigmoid were analyzed as sigmoid resections and all surgical segmental resections of the rectum (e.g., low anterior resection, abdominoperineal resection) were analyzed as Total Mesorectal Excision (TME).

Retrospectively analyzed ESD procedures in the completion surgery group were performed at the discretion of an experienced endoscopist (AK, WG, PD, LM, JH, JB). An en bloc resection was defined as macroscopic removal of the lesion in a single piece. Reasons for possible early termination of the ESD without complete lesion removal or conversion to a different resection technique were recorded.

Histology

Tumor stages were histologically confirmed and defined according to the TNM classification: pT1 as invasion through the muscularis mucosae and into, but not beyond the submucosa and pT2 as invasion into the muscularis propria.[16] In case ESD resection was incomplete but completion surgery showed no residual cancer in the surgical specimen, the cancer was staged as pT1. Tumor radicality was subdivided into positive resection margins (R1), unsure radicality (Rx) and radical resection (R0) defined as cancer-free deep and lateral resection margins at histology.

Statistical analysis

Data were analyzed using SPSS 24 (SPSS, Chicago, IL, USA). Categorical data are expressed as frequencies and percentages. Continuous data are expressed as mean with standard deviation, when normally distributed, and as median with interquartile range (IQR) if data was not distributed normally. The Pearson χ^2 was used to compare categorical data. Continuous variables were compared using the Mann–Whitney U test. Morbidity outcomes and the amount of harvested lymph nodes were compared between the groups, using logistic regression. In our analysis the amount of harvested lymph nodes was dichotomized with a cut-off of 12. Differences in baseline characteristics were addressed by the use of propensity adjustment; which corrects for these differences without an undesirable reduction in sample size.[17] To estimate the propensity score, logistic regression was performed with the following variables: age, sex, body mass index, American Society of Anesthesiologists (ASA) score, CRC location (sigmoid, rectosigmoid or rectum), modality of procedure (laparotomy, laparoscopy, transanally or robot-assisted) and type of surgery (TME or sigmoid resection). Missing data on propensity score variables or outcome variables were imputed, under the assumption that data were missing (completely) at random. A total of 10 datasets were imputed. A p-value ≤ 0.05 was considered statistically significant. A subgroup analysis was performed in the subgroup of TMEs.

Results

Patient characteristics

A total of 411 patients were included in the study; 54 patients in the CS group and 357 patients in the PS group. A flow diagram of the patient selection process is shown in Figure 1. Baseline characteristics of both groups, prior to propensity score adjustment, are shown in Table 1. Demographic characteristics did not differ significantly between both groups. ASA-score and tumor location did differ significantly. Patients in the CS group mainly underwent a TME (37/54, 68.5%) whilst patients in the PS group were mainly treated by a sigmoidal resection (221/357, 61.9%). CS and PS were mostly performed laparoscopically (81.5% and 76.8%, respectively).

Figure 1. Flow diagram of patient selection. *ESD* endoscopic submucosal dissection, *CRC* colorectal cancer.

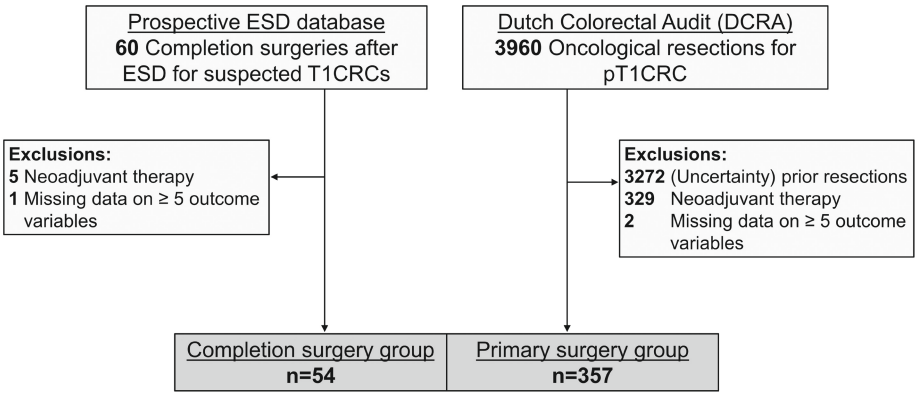

Table 1. Baseline characteristics of study participants prior to propensity score adjustment.

	Completion surgery (n=54)	**Primary surgery** (n=357)	**P value**
Sex, male	35 (64.8)	209 (58.5)	0.382
Age, years, mean (SD)	66.9 (8.63)	67.1 (9.16)	0.258
BMI, kg/m^2, mean (SD)	28.4 (5.67) *Unknown (n=9)*[1]	27.6 (4.61) *Unknown (n=10)*[1]	0.169
ASA-score			
I	10 (18.5)	63 (17.6)	
II	40 (74.1)	207 (58.0)	0.043
III	4 (7.4)	86 (24.1)	
IV	0 (0)	1 (0.3)	
Tumor location			
Sigmoid	15 (27.8)	213 (59.7)	<0.001
Rectosigmoid	14 (25.9)	35 (9.8)	
Rectum	25 (46.3)	109 (30.5)	
Type of surgery			
Sigmoid resection	17 (31.5)	221 (61.9)	<0.001
TME	37 (68.5)	136 (38.1)	
Surgical approach			
Laparoscopic	44 (81.5)	274 (76.8)	
Open	3 (5.6)	10 (3.1)	0.646
taTME	2 (3.7)	11 (3.1)	
Robot-assisted	5 (9.3)	46 (12.9)	
		Unknown (n=16)[1]	

[1] Prior to analyses, missing data were imputed, using multiple imputations with 10 iterations. *SD* standard deviation, *BMI* body mass index, *ASA* American society of anesthesiology, *taTME* trans-anal total mesorectal excision.

ESD characteristics

ESDs in the CS group were en bloc in 35/54 patients (64.8%). In 13 patients (24.1%), the ESD was terminated without complete tumor removal due to the suspicion of deep submucosal invasion during the procedure. In six patients (11.1%), the ESD procedure was converted to a piecemeal endoscopic mucosal resection (pEMR). Conversion to pEMR was decided as a result of difficult endoscopic access in one patient and in five patients due to the presence of fibrosis. Five ESDs were complicated by a microperforation or macroperforation. All were managed endoscopically, either by hemoclips (four patients) or an over-the-scope clip (one patient). At histological assessment, 39 cancers were staged as pT1 (72.2%) and 15 as pT2 (27.8%). Of the 35 patients with an en bloc resection, 15 patients had a R0 resection (42.9%). Additional clinical data of the completion surgery group are shown in Table 2.

Table 2. Clinical data of the completion surgery group.

	Completion surgery group (n=54)
Tumor characteristics	
Diameter polyp, mm (IQR)	25.0 (22.5) *Unknown (n=4)*
Gross morphology Sessile Flat Pedunculated	 35 (64.8) 12 (22.3) 4 (7.4) *Unknown (n=3)*
Staging MRI performed prior to ESD	10 (18.5)[1]
Technical details ESD	
Duration, median (IQR)	129 minutes (103) *Unknown (n=11)*
Perforation (microperforation or perforation)	5 (9.3)
En bloc Yes No	 35 (64.8) 19 (35.2)
Radicality R0 R1/Rx	 15 (27.8) 39 (72.2)
Tumor stage ESD specimen pT1 pT2	 39 (72.2) 15 (27.8)
Subsequent eFTR performed	3 (5.6)
Completion surgery	
Indication additional therapy[2] Not R0 resection High-risk histology	 39 (72.2) 15 (27.8)
Time to surgery, days, median (IQR)	56.5 (37)

Values are *n* (%) unless otherwise defined.
[1] For patients eventually undergoing TME this was 10/37 (27.0%). Specific anatomic location within the rectum was reported in 6 patients. [2] In case a surgical specimen showed both Rx/R1 and an additional high-risk criterium, the indication was scored as *not R0 resection*. *ESD* endoscopic submucosal dissection, *IQR* interquartile range, *MRI* magnetic resonance imaging, *pEMR* piecemeal endoscopic mucosal resection, *eFTR* endoscopic full-thickness resection.

Outcomes of completion Surgery

The indication for completion surgery was an incomplete resection in 39 patients (72.2%) and the presence of high-risk features in 15 (27.8%). Details on the high-risk features of the pT1CRC subgroup are shown in Supplementary Table 1. All patients underwent a radical (R0) oncological resection. In the surgical specimen, a local endoluminal cancer rest was found in 19/39 (48.7%) non-radical (Rx/R1) ESD resections. More information regarding local endoluminal cancer rests is shown in Figure 2. On average, 15.5 lymph nodes were harvested (SD = 10.0). The stoma rate was 20.4% (11 patients), of which three were temporary. Adverse events occurred in 13 patients (24.1%). In nine patients these were classified as surgical adverse events. Anastomotic leak was the most common, occurring in six patients (11.1%). All surgical adverse events required a reintervention. No patients died within 90 days after completion surgery. More outcome variables of the CS group are shown in Table 3.

Figure 2. Outcomes of the completion surgery group. *ESD* endoscopic submucosal dissection, *R0* radical resection, *Rx* unsure radicality, *R1*, non-radical.

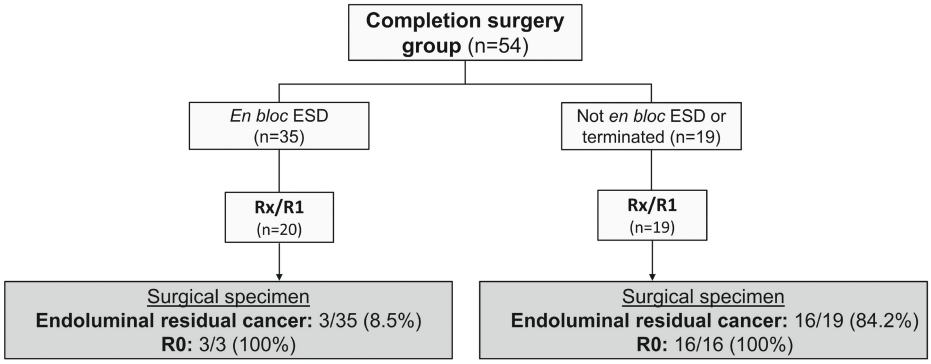

Table 3. Detailed outcome variables before propensity score adjustment for completion surgery and the primary surgery groups.

	Completion Surgery (*n* = 54)	**Primary Surgery** (*n* = 357)
Stoma after resection	11 (20.4)	43 (12.0)
Temporary ileostomy	3	23
Permanent ileostomy	0	1
Temporary colostomy	0	1
Permanent colostomy	8	18
Adverse events < 90 days	13 (24.1)	76 (21.3)
Surgical adverse events	9 (16.7)	50 (14)
Anastomotic leak	6	19
Abscess	0	8
Bleeding	0	1
Ileus	2	11
Fascial dehiscence	0	0
Perforation	0	2
Urethral or bladder injury	2	1
Surgical site infection	0	8
Non-surgical adverse events	6 (11.1)	42 (11.8)
Pulmonary	1	12
Cardiac	1	5
Thrombotic	0	3
Infectious	1	10
Neurological	2	0
Other	4	18
Reintervention [1]	9 (16.7)	31 (8.7)
Laparotomy	2	10
Laparoscopy	5	11
Endoscopy	1	2
Radiology	0	1
Other	1	4
		Unknown (n = 3)
Stoma by reintervention [1]	6 (11.1)	18 (5.0)
Temporary ileostomy	4	7
Permanent ileostomy	1	0
Temporary colostomy	1	4
Permanent colostomy	0	7
Unknown	0	3
ICU admission [2]	1 (1.9)	17 (4.8) *Unknown (n = 4)*
Median stay, days (range)	4	2 (1–12)
Permanent injury	2 (3.7)	1 (0.3)
Lymph nodes harvested, mean (SD)	15.5 (10.0)	15.66 (7.9)
90-day mortality	0	1 (0.3)

Values are *n* (%) unless otherwise defined.
[1] As result of a surgical adverse event. [2] As result of an adverse event.
ICU intensive care unit, *SD* standard deviation.

Outcomes of primary Surgery

An overview of the outcome variables of the PS group is shown in Table 3**.** The average number of harvested lymph nodes in the PS group was 15.7 (SD = 7.9). The stoma rate was 12.0% (43 patients), of which 24 were temporary. Adverse events occurred in 76 patients (21.3%). In 50 these were classified as surgical adverse events. Anastomotic leak was the most common, occurring in 19 patients (5.3%). Within 90 days after primary surgery one patient died (0.3%).

Comparison between completion surgery and primary surgery

Outcomes of the comparison between the CS group and PS group after propensity score adjustment are shown in Table 4. No statistical difference was observed in the number of patients in which ≥12 lymph nodes were harvested (OR 0.687; 95%-CI 0.365–1.293, *p* = 0.245). Additionally, no statistical difference was observed in stoma rate (OR 0.864 95%-CI 0.298–2.502, *p* = 0.787), the overall adverse event rate (OR 1.192; 95%-CI 0.514–2.763, *p* = 0.682) or the occurrence of surgical adverse events (OR 1.343; 95%-CI 0.527–3.422, *p* = 0.537). Additionally, no statistical difference was observed for the other morbidity-related outcomes. The 90-day mortality could not be compared because no events occurred in the completion group.

Table 4. Comparison between completion surgery and primary surgery groups.

Outcome Variable	Odds Ratio (95% CI)	*p* Value
Lymph nodes harvested[1]	0.687 (0.365–1.293)	0.245
Stoma after surgery	1.298 (0.587–2.872)	0.519
Adverse event < 90 days	1.162 (0.570–2.370)	0.679
Surgical adverse event	1.133 (0.498–2.576)	0.767
Reintervention required	1.572 (0.661–3.737)	0.306
Stoma by reintervention	1.864 (0.651–5.335)	0.246
ICU admission as result of an adverse event	0.210 (0.025–1.737)	0.148
Permanent injury	2.937 (0.246–35.115)	0.391
90-day mortality	NA	NA

The primary surgery group was used as reference for the regression analysis.
[1] Variable was dichotomized, using 12 lymph nodes as cut-off.
CI confidence interval, *ICU* intensive care unit.

Rectal surgery subgroup

In total, 37 patients from the CS group and 136 patients from the PS-group underwent a TME. The average number of harvested lymph nodes in the CS group and PS-group were 16.6 (SD = 11.7) and 16.3 (SD = 8.8), respectively. Stoma rate was 24.3% and 22.8%, respectively. Adverse events occurred in 29.7% and 27.2%, respectively. In both groups, anastomotic leak was the most common adverse event, which occurred in 6 (16.2%) and 12 (8.8%) patients, respectively. The 90-day mortality of both groups was zero.

After propensity score adjustment, no statistical association was found between the type of resection (completion or primary) and the number of harvested lymph nodes and morbidity-related outcomes (Supplementary Table 2).

Discussion

This study evaluated the influence of prior ESD on the surgical morbidity and mortality of completion surgery in suspected T1CRCs in a Western setting. After propensity score adjustments for differences at baseline, no significant difference was seen in 90-day surgical morbidity or survival between the Completion Surgery (CS) group and the Primary Surgery (PS) group. Our findings suggest that ESD does not compromise morbidity and 90-day mortality of completion surgery.

Previous studies related to this topic have only reported outcomes of CS after ESD without comparing outcomes to a PS group,[18] or reported outcomes of completion surgery after endoscopic resections in general.[19] Compared to the only other study reporting results of a cohort of patients undergoing CS following ESD, our overall adverse event rate of 24.1% in the CS-group appears to be slightly higher than the reported 17%.[18] However, the proportion of patients with rectal cancers, associated with a higher risk of adverse events,[20] was considerably higher in our study (68.5% vs. 37.7%). This study did not compare their CS group to a PS group and therefore did not answer the question of whether a prior ESD increases the morbidity of completion surgery.

ESD is a complex endoscopic resection technique with generally longer procedure times and a higher chance of coagulation-induced deep thermal injury, compared to more conventional snare-based endoscopic resection techniques.[21,22] Therefore, the influence on completion surgery for ESD should be studied separately from other snare-based techniques and ESD might show more resemblance to local surgical resection techniques, such as TEM or TAMIS. The influence of these local surgical resections on the morbidity of completion surgery has been studied more frequently. A recent meta-analysis on this subject reported a significant increase in adverse events that required a reintervention if a surgical resection was preceded by a local surgical resection.[12] This is in contrast to our results, where no increase in adverse event rate was observed between the CS group and PS group. The reported overall adverse event rate of 37.4% after completion TME preceded by local surgical resection was also higher than the 29.7% (TME subgroup only) found in our study. These differences might be explained by the difference in the dissection plane. In contrast to the full-thickness or inter-muscular local surgical resections, the submucosal dissection plane of ESDs is more superficial. Any possible inflammatory response that might cause fibrosis and adhesions might be less extensive after ESD, due to the more superficial dissection plane of the submucosa.

In contrast, our results are in line with the previously mentioned meta-analysis that compared the morbidity of completion surgery after prior endoscopic resection to primary surgery.[19] This study showed that prior endoscopic resections did not appear to increase surgical morbidity. However, as mentioned before, this study did not focus on ESD and mainly studied the influence of more conventional snare-based endoscopic resections. This study reports the largest cohort of patients undergoing completion surgery after ESD with a comparison to an adjusted primary surgery group.

The quality of completion surgery also does not appear to be negatively affected by ESD. Firstly, the lymph node yield did not differ between the groups. Using the previously reported quality indicator of 12 lymph nodes as a cut-off point, our study found no significant difference in lymph node yield between the CS-group and the PS-group.[23] In contrast to our results, local surgical resections did appear to significantly reduce the number of harvested lymph nodes.[12] Secondly, prior local surgery was associated with an increase in incomplete mesorectal excisions, using previously described grading of the mesorectum.[24] Although reporting and comparing mesorectal grading was not possible in our dataset due to missing data, we did observe that all completion surgeries were radical (R0) resections. This suggests that the quality of completion surgery may also be unaffected by prior ESD.

This study has some limitations. Firstly, due to the rarity of this clinical situation, the number of patients in the completion surgery group is limited. This should be taken into account when interpreting the results of the comparison. Secondly, due to our study's retrospective nature, there is an inherent risk of selection bias, which we have tried to minimize by using propensity score adjustment. Nevertheless, residual confounding cannot be excluded entirely, especially because some relevant characteristics were unavailable, such as the exact tumor location within the rectum, which might be related to surgical complexity.[25] Additionally, since the data used for analysis were collected from different centers, possible variations in the quality of surgical procedures and differences in medical personnel across centers may introduce a form of selection bias. Thirdly, the DCRA is a self-reported surgical database, which brings a risk of under-registration. This database was also not specifically designed for this study, which is why some relevant information, for example on histological high-risk features, was not available for the primary surgery group. In addition, we had to exclude 2876 patients, because it was not clearly stated if a local resection took place. Although missingness was unlikely to be related to the outcome, we were not able to completely exclude the possibility of some selection bias. Fourthly, ESDs were included starting from 2014, when the procedure was still being introduced in the West. As a result, ESD performance might be slightly inferior to performance in current practice. However, by selecting only ESDs after which completion surgery was performed and thus, excluding all definitive ESD procedures, the quality of included ESDs is not representative for the general ESD performance in these centers. Lastly, due to unavailable data, we were unable to study

the influence of a prior ESD on functional outcomes or procedure times of completion surgery.

This study has implications for clinical care as it adds to the previous evidence that it is safe to perform ESDs for suspected T1CRCs without compromising completion surgery. The long-term oncological safety of this strategy was previously reported.[7,8,11] Additionally, it was previously reported that the perceived time to recovery after completion surgery does not appear to differ from primary surgery.[26] Our current study shows that ESDs for suspected T1CRCS do not appear to increase surgical morbidity and 90-day mortality. Taken together it seems justified to perform ESD in all patients with a suspected T1CRC, to prevent extensive surgery for the substantial number of patients with a low-risk T1CRC. To increase the validity of the present study, performing a follow-up clinical trial may be considered.

Conclusions

This study suggests that ESD does not adversely affect the morbidity and 90-day mortality of completion surgery.

Supplemental materials

Supplemental Table 1. Histological high-risk features of pT1CRC patients in the completion surgery group.

Histological feature	**pT1CRC completion surgery group** (n=39)
Invasion depth	
Invasion Sm2/3 or >1000µm	17 (60.7)
Superficial	4 (14.3)
Not assessable	7 (25)
	Not desribed (n = 11)
Lymphovascular invasion	
Present/suspect	20 (60.6)
Absent	13 (39.4)
	Not described (n = 6)
Differentiation grade	
Poor/Mucinous	5 (14.3)
Well/Moderate	30 (85.7)
	Not described (n = 4)
Budding	
High grade	7 (30.4)
Absent or low grade	12 (52.2)
Not assessable	4 (17.4)
	Not desribed (n = 16)

CRC Colorectal cancer.

Supplemental Table 2. Comparison completion TME and primary TME.

Outcome variable	**Odds ratio** (95% CI)	***P* value**
Lymph nodes harvested[1]	0.997 (0.434-2.287)	0.993
Stoma after surgery	1.532 (0.648-3.623)	0.331
Adverse events <90 days	1.298 (0.557-3.023)	0.546
Surgical adverse events	1.376 (0.532-3.558)	0.510
Reintervention required	1.659 (0.628-4.383)	0.307
Stoma by reintervention	2.491 (0.779-7.965)	0.124
ICU admission due to complication	0.270 (0.031-2.323)	0.233
Permanent injury	*NA, no events*	*NA*
90-day mortality	*NA, no events*	*NA*

The primary surgery group was used as reference for the regression analysis.
[1] Variable was dichotomized, using 12 lymph nodes as cut-off.
TME total mesorectal excision, *CI* confidence interval, *ICU* intensive care unit, *NA* not applicable.

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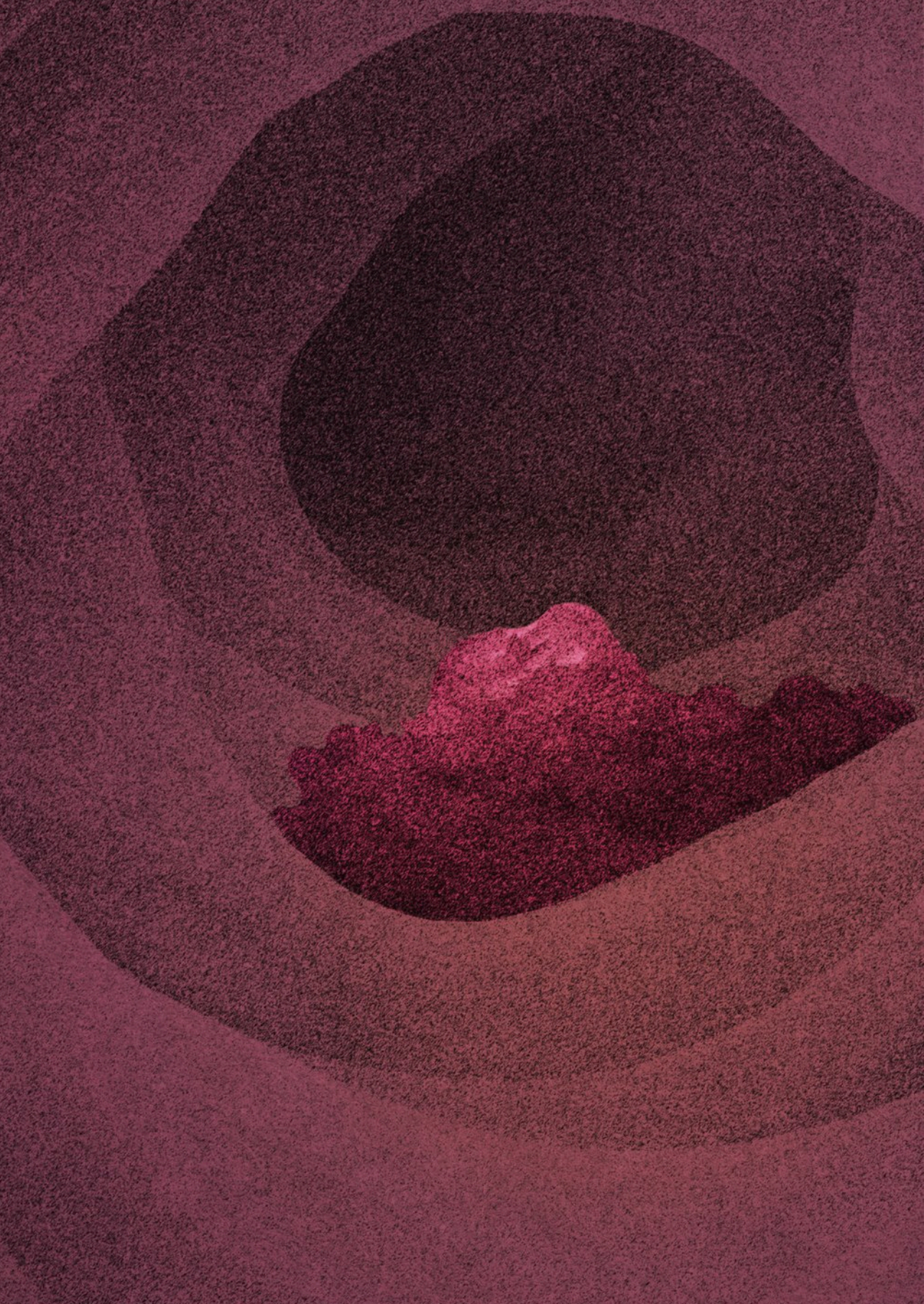

CHAPTER 7

Risk of recurrence after local resection of T1 rectal cancer: a meta-analysis with meta-regression

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Surgical Endoscopy 2022

Abstract

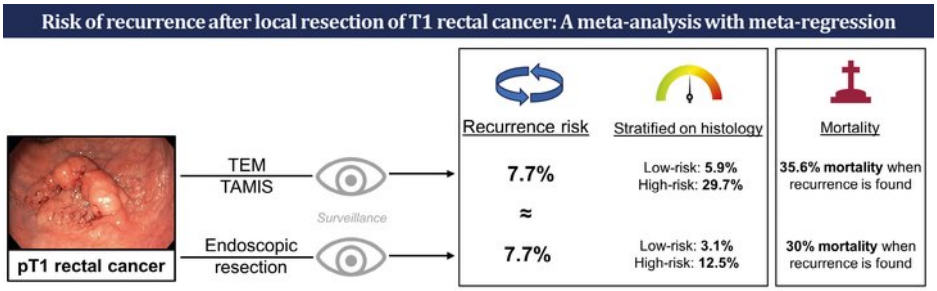
Background: T1 rectal cancer (RC) patients are increasingly being treated by local resection alone but uniform surveillance strategies thereafter are lacking. To determine whether different local resection techniques influence the risk of recurrence and cancer-related mortality, a meta-analysis was performed.

Methods: A systematic search was conducted for T1RC patients treated with local surgical resection. The primary outcome was the risk of RC recurrence and RC-related mortality. Pooled estimates were calculated using mixed-effect logistic regression. We also systematically searched and evaluated endoscopically treated T1RC patients in a similar manner.

Results: In 2585 unique T1RC patients (86 studies) undergoing local surgical resection, the overall pooled cumulative incidence of recurrence was 9.1% (302 events, 95% CI 7.3–11.4%; I^2 = 68.3%). In meta-regression, the recurrence risk was associated with histological risk status ($p < 0.005$; low-risk 6.6%, 95% CI 4.4–9.7% vs. high-risk 28.2%, 95% CI 19–39.7%) and local surgical resection technique ($p < 0.005$; TEM/TAMIS 7.7%, 95% CI 5.3–11.0% vs. other local surgical excisions 10.8%, 95% CI 6.7–16.8%). In 641 unique T1RC patients treated with flexible endoscopic excision (16 studies), the risk of recurrence (7.7%, 95% CI 5.2–11.2%), cancer-related mortality (2.3%, 95% CI 1.1–4.9), and cancer-related mortality among patients with recurrence (30.0%, 95% CI 14.7–49.4%) were comparable to outcomes after TEM/TAMIS (risk of recurrence 7.7%, 95% CI 5.3–11.0%, cancer-related mortality 2.8%, 95% CI 1.2–6.2% and among patients with recurrence 35.6%, 95% CI 21.9–51.2%).

Conclusions: Patients with T1 rectal cancer may have a significantly lower recurrence risk after TEM/TAMIS compared to other local surgical resection techniques. After TEM/TAMIS and endoscopic resection the recurrence risk, cancer-related mortality and cancer-related mortality among patients with recurrence were comparable. Recurrence was mainly dependent on histological risk status.

Graphical abstract



Introduction

The introduction of population-based screening has resulted in an increased number of early invasive, or T1, rectal cancers (T1RC).[1] Over the last years, a shift can be observed from major surgery towards local, organ-preserving endoscopic or surgical resection techniques as primary treatment for these tumors.

The decision whether to perform additional total mesorectal excision (TME) after local resection mainly depends on the oncological risk (which is based on histological high-risk features for lymph node metastasis (LNM)[2]), operative risk and patient preferences. Considering the limited accuracy of the histological risk stratification models, and the significant morbidity and decrease in quality of life that are associated with TME, there has been an increased tendency towards close-surveillance strategies after local resection of T1RC.[3-6]

Surveillance after local resection of T1RC is currently quite heterogeneous,[7] and needs to be optimized to improve the efficacy of surveillance. To determine the optimal surveillance strategy, it is important to determine the risk, type and prognosis of cancer recurrences that could occur. This meta-analysis aims to estimate the cumulative incidence of RC recurrence and RC-related mortality for patients with local surgically resected T1RC and to compare this with results of endoscopically treated T1RC patients.

Materials and methods

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[8] Information regarding the search strategy, data extraction, definitions and classifications, and risk of bias assessment can be found in the Supplementary methods. Approval of the institutional review board (IRB) and written consent was not needed.

Selection criteria for local surgical resection

A systematic literature search was conducted in PubMed, Embase, Web of Science and Cochrane Library from inception until May 19, 2021. Inclusion criteria were: 1. histologically confirmed pT1RCs 2. local surgical resection alone, 3. the proportion of recurrences after local surgical resection of T1RCs was reported 4. original peer-reviewed articles. Exclusion criteria were: 1. prior or additional therapy (e.g., endoscopic resection, oncological surgery, chemotherapy or radiotherapy), 2. hereditary predisposition for CRC, 3. inflammatory bowel disease, 4. studies with < 5 patients with T1RC undergoing local surgical resection, 5. studies without original patient data (e.g., reviews or meta-analyses), 6. conference abstracts, 7. animal studies and 8. non-English

or non-German articles. In case of overlapping cohorts, the cohort with the largest number of patients, or covering the largest period of time was selected.

T1RCs were defined as rectal tumors with histologic tumor invasion through the muscularis mucosae and into, but not beyond, the submucosa. Local surgical resection was defined as any type of local resection that was used to excise a rectal tumor without lymph node dissection, and that did not use flexible endoscopy (i.e., no endoscopic submucosal dissection (ESD), endoscopic full-thickness resection (eFTR), endoscopic mucosal resection (EMR), or snare polypectomy). High-risk criteria for LNM defined by The Japanese Society for Cancer of the Colon and Rectum (JSCCR) include: positive resection margins, deep submucosal invasion, grade 3 differentiation, lymphovascular invasion and high-grade tumor budding.[2]

Selection criteria for local endoscopic resection

Data of endoscopically treated T1RC patients were extracted from our previous meta-analysis on recurrences after local endoscopic resection of T1 colorectal cancer.[9] This search was updated until May 19, 2021 and additional data regarding primary outcomes or main study characteristics for the subgroup of T1RC patients were requested from the corresponding authors. The in- and exclusion criteria of the current analysis were similar to those of the previous analysis,[9] except for treatment and location (Supplementary Table 1).

Data acquisition

Data extraction and risk of bias assessment were independently performed by 3 authors (ND, HD, PO). In case of disagreement without consensus after discussion, a fourth assessor (JB) was decisive. Relevant study-level parameters and individual patient-level data of recurrence cases were extracted. The risk of bias was assessed using a modified Newcastle–Ottawa Scale.[10] An additional random data check was performed by the decisive assessor to ensure the data quality.

Study outcomes

The primary outcome was the cumulative incidence of RC recurrence (locoregional or distant) and RC-related mortality during follow-up. Locoregional recurrence was defined as endoluminal cancer at the primary resection site or pelvic LNM. Distant recurrence was defined as any metastasis outside the pelvic area. Secondary outcomes were the cumulative incidence of locoregional RC recurrence only, any locoregional RC recurrence and any distant recurrence.

Statistical analysis

All analyses were performed in R v4.1.0[11] using the package *metafor v3.0.1*.[12] Cumulative incidences of all study outcomes were modeled on the logit scale using mixed-effects logistic regression.[13] Thereafter, results were transformed back to proportions and

presented as point estimates with 95%-confidence intervals (95% CI). The risk of publication bias was examined using a funnel plot with the square root of the study size on the y-axis.[14]

Statistical heterogeneity was quantified using I^2 statistic and tau-squared (τ^2). Univariable meta-regression and subgroup analyses were performed to explore possible sources of heterogeneity with predefined potential predictors: study characteristics (e.g., publication year, study design), individual items from the risk of bias assessment, follow-up characteristics (e.g., duration and intensity), and clinical characteristics (e.g., resection technique, histology). Only studies with subgroups of ≥ 5 patients, for whom the exact number of events could be determined, were included in meta-regression and subgroup analyses. Meta-regression was only performed when at least 10 studies could be analysed.[15] p values < 0.05 were considered statistically significant.

Results

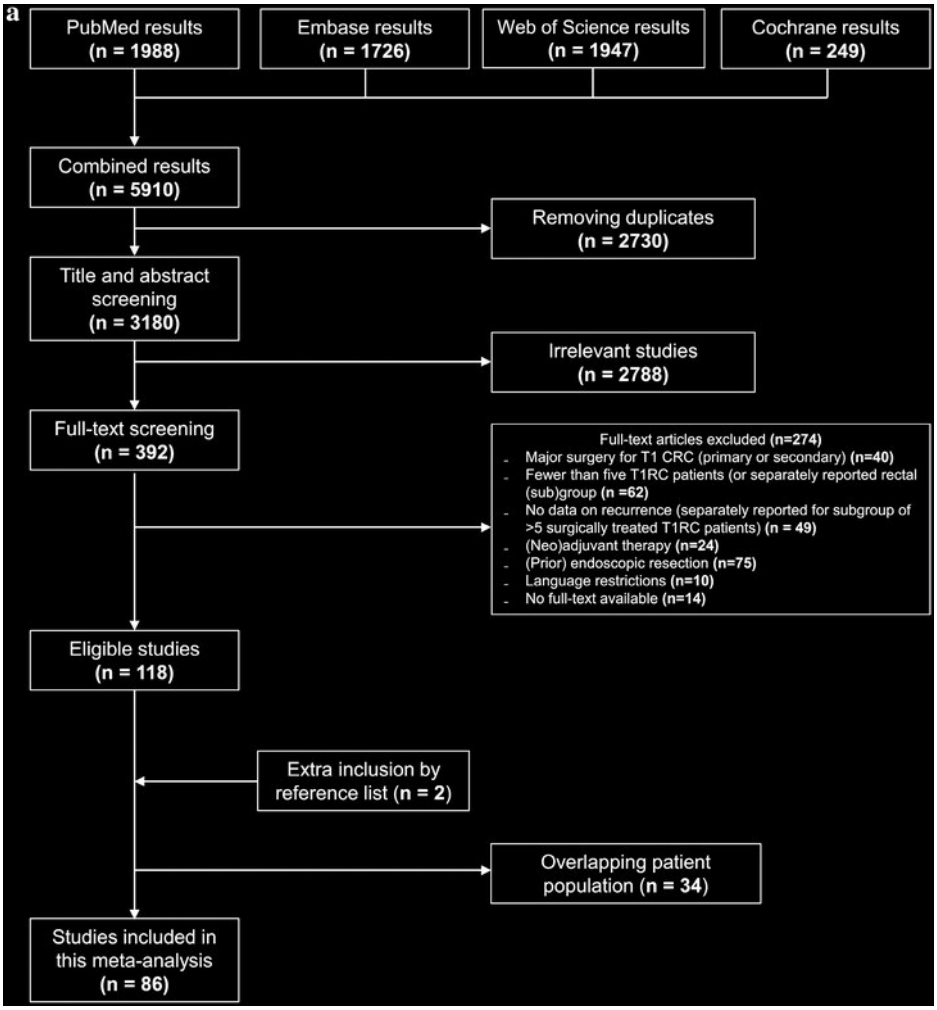
Study characteristics for local surgical resection

Our search identified 5910 articles, of which 86 reported unique patient cohorts and were included (Figure 1a).[16-101] These studies consisted of 2585 patients undergoing local surgical resection for T1RC, with data on the cumulative incidence of recurrence. Eighty-five studies also reported separate incidences of locoregional and distant recurrences.

The extracted data and risk of bias assessment of the included studies are shown in Supplementary analyses. Most studies were performed in Europe (46 studies, n = 1506 patients), followed by North America (20 studies, n = 608), Asia (17 studies, n = 438), South America (2 studies, n = 15) and Australia (one study, n = 618). No obvious asymmetry was observed in the funnel plot (Supplementary Figure 1).

In 41 studies the transanal endoscopic microsurgery (TEM) technique was investigated and transanal minimally invasive surgery (TAMIS) in 4. The majority of patients in the remaining 41 studies underwent other local surgical resection techniques with direct visualization; these were grouped as “local excision” (LE; e.g., Park method or using the Ferguson anoscope). Fifty-five studies reported data on the resection plane; almost all patients in these studies underwent a full-thickness resection (99.2%). The mean and minimum follow-up could be determined in 15 (range, 18.2–72.5) and 51 studies (range 1–60), respectively. Complete data on follow-up schemes (i.e., which follow-up modalities and intervals per modality) was reported in 42 studies; schemes were classified as “not strict” in 6 (14.3%), “strict” in 13 (31.0%), and “very strict” in 23 studies (54.8%). The definitions used for these groups are shown in the Supplementary methods. A flow diagram of the study process is shown in Figure 2.

Figure 1. Flow diagram of the selection process for studies on local surgical resection (**a**) and endoscopic resection (**b**). *(C)RC* (colo)rectal cancer



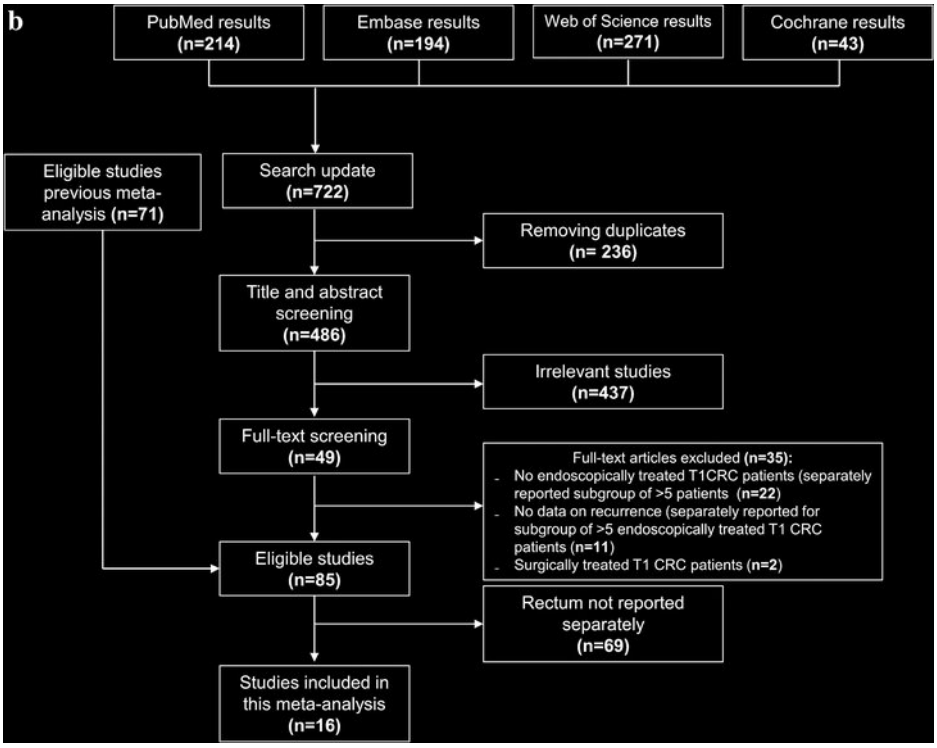
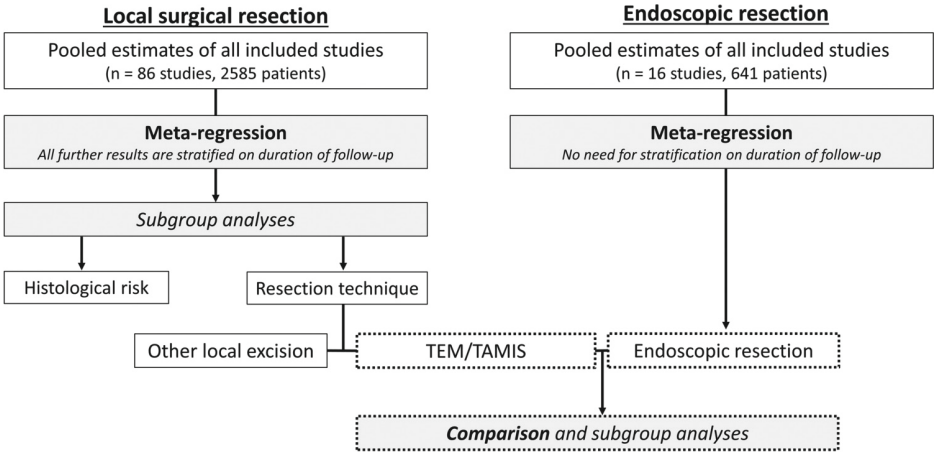

b
PubMed results (n=214)
Embase results (n=194)
Web of Science results (n=271)
Cochrane results (n=43)
Eligible studies previous meta-analysis (n=71)
Search update (n=722)
Removing duplicates (n= 236)
Title and abstract screening (n=486)
Irrelevant studies (n=437)
Full-text screening (n=49)
Full-text articles excluded (n=35):
- No endoscopically treated T1CRC patients (separately reported subgroup of >5 patients (n=22)
- No data on recurrence (separately reported for subgroup of >5 endoscopically treated T1 CRC patients (n=11)
- Surgically treated T1 CRC patients (n=2)
Eligible studies (n=85)
Rectum not reported separately (n=69)
Studies included in this meta-analysis (n=16)

Figure 2. Flow diagram of the study process. *TEM* transanal endoscopic microsurgery, *TAMIS* transanal minimally invasive surgery



Pooled estimates of all included studies

Overall, 302 out of 2585 patients experienced recurrence after local surgical resection. The pooled cumulative incidence of any RC recurrence was 9.1% (95% CI 7.3–11.4%; I^2 = 68.3%; Figure 3).

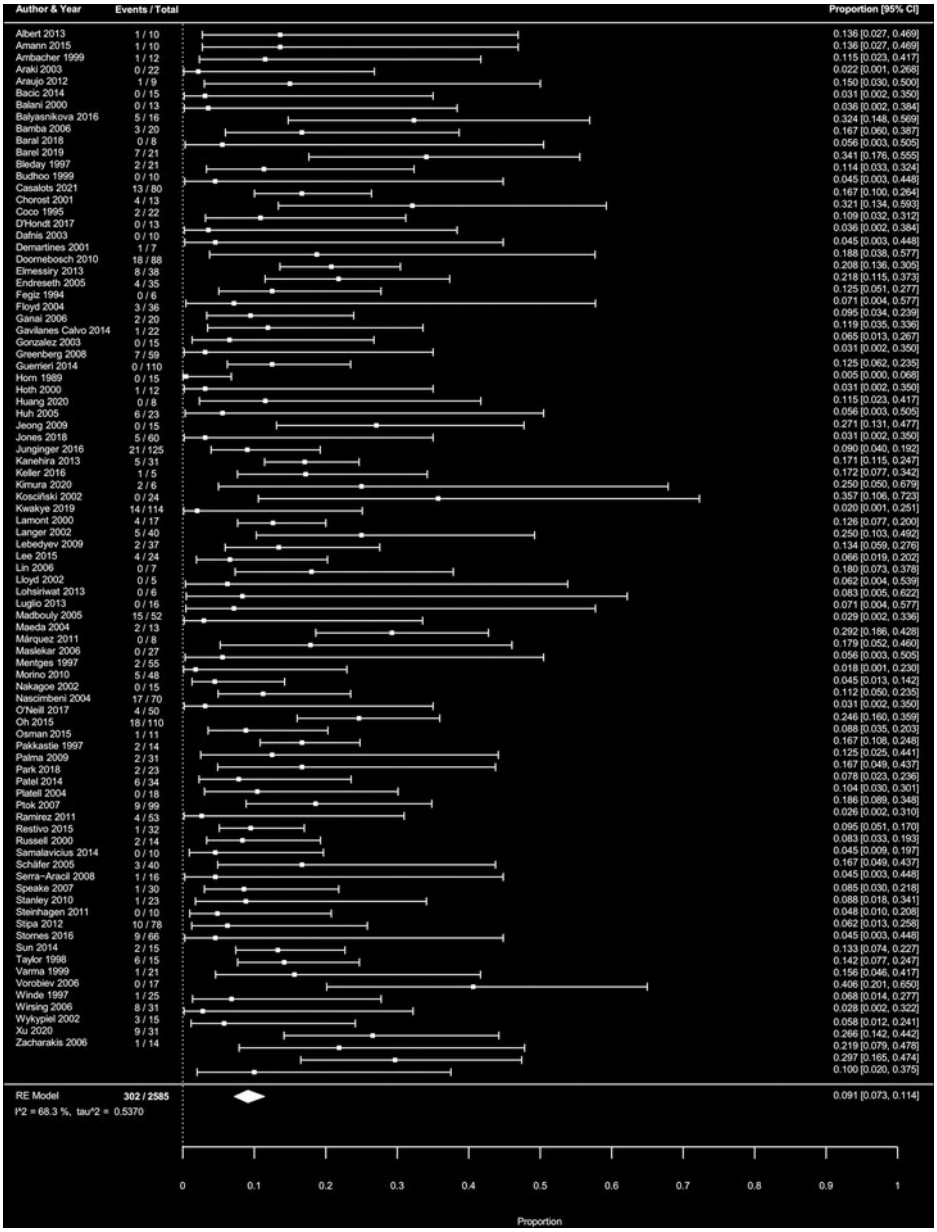
Meta-regression

In meta-regression, histological risk status (low-risk vs. high-risk) and, local surgical resection technique (TEM/TAMIS vs. other local surgical excisions) were associated with the risk of recurrence (Supplementary Tables 2 and 3). Therefore, subgroup analyses were performed for histological risk status and local surgical resection technique. Further analyses were stratified according to the duration of follow-up because risk of recurrence increased with longer mean follow-up duration (Supplementary Table 2). Results for studies with ≥ 2-year follow-up are shown below; results for all studies, for studies with a ≥ 5 years follow-up and detailed information regarding the meta-regression results are shown in Supplementary results.

Pooled estimates of studies with ≥ 2 years follow-up

The pooled cumulative incidence of any RC recurrence was 9.2% (194/1713 events; 95% CI 7.1–11.9%; I^2 = 60.8%; Supplementary Figure 2). Pooled incidences of all secondary outcomes are shown in Supplementary analyses. The pooled incidence of RC-related mortality was 1.9% (31/898 events, 27 studies; 95% CI 0.9–4.2%; I^2 = 69.3%; Supplementary Figure 3). The RC-related mortality rate among patients with recurrence was 28.7% (31/108). All of these patients died of disease progression.

Figure 3. Forest plot with cumulative incidences of any rectal cancer recurrence after local surgical resection. To visualize incidence estimates of studies with 0 events, a continuity correction of + 0.5 was applied. Values of the pooled estimates, I^2 and τ^2 are calculated using a model without continuity correction.

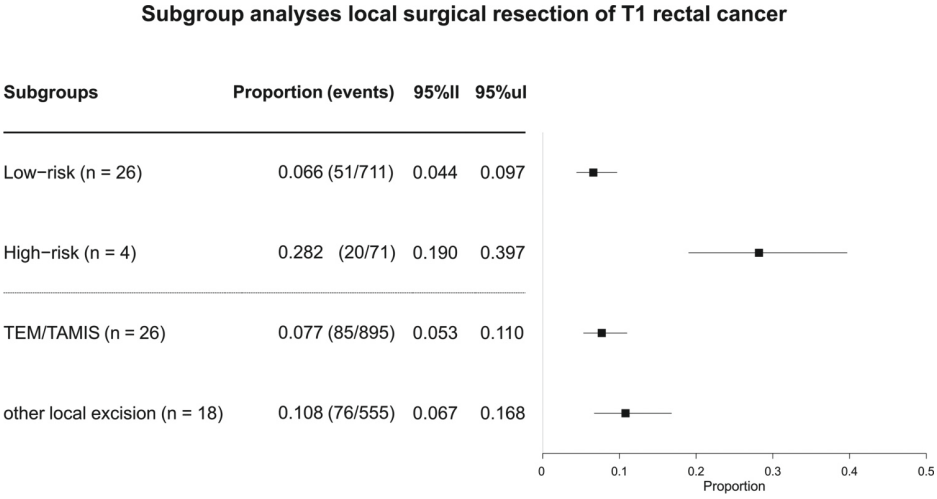


Subgroup analyses in studies with ≥ 2 years follow-up

Low-risk versus high-risk

Twenty-six studies reported a subgroup of ≥ 5 patients with low-risk T1RC and sufficient data on recurrence, and 4 studies did so for high-risk T1RCs. The definitions of low- and high-risk T1RCs were diverse. Most studies used 3 risk criteria: differentiation grade was used the most and tumor budding the least (Supplementary Figure 4). The cumulative incidence of any RC recurrence was 6.6% for low-risk T1RCs (51/711 events; 95% CI 4.4–9.7%; I^2 = 22.4%) and 28.2% for high-risk T1RCs (20/71 events; 95% CI 19–39.7%; I^2 = 0.0%) (Figure 4).

Figure 4. Forest plot with cumulative incidences of any rectal cancer recurrence after local surgical resection with subgroups based on histological risk status and local surgical resection technique. *95%ll* 95% confidence interval lower limit, *95%ul* 95% confidence interval upper limit, *TEM* transanal endoscopic microsurgery, *TAMIS* transanal minimally invasive surgery.



TEM/TAMIS versus local excision

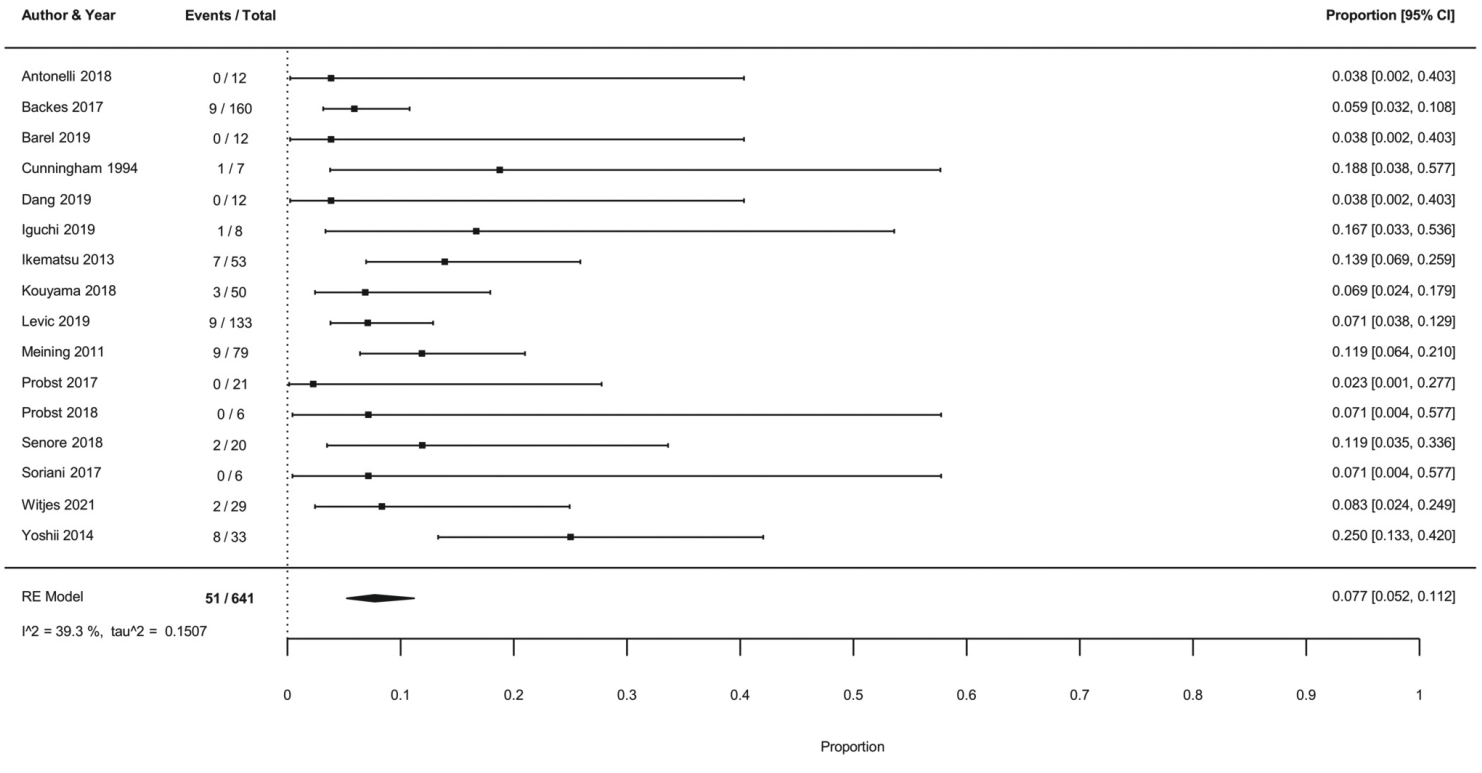
The cumulative incidence of RC recurrence was 7.7% after TEM/TAMIS (85/895 events; 95% CI 5.3–11.0%; I^2 = 47.7%) and 10.8% after local surgical excision techniques with direct visualization (76/555 events; 95% CI 6.7–16.8%; I^2 = 65.3%) (Figure 4). This difference was mainly due to an increased incidence of endoluminal local-site recurrences; 4.7% for the TEM/TAMIS (50/859 events; 95% CI 2.9–7.6%; I^2 = 44.2%) and 7.2% for local excision (38/480 events; 95% CI 4.2–12%; I^2 = 29.9%). This subgroup analyses confirmed that TEM/TAMIS is superior to other local surgical excision techniques with regard to recurrence. Outcomes of the TEM/TAMIS technique will therefore be compared to the endoscopic data. Secondary outcomes for all subgroup analyses are detailed in Supplementary results and Supplementary analyses.

TEM/TAMIS versus endoscopic resection

The previous meta-analysis and search update yielded 16 eligible studies with 641 patients and 51 recurrences (Figure 1B, Supplementary analyses) .[26,102-116] The studied endoscopic resection techniques included ESD, eFTR, EMR, and snaring polypectomy. "Very strict" follow-up schemes were reported in 50.0% (13/26) of the TEM/TAMIS studies and in 37% (10/27) of the endoscopic studies (Supplementary Figure 5). The pooled incidence of RC recurrence was comparable between endoscopically treated (7.7%; 95% CI 5.2–11.2%; I^2 = 39.3%; Figure 5) and TEM/TAMIS-treated patients with ≥ 2 years follow-up (7.7%). Also after correcting for the proportion of low- and high-risk T1RCs, meta-regression showed no statistical difference between TEM/TAMIS and endoscopic resection (p = 0.244).RC-related mortality was also comparable between endoscopically treated (2.3%; 95% CI 1.1–4.9%; I^2 = 18.4%) and TEM/TAMIS-treated patients (2.8%; 95% CI 1.2–6.2%; I^2 = 48.9%) and among the recurrence cases (30.0% versus 35.6%, respectively). The timing of the recurrences after endoscopic resection is shown in Supplementary Figure 6. The overall pooled incidence of RC recurrence after TEM/TAMIS and endoscopic resections combined was 7.7% (136/1536 events, 95% CI 5.9–10.0%; I^2 = 46.2%).

The risk of recurrence for low-risk T1RC was 5.9% after TEM/TAMIS (27/406 events, 95% CI 3.4–10.0%; I^2 = 24.1%) and 3.1% after endoscopic resection (4/128 events, 95% CI 1.2–8.0%; I^2 = 0.0%). Twenty-four of these low-risk recurrences were endoluminal (2 with synchronous locoregional LNM; 9 also presented with distant metastasis at the time of the local recurrence or later), the other 7 were distant metastasis. For 29 of the 31 low-risk T1RC recurrences it was stated that the local resection was complete. For the other 2 recurrence cases this was not stated explicitly. For high-risk T1RCs the risk of recurrence was 29.7% after TEM/TAMIS (11/37 events, 95% CI 17.3–46.1%; I^2 = 0.0%) and 12.5% after endoscopic resection (25/200 events, 95% CI 8.6–17.8%; I^2 = 0.0%). In 29 of the 43 studies on local endoscopic resections for T1RC, 4–5 JSCCR risk criteria were used; for studies on TEM/TAMIS this was 5 of the 33 studies (Supplementary Figure 4). Other secondary outcomes are shown in Supplementary results.

Figure 5. Forest plot with cumulative incidences of any RC recurrence after endoscopic resection. To visualize incidence estimates of studies with 0 events, a continuity correction of + 0.5 was applied. Values of the pooled estimates, I^2 and τ^2 are calculated using a model



Discussion

This meta-analysis is the first to meticulously analyze the long-term outcomes of T1RC patients treated by local surgical resection, and to relate these outcomes to those of endoscopically treated T1RC patients. The overall recurrence risk after local surgical resection of T1RC was found to be around 9%.

Meta-regression analysis demonstrated that the risk of recurrence was significantly affected by several factors, including resection technique. In line with previous studies,[117] our subgroup analyses confirmed that TEM/TAMIS (7.7%) is superior to other local surgical excision techniques using direct visualization (10.8%) with regard to recurrence. Although TEM/TAMIS were introduced later, it is unlikely that this biased the results because meta-regression showed no association between publication year and risk of recurrence. Instead, the difference could mainly be attributed to an increased risk of endoluminal local-site recurrences. This suggests that the oncological superiority of TEM/TAMIS is most likely explained by the camera-assisted visualization, and the use of a pneumorectum, which allows for improved visualization of tumor margins and increases the chance of achieving a complete resection. Tumor height may also have influenced the outcome of local surgical resections. Unfortunately data on tumor height was scarcely reported and could not always be extracted for the correct subgroup, therefore it was not possible to further stratify our results.

Another factor that significantly influenced the recurrence risk was histological risk status. This was in accordance with findings of our previous meta-analysis.[9] In subgroup analyses the difference between low- and high-risk tumors was confirmed for both TEM/TAMIS-treated (5.9% recurrence risk for low-risk T1RC vs. 29.7% for high-risk T1RC) and endoscopically treated patients (3.1% recurrence risk for low-risk T1RC vs. 12.5% for high-risk T1RC). There appears to be a difference in the risk of recurrence for high-risk T1RC treated by TEM/TAMIS or endoscopic resection (TEM/TAMIS: 11/37 events in 2 studies, endoscopic resection: 25/200 events in 8 studies). Due to the limited number of studies included in this subgroup analysis, it was not possible to draw any valid conclusions on these findings.

When comparing TEM/TAMIS to endoscopic resections, we observed that overall recurrence rates (7.7% and 7.7%, respectively), RC-related mortality rates (2.8% and 2.3%, respectively) and mortality rates among recurrences (35.6% and 30.0%, respectively) were quite similar. A randomized non-inferiority trial is pending to confirm these results.[118] Despite the similarities in oncological outcomes, we found that risk stratification and follow-up varied considerably between local surgically and endoscopically treated T1RC patients. Firstly, the number of JSCCR criteria used for risk stratification were quite different, which makes it difficult to compare recurrence risks stratified by histology. Two-third of studies on endoscopic resections used > 3 criteria

to define high-risk tumors, but among studies on TEM/TAMIS only ~ 15% used > 3 criteria. This has most probably caused an overestimation of the recurrence risk in the group of TEM/TAMIS-treated low-risk T1RC, as some of these patients would have been classified as high-risk if more JSCCR criteria had been used. However, it was impossible to draw any valid conclusions on the clinical relevance of each high-risk criterion from these results, as the available data did not allow us to study the criteria individually. More universal histological assessment of T1RC by a dedicated pathologist is therefore warranted. Secondly, the reported follow-up schemes of TEM/TAMIS-treated T1RC patients were often much stricter than the schemes of endoscopically treated patients (Supplementary Figure 6), but compliance to these schemes were rarely reported. Considering the comparable outcomes of TEM/TAMIS and endoscopic resection, it appears that at a certain point further intensifying the follow-up, using current follow-up modalities, might not necessarily lead to increased detection of recurrences or improved prognosis of T1RC patients. However, the optimal surveillance intensity in terms of clinical outcomes remains to be elucidated.

The risk of recurrence after local resection seems higher for T1 cancers in the rectum compared to T1 cancers throughout the colon. Here, we found a risk of recurrence for rectal T1 cancers of 7.7% (after endoscopic resection or TEM/TAMIS), which is higher than the 3.3% for endoscopically treated T1 cancers at sites throughout the colorectum.[9] A similar difference was seen in the subgroup of low-risk (endoscopically treated T1 colorectal cancer: 0.7%; endoscopically or TEM/TAMIS-treated low-risk T1 rectal cancer: 3.1–5.9%) and high-risk cancers (endoscopically treated T1 colorectal cancer: 7.0%; endoscopically or TEM/TAMIS-treated low-risk T1 rectal cancer: 12.5–29.7%). These results suggest rectal T1 cancers are associated with worse outcomes compared to colonic T1 cancers, independent of histological risk status. Plausible contributing factors include differences in anatomic structures and tumor biology.[119]

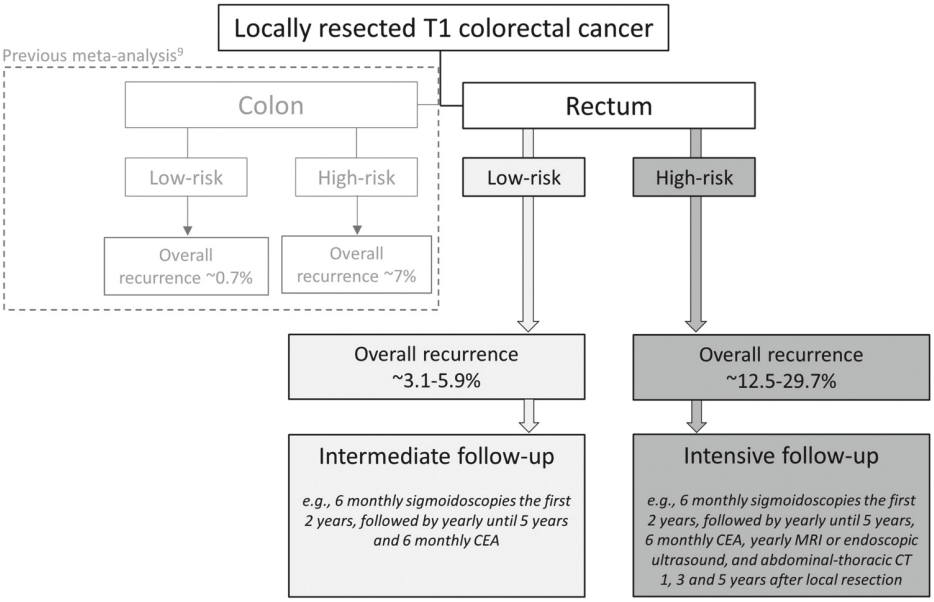
The most important limitation of this meta-analysis relates to the quality of the included studies. The selection of studies for this meta-analysis was performed as thoroughly as possible, to prevent the exclusion of important studies. However, several studies did not specifically study T1RC patients treated by local resection alone. Therefore, data on patient, treatment, tumor size, tumor height, histological, follow-up and individual recurrence characteristics could not always be fully extracted. This resulted in a smaller number of studies in various subgroup analyses and for some studies in not receiving the maximum assessment scores on risk of bias. Secondly, there was some statistical heterogeneity, which could be expected a priori considering the heterogeneity in the resection techniques and follow-up. Therefore, we performed extensive meta-regression and subgroup analyses, which yielded lower heterogeneity estimates. Lastly, the definition of the rectum was left to the discretion of the authors of included studies, to avoid exclusion of many relevant articles that did not clearly state a definition. However, due to the technical limitations of transanal local excisions

proximal to the rectum, it is not likely that cancers outside the rectum were included in this meta-analysis.

Clinical implications

Based on our study findings, we propose the following surveillance recommendations and key points for future research. Firstly, T1RC patients should be offered a different follow-up than T1 colon cancer patients and the surveillance should be stratified for histological risk status. There is no need to stratify surveillance for local resection technique when the T1RC is removed endoscopically or by TEM/TAMIS. All T1RCs that are removed locally should be offered surveillance (provided that possible findings will have clinical consequences) because even for low-risk T1RCs the recurrence risk is 3.1–5.9%. Patients with locally resected low-risk T1RC should be offered surveillance rather than completion TME because we think that in these patients the potential drawbacks from oncological surgery are greater than the possible benefits. We propose a 5-year moderately intensive follow-up scheme that should focus on the local-endoluminal site where most recurrences seem to develop (e.g., 6 monthly (recto)sigmoidoscopies the first 2 years, and then yearly until 5 years; and 6 monthly CEA). Patients with high-risk T1RC should be offered completion TME surgery because of the relatively high-risk of recurrence, as is recommended in current guidelines.[2,120] If oncological surgery is not feasible we propose a 5-year intensive follow-up scheme focusing on the detection of endoluminal, locoregional lymph node and distant recurrences (e.g., 6 monthly (recto) sigmoidoscopies the first 2 years, and then yearly until 5 years; 6 monthly CEA; yearly MRI or endoscopic ultrasound, and abdominal-thoracic computed tomography at 1, 3 and 5 years). This follow-up scheme only seems beneficial for those patients in whom salvage surgery or treatment of metastases seems feasible in the future. An overview of our main study findings and surveillance recommendations is shown in Figure 6. Further prospective studies are necessary to study the optimal method, the optimal timing, cost-effectiveness of surveillance and the impact of surveillance on the prognosis.

Figure 6. Overview of the main study findings and surveillance recommendations. *CEA* carcinoembryonic antigen, *MRI* magnetic resonance imaging, *CT* computed tomography.



Conclusion

Patients with T1 rectal cancer may have a significantly lower recurrence risk after TEM/TAMIS compared to other local surgical resections. After TEM/TAMIS and endoscopic resection the recurrence risk, cancer-related mortality and cancer-related mortality among patients with recurrence were comparable. Recurrence was mainly dependent on histological risk status. Based on our findings we propose a more uniform histology-based surveillance strategy for T1 rectal cancer patients treated by local resection alone.

Supplemental materials

Supplementary methods

Search strategy

A systematic literature search was conducted in the electronic databases of PubMed, Embase, Web of Science and Cochrane Library from inception until May 19, 2021. The strategy included terms for "T1 rectal cancer", "local surgical resection" and "recurrence". Duplicates were removed and the eligibility of the studies was independently assessed by 3 authors (ND/HD/JK). A fourth assessor (JB) was decisive in case of disagreement after discussion. The detailed search strategies per database are shown below.

PubMed: n =1988 hits on May 19, 202

("Colorectal Neoplasms"[Mesh] OR (("Intestine, Large"[Mesh] OR large intestin*[tw] OR "Colon"[tw] OR "colonic"[tw] OR "colorectal"[tw] OR "Rectum"[tw] OR "rectal"[tw] OR "cecum"[tw] OR "coecum"[tw] OR "cecal"[tw] OR "coecal"[tw] OR "large bowel"[tw] OR lower gastro*[tw]) AND ("Neoplasms"[Mesh:NoExp] OR Neoplas*[tw] OR "Carcinoma"[Mesh:NoExp] OR carcinoma*[tw] OR "Adenocarcinoma"[Mesh:NoExp] OR Adenocarcinoma*[tw] OR "cancer"[tw] OR "cancers"[tw] OR "Polyps"[Mesh:NoExp] OR "Intestinal Polyps"[Mesh] OR "polyp"[tw] OR "polyps"[tw] OR "tumor"[tw] OR "tumors"[tw] OR "tumour"[tw] OR "tumours"[tw] OR malignan*[tw] OR dysplas*[tw]))) AND ("T1"[tw] OR "T 1"[tw] OR "cT1"[tw] OR "c T1"[tw] OR "pT1"[tw] OR "p T1"[tw] OR "early"[ti] OR "stage I"[tw] OR "stage 1"[tw] OR "stage1"[tw] OR submucosa*[tw] OR "Dukes A"[tw] OR "Stage A"[tw]) AND ("Transanal Endoscopic Microsurgery"[Mesh] OR "transanal endoscopic microsurgery"[tw] OR "transanal endoscopic microsurg*"[tw] OR "trans anal endoscopic microsurgery"[tw] OR "trans anal endoscopic microsurg*"[tw] OR (("transanal"[tw] OR transanal*[tw] OR "trans-anal"[tw] OR trans-anal*[tw]) AND ("microsurgery"[tw] OR "microsurg*"[tw] OR "micro surgery"[tw] OR "micro surg*"[tw] OR "Microsurgery"[Mesh])) OR "Transanal Endoscopic Surgery"[mesh] OR "transanal minimally invasive surgery"[tw] OR "transanal minimal invasive surgery"[tw] OR "transanal minimally invasive"[tw] OR "transanal minimal invasive"[tw] OR (("transanal"[tw] OR transanal*[tw] OR "trans-anal"[tw] OR trans-anal*[tw]) AND ("Minimally Invasive Surgical Procedures"[mesh:noexp] OR "minimal invasive"[tw] OR "minimally invasive"[tw])) OR "TAMIS"[tiab] OR rectoscop*[tw] OR "Proctoscopy"[Mesh] OR proctoscop*[tw] OR polypect*[tw] OR (("locally"[tw] OR "local"[tw] OR transana*[tw] OR "full thickness"[tw] OR "full-thickness"[tw]) AND (resect*[tw] OR dissect*[tw] OR excis*[tw]))) AND ("Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh] OR Recurren*[tw] OR "Disease Progression"[Mesh:NoExp] OR progress*[tw] OR relaps*[tw] OR reoccur*[tw] OR reappear*[tw] OR return*[tw] OR "Neoplasm, Residual"[Mesh] OR residual*[tw] OR incomplete resect*[tw] OR "Reoperation"[Mesh] OR Reoperat*[tw] OR "Neoplasm Metastasis"[Mesh] OR metastas*[tw] OR "metastatic"[tw]) NOT

("Case Reports" [Publication Type] OR "case report"[ti] OR "case reports"[ti]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

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(colon tumor/ or exp colon cancer/ or colon polyp/ or colorectal tumor/ OR rectum tumor/ OR exp rectum cancer/ OR rectum polyp/ OR ((exp large intestine/ OR large intestin*.ti,ab. OR "cecum".ti,ab. OR "coecum".ti,ab. OR "cecal".ti,ab. OR "coecal".ti,ab. OR "Colon".ti,ab. OR "colonic".ti,ab. OR "colorectal".ti,ab. OR "Rectum".ti,ab. OR "rectal".ti,ab. OR "large bowel".ti,ab. OR lower gastro*.ti,ab.) AND (neoplasm/ OR Neoplas*.ti,ab. OR carcinoma/ OR carcinoma*.ti,ab. OR adenocarcinoma/ OR Adenocarcinoma*.ti,ab. OR "cancer".ti,ab. OR "cancers".ti,ab. OR polyp/ OR exp intestine polyp/ OR "polyp".ti,ab. OR "polyps".ti,ab. OR "tumor".ti,ab. OR "tumors".ti,ab. OR "tumour".ti,ab. OR "tumours".ti,ab. OR malignan*.ti,ab. OR malignant neoplasm/ OR dysplasia/ or gastrointestinal dysplasia/ OR dysplas*.ti,ab.))) AND ("T1".ti,ab. OR "T 1".ti,ab. OR "cT1".ti,ab. OR "c T1".ti,ab. OR "pT1".ti,ab. OR "p T1".ti,ab. OR "early".ti. OR "stage I".ti,ab. OR "stage 1".ti,ab. OR "stage1".ti,ab. OR submucosa/ OR submucosa*.ti,ab. OR "Dukes A".ti,ab. OR "Stage A".ti,ab.) AND ("Transanal Endoscopic Microsurgery"/ OR "transanal endoscopic microsurgery".ti,ab OR "transanal endoscopic microsurg*".ti,ab OR "trans anal endoscopic microsurgery".ti,ab OR "trans anal endoscopic microsurg*".ti,ab OR (("transanal".ti,ab OR transanal*.ti,ab OR "trans-anal".ti,ab OR trans-anal*.ti,ab) AND ("microsurgery".ti,ab OR "microsurg*".ti,ab OR "micro surgery".ti,ab OR "micro surg*".ti,ab OR exp "Microsurgery"/)) OR "transanal minimally invasive surgery".ti,ab OR "transanal minimal invasive surgery".ti,ab OR "transanal minimally invasive".ti,ab OR "transanal minimal invasive".ti,ab OR (("transanal".ti,ab OR transanal*.ti,ab OR "trans-anal".ti,ab OR trans-anal*.ti,ab) AND ("Minimally Invasive Surgery"/ OR "minimal invasive".ti,ab OR "minimally invasive".ti,ab)) OR "TAMIS".ti,ab OR rectoscopy/ OR rectoscop*.ti,ab. OR proctoscop*.ti,ab. OR polypectomy/ OR polypect*.ti,ab. OR local excision/ OR ((local therapy/ OR "locally".ti,ab. OR "local".ti,ab. OR "transanal*".ti,ab OR "full-thickness".ti,ab) AND (resect*.ti,ab. OR dissection/ OR dissect*.ti,ab. OR excision/ OR excis*.ti,ab.))) AND (recurrent disease/ OR tumor recurrence/ OR Recurren*.ti,ab. OR progress*.ti,ab. OR relapse/ OR relaps*.ti,ab. OR reoccur*.ti,ab. OR reappear*.ti,ab. OR return*.ti,ab. OR minimal residual disease/ OR residual*.ti,ab. OR incomplete resect*.ti,ab. OR reoperation/ OR Reoperat*.ti,ab. OR exp metastasis/ OR metastas*.ti,ab. OR "metastatic".ti,ab.) NOT (case report/ OR "case report".ti. OR "case reports".ti.) NOT (animal/ NOT human/) NOT ("conference abstract" OR "conference review").pt.

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TS=((large intestin* OR "Colon" OR "colonic" OR "colorectal" OR "Rectum" OR "rectal" OR "cecum" OR "coecum" OR "cecal" OR "coecal" OR "large bowel" OR lower gastro*) AND (Neoplas* OR carcinoma* OR Adenocarcinoma* OR "cancer" OR "cancers" OR "polyp" OR "polyps" OR "tumor" OR "tumors" OR "tumour" OR "tumours" OR malignan* OR dysplas*)) AND (TS=("T1" OR "T 1" OR "cT1" OR "c T1" OR "pT1" OR "p T1" OR "stage

I" OR "stage 1" OR "stage1" OR submucosa* OR "Dukes A" OR "Stage A") OR TI="early") AND TS=("Transanal Endoscopic Microsurgery" OR "transanal endoscopic microsurgery" OR "transanal endoscopic microsurg*" OR "trans anal endoscopic microsurgery" OR "trans anal endoscopic microsurg*" OR (("transanal" OR transanal* OR "trans-anal" OR trans-anal*) AND ("microsurgery" OR "microsurg*" OR "micro surgery" OR "micro surg*" OR "Microsurgery")) OR "transanal minimally invasive surgery" OR "transanal minimal invasive surgery" OR "transanal minimally invasive" OR "transanal minimal invasive" OR (("transanal" OR transanal* OR "trans-anal" OR trans-anal*) AND ("Minimally Invasive Surgery" OR "minimal invasive" OR "minimally invasive")) OR "TAMIS" OR rectoscop* OR proctoscop* OR polypect* OR (("locally" OR "local" OR "transanal*" OR "full-thickness") AND (resect* OR dissect* OR excis*))) AND TS=(Recurren* OR progress* OR relaps* OR reoccur* OR reappear* OR return* OR residual* OR incomplete resect* OR Reoperat* OR metastas* OR "metastatic") NOT TI=("mouse" OR "mice" OR "murine" OR "rat" OR "rats" OR "animal" OR "animals" OR "rodent" OR "rodents") Refined by: [excluding] DOCUMENT TYPES: (MEETING ABSTRACT). Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI.

Cochrane Library: n =249 hits on May 19, 2021

(((large intestin* OR "Colon" OR "colonic" OR "colorectal" OR "Rectum" OR "rectal" OR "cecum" OR "coecum" OR "cecal" OR "coecal" OR "large bowel" OR lower gastro*) AND (Neoplas* OR carcinoma* OR Adenocarcinoma* OR "cancer" OR "cancers" OR "polyp" OR "polyps" OR "tumor" OR "tumors" OR "tumour" OR "tumours" OR malignan* OR dysplas*)) AND ("T1" OR "T 1" OR "cT1" OR "c T1" OR "pT1" OR "p T1" OR "stage I" OR "stage 1" OR "stage1" OR submucosa* OR "Dukes A" OR "Stage A" OR "early") AND ("Transanal Endoscopic Microsurgery" OR "transanal endoscopic microsurgery" OR "transanal endoscopic microsurg*" OR "trans anal endoscopic microsurgery" OR "trans anal endoscopic microsurg*" OR (("transanal" OR transanal* OR "trans anal" OR trans anal*) AND ("microsurgery" OR "microsurg*" OR "micro surgery" OR "micro surg*" OR "Microsurgery")) OR "transanal minimally invasive surgery" OR "transanal minimal invasive surgery" OR "transanal minimally invasive" OR "transanal minimal invasive" OR (("transanal" OR transanal* OR "trans anal" OR trans anal*) AND ("Minimally Invasive Surgery" OR "minimal invasive" OR "minimally invasive")) OR "TAMIS" OR rectoscop* OR proctoscop* OR polypect* OR (("locally" OR "local" OR "transanal" OR "transanal*" OR "full thickness") AND (resect* OR dissect* OR excis*))) AND (Recurren* OR progress* OR relaps* OR reoccur* OR reappear* OR return* OR residual* OR incomplete resect* OR Reoperat* OR metastas* OR "metastatic") NOT ("mouse" OR "mice" OR "murine" OR "rat" OR "rats" OR "animal" OR "animals" OR "rodent" OR "rodents")):ti,ab,kw NOT (meeting abstract OR conference abstract):

The search strategy for studies regarding the endoscopic resections for T1CRC was previously published.[9] For this meta-analysis, the search was updated until May 19,

2021, the subset of patients with rectal lesions was selected and additional data regarding this subgroup was requested from corresponding authors.

Data extraction

The following data were extracted: study characteristics (year of publication, single- or multi-center, study design, inclusion period, geographical location) patient characteristics (number of patients undergoing local surgical resection for T1RC, sex, age, comorbidity), treatment characteristics (treatment modality used for local resection, resection plane, anatomical approach of the resection), tumor characteristics (size, distance to the anal verge/dentate line), histological characteristics (low- or high-risk T1RC, high-risk definition, resection margin status, number of patients with lymphovascular invasion (LVI), deep submucosal invasion, high-grade tumor budding, grade 3 differentiation), follow-up characteristics and outcomes (follow-up modalities used, frequency per follow-up modality, mean and minimum follow-up duration, number of locoregional or distant recurrences, RC-related mortality). For all individual recurrence cases, we also extracted available patient-level data on all aforementioned clinical characteristics, and recurrence management and outcomes.

For the subgroup of patients who were treated endoscopically, individual patient-level recurrence data, study characteristics, the total number of patients undergoing local endoscopic resection, follow-up characteristics, and outcomes were extracted. For practical reasons data on individual JSCCR features and follow-up duration specifically for T1RC were not collected.

When only median values and ranges were reported for continuous variables, the mean was estimated using the approximation method described by Luo and others.[102]

Definitions and Classifications

Studies were classified as retrospective when this was explicitly or implicitly stated (e.g., “patient records were reviewed” or concluding that “prospective studies will be needed”). Studies that reported a retrospective analysis of prospectively collected data were classified as prospective. Studies were categorized as single-center when all authors were from 1 hospital and if it was not clearly stated in the manuscript how many centers the patients were included from. All four papers in which discrepancies were found in between the text and tables/figures,[23, 44, 81] were discussed in detail by two assessors (ND, HD) until consensus was reached.

The TEM and TAMIS techniques are well described in literature, first by Buess and Atallah.[103, 104] The Gasless Transanal Endoscopic Surgery (GTES)[96] and Video Endoscopic Transanal Rectal Tumour Excision (VTEM)[71] were analyzed with the TEM group because of their similarities to TEM. Minimally Invasive Transanal Surgery (MITAS)[66] was analyzed with TAMIS for the same reason. All other local surgical resection techniques using direct

visualization (e.g., Parks technique, Stuart technique, the use of Ferguson's anoscope, transanal endoscopic operation, or undefined local surgical resections) were grouped as "other local excisions". Some papers reported more than one treatment modality. Patients for whom it was implicitly stated that they had undergone prior (endoscopic) resection (e.g., "no tumor rest was found in the specimen") were excluded from this meta-analysis. However, for one study it could not be ruled out that 1 of the 20 included patients was a case of T1 recurrence after endoscopic polypectomy.[124] We chose to include this study to prevent loss of relevant data.

For each study, the high-risk definitions were classified based the number of JSCCR histological high-risk criteria that were used (i.e., grade 3 differentiation, deep submucosal invasion, high-grade tumor budding, LVI, and positive resection margins).[2] Grade 3 differentiation was defined as poorly differentiated adenocarcinoma, mucinous, or signet ring cell carcinoma.[125] Deep submucosal invasion was defined as Kikuchi level ≥Sm2 or an invasion depth ≥1000 μm.[126] High-grade tumor budding was defined as ≥Bd2.[127] LVI was categorized into "present" or "absent" and was defined as CRC cells within an endothelial or internal elastic lamina-confined lumen.[125] Resection margins were classified as R0 (no dysplastic cells at the resection margins), Rx (margins could not be assessed with certainty), or R1 (dysplastic cells close to or at the resection margins). Rx and R1 were then categorized as "not-R0" due to the fact that the exact number of Rx and R1 resections were often difficult to determine for the subgroup of interest and because of the varying definitions of R1 across the different studies.

Follow-up intensity was compared by grouping studies together based on the number of follow-up modalities used and the intervals per modality. Schemes with a mean of ≤2-3 modalities per year or only one modality (e.g., "3 monthly sigmoidoscopies for at least 5 years")[28] were classified as "not strict", schemes with a mean of 2-4 modalities per year and at least 2 different modalities used (e.g., "3 monthly colonoscopies and CEA for 2 years, followed by yearly for 5 years")[18] as "strict" and schemes with ≥4 modalities per year and the use of at least 3 different modalities (e.g., "3 monthly proctoscopies, chest X-ray, abdominal ultrasound scanning, CEA and rectal intraluminal ultrasound for 2 years, followed by 6 monthly for 5 years")[44] as "very strict". When the follow-up duration was not reported separately for the subgroup of locally treated T1 patients, overall follow-up durations of the population that came closest to the population of interest (both in numbers and in treatment modality) were extracted and used in sensitivity analyses.

Risk of Bias Assessment

A modified Newcastle-Ottawa Scale for cohort studies was used to assess the risk of bias.[10] The items "Comparability of cohorts" and "Selection of the non-exposed cohort" were excluded because no comparative outcome measures were meta-analyzed. "Ascertain of exposure" was excluded because only patients with histologically

confirmed T1RCs were included. The item "Was follow-up long enough for outcomes to occur" was adjusted to "Information on follow-up duration of analyzed patients with T1RC reported" (0, no; 1, yes). Reported follow-up durations were included in meta-regression analyses as continuous variables. "Information on follow-up intensity reported" was also added as an item (0, no; 1, yes; the number of modalities is reported; 2, yes; both the number of modalities and the frequency of use are reported; included as categorical variables in meta-regression analyses) because recurrence incidence, location, and time to recurrence largely depend on the number of follow-up modalities used and the frequency thereof. The influence of every individual risk of bias item on the study outcomes was evaluated using meta-regression analyses. It has been shown that the use of combined scores of all individual risk of bias items to identify the level of quality can be problematic.[128] Therefore, no overall scores were included in our analyses.

Supplementary results

All additional forest plots are displayed in Supplementary analyses.

Individual recurrence cases

The type of recurrence was reported for 288 recurrence cases (192 locoregional, 43 distant, 53 both). The time to recurrence was reported in 152 cases (Supplementary Figure 7). In 26 cases it was reported which modality detected the recurrence: 12 via endoscopy/endoscopic-ultrasound, 7 via magnetic resonance imaging (MRI), 5 via clinical exam, and 1 via serum Carcinoembryonic Antigen (CEA). The management of recurrences was reported in 153 cases(Supplementary Figure 8). Of the 100 patients with only endoluminal recurrence, most underwent additional TME (n=74) or a local re-excision (n=16), with or without (neo)adjuvant therapy. The ten other patients received (chemo)radiation therapy without resection, palliative care or no treatment. The T-stage of the recurrences was reported in 42 cases (9 T2; 28 T3; 3 T4). The N- and M-stage of recurrences were rarely reported. In 33 recurrence cases with data on both the time to recurrence and time to RC-related death, the median time from recurrence to RC-related death was 13 months (range, 0-104;Supplementary Figure 9).

Meta-regression

None of the study characteristics, risk of bias assessment items, and follow-up intensity were significantly associated with the risk of recurrence (all $p>0.1$) Supplementary table 2. Follow-up duration (15 studies) and reporting on follow-up scheme (reported vs. not reported, 86 studies) were not significant ($p=0.06$). In 59 studies a mean duration of follow-up was reported for a group of patients that included all locally treated T1 cancers but also included other patients (e.g., also including some patients receiving adjuvant therapies, T2 cancers, etc.). When this mean duration of follow-up was used in a sensitivity analysis a positive significant association between follow-up duration and risk of recurrence was found ($p=0.0001$). Therefore, further analyses were stratified

according to the duration of follow-up. Of all clinical characteristics, histological risk profile showed the most significant association with the cumulative incidence of RC recurrence (p=0.0004), followed by treatment modality (p=0.0037 for LE vs. TEM/TAMIS). (Supplementary Table 3).

Subgroup analyses stratified on follow-up duration

All studies

The pooled incidences of locoregional recurrence only, any locoregional recurrence and any distant recurrence were 6.5% (95%-CI 5.1-8.3%, I^2 = 52.5%), 7.7% (95%-CI 6.0-9.8%, I^2 = 66.5%) and 2.6% (95% CI 1.8-3.8%, I^2 = 57.7%), respectively. The pooled incidence of RC-related mortality was 2.0% (55/1468 events, 52 studies; 95%-CI 1.1-3.8; I^2 = 75.2%). The RC-related mortality rate among patients with recurrence was 31.4% (55/175). Besides one patient with direct postoperative mortality after salvage TME (patient ID 12571 no. 2; Supplementary analyses; dataset), all of these patients died of disease progression.

≥ 2 years follow-up

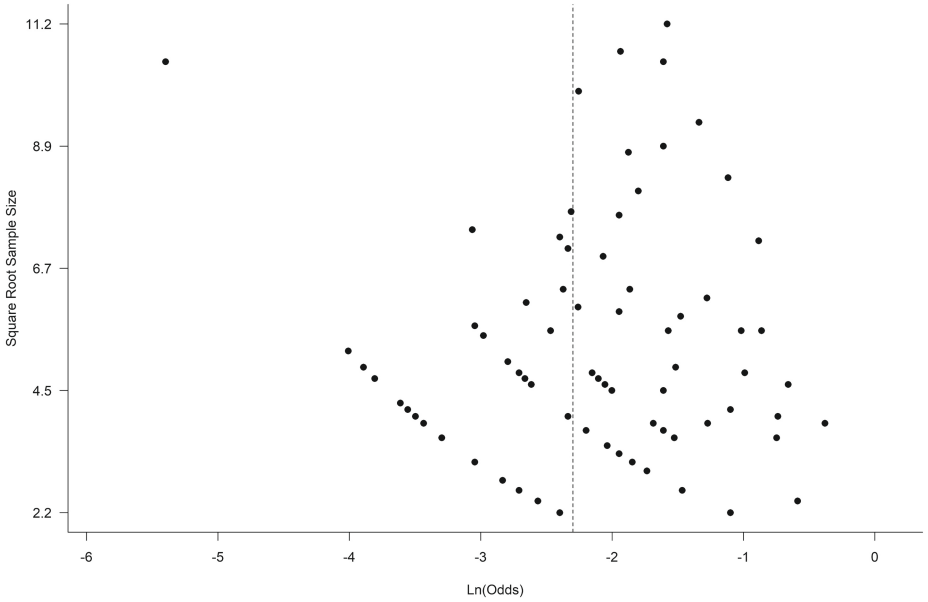
The pooled incidences of locoregional recurrence only, any locoregional recurrence and any distant recurrence were 6.5% (95%-CI 4.9-8.6% I^2 = 43.1%), 7.5% (95%-CI 5.7-10.0%, I^2 = 56.2%) and 3.1% (95%-CI 2.1-4.5%, I^2 = 40.8%), respectively.

≥ 5 years follow-up

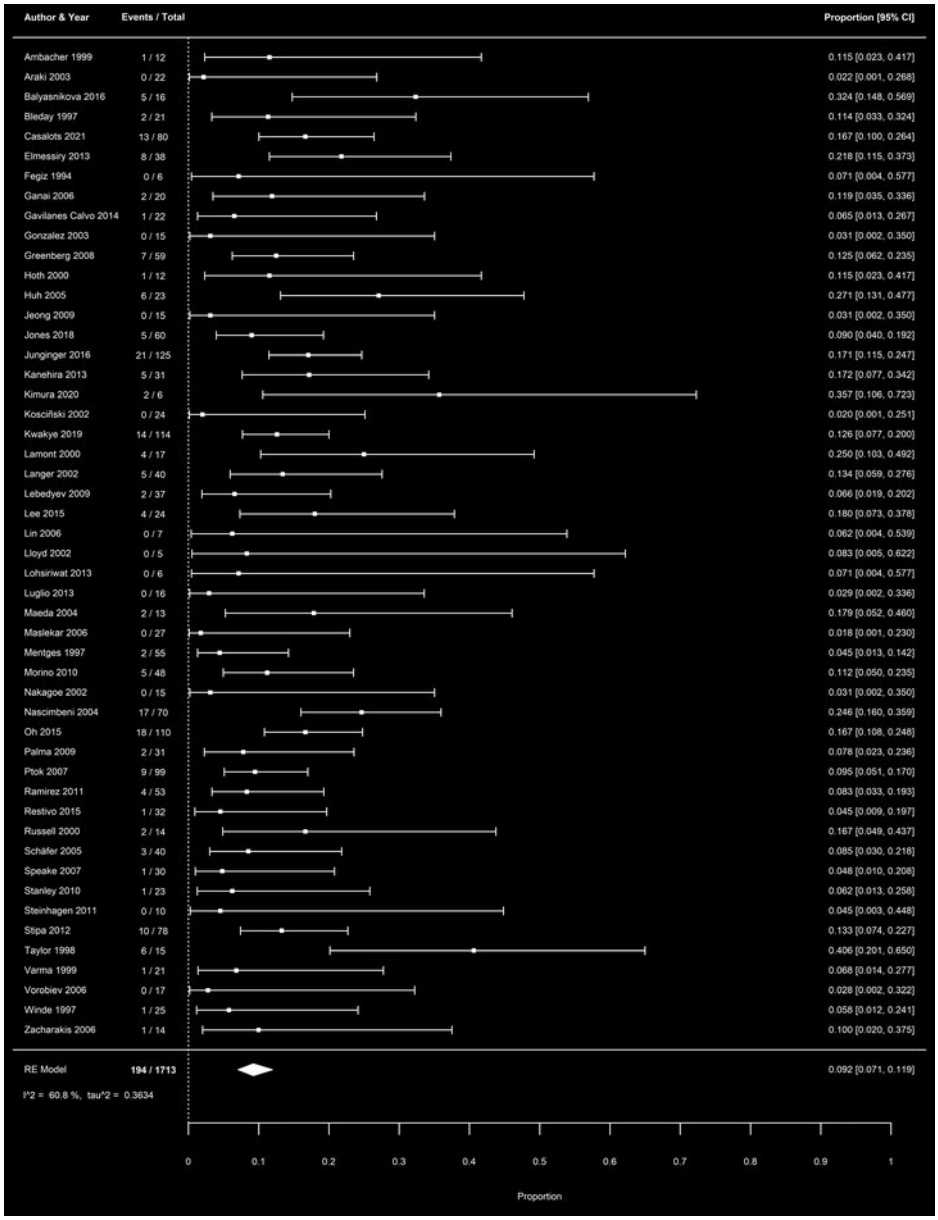
The pooled cumulative incidence of any RC recurrence was 13.2% (95%-CI 10.5-16.6%; I^2 = 24.4%). The pooled incidences of locoregional recurrence only, any locoregional recurrence and any distant recurrence were 8.3% (95%-CI 6.7-10.3%, I^2 = 0.0%), 10.3% (95%-CI 7.9-13.3%, I^2 = 8.4%) and 4.9% (95%-CI 3.3-7.3%, I^2 = 35.6%), respectively. The pooled incidence of RC-related mortality was 3.4% (22/489 events, 9 studies; 95%-CI 1.5-7.1%; I^2 = 59.4%). The RC-related mortality rate among patients with recurrence was 31.4% (22/70). All of these patients died of disease progression.

Supplementary figures

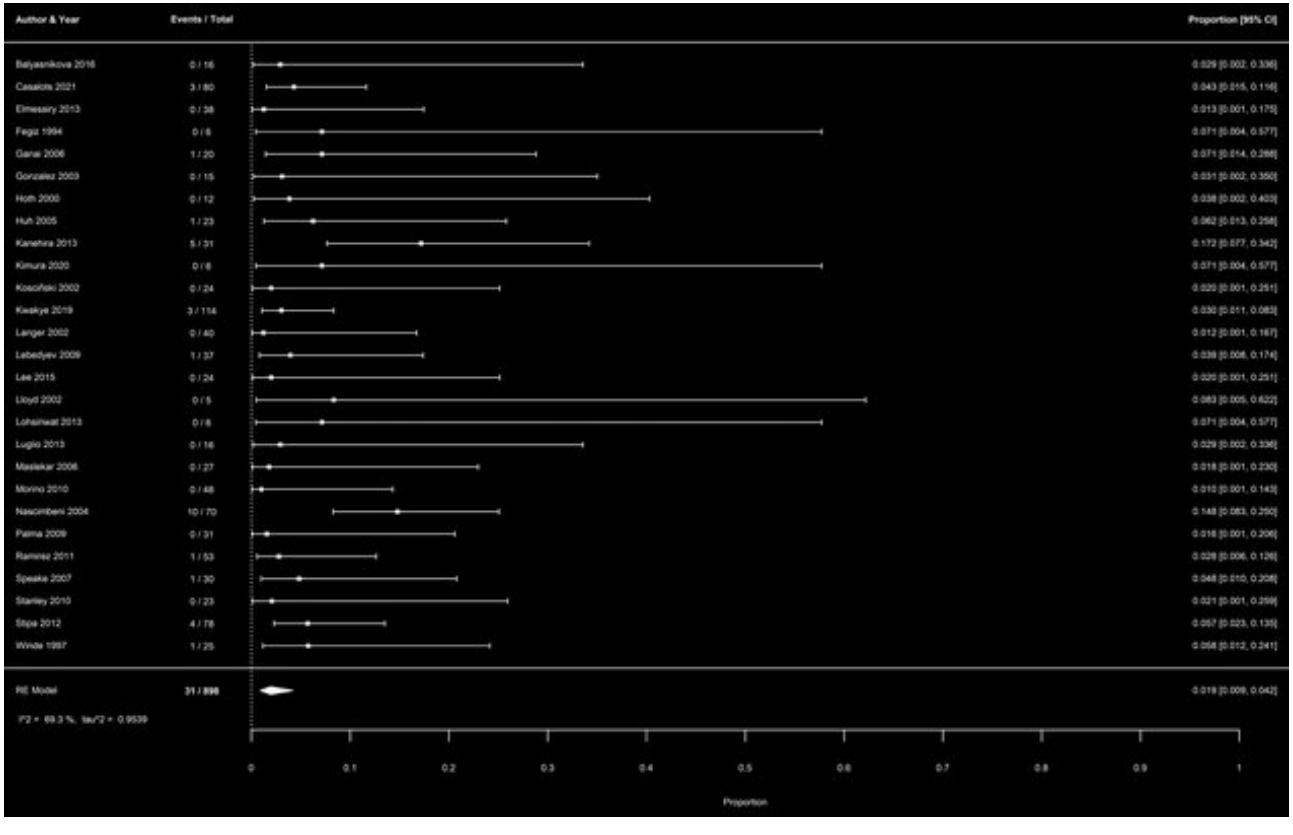
Supplementary figure 1. Funnel plot for the cumulative incidence of any rectal cancer recurrence. The points correspond to the incidences of individual studies, and the vertical line in the funnel plot indicates the summary estimate. To visualize incidence estimates of studies with 0 events, a continuity correction of +0.5 was applied.



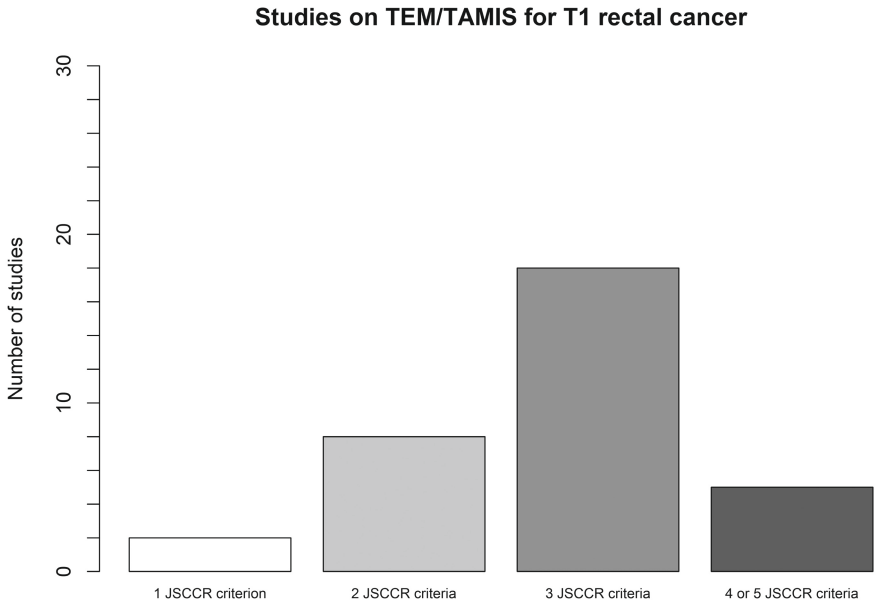
Supplementary figure 2. Forest plot with cumulative incidences of any RC recurrence after local surgical resection in patients with ≥2 years follow-up. To visualize incidence estimates of studies with 0 events, a continuity correction of +0.5 was applied. Values of the pooled estimates, I^2 and τ^2 are calculated using a model without continuity correction.

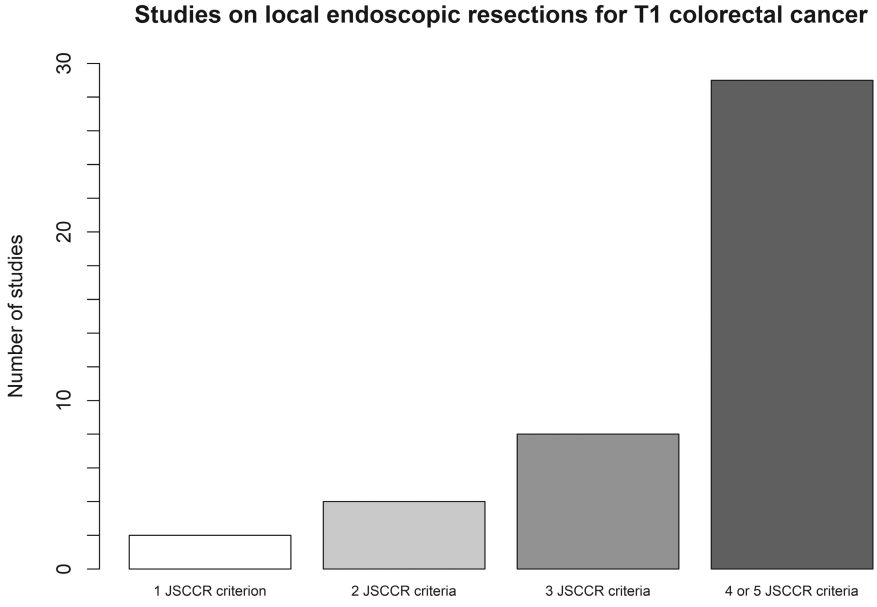


Supplementary figure 3. Forest plot with cumulative incidences of rectal cancer-related mortality after local surgical resection in patients with ≥2 years follow-up. To visualize incidence estimates of studies with 0 events, a continuity correction of +0.5 was applied. Values of the pooled estimates, I^2 and τ^2 are calculated using a model without continuity correction.

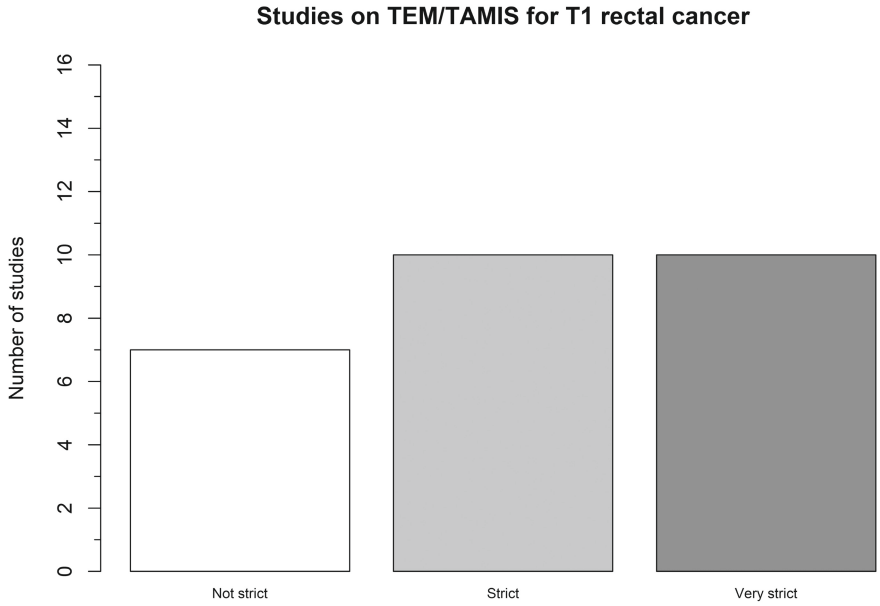


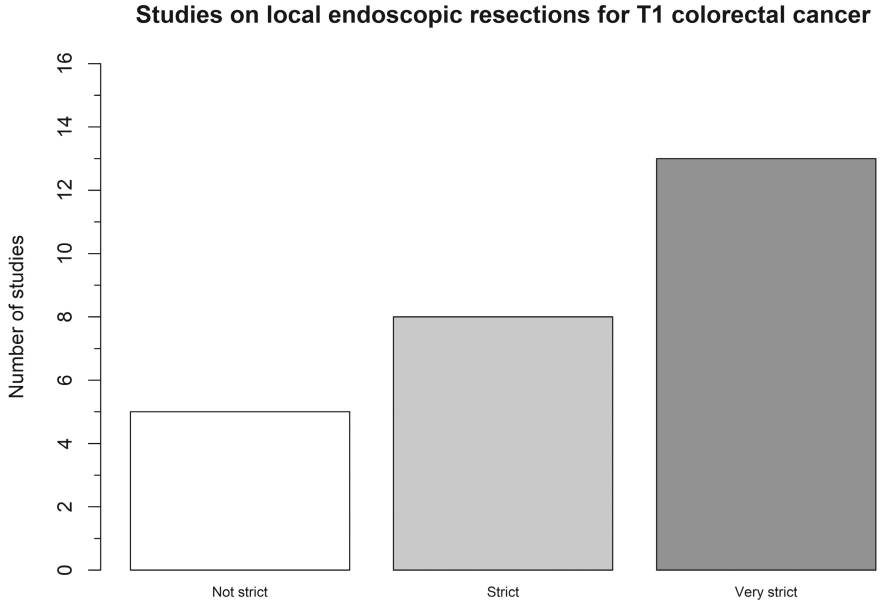
Supplementary figure 4. Number of JSCCR criteria used for histological risk stratification for studies on TEM/TAMIS and endoscopic resection. *TEM* transanal endoscopic microsurgery, *TAMIS* transanal minimally invasive surgery, *JSCCR* Japanese Society for Cancer of the Colon and Rectum.



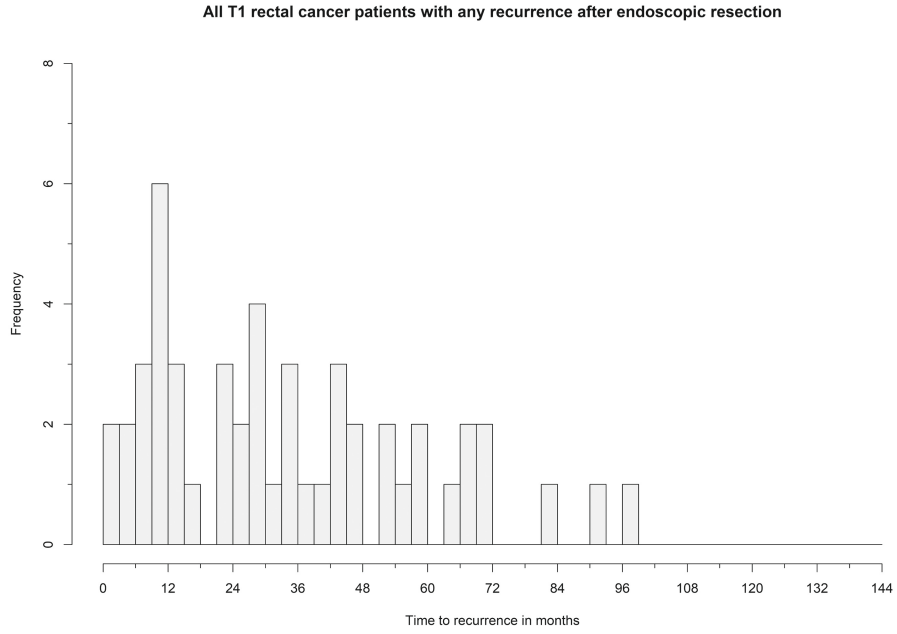


Supplementary figure 5. Strictness of follow-up for studies on endoscopic resection and TEM/TAMIS. *TEM* transanal endoscopic microsurgery, *TAMIS* transanal minimally invasive surgery.

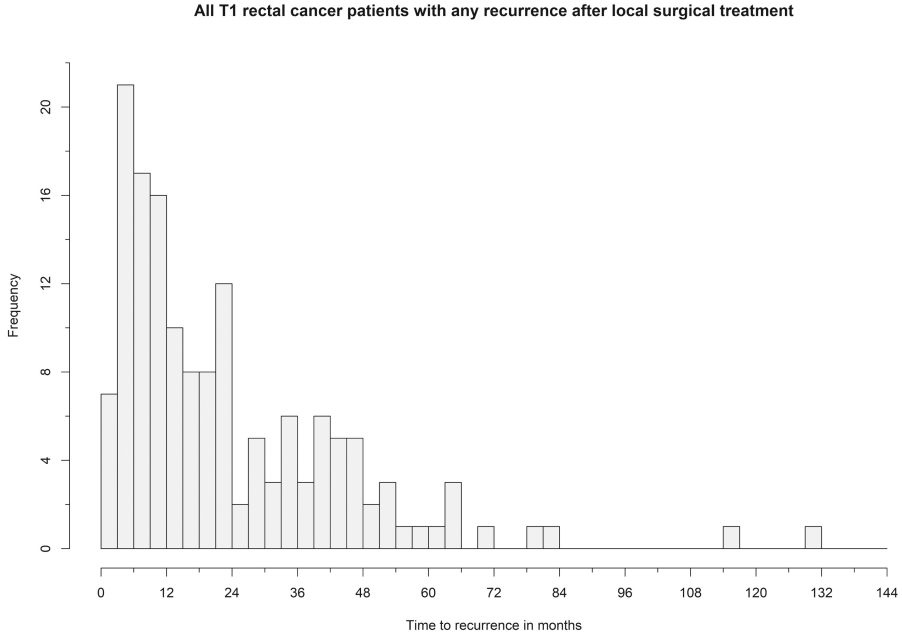




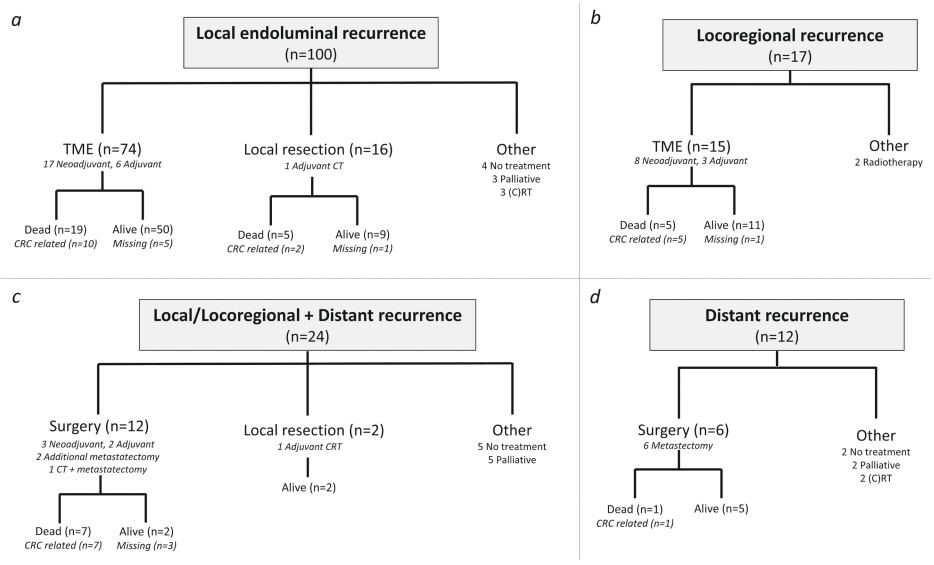
Supplementary figure 6. Time to any rectal cancer recurrence after endoscopic resection.



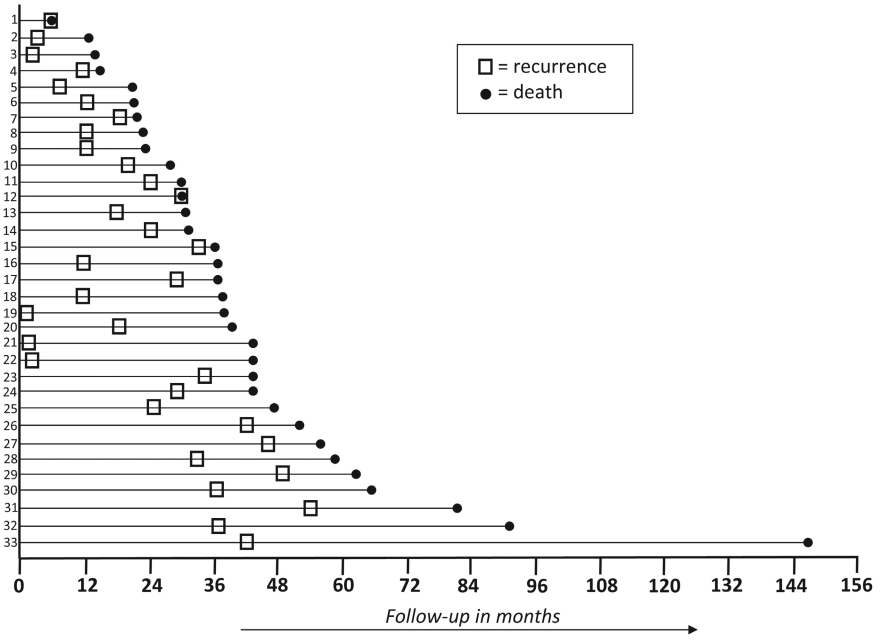
Supplementary figure 7. Time to any rectal cancer recurrence after local surgical resection.



Supplementary figure 8. Treatment of recurrence after local surgical resection. **a.** local endoluminal recurrence, **b.** locoregional recurrence, **c.** local/locoregional + distant recurrence, **d.** distant recurrence. *TME* total mesorectal excision, *CRT* chemoradiotherapy.



Supplementary figure 9. Time between rectal cancer recurrence and rectal cancer-related mortality.



Supplementary tables and analyses
Supplementary tables and supplementary analyses can be found online at Surgical Endoscopy (https://link.springer.com/journal/464).

Supplementary table 1. In- and exclusion criteria for the endoscopic sub-section.

Supplementary table 2. Meta-regression with study characteristics and risk of bias.

Supplementary table 3. Meta-regression with clinical characteristics.

Supplementary analyses. Including: extracted data and risk of bias assessment of the included studies, pooled incidence of all secondary outcomes, and forest plots of all subgroup analyses

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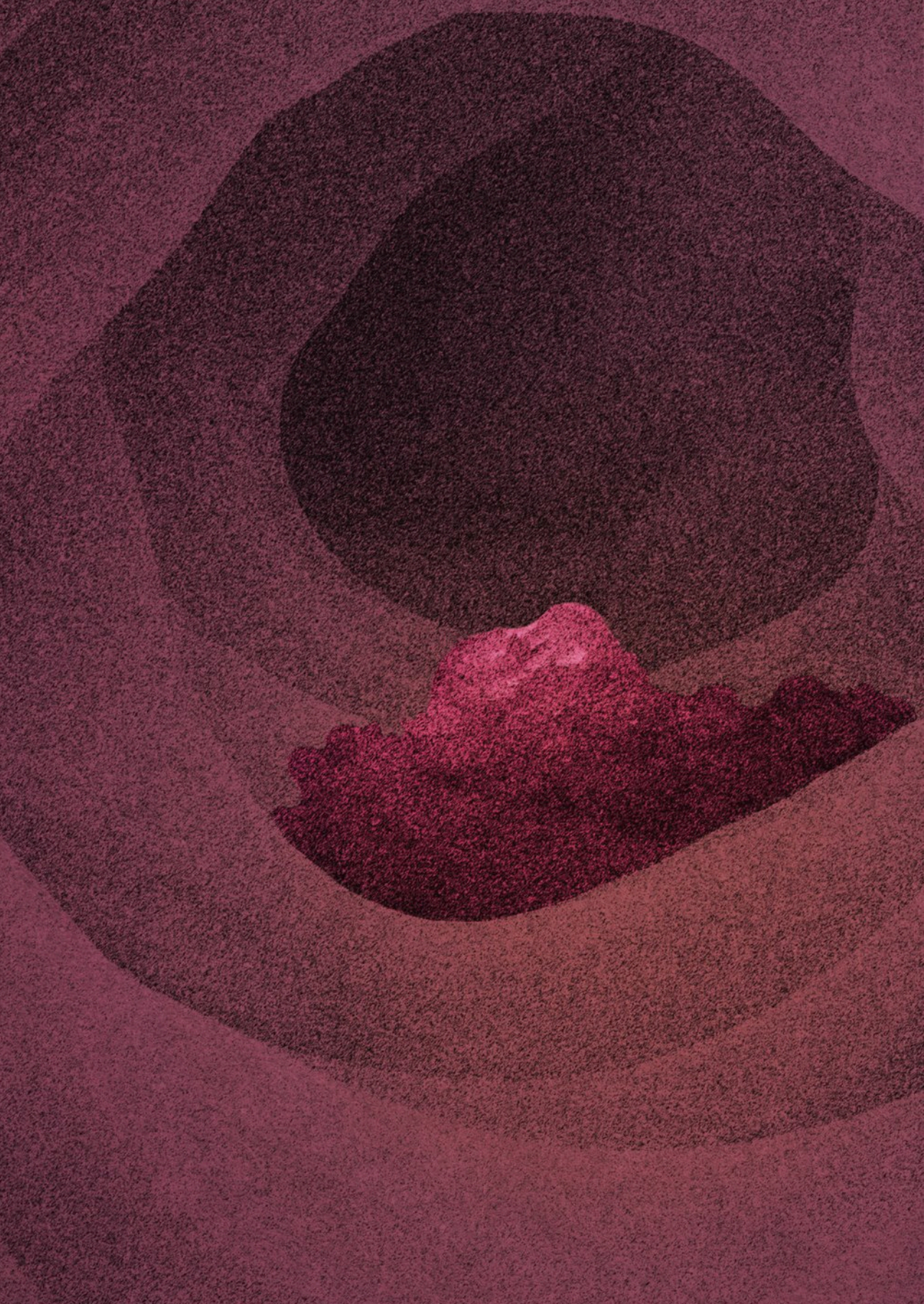
PART III

Patient empowerment



CHAPTER 8

T1 colorectal cancer patients' perspective on information provision and therapeutic decision-making after local resection

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United European Gastroenterology Journal 2024

Abstract

Background: Decision-making after local resection of T1 colorectal cancer (T1CRC) is often complex and calls for optimal information provision as well as active patient involvement.

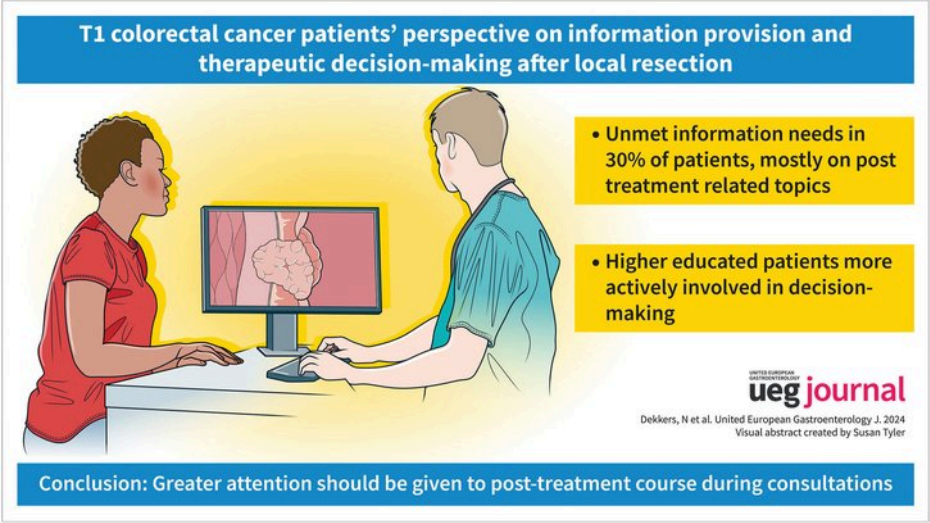
Objective: The aim was to evaluate the perceptions of patients with T1CRC on information provision and therapeutic decision-making.

Methods: This multicenter cross-sectional study included patients who underwent endoscopic or local surgical resection as initial treatment. Information provision was assessed using the EORTC QLQ-INFO25 questionnaire. In patients with high-risk T1CRC, we evaluated decisional involvement and satisfaction regarding the choice as to whether to undergo additional treatment after local resection, and the level of decisional conflict using the Decisional Conflict Scale.

Results: Ninety-eight patients with T1CRC were included (72% response rate; 79/98 endoscopic and 19/98 local surgical resection; 45/98 high-risk T1CRC). Median time since local resection was 28 months (IQR 18); none had developed recurrence. Unmet information needs were reported by 29 patients (30%; 18 low-risk, 11 high-risk), mostly on post-treatment related topics (follow-up visits, recovery time, recurrence prevention). After local resection, 24 of the 45 high-risk patients (53%) underwent additional treatment, while others were subjected to surveillance. Higher-educated patients were more often actively involved in decision-making (93% vs. 43%, $p = 0.002$) and more frequently underwent additional treatment (79% vs. 40%, $p = 0.02$). Decisional conflict ($p = 0.19$) and satisfaction ($p = 0.78$) were comparable between higher- and lower-educated high-risk patients.

Conclusion: Greater attention should be given to the post-treatment course during consultations following local T1CRC resection. The differences in decisional involvement and selected management strategies between higher- and lower-educated high-risk patients warrant further investigation.

Graphical abstract



Key summary

Summarize the established knowledge on this subject

- Local organ-sparing resection techniques have emerged as first-line treatment for T1 colorectal cancer
- Therapeutic decision-making after local resection of T1 colorectal cancer is often complex (i.e. additional treatment vs. surveillance)
- T1 colorectal cancer patients' perspective on information provision and decision-making has never been studied

What are the significant and/or new findings of this study?

- Post-treatment care was identified as the area with the most unmet information needs among locally treated T1 colorectal cancer patients.
- The importance for clinicians to take the educational background of patients into account during consultations and decision-making.
- Satisfaction with decision-making remained consistent regardless of whether patients opted for additional treatment or surveillance.

Introduction

In recent years, local organ-sparing tumor resection has emerged as the first-line treatment for early invasive colorectal cancer (T1CRC).[1] Subsequent management typically involves either additional oncological surgery or surveillance, with the choice depending on balancing the estimated risk of residual or recurrent disease against the potential harms associated with further treatment.[2] The decision-making process can be intricate when a clearly superior option is lacking, a scenario frequently encountered in T1CRC cases with ≥1 histological high-risk features. Patients with high-risk T1CRC face a relatively increased risk of lymph node metastasis, albeit modest in absolute terms (~15%).[2] In these cases, active patient involvement in the decisional process can be important to determine the most suitable treatment choice for that individual patient.[3]

A prerequisite for making an informed decision is providing patients with comprehensive and understandable information about the disease and its clinical management. However, particularly in the context of cancer care, adequate information provision can be difficult for several reasons. Firstly, medical information may be emotionally charged, especially regarding aspects such as the risk of disease recurrence and survival.[4] Secondly, the information provided by physicians may not always align with patients' preferences, potentially leaving out certain topics that patients wish to have more information about.[5, 6] Thirdly, medical information often contains numerous considerations and nuances that may be complex for non-experts to understand and interpret. As previously emphasized, this challenge is notably apparent in the management of T1CRCs.

Currently, it remains unclear how patients with T1CRC perceive the provided information and its comprehensiveness. In addition, empirical data on the views of patients with T1CRC regarding decisional involvement and satisfaction are lacking. Therefore, this study aimed to explore the patient's perspective on information provision and the decision-making process following local resection of T1CRC.

Materials and methods

Population

We conducted a cross-sectional multicenter study in patients selected according to the following inclusion criteria.

1. Diagnosed with T1CRC (defined as histologically proven tumor invasion through the muscularis mucosae and into, but not beyond, the submucosa)
2. Initial endoscopic or local surgical resection was performed at the Leiden University Medical Center (tertiary hospital) or Isala Hospital (community hospital) between January 2018 and December 2021.

3. Provided written informed consent.

Patients were excluded if they could not read Dutch. The study was approved by the Medical Ethical Committees of Leiden University Medical Center (N21.083) and Isala Hospital (20210910).

Clinical variables

Demographic patient characteristics (age, sex, comorbidity) and clinical data (morphology and location of T1CRC; type and timing of local resection; histology parameters: high-risk features, completeness of the resection) were collected from the hospital electronic medical records. In the high-risk subgroup, we also assessed whether patients were referred to a surgeon.

Patients' educational level was collected through a self-reported questionnaire. Higher educational level was defined as completion of at least a bachelor's degree. Physical status was determined using the American Society of Anesthesiologists (ASA) physical status classification system and the Charlson Comorbidity Index (CCI). Completeness of the local resection was classified as either R1 (microscopic positive resection margins), Rx (uncertain resection margins), or R0 (complete resection), the latter being defined as histologically proven cancer-free (≥0.1 mm margin) deep and lateral resection margins. T1CRCs were classified as high-risk if ≥1 histological high-risk feature for lymph node metastasis was present. At the time this study was conducted, the high-risk features were grade three differentiation, lymphovascular-invasion, high-grade tumor budding (≥Bd2), R1 or Rx resection margins of the invasive component, and deep submucosal invasion (Haggitt 4, ≥Sm1 or ≥1000 µm invasion depth).[7] Patients who underwent oncological surgery or chemoradiotherapy[8] after local resection were categorized as 'additional treatment', while patients who did not undergo these treatments were categorized as 'close monitoring'. Secondary local scar resection was not regarded as 'additional treatment' since its purpose is mainly to enhance local control rather than addressing potential lymph node metastases.

Questionnaires

Patients' perception on information provision, satisfaction and needs

Information provision, satisfaction and needs were assessed in all patients using the validated Dutch version of the EORTC QLQ-INFO25 (INFO25).[9] The INFO25 consists of 25 items, and the items regarding provided information are organized in four multi-item scales: Information about the disease (four items), medical tests (three items), treatment (six items), other services (four items) and two single items (lifestyle and nutritional advice, things you can do to help yourself get better). Six additional items assess information needs and satisfaction. The response format for most questions is a four-point Likert scale (1—Not at all, 2—A little, 3—Quite a bit, 4—Very much), except for four items (20, 21, 23, and 24), which have a dichotomous (yes/no) scale. All scores

were linearly transformed into a score from 0 to 100.[10] A higher score on a certain item indicates a higher level of information received, greater desire for more information, or greater satisfaction. The questionnaire was slightly modified to make it more applicable to the situation of patients with T1CRC. The modifications are described in detail in the Supplementary Methods.

Patients' perception on decision-making

Patients with a high-risk T1CRC were asked to answer several additional questions. The patient's experience on how the decision to either opt for or opt out of additional treatment was assessed in two pre-questions. The first question assessed the level of decisional involvement: "Did you feel like you had a choice regarding whether or not to undergo additional treatment?". If patients answered affirmatively, they were asked to choose between the following two statements: a. "I had a choice, and I made the decision myself" or b. "I had a choice, but I let the physician make the decision". The second question assessed the level of decisional satisfaction: "Are you satisfied with the way in which the treatment policy was determined?". The response format for the second question was a four-point Likert scale (1-Not at all, 2-A little, 3-Quite a bit, 4-Very much), which was linearly transformed to a 0–100 scale for analyses. In line with a previous study,[11] patient involvement in decision-making was classified as 'active' if patients reported making the decision themselves. It was classified as 'passive' if patients reported allowing their physician to decide or if they indicated they had never experienced having a choice.

Perceptions on the extent of decisional conflict were assessed in patients who indicated that they had experienced a moment of choice (either active or passive) using the Dutch version of the validated Decision Conflict Scale (DCS).[12] The DCS is a 16-item questionnaire that measures five dimensions of decision-making: Informed subscale (three items), values clarity subscale (three items), support subscale (3 items), uncertainty subscale (three items) and effective decision subscale (four items). The response format for all questions is a five-point Likert scale (0−Strongly agree, 1−Agree, 2−Neither agree nor disagree, 3−Disagree, 4-Strongly disagree). All scores were linearly transformed into a score from 0 to 100, with lower scores indicating a lower level of decisional conflict.

Procedures

The consultation procedure in the outpatient clinic was not standardized; instead, the standard of care was assessed. Generally, the consultation procedure was similar in both hospitals. Initially, patients underwent a primary consultation where a healthcare professional briefed the patient on the upcoming colonoscopy or on local treatment directly, depending on the available information. If a colonoscopy was performed and revealed the need for a more extensive local resection (e.g., endoscopic submucosal dissection), a second consultation took place to obtain informed consent. Following

local resection and pathological examination, patients returned to the outpatient clinic for the results within ± two weeks. For low-risk T1 CRC cases follow-up was discussed. High-risk cases were usually discussed in a multidisciplinary team before different treatment strategies were discussed with the patient in the outpatient clinic (additional treatment vs. monitoring). Additionally, high-risk patients were often referred for surgical consultation prior to decision-making. The healthcare professionals involved in abovementioned consultations were mostly (i.e. >95%) gastroenterologists or surgeons, and in some cases, a resident or a physician assistant.

Follow-up in both hospitals was generally conducted in a similar manner, in accordance with the national colorectal cancer guideline.[13] The follow-up protocol was most stringent for the high-risk group that opted for close surveillance.

The questionnaires were sent to the patients' home addresses along with a consent form and a stamped return envelope. Patients who did not return the questionnaire within a month were contacted by telephone to confirm the receipt of the study documents and to determine their willingness to participate.

Statistical analyses

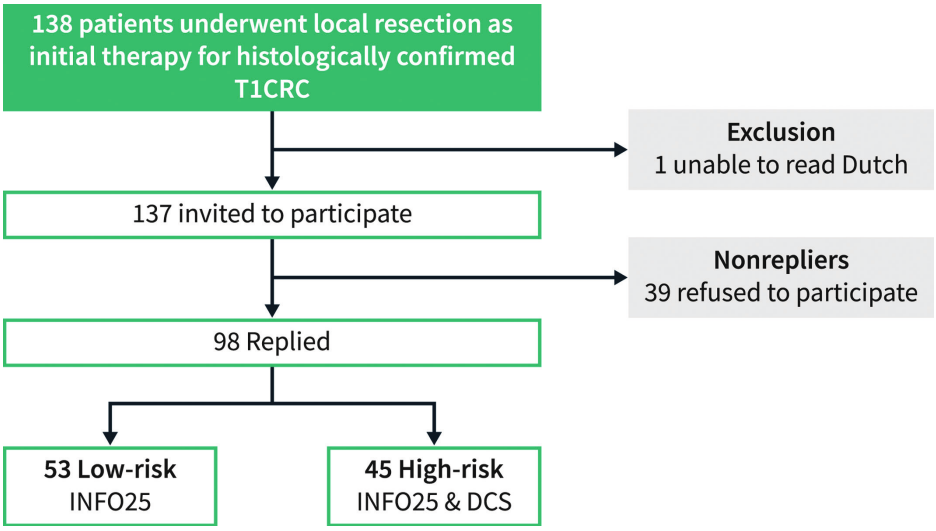
Nominal and ordinal variables were expressed as frequencies and percentages and continuous variables as medians and interquartile ranges (IQR). Continuous variables were compared using the Mann–Whitney *U* test. Categorical data were compared using the chi-squared test or Fisher›s exact test, as appropriate. Linear or logistic regression were used to evaluate associations between variables.

Based on the results of the validation study, subgroup analyses of the INFO25 scores were performed based on sex, age and educational level.[9] Additionally, we stratified the INFO25 analyses based on histological risk status. Regarding the decision-making process, we explored the association between decisional involvement/satisfaction and adopted treatment policy, sex, age, comorbidity index, tumor location, and total INFO25 score. For the DCS scores, subgroup analyses were performed based on patients› perceived degree of decisional involvement and the treatment decision that was made. Sensitivity analyses were performed to evaluate the impact of the time interval between local resection and questionnaire completion on the results. The median time interval was used as a cut-off to form two groups with similar numbers of participants, thereby minimizing the power reduction of these analyses. SPSS version 24.0 was used for all statistical analyses. A p-value <0.05 was considered statistically significant.

Results

A total of 137 patients fulfilled the selection criteria and were invited to participate. The response rate was 71.5% (98/137) (Figure 1). The median interval between local resection and study participation was 28 months (IQR 18). Of the 98 patients, 45 underwent local resection for a high-risk T1CRC. Patients' demographic and clinical characteristics, stratified on histological risk status, are summarized in Table 1. Ethical approval does not permit publishing data on non-responders. There is no indication for exclusion not at random.

Figure 1. Flow-chart of patient selection. *CRC* colorectal cancer, *DCS* Decision conflict scale, *INFO25* EORTC QLQ-INFO25.



Tables 1. Baseline characteristics.

	All patients (n=98)	Low-risk (n=53)	High-risk (n=45)
Patient characteristics			
Age, years, mean (SD)	64.9 (7.9)	64.1 (8.4)	65.7 (7.3)
Sex, male	62 (63.3)	33 (62.3)	29 (64.4)
Charlson Comorbidity Index, median (IQR)	2.0 (1)	3.0 (3)	2.0 (1)
Educational level, high	24 (24.7)	10 (18.9)	14 (31.1)[a]
Tumor and treatment characteristics			
Gross polyp morphology			
Pedunculated	33 (33.7)	24 (45.3)	9 (20)
Non-pedunculated	65 (66.3)	29 (54.7)	36 (80)
Tumor location, rectum	42 (46.9)	17 (32.1)	25 (55.6)
Local resection technique			
Snaring	32 (32.7)	23 (43.4)	9 (20)
EMR	11 (11.2)	4 (7.5)	7 (15.6)
ESD	27 (27.6)	12 (22.6)	15 (33.3)[b]
eFTR	9 (9.2)	3 (5.7)[c]	6 (13.3)
TEM/TAMIS	10 (10.2)	5 (9.4)	5 (11.1)
CAL-WR	9 (9.2)	6 (11.3)	3 (6.7)
Timing of local resection			
Direct (during index procedure)	36 (36.7)	24 (45.3)	12 (26.7)
Rescheduled after initial detection	62 (63.3)	29 (54.7)	33 (73.3)
Time interval resection to questionnaire, months, median (IQR)	28 (18.0)	28 (18.0)	28 (18.0)

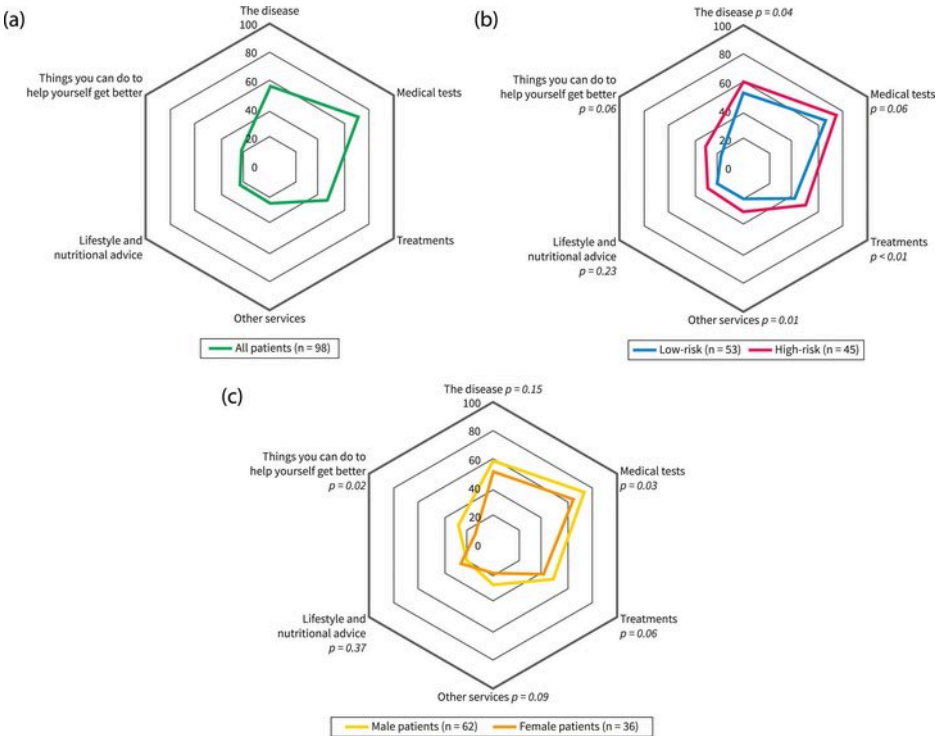
All values are *n* (%) unless otherwise defined. Higher educational level was defined as completion of at least a bachelor›s degree.

[a] One patient refused to complete the question regarding educational level.[b] One patient underwent a hybrid ESD-EMR procedure.[c] One patient underwent a hybrid eFTR-EMR procedure. *ASA* American Society of Anesthesiologists, *CAL-WR* colonoscopic-assisted laparoscopic wedge resection, *eFTR* endoscopic full-thickness resection, *EMR* Endoscopic mucosal resection, *ESD* Endoscopic submucosal dissection, *IQR* interquartile range, *TAMIS* transanal minimally invasive surgery, *TEM* transanal endoscopic microsurgery, *SD* standard deviation.

Information provision, satisfaction, and needs (EORTC QLQ-INFO25)

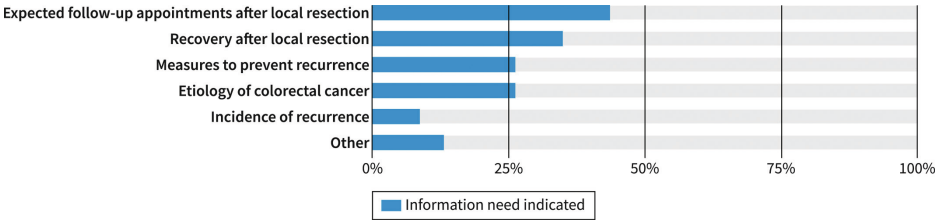
The mean scores of all subscales and single INFO25 items are presented in Figure 2 and Supplementary Table 1. Patients reported having received the most information on the 'medical test' subscale, scoring an average of 71 out of 100 points. Patients reported having received the least information on 'things you can do to help yourself get better' (mean score 23.5). Of the single items, patients reported having received the most information about the initial local resection (mean score 73.8) and the least about potential avenues for professional psychological support (mean score 11.6).

Figure 2. Visual representation of the amount of information that was provided on the various disease topics of the INFO25 questionnaire. Comparisons were made by (**a**) Overall; (**b**) Grouped by histological risk-status; (**c**) Grouped by sex. Scale 0–100: ranging from 'not at all' to 'very much'.



The mean scores of the overall satisfaction level (item 22) and the perceived helpfulness of the received information (item 25) were 67.0 and 71.1 out of 100 points, respectively. Sixty-nine patients (70.4%) reported no need for additional information. Among the 29 patients expressing a need for more information (15 males and 14 females; 18 low-risk, 11 high-risk T1CRC), 23 specified the specific topics where their information needs were unmet. The most mentioned topics were 'expected follow-up appointments after local resection' (10/23) and 'recovery after local resection' (8/23) (Figure 3). In addition to the information being provided verbally, 39 patients (39.8%) indicated a preference for receiving additional information on paper and 24 (24.5%) preferred to receive additional information digitally.

Figure 3. Topics with unmet information needs in 23 patients who specified on what topics they wished to have received more information on. The category 'other' was utilized to categorize responses that were provided only once and did not fit into the other predefined categories.



In exploratory subgroup analyses, patients with high-risk T1CRC scored higher on multiple INFO25 scales, indicating that high-risk patients experienced receiving more information compared with patients diagnosed with low-risk T1CRC (Figure 2b). Satisfaction with the provided information and reported needs for more information were comparable between high-risk and low-risk patients (Supplementary Table 2). Moreover, women scored lower than men on multiple INFO25 scales (Figure 2c), including 'medical tests' ($p = 0.03$) and 'things you can do to help yourself get better' ($p = 0.02$). With regard to information provision, women reported lower satisfaction scores than men (60.2 vs. 71.0, $p = 0.04$) (Supplementary Table 2). No statistical differences were observed between younger (≤65 years) and older patients (>65) or between patients with a higher and lower educational level (Supplementary Table 3). Sensitivity analyses showed that the total INFO25 score was not significantly influenced by the time interval between local resection and questionnaire completion (short vs. long interval: 40.3 and 37.8, $p = 0.43$).

Therapeutic decision-making in patients with a high-risk T1CRC

The decision-making process was evaluated in the 45 patients with locally resected high-risk T1CRC (baseline characteristics and clinical outcomes shown in Table 2). After a median follow-up of 28 months (IQR 18), no recurrences or mortality were observed.

The treatment strategies following local resection included oncological resection ($n = 18$), chemoradiotherapy in early stage rectal cancer as part of a clinical trial ($n = 6$), and close monitoring ($n = 21$; 6 treated with additional local scar resection and 15 no further treatment). In the close monitoring group, 12 patients (57.1%) exclusively consulted a gastroenterologist, and 9 patients (42.9%) were referred for consultation with a surgeon. Nineteen of the 21 patients (90.5%) were discussed in a multidisciplinary team meeting. Higher-educated patients were more likely to undergo additional treatment than lower-educated patients ($p = 0.02$). There was no significant association between the adopted strategy after local resection and other variables, such as the patient›s sex, tumor location, comorbidity index and time interval between local resection and questionnaire completion.

Table 2. Baseline characteristics of patients with a high-risk T1 colorectal cancer.

	Additional treatment (n=24)	**Close monitoring** (n=21)	**P-value**
Baseline characteristics			
Sex, male	15 (62.5)	14 (66.7)	>0.99
Educational level, high	11 (45.8)	3 (14.3)	0.02
Tumor location, rectum	11 (45.8)	14 (66.7)	0.23
Charlson Comorbidity Index, median (IQR)	2.0 (1)	3.0 (2)	0.16
High-risk features			
Rx	0	3 (14.3)	0.38
R1	5 (20.8)	5 (23.8)	
Other JSCCR high-risk feature(s)	15 (62.5)	10 (47.6)	
Both	4 (16.7)	3 (14.3)	
Time interval since treatment, <28 months	7 (29.2)	12 (57.1)	0.08
Extent of decision involvement, active	17 (70.8)	10 (47.6)	0.14
Outcome of treatment strategy			
TNM-stage[a]			
T1N0M0, without residual tumor rest	16	*NA*	*NA*
T1N1M0, with residual tumor rest	1		
Underwent CRT (i.e. no TNM)	6		
Cancer recurrence, yes	0*	0	> 0.99

Patients who underwent oncological resection (*n* = 18) or chemoradiotherapy (*n* = 6) after local resection were categorized as 'additional treatment', while patients who underwent an additional local scar resection (*n* = 6) or refrained from any additional treatment were grouped together as 'close monitoring'. All values are *n* (%) unless otherwise defined.

[a] Follow-up data of one patient was missing.

CRT chemoradiotherapy, *IQR* interquartile range, *JSSCR* Japanese Society of Cancer of the Colon and Rectum, *TNM* Tumor Nodes and Metastases classification of malignant tumors.

Figure 4 presents a visual depiction of the therapeutic decision-making process and patient involvement, categorized by the adopted treatment policy following local resection. From the patient's perspective, 27 individuals (60.0%) opted for the treatment policy themselves after local resection (an 'active' role). Meanwhile, 9 patients deferred the decision to their physician (a 'passive' role), and an additional 9 patients felt they were not offered a choice (also a 'passive' role). In univariable analyses, higher-educated patients were more likely to experience active involvement in decision-making than lower-educated patients ($p = 0.002$) (Table 3). No significant association was found between the level of patient›s involvement in decision-making and the adopted treatment strategy (additional treatment or close monitoring), sex, age, comorbidity

index, tumor location, total INFO25 score, and time interval between local resection and questionnaire completion (Supplementary Table 4).

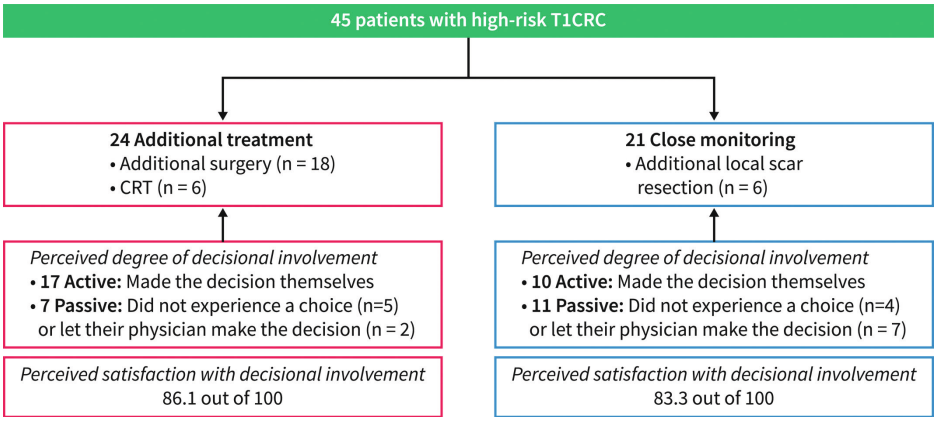
Table 3. Implemented treatment policy after local resection and extent of patient involvement with regard to this decision, stratified for educational level. The p-value studying the association between educational level - additional treatment (yes/no) and extent of decisional involvement (active/passive).

	Additional treatment		**Close monitoring**		
	Active patient involvement (n=16)	**Passive patient involvement (n=7)**	**Active patient involvement (n=10)**	**Passive patient involvement (n=11)**	**P-value**
Low level of education (n=30)	6 (37.5)	6 (85.7)	7 (70)	11 (100)	*0.004*
High level of education (n=14)	10 (62.5)	1 (14.3)	3 (30)	0 (0)	

Patients who underwent oncological resection (n = 18) or chemoradiotherapy (n = 6) after local resection were categorized as 'additional treatment', while patients who underwent an additional local scar resection (n = 6) or refrained from any additional treatment were grouped together as 'close monitoring'. The extent to which patients were involved in decision-making was categorized as 'active' if patients reported to have made the decision themselves, and 'passive' if patients reported to have let their physician make the decision or if patients reported that they never felt that they were given a choice. Higher educational level was defined as completion of at least a bachelor's degree. One patient who did not provide their educational level was excluded from this subgroup analysis.
All values are n (%) unless otherwise defined

Overall, most patients expressed high levels of decisional satisfaction, with 27 (61.4%) reporting being 'very much' satisfied, 14 (31.8%) being 'quite a bit' satisfied and 3 (6.8%) being 'a little' satisfied with the decision-making process. One patient couldn't recall her level of decisional satisfaction. Decisional satisfaction did not differ between higher- and lower-educated patients (83.3 vs. 85.6; $p = 0.78$), as well as between patients with active and passive decisional involvement (86.4 vs. 82.4; $p = 0.43$), patients receiving additional treatment or close monitoring (86.1 vs. 83.3; $p = 0.76$) and patients receiving additional chemoradiotherapy or surgical resection (83.3 vs. 87.0; $p = 0.97$).

Figure 4. Overview of the therapeutic decision-making in patients with high-risk T1 colorectal cancer. *CRC* colorectal cancer, *CRT* chemoradiotherapy.



Decisional conflict (decisional conflict scale)

The assessment of decisional conflict was conducted among the 36 high-risk patients who reported having had a choice in therapeutic decision-making. Overall, the mean total DCS was 16.7 out of 100 (SD 14.9). DCS domain scores and total DCS were comparable between patients with active and passive decisional involvement (Supplementary Table 5). Likewise, there was no significant association between the total DCS score and the adopted treatment strategy (additional treatment or close monitoring), type of additional treatment (chemoradiotherapy or additional surgical resection), sex, age, comorbidity index, tumor location, total INFO25 score, and time interval between local resection and questionnaire completion (Supplementary Table 6).

Discussion

Overall, our study indicates that most patients with T1CRC express satisfaction with the information provided after local tumor resection but may require additional details about the post-treatment course. Similarly, satisfaction levels concerning the decision-making process were high among patients with high-risk T1CRC, irrespective of their level of involvement in decision-making or the adopted treatment approach. However, the degree of decisional involvement varied considerably among patients with different educational backgrounds, with higher-educated patients more often actively choosing additional surgery after local resection of a high-risk T1CRC. To our knowledge, this is the first study to present empirical data on the perspectives of patients with T1CRC regarding information provision and the decision-making process following local T1CRC resection.

The high INFO25 scores on the disease, medical test and local treatment-related items indicate that current information provision mainly centers around the primary objective of the outpatient consultation following local T1CRC treatment. This goal entails informing the patient about the histological outcomes of the tumor resection and determining the subsequent management strategy. Considering the high satisfaction scores[14, 15] and low levels of decisional conflict,[12, 16] most of the information provided by physicians seems to align well with the patient›s preferences. However, we did identify some subgroups and topics with unmet information needs. First, a substantial proportion of (both low and high-risk) patients required more details on the post-treatment course, and in particular the type and frequency of follow-up visits, the estimated recovery time after local or surgical resection, and possible measures for preventing disease recurrence. Comparable information needs were also found in patients who underwent primary surgery for stage I-III CRC,[17] indicating that the post-treatment course is an aspect of CRC care that is frequently neglected. To enhance patient-provider communication in the future, we propose that greater attention should be given to post-treatment topics in the outpatient clinic. However, the lack of specific scientific evidence on certain topics, such as recovery and prevention, may also contribute to clinicians› limited information provision. Therefore, future research in the field of T1CRC should focus on addressing these aspects of treatment.

Our data also reveal that women with T1CRC reported having received less information on multiple topics than men, as well as being less satisfied with the provided information. Such a difference was also found in multiple other cancer patient populations,[9, 18, 19] including patients with surgically treated colorectal cancer.[20] Possible explanations for these findings might involve gender bias among clinicians,[21-23] leading to suboptimal information provision to women. Besides, women might also exhibit a greater demand for information in response to a medical diagnosis.[24, 25] This coping style is typically referred to as "monitoring"[26] and is associated with lower levels of satisfaction with the received healthcare and information.[24, 27-29] To further improve information provision after local T1CRC treatment, clinicians need to be aware of possible gender bias affecting their communication as well as the potentially higher information demands among female patients.

In our study, decisional satisfaction following local tumor resection did not differ according to the degree of decisional involvement and the adopted management strategy. This was not unexpected, considering the wide variability in patient preferences regarding decisional involvement[30, 31] and the fact that the vast majority of both surgically and locally treated patients with T1CRC do not experience cancer recurrence or adverse events.[32-34] However, we found striking differences in the decisional process between higher- and lower-educated patients. More highly educated patients were twice as likely to report active decisional involvement and to opt for additional treatment. While the high levels of decisional satisfaction suggest that lower-

educated patients do not strongly desire active involvement in the decision-making process, it must be kept in mind that the abovementioned differences may also arise from possible systemic inequities in health literacy.[35-37] Therefore, clinicians should not presume that lower-educated patients prefer passive decisional involvement. Instead, they should actively explore the reasons behind the patient›s choice not to be involved in decision-making, and address possible low literacy levels by tailoring their communication strategy. For example, they could develop tailored educational materials or decisional aids, such as patient educational videos on T1 colorectal cancer.[3]

The explanations for the difference in management strategies between lower- and higher-educated patients with high-risk T1CRC may be two-fold. On the one hand, lower-educated patients with passive decisional involvement might be less likely to undergo additional treatment due to a higher prevalence of comorbidities that render them less suitable for surgical interventions.[38-40] Recent studies have shown that in comorbid patients with locally resected high-risk T1CRC, additional surgery may not result in a long-term survival benefit compared with a close monitoring approach.[34, 41-43] In light of these findings, the considerable proportion of lower-educated high-risk patients subjected to close monitoring might actually reflect the recent trend among physicians to refrain from additional surgical resections for comorbid patients more frequently. Unfortunately, the data did not allow us to substantiate this hypothesis with sufficiently powered subgroup analyses. On the other hand, higher-educated patients may be more inclined to actively choose additional treatment because of their higher level of health literacy. As a result, they are more likely to seek out health information themselves,[44-46] and prefer active involvement in the decisional process.[47-49] Given that most guidelines do not (yet) consider the very recently published papers mentioned above[34, 41-43] and still recommend surgery in all cases of high-risk T1CRC, it seems reasonable that higher-educated patients more frequently opt for additional treatment. To confirm that decision-making after local T1CRC treatment does not depend on educational level but is confounded by other factors, in-depth interview studies with both patients and clinicians are needed.

Several limitations of this study should be acknowledged. Firstly, the sample size is limited, particularly in the high-risk subgroup, which should be taken into account when interpreting the results. Secondly, both response and recall bias may have influenced the results, although the response rate of our study is quite high (71.5%)[50] and the time interval between local resection and questionnaire completion did not influence the outcomes in sensitivity analyses. Thirdly, various (types of) physicians provided non-standardized information in the outpatient consultations after local resection. Given the importance of information framing in patient understanding and decision-making,[51] this lack of uniformity may have affected the study findings and conclusions to a certain degree. Lastly, the extent of decisional involvement most likely exists on a spectrum broader than the options examined in this study. Future research would benefit from

a validated questionnaire to thoroughly investigate this aspect. Unfortunately, such a tool is not yet available.

Conclusion

From the patient's perspective, the information provided after local T1CRC resection seems to align well with the primary objective of the consultation, but some patients may require more details on certain items, for example, post-treatment course and follow-up. Although patient satisfaction with the decision-making process following local resection of high-risk T1CRC was high, decisional involvement and management strategies differed considerably between patients of different educational backgrounds. Our results provide valuable insights that can aid physicians in optimizing information provision and shared decision-making in the outpatient clinic.

Supplemental materials

Supplementary methods

Authors have slightly modified the validated INFO25 questionnaire to make it more suitable to the situation of current situation. Q21 'have you received information on CD or tape/video?' have been replaced by 'have you received information digitally'. Authors have combined Q14 'the amount of information on additional help outside the hospital (e.g., help with daily activities, self-help groups, district nurses)' and Q15 'the amount of information on rehabilitation services (e.g., physiotherapy, occupational therapy)' to Q14 'the amount of information on Additional help outside the hospital (e.g., (pelvic) (physiotherapy, home care products)'. 'The amount of information on the physical recovery time after removal of the polyp' was added as Q15. Q18 'the amount of information provided on different places of care' was removed because we did not find them applicable for T1CRC patients. Instead, 'the amount of information on lifestyle and nutritional advice' (Q18) was assessed. Additionally, we assessed the preferred method of information provision in a question with checkbox fields (provided options: verbally by the physician, by phone, on paper, digitally, other). Results of this question were not incorporated in the total INFO25 score because both the content and the format of the question did not resemble any questions in the validated INFO25 questionnaire. The translated version of the INFO25 and DCS, including pre-questions, are added as supplementary documents.

Supplementary tables

EORTC QLQ-INFO25 item	**All patients** (n=98)
How much information did you receive on…	
… the disease;	56.9 (20.8)
- The diagnosis of your disease? (1)	68.4(22.6)
- The extent (spread) of your disease? (2)	60.2 (28.6)
- The possible causes of your disease? (3)	30.6 (32.7)
- Whether the disease is under control? (4)	68.4 (24.1)
… medical tests;	71.0 (22.0)
- The purpose of any medical tests you have had or may undergo? (5)	69.1 (24.5)
- The procedures of the medical tests? (6)	71.4 (24.9)
- The results of the medical tests you have already received? (7)	72.4 (24.9)
… treatments;	46.1 (19.4)
- The initial local resection of the polyp (by a gastroenterologist or surgeon)? (8)	73.8 (23.6)
- The expected benefit of the treatment? (9)	71.8 (23.1)
- The possible side-effects of your treatment? (10)	46.6 (33.4)
- The expected effects of the treatment on disease symptoms? (11)	46.6 (33.1)
- The effects of treatment on social and family life? (12)	24.8 (28.0)
- The effects of the treatment on sexual activity? (13)	12.9 (25.6)
… other services;	25.3 (21.8)
- Additional help outside the hospital (e.g., physiotherapy, domiciliary care)? (14)	14.3 (27.1)
- Time of physical recovery after local resection? (15)	49.0 (31.5)
- Aspects of managing your illness at home? (16)	26.2 (30.4)
- Possible professional psychological support? (17)	11.6 (24.5)
… lifestyle and nutritional advice (18)	24.5 (30.9)
… things that you can do to help yourself get well (e.g., rest, contact with others)? (19)	23.5 (30.7)

Supplementary Table 1. Summary of the single items on perceived amount of received information of the EORTC QLQ-INFO25 questionnaire. Scores on a 4-point Likert scale were transformed to a linear 0-100 score; higher scores indicate a higher amount of information provided. Values are presented as means (standard deviation).

Supplementary Table 2. Summary of the EORTC QLQ-INFO25 results of the entire cohort and subgroups based on sex and histological risk status. The response of all items was a 4-point Likert scale or dichotomous (yes/no). Scores were transformed to a linear 0-100 scale; Higher scores indicate a higher level of information received (items 1-19), a higher proportion of patients receiving additional info (20,21), a higher satisfaction with the amount of information (item 22), higher desire for more or less information (items 23, 24). Values are presented as means (standard deviation).

EORTC QLQ-INFO25 Scale or item	Low-risk (n=53)	High-risk (n=45)	P-value	Female (n=36)	Male (n=62)	P-value
How much information did you receive on						
- the disease (items 1-4)	53.5 (18.5)	60.9 (22.8)	0.04	52.1 (21.4)	59.7 (20.1)	0.15
- medical tests (items 5-7)	67.3 (22.6)	75.3 (20.8)	0.06	65.1 (21.4)	74.4 (21.8)	0.03
- treatments (items 8-13)	41.6 (18.4)	51.4 (19.3)	<0.01	41.2 (16.8)	48.9 (20.3)	0.06
- other services (items 14-17)	20.9 (21.4)	30.4 (21.3)	0.01	19.7 (17.2)	28.5 (23.6)	0.09
- lifestyle and nutritional advice (item 18)	20.8 (28.7)	28.9 (33.0)	0.23	26.3 (31.4)	21.3 (30.0)	0.37
- things you can do to help yourself get better (item 19)	17.6 (26.6)	30.4 (34.0)	0.06	14.8 (30.0)	28.5 (31.9)	0.02
Did you also receive written information? (item 20)*	37.7 (48.9)	46.7 (50.5)	0.37	41.7 (50.0)	41.9 (49.7)	0.98
Did you also receive digital information? (item 21)*	13.2 (34.2)	11.1 (31.8)	0.75	0 (0)	19.4 (39.8)	0.01
Satisfaction with the information received (item 22)	62.9 (25.9)	71.9 (21.3)	0.08	60.2 (26.2)	71.0 (22.2)	0.04
Wish you had received more information (item 23)*	34.0 (47.8)	24.4 (43.5)	0.31	39.9 (49.4)	24.2 (43.2)	0.13
Wish you had received less information (item 24)*	0 (0)	2.2 (14.9)	0.28	2.8 (16.7)	0 (0)	0.19
Overall helpfulness of information (item 25)	66.7 (24.5)	76.3 (20.9)	0.05	66.7 (23.9)	73.7 (22.7)	0.18
Total INFO25 score	36.2 (12.4)	42.3 (11.8)	0.01	35.1 (10.9)	41.2 (12.8)	0.03

**Items with a yes/no answer*

Supplementary Table 3. Summary of the EORTC QLQ-INFO25 results of the entire cohort and subgroups based on age and educational level. The response of all items was a 4-point Likert scale or dichotomous (yes/no). Scores were transformed to a linear 0-100 scale; Higher scores indicate a higher level of information received (items 1-19), a higher proportion of patients receiving additional info (20,21), a higher satisfaction with the amount of information (item 22), higher desire for more or less information (items 23, 24). Values are presented as means (standard deviation).

EORTC QLQ-INFO25 Scale or item	**≤65 years** (n=50)	**>65 years** (n=48)	**P-value**	**Higher educational level** (n=24)	**Lower educational level** (n=73)	**P-value**
How much information did you receive on						
- the disease (items 1-4)	56.8 (19.5)	56.9 (22.3)	0.99	57.6 (18.4)	56.5 (21.8)	0.88
- medical tests (items 5-7)	70.7 (20.7)	71.3 (23.6)	0.55	74.5 (16.9)	69.4 (23.3)	0.47
- treatments (items 8-13)	47 (19.8)	45.1 (19.1)	0.59	47.0 (20.2)	45.5 (19.2)	0.72
- other services (items 14-17)	26.0 (20.0)	24.5 (23.7)	0.41	28.1 (24.7)	24.4 (21.0)	0.63
- lifestyle and nutritional advice (item 18)	27.3 (30.6)	21.5 (31.1)	0.23	22.2 (21.2)	24.2 (32.5)	0.67
- things you can do to help yourself get better (item 19)	24.7 (29.2)	22.2 (32.5)	0.49	23.6 (26.9)	23.7 (32.1)	0.75
Did you also receive written information? (item 20)*	48 (50.5)	35.4 (48.3)	0.21	41.7 (50.4)	41.1 (49.5)	0.96
Did you also receive digital information? (item 21)*	4 (19.8)	20.8 (41.0)	0.01	20.8 (41.5)	9.6 (29.6)	0.15
Satisfaction with the information received (item 22)	63.3 (24.5)	70.8 (23.4)	0.10	66.7 (19.7)	66.7 (24.5)	0.94
Wish you had received more information (item 23)*	30.0 (46.3)	29.1 (45.9)	0.93	27.4 (44.9)	37.5 (49.5)	0.35
Wish you had received less information (item 24)*	0 (0)	2.1 (14.4)	0.31	0 (0)	1.37 (11.7)	0.57
Overall helpfulness of information (item 25)	70.0 (22.6)	72.2 (24.1)	0.54	69.9 (23.7)	75 (22.5)	0.37
Total INFO25 score	39.0 (11.8)	39.0 (13.2)	0.70	40.9 (12.0)	38.2 (12.6)	0.44

**Items with a yes/no answer*

Supplementary Table 4. Univariable analyses on the degree of involvement in the decision-making process for all patients with high-risk T1 colorectal cancer. Active involvement included patients who indicated to have made the final decision themselves. Passive involvement included patients who did not experience shared decision-making or let their physician decide. Values are n (%) unless otherwise specified. *CCI* Charlson Comorbidity Index, *EMR* electronic medical records, *INFO25* EORTC QLQ-INFO25 questionnaire, *IQR* interquartile range.

		Active involvement (n=27)	**Passive involvement** (n=18)	**P-value**
INFO25 total, median (IQR)		39.1 (19.7)	43.3 (6.8)	0.41
Age, median (IQR)		65 (8)	69 (13)	0.72
CCI, median (IQR)		2.0 (1)	3.0 (3)	0.12
Sex	Female	10 (62.5)	6 (37.5)	1.0
	Male	17 (58.6)	12 (41.4)	
Educational level	Lower	13 (43.3)	17 (46.7)	0.002
	Higher	13 (92.9)	1 (7.1)	
Location	Rectum	13 (52)	12 (48)	0.36
	Non-rectum	14 (70)	6 (30)	
Treatment after local resection	Additional treatment	17 (70.8)	7 (29.2)	0.14
	Close surveillance	10 (47.6)	11 (53.4)	
Time interval since treatment	<28 months	10 (52.6)	9 (47.4)	0.54
	≥28 months	17 (65.4)	9 (34.6)	

Supplementary Table 5. Results of the Decision Conflict Scale categorized by perceived level of involvement in decision-making. The DCS evaluates decision-making using 16 items that are categorized in 5 domains of decision-making. The response format was a 5-point Likert scale (from strongly Agree [1] to strongly Disagree [5]) that was linearly transformed to a 0-100 scale; lower scores contribute to a lower overall level of decisional conflict. Values are presented as means (standard deviation). *DCS* Decision Conflict Scale

Decision conflict items and domains	**All patients** (n=36)	**Active role** (n=27)	**Passive role** (n=9)	**P-value**
Informed domain (items 1-3) [a]	16.2 (14.6)	14.2 (13.6)	22.2 (16.7)	0.20
Values clarity domain (items 4-6) [b]	15.3 (14.4)	12.9 (13.7)	22.2 (15.0)	0.15
Support domain (items 7-9) [c]	18.5 (18.9)	14.8 (15.6)	29.6 (24.3)	0.07
Uncertainty domain (items 10- 12) [d]	17.6 (20.5)	14.8 (15.6)	25.9 (30.7)	0.39
Effective decision (items 13-16) [e]	16.0 (20.1)	13.0 (13.9)	25.0 (32.0)	0.39
Total DCS score[f]	16.7 (14.9)	13.9 (11.8)	25 (20.4)	0.12

[a] *Score ranges from 0 (feels extremely informed) to 100 (feels extremely uninformed).*
[b] *Score ranges from 0 (feels extremely clear about personal values for benefits & risks) to 100 (feels extremely unclear about personal values).*
[c] *Score ranges from 0 (feels extremely supported in decision-making) to 100 (feels extremely unsupported in decision-making).*
[d] *Scores ranged from 0 (feels extremely certain about the best choice) to 100 (feels extremely uncertain about the best choice).*
[e] *Score ranges from 0 (good decision) to 100 (bad decision).*
[f] *Score range from 0 (no decisional conflict) to 100 (extremely high decisional conflict).*

Supplementary Table 6. Univariable analyses of the total score of the Decision Conflict Scale. Values are mean (standard deviation). Scores on the Decision Conflict Scale were linearly transformed to a 0-100 scale; lower scores contribute to a lower overall level of decisional conflict.

		Total DCS score (n=36)	**P-value**
Sex	Female (n=12)	16.0 (15.0)	0.87
	Male (n=24)	17.0 (15.0)	
Education*	Higher (n=13)	13.2 (11.2)	0.19
	Lower (n=22)	19.2 (16.7)	
Age	≤65 years (n=17)	14.7 (13.0)	0.63
	>65 years (n=19)	18.4 (16.6)	
Additional treatment	No (n=17)	19.7 (17.9)	0.55
	Yes (n=19)	14.0 (11.6)	
Type of additional treatment	Chemoradiotherapy (n=6)	10.9 (11.8)	0.60
	Segmental resection (n=13)	15.4 (11.7)	
Degree of involvement	Active (n=27)	13.9 (11.8)	0.12
	Passive (n=9)	25.0 (20.4)	
Time interval since treatment	<28 months (n=17)	18.1 (17.1)	0.94
	≥28 months (n=19)	15.4 (13.0)	

Values are presented as means (standard deviation). *One patient did not provide their educational level. *DCS* Decision Conflict Scale.

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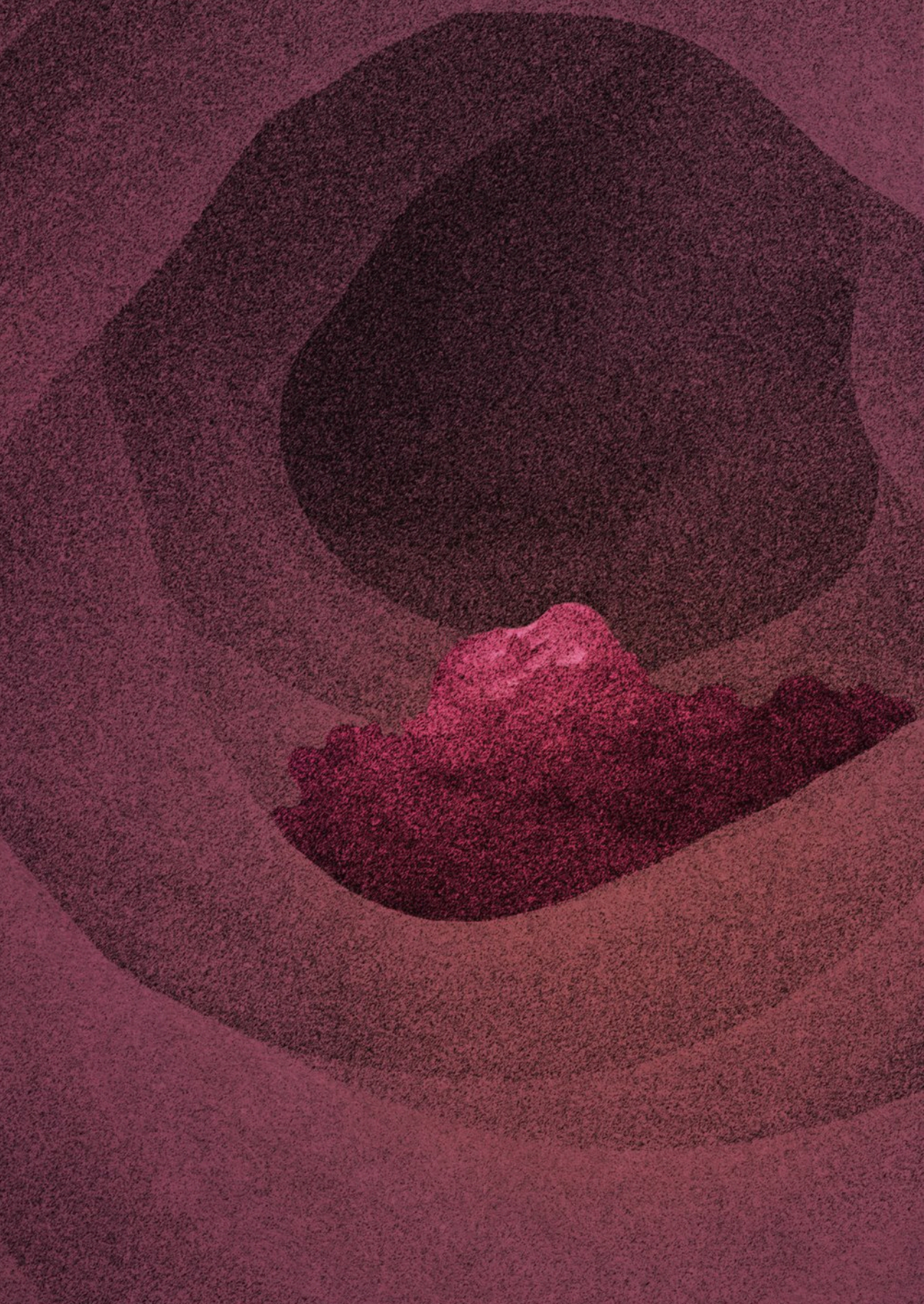


CHAPTER 9

Patient educational videos on T1 colorectal cancer

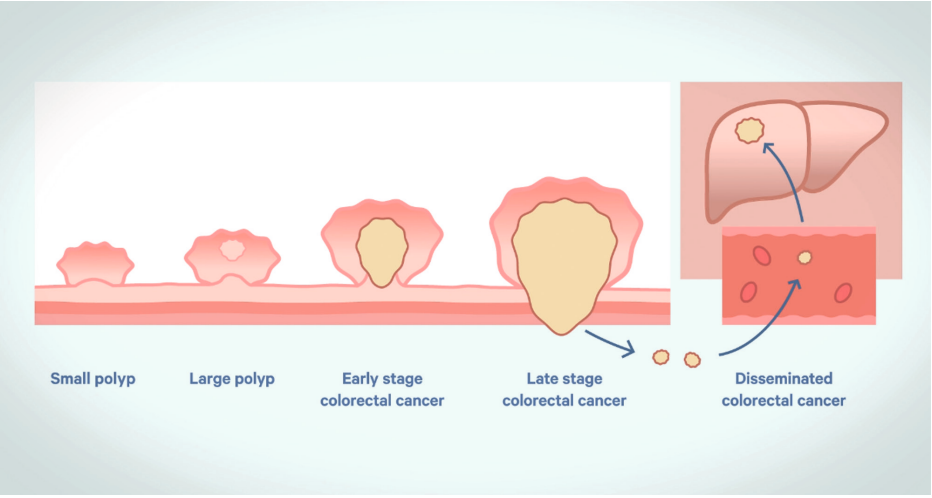
Nik Dekkers, Hao Dang, Jolein van der Kraan, James C. H. Hardwick, Alexandra M. J. Langers, Jurjen J. Boonstra

VideoGIE 2023

Educational videos

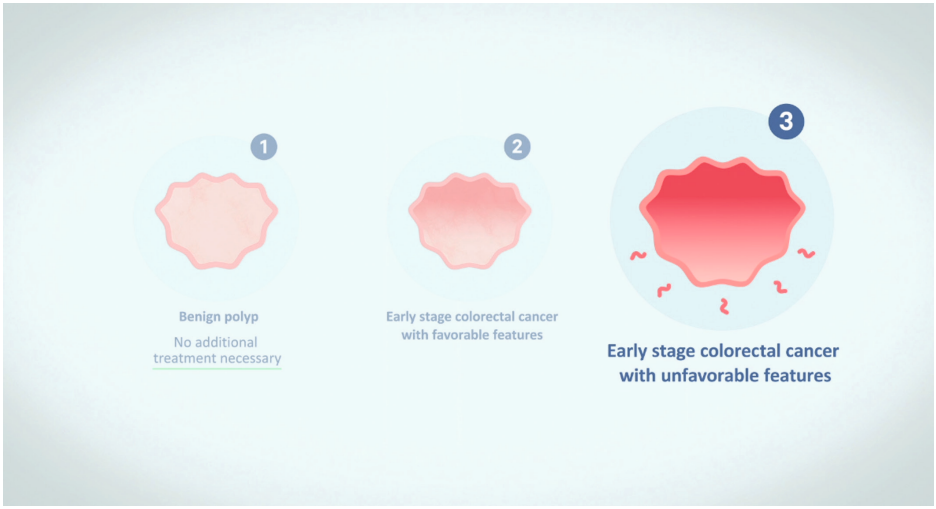
This study provides a structured and informative overview of the journey of patients with T1 colorectal cancer (T1CRC) in 3 distinctive videos.

Video 1. "Colorectal cancer: how does it develop and how can you detect it?"
The first video (Video 1, available online at www.videogie.org) provides a general introduction to colorectal cancer. This video discusses how colorectal cancer develops and how early forms can be intercepted. It serves as a preamble for the following video on polyps with suspected T1CRC.



Still from Video 1 showing the progression from benign polyp to metastatic colorectal cancer

Video 2. "A polyp suspected to be colorectal cancer, what now?"
The second video (Video 2, available online at www.videogie.org) applies to all patients with a polyp suspected for T1CRC. This video discusses the following topics: the uncertainty of a T1CRC diagnosis prior to removal, the necessity of an en bloc complete removal using local resection techniques, and the 3 possible histological outcomes after local resection of a polyp that is suspected to be CRC. For patients with a histologically confirmed T1CRC (scenarios II & III in the video), we then discuss the considerations of whether to undergo additional treatment after local resection.



Still from Video 2 illustrating the possible histological outcomes following resection of a polyp suspected of being T1CRC

Video 3. "Early stage colon cancer with unfavorable features, what now?"

The third video (Video 3, available online at www.videogie.org) provides additional information that is only applicable to patients with a high-risk T1CRC (scenario III). This video discusses the following topics: benefits, disadvantages and nature of additional treatment, the influence of tumor location on surgical morbidity, refraining from additional treatment, and follow-up.

Still from Video 3 illustrating a discussion between a clinician and a patient regarding additional treatment or surveillance for a T1CRC with unfavorable features.

Adobe Illustrator and Adobe After Effects (both from Adobe Inc, San Jose, Calif, USA) were used to generate and refine the storyboard and to create the animation videos. All graphics, images, and videos are completely original. In the context of improving the quality of patient care, we have also asked a panel of 13 patients with (suspected) T1CRCs to share their opinion about these educational videos (see Table 1 for the results).

Table 1. Feedback of 14 patients

	All patients (n=14)
How understandable was the content of this video? *mean score out of 10*	9.4
What did you think of the pace of this video?	
Too slow	0
Good	14 (100)
Too fast	0
Did this video improve the understanding of your disease? *yes*	9 (64.3)
Do you think this video is a useful addition to the physician's consultation? *yes*	12 (85.7)
Would you recommend a future patient to watch this video? *yes*	14 (100)
What do you think is the preferred timing to show patients this video?	
Prior to consultation*	5 (35.7)
During consultation	4 (28.6)
After consultation	5 (35.7)

Values are n (%) unless otherwise defined.
* All 14 reviewers indicated that a health care professional should introduce the possibility of a cancer diagnosis in person, prior to showing these videos.

Discussion

The most complex decisional moment for patients with T1CRC is the decision to either proceed to additional treatment after local resection or to refrain from further treatment. Because of the complexity of this decision, a large proportion of these videos is devoted to this moment. Patients and their treating physician will have to weigh the benefits and disadvantages of additional treatment. The disadvantage of undergoing additional treatment is the risk of treatment-related morbidity and mortality, which depends on the type of additional treatment and the patient's fitness. The benefit of additional treatment is reduction of the oncological risk, which includes reducing the risk of lymph node metastases (LNM) and disease recurrence. The current risk stratification model for LNM stratifies patients with T1CRC based on the absence or presence of 1 or more histological high-risk features.[1] This model stratifies patients with T1CRC into low-risk (favorable features, scenario II) and high-risk (1 or more unfavorable

features, scenario III) for LNM. T1CRCs with high-risk features also have an increased risk of disease recurrence after endoscopic resection, which is approximately 7% to 12.5%, whereas the risk of disease recurrence after endoscopic resection of a low-risk T1CRC is approximately 0.7% to 3.1%.[2,3]

If the possible disadvantages of additional treatment do not appear to outweigh the potential benefits, refraining from additional treatment can be the best option. This is generally the case for patients with a low-risk T1CRC (scenario II) because of their overall low benefit from additional treatment. In patients with high-risk T1CRC (scenario III), the decision to undergo additional treatment can be more challenging. Current guidelines recommend additional oncological resection after local resection of a high-risk T1CRC because of the higher oncological risk.[1,4] Nevertheless, even for high-risk T1CRCs, the absolute risk for LNM or disease recurrence can still be considered relatively low.[5] When using the above-mentioned risk stratification model, more than 80% of patients with a high-risk T1CRC referred for oncological resection turn out not to have LNM, despite being exposed to the risk of surgical morbidity and mortality.[5] As a result, an increased tendency can be observed to refrain from additional treatment after local resection of T1CRC.[6] Video 3 provides a summary of the aforementioned considerations, specifically for patients with a high-risk T1CRC for whom this decisional moment is most complex.

The absolute risk for LNM or disease recurrence varies greatly between patients, especially in the high-risk group. The recurrence risk of an individual patient depends on many different factors, including the number of high-risk features present and tumor location.[2,3] Because we aimed to create videos that are applicable for all patients with T1CRC, we deliberately chose not to mention the absolute risk percentages.

Conclusion

The educational videos in this study provide patient information about T1CRC and illustrate the different steps in the treatment of a polyp suspected to be colorectal cancer. They also address the considerations to opt for or refrain from additional treatment after local resection. Based on patient feedback, we believe that implementation of these videos might support the shared decision-making process, which is often complex in patients with T1CRC.

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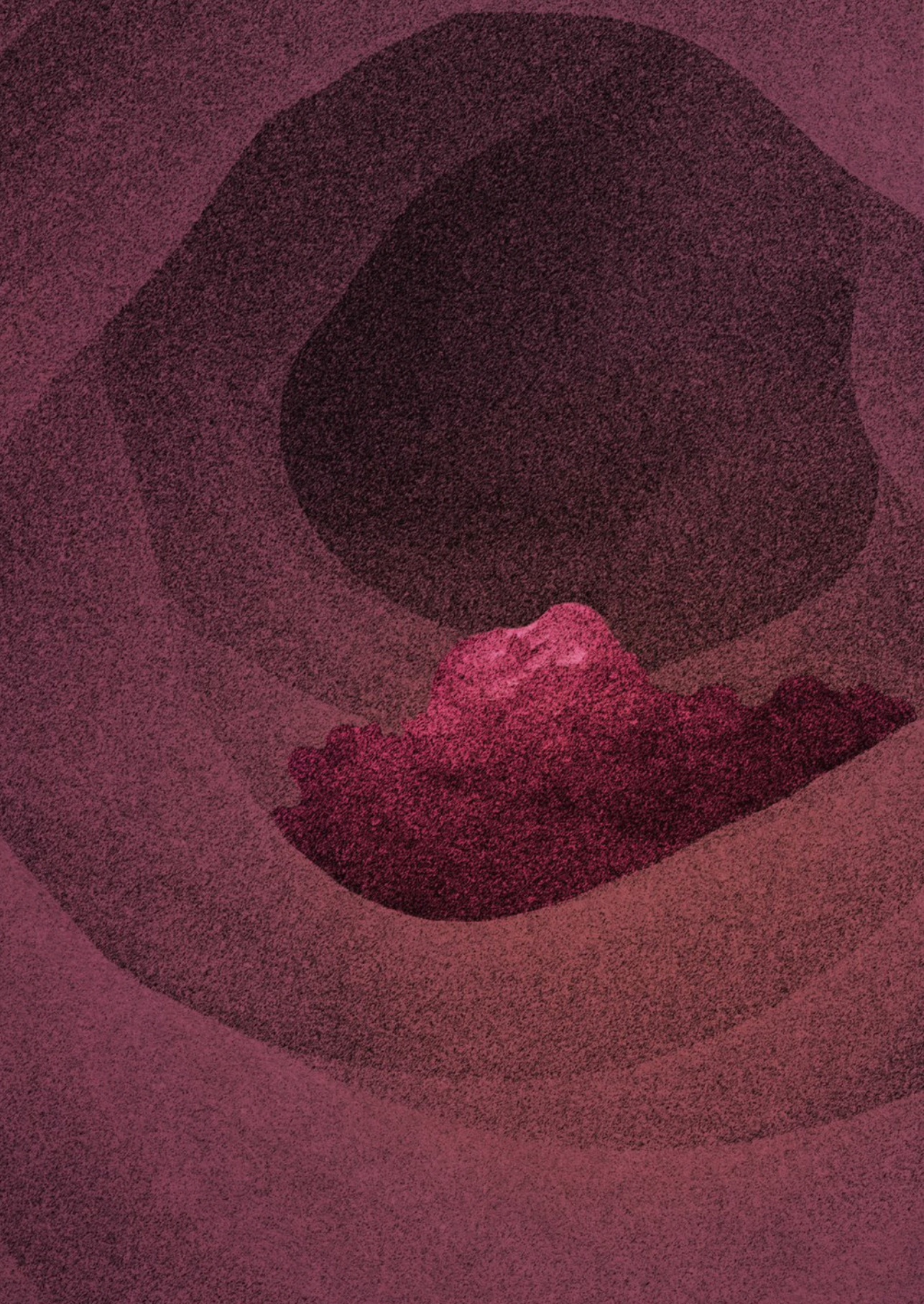

CHAPTER 10

Thesis summary and future perspectives

Thesis summary

Following the implementation of nationwide screening programs, the incidence of large rectal adenomas and early-invasive colorectal cancers (T1CRC) has increased, highlighting the urgency of addressing the many challenges and unanswered questions in their clinical management. In this thesis, we aimed to advance care for these patients by focusing on three main areas: optical diagnosis and local treatment (Part I), treatment strategies after local treatment (Part II), and patient empowerment (Part III). This chapter summarizes the main findings and discusses future perspectives.

Part I: Optical diagnosis & local treatment

Accurate real-time identification of high-grade dysplasia (HGD) or T1CRC in lesions is crucial for selecting the appropriate local resection technique and reducing the need for major oncological resections. Current optical diagnosis methods lack optimal accuracy, and standard imaging techniques like endoscopic ultrasound or magnetic resonance imaging are of little added value. Fluorescence-optical imaging is a promising technique that highlights tumor-specific markers by using fluorescent dyes, possibly enabling direct visualization of abnormal tissue during endoscopy. In **chapter 3**, we explored the in vitro feasibility of this approach by staining colorectal lesions for various tumor-specific targets. Among carcinoembryonic antigen (CEA), c-mesenchymal-epithelial transition factor (c-MET), epithelial cell adhesion molecule (EpCAM), folate receptor alpha (FRα), and integrin alpha-v beta-6 (αvβ6), CEA most consistently showed differential expression in (pre-)cancerous tissue compared to adjacent benign tissue, with a sensitivity of 65% and a specificity of 75%. A follow-up study using CEA-targeted fluorescence-guided endoscopy is needed to confirm these results in vivo.

Chapter 4 and 5 focus on endoscopic submucosal dissection (ESD) and transanal minimally invasive surgery (TAMIS); two minimally invasive approaches suitable for local en bloc resection of large rectal lesions and T1 rectal cancer. Both techniques are considered standard of care, but their relative merits remain unclear, due to the lack of randomized trials. **Chapter 4** presents the study protocol of the TRIASSIC study. In this randomized trial, 198 patients with a large non-pedunculated rectal adenoma or T1 rectal cancer will be allocated to either TAMIS or ESD. As the first randomized trial of its kind, it evaluates the clinical and economic impact of both techniques. The primary endpoint is cumulative recurrence at 12 months to assess non-inferiority of ESD compared to TAMIS. Secondary outcomes include radicality, quality of life, complication rates and cost-effectiveness.

In addition to these clinical and economic outcomes, rehabilitation of physical activity is an important functional outcome of these procedures. Despite its potential relevance, for example in preoperative counseling, physical recovery after ESD and TAMIS has

never been studied quantitatively. In **Chapter 5**, we report the results of an ancillary study of the TRIASSIC trial in which physical recovery after ESD and TAMIS was quantitively assessed and compared. In a subgroup of forty patients, smartwatches were used to monitor physical activity. The mean recovery time after ESD (13.9 days) was found to be non-inferior to that of TAMIS (21.0 days). Post-procedural pain was associated with decreased physical activity, and moderate to severe pain scores were more commonly reported after TAMIS. Larger lesion size and proximity to the dentate line were identified as potential preoperative risk factors for slower recovery. Notably, despite the assumed minimally invasive nature of the procedures, 20% of patients had not recovered within the four-week monitoring period. This study provides valuable information to improve personalized information provision in outpatient clinics and identified opportunities for optimizing postoperative recovery by highlighting the impact of pain, lesion characteristics, and anatomical location on recovery trajectories.

Part II: Treatment strategies after local resection

Over the years, the development of advanced local resection techniques such as ESD and TAMIS has shifted the primary treatment of lesions suspected for T1CRC from an upfront oncological resection to a less invasive, two-step approach, starting with a local resection. Thereafter, histological features associated with an incomplete resection or increased risk of metastasis inform the decision whether completion surgery is warranted.

Establishing the safety of this two-step approach requires evaluating how initial local resection influences the outcome of subsequent completion surgery, something that had not yet been examined for ESD. In **Chapter 6**, the impact of ESD on morbidity and mortality of completion surgery was evaluated. After propensity score adjustment, outcomes of 357 patients who underwent primary surgery, derived from a nationwide surgical database, were compared to 54 patients who underwent completion surgery after ESD for suspected T1CRC (pT1-2), collected from a prospective multicenter database. ESD did not increase the morbidity or 90-day mortality of completion surgery. Adverse event rates were 21.3% for primary surgery and 24.1% for completion surgery. In the subgroup of rectal cancers, these adverse event rates were higher but still similar at 27.2% and 29.7%, respectively. These findings confirm that ESD can safely be used as an initial approach in suspected T1CRC, helping to avoid unnecessary oncological surgery in a substantial number of patients.

To better understand long-term outcomes and guide follow-up care, **chapter 7** presents a meta-analysis comparing oncological outcomes after local surgical and endoscopic treatment of T1 rectal cancer. The pooled cumulative incidence of recurrence was similar after transanal endoscopic microsurgery (TEM) or TAMIS and endoscopic resection, both at 7.7%. Cancer-related mortality among patients with recurrence was

also comparable (35.6% vs 30%). Patients with high-risk histological features had a substantially higher recurrence rate (29.7% vs 12.5%) than those with low-risk tumors (5.9% vs 3.1%). Notably, recurrence appeared more frequent in locally treated T1 rectal cancers compared to T1 cancers throughout the colon reported in another meta-analysis (0.7% for low-risk and 7% for high-risk). These findings support the development of evidence-based surveillance strategies after local resection of T1 rectal cancer.

Part III: Patient empowerment

Part III of this thesis explores the perspective of T1CRC patients on the management of their disease and introduces educational videos to empower patients in their patient journey.

A necessary first step towards more patient-centered care is to understand patients' experiences with current clinical practice, as it may reveal opportunities for improvement and guide further research. **Chapter 8** explored T1CRC patients' perspective on the information they received during their treatment. Additionally, we studied how patients in the high-risk subgroup experienced the decision-making process after local resection, specifically the decision to undergo or refrain from additional surgery. Although patients were generally satisfied with the information received, several patients reported unmet information needs, particularly concerning post-treatment care. Decisional satisfaction was also high. Strikingly, a lack of involvement in the decision-making process did not correlate with dissatisfaction. Educational level appeared to influence both the extent of involvement and the outcome: higher-educated patients were more likely to actively choose for additional surgery. Whereas lower-educated patients were more likely to be more passively involved in the decision-making process and refrain from additional surgery. These findings suggest that clinicians may benefit from proactively addressing post-treatment care and adopting a personalized approach to shared decision-making.

Finally, in **chapter 9**, we introduce patient educational videos on T1CRC. Three videos provide a structured and informative overview of the patient journey for T1CRC patients, including: "Colorectal cancer: how does it develop and how can you detect it", "A polyp suspected to be colorectal cancer: what now?", and "Early-stage colon cancer with unfavorable features: what now?". A panel of fourteen patients reviewed the videos, and all indicated they would recommend them to future patients. We believe that integrating these videos into T1CRC care may support shared decision-making by providing accessible information that can help patients engage in their care to the extent they prefer.

Future perspectives

I. Optimizing optical diagnosis of T1 colorectal cancer

Improving the accuracy of optical diagnosis is key to increasing the curative potential of local resections. Multiple approaches can be considered for improvement, including the development of novel techniques and optimization of current practices through education and expert consultation.

Novel techniques

Fluorescence-guided imaging is a promising innovation that uses targeted fluorescent agents to visualize specific molecular markers, either through near-infrared light or other fluorophores. In endoscopy, it has already been used to enhance detection and assess treatment response in advanced rectal cancer,[1, 2] but its role in optical diagnosis of T1CRC remains unexplored. The study presented in **Chapter 5** demonstrated in vitro feasibility, identifying carcinoembryonic antigen as the most accurate molecular target for detecting (pre)cancerous cells within otherwise benign lesions. The next step towards clinical application is in vivo testing, focusing on dose optimization of a fluorophore-conjugated anti-carcinoembryonic antigen antibody like SGM-101,[3] which is currently being conducted. If feasibility is confirmed in vivo, larger trials will be needed to assess diagnostic performance, added value over standard imaging, and clinical applicability in high-risk scenarios such as piecemeal resections and suspected recurrence. Current practical limitations of this technique include the lack of a high-quality flexible fluorescence endoscope, which means rigid laparoscopic systems are needed, limiting the use of the technique to rectal lesions. In addition, a separate hospital visit is required for intravenous tracer injection, which may reduce scalability and broader implementation. The ultimate aim is to create a simple, user-friendly system with a topical fluorescent dye and a single-button light filter on a standard endoscope, making fluorescence imaging part of everyday practice.

Artificial intelligence (AI) is a rapidly evolving technique that also has the potential to enhance optical diagnosis. Initially, AI applications in endoscopy focused on computer-aided detection, which demonstrated improved adenoma detection rates.[4] However, there has been an increasing interest in also applying AI to support optical diagnosis of T1CRC. Several studies have explored computer-aided diagnosis for T1CRC invasion depth with promising results, but each model has their limitations.[5] One model demonstrated high sensitivity (91.2%) for non-invasive and superficially invasive lesions, yet sensitivity dropped to 51.5% for deeper invasion.[6] A more recent system developed using only white-light images, showed satisfactory accuracy for diagnosing deeply invasive T1CRC, comparable to expert endoscopists,[7] though its performance was based on optimal thresholds from training data and requires cross-validation. The COMET-T1CRC project is the first Dutch effort to develop an AI system trained on endoscopic images and videos to improve optical diagnosis of T1CRC. Looking ahead, AI may also

facilitate interpretation of molecular imaging during fluorescence-guided endoscopy to enhance diagnostic accuracy.

Improving current practice

Structured training and digital learning platforms are promising tools to enhance optical diagnosis in its current form. Their effectiveness is supported by a recent position statement from the European Society of Gastrointestinal Endoscopy, which concluded that structured training improves lesion recognition, particularly when combined with extensive in vivo experience.[8] In addition, a multicenter study showed that an e-learning program on T1CRC recognition improved detection rates and resulted in more complete en bloc resections.[9] Several educational modules on T1CRC are already freely available, including one from the United European Gastroenterology,[10] and our Dutch polypectomy e-learning, which features a dedicated section on optical assessment (**chapter 2**). To maximize their value, educational resources should be actively promoted and integrated into routine endoscopy training.

Regional expert panels offer another way to improve optical diagnosis for larger or complex colorectal lesions. These panels enable expert review via shared endoscopic images and provide guidance on treatment strategy. Key challenges include recognizing potentially malignant lesions as such and ensuring high-quality imaging. Ideally, this includes white-light overview images and advanced imaging of areas with abnormal morphology or surface patterns. The feasibility and value of such panels were demonstrated in a recent study,[11] and applied in the TRIASSIC trial (**chapter 3**).

While structured training and expert panels likely improve optical diagnosis, their impact is limited by the presence of covert cancers. Technical innovations such as the aforementioned fluorescence imaging and AI therefore remain essential. Until diagnostic certainty of optical diagnosis improves, at-risk lesions should be resected en bloc to ensure oncological safety and avoid unnecessary morbidity from oncological surgery.

II. Shaping the optimal local approach for non-pedunculated rectal adenomas and superficially invasive T1 rectal cancer

Based on the first randomized comparisons between ESD and TAMIS in a Western setting, their relative merits have become clearer. Initial results from the TRIASSIC study (protocol in **Chapter 3**),[12] demonstrated non-inferiority of ESD for local recurrence at 12 months, even showing superiority (0 recurrences in the ESD group vs. 6 in the TAMIS group, -6.4% risk difference, 95% CI -11.3 to -1.4). Complication rates were similar between both groups (22.0% for ESD vs. 20.4% for TAMIS; p=0.33). ESD was associated with lower initial procedural costs (€2,628 vs. €3,365; p<0.001), while total healthcare costs over a one year period were comparable (€7,135 for ESD vs. €7,216 for TAMIS). The ancillary study (**chapter 4**) also demonstrated non-inferiority of ESD in terms of

postoperative physical recovery, with a seven-day shorter mean recovery time (13.9 days vs. 21.0 days). Beyond these clinical and economic outcomes, ESD seems to offer an important practical advantage in terms of anatomical flexibility. While ESD can be performed throughout the colorectum by experienced operators, TAMIS is limited to the rectum due to the rigidity of its instruments.[13] However, even within the rectum, ESD appears more versatile. In the TRIASSIC study, the TAMIS procedure was aborted In 5% of due to anatomical constraints that did not hinder ESD.

These findings highlight the potential of ESD in the treatment of non-pedunculated rectal adenomas and T1 rectal cancer. Nevertheless, widespread implementation in Western clinical practice is still limited.

Towards broader clinical use of ESD in Western healthcare

One important obstacle hindering widespread implementation is the technical complexity of ESD, which demands extensive hands-on experience and is associated with a much longer learning curve compared to local surgical approaches.[14, 15] Although theoretical courses, simulation-based exercises, and hands-on training programs (often using animal models) are increasingly available,[16] these resources alone are often insufficient for achieving safe and effective clinical performance, and transitioning to human cases remains challenging.[17, 18] Supervised training by ESD experts has been shown to shorten the learning curve and improve outcomes,[19, 20] and is therefore strongly endorsed by the European Society of Gastrointestinal Endoscopy as a key component to ESD training.[16] However, due to a shortage of experienced ESD endoscopists in the West, and lack of practical guidelines on how to implement such mentorships programs, standardized training programs are not widely available in Europe or North America. A proposed solution is the formal establishment of regional or national expert networks, alongside international fellowship programs to increase access to expert supervised training and accelerate ESD training. Efforts to formalize and expand such training infrastructure will be essential to make ESD a more viable and accessible option in Western clinical practice.

A second barrier hampering ESD adoption in Western countries is the long procedure time combined with relatively low reimbursement rates.[21, 22] This issue is particularly prominent outside academic centers, where such constraints are likely most pressing. The time required for a single ESD procedure, especially in the beginning, often competes with the opportunity to perform multiple other endoscopic interventions within the same timeframe, which cumulatively yield higher reimbursement. Prospective comparative data, such as those expected from the TRIASSIC trial, are necessary to support more appropriate reimbursement models for ESD and thereby help to overcome this important barrier.

III. Towards more patient-centered care in T1 colorectal cancer

By exploring T1CRC patients' perspectives on information provision and decision-making after local resection (**chapter 8**), several important directions towards more patient-centered care were identified that require attention from healthcare professionals.

The identified unmet information needs highlight opportunities for improvement. These needs mainly concerned post-treatment care (including follow-up, recurrence risk, and recovery after local resection). These unmet needs may reflect both clinicians' unawareness of patients' priorities, but potentially also a lack of available evidence at the time. Recent developments now offer clinicians guidance to better address these topics during consultations. Regarding follow-up and recurrence, the updated national guideline offers clear follow-up recommendations, even for high-risk patients who forgo additional treatment.[23] Additionally, two meta-analyses, that have since been published, provide additional insights regarding risk of recurrence. One on recurrence after endoscopic resection of T1CRC,[24] and one specifically on T1 rectal cancer showing notably higher recurrence rates (**chapter 3**), emphasizing the need for tumor location-specific counseling. Regarding recovery, the study in **chapter 5** adds objective data on physical recovery after ESD and TAMIS that can help patients form realistic expectations during pre-treatment consultations. This study's methodology could be extended to other local resection techniques to further reduce information needs regarding recovery. Together, these insights enable clinicians to engage in more patient-centered communication that aligns with patients' priorities.

Regarding decision-making after local resection, many patients reported satisfaction with the process, but not all felt actively involved. Interestingly, the lack of decisional involvement did not correlate with dissatisfaction, suggesting that preferences for involvement may vary among these T1CRC patients. Some may thus prefer a more conventional or paternalistic decision-making style, in which the healthcare professional makes decisions on behalf of the patient, as was reported previously in patients receiving care across various medical disciplines.[25] Efforts to improve decision-making in T1CRC care should therefore not only encourage patient involvement, but perhaps even more importantly, focus on identifying and respecting each individual's preferred role in the process. Still, the association between educational level, extent of decisional involvement, and even decision outcomes warrants attention, as it may reflect underlying inequalities in communication and understanding rather than differences in preferred decision-making style. Communication should therefore be tailored to varying levels of literacy to help ensure that all patients, regardless of educational background, receive adequate support to participate in decision-making, if they wish to do so.

A promising way to help bridge disparities related to educational background is through educational interventions.[26] For example, the patient educational videos on T1CRC care pathway presented in **chapter 9** could be integrated into routine care, perhaps

as preparation for the consultation or as a reference afterwards. By providing clear, repeatable information, these videos may empower patients to engage with their care in a way that suits their individual preferences.

Meaningful progress towards patient-centered care requires the active integration of patients' perspectives not only into clinical practice, but also into research. This means looking beyond traditional study outcomes to also consider patients' concerns, needs, and preferences. As diagnostics and local treatments for T1CRC continue to evolve, future research must give equal priority to what matters most to patients.

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APPENDICES

Nederlandse samenvatting

Dikkedarmkanker is een van de meest voorkomende vormen van kanker en wereldwijd de op één na belangrijkste oorzaak van sterfte door kanker. In 2023 kregen in Nederland ongeveer 12.000 mensen deze diagnose van wie circa 3.000 met endeldarmkanker. Dikkedarmkanker ontstaat meestal uit goedaardige voorstadia, zogenaamde poliepen. Hoewel alle poliepen uiteindelijk kwaadaardig kunnen worden, ontwikkelt slechts een deel zich daadwerkelijk tot kanker. Het proces waarbij gezond darmslijmvlies via poliepen verandert in dikkedarmkanker duurt doorgaans tien tot vijftien jaar. Dit biedt mogelijkheden voor vroegtijdige opsporing en behandeling met als doel de sterfte te verminderen.

Dikkedarmkanker geeft vaak pas klachten in een vergevorderd stadium, zoals een veranderd ontlastingspatroon of bloedverlies. Grote poliepen of vroegstadium dikkedarmkanker geeft dus vaak geen klachten. Wel kan dit kleine hoeveelheden bloedverlies geven, die met het blote oog nog niet op te merken zijn. Om de ziekte eerder op te sporen zijn er daarom testen ontwikkeld om die kleine hoeveelheden bloed in de ontlasting aan te kunnen tonen. Tegelijkertijd zijn er speciale technieken ontwikkeld om juist deze grote poliepen of vroege vormen van darmkanker nog plaatselijk, darmsparend, te verwijderen. In vergelijking met meer traditionele grotere operaties, waarbij een deel van de darm wordt weggehaald, zijn deze plaatselijke methodes minder ingrijpend en belastend voor patiënten. Deze ontwikkelingen hebben in 2014 geleid tot de invoering van het bevolkingsonderzoek naar darmkanker in Nederland, met als doel sterfte aan dikkedarmkanker te verminderen via vroege opsporing en behandeling.

Sinds de invoering van het bevolkingsonderzoek naar dikkedarmkanker wordt de ziekte inderdaad vaker in een vroeg stadium ontdekt. Daardoor zien we meer patiënten met grotere poliepen of met vroegstadium dikkedarmkanker (T1CRC). In de zorg voor deze patiëntengroep bestaan momenteel nog diverse uitdagingen, zoals het beter herkennen van T1CRC, het kiezen van de meest geschikte plaatselijke (lokale) behandeling en de meest optimale zorg daarna. Dit proefschrift beoogt aan de hand van drie hoofdthema's de zorg voor deze patiëntengroep te verbeteren en meer patiëntgericht te maken: Optische diagnostiek en lokale behandeling (deel I), behandelstrategieën na lokale behandeling (deel II), en versterken van de regie van patiënten (deel III).

Na een algemene introductie van het onderzoek (**Hoofdstuk 1**) en een e-learning over het verwijderen van poliepen (poliepectomie) voor vakgenoten (**Hoofdstuk 2**) komen bovenstaande drie delen aan bod.

Deel I: Optische diagnostiek en lokale behandeling

Optische diagnostiek

Een inschatting maken tijdens een darmonderzoek of een poliep volstrekt goedaardig is of dat er sprake kan zijn van (vroegstadium) dikkedarmkanker op basis van hoe de poliep eruit ziet noemen we optische diagnostiek. Nauwkeurige optische diagnostiek is belangrijk omdat de kans op kanker bepaalt hoe een afwijking het beste weggehaald kan worden. Als kanker niet herkend wordt kan dit leiden tot een onvolledige manier van weghalen, waardoor grotere belastende operaties alsnog nodig kunnen zijn die wellicht voorkomen hadden kunnen worden. Momenteel is de nauwkeurigheid van de optische diagnostiek suboptimaal.

Fluoresence optical imaging is een techniek waarbij met behulp van lichtgevende kleurstoffen (fluorescentie) bepaalde eiwitten in het lichaam zichtbaar gemaakt kunnen worden. Door een kleurstof te koppelen aan een eiwit dat specifiek aanwezig is in kankercellen kunnen bijvoorbeeld kwaadaardige gebieden opgelicht worden. Theoretisch zou deze techniek ook tijdens een darmonderzoek gebruikt kunnen worden om goedaardige van kwaadaardige poliepen te onderscheiden en daarmee de optische diagnostiek te verbeteren. In **Hoofdstuk 3** onderzochten we in het laboratorium of deze techniek haalbaar lijkt en welke eiwitten dan geschikt zijn als doelwit voor fluoresentie geleide endoscopie om optische diagnostiek van T1CRC te verbeteren. We onderzochten vijf verschillende eiwitten: carcinoembryonic antigen, mesenchymal-epithelial transition factor, epithelial cell adhesian molecule, folate receptor alpha en integrin alpha-v beta-6. Carcinoembryonic antigen bleek het meest betrouwbaar verschil te laten zien tussen (voorlopers van) kanker en het omliggende goedaardige weefsel. Dit eiwit had een sensitiviteit van 65% voor verdacht weefsel en een specificiteit van 75%.

Lokale behandeling

Hoofdstuk 4 en 5 richten zich op twee technieken voor lokale behandeling van grotere goedaardige poliepen en T1CRC. Endsocopische submucoale dissectie (ESD) en transanaal minimaal invasieve chirurgie (TAMIS) waarbij de eerste doorgaans door een Maag-Darm-Leverarts zal worden uitgevoerd en de tweede door een chirurg. De technieken lijken erg op elkaar maar zijn net anders in uitvoering, zoals het snijvlak waarin gesneden wordt dat dieper is voor de TAMIS. Beide technieken zijn momenteel standaard zorg in Nederland en maken het mogelijk om afwijkingen in hun geheel te verwijderen in een poging om een grote buikoperatie te voorkomen. Omdat beide technieken nog nooit direct met elkaar vergeleken zijn, zijn de relatieve voor- en nadelen onbekend.

Hoofdstuk 4 beschrijft het onderzoeksprotocol van de TRIASSIC studie. In dit onderzoek worden 198 patiënten met een grote poliep of T1 kanker in de endeldarm willekeurig ingedeeld voor een behandeling met TAMIS of ESD. Het primaire doel van de studie is

om te onderzoeken of ESD even goed werkt als TAMIS in het voorkomen van terugkeer van ziekte (recidief) binnen twaalf maanden. Daarnaast wordt gekeken naar hoe vaak het lukt om afwijkingen volledig te verwijderen, de kwaliteit van leven, kans op complicaties en de kosten van beide behandelingen.

In **Hoofdstuk 5** beschrijven we de uitkomsten van een zij-studie binnen deze TRIASSIC studie, waarin we het lichamelijk herstel na ESD en TAMIS hebben onderzocht en met elkaar vergeleken. Veertig patiënten droegen na de ingreep vier weken lang een smartwatch, waarmee hun dagelijkse beweging werd bijgehouden die vergeleken werd met hun activiteitsniveau 14 dagen voorafgaand aan de ingreep. Gemiddeld duurde het herstel na ESD 14 dagen, wat in ieder geval vergelijkbaar of zelfs iets korter was dan het herstel na TAMIS, dat gemiddeld 21 dagen duurde. Patiënten die na de ingreep meer pijn hadden bewogen minder. Matig tot ernstige pijn kwam vaker voor na TAMIS. Ook bleek dat grotere afwijkingen en afwijkingen die dichterbij de anus lagen het herstel vertraagden. Tevens was het opvallend dat, ondanks dat beide ingrepen als minimaal belastend worden beschouwd, 20% van de patiënten na vier weken nog niet volledig was hersteld. Deze inzichten helpen om patiënten in de toekomst beter voor te lichten over wat ze na de ingreep kunnen verwachten.

Deel II: Behandelstrategieën na lokale behandeling

Bij verdenking op een T1CRC kiezen artsen vaak voor een stapsgewijze behandelaanpak: Eerst wordt geprobeerd om de tumor lokaal weg te halen (bijvoorbeeld met een ESD of TAMIS), waarna op basis van pathologisch onderzoek een afweging gemaakt dient te worden tussen een aanvullende behandeling, meestal buikoperatie, of afzien hiervan. Het gaat hierbij om een afweging tussen de voordelen van aanvullende behandeling (oncologische risico verminderen) en de nadelen (risico's van de aanvullende behandeling). Er is sprake van een verhoogd oncologisch risico als de lokale behandeling niet compleet was of als er aanwezigheid is van zogenaamde hoog risico kenmerken die geassocieerd zijn met lymfeklieruitzaaiingen. De lymfeklieren zijn namelijk niet weggehaald met alleen een lokale behandeling. De nadelige gevolgen van een aanvullende operatie zijn het meest uitgesproken in de endeldarm, waarbij het belangrijkste risico het aanleggen van een blijvend stoma is. Als de lokale behandeling volledig is en er geen hoog risico kenmerken aanwezig zijn, kan veilig afgezien worden van een grote operatie en de daarbij behorende nadelige gevolgen. Ook bij patiënten die wel een verhoogd oncologisch risico hebben kan afgezien worden van aanvullende behandeling, bijvoorbeeld omdat door de conditie van een patiënt de aanvullende behandeling te risicovol is of omdat dit de wens van de patiënt is.

In **Hoofdstuk 6** onderzochten we of een eerdere ESD de uitkomst van een eventuele latere buikoperatie negatief beïnvloedt. Dit deden we door de volgende

patiëntengroepen met elkaar te vergelijken: 54 patiënten die na een ESD alsnog een buikoperatie ondergingen, en 357 patiënten die direct een buikoperatie kregen zonder voorafgaande ESD. Omdat de patiënten in beide groepen op sommige punten van elkaar verschilden, hebben we een statistische methode gebruikt, genaamd propensity score adjustment. Daarmee konden we corrigeren voor de verschillen, zodat de groepen beter met elkaar te vergelijken waren.

Uit de analyse bleek dat een eerdere ESD de uitkomsten van de daaropvolgende buikoperaties niet verslechterde. De kans op complicaties of overlijden binnen 90 dagen was vergelijkbaar in beide groepen. Dit bevestigt dat het veilig is om bij een vermoeden van T1CRC eerst een minder ingrijpende ESD-behandeling te proberen. Als uit de weefselanalyse blijkt dat aanvullende chirurgie toch nodig is, kan die alsnog veilig plaatsvinden. Tegelijkertijd biedt deze aanpak de mogelijkheid om een buikoperatie te vermijden bij de patiënten waar dit niet nodig of wenselijk blijkt.

In **Hoofdstuk 7** presenteren we de resultaten van een meta-analyse waarbij we oncologische uitkomsten na lokale chirurgische behandeling vergelijken met endoscopische behandeling van T1 kanker in de endeldarm. De kans op terugkeer van ziekte, de recidiefkans, was vergelijkbaar tussen de groep patiënten die TAMIS of vergelijkbare transanal endoscopic microsurgery ondergingen en de groep patiënten die een endoscopische resectie kreeg. Die kans bleek 7.7% in beide groepen. Ook in de patiënten die een recidief kreeg, was de kans op overlijden als gevolg van kanker vergelijkbaar (35.6% vs. 30%). Patiënten met hoog risicokenmerken voor lymfeklieruitzaaiingen hadden een substantieel hogere kans op een recidief (29.7% vs. 12.5%) dan patiënten met een laag-risico tumor (5.9% vs. 3.1%). Opvallend was dat recidieven vaker voorkwamen bij lokaal behandelde kankers in de endeldarm in vergelijking met T1 kankers vanuit de gehele dikke darm, zoals gerapporteerd werd in een eerdere vergelijkbare meta-analyse (0.7% voor laag-risico en 7% voor hoog-risico). Deze bevindingen helpen artsen om een duidelijk vervolgplan te maken voor patiënten die met een lokale behandeling zijn behandeld voor een T1 kanker van de endeldarm.

Deel III: Versterken van de regie van patiënten

Een belangrijke eerste stap richting meer patiëntgerichte zorg is het begrijpen van de ervaringen van patiënten met de huidige zorg. In **Hoofdstuk 8** hebben we onderzocht hoe T1CRC patiënten de informatievoorziening tijdens hun behandeling hebben ervaren. Daarnaast hebben we bij patiënten met een hoog-risico tumor onderzocht hoe zij de beslissing hebben ervaren om wel of geen aanvullende behandeling te ondergaan na de lokale behandeling. Hierbij waren de belangrijkste vragen hoe betrokken zij zich voelden bij deze beslissing en of zij tevreden waren hierover.

Hoewel de meeste patiënten over het algemeen tevreden waren met de informatie die zij ontvingen, gaven meerdere patiënten aan dat zij toch bepaalde informatie misten, vooral over de periode na de behandeling. Ook over het proces van medische besluitvorming waren de meeste patiënten tevreden. Opvallend was dat het ervaren hebben van een minder betrokken rol tijdens deze besluitvorming niet leidde tot ontevredenheid. Het opleidingsniveau van een patiënt leek een belangrijke rol te spelen in het proces van besluitvorming: hoger opgeleide patiënten voelden zich vaker actief betrokken en de uiteindelijke keuze resulteerde bij hen vaker in het ondergaan van een aanvullende behandeling, terwijl lager opgeleide patiënten zich juist vaker minder betrokken voelden en de uiteindelijke keuze vaker resulteerde in het afzien van aanvullende behandeling. Deze bevindingen suggereren dat om de zorg te verbeteren zorgverleners tijdens de informatievoorziening meer aandacht zouden moeten besteden aan de periode na de plaatselijke behandeling. Wat betreft de besluitvorming is het van belang is om de mate van betrokkenheid af te blijven stemmen met de individuele wensen en behoeften van de patiënt.

In **Hoofdstuk 9** introduceren we educatieve video's voor patiënten met een T1CRC. In drie video's wordt een overzichtelijke uitleg gegeven over wat patiënten met T1CRC kunnen verwachten tijdens hun behandeling. De titels van de video's zijn: "Colorectal cancer: how does it develop and how can you detect it", "A polyp suspected tob e colorectal cancer: what now?", en "Early-stage colon cancer with unfavorable features: what now?". Veertien patiënten hebben de video's geëvalueerd en allemaal gaven ze aan de video's aan toekomstige patiënten aan te raden. Door duidelijke en makkelijk te begrijpen informatie aan te bieden, verwachten wij dat het gebruik van deze video's in de zorg patiënten helpt om, als zij dat willen, meer regie te nemen in hun zorg.

Tot slot worden in **Hoofdstuk 10** de belangrijkste bevindingen van dit proefschrift samengevat. Daarnaast wordt vooruitgekeken naar hoe de zorg voor patiënten met een poliep in de endeldarm of T1CRC verder kan worden verbeterd en welke stappen en onderzoeken daarvoor nodig zijn.

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List of publications

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1. **Dekkers N***, Zonoobi E*, Dang H, Warmerdam MI, Crobach S, Langers AMJ, van der Kraan J, Hilling DE, Peeters KCMJ, Holman FA, Vahrmeijer AL, Sier CFM, Hardwick JCH, Boonstra JJ. Colorectal polyps: Targets for fluorescence-guided endoscopy to detect high-grade dysplasia and T1 colorectal cancer. United European Gastroenterol J. 2023 Apr;11(3):282-292. doi: 10.1002/ueg2.12375. Epub 2023 Mar 17. PMID: 36931635; PMCID: PMC10083466. **Shared first*
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Dankwoord

Wat ben ik blij om na al die jaren eindelijk te kunnen schrijven dat het zo ver is, mijn proefschrift is klaar. Ik ben iedereen die hieraan heeft bijgedragen enorm dankbaar.

Allereerst dank aan de patiënten voor hun bereidheid om, in een vaak onzekere tijd, mee te willen doen aan één, twee en soms zelfs drie van de studies die in mijn proefschrift zijn opgenomen.

Ook wil ik mijn promotieteam bedanken. Prof. dr. Hardwick, James, dank voor je vertrouwen in mij aan de start van mijn PhD. Hoewel het traject anders liep dan we beiden hadden verwacht, ben ik blij dat we mijn proefschrift uiteindelijk toch samen op deze manier tot een goed einde kunnen brengen. Dr. Doornebosch, Pascal, bedankt dat jij met James mijn PhD mogelijk hebt gemaakt en voor jouw input vanuit chirurgisch perspectief. Dr. Boonstra, Jurjen, bedankt voor jouw onmisbare begeleiding en samenwerking de afgelopen jaren. Ik ben trots op de projecten die we samen hebben bedacht, uitgevoerd en afgerond, en heb zowel op professioneel als persoonlijk vlak veel van je geleerd, waarvoor ik je zeer dankbaar ben.

Richard, paranimf, dank voor de fijne samenwerking en je onmisbare input. Daarnaast dank voor de gezelligheid buiten de wondere wereld van de poliepen, de duizend stickers die je me gestuurd hebt (‘finally my friend’), en je luisterende oor tijdens de mindere momenten.

Elma, paranimf, al sinds de eerste klas Nederlands een van mijn meest favoriete mensen. Of het nu gaat om series kijken, concerten bezoeken, of spelletjes spelen, alles is met jou een feestje en met jouw creatieveling Phil erbij is het alleen maar gezelliger geworden. Dank dat je er altijd voor mij bent.

Al mijn vrienden en ‘schoon’vrienden, bedankt voor jullie steun en afleiding. Nienke (en haar Joost), dank voor het lief en leed dat we hebben gedeeld, zowel op als buiten de werkvloer. Lisette, dank voor de vele gezamenlijke focussessies, of juist voor de zeer nodige afleiding. Tess, wat hebben we heerlijk tegen elkaar aan kunnen zeuren over onze niet altijd soepel verlopende projecten; bedankt voor je humor en relativeringsvermogen. Martine, dank dat ik altijd met Alex en de hond(en) mocht komen spelen. Phil, bedankt voor het maken van de omslag van mijn boekje. Matthijs, bedankt voor jouw hulp bij het horloge project.

Mijn mede-onderzoekers, zonder wie mijn tijd in het LUMC een stuk minder kleurrijk zou zijn geweest: bedankt Noor, Laura, Sarah O, Lola, Roberta, Jelte, Maaike, Tom, Marieke en Mark. Vera en Emilie, bedankt voor het meest hartelijke ontvangst dat je je toe kan wensen, en ook voor jullie gezelligheid in ons verder vrij sfeerloze hok.

Mede-murmellianen Anna en Annelotte, bedankt voor deze enorm gezellige reünie. Megan, dank voor jouw aanstekelijke enthousiasme voor de MDL en je behulpzaamheid. Oncollega Derk, dank voor de subway-sessies. Anke, juf Ank, wat een feest om kamergenoten met jou te zijn geweest; bedankt voor je gezelligheid binnen en buiten het LUMC. Susan, dank voor de gezellige koffie- en (vega)kroketmomenten. Sarah H, dank voor je humor en dat je mij nooit hebt willen uitleggen wat nanostring is. Tessa, dank voor jouw oprechte interesse; ik kan niet wachten tot we weer collega's zijn in LUMC. Daan, bedankt voor de (tussen ons) soepele overname van de projecten.

Alexandra, dank voor jouw feilloze feedback en voor het aanstekelijke enthousiasme dat jij en Jolein hebben voor onderwijs.

Anne, Gawain, Katinka, Philip en Manon dank voor jullie inzet.

Judith, Jolanda, Riena, Sarita, Suzan en Niki bedankt voor jullie gezelligheid en ondersteuning.

Ook wil ik iedereen bedanken die heeft meegewerkt aan de uitvoering van de TRIASSIC-studie en de studies die in dit proefschrift zijn opgenomen. Barbara, Marinke en Leon, dank voor jullie bijzonder actieve bijdrage aan de verschillende studies waaraan jullie hebben deelgenomen.

Ik wil mijn (oud)collega's en opleiders van de Interne geneeskunde en MDL bedanken voor de ruimte die jullie mij hebben gegeven de afgelopen jaren en voor de begeleiding en gezelligheid op de werkvloer. In het bijzonder: Zure zusje Sanne, wat een geluk dat wij onze opleiding samen opgescheept zitten, cocktailmasters Michel en Yannick, en buurvrouw Dieuwke. Berbel en Rianne, bedankt voor onze vele koffierondjes.

Ook wil ik mijn (schoon)familie bedanken voor hun steun de afgelopen jaren. In het bijzonder mijn zussen Lorenze en Sandrijn en mijn ouders Gerard en Els (en hun partners Marjo en Marc). Bedankt voor jullie steun en altijd oprechte interesse in waar ik mee bezig ben. Ik ben blij dat nu dit erop zit, ik jullie vaker op kan komen zoeken.

Lieve Lorân, bedankt voor jouw onmisbare steun, geduld en betrokkenheid. Je moedigt me aan, steunt me en zorgt voor afleiding op precies de juiste momenten. Dank voor wie je bent en voor het zoveel leuker maken van mijn leven. Ik hou van je.

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Nik Dekkers was born on the 29 June 1993 in Alkmaar, the Netherlands. He graduated from the Murmellius Gymnasium in Alkmaar in 2011. That same year, he began studying medicine at Leiden University. During his studies, he took elective courses in education and medical ethics. His first experience in research was his scientific internship studying the role of mucosal inflammation in the recurrence risk of primary sclerosing cholangitis in patients with ulcerative colitis. This project was led by dr. Jeroen Maljaars and carried out at the Leiden University Medical Center and the University Hospital Leuven. After completing his final clinical rotation in Internal Medicine and in Gastroenterology and Hepatology at the Haga Hospital, he obtained his Master's degree in Medicine in 2017. After graduation, he worked as a resident not in training at the Haga Hospital, first in Internal Medicine and later in Gastroenterology and Hepatology.

In 2019, he started his PhD at the Department of Gastroenterology and Hepatology at Leiden University Medical Center under the direct supervision of prof. James Hardwick and dr. Jurjen Boonstra. The main focus of his thesis was large rectal adenomas and T1 colorectal cancer. During his PhD, Nik coordinated the randomized TRIASSIC trial, which compared the effectiveness, safety, and cost-effectiveness of endoscopic submucosal dissection and transanal minimally invasive surgery. Alongside his scientific work, he was also actively involved in developing educational materials and courses for both healthcare professionals and patients. Under the supervision of dr. Jurjen Boonstra, he obtained a Gastrostart grant for the project "*Fluorescent-guided imaging in the rectum: is it possible to let an early rectal cancer glow in the dark*". As part of the study team of the TRIASSIC trial, Nik was awarded a best abstract award for the trial results at both the Dutch Digestive Disease Days and the United European Gastroenterology week.

In 2023 Nik started his residency in Gastroenterology and Hepatology and is currently working at the Haga hospital. He lives in The Hague with his husband Lorân, where he enjoys life both inside and outside of medicine.