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

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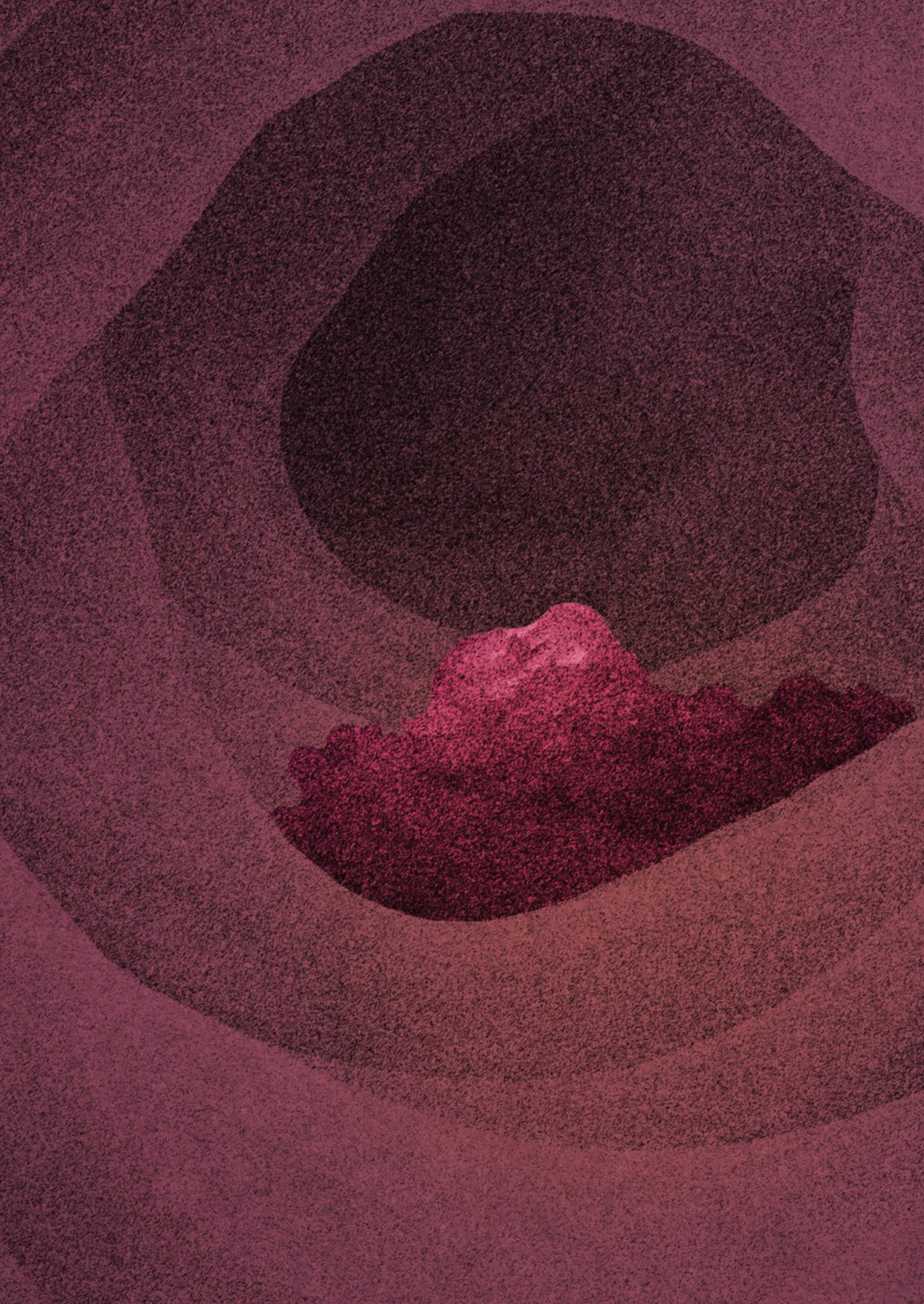

CHAPTER 10

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.

References:

1. Burggraaf J, Kamerling IM, Gordon PB, Schrier L, de Kam ML, Kales AJ, et al. Detection of colorectal polyps in humans using an intravenously administered fluorescent peptide targeted against c-Met. Nat Med. 2015;21(8):955–61.
2. Tjalma JJJ, Koller M, Linssen MD, Hartmans E, de Jongh SJ, Jorritsma-Smit A, et al. Quantitative fluorescence endoscopy: an innovative endoscopy approach to evaluate neoadjuvant treatment response in locally advanced rectal cancer. Gut. 2020;69(3):406–10.
3. Gutowski M, Framery B, Boonstra MC, Garambois V, Quenet F, Dumas K, et al. SGM-101: An innovative near-infrared dye-antibody conjugate that targets CEA for fluorescence-guided surgery. Surg Oncol. 2017;26(2):153–62.
4. Maas MHJ, Neumann H, Shirin H, Katz LH, Benson AA, Kahloon A, et al. A computer-aided polyp detection system in screening and surveillance colonoscopy: an international, multicentre, randomised, tandem trial. The Lancet Digital Health. 2024;6(3):e157–e65.
5. Bai J, Liu K, Gao L, Zhao X, Zhu S, Han Y, et al. Computer-aided diagnosis in predicting the invasion depth of early colorectal cancer: a systematic review and meta-analysis of diagnostic test accuracy. Surgical Endoscopy. 2023;37(9):6627–39.
6. Luo X, Wang J, Han Z, Yu Y, Chen Z, Huang F, et al. Artificial intelligence-enhanced white-light colonoscopy with attention guidance predicts colorectal cancer invasion depth. Gastrointest Endosc. 2021;94(3):627–38.e1.
7. Nemoto D, Guo Z, Katsuki S, Takezawa T, Maemoto R, Kawasaki K, et al. Computer-aided diagnosis of early-stage colorectal cancer using nonmagnified endoscopic white-light images (with videos). Gastrointest Endosc. 2023;98(1):90–9.e4.
8. Dekker E, Houwen B, Puig I, Bustamante-Balén M, Coron E, Dobru DE, et al. Curriculum for optical diagnosis training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2020;52(10):899–923.
9. Meulen LWT, Haasnoot KJC, Vlug MS, Wolfhagen FHJ, Baven-Pronk M, van der Voorn M, et al. Effect of optical diagnosis training on recognition and treatment of submucosal invasive colorectal cancer in community hospitals: a prospective multicenter intervention study. Endoscopy. 2024;56(10):770–9.
10. Langers AMJ, Boonstra JJ, Hardwick JCH, Dang H. (2020). Management of T1 colorectal cancer [Online course]. United European Gastroenterology. Updated February 2023. https://ueg.eu/p/198
11. Zwager LW, Bastiaansen BAJ, Dekker E, Fockens P. Setting up a regional expert panel for complex colorectal polyps. Gastrointest Endosc. 2022;96(1):84–91.e2.
12. Verhoeven D, Dekkers N, Boonstra JJ, Moons LG, Hompes R, Bastiaansen BA, et al. Multicenter, randomized non-inferiority trial comparing TRansanal minimal InvAsive Surgery (TAMIS) and endoscopic Submucosal dIsseCtion (ESD) for resection of non-pedunculated rectal lesions. Endoscopy. 2025;57(S 02):OP054.
13. Atallah S, Albert M, Larach S. Transanal minimally invasive surgery: a giant leap forward. Surg Endosc. 2010;24(9):2200–5.
14. Khalaf MA, Ayoub F, Staggers KA, El-Haj JW, Jawaid S, Othman MO. Learning curve for endoscopic submucosal dissection (ESD) in the United States: Large, untutored, single-operator experience. Endosc Int Open. 2024;12(7):E905–e13.

15. Li X, Guo S, Yao K, Ge Z, Li Y, Hu J, et al. Learning curve of transanal minimally invasive surgery for rectal neoplasm. Front Oncol. 2025;15:1545589.
16. Pimentel-Nunes P, Pioche M, Albéniz E, Berr F, Deprez P, Ebigbo A, et al. Curriculum for endoscopic submucosal dissection training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2019;51(10):980–92.
17. Barbour JA, O'Toole P, Suzuki N, Dolwani S. Learning endoscopic submucosal dissection in the UK: Barriers, solutions and pathways for training. Frontline Gastroenterol. 2021;12(7):671–6.
18. Schlachterman A, Yang D, Goddard A, Gotoda T, Draganov PV. Perspectives on endoscopic submucosal dissection training in the United States: a survey analysis. Endosc Int Open. 2018;6(4):E399–e409.
19. Yamamoto S, Radomski T, Shafazand M. Implementation of mentor-assisted colorectal endoscopic submucosal dissection in Sweden; learning curve and clinical outcomes. Scand J Gastroenterol. 2018;53(9):1146–52.
20. Draganov PV, Chang M, Coman RM, Wagh MS, An Q, Gotoda T. Role of observation of live cases done by Japanese experts in the acquisition of ESD skills by a western endoscopist. World J Gastroenterol. 2014;20(16):4675–80.
21. Dahan M, Pauliat E, Liva-Yonnet S, Brischoux S, Legros R, Tailleur A, et al. What is the cost of endoscopic submucosal dissection (ESD)? A medico-economic study. United European Gastroenterol J. 2019;7(1):138–45.
22. Iqbal S, Ali A, Razzaq A, Shahzad E. Lack of proper reimbursement is hampering adoption of minimally invasive gastrointestinal endoscopy in North America. World J Gastrointest Endosc. 2020;12(1):49–52.
23. Nederlandse Vereniging van Maag-Darm-Leverartsen (NVMDL). Richtlijn colorectaal carcinoom. 2024.
24. Dang H, Dekkers N, le Cessie S, van Hooft JE, van Leerdam ME, Oldenburg PP, et al. Risk and Time Pattern of Recurrences After Local Endoscopic Resection of T1 Colorectal Cancer: A Meta-analysis. Clin Gastroenterol Hepatol. 2022;20(2):e298–e314.
25. Driever EM, Stiggelbout AM, Brand PLP. Patients' preferred and perceived decision-making roles, and observed patient involvement in videotaped encounters with medical specialists. Patient Educ Couns. 2022;105(8):2702–7.
26. Chatterjee A, Strong G, Meinert E, Milne-Ives M, Halkes M, Wyatt-Haines E. The use of video for patient information and education: A scoping review of the variability and effectiveness of interventions. Patient Educ Couns. 2021;104(9):2189–99.