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Endoscopic intermuscular dissection for deep submucosal invasive cancer in the rectum: a new endoscopic approach

Authors

Leon M. G. Moons[1,*], Barbara A. J. Bastiaansen[2,*], Milan C. Richir[3], Wouter L. Hazen[4], Jurriaan Tuynman[5], Sjoerd G. Elias[6], Ruud W M. Schrauwen[7], Frank P. Vleggaar[1], Evelien Dekker[2], Philip Bos[8], Arantza Fariña Sarasqueta[9], Miangela Lacle[10], Roel Hompes[5], Paul Didden[1]

Institutions

1 Department of Gastroenterology & Hepatology, UMC Utrecht, Utrecht, The Netherlands
2 Department of Gastroenterology & Hepatology, Amsterdam UMC, Amsterdam, The Netherlands
3 Department of Surgery, UMC Utrecht, Utrecht, The Netherlands
4 Department of Gastroenterology & Hepatology, Elizabeth Tweesteden Ziekenhuis, Tilburg, The Netherlands
5 Department of Surgery, Amsterdam UMC, Amsterdam, The Netherlands
6 Department of Epidemiology, Julius Center for Health Sciences and Primary Care, Utrecht, The Netherlands
7 Department of Gastroenterology & Hepatology, Bernhoven, Uden, The Netherlands
8 Department of Gastroenterology & Hepatology, Gelderse Vallei, Ede, The Netherlands
9 Department of Pathology, Amsterdam UMC, Amsterdam, The Netherlands
10 Department of Pathology, UMC Utrecht, Utrecht, The Netherlands

submitted 12.1.2021
accepted after revision 24.1.2022
published online 24.1.2022

Bibliography
Endoscopy 2022; 54: 993–998
DOI 10.1055/a-1748-8573
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Figs. 1 s, 2 s
Supplementary material is available under https://doi.org/10.1055/a-1748-8573

Corresponding author
Leon M.G. Moons, MD, Dept Gastroenterology & Hepatology, UMC Utrecht, Heidelberglaan 100, Utrecht 3508GA, The Netherlands
l.m.g.moons@umcutrecht.nl

ABSTRACT

Background The risk of lymph node metastasis associated with deep submucosal invasion should be balanced against the mortality and morbidity of total mesorectal excision (TME). Dissection through the submucosa hinders radical deep resection, and full-thickness resection may influence the outcome of completion TME. Endoscopic intermuscular dissection (EID) in between the circular and longitudinal part of the muscularis propria could potentially provide an R0 resection while leaving the rectal wall intact.

Methods In this prospective cohort study, the data of patients treated with EID for suspected deep submucosal invasive rectal cancer between 2018 and 2020 were analyzed. Study outcomes were the percentages of technical success, R0 resection, curative resection, and adverse events.

Results 67 patients (median age 67 years; 73 % men) were included. The median lesion size was 25 mm (interquartile range 20–33 mm). The rates of overall technical success, R0 resection, and curative resection were 96 % (95 %CI 89 %–99 %), 81 % (95 %CI 70 %–89 %), and 45 % (95 %CI 33 %–57 %). Only minor adverse events occurred in eight patients (12 %).

Conclusion EID for deep invasive T1 rectal cancer appears to be feasible and safe, and the high R0 resection rate creates the potential of rectal preserving therapy in 45 % of patients.

* Contributed equally to this manuscript.

Introduction

Deep submucosal invasive rectal cancer is considered an indicator for total mesorectal excision (TME) [1]. However, recent reports have shown that deep submucosal invasion is associated with low rates of lymph node metastasis (LNM; 1.3 %–2.5 %) when high grade tumor budding (Bd2–3), lymphovascular invasion, and poor differentiation are absent [2–4]. This limited risk must be balanced against the TME mortality (1 %–1.5 %) and post-TME recurrence (3 %–6 %) [5]. A local excision of a suspected deep submucosal invasive rectal cancer – as a "total excisional biopsy" – can therefore be seen as a first step to organ preservation.

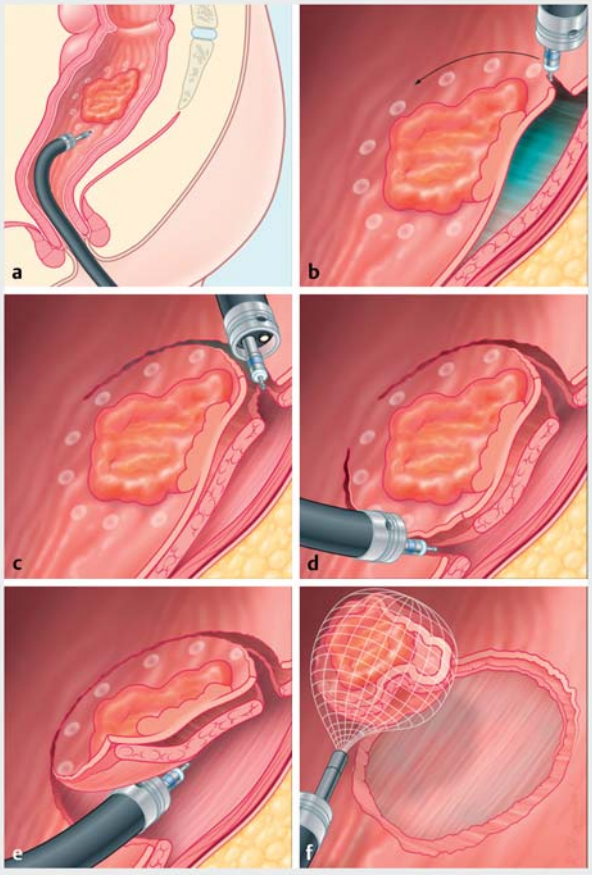
Endoscopic submucosal dissection (ESD) for superficial invasive T1 cancer can provide high R0 resection rates up to 92 %; however, the deep margin R0 rates drop to 62 %–64 % when deep submucosal invasion turns out to be present [6, 7]. Transanal endoscopic surgery (TES [6, 7]) usually comprises a full-thickness resection. While superior control of the deep margin is obtained, a full-thickness excision distorts the embryological plane for future completion of TME, particularly in rectal areas with minimal fat coverage. Post-TES, completion TME was associated with an increased re-intervention rate and incomplete mesorectal excision [8], and impaired quality of the TME specimen due to extensive fibrosis [9].

Endoscopic dissection in between the inner (circular) and outer (longitudinal) part of the muscularis propria was recently described in rectal lesions with severe submucosal fibrosis [10]. Dissection through this intermuscular space would enable the attainment of R0 deep resection margins for T1 rectal cancer with deep submucosal invasion, whilst securing the integrity of the rectal wall, leaving possible future TME planes intact. In this study, we report on the technical feasibility, R0 resection rate, and short-term clinical outcome of this new approach, called endoscopic intermuscular dissection (EID), for T1 rectal cancers with optical suspicion of deep submucosal invasion.

Methods

Study design

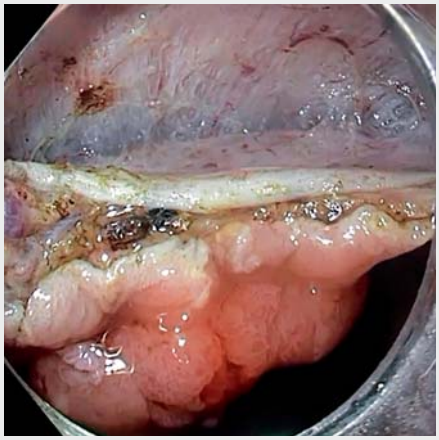
All consecutive patients treated with EID between November 2018 and July 2020 at UMC Utrecht or Amsterdam UMC were included in a prospective registry. The indication for EID was suspicion of T1 rectal cancer with deep submucosal invasion, based on optical imaging using the optical model [11]. The optical features were prospectively recorded in a standardized endoscopy report. Patients were deemed unsuitable for EID when suspect lymph nodes (> 9 mm in short axis, or 5–8 mm in combination with two malignant morphological criteria) were observed on rectal magnetic resonance imaging (MRI). A multidisciplinary decision was made to proceed to a local excision, and subsequently informed consent was obtained. The analysis of the prospective registry was approved by the medical ethics review committee of the University Medical Center Utrecht (METC 20–119/C).



▶ **Fig. 1** Schematic representation of the endoscopic intermuscular dissection (EID) procedure illustrating: **a** a rectal lesion suspected of having deep submucosal invasion in the mid-rectum; **b** a partial circumferential cut of the mucosa, which is performed to gain access to the submucosal space; **c,d** the circular muscularis propria being cut at the luminal edge of the lesion to gain access to the intermuscular space; **e** the intermuscular space being dissected to remove the specimen en bloc, including the circular part of the muscularis propria; **f** the specimen being removed using a retrieval net, leaving the longitudinal part of the muscularis propria exposed.

Endoscopic intermuscular dissection (EID) procedure

First, a mucosal incision was made approximately 5 mm around either the proximal or distal side of the lesion, followed by submucosal dissection to expose the muscle layer. A selective myotomy of the circular muscularis propria was then performed, exposing the longitudinal muscle fibers (▶ **Fig. 1**). A lifting solution was used to slightly expand the intermuscular space before dissection was started. The procedure was continued from the opposite site, until intermuscular dissection was completed (▶ **Fig. 1**; ▶ **Video 1**). The post-EID defect was not routinely closed.



Video 1 This video shows the endoscopic intermuscular dissection (EID) of a pT1Sm2 lymphovascular invasion-positive, Bd3, G1 rectal cancer at 1 cm from the dentate line.
Online content viewable at:
https://doi.org/10.1055/a-1748-8573

Histological assessment and definitions

Tumor differentiation, and presence of lymphovascular invasion and tumor budding were assessed by a dedicated gastrointestinal pathologist. The presence of circular muscle fibers beneath the invasive front was reported. Depth of invasion was measured, using the Kikuchi classification, as Sm1, Sm2, or Sm3, with ≥ Sm2 being considered to be deep submucosal invasion. R0 resection was defined as tumor-free lateral and deep resection margins. R1 resection was defined as margin involvement with microscopic tumor (**Fig. 1 s**, see online-only Supplementary material).

Follow-up

Adverse events (AEs) were recorded 14 days after EID, when patients were contacted to discuss the final result after multidisciplinary team discussion. Patients with carcinoma in situ/high grade dysplasia or a curative resection of T1Sm1 cancer were followed according to a low risk protocol, consisting of full colonoscopy with scar surveillance after 12 and 48 months. Patients with a non-curative resection were offered adjuvant treatment. Patients with a curative resection of T1Sm2/3 cancer were counselled on the risks and benefits of adjuvant treatment. If patients decided against completion surgery, intense protocolled surveillance was offered with scar inspection, MRI, and carcinoembryonic antigen (CEA) every 6 months for a period of 2 years, followed by annual examinations (endoscopy and MRI) and 6-monthly CEA measurements up to 5 years.

Study outcomes

The two main study outcomes were: (i) technical success, defined as en bloc resection with successful intermuscular dissection; and (ii) the proportion of R0 resections. Secondary outcomes were: the proportion of curative resections, defined as an R0 resection in the absence of histological risk factors (lymphovascular invasion, high grade tumor budding, and poor differentiation); and the occurrence of periprocedural complications. Complications were recorded according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon.

Data management and statistical analysis

Study data were collected and analyzed at the coordinating study center. All data were stored according to an evaluated data management plan (METC 20–119C). The database was created and statistical calculations were performed using IBM SPSS, version 25 (SPSS Inc., IBM Corp., Chicago, Illinois, USA). Descriptive statistics were expressed as a median with interquartile range (IQR) or as a proportion. Wilson's 95 %CIs were calculated.

Results

Patient characteristics and preprocedural assessment

In total, 67 patients were eligible for EID between November 2018 and July 2020. Detailed patient and lesion characteristics are provided in ▶ **Table 1**.

Technical success

Macroscopic complete en bloc resection with EID was achieved in 64/67 patients (96 %; 95 %CI 89 %–99 %). In three patients, the procedure was prematurely aborted because of failure to identify the intermuscular plane (R2 resection). In all three, the surgical specimen confirmed invasion into the muscularis propria (T2). Intermuscular dissection was achieved in 56/64 patients (88 %) (▶ **Table 2**). In eight, a partial full-thickness excision occurred, with seven of these being closed by either multiple hemoclips (n = 3), over-the-scope clips (n = 1), or endoscopic suturing (n = 3). R0 resection was achieved in of the eight patients.

In another eight patients, focal accidental injury of the longitudinal muscle occurred, with six of the defects being approximated with one hemoclip. The mean (SD) procedure time was 110 (51) minutes.

R0 resection and curative resection

Overall, R0 resection was achieved in 54/67 patients (81 %; 95 % CI 70 %–89 %), and curative resection in 30/67 (45 %; 95 %CI 33 %–57 %) patients. More detailed subgroup analysis is provided in ▶ **Table 2**.

Adverse events

Overall, AEs occurred in eight procedures (12 %; 95 %CI 5 %–22 %) and all were classified as minor to moderate. They included: moderate perianal pain in three patients (4 %) and inflammatory response (fever, pain, elevated C-reactive protein, perirectal air without a fluid collection) in three patients (4 %), all of which could be treated conservatively with intravenous antibiotics and/or analgesics. In addition, there was one patient with delayed bleeding and one with rectal stenosis that needed dilation.

▶ **Table 1** Characteristics of the 67 patients who underwent endoscopic intermuscular dissection and the lesions treated.

Age, median (IQR), years	67 (60–73)
Sex, male, n (%)	49 (73 %)
ASA score III/IV, n (%)	16 (24 %)
Lesion size, median (IQR), mm	25 (20–33)
Resected specimen size, median (IQR), mm	39 (33–46)
Size of the cancerous component, median (IQR). mm	14 (9–18)
Distance to the dentate line, median (IQR), cm	3 (1.5–10)
Paris classification, n (%)	
▪ Is	39 (58 %)
▪ IIa + IIc	16 (24 %)
▪ IIa + Is	4 (6 %)
▪ IIa	8 (12 %)
Non-granular type, n (%)	53 (79 %)
Depression present, n (%)	61 (91 %)
Easy friability present, n (%)	42 (63 %)
Hiroshima classification, n (%)	
▪ C1	10 (15 %)
▪ C2	22 (33 %)
▪ C3	35 (52 %)
Preoperative MRI performed, n (%)	60 (90 %)
▪ Lymph nodes 5–8 mm, n (%)	6 (10 %)
▪ T1/T2, n (%)	50 (83 %)
▪ T2 deep/T3a, n (%)	10 (17 %)

IQR, interquartile range; ASA, American Society of Anesthesiologists; MRI, magnetic resonance imaging.

Follow-up

A detailed flow chart of treatment strategies and follow-up after EID is provided in Fig. 2 s. There were 17 patients (65 %) who underwent completion TME, 11 (74 %) with low anterior resections, and six (27 %) with abdominoperineal excisions. After low anterior resection, two patients developed anastomotic dehiscence that necessitated a permanent stoma, and one patient developed a rectal stenosis. LNM was observed in 7/18 TME patients (39 %). This high proportion of lymph node-positive cases is caused by a bias towards high risk patients (more patients with T2 and with ≥ 2 histological risk factors). In all surgical specimens, no residual luminal cancer was found, except for in the three aborted cases. Of the 18 patients with two or more histological risk factors, 15 underwent adjuvant treatment (surgery or chemoradiation), while 44 % of the cases with only one feature chose a wait-and-see strategy. One case with a pT1Sm3 tumor with lymphovascular invasion developed an extraluminal recurrence that was detected by MRI at 18 months and could be treated by salvage surgery with curative intent.

▶ **Table 2** Outcomes of the endoscopic intermuscular dissection procedure.

Parameter	n/N (%)	95 %CI
Technical success		
▪ Overall	64/67 (96 %)	89 %–99 %
▪ pT1	44/45 (98 %)	90 %–100 %
▪ pT1 with deep submucosal invasion	39/40 (98 %)	89 %–100 %
R0 rate		
▪ Overall	54/67 (81 %)	70 %–89 %
▪ Technically successful cases	54/64 (84 %)	74 %–92 %
▪ pT1	41/45 (91 %)	80 %–97 %
▪ pT1 with deep submucosal invasion	36/40 (90 %)	78 %–97 %
Curative resection rate		
▪ Overall	30/67 (45 %)	33 %–57 %
▪ Technically successful cases	30/64 (47 %)	35 %–59 %
▪ pT1	22/45 (49 %)	35 %–63 %
▪ pT1 with deep submucosal invasion	18/40 (45 %)	30 %–60 %
Depth of invasion		
▪ Tis	8/67 (12 %)	
▪ Sm1	5/67 (8 %)	
▪ Sm2	13/67 (19 %)	
▪ Sm3	27/67 (40 %)	
▪ T2	14/67 (21 %)	
Histological risk factors		
▪ Lymphovascular invasion (present)	30/67 (45 %)	
▪ High grade tumor budding (Bd2–3)	19/67 (28 %)	
▪ Poor differentiation	5/67 (7 %)	
Adjuvant treatment	26/67 (39 %)	
▪ TME surgery	17 (65 %)	
▪ Chemoradiotherapy	8 (31 %)	
▪ Completion TAMIS	1 (4 %)	
Surveillance	41/67 (61 %)	
▪ Intensive follow-up of non-curative cases	11 (27 %)	
▪ Intensive follow-up of pT1Sm2/3 cases*	18 (44 %)	
▪ Low risk cases (Tis + pT1Sm1)	12 (29 %)	

Tis, carcinoma in situ; TME, total mesorectal excision; TAMIS, transanal minimally invasive surgery.

Discussion

This is the first study to evaluate the feasibility and safety of EID for suspected deep submucosal invasive rectal cancer. An overall technical success rate of 96 % and R0 resection rate of 81 % was reached. The R0 resection rate for pT1Sm2/3 lesions was 90 %.

This high rate of complete resection for pT1 lesions with deep submucosal invasion qualifies EID as an attractive endoscopic local staging technique. Comparing the performance of EID to ESD in this setting is difficult, because ESD is generally not commenced for lesions with optical features of deep submucosal invasion. However, we believe ESD outcomes would be expected to be less favorable, as studies have shown a significant drop in R0 resection rate to 64 % for ESD when unexpected deep submucosal invasion was found to be present [6, 7]. A failed ESD due to the muscle retraction sign and non-lifting is known to be associated with Sm3 invasion. Nearly half of all rectal cancers with deep submucosal invasion did not show other histological risk features for LNM, leading to an overall curative resection rate of 45 %, suggesting a number needed to treat of 2.2 to directly prevent TME. Future studies addressing the long-term oncological outcomes should evaluate full-thickness resection versus an intermuscular dissection in a comparative matter, including further study on the potential negative consequences for those who need to undergo completion TME [12]. We assume that intermuscular dissection might prove superior compared with full-thickness resection.

Better case selection for EID could improve its effectiveness, preventing over- as well as undertreatment. EID should therefore preferably be limited to the excision of T1 rectal cancer with deep submucosal invasion. However, differentiation between T1Sm2/3 and T2 cancers with either MRI, endoscopic ultrasound (EUS), or optical diagnosis is challenging. Optical diagnosis been designed to recognize submucosal invasive cancer and to discriminate superficial from deep submucosal invasion. Therefore, none of the currently available classifications are suitable or validated for differentiating T1Sm2/3 from T2/T3 cancers.

This problem arises not only in the rectum with the introduction of TES and now EID, but is also a contemporary problem with the introduction of endoscopic full-thickness resection (EFTR), where 28.6 % of the removed CRCs showed T2/T3 invasion [13]. Therefore, optical diagnosis should be redesigned to differentiate between T1 and T2 cancers. MRI and EUS are both used as effective methods for locoregional staging of rectal cancer; however, their accuracy in daily practice to differentiate between T1 and ≥ T2 rectal cancers is disappointing. In recent reports, MRI significantly overestimated the risk of invasion and LNM in American Joint Committee on Cancer (AJCC) stage I rectal cancer on a community level [14, 15]. For EUS, a similar risk of under- and overestimation has been observed [15, 16]. As technology and training for both imaging modalities progresses further, we expect improved accuracy for early T-staging to be possible in the future [17].

This study has several limitations. First, as we included all consecutive cases from the start, a learning curve cannot be excluded. A comparison of the first 10 patients to the remaining patients did not detect a difference in the technical success and R0 resection rates. It remains to be seen what level of experience is required to start performing EIDs, or to perform EIDs at the highest quality, as the space for dissection is small and structures need to be discriminated well. We encountered 12 % of cases with unintentional small perforations of the longitudinal muscularis propria. Although muscle defects can be closed endoscopically and leaving them open will not cause more complications [18], the potential advantage of EID over full-thickness resection might be compromised by a higher level of perforation and mesorectal inflammation.

A second limitation of our study is the duration of follow-up, which hampers conclusions on the long-term oncological safety of EID. There are however many reports on the long-term safety of local full-thickness resection in well-selected patients and we believe that EID is unlikely to have inferior outcomes compared with TES. The absence of standardized questionnaires on quality of life and functional outcome at different time points during the first 3 months is a third limitation. Although all patients affirmed an uneventful recovery at 14 days after the EID and did not report remaining symptoms, the absence of a structured questionnaire may have missed some unreported functional loss.

Although questions on long-term oncologic outcomes and proper case selection need further study, we have shown that EID is a promising new endoscopic technique for the resection of deep submucosal invasive T1 rectal cancers.

Competing interests

Leon M. G. Moons is a consultant for Boston Scientific, Barbara A. J. Bastiaansen is a consultant for OVESCO.

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