Original research

Results of endoscopic intermuscular dissection for deep submucosal invasive rectal cancer: a three-year follow-up study

Lisa van der Schee ,[1,2] Sander C Albers,[3,4,5] Paul Didden,[1] Miangela M Lacle,[2] Arantza Farina Sarasqueta,[6] Milan C Richir,[7] Martijn P W Intven,[8] Jurriaan B Tuynman,[5,9] Roel Hompes,[5,9] Evelien Dekker ,[3,4,5] Frank P Vleggaar,[1] Barbara A J Bastiaansen,[3,4,5] Leon M G Moons [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Leon M G Moons;
L.M.G.Moons@umcutrecht.nl

LvdS and SCA are joint first authors.

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ABSTRACT

Background Endoscopic intermuscular dissection (EID) is a promising new technique for managing rectal deep submucosal invasive cancer (D-SMIC), but long-term outcome data are currently lacking.

Objective This multicentre study evaluated the three-year oncological outcomes of EID, focusing specifically on patients with rectal D-SMIC who underwent active surveillance following the procedure.

Design Data from consecutive, prospectively recorded EID procedures for suspected rectal D-SMIC—based on optical diagnosis—performed at two academic centres between 2019 and 2023 were analysed. D-SMIC was defined as submucosal invasion of sm2–sm3 depth. Histological risk factors included poorly differentiated tumours (G3), lymphovascular invasion, high-grade tumour budding and positive or indeterminate resection margins (R1/Rx). Study outcomes included three-year rates of locoregional recurrence (intramural and nodal), distant recurrence (metastatic disease), non-salvageable recurrence, cancer-specific mortality and secondary rectal surgery. Cumulative incidence was estimated using the Aalen-Johansen method.

Results Among the 188 included cases, EID achieved an en bloc resection rate of 94.1% and R0 resection rate of 82.5%, respectively. Of the 177 procedures that were completed, 16% showed non-invasive histology (low-grade dysplasia/high-grade dysplasia; 20/177=11%) or superficial submucosal invasive cancer (sm1, 9/177=5%), and 31% (54/177) showed deeper (≥pT2) invasion. The remaining 94 D-SMIC cases (53%) represented the main target group. Of these, 37% (n=35) were classified as low risk (no histological risk factors), 34% (n=32) as intermediate risk (one risk factor) and 29% (n=27) as high risk (≥2 risk factors). Active surveillance was initiated in all low-risk patients, in 72% of the intermediate-risk cases and in 22% of the high-risk group. The remaining patients underwent completion surgery or adjuvant chemoradiotherapy. At three years, locoregional recurrence occurred in 7% (1/35, 95% CI 1% to 28%) of low-risk and 13% (2/15, 95% CI 2% to 35%) of intermediate-risk patients managed with active surveillance. All were successfully salvaged. Among the six high-risk patients under surveillance, locoregional recurrence was seen in two. No distant recurrences or cancer-specific deaths occurred in any D-SMIC group. Secondary rectal surgery was finally performed in 5.3%, 25.0% and 59.6% of the low, intermediate and high-risk groups, respectively.

Conclusion Despite the challenges associated with accurate preoperative staging, EID followed by active surveillance may offer a viable alternative to radical surgery for patients with low- and intermediate-risk rectal D-SMIC, avoiding rectal surgery in most cases while maintaining oncological safety.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Endoscopic intermuscular dissection (EID) shows promise for treating rectal deep submucosal invasive cancer (D-SMIC). Although recent evidence suggests deep invasion alone is not an independent risk factor for lymph node metastasis, current guidelines still recommend radical surgery for all D-SMIC cases, even without additional risk factors—raising concerns about overtreatment and surgery-related morbidity.

WHAT THIS STUDY ADDS

⇒ Local excision with EID, followed by active surveillance, demonstrated favourable three-year oncological outcomes and high rectal preservation rates in low and intermediate-risk patients with D-SMIC. Active surveillance allows early detection of locoregional recurrence and enables effective salvage treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may guide future research on optimal initial treatment for rectal D-SMIC, supporting a shift from radical surgery to local excision with active surveillance in low and intermediate-risk patients. The aim is to reduce overtreatment and better preserve quality of life.

INTRODUCTION

The implementation of colorectal cancer screening programmes has increased the detection of early-stage rectal cancer (cT1-2N0M0), prompting

growing interest in organ-preserving strategies and a shift toward local excision as the preferred initial treatment approach.[1–3] Endoscopic intermuscular dissection (EID) has recently emerged as a novel endoscopic local excision technique for rectal cancer with suspected deep submucosal invasion. Adapted from endoscopic submucosal dissection, EID involves dissection within the intermuscular plane of the muscularis propria to achieve tumour-free (R0) deep resection margins. In our previous study on EID for suspected deep submucosal invasive cancer (D-SMIC), we reported promising technical and short-term oncological outcomes, including a 90% R0 resection rate for rectal D-SMIC.[4]

Deep submucosal invasion has traditionally been considered an independent risk factor for lymph node metastasis (LNM) and/or intramural recurrence, with total mesorectal excision (TME) recommended as the standard treatment for surgically fit patients.[5–9] However, recent data suggest that the risk of LNM in colorectal D-SMIC is relatively low (2.6–5%) when additional histological risk factors are absent.[10 11] This raises the question of whether TME is necessary for all patients with D-SMIC, especially considering that nearly 40% of cases lack other histopathological risk factors.[4 10 12]

Current risk stratification for pT1 rectal cancer does not account for the number of histological risk factors, leading to wide variability in locoregional recurrence rates within the high-risk group (2.6–23.6%).[10 13 14] Studies show that the risk of synchronous LNM and/or recurrence increases with the cumulative number of risk factors.[15–19] In D-SMIC with no more than one additional risk factor, the recurrence risk may be limited. Given the morbidity associated with TME—often without oncological benefit when completion TME (cTME) specimens show no residual cancer—less invasive strategies should be considered for selected high-risk patients.[20–23]

Therefore, the aim of this study is to assess three-year oncological outcomes of EID in a prospective cohort of patients with suspected rectal D-SMIC. While all consecutive cases are included, the focus is on patients with D-SMIC with no (low-risk) or one (intermediate-risk) histological risk factor who were managed with active surveillance alone after EID.

METHODS

Study design and population

Data from consecutive and prospectively recorded EID procedures for suspected rectal D-SMIC at two academic centres between January 2019 and March 2023 were analysed. EID was performed for suspected D-SMIC based on advanced imaging (OPTICAL score ≥40%, Hiroshima C2/3, Japan NBI Expert Team (JNET) 3, NBI International Colorectal Endoscopic (NICE) III and/or Kudo Vn), or for a non-lifting lesion with features suggestive of submucosal invasion.[24] Optical features were prospectively recorded in a standardised endoscopy report. Preoperative biopsies were generally withheld to preserve the integrity of the definitive histopathological evaluation. In case biopsies were taken, the gross macroscopic appearance was prioritised over the preoperative histology.

Cases were considered unsuitable for EID if the baseline MRI indicated a tumour location at or above the sigmoid take-off, or if malignant lymph nodes or other adverse features, such as extramural venous invasion or tumour deposits, were identified. Lymph nodes on MRI were considered suspicious for malignancy if they were >9 mm in short axis, or 5–9 mm in combination with two other malignant morphological criteria (eg, irregular borders, mixed signal intensity, round shape). Patients were excluded if there was clear evidence of extramural invasion (>T2) on MRI. In cases of T-stage (T1/T2) discrepancy between MRI and optical diagnosis, endoscopic evaluation was leading. Prior to treatment, all patients were discussed at the local multidisciplinary tumour board meeting and informed consent was obtained.

Patient involvement

Patients were not involved in the design or conduct of this study. However, patient representatives contributed to the development of the active surveillance schedule within the Dutch colorectal cancer guideline used in this study.[25] Study results will be disseminated to the patient community through Stichting Darmkanker (www.stichtingdarmkanker.nl), the Dutch colorectal cancer patient organisation.

Outcomes and definitions

The primary objective of this study was to evaluate the three-year oncological outcomes, including secondary surgery rates, in patients with rectal D-SMIC (sm2/sm3 infiltration per Kikuchi classification) with no additional histological risk factors (low risk) or one (intermediate risk) who chose active surveillance instead of adjuvant treatment, such as cTME or adjuvant chemoradiotherapy (CRT).

Secondary objectives included:

1. Evaluation of the three-year oncological outcomes and the corresponding secondary rectal surgery rates in the remaining patient population, namely:
   a. Non-invasive lesions (low-grade dysplasia (LGD) and high-grade dysplasia (HGD)).
   b. Superficial submucosal invasive cancer (S-SMIC, defined as Kikuchi sm1).
   c. D-SMIC with two or more risk factors (high risk).
   d. ≥pT2 cancers.
2. Adverse events within 30 days after the procedure.

All resection specimens were assessed by dedicated GI pathologists. EID specimens with HGD or LGD were grouped as non-invasive. Submucosal infiltration depth was assessed according to the Kikuchi classification (sm1/sm2/sm3). Histological risk factors included high-grade tumour differentiation (G3), positive lymphovascular invasion, tumour budding grades II–III, microscopic margin involvement (R1) and/or indeterminate resection margin (Rx). R1 resection was defined as cancer involvement within <0.1 mm of the lateral and/or deep margin.

Patients with histologically confirmed D-SMIC were stratified according to the number of histological risk factors:

a. 'low-risk': no histological risk factors.
b. 'intermediate-risk': one histological risk factor.
c. 'high-risk': two or more histological risk factors.

The oncological outcomes were the three-year locoregional recurrence rate, three-year distant recurrence rate, three-year non-salvageable recurrence rate and three-year cancer-specific mortality. Follow-up time was calculated from the EID procedure to the last recorded follow-up visit related to rectal cancer treatment or, if the patient had died, to the date of death. Locoregional recurrence was defined as intramural cancer recurrence, tumour deposits and/or mesorectal or lateral LNM during follow-up. Distant recurrence referred to any cancer recurrence outside the locoregional area. Non-salvageable recurrence was defined as cancer recurrence without curative treatment options. Examples of salvage recurrence therapies include local re-excision, TME, local ablation therapy, stereotactic radiotherapy or metastasectomy for oligometastatic disease. Three-year

cancer-specific mortality was defined as the percentage of patients who died from rectal cancer or rectal cancer treatment-related complications within three years of EID. Death from metachronous colorectal cancer or other unrelated causes was considered a competing event for all outcomes. Secondary surgery rate was defined as the proportion of patients who underwent either cTME after EID or salvage TME for locoregional cancer recurrence during follow-up.

Patients for whom histopathology was not obtained due to discontinuation of the EID procedure were only included in the description of baseline characteristics and procedural outcomes.

Adverse events

All 30-day procedure-related adverse events resulting in unplanned postprocedural hospitalisation >3 hours, emergency department visit, readmission or intervention were recorded. This included all interventions such as blood transfusions and endoscopic, angiographic or surgical procedures. The severity of adverse events was graded according to the AGREE classification.[26]

Table 1 Patient demographics and lesion characteristics

Characteristic	Total (n=188)
Age, years, mean (SD)	66 (9.9)
Sex, male, n (%)	125 (66.5)
ASA scores I–II, n (%)	159 (84.6)
Estimated diameter of lesion*, mm, median (p25–p75)	25 (20–30)
Lesion location*, n (%)	
Distal rectum (0–5 cm from anal verge)	107 (56.9)
Mid-rectum (6–10 cm from anal verge)	40 (21.3)
Proximal rectum (>10 cm from anal verge)	41 (21.8)
Distance from anal verge*, cm, median (p25–p75)	5 (2–10)
Granularity, n (%)	
Non-granular	150 (80.6)
Granular	28 (15.1)
Mixed granular	7 (3.8)
Missing	2
Depression present, n (%)	170 (90.4)
Easy friability present, n (%)	128 (68.1)
Hiroshima classification, n (%)	
C1	20 (12.4)
C2	72 (44.7)
C3	69 (42.9)
Missing	27
Kudo's pit pattern, n (%)	
IV	6 (3.3)
V (not further specified)	1 (0.6)
Vi	63 (34.6)
Vn	112 (61.5)
Missing	6
Preoperative MRI, n (%)	
cTx	8 (4.7)
cT1	11 (6.4)
cT1-2	110 (64.0)
cT2	36 (20.9)
cT3a/b	7 (4.1)
Missing	16

*As measured during endoscopy.
ASA, American Society of Anesthesiologists.

Follow-up

Final histopathology and post-EID management were reviewed by the multidisciplinary tumour board at the performing centre. Treatment decisions followed a shared decision-making process with the patient. Endoscopic surveillance was advised for non-invasive or S-SMIC without histological risk factors, including colonoscopy at one and years post-EID.[25] Active surveillance was recommended for low-risk patients with D-SMIC and also initiated in intermediate or high-risk D-SMIC and ≥pT2 cases who declined adjuvant treatment. This included endoscopic scar surveillance, imaging and carcinoembryonic antigen (CEA) monitoring over five years per Dutch colorectal cancer guideline (see online supplemental table 1).[25] Additional cross-sectional imaging was performed when clinically indicated, such as with elevated CEA. For patients undergoing cTME, follow-up was based on nodal status per guideline.[25] Additionally, patients with pT1 rectal cancer and one or more risk factors, or pT2 without risk factors, were offered participation in the TESAR trial (NCT02371304), comparing adjuvant CRT with cTME.[27]

Statistics

Study data were collected by two members of the study team (LvdS and SCA) at the two participating study centres and entered into an electronic data capture system (Castor EDC). Descriptive statistics were presented as mean with SD for normally distributed data, median with IQR or p25–p75 for non-normally distributed data or as numbers with percentages. We used the Aalen-Johansen estimator to estimate the cumulative incidence of three-year locoregional recurrence rate, distant recurrence rate, non-salvageable recurrence rate, cancer-specific mortality rate and secondary rectal surgery rate. We chose the Aalen-Johansen estimator instead of the Kaplan-Meier method because the latter may overestimate the cumulative incidence of the outcome of interest in the presence of competing events (eg, if a person dies of a cause unrelated to rectal cancer before experiencing a cancer recurrence, this is considered a competing event). The 95% CIs for all outcomes were obtained using the 'survfit' function within the 'Survival' package in R using the log-log method. Analyses were performed using SPSS V.28.0.1.1 and R statistical software V.4.4.0.

RESULTS

Procedural outcomes

A total of 188 patients underwent EID for suspected rectal D-SMIC between January 2019 and March 2023 at two Dutch academic centres. Detailed patient demographics and lesion characteristics are provided in table 1.

Technical success and R0 resection

Complete macroscopic *en bloc* resection was achieved in 177/188 patients (94.1%). In the remaining 11 patients, the EID procedure was discontinued due to more advanced tumour invasion than initially anticipated. These patients were referred for TME and/or neoadjuvant CRT. The overall R0 resection rate for the completed EID procedures was 82.5% (146/177) or 77.6% (146/188) for the entire group. Only one patient had an indeterminate (Rx) resection margin. Of all R0 resected malignant tumours, 39.7% (50/126) had a free resection margin between 0.1 and 1 mm, while the remaining had a free margin of >1 mm. For specifically pT1 cancers and the D-SMIC subgroup, the R0 resection rates were 92.2% (95/103) and 91.5% (86/94), respectively. Further details are presented in table 2.

Table 2 Procedural and histopathological outcomes of endoscopic intermuscular dissection

	Overall	Non-invasive and S-SMIC	D-SMIC	T2 or more
Technical success*, n (%)	177/188 (94.1)	29/29 (100)	94/98 (95.9)	54/59 (91.5)
Adverse events*†, n (%)				
Overall	35/188 (18.6)	3/29 (10.3)	19/98 (19.4)	13/59 (22.0)
Grades I–II	30/188 (16.0)	3/29 (10.3)	16/98 (16.3)	11/59 (18.6)
Grades IIIa/b–IV	4/188 (2.1)	0/29 (0)	3/98 (3.1)	1/59 (1.7)
Grade V	1/188 (0.5)	0/29 (0)	0/98 (0)	1/59 (1.7)
R0 resection, n (%)	146/177 (82.5)	29/29 (100)	86/94 (91.5)	31/54 (57.4)
Histological risk factors, n (%)				
No risk factors	63/177 (35.6)	28/29 (96.6)	35/94 (37.2)	7/54 (13.0)
Lymphovascular invasion	81/177 (45.8)	1/29 (3.4)	46/94 (48.9)	34/54 (63.0)
High-grade tumour budding	60/177 (33.9)	0/29 (0)	31/94 (33.0)	29/54 (53.7)
High-grade differentiation	17/177 (9.6)	0/29 (0)	9/94 (9.6)	8/54 (14.8)

*Two patients were excluded from subgroup analysis due to unknown depth of invasion after neoadjuvant chemoradiotherapy prior to surgery.
†According to the AGREE classification.
D-SMIC, deep submucosal invasive cancer; R0, tumour free; S-SMIC, superficial submucosal invasive cancer.

Adverse events

Adverse events occurred in 35 of 188 EID procedures (18.6%), with four cases (2.1%) classified as grade IIIa per AGREE classification. These included two patients requiring endoscopic dilatation for rectal stenosis after resection of an 80% circumferential lesion, one with delayed bleeding on day six after restarting anticoagulants who underwent diagnostic endoscopy without intervention, and one readmitted for opioid pain management. MRI revealed the presence of pneumorectum which was managed conservatively. One patient (0.5%) with an autoimmune disease on high-dose corticosteroids developed gram-negative sepsis and died (grade V), without evidence of abscess formation or perforation. The remaining 30 events (16.0%) were grades I–II.

Risk stratification

Histopathology identified adenocarcinoma in 157/177 (88.7%) of the EID specimens, while 20 (11.3%) had non-invasive histology. Of the adenocarcinomas, 103 (65.6%) were pT1 and 54 (34.4%) were ≥pT2. Within the pT1 group, nine of 103 (8.7%) were S-SMIC and 94 (91.3%) were D-SMIC. Of the 94 D-SMIC cases, 35 (37.2%) were classified as low risk, 32 (34.0%) as intermediate risk and 27 (28.7%) as high risk. An overview of histopathological findings and risk stratification is shown in table 2.

Treatment strategy after EID

Of the 177 patients, 70 (39.5%) received adjuvant treatment as advised by the multidisciplinary tumour board and through shared decision-making; the remaining 107 (60.5%) patients opted for surveillance only. A detailed overview of treatment strategies after EID, including histopathological outcomes of cTME for D-SMIC, is provided in table 3 and online supplemental figure 1.

Three-year oncological outcomes

Detailed data on all cancer recurrences within three years of EID for the cohort of 177 patients with en bloc resected tumours are presented in online supplemental table 2. In the following section, outcomes are described according to histological risk profile and depth of infiltration.

Non-invasive histology and S-SMIC (T1 sm1)

Histological assessment after EID identified non-invasive histology in 20 (11.3%) patients and S-SMIC in nine (5.1%), all managed with surveillance. No cancer recurrences were observed during a median follow-up of 12 months (IQR 21), resulting in a three-year locoregional, distant and non-salvageable recurrence rate of 0% (95% CI 0.0% to 0.0%). The three-year cancer-specific mortality and secondary surgery rates were both 0% (95% CI 0.0% to 0.0%).

Table 3 Treatment strategy after completed endoscopic intermuscular dissection

Treatment strategy	Total cohort	D-SMIC low risk	D-SMIC intermediate risk	D-SMIC high risk
Adjuvant treatment, n/N (%)	70/177 (39.5)	0/35 (0)	10/32 (31.3)	21/27 (77.8)
Completion TME, n/N (%)	53/177 (29.9)	0/35 (0)	7/32 (21.9)	15/27 (55.6)
Residual cancer*	21/53 (39.6)	–	2/7 (28.6)	8/15 (53.3)
Chemoradiotherapy, n/N (%)	16/177 (9.0)	0/35 (0)	2/32 (6.3)	6/27 (22.2)
Completion TAMIS, n/N (%)	1/177 (0.6)	0/35 (0)	1/32 (3.1)	0/27 (0)
Residual cancer*	0/1 (0)	–	0/1 (0)	–
Surveillance only, n/N (%)	107/177 (60.5)	35/35 (100)	23/32† (71.9)	6/27 (22.2)

*Residual cancer defined as presence of tumour deposits and intramural and/or nodal adenocarcinoma.
†One patient who underwent completion TAMIS with no residual cancer was additionally assigned to the surveillance group.
D-SMIC, deep submucosal invasive cancer; TAMIS, transanal minimally invasive surgery; TME, total mesorectal excision.

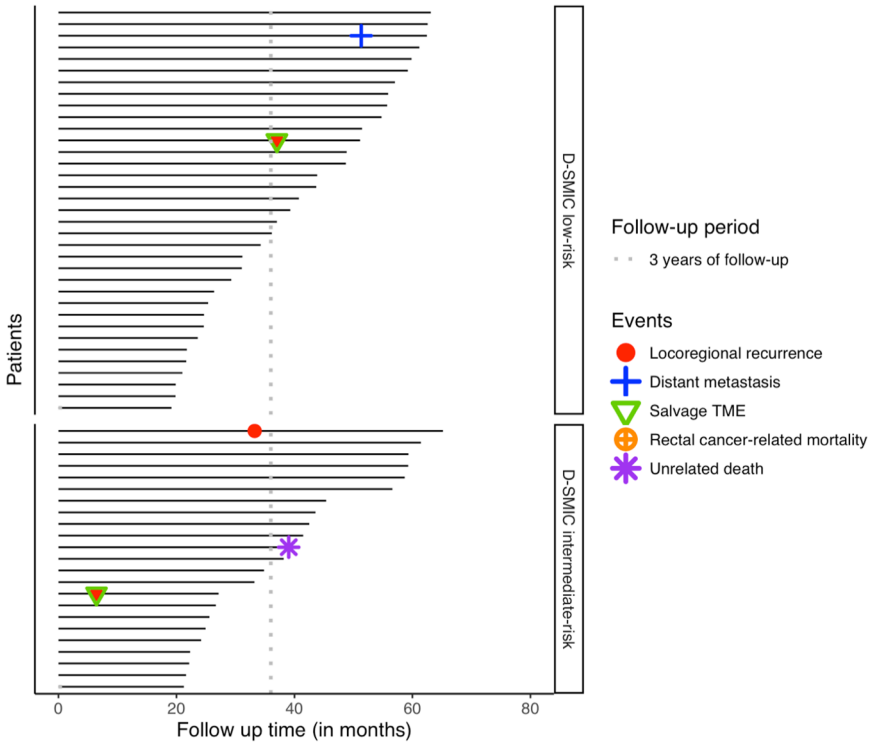

Figure 1 Event plot of 58 patients with rectal D-SMIC who opted for active surveillance after EID, stratified according to the presence of a histological risk factor. Time 0 was set at the time of EID. The vertical dotted line represents the three-year follow-up moment. The single distant metastasis was not included in the description of the three-year outcomes, as this metastasis developed after 51 months (solitary lung metastasis for which salvage radiotherapy was given). D-SMIC, deep submucosal invasive cancer; EID, endoscopic intermuscular dissection; TME, total mesorectal excision.

Low-risk D-SMIC (T1 sm2/3 without histological risk factors)

All 35 patients with low-risk D-SMIC underwent active surveillance after EID, with a median follow-up of 31 months (IQR 29). One locoregional recurrence was detected on MRI at 37 months, resulting in a three-year locoregional recurrence rate of 7.1% (95% CI 0.5% to 27.5%) (figure 1). This recurrence was successfully treated with salvage abdominoperineal resection, which revealed two LNMs and one tumour deposit. No distant metastases were observed within three years, resulting in a three-year distant and non-salvageable recurrence rate of 0.0% (95% CI 0.0% to 0.0%) for both outcomes. In addition, the three-year cancer-specific mortality rate was 0% (95% CI 0.0% to 0.0%), and the three-year secondary surgery rate was 5.3% (95% CI 0.8% to 35.0%).

Intermediate-risk D-SMIC (T1 sm2/3 with one histological risk factor)

Of the 32 patients with intermediate-risk D-SMIC, seven (21.9%) underwent cTME, with residual cancer detected in two (28.6%). Two (6.3%) patients received adjuvant CRT, while 23 (71.9%) opted for active surveillance, including one who required additional scar resection via transanal minimally invasive surgery (TAMIS) for an R1 vertical margin without other risk factors. Histological evaluation of the resected scar

Table 4 Three-year oncological outcomes of patients who underwent EID for histologically confirmed rectal D-SMIC

	Locoregional recurrence rate % (95% CI)	Distant recurrence rate % (95% CI)	Non-salvageable recurrence rate % (95% CI)	Cancer-specific mortality % (95% CI)	Secondary surgery rate % (95% CI)
D-SMIC low risk* (n=35)					
Total (n=35)	7.1 (0.5 to 27.5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	5.3 (0.8 to 35)
Active surveillance only (n=35)	7.1 (0.5 to 27.5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	5.3 (0.8 to 35)
D-SMIC intermediate risk* (n=32)					
Total (n=32)	9.2 (1.4 to 26.4)	3.1 (0.2 to 13.7)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	25.0 (11.8 to 40.7)
Active surveillance only (n=23)	13.0 (1.8 to 35.4)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	4.4 (0.3 to 18.2)
D-SMIC high risk* (n=27)					
Total (n=27)	8.2 (1.4 to 22.9)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	59.6 (38.8 to 75.3)
Active surveillance only (n=6)	33.3 (4.6 to 67.8)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	20.0 (0.8 to 58.1)

*Low risk denotes no additional histological risk factor other than deep submucosal invasion; intermediate risk denotes having one additional histological risk factor other than deep submucosal invasion; high risk denotes having two or more additional histological risk factors other than deep submucosal invasion.
D-SMIC, deep submucosal invasive cancer; EID, endoscopic intermuscular dissection.

confirmed the absence of residual adenocarcinoma. The oncological outcomes and secondary surgery rate of all 32 patients are presented in table 4.

In the 23 patients who received no additional treatment, median follow-up was 30 months (IQR 22). Two locoregional recurrences occurred within three years, resulting in a three-year locoregional recurrence rate of 13.0% (95% CI 1.8% to 35.4%) (figure 1). One patient had an intramural recurrence at six months and was successfully treated with salvage TME (pT2N0). The other patient had a solitary LNM on MRI at 33 months and was treated with stereotactic radiotherapy. Both patients have remained in remission to date. No distant recurrences were observed, resulting in a three-year distant and non-salvageable recurrence rate of 0.0% (95% CI 0.0% to 0.0%). The three-year cancer-specific mortality rate was 0% (95% CI 0.0% to 0.0%), and the three-year secondary surgery rate was 4.4% (95% CI 0.3% to 18.2%).

High-risk D-SMIC (T1 sm2/3 with two or more histological risk factors)

Among the 27 patients with high-risk D-SMIC, 15 (55.6%) underwent cTME, which revealed residual cancer in eight (53.3%) (table 3). Six (22.2%) patients received adjuvant CRT, while the remaining six (22.2%) opted for active surveillance. The median follow-up duration was 36 months (IQR 22). In the overall group, the three-year locoregional recurrence rate was 8.2% (95% CI 1.4% to 22.9%). In the six patients who chose active surveillance, this rate was 33.3% (95% CI 4.6% to 67.8%) due to two intramural recurrences. Both locoregional recurrences were successfully managed with salvage therapy. No distant recurrences were observed within three years, resulting in a 0% cancer-specific mortality rate. The three-year secondary surgery rate was 59.6% (95% CI 38.8% to 75.3%) in the overall group and 20.0% (95% CI 0.8% to 58.1%) in the active surveillance group.

pT2 or beyond

Histological analysis revealed pT2 rectal cancer in 49 patients (27.7%) and pT3 in five patients (2.8%). R0 resection by EID was achieved in 31/54 cases (table 2). Among these 54 patients, 31 (57.4%) underwent cTME, with residual cancer detected in ten (32.3%). Eight patients (14.8%) received adjuvant CRT, whereas the remaining 15 patients (27.8%) opted for active surveillance. The median follow-up duration was 29 months (IQR 17). Among all 54 patients, the three-year locoregional and distant recurrence rates were 7.6% (95% CI 2.4% to 16.6%) and 14.2% (95% CI 6.2% to 25.4%), respectively. Four out of seven recurrences were non-salvageable (8.3% (95% CI 2.6% to 18.3%)), all of which occurred in patients who received additional treatment after EID (cTME or adjuvant CRT) (online supplemental table 2). At three years, cancer-specific mortality was 7.9% (95% CI 3.1% to 20.2%). Two patients died due to cancer recurrence and one death was treatment related. Of the subgroup of 15 patients who chose active surveillance after EID (all pT2 with varying numbers of histological risk factors), the three-year locoregional recurrence rate was 7.2% (95% CI 0.5% to 27.6%), with no distant recurrences observed. Specifically, in the 31 patients with pT2 rectal cancer in whom an R0 resection was achieved, seven had no additional risk factors. Of the four patients with no risk factors who opted for surveillance only after EID, no locoregional or distant recurrences were observed during follow-up.

DISCUSSION

This is the first study to report three-year oncological outcomes following EID for suspected rectal deep submucosal invasive cancers (D-SMIC, defined as sm2–3 invasion), which are currently considered non-curative by local excision alone. Lesions were selected primarily based on endoscopic appearance, with less emphasis on MRI findings (<cT3a was allowed) and typically without preprocedural biopsies. Final histology revealed that just over half of the cases were confirmed as D-SMIC, thereby underlining the limitations of preprocedural staging. In these patients, the three-year outcomes of EID, followed by active surveillance (without secondary surgery), were excellent when no additional histological risk factors were present (7% locoregional recurrence), and still favourable with one risk factor (13% locoregional recurrence), with all recurrences being successfully treated and no cancer-related deaths. Importantly, no distant metastases occurred in either group, suggesting organ-sparing treatment did not compromise systemic control. EID demonstrated a 94.1% technical success rate across all cases and a 91.5% R0 resection rate among confirmed D-SMIC cases, supporting its effectiveness for endoscopic removal of rectal D-SMIC. Adverse events were infrequent. These findings challenge the current paradigm that deep submucosal invasion alone warrants cTME and suggest that such an approach may represent overtreatment. Our data may change the management of a subgroup of early rectal cancers, and several results warrant further commentary and discussion.

Patients with pT1 rectal cancer and one or more histological risk factors are typically classified as 'high-risk'. However, this category is heterogeneous, as reflected by reported locoregional recurrence rates ranging from 13.6% (95% CI 8.0% to 22.0%) to 23.7% (95% CI 13.2% to 38.8%) in studies with at least two years of follow-up.[13 14] A key contributor to this variability is that the current risk stratification system does not consider the cumulative number of histological risk factors—despite evidence that the risk of LNM and locoregional recurrence increases with each additional factor.[15 19] This limitation hinders the ability to make individualised treatment decisions after diagnostic local excision. In our study, patients with low and intermediate-risk D-SMIC showed lower locoregional recurrence rates than previously reported in high-risk pT1 cohorts. These findings highlight the clinical value of incorporating the number of histological risk factors to better identify patients who may benefit from adjuvant treatment, while minimising overtreatment in low-risk individuals.

This study adds to the existing evidence that submucosal invasion beyond sm1 or >1000 µm does not independently increase oncological risk.[10 11 15] Although often considered a high-risk feature, deep submucosal invasion (sm2/3 or >1000 µm) was not associated with increased recurrence in the absence of additional histological risk factors. Recurrence rates in low-risk patients with D-SMIC were comparable to those reported in low-risk S-SMIC cohorts, reinforcing the notion that invasion depth alone does not drive cancer recurrence.[13 28] Even among the small subset of patients with completely resected pT2 cancers and no additional histological risk factors, three-year outcomes remained favourable, consistent with earlier reports.[29–31] Therefore, endoscopic suspicion of deep submucosal invasion should not automatically prompt radical surgery. Rather, treatment decisions should be guided by the presence and number of additional histological risk factors identified after diagnostic local excision.

When comparing locoregional recurrence rates between EID and minimally invasive local surgery, literature shows that a significant portion of locoregional recurrences after surgical

(transmural) local excision of rectal cancer are intramural.[13 14] A recent meta-analysis linked local excision technique to recurrence risk, with improved outcomes for advanced transanal resection methods like transanal endoscopic microsurgery (TEM) or TAMIS compared with older techniques.[14] However, recurrence rates for high-risk pT1 cancer after TEM/TAMIS remain high (29.9%) and exceed those seen after endoscopic resection (12.5%).[14] Even in superficial pT1 cases without risk factors, recurrence rates up to 23.3% have been reported following TEM/TAMIS.[32] These high intramural recurrence rates may result from intraoperative seeding of tumour cells into perirectal fat during full-thickness excision, although this remains entirely speculative.[33–36] Intermuscular dissection preserves rectal wall integrity, potentially reducing this risk. In our study, no intramural recurrences were seen in low-risk rectal D-SMIC or S-SMIC groups, and only one occurred in the intermediate-risk group after an Rx resection. Comparative studies are needed to assess whether EID reduces intramural recurrence risk compared with full-thickness excision.

While both cTME and adjuvant CRT reduce locoregional recurrence in high-risk rectal cancer, neither significantly lowers the risk of distant metastasis—the main cause of cancer-related mortality.[13 37 38] Reported distant recurrence rates range from 2.8% to 11.3%, reflecting the heterogeneity within the high-risk T1 group.[13 14 32 39] In our study, no distant metastases occurred in the low or intermediate-risk D-SMIC groups over three years, and all (n=3) locoregional recurrences were successfully salvaged. These results suggest that active surveillance after EID for D-SMIC with up to one risk factor may offer a safe alternative to radical surgery in most cases. However, further data are needed to clarify the role of adjuvant CRT in high-risk D-SMIC, particularly regarding long-term functional outcomes and quality of life.

An alternative organ-preserving strategy for rectal cancer is neoadjuvant CRT, followed by watchful waiting.[40] However, complete response rates remain variable (40–60%), and non-responders still require surgery, increasing the risk of treatment-related morbidity.[41–43] Neoadjuvant therapy may also lead to overtreatment in patients who could have been managed with local excision alone, exposing them to unnecessary toxicity. In our study, 16% of lesions were non-invasive or low-risk S-SMIC, and 37% of D-SMIC had no histological risk factors, requiring no further treatment. Unlike neoadjuvant strategies, a local excision-first approach enables histology-driven decisions for further management.

Several limitations should be considered when interpreting our results. First, although this study includes a large EID cohort, the key subgroups of interest—patients with rectal D-SMIC and no or one histological risk factor—remain relatively small, limiting statistical power and multivariable analysis. Nonetheless, this is the first study to report three-year oncological outcomes of EID for rectal D-SMIC, showing locoregional and distant recurrence rates comparable to or lower than those reported in previous literature. Second, we defined an R0 resection as a tumour-free margin of at least 0.1 mm, whereas both the ESGE and the International Collaboration on Cancer Reporting define it as at least 1.0 mm following endoscopic or surgical local excision.[9 44] However, the clinical relevance of this threshold has been questioned. A previous study reported comparable rates of residual intramural cancer for lesions resected with margins of ≥1.0 mm and those with margins as small as 0.1 mm.[45] Our findings are consistent with this; a substantial proportion of lesions in our cohort had resection margins between 0.1 and 1.0 mm, yet there was no associated increase in the risk of intramural recurrence. Third, the three-year follow-up is shorter than the standard five-year surveillance period, potentially underestimating recurrence. However, since most recurrences occur within the first three years, the number of late events is likely limited.[28] Finally, the prediction of invasion depth prior to resection was poor. In our cohort, histological assessment confirmed cancer in 88.7% of lesions that strongly suggested malignancy. However, only 53.1% of lesions were confirmed as deep submucosal invasive, while approximately one-third of lesions were ultimately staged as ≥pT2. These findings confirm previously reported limitations in the accuracy of both endoscopic assessment and MRI for distinguishing D-SMIC from pT2 rectal cancer.[46 47] Although the rate of overtreatment of superficial or non-invasive lesions (16%) may be considered acceptable given the safety of EID and the need for en bloc resection, the rate of undertreatment of ≥pT2 cancers (30%) is more concerning. Despite comparable oncological outcomes being reported for cTME and primary TME,[48 49] full-thickness excision in pT2 cancers may offset the benefits of EID, particularly with regard to preserving the TME plane. Perirectal fibrosis induced by full-thickness local excision, especially in anatomical regions with minimal mesorectal fat, has been associated with higher ostomy rates and incomplete TME specimens.[49 50] Structured MRI assessment may improve selection. An earlier study showed high diagnostic accuracy when ≥1 mm of preserved muscularis propria was used as a criterion for intermuscular dissection on MRI,[51] which was recently reconfirmed in a larger setting.[52] Despite its limitations, this study provides a valuable foundation for a larger prospective trial to confirm the oncological safety of active surveillance after EID in low and intermediate-risk rectal D-SMIC. The effects of EID on cTME quality, patients' quality of life and functional outcomes are still being explored in the ongoing prospective multicentre ICON trial (Dutch Trial Register NL8409).

In conclusion, this is the first study to report -year oncological outcomes of EID in rectal D-SMIC. While further validation is needed, active surveillance appears to be a safe alternative to radical surgery for patients with deep submucosal invasion and no more than one histological risk factor, enabling rectal preservation in most cases.

Author affiliations
[1]Gastroenterology & Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands
[2]Pathology, University Medical Center Utrecht, Utrecht, The Netherlands
[3]Gastroenterology & Hepatology, Amsterdam University Medical Center, Amsterdam, The Netherlands
[4]Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands
[5]Cancer Center Amsterdam, Amsterdam, The Netherlands
[6]Pathology, Amsterdam University Medical Center, Amsterdam, The Netherlands
[7]Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[8]Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[9]Surgery, Amsterdam University Medical Center, Amsterdam, The Netherlands

Contributors LMGM, BAJB, LvdS and SCA conceived and designed the study. LvdS and SCA were responsible for acquisition and analysis of the data. All authors (LvdS, SCA, PD, MML, AFS, MR, MI, JBT, RH, ED, FV, BAJB, LMGM) were involved in interpretation of the analyses. LvdS, SCA, BAJB and LMGM drafted the manuscript. In addition, each author has been involved in critically revising it for important intellectual content. Lastly, all authors have given their final approval of the version to be published. LMGM is the guarantor.

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ORCID iDs
Lisa van der Schee https://orcid.org/0000-0002-1296-4574
Evelien Dekker https://orcid.org/0000-0002-4363-0745
Leon M G Moons https://orcid.org/0000-0002-6913-9954

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