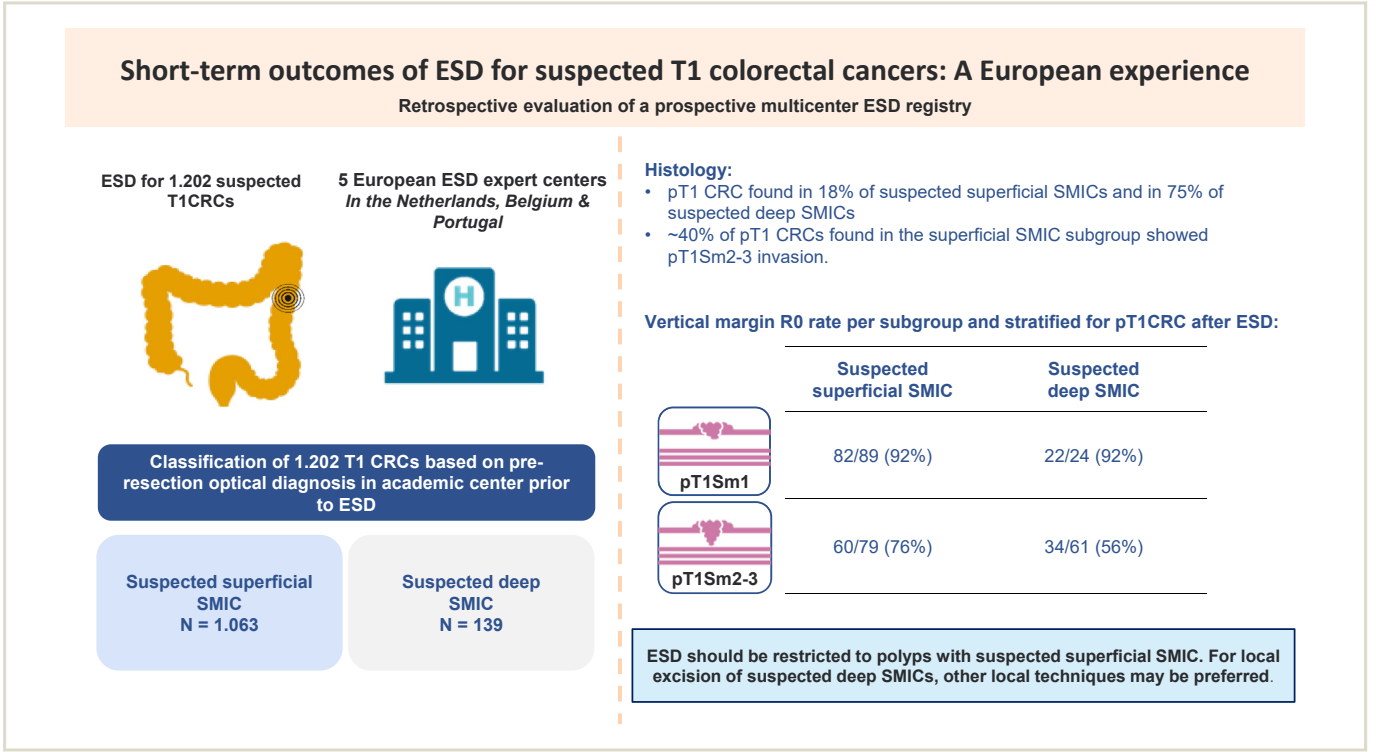
Short-term outcomes of endoscopic submucosal dissection for suspected T1 colorectal cancers: a European experience

Rixta A. H. van Eijck van Heslinga, MD,[1] Paul Didden, MD, PhD,[1] Arjun D. Koch, MD, PhD,[2] Jurjen J. Boonstra, MD, PhD,[3] Arnaud Lemmers, MD, PhD,[4] Mariana Figueiredo Ferreira, MD,[4] Joao Santos-Antunes, MD, PhD,[5] Wilmar de Graaf, MD, PhD,[2] James C. H. Hardwick, MD, PhD,[3] Sjoerd G. Elias, MD, PhD,[6] Miangela M. Lacle, MD, PhD,[7] Leon M. G. Moons, MD, PhD[1]

Utrecht, Rotterdam, Leiden, The Netherlands; Brussels, Belgium; Porto, Portugal

GRAPHICAL ABSTRACT



Background and Aims: The indication for primary surgery on suspected deep submucosal invasive colorectal carcinoma (d-SMIC) is debatable. Consequently, local excision techniques, such as endoscopic submucosal dissection (ESD), are increasingly attempted in such patients. This study retrospectively evaluated the effectiveness of ESD in obtaining a free vertical margin (VM)-R0 in suspected d-SMIC compared with suspected superficial SMIC (s-SMIC).

Current affiliations: Department of Gastroenterology and Hepatology (1), Department of Pathology (7), University Medical Center Utrecht, Utrecht, The Netherlands; Department of Gastroenterology and Hepatology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands (2), Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands (3), Department of Gastroenterology and Hepatopancreatology, Erasme Hospital, Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels, Belgium (4), Department of Gastroenterology, Faculty of Medicine, Centro Hospitalar Universitario Sao Joao, Porto, Portugal (5), Department of Epidemiology, Julius Center for Health Sciences and Primary Care, Utrecht, The Netherlands (6).

Corresponding author: Leon M. G. Moons, MD, PhD, Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Heidelberglaan 100, 3508 GA Utrecht, The Netherlands. E-mail: l.m.g.moons@umcutrecht.nl.

Methods: ESDs for suspected T1 colorectal cancer (CRC) in treatment-naïve polyps were included between 2011 and 2022 in 5 European tertiary referral centers. Based on optical assessment, lesions were categorized into suspected d-SMIC or s-SMIC. Main outcomes were the VM-R0 rate, en bloc resection rate, and adverse event rate. An adjusted risk ratio for VM-R1 resections within the suspected d-SMIC group was calculated.

Results: In the suspected s-SMIC group (n = 1063), en bloc resection rate, VM-R0 rate, proportion of pT1 CRC, and adverse even rate were 90.5% (95% CI, 88-92), 90.6% (95% CI, 88-92), 18.0%, and 3.6% (IQR, 2-5), respectively. In the suspected d-SMIC group (n = 139), these values were 61.9% (IQR, 54-70), 55.4% (IQR, 47-63), 74.8%, and 5.8% (IQR, 2-10), respectively. Compared with suspected s-SMIC cases, the VM-R0 rate of suspected d-SMIC cases particularly decreased for pT1Sm2-3 (75.9% vs 55.7%). None of the investigated features (age, sex, polyp location, size, morphology, and Hiroshima classification) predicted a VM-R1 resection in suspected d-SMIC cases.

Conclusions: ESD performed on polyps with suspected d-SMIC showed lower VM-R0 rates for pT1Sm2-3 cases compared with suspected s-SMIC cases. This should be taken into account when selecting the optimal resection technique for suspected d-SMIC cases. (Gastrointest Endosc 2026;103:147-55.)

In contrast to the American Society for Gastrointestinal Endoscopy and the European Society of Gastrointestinal Endoscopy guidelines, deep submucosal invasion at histology (>1000 mm or Sm2-Sm3 invasion) is no longer considered a strong indication for completion surgery in the Netherlands. When Sm2-3 and/or >1000-mm invasion is the sole risk factor, the risk of lymph node metastasis and distant metastasis is expected to be only 3% to 5% and 1%, respectively.[1,2] It is debatable whether completion surgery with a mortality rate of 1% to 1.7% and persistent risk of distant metastasis will result in an increased 5-year cancer-specific survival.[3-7] Consequently, local excision is increasingly attempted on lesions with optical features of suspected deep submucosal invasive carcinoma (d-SMIC). This might be justified for several reasons. First, despite suspected d-SMIC, a significant subgroup will only contain a superficial invasive cancer or even intramucosal carcinoma because of an overestimation of histology. Second, approximately 40% of d-SMIC cases will only show deep submucosal invasion as the sole histologic risk factor. For this subgroup, active surveillance with salvage surgery once the cancer recurs might be a valid alternative to completion surgery.[8] Third, particularly in the rectum, local excision of radical (R0) resected high-risk T1 rectal cancers can be completed with adjuvant chemoradiotherapy.[9] Organ preservation with local excision therefore starts with an en bloc local excision with free vertical resection margins.

Colorectal endoscopic submucosal dissection (ESD) is often performed for polyps at risk of early colorectal cancer (CRC). However, it is unknown whether ESD is an appropriate technique to remove T1 CRCs with suspected d-SMIC. In most systematic reviews and international guidelines, the reported R0 resection rate of ESD is dominated by the results of ESD on noninvasive polyps.[10] Little is known about the R0 rate of ESD in T1 CRCs specifically. Notably, these results are often derived from cohorts of polyps selected for ESD based on the optical diagnosis of suspected superficial SMIC (s-SMIC).[11-13] It is likely that this subgroup exhibits a different distribution of pT1Sm1 versus pT1Sm2-3 or even pT2 cancers compared with the suspected d-SMIC group. ESD has been associated with lower R0 rates in cases of deep submucosal invasion (>1000 mm or Sm2-Sm3 invasion), ranging from 47% to 64%, mainly because of positive vertical margins (VMs).[14-16] Whether these results can be extrapolated to polyps suspected of d-SMIC is unknown. Therefore, it is important to assess the outcomes of ESD for suspected T1 CRCs and within specific subgroups with varying anticipated depths of submucosal invasion. In this study, we compared the en bloc resection rate, the VM-R0 resection rate, and the adverse event rate of colorectal ESD in cases suspected for s-SMIC and d-SMIC.

METHODS

Patients and study design

This multicenter, retrospective analysis was conducted on a prospective, observational cohort of colorectal ESDs in 3 Dutch tertiary referral centers between 2011 and 2022 and 2 additional European cohorts between 2015 and 2022 from 2 ESD expert centers (Erasme in Belgium and São João in Portugal). Patients were included based on (1) a suspicion of a T1 CRC in a treatment-naïve nonpedunculated lesion (suspicion was based on >20-mm size and location in the rectum or sigmoid, and/or on the presence of optical features predictive of a T1 CRC at optical imaging (enhanced imaging) irrespective of size and location), and if (2) the lesion was deemed suitable for ESD based on the still images before referral, and (3) an attempt for ESD had been made.

Evaluation endoscopies solely to verify suitability for ESD are not routinely performed in the Netherlands. Treatment

decisions are typically made based on still images and, occasionally, videos provided by the referring centers. Optical reassessment of the referred suspected polyps in the expert center is assessed just before ESD. Standard optical assessment consists of evaluation with white-light imaging supported by near focus if available, followed by using an enhanced imaging technique such as narrow-band imaging, blue-light imaging, or flexible spectral imaging color enhancement, depending on the endoscope used. In most cases, enhanced imaging will be supported by near focus if available. Whether near focus was used or not was not registered as a parameter in the prospective ESD registry.

Zoom endoscopes are not available in Europe and were therefore not used. Chromoendoscopy using indigo carmine and crystal violet is not performed in the Netherlands. Pit pattern analysis was performed with narrow-band imaging or blue-light imaging supported with near focus if available. The decision to perform an ESD despite optical features suggestive of deep submucosal invasion was based on various aspects, including the impact of surgery on the patient, polyp location in the colon, size of the most invasive area of the polyp, uncertainty of optical diagnosis, estimation that an R0 resection could potentially be achieved, and absence of alternative local excision techniques available at that time.

Suspected depth of invasion based on optical diagnosis

Based on the preresection optical diagnosis in the referral center, patients were classified into 2 subgroups: suspected s-SMIC or suspected d-SMIC. The suspicion of s-SMIC was based on location (rectum and sigmoid), size, morphology (nongranular, mixed granular), and/or enhanced imaging features (such as an OPTICAL score of 10%-40%,[17] Japan NBI Expert Team type 2B, Kudo Vi, or Hiroshima C1). Suspicion of d-SMIC was based on the presence of enhanced imaging features indicative of deeper invasion (OPTICAL score >40%,[17] Japan NBI Expert Team type 3, Kudo Vn, and/or Hiroshima C2-C3).

Medical ethical approval

The study was approved by the local medical ethics committees of all centers (UMCU [19–228/C], LUMC [G18.097/SH/sh], Erasmus MC [19-0678], Erasme Hospital [P2020/186], and São João [255/2020]) and was carried out in accordance with the Declaration of Helsinki. All patients were informed about the ESD procedure and periprocedural risks by their treating physician, and informed consent for the procedure was obtained. Patients were not involved in the design, conduct, or reporting of this study.

Data collection

In each participating center, study variables were registered in Castor Electronic Data Capture (EDC) system (Castor EDC, Amsterdam, the Netherlands; https://www.castoredc.com). Patient characteristics included sex, age, and physical status according to the American Society of Anesthesiologists classification system. Polyp characteristics included lesion size, location, optical diagnosis, and final histologic outcome. The proximal colon was defined as the cecum and ascending and transverse colon including the splenic flexure. The distal colon was defined as the descending and sigmoid colon. A rectal lesion was defined as a lesion within 15 cm from the anal canal. T1 CRC was classified based on submucosal invasion according to the Kikuchi level (ie, Sm1 or *<1000* μm, Sm2-3 or *≥1000* μ*m),* with Sm2-3 considered as d-SMIC. T1 CRC in which the invasion depth was unable to be determined was described as $T1Sm_x$.

Endpoints and definitions

The main outcome was the radical VM-R0 resection rate of pT1 CRCs, defined as both a CRC and high-grade dysplasia (HGD)-free VM. We restricted our analysis to CRC and HGD, because a positive VM for low-grade dysplasia entails no further treatment consequences for the patient. The VM was the main focus because the importance of a positive horizontal margin after an en bloc ESD seems low, with recurrence rates as low as 2.2%.[18] Secondary outcomes of interest were en bloc resection rate for pT1 CRCs, defined as a 1-piece ESD of the entire lesion as observed endoscopically; R0 resection rate for pT1 CRCs, defined as both a CRC and HGD-free vertical and horizontal resection margin; and procedure-related adverse events (graded according to the AGREE classification).

Statistical analysis

Baseline characteristics were analyzed using standard descriptive statistics. Categorical data are presented as frequencies and percentages and continuous data as mean (SD) or median (IQR) for normally distributed and skewed data, respectively. R0 and en bloc resection rates were calculated for the suspected s-SMIC and d-SMIC groups, expressed in frequencies and percentages with 95% CI using the Wilson procedure.

Risk factors for a VM-R1/Rx resection within suspected d-SMIC cases were identified using univariate and multivariable Poisson regression analysis with robust SEs. Potential risk factors were age (>70 vs ≤70 years), sex (female vs male), polyp location (colon vs rectum), polyp size (≥30 vs <30 mm), morphology (protruded vs flat), and Hiroshima classification (C3 vs C2) and were expressed in risk ratios with 95% CIs. The association of suspected d-SMIC cases and VM-R1/Rx resection, adjusted for the same risk factors, was calculated using multivariable Poisson regression analysis with robust SEs.

A 2-sided $P < .05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA). Data presented conform to the STROBE and ICMJE guidelines for cohort studies.

RESULTS

Baseline characteristics

A total of 1202 consecutive patients from 5 European tertiary referral centers for colorectal ESD were included in the analysis. Based on the optical assessment in the tertiary referral center just before ESD, 1063 patients (88.4%) were classified as suspected s-SMIC, with 658 patients treated in the Netherlands, 174 in Belgium, and 231 in Portugal. The remaining 139 patients (11.6%) were classified as suspected d-SMIC, all of whom were treated in the Netherlands. Examples of suspected s-SMIC and d-SMIC cases are shown in Figure 1.

Patient and polyp characteristics of both subgroups are provided in Table 1. The median lesion size was 30 mm (IQR, 25-50) in the suspected s-SMIC group and 25 mm (IQR, 20-31 mm) in the suspected d-SMIC group. Suspected s-SMIC cases were more often located in the rectum (63.9% vs 40.3%). Histology revealed that the proportion of cancers, pT1sm2-3, and pT2 CRC increased from 20.0% (209/1047), 7.5% (79/1047), and 2.0% (21/1047) in the suspected s-SMIC group to 90.8% (119/131), 46.6% (61/131), and 16.0% (21/131) in the suspected d-SMIC group. Within the suspected s-SMIC group, the prevalence of cancers was comparable across the contributing countries, with 23.1% in the Netherlands, 19.5% in Belgium, and 11.1% in Portugal. In 16 s-SMIC cases and 8 d-SMIC cases, histology was not obtained because of technical failure of ESD, and the final histology after surgery was unknown.

En bloc resection

In the suspected s-SMIC group, en bloc resection was achieved in 962 of 1063 patients (90.5%; 95% CI, 88-92). In the suspected d-SMIC group, the en bloc resection rate decreased to 86 of 139 patients (61.9%; 95% CI, 54-70). Among the suspected d-SMIC cases where an en bloc resection was not achieved, 26 of 53 (65%) were converted into piecemeal EMR or hybrid ESD or were accepted as macroscopic incomplete ESD, and 27 of 53 (35%) were aborted. En bloc resection rates for the 2 subgroups according to histologic invasion depth are shown in Table 2. In both subgroups, a decrease in the en bloc resection rate was seen in tumors with increasing depth in the wall of the colorectum. The en bloc resection rate for pT1Sm2-3 cases was lower in the suspected d-SMIC group compared with the suspected s-SMIC group (72.1% vs 86.1%).

VM-R0 resection

In the suspected s-SMIC group, a VM-R0 resection was achieved in 963 of 1063 patients (90.6%; 95% CI, 88-92). In comparison, in the suspected d-SMIC group, a VM-R0 resection was achieved in 77 of 139 patients (55.4%; 95% CI, 47-63). VM-R0 rates for both groups stratified for histologic invasion depth are shown in Table 2. The VM-R0 rate for pT1CRCs was substantially lower within the suspected d-SMIC subgroup compared with the suspected s-SMIC group (61.2% vs 79.3%), and this difference was particularly pronounced in pT1sm2-3 cases (55.7% vs 75.9%).

Multivariable regression analysis showed that suspected d-SMIC was significantly associated with a VM-R1/Rx resection after adjusting for age, sex, polyp location, size, morphology, and Hiroshima classification (adjusted risk ratio, 4.18; 95% CI, 2.81-6.22; $P < .001$) (data not shown). Multivariable regression analysis also showed that within suspected d-SMIC cases, none of the investigated variables were independently associated with a VM-R1/Rx (Table 3).

Adverse events

Procedure-related adverse events occurred in 3.6% of patients (38/1036; IQR, 2-5) in the suspected s-SMIC group and 5.8% of patients (8/139; IQR, 2-10) in the suspected d-SMIC group. Perforation occurred in 15 ESD procedures (1.5%), including 8 intraprocedural and 7 postprocedural perforations, and was similar for suspected d-SMIC versus suspected s-SMIC cases (2.1% vs 1.1%, respectively). Eight of 15 perforations required emergency surgery, whereas 7 were managed conservatively with antibiotics and/or observation or repeated colonoscopy with endoscopic clips. Postprocedural bleeding occurred in 30 ESDs (2.5%) and was not higher for lesions suspected for d-SMIC when compared with lesions suspected for s-SMIC (2.8% vs 2.5%, respectively). In none of these patients surgical intervention was required.

DISCUSSION

In this well-sized, multicenter, observational cohort study, en bloc resection and VM-R0 rates of ESD for the treatment of pT1 CRCs were very acceptable for pT1 CRCs within the group of suspected s-SMIC, even for pT1Sm2-3 CRCs. However, when expanding the indication for ESD to lesions suspected for d-SMIC, resections more often failed, and the VM-R0 rate for pT1Sm2-Sm3 cases was lower (76% vs 56%) within the suspected d-SMIC subgroup compared with the suspected s-SMIC group.

In accordance with current practice in the Netherlands, where deep submucosal invasion as the sole risk factor is not considered an indication for completion surgery, ESD has been performed in suspected d-SMICs. This approach is not in line with international guidelines, which advise against local excision and advocate for primary surgical resection. This cohort shows the results of this attempt to be organ preserving within d-SMIC cases.

Our cohort of suspected s-SMIC cases demonstrates results consistent with those of large ESD cohorts.[18,19] The overall en bloc and R0 resection rates in a prospective Japanese cohort were slightly higher than in our cohort (97% vs 90%, respectively).[19] However, the prevalence of cancer

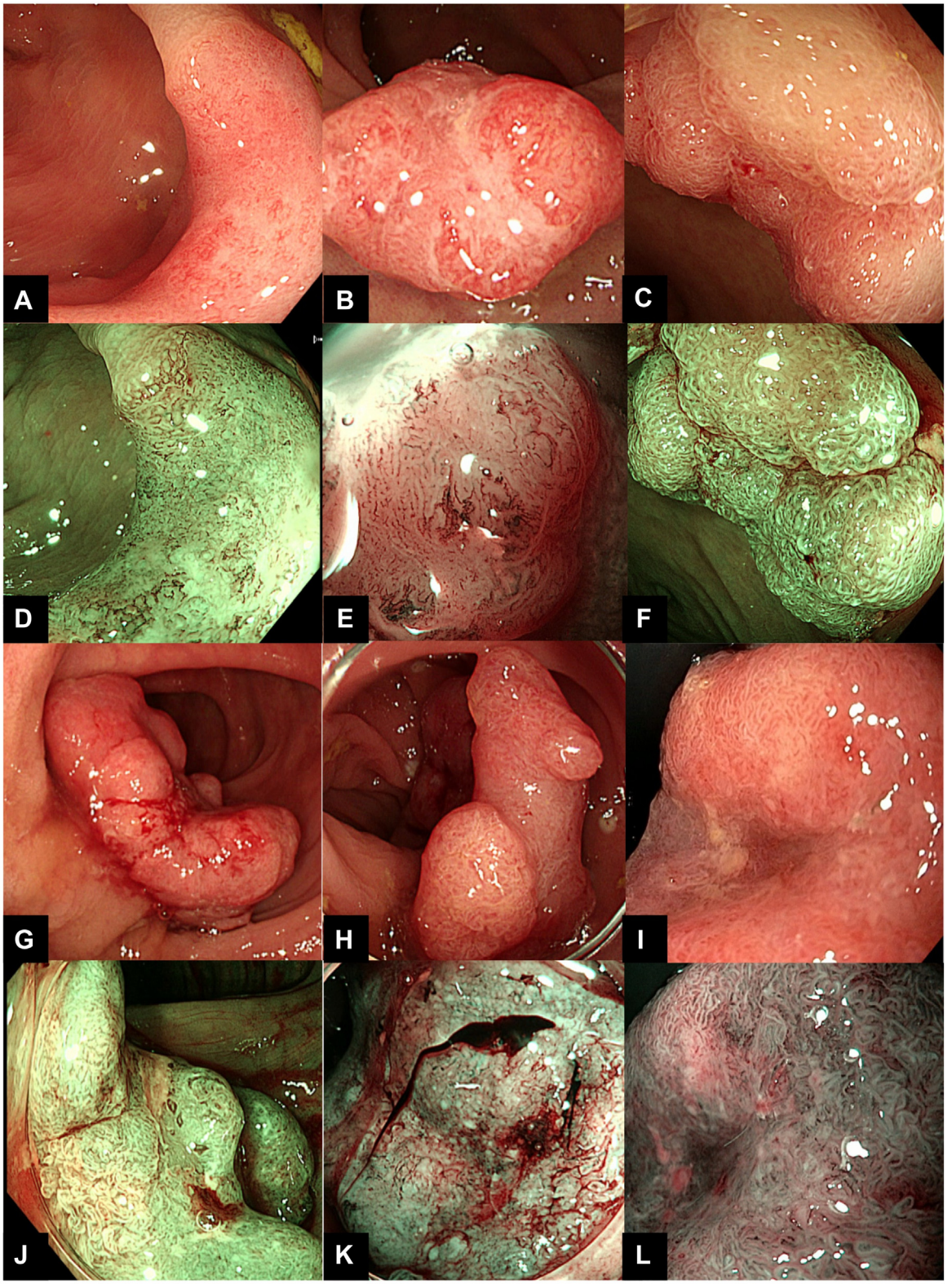


Figure 1. Overview of representative images of the different subgroups containing both a white-light image and narrow-band image (near focus) of the most suspected area. **A** and **D,** A 30-mm nongranular Paris IIa polyp with a slightly disturbed vascular pattern (Hiroshima C1/Japan NBI Expert Team [JNET] type 2B) in the center. Histology showed a pT1Sm1 lymphovascular invasion (LVI) negative, Bd1, G1/2 transverse colon cancer. **B** and **E,** A 15-mm Paris Is, nongranular midrectal polyp with disturbed vascular pattern (Hiroshima C2/JNET type 3). Histology showed an R0 resection of a tubular adenoma with high-grade dysplasia. **C** and **F,** A 20-mm nongranular, Paris 0-IIa+IIc, Hiroshima C1/JNET type 2B polyp with central Kato IV nonlifting in the transverse colon. Histology showed an R1 resection of a pT1Sm2-3 LVI negative, Bdx, G1/2 differentiated cancer. **G** and **J,** Histology showed a sessile

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TABLE 1. Baseline characteristics and histological outcomes of patients treated with colorectal endoscopic submucosal dissection for suspected s-SMIC and suspected d-SMIC based on optical diagnosis

	Suspected s-SMIC				Suspected d-SMIC
	Overall (n = 1063)	Netherlands (n = 658)	Belgium (n = 174)	Portugal (n = 231)	Netherlands (n = 139)
Sex, male	605 (56.9)	383 (58.2)	95 (54.6)	127 (56.0)	88 (63.6)
Mean age, y (SD)	67 (10.7)	69 (10.3)	66 (10.8)	65 (11.0)	66 (9.7)
Median polyp size, mm (IQR)	30 (25-50)	30 (25-50)	35 (25-40)	40 (30-50)	25 (20-31)
Polyp location					
Proximal colon	164 (15.4)	139 (21.1)	14 (8.0)	11 (4.8)	24 (17.3)
Distal colon	220 (20.7)	157 (23.9)	23 (13.2)	40 (17.3)	59 (42.4)
Rectum	679 (63.9)	362 (55.0)	137 (78.7)	180 (77.9)	56 (40.3)
Histology					
Adenoma with low-grade dysplasia	367 (35.1)	241 (37.2)	54 (31.0)	72 (32.0)	—
Adenoma with high-grade dysplasia	471 (45.0)	257 (39.7)	86 (49.4)	128 (56.9)	12 (9.2)
T1 colorectal cancer	188 (18.0)	135 (20.8)	28 (16.1)	25 (11.1)	98 (74.8)
Sm1	89 (8.5)	58 (9.0)	11 (6.3)	20 (8.9)	24 (18.3)
Sm2-3	79 (7.5)	60 (9.3)	14 (8.0)	5 (2.2)	61 (46.6)
Sm_x	20 (1.9)	17 (2.6)	3 (1.7)	0 (0)	13 (9.9)
≥T2 colorectal cancer	21 (2.0)	15 (2.3)	6 (3.4)	0 (0)	21 (16.0)
Unknown*	16	10	0	6	8

Values are n (%) unless otherwise defined.
d-SMIC, deep submucosal invasive cancer; *s-SMIC*, superficial submucosal invasive cancer; –, indicates that the variable was not present.
*In these cases, histology was not obtained because of technical failure of endoscopic submucosal dissection.

TABLE 2. Outcomes of colorectal endoscopic submucosal dissection for suspected s-SMIC and suspected d-SMIC stratified for the histological outcome after colorectal endoscopic submucosal dissection

		Overall*	High-grade dysplasia	pT1Sm1	pT1Sm2-3	pT1Smx	≥pT2
Suspected s-SMIC	En bloc resection	962/1063 (90.5)	439/471 (93.2)	83/89 (93.3)	68/79 (86.1)	12/20 (60.0)	10/21 (47.6)
	R0 resection	879/1063 (82.7)	370/471 (78.6)	75/89 (84.3)	57/79 (72.2)	6/20 (30.0)	4/21 (19.0)
	Vertical margin-R0 resection	963/1063 (90.6)	441/471 (93.6)	82/89 (92.1)	60/79 (75.9)	7/20 (35.0)	6/21 (28.6)
Suspected d-SMIC	En bloc resection	86/139 (61.9)	12/12 (100)	22/24 (91.7)	44/61 (72.1)	5/13 (38.5)	3/21 (14.3)
	R0 resection	73/139 (52.5)	11/12 (91.7)	21/24 (87.5)	33/61 (54.1)	4/13 (30.8)	4/21 (19.0)
	Vertical margin-R0 resection	77/139 (55.4)	11/12 (91.7)	22/24 (91.7)	34/61 (55.7)	4/13 (30.8)	6/21 (28.6)

Values are n/N (%).
d-SMIC, deep submucosal invasive cancer; *s-SMIC*, superficial submucosal invasive cancer.
*Including cases with low-grade dysplasia.

in the Japanese cohort was only 15%, compared with 30% in the present cohort. When comparing the outcomes of the Japanese cohort specifically to the subgroup of pT1Sm1 and HGD cases, the difference was minimal, and the difference in the overall VM-R0 rate between both cohorts can mainly be attributed to the higher number of pT1Sm2-3 and T2 cases in our cohort. Similar findings were observed when comparing the German prospective cohort of colorectal ESDs with our cohort,[19] confirming that the quality of ESD aligns with those recently published by other expert centers. This also concerns the risk of adverse events, which were in an acceptable range.

Expanding the use of ESD for the local excision of suspected d-SMIC cases, however, was associated with substantial lower en bloc and VM-R0 resection rates, particularly in pT1Sm2-3 cases. One could argue that a diagnostic excision as a final staging procedure is acceptable. A local excision has been shown not to influence oncologic outcomes[20] and was

polyp (Paris Is), nongranular surface morphology, protrusions, demarcated depression with vascular disturbance (Hiroshima C2/JNET type 3). Histology showed an R0 resection of a pT1Sm2-3 LVI negative, Bd1, G1/2 differentiated rectosigmoid cancer. **H** and **K,** a 20 × 20-mm Paris 0-Is+IIa+IIc, Hiroshima C3/JNET type 3, lesion in the sigmoid. Histology showed an R0 resection of a pT1Sm2-3, LVI positive, Bd1, G1/2 differentiated sigmoid cancer. **I** and **L,** A sessile (Paris Is), nongranular polyp with clear central depression. The center shows a more severely disturbed vascular pattern (Hiroshima C2/JNET type 3). Histology showed an R1 resection of a pT1Sm2-3, LVI positive, Bd3, G1/2 differentiated sigmoid cancer.

TABLE 3. Univariate and multivariate analysis of risk factors associated with an R1/Rx vertical resection margin among 139 cases with deep submucosal invasive cancer

	R1/Rx vertical margins (%)	Univariate analysis risk ratio (95% CI)	*P* value	Multivariate analysis risk ratio (95% CI)	*P* value
Age					
≤70 y	41.4	Reference		Reference	
>70 y	50	1.21 (0.7-2.0)	.31	0.98 (0.5-1.9)	.96
Sex					
Male	47.7	Reference		Reference	
Female	39.2	1.21 (0.7-2.1)	.47	1.46 (0.7-2.9)	.29
Polyp location					
Rectum	39.3	Reference		Reference	
Colon	48.2	1.23 (0.7-2.1)	.44	1.33 (0.6-2.7)	.43
Polyp size					
<30 mm	35.9	Reference		Reference	
≥30 mm	55.7	1.5 (0.9-2.6)	.08	1.62 (0.8-3.1)	.14
Gross morphology					
Flat	41.3	Reference		Reference	
Protruded	45.2	1.0 (0.5-1.9)	.91	1.3 (0.6-2.8)	.96
Hiroshima classification					
C2	40.5	Reference		Reference	
C3	41.9	1.1 (0.6-1.9)	.91	0.97 (0.4-2.1)	.94

not associated with a higher percentage of emergency surgery or post-ESD bleeding in the current cohort. Furthermore, a significant proportion of 28% within the suspected d-SMIC subgroup only showed HGD or pT1Sm1 CRC. This could perhaps even increase to 43% if only cases with a small focus (<15 mm) of deep submucosal invasion would be selected for ESD.[21] Even trying to resect a selected group of suspected d-SMIC may be justified to prevent surgery on HGD and pT1Sm1 CRCs without risk factors.[22] On the other hand, an R1/Rx resection interferes with optimal risk stratification as it interferes with optimal evaluation of the invasive front and is associated with an increased risk of local recurrence.

More recently, endoscopic intermuscular dissection (EID) was introduced as an alternative for ESD for suspected d-SMIC in the rectum, showing a much higher VM-R0 rate for pT1Sm2-3 cases of 94%.[23] Similar results have been presented for full-thickness resection techniques in the colon, such as endoscopic full-thickness resection or colonoscopy-assisted laparoscopic wedge resection.[24-26] Although a formal direct comparison between these techniques and ESD has not been performed, our findings raise concerns whether ESD is the most appropriate technique as a first-line treatment of suspected d-SMICs given the availability of other techniques such as EID or endoscopic full-thickness resection.

This study also has some important limitations that should be addressed. First, the database included only cases in which an attempt of ESD had been made, which may have introduced selection bias within the d-SMIC cases, which were selected for an attempt with ESD. Although this provides a good overview, it is unclear how many cases were discussed or presented by referral centers and were disapproved for ESD based on the photos or videos. Furthermore, the decision to refer a lesion for a local excision with ESD is often performed in the referring hospital. This may have caused a selection bias toward cases with a more favorable appearance and therefore a higher chance of achieving an VM-R0 rate. This is supported by the finding that the proportion of pT2 cancer was shown to be lower than reported for EID cases (16% vs 25%). Cancers with a more invasive aspect may have been sent for surgery directly. It might therefore be that performing ESD on all cases with suspected d-SMIC cases may result in a lower en bloc resection rate and VM-R0 resection rate than reported in this study. The observed 55% VM-R0 rate for pT1Sm2-3 cases may therefore even be an overestimation.

Second, different types of endoscopes and classification techniques were used during the study to determine optical diagnosis. Although the standard assessment with white-light imaging, enhanced imaging with narrow-band imaging, blue-light imaging or flexible spectral-imaging color enhancement, and near focus, if available, would most likely have been used. The individual optical parameters, but not the use of zoom of near focus, were a parameter

in the prospective ESD registry. The value of the individual parameters or the use of near focus cannot be evaluated from this study. This approach, however, reflects the current standard of care in Western Europe facilities, because chromoendoscopy with zoom endoscopes are unavailable. The current distribution of noninvasive, superficial invasive, and deep invasive lesions within the selection of suspected d-SMICs is comparable with other cohorts, and most indeed concerned deep T1 or T2 cancers. We therefore believe that the use of near-focus or zoom endoscopes will not change the conclusion of this study that ESD is less sufficient to remove suspected deep submucosal invasive T1 CRCs. In recent publications, the proportion of T1b within the T1 CRCs removed by endoscopy within the selection of superficial invasive CRCs remained approximately 50%. Although the R0 rate was higher, it might still be considered suboptimal when potential candidates for organ preservation are missed.

Third, we did not distinguish pT1Sm2 and pT1Sm3 cases. Given the absence of the muscularis propria in the resection specimen, stratifying the cancers into Sm2 and Sm3 based on the measured depth of submucosal invasion was not reliable. The depth of submucosal invasion was determined differently among pathology centers. Some pathologists used the Ueno criteria, which measures invasion depth from the surface to the deepest point of invasion in absence of an identifiable muscularis mucosa. Some pathologists use the anticipated line of the muscularis mucosa to the deepest point of invasion to estimate the depth of invasion. Because the method of determining the depth of invasion was not mentioned in the pathology report, it was not possible to correct for this methodologic difference. The depth of invasion may also be influenced by gross morphology of the polyp, with bulky lesions having larger tumor bulks. It is likely, however, that the proportion of Sm2 and Sm3 within the pT1Sm2-3 subgroups differs between the suspected d-SMIC and suspected s-SMIC, reflected by the difference in VM-R0 rate.

Fourth, we excluded 139 cases for the optical reassessment because of missing data on the optical diagnosis. The excluded subgroup contained a large group of aborted ESDs. This may have caused a bias toward a higher en bloc resection and VM-R0 rates within the remaining subgroups. Because most failed cases showed deep submucosal or muscular invasion, this especially concerns the suspected d-SMIC subgroup. Because of the high proportion of missing cases, we did not correct for missing data with imputation.

In conclusion, ESD is a successful technique for removing pT1 CRCs, with an R0 resection achieved in a well-selected group of polyps. ESD should be restricted to polyps with suspected s-SMIC. When a local excision is performed for suspected d-SMICs, other techniques that dissect a layer deeper, such as intermuscular (EID, transanal minimally invasive surgery) or full-thickness techniques (endoscopic full-thickness resection, colonoscopy-assisted laparoscopic wedge resection) may be preferred. When removing suspected polyps with local excision, lesion size, diameter of the malignant focus, suspected depth of invasion at optical diagnosis, and location in the colon or rectum should be taken into account to select the proper resection technique.

DISCLOSURE

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Abbreviations: CRC, colorectal cancer; d-SMIC, deep submucosal invasive carcinoma; EID, endoscopic intermuscular dissection; ESD, endoscopic submucosal dissection; HGD, high-grade dysplasia; s-SMIC, superficial submucosal invasive carcinoma; VM, vertical margin.

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