Thieme

Endoscopic submucosal dissection for early rectal neoplasia: experience from a European center

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submitted 21.2.2016
accepted after revision 9.8.2016

Bibliography
DOI http://dx.doi.org/10.1055/s-0042-118449
Published online: 14.11.2016 | Endoscopy 2017; 49: 222–232

ISSN 0013-726X

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ABSTRACT

Background and study aims Endoscopic resection is a curative treatment option for large nonpedunculated colorectal polyps (LNPCPs). Endoscopic submucosal dissection (ESD) allows en bloc resection but ESD experience is still limited outside Asia. The aim of our study was to evaluate the role of ESD in the treatment of early rectal neoplasia in a European center.

Patients and methods 330 patients referred for endoscopic resection of rectal LNPCPs were included prospectively.

Results ESD was performed for 302 LNPCPs (median diameter 40 mm). Submucosal invasive cancer (SMIC) was present in 17.2 % (n = 52). SMIC was associated with Paris type (54.5 % among type 0-Is lesions, 100 % of 0-Is-IIc type, 0 % of 0-IIa, 14.9 % of 0-IIa-Is, and 59.3 % of 0-IIa-IIc type; $P < 0.001$) and with surface pattern (71.4 % among nongranular plus mixed surface lesions, 17.9 % of lesions with granular surface and nodule ≥ 10 mm). For SMICs, resection rates were en bloc 81.4 %, R0 65.1 %, and curative 30.2 %. Curative resection rate improved from 13.6 % to 47.6 % over the study period ($P = 0.036$). The reason for 83.3 % (25/30) of noncurative resections was submucosal invasion exceeding 1000 µm. For benign lesions (n = 250, 82.8 %), the R0 resection increased from 55.2 % to 84.8 % over the study period ($P < 0.001$). Recurrence rate was 4.8 %, bleeding rate 5.2 %, and perforation rate 0.8 % (all complications managed conservatively). Median follow-up was 35 months.

Conclusions The majority of rectal LNPCPs are benign lesions. ESD offers high R0 resection and low recurrence rates but EMR may be appropriate. In lesions with a risk for SMIC, ESD should be offered to achieve R0 resection. Despite high rates of R0 resection the curative resection rate of ESD for rectal SMIC is < 50 %. Pretherapeutic lesion selection needs improvement.

Introduction

Endoscopic resection has been shown to be effective in reducing the incidence of colorectal cancer (CRC) [1]. Endoscopic mucosal resection (EMR) is a well-established and safe technique for the removal of colorectal adenomas [2]. However, in sessile lesions with a diameter exceeding 20 mm, also called large nonpedunculated colorectal polyps (LNPCPs), EMR often leads to piecemeal resection. After piecemeal resection, histopathological assessment of R0 resection is near impossible and the risks of incomplete resection and recurrence are increased [2, 3]. Endoscopic submucosal dissection (ESD) has been developed to overcome this problem and allows en bloc resection of lesions, regardless of their size. Large studies from Japan have reported high en bloc resection rates, R0 resection rates of up to 90 %, and recurrence rates as low as 2 % after ESD for large colorectal lesions [4, 5].

However, ESD is technically difficult and time-consuming, and there is a learning curve for inexperienced endoscopists, especially western endoscopists [6, 7]. Western data on colorectal ESD are limited and the role of ESD for colorectal lesions is, at present, not well-defined.

The balance between the advantages and disadvantages of ESD should be considered, especially for removal of early submucosal invasive cancers (SMICs), as these should be resected en bloc with histopathological confirmation of R0 status to minimize risk of recurrence [8]. For endoscopic resection of benign lesions, EMR might be sufficient and if recurrence occurs, repeat EMR is effective in most cases [2].

Endoscopic resection of SMICs is accompanied by two major problems. First, prior to resection the risk that a lesion has submucosal invasion is not always known, therefore, selection of the best resection method can be difficult. However, sufficient histopathological assessment can only be obtained after resection. Second, endoscopic resection can be judged curative only

after fulfillment of the pathological low risk criteria with a negligible risk for lymph node metastasis (LNM) [8]. Low risk criteria for sessile SMICs have been defined as submucosal invasion of less than 1000 µm, exclusion of poor differentiation, exclusion of lymphovascular invasion, and exclusion of tumor budding. When one of these criteria is not fulfilled, endoscopic resection might be inadequate and surgical resection with lymph node dissection is recommended [8]. At present, accurate evaluation of these criteria is impossible prior to resection. To date, very little data are available from the western world regarding the efficacy of colorectal ESD, especially in SMICs. In two small European studies the curative resection rates for early rectal cancers were 0 % and 7.1 % during the ESD learning curve [7, 9].

The aim of the following study was to analyze a large number of rectal LNPCPs with regard to their risk of malignancy and to evaluate the potential role of ESD, in a European center, with a focus on early rectal cancers and going beyond the ESD learning curve.

Patients and methods

The study was conducted as a single-center uncontrolled study in a German referral center (Department of Gastroenterology, Klinikum Augsburg, Germany). The study was approved by the Institutional Review Board of Klinikum Augsburg, Germany. From October 2004 to March 2016 all patients referred for endoscopic resection of a LNPCP located in the rectum were included. Data were collected prospectively.

Inclusion criteria for ESD

These were:

- Endoscopic diagnosis of a LNPCP
- Location in the rectum (0 – 15 cm from the anal verge)
- Lesion diameter > 20 mm
- Age > 18 years
- American Society of Anesthesiologists (ASA) score I – III
- Written informed consent after patients had received detailed information about the ESD procedure and alternative treatment options (EMR, surgery).

Exclusion criteria

- Suspected invasion into or beyond the deep submucosal layer after diagnostic workup (> T1sm3 carcinoma)
- Submucosal tumor
- Circumferential lesion
- Recurrence after surgical pretreatment
- Ulcerated lesion
- Poor differentiation or lymphovascular invasion shown in a biopsy
- Concomitant malignant disease without curative treatment option.

Diagnostic workup

Video endoscopy with white-light and narrow band imaging (NBI) was performed. Scope types changed over the study period (GIF-Q160 and XGIF-240FZ from 2004 to 2007, GIF-Q180 from 2008 to 2012, GIF-HQ190 from 2012 to 2016; Olympus Medical Systems, Tokyo, Japan). From 2012 full high definition systems (scopes, monitors, cables) were used.

Chromoendoscopy with indigo carmine was used to improve the visualization of the lesion border and the lesion surface pattern (pit pattern). Lesions were classified according to the Paris classification, the classification of laterally spreading tumors (LST), and the pit pattern classification [10, 11, 12]. In addition, from 2013 the Sano classification of the capillary pattern was evaluated [13].

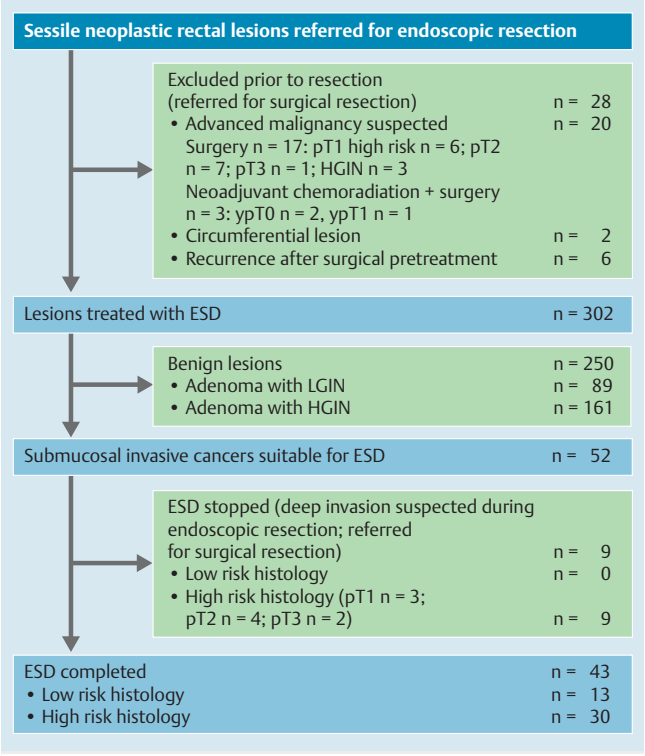
When SMIC was suspected by morphological criteria (Paris type 0-Is, 0-Is-IIc, 0-IIa-Is, 0-IIa-IIc and/or pit pattern type V and/or capillary pattern type IIIB), biopsies were taken to rule out poor differentiation or lymphovascular invasion, and endoscopic ultrasound (EUS) was performed to rule out advanced cancer (> T1) and LNM. When cancer was confirmed prior to or after resection, a computed tomography (CT) scan of the chest and abdomen was performed.

In lesions judged to be benign by macroscopic criteria, EUS was not performed and biopsies were not routinely taken prior to endoscopic resection. After the diagnostic workup, if adenoma or early SMIC without high risk criteria was suspected, ESD was performed. When advanced cancer (> T1) or T1 cancer with high risk criteria was suspected, endoscopic resection was not performed and surgical resection was recommended.

ESD procedure

ESD was performed using conventional video endoscopes (GIF-1TQ160, GIF-H180J, GIF-HQ190, GIF-1TH190; Olympus). A transparent cap at the tip of the endoscope was used. Procedures were performed under insufflation with carbon dioxide from 2011. Submucosal injection was done using a mixture of saline, epinephrine (1 : 100 000), glycerol (10 %), and a small amount of indigo carmine solution. Additionally, in cases with severe fibrosis, hyaluronic acid (Sigmavisc; Hyaltech, Livingston, UK) was injected. During ESD, large visible vessels or bleeding sites were coagulated with the Coagrasper (FD-410 LR; Olympus). Remaining visible vessels after completion of ESD were coagulated routinely. In large vessels additional clipping was done to prevent delayed bleeding. When transmural perforations (view into the perirectal space or the peritoneal cavity) or dehiscent muscle fibers (without view into the perirectal space or the peritoneal cavity) were seen, hemoclips were used for closure. In these patients antibiotics were administered intravenously for 72 hours. In cases with transmural perforations a surgeon was informed and the postinterventional management was interdisciplinary.

For the different steps of the resection procedure the VIO 300 D electrosurgical generator (ERBE Elektromedizin, Tübingen, Germany) was used (endocut I mode 60–80 W for cutting, and spray coag mode 60 W for coagulation). After the initial learning period, the ESD procedure was carried out in a standardized way using the hook-knife (KD-620LR; Olympus), as reported previously [7]. In the first study period, after circular incision and partial submucosal dissection, the use of a snare was permitted, if possible, to complete en bloc resection, in order to accelerate the procedure (hybrid ESD). However, after 50 re-



▶ **Fig. 1** Patients referred for endoscopic resection of large non-pedunculated colorectal polyps. ESD, endoscopic mucosal dissection; HGIN, high grade intraepithelial neoplasia; LGIN, low grade intraepithelial neoplasia.

sections the use of hybrid ESD was stopped because of a high rate of piecemeal resections, as previously reported [7].

Sedation with midazolam, pethidine, and propofol, under continuous cardiorespiratory monitoring, was administered by a second physician,. In accordance with common German practice after EMR of LNPCPs, patients stayed in the hospital for 48–96 hours after ESD. In the first 34 resections, control endoscopies were performed routinely after 24–48 hours. During the further study routine control endoscopies were not performed.

An equal number of ESD procedures were performed by two endoscopists (A.P., H.M.). At the beginning of the study neither endoscopist had ESD experience. By the end of the study both endoscopists had performed about 400 ESD procedures each (esophageal, gastric, and colorectal).

Definitions and follow-up

En bloc resection was defined as resection of the targeted area in one piece. Resection in one piece, with histopathological confirmation that the vertical margin and the horizontal margin were free of neoplasia was classified as R0 resection.

In benign lesions, R0 resection was classified as curative resection.

In SMICs, ESD was judged curative when R0 resection was achieved and histopathological diagnosis confirmed that low risk criteria were fulfilled. When R0 resection could not be confirmed or low risk criteria were not fulfilled, resection was judged noncurative and additional surgery with lymph node dissection was recommended. After curative ESD of SMICS, follow-up endoscopies including white-light endoscopy and NBI were performed after 3, 6, 12, 18 and 24 months and annually thereafter for 5 years. Additionally in patients not treated surgically, despite high risk histological findings, EUS was performed. After ESD of benign lesions, follow-up endoscopies were performed after 3 and 12 months. Follow-up recommendations were given according to a local protocol.

Histopathological workup

ESD specimens were minimally stretched and fixed on cork with needles. Specimen size was measured and specimens were sent for histopathological assessment.

The specimens were cut into thin parallel sections of 3-mm thickness, or less. The formalin fixation of these stretched large specimens facilitated an optimal orientation during paraffin embedding. Embedding in a 90-degree orientation enabled an excellent evaluation of the slides with regard to involvement of the lamina muscularis mucosae and the depth of invasion. Pathological reporting included the lesion diameter, invasion depth, differentiation, and presence or absence of lymphovascular invasion and tumor budding. R0 or R1 status was described for the vertical and horizontal margins.

SMIC was diagnosed when invasion was seen beyond the lamina muscularis mucosae. Intramucosal lesions were classified as adenoma with low grade or high grade intraepithelial neoplasia (LGIN or HGIN). Surgical specimens, after noncurative endoscopic resection, were analyzed for residual cancer and LNM. When SMIC was diagnosed, the patient's management was discussed by an interdisciplinary panel of gastroenterologists and surgeons.

Complications

Complications were defined as bleeding, perforation, stenosis, or death. Bleeding during ESD was considered to be a complication when it was severe, leading to premature termination of endoscopic resection. Bleeding with clinical signs observed after ESD (rectal bleeding or hemoglobin drop > 2 g/dL) was defined as delayed bleeding [14]. Transmural perforation was defined as an obvious endoscopic view into the perirectal space or the peritoneal cavity, or when postinterventional imaging showed extravasation of the contrast medium.

Statistical analysis

A *t* test or Mann–Whitney rank sum test was used to compare numeric values. For the comparison of categorical data, chi-squared or Fishers's exact test were employed, depending on the expected frequency of the observations. P values < 0.05 were considered to be statistically significant. A Bonferroni–Holm correction was performed to adjust the alpha level in cases of multiple comparisons. Calculations were performed using the software package Sigma Plot 13.0 (Systat Software, San Jose, USA).

▶ **Table 1** Morphological features and risk for submucosal invasion in 330 large nonpedunculated colorectal polyps referred for endoscopic resection.

	n (%)	Diameter, median (range), mm	LGIN, n	HGIN, n	SMIC, n	Risk for cancer, % (95 %CI%)
Paris type						
▪ 0-Is	22 (6.7 %)	27.5 (18 – 80)	0	10	12	54.5 % (43.7 % – 73.1 %)
▪ 0-Is-IIc	10 (3.0 %)	30 (20 – 40)	0	0	10	100 % (72.3 % – 100 %)
▪ 0-IIa	63 (19.1 %)	39 (20 – 135)	44	19	0	0 % (0 % – 5.8 %)
▪ 0-IIa-Is	208 (63.0 %)	50 (20 – 115)	46	131	31	14.9 % (10.7 % – 20.4 %)
▪ 0-IIa-IIc	27 (8.2 %)	30 (20 – 70)	1	10	16	59.3 % (40.1 % – 75.5 %)
LST type						
Granular	267 (80.9 %)	45 (18 – 135)	89	154	24	9.0 % (6.1 % – 13 %)
Without nodule	61		43	18	0	0 %
Small nodule (< 10 mm)	83		28	53	2	2.4 %
Large nodule (> 10 mm)	123		18	83	22	17.9 %
Nongranular	55 (16.7 %)	30 (19 – 70)	211	15	38	69.1 % (56.0 % – 79.7 %)
Pseudodepressed	34		1	8	25	73.5 %
Flat/elevated	21		1	7	13	61.9 %
Mixed (granular and nongranular)	8 (2.4 %)	60 (30 – 80)	0	1	7	87.5 % (52.9 % – 97.8 %)
All	330	40 (18 – 135)	91	170	69	20.9 % (16.9 % – 25.6 %)

LST, laterally spreading tumor; LGIN, low grade intraepithelial neoplasia; HGIN, high grade intraepithelial neoplasia; SMIC, submucosal invasive cancer; 95 %CI, 95 % confidence interval

Results

Patient and lesion characteristics

▶ **Fig. 1** gives an overview of the study population. Over a 140-month period, 330 patients referred for endoscopic resection of LNPCPs were enrolled (59 % men; median age 66.1 years, range 29–88 years). A total of 28 patients (8.5 %) were excluded. In 20 of these, advanced cancer was suspected macroscopically (6 nongranular LSTs with ulceration, 14 granular LSTs with a large nodule showing ulceration, pit pattern type V, and capillary pattern type IIIB); and 8 patients with benign lesions were excluded (6 lesions after surgical pretreatment, 2 circumferential lesions).

ESD was therefore performed in 302 patients (91.5 %). In 223 of the resected lesions, biopsies had been taken by the referring physician (73.8 %). A total of 32 lesions (10.6 %) were residual or recurrent lesions after previous EMR.

Resected lesions showed benign histology in 250 patients (82.8 %), while the remaining 52 were diagnosed as SMICs (17.2 %).

The median diameter of the LNPCP lesions was 40 mm (range 18–135 mm) (▶ **Table 1**). The predominant lesion type was Paris type 0-IIa-Is (63.0 %), followed by 0-IIa (19.1 %). The risk for SMIC was high in Paris 0-Is (54.5 %), Paris 0-Is-IIc (100 %), and Paris 0-IIa-IIc lesions (59.3 %). In the most frequent subtype 0-IIa-Is, SMIC was diagnosed in 14.9 % of lesions. Paris 0-IIa lesions did not contain SMIC. The risk for submucosal invasion was significantly different between the Paris types ($P < 0.001$).

According to Kudo's classification of laterally spreading tumors (LSTs), 267 lesions showed a granular surface (80.9 %), 55 showed a nongranular surface (16.7 %), and 8 were mixed lesions (2.4 %). Of the nongranular lesions, 34 were pseudodepressed lesions. The risk for SMIC was 71.4 % (45/63) in lesions containing a nongranular surface (nongranular-only and mixed-type lesions), while it was 9.0 % (24/267) in granular-type lesions ($P < 0.001$).

The distribution of lesions and their risk for submucosal invasion is shown in ▶ **Table 1**.

Technical success of ESD (all lesions)

With regard to all resections, en bloc resection was possible in 243 patients (80.5 %). In 50 lesions piecemeal resection had to be performed (16.6 %). The remaining 9 resections were stopped because of non-lifting and suspected deep submucosal invasion, only recognizable after submucosal dissection had been started (2.9 %).

In residual/recurrent lesions after previous EMR en bloc resection was possible in 56.3 % (18/32), while it was possible in 83.3 % (225/270) of treatment-naïve lesions ($P<0.005$). In treatment-naïve lesions with previous biopsy, the en bloc resection rate was 79.4 % (177/223) compared to 93.6 % (44/47) in lesions without previous biopsy ($P=0.002$).

ESD in submucosal invasive cancers (SMICs)

Clinical characteristics

After diagnostic work-up, 52 lesions later classified as SMICs were judged suitable for ESD (patients, 65.4 % men; median age 67.7 years, range 39–88 years).

In 9 of these patients ESD had to be stopped because of non-lifting and suspected deep submucosal invasion, only recognizable after submucosal dissection had been started. In all of these lesions cancer had been suspected macroscopically but could not be confirmed by biopsy (7 Paris 0-IIa-Is lesions, 1 Paris 0-Is lesion with a granular surface, and 1 Paris 0-Is-IIc lesion with a nongranular surface). Of these lesions, 7 were encountered within the first half of the study period. After the endoscopic resection was halted, the patients were treated surgically (▶ **Fig. 1**).

In the remaining 43 patients, ESD could be completed. ▶ **Table 2** shows the patient and lesion characteristics.

Resection rates, complications, and learning curve

En bloc resection was possible in 35 of 43 ESD procedures (81.4 %), R0 resection in 28 (65.1 %), and curative resection in 13 (30.2 %) (▶ **Table 3**). R0 resection could not be confirmed in 15 lesions (34.9 %). This was because of R1 evaluation at the vertical margins in all 15 lesions and additionally at the horizontal margin in 6 lesions which had not been resected en bloc. The main reason for noncurative resection was submucosal invasion exceeding 1000 µm in 25 of 30 lesions (83.3 %). The rate for curative resection was higher for Paris type 0-II lesions compared to 0-I lesions (37.5 % vs. 9.1 %; $P=0.031$).

Within the first 48 hours 2 bleedings were observed and were treated with endoscopic clipping. In 3 cases hemoclips were used during ESD to close muscle fiber dehiscences. In a further 18 patients, hemoclips were used to prevent delayed bleeding. Transmural perforations or other complications were not observed.

The chance for low risk histological results and therefore, for curative endoscopic resection of SMICs, was highest when cancer was diagnosed after endoscopic resection and had not been suspected prior to resection (38.5 %). All lesions with biopsy-

▶ **Table 2** Resection of submucosal invasive cancers resected by endoscopic submucosal dissection (ESD): patient and lesion characteristics.

	Cancers resected with ESD (n = 43)
Patient characteristics	
Sex, male : female, n	26 : 17
Age, median (range), years	68.8 (39 – 88)
ASA status: I; II; III	26; 13; 4
Lesion characteristics	
Diameter, median (range), mm	35 (20 – 90)
Paris type, n (%)	
▪ 0-Is	7 (16.3 %)
▪ 0-Is-IIc	4 (9.3 %)
▪ 0-Is-IIa	18 (41.9 %)
▪ 0-IIa-IIc	14 (32.6 %)
Location (lesion distal margin), n (%)	
▪ Distal rectum (< 5 cm from the anal verge)	10 (23.3 %)
▪ Mid rectum (5 – 10 cm)	12 (27.9 %)
▪ Proximal rectum (> 10 cm)	21 (48.8 %)
Clinical situation, n (%)	
Cancer confirmed by biopsy	5 (11.6 %)
Cancer suspected by morphological criteria* (but biopsy-negative)	25 (58.1 %)
Cancer not suspected prior to endoscopic resection	13 (30.2 %)
Histology, n (%)	
Invasion depth	
▪ pT1 ≤ 1000 µm	17 (39.5 %)
▪ pT1 > 1000 µm	25 (58.1 %)
▪ pT2	1 (2.3 %)
Differentiation	
▪ G1	2 (4.7 %)
▪ G2	37 (86 %)
▪ G3	4 (9.3 %)
Lymphovascular invasion, n (%)	
▪ L0	40 (93 %)
▪ L1	3 (7 %)
▪ Budding	2 (4.7 %)

ASA. American Society of Anesthesiologists.
* Paris type 0-Is, 0-Is-IIc, 0-IIa-Is, 0-IIa-IIc, and/or pit pattern type V and/or capillary pattern type IIIB

▶ **Table 3** Endoscopic submucosal dissection of 43 submucosal invasive cancers (SMICs): resection rates, according to Paris classification.

	n	Median diameter, mm	Clinical situation regarding cancer, n			Resection, n (%)		
			Biopsy-proven	Suspected but biopsy-negative*	Not suspected	En bloc	R0	Curative
Paris type								
▪ 0-Is	7	23	3	4	0	6 (85.7 %)	4 (57.1 %)	1 (14.3 %)
▪ 0-Is-IIc	4	28	1	3	0	1 (25 %)	1 (25 %)	0
▪ 0-IIa-Is	18	58	1	5	12	15 (83.3 %)	13 (72.2 %)	6 (33.3 %)
▪ 0-IIa-IIc	14	32	0	13	1	13 (92.9 %)	10 (71.4 %)	6 (42.9 %)
All	43	41.2 (range 20 – 90)	5	25	13	35 (81.4 %) (95 %CI 67.4 % – 90.3 %)	28 (65.1 %) (95 %CI 50.2 % – 77.6 %)	13 (30.2 %) (95 %CI 18.6 % – 45.1 %)

95 %CI, 95 % confidence interval
* Paris type 0-Is, 0-Is-IIc, 0-IIa-Is, 0-IIa-IIc and/or pit pattern type V and/or capillary pattern type IIIB

▶ **Table 4** Low risk versus high risk histology, according to clinical situation, in 43 submucosal invasive cancers (SMICs) resected by endoscopic submucosal dissection (ESD).

	n	Histological findings, n (%)	
		Low risk	High risk
Clinical situation			
Cancer confirmed by biopsy	5	0 (0 %)	5 (100 %)
Cancer suspected by morphological criteria* (but biopsy-negative)	25	8 (32 %)	17 (68 %)
Cancer not suspected prior to resection	13	5 (38.5 %)	8 (61.5 %)
All lesions	43	13 (30.2 %) (95 %CI 18.6 – 45.1)	30 (69.8 %) (95 %CI 54.9 – 81.4)

95 %CI, 95 % confidence interval
* Paris type 0-Is, 0-Is-IIc, 0-IIa-Is, 0-IIa-IIc and/or pit pattern type V and/or capillary pattern type IIIB).

confirmed cancer showed high risk histology (▶ **Table 4**). ▶ **Fig. 2** shows examples of ESD in early rectal cancer.

Resection rates were analyzed separately for the first half of the study (resections 1 – 22; 10/2005 – 07/2013) and the second half of the study (resections 23 – 43; 07/2013 – 03/2016). The en bloc resection rate increased from 72.7 % (16/22) to 90.5 % (19/21) and the R0 resection rate increased from 54.5 % (12/22) to 76.2 % (16/21), underlining the learning curve for ESD technique. The differences were not statistically significant because of the small case numbers. The curative resection rate increased significantly from 13.6 % (3/22) to 47.6 % (10/21) (P = 0.036; ▶ **Table 5**).

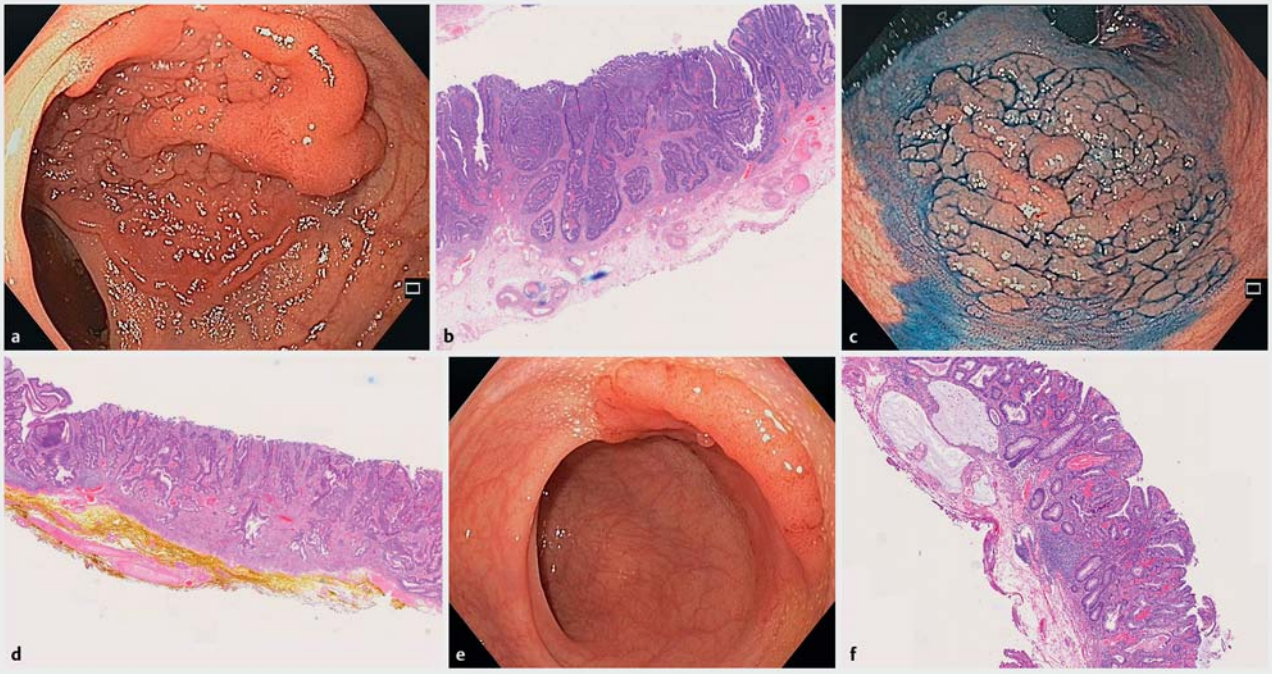
Follow-up

A total of 13 patients with SMICs with low risk histology entered follow-up.

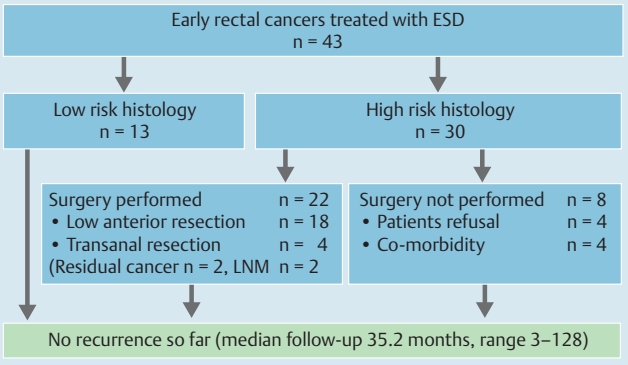
In the remaining 30 patients, surgery was performed in 22, whilst 8 patients entered follow-up without surgical resection because of the patient's refusal or severe co-morbidity. A total of 18 patients underwent low anterior resection including lymph node dissection. In the remaining 4 surgical patients, transanal full-thickness resection was performed to rule out residual cancer, but more extensive surgery, including lymph node dissection, was not performed because of patient refusal.

Surgical specimens showed residual cancer in 2 patients after R1 resection at the vertical margin (9.1 %). LNM was found in another 2 patients out of 18, after lymph node dissection (11.1 %). LNM was diagnosed after R0 resection of a G3L0V0 cancer with a submucosal invasion depth of 2000 µm and after R1 resection (vertical margin) of a G2L0V0 cancer with a submucosal invasion depth of > 1400 µm.

After a median follow-up of 35.2 months (range 3–128), no local recurrence and no metastasis were observed after treatment of SMICS (▶ **Fig. 3**).



▶ **Fig. 2** Endoscopic findings in early rectal cancer and corresponding histology. **a** Paris type 0-IIa-Is; granular and nongranular surface; **b** corresponding histology for **a**, pT1a, sm invasion 700 µm, L0V0G2, R0. **c** Paris type 0-IIa-Is; granular surface; **d** corresponding histology for **c**, pT1a, sm invasion > 1000 µm L1V0G2, Rx at the vertical margin, tumor budding. **e** Paris type 0-IIa-IIc, nongranular surface; **f** corresponding histology for **e**, pT1a, sm invasion 760 µm, L0V0G2, R0.



▶ **Fig. 3** Clinical course and follow-up in 43 patients with submucosal invasive cancers (SMICs) who underwent endoscopic submucosal dissection (ESD). LNM, lymph node metastasis.

ESD in benign lesions and learning curve

ESD was performed in 250 benign rectal LNPCPs. Over the whole study period the en bloc resection rate was 83.2 % (208/250) and the R0 resection rate was 70 % (175/250).

The bleeding rate was 5.2 % (13/250) and the perforation rate was 0.8 % (2/250). Bleedings occurred within the first 48 hours in 10 patients and on day 6, 8, and 10 in the remaining 3. Perforation was noticed during ESD in 1 patient (the lesion being resected had been a recurrence after previous EMR) and 48 hours after ESD, during a routine control endoscopy, in 1 more. All bleedings and the two perforations were treated with endoscopic clipping.

In 26 cases hemoclips were used during ESD to close muscle fiber dehiscences. In another 69 patients hemoclips were used to prevent delayed bleeding. There was no need for surgical intervention or blood transfusion. The use of clips to prevent delayed bleeding decreased significantly over time.

The total recurrence rate after ESDs for benign lesions was 4.8 % (12/250). It was 0.5 % (1/208) after en bloc resection and 26.2 % (11/42) when en bloc resection was not achieved and the resection had to be completed in a piecemeal fashion. Of the recurrences, 10 were successfully removed with snare resection or argon plasma coagulation. The remaining 2 recurrences were treated with transanal surgical resection. Endoscopic resection was judged impossible because of severe submucosal scarring; both lesions had been recurrences after initial EMR.

The median follow-up for benign lesions was 34.8 months (3–140). A clear learning curve could be shown, resulting in significant improvement of the resection rates (▶ **Table 6**).

Discussion

CRC continues to be one of the most frequent cancers in the western world. Screening colonoscopies have been introduced in several countries over the last decade and have been shown to be effective in detecting premalignant adenomas and CRCs at an earlier stage. In a large German study involving 2821 392 screening colonoscopies, premalignant precursor lesions were

▶ **Table 5** Endoscopic submucosal dissection (ESD) in rectal submucosal invasive cancers.

	First study period (10/2005 – 07/2013) Resections 1 – 22	Second study period (07/2013 – 03/2016) Resection 23 – 43	*P* value
Diameter, median (range), mm	30 (20 – 90)	40 (20 – 90)	0.146
En bloc or piecemeal resection, n (%)			0.240
▪ En bloc	16 (72.7 %)	19 (90.5 %)	
▪ Piecemeal	6 (27.3 %)	2 (9.5 %)	
R0 or R1 resection			0.243
▪ R0	12 (54.5 %)	16 (76.2 %)	
▪ R1	10 (45.5 %)	5 (23.8 %)	
Curative resection (R0 resection with low risk histology)	3 (13.6 %)	10 (47.6 %)	0.036

▶ **Table 6** Endoscopic submucosal dissection (ESD) in benign rectal large nonpedunculated colonic polyps.

	First study period (10/2004 – 07/2013) Resections 1 – 125	Second study period (07/2013 – 03/2016) Resections 126 – 250	*P* value
Diameter, median (range), mm	40 (18 – 120)	45 (20 – 115)	0.086
En bloc resection, n (%)	94 (75.2 %)	114 (91.2 %)	0.001
R0 or R1 resection			< 0.001
▪ R0	69 (55.2 %)	106 (84.8 %)	
▪ R1	56 (44.8 %)	19 (15.2 %)	
Recurrence, n (%)	8 (6.4 %) (95 %CI 3.2 % – 12.1 %)	4 (3.2 %) (95 %CI 1.3 % – 7.9 %)	0.375
After en bloc ESD	1/94 (1.1 %)	0/114	
After piecemeal resection	7/31 (22.6 %)	4/11 (36.4 %)	
Complications, n (%)			
▪ Bleeding	10 (8 %)	3 (2.4 %)	0.087
▪ Transmural perforation	1 (0.8 %)	1 (0.8 %)	1.0
Intraprocedural clipping:	67 (53.6 %)	28 (22.4 %)	< 0.001
▪ Dehiscence of muscle fibers	15	11	0.534
▪ Prophylaxis of delayed bleeding	52	17	< 0.001

found in 19.4 % and cancers in 0.9 %. Of the cancers, 47.3 % were detected at an early stage, UICC I [15]. Early CRC (pT1) shows an excellent prognosis and endoscopic resection can be performed with curative intent when low risk pathological criteria with a negligible risk for LNM are fulfilled. Low risk criteria for colorectal SMICs have been defined as submucosal invasion of less than 1000 µm and exclusion of poor differentiation, lymphovascular invasion, and budding. When low risk criteria are not fulfilled, endoscopic resection is judged inadequate and surgical resection with lymph node dissection is recommended. A meta-analysis demonstrated a 1.9 % risk for LNM in pT1 cancers with low risk criteria, while the risk was 14.6 % beyond these criteria [16]. Yoda et al. reported a 5-year recurrence-free survival of 98 % and a recurrence rate of 0.8 % after endoscopic resection of low risk SMICs [17]. Ikematsu et al. analyzed follow-up data on 549 early colonic and 209 early rectal cancers after endoscopic resection. After endoscopic resection of low risk cancers the recurrence rate was 0 % for colonic and 6.3 % for rectal lesions after 5 years [18]. Therefore, endoscopic resection for SMICs with low risk criteria is widely accepted and

recommended in recently published international guidelines [8, 19].

To achieve curative treatment by endoscopic resection it is crucial to estimate a lesion's risk of malignancy and the depth of submucosal invasion, prior to therapeutic decisions. Biopsies are known to be unreliable for the correct diagnosis of submucosal invasive cancers because of superficiality and sampling errors [20]. Therefore, the risk for SMIC and for deep submucosal invasion should be identified by morphologic features [12, 13, 21]. In previous studies, an increased risk of malignancy has been seen in the following lesions: those of Paris-type 0-IIc or 0-IIa-IIc, laterally spreading tumors (LSTs) with a nongranular surface, LSTs with a granular surface and a dominant nodule (Paris 0-IIa-Is), and lesions with irregularities of the surface pattern (such as pit pattern type V) or the vascular pattern (such as capillary pattern type III) [19, 22]. Recently, Yamada et al. described a 39 % risk for SMIC in nongranular-type lesions and a 19 % risk in granular-type lesions. In nongranular-type lesions the risk was highest under depressed areas, while it was highest under large nodules (> 10 mm) in granular-type lesions [23]. However, while the Paris classification and evaluation of surface pattern (granular-type versus nongranular-type) are easy to apply, correct assessment of pit pattern type V might be difficult, with limited interobserver agreement [24].

When malignancy is suspected in colorectal neoplasia, en bloc resection is strongly recommended to improve histopathological assessment of R0 resection and to minimize the risk of recurrence [19]. ESD has been shown to achieve higher en bloc resections compared to EMR and might be considered the treatment of choice for lesions with suspected malignancy [5]. However, ESD is technically difficult, time-consuming and requires a learning curve, especially for western endoscopists [6] [7]. Currently, little data on colorectal ESD have been published from the western world and are mainly restricted to rectal lesions [7, 9]. To date in the western world, the role of colorectal ESD is not well defined and its potential benefit for SMICs, but also for benign lesions, is unknown.

In our single-center study we analyzed 330 rectal LNPCPs referred for endoscopic resection to a European center. If lesion diameter exceeded 20 mm, ESD was performed to avoid piecemeal resection. In lesions resected endoscopically the rate of SMIC was 17.2 %. Large Japanese studies have reported similar rates of SMIC, from 17.1 % to 19.6 % [4, 25, 26]. In our study granular-type lesions accounted for 80.9 %, while 19.1 % showed a wholly or partly nongranular surface. The distribution is similar to that reported in a study by Yamada et al. (74.7 % granular-type versus 25.3 % nongranular type in rectal lesions) [23]. The risk of submucosal invasion was strongly associated with the lesion morphology. Similarly to the data of Yamada et al., the risk for SMIC was highest in nongranular and partly nongranular-type lesions (71.4 %) and in granular-type lesions with a large nodule exceeding 10 mm (17.9 %). In granular-type lesions without nodules or with small nodules of less than 10 mm, the rates for SMIC were 0 % and 2.4 %, respectively. These latter two groups accounted for 47.7 % (144/302) of all lesions assessed as suitable for ESD.

Furthermore, Paris types 0-Is, 0-Is-IIc, 0-IIa-Is, and 0-IIa-IIc were associated with SMIC with risks of 54.5 %, 100 %, 14.9 %, and 59.3 %, respectively. Paris type 0-IIa exhibited no risk for SMIC.

In 52 of the SMICs, ESD had seemed possible after diagnostic work-up. Biopsies had confirmed cancer in only 5 lesions prior to resection (9.6 %). In 34 lesions cancer was suspected by morphological features but biopsies could not confirm this (73.5 %). A total of 13 cancers were diagnosed only after analysis of the resection specimen and had not been suspected prior to ESD (25 %). These cancers were mainly diagnosed within nodules in 0-IIa-Is lesions (92.3 %). Despite pretherapeutic estimation of resectable pT1 cancer, ESD had to be stopped in 9 cases because of deep submucosal invasion or invasion into the proper muscular layer, which was only diagnosed during ESD.

The findings reflect the difficulties in the pretherapeutic assessment of LNPCPs, even after morphological analysis and biopsy, especially whist endoscopists gain initial experience.

The enrolment over a 12-year period included our ESD learning curve at the beginning of the study period. In our previous study, on the learning curve for ESD in large sessile lesions of the rectosigmoid, 14 early cancers were included and only 1 procedure achieved curative resection (7.1 %) [7]. Large Asian studies on ESD for colorectal early cancers report higher rates of curative resection but, also, submucosal invasion exceeding 1000 µm is reported to be as high as 46.8 %–47.4 % in these studies [4, 25].

In our study, ESD was completed in 43/52 SMICs and the curative resection rate was 30.2 % for the whole study period. As previously reported from Japan, the main reason for noncurative resection was submucosal invasion exceeding 1000 µm, in 25 of 30 noncurative resections (83.3 %). The curative resection rate improved significantly from the first to the second study half (13.6 % versus 47.6 %). The en bloc resection rate increased from 72.7 % to 90.5 % and the R0 resection rate increased from 54.5 % to 76.2 %, underlining the learning curve for the ESD technique. The improvement of the curative resection rate reflects the learning curve in lesion selection. The main reason may be the improvement in imaging technology that became available in recent years (e. g. high definition systems, magnifying endoscopy, narrow-band imaging [NBI]). Full high definition systems (scopes, monitors, cables) became available during the second study period and also may have contributed to the improvement. Another possible reason for the increasing rate of curative resections is the improved knowledge of lesion risk for SMIC according to morphological features (Paris classification, LST classification, pit pattern, and Sano classification).

For lesions known to have a risk for SMIC, en bloc resection should be aimed at, and ESD might be the ideal resection method. As suggested by Yamada et al., our data confirm the recommendation for ESD in nongranular-type lesions and granular-type lesions with large nodules. At present, because of limited experience, colorectal ESD should be offered in specialized centers in the western world.

However, despite progress in diagnostic technology and in resection technique, the pretherapeutic diagnosis of the inva-

sion depth remains a problem and further improvement is strongly needed. In a substantial proportion of cases, ESD of SMICs remains a diagnostic resection and must be seen as an optimized staging procedure, which facilitates the decision for surgical resection on the basis of accurate histopathological staging. However, because cancer is not confirmed in the majority of cases prior to resection, we recommend ESD as the first treatment in these lesions to avoid surgical overtreatment with its potential morbidity. In high risk lesions there is no disadvantage for the patient in a recommendation for surgical resection after endoscopic resection [27].

In contrast to lesions with a risk for SMIC, the real benefit of ESD in benign LNPCPs is not clear at present. The majority of LNPCPs show benign histology without submucosal invasion (250 lesions, accounting for 82.8 % in our study). For these lesions EMR has been shown to be effective over the long term, despite substantial rates of piecemeal resections and recurrences [2, 3]. Our data show an R0 resection rate of 70 % for benign lesions with a clear improvement over time (84.8 % in the second study period) and a recurrence rate of 4.8 %. One possible reason for the discrepancy between R0 resection and recurrence rate could be the coagulation damage to the margin of the specimen, which makes diagnosis of R0 resection difficult. The low recurrence compared to EMR data seems to be the major advantage of ESD in benign lesions. However, ESD has not gained widespread use in the western world and involves a learning curve. Looking at the good long-term data after EMR, it is not justifiable at present to recommend ESD for benign LNPCPs, based only on lower recurrence rates. Depending on local expertise, EMR seems adequate for lesions without a substantial risk for SMIC. Suitable lesions are granular-type lesions without nodules or with small nodules < 10 mm; these represent the majority of LNPCPs in our study.

In conclusion, ESD was shown to be a safe technique which can achieve high rates of R0 resection in rectal LNPCPs. The estimation of the risk that a lesion harbors SMIC is crucial in determining the optimal resection method. ESD should be offered for lesions with a risk of SMIC, to achieve R0 resection, optimize the histopathological diagnosis, and minimize the recurrence risk. However, further improvement of the pretherapeutic diagnosis is needed for a better curative resection rate. The majority of rectal lesions show a low risk for SMIC. ESD also offers the advantage of a low recurrence rate in these lesions but EMR might be adequate as well. The role of colorectal ESD needs to be further defined when ESD more widely disseminated in the western world.

Limitations of our study are the restriction to rectal lesions and the lack of randomization to a control group treated with EMR or surgically. Another limitation is the 12-year period of study enrolment with a change of the methodology over time. During this time endoscopist experience, imaging technology (scope types, high definition, NBI), and knowledge of surface topography improved dramatically. The study can give an overview of the development of rectal ESD in a western center over the last decade. By analyzing different study periods separately, the study also describes the results which can be obtained with current knowledge and technology. The data may be helpful in further defining the role of colorectal ESD in the western world. However, further studies are urgently needed on colorectal ESD, especially for lesions outside the rectum where lesion distribution might be different and there is a greater risk of complication associated with ESD.

Competing interests

None

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