

Long-term follow-up after colorectal endoscopic submucosal dissection in 182 cases



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submitted 4.8.2020

accepted after revision 20.10.2020

Bibliography

Endoscopy International Open 2021; 09: E258–E262

DOI 10.1055/a-1321-1271

ISSN 2364-3722

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ABSTRACT

Background and study aims We previously reported a case series of our first 182 colorectal endoscopic submucosal dissections (ESDs). In the initial series, 155 ESDs had been technically feasible, with 137 en bloc resections and 97 en bloc resections with free margins (R0). Here, we present long-term follow-up data, with particular emphasis on cases where either en bloc resection was not achieved or en bloc resection resulted in positive margins (R1).

Patients and methods Between September 2012 and October 2015, we performed 182 consecutive ESD procedures in 178 patients (median size 41.0 ± 17.4 mm; localization rectum vs. proximal rectum 63 vs. 119). Data on follow-up were obtained from our endoscopy database and from referring physicians.

Results Of the initial cohort, 11 patients underwent surgery; follow-up data were available for 141 of the remaining 171 cases (82,5%) with a median follow-up of 2.43 years (range 0.15–6.53). Recurrent adenoma was observed in 8 patients (n = 2 after margin positive en bloc ESD; n = 6 after fragmented resection). Recurrence rates were lower after en bloc resection, irrespective of involved margins (1.8 vs. 18,2%; P < 0.01). All recurrences were low-grade adenomas and could be managed endoscopically.

Conclusions The rate of recurrence is low after en bloc ESD, in particular if a one-piece resection can be achieved. Recurrence after fragmented resection is comparable to published data on piecemeal mucosal resection.

Introduction

Endoscopic resection of colorectal neoplasia is a cornerstone of colorectal cancer prevention. Ideally, neoplastic lesions should be resected in one piece with negative horizontal and vertical margins [1]. However, that cannot reliably be achieved for lar-

ger flat or sessile lesions if the current standard, i. e. endoscopic mucosal resection (EMR), is applied. Thus, these lesions are removed in fragments, which carries a risk for recurrent adenoma of 15% to 40% [2–5]. Moreover, because the risk for high-grade dysplasia or invasive cancer is associated with the size of the lesion, a fragmented resection can make histological diagnosis

impossible, with the consequences of either misdiagnosis of a low-risk situation or unnecessary additional surgery [6].

Endoscopic submucosal dissection (ESD), initially established for the treatment of stomach cancer, has also been adopted for resection of colorectal lesions. It is technically demanding, associated with longer procedure times, and also carries a slightly higher risk for relevant perforations, but ESD can achieve en bloc resections even in very large lesions [1, 7]. In Japan, colorectal ESD is a standard treatment for suspicious lesions that are difficult to remove in one piece or for very large lesions that carry a high risk of high-grade dysplasia or invasive cancer and have a high recurrence rate [6]. ESD has also been included in recent guidelines from Europe and the United States [8–10].

We have previously reported short-term results after ESD for 182 colorectal flat or sessile lesions >20 mm [11]. The data included our learning curve and the effectiveness was relatively modest. Thus, ESD was technically feasible in 155 of 182 cases with an overall en bloc resection rate of 137 of 182. Moreover, in 40 of 137 en bloc resected specimens, microfocal involvement of lateral margins was diagnosed, in particular, in lesions larger than 50 mm. Here, we present long-term follow-up for this cohort, with particular attention to recurrence rates relative to size of the resected lesions and outcome of the initial ESD procedure.

Patients and methods

Data on method and short-term outcome have been published previously [11]. Briefly, in our initial series, 182 consecutive ESD procedures had been performed for colorectal neoplastic lesions >20 mm (mean size 41.0 ± 17.4 mm). Lesions were located in the cecum (n=43), right-sided colon (n=65), left-sided colon (n=11) or rectum (n=63). We had observed a low complication rate (microperforation 9.3%, delayed bleeding 2.7%, no emergency surgery, no 30-day mortality). Informed consent had been obtained from all patients and the study had been approved by the Ethics Committee of the University of Bonn (registration number 35613) and was conducted according to the Declarations of Helsinki.

Collection of follow-up data and data analysis

Data on follow-up were collected from our own database or from endoscopy reports of the referring physicians. Rates of recurrence were calculated for patients that had at least one endoscopic control documented. In cases of several endoscopic controls, the latest control was used to calculate the follow-up interval. The Kaplan-Meier method was used to estimate the cumulative rate of recurrent neoplasia. We used a log-rank test to assess the relative effectiveness of the initial ESD procedure (i. e., ESD en bloc versus fragmented resection) on the rate of recurrent lesions.

Results

Data availability for follow-up

We initially attempted ESD on 182 consecutive colorectal neoplastic lesions >20 mm in 178 patients. Eleven patients underwent surgery for various reasons and were not available for endoscopic follow-up (see below). Of the remaining 171 patients, 41 had at least one endoscopic control (median number of control endoscopies 1; range 1–5) and the median follow-up time was 2.43 years (range 0.15–6.53). The outcome was analyzed in two groups according to the outcome of the initial ESD procedure. Group 1 (ESD en bloc) included procedures with en bloc resection (n=108), either with free or with microscopically involved margins. Group 2 (ESD not en bloc or converted to EMR) included all cases where en bloc resection could not be achieved (n=33), either because the ESD procedure could be done but was not completed as one-piece resection (ESD not en bloc) or because ESD was technically not feasible and the procedure was finished as piecemeal EMR (converted to EMR) (► Fig. 1).

Patients with recurrent adenoma

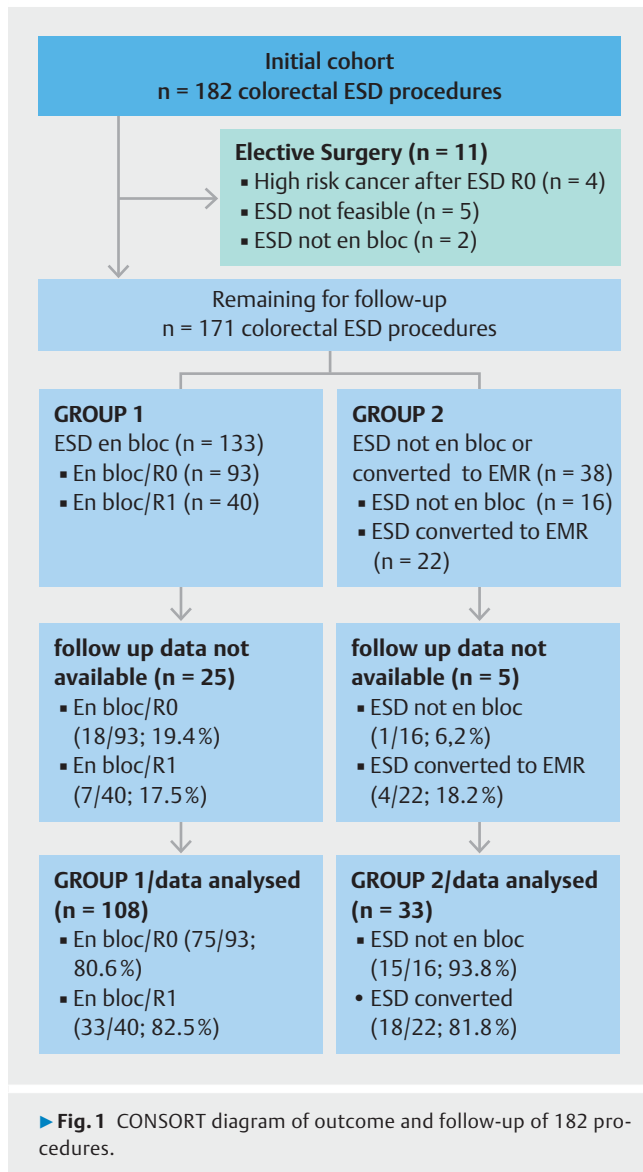
We observed recurrent adenomas in two patients in Group 1 (after 215 and 1250 days) and six patients in Group 2 (after 129, 179, 195, 296, 333 and 1153 days), thus the recurrence rates were significantly lower after an initial ESD en bloc versus fragmented resection (► Table 1 and ► Fig. 2). We did not have sufficient data to analyze for a possible correlation between recurrence and length of the R1 margin (in margin positive en bloc resections) or between recurrence and the number of resected pieces (in cases converted to EMR). All recurrences could be retreated endoscopically with documented treatment success in six patients and two patients without sufficient follow-up data (► Table 2).

Outcome of patients who underwent surgery

Eleven patients underwent surgery (► Table 3). In four patients, surgery was performed after previous en bloc/R0 ESD due to a histological diagnosis of high-risk pT1 cancer. No residual cancer or lymph node metastasis was detected in these four surgical specimens. The other seven patients underwent surgery after fragmented resection of invasive cancer (n=2: no residual cancer in the surgical specimen) or due to failed endoscopic resections (n=5: with a single small high-risk cancerous component in a patient referred for surgery for high-grade adenoma).

Outcome of patients with invasive cancer

In the initial series, invasive cancer was diagnosed in 13 patients. ESD was curative in five of 13 (38.4%) and all patients are alive without recurrence or metastatic disease during follow-up. The aforementioned four patients who underwent surgery after R0 ESD because of high-risk features also had no residual cancer or lymph node metastasis. Another two patients had fragmented endoscopic resections (Rx) of high-risk invasive cancer and negative histology after surgery. Only one patient had an incidental invasive cancer in a high-grade dysplasia



(Patient #7, ► **Table 3**) – and another refused surgery for high-risk cancer and was lost to follow-up.

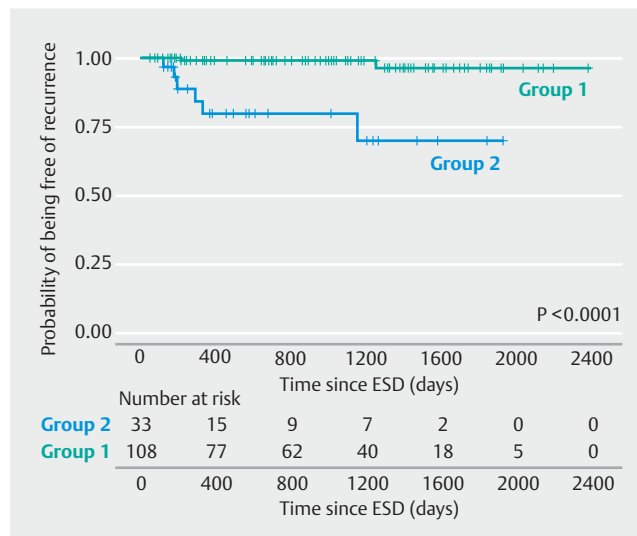
Discussion

The main findings of this long-term follow-up of our initial colorectal ESDs series are: (1) a recurrence rate less than 2% in cases where en bloc resection was achieved (irrespective of an involvement of resection margins); (2) a recurrence rate of roughly 20% after procedures that did not result in a one-piece specimens; (3) a recurrence pattern that was amenable to repeated endoscopic treatment; and (4) a curative resection for five of 13 cases of invasive cancer with no residual cancer after surgery for en bloc/R0 resection of high-risk early cancers and only one invasive cancer in a surgical specimen, after resection of an adenoma with high-grade dysplasia that could not be removed completely.

► **Table 1** Recurrences according to the outcome of the initial procedure.

Initial procedure	Recurrence (rate)
Group 1 ESD en bloc	2/108 (1.8%)
ESD en bloc/R0	0/75 (0.0%)
ESD en bloc/R1	2/33 (6.1%)
Group 2 ESD not en bloc or converted to EMR	6/33 (18.2%)
ESD not en bloc	2/15 (13.3%)
ESD converted to EMR	4/18 (22.2%)

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.



► **Fig. 2** Kaplan-Meier of recurrence stratified for the outcome of the initial procedure.

Recurrence after piecemeal EMR is a problem [2, 5, 12] and the risk of recurrence increases with the size of the lesion [2, 3, 5]. Also, incomplete adenoma resection has a significant impact on risk of interval cancer [13]. Thus, follow-up endoscopy is recommended in current guidelines, but compliance with this recommendation is far from perfect [4]. Although encouraging reports have been published on reduction in recurrence after coagulation of the mucosal defect margins [14], even a low recurrence rate after fragmented resection will not avoid control endoscopies. The very low recurrence rate of <math>< 2\%</math> reported here after successful one-piece resection (irrespective of involved margin), however, might allow for a more relaxed endoscopic follow-up schedule. In fact, we did not observe a single recurrence after en bloc R0 resection. Moreover, incidence of recurrence after failed ESD attempts, which resulted in a fragmented resection, is in the range of published data for piecemeal EMR. As reported in studies on piecemeal EMRs, most recurrences were small and all could be treated endoscopically by repeat resection or ablation. With the advent of endoscopic full-thickness resection, en bloc R0 resections have become

► **Table 2** Outcome of patients with recurrent neoplasia.

Localiza-tion	Size	Initial ESD	Recurrence, size and histology	Management	Outcome
Rectum	80 mm	En bloc/R1	25 mm; tubular villous adenoma, low-grade dysplasia	EMR (R0)	No residual adenoma during follow-up
Cecum	55 mm	En bloc/R1	2 mm; tubular adenoma, low-grade dysplasia	Biopsy only	No residual adenoma during follow-up
Ascending	30 mm	Converted to EMR	10 mm; tubular adenoma, high-grade dysplasia	EMR/APC	No residual adenoma during follow-up
Cecum	50 mm	Converted to EMR	10 mm; tubular adenoma, low-grade dysplasia	EMR/APC (2x)	No residual adenoma during follow-up
Rectum	60 mm	Converted to EMR	15 mm; tubular adenoma, low-grade dysplasia	EMR/APC (3x)	No residual adenoma during follow-up
Rectum	70 mm	Converted to EMR	10 mm; tubular villous adenoma, high-grade dysplasia	EMR/APC	No follow-up data available
Cecum	60 mm	Converted to EMR	10 mm; tubular adenoma, low-grade dysplasia	EMR/APC	No follow-up data available
Cecum	25 mm	Converted to EMR	5 mm; tubular adenoma, low-grade dysplasia	EMR/APC	No residual adenoma during follow-up

Endoscopic submucosal dissection; EMR, endoscopic mucosal resection; APC, argon plasma coagulation.

► **Table 3** Outcome of patients who underwent surgery.

	Localiza-tion	Initial ESD	Histology after ESD	Surgical procedure	Final histology
#1	Rectum	ESD en bloc	pT1 (sm ³ ¹ -1500 μm), L1, V0, R0-G3 (high risk)	Low anterior rectal resection	No residual cancer
#2	Rectum	ESD en bloc	pT1 (sm ³ -3000 μm), L0, V0, R0-G2 (high risk)	Low anterior rectal resection	No residual cancer
#3	Rectum	ESD en bloc	pT1 (sm ³ -2400 μm), L0, V0, R0-G2 (high risk)	Low anterior rectal resection	No residual cancer
#4	Sigmoid	ESD en bloc	pT1 (sm ¹), L1, V0, R0-G3 (high risk)	Sigmoid colectomy	No residual cancer
#5	Ascending	ESD not en bloc	pT1 (sm ¹), L1, V0, Rx-G2 (high risk)	Right hemicolectomy	No residual cancer
#6	Transverse	ESD not en bloc	pT1 (sm ³ -1300 μm), L0, V0, Rx-G1 (high risk)	Transverse colectomy	No residual cancer
#7	Sigmoid	Converted to EMR	Tubular villous adenoma, high grade	Sigmoid resection	pT1(sm ³ -1800 μm), pN0, L0, V0, R0-G1
#8	Cecum	Converted to EMR	Tubular adenoma, low grade	Ileo-cecal resection	Recurrence, low-grade adenoma
#9	Ascending	Converted to EMR	Tubular-villous adenoma, low grade	Right hemicolectomy	No residual adenoma
#10	Rectum	Converted to EMR	Tubular-villous adenoma, low grade	Low anterior rectal resection	Recurrence, low-grade adenoma
#11	Cecum	Converted to EMR	Tubular-villous adenoma, low grade	Right hemicolectomy	Recurrence, low-grade adenoma

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.

¹ Submucosal infiltration depth: sm¹ < 1000 μm; sm³ ≥ 1000 μm

available for most recurrences and will likely replace thermal ablation in such cases [15]. Finally, in our case series, en bloc

resection by ESD avoided surgery in five of 13 patients with invasive cancer and with better technical expertise, the method

has the potential to even further reduce the need of additional surgery in T1 cancers [16].

The study has limitations, mainly due to the retrospective design and the incomplete follow-up, which also has been reported in prospective studies [4] and somehow reflects the real-life situation that not all patients present for recommended endoscopic control. The strength of the study is its long follow-up, the relatively large sample size (at least in comparison with other non-Asian studies), and its conduction under the conditions of a Western endoscopy unit without continuous access to expert supervision.

Conclusion

In summary, the data presented here should encourage Western endoscopists to take the trouble to perform colorectal ESD. While ESD is time-consuming, it carries only a moderate complication rate and comes with the reward of very low recurrence rates. In fact, even a conversion to fragmented resection does not seem to confer a disadvantage to the patient.

Competing interests

The authors declare that they have no conflict of interest.

References

- [1] Dumoulin FL, Hildenbrand R. Endoscopic resection techniques for colorectal neoplasia: Current developments. *World J Gastroenterol* 2019; 25: 300–307
- [2] Belderbos TD, Leenders M, Moons LM et al. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. *Endoscopy* 2014; 46: 388–402
- [3] Briedigkeit A, Sultanie O, Sido B et al. Endoscopic mucosal resection of colorectal adenomas >20 mm: Risk factors for recurrence. *World J Gastrointest Endosc* 2016; 8: 276–281
- [4] Knabe M, Pohl J, Gerges C et al. Standardized long-term follow-up after endoscopic resection of large, nonpedunculated colorectal lesions: a prospective two-center study. *Am J Gastroenterol* 2014; 109: 183–189
- [5] Seidel J, Färber E, Baumbach R et al. Complication and local recurrence rate after endoscopic resection of large high-risk colorectal adenomas of ≥ 3 cm in size. *Int J Colorectal Dis* 2016; 31: 603–611
- [6] Tanaka S, Kashida H, Saito Y et al. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc* 2020; 32: 219–239
- [7] Fuccio L, Hassan C, Ponchon T et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. *Gastrointest Endosc* 2017; 86: 74–86.e17
- [8] Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; 47: 829–854
- [9] Kaltenbach T, Anderson JC, Burke CA et al. Endoscopic removal of colorectal lesions—recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Gastrointest Endosc* 2020; 158: 1095–1129
- [10] Schmiegel WP C. Leitlinienprogramm Onkologie: S3-Leitlinie Koloroktales Karzinom, Langversion 2.1, 2019, AWMF Registrierungsnummer: 021/007OL. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF; 2019; https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Kolorektales_Karzinom/Version_2/LL_KRK_Langversion_2.1.pdf (23.01.2020)
- [11] Sauer M, Hildenbrand R, Oyama T et al. Endoscopic submucosal dissection for flat or sessile colorectal neoplasia >20 mm: A European single-center series of 182 cases. *Endosc Int Open* 2016; 4: E895–E900
- [12] Pohl H, Srivastava A, Bensen SP et al. Incomplete polyp resection during colonoscopy—results of the complete adenoma resection (CARE) study. *Gastroenterology* 2013; 144: 74–80.e71
- [13] Chiu SY, Chuang SL, Chen SL et al. Faecal haemoglobin concentration influences risk prediction of interval cancers resulting from inadequate colonoscopy quality: analysis of the Taiwanese Nationwide Colorectal Cancer Screening Program. *Gut* 2017; 66: 293–300
- [14] Klein A, Tate DJ, Jayasekaran V et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. *Gastroenterology* 2019; 156: 604–613.e603
- [15] von Helden A, Hildenbrand R, Sido B et al. Endoscopic full-thickness resection using an over-the-scope device for treatment of recurrent/residual colorectal neoplasia: a single-center case series. *BMC Gastroenterol* 2019; 19: 121
- [16] Tomiki Y, Kawai M, Kawano S et al. Endoscopic submucosal dissection decreases additional colorectal resection for T1 colorectal cancer. *Med Sci Monit* 2018; 24: 6910–6917