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 larger flat or sessile lesions if the current standard, i.e. endoscopic mucosal resection (EMR), is applied. Thus, these lesions are resected 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 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.
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 specimen; (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.

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 < 2% 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

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

**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. 1** CONSORT diagram of outcome and follow-up of 182 procedures.

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

| Table 2 | Outcome of patients with recurrent neoplasia. |
|---------|-----------------------------------------------|
| **Localization** | **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. |
|---------|-------------------------------------------|
| **Localization** | **Initial ESD** | **Histology after ESD** | **Surgical procedure** | **Final histology** |
| #1 Rectum | ESD en bloc | pT1 (sm3–1500 µm), L1, V0, R0-G3 (high risk) | Low anterior rectal resection | No residual cancer |
| #2 Rectum | ESD en bloc | pT1 (sm3–3000 µm), L0, V0, R0-G2 (high risk) | Low anterior rectal resection | No residual cancer |
| #3 Rectum | ESD en bloc | pT1 (sm3–2400 µm), L0, V0, R0-G2 (high risk) | Low anterior rectal resection | No residual cancer |
| #4 Sigmoid | ESD en bloc | pT1 (sm1), L1, V0, R0-G3 (high risk) | Sigmoid colectomy | No residual cancer |
| #5 Ascending | ESD not en bloc | pT1 (sm1), L1, V0, Rx–G2 (high risk) | Right hemicolectomy | No residual cancer |
| #6 Transverse | ESD not en bloc | pT1 (sm3–1300 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(sm3–1800 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 hemicolecotomy | 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 hemicolecotomy | Recurrence, low-grade adenoma |

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

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

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