

Feasibility of endoscopic submucosal dissection for recurrent colorectal tumors after endoscopic mucosal resection

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Abstract

Background : Colorectal recurrent lesions after endoscopic mucosal resection (EMR) often contain severe fibrosis. In such lesions, repeat EMR is often difficult and endoscopic piecemeal mucosal resection (EPMR) has a high risk of repeated recurrence, while surgery is considered overtreatment. Whether ESD can be used safely and reliably to treat such difficult lesions has not been adequately verified. We analyzed the treatment outcomes of ESD for recurrent lesions after EMR.

Methods : Among 653 colorectal ESD conducted in our institution between April 2012 and August 2017, 27 consecutive patients underwent the procedure for recurrent lesions after EMR. Treatment outcomes including en bloc resection rate, R0 resection rate, and curative resection rate; complications were analyzed.

Results : Treatment outcomes of the 27 patients were as follows: en bloc resection rate 81.5%, R0 resection rate 74.1%, curative resection rate 74.1%, median procedure time 47 min (range 10–210 min), perforation rate 0%, and delayed bleeding rate 3.7%. The corresponding rates for 626 patients who underwent colorectal ESD during the same period for lesions other than recurrence after EMR were 97.2%, 95.5%, 88.7%, 37 min (7–225 min), 0.5%, and 2.8%. There were no differences in complication rates. Treatment outcomes including en bloc resection rate were inferior in the recurrence group compared to non-recurrent group, but no local recurrence was found in all patients.

Conclusions : Colorectal ESD is feasible for recurrent colorectal lesions after EMR. The procedure is safe and achieves good treatment outcomes with no local recurrence. (*Acta gastroenterol. belg.*, 2019, 82, 375-378).

Keywords : ESD, colorectal, salvage, recurrent, residual

Abbreviations : EMR Endoscopic mucosal resection ; EPMR Endoscopic piecemeal mucosal resection ; ESD Endoscopic submucosal dissection.

Introduction

High curability has been reported for endoscopic submucosal dissection (ESD), and ESD is considered an effective procedure for treating gastrointestinal cancers (1-3). In the initial stage of clinical application, technical difficulty and high complication rate have been reported as issues of ESD. However, with advances in device and technical improvement, the procedure has been standardized and treatment outcome has improved dramatically compared with the past (4-9). However, lesions that are difficult to treat by ESD still exist, and among them, fibrosis is considered the most difficult factor (10-12). Fibrosis is always found in recurrent lesions after endoscopic mucosal resection (EMR), although the causes and severity of fibrosis vary. In many

recurrent cases, fibrosis is severe. In such lesions, *en bloc* resection is difficult to achieve by repeat EMR. While endoscopic piecemeal mucosal resection (EPMR) is an alternative option, the risk of recurrence ranges from 2.7 to 27.2%, and is high compared to *en bloc* resection (13-15). Since an accurate pathological diagnosis including depth of invasion is often difficult, caution is needed in deciding indications. On the other hand, surgical treatment is considered an overtreatment, considering that the lesions are early cancers or precancerous tumors. ESD is potentially useful for recurrent lesions. A sub-analysis of a small number of patients who underwent endoscopic resection for local recurrent lesions after prior endoscopic resection suggested that ESD may be effective (16). However, whether ESD is safe and reliable for such difficult lesions has not been adequately validated. In the present study, we focused on salvage ESD for recurrent lesions after EMR, and analyzed the treatment outcomes and evaluated its feasibility.

Patients and Methods

Patients

Among 653 colorectal ESD performed in our institution between April 2012 (when colorectal ESD was approved for health insurance coverage) and August 2017, 27 consecutive patients (27 lesions) underwent the procedure for recurrence after EMR. In all these patients, the initial treatment was EMR performed in other hospitals. Within this period, there was no case of conversion to surgical treatment due to technical reason. All patients provided written informed consent. The study was approved by the ethics committee of Chiba Cancer Center and carried out in accordance with the World Medical Association's Declaration of Helsinki. This study is a retrospective study showing the outcome of salvage ESD for recurrent lesions of EMR.

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Indication

According to the Japanese guidelines for the treatment of colorectal cancers, intramucosal cancer and submucosal cancer less than 1,000 μm without lymphovascular invasion or a poorly differentiated component are indicated for endoscopic treatment, because there is no risk of metastasis. Diagnosis of these lesions were based on pit pattern analysis with magnifying chromoendoscopy. Since the subjects in this study had recurrent lesions after EMR, ESD treatment was selected when the lesions were judged to be difficult to treat by EMR, and were diagnosed as mucosal cancer, superficial submucosal cancer, or adenoma.

ESD procedure

The procedures were performed by two expert endoscopists who had experience of performing over 500 esophageal, gastric or colorectal ESD. The devices used in ESD are shown in Figure 1. The Dual knife (Olympus Co., Tokyo, Japan) was used as the main device, and was combined with the SB Knife Jr (Sumitomo, Japan) as the second knife depending on the circumstances. The Dual knife is a needle type knife with a 1.5 mm tip. The SB Knife Jr is a scissors-type knife, and is insulated around the knife. Sodium hyaluronate acid was used for injection into the submucosal layer, and a high frequency electrosurgical generator VIO300D (ERBE, Germany) was used for ESD. In the present study, as a strategy to overcome severe fibrosis in lesions recurring after EMR, we used the Short ST Hood (Fujifilm, Japan) as a transparent hood to facilitate the approach to the narrow submucosal layer with fibrosis. As treatment strategy, we started cutting on the anal side and away from the scar. After the dissection of the anal side, we then performed

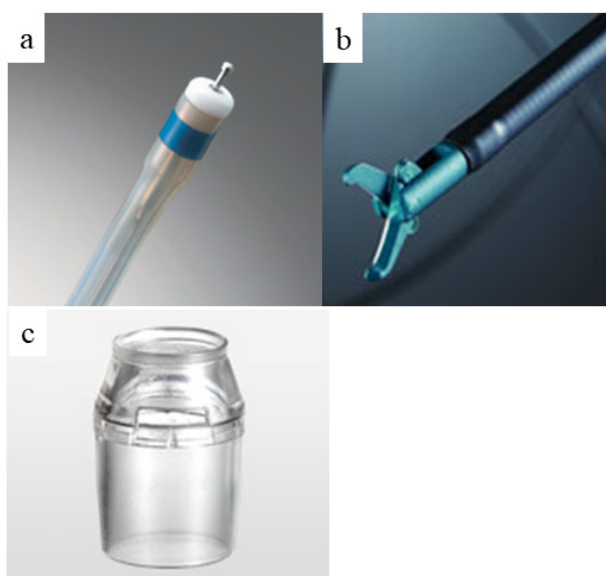


Figure 1. — Devices used in endoscopic submucosal dissection in the present study: (a) Dual knife, (b) SB Knife Jr, (c) Short ST Hood.

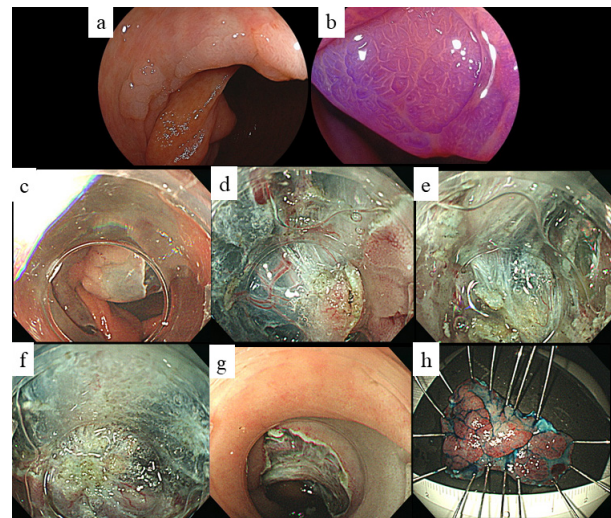


Figure 2. — A case of recurrent lesion after endoscopic mucosal resection in ascending colon. (a, b) Recurrent lesion in ascending colon, (c) circumferential cutting, (d) submucosa with mild fibrosis, (e, f) submucosa with severe fibrosis, (g) dissection completed after treatment time of 90 min, (h) pathological finding indicated complete resection; high grade dysplasia.

circumferential cutting and dissection sequentially. During this procedure, the region with less fibrosis was first dissected, and the part with severe fibrosis was approached at the end. This strategy facilitated the approach to the narrow submucosal layer with severe fibrosis (Figure 2). Although the Dual knife was used as the main device, the SB Knife Jr was used in combination when the scope was oriented vertically to the muscular layer, because of the high risk of perforation (Figure 3).

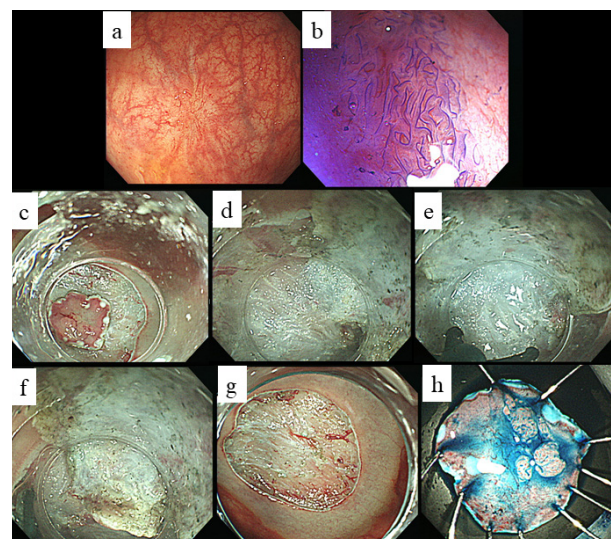


Figure 3. — A case of recurrent lesion after endoscopic mucosal resection in sigmoid colon. (a, b) Recurrent lesion in sigmoid colon, (c) circumferential cutting, (d) submucosa with severe fibrosis, (e, f) site at which the scope is oriented vertically to the muscular wall (SB Knife Jr was used), (g) dissection completed after treatment time of 90 min, (h) pathological finding indicated complete resection; high grade dysplasia.

Moreover, clipping was not done to close the ulcer after dissection.

Follow-up evaluation

When a negative margin was gotten by ESD, colonoscopy was performed one year later. When the margin was unknown or positive, colonoscopy was performed 3 to 6 months later. Endoscopic examination was conducted using dye spraying, or a biopsy was performed. Colonoscopic follow-up was continued once a year.

Statistical analysis

Treatment outcomes were evaluated by analyzing *en bloc* resection rate, R0 resection rate, and curative resection rate. Procedural complications were analyzed as perforation rate and delayed bleeding rate. Furthermore, local recurrence rate was also analyzed.

The data are presented in percentage or median and range. Chi-square test was used to compare the *en bloc* resection rate and rates of procedure-related complications between two groups. Mann-Whitney's U test was used to compare the procedure time between two groups. A p value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using StateMate IV (ATMS, Tokyo, Japan).

Results

The clinicopathological features of the 27 recurrent lesions after EMR are shown in Table 1. Treatment outcomes for these cases were as follows: *en bloc* resection rate was 81.5%; R0 resection rate was 74.1%; curative resection rate was 74.1%; median tumor diameter was 20 mm (range, 1-53 mm); median diameter of resected specimen was 27 mm (range, 12-55 mm); and median procedure time was 47 min (range, 10-210 min). For procedural complications, perforation rate was 0% and delayed bleeding rate was 3.7%. All bleeding cases were successfully treated using endoscopic coagulation. During ESD, the SB Knife Jr was used as a second knife in 11 cases (40.7%). Pathological examination of the resected specimens revealed high grade dysplasia in 20 cases and low grade dysplasia in 7 cases.

Treatment outcomes of 626 patients who underwent colorectal ESD during the same period for lesions other than recurrence after EMR were: *en bloc* resection rate 97.2%; R0 resection rate 95.5%; curative resection rate 88.7%; median procedure time 37 min (range, 7-225 min); perforation rate 0.5% and delayed bleeding rate 2.8%.

The *en bloc* resection rate, R0 resection rate, and curative resection rate were significantly lower in recurrent lesions than in non-recurrent lesions ($p < 0.001$, < 0.001 , and < 0.05 , respectively). Delayed bleeding rate and perforation rate were not significantly different

Table 1. — Clinicopathological features of 27 cases of recurrent colorectal tumor after endoscopic mucosal resection.

Age, median(y)(range)	72(52-88)
Location(C/A/T/D/S/R)*	0/2/4/3/3/15
Resected size, median(mm)(range)	27(12-55)
Morphology; Is/IIa(LST-G/NG)	4/23(14/9)
Pathological finding(HGD/LGD)**	20/7

*C : cecum, A : Ascending, T : Transverse, D : Descending, S : Sigmoid, R : Rectum **HGD : high grade dysplasia, LGD : low grade dysplasia.

Table 2. — Treatment outcomes and complications in 27 cases of recurrent tumor after endoscopic mucosal resection and 626 non-recurrent cases

	Recurrent cases (N=27)	Others (N=626)	P value
Median tumor size (mm)(range)	20(1-53)	22(2-101)	N.S
Median procedure time (min)(range)	47(10-210)	37(7-225)	$p < 0.001$
En bloc resection	81.5%	97.2%	$p < 0.001$
R0 resection	74.1%	95.5%	$p < 0.001$
Curative resection	74.1%	88.7%	$p < 0.05$
Use of SB knife Jr	40.7%	18.5%	$P < 0.01$
Complication			
Perforation	0%	0.5%	N.S
Bleeding	3.7%	2.8%	N.S
Local recurrence	0%	0%	N.S

between recurrent and non-recurrent lesions. During a median follow-up period of 33 months (range, 3-64 months), there was no local recurrence in all the patients studied (Table 2).

Discussion

Improvements in endoscopic devices have decreased complication rates of ESD, such as perforation. In addition, after gradual evolution, the technique is now widely accepted for the management of large colorectal neoplasms in Japan. However, the presence of fibrosis has been reported to be a factor contributing to treatment difficulty and also a risk factor of perforation (10-12). Particularly, fibrosis is always present in recurrent lesions after EMR, and these lesions are considered to be very difficult to treat. In this study, we analyzed the treatment outcomes of ESD for recurrent lesions after EMR, and verified that ESD can be performed safely and effectively even in post-EMR recurrent lesions with severe fibrosis. A previous study reported the usefulness of ESD for recurrent lesions after gastric EMR (17). Sakamoto reported treatment strategies for recurrent lesions after colorectal EMR. They treated recurrent or residual colorectal lesions with EMR in 58 cases and with ESD in 9 cases, and reported *en bloc* resection rates of 39% and 56%, respectively, indicating a higher rate for ESD. However, only a small number of cases underwent ESD in that study, and the cases were not consecutive. In the

present study, we treated all recurrent lesions after EMR with ESD, and analyzed a large number of consecutive cases.

On the other hand, although EPMR appears to be a possible alternative option, repeated treatments pose physical and economical burdens to patients. Furthermore, several case studies suggest that residual tumor cells after incomplete EMR or polypectomy may acquire greater malignancy (18-20). Additionally, full thickness resection is the candidate for the treatment. But we think it is not adequate for epithelial tumors, because there are the possibility of dissemination. The exposure of tumor to peritoneal lumen should be avoided. Even if the lesion is thought to be benign, colorectal tumor sometimes contain cancer. Before treatment, it is difficult to diagnose them completely. Therefore, ESD with high *en bloc* resection rate and no recurrence is considered to be safe and the most appropriate treatment.

In the present study, the tumor size was accidentally similar in the both groups. Although the *en bloc* resection rate of ESD for recurrent lesions was slightly lower than that for non-recurrent lesions, there was no local recurrence. As a possible reason for this result, we propose the following. In ESD, the extent of resection is determined completely by circumferential cutting. In EMR, however, resection by snare does not guarantee that the tumor together with surrounding normal mucosa are being resected. On the other hand, in the case of piecemeal resection in ESD, since the extent of resection include both tumor and surrounding normal mucosa, the risk of residual tumor is reduced.

The results of this study may potentially alter the management paradigm of treatment strategy for recurrent lesions after EMR. However, since ESD were performed by expert endoscopists in the present study, the results may not be generalized to all institutions. Since fibrosis has been reported to be a risk factor of perforation also in colorectal ESD, this procedure should be performed by endoscopists who are sufficiently competent in endoscopic procedures. Another limitation is the retrospective and single-center design of the study. And the study did not show the comparison with the matched group. Further prospective studies in multicenter are required to validate the present findings.

In conclusion, this study suggests that ESD may be effective as a salvage therapy for the treatment of residual or recurrent colorectal tumors.

Disclosure

Drs. Suzuki, Kitagawa, Nankinzan, Hara, and Yamaguchi have no conflicts of interest or financial ties to disclose.

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