Treatment strategy for recurrent or residual colorectal tumors after endoscopic resection

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Abstract

Background Piecemeal resection of colorectal neoplasms is associated with a higher risk of recurrent or residual tumors, but nearly all such cases can be cured by additional endoscopic resection (ER). Although the adoption of endoscopic submucosal dissection (ESD) for colorectal neoplasm is continuing, the safety of this treatment for recurrent or residual tumors has not been fully assessed. We evaluated salvage therapy for the treatment of recurrent or residual tumors, and propose an endoscopic treatment strategy for these tumors.

Methods This retrospective study was conducted for 60 consecutive patients who had with locally recurrent or residual tumor after ER between January 2004 and October 2005. Endoscopic treatment strategy, treatment results, complications and clinical outcomes were recorded.

Results Among 69 lesions in 60 patients, 67 were treated endoscopically, whereas 2 required surgical treatment. Of these 67, 87% (58/67) were resected by endoscopic mucosal resection (EMR) and 13% (9/67) by ESD. En bloc resection rate was 39% (23/58) in the EMR group and 56% (5/9) in the ESD group. One limitation of this study is that it was a single-center retrospective analysis.

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Conclusions ESD is safe and effective for the treatment of recurrent or residual colorectal tumors. However, because of its technical difficulty, the en bloc resection rate is lower than that for the treatment of nonrecurrent lesions.

Abbreviations

ER	Endoscopic resection
EMR	Endoscopic mucosal resection
EPMR	Endoscopic piecemeal mucosal resection
ESD	Endoscopic submucosal dissection
TEM	Transanal endoscopic microsurgery
HGD	High grade dysplasia

Thanks to its minimal invasiveness, relative safety, and cost-effectiveness, endoscopic mucosal resection (EMR) is now widely used for the treatment of colorectal tumors. However, because of the limitations in snare size and the technical difficulty of en bloc resection, it is not used to treat lesions larger than 20 mm in diameter [1], which are instead resected by using endoscopic piecemeal mucosal resection (EPMR). A method newly developed in Japan called endoscopic submucosal dissection (ESD) does allow the en bloc resection of larger lesions; however, because of its technical difficulty in the colorectum, its use for cancers at these sites is not high [2–5, 20].

The risk of residual tumor with EPMR (2.7–27.2%) is greater than that with en bloc resection [6, 16]. Moreover, complete retrieval of all specimens and histological determination of the depth of cancer invasion in EPMR are

sometimes difficult [6–13]. It has been speculated that additional endoscopic treatment can achieve complete remission in most recurrent or residual tumors, but methods and safety in the treatment of these tumors have not been fully assessed. We evaluated salvage endoscopic therapy for the treatment of recurrent or residual tumors. We also propose an endoscopic treatment strategy for these tumors.

Patients and methods

We retrospectively analyzed a database of all patients who underwent endoscopic treatment, including transanal endoscopic microsurgery (TEM), at our institution from January 2004 to October 2005 and identified all cases of local recurrent or residual tumors.

Sixty-nine colorectal tumors in 60 patients fulfilled the criteria of this study. In all, 67 lesions underwent endoscopic treatment, whereas two other patients who did not receive appropriate endoscopic surveillance required surgical treatment because the recurrent lesions were endoscopically diagnosed as invasive cancer. Of the 67 lesions, 58 were treated by EMR, and 9 that were technically difficult to remove by EMR were treated by ESD (Fig. 1). With regard to the initial treatment, 47 of the 58 EMR-treated lesions were residual or recurrent tumors treated at our and 9 other hospitals, and 4 of the ESD lesions were treated at our hospital and 5 at other hospitals.

Clinical indication of endoscopic treatment

Evidence regarding the clinical indications for endoscopic treatment is growing. First, it has been reported that intramucosal colorectal cancers show no lymph node metastasis. Second, some reports have revealed that lesions with submucosal invasion limited to less than 1,000 μm without lymphovascular invasion or a poorly differentiated component do not involve lymph node metastasis. Moreover, the depth of invasion of colorectal neoplasms can be

Fig. 1 Follow-up of 69 colorectal lesions after initial treatment

predicted using pit pattern analysis with magnifying chromoendoscopy. Endoscopic treatment for colorectal lesions is therefore based on the conventional endoscopic and pit pattern findings of a noninvasive pattern [14]. With regard to endoscopic management after resection, follow-up colonoscopy is required only for the observation of treatment sites after endoscopic resection for high-grade dysplasia/intramucosal cancer, which also is the case with adenoma. In contrast, borderline cases (i.e., invasion depth of approximately 1,000 μm) or EPMR cases, in which the histology of the tumor cannot be precisely assessed, require extensive assessment (e.g., CT scan, abdominal ultrasonography, tumor markers) to determine the presence of metastatic disease.

Treatment strategy and techniques

EMR

In this study, several endoscopic procedures were used in the EMR group, including hot biopsy, snare polypectomy, and conventional EMR. These methods were chosen according to the size and endoscopic features of the polyp. Hot biopsy forceps are suitable for the excision of adenomas up to 5 mm in size, and snare polypectomy for pedunculated or semipedunculated polyps larger than 6 mm. Indications for EMR include flat-type adenomas, including those with severe dysplasia, as well as early colorectal cancers diagnosed as having a noninvasive pattern by magnifying chromoendoscopy [14]. Conventional EMR procedures were performed using the well-recognized general method of tangential submucosal injection of normal saline or glycerol.

ESD

Candidates for ESD were large lesions >20 mm that were technically unsuitable for conventional EMR due to the presence of extensive submucosal fibrosis. The technique has been standardized for early gastric cancer and is described in detail elsewhere [15]. For ESD of colorectal neoplasms, we developed a bipolar needle knife (B-knife) (Zeon Medical Inst., Tokyo, Japan), in which the electric current is localized to the needle tip, and an insulation-tipped knife (IT-knife), which allows safe dissection (Olympus Co, Tokyo, Japan).

ESD is performed as follows. Glycerol and sodium hyaluronate acid are first injected into the submucosal layer under the tumor. Initial incision of the mucosa is made with the B-knife outside the lesion edge on the elevation caused by the submucosal injection. After completion of a circumferential incision, additional submucosal injection of the same solution is made before submucosal dissection to
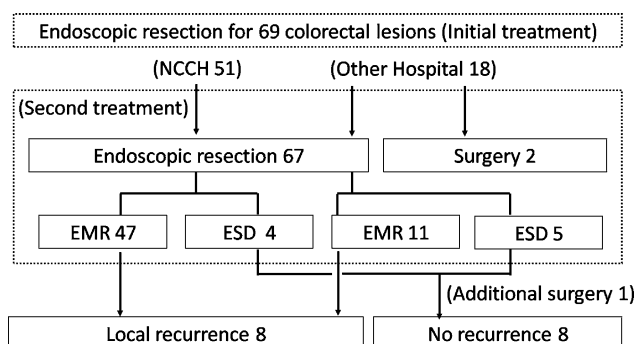
prevent perforation. The IT knife or B-knife is then used to dissect the submucosal layer (Fig. 2).

Sedation

ESD procedures in our hospital are performed under conscious sedation in an endoscopy room. Intravenous injections of 2–3 mg of Midazolam and 15 mg of pentazocine are administered in all cases. An additional 2 mg of midazolam is given as necessary at the endoscopist's discretion.

Pathological evaluation

We defined resections as en bloc (namely, resection of the tumor in one piece) or piecemeal, in which the lesion was removed in multiple fragments. All resected specimens were fixed in 10% buffered formalin. En bloc specimens and, where possible, larger piecemeal specimens were further cut into 2-mm-wide slices. The fragments or slices were embedded in paraffin, cut into 3-µm sections, stained with hematoxylin–eosin, and microscopically examined for histologic type by pathologists specializing in gastrointestinal pathology.

Fig. 2 **A** Conventional image of a sigmoid colon, flat-type (0-IIa), high-grade dysplasia. **B** Chromoendoscopy image using indigo carmine. **C** Circumferential incisions were made into the adjacent mucosa using the bipolar needle knife (ball tip type) to permit submucosal access. **D** After initial dissection, dense fibrotic bands was seen beneath the center of the lesion. **E** After submucosal dissection, a snaring technique was applied to achieve final dissection. **F** En bloc resection was achieved without complications
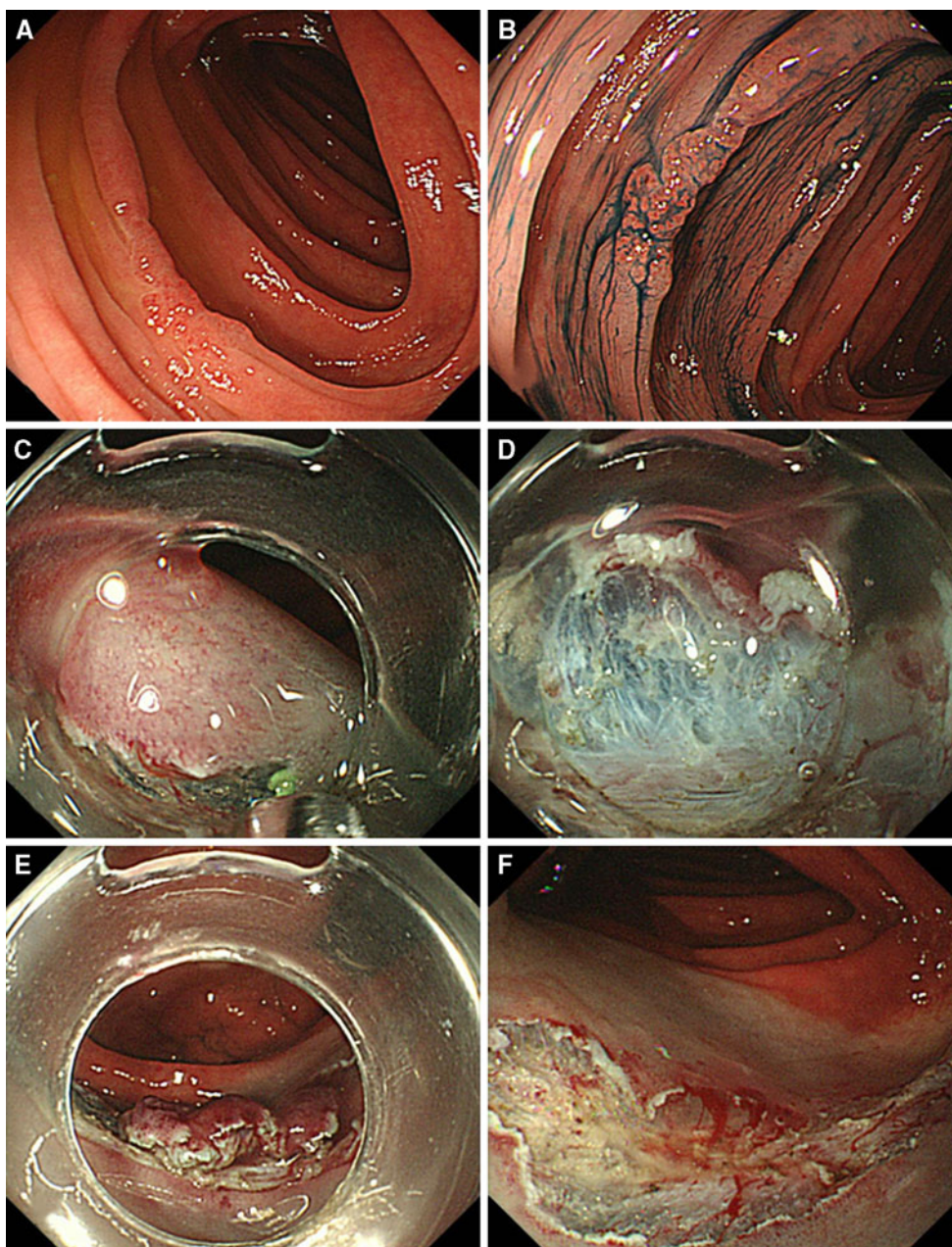
Statistical analysis

Comparisons were performed with the Pearson χ^2 or the Fisher exact test for categorical data. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Analysis was performed with Statview statistical software (Statview Software version 5.0; Abacus Concepts, Berkeley, CA).

Ethical considerations

Written, informed consent was obtained from all patients who underwent colonoscopy examination and any form of treatment.

Results

Treatment results, complications, and clinical outcomes are summarized in Table 1. Lesions in the ESD group was significantly larger than those in the EMR group ($P = 0.001$). There was no statistically significant difference in the rates of en bloc and piecemeal resection between the two groups.

En bloc resection rate

ESD led to en bloc resection in 5 of 9 lesions (56%)—a higher rate than the 23 of 58 lesions (39%) in EMR group, despite the significantly larger tumor size in the ESD group. Nevertheless, this difference between the groups was not statistically significant (Table 1).

Complications

One perforation (2%) occurred in the EMR group. This perforation was small and was successfully treated

Table 1 Treatment results and complications, and clinical outcomes in 67 cases of recurrent or residual colorectal tumor after mucosal or submucosal endoscopic resection

	EMR ($n = 58$)	ESD ($n = 9$)
Mean tumor size (mm)	7.8 ± 6.4*	25.3 ± 19.6
En bloc or piecemeal		
En bloc resection	23 (39)	5 (56)
Piecemeal resection	35 (61)	4 (44)
Complications		
Perforation	1 (2)	0 (0)
Bleeding	1 (2)	1 (11)
Rate of recurrence	8 (14)	0 (0)

Data are means ± standard deviations or numbers with percentages in parentheses

* $P = 0.001$

endoscopically using endoclips. One patient in each group developed bleeding. All bleeding episodes were successfully treated using endoclips or coagulation.

Clinical outcomes

We reviewed all patients who underwent endoscopic resection for recurrent lesions at 6 months after surgery. No cases of recurrent or residual lesions were seen in the ESD group compared with eight recurrences (14%) from lesions treated by EMR (Fig. 1). Most cases of recurrence were intramucosal neoplasm and were treated with additional conventional EMR or coagulation. All patients with recurrence achieved complete remission.

Comparison of pathological characteristics between initial and recurrent or residual tumors

Of the total of 67 initial lesions, 21% (14/67) were adenomas, 58% (39/67) were high-grade dysplasia (HGD), and 4% (3/67) were submucosal cancer invading as far as the superficial layer of the submucosa (SM1: <1,000 μm). In contrast, for recurrent or residual lesions, among cases in which the initial lesion was adenoma, 71% (10/14) were adenomas and 29% (4/14) were HGD; whereas among cases in which the initial lesion was carcinoma, 54% (28/52) were adenomas, 19% (10/52) were HGD, and 2% (1/52) were invasive submucosal cancer without distant or lymph-node metastasis (Table 2).

Discussion

In this study, we found that ESD is a safe and effective treatment for recurrent or residual colorectal tumors. However, because of the technical difficulty of this procedure, the en bloc resection rate is lower than that in the treatment of nonrecurrent lesions. These findings provide further evidence for the clinical usefulness of ESD in a variety of conditions and sites.

Among the benefits of ESD, this procedure is suitable for use in endoscopic salvage procedures for recurrent lesions.

Table 2 Pathological characteristics of initial and recurrent or residual lesions

Initial lesions	Recurrent or residual lesions			
	Adenoma	HGD	SM Ca.	Unknown
Adenoma	10	4	0	0
HGD	25	10	1	3
SM Ca.	3	0	0	0
Unknown	7	4	0	0

Furthermore, appropriate colonoscopic surveillance allows the achievement of complete cure by repeated conventional endoscopic treatment (hot biopsy, EMR, argon plasma coagulation, etc), even for recurrent or residual tumors.

These benefits emphasize the importance of a suitable follow-up period [16], which is currently considered to be 6 months after EPMR. In our study, most (88%) lesions recurring after initial treatment were diagnosed at the first follow-up colonoscopy within 6 to 12 months (Fig. 3). Surveillance at an inappropriate interval after EPMR, in contrast, would hamper the achievement of remission by conventional endoscopic treatment for almost all recurrent or residual tumors. Until recently, treatment for such lesions (i.e., those >20 mm or with severe fibrosis) was limited to surgical therapy. In our case series, however, the ESD technique enabled complete resection in these cases. Improvements in endoscopic devices and instruments have decreased complication rates with ESD, such as perforation, and after gradual evolution the technique is now widely accepted for the management of large colorectal neoplasms in Japan. The B-knife, for example, has been designed so that the high-frequency current sent to the muscle layer is reduced, enabling better control and greater endoscopist safety, whereas the return current from the knife toward the sheath tip results in greater patient safety [16–20]. However, because of its technical difficulty, longer procedure time, and increased risk of complications, it is not yet in universal use. Moreover, repeat endoscopic resection for recurrent tumor after endoscopic treatment or TEM is markedly difficult because of the development of submucosal fibrosis at the site of the previous treatment [21]. In this study, five of the nine lesions that underwent ESD (56%) were performed by en bloc resection. Although satisfactory, this rate is nevertheless lower than that in our previous series of patients who underwent ESD for primary colorectal cancer (168/200 patients; 84%) [20]. We consider that the technical difficulty of ESD makes its broad application to recurrent or residual tumor unfeasible, although not impossible. The treatment of these lesions is likely best performed using simple EMR and requires a proper surveillance interval after EPMR. In several previous reports [23–25], incomplete endoscopic resection for submucosal cancer was associated with an increased risk of rapid growth of residual tumor. Accurate histopathological evaluation of the resected specimen is therefore crucial to determine a surveillance strategy.

An important unanswered question is the clinicopathological features of recurrent or residual tumor. Several previous studies assumed that residual tumor cells had acquired greater malignancy after EMR, and the development of residual cancer after EMR or polypectomy has been described [22–25]. In one study, 11.4% of local recurrent tumors after EPMR consisted of HGD, even though the excised specimens were diagnosed as benign adenomas [26]. However, none of these cases revealed any evidence of invasive cancer in the locally recurrent tumor, or distant or lymph node metastasis.

Although the present results indicate the acceptability of additional endoscopic treatment after EPMR for adenoma, objections may arise in the case of carcinoma. Upon histopathological comparison of the initial and recurrent tumors in our series, the recurrent or residual tumors were mainly adenoma, and the histological grade of atypia did not increase in almost any case, even when the initial treatment was HGD. This can be explained as follows: almost all lesions of colorectal neoplasm, especially LST-G, were cancer in adenoma, and local recurrence or residual tumor might have resulted from incomplete resection at the initial treatment, i.e., positive resection margins. On this basis, very few residual or recurrent tumors may present a serious clinical problem.

Several limitations of our study warrant mention. First, ESD in the colon can presently be performed by expert colonoscopists in only a limited number of specialized hospitals, and broader application in general centers may be difficult. Second, this was a retrospective study conducted at a single institution, and the validity of this treatment for recurrent or residual tumors requires confirmation in multicenter trials.

In conclusion, this study suggests that ESD may be effective in salvage therapy for the treatment of residual or recurrent tumors. Operator skill requirements are high, however, and widespread application is presently difficult. The achievement of complete remission after endoscopic piecemeal resection is dependent on suitable surveillance procedures.
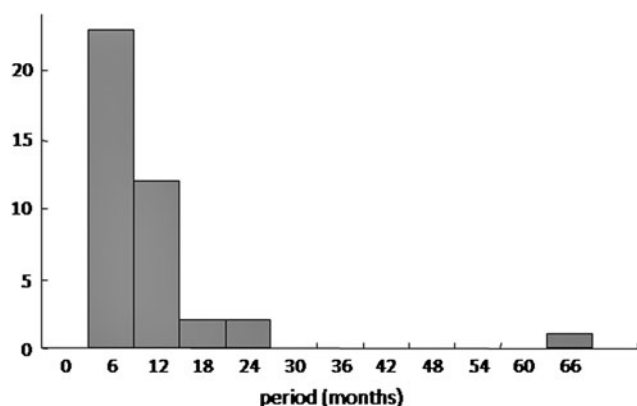
Fig. 3 Time between initial treatment and the detection of residual or recurrent tumor

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