



# Treatment strategy for local recurrences after endoscopic resection of a colorectal neoplasm

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## Abstract

**Background and Aim** Endoscopic salvage treatment for recurrent or residual neoplasms is sometimes technically challenging, and information in choice of treatment methods is lacking. This study aimed to clarify the appropriate treatment strategy for local recurrence after endoscopic resection (ER).

**Methods** Seventy-four patients with 74 lesions who received endoscopic treatment for local recurrence after ER for colorectal epithelial neoplasms between January 2010 and December 2016 were enrolled. Patients with hyperplastic polyp, sessile-serrated adenoma/polyp, and submucosal invasive cancer in their initial ER were excluded. Treatment methods, treatment outcomes, and recurrence rate were evaluated for each recurrence based on the preoperative endoscopic diagnosis (adenomatous or cancerous).

**Results** Forty-nine of the 74 patients diagnosed with adenomatous recurrence were treated using cold polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) in 15, 26, and 8 patients, respectively. Cold polypectomy was applied only to diminutive lesions. EMR and ESD en bloc resection rates were 53.8 and 100%, respectively ( $p=0.030$ ). Two patients (7.7%) in the EMR group developed local recurrence, but an additional ER achieved complete resection. Meanwhile, the remaining 25 patients diagnosed with cancerous recurrence were treated via EMR and ESD for 7 and 18 patients, respectively. EMR and ESD en bloc resection rates were 28.6 and 83.3%, respectively ( $p=0.017$ ). Three patients (42.9%) in the EMR group developed recurrence.

**Conclusions** Selecting appropriate treatment methods for adenomatous recurrence could be decided based on estimated pathology and lesion size. ESD was effective for cancerous recurrence to achieve complete disease control.

**Keywords** Cold polypectomy · Colorectal neoplasm · Endoscopic mucosal resection · Endoscopic submucosal dissection · Local recurrence

Endoscopic detection and removal of colorectal adenomas reduces the incidence of colorectal carcinoma and the associated mortality [1, 2]. Endoscopic mucosal resection (EMR) is now established as a safe and simple treatment method for colorectal epithelial neoplasm. However, large and flat lesions more than 2 cm in size often require piecemeal resection. There are several reports that piecemeal resection was a risk factor for local recurrence [3–9]. Conversely,

endoscopic submucosal dissection (ESD) is effective for en bloc resection of superficial colorectal tumors regardless of tumor size or location. The local recurrence rate in the ESD group was significantly lower than that of the EMR group (1.4% vs. 6.8%,  $p < 0.01$ ) in a multicenter prospective study in Japan [10].

Along with ESD spread, its efficacy for local recurrence has been reported [11–16]. According to the Japan Gastroenterological Endoscopy Society (JGES) guidelines for colorectal ESD and EMR [17], local residual or recurrent early carcinomas after endoscopic resection (ER) is one of the indications for ESD for colorectal tumors. Additionally, ESD can resect lesions with a positive non-lifting sign (including adenomas) for which EMR is generally difficult to

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apply and for which en bloc resection is desirable. However, the appropriate treatment strategy for these lesions, including ESD, remains unclear. Furthermore, cold polypectomy (CP) for low-grade dysplasia less than 10 mm has become widespread [18, 19], but there is no report of whether CP is acceptable for small recurrent lesions. This study aimed to clarify the treatment method and results of recurrent lesions, and to propose a strategy for the endoscopic treatment of local recurrent lesions.

## Materials and methods

### Patients and study design

A total of 74 patients with 74 lesions who received endoscopic treatment for local recurrence after an initial ER for colorectal epithelial neoplasms at our tertiary cancer center between January 2010 and December 2016 were enrolled. Patients with pathological diagnosis of hyperplastic polyps, sessile-serrated adenoma/polyps, or submucosal invasive cancers in their initial ER were excluded. Seven patients who underwent surgery were also excluded. The form of the local recurrence was divided into adenomatous recurrence and cancerous recurrence according to their preoperative endoscopic diagnosis.

We analyzed the procedural outcomes and recurrence rate according to the recurrent forms (adenomatous or cancerous) of the preoperative endoscopic diagnoses. A first surveillance colonoscopy after endoscopic treatment was carried out after at least 6 months up to 1 year. This retrospective study was approved by the institutional review board of our hospital (28-J88-28-1-3).

### Diagnosis of local recurrence

All the colonoscopies were performed using a high-resolution endoscope equipped with a magnification function (CF-H260AZI, PCF-Q260AZI, CF-HQ290ZI, PCF-H290ZI; Olympus, Tokyo, Japan). ER scars were carefully evaluated during colonoscopy. When an elevated lesion was detected in the scar or in the edge of the scar, it was necessary to diagnose whether it was neoplastic, non-neoplastic, or a non-invasive cancer. If a neoplastic recurrence was suspected in white light imaging (WLI), the lesion was evaluated using magnifying narrow-band imaging (NBI) according to Sano's classification [20] and the Japan NBI expert team (JNET) classification [21]. We decided that JNET Type 3 was the indication for surgical resection; Type 2B added pit pattern diagnosis based on Kudo's classification using magnifying chromoendoscopy and 0.05% crystal violet staining for excluding invasive cancer [22]. JNET Type 1 was considered non-neoplastic; thus, there was no need for resection.

The recurrence forms were defined as adenomatous recurrence (Fig. 1A–D): JNET Type 2A/ Kudo's Type III and IV pit pattern and cancerous recurrence (Fig. 2A–D): JNET Type 2B/ Kudo's Type V pit pattern.

### Endoscopic treatment for recurrent lesions

Detected recurrent lesions were treated by an endoscopist. The selection of endoscopic treatments included CP, EMR, and ESD. The indication for ESD was a lesion that was difficult to resect using conventional EMR with a snare, showing a positive non-lifting sign due to severe fibrosis or larger lesions and requiring hospitalization.

CP techniques such as cold biopsy forceps polypectomy and cold snare polypectomy are preferred for most diminutive polyps [18]. CP was performed using jumbo forceps (Radial Jaw 4 Jumbo Biopsy Forceps; Boston Scientific, Marlborough, MA, USA) or a captivator II snare (Boston Scientific, Natick, MA, United States). Regarding EMR, a captivator II snare and a high-frequency snare (SD-12L-1; Olympus, Tokyo, Japan) were used. The main devices for ESD were Dual knife (KD-650Q; Olympus) and ITknife nano (KD-612; Olympus). We used a high-frequency surgical generator (VIO300D; ERBE, Tübingen, Germany) and a CO<sub>2</sub> insufflation system (UCR; Olympus) during the procedure. A mixture of 0.4% sodium hyaluronate solution (Muco Up; Boston Scientific Japan, Tokyo, Japan) and 10% glycerol solution tinged with indigo carmine was injected into the submucosal layer during the ESD procedure.

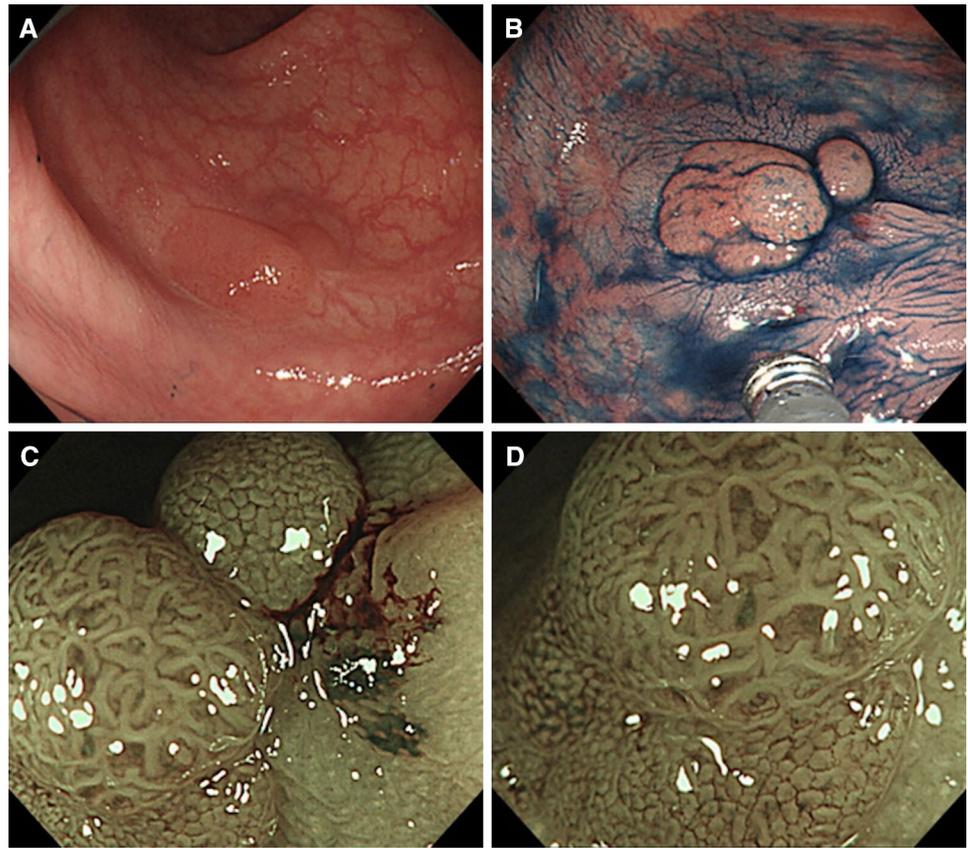
### Statistical analysis

Categorical variables were analyzed using the chi-squared test or Fisher's exact test. All tests were two-sided, and a *p* value < 0.05 was considered significant. Analyses were performed using JMP software version 11.0 (SAS Institute Inc., Cary, NC, USA).

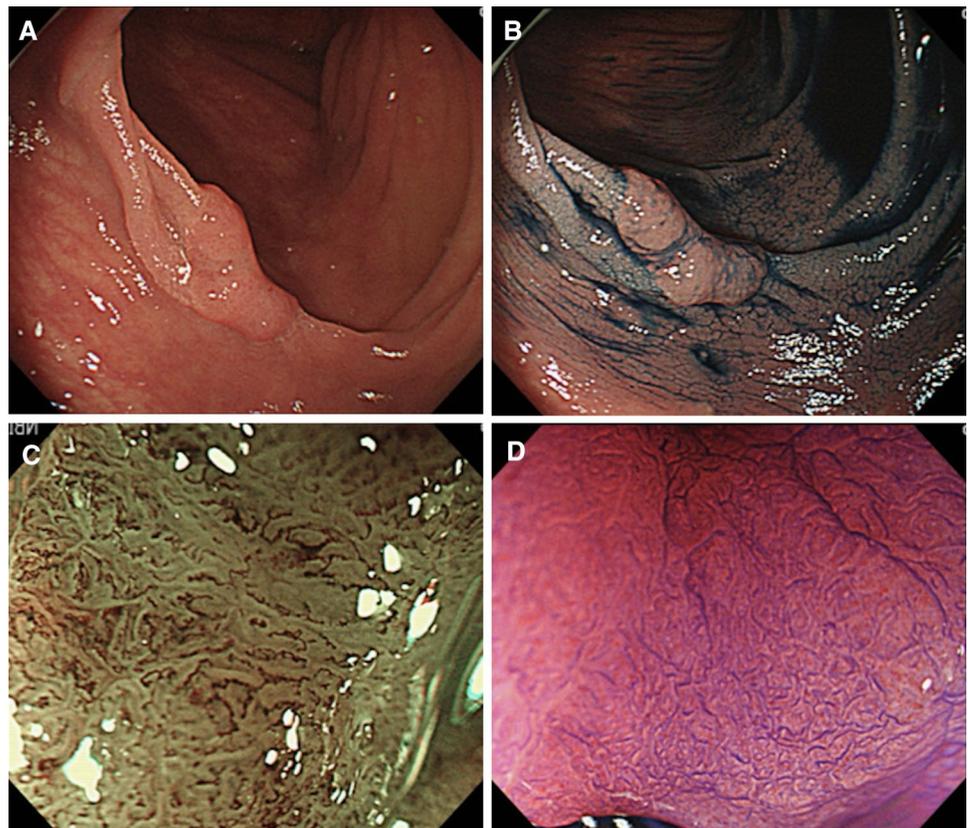
## Results

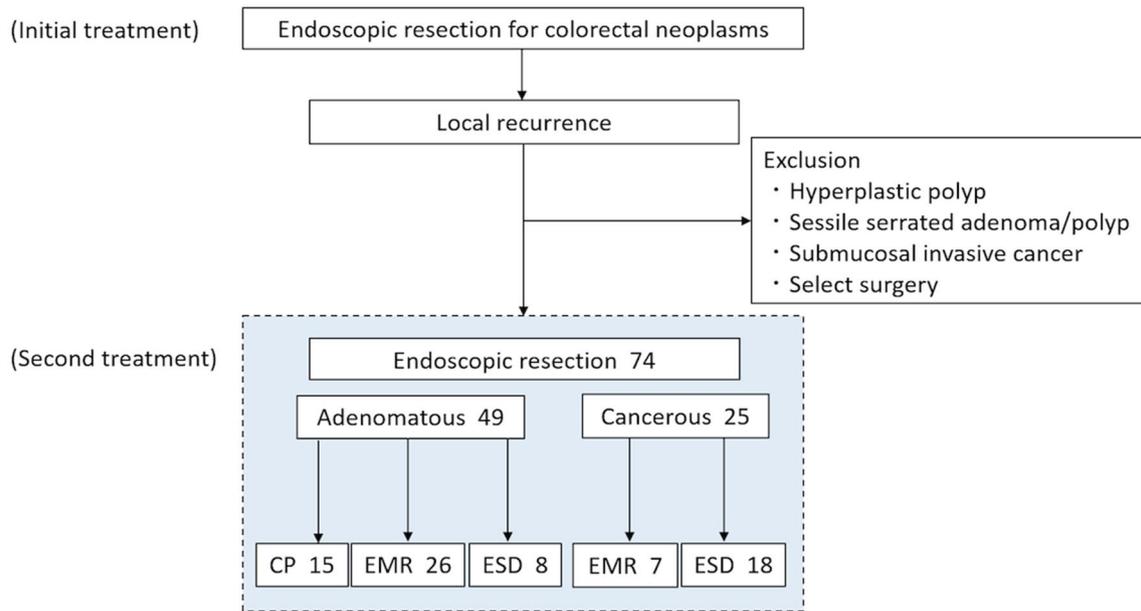
A total of 74 patients with 74 lesions underwent endoscopic treatment for local neoplastic recurrence. Of the 74 lesions, 49 lesions were diagnosed as adenomas and 25 as cancers. The second endoscopic treatment flow is shown in Fig. 3. The second treatments for local recurrence were CPs in 15 cases, EMRs in 33 cases, and ESDs in 26 cases. Next, we analyzed the treatment outcomes according to the recurrent forms of the preoperative endoscopic diagnoses. Forty-nine patients diagnosed with adenomatous recurrence were treated using CP, EMR, or ESD in 15, 26, and 8 patients, respectively. A comparison between the EMR and ESD group is shown in Table 1. The tumor size was significantly

**Fig. 1** Diagnosis of adenomatous recurrence: **A** WLI shows that the elevated lesion, 12 mm in size, is detected in the sigmoid colon; **B** The scar on the right side of the lesion became clear using chromoendoscopy with indigo carmine staining; **C**, **D** NBI magnifying showed that JNET is classified as Type 2A because of regular microvessel and surface patterns



**Fig. 2** Diagnosis of cancerous recurrence: **A** WLI shows that the elevated lesion, 16 mm in size, is detected in the ascending colon; **B** The scar on the right side of the lesion became clear using chromoendoscopy with indigo carmine staining. The surface structure of this lesion was rough; **C** NBI magnifying showed that JNET is classified as Type 2B; **D** Kudo's classification with magnifying chromoendoscopy is classified as VI pit pattern with mild irregularity





**Fig. 3** Second treatment flow using endoscopic treatment. *CP* cold polypectomy, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

**Table 1** Treatment outcomes of EMR and ESD in 49 recurrent adenomas

	EMR (n=26)	ESD (n=8)	p value
Lesion size [mean (range), mm]	6.4 (3–12)	23.0 (14–35)	<0.001
En bloc resection rate (%)	53.8 (14/26)	100.0 (8/8)	0.030
R0 resection rate (%)	26.9 (7/26)	50.0 (4/8)	0.388
Recurrence rate (%)	7.7 (2/26)	0.0 (0/8)	N/A

*EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *N/A* not applicable

larger in the ESD group than in the EMR group ( $p < 0.001$ ); EMR was not applied for lesions above 15 mm in size. The en bloc resection rates of the EMR and ESD groups were 53.8 and 100%, respectively ( $p = 0.030$ ). Two patients (7.7%) in the EMR group developed local recurrence; however, an additional ER achieved curative resection. CP was applied only to diminutive (<5 mm) lesions and there was no recurrence.

Of 25 patients diagnosed with cancerous recurrence, seven were treated using EMR and 18 using ESD (Table 2). No patient in this group was treated using CP. The tumor size was significantly larger in the ESD group than in the EMR group ( $p < 0.001$ ). The en bloc resection rates of the EMR and ESD groups were 28.6 and 83.3%, respectively ( $p = 0.017$ ). Surgery was performed in addition to non-curative resection for three lesions in the ESD group. All cases in the EMR group were mucosal cancer and no additional surgery was performed. The reasons for non-curative

**Table 2** Treatment outcomes of EMR and ESD in 25 recurrent cancers

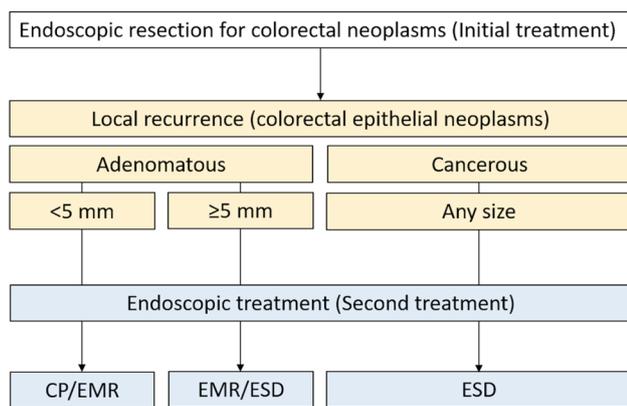
	EMR (n=7)	ESD (n=18)	p value
Lesion size [mean (range), mm]	9.3 (5–15)	23.7 (8–45)	0.006
En bloc resection rate (%)	28.6 (2/7)	83.3 (15/18)	0.017
R0 resection rate (%)	28.6 (2/7)	66.7 (12/18)	0.178
Additional surgery rate (%)	0.0 (0/7)	16.7 (3/18)	N/A
Recurrence rate (%)	42.9 (3/7)	0.0 (0/18)	N/A

*EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *N/A* not applicable

resection were piecemeal resection or lateral margin positive, and argon plasma coagulation (APC) was added in five cases. Three patients (42.9%) in the EMR group developed recurrence; the first patient required surgery because of the invasive local recurrence; the second patient required chemotherapy because of distant metastasis; and the third patient was followed up because of severe comorbidities.

## Discussion

We reported the treatment and results of the recurrence of 74 local neoplastic lesions after a first ER and summarized an endoscopic treatment strategy for recurrent lesions. These lesions often present with a non-lifting sign and treatment can be difficult. In this retrospective study, we discussed the need to distinguish between treatments depending on



**Fig. 4** Our strategy of endoscopic treatment for a local neoplastic recurrence. *CP* cold polypectomy, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

whether the recurrence is an adenoma or cancer. Based on the experience of recurrence in three patients who underwent EMR, we suggest that treatment of cancerous recurrence should be done with caution. The en bloc resection rate in the EMR group was significantly lower than in the ESD group, and frequent surveillance colonoscopies are required in incomplete resection cases. ESD is a useful method not only for large cancerous recurrence but also for small cancerous recurrence aimed at en bloc resection with negative margins.

If complete snare resection was not possible in EMR, the residual lesions were additionally removed by biopsy forceps or APC (at 30–40 W and 0.5–1 L flow depending on lesion location). Ablation is less controlled and less reliable than excision and does not provide tissue for histology. APC is one of the risk factors for local recurrence and Holmes et al. and Moss et al. recommend that recurrent lesions be resected via snare ablation rather than APC [23, 24]. In this study, APC was performed in 76.5% (13/17) (nine adenomatous recurrence, four cancerous recurrence) of patients in the EMR group for lesions which could not be completely resected. Among the cancerous recurrence cases, APC was performed more than once in patients with advanced local recurrence and distant metastasis occurred.

We proposed an endoscopic treatment strategy for local neoplastic recurrent (colorectal epithelial neoplasm) lesions, as shown in Fig. 4. Diminutive adenomatous recurrence (<5 mm) can be easily treated endoscopically in a single session and is not a significant clinical problem. For large lesions, snare resection is technically difficult; thus, EMR or ESD can be performed depending on the size. However, with regards to cancerous recurrence, conventional EMR with unknown margin evaluation should be avoided and ESD aimed at complete en bloc resection should be selected. In the short-run, ESD is more time consuming resulting in

higher healthcare costs, but is cost-effective long-term due to a lower patient burden, higher number of R0 resections, and lower recurrence rate with less need for repeat procedures [25].

ESD enables complete removal of recurrent lesions but presents some technical difficulties and is time consuming. In recent years, underwater endoscopic mucosal resection (UEMR) has received attention as a new method [26–28] and we have reported a case involving the utilization of UEMR [29]. UEMR allowed us to “float” the lesion away from the muscularis layer, allowing wide-field resection of the entire lesion and scars; moreover, UEMR eliminated the need for gravity. Although UEMR was not included in this study, it may become more popular than traditional EMR as a convenient and useful therapy in the future.

Desomer et al. reported that accurate endoscopic detection of recurrent lesions in a post-EMR scar can be performed using a standardized imaging protocol, which incorporates high-definition white light and NBI. This results in real-time, accurate recurrent lesion detection, allowing immediate and appropriate treatment [30]. Lesions suspected of invasive cancer are not indicated for endoscopic treatment; preoperative endoscopic diagnosis is important to realize our proposed strategy. If cancerous recurrence is suspected, magnification after crystal violet staining should also be observed in addition to NBI. Imai et al. mentioned that the presence of a deep semilunar fold, a fold convergence, and poor colonoscope operability were the strongest risk indicators of the failure of en bloc resection in ESD for colonic lesions [31]. Regarding recurrent lesions with such characteristics, surgical resection should also be recommended to patients as a treatment option.

Our study has some limitations. First, it was retrospective, conducted at a single tertiary cancer center. Second, there is selection bias regarding the treatment method as it was not randomized. Third, presently, ESD of the colon can only be performed by expert colonoscopists in a limited number of specialized hospitals and broader application in general centers may be difficult.

In conclusion, this study suggests that the selection of ER for local adenomatous recurrence could be based on lesion size. ESD is desirable for local cancerous recurrence to achieve complete disease control.

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### Compliance with ethical standards

**Disclosures** Sayo Ito, Kinichi Hotta, Kenichiro Imai, Yuichiro Yamaguchi, Yoshihiro Kishida, Kohei Takizawa, Naomi Kakushima, Noboru Kawata, Masao Yoshida, Hirotoishi Ishiwatari, Hiroyuki Matsubayashi, and Hiroyuki Ono have no conflicts of interest or financial ties to disclose.

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