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Applicability of endoscopic submucosal dissection after unsuccessful endoscopic mucosal resection in colorectal laterally spreading tumors: a single center experience

Kolorektal lateral yayılımlı tümörlerde başarısız endoskopik mukozal rezeksiyon sonrası endoskopik submukozal diseksiyonun uygulanabilirliği: tek merkez deneyimi

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ABSTRACT

Aim: Endoscopic mucosal resection might technically be unsuccessful (interrupted endoscopic mucosal resection) in some cases when treating large colorectal laterally spreading tumors. In the literature, data on the outcomes of the endoscopic submucosal dissection method in endoscopic mucosal resection interrupted tumors are lacking. In this study, we evaluated the results of patients who underwent endoscopic submucosal dissection for endoscopic mucosal resection interrupted laterally spreading tumors.

Materials and Methods: Between February 2019 and April 2021, 8 patients with endoscopic mucosal resection interrupted colorectal laterally spreading tumors underwent endoscopic submucosal dissection. The primary endpoint was en bloc, R0, and curative resection rates of endoscopic submucosal dissection.

Results: In all cases, endoscopic submucosal dissection was successfully completed. The mean tumor size was 61.5 mm (35–100 mm). The rate of en bloc resection, R0 resection and curative resection was 100%, 87.5% and 87.5% respectively. Intra-procedural perforation occurred in 1 patient (12.5%) and was successfully treated with clip application. Delayed bleeding occurred in 1 patient (12.5%), and was successfully treated with endoluminal hemostasis. Furthermore, histopathological examination revealed that laterally spreading tumors in 4 patients (50.0%) had submucosal invasion. Surgical resection was performed after endoscopic submucosal dissection in 1 patient owing to the presence of deep submucosal invasion.

Conclusion: Endoscopic submucosal dissection is an effective and relatively safe method in endoscopic mucosal resection interrupted colorectal laterally spreading tumors.

Keywords: Interrupted endoscopic mucosal resection, endoscopic submucosal dissection, laterally spreading tumors.

ÖZ

Amaç: *Geniş kolorektal lateral yayılımlı tümörlerin tedavisinde endoskopik mukozal rezeksiyon bazı durumlarda teknik olarak başarısız (tamamlanmamış endoskopik mukozal rezeksiyon) olabilir. Endoskopik mukozal rezeksiyon tamamlanmamış tümörlerde endoskopik submukozal diseksiyon yönteminin uygulanabilirliği ile ilgili literatürde kısıtlı veri mevcuttur. Biz bu çalışmada tamamlanmamış endoskopik mukozal rezeksiyon sonrasında endoskopik submukozal diseksiyon uyguladığımız kolorektal lateral yayılımlı tümörlü hastaların sonuçlarını analiz ettik.*

Gereç ve Yöntem*: Şubat 2019- Nisan 2021 tarihleri arasında endoskopik mukozal rezeksiyon tamamlanmamış kolorektal lateral yayılımlı tümörlerde endoskopik submukozal diseksiyon uygulanan 8 hasta çalışmaya dahil edildi. Primer sonlanım noktası olarak endoskopik submukozal diseksiyon ile en bloc, R0 ve küratif rezeksiyon oranlarına bakıldı.*

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Bulgular: *Tüm hastalarda endoskopik submukozal diseksiyon başarı ile tamamlandı. Ortalama tümör çapı 61,5 mm (35-100 mm) idi. En bloc, R0 ve küratif rezeksiyon oranları sırayla %100, %87,5 ve %87,5'du. Uygulama esnasında perforasyon bir (%12,5) hastada görüldü ve klip uygulanarak tedavi edildi. Gecikmiş kanama bir (%12,5) hastada izlendi ve endoluminal hemostaz sağlandı. Histopatolojik incelemede lateral yayılımlı tümörlerin dördünde (%50,0) submukozal invazyon izlendi. Derin submukozal invazyon nedeniyle bir hastada endoskopik submukozal diseksiyon sonrasında cerrahi rezeksiyon uygulandı.*

Sonuç: *Endoskopik mukozal rezeksiyon tamamlanmamış kolorektal lateral yayılımlı tümörlerde endoskopik submukozal diseksiyon etkili ve oldukça güvenilir bir yöntemdir.*

Anahtar Sözcükler: *Başarısız endoskopik mukozal rezeksiyon, endoskopik submukozal diseksiyon, lateral yayılımlı tümör.*

INTRODUCTION

Piecemeal resection of large colorectal laterally spreading tumors (LST; up to 130 mm in size) with endoscopic mucosal resection (EMR) is technically possible; nevertheless, the development of residue or recurrence is the major problem observed in up to 55% cases in the follow-up period (1). Technically, it is difficult to repeat the application of EMR in residual or recurrent lesions because of the dense submucosal fibrosis (2–4). Endoscopic submucosal dissection (ESD) is the recommended salvage treatment procedure in these lesions as it can provide en bloc resection despite the presence of submucosal fibrosis (5).

Although large LSTs can be treated by EMR, it may fail (EMR interrupted) in some cases, such as those with positive non-lifting sign, poor endoscope operability, difficult locations (i.e., involvement of ileocecal valve or appendiceal orifice or the extension of the rectum to the dentate line), assessed as high risk for submucosal invasive cancers after commencing EMR, anesthetic reaction (1, 2). Similar to residual or recurrent lesions, severe submucosal fibrosis is an expected finding in EMR interrupted tumors (2). However, apart from residual or recurrent lesions, there is no consensus in the literature about the treatment of EMR interrupted tumors.

In this study, we aimed to demonstrate the feasibility of ESD in EMR interrupted colorectal LSTs.

MATERIALS and METHODS

Between February 2019 and April 2021, a total of 8 colorectal LSTs in 8 patients who had a history of interrupted EMR underwent en bloc resection with ESD were eligible for inclusion.

Interrupted EMR was defined as the termination of EMR owing to various reasons including positive non-lifting sign, extension to the anal canal, or depressed appearance.

En bloc resection of lesions that could not be achieved with ESD and local residual/recurrent lesions were not included in the study. ESD indications were evaluated according to the Japan Gastroenterological Endoscopy Society guideline (5). Written consents were obtained from all participants

Pre-ESD assessment:

All lesions were initially detected using conventional methods and were then examined using the narrow band imaging (NBI) system without magnification to evaluate endoscopic surface, vascular features and color (NICE [NBI International Colorectal Endoscopic] classification) (6). Lesion size and location was noted. Cecum, ascending colon and transverse colon as right colon, descending colon and sigmoid colon were defined as left colon. LSTs were also classified according to the LST classification (4).

ESD equipment and procedure:

All ESDs were carried out by a single operator (A.M.B.) experienced in colorectal ESD. The procedures were performed under conscious sedation using intravenous midazolam and fentanyl or deep sedation with propofol. All ESDs were performed using Olympus equipment (Olympus Exera processors and 180–190 series endoscopes). Carbon dioxide insufflation was used for all procedures. Sodium hyaluronate acid with a small amount of methylene blue dye was used for the injection into the submucosal layer. According to the appearance of the submucosal layer, mild fibrosis was grouped as F0 (no fibrosis) or F1 (submucosal layer appears blue transparent), and severe fibrosis was grouped as F2 (severe fibrosis; submucosal layer looks like a white muscle layer) (7). A small size type transparent hood (ST hood) (Fujifilm, Japan) was used for all ESDs. ESD was

performed using a 1.5-mm long Flush knife (DK2620J-B15S; FTS, Tokyo, Japan) powered by a high-frequency electrosurgical unit (VIO 200D, ERBE Elektromedizin, Tübingen, Germany). Pocket-creation method was used during ESD (8). In cases where adequate elevation could not be achieved owing to intense submucosal fibrosis, traction was applied with the multi-loop method (9).

Intra-procedural bleeding was defined as bleeding lasting longer than 60 seconds during ESD. Post-procedural bleeding was defined as a decrease in hemoglobin value >2 g/dL with rectal bleeding after ESD compared to the preoperative value. It was grouped as intraoperative perforation if occurs during ESD and delayed perforation if occurs after ESD (10). No clip was applied to the ESD ulcer after dissection. Procedure time was calculated as the time between injection and complete dissection.

Histopathological examination:

Histological findings were reported according to the Vienna classification (11). According to the Japanese Classification, pathological diagnoses were T1a when the invasion depth was <1,000 μm and T1b when the depth invasion depth 1,000 μm (12). En bloc resection was defined as resection in one piece. R0 resection was defined horizontal and vertical margins free from any type of neoplasia. Curative resection was described as en bloc resection with negative vertical (the invasion depth <1,000 μm) and lateral margins, without lymphovascular infiltration (13). Additional surgery was recommended when these criteria were not met.

Follow-up evaluation:

Control colonoscopies were planned at 3 and 12 months after ESD. Biopsy specimens were not routinely taken from the ESD scar unless there was a suspicion of recurrence in the control colonoscopy.

Measured outcomes:

The primary endpoint of our study was to evaluate en bloc, R0 and curative resection rates of ESD in EMR interrupted LSTs. Secondary endpoints were submucosal fibrosis frequency, the rate of traction method requirement, ESD-related complication rates, and histopathological correlation after EMR–ESD.

RESULTS

ESD was applied to 8 colorectal LSTs with EMR interrupted. Patient details are outlined in Table-1, 2. The female ratio was 25% (2/8). The median age of the patients was 62.5 years (48–83 years). The mean period from the interrupted EMR to ESD was 18 days (1–90 days). Interrupted EMR was caused by positive non-lifting sign in 5 lesions, technical failure due to flat structure and extension to the anal canal in 2 lesions, and technical failure due to depressed appearance in 1 lesion. Mean size (the maximum diameter) of resected tumors was 61.5 mm (35–100 mm). 6/8 (75%) of LSTs were granular (LST-G) and all LST-G lesions were mixed (LST-GM). One of the non-granular LST (LST-NG) was pseudo-depressed (LST-NG-PD) type. Four lesions were in the rectum, 1 lesion was in the left colon and 3 lesions were in the right colon. The 2 lesions in the rectum were also extending to the anal canal. All LSTs were evaluated as NICE type 2. The non-lifting sign was positive in 6/8 (75%) of the lesions. Severe fibrosis was observed in 7/8 (87.5%) of LSTs. Traction method (12.5%) was only used in one patient. The en bloc resection, the R0 resection and the curative resection rates were 100%, 87.5% and 87.5% respectively (Table-3). The mean procedure duration is 134 minutes (25–300 minutes) (Table-2). Intra-procedural perforation (2 × 2 mm) was observed as a complication in 1 patient (12.5%). It was closed with metal clips. Delayed bleeding was observed in one patient (12.5%). The bleeding complication was controlled by monopolar hemostatic forceps with soft coagulation (Table-3). In the histopathological examination, 1 LST was diagnosed as traditional serrated adenoma, 1 as tubulovillous adenoma with high-grade dysplasia, 2 as carcinoma in situ, and 4 as adenocarcinoma (T1). Of the T1 tumors, 3 were evaluated as T1a and 1 as T1b (Table-2). Right hemicolectomy was performed for T1b LST. No residual tumor and metastatic lymph node were observed in the pathological examination of the specimen. Comparison histopathology after EMR and ESD showed that results were correlated in only 2 LSTs (25%). Mean follow-up for all patients was 15.5 (3–26) months (Table-2). No recurrence was observed in the 3rd-month and 1st-year colonoscopies of 6 patients with a follow-up period longer than 1 year. Except for the patient who underwent surgery, no recurrence was observed in the 3rd-month control colonoscopy of the other patient with a follow-up period of less than 1 year.

Table-1. Clinicopathological features.

Variables	EMR interrupted tumors (n=8)
Sex, male/female (n)	6/2
Age (year), mean (range)	62.5±4.89 (48-83)
Time period from EMR to ESD (day), mean (range)	18 (0-90)
Location (n)	
Right colon	3
Left colon	1
Rectum	4
Tumor size (mm), mean (range)	61.5 (35-100) mm
LST subtype (n)	
LST-G	6
LST-NG	2
Submucosal fibrosis (n)	
Mild (F0/F1)	1
Severe (F2)	7
Final histopathologic diagnosis (n)	
LGD	0
HGD	1
Tis	2
T1a (<1,000 μm)	3
T1b (1,000 μm≤)	1
TSA	1

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LST, lateral spreading tumor; LST-G, lateral spreading tumor granular; LST-NG, lateral spreading tumor non-granular; LGD, low grade dysplasia; HGD, high grade dysplasia; Tis, diminutive intramucosal invasive.

Table-2. Endoscopic submucosal dissection for the treatment of endoscopic mucosal resection interrupted lateral spreading tumors: patient characteristics and outcomes.

Patient#	Age, years	Sex	LST type	Site	Tumor size, mm	EMR-ESD interval, day	ESD time, minutes	Resection	Pathological findings	Complication
1	77	M	NG-F	SC	35x20	1	25	En bloc	T1a	None
2	48	M	G-M	AC	50x45	15	150	En bloc	T1b	None
3	55	M	G-M	C	45x37	0	140	En bloc	Tis	None
4	61	M	G-M	R	95x75	30	300	En bloc	T1a	Minor perforation
5	57	M	G-M	R	100x65	90	170	En bloc	T1a	None
6	83	F	G-M	R-DL	70x62	7	180	En bloc	TSA	None
7	56	F	G-M	R-DL	55x40	10	70	En bloc	HGD	None
8	63	M	NG-PD	HF	42x35	40	40	En bloc	Tis	Delayed bleeding

M, male; F, female; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LST-G-NM, Laterally spreading tumor, granular-nodular mixed; LST-NG-F, Laterally spreading tumor non-granular-flat elevated; LST-NG-PD, Laterally spreading tumor non-granular-pseudo depressed; SC, sigmoid colon; AC, ascending colon; C, caecum; R, rectum; R-DL, rectum involving the dentate line; HF, hepatic flexure; HGD, high grade dysplasia; Tis, diminutive intramucosal invasive.

Table-3. Endoscopic submucosal dissection (ESD) outcomes.

Variables	Salvage ESD performed (n=8)
Procedure time (min), mean (range)	134±83.7(25-300)
En bloc resection (n, %)	8 (100)
R0 resection (n, %)	7 (87.5)
Curative resection (n, %)	7 (87.5)
Complication (n, %)	2 (25)
Postoperative bleeding	1 (12.5)
Intraoperative perforation	1 (12.5)
Delayed perforation	0

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

DISCUSSION

Considering that colorectal ESD provides high en bloc resection rate (84–95%) and low recurrence risk (0-2%), it is an ideal treatment option for LSTs larger than 2 cm (5, 14). JGES guideline stated that another important indication of ESD is local residual or recurrent tumors following endoscopic resection (ESD or EMR) (5). ESD efficacy and safety in the treatment of colorectal local residual or recurrent tumors has been shown in many studies (2). However, unlike residual or recurrent lesions, there is only one study on the applicability of ESD treatment in EMR interrupted tumors (2). In the case series of Tanaka et al. that included 21 patients who underwent ESD for EMR interrupted tumors, en bloc, R0, curative resection rates were 86%, 86%, and 76%, respectively. The mean LST size in this study was 22 mm (6–30 mm) (2). Our study is important as it is the second study in which EMR interrupted tumors were treated with ESD. In our case series, the en bloc, R0 and curative resection rates were similar (100%, 87.5%, and 87.5%, respectively) although the mean size of the tumors was almost 3 times larger. In this respect, it has been shown that ESD can be a salvage treatment even if the lesion diameter is large in EMR interrupted LSTs (Figure 1-5).

The JGES guideline does not recommend biopsy sampling in the differentiation adenoma/adenocarcinoma prior to colorectal endoscopic resection to prevent development of submucosal fibrosis (5). Biopsy sampling before treatment may increase the risk of fibrosis and has limited the diagnostic benefits (sensitivity, specificity and diagnostic accuracy rates of 36.6%, 90.5%, and 54.8%, respectively) (15).

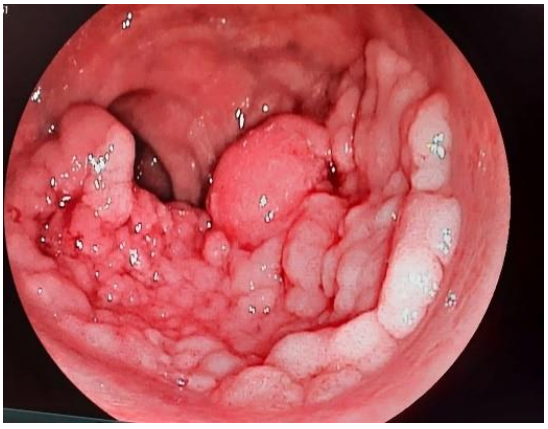

Figure-1. 100 × 65 mm LST-GM type lesion covering ¾ of the lumen in the rectum.

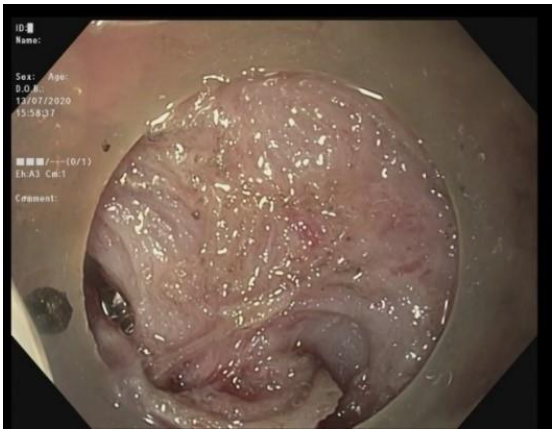

Figure-2. The lesion referred for ESD had a history of multiple biopsy and incomplete resection with EMR. LST, which had severe submucosal fibrosis during ESD.

Submucosal fibrosis is an expected condition in the presence of residue or recurrence after EMR/ESD or similarly in tumors with interrupted EMR (2).

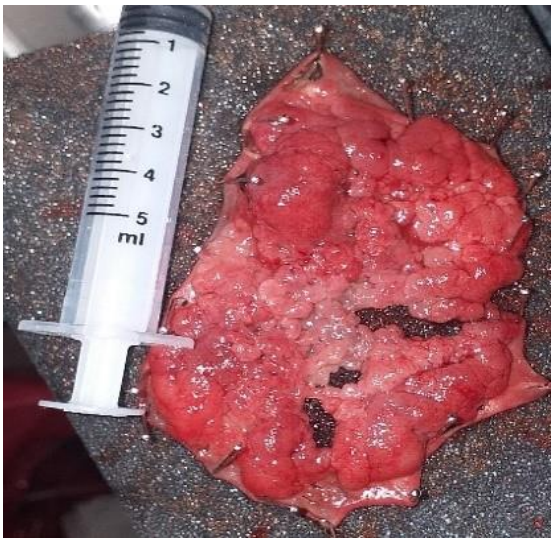

Figure-3. LST was resected en bloc with ESD.

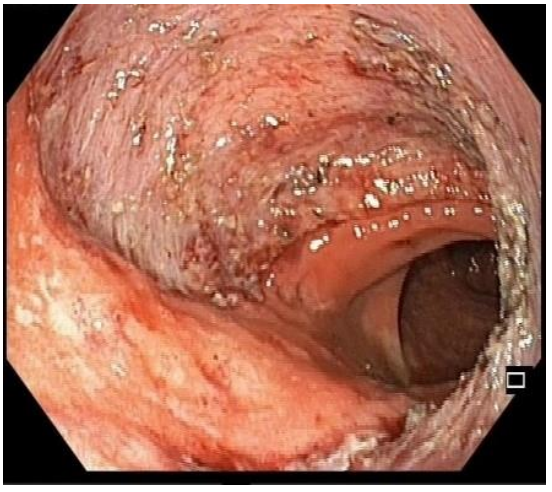

Figure-4. No complication was observed after ESD.

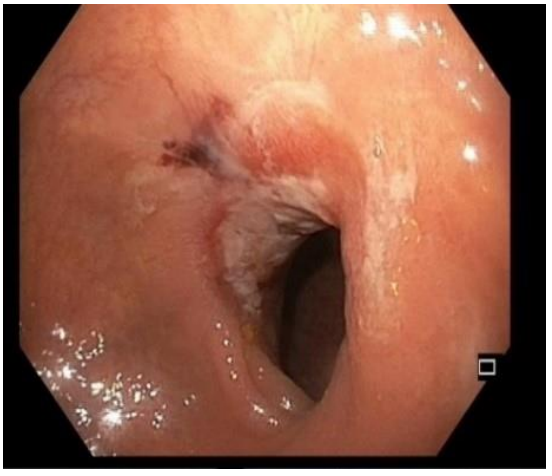

Figure-5. No recurrence was observed at the 3rd-month control colonoscopy after ESD.

In our case series, severe submucosal fibrosis was observed in most of the patients (87.5%). In addition, the correlation between the tissues removed by EMR with the final histopathology after ESD was examined and the diagnosis did not change in only 2 patients (25%). Therefore, our study showed that partial resection with EMR causes severe submucosal fibrosis and tissue samples obtained with EMR mostly did not reflect the lesion overall.

Guidelines recommend chromoendoscopy to predict deep submucosal invasion when planning treatment before endoscopic resection (5, 16, 17). The introduction of chromoendoscopy methods has enabled the in vivo diagnosis of LSTs; therefore, submucosal fibrosis that may occur after unnecessary biopsies and/or mucosal resections can be prevented. In this study, it was observed that none of the patients referred for ESD underwent chromoendoscopic examination prior to EMR. In our study, all lesions were found to be NICE type 2 in the chromoendoscopy evaluation before ESD, and curative resection was achieved in all but one patient. In conclusion, this study showed that chromoendoscopy rather than biopsy or tissue sampling by EMR is more critical in the treatment decision in colorectal LSTs with EMR interruption. In addition, this study reiterates that chromoendoscopic methods should be used more widely by therapeutic endoscopists.

Reportedly, the most common cause of interrupted EMR etiology is positive non-lifting sign. The non-lifting sign is a rapid and practical method for evaluating submucosal invasion. EMR is contraindicated in colorectal tumors with positive non-lifting sign owing to the risk of submucosal invasion. However, non-lifting sign has a specificity of 98.4% for T1b, while sensitivity (61.5) is low (18). Therefore, the non-lifting sign is insufficient to differentiate between resectable T1a tumors and T1b tumors. Severe submucosal fibrosis is also one of the conditions in which the non-lifting sign is positive (19). In our case series, although the most common cause of interrupted EMR etiology was non-lifting sign, T1b was observed in only 1 patient in the non-lifting sign etiology.

In the presence of severe submucosal fibrosis in the ESD procedure, the separation of the muscle and the submucosal layer during submucosal dissection becomes difficult, leading to prolongation of the procedure and an increased risk of complications (15, 20). Recently, with the development of ESD techniques (Pocket-creation method, traction methods), injection knives and caps developed for submucosal fibrosis such as ST hoods, ESD has become easier and safer in LSTs with severe submucosal fibrosis (2, 8, 9, 21). Apart from submucosal fibrosis in interrupted EMR tumors, one of the technical difficulties of ESD is tissue defects in the middle and/or margin of the lesion. In this respect, there may be difficulty in orientation during submucosal dissection or the existing tissue defect may be perceived as ESD-related mucosal damage. As we demonstrated in the present study, repetitive submucosal injections with a knife in areas where integrity is lost due to tissue defect and dissection of the non-fibrosis primarily area will help find the correct incision line. ESD was technically successful in all cases with the equipment and treatment strategy preferred in our series. Intra-procedural minor perforation was observed in only 1 patient, which was treated with an endoclip.

The present study has several limitations. Our study included a limited number of cases and all ESDs were carried out by a single experienced operator. The included tumors in our cases were technically difficult, and the results may not be relevant if the technique is carried out by inexperienced endoscopists. Another negative aspect about the results of this study were based on the fibrosis in the endoscopic findings during the ESD. Histologic evaluation is often more objective than clinical evaluation. Another shortcoming of the study is the short follow-up period after ESD. Because of the previous history of resection with snare, even if the lesion was resected en bloc with ESD, it should be considered as a piecemeal resection. In addition, there may be tissues that cannot be sent to pathology during the previously performed EMR. Therefore, prospective studies evaluating long-term follow-ups that can assess recurrence are needed. In addition, there is no clear opinion about the optimal time to ESD application after incomplete EMR intervention. The ESD application time interval in our study is quite wide. Thus, multicenter, prospective studies are needed.

In conclusion, ESD in EMR interrupted LSTs is technically difficult, but it is very effective method when applied by experienced endoscopists.

Statement of Ethics

The authors have no ethical conflicts to disclose. All patients gave their written consent.

Conflict of interest statement: The authors have no conflicts (financial, professional, or personal) to declare.

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