REVIEW

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Indications for and Technical Aspects of Colorectal Endoscopic Submucosal Dissection

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Due to the widespread acceptance of gastric and esophageal endoscopic submucosal dissections (ESDs), the number of medical facilities that perform colorectal ESDs has grown and the effectiveness of colorectal ESD has been increasingly reported in recent years. The clinical indications for colorectal ESD at the National Cancer Center Hospital, Tokyo, Japan include laterally spreading tumor (LST) nongranular type lesions >20 mm and LST granular type lesions >30 mm. In addition, 0-IIc lesions >20 mm, intramucosal tumors with nonlifting signs and large sessile lesions, all of which are difficult to resect *en bloc* by conventional endoscopic mucosal resection (EMR), represent potential candidates for colorectal ESD. Rectal carcinoid tumors less than 1 cm in diameter can be treated simply, safely, and effectively by endoscopic submucosal resection using a ligation device and are therefore not indications for ESD. The *en bloc* resection rate was 90%, and the curative resection rate was 87% for 806 ESDs. The median procedure time was 60 minutes, and the mean size for resected specimens was 40 mm (range, 15 to 150 mm). Perforations occurred in 23 (2.8%) cases, and postoperative bleeding occurred in 15 (1.9%) cases, but only two perforation cases required emergency surgery (0.25%). ESD was an effective procedure for treating colorectal tumors that are difficult to resect *en bloc* by conventional EMR. ESD resulted in a higher *en bloc* resection rate as well as decreased invasiveness in comparison to surgery. Based on the excellent clinical results of colorectal ESDs in Japan, the Japanese healthcare insurance system has approved colorectal ESD for coverage. **(Gut Liver 2013;7:263-269)**

Key Words: Endoscopic submucosal dissection; Endoscopic mucosal resection; Colorectum; Laterally spreading tumor granular type; Laterally spreading tumor nongranular type

INTRODUCTION

Traditionally, endoscopic mucosal resection (EMR)[1-5] and surgery have been the only available treatments for large colorectal tumors even those detected at an early stage. In Japan, EMR is indicated for the treatment of colorectal adenomas, intramucosal and submucosal superficial (superficial submucosal cancer, SM1; invasion <1,000 μm from the muscularis mucosae) cancers because of the negligible risk of lymph node (LN) metastasis[6] and excellent clinical outcome results.[2-4]

The endoscopic submucosal dissection (ESD) procedure, which enables *en bloc* resection of large tumors, is accepted as a standard minimally invasive treatment for early gastric and esophageal cancers in Japan. Due to the widespread acceptance of gastric and esophageal ESDs, the number of medical facilities that perform colorectal ESDs has been growing and the effectiveness of colorectal ESD has been increasingly reported in recent years.[5-15]

Until the spring of 2012, colorectal ESDs had been performed in Japan in accordance with advanced medical treatment system no. 78 approved by the Japanese Ministry of Health, Labor and Welfare in 2009 which distinguishes colorectal ESD from gastric and esophageal ESDs because of its greater technical difficulty. The indications for colorectal ESD under this system were defined as 1) early colorectal cancers >20 mm difficult to treat *en bloc* by EMR; and 2) adenomas with nonlifting sign or residual tumors >10 mm difficult to treat by EMR.[16]

All candidate lesions for ESD had to be confirmed as being an intramucosal tumor using magnification colonoscopy[17-19] or endoscopic ultrasonography (EUS) before performing the procedure. Over 150 institutions had started performing colorectal ESDs in accordance with the advanced medical treatment system utilizing recent improvements in ESD-related instruments

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and devices as well as various other technical innovations. In fact, a total of 3,006 colorectal ESDs were performed in 143 institutions during a recent 1-year period using this advanced medical treatment system. Based on the excellent clinical results of colorectal ESDs in Japan, the Japanese healthcare insurance system has approved colorectal ESD for coverage and set the cost at 183,700 Japanese yen which is approximately three times higher than the cost for conventional EMR. Most patients younger than 75 years of age receive a 70% reduction in the treatment cost under the universal health insurance system in Japan.

INDICATIONS FOR COLORECTAL ESD

The indications for colorectal ESD approved by the Japanese government's medical insurance system are colorectal adenomas and cancers with a maximum tumor size of 2 to 5 cm taking into account the procedure's technical standardization and safety throughout Japan at the present time.

Based on our previous clinicopathological analyses of laterally spreading tumors (LSTs),[4,17] LST nongranular type (LST-NG) lesions have a higher rate of SM invasion which can be difficult to predict endoscopically. Approximately 30% of LST-NGs with SM invasion are multifocal and such invasions are primarily SM1 which is especially difficult to predict before endoscopic treatment. LST-granular type (LST-G) lesions have a lower rate of SM invasion and most such invasions are found under the largest nodule or depression and are easier to predict endoscopically.[4,17] LST-Gs >20 mm can be treated by planning endoscopic piecemeal mucosal resection (EPMR) rather than ESD with the area having the largest nodule resected first before resection of the remaining tumor. LST-Gs >30 mm are possible candidates for ESD, however, because they have a higher SM invasion rate and are more difficult to treat even by EPMR. Consequently, they are treated by either EPMR or ESD depending on the individual endoscopist's judgment.

0-IIc lesions >20 mm, intramucosal tumors with nonlifting sign and large sessile lesions, all of which are difficult to resect *en bloc* by conventional EMR, are also potential candidates for colorectal ESD. Rectal carcinoid tumors less than 1 cm in diameter can be treated by endoscopic submucosal resection using a ligation device safely, effectively, and easily so not an indication for ESD (Table 1).[20,21]

ESTIMATING DEPTH OF INVASION

A noninvasive pattern (Table 1)[18,19] and Sano's type II or IIIA capillary pattern[22] should be confirmed in each lesion indicating that the lesion is suitable for EMR or ESD with the estimated invasion depth being less than SM1. No biopsies are performed before ESD because they can cause fibrosis and may interfere with SM lifting.

ESD PROCEDURE AT NATIONAL CANCER CENTER HOSPITAL

1. Materials

1) Endoscope system

Water jet endoscope (PCF-Q260JI and GIF-Q260J; Olympus Medical Systems Co., Tokyo, Japan) with water jet pump system (OFP1; Olympus Medical Systems CO.).

2) ESD Knives

Ball-tip bipolar needle knife with water jet function (Jet B-knife; XEMEX Co., Tokyo, Japan) (Fig. 1A).

Newly developed insulation-tipped electrosurgical knife (IT knife nano, KD-612Q; Olympus Optical Co., Tokyo, Japan)[23] in which the insulation-tip is smaller and the short-blade is designed as a small disk to reduce the burning effect on the muscle layer (Fig. 1B).

Table 1. Indications for Colorectal ESD at National Cancer Center Hospital

Indication	Tumor size, mm			
	<10	10-20	20-30	>30
0-IIa, IIc, IIa+IIc (LST-NG)*	EMR	EMR	ESD	ESD
0-Is+IIa (LST-G)†	EMR	EMR	EMR	ESD
0-Is (Villous)	EMR	EMR	EMR	ESD
Residual or recurrent tumor‡	EMR	EMR/ESD	ESD	ESD
Rectal carcinoid tumor§	EMR	ESD/Surgery	Surgery	Surgery

Noninvasive pattern by chromomagnified colonoscopy.
ESD, endoscopic submucosal dissection; LST-NG, laterally spreading tumor nongranular type; EMR, endoscopic mucosal resection; LST-G, laterally spreading tumor granular type.
*0-IIa, IIc, IIa+IIc (LST-NGs) >20 mm; †0-Is+IIa (LST-G) >30 mm; ‡Intramucosal tumors with nonlifting sign and large sessile lesions which are difficult to resect *en bloc* by conventional EMR; §Rectal carcinoid tumors less than 1 cm in diameter can be treated by endoscopic submucosal resection using a ligation device simply, safely, and effectively so not an indication for ESD.

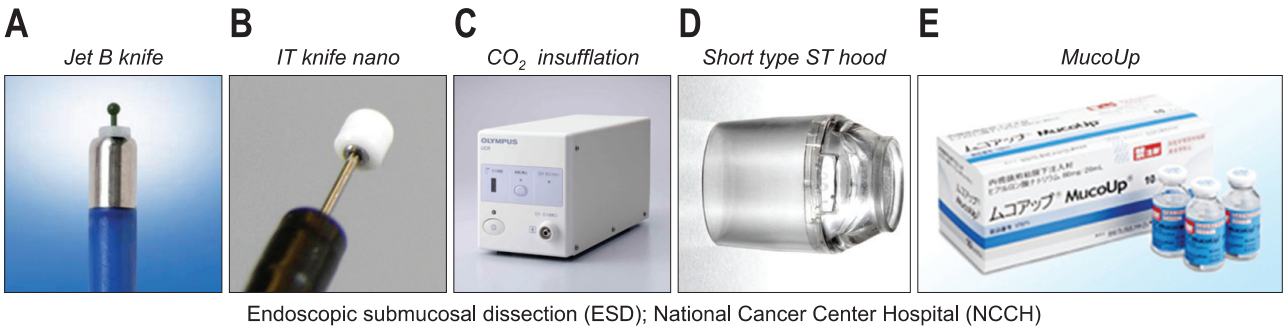

Fig. 1. Procedures were primarily performed using (A) a ball-tip bipolar needle knife (B-knife; XEMEX Co.) and (B) an insulation-tipped electrosurgical knife nano (IT Knifenano; Olympus Optical Co.) (C) with CO_2 insufflation instead of air insufflation to reduce patient discomfort. (D) A short-type ST hood was used from the start of each colorectal endoscopic submucosal dissection (ESD) to access the narrow submucosal (SM) layer more easily and to provide counter-traction for the resected specimen. Following the injection of Glyceol® (Chugai Pharmaceutical Co., Ltd.) and (E) MucoUp® (Seikakagu Co.; 0.4% hyaluronic acid) into the SM layer, a circumferential incision was made using the B-knife and then ESD was performed using both the B-knife and the IT knife (A, B).

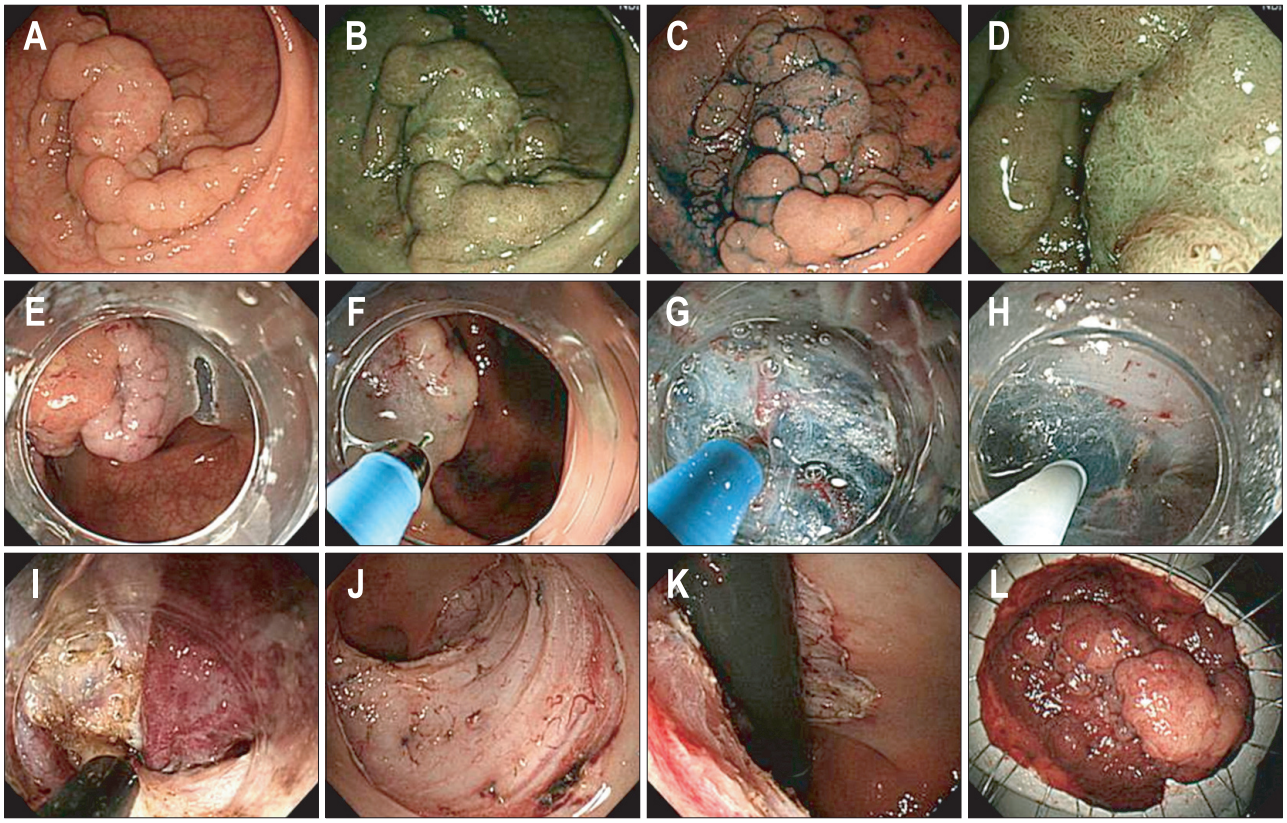

Fig. 2. Endoscopic submucosal dissection (ESD) procedure. (A) The tumor granular (LST-G) type lesion, which was 40×50 mm in size and located in the sigmoid colon, was laterally spreading type (straight view). (B, C, D) A noninvasive pattern and Sano's type IIIA capillary pattern were confirmed for this lesion indicating that the lesion was suitable for ESD with an estimated invasion depth of less than superficial submucosal cancer (SM1). No biopsies were performed prior to ESD because they could have caused fibrosis and may have interfered with the submucosal (SM) lifting. (C) Lesion margins were delineated prior to ESD using 0.4% indigo-carmine dye spraying. (E) Straight view of the lesion after half partial-marginal resection of the oral side. (F) Additional marginal resection of the anal side to be performed with the Jet B-knife using a straight view. (G) Following the injection of Glycerol® (Chugai Pharmaceutical Co., Ltd.) and sodium hyaluronate acid solution into the SM layer, a half-circumferential incision (anal side) was performed with the jet B-knife using a retroflex view. Following the circumferential incision, SM dissection was performed using the same Jet B-knife. (H) An additional SM injection of Glyceol® and MucoUp® (Seikakagu Co.) was performed to avoid perforation. (I) The SM dissection from the outside to the inside of lesion was easily performed using the IT Knifenano. (J, K) The ulcer bed after a successful *en bloc* resection was completed in 1.5 hours. (L) The resected specimen was 60×40 mm in diameter with tumor-free margins.

3) CO_2 regulator

CO_2 regulator (UCR; Olympus Medical Systems Co.) or Gas Regulator (Crown, Model FR-IIS-P; Yutaka Engineering, Tokyo, Japan) (Fig. 1C).[11]

4) Distal attachment

ST hood short-type (DH-28GR and 29CR; Fujifilm Medical Co., Tokyo, Japan) (Fig. 1D).

5) Bipolar hemostatic forceps

HemoStat-Y (H-S2518; Pentax Co., Tokyo, Japan).

6) SM injection solution

Mixtures of two solutions were prepared before ESD to create a longer lasting SM fluid cushion.

1) Solution 1: Indigo carmine dye (2 mL of 1%) and epinephrine (1 mL of 0.1%) were mixed with 200 mL Glyceol® (10% glycerin and 5% fructose; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan)[24] in a container and the solution was then drawn into a 5 mL disposable syringe.

2) Solution 2: MucoUp® (Seikakagu Co., Tokyo, Japan)[14] Fig. 1E was drawn into another 5 mL syringe.

During the actual ESD procedure, a small amount of solution 1 was injected into the SM layer first to confirm the appropriate SM layer elevation and then solution 2 was injected into the properly elevated SM layer. Finally, a small amount of solution 1 was injected again to flush any residual amount of solution 2.

DETAILED COLORECTAL ESD PROCEDURES

The procedures were primarily performed using a Jet B-knife and an IT knife nano[23] with CO_2 insufflation instead of air insufflation to reduce patient discomfort. An ST hood short-type was used from the start of each colorectal ESD in order to creep into the narrow SM layer more easily and provide counter-traction for the resected specimen (Fig. 1).

1) The margins of the lesion were delineated before ESD using narrow band imaging and 0.4% indigo carmine dye spray (Fig. 2A-C). Sano's type IIIA capillary pattern[22] were confirmed in this large nodule indicating that this lesion was suitable for ESD with the estimated invasion depth being less than SM1 (Fig. 2D). After formation of the SM fluid cushion, an initial incision was made with the Jet B-knife at the oral side of the lesion (Fig. 2E). In colorectal cases, it is unnecessary to actually mark around lesions because tumor margins can be visualized clearly with indigo carmine dye spraying.

2) The Jet B-knife was then inserted into the initial incision and an electrosurgical current was applied in Endocut mode (50 W) using a standard electrosurgical generator (ICC200; ERBE, Tubingen, Germany) to continue the marginal incision around the oral side of the lesion (Fig. 2F and G).

3) After partial marginal resection of the oral side to ensure adequate SM lifting, SM dissection was begun with the same Jet B-knife using the retroflex view (Fig. 2G).

4) Additional SM injection of Glyceol® and MucoUp® was performed to avoid perforation (Fig. 2H).

5) After the lesion was partially dissected so that the SM layer could be adequately visualized, an IT knife nano (Fig. 2I) was used to complete the dissection of the SM layer quickly and safely. Repeated injection of the previously indicated solutions into the SM layer were made to maintain the SM fluid cushion so as to minimize the risk of perforation.

6) Hemostat-Y forceps were used in bipolar mode (25 W) to control visible bleeding and minimize the risk of any burning effect on the muscle layer. The patient's position was changed as necessary to facilitate adequate visualization of the tissue plane and dissection continued until the lesion was completely excised.

7) After the colorectal ESD was completed, routine colonoscopic review to detect any possible perforation or exposed vessels was conducted and minimum coagulation was performed using the hemostat-Y forceps on nonbleeding visible vessels to prevent postoperative bleeding (Fig. 2J and K).

8) The resected specimen was stretched and fixed to a board using small pins (Fig. 2L).

CLINICAL OUTCOMES OF ESDS AT NATIONAL CANCER CENTER HOSPITAL

The *en bloc* resection rate was 90% and the curative resection rate was 87% for 806 ESDs. There were a total of 628 (78%) carcinomas and the curative resection rate was 87% (702/806). The other 104 cases (13%) were diagnosed as SM deep and/or lymphovascular invasion and additional surgery was recommended for most such noncurative cases. The median procedure time was 60 minutes with a mean of 100 minutes and the mean size of resected specimens was 40 mm (range, 20 to 150 mm).

In our previously reported prospective multicenter study, multivariate analysis revealed that large tumor size ≥50 mm and a lower experience level in which <50 ESDs were performed were

Table 2. Clinical Outcomes of Colorectal Endoscopic Submucosal Dissections Performed at the National Cancer Center Hospital

Variable	Value
Year	2004–2012
Total no.	806
Rectum	214 (27)
Age, yr	66±10
Tumor size, mm	37±18
Procedure time (median), min	100±70 (60)
En bloc resection	728 (90)
Snare use	193 (24)
Cancer	628 (78)
Curative resection	702 (87)
Perforation	23 (2.8)
Delayed bleeding	15 (1.9)

Data are presented as mean±SD or number (%).

independent factors for a significantly increased risk of complications.[25] The postoperative bleeding rate for colorectal ESD was 1.9% (15/806) and the perforation rate was 2.8% (23/806), but only one immediate and one delayed perforation required emergency surgery (Table 2).

TECHNICAL PROGRESS OF COLORECTAL ESD

Until recently, colorectal ESDs had been performed mainly in Japan[10-16,23,25-27] because of the procedure's technical difficulty and the fact that ESD is most frequently used to treat early gastric cancer, which is much more common in Japan than in Western countries,[28] although some trained endoscopists have started to do colorectal ESDs in other Asian countries including South Korea,[16,29,30] Europe,[31,32] and the United States.[33]

In order to reduce the perforation rate for colorectal ESD, the use of specialized knives,[7,23] distal attachments,[14] and hypertonic solutions (Glycerol®[24] and MucoUp®[14]), which produce longer lasting and higher SM elevation cushions, are necessary for safer ESDs because of the thinner colonic wall. The Jet B-knife is safer because electric current is limited to the needle, the bipolar system prevents electric current from passing to the muscle layer and the new water-jet function with which SM injection is possible reduces the need for more frequent device changes.

ESD enables treatment of even recurrent lesions after incomplete endoscopic resections as well as large colorectal LSTs >10 cm in diameter.[34] It is important, therefore, to examine lesions carefully and diagnose them accurately before treatment using chromomagnification colonoscopy[17,18] in order to reduce unnecessary noncurative resections of SM deep invasive cancers.[6]

COMPARISON BETWEEN ESD AND EMR

The primary advantage of ESD compared to EMR is a higher *en bloc* resection rate for large colonic tumors that had been treated by surgery previously. Consequently, ESD has a lower recurrence rate compared to EMR (2% vs 14%) and also provides a better quality of life for patients compared with surgery.[35] Future studies should be designed to compare the clinical outcomes between ESD and surgery rather than between ESD and EMR because the indications for ESD and EMR are different as are the relevant tumor characteristics.

Until quite recently, EPMR had been considered a feasible treatment for colorectal LSTs because of a low local recurrence rate for such tumors and repeat endoscopic resection was considered sufficient for most local recurrent tumors.[9] In our case series,[35] EPMR also was effective in treating many LST-Gs ≥20 mm, but three cases (1.3%) required surgery after such piecemeal resections including two cases of invasive recurrence. Based on our results, EPMR cases in which accurate histological evaluation would be difficult should be considered for ESD or laparoscopic-assisted colorectal (LAC) surgery.[36]

RECOMMENDATIONS ON POST-ESD CARE

Supported by our comparative data analysis between ESD and EMR, follow-up endoscopy is recommended after 1 year for curative *en bloc* ESD cases and after 6 months for piecemeal ESD cases considering local recurrence rates.[9,35] Even for pathologically curative resection cases, computed tomography or EUS examination is recommended for SM1 and piecemeal resection cases to detect LN metastasis or distant metastasis. Surgery is recommended for SM deep cancer or deeper invasion and when lymphovascular invasion or poorly differentiated cancer is diagnosed histologically.[6]

COMPARISON OF ESD AND LAC

LAC is one of the minimally invasive alternatives to open surgery for colorectal cancers while ESD is another such alternative. Comparative effectiveness data on ESD versus LAC resection of early colorectal cancer has been unavailable although such information would be most enlightening given the considerable differences in the potential benefits and risks between the two procedures.

We decided to compare ESD with LAC, therefore, as minimally invasive treatments for early colorectal cancer.[36] This comparison indicated that ESD was safe and provided an excellent prognosis because the bowel conservation rate was higher than 90% and the 3-year survival rate for ESD was comparable to that of LAC despite different indications for ESD and LAC. In terms of the length of hospital stay and time to oral intake after the procedures, both periods were shorter for the ESD group than for the LAC group. ESD and LAC have quite different indications, however, so if the primary indications are a noninvasive colorectal lesion diagnosed preoperatively as intramucosal to SM1 (<1,000 μm), the patient's quality of life following treatment for such an early colorectal cancer would probably be better with ESD.

Although there have been some cases requiring additional surgical resection after endoscopic resection for SM invasive cancer, surgery for adenomas, intramucosal and SM1 cancers after the introduction of ESD has been necessary in only 1% of cases which is a significantly lower figure than the 20% rate for such surgeries before the introduction of ESD.[37] In other words, colorectal ESD has succeeded in reducing over surgery of mucosal carcinomas and improving the overall quality of life for most patients.

ESTABLISHMENT OF SYSTEMATIC TRAINING FOR COLORECTAL ESD

Probst *et al*.[32] reported ESD performed in the distal colon is feasible with acceptable complication risks in a European setting. They also indicated resection rates were not as high as

those reported in Japanese studies although a clear learning curve was evident from their results.

Establishment of a systematic training program for technically more difficult colorectal ESD together with further development and refinement of the instruments, devices, equipment, and injection solutions used in the procedure are encouraged to facilitate increased use of colorectal ESD not only in Japan, but in the rest of the world where clinical experience using ESD is much less than in this country.

CONCLUSIONS

ESD is a safe and effective procedure for treating colorectal LST-NGs >20 mm, LST-Gs >30 mm, 0-IIc lesions >20 mm, intramucosal tumors with nonlifting sign and large sessile lesions, which are all difficult to resect *en bloc* using conventional EMR, providing a higher *en bloc* resection rate as well as being less invasive than surgery. Establishment of a systematic training program for technically more difficult colorectal ESD in addition to further development and refinement of ESD-related instruments, devices, equipment, and injection solutions will help facilitate increased use of colorectal ESD throughout the world.

CONFLICTS OF INTEREST

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