Surg Endosc (2014) 28:2120–2128
DOI 10.1007/s00464-014-3443-8

Endoscopic submucosal dissection for colorectal neoplasia during the clinical learning curve

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Received: 27 August 2013 / Accepted: 13 January 2014 / Published online: 11 February 2014

Abstract
Background The efficacy of colorectal endoscopic submucosal dissection (ESD) has been reported mainly from Japanese referral centers. However, ESD is technically difficult and associated with a higher risk of adverse events than endoscopic mucosal resection, especially for novices performing colorectal ESD with little experience in gastric ESD. The current study evaluated the results of colorectal ESD during the clinical learning curve by retrospectively examining the results of colorectal ESD performed by four endoscopists who had experience with fewer than five cases of gastric ESD.
Methods The study retrospectively investigated the first 20 cases managed by each endoscopist, for a total of 80 cases. The main outcome measurements were procedural time, en bloc resection rate with tumor-free margins (R0 resection rate), and adverse events rate. From among clinicopathologic characteristics, factors that affected main outcome measurements were identified.
Results Of the 80 cases (56 colonic and 24 rectal lesions; 44 granular laterally spreading tumors (LSTs) and 23 nongranular LSTs, 5 depressed, and 8 protruding), 54 cases (67.5 %) had resection using a standard tip-type knife, and 26 cases (32.5 %) had resection using a small scissors-type knife. The mean tumor diameter was 34.9 ± 14.1 mm, and the mean procedural time was 108.8 ± 53.4 min. The resection in 75 cases (93.8 %) was performed en bloc, and the R0 resection rate was 75 % (60/80). Perforation occurred in six cases (7.5 %) and postoperative hemorrhage in three cases (3.8 %). Multivariate analyses showed that colonic lesions and larger lesions (≥40 mm) were significantly associated with prolonged procedural time (≥90 min). Use of the scissors-type knife was significantly associated with a higher R0 resection rate. Perforation occurred only in colonic lesions.
Conclusions For novices in colorectal ESD, beginning with rectal and smaller lesions may be advisable. Also, using scissors-type knives may increase the R0 resection rate.

Keywords Colorectal neoplasia · Endoscopic submucosal dissection · ESD · Novices · En bloc resection · R0 resection · Perforation

The efficacy of endoscopic submucosal dissection (ESD) for en bloc resection of mucosal lesions of gastrointestinal neoplasia has been widely reported, especially for early gastric tumors. It enables resection of almost all mucosal and slightly submucosal invasive tumors regardless of their size and shape, even in the colon [1].

The efficacy of colorectal ESD performed by experienced endoscopists has been reported mainly from Japanese referral centers [2–8]. However, colorectal ESD is not established to date as a standard therapy because of its technical difficulty and high risk of adverse events, especially for novices performing colorectal ESD. Indeed, the rate of perforation during colorectal ESD is reported to be higher than for endoscopic mucosal resection (EMR), even in referral centers [9, 10]. Although most cases have been managed conservatively with endoscopic clipping closure and although the per lesion summary estimate of surgery after ESD-related adverse events is reported to be only 1 % (95 % confidence interval (CI) 0–1 %) [11], the higher risk

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of perforation than for EMR has prevented the widespread use of colorectal ESD.

The following three points represent the main difficulties with the performance of colorectal ESD that are not seen with gastric ESD:

(1) Very thin walls present a high risk of perforation.
(2) Enterobacterium-induced, serious peritonitis may develop in the event of perforation.
(3) The lumen is narrow and angulated, causing poor operability by endoscopy and generating a higher level of difficulty [1].

Therefore, colorectal ESD is very difficult to perform, both for novices performing colorectal ESD in Japan who have little experience with gastric ESD and for skilled endoscopists in Western countries, where early gastric neoplasia is relatively rare [12]. Extensive experience with gastric ESD before the performance of colorectal ESD has been recommended [8, 13].

A questionnaire survey sent to 1,356 institutions in Japan showed that endoscopists performing colorectal ESD also had performed gastric ESD in 92.9 % of these institutions. Additionally, only endoscopists with skills above a certain level were permitted to perform colorectal ESD in 92.3 % of the same institutions [8]. These results reflect a general belief that colorectal ESD is more difficult to perform than gastric ESD.

To improve the efficacy and safety of colorectal ESD, the development of devices or the improvement of current devices may be required. Standard tip-type knives (Flex Knife or Dual Knife; Olympus Optical Co., Tokyo, Japan) may require that endoscopists who perform colorectal ESD have adequate experience to avoid perforation.

Honma et al. [14] developed a scissors-type grasping device consisting of stag beetle (SB) knives (Sumitomo Bakelite, Tokyo, Japan) that enable resection of tumors without endoscopic movement. These standard and short SB knives have been effective for ESD in the stomach, esophagus, and colon. These authors also developed the SB Knife Jr, specialized for colorectal ESD [15]. The SB Knife Jr has smaller blade tips than standard and short SB knives, and its blades are tapered to enable more accurate and safe ESD procedures. Oka et al. [16] also reported that the SB Knife Jr yielded better results than the Hook Knife in terms of complete en bloc resection and avoidance of perforation. This device may be especially useful for novices performing colorectal ESD.

The current study evaluated the results of colorectal ESD during the clinical learning curve by retrospectively examining the results of colorectal ESD performed by four endoscopists who had little experience with gastric ESD. The study also aimed to identify factors that affected the treatment outcomes.

Materials and methods

Indication criteria for colorectal ESD

The recommended indications for colorectal ESD are as follows:

(1) Lesions difficult to remove en bloc with a snare EMR such as nongranular laterally spreading tumors (LSTs), particularly the pseudo-depressed type, lesions with a type V_I pit pattern, and large lesions of the protruding type suspected to be carcinomas
(2) Lesions with fibrosis due to biopsy or peristalsis
(3) Sporadic localized lesions involving chronic inflammation such as ulcerative colitis
(4) Local residual carcinoma after EMR [17].

Because indications 2, 3, and 4 often have a high degree of fibrosis, the ESD procedure for these lesions may possibly be accompanied by adverse events if performed by novices in colorectal ESD. We therefore excluded these lesions in this evaluation.

ESD procedure

Details of the colorectal ESD procedure have been described previously [1–7, 18]. Some of differences between our method and other reported methods are described in the following sections.

Preparation

Patients were instructed to restrict their intake of fiber-rich foods on the day before colorectal ESD and to drink 10 mL of 0.75 % sodium picosulfate solution (Laxoberon; Teijin Pharma Co, Ltd, Tokyo, Japan) after dinner. On the morning of the procedure, 2 L of an isotonic polyethylene glycol electrolyte solution (Niflec; Ajinomoto Pharma Co, Ltd, Tokyo, Japan) with 10 mL of dimeticon (Gascon; Kissei Pharmaceutical, Matsumoto, Japan) was used to achieve good bowel preparation.

Sedative agents

For the purpose of sedation, 15 mg of pentazocine and 2–3 mg of midazolam were administered intravenously before the ESD procedure.

Endoscopic system

Colorectal ESD was performed using single-channel, ultraslim endoscopes with a water jet system: PCF-Q260JI (outer diameter, 10.5 mm; Olympus Optical Co.) for lesions in the proximal colon (from the cecum to the

descending colon) and GIF-Q260J (outer diameter 9.8 mm; Olympus Optical Co.) for lesions of the sigmoid colon or rectum. Disposable attachments for the tips of the endoscopes (Elastic touch F-030 or F-025; Top Co., Tokyo, Japan) also were used.

High-frequency generator

We used the ICC 200 high-frequency generator (ERBE, Tübingen, Germany). The settings were endocut mode (effect 2, 60 W) for mucosal incision, forced mode (40 W) for submucosal dissection, and soft-coagulation mode (50 W) for hemostasis. We also used the ESG-100 (Olympus Optical Co.) with the SB Knife Jr. The settings were endocut mode (pulse cut fast, 35 W) for mucosal incision and submucosal dissection and soft-coagulation mode (50 W) for hemostasis.

Local injection

A solution of sodium hyaluronate was required for successful performance of mucosal incision and submucosal dissection. We used a mixture comprising a solution of sodium hyaluronate (MucoUp; SEIKAGAKU Co., Tokyo, Japan) and a small volume of epinephrine and indigo carmine.

Knives for incision and dissection

The knives used for mucosal incision and submucosal dissection were standard tip-type knives (Dual Knife; Olympus Optical Co.) or scissors-type knives (SB Knife Jr; Sumitomo Bakelite Co., Tokyo, Japan). We began to use both the Dual Knife and the SB Knife Jr in almost the same phase of the study period.

Instruction of ESD

Each endoscopist in the current study had expertise in therapeutic endoscopy, with experience in managing more than 2,000 cases of total colonoscopy and more than 300 cases of EMR or endoscopic piecemeal mucosal resection (EPMR). Before performing colorectal ESD, each endoscopist had served as an assistant to senior endoscopists for more than 20 cases of colorectal ESD and had undergone training using animal models. They had acquired sufficient knowledge of the ESD procedure during the same period. They also had experienced fewer than five cases of gastric ESD when they began to perform colorectal ESD.

In the current study, for safe performance of colorectal ESD, most of the rectal lesions were resected in the first half of the case series of each endoscopist. In addition, all ESD procedures were supervised by a senior endoscopist with experience of more than 50 cases of colorectal ESD. The senior endoscopist assumed only verbal control of the ESD procedure. However, when a perforation occurred, the subsequent ESD procedure was performed by the senior endoscopist. As a result, the self-completion rate was the same as the rate without perforation.

Study subjects

Colorectal ESD was performed at the Tohoku University Hospital between July 2009 and April 2013 by four endoscopists. The first 20 consecutive cases managed by each endoscopist were evaluated retrospectively. All tumors were larger than 20 mm in diameter. Cases involving neuroendocrine tumors (NETs) or carcinoids were excluded because the histologic characteristics of NET are different from those of adenocarcinomas or adenomas. Written informed consent for the ESD procedure was obtained from all the participants under the protocol approved by the Tohoku University Hospital Committee for Clinical Investigation.

According to the Paris endoscopic classification [19], a macroscopic type of tumor was classified as protruding (0-I) or as nonprotruding and excavated (0-II). The type 0-II lesions were subdivided into slightly elevated (IIa) or depressed (IIc, IIa + IIc) lesions. The IIa lesions larger than 20 mm in diameter were called "LSTs," and the LSTs were categorized as either the granular (LST-G) or nongranular (LST-NG) type [2–7].

The procedural time was defined as the total time from the onset of the mucosal incision to the end of the submucosal dissection. After the ESD procedure, if the tumor had been resected in a single piece, the resection was endoscopically judged to be an en bloc resection. The resected specimens were fixed in 10 % buffered formalin, paraffin-embedded, sliced at intervals of 2 mm, and microscopically reviewed in accordance with the Vienna classification [20]. Due to the high risk of lymph node metastasis, colectomy was recommended in cases with massive submucosal invasion of more than 1,000 μm, poorly differentiated adenocarcinoma, or vessel infiltration [19, 21].

The grade of resection was histopathologically evaluated as R0 (complete) resection in cases in which the tumor was resected en bloc and the lateral and basal margins were free of tumor cells [2]. In other cases, resection was defined as R1 (incomplete) or Rx (not evaluable) [2].

In this study, procedure-related mortality was defined as any death within 30 days after the ESD. Delayed postoperative hemorrhage was defined as clinical evidence of bleeding manifested by melena or hematochezia that required endoscopic hemostasis within 0 to 14 days after the procedure [5].

We examined the clinicopathologic characteristics of cases such as age, gender, location (rectum or colon),

Table 1 Clinicopathologic characteristics of patients

No. of patients	*n* (%)
Gender	
Male	54 (67.5)
Female	26 (32.5)
Age (years)	
Mean age	68.1 ± 9.9
Disease location	
Colon	56 (70.0)
(Cecum)	(7.5)
(Ascending colon)	(30.0)
(Transverse colon)	(17.5)
(Descending colon)	(2.5)
(Sigmoid colon)	(12.5)
Rectum	24 (30.0)
Macroscopic type	
LST-G	44 (55.0)
LST-NG	23 (28.8)
Depressed	5 (6.2)
Protruding	8 (10.0)
Tumor size (mm)	
Mean tumor size	34.9 ± 14.1
(≥40 mm)	(30.0)
(<40 mm)	(70.0)
Histologic type	
Adenocarcinoma	39 (48.8)
(Noninvasive intramucosal tumors)	(42.5)
(Submucosal invasive carcinoma)	(6.3)
Adenoma	41 (51.2)

LST-G granular-type laterally spreading tumors, *LST-NG* non–granular-type laterally spreading tumors

macroscopic type of tumor (LST-G, LST-NG, depressed, protruding), tumor size, and histologic type (adenocarcinomas or adenomas) as well as the knife type used (Dual Knife or SB Knife Jr). The main outcome measurements of this study were procedural time, en bloc resection rate with tumor-free margins (R0 resection rate), and adverse events rate. Among the clinicopathologic characteristics, factors that affected the main outcome measurements were identified using multivariate analyses.

Statistical analysis

Quantitative data are presented as mean ± standard deviation. Discrete variables are presented as median and range. All statistical analyses were performed using the JMP version 9 (SAS Institute Inc., Cary, NC, USA). Differences among groups were evaluated using the chi-square test or Fisher's exact probability test, as appropriate. A multiple logistic regression method that included all possible variables was used. The level of statistical significance was set at a P value lower than 0.05.

Results

Clinicopathologic characteristics of the 80 patients

The 80 cases in this study included 54 men (67.5 %) and 26 women (32.5 %). The mean age of the entire group was 68.1 ± 9.9 years. The patients in 29 cases (36.3 %) had histories of prior abdominal surgery. Tumors were located at the rectum in 24 cases (30 %) and at the colon in 56 cases (70 %). In terms of macroscopic type, 44 cases (55 %) were identified as LST-G, 23 cases (28.8 %) as LST-NG, 5 cases (6.2 %) as depressed and 8 cases (10 %) as protruding (Table 1).

In all cases, good bowel preparation was achieved early in the afternoon before the colorectal ESD. The mean tumor diameter in the entire group was 34.9 ± 14.1 mm. Of the 80 cases, 24 (30 %) had a tumor diameter of 40 mm or larger and 56 (70 %) had a tumor diameter smaller than 40 mm. Histopathology showed that 39 patients (48.8 %) had adenocarcinomas and 41 patients (51.2 %) had adenomas (Table 1). Five patients had submucosal invasion. Three of these five patients had lymphatic invasion, venous invasion, or massive submucosal invasion greater than 1,000 μm and underwent colectomy.

The Dual Knife was used in 54 cases (67.5 %) and the SB Knife Jr in 26 cases (32.5 %). Of the 54 cases in which the Dual Knife was used, 12 (22.2 %) required another knife or snare. On the other hand, of the 26 cases in which the SB Knife Jr was used, only 2 cases (7.7 %) required another knife or snare ($P = 0.089$, Fisher's exact test).

Main outcome measurements of colorectal ESD

The mean procedural time for the 80 cases was 108.8 ± 53.4 min. For 47 (58.8 %) of these 80 cases, the procedural time was 90 min or longer. The en bloc resection (endoscopic) rate was 93.8 % (75/80), and the R0 resection (histologic) rate was 75 % (60/80).

Perforations occurred during six ESD procedures (7.5 %), which were managed by conservative medical treatment with bowel rest and intravenous antibiotics after the endoscopic closure. Delayed postoperative hemorrhage occurred in three cases (3.8 %) and was treated by endoscopic hemostasis. Therefore, the rate of all ESD-induced adverse events was 11.3 % (9/80). No deaths occurred within 30 days after the ESD.

When the 80 cases were divided into the 40 cases in the first half of the study and the 40 cases in the second half, the en bloc resection rate was 87.5 % (35/40) for the first half and

Table 2 Possible variables that affected the prolonged procedural duration (≥90 min)

	Prolonged procedural duration (≥ 90 min) *n* (%)	*P* value[a]	Multivariate analysis			
			OR[b]		*P* value[b]	95 % CI[b]
Disease location						
Colon	36/56 (64.3)	0.12	3.61	0.04	1.05	14.71
Rectum	11/24 (45.8)		1			
Macroscopic type						
LST-G	28/44 (63.6)	0.21	3.20	0.22	0.50	25.32
LST-NG	14/23 (60.9)		3.79	0.19	0.52	35.27
Depressed	2/5 (40.0)		2.82	0.45	0.19	44.23
Protruding	3/8 (37.5)		1			
Tumor size (mm)						
≥40	21/24 (87.5)	0.0006	14.74	<0.0001	3.58	89.36
<40	26/56 (46.4)		1			
Histologic type						
Adenocarcinoma	21/39 (53.9)	0.38	0.97	0.96	0.32	2.98
Adenoma	26/41 (63.4)		1			
Knife type						
SB Knife Jr	16/26 (61.5)	0.73	1.23	0.70	0.42	3.73
Dual Knife	31/54 (57.4)		1			

OR odds ratio, *CI* confidence interval, *LST-G* granular-type laterally spreading tumors, *LST-NG* non–granular-type laterally spreading tumors

[a] The chi-square test or Fisher's exact probability test was used

[b] The multiple logistic regression method was used

100 % (40/40) for the second half of the study. Similarly, the R0 resection rate increased from 60 % (24/40) in the first half to 90 % (36/40) in the second half of the study. Perforation occurred only in the first half of the study. No case of perforation occurred in the second half of the study.

Factors that affected the prolonged procedural duration (≥90 min)

Among the clinicopathologic characteristics including the location, macroscopic type, tumor size, histologic type, and knife type, the colonic lesions required longer procedural durations than rectal lesions, but the difference was not significant. Significantly more cases with larger lesions (≥40 mm) required prolonged procedural durations than cases with smaller lesions. The procedural duration did not differ significantly in terms of macroscopic type, histologic type, or knife type (Table 2). The procedural duration also was correlated positively with the tumor diameter ($r = 0.566$; $P < 0.0001$).

Multivariate analyses showed that colonic lesions and larger lesions (≥40 mm) were independent predictors of prolonged procedural duration (≥90 min), with respective adjusted odds ratios (ORs) of 3.61 (95 % CI 1.05–14.71) and 14.74 (3.58–89.36). No other factors were associated with prolonged procedural duration (Table 2).

Factors that affected the R0 resection rate

Among the clinicopathologic characteristics examined, the R0 resection rate in the SB Knife Jr group was higher than in the Dual Knife group, but the difference was not significant. The other factors examined did not differ (Table 3). Multivariate analyses showed that use of the SB Knife Jr was significantly associated with the R0 resection rate, with an adjusted OR of 3.91 (95 % CI 1.10–18.81). No other factors had a significant influence on the rate of R0 resection (Table 3).

Factors that affected the adverse events rate

All six cases with perforation had colonic lesions. The rate of perforation in the SB Knife Jr group was lower than in the Dual Knife group, but the difference was not significant (Table 4). All three patients who experienced delayed postoperative hemorrhage had larger lesions (≥40 mm) (Table 4). Because the number of cases with perforation or delayed postoperative hemorrhage was very small, multivariate analyses could not be performed.

Discussion

The efficacy of colorectal ESD performed by experienced endoscopists has been reported mainly from Japanese referral centers [2–8]. On the other hand, there have been few reports on colorectal ESD from Western countries [22, 23].

Because of the technical difficulty and the high risk of adverse events, colorectal ESD has not been established to date as a standard therapeutic method. For novices performing colorectal ESD, experience with gastric ESD

Table 3 Possible variables that affected the R0 resection rate

	R0 resection *n* (%)	*P* value[a]	Multivariate			
			OR[b]	*P* value[b]	95 % CI[b]	
Disease location						
Colon	44/56 (78.6)	0.26	1.90	0.29	0.58	6.27
Rectum	16/24 (66.7)		1			
Macroscopic type						
LST-G	33/44 (75.0)	0.87	0.81	0.81	0.10	4.48
LST-NG	18/23 (78.3)		0.87	0.89	0.09	6.11
Depressed	3/5 (60.0)		0.33	0.40	0.02	4.57
Protruding	6/8 (75.0)		1			
Tumor size (mm)						
≥40	18/24 (75.0)	>0.99	1.16	0.81	0.35	4.17
<40	42/56 (75.0)		1			
Histologic type						
Adenocarcinoma	29/39 (74.3)	0.90	1.43	0.55	0.45	4.78
Adenoma	31/41 (75.6)		1			
Knife type						
SB Knife Jr	23/26 (88.5)	0.06	3.91	0.03	1.10	18.81
Dual Knife	37/54 (68.5)		1			

OR odds ratio, *CI* confidence interval, *LST-G* granular-type laterally spreading tumors, *LST-NG* non–granular-type laterally spreading tumors

[a] The chi-square test or Fisher's exact probability test was used

[b] The multiple logistic regression method was used

Table 4 Possible variables that affected the adverse events rate

	Perforation *n* (%)	*P* value[a]	Delayed postoperative hemorrhage *n* (%)	*P* value[a]
Disease location				
Colon	6/56 (10.7)	0.17	1/56 (1.8)	0.21
Rectum	0/24 (0.0)		2/24 (8.3)	
Macroscopic type				
LST-G	5/44 (11.4)	0.51	2/44 (4.5)	0.41
LST-NG	1/23 (4.3)		0/30 (0.0)	
Depressed	0/5 (0.0)		0/9 (0.0)	
Protruding	0/8 (0.0)		1/12 (8.3)	
Tumor size (mm)				
≥40	2/24 (8.3)	>0.99	3/24 (12.5)	0.02
<40	4/56 (7.1)		0/56 (0.0)	
Histologic type				
Adenocarcinoma	4/39 (10.3)	0.43	1/39 (2.6)	>0.99
Adenoma	2/41 (4.9)		2/41 (4.9)	
Knife type				
SB Knife Jr	1/26 (3.8)	0.66	1/26 (3.8)	>0.99
Dual Knife	5/54 (9.3)		2/54 (3.7)	

LST-G granular-type laterally spreading tumors, *LST-NG* non–granular-type laterally spreading tumors

[a] The chi-square test or Fisher's exact probability test was used

has been recommended before colorectal ESD is attempted [8, 13]. A panel of experts gathered in Europe similarly stated that ESD should be performed in a step-up approach, starting with lesions presenting in the rectum or the distal stomach, moving on to those in the colon and proximal stomach, and finally to lesions in the esophagus [24].

However, it is difficult for endoscopists in Western countries to perform sufficient gastric ESD procedures to gain such experience because fewer early gastric neoplasias occur in Western countries than in Japan [12]. Therefore, the current data on colorectal ESD during the clinical learning curve may be of great use. In addition, the endoscopists in the current study had experience with

fewer than five cases of gastric ESD when they began to perform colorectal ESD. This is a unique point of this study, and the settings of this study were almost the same as those in Western countries.

Needless to say, the experiences of the four endoscopists in the current study were few. Many experts have recommended that novices should experience 20–50 supervised (gastric) ESD cases before starting to perform colorectal ESD [8, 13, 25, 26]. However, because of the very thin wall of the colorectum, colorectal ESD generally requires more delicate control than procedures for the gastric wall. Therefore, it may be better for endoscopists with expertise in colonoscopy or colorectal EMR/EPMR to start colorectal ESD before becoming too familiar with gastric ESD.

On the other hand, similar reports have described novices performing colorectal ESD in Western countries [27, 28]. However, most cases involved rectal lesions, and two endoscopists had a certain amount of experience with gastric and esophageal lesions [27]. In a study reported by Iacopini et al. [28], ESD procedures were performed by only one endoscopist.

For the 80 cases examined in this study, the R0 resection rate was 75 % (60/80), and no ESD-induced fatalities occurred. The lateral margin was judged to be positive when the tumor existed in the first or end slice, even if the lateral and basal margins were free of tumor cells in all slices. Therefore, the R0 resection rate may be lower than in previous studies [2–8]. However, the en bloc resection rate (93.8 %, 75/80) was not low, even compared with previous reports involving expert endoscopists [2–8].

If endoscopists set up slightly larger lateral margins, the R0 resection rate will be satisfactory (close to the en bloc resection rate of 93.8 %). Additionally, in the metaanalysis of ESD versus transanal endoscopic microsurgery (TEM), TEM was reported to achieve a higher R0 resection rate [29]. However, other studies have reported that both ESD and TEM are effective and safe [30, 31].

Clinicians should select ESD or TEM as appropriate, taking their respective advantages into consideration. Although ESD enables minimal invasiveness and avoidance of anesthesia, it has the possibility of additional surgery in cases of massive submucosal invasion.

With regard to adverse events, perforation during the ESD procedure occurred in six cases and delayed postoperative hemorrhage in three cases. All were treated by endoscopic closure and hemostasis. These results indicate that colorectal ESD is feasible and safe during the clinical learning curve.

In terms of factors related to prolonged procedural durations (≥90 min), multivariate analyses showed that colonic lesions and larger lesions (≥40 mm) were significantly associated with prolonged procedural durations. Colonic lesions generally have poor operability by endoscopy and were expected to require higher levels of endoscopic skill and longer procedural durations than rectal lesions. Indeed, Niimi et al. [26] have recommended a training system for colorectal ESD from the rectum to the colon. It stands to reason that larger lesions would be associated with longer procedural durations. In fact, the procedural durations were positively correlated with the tumor diameter. It was reported that lesions measuring 40 mm or larger should have been resected by experienced endoscopists due to prolonged procedural durations [32].

As for factors that affected the R0 resection rate, that of the colon was slightly higher than that of the rectum in the current study. This point was in conflict with those of previous reports. As mentioned in the "Materials and methods" section, most of the rectal lesions were resected in the first half of the case series of each endoscopist. Because of the low endoscopic skill and small margins, the R0 resection rate of the rectum might decrease. If rectal and colonic lesions were resected equally, the location might have a significant influence on the R0 resection rate in multivariate analyses.

As mentioned at the beginning of this report, the SB Knife Jr may be useful for novices with expertise in performing colorectal ESD. The usefulness of another scissors-type knife also has been reported [33]. Although the current study showed no significant difference in the procedural time between the Dual Knife group and the SB Knife Jr group, use of the SB Knife Jr was associated with an increased rate of R0 resection. Because the burning effect of the SB Knife Jr during the incision is moderately strong, we might have set up larger margins, which might have led to the higher R0 resection rate.

Although the problem of the burning effect exists, it is important for novices to perform colorectal ESD safely from all aspects. Indeed, although 22.2 % of the Dual Knife group required another knife or snare because of technical difficulties, only 7.7 % of the SB Knife Jr group required another knife or snare.

Our study had some limitations. First, our study could not exclude selection bias in terms of the knife type and location. The knife for colorectal ESD was not selected randomly, so we might have preferred the SB Knife Jr for lesions presenting perpendicularly to the scope. To evaluate the usefulness of the SB Knife Jr, a prospective cohort study should be performed. As for the location, if rectal and colonic lesions are resected equally, we might be able to exclude selection bias.

Second, because a senior endoscopist observed colorectal ESD performed by novices, the results of colorectal ESD might have been influenced by the skill of the senior endoscopist. Because the endoscopists in the current study had little experience with ESD, supervision by senior

endoscopists was necessary to reduce the risk of adverse events.

Third, we are not able to exclude the effect of fibrosis, which might have affected the main outcome measurements. However, the number of lesions with moderate to severe fibrosis was small because we excluded lesions with fibrosis due to biopsy or peristalsis, sporadic localized lesions in chronic inflammation, and local residual carcinoma after EMR.

The ESD procedure is technically challenging for novices. However, the efficacy and the safety of colorectal ESD were demonstrated in the current study. It may be better for novices performing colorectal ESD to begin with rectal and smaller lesions in order to reduce adverse events. In addition, use of the SB Knife Jr may increase the R0 resection rate. We hope the current study will be useful for novices in colorectal ESD. In the future, a prospective study should be undertaken to determine the efficacy and safety of colorectal ESD.

Acknowledgments We thank Dr. Rintaro Moroi and Dr. Hitoshi Nagasawa for data collection. We also thank Dr. Shoichi Kayaba and Dr. Manabu Shiraki for providing helpful advice concerning colorectal ESD.

Disclosures Hisashi Shiga, Katsuya Endo, Masatake Kuroha, Yoichi Kakuta, Seiichi Takahashi, Yoshitaka Kinouchi, and Tooru Shimosegawa have no conflicts of interest or financial ties to disclose.

Funding This study was not supported by grants from governmental agencies, private sources, or manufacturers of drugs or equipment.

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