２．学会誌・雑誌等における論文掲載

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Involvement of NADPH oxidases in suppression of cyclooxygenase-2 promoter-dependent transcriptional activities by sesamol.	Shimizu S, Ishigamori R, Fujii G, Takahashi M, Onuma W, Terasaki M, Yano T, Mutoh M.	J Clin Biochem Nutr.	in press	国外
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機関名　広島大学病院　内視鏡診療科　田中信治

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発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
大腸SM癌に対する完全摘除生検としてのESDの意義 【シンポジウム】	朝山直樹，田中信治，岡志郎，中土井鋼一，茶山一彰.	福島市（第10回日本消化管学会総会学術集会）	2014.2.14-2.15	国内
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機関名　国立がん研究センター中央病院 内視鏡科　松田尚久

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機関名　和歌山県立医科大学　竹下達也

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機関名　京都府立医科大学　酒井敏行

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機関名　静岡県立大学　食品栄養環境科学研究院　食品環境研究センター　若林敬二

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研究成果の刊行物・別冊

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ORIGINAL ARTICLE

Factors associated with technical difficulties and adverse events of colorectal endoscopic submucosal dissection: retrospective exploratory factor analysis of a multicenter prospective cohort

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Abstract
Background Colorectal endoscopic submucosal dissection (C-ESD) is a promising but challenging procedure. We aimed to evaluate the factors associated with technical difficulties (failure of *en bloc* resection and procedure time, ≥2 h) and adverse events (perforation and bleeding) of C-ESD.

Methods We conducted a retrospective exploratory factor analysis of a prospectively collected cohort in 15 institutions. Eight-hundred sixteen colorectal neoplasms larger than 20 mm from patients who underwent C-ESD were included. We assessed the outcomes of C-ESD and risk factors for technical difficulties and adverse events.

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Results Of the 816 lesions, 767 (94 %) were resected *en bloc*, with a median procedure time of 78 min. Perforation occurred in 2.1 % and bleeding in 2.2 %. Independent factors associated with failure of *en bloc* resection were low-volume center (<30 neoplasms), snare use, and poor lifting after submucosal injection. Factors significantly associated with long procedure time (≥2 h) were large tumor size (≥4 cm), low-volume center, less-experienced endoscopist, CO_2 insufflation, and use of two or more endoknives. Poor lifting was the only factor significantly associated with perforation, whereas rectal lesion and lack of a thin-type endoscope were factors significantly associated with bleeding. Poor lifting after submucosal injection occurred more frequently for nongranular-type laterally spreading tumors (LST) and for protruding and recurrent lesions than for granular-type LST (LST-G).
Conclusions Poor lifting after submucosal injection was the risk factor most frequently associated with technical difficulties and adverse events on C-ESD. Less experienced endoscopists should start by performing C-ESDs on LST-G lesions.

Keywords Colonoscopy · Colorectal neoplasm · Endoscopic gastrointestinal surgery · Endoscopic submucosal dissection

Introduction

Endoscopic resection is a noninvasive, standard treatment for patients with superficial colorectal neoplasms (adenoma/early cancer) without risk of lymph node metastasis [1–3]. Small colorectal neoplasms can be removed easily with conventional polypectomy or endoscopic mucosal resection (EMR). However, conventional EMR may result in piecemeal resection (i.e., tumor resection in multiple fragments) of large-sized tumors [4–6]. Limitations of piecemeal resection include incomplete histological assessment of the specimen and a greater risk of tumor recurrence [7]. Indeed *en bloc* resection (i.e., resecting the entire tumor in one piece) is preferred for precise histological assessment of the resected specimen and to ensure elimination of any residual tumor [4].

Endoscopic submucosal dissection (ESD), of superficial gastrointestinal neoplasms results in high *en bloc* resection rates, regardless of tumor size, location, or fibrosis in the submucosa (SM) [1]. However, colorectal ESD is associated with technical difficulties resulting in poor outcomes, such as failure of *en bloc* resection and long procedure time [8]. Additionally, the adverse events of colorectal ESD (e.g., perforation and bleeding) may be quite severe [9]. These technical difficulties and adverse events may be associated with lesion characteristics, type of endoscopic device, and operator experience. Limitations in attempting to perform colorectal ESD may be due to a lack of information on these technical difficulties and adverse events. Assessing factors associated with such technical difficulties and adverse events may help in formulating training programs for colorectal ESD and treatment strategies for large colorectal tumors. Although several large case-series have assessed the feasibility and efficacy of colorectal ESD, these were retrospective analyses in well-experienced single centers [10, 11]. Outcomes of colorectal ESD were also assessed in a prospective multicenter study, but those centers were all advanced institutions [12]. Therefore, the outcomes of colorectal ESD performed at institutions with various levels of experience have not yet been evaluated.

Considering that the rates of adverse events and tumor recurrence following EMR and ESD had never been directly compared, we performed a prospective cohort study comparing EMR and ESD for large (≥20 mm) colorectal neoplasms [13, 14]. In the prospectively collected cohort, there was a large number of ESD procedures (816 ESDs vs. 1,029 EMRs). Therefore, we retrospectively explored the factors associated with technical difficulty and adverse events on colorectal ESD in the cohort.

Patients and methods

This retrospective analysis involved the patients undergoing colorectal ESD in the prospectively selected patients undergoing colorectal endoscopic resection at 18 tertiary institutions with various levels of experience. The study was performed by the Japanese Society for Cancer of the Colon and Rectum to compare recurrence rates after EMR and ESD for colorectal neoplasms ≥20 mm [13, 14]. The study protocol was approved by the institutional review board of each center and registered in the University Hospital Medical Information Network Clinical Trials Registry as number UMIN 000001642. This manuscript followed the STROBE

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guidelines [15]. All the authors had reviewed and approved the final manuscript.

Study participants

Consecutive patients >20 years old with superficial colorectal neoplasms ≥20 mm in diameter undergoing endoscopic resection between October 2007 and December 2010 were eligible for inclusion in the original cohort trial. Lesions predicted to be noninvasive neoplasms and carcinomas with minute (<1,000 μm) SM invasion, thought to have no risk of lymph node metastasis, were removed by endoscopic resection. The subjects in that trial who underwent ESD were included in this retrospective exploratory factor analysis (Fig. 1). The choice between EMR and ESD was made by each participating colonoscopist, based on the proposed guidelines of the Colorectal ESD Standardization Implementation Working Group [16, 17]. Lesions with contraindications to endoscopic resection, as determined by the colonoscopist, including lesions involving the orifice of the appendix, those encompassing the entire circumference of the colonic wall, those showing massive invasion of the ileum, and lesions inaccessible by colonoscopy, were excluded and treated by surgical colectomy. Written informed consent was obtained from each patient.

Procedures

All procedures were performed by colonoscopists who had been physicians for at least 5 years and were either board-certified by the Japanese Gastroenterological Endoscopy Society (JGES) or had knowledge and endoscopic techniques equal to that of board-certificated colonoscopists. Therefore, no trainees were involved in any of these cases. Endoscopic devices (endoknives), endoscopes, endoscopic systems, and medications were not regulated by the study protocol, and all procedures were performed according to each institution's standard procedure. Patients were considered admitted to hospital when they underwent ESD. Although the fasting and hospitalization periods and examination after colonic ESD were determined according to each institution's protocol, in Japan the usual fasting period is 2 days, including the day on which ESD is performed, and the hospitalization period is 7 days with blood tests performed the day after ESD. The histopathology of each resected specimen was assessed at each institution, following the Japanese classification of colorectal carcinoma [2]. Lesions histopathologically diagnosed as low/high-grade adenoma, intramucosal carcinoma, or carcinoma with minute SM invasion (<1,000 μm), without high pathologic risk features (lymph-vascular involvement and/or poorly differentiated adenocarcinoma), were regarded as curable because they had no risk of lymph node metastasis. By contrast, lesions histopathologically diagnosed as carcinoma with deep SM invasion (≥1,000 μm) or with high-risk pathologic features were regarded as incurable, and these patients were referred for additional surgery, including lymph node dissection.

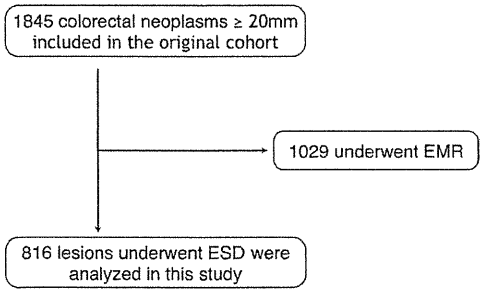

Fig. 1 Study design, showing a flow diagram of enrolled subjects

Data collection and measured outcomes

Detailed data sheets on each participating patient were completed by the investigators and faxed to the independent data center. Information about endoscopic resection (e.g., endoscopic devices, endoscopes, and medications) was collected after the procedure. Data included patient characteristics (age and sex), diagnostic modality prior to endoscopic resection (with or without magnifying endoscopy), tumor characteristics (location, estimated size, type, and history of biopsy), institution, the experience of each colonoscopist (<11 or ≥11 years), fluid injected to form a SM cushion (sodium hyaluronate or others), type of power source used for electrical cutting and its setting, type of electrosurgical endoknife, type of insufflation gas (CO_2 or air), lifting condition after SM injection (good or poor), completeness of the endoscopic resection (*en bloc*, piecemeal, or unresected), diagnostic modality for assessment of residual tumor after endoscopic resection (with or without magnifying endoscopy), procedure time (from the beginning of SM injection until lesion removal), adverse events (perforation, bleeding, and others), treatments administered for adverse events and their outcomes, histopathological diagnosis of the resected specimen (histological type, lymph-vascular involvement, and tumor involvement on the lateral and proximal margins) according to the Japanese classification of colorectal carcinoma [2], and additional therapy for incurable lesions.

Outcomes indicating technical difficulties included failure of *en bloc* resection and procedure time and adverse events included perforation and bleeding. The factors associated with each were also evaluated.

Definitions

ESD was defined as endoscopic dissection of a colorectal tumor using an electrosurgical endoknife, consisting of circumferential mucosal cutting and SM dissection or

circumferential SM incision prior to EMR (CSI-EMR) [18], as it was difficult to distinguish whether CSI-EMR was initially planned prior to the procedure or was used to rescue a procedure which was difficult to complete. As ESD is intended for *en bloc* resection, a failed procedure was defined as failure of *en bloc* resection (i.e., piecemeal resection or incomplete procedure). Tumors were classified as being located on the colon (cecum, ascending, transverse colon, descending or sigmoid colon) or the rectum. Endoknives were classified into three categories (needle knife, IT knife, and scissors types), as well as with or without water-jet function. Tumors were classified into five categories, based on the Paris classification and models of tumor growth during the development of colorectal neoplasia [3, 19]. The five types were: (1) granular-type laterally spreading tumor (LST-G), (2) nongranular-type laterally spreading tumor (LST-NG), (3) protruding tumor, (4) recurrent tumor after endoscopic resection, and (5) unclassified. Lifting conditions after SM injection were assessed as good or poor [20]. Histopathological diagnoses were based on the Japanese classification and were re-classified according to the Vienna classification [21]. Low-grade adenomas according to the Japanese classification were equivalent to noninvasive low-grade neoplasias according to the Vienna classification, whereas high-grade adenomas and intramucosal carcinomas according to the Japanese classification were equivalent to noninvasive high-grade neoplasias according to the Vienna classification. Based on the median number of ESDs performed at each institution during the study period (30 cases/3 years; i.e., 10 cases/year), institutions were classified as low (<30 lesions) and high (≥30 lesions) volume centers. Colonoscopists were classified as those who were less (<11 years) and more (≥11 years) experienced, because it takes at least 5 years to be a board-certified member of JGES and it is thought that it takes more 5 years to experience enough ESD cases. Procedure time >2 h was defined as long, because 30 % of the ESDs needs procedure time >2 h, and it can be said they are relatively difficult cases than average. Lesion size was classified as <40 and ≥40 mm. A bleeding episode was defined as bleeding resulting in (1) apparent hematochezia or melena after the procedure, (2) a ≥2-g/dL decrease in hemoglobin concentration, or (3) a blood transfusion (the decision for transfusion was left each institution's criterion and 7.0 g/dL in hemoglobin concentration is generally accepted as a criterion for transfusion). Perforation was defined as a full-thickness defect of the colonic wall with visible peritoneal fat or the presence of extra-gastrointestinal air on X-ray or abdominal computed tomography. Although observation period for delayed adverse events was not defined, the patients were generally followed up for at least one year because the follow-up period of the original cohort study was one year. Therefore, we could collect the information about late adverse events for two to four weeks [22].

Sample size estimation and statistical analysis

This study was a retrospective exploratory factor analysis of a prospective cohort study. The cohort involved 1,845 colorectal neoplasms ≥20 mm in diameter. The lesions from patients who underwent ESD were included to this exploratory analysis. Multiple lesions in the same patient were counted as independent lesions.

All data were collected and analyzed at an independent data center. Continuous, parametric variables are reported as means (standard deviation (SD)) and nonparametric data as medians (interquartile range (IQR) or range). Categorical variables were reported as incidence or rates (%) and compared using the χ^2 test or Fisher's exact test, as appropriate. Univariate and multivariate logistic regression analyses were performed to examine the factors associated with technical difficulty (failure of *en bloc* resection and procedure time, >2 h), whereas the number of adverse events (perforation and bleeding) was too small for multivariate analysis and only univariate analysis was done to examine the factors associated with adverse events. Variables with p values for association ≤0.2 on univariate analysis were considered potential risk factors in multivariate logistic regression analysis. All statistical analyses were performed using JMP version 10 (SAS Institute Inc, Cary, NC). All analysis were exploratory and P values were two-tailed, with $p<0.05$ defined as statistically significant.

Results

Study design and baseline patient characteristics

The participants' flow is shown in Fig. 1. Between October 2007 and December 2010, 1,845 colorectal neoplasms ≥20 mm in diameter were enrolled in the prospective cohort study. Of these, 816 lesions underwent colorectal ESD and were included in this analysis, and the remainder underwent conventional EMR.

Baseline patient characteristics are shown in Table 1. ESD procedures were performed at 15 of the 18 participating institutions, with a median of 30 lesions (IQR, 11–94 lesions) treated per center. The median lesion size was 35 mm (IQR, 28–47 mm). Almost two thirds of the lesions (64 %) were located in the colon. LST-G was the most frequent type (56 %), with 55 % of the lesions biopsied prior to ESD. Approximately 90 % of the lesions were removed by colorectal ESD at a high-volume center, with 65 % of these procedures performed by more experienced colonoscopists. One fourth of the lesions (25 %) showed poor lifting after SM injection.

Table 1 Baseline demographic and clinical characteristics of the study subjects

		Number		Percent	
Number of lesions		816			
Sex (male/female)		468:348			
Mean age (year (±SD))		67 (±10)			
Median tumor size, mm (IQR)		35 (28–47)			
Tumor location					
Colon	Cecum	520	71	64 %	9 %
	Ascending colon		152		19 %
	Transverse colon		144		18 %
	Descending colon		32		4 %
	Sigmoid colon		121		15 %
Rectum		296		36 %	
Type					
LST-G		459		56 %	
LST-NG		281		34 %	
Protruding		59		7 %	
Recurrent tumor after ER		5		1 %	
Unclassified		12		2 %	
Institution					
High-volume (≥30 patients), 8 institutions		715		88 %	
Low-volume (<30 patients), 7 institutions		101		12 %	
Experience of endoscopist					
More experienced (≥11 years)		531		65 %	
Less experienced (<11 years)		285		35 %	
Lifting after submucosal injection					
Good		608		75 %	
Poor		208		25 %	

Abbreviations: *IQR* interquartile range, *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection

Procedures for colorectal ESD

Almost all procedures used CO_2 gas and sodium hyaluronate (Table 2). Various types of electrosurgical endoknives were used. Of the colorectal ESDs, 68 % required one electrosurgical endoknife, with the remaining 32 % requiring two or more. Endoknives with water-jet function were used to remove 29 % of the colorectal ESDs, with only 5 % requiring an endoscopic snare. Most of the colonoscopists (86 %) preferred to use a thin endoscope (thin caliber colonoscope or gastroscope). A gastroscope was used in 25 % of the procedures, whereas endoscopes equipped with a water-jet function were utilized in 70 %.

Therapeutic outcomes

Therapeutic outcomes are shown in Table 3. The median procedure time was 78 min (IQR, 50–120 min). Procedure times were longer than 2 h for 30 % of the lesions and longer than 3 h for about 10 %. We found that 57 % of the lesions were noninvasive high-grade neoplasms, 24 % were noninvasive low-grade neoplasms, and 18 % were invasive adenocarcinomas, including 7 % that were unexpectedly deep (≥1,000 μm) invasive SM cancers. These latter tumors were regarded as incurable by endoscopic local resection and were referred for additional surgery. Almost all the tumors (94 %) were resected *en bloc*, with 6 % requiring piecemeal resection or surgical colectomy.

Perforation occurred in 17 patients (2.1 %). Although most perforations were treated endoscopically using endoclips without surgical intervention, one required emergency surgery. Bleeding occurred in 20 patients (2.2 %), with most (19 patients) being postoperative. One patient with severe uncontrolled intraoperative bleeding required emergency surgery. There were no fatal adverse events.

Factors associated with difficulty and adverse events of colorectal ESD

Tables 4, 5, 6, and 7 show the results of univariate and multivariate analyses of factors associated with technical

Table 2 Devices used for colorectal endoscopic submucosal dissection

	Number	Percent
CO_2	693	85 %
Sodium hyaluronate	788	97 %
Electrosurgical endoknife (multiple choice answers)		
Needle type[a]	806	98 %
IT type[b]	169	21 %
Scissors type[c]	32	4 %
Endoknife with water-jet function	238	29 %
Number of electrosurgical endoknives used		
1	558	68 %
≥2	258	32 %
Snare used	42	5 %
Thin-caliber endoscope (Gastroscope)	703 (205)	86 % (25 %)
Water-jet endoscope	568	70 %

[a] Includes Flushknife (DK2618JN, Fujifilm Medical, Tokyo, Japan), Flushknife BT (DK2618JB, Fujifilm Medical), Dual knife (KD-650Q, Olympus Co, Tokyo, Japan), Hook knife (KD-620QR, Olympus), Flex knife (KD-630 L, Olympus), needle-type bipolar needle knife (BSBK21S45, Xeon Medical Co, Tokyo, Japan), and ball-tipped bipolar needle knife (BSBK21B35, Xeon Medical)

[b] Includes IT knife (KD-610 L, Olympus), IT knife 2 (KD-611 L, Olympus), and IT knife nano (KD-612Q, Olympus)

[c] Includes SB knife (MD-47706, Sumitomo Bakelite, Tokyo, Japan) and SB knife Jr. (MD-47703, Sumitomo Bakelite)

difficulties (failure of *en bloc* resection and long procedure time) and adverse events (perforation and bleeding). Univariate analysis showed that protruding type tumor, low-volume center (<30 neoplasms), lack of sodium hyaluronate use, snare use, poor lifting after SM injection, noninvasive high-grade dysplasia and deeply invasive carcinoma (≥1,000SMμm) were possible risk factors associated with failure of *en bloc* resection. Multivariate analysis showed that low-volume center, snare use, and poor lifting after SM injection were independent risk factors associated with failure of *en bloc* resection (Table 4). Factors associated with long procedure time (≥2 h) on univariate analysis included large tumor size (≥4 cm), colonic lesion, LST-NG, protruding-type tumor, low-volume center (<30 lesions), less-experienced endoscopist, CO_2 use, use of two or more electrosurgical endoknives, snare use, noninvasive high-grade neoplasm and deeply invasive carcinoma (≥1,000 μm). On multivariate analysis, large tumor size, low-volume center, less-experienced endoscopist, CO_2 use, and use of two or more electrosurgical endoknives were independent risk factors for long procedure time (Table 5).Univariate analysis showed that poor lifting after SM injection was the only risk factor associated with perforation (Table 6). Factors associated with bleeding on univariate analysis included rectal lesions and lack of thin-type endoscope (Table 7).

Poor lifting after SM injection occurred more frequently in LST-NG and in protruding and recurrent lesions than in LST-G, with the incidence of poor lifting after SM injection being extremely high (80 %) for recurrent lesions, although the incidence of poor lifting was not related to history of biopsy (Table 8).

Table 3 Clinical outcomes of colorectal endoscopic submucosal dissection

	Number	Percent
Median procedure time (min (range))	78 (50–120)	
Procedure time ≥2 h	240	30 %
Histology		
Noninvasive low-grade neoplasm	195	24 %
Noninvasive high-grade neoplasm	466	57 %
SM <1,000 μm	88	11 %
SM ≥1,000 μm	62	7 %
Unknown	5	1 %
Completeness of the procedure		
En bloc resection	771	94 %
Piecemeal resection	44	5 %
Unresected	1	1 %
R0 resection	638	78 %

Abbreviation: *SM* submucosa

Discussion

We found that colorectal ESD yielded satisfactory outcomes in this prospective cohort treated at several participating institutions with various levels of experience. Acceptable outcomes of colorectal ESD have also been reported in western countries, but improvements are needed because of its technical difficulties [23]. Adverse events such as perforation and bleeding [13] have been reported, as have failure of *en bloc* resection and long procedure time. We therefore assessed factors independently associated with these technical difficulties and adverse events.

We found that poor lifting after SM injection was independently associated with failure of *en bloc* resection and with increased perforation. Poor lifting after SM injection is thought to be associated with fibrosis in the SM layer. In single center trials, fibrosis was reported related to failure of *en bloc* resection and perforation [20]; and tumor size and the presence of fibrosis were found to be independent risk factors for perforation [24, 25]. Although a multicenter trial showed that only large tumor size and performance of the procedure at a low-volume institution were risk factors for perforation and postoperative bleeding, that trial did not assess lifting condition or fibrosis [13]. Our finding, that poor lifting was a significant risk factor for failure of *en bloc* resection and

Table 4 Univariate ($p \leq 0.2$) and multivariate logistic analyses of factors associated with failure of *en bloc* resection during colorectal endoscopic submucosal dissection

	Univariate analysis			Multivariate analysis		
Variable	*En bloc* resection	Failure of *en bloc* resection	*p* value	Adjusted OR	95 % CI	*p* value
Institution (*n*; %)						
High volume (≥30 patients)	682/715 (95)	33/715 (5)				
Low volume (<30 patients)	89/101 (88)	12/101 (12)	0.0008	5.52	2.25–13.37	0.0003
Snare						
−	744 /774 (95)	30/774 (4)				
+	27/42 (64)	15/42 (36)	<0.001	25.32	10.37–63.94	<0.0001
Lifting condition after SM injection						
Good	590/608 (97)	18/608 (3)				
Poor	181/208 (87)	27/208 (13)	<0.001	10.74	4.49–25.18	<0.0001

Abbreviations: *OR* odds ratio, *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

adverse events, was similar to the results of these earlier trials. The causes of fibrosis are not completely known, but we frequently observed the lesions with poor lifting in LST-NG and in protruding and recurrent lesions. These findings suggest that endoscopists in low-volume centers should start by performing colorectal ESDs on LST-G lesions.

We also found that performance of ESD at a low-volume institution was an important risk factor for failure of *en bloc* resection and long procedure time. Similarly, another study reported that the total number of ESDs performed per institution was inversely associated with the incidence of adverse events [13]. In this study, institutions performing fewer than ten colorectal ESDs per year were regarded as low-volume centers and these institutions should be selective in performing colorectal ESD. Unfortunately, we could not collect the colorectal ESD volume of each colonoscopist and we had to assess the experience of ESD by each institution, not by each colonoscopist. However, since colorectal ESD is a technically challenging and relatively rare procedure, we expect that within each institution such cases are performed by

Table 5 Univariate ($p \leq 0.2$) and multiple regression analyses of factors associated with longer procedure time (≥2 h) during colorectal endoscopic submucosal dissection

	Univariate analysis			Multivariate analysis		
Variable	<2 h	≥2 h	*p* value	OR	95 % CI	*p* value
Tumor size (%)						
<4 cm	396/477 (83)	81/477 (17)				
≥4 cm	180/339 (53)	159/339 (47)	<0.0001	4.97	3.35–7.47	<0.0001
Institution (*n* (%))						
High volume (≥30 patients)	516/715 (72)	199/715 (28)				
Low volume (<30 patients)	60/101 (59)	41/101 (41)	0.01	2.75	1.59–4.78	0.0003
Endoscopist						
Experienced	400/531 (75)	131/531 (25)				
Less experienced	176/285 (62)	109/285 (38)	<0.0001	2.31	1.61–3.34	<0.0001
CO_2						
−	98/123 (80)	25/123 (20)				
+	478/693 (69)	215/693 (31)	0.02	2.02	1.17–3.61	0.012
Number of electrosurgical endoknives used						
1	425/558 (76)	133/558 (24)				
≥2	151/258 (58)	107/258 (42)	<0.0001	2.48	1.70–3.62	<0.0001

Abbreviations: *OR* odds ratio, *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

Table 6 Univariate analysis of factors associated with perforation during colorectal endoscopic submucosal dissection

Variable	Univariate analysis		
	Perforation (−)	Perforation (+)	*p* value
Institution (*n* (%))			
High volume (≥30 patients)	702/715 (98)	13/715 (2)	
Low volume (<30 patients)	97/101 (96)	4/101 (4)	0.15
Snare			
−	760/774 (98)	14/774 (2)	
+	39/42 (93)	3/42 (7)	0.05
Lifting condition after submucosal injection			
Good	601/608 (99)	7/608 (1)	
Poor	198/208 (95)	10/208 (5)	0.003

Abbreviations: *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

Table 8 Relationship between poor lifting after submucosal injection and lesion characteristics

	Poor lifting after SM injection		*p* value
	Incidence (%)	*n*	
Type			
LST-G	16 %	(73/459)	<0.01
LST-NG	38 %	(108/281)	
Protruding	32 %	(19/59)	
Recurrent	80 %	(4/5)	
Unclassified	33 %	(4/12)	
History of biopsy			
Positive	27 %	(119/446)	0.42
Negative	24 %	(89/370)	

Abbreviations: *SM* submucosa, *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor

or with the assistance of the most experienced ESD operator whenever possible. Therefore, we believe that the institutional experience with colorectal ESD is an accurate and adequate surrogate marker for the colonoscpists' ESD experience.

The mechanisms by which rectal location and lack of use of a thin-type endoscope enhance bleeding are unclear. Lesion location in the colon has been reported to be a significant risk factor for delayed bleeding following colonic EMR for large lesions [26]. By contrast, we found that the risk of bleeding was lower for lesions in the colon than the rectum. Differences between the two studies may be due to differences in the resection method (EMR vs. ESD), the race or ethnic background of the patients, and/or lesion characteristics. However, we found that the incidence of bleeding after endoscopic resection for large superficial colorectal tumors was lower (2.2 %) than previously reported (7 %) [26]. This difference may have been due to post-ESD coagulation (PEC), which uses a coagulation forceps to prevent bleeding by visible blood vessels in the resection area [27]. As PEC is not usually performed after conventional EMR, it may explain the reduced bleeding rate after ESD and the different characteristics of bleeding after EMR and ESD. Additionally, thin-type endoscopes are flexible, making it easier for them to access any part of mucosal defects after colorectal ESD. Use of these endoscopes would better detect visible vessels on the mucosal defect after colorectal ESD, resulting in a reduction in bleeding rate due to easier coagulation. Moreover, CO_2 and multiple endoknives use were also independent risk factors for longer ESD procedure time in our study, although CO_2 was reported to reduce the procedure time of colorectal ESD and endoknives are generally used to make the procedure easier [28]. We suppose these are not causative factors but rather than the opposite, symptoms of an expected complicated clinical situation. That is, the endoscopists may tend to use CO_2 or multiple endoknives for especially difficult cases.

Table 7 Univariate analysis of factors associated with bleeding during colorectal endoscopic submucosal dissection

Variable	Univariate analysis		
	Bleeding (−)	Bleeding (+)	*p* value
Location (*n* (%))			
Colon	513/520 (99)	7/520 (1)	
Rectum	285/296 (96)	11/296 (4)	0.04
CO_2			
−	117/123 (95)	6/123 (5)	
+	679/693 (98)	14/693 (2)	0.1
Thin-type endoscope			
−	105/113 (93)	8/113 (7)	
+	691/703 (98)	12/703 (2)	0.003

Abbreviations: *LST-G* granular-type laterally spreading tumor, *LST-NG* nongranular-type laterally spreading tumor, *ER* endoscopic resection, *SM* submucosa

Although our prospectively collected large sample size was one of the strengths of this trial, our results may have been limited by selection bias. Our study subjects consisted of consecutive patients who underwent endoscopic resection in a prospective cohort trial, but more than half the subjects screened underwent EMR [16, 17]. Flat-type lesions, rectal lesions, and SM cancers were more frequently removed by ESD than by EMR. Additionally, the mean lesion size was larger in the ESD than in the EMR group (39.4 vs. 26.4 mm). Despite any possible selection bias, however, the *en bloc* resection rate was greater for ESD than for conventional EMR (94.5 vs. 56.9 %). Moreover, of the 816 lesions removed by ESD, 140 (17.2 %) showed unfavorable results (failure of