Predictive factors for technically difficult endoscopic submucosal dissection in the colorectum

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Background and study aims: Because of technical difficulty, colorectal endoscopic submucosal dissection (CR-ESD) is not widely performed. We aimed to determine risk factors for such technical difficulty as defined by long procedure duration (≥ 150 min), perforation, and piecemeal resection.
Patients and methods: Patients with consecutive colorectal tumors treated with ESD between April 2006 and December 2010 were enrolled in a prospective cohort study. For prediction of technical difficulty, three types of factor were investigated: tumor location, tumor type, and colonoscopy-related. Cases were subsequently categorized into earlier and later periods (April 2006 – August 2008, 123 lesions; September 2008 – December 2010, 124 lesions). Variables were analyzed using multiple logistic regression, with subgroup analyses for each period.
Results: 247 lesions were analyzed. Flexure location was an independent risk factor for technical difficulty as measured by longer procedure duration (odds ratio [OR] 4.1, 95 % confidence interval [95 %CI] 1.1 – 14.9), piecemeal resection (4.7, 1.1 – 17.2), or perforation (8.8, 1.1 – 56.8). Tumor with scarring or locally recurrent was a risk factor for longer procedure duration (4.7, 1.7 – 13.7), and for piecemeal resection (7.8, 2.4 – 25.0). Tumor of size ≥ 50 mm or spreading across ≥ 2 folds was the strongest independent risk factor for longer duration (6.3, 2.8 – 15.4), and was an independent risk factor for longer duration in both time periods (earlier, 3.3, 1.1 – 10.4; later, 27.4, 7.4 – 138.0). Flexure location was an independent risk factor for perforation (13.9, 1.5 – 129.1) and for piecemeal resection (5.1, 0.9 – 25.2) in the earlier but not the later period.
Conclusions: Factors predicting technical difficulty of CR-ESDs were clarified. Their importance was influenced by the increasing experience of the endoscopist.

Introduction

Endoscopic mucosal resection (EMR) for early stage gastrointestinal tumors is potentially curative [1]. However, this endoscopic technique is inadequate for en bloc resection of lesions 20 mm or greater in size because incomplete removal and local recurrence can occasionally be associated with a piecemeal EMR [2,3]. Endoscopic submucosal dissection (ESD) which has been developed in Japan, enables direct submucosal dissection, so that early-stage gastrointestinal tumors can be removed with a high en bloc resection rate. This enhances the potential of curative resection with accurate histological assessment despite large tumor size, presence of severe scarring, or location in a difficult position [4 – 9]. Initially used for gastric tumors, ESD has subsequently been applied to colorectal epithelial neoplastic lesions. However, colorectal ESD (CR-ESD) is a technically challenging and demanding procedure because the lumen of the colorectum is relatively small, tortuous and angulated. In addition, the colorectal wall is thinner compared to the stomach so underestimation of the depth of the submucosal layer can result in a higher risk for perforation during the dissection phase of the submucosal layer. Consequently, a longer procedure time is required [7, 10 – 12].

For adaptation and continued development of skills for this procedure, considerable expert guidance and hands-on experience is necessary for optimal performance and success. However, a suitable high level training environment has not been established as yet. Taking these factors into consideration, appropriate training in a well-recognized established program and sufficient opportunities to improve technical skills in a clinical setting are essential for endoscopists.

To improve the quality of CR-ESD outcomes and training, it is crucial that factors predicting the level of procedural difficulty are evaluated. How-

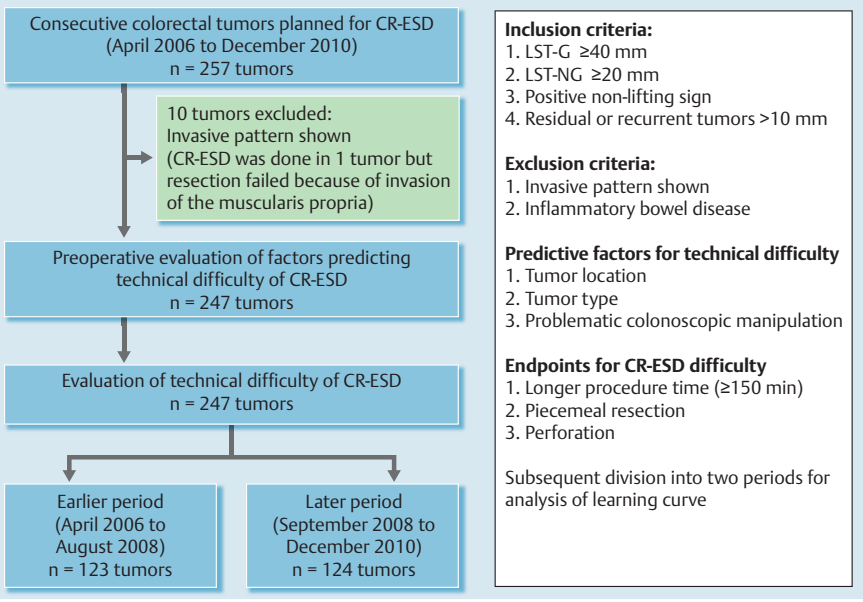

Fig. 1 Factors predicting technical difficulty in colorectal endoscopic submucosal dissection (CR-ESD): study design. LST-G, laterally spreading tumor of granular type; LST-NG, laterally spreading tumor of nongranular type.

ever, to date there has been no prospective analysis of predictors of the technical difficulty, safety, efficacy, and limitations of CR-ESD.

Previously several investigators had reported indications for CR-ESD; however, their analyses were primarily based on clinicopathological features of colorectal lesions [13, 14]. The aim of this study was to prospectively assess the risk factors associated with technical difficulty in CR-ESD.

Patients and methods

Study population

This was a prospective cohort study, using a prospectively completed database of 242 consecutive patients with 257 lesions, referred to the Okayama University Hospital with an indication for CR-ESD, between April 2006 and December 2010 (**Fig. 1**).

This study was approved by the institutional review board of Okayama University Hospital. Written informed consent was obtained from all patients

Exclusion and inclusion criteria

A total of 10 tumors in 10 patients were excluded because surface patterns were suggestive of deep invasion and lymph node metastasis. Lesions were regarded as having an invasive pattern when high magnification chromoendoscopy showed irregular and distorted epithelial crests in a demarcated area, suggesting that the lesion exhibited deep submucosal invasion with risk of lymph node metastasis [15 – 17].

Inclusion criteria were the presence of:

(i) Laterally spreading tumors of granular type (LST-G) and size ≥ 40 mm, with even or uneven nodules on the surface; and

(ii) LSTs of nongranular type (LST-NGs) of size ≥ 20 mm with a smooth surface.

(iii) Lesions showing the "nonlifting" sign.

(iv) Residual or recurrent tumors of size > 10 mm following EMR.

Criteria (i) and (ii) were defined because LST-NG lesions ≥ 20 mm and LST-G lesions ≥ 40 mm have a higher submucosal invasion rate and are difficult to treat even using a piecemeal EMR technique [6, 7, 12, 16, 18].

Preparation and sedation

Adequate bowel preparation was required before colorectal ESD. Patients were restricted to a low fiber diet the day before treatment, and 10 mL of 0.75 % sodium picosulfate solution (Laxoberon; Teijin Pharma Co, Tokyo, Japan) was taken the night before ESD. An isotonic polyethylene glycol electrolyte solution (3 L of Muben; Takeda Pharma Co, Tokyo, Japan) were administered on the morning of the procedure.

Conscious sedation was maintained for the duration of each procedure by the administration of intravenous midazolam (2 – 3 mg).

ESD procedure

All procedures were performed by a single, highly experienced colonoscopist (T.U.) who had previously performed 50 CR-ESDs since January 2004 at another institution.

Carbon dioxide insufflation was used [19]. Single-channel gastroscopes (GIF 260, 260 J, Q240Z; Olympus) and colonoscopes (PCF 260AI, 260 J, and 240ZI; Olympus Co.) were used for rectal and colonic ESD, respectively. Electrosurgical knives and a high frequency automated electrosurgical generator (Erbotom ICC 200; ERBE Elektromedizin Ltd, Tübingen, Germany). in endocut or forced coagulation mode were used.

After submucosal injection of glycerol (Chugai Pharma, Tokyo, Japan), a circumferential incision in the mucosa was made using a needle knife (B-Knife; XEMEX, Tokyo, Japan) or a DualKnife (Olympus) with bipolar current. A mixture of glycerol and sodium hyaluronate acid solution (Suvenyl; Chugai Pharma) containing a small amount of indigo carmine dye was then injected into the submucosal layer to lift the lesion and the thickened submucosal layer was incised using a B-knife or DualKnife. Submucosal injection was repeated after an incision of a few centimeters of the mucosa to facilitate a consistent lifting of the cushion away from the muscle layer while the submucosal connective tissue was dissected. We sometimes combined the use of other electrosurgical knives, namely an insulation-tipped knife (IT Knife; Olympus) or the Mucosectom (Pentax Co, Tokyo, Japan) during submucosal incision and for a safer cut into any submucosal scar or fibrosis, respectively. The B-Knife was routinely used, sometimes combined with the IT Knife, until the end of April 2009,

while from April 2009, the endoscopist mostly used a Dual knife. After ESD, the resected specimen was retrieved using either a net, a sliding tube, or an anoscope with suction. The ulcer base was irrigated with water and any exposed vessels on the ulcer base were treated with coagulation forceps to prevent delayed bleeding.

Any perforation that was noted during the procedure was successfully managed immediately by endoscopic closure using endoclips. All cases of recognized immediate perforation were completed by CR-ESD after endoscopic closure of perforations with endoclips. These patients were managed successfully with subsequent conservative treatment which included fasting and intravenous antibiotics for a few days.

Histopathological evaluation

The resected specimens were fixed in a 10 % buffered formalin solution. Paraffin-embedded samples were then sliced into 2- to 3-mm sections and were stained using hematoxylin and eosin. Histopathological diagnoses were based on the Vienna classification [20].

Variables investigated

Technical difficulty endpoints

After the preoperative examination and documentation of the predictive factors, the technical difficulty of CR-ESD was evaluated during performance of the procedure.

Technical difficulty in performing CR-ESD was defined by any one of three end points:

- Long procedure time (gt; 150 minutes)
- Occurrence of perforation
- Piecemeal resection.

The definition of long procedure time was based on the average operation time of laparoscopic surgery [21,22]. The reason for these endpoints was that we think that CR-ESD is advantageous only if relatively longer procedure time, piecemeal resection, or perforation are avoided.

Factors predicting technical difficulty: selection and definition

The following factors were considered to be potentially predictive of technical difficulty.

1. Colorectal location
- Proximal colon vs. rectum, or distal colon vs. rectum
- Flexure vs. other areas (**Fig. 2a,b**)
- Location type 3: Bauhin's valve or dentate line vs. others (**Fig. 2c,d**).

The proximal colon was considered to be the cecum, ascending colon, hepatic flexure, and transverse colon, and the distal colon to be the splenic flexure, descending colon, and sigmoid colon. The flexures included the hepatic flexure, splenic flexure, the junction of the sigmoid and the descending colon, and the rectosigmoid junction. Tumor location on Bauhin's valve or on the dentate line was defined as a predictive factor, since tumors in these locations have a rich blood supply and resection time is usually longer because of frequent bleeding during the procedure [26].

2. Tumor type
- Tumor extent > 50 mm or spreading across two or more folds (**Fig. 2e, f**)
- Tumor with scarring or arising from local recurrence (**Fig. 2g, h**)
- Tumor type LST-NG.

Tumor size ≥ 50 mm was defined as a predictive factor based on the difficulty presented by tumors of larger size for attempting endoscopic resection [2].

3. Colonoscope maneuverability
- Failure to achieve a retroflexed position
- Deep breathing by patient, or poor manipulation of the colonoscope.

Failure to achieve a retroflexed position was defined as occurring when the endoscopist was unable to visualize the oral side of the lesion with a retroflexed position of the colonoscope. Deep breathing or poor manipulation of colonoscope was defined as the endoscopist's subjective experience of encountering significant difficulty reaching the lesion because of deep breathing by the patient. The movement of the colon during such respiration resulted in inability to achieve proper manipulation of the colonoscope before the CR-ESD, by the same endoscopist who then performed the CR-ESD.

4. Learning curve
- earlier period vs. later period.

To investigate the effect of a learning curve for CR-ESD, the variable of later period vs. earlier period was included. Procedures were subsequently categorized, with 123 lesions resected during the early period between April 2006 and August 2008 and 124 lesions during the late period between September 2008 and December 2010) (**Fig. 1**).

Statistical analysis

Continuous variables are presented as medians and interquartile range (IQR). Continuous variables were compared using the Mann – Whitney *U* test, and dichotomous variables were examined using Fisher's exact test and logistic regression. In order to extract significant factors for each of the three technical difficulty end points (long procedure time ≥ 150 min, perforation, or piecemeal resection), multivariate analyses were done using logistic regression analysis with backward stepwise selection, with $P = 0.15$ as the level for including variables, and $P = 0.10$ for exclusion of variables. The significance level was set at $P < 0.05$ Analyses were done using JMP software version 8.0 (SAS Institute, Cary, North Carolina, USA).

To investigate any learning curve effect on performance of CR-ESD with regard to technical difficulty, the variable of later period vs. earlier period was examined using univariate logistic regression analyses and stepwise multiple logistic regressions for all periods, and subgroup analyses for each period were done.

Results

Table 1 shows the characteristics of the study population and the lesions. For the 247 colorectal lesions in this study, the en bloc resection rate was 93.1 % (230/247), the R0 resection rate was 92.3 % (228/247), and the curative resection rate was 92.3 % (228/247). The median procedure time was 60 minutes (IQR 40 – 120 minutes) with median resected tumor size of 35 mm (IQR 23 – 46 mm). Five perforations (2.0 %) occurred during ESD and were successfully managed by endoscopic closure and conservative management without the need for surgical intervention.

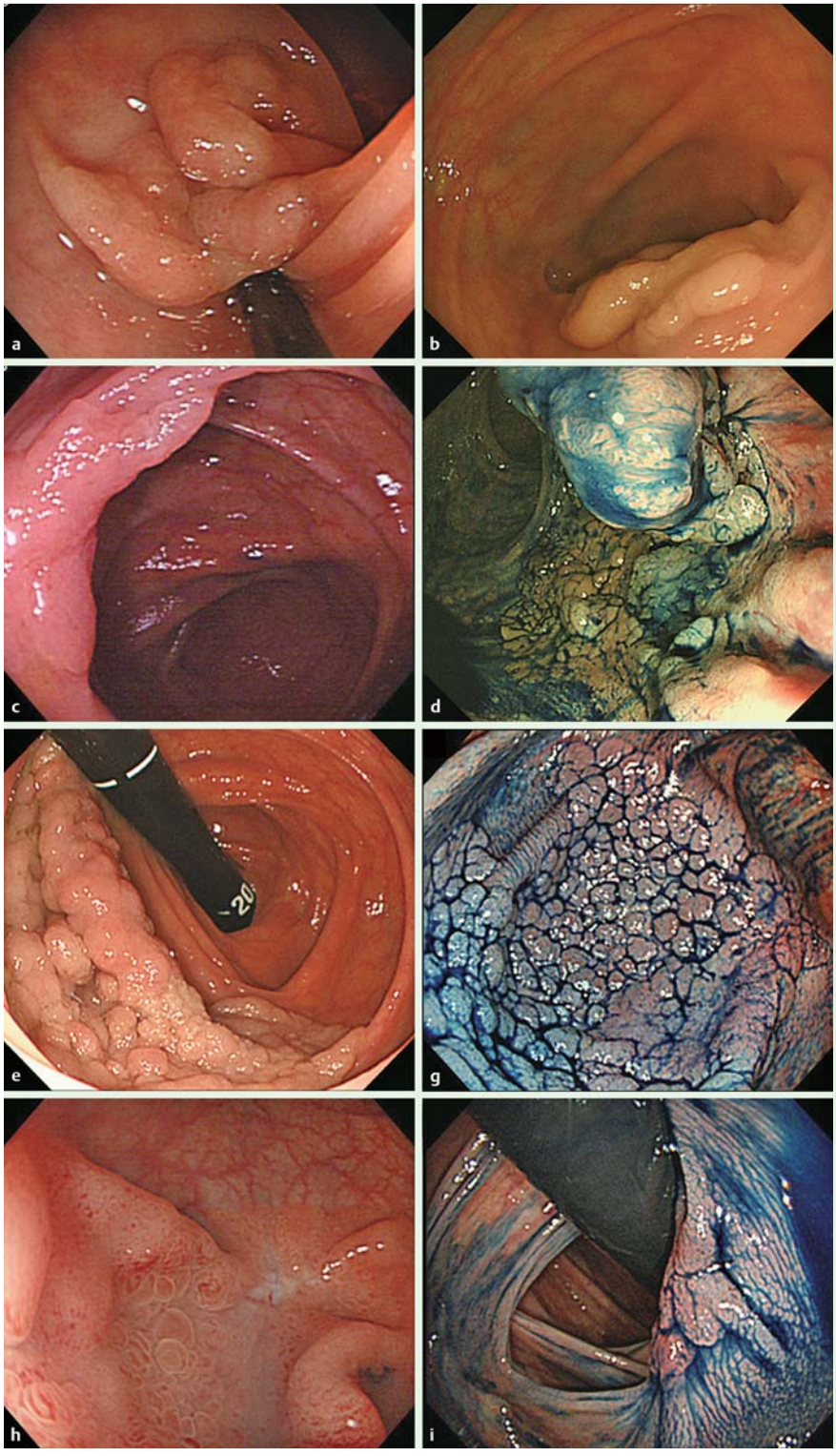

Fig. 2 Factors predictive of difficult colorectal endoscopic submucosal dissection (CR-ESD): representative endoscopic examples. **a, b** Flexure location (hepatic flexure, splenic flexure, junction of sigmoid and descending colon, or rectosigmoid). **c, d** Location on Bauhin's valve or dentate line. **e, f** Tumor extent ≥ 50 mm or spreading across two or more folds. **g, h** Tumors with scarring or that arose from local recurrence.

Learning curve: univariate analysis

Based on the analysis according to earlier and later periods (123 and 124 lesions, respectively), the procedure time was significantly improved (earlier period, median 80 min, IQR 50 – 140; later period, median 55 min, IQR 31 – 90; $P = 0.0002$). Nonsignificant tendencies for improvement in the later period were shown for rates of en bloc resection (earlier vs. later 91.1 % vs 95.2 %), R0 resection (90.2 % vs. 94.4 %), curative resection (90.2 % vs. 94.4 %), and perforation (3.3 % vs. 0.8 %).

Factors predicting technical difficulty: univariate and multivariate analysis

Table 2 summarizes the results of the univariate and multivariate analysis for factors predicting difficulty with CR-ESD. Results for variables meeting the *P*-level criteria are shown in bold, and the multivariate analysis columns show only the variables selected using those criteria.

Multivariate analysis showed that location of tumor at a flexure was an independent risk factor for technical difficulty at CR-ESD with regard to all three end points: longer procedure time (odds

	All	Early period	Later period
CR-ESD procedures, n	247	123	124
Patient and tumor characteristics			
Age, median (IQR), years	70 (62 – 75)	70 (63 – 77)	70 (61 – 75)
Sex, male, n (%[1])	165 (66.8)	87 (70.7)	78 (62.9)
Tumor size, median (IQR), mm	35 (23 – 46)	35 (23 – 50)	33 (23 – 43)
ESD procedure outcome			
Resection type, n (%[1])			
En bloc	230 (93.1)	112 (91.1)	118 (95.2)
R0 en bloc	228 (92.3)	111 (90.2)	117 (94.4)
Curative	228 (92.3)	111 (90.2)	117 (94.4)
Procedure time			
Duration, median (IQR), minutes	60 (40 – 120)	80 (50 – 140)	55 (31 – 90)
Longer than 150 minutes, n (%[1])	45 (18.2)	29 (23.6)	16 (12.9)
Complications, n (%[1])			
Perforations	5 (2.0)	4 (3.3)	1 (0.8)
Post procedure bleeding	1 (0.4)	1 (0.8)	0 (0.0)
Factors associated with difficulty, n (%[1])			
Tumor location			
Colon			
Proximal colon			
Bauhin's valve	8 (3.2)	5 (4.1)	3 (2.4)
Hepatic flexure	12 (4.9)	7 (5.7)	5 (4.0)
Other	99 (40.1)	39 (31.7)	60 (48.4)
Distal colon			
Splenic flexure, sigmoid – descending colon junction	4 (1.6)	0 (0.0)	4 (3.2)
Other	48 (19.4)	26 (21.1)	22 (17.7)
Rectum			
Dentate line	12 (4.9)	5 (4.1)	7 (5.7)
Rectosigmoid flexure	3 (1.2)	3 (2.4)	0 (0.0)
Other	61 (24.7)	38 (30.9)	23 (18.6)
Tumor type			
Tumor size ≥ 50 mm or spreading across ≥ 2 folds	75 (30.4)	44 (35.8)	31 (25.0)
With scarring or from local recurrence	33 (13.4)	13 (10.6)	20 (16.1)
LST-NG	95 (38.5)	43 (35.0)	52 (42.0)
Colonoscopic manipulation difficulty			
Failure to achieve a retroflexed position	83 (33.6)	27 (22.0)	56 (45.2)
Deep breathing by patient, or poor manipulation	63 (25.5)	27 (22.0)	36 (29.0)

IQR, interquartile range; LST-NG, laterally spreading tumor of nongranular type.
[1] % of total or of period subgroup

Table 1 Factors predicting technical difficulty in colorectal endoscopic submucosal dissection (CR-ESD): baseline characteristics of patients and tumors, and procedure outcomes.

ratio [OR] 4.1, 95% confidence interval [95%CI] 1.1 – 14.9; *P*= 0.03) piecemeal resection (OR 4.7, 95%CI 1.1 – 17.2; *P*=0.037), and perforation (OR 8.8, 95%CI 1.1 – 56.8; *P*=0.022).

Presence of scarring or local recurrence was a risk factor with regard to the two end points of longer procedure time (OR 4.7, 95% CI 1.7 – 13.7; *P*=0.0034) and piecemeal resection (OR 7.8, 95%CI 2.4 – 25.0; *P*=0.0008).

Tumor extent ≥ 50 mm or spreading across two or more folds was the independent risk factor with the highest odds ratio for longer procedure time (OR 6.3, 95%CI 2.8 – 15.4; *P*<0.0001), but it was not a significant risk factor for piecemeal resection or for perforation. Tumor location on Bauhin's valve or the dentate line was also an independent risk factor for longer procedure time (OR= 3.7, 95%CI 1.1 – 13.1], *P*=0.035).

Risk of longer procedure time was significantly lower in the later period (**Table 2**) according to univariate analysis (OR 0.5, 95%CI 0.2 – 0.9; *P*=0.032), whereas multivariate analysis showed a non-significant tendency of lower risk (OR 0.5, 95%CI 0.2 – 1.0; *P*= 0.058).

Learning curve: multivariate subgroup analysis

The subgroup multivariate analyses for factors predicting technical difficulty with CR-ESD, stratified for the earlier and later periods, are summarized in **Table 3** and **Table 4**, respectively.

In the earlier period, tumor location at a flexure was an independent risk factor for perforation (OR 13.9, 95%CI 1.5 – 129.1; *P*= 0.014) and for piecemeal resection (OR 5.1, 95%CI 0.9 – 25.2; *P*= 0.049); however, this was not identified as a risk factor in the later period. Similarly, in the earlier period, presence of scarring with the tumor or local recurrence was an independent risk factor for both piecemeal resection (OR 6.1, 95%CI 1.3 – 26.1; *P*= 0.015) and for longer procedure time (OR 14.7, 95%CI 3.1 – 91.3; p=0.0016), and deep breathing or poor manipulation was an independent risk factor for longer procedure time (OR 9.5, 95%CI 1.9 – 61.7; *P*=0.0099); these were not identified as risk factors in the later period.

Tumor extent ≥ 50 mm or spreading across two or more folds was an independent risk factor for longer procedure time in both periods (earlier, OR 3.3, 95%CI 1.1 – 10.4, *P*=0.038; later, OR 27.4, 95%CI 7.4 – 138.0, *P*<0.0001). Tumor location on Bauhin's valve or the dentate line was an independent risk factor for longer procedure time in the earlier period (OR 10.9, 95%CI 1.6 – 97.8; *P*=

Table 2 Prediction of technical difficulty in colorectal endoscopic submucosal dissection (CR-ESD): univariate and multivariate analysis of possible factors.

Variable categories, and variables	Procedure time ≥ 150 min						Piecemeal resection						Perforation					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	95 %CI	*P*	OR	95 %CI	*P*	OR	95 %CI	*P*	OR	95 %CI	*P*	OR	95 %CI	*P*	OR	95 %CI	*P*
Location																		
Rectum (reference)	1.0						1.0			1.0			1.0					
Proximal colon (vs. rectum)	**0.4**	**0.2 – 0.9**	**0.021**				1.8	0.6 – 6.8	0.30	**2.6**	**0.9 – 8.7**	**0.086**	2.6	0 – 0	0.36			
Distal colon (vs. rectum)	**0.3**	**0.1 – 0.7**	**0.0061**				0.7	0.1 – 3.8	0.71				0.0001	0 – 8.5	0.31			
Flexure (hepatic, splenic, sigmoid – descending colon junction, or rectosigmoid, vs. other lesions)	2.2	0.7 – 6.0	0.12	**4.1**	**1.1 – 14.9**	**0.032**	**4.4**	**1.1 – 4.3**	**0.034**	**4.7**	**1.1 – 17.2**	**0.037**	**8.8**	**1.1 – 56.8**	**0.0022**	**8.8**	**1.1 – 56.8**	**0.0022**
Bauhin's valve or dentate line (vs. other lesions)	**4.3**	**1.6 – 11.3**	**0.0025**	**3.7**	**1.1 – 13.1**	**0.035**	2.7	0.6 – 9.3	0.18				2.9	0.1 – 21.1	0.40			
Tumor type																		
Tumor size ≥ 50 mm or spreading across ≥ 2 folds	**7.0**	**3.5 – 14.4**	**< 0.0001**	**6.3**	**2.8 – 15.4**	**< 0.0001**	1	0.3 – 2.7	0.93				3.5	0.6 – 27.3	0.17			
Tumors with scarring or from local recurrence	**3.7**	**1.6 – 8.1**	**0.0019**	**4.7**	**1.7 – 13.7**	**0.0034**	**5.5**	**1.9 – 15.6**	**0.0029**	**7.8**	**2.4 – 25.0**	**0.0008**	1.6	0.1 – 11.5	0.68			
LST-NG	**0.05**	**0.00 – 0.2**	**< 0.0001**	**0.1**	**0.02 – 0.4**	**0.0045**	0.5	0.1 – 1.4	0.18				0.4	0.02 – 2.7	0.37			
Colonoscopic manipulation difficulty																		
Failure to achieve a retroflexed position	0.9	0.4 – 1.7	0.70				1.1	0.4 – 3.0	0.88				1.3	0.2 – 8.1	0.76			
Deep breathing or poor manipulation	1.2	0.6 – 2.5	0.57				1.7	0.5 – 4.6	0.34				0.00007	0 – 1.4	0.084			
Period																		
Later period	**0.5**	**0.2 – 0.9**	**0.032**	0.5	0.2 – 1.0	0.058	0.5	0.2 – 1.4	0.20	0.4	0.1 – 1.2	0.099	0.2	0.01 – 1.7	0.16			

OR, odds ratio; 95 %CI, 95 % confidence interval; LST-NG, laterally spreading tumor nongranular type.

Table 3 Earlier period of study: significant factors for predicting technical difficulty in colorectal endoscopic submucosal dissection (CR-ESD) in the earlier study period: stepwise multivariate logistic regression analysis.

Variable categories, and variables	Procedure time ≥ 150 min			Piecemeal resection			Perforation		
	OR	95 %CI	*P*	OR	95 %CI	*P*	OR	95 %CI	*P*
Location									
Rectum (reference)	1.0								
Proximal colon (vs. rectum)	**0.2**	**0.03 – 0.8**	**0.042**						
Distal colon (vs. rectum)	0.2	0.03 – 1.1	0.081						
Flexure (hepatic, splenic, sigmoid – descending colon junction, or recto-sigmoid, vs. other lesions)				**5.1**	**0.9 – 25.2**	**0.049**	**13.9**	**1.5 – 129.1**	**0.014**
Bauhin's valve or dentate line (vs. other lesions)	**10.9**	**1.6 – 97.8**	**0.02**						
Tumor type									
Tumor size ≥ 50 mm or spreading across ≥ 2 folds	**3.3**	**1.1 – 10.4**	**0.038**						
Tumors with scarring or from local recurrence	**14.7**	**3.1 – 91.3**	**0.0016**	**6.1**	**1.3 – 26.1**	**0.015**			
LST-NG	**0.1**	**0.02 – 0.6**	**0.025**						
Colonoscopic manipulation difficulty									
Deep breathing or poor manipulation	**9.5**	**1.9 – 61.7**	**0.0099**						

OR, odds ratio; 95 %CI, 95 % confidence interval; LST-NG, laterally spreading tumor nongranular type.

Table 4 Later study period: significant factors for predicting technical difficulty in colorectal endoscopic submucosal dissection (CR-ESD): stepwise multivariate logistic regression analysis.

Variable categories, and variables	Procedure time ≥ 150 min			Piecemeal resection			Perforation		
	OR	95 %CI	*P*	OR	95 %CI	*P*	OR	95 %CI	*P*
Location									
Bauhin's valve or dentate line (vs. other lesions)				**6.9**	**0.9 – 41.4**	**0.040**			
Tumor type									
Tumor size ≥ 50 mm or spreading across ≥ 2 folds	**27.4**	**7.4 – 138.0**	**<0.0001**						
Colonoscopic manipulation difficulty									
Failure to achieve a retroflexed position	0.3	0.07 – 1.0	0.069						

OR, odds ratio; 95 %CI, 95 % confidence interval; LST-NG, laterally spreading tumor nongranular type.

0.02), and an independent risk factor for piecemeal resection in the later period (OR 6.9, 95 %CI 0.9 – 41.4; *P* = 0.040).

Discussion

Because of improvements and refinements in ESD techniques and devices and increased expertise of endoscopists, performance of ESD in the colorectum has gradually come about. However, limitations such as technical difficulty, longer procedure time, and increased risk of perforation are still major concerns regarding this procedure [7, 10 – 12]. Because the technical challenges vary according to patient and lesion characteristics, for successful ESD it is important that in each case an attempt is made beforehand to predict the likely technical difficulty.

We defined long procedure time (in this study, as compared with the average operation time for laparoscopic surgery [21, 22]), perforation, and piecemeal resection as end points that marked technical difficulty. Procedure duration is a potentially important surrogate marker for difficulty. In addition, difficult procedures take longer because of the attempt to avoid major complications, mainly perforation, requiring careful consideration of each step during incision and dissection. ESD can result in a high en bloc resection rate, enhancing the possibility of potentially curative resection with accurate histological assessment, but some difficult procedures are considered to be unsuccessful because they result in unintended piecemeal resection. Difficult ESD procedures entail more device exchanges for tissue elevation, more bleeding, and more time; this also has very important implications in most health care environments because of the associated cost.

We defined three categories of factors that might predict technical difficulty: location of tumors, tumor type, and colonoscopic manipulation before the CR-ESD itself.

Our study shows that location of the tumor at a flexure was an independent risk factor for all three technical difficulty end points, and the presence of tumors with scarring or arising from local recurrence was an independent risk factor for long procedure time and for piecemeal resection. Contrary to our expectation, tumor size was not an risk for perforation or piecemeal resection, but it had the highest odds ratio as an independent risk factor for longer procedure time. The risk for longer procedure time tended to be lower in the later period.

Based on the subanalyses done for the earlier and later periods, in the earlier period flexure location was an independent risk factor for perforation and for piecemeal resection, and the presence of a tumor with scarring or from local recurrence was identified as a risk factor with the highest odds ratios for long procedure time

and for piecemeal resection. However, these were not identified as risk factors in the later period. We recommend a step-by-step process when attempting to introduce CR-ESD into practice: we consider that tumors located at flexures or associated with scarring or from local recurrence are not good candidates for CR-ESD in the early period of its adoption.

With regard to risk factors associated with technical difficulty for ESD, Imagawa et al. reported the degrees of technical difficulty for ESD in the stomach. Their analysis showed that larger tumor size, location, and ulceration were associated with greater difficulty of gastric ESD [23]. However there are few reports that describe the risk factors for technical difficulty of CR-ESD, although some recent reports have demonstrated risk factors for complications related to CR-ESD [12, 24]. Isomoto et al. reported that the presence of fibrosis and right-side colonic location of tumor were independent risk factors for incomplete resection, and the presence of fibrosis and tumor size ≥ 31 mm were independent risk factors for perforation [24]. Saito et al. reported that tumor size ≥ 50 mm was an independent risk factor for complications including immediate or delayed perforation and post-procedure bleeding, but in that multicenter study a larger number of ESDs performed at an institution was associated with a decreased risk of complications [12], reflecting the importance of more experience. In the present study, the tumor size or presence of scarring with the lesion were not risk factors for perforation, but were associated with longer procedure time. ESD for tumors in the colorectal area requires more technical skill because of the unique anatomical characteristics of the colon with its flexures.

Some investigators have described criteria for introduction of CR-ESD that are based on analysis of endoscopists' learning curves [13, 14]. If the procedure is predicted to be very difficult, then ESD should be first attempted and mastered in the distal stomach before CR-ESD is attempted [25, 26]. However, it is recognized that in Western countries this is not feasible because of the low prevalence of early gastric cancer. Therefore, the rectum is considered an easy and safe location for beginning to perform ESD compared with the colon [10, 14, 25, 27 – 29]. To date, a strict evaluation regarding the difficulty of colorectal ESD has not been performed. Even rectal tumors are not recommended as an introduction to the procedure if they involve cutting and dissecting close to or on the dentate line, or if they are large laterally spreading tumors ≥ 50 mm As the expertise of the endoscopist improves, progression to ESD of colonic tumors without scarring and not located on flexures is scarring is recommended. ESD of tumors located at flexures requires significant experience and there may be other factors that require attention in the pre-procedure prediction of level of technical difficulty.

CR-ESD procedures are considered to be more technically difficult and result in a higher risk of peritonitis when compared with gastric ESDs. Even at specialized Japanese centers, complication rates are significantly different according to the number of ESDs performed at an institution [12]. Training at high volume centers under expert supervision and the use of animal training models will provide considerable support for the introduction and technical improvement of CR-ESDs [28, 30].

A limitation of our study was that all the ESDs were performed by a single endoscopist. Further studies with a larger number of ESD procedures and inclusion of endoscopists with different experience will be necessary to confirm our results. In our study, only one case in which endoscopic resection could not be completed (see **Fig. 1**) met the existent inclusion criteria, but this case fulfilled the exclusion criterion of a positive invasive pattern before the procedure was conducted and was excluded from the study. Therefore, definitive exclusion criteria for CR-ESD based on technical difficulty cannot be determined from our study. Nevertheless we think that if the preoperative evaluation shows likely outcomes for CR-ESD of longer procedure time than the average for laparoscopic surgery, or of piecemeal resection, or of perforation, then CR-ESD should be avoided as it is then not sufficiently advantageous. Therefore, strict evaluation of the technical difficulty of CR-ESD on the basis of those end points is felt to be absolutely necessary. In addition, our results show that even experienced endoscopists should not attempt CR-ESD of tumors with the combined risk factors of flexure location and association with scarring or local recurrence.

In conclusion, predictive factors for technical difficulty of CR-ESD were clarified. However, because of the learning curve for performance of CR-ESD, the influence of factors predicting degree of difficulty differed according to the experience of the endoscopist. In addition to clinicopathological features of colorectal lesions, the indications for CR-ESD should be determined by the predicted technical difficulty and the experience of the endoscopist.

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