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Predictive factors associated with technical difficulty in colorectal endoscopic submucosal dissection

A Honam Association for the Study of Intestinal Disease (HASID) multicenter study

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Abstract

Colorectal endoscopic submucosal dissection (ESD) is a promising but challenging procedure. It is not widely performed due to its technical difficulty. We aimed to find the predictive factors associated with technical difficulty in colorectal ESD before the procedure. Clinical data from patients who underwent ESD for colorectal tumors in 5 hospitals in Honam province of South Korea between 2015 and 2020 were reviewed retrospectively. Technically difficult colorectal ESD procedure was defined in 3 points. Long procedure time (longer than 60 minutes), occurrence of perforation, and failure of en bloc resection. Factors associated with technically difficult ESD were included as main outcome measure. 1446 patients were identified and their data were analyzed. Median procedure time was 30.0 minutes and median long axis of the tumor was 20.1 mm. Technically difficult procedures including long procedure time were 231 cases (16.0%), perforation occurred in 34 cases (2.3%), and en bloc resection was done in 1292 cases (89.3%). Tumor size larger than 35 mm (odd ratio [OR]: 1.474, $P = .047$), central depression or ulceration in the lesion (OR: 1.474, $P = .013$), previous endoscopic mucosal resection (EMR) or polypectomy procedure (OR: 2.428, $P = .020$) were associated with technically difficult ESD. Descending colon-located tumor (OR: 5.355, $P < .001$), and use of IT knife (OR: 4.157, $P = .003$) were associated with perforation. Recognizing factors associated with technically difficult ESD can help in planning the ESD procedure beforehand.

Abbreviations: CI = confidence interval, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, IQR = interquartile range, IT = insulated tipped, LST = laterally spreading tumor, LST-G = laterally spreading tumor granular type, LST-NG = laterally spreading tumor nongranular type.

Keywords: colorectal tumor, endoscopic submucosal dissection, perforation, procedure time

1. Introduction

Endoscopic submucosal dissection (ESD) has been used in the treatment of premalignant and early malignant GI tract lesions, especially in size larger than 20 mm allowing en bloc resection.[1,2] Compared to conventional endoscopic resection, ESD has higher potential for curative resection, allowing detailed histologic evaluation of the specimen[3,4] and accurate judgment of resection margin.[5] However, colorectal ESD is technically more difficult compared to esophageal and gastric ESD because of the thin walls, presence of folds and flexures, and peristalsis of the colon.[6,7] This technical difficulty leads to longer procedure time, occurrence of complications such as perforation, and failure of en bloc resection. Risk stratification for difficult ESD before the procedure is of great value in

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arranging the procedure schedule and improving the quality of colorectal ESD outcomes. However, current data on risk factors associated with technical difficulty in colorectal ESD are limited and only a few validated tools are available to predict the level of difficulty. In this study, we aimed to find the predictive factors associated with technical difficulty in colorectal ESD before the procedure with a large number of cases.

2. Materials and methods

2.1. Study population

A total of 1446 patients who underwent ESD at 5 tertiary medical centers (Chonnam National University Hospital, Chonnam National University Hwasun Hospital, Jeonbuk National University Hospital, Chosun University Hospital and Wonkwang University Hospital) located in Honam province in South Korea, between January 2015 to December 2020 were retrospectively enrolled. The hospitals are affiliated with the Honam Association for the Study of Intestinal Diseases. Medical records were collected and analyzed retrospectively to extract pre-procedural characteristics and procedural outcomes. Pre-procedural characteristics included age, sex, past medical history, tumor size and location, morphology of the tumor, and previous endoscopic mucosal resection (EMR) or polypectomy history of the patients. Procedural outcomes included completeness of endoscopic resection (en bloc or piecemeal), rate of R0 resection, procedure time (from start of submucosal injection to complete removal of the lesion), presence of fibrosis, lifting condition after submucosal injection (poor or good), complications including perforation, bleeding and postcoagulation syndrome, and histopathological diagnosis of the resected specimen. The study protocol was approved by the ethical review boards of 5 participating institutions (Chonnam National University Hospital [IRB No. CNUH-2022-060], Chonnam National University Hwasun Hospital [IRB No. CNUHH-2022-208], Chosun University Hospital [IRB No. CHOSUN 2022-03-006-001], Chonbuk National University Hospital [IRB No. CNU 2022-12-057], and Wonkwang University Hospital [IRB No. WKUH 2022-10-007]), and all patients provided written informed consent for ESD before the procedure.

2.2. Indication for ESD

Indications for colorectal tumors treated with ESD were in accordance with the Korean Journal of Gastroenterology guidelines.[8] Clinically diagnosed intramucosal neoplasm, regardless of cancer or adenomas, or invasive carcinoma with superficial submucosal invasion (SM1; <1000 μm from muscularis mucosa) using chromoendoscopy or magnification, lesions larger than 20 mm of any macroscopic type, lesions that are unsuitable for EMR such as recurrence of the lesion previously treated by endoscopic resection. Although many neuroendocrine tumors in the rectum were treated with ESD, they were not included in this study.

2.3. ESD procedure

All the colorectal ESD procedures were performed by experienced endoscopists who had performed over 200 procedures of gastric ESD. The endoscopes (such as PCF-Q260JI, CF-H260AI, CF-HQ290I, CF-H290I; all from Olympus, Tokyo, Japan) were chosen in accordance with the location and features of the lesions. Indigo carmine dye was used to delineate the margin of the lesions. The mucosa was marked circumferentially using the tip of a needle knife (Dual knife; Olympus, Tokyo, Japan) with a 3 to 5 mm safety margin. A mixture of methylene blue and epinephrine diluted with normal saline was injected into submucosa to lift the lesion. Mucosal incision and submucosal dissection were done with careful hemostasis using a needle knife (Dual knife; Olympus, Tokyo, Japan) or insulated tipped knife (IT knife; Olympus, Tokyo, Japan). Then coagulation of visible vessels in the artificial ulcer was done.

2.4. Definitions and outcomes

Technically difficult ESD was defined as any 1 of 3 endpoints; long procedure time (more than 60 minutes), occurrence of perforation (including both intra-procedural and delayed perforation), and failure of en bloc resection. Tumor location was divided into 6 areas; cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The macroscopic morphology of tumor was classified into laterally spreading tumor (LST) and protruded-type. LSTs were subdivided into LST-granular type (LST-G), and LST-nongranular type (LST-NG). En bloc resection was defined as an excision of the tumor in 1 piece without fragmentation. R0 resection was defined as a histologically complete resection with no risk of lymph node metastasis.[9]

Post-procedural bleeding was defined as bleeding requiring transfusion or emergency endoscopy or that reduced the hemoglobin level by more than 2 g/dL, 6 hours to 30 days after the procedure. Immediate perforation was diagnosed by endoscopically observed extraluminal space during the procedure. Delayed perforation was diagnosed by the presence of free air on X-ray or computed tomography taken after the procedure. Post coagulation syndrome was diagnosed when there were signs of inflammation such as abdominal pain, fever (≥37.8°C), leukocytosis (≥10,000 cells/μL), or elevation of C-reactive protein level (≥0.5 mg/dL), 6 to 24 hours after ESD without evidence of perforation.

2.5. Statistical analysis

Nonnormally distributed variables were reported as medians (interquartile range [IQR]). Categorical variables were expressed as frequencies and percentages. The Mann–Whitney *U* test, the Student *t* test, chi-square test, or the analysis of variance were used as appropriate. Using a logistic regression model, we determined predictive factors associated with technically difficult ESD, perforation, long procedure time, and piecemeal resection. Statistical significance was set at $P < .05$. All data were analyzed using Statistical Package for the Social Sciences, version 27.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Characteristics of enrolled patients and the lesions

Pre-procedural baseline characteristics of enrolled patients and lesions are summarized in Table 1. The median age was 66.1 (IQR 57.7–73.8) years, median tumor size was 20.1 (15–29) mm on long axis and 16.5 (10–25) mm on short axis. 662 (45.8%) were LST-G, 438 (30.3%) were LST-NG and 346 (23.9%) were protruded-type. 29 (2.1%) patients had previous EMR or polypectomy for the lesion. IT knife was used during the procedure in 69 (4.8%) patients.

Among 1446 patients, 398 (27.5%) patients were categorized as patients who had difficult ESD, and 1048 (72.5%) patients were categorized as patients who had non-difficult ESD. There were no significant differences in age, sex, previous medical history such as hypertension, diabetes mellitus, ischemic heart disease, cerebral vascular accident, chronic kidney disease, and liver cirrhosis between 2 groups. There were no significant differences in tumor size, tumor location, and morphology of the tumor between 2 groups. However, there were significant differences in presence of central depression or

ulceration in the lesion, previous EMR or polypectomy history, and use of IT knife between 2 groups (P = .003, P = .012, P < .001, respectively).

3.2. Procedural outcome of enrolled patients

Procedural outcomes of enrolled patients are summarized in Table 2. En bloc resection was achieved in 1292 (89.3%) patients and R0 resection was achieved in 1167 (80.7%) patients. R0 resection rate was significantly lower in difficult ESD group compared to non-difficult ESD group (70.9% vs 84.4%, P < .001). The rate of fibrosis and poor lifting sign was higher in difficult ESD group compared to non-difficult ESD group (43.7% vs 28.3%, P < .001 and 40.0% vs 23.9%, P < .001, respectively). Immediate perforation occurred in 25 (1.7%) patients and delayed perforation occurred in 9 (0.6%) patients. Post-procedural bleeding happened in 34 (2.4%) patients and post-coagulation syndrome was diagnosed in 41 (2.8%) patients

Table 1

Pre-procedural baseline characteristics of enrolled patients and lesions.

	Total (n = 1446)	Difficult ESD (n = 398)	Non-difficult ESD (n = 1048)	P value
Age (yr), median (IQR)	66.1 (57.7–73.8)	65.8 (57.1–73.2)	66.3 (58.0–74.0)	.233
Female, n (%)	581 (40.2)	149 (37.4)	432 (41.2)	.190
Hypertension, n (%)	577 (39.9)	160 (40.2)	417 (39.8)	.672
Diabetes mellitus, n (%)	284 (19.6)	83 (20.9)	201 (19.2)	.474
Ischemic heart disease, n (%)	65 (4.5)	17 (4.3)	48 (4.6)	.800
Cerebral vascular accident, n (%)	12 (3.0)	32 (3.1)	44 (3.0)	.970
Chronic kidney disease, n (%)	25 (1.7)	4 (1.0)	21 (2.0)	.193
Cirrhosis, n (%)	11 (0.8)	3 (0.8)	8 (0.8)	.985
Use of antithrombotics, n (%)	164 (11.3)	43 (10.8)	121 (11.5)	.691
Tumor size, median (IQR)				
Long axis (mm)	20.1 (15–29)	20.0 (15–30)	20.0 (15–28)	.869
Short axis (mm)	16.5 (10–25)	17.0 (10–25)	16.0 (10–25)	.795
Size larger than 30 mm	257 (17.8)	82 (20.6)	175 (16.7)	.083
Size larger than 40 mm	90 (6.2)	30 (7.5)	60 (5.7)	.203
Tumor location				
Cecum	145 (10.0)	53 (13.3)	92 (8.8)	
Ascending colon	341 (23.6)	90 (22.6)	251 (24.0)	
Transverse colon	243 (16.8)	68 (17.1)	175 (16.7)	
Descending colon	79 (5.5)	28 (7.0)	51 (4.9)	
Sigmoid	263 (18.2)	71 (17.8)	192 (18.3)	
Rectum	375 (25.9)	88 (22.2)	287 (27.4)	
Anal verge involvement (n = 376)	9 (2.4)	2 (1.9)	7 (2.6)	.725
Morphology				
LST-granular type	662 (45.8)	185 (46.4)	477 (45.6)	.935
LST-nongranular type	438 (30.3)	118 (29.6)	320 (30.5)	
Protruded	346 (23.9)	95 (23.9)	251 (24.0)	
Central depression or ulceration, n (%)	245 (16.9)	86 (21.6)	159 (15.2)	.003
Previous EMR or polypectomy, n (%)	29 (2.1)	14 (3.7)	15 (1.5)	.012
Use of IT knife	69 (4.8%)	33 (8.3)	36 (3.4)	<.001

EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, IQR = interquartile range, IT = insulated tipped, LST = laterally spreading tumor.

Table 2

Procedural outcome of enrolled patients.

	Total (n = 1446)	Difficult ESD (n = 398)	Non-difficult ESD (n = 1048)	P value
En bloc resection, n (%)	1292 (89.3)	244 (61.3)	1048 (100)	
R0 resection, n (%)	1167 (80.7)	282 (70.9)	885 (84.4)	<.001
Procedure time (min), median (IQR)	30.0 (17.6–50.0)	37.9 (24.2–60.0)	27.8 (16.1–45.3)	<.001
Procedure time > 60 min	231 (16.0)			
Fibrosis	471 (32.5)	174 (43.7)	297 (28.3)	<.001
Poor lifting sign	413 (28.5)	163 (40.0)	250 (23.9)	<.001
Hybrid ESD, n (%)	280 (19.4)	104 (26.1)	176 (16.8)	<.001
Complications				
Perforation				
Immediate perforation	25 (1.7)	25 (6.3)	0	
Delayed perforation	9 (0.6)	9 (2.3)	0	
Post-procedural bleeding	34 (2.4)	6 (1.5)	28 (2.7)	.192
Postcoagulation syndrome	41 (2.8)	16 (4.0)	25 (2.4)	.094
Pathologic diagnosis				
Hyperplastic polyp	30 (2.1)	8 (2.0)	22 (2.1)	.789
Adenoma with dysplasia	1044 (72.2)	280 (70.4)	764 (72.9)	
Intramucosal or superficial submucosal carcinoma	271 (18.7)	80 (20.1)	191 (18.2)	
Deep submucosal carcinoma	101 (7.0)	30 (7.5)	71 (6.8)	
Operation, n (%)	82 (5.9)	28 (7.3)	54 (5.3)	.166

ESD = endoscopic submucosal dissection, IQR = interquartile range.

which were not significantly different between 2 groups. There was no significant difference in pathologic diagnosis between 2 groups.

3.3. Factors associated with long procedure time (>60 minutes)

Table 3 shows the factors associated with long procedure time. In univariate logistic regression analysis, tumor size, size larger than 30 mm, protruded lesion, history of previous EMR or polypectomy, use of IT knife and hybrid ESD were associated with long procedure time (OR: 1.021 [95% Confidence interval (CI): 1.009–1.032], $P < .001$; OR: 1.866 [95% CI: 1.341–2.595], $P < .001$; OR: 1.716 [95% CI: 1.264–2.330], $P = .001$; OR: 2.880 [95% CI: 1.320–6.281], $P = .008$; OR: 1.777 [95% CI: 1.008–3.131], $P = .047$; OR: 1.871 [95% CI: 1.357–2.580], $P = .001$, respectively). In multivariate logistic regression analysis, size larger than 30 mm, protruded lesion, history of previous EMR or polypectomy and hybrid ESD were associated with long procedure time (OR: 1.680 [95% CI: 1.073–2.632], $P = .023$; OR: 1.680 [95% CI: 1.167–2.242], $P = .004$; OR: 2.512 [95% CI: 1.123–5.618], $P = .025$; OR: 1.818 [95% CI: 1.292–2.558], $P = .001$, respectively).

3.4. Risk factors of perforation including both immediate and delayed perforation

Table 4 shows the risk factors of perforation including both immediate and delayed perforation. In univariate logistic regression analysis, presence of central depression or ulceration in the lesion, descending colon-located tumor compared to non-descending colon-located tumor, use of IT knife were significant independent risk factors for perforation (OR: 2.179 [95% CI: 1.024–4.639], $P = .043$; and OR: 5.014 [95% CI: 2.106–11.940], $P < .001$; OR: 4.762 [95% CI: 1.898–11.949], $P = .001$, respectively). In multivariate logistic regression analysis, descending colon-located tumor, use of IT knife were significant independent risk factors for perforation (OR: 5.355 [95% CI: 2.207–12.993], $P < .001$; and OR: 4.157 [95% CI: 1.599–10.805], $P = .003$, respectively).

3.5. Factors associated with piecemeal resection

Table 5 shows the factors associated with piecemeal resection. In univariate logistic regression analysis, presence of central depression or ulceration in the lesion, presence of fibrosis and poor lifting sign, LST and tumor size larger than 30 mm were associated with piecemeal resection (OR: 1.935 [95% CI: 1.314–2.851], $P = .001$; OR: 3.686 [95% CI: 2.612–5.202], $P < .001$; OR: 4.219 [95% CI: 2.990–5.953], $P < .001$; OR: 2.408 [95% CI: 1.466–3.955], $P = .001$; OR: 0.583 [95% CI: 0.350–0.972], $P = .039$, respectively). In multivariate logistic regression analysis, presence of poor lifting sign, LST, and tumor size were associated with piecemeal resection. (OR: 3.278 [95% CI: 1.569–6.848], $P = .002$; OR: 2.291 [95% CI: 1.379–3.805], $P = .001$, respectively).

3.6. Factors associated with technically difficult ESD

Table 6 shows the factors associated with technically difficult ESD. In univariate logistic regression analysis, presence of central depression or ulceration, history of previous EMR or polypectomy for the lesion and use of IT knife were significant factors for technically difficult ESD (OR: 1.541 [95% CI: 1.151–2.064], $P = .004$; OR: 2.537 [95% CI: 1.213–5.308], $P = .013$; and OR: 2.542 [95% CI: 1.561–4.137], $P = .001$, respectively). In multivariate logistic regression analysis, presence of central depression or ulceration, history of previous EMR or polypectomy for the lesion and use of IT knife were significant factors for technically difficult ESD (OR: 1.474 [95% CI: 1.086–2.001], $P = .013$; OR: 2.428 [95% CI: 1.150–5.128], $P = .020$; and OR: 2.578 [95% CI: 1.545–4.301], $P < .001$, respectively).

4. Discussion

Performance of colorectal ESD has been gradually improved along as new endoscopic instruments have been developed and novel ESD techniques such as traction-assisted ESD and pocket creation methods have been proposed.[10,11] However, colorectal ESD is still technically difficult with a steep learning curve compared to gastric ESD.[3] And so, it is important

Table 3

Factors associated with long procedure time (>60 min).

	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	*P* value	Odd ratio (95% CI)	*P* value
Tumor size (long axis)	1.021 (1.009–1.032)	<.001	1.003 (0.989–1.017)	.694
Size larger than 30 mm	1.866 (1.341–2.595)	<.001	1.680 (1.073–2.632)	.023
Protruded lesion (non-LST)	1.716 (1.264–2.330)	.001	1.618 (1.167–2.242)	.004
Previous EMR or polypectomy	2.880 (1.320–6.281)	.008	2.512 (1.123–5.618)	.025
Use of IT knife	1.777 (1.008–3.131)	.047	1.7433 (0.953–3.152)	.072
Hybrid ESD	1.871 (1.357–2.580)	.001	1.818 (1.292–2.558)	.001

CI = confidence interval, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, IT = insulated tipped, LST = laterally spreading tumor.

Table 4

Risk factors of perforation.

	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	*P* value	Odd ratio (95% CI)	*P* value
Central depression or ulceration	2.179 (1.024–4.639)	.043	1.838 (0.820–4.119)	.139
Descending colon location	5.014 (2.106–11.940)	<.001	5.355 (2.207–12.993)	<.001
Use of IT knife	4.762 (1.898–11.949)	.001	4.157 (1.599–10.805)	.003
Fibrosis	1.982 (0.992–3.958)	.053	1.540 (0.730–3.250)	.257

CI = confidence interval, IT = insulated tipped.

to assess the difficulty before the procedure to improve the treatment outcome of colorectal ESD. There has been an effort to make a pre-procedural scoring system to predict the difficulty of the procedure.[12,13] But there are still limitations. In this study, we aimed to find the predictive factors associated with technical difficulty in colorectal ESD before the procedure in the largest number of patients to our knowledge.

We defined technically difficult colorectal ESD procedure in 3 points. Long procedure time (more than 60 minutes), occurrence of perforation (including both intra-procedural and delayed perforation) and failure of en bloc resection. Generally, difficulty of ESD has been defined using various factors such as long procedure time or slow-dissection speed,[14–17] incomplete resection,[7,15–18] adverse events such as perforation.[7,17,18] Among a total of 1446 lesions, 398 lesions were classified as difficult ESD, and 1048 lesions were classified as non-difficult ESD. There were no significant differences in patient factors such as age, sex, past medical history. Concerning the tumor characteristics, there were no significant differences in size, tumor location, and morphology of the tumor.

Usually, difficult cases take longer procedure time due to technical difficulties and to avoid adverse events such as perforation. Also, many previous studies defined technical difficult procedures using long procedure time.[19–21] ESD procedure time with various cutoff values has been widely used. We set more than 60 minutes as the cutoff value of long procedure time for the following reasons. First, most of the previous studies set longer than 60 minutes as the long procedure time as it was median procedure time of previous studies.[7,19] In this registry data, median procedure time was 30 minutes and IQR was 50 minutes. As setting 30 minutes which is our median time seemed too short, we set 60 minutes which was close to IQR of our registry. Second, in real practice, 60 minutes seemed acceptable for both endoscopist and patient. About 231 cases (16.0 %) took more than 60 minutes to finish the procedure. In multivariate logistic regression analysis, size larger than 30 mm, protruded lesion, history of previous EMR or polypectomy and hybrid ESD was associated with long procedure time. Previous studies reported that size larger than 30 mm, especially size larger than 50 mm was associated with long procedure time[12,19] which was consistent with our study. In this study, protruded-type tumor morphology was associated with longer procedure time compared to LSTs. Kaosombatwattana et al reported that protruded-type tumor morphology had a higher possibility of severe fibrosis.[13] However, Li et al[12] reported that protruded-type tumor morphology was not associated with difficult procedures, but LST-NG was an independent predictor of technical difficult ESD. In this study, previous forceps biopsy did not affect the treatment outcome. But history of EMR or polypectomy was associated with longer procedure time. This may be due to fibrosis made after EMR or polypectomy. Although hybrid ESD procedure was associated with long procedure time in this study, this may be due to selection bias that we usually perform hybrid ESD when there is poor lifting sign at the center.

Next, we analyzed factors associated with perforation. In univariate analysis, central depression or ulceration in the lesion, descending colon location compared to other locations and use of IT knife was associated with perforation. In multivariate analysis, only descending colon location compared to other locations and use of IT knife was associated with perforation. However, these results were not consistent with systematic review and meta-analysis done by Santos et al They reported that right colon location was associated with perforation with OR of 2.35 (95% CI: 1.58–3.50). Also, they reported that larger size of tumor and the presence of fibrosis were associated with perforation.[22] However, size nor presence of fibrosis was associated with perforation in this study.

Piecemeal resection[23–26] and histological incomplete resection[24,26] are well-known risk factors for local recurrence. In this study, 154 lesions were piecemeal resected. Also, R0 resection rate was significantly lower in difficult ESD group compared to non-difficult ESD group. Presence of central depression or ulceration in the lesion and size larger than 30 mm were statistically significant factors associated with piecemeal resection in univariate analysis but not in multivariate analysis. Poor lifting sign and LST were statistically significant factors associated with piecemeal resection in multivariate analysis. Generally, in the absence of prior endoscopic procedure, poor lifting sign means deep submucosal invasion of the cancer.[27] Prior endoscopic procedures such as

Table 5

Factors associated with piecemeal resection.

	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	*P* value	Odd ratio (95% CI)	*P* value
Central depression or ulceration	1.935 (1.314–2.851)	.001	1.191 (0.785–1.808)	.410
Fibrosis	3.686 (2.612–5.202)	<.001	1.237 (0.588–2.601)	.575
Poor lifting sign	4.219 (2.990–5.953)	<.001	3.278 (1.569–6.848)	.002
Laterally spreading tumor	2.408 (1.466–3.955)	.001	2.291 (1.379–3.805)	.001
Size larger than 30 mm	0.583 (0.350–0.972)	.039	0.603 (0.357–1.020)	.059

CI = confidence interval.

Table 6

Factors associated with technically difficult ESD.

	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	*P* value	Odd ratio (95% CI)	*P* value
Size larger than 35 mm	1.473 (1.029–2.109)	.034	1.474 (1.005–2.099)	.047
Central depression or ulceration	1.541 (1.151–2.064)	.004	1.474 (1.086–2.001)	.013
Previous EMR or polypectomy	2.537 (1.213–5.308)	.013	2.428 (1.150–5.128)	.020
Use of IT knife	2.542 (1.561–4.137)	.001	2.578 (1.545–4.301)	<.001

CI = confidence interval, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, IT = insulated tipped.

biopsy, polypectomy, submucosal injection, and EMR can also lead to fibrosis and result in poor lifting signs.[28] Submucosal fibrosis carries the risk of cutting through muscularis propria layer leading to perforation which makes the procedure more difficult. Other studies reported that presence of fold convergence, protruding type lesion, less-experienced endoscopist, and tumor size larger than 50 mm were associated with failure of en bloc resection.[7,18]

Lastly, we analyzed factors associated with technically difficult ESD. In this study, size larger than 35 mm, presence of central depression or ulceration and previous EMR or polypectomy procedure were significant factors associated with technically difficult ESD. We previously found that larger size and previous EMR or polypectomy were associated with long procedure time. Central depression or ulceration in the lesion may be associated with deep submucosal invasive cancer and the presence of fibrosis at the center. It is well known that the rate of submucosal invasive carcinoma is highest in the LST-NG-pseudo-depressed type.[29] Also, in the upper GI tract neoplasia, depressed type tumor was associated with submucosal fibrosis leading to a difficult ESD procedure.[30,31]

There are some limitations in this study. First, as the study design was a retrospective cohort study, selection biases were inevitable. Second, we did not analyze the endoscopist experience in this study. Although all endoscopist were experienced endoscopists who had performed over 200 procedures of gastric ESD, there may be difference in the procedure during their early-time colorectal ESD and late time colorectal ESD. Third, the location of the tumor was not analyzed in more detail. Although previous studies reported that lesions over the folds or in flexure locations were associated with technical difficulty, we did not analyze these points. However, we found predictive factors associated with technical difficulty in colorectal ESD before the procedure in the largest number of patients to our knowledge.

In conclusion, we found that tumor size larger than 35 mm, presence of central depression or ulceration in the lesion, previous EMR, or polypectomy were significant factors associated with technically difficult ESD. Recognizing these factors can help in planning the ESD procedure beforehand.

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