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Predictive factors for technically difficult endoscopic submucosal dissection in large colorectal tumors

COLON

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ABSTRACT

Background/Aims: Endoscopic submucosal dissection (ESD) for colorectal tumors is dangerous, particularly those that are large. However, the technical difficulty in resecting large tumors in the colonrectum has seldom been investigated.

Materials and Methods: Between October 2012 and January 2015, 36 consecutive large colorectal tumors were resected by ESD at the endoscopic center of PLA Army General Hospital. Five factors were investigated in predicting the technical difficulty in resecting such tumors.

Results: En bloc resection, complete (R0) resection, and curative resection rates were 83.33% (30/36), 80.56% (29/36), and 77.78% (28/36), respectively. Tumor location in a flexure was risk a factor for difficult ESD in the colonrectum as measured by perforation (4.55, 0.09–6.25), non-en bloc resection (4.94, 0.10, 9.45), and dissection speed (β±SE: 1.75±0.05). When tumor size increased, the perforation rate also increased (9.93, 0.96–10.32).

Conclusion: ESD was more technically demanding in flexures for resecting large colorectal tumors, and for large tumor effective technique to close perforation is essential. Our study will guide endoscopists in using ESD to remove large colorectal tumors.

Keywords: Endoscopic submucosal dissection, risk factors, dissection speed, perforation, en bloc resection

Original Article

INTRODUCTION

Early-stage tumors in the gastrointestinal tract can be resected en bloc using endoscopic submucosal dissection (ESD), despite their large size (1,2). This enables a detailed histological evaluation, the accurate judgment of resected margins, and a high rate of curative resection even with the presence of scarring or difficult location (3,4). However, colorectal ESD (CR-ESD) remains a challenging technique for the relatively small, tortuous, and angulated colorectal lumen. Further, the colon has a thinner wall than the stomach, which can result in a high risk of perforation (5). Recently, some new methods have been introduced to overcome these drawbacks, such as hybrid ESD, circumferential incision accompanied by snaring (precutting EMR), and wide-field (WF) EMR (6-8). However, for large tumors, ESDS, cutting EMR, and WF EMR are not suitable because of technical demanding with complete histopathological evaluation (6). ESD can be the first choice to remove large colorectal lesions for obtaining a high en bloc resection rate. There has been no study evaluating factors affecting technical difficulty and limitations of large-sized CR-ESD. The purpose of this study was to examine predictive factors for technical difficulty in large-sized CR-ESD.

MATERIALS AND METHODS

Patients

This was a retrospective study using a database of 36 patients with large tumor sizes (>10 cm^2) from October 2012 to January 2015 and who had been referred to PLA Army General Hospital for ESD. This study was approved by the Institutional Review Board of PLA Army General Hospital. All patients provided informed con-

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sent. Inclusion criteria were lesions with large elevated type, granular-type laterally spreading tumors (LSTs) (LST-Gs), and nongranular-type LSTs (LST-NGs) and a tumors size of >10 cm^2. Exclusion criteria were lesions suggestive of a deep submucosal invasion by magnification chromoendoscopy. Clinicopathological features are summarized in Table 1.

ESD

The detection of lesions was done using a PCF-Q260AI endoscope (Olympus; Japan) and a high-magnification endoscope (PCF-Q260AZI, Olympus; Japan) for interested lesion identification before ESD. When performing ESD, all patients were sedated under anesthesia with propofol. A transparent hood was attached to the tip of a GIF-260J or PCF-Q260JI endoscope (Olympus; Japan) for ESD. Injection needles (MTW; Wesel, Germany) were used to inject sodium hyaluronate (Shanghai, China) into the submucosal layer, and an endoknife (Olympus; Japan) was used for making a mucosal incision and for lesion dissection (Figure 1). Any injection of sodium hyaluronate without mucosal lifting was defined as "nonlifting." When performing ESD, carbon dioxide was insufflated to reduce patient discomfort. Procedure time was defined as from the time of the submucosal injection to the complete resection. Two endoscopists with at least 30 years of experience in CR-ESD performed all procedures.

Table 1. Characteristics of the colorectal tumors in 36 patients

Characteristic	Colorectal tumors (n=36) (%)
Age, mean±SD (range)	62±8.01 (43–78)
Sex (male/female)	13/23
Tumor size (cm^2) (range)	27.51±24.37 (10–100)
Tumor location, n (%)	
Rectum	21 (58.3)
Left colon	1 (2.8)
Right colon	6 (16.7)
Flexure	8 (22.2)
Macroscopic type, n (%)	
LST-NG	8 (22.2)
LST-G (mix)	11 (30.6)
LST-G (homo)	9 (25.0)
Protruding (Is)	8 (22.2)
Histology, n (%)	
Adenoma	17 (47.2)
Adenocarcinoma-m	15 (41.7)
Adenocarcinoma-sm	4 (11.1)
Nonlifting sign, n (%)	
Negative	33 (91.7)
Positive	3 (8.3)

LST-NG: nongranular type-laterally spreading tumors; LST-G: granular type-laterally spreading tumors; m: mucosal; sm: submucosal; SD: standard deviation

Clinicopathological characteristics

The macroscopic type was granular-type LSTs, LST-NGs, and protruding tumor (Is). LSTs were first divided into LST-Gs or LST-NGs. LST-Gs were then subdivided into homogenous-type (homo) and nodular mixed-type (mix) tumors (8). Tumor location was divided into four parts, the rectum, left colon, right colon, and flexures (hepatic junction, splenic junction, sigmoid and descending colon junction, and rectosigmoid junction), according to Hori et al. (9).

Variables for Technical difficulty

Using the method by Hori et al. (9) with revision slight modification, dissection speed (min/cm^2), perforation, and en bloc resection were chosen as variables of technical difficulty for large-sized CR-ESD. Indicators for ESD being a superior technique than other interventions (ESDS, EMR-P, WF EMR, and surgery) would be quicker procedure speed, en bloc resection, and no perforation. Size was postoperatively determined. Lesion size (cm^2)=Π×major axis of the lesion (cm)×minor axis of the lesion (cm)/4. The calculation for ESD speed was area/time.

Histopathological evaluation

After successful resection of the specimen, it was laid out and adhered with pins on a foam plastic board and measured before being soaked in formaldehyde solution. Pathologists conducted successive parallel 2-mm interval slices. En bloc resection was a lesion dissected with one piece. Complete (R0) resection was a tumor free from lateral and vertical margins. Curative resection was R0 resection without an unfavorable histopathological evaluation (tumor budding, poor differentiation, or lymphovascular invasion) or submucosal invasion deeper than 1,000 μm.

Statistical analysis

SPSS 15.0 (SPSS Inc.; Chicago, IL, USA) was used to perform statistical analysis. Continuous variables were described with the

Table 2. Outcomes of colorectal ESD (n=36)

Characteristic	Colorectal tumors (n=36) (%)
Procedure speed (min/cm^2), mean±SD (range)	0.30±0.16 (0.13-0.91)
Procedure time (min), mean±SD (range)	94.5±67.2 (24–300)
En bloc resection, n (%)	30 (83.3%)
Complete resection, n (%)	29 (80.6%)
Curative resection, n (%)	28 (77.8)
Perforation, n (%)	4 (11.1%)
Delayed bleeding, n (%)	1 (2.8%)
Median follow-up (months), mean±SD (range)	14.23±8.07 (3–30)
Local recurrence, n (%)	3 (8.33)

ESD: endoscopic submucosal dissection; Complete resection: en bloc resection was tumor-free lateral and vertical margins on histological examination; Curative resection: en bloc resection without lymphovascular involvement; SD: standard deviation

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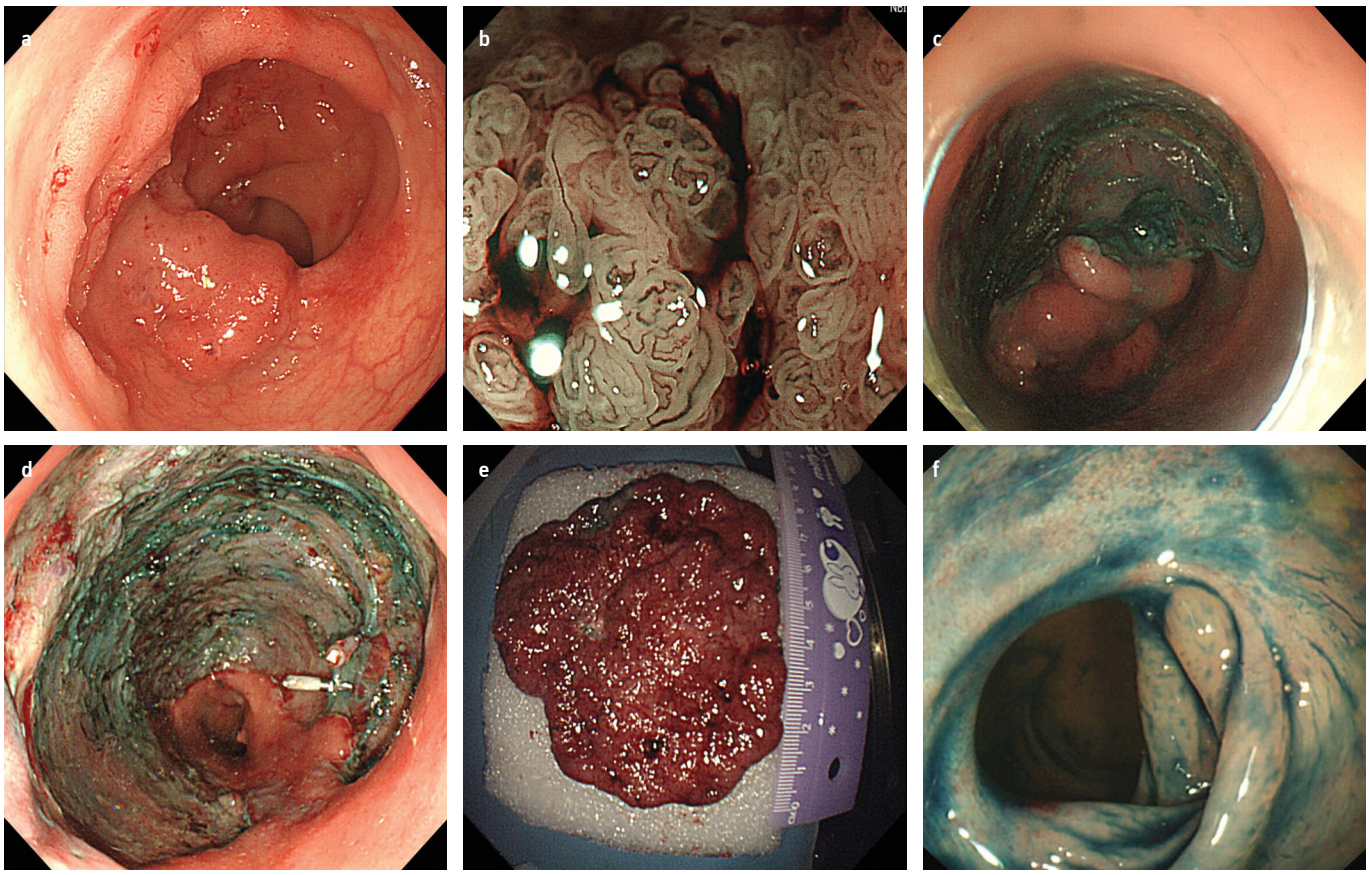

Figure 1. a-f. Cap-assisted colonoscopy for a large size colorectal ESD. Laterally spreading and nearly circumferential tumors of the rectum (a). Nar¬row-band image view (b). Mucosal incision and dissection (c). A huge ulcer was created by ESD (d). One piece of the resected specimen was 100×100 mm (e). Indigo carmine dye spraying revealed no local recurrence 14 months after ESD (f).

independent two-sample t-test. Categorical variables were described with Fisher's exact test. Significant factors for perforation and en bloc resection were analyzed using logistic regression. Linear regression analysis was used to evaluate dissection speed.

RESULTS

Patient characteristics and treatment results

Table 1 and 2 list patient characteristics and outcomes. En bloc resection, R0 resection, and curative resection rates was 83.3% (30/36), 80.6% (29/36), and 77.8% (28/36), respectively. The median procedure speed was 0.30±0.16 min/cm^2. Four patients (11.1%) suffered from immediate perforation, three were successfully closed during or after ESD, two were closed using several endoclips, and one was closed using an endoscopic purse-string suture (10). For the last patient, when the perforation was observed, we used endoclips to close it and successfully resected by second ESD procedure two weeks later. No surgical intervention was needed. Among four patients with submucosal invasion, only one had submucosal invasion deeper than 1,000 µm and was referred for surgery. Among the 36 patients who underwent ESD, 31 were followed up; the median follow-up period was 14 months (range, 3–30 months). Local recurrence occurred in three patients during this period; all these patients were successfully treated by a second ESD.

Comparison between large size and conventional ESD

Comparison of patient characteristics and treatment results between large- and small-sized colorectal tumor groups are described in Table 3. In the large- and small-sized colorectal tumor groups, the en bloc resection rates were 83.33% vs 97.40% (p=0.007), mean procedure times were 94.5±67.2 min vs 36.27±22.67 min (p<0.001), and median ESD speeds were 0.30±0.16 min/cm^2 vs 0.14±0.13 min/cm^2 (p<0.001). Immediate perforation occurred in four and three patients (11.11% vs. 3.90%; p=0.287) during the ESD procedure in the large- and small-sized colorectal tumor groups, respectively. Histologically, there were 17 and 40 adenomas (47.22% vs 51.95%), 15 and 32 adenocarcinomas-m (41.67% vs 41.56%), and four and five adenocarcinomas with submucosal invasion (11.11% vs 6.49%) (p=0.501) in the large- and small-sized colorectal tumor groups, respectively.

Factors for technical difficulty

Table 4, 5, and 6 summarize the results of factors predicting difficulty large-sized CR-ESD. Tumor location in a flexure (recto-sigmoid, sigmoid, and descending colon junction, splenic, and hepatic junction) was technically demanding for difficult ESD in colonrectum as measured by perforation (4.55, 0.09–6.25), non en bloc resection (4.94, 0.10–9.45), and dissection speed (β±SE: 1.75±0.05). Tumor size was the strongest risk factor for

Table 3. Comparison between large size and conventional ESD

Characteristics	Tumor size ≥4.0 cm (n=36)	Tumor size <4.0 cm (n=77)	p
Age, mean±SD	62.0±8.01	62.70±14.01	0.593
Sex (male/female)	13/23	46/31	0.009
Tumor size (cm^2), mean±SD	27.51±24.37	3.03±1.27	<0.001
Tumor diameter (cm), mean±SD	5.48±2.27	2.21±0.39	<0.001
Tumor location, n (%)			0.010
Rectum	21 (58.3)	27 (35.06%)	t
Left colon	1 (2.8)	10 (12.99%)	
Right colon	6 (16.7)	25 (32.47%)	
Flexure	8 (22.2)	15 (19.48%)	
Macroscopic type, n (%)			0.075
LST-NG	8 (22.22%)	28 (36.36%)	
LST-G	20 (55.56%)	25 (32.47%)	
Protruding (Is)	8 (22.22%)	24 (31.17%)	
Histology			0.501
Adenoma	17 (47.22%)	40 (51.95%)	
Adenocarcinoma-m	15 (41.67%)	32 (41.56%)	
Adenocarcinoma-sm	4 (11.11%)	5 (6.49%)	
Resection type, n (%)			
En bloc resection	30 (83.33%)	75 (97.40%)	0.007
Complete resection	29 (80.56%)	73 (94.80%)	0.041
Curative resection	28 (77.78%)	71 (92.21%)	0.136
Procedure time (min) , mean±SD	94.5±67.2	36.27±22.67	<0.001
Procedure speed (cm^2/min) , mean±SD	0.30±0.16	0.14±0.13	<0.001
Complications, n (%)			
Perforation	4 (11.11%)	3 (3.90%)	0.287
Delayed bleeding	0 (0)	0 (0)	

LST-NG: nongranular type-laterally spreading tumors; LST-G: granular type-laterally spreading tumors; m: mucosal; sm: submucosal; SD: standard deviation

Table 4. Prediction of technical difficulty for perforation: univariate and multivariate analyses

	Univariate		Multivariate	
	OR (95% CI)	p*	OR (95% CI)	p*
Tumor size (mm)	9.44 (0.91, 9.84)	0.01	9.93 (0.96, 10.32)	0.03
Tumor location				
Rectum	1		1	
Left colon	0.911 (0.93,1.16)	0.57	2.66 (0.5, 20.18)	0.12
Right colon	0.143 (0.02, 1.16)	0.07	0.207 (0.02, 1.88)	0.33
Flexure	1.76 (0.05, 2.60)	0.01	4.55 (0.09, 6.25)	0.02
Macroscopic type				
Is		1		
LST-NG	0.500 (0.09, 2.73)	0.42		
LST-G	1.720 (0.51, 1.93)	0.78		
Histology				
Adenoma	1		1	
Adenocarcinoma-m	1.71 (0.11, 2.54)	0.01	0.154 (0.02, 1.44)	0.10
Adenocarcinoma-sm	7.66 (0.95, 9.83)	0.001	1.028 (0.98, 1.08)	0.22
Nonlifting sign				
Negative	1			
Positive	1.57 (0.3, 14.1)	0.61		

OR:odds ratio; 95% CI: 95% confidence interval; m: mucosal; sm: submucosal; LST-NG: nongranular type-laterally spreading tumors; LST-G: granular type-laterally spreading tumors
*Logistic regression analysis was used.

perforation (9.93, 0.96–10.32). Adenocarcinoma-sm (β±SE: 0.605±0.043) and tumor size (β±SE: 0.003±0.001) were independent factors for slow dissection speed, but with little effect for low β values.

DISCUSSION

EMR, ESD, and the recently introduced ESDS, EMR-P, and WF EMR (6,7) are minimally invasive treatments for early-stage gastrointestinal tumors. EMR is ideal for lesions with diameters between 5 mm and 20 mm. EPMR, ESDS, EMR-P, and WF EMR are acceptable treatment modalities for lesions with diameters larger than 20 mm. However, given the nature of these procedures, the pathological assessment is not as complete and the risk of recurrence increases. ESD can achieve en bloc resection of mucosal lesions with diameters larger than 20 mm. However, for tumors with diameters larger than 30 or 40 mm, no study has been conducted to discuss the challenges and limitations of ESD.

In agreement with Kim et al. (6), we defined dissection speed, perforation, and en bloc resection as factors for technical difficulty. Large tumor size is a potentially important factor for long procedure duration. In addition, lesion location requiring a careful incision and dissection will make the procedure duration much longer for avoiding perforation and bleeding. The en bloc resection rate is much higher, offering an accurate histological assessment and enhancing the possibility of curative resection. Our study shows that tumors located at flexures were independent risk factor for all measures of difficulty that were defined. Tumor size was a strongest risk factor for perforation.

Mizushima et al. (11) reported technically difficult ESD based on location, and their analysis suggested that sigmoid colon was more technical demanding for CR-ESD. However, there have been no reports that describe risk factors for technical difficulty of large-sized CR-ESD. Jung da et al. (12) reported nine giant colorectal LST lesions larger than 10 cm for which ESD was performed, with a higher en bloc and curative resection

Table 5. Prediction of technical difficulty for en bloc resection: univariate and multivariate analyses

	Univariate		Multivariate	
	OR (95% CI)	p*	OR (95% CI)	p*
Tumor size (mm)	1.31 (1.03, 1.06)	0.03	0.987 (0.955, 1.020)	0.44
Tumor location				
Rectum	1			
Left colon	7 (0.82, 56.89)	0.07		
Right colon	2 (0.37, 10.91)	0.42	0.97 (0.06, 36.19)	0.98
Flexure	4 (1.34, 11.96)	0.01	4.94 (0.10, 9.45)	0.04
Macroscopic type				
Is	1			
LST-NG	1.07 (0.2, 5.68)	0.94		
LST-G	1.75 (0.2, 15.41)	0.61		
Histology				
Adenoma	1		1	
Adenocarcinoma-m	4 (1.13, 14.17)	0.03	1.133 (0.176, 7.289)	0.69
Adenocarcinoma-sm	0.62 (0.59, 1.20)	0.99	0.447 (0.36, 0.991)	0.89
Nonlifting sign				
Negative	1			
Positive	1.50 (0.42, 5.31)	0.53		

OR: odds ratio; 95% CI: 95% confidence interval; m: mucosal; sm: submucosal LST-NG: nongranular type-laterally spreading tumors; LST-G: granular type-laterally spreading tumors
*Logistic regression analysis was used.

Table 6. Prediction of technical difficulty for procedure speed: univariate and multivariate analyses

	Univariate		Multivariate	
	β±SE	p*	β±SE	p*
Tumor size (mm)	0.103±0.001	0.014	0.003±0.001	0.008
Tumor location (rectum)				
Left colon	−0.094±0.168	0.580	−0.291±0.132	0.200
Right colon	−0.149±0.07	0.039	−0.031±0.060	0.616
Flexure	1.081±0.062	0.036	1.753±0.054	0.008
Macroscopic type (Is)				
LST-NG	0.042±0.066	0.53		
LST-G	−0.042±0.066	0.53		
Histology (adenoma)				
Adenocarcinoma-m	−0.057±0.088	0.516	−0.039±0.074	0.605
Adenocarcinoma-sm	0.124±0.052	0.023	0.605±0.043	0.021
Nonlifting sign(N)	0.057±0.100	0.571		

m: mucosal; sm: submucosal LST-NG: nongranular type-laterally spreading tumors; LST-G: granular type-laterally spreading tumors; SE: standard error; β: beta
*Linear regression analysis was used.

rate (88.9% and 100%), respectively. After follow-up, no local recurrences and tumor distant metastases were found. Repici et al. (13) reported 40 consecutive patients with rectal LSTs larger than 3 cm who underwent ESD. Higher en bloc and curative resection rates were achieved (90% and 80%, respectively). Perforation occurred in one patient (2.5%), which was conservatively managed. In these two studies, independent risk factors for complications and predictive factors for technical difficulty were not evaluated.

Colorectal endoscopic submucosal dissection is considered to be more technical demanding with a high perforation rate. A study reported that submucosal fibrosis, long procedure time, tumor size, tumor location of a flexure, and an inexperienced operator were risk factors for complication (14-16). In our study, we looked at large tumors (>10 cm^2) and found that tumor size was technically demanding for perforation, which is consistent with what was observed in previous studies (14-16). However, a recent study found that when ESD were performed before 2010, tumor size might be technically demanding for perforation, but when ESD was performed after 2010 in the same institution, the results were different (11). Our data were collected from the beginning of performing CR-ESD; therefore, a performance learning curve must be considered.

Endoscopists may worry about stenosis following ESD of large tumors in the colorectum. Abe et al. (17) reported that in 26 lesions with rectal mucosal defects larger than three-quarters of the circumference after ESD, stenosis occurred in only one patient who was clinically asymptomatic without prophylactic endoscopic balloon dilation. In our study on 36 patients with large tumors (>10 cm^2) undergoing ESD, stenosis did not occur.

Some limitations of our study were that all ESDs were performed by only two endoscopists, the small number of patients, and the retrospective nature. Prospective studies, larger number of patients, and different levels of endoscopists are required.

In conclusion, we found factors for estimating the technical demanding of large-sized CR-ESD. ESD is a safe and effective procedure for the curative resection of large tumors in the colorectum. However, ESD for a tumor located at a flexure was more technically demanding, suggesting that lesions in these areas would be difficult to remove. Tumor size was the strongest risk factor for a complication of perforation. Our results can provide endoscopists useful information for suitable lesion selection for performing ESD, particularly inexperienced endoscopists.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of PLA Army General Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.H., X.W.; Design - J.S.; Supervision - J.S.; Materials - X.W.; Data Collection and/or Processing - Y.H.; Analysis

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