



Predictors of technical difficulty during endoscopic submucosal dissection of superficial esophageal cancer

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Abstract

Background Endoscopic submucosal dissection (ESD) is the standard treatment for superficial esophageal cancer (SEC); however, it is sometimes technically difficult. Our aim was to identify the predictors of technical difficulty during ESD for SEC.

Methods We reviewed the records of patients who underwent ESD for superficial esophageal squamous cell carcinomas at a tertiary cancer center between April 2008 and March 2016. Patients undergoing ESD after esophagectomy or for residual/recurrent lesions were excluded. Preoperative factors such as tumor subsite, localization, preoperative size, macroscopic type, endoscopic depth of invasion, and treatment for synchronous multiple SECs or previous history of radiation therapy were analyzed. Logistic regression analysis was performed to identify the predictors of technical difficulty, defined as (1) long procedure time (≥ 120 min), (2) adverse events (perforation, pneumomediastinum), or (3) incomplete resection (piecemeal resection, positive or indeterminate vertical margin).

Results A total of 679 lesions in 511 patients were analyzed. Difficulty was experienced in 60 cases. The procedure time was > 120 min in 43 (6.3%) patients, adverse events occurred in 16 (2.8%), and incomplete resection occurred in 17 (2.5%). Multivariate logistic regression revealed that tumors in the left esophageal wall (OR 2.15; 95% CI 1.17–3.91; $p=0.014$) and those encompassing $\geq 1/2$ its circumference (OR 5.06; 95% CI 2.40–11.34; $p<0.001$) were independently associated with difficulty.

Conclusions Tumors in the left esophageal wall and tumors measuring $> 1/2$ of the esophageal circumference are predictors of difficult esophageal ESD. These results may contribute to better patient selection according to each endoscopist's skill.

Keywords Endoscopic submucosal dissection · Incomplete resection · Technical difficulty · Clinical outcomes

Endoscopic submucosal dissection (ESD) enables direct submucosal dissection of early-stage esophageal tumors with a high en bloc resection rate. Esophageal ESD is superior to conventional endoscopic mucosal resection (EMR) via en bloc resection as it facilitates accurate pathological diagnosis. In addition, en bloc R0 resections achieved by esophageal ESD are associated with a lower local recurrence

rate than piecemeal resection by conventional EMR [1–5]. In Japan, esophageal ESD has been eligible for health insurance reimbursement since April 2008 and has become widely accepted as the standard treatment for superficial esophageal cancer (SEC).

Esophageal ESD is more challenging than conventional EMR due to the narrow esophageal lumen, with thin walls, which is significantly affected by respiratory fluctuation and cardiac pulsation. Therefore, esophageal ESD is occasionally associated with a longer procedure time, failure of en bloc resection, or adverse events, such as perforation and pneumomediastinum [6–11]. Several studies have reported predictive factors associated with technically difficult gastric or colorectal ESD [12–16]. Understanding these factors could help stratify lesions according to their difficulty. In

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addition, taking these factors into consideration, appropriate training in a well-recognized established program and sufficient opportunities to improve technical skills in a clinical setting have been recognized as essential for trainee endoscopists.

To improve the quality of esophageal ESD outcomes and training, it is crucial that the factors associated with the level of procedural difficulty are determined. However, to date there has been no retrospective analysis of predictors of technical difficulty, safety, efficacy, or limitations of esophageal ESD. The aim of this study was to identify the preoperative indicators associated with technical difficulty during esophageal ESD.

Materials and methods

Patients

We reviewed the records of 747 lesions in 556 consecutive patients who underwent ESD for superficial esophageal squamous cell carcinomas (SCC) at a tertiary cancer center between April 2008 and March 2016. At our institution, the ESD database records data on patient and lesion characteristics, procedure outcomes, pathology results, and postoperative clinical course; all data were prospectively recorded by the endoscopist who performed the ESD. Written informed consent was obtained from all patients. This retrospective study was approved by the Shizuoka Cancer Center institutional review board (28-J14-28-1-3).

Indications for ESD

The indication for esophageal ESD was a clinical diagnosis of cT1a carcinoma without lymph node metastasis. In this study, we only selected lesions with a preoperative diagnosis of SCC. For patients with a poor performance status and/or preference for less invasive therapy, ESD was selected as an initial treatment even if the lesion was clinically diagnosed as a submucosal invasive esophageal cancer without lymph node or distant metastasis (cT1bN0M0). These indications were determined by esophagogastroduodenoscopy (EGD), endoscopic ultrasonography (EUS), and computed tomography (CT) scans for lesions with a high likelihood of submucosal invasion [17].

We excluded patients that had undergone previous esophagectomy due to their differing anatomic features. We also excluded patients with local residual or recurrent lesions after endoscopic resection (ER), as severe fibrosis beneath these lesions would be expected. We also excluded simultaneous ESD for multiple lesions, because it would have been difficult to evaluate the technical difficulty of each lesion.

ESD procedure

The ESD procedure was performed in hospitalized patients under deep conscious sedation by intravenous anesthesia. Patients received 10 mg diazepam and 35 mg pethidine hydrochloride for induction of anesthesia. In addition, dexmedetomidine hydrochloride was continuously infused for sedation. Cardiopulmonary function was monitored throughout the procedure. Additional midazolam was administered to maintain continuous sedation as needed throughout the procedure. During the procedure, patients were set in the left lateral decubitus position. ESD was performed by using a single-channel upper gastrointestinal endoscope with a water-jet function (GIF-Q260J, Olympus, Tokyo, Japan) and a transparent cap attached to its tip. An insulated-tip knife (IT knife nano, KD-612; Olympus) was used during the procedure for mucosal incision and submucosal dissection. Hemostatic forceps (Coagrasper; Olympus) were used for hemostasis of procedural bleeding. We also used an electrosurgical generator (VIO300D; ERBE, Tübingen, Germany) and carbon dioxide insufflation system (UCR; Olympus). A solution of 0.4% sodium hyaluronate acid (Muco Up®; Johnson & Johnson, New Brunswick, NJ, USA) tinged with indigo carmine was injected into the submucosal layer. Since April 2010, clip traction has been at the discretion of the endoscopist [18–20]. A rotatable clip releaser (Olympus), a clip (HX-610-090; Olympus), and a thread (REACH; Johnson & Johnson; approximately 2 m in length) were used for clip traction. The thread was tied to the claw of the clip and was applied to the oral edge of the lesion after circumferential mucosal incision was completed. The ESDs in this study were mainly performed by skilled endoscopists with experience of > 40 gastric ESDs, but some procedures were performed by trainee endoscopists. The trainee endoscopists were supervised by skilled endoscopists during the procedure.

Definition

Difficult cases of esophageal ESD were defined as those meeting any of the following criteria: (1) long procedure time (> 120 min), (2) occurrence of adverse events (perforation, pneumomediastinum), or (3) incomplete resection (piecemeal resection, positive or indeterminate vertical margins assessed by + histopathologic diagnosis of the ESD specimen). En bloc resection was defined as removal of an intact tumor with macroscopically free lateral margins. Perforation during ESD was defined as: (1) endoscopic observation of a perforation site, and (2) the presence of pneumomediastinum on upright chest X-ray or

CT with simultaneous clinical symptoms (i.e., chest pain, high fever). Pneumomediastinum was defined as the presence of extraluminal air within the mediastinum on chest X-ray or CT without endoscopic findings of perforation.

Measurements

The following preoperative variables were noted: tumor subsites, macroscopic type, preoperative depth of invasion, previous radiation/chemoradiation therapy, and treatment for synchronous multiple esophageal cancers. The endoscopic appearance of the tumors was classified according to the Japanese Classification of Esophageal Cancer, tenth edition [21]. All lesions were also classified into two groups: elevated or flat (0–I, IIa, IIb) and depressed (0–IIc, III). The invasion depth was determined by either EGD, chromoendoscopy with iodine staining, magnifying endoscopy using narrow-band imaging system, and occasionally, EUS [22, 23].

Statistical analysis

The Fisher exact test was used to compare categorical variables, as appropriate. We calculated odds ratios (ORs) using cross tables in the univariate analysis. Associations between clinical and endoscopic variables of participants and difficult ESD were tested by multivariable logistic regression. ORs and 95% confidence intervals (95% CIs) were calculated to evaluate the predictors of difficult ESD. All statistical analyses were carried out with JMP software (version 8.0; SAS Institute Inc., Cary, NC, USA).

Results

A flow diagram of the patients' clinical course is shown in Fig. 1. A total of 679 lesions in 511 patients were analyzed. Demographic and clinical data are shown in Table 1. The

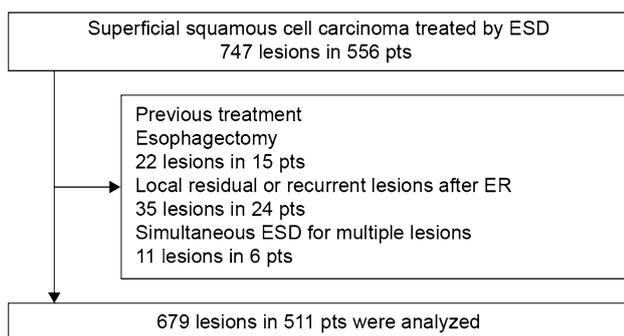


Fig. 1 Flow diagram illustrating the study protocol. ESD endoscopic submucosal dissection, ER endoscopic resection

Table 1 Baseline characteristics of 511 patients with 679 lesions

Age (years), median (range)	69 (40–87)
Sex, male/female, no.	445/66
Tumor subsites, no. (%)	
Middle esophagus	393 (57.9)
Upper esophagus	114 (16.8)
Lower esophagus	172 (25.3)
Localization, no. (%)	
Posterior wall	227 (33.4)
Right wall	183 (27.0)
Anterior wall	94 (14.1)
Left wall	175 (25.5)
Median tumor size, mm (range)	20 (3–130)
Tumor size \geq 30 mm, no. (%)	229 (33.7)
Circumference of the lesion, no. (%)	
< 1/2	563 (82.9)
\geq 1/2	116 (17.1)
Macroscopic type, no. (%)	
Elevated–flat	61 (9.0)
Depressed	618 (91.0)
Preoperative depth of invasion, no. (%)	
cT1a	633 (93.2)
cT1b	46 (6.8)
Synchronous multiple SEC, no. (%)	154 (22.7)
Previous radiation/chemoradiation therapy, no. (%)	53 (7.8)
Use of clip traction technique, no. (%)	139 (20.5)

SEC superficial esophageal cancer, cT1a EP+LPM+MM, cT1b SM1+SM2, EP epithelium, LPM lamina propria mucosa, MM muscularis mucosa, SM1 submucosa 1 (SM < 0.2 mm), SM2 submucosa 2 (SM > 0.2 mm)

patients were 445 males and 66 females with a median age of 69 (range 40–87) years. Lesions were mainly located in the middle esophagus (57.9%), followed by the upper esophagus (16.8%) and lower esophagus (25.3%). The average tumor size was 20 (range 3–130) mm, and 229 lesions (33.7%) were larger than 30 mm. Depressed type tumors were the most common macroscopic type (618 cases, 91.0%). There were 139 cases (20.5%) in which clip traction was employed (Table 2).

Procedure-related outcomes of esophageal ESD

Overall procedural outcomes are shown in Table 3. The median procedure time was 40 min (range 8–320 min). The en bloc resection rate was 99.6% (676/679) and the curative resection rate was 85.6% (581/679). Perforations and pneumomediastinum occurred in 8 (1.2%) patients each. These adverse events were successfully managed conservatively without surgical intervention. No cases had to be discontinued due to intraoperative adverse events. The most frequent histological type of resected lesions was SCC (661/679, 97.3%). Positive

Table 2 Characteristics of lesions resected using the clip traction method

	No clip traction (n = 540)	Clip traction (n = 139)	p value
Tumor subsite, no. (%)			0.629
Middle esophagus	313 (58.0)	80 (57.6)	
Upper esophagus	95 (17.6)	19 (13.7)	
Lower esophagus	132 (24.4)	40 (28.8)	
Localization, no. (%)			0.303
Posterior wall	193 (35.7)	34 (24.5)	
Right wall	144 (26.7)	39 (28.1)	
Anterior wall	71 (13.1)	23 (16.5)	
Left wall	132 (24.4)	43 (30.9)	
Tumor size ≥ 30 mm, no. (%)	139 (25.7)	90 (64.7)	<0.001
Circumference of the lesion, no. (%)			<0.001
$\geq 1/2$	61 (11.3)	55 (39.6)	
Macroscopic type, no. (%)			0.795
Elevated–flat	51 (9.4)	10 (7.2)	
Depressed	489 (90.6)	129 (92.8)	
Preoperative depth of invasion, no. (%)			1.000
cT1a	503 (93.1)	130 (93.5)	
cT1b	37 (6.9)	9 (6.5)	
Synchronous multiple SEC, no. (%)	127 (23.5)	27 (19.4)	0.364
Previous radiation/chemoradiation therapy, no. (%)	43 (8.0)	10 (7.2)	0.861

SEC superficial esophageal cancer, cT1a EP+LPM+MM, cT1b SM1+SM2, EP epithelium, LPM lamina propria mucosa, MM muscularis mucosa, SM1 submucosa 1 (SM < 0.2 mm), SM2 submucosa 2 (SM > 0.2 mm)

or indeterminate vertical margins were observed in 14 (2.1%) cases.

Factors associated with technical difficulty during esophageal ESD

Table 4 summarizes the results of the univariate analysis for factors predicting difficulty with esophageal ESD. Lesions in the left wall of the esophagus ($p < 0.004$) were more frequently associated with technical difficulty than other localizations. In addition, tumor size (larger than 30 mm, $p < 0.001$) and circumference of the lesion (more than half of the esophagus, $p < 0.001$) were significantly associated with technical difficulty. Table 5 summarizes the results of the multivariate analysis of factors predicting difficulty during esophageal ESD. Localization in the left wall (OR 2.15; 95% CI 1.17–3.91; $p = 0.014$), and a circumference of more than half of the esophagus (OR 5.06; 95% CI 2.40–11.34; $p < 0.001$) were the two independent factors associated with difficulty.

Discussion

With the constant improvements in operative technique, the refinement of ESD devices, and the increased expertise of endoscopists, esophageal ESD has become a widely

accepted procedure. As numerous endoscopists perform EMR and ESD, it is important to determine the risks and outcomes of procedure-related adverse events (i.e., bleeding, pneumonia, stenosis, perforation). Particularly in ESD of superficial-spreading esophageal cancer, the procedure-related risk is expected to be higher than that of EMR [24, 25]. Previous studies of gastric ESD have reported that technical challenges vary according to clinicopathologic factors such as the location, size, and depth of tumor invasion [26, 27]. However, the predictors of technical difficulty and the limitations of esophageal ESD have been scarcely investigated.

The en bloc resection rate of 99.6% and en bloc curative resection rate of 85.6% in this study were consistent with recent studies (95.1% and 89.4%, respectively) [7]. In previous studies, the rate of perforation during esophageal ESD was reported as 0–6.9%, which is also comparable to that of this study [6, 28–30]. Although previous reports had indicated that procedures performed early in the learning curve and low volume institutions were significantly independent risk factors for perforation during esophageal ESD [28], little research has been done to assess the risk factors for perforation with respect to lesion characteristics.

Long procedure time is one of the limitations of esophageal ESD compared to EMR [2, 24]. Tsujii et al. reported that the median procedure time of esophageal ESD was

Table 3 Procedure-related outcomes of esophageal ESD

Difficult cases, no. (%)	60 (8.8)
Procedure time, min, median (range)	40 (8–320)
Longer than 120 min, no. (%)	43 (6.3)
Resection type, no. (%)	
En bloc resection	676 (99.6)
Piecemeal resection	3 (0.4)
Adverse events, no. (%)	16 (2.4)
Perforation, no. (%)	8 (1.2)
Pneumomediastinum, no. (%)	8 (1.2)
Incomplete resection, no. (%)	14 (2.1)
Depth of tumor invasion, no. (%)	
EP	226 (33.3)
LPM	281 (41.4)
MM	100 (14.7)
SM1	18 (2.7)
SM2	54 (8.0)
Pathological diagnosis, no. (%)	
Squamous cell carcinoma	661 (97.3)
Intraepithelial neoplasia	9 (1.3)
Basaloid-(squamous) carcinoma	4 (0.6)
Adenocarcinoma	5 (0.7)
Curative resection, no. (%)	581 (85.6)

Difficult cases were defined as those with procedure time ≥ 120 min, failure of en bloc resection, occurrence of adverse events such as perforation and pneumomediastinum, or incomplete resection (piecemeal resection, positive or indeterminate vertical margins assessed by histopathologic diagnosis of the ESD specimen). En bloc resection was defined as tumor removal in a single piece with macroscopically tumor free lateral margins

EP epithelium, LPM lamina propria mucosa, MM muscularis mucosa, SM1 submucosa 1 (SM < 0.2 mm), SM2 submucosa 2 (SM > 0.2 mm)

90 min (range 12–450 min) [28]. In our study, the median procedure time was 40 min (range 8–320 min). Therefore, we defined a difficult ESD as a procedure requiring more than 120 min, three times the median procedure time. Our shorter procedure times may be due to our experience as a high volume center. Difficult cases often take a longer time as the endoscopist attempts to avoid major adverse events, mainly perforation, by carefully considering each step during mucosal incision and submucosal dissection. Therefore, procedure time may be a potentially important surrogate marker for technical difficulty.

In the present study, we showed that lesions located on the left wall of the esophagus were significantly associated with difficult esophageal ESD. During esophageal ESD, patients are usually placed in the left lateral decubitus position. Therefore, lesions on the left wall are prone to sinking under the water. In addition, it is difficult to create an effective countertraction because the mucosal flap would remain on the left side due to gravity. In this study, patients were set in the left lateral decubitus position during the procedure. If

Table 4 Univariate analysis of factors associated with difficulty during ESD

Variables	Difficult cases, no. (%)	OR	(95% CI)	<i>p</i> value
Tumor subsite				
Middle esophagus	29/393 (7.3)	1		
Upper esophagus	10/114 (8.7)	1.21	(0.51–2.65)	0.689
Lower esophagus	21/172 (12.2)	1.74	(0.91–3.28)	0.076
Localizations				
Posterior wall	11/227 (4.8)	1		
Right wall	16/183 (8.7)	1.89	(0.79–4.60)	0.160
Anterior wall	10/94 (10.6)	2.33	(0.85–6.30)	0.080
Left wall	23/175 (13.1)	2.96	(1.34–6.95)	0.004
Tumor size (mm)				
< 30	22/450 (4.9)	1		
≥ 30	38/229 (16.6)	3.86	(2.16–7.06)	< 0.001
Circumference of the lesion				
< 1/2	29/563 (5.2)	1		
$\geq 1/2$	31/116 (26.7)	6.69	(3.70–12.15)	< 0.001
Macroscopic type				
Elevated/flat	3/61 (4.9)	1		
Depressed	57/618 (9.2)	1.96	(0.61–10.10)	0.347
Preoperative depth of invasion				
cT1a	53/633 (8.4)	1		
cT1b	7/46 (15.2)	1.96	(0.71–4.73)	0.171
Synchronous multiple SEC				
No	48/525 (9.1)	1		
Yes	12/154 (7.8)	0.84	(0.39–1.66)	0.747
Previous radiation/chemoradiation therapy				
No	54/626 (8.6)	1		
Yes	6/53 (11.3)	1.35	(0.45–3.37)	0.454

OR odds ratio, CI confidence interval, SEC superficial esophageal cancer, cT1a EP+LPM+MM, cT1b SM1+SM2, EP epithelium, LPM lamina propria mucosa, MM muscularis mucosa, SM1 submucosa 1 (SM < 0.2 mm), SM2 submucosa 2 (SM > 0.2 mm)

esophageal ESD had been performed with the patients in a different position, such as the supine or prone positions, the effects of gravity would have been different and so might have been the outcomes. To overcome these disadvantages, previous reports have suggested that clip traction is effective in improving the safety of esophageal ESD and contributes to shortening of the procedure time [18, 19]. With this method, we could apply adequate tension to the lesion and achieve better vision and more space in the submucosal tissue. Direct vision is also useful to recognize bleeding sites and vessels that need to be cauterized. These advantages appear to improve the applicability of esophageal ESD.

Lesions extending to more than half of the circumference were another significant factor associated with a difficult ESD. In this study, the number of cases performed using

Table 5 Multivariate analysis of factors associated with difficulty during ESD

Variables	OR	(95% CI)	<i>p</i> value
Tumor subsite			
Lower esophagus (vs. other lesions)	1.60	(0.86–2.91)	0.128
Localization			
Left wall (vs. other lesions)	2.15	(1.17–3.91)	0.014
Tumor size (mm)			
≥ 30 (vs. <30)	1.65	(0.72–3.58)	0.222
Circumference of the lesion			
≥ 1/2 (vs. <1/2)	5.06	(2.40–11.34)	<0.001
Macroscopic type			
Depressed (vs. elevated/flat)	2.51	(0.80–11.29)	0.122
Preoperative depth of invasion			
cT1b (vs. cT1a)	1.61	(0.56–4.13)	0.355
Synchronous multiple SEC			
Yes (vs. No)	1.25	(0.59–2.50)	0.538
Previous radiation/chemoradiation therapy			
Yes (vs. No)	1.52	(0.52–3.84)	0.415

OR odds ratio, CI confidence interval, SEC superficial esophageal cancer, cT1a EP+LPM+MM, cT1b SM1+SM2, EP epithelium, LPM lamina propria mucosa, MM muscularis mucosa, SM1 submucosa 1 (SM < 0.2 mm), SM2 submucosa 2 (SM > 0.2 mm)

the clip traction method was 139 (20.5%). Lesion localization was not different between the cases that employed clip traction and those that did not. However, more lesions with a larger diameter or circumference were operated upon using the clip traction method. Lesions extending to more than half of the circumference are likely to have large diameters. This result shows that despite the use of clip traction, it is difficult to obtain good traction in large-circumference lesions and, therefore, ESD for these lesions is considered difficult.

Esophageal ESD procedures are considered to be more technically difficult and carry a higher risk of perforation compared to gastric ESD. Even at specialized Japanese centers, complication rates are significantly different according to the number of ESDs performed at each institution [28]. Training at high volume centers under expert supervision and the use of animal training models will provide considerable support to the adoption and technical improvement of esophageal ESD. Our results indicate that the technical difficulty of operating on each lesion can be predicted preoperatively, which will greatly affect the accurate stratification of lesions during stepwise training for esophageal ESD.

There are several limitations to this study. First, we performed a retrospective analysis in a single tertiary cancer center setting. Second, less-experienced endoscopists at our institution had on-site assistance by endoscopists that were highly experienced in esophageal ESD. Furthermore, the endoscopists who performed the procedure included both trainees and skilled endoscopists. However, we believed

that this was acceptable as it reflects daily clinical practice. Third, one of the definitions of incomplete resection, a criterion for technical difficulty, was positive or indeterminate vertical margins. Although positive or indeterminate vertical margins might have been attributable to preoperatively unexpected submucosal infiltration, we included this definition to incorporate the issue of inability to technically perform the dissection or detachment by making an incision in a lesion or cutting it at a certain depth. Another limitation is that we did not consider the learning curve during the study period. Technical improvements in ESD resulted in different en bloc resection and perforation rates between the initial experience and more recent cases. Nevertheless, the large population in our study provides a good source for analyzing this factor.

In conclusion, the predictive factors for technical difficulty of esophageal ESD were identified. Understanding these factors could help to accurately stratify lesions that are more difficult and prone to failure of en bloc resection or perforation. These results provide useful information for the selection of suitable lesions for complete resection by ESD, especially for inexperienced operators.

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Compliance with ethical standards

Disclosures Drs. Hiromasa Hazama, Masaki Tanaka, Naomi Kakushima, Yohei Yabuuchi, Masao Yoshida, Noboru Kawata, Kohei Takizawa, Sayo Ito, Kenichiro Imai, Kinichi Hotta, Hirotoishi Ishiwatari, Hiroyuki Matsubayashi, Keita Mori, and Hiroyuki Ono have no conflicts of interest or financial ties to disclose.

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