



Factors associated with technical difficulty of endoscopic submucosal dissection for early gastric cancer that met the expanded indication criteria: post hoc analysis of a multi-institutional prospective confirmatory trial (JCOG0607)

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Abstract

Background There are few reports on the technical difficulty of gastric endoscopic submucosal dissection (ESD). The aim of this study was to investigate the factors associated with the technical difficulty of ESD for early gastric cancer (EGC) using the data from the multicenter non-randomized confirmatory trial of expanded indication criteria of ESD (JCOG0607).

Methods The major inclusion criteria were as follows: (1) histologically proven intestinal-type adenocarcinoma; (2) cT1aN0M0; (3) lesion without finding of ulcer (UL-negative) with > 2 cm in size, or UL-positive with ≤ 3 cm; (4) age 20–75 years. The difficult case was defined as ESD taking ≥ 120 min, piecemeal resection, and/or developing perforation during procedure.

Results Between June 2007 and October 2010, 470 patients were enrolled from 29 institutions. Median procedure time was 79 (range 14–462) min, and it was ≥ 120 min in 127 patients. Twelve patients developed perforation during ESD, and the procedure time was ≥ 120 min in 9 of them. Therefore, 130 patients (27.7%) were identified as difficult cases. Multivariable analysis showed that UL-negative with > 5 cm (vs. UL-negative with ≤ 3 cm, odds ratio, 24.993; 95% CI 6.130–101.897, $p < 0.0001$) had the largest odds ratio and followed by UL-negative with 3–5 cm upper or middle portion of stomach and age ≤ 60 years were significantly associated with difficulty.

Conclusions UL-negative lesion with > 3 cm, upper or middle portion of stomach and age ≤ 60 years were independent factors associated with technical difficulty of ESD for EGC. Trial registered number was UMIN000000737.

Keywords Early gastric cancer · Endoscopic submucosal dissection · Technical difficulty

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Introduction

While gastric cancer remains one of the leading causes of cancer death, mortality reduction through early detection with nation-wide endoscopic screening has been successful mainly in Japan and Korea [1, 2]. Small intramucosal gastric cancer can be easily treated by endoscopic mucosal resection without lymph node dissection. However, in lesions with large size or with ulceration, it is technically difficult to perform endoscopic resection. Endoscopic submucosal dissection (ESD) is now widely indicated for early gastric cancer (EGC) and enables the removal of whole lesions in en bloc fashion regardless of its size and concomitant ulceration (UL-positive) [3].

We previously reported that, in the clinical trial (JCOG0607) of ESD for expanded indication, UL-negative tumor with > 2 cm in size or UL-positive tumor with ≤ 3 cm in size, showed equivalent survival to those that underwent surgery with lymph node dissection [4]. Based on these results, the indication was expanded to T1a intestinal type gastric adenocarcinoma with UL-negative > 2 cm size or UL-positive ≤ 3 cm size in the clinical guidelines published by Japanese Gastric Cancer Association in 2018.

Clinically, expanded indication might raise the problem of longer procedure time to complete. For example, procedure time longer than 120 min in ESD for EGC was reported as a risk factor of aspiration pneumonia [5]. In addition, perforation is also related with longer procedure time, less completion of ESD. While longer procedure time might be caused by technical difficulty, there were few reports on technical difficulty of ESD for expanded indication of EGC [6, 7]. As for the technical aspects of the JCOG0607 trial, most of the lesions (91.7%: 431/470) could be completely resected in en bloc fashion, and the median procedure time was 79 min. However, the procedure time of ESD widely ranged from 14 to 462 min [4].

The aim of this supplementary study was to explore the factors associated with the technical difficulty of ESD for EGC, which met the expanded indication criteria using the data from JCOG0607.

Methods

This post hoc analysis used the data collected in a multi-institutional prospective confirmatory trial of ESD for EGC which met the expanded indication criteria (JCOG0607). The primary endpoint of JCOG0607 was the 5-year overall survival rate after ESD with an intention to treat analysis. JCOG0607 complied with the Declaration

of Helsinki requirements, which was approved by the institutional review board of all participating hospitals, and registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000000737). The informed consent about the secondary use of the data was obtained from the enrolled patients at the registration to JCOG0607.

Inclusion criteria of JCOG0607 and the definition of difficult case in this study

The key indication criteria of JCOG0607 were as follows: (1) primary and single histologically proven intestinal-type adenocarcinoma of the stomach, (2) endoscopically diagnosed mucosal tumor and absence of lymph node and distant metastasis (cT1aN0M0) in computed tomography (CT) of abdomen, (3) UL-negative tumor with > 2 cm in size or UL-positive tumor with ≤ 3 cm in size, (4) age of 20–75 years, (5) Eastern Cooperative Oncology Group performance status of 0 or 1, (6) no prior gastrectomy and no reconstructive surgery using the stomach after resection of esophageal cancer, (7) no prior chemotherapy or radiation therapy for any other malignancies, (8) high possibility of en bloc resection with ESD, and (9) provision of written informed consent [4]. The difficult case was defined as ESD taking 120 min or longer, and/or piecemeal resection and/or developing perforation during the procedure. In JCOG0607, the procedure time was defined from the start of marking to the end of resection, and the perforation was diagnosed as follows: (1) mesenteric fat was observed with endoscopy during ESD or, (2) free air was detected with X-ray or CT of abdomen. The easy case was defined as ESD taking less than 120 min with en bloc resection without perforation during procedure.

ESD procedure and trial profile of JCOG0607

In JCOG0607, all ESD procedures were performed by certified endoscopists as operator or supervisor, who had experienced 100 cases of gastric ESD or more. ESD was performed in a manner previously reported [8, 9]. The device for ESD depended on the operators' choices such as IT-knife[®], Hook knife[®], Flush knife[®], and others. After the completion of ESD, all resected materials were evaluated by experienced pathologists at each participating institution.

Statistical analysis

All data including procedure time were collected prospectively. Univariable and multivariable analyses of the proportion of difficult cases were performed with following categorized variables: age, sex, location (U: upper, M: middle, L: lower), circumference location (on greater curvature, non-spreading to greater curvature), macroscopic

type (protruded, depressed, mixed), tumor size and UL finding, device, institution, and registration periods. Institution was classified into three groups depending on the numbers of registered patients, and the whole registration period was divided into three periods (first 1/3 period: June 2007–June 2008, middle 1/3 period: June 2008–June 2009, last 1/3 period: June 2009–Oct 2010). As for age, the proportion of difficult cases was compared among 4 categories of age (≤ 60 years, 61–65 years, 66–70 years, > 71 years) to set the cut-off for categorizing to be used in univariable and multivariable analyses. Because of the indication criteria of JCOG0607, all lesions > 3 cm ($n = 111$) were UL-negative and all lesions with UL-positive were ≤ 3 cm ($n = 207$), it is difficult to analyze size and UL finding as each variables in multivariable analysis due to high correlation. Therefore, we used four categories combining size and UL finding (UL-negative and ≤ 3 cm, UL-negative and 3–5 cm, UL-negative and > 5 cm, UL-positive) in this study. As reference, univariable analysis using tumor size as continuous variable was performed, and the proportion of difficult case was compared among the five categories of tumor size (≤ 2 cm, 2–2.5 cm, 2.5–3 cm, 3–5 cm, > 5 cm).

Odds ratios were estimated using logistic regression model using the above-mentioned variables. Fisher's exact test was also used for univariable analyses. All p values were two-sided. Statistical analyses were performed by a biostatistician of the JCOG Data Center using SAS version 9.4.

Results

Between June 2007 and October 2010, 470 patients were enrolled and all of them underwent ESD in JCOG0607. This post hoc analysis included all 470 patients. As for cutting devices for ESD, IT-knife or IT-knife 2 were predominant (82.3%: 387/470), and approximately 75% of the patients (355/470) enrolled were from the top one-third active institutions. ESD was stopped during the procedure in one case because of perforation. The procedure time was 120 min or longer in 127 patients, and 9 of them were complicated even with perforation during ESD. Moreover, 3 cases developed perforation with their procedure time less than 120 min. In total, 130 (27.7%) cases were classified as difficult cases, whereas the other 340 cases were easy cases (Fig. 1). All patients' and lesions' characteristics in both difficult and easy groups are summarized in Table 1. The details related to ESD procedure are summarized in Table 2. The median procedure time was 61.5 (range 14–119) min in easy cases and 157.5 (range 48–462) min in the difficult cases. The histogram of the procedure time in each group was presented in Fig. 2.

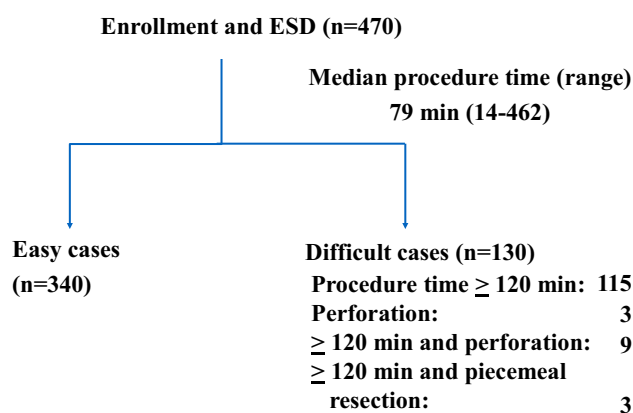


Fig. 1 The patients' flow diagram

Table 1 Patients' and lesions' characteristics

	Total (n=470)
Median age (y-o, range)	65 (40–75)
Gender	
M	385
F	85
Location	
U	71
M	255
L	144
Tumor size (cm)	
Median	2.5
Range	0.5–13
Macroscopic type	
Protruded	155
Depressed	258
Mixed	57
Ulceration or scar	
Presence (UL+)	207
Absence (UL–)	263
Tumor size and finding of UL	
UL(–) and ≤ 3 cm	152
UL(–) and > 3 cm	111
UL (+) (< 3 cm)	207

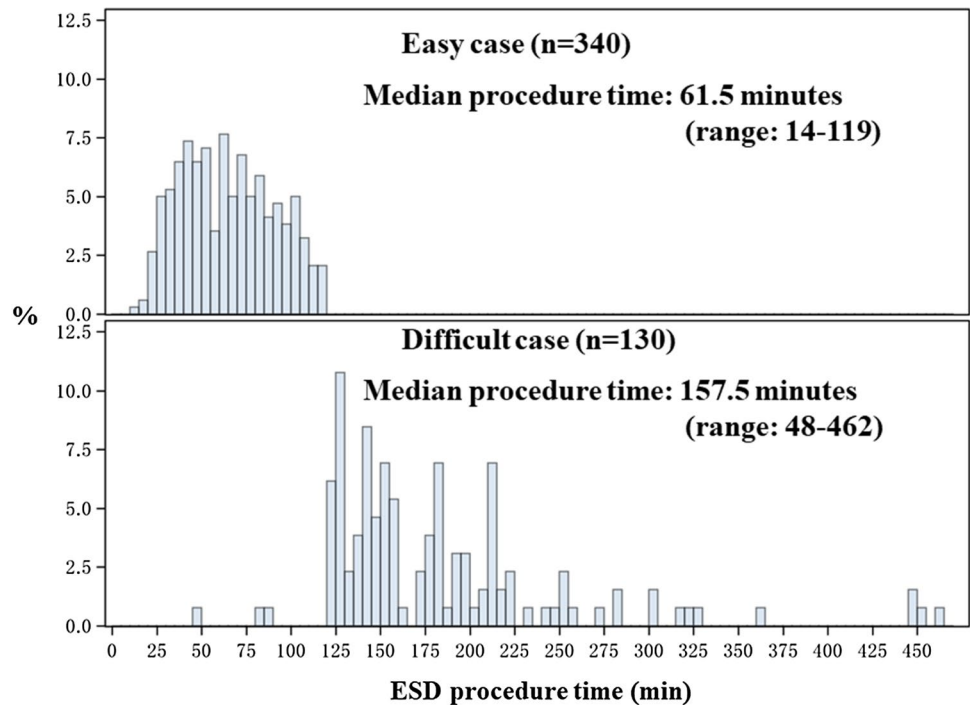
Univariable analysis of factors associated with technical difficulty

The results of the univariable analyses for the technical difficulty are presented in Table 3. As for age, the proportion of difficult cases was 33.3% (47/141) in patients aged ≤ 60 years, 25.5% (28/110) in those aged 61–65 years, 24.0% (29/121) in those aged 66–70 years, and 26.5% (26/98) in those aged > 71 years. The proportions of difficult cases were consistent in patients > 60 years while it was

Table 2 Details of ESD procedure

	Easy cases (n=340)	Difficult cases (n=130)	Total (470)	% of difficult cases
Median procedure time (min)	61.5	157.5	79	
Range (min)	14–119	48–462	14–462	
Main device using in ESD (IT-knife/non IT-knife)				
IT-knife or IT-knife 2	283	104	387	26.9
Others (Hook knife, flush knife, flex knife, etc.)	57	26	83	31.3
Institution (number of enrollment)				
Top 1/3	257	98	355	27.6
Middle 1/3	67	26	93	28.0
Lower 1/3	16	6	22	27.2
Registration period				
First 1/3 period (2007/6/8–2008/6/7)	107	49	156	31.4
Middle 1/3 period (2008/6/8–2009/6/7)	109	35	144	24.3
Last 1/3 period (2009/6/8–2010/10/4)	126	44	170	25.9

Fig. 2 The histogram of procedure time in each groups



relatively higher in patients ≤ 60 years old. In univariable analysis using categorized variable for age ≤ 60 years (odds ratio 1.482; 95% CI 0.964–2.277; *p* = 0.0727), location of upper 1/3 in stomach (odds ratio 2.433; 95% CI 1.297–4.564; *p* = 0.0056), UL-negative tumor of 3–5 cm size (odds ratio 3.444; 95% CI 1.938–6.122, *p* < 0.0001), and UL-negative and > 5 cm size (odds ratio 17.711; 95% CI 4.685–66.959, *p* < 0.0001) were significantly associated with technical difficulty. As reference, univariable analysis of tumor size (cm) as the continuous variable was performed and an odds ratio was 1.364 (95% CI 1.240–1.501, *p* < 0.0001), the proportion

of the difficult case was related to the tumor size: 16.7% (23/138) in ≤ 2 cm, 21.3% (26/122) in > 2 cm and ≤ 2.5 cm, 27.3% (27/99) in > 2.5 cm and ≤ 3 cm, 43.8% (42/96) in > 3 cm and ≤ 5 cm, and 80.0% (12/15) in > 5 cm.

Multivariable analysis of factors associated with technical difficulty

In multivariable analysis, age ≤ 60 years (odds ratio 1.755; 95% CI 1.101–2.799; *p* = 0.0181), location of upper 1/3 (odds ratio 3.192; 95% CI 1.579–6.452; *p* = 0.0012) and

Table 3 The univariable and multivariable analyses for the technical difficulty

	Proportion of difficult case		<i>p</i> value	Univariable analysis			Multivariable analysis		
				Odds ratio	(95% CI)	<i>p</i> value	Odds ratio	(95% CI)	<i>p</i> value
Age (years)									
> 61	83/329	25.2%		1		0.0727	1		0.0181
≤ 60	47/141	33.3%	0.0911	1.482	0.964–2.277		1.755	1.101–2.799	
Gender									
Female	19/85	22.4%		1		0.2285	1		
Male	111/385	28.8%	0.2837	1.407	0.807–2.453		1.542	0.835–2.848	0.1667
Location									
L	29/144	20.1%		1			1		
M	74/255	29.0%		1.621	0.994–2.643	0.0527	1.764	1.017–3.061	0.0433
U	27/71	38.0%	0.0171	2.433	1.297–4.564	0.0056	3.192	1.579–6.452	0.0012
Circumferential location									
Non-spreading to greater curvature	117/406	28.8%		1			1		
On greater curvature	13/64	20.3%	0.1778	0.630	0.330–1.201	0.1606	0.703	0.346–1.426	0.3284
Macroscopic type									
Protruded	54/155	34.8%		1			1		
Depressed	62/258	24.0%		0.592	0.382–0.916	0.0185	0.669	0.369–1.211	0.1838
Mixed	14/57	24.6%	0.0553	0.609	0.306–1.211	0.1574	1.004	0.458–2.204	0.9915
Tumor size and UL									
UL (–) and ≤ 3 cm	28/152	18.4%		1			1		
UL (–) and 3–5 cm	42/96	43.8%		3.444	1.938–6.122	< 0.0001	3.765	2.052–6.908	< 0.0001
UL (–) and > 5 cm	12/15	80.0%		17.711	4.685–66.959	< 0.0001	24.993	6.130–101.897	< 0.0001
UL (+) (≤ 3 cm)	48/207	23.2%	< 0.0001	1.337	0.793–2.253	0.2755	1.683	0.916–3.091	0.0933
Device									
IT knife or IT knife 2	104/387	26.9%		1			1		
Others	26/83	31.3%	0.4191	1.241	0.741–2.078	0.4112	1.256	0.669–2.360	0.4779
Institution (number of enrollment)									
Top 1/3	98/355	27.6%		1			1		
Middle 1/3	26/93	28.0%		1.018	0.612–1.693	0.9461	1.131	0.620–2.066	0.6880
Lower 1/3	6/22	27.3%	1.0000	0.983	0.374–2.586	0.9731	1.003	0.350–2.878	0.9951
Registration period									
First 1/3 period	49/156	31.4%		1			1		
Middle 1/3 period	35/144	24.3%		0.701	0.421–1.167	0.1718	0.706	0.406–1.229	0.2183
Last 1/3 period	46/170	27.1%	0.3804	0.810	0.502–1.307	0.3881	0.856	0.507–1.446	0.5607

middle 1/3 of the stomach (odds ratio 1.764; 95% CI 1.017–3.061), UL-negative tumor of 3–5 cm size (odds ratio 3.765; 95% CI 2.052–6.908; $p < 0.0001$) and UL-negative tumor of > 5 cm size (odds ratio 24.993; 95% CI 6.130–101.897, $p < 0.0001$) were significantly associated with technical difficulty.

Discussion

This is the first report that evaluated the technical difficulty of gastric ESD for expanded indication criteria using data of a multi-institutional prospective study. Although this

supplementary study was not pre-planned, all data used in this post hoc analysis had been already collected prospectively, including the ESD procedure time and adverse events. This study demonstrated that the UL-negative tumor with > 5 cm size showed the largest odds ratio, followed by UL-negative tumor of 3–5 cm size, upper or middle 1/3 location and age ≤ 60 years, as a significant risk factor of difficult ESD taking ≥ 120 min or complicated with perforation.

Tumors with large size or located in the upper part of the stomach were known factors associated with technical difficulty, as described in previous reports [6, 7, 10]. The procedure of ESD generally consists of the following three major processes; (1) cutting the surrounding of the lesion,

(2) dissection of submucosal layer beyond the lesion, and (3) hemostasis for intraoperative bleeding. During the process of dissection of the submucosal layer, minor and/or major bleeding make complicated the procedure in some cases. In other words, dissection of the submucosal layer and hemostasis were procedures performed alternately and repeatedly. Management of bleeding includes the steps of searching the bleeding spot and stopping bleeding, which results in time consuming. The risk of bleeding is getting higher with the larger size of dissected area. Thus, it is reasonable that lesion size is the most important risk factor of difficulty in ESD. Goto et al. reported that both the presence of ulcerative findings and tumor size larger than 2 cm were the significant predictors for procedure time longer than 120 min [6]. Nagata et al. also described that ulcerative change was related to longer procedure time [7]. In this study, UL-positive was not a significant factor for technical difficulty by multivariable analysis, probably because all UL-positive lesions were less than 3 cm in size. It is considered that the recent ESD technique using new devices might conquer the difficulty due to the presence of ulceration in relatively small (< 3 cm) lesions.

Similar to this study, there have been some reports that EGC in located in the upper or middle part of the stomach required a significant longer ESD procedure time than those located in the lower stomach [6, 10]. It is considered that technical difficulty due to location cannot be resolved only by improvement of cutting device. Moreover, tangential approach is required when dissecting the submucosal layer beneath the lesion especially on greater curvature in upper stomach. Recently, some investigators reported the innovative methods using traction devices when dissecting the submucosal layer to resolve the technical difficulty in gastric ESD [11–14]. Yoshida et al. conducted a multi-center randomized control trial of conventional ESD versus dental floss clip traction assisted ESD (DFC-ESD) for early gastric neoplasm [15]. While DFC-ESD failed to significantly reduce the procedure time compared with the conventional method in the analysis of all enrolled lesions, DFC traction tended to shorten the procedure time at the area of greater curvature of the middle or upper part of the stomach in a subset analysis. As the traction device was generalized after the study period, most of the cases were performed without those tools. These new traction devices, which are used recently, may solve the technical difficulty related to the location of lesion in gastric ESD.

Age of ≤ 60 years was one of the risk factors associated with technical difficulty in this study. There are few reports comparing the procedure time between elderly and young patients in gastric ESD. Iwai et al. reported the retrospective comparative study between elderly (≥ 80 years) and non-elderly (< 80 years) patients to assess short- and long-term outcome of gastric ESD [16]. There was no significant

difference in the procedure time and incidence of perforation between the two groups; however, it might be difficult to refer the results of their study into our study. Because it was the retrospective analysis of their daily practical data, the lesions' characteristics of each group were different. Meanwhile, somatotype and mucosal condition might explain the reason for the differences in the findings between young and elderly patients. High body mass index (BMI) was reported as significantly associated with long operation time in gastrectomy due to thick abdominal wall and massive adipose tissue in clinical setting [17]. Thick gastric wall or increased adipose tissue in the submucosal layer might be associated with long procedure time in ESD as well as gastrectomy. In general, gastric atrophy increased with age especially in *Helicobacter pylori*-infected stomach [18], and decreased gastric mucosal blood flow with aging as reported in experimental models [19]. The difference in the degree of gastric atrophy or mucosal blood flow with age can affect the prevalence of technical difficulty. However, it cannot conclude that these factors affect the difficulty of ESD because information of patients' physics (e.g. BMI), degree of gastric atrophy, and *H. pylori* infection status were not collected in JCOG0607. This is one of the major limitations of this study, and further investigation is necessary to elucidate this issue.

Moreover, the second limitation was that there was no control group, including small (< 2 cm) and UL-negative lesions because of the indication criteria of JCOG0607. Therefore, fair comparison of the technical difficulty between UL-positive and -negative cases of same size could not be performed. Finally, information about the specific time required for each step of the procedure is lacking. These data may contribute to the clear identification of risk factors and the developing of new devices for ESD. To know the accurate time allotted for each step based on the technical aspects will also be when training young endoscopists and for the prediction of procedure time. Furthermore, it may have an educational benefit in the case selection for novice operator or in providing information about the operation time for patients and their family members before the procedure.

In conclusion, UL negative tumor > 3 cm size, location in the upper or middle part of the stomach, and age of 60 years or younger were the independent risk factors associated with technical difficulty in ESD for EGC, which met the expanded indication criteria. While traction devices including dental floss clip may be supportive to conquer the factors related to lesion's location in technical difficulty, we should continue to make an effort to innovate other devices or methods to reduce adverse events related to long procedure time of gastric ESD.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest related to this article.

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