Hospital volume and adverse events following esophageal endoscopic submucosal dissection in Japan

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ABSTRACT

Background and study aims   Esophageal endoscopic submucosal dissection (ESD) has gradually acquired popularity as a minimally invasive surgery for early cancers not only in Japan, but also in other countries. However, most reported outcomes have been based on relatively small samples of patients from specialized centers. Therefore, the association between hospital volume and the rate of adverse events following esophageal ESD has been poorly understood.
Patients and methods   Using a nationwide administrative database in Japan, we identified patients who underwent esophageal ESD between 1 July 2007 and 31 March 2013. Hospital volume was defined as the number of esophageal ESD procedures performed per year at each hospital and was categorized into quartiles.
Results   In total, 12 899 esophageal ESD procedures at 699 institutions were identified during the study period. Perforation and perforation-related disorders were observed in 422 patients (3.3 %), and one patient died after perforation. There was a significant association between a lower hospital volume and a higher proportion of adverse events following esophageal ESD. Although not statistically significant, a similar tendency was observed in the occurrence of blood transfusion within 1 week after ESD and all-cause in-hospital death. Multivariable logistic regression analysis showed that hospitals with very high case volumes were less likely to experience adverse events following esophageal ESD than hospitals with very low volumes.
Conclusions   The proportion of perforation and perforation-related disorders following esophageal ESD was permissibly low, and there was a linear association between higher hospital volume and lower rates of adverse events following esophageal ESD.

Introduction

Endoscopic submucosal dissection (ESD) for the treatment of early esophageal cancers is a well-established minimally invasive surgical procedure worldwide [1–4]. Compared with endoscopic mucosal resection (EMR), esophageal ESD is advantageous because it allows en bloc resection, enabling precise histopathological evaluation regardless of lesion size or configuration; this results in a lower local recurrence rate and a higher long-term survival rate [5–8].

However, esophageal ESD is technically more difficult than esophageal EMR. Previous studies have suggested that esophageal ESD is more likely to lead to a higher frequency of adverse events compared with EMR [9,10]. Among the adverse events

associated with esophageal ESD is perforation, which is a severe condition that may result in death, although this is rare [5,6, 10,11].

Almost all previous reports describing adverse events associated with esophageal ESD involved relatively small samples and only included patients treated at specialized centers, resulting in low generalizability. Using a nationwide database, we recently reported two important findings regarding adverse events following colorectal ESD: 1) the rate of postoperative bleeding associated with colorectal ESD was slightly higher than that in previous studies, which were mainly performed at specialized centers; and 2) hospital volume was inversely related to the rate of adverse events associated with colorectal ESD

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[12]. Another nationwide study of 27 385 gastric ESD procedures showed similar results [13]. However, no studies have addressed the adverse events associated with esophageal ESD in a nationwide setting, and the relationships between hospital volume and the occurrence of adverse events associated with esophageal ESD have been poorly understood.

In the present study, we examined the occurrence rate of perforation and perforation-related disorders following esophageal ESD, and clarified the relationships between hospital volume and adverse events following esophageal ESD using a national inpatient database in Japan.

Patients and methods

Design and setting

This was a retrospective cohort study using the Japanese Diagnosis Procedure Combination (DPC) database, which is a nationwide, large-scale, administrative database.

DPC database

The details of the DPC database have been described elsewhere [14]. In summary, the DPC database includes inpatient claims and discharge abstracts. Data were compiled from 1 July to 31 December each year from 2007 to 2010, and for the whole of each year since 2011. The 2012 database includes data on approximately 6.8 million inpatients, which accounted for approximately 50 % of all inpatient admissions to acute-care hospitals in Japan. The following data are included in the database: unique identifier for each hospital; type of hospital (academic or nonacademic); patient age and sex; diagnoses, co-morbidities, and adverse events coded according to the International Classification of Diseases 10th revision (ICD-10) codes; surgical procedures; implementation of radiotherapy; type of anesthesia; drugs used; and discharge status. Postadmission adverse events are clearly differentiated from preadmission co-morbidities. Attending doctors are responsible for recording the diagnoses with reference to the medical charts.

Informed consent was waived for this study because of the anonymous nature of the data. The study was approved by the institutional review board of The University of Tokyo.

Patient selection

Using unique Japanese surgical procedure codes, we identified patients who underwent esophageal ESD between 1 July 2007 and 31 March 2013. The following background patient data were collected: age and sex, diagnoses, co-morbidities at admission and adverse events after admission, surgical procedures, implementation of radiotherapy, use of general anesthesia, use of antithrombotic agents, use of anticancer drugs, and in-hospital mortality.

Co-morbidities included in the study were as follows: cardiac diseases including ischemic heart diseases (ICD-10 codes I20 – 25) and heart failure (I50), chronic obstructive pulmonary disease including emphysema (J43) and other chronic obstructive pulmonary disease (J44), renal failure (N17 – 19), liver cirrhosis including alcoholic cirrhosis (K70.3) and fibrosis and cirrhosis (K74), and diabetes mellitus (E10 – 14). Based on Japanese text

data combined with ICD-10 codes (C15.5), esophageal adenocarcinoma in Barrett's esophagus was distinguished from esophageal squamous cell carcinoma

We identified antithrombotic agents and anticancer drugs used during hospitalization for each patient. Antithrombotic agents comprised antiplatelet and anticoagulant drugs. The antiplatelet drugs included aspirin, clopidogrel, ticlopidine, cilostazol, icosapentate, beraprost, sarpogrelate, and dipyridamole, and the anticoagulant drugs included heparin, warfarin, and dabigatran. Anticancer drugs included fluorouracil, cisplatin, and nedaplatin. Preoperative chemoradiotherapy was defined as the combination of chemotherapy (using the abovementioned anticancer drugs) with radiotherapy performed for the treatment of esophageal cancers before the performance of ESD.

Hospital volume was defined as the number of esophageal ESD procedures performed annually at each hospital, and was categorized into quartiles (very low, low, high, and very high) so that the numbers of patients in the four groups were almost equal.

Outcomes

The primary outcome was perforation and perforation-related disorders following esophageal ESD. Perforation was identified using the following ICD-10 codes: esophageal perforation (K22.3); other postprocedural disorders of the digestive system, not elsewhere classified (K91.8); accidental puncture and laceration during a procedure, not elsewhere classified (T81.2); and other adverse events of procedures, not elsewhere classified (T81.8). Perforation-related disorders included the following conditions: mediastinitis including diseases of the mediastinum, not elsewhere classified (J98.5) and infection following a procedure, not elsewhere classified (T81.4); abscessation of the mediastinum (J85.3); interstitial emphysema (J98.2); traumatic subcutaneous emphysema (T79.7); and pneumothorax, unspecified (J93.9). We checked the Japanese text data for the diagnoses to confirm the accuracy of the ICD-10 codes. The records of re-admission within 2 weeks after the initial discharge were examined to investigate delayed perforation.

Secondary outcomes were all-cause in-hospital mortality and blood transfusion within 1 week after esophageal ESD. The compound end point was defined as at least one adverse event including perforation, perforation-related disorders, in-hospital death, or blood transfusion within 1 week after esophageal ESD.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, New York, USA). The chi-squared test was used for categorical data, and Student's t test was used for continuous data. The association between hospital volume and the compound end point was examined using a multivariable logistic regression analysis with adjustment for age, sex, type of hospital, cardiac diseases, chronic obstructive pulmonary disease, liver cirrhosis, renal failure, diabetes mellitus, preoperative chemoradiotherapy, general anesthesia, carcinoma in Barrett's esophagus, and use of antithrombotic agents.

	Hospital case volume per year				Total	P value
	≤8	9–17	18–38	≥39		
ESD procedures, n	3342	3153	3057	3347	12 899	
Institutions, n	552	89	41	17	699	
Female sex, n (%)	494 (14.8)	441 (14.0)	391 (12.8)	454 (13.6)	1780 (13.8)	0.13
Age, n (%), years						
≤49	67 (2.0)	63 (2.0)	48 (1.6)	87 (2.6)	265 (2.1)	<0.001
50–59	378 (11.3)	406 (12.9)	410 (13.4)	463 (13.8)	1657 (12.8)	
60–69	1160 (34.7)	1107 (35.1)	1186 (38.8)	1285 (38.4)	4738 (36.7)	
70–79	1356 (40.6)	1271 (40.3)	1173 (38.4)	1192 (35.6)	4992 (38.7)	
≥80	381 (11.4)	306 (9.7)	240 (7.9)	320 (9.6)	1247 (9.7)	
Co-morbidities, n (%)						
Cardiac disease	255 (7.6)	157 (5.0)	181 (5.9)	139 (4.2)	732 (5.7)	<0.001
COPD	58 (1.7)	60 (1.9)	39 (1.3)	37 (1.1)	194 (1.5)	0.03
Liver cirrhosis	74 (2.2)	51 (1.6)	34 (1.1)	50 (1.5)	209 (1.6)	0.01
Renal failure	57 (1.7)	43 (1.4)	27 (0.9)	33 (1.0)	160 (1.2)	0.01
Diabetes mellitus	438 (13.1)	325 (10.3)	269 (8.8)	300 (9.0)	1332 (10.3)	<0.001
Carcinoma in Barrett's esophagus, n (%)	135 (4.0)	121 (3.8)	69 (2.3)	88 (2.6)	413 (3.2)	<0.001
General anesthesia, n (%)	530 (15.9)	496 (15.7)	707 (23.1)	574 (17.1)	2307 (17.9)	<0.001
Preoperative chemoradiotherapy, n (%)	19 (0.6)	34 (1.1)	37 (1.2)	29 (0.9)	119 (0.9)	0.04
Antithrombotic agents, n (%)	131 (3.9)	119 (3.8)	105 (3.4)	149 (4.5)	504 (3.9)	0.20

ESD, endoscopic submucosal dissection; COPD, chronic obstructive pulmonary disease.

The regression model was fitted with a generalized estimated equation to adjust for within-hospital clustering effects. A P value of <0.05 was regarded as statistically significant.
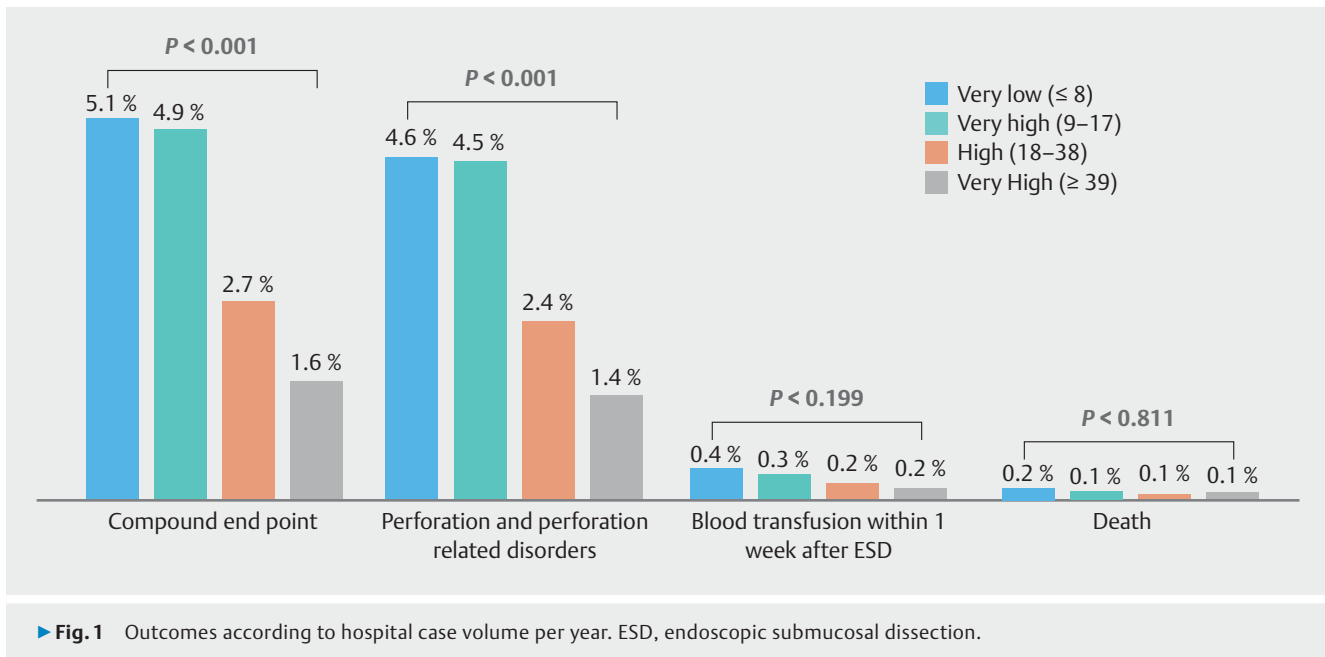
Results

In total, 12 899 esophageal ESD procedures in 699 hospitals were identified during the study period. With respect to hospital case volume, the patients were divided into very low volume (≤8), low volume (9–17), high volume (18–38), and very high volume (≥39).

The patient background data according to the four hospital volume groups are shown in ► **Table 1**. Overall, approximately 80 % of hospitals had very low case volumes. The most frequent age groups were 60–69 and 70–79 years in all hospital volume groups. Higher-volume hospitals were more likely to have smaller proportions of patients with co-morbidities than lower-volume hospitals. Carcinoma in Barrett's esophagus accounted for 3.2 % of all ESD procedures. There was no linear trend between hospital volume and the proportion of patients receiving general anesthesia.

The rate of perforation and perforation-related disorders was 3.3 % (n = 422). Among these patients, 7 (1.7 %) underwent open thoracotomy for treatment of esophageal perforation. There was a linear association between a lower hospital volume and a higher proportion of these outcomes. The proportions of blood transfusion within 1 week after esophageal ESD and all-cause in-hospital death were 0.3 % and 0.1 %, respectively. Hospitals with very low case volumes had a higher proportion of blood transfusion within 1 week after esophageal ESD than hospitals with very high case volumes, although the difference was not statistically significant (► **Fig. 1**). Of the 16 in-hospital deaths, 8 patients died within 4 weeks after esophageal ESD, 5 received a blood transfusion within 1 week after esophageal ESD, and 1 developed perforation and perforation-related disorders following esophageal ESD.

Factors associated with a higher occurrence of the compound end point were a lower hospital volume and female sex. Compared with the hospitals with very low case volumes, the odds ratio for the compound end point in hospitals with a very high case volume was 0.31 (95 % confidence interval 0.12–0.81; P = 0.02). The patients who underwent esophageal ESD under general anesthesia were more likely to have the compound end point, but this was not statistically significant (► **Table 2**).

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▶ Fig. 1 Outcomes according to hospital case volume per year. ESD, endoscopic submucosal dissection.

Discussion

Using a national inpatient database in Japan, we clarified that hospital case volume was inversely related to the proportion of perforation and perforation-related disorders following esophageal ESD. The relatively low rate of perforation and perforation-related disorders was consistent with the findings of previous small studies [7, 11]. Multivariable logistic regression analysis showed that hospitals with very high case volumes had a significantly lower rate of adverse events following esophageal ESD than hospitals with very low case volumes.

Early detection and treatment of esophageal cancers are desired for curative care. Recent advances in endoscopic technology, such as magnifying observation and narrow-band imaging, have enabled more frequent detection of early esophageal cancers than has been achieved in the past. In addition, ESD for early esophageal cancers has gradually acquired popularity as a minimally invasive intervention with good clinical outcomes. In a recent meta-analysis including 15 studies of esophageal ESD, the pooled estimates of complete and en bloc resection rates were 89.4% and 95.1%, respectively [15].

However, because of the narrowness of the esophageal lumen and movement derived from heartbeats, esophageal ESD requires a more highly skilled technique compared with gastric ESD. Moreover, the risk of perforation after esophageal ESD is considered to be higher than that after gastric ESD because the esophageal wall is thinner than the gastric wall [15]. However, based on data from 699 institutions nationwide, the present study showed that the proportion of perforation and perforation-related disorders following esophageal ESD was permissibly low at 3.3%. Most perforations following ESD are treated successfully with conservative management including endoscopic closure, fasting with intravenous fluid therapy, and intravenous antibiotics. In fact, only one patient with perforation died in the present study.

Several recent reports have shown promising results of ESD for the treatment of esophageal adenocarcinoma [16, 17]; however, most of the published studies of esophageal ESD have focused on squamous cell carcinoma. This is probably because most studies of esophageal ESD were conducted in Japan, and the incidence of esophageal adenocarcinoma in Japan is markedly lower than that in Western countries [18]. Several reports have shown that the percentage of esophageal adenocarcinoma among all esophageal cancers in Japan is approximately 4% [19, 20], which is consistent with the present results. Interestingly, the present study suggests that the proportion of adverse events following ESD for esophageal adenocarcinoma is comparable to that for squamous cell carcinoma.

The present study clearly showed a linear association between a lower hospital case volume and higher rate of adverse events following esophageal ESD. This trend is similar to that found in previous studies of gastric ESD and colorectal ESD [12, 13]. In particular, the proportion of perforation and perforation-related disorders in hospitals with very low case volumes was more than three times higher than that in hospitals with very high case volumes. There is no universal standard for training of esophageal ESD in Japan, and each institution has its original training program. Higher-volume centers may have better training programs, possibly resulting in better outcomes in these centers.

Multivariable logistic regression analysis showed that factors associated with adverse events following esophageal ESD were hospital volume and female sex. The reason for higher complication rates in women remains unclear. However, there is a plausible explanation for this trend. Heavy drinking and smoking, which are more common in men, are major causes of esophageal cancers. These conditions sometimes result in chronic inflammation of the esophagus, leading to thickening of the esophageal submucosa, which may be associated with a

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► **Table 2** Multivariable logistic regression analyses of the compound end point, defined as at least one complication (perforation, perforation-related disorders, in-hospital death, or blood transfusion within 1 week after esophageal ESD).

	OR	95 %CI	*P* value
Hospital volume (procedures/year)			
Very low (≤8)	Reference		
Low (9 – 17)	1.02	0.67 – 1.56	0.92
High (18 – 38)	0.57	0.28 – 1.15	0.12
Very high (≥39)	0.31	0.12 – 0.81	0.02
Age in years			
≤49	Reference		
50 – 59	0.85	0.43 – 1.66	0.63
60 – 69	0.90	0.49 – 1.65	0.73
70 – 79	1.02	0.56 – 1.86	0.95
≥80	1.04	0.55 – 2.00	0.90
Female sex	1.61	1.29 – 2.01	<0.001
Type of hospital			
Nonacademic	Reference		
Academic	0.74	0.41 – 1.35	0.32
Cardiac diseases	0.88	0.56 – 1.38	0.57
COPD	0.74	0.29 – 1.88	0.53
Liver cirrhosis	1.25	0.57 – 2.73	0.57
Renal failure	1.55	0.79 – 3.05	0.21
Diabetes mellitus	1.11	0.84 – 1.47	0.45
Preoperative chemora-diotherapy	1.57	0.56 – 4.40	0.39
General anesthesia	1.42	0.95 – 2.14	0.09
Carcinoma in Barrett's esophagus	0.65	0.23 – 1.81	0.41
Antithrombotic agents	1.39	0.87 – 2.23	0.17

OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

lower rate of esophageal perforation related to ESD procedures.

No co-morbidities in the present study were significantly associated with adverse events after esophageal ESD. Conversely, esophageal ESD under general anesthesia was more likely to be associated with procedure-related adverse events, although this was not statistically significant. There is a plausible explanation for this trend. Gastrointestinal endoscopists who perform ESD usually select general anesthesia based on the preoperative findings of the lesion. In other words, the use of general anesthesia may be a surrogate marker of a more time-consuming procedure and more complicated lesions in esopha-

geal ESD, including large lesions, circumferential lesions, and lesions on a scar.

The present study has several limitations. First, the DPC database lacks some information about clinicopathological features in esophageal ESD, such as the location, size, configuration, circumferential involvement, depth of lesions, submucosal invasion, submucosal adhesion, and the presence of scar tissue. However, a recent study conducted in Japan, which included 368 esophageal ESDs among 11 hospitals, suggested that there were no differences in lesion factors between the high-volume centers and low-volume centers [21]. The database also lacks data regarding experience of the endoscopists who perform ESD procedures, number of endoscopists working at the hospital, types of endoscopy knives used, use of carbon dioxide insufflation vs. room air insufflation, and duration of the procedure. That is, there was no information on learning curve of ESD procedures. We adjusted for type of hospitals (academic or nonacademic hospitals) because academic hospitals are generally likely to have more junior trainees. Differences in clinicopathological features may not have caused overestimation of the volume – outcome relationship because endoscopists with less experience may not have attempted ESD for patients with more complicated lesions [22]. Some experienced endoscopists may perform esophageal ESD in low-volume centers as a part-time job. However, such a situation may be rare, and may not significantly affect our results.

Second, the DPC database lacks some important details regarding the clinical outcomes after esophageal ESD, such as the rates of en bloc resection, curative resection, and local recurrence. In addition, the database does not include information on the occurrence of post-ESD stenosis or long-term mortality. Third, recorded diagnoses in inpatient databases are generally less-well validated than those in planned prospective cohorts or registries.

In conclusion, based on a national administrative database, we verified that the proportion of perforation and perforation-related disorders following esophageal ESD is low, and that a linear association exists between higher hospital case volume and lower rates of adverse events following esophageal ESD.

Acknowledgment

Competing interests

None

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