Diseases of the Esophagus (2017) **30**, 1–8
DOI: 10.1093/dote/dox057

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Changes in esophageal motility after endoscopic submucosal dissection for superficial esophageal cancer: a high-resolution manometry study

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SUMMARY. **The effect of endoscopic submucosal dissection (ESD) on esophageal motility remains unknown. Therefore, the aim of this study is to elucidate changes in esophageal motility after ESD along with the cause of dysphagia using high-resolution manometry (HRM). This is a before-and-after trial of the effect of ESD on the esophageal motility. Twenty patients who underwent ESD for superficial esophageal carcinoma were enrolled in this study. Patients filled out a questionnaire about dysphagia and underwent HRM before and after ESD. Results before and after ESD were compared. Data were obtained from 19 patients. The number of patients who complained of dysphagia before and after ESD was 1/19 (5.3%) and 6/19 (31.6%), respectively ($P = 0.131$). Scores from the five-point Likert scale before and after ESD were 0.1 ± 0.5 and 1.0 ± 1.6, respectively ($P = 0.043$). The distal contractile integral (DCI) before and after ESD and the number of failed, weak, or fragmented contractions were not significantly different. However, in five patients with circumferential ESD, DCI was remarkably decreased and the frequency of fail, weak, or fragmented contractions increased. Univariate regression analysis showed a relatively strong inverse correlation of ΔDCI with the circumferential mucosal defect ratio $\{P < 0.01$, standardized regression coefficient $(r) = -0.65\}$, the number of stricture preventions ($P < 0.01$, $r = -0.601$), and the number of stricture resolutions ($P < 0.01$, $r = -0.77$). This HRM study showed that impairment of esophageal motility could be caused by ESD. The impairment of esophageal motility was conspicuous, especially in patients with circumferential ESD and subsequent procedures such as endoscopic triamcinolone injection and endoscopic balloon dilatation. Impaired esophageal motility after ESD might explain dysphagia.**

KEY WORDS: **dysphagia, endoscopic submucosal dissection, esophageal cancer, esophageal motility, high-resolution manometry (HRM).**

INTRODUCTION

Endoscopic submucosal dissection (ESD) for esophageal cancer (EC) is a minimally invasive procedure compared with esophagectomy or chemoradiotherapy and it enables en-bloc resection of circumferential EC. Consequently, ESD results in precise histopathological assessment and a low local recurrence rate.[1,2] Although circumferential extension of more than three quarters of the resected lesion for ESD is a risk factor for postoperative strictures of the esophagus,[3,4] procedures to prevent and resolve strictures, such as endoscopic balloon dilatation (EBD), endoscopic triamcinolone injection (ETI), and oral administration of prednisolone have made it possible to avoid postoperative strictures more effectively.[5–7] However, some patients complain of dysphagia after ESD even when postoperative strictures are absent. In those cases, esophageal motility impaired by ESD might be related to the symptoms. Previously, we investigated esophageal motility after ESD using high-resolution manometry (HRM) and found that patients with circumferentially large ESD requiring stricture preventions tended to have

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impaired esophageal motility after ESD, resulting in dysphagia.[8] However, to the best of our knowledge, there are no reports that prospectively compare esophageal motility before and after ESD. Therefore, the aim of this study is to elucidate the esophageal motility before and after ESD and the cause of dysphagia using HRM.

METHODS

Patients

This is a before-and-after trial of the effect of ESD on esophageal motility. Twenty patients who underwent ESD for superficial EC between September 2013 and February 2015 at Niigata University Hospital were enrolled in this study. The study protocol is shown in Figure 1. After enrollment, each patient underwent HRM and filled out a questionnaire on dysphagia before ESD. ESD was performed on admission. When the circumferential extension of the resected lesion was less than three quarters of the esophageal circumference, endoscopy was performed 3 months after ESD. When scarring of the ESD ulcer was confirmed by endoscopy 3 months after ESD, patients underwent a second HRM and filled out the questionnaire again. We defined 'circumferential ESD' as the condition where the resected lesion spanned more than three quarters of the esophageal circumference. In patients who had undergone circumferential ESD, ETI was performed several times until epithelization of the esophageal mucosa without stricture was confirmed or postoperative stricture occurred; this procedure was defined as a stricture prevention. We used triamcinolone acetonide (10 mg/mL) just after ESD, according to our provisional report.[6] We counted the number of stricture preventions and used it in the analysis. Once postoperative stricture occurred, we repeated EBD with a balloon dilator ($\varphi = 18$–20 mm, CRE Fixed Wire Balloon Dilators; Boston Scientific Japan Co., Tokyo, Japan) once a week until the stenosis disappeared. If possible, we added ETI to the laceration made by EBD. These procedures were defined as a stricture resolution. We counted the number of EBD with or without ETI as the number of stricture resolutions. A postoperative stricture was defined when one of the endoscopes used {Q260J, H260, H260Z, H290, H290Z (φ = 9.8–10.8 mm; Olympus)} could not pass through the ESD scar after epithelization of the esophageal mucosa. The disappearance of the postoperative stricture was declared when scaring of the esophagus was confirmed by endoscopy and when one of the endoscopes could pass through the ESD scar. Patients who had circumferential ESD underwent a second HRM and filled out the questionnaire after the disappearance of the postoperative stricture. Patients who had a residual tumor after ESD and underwent additional therapy (surgery, chemotherapy, and/or radiation) were excluded from this study. The patients who could not achieve 10 water swallows during HRM were also excluded from the study. Written informed consent was obtained before enrollment. The study protocol was approved by the Niigata University Institutional Ethics Committee and was carried out in accordance with the Declaration of Helsinki. This study was listed in the UMIN Clinical Trials Registry (UMIN000022890).

ESD procedure

ESD procedures were performed as previously reported using a single-channel upper gastrointestinal

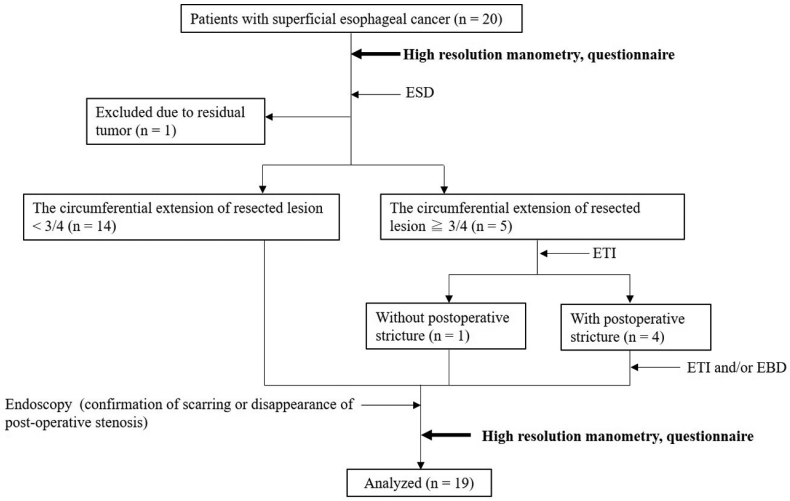

Fig. 1 Flow chart of the participants in the study. Twenty patients were enrolled, underwent HRM, and answered a questionnaire before ESD. After ESD, one patient was excluded because he needed additional therapy due to a residual tumor. Five patients with circumferential ESD (circumferential extent of the resected specimen >3/4) underwent ETI or EBD. After confirmation of scaring of the ulcers and disappearance of the postoperative strictures, patients underwent HRM and answered a questionnaire again. Nineteen patients were included in the analysis.

endoscope (GIF Q260J; Olympus, Tokyo, Japan) and a Hook knife (Olympus, Tokyo, Japan).[9] An electrosurgical current was applied using a standard electrosurgical generator (VIO 300D; ERBE, Tübingen, Germany). The margin of the lesion was circumferentially dotted using the hook knife in the forced coagulation mode (35 W, effect 2). After the injection of a 10% glycerin solution containing 0.005 mg/mL epinephrine into the submucosal layer, a mucosal incision was made using the hook knife in the dry cut mode (60 W, effect 4). Then, the submucosal layer was dissected longitudinally from the oral to anal direction with the hook knife in swift (60 W, effect 4) or spray (60 W, effect 2) coagulation mode. The longitudinal mucosal defect size (mm) and circumferential mucosal defect ratio (%) to the whole circumference of the esophagus were retrospectively evaluated by the endoscopic images from the ESD.

High-resolution manometry protocol

Manometric data were obtained using a combined solid-state manometry assembly with 36 circumferential sensors spaced at 1 cm intervals (Star Medical Inc., Tokyo, Japan). The outer diameter of the catheter was 4.66 mm. After overnight fasting, the patients underwent HRM. The HRM catheter was placed transnasally and the three most distal sensors were positioned in the stomach. After deciding on the catheter position, the catheter was fixed on the nose. A total of 10 water (5 mL) swallows at 20 s intervals were recorded in the left lateral decubitus position. The manometric data were analyzed using the original software (Star Medical, Inc.), which could calculate parameters defined by the Chicago classification version 3.[10] We calculated the distal contractile integral (DCI) and peristalsis break by topography and then classified each contraction as normal, weak, failed, or fragmented. In the Chicago classification, DCI is defined as follows: amplitude × duration × length (mmHg-s-cm) of the distal esophageal contraction of more than 20 mmHg from the proximal to distal pressure troughs in the topography. A weak contraction is defined as a contraction with a DCI > 100 but <450 mmHg-s-cm and failed contraction is defined as a contraction with a DCI < 100 mmHg-s-cm. A fragmented contraction is defined as a contraction with a normal DCI (450–8000 mmHg-s-cm) and a peristalsis break >5 cm in the 20 mmHg isobaric contour. In several reports, weak or failed contractions and fragmented contractions were related to a decline in esophageal function.[10–13] These metrics were used as an indicator of impaired esophageal motility in this study. DCI was calculated in all patients and the number of weak, failed, and fragmented contractions in the 10 swallows was counted. ΔDCI was calculated by subtracting DCI before ESD from DCI after ESD. The results of the HRM were compared before and after ESD.

Symptom assessment

Before HRM, patients were asked to fill out a questionnaire to investigate whether they have dysphagia. The frequency of dysphagia was quantified using a five-point Likert scale (0 = none, 1 = rarely, 2 = several times a month, 3 = several times a week, and 4 = everyday). The scores from the five-point Likert scale were compared before and after ESD.

Statistical analysis

Categorical data were expressed as number (*n*) and percentage (%). Continuous data were expressed as mean ± standard deviation (SD) if normally distributed and as median and range if not normally distributed. The McNemar's chi-square test was used for categorical data and the Wilcoxon signed-rank test was used for numerical data. Univariate linear regression analysis was used to evaluate the correlation of ΔDCI with circumferential mucosal defect ratio, longitudinal mucosal defect size, the number of stricture preventions, and the number of stricture resolutions. Power analysis was performed on the comparison of five-point Likert scale of matched pairs of study subjects in a nonparametric method. We predicted that the standard deviation of difference was 1.0, and the true difference in the mean was 0.75. Therefore, to obtain 80 percent power and detect differences at an alpha level of 5%, 17 samples were needed for this study. After that, considering the occurrence of drop outs, 20 samples were taken as the final sample size. SPSS statistics for Windows, version 21.0 (IBM Corp., Armonk, NY) was used for the statistical analyses. *P*-values < 0.05 were considered statistically significant.

RESULTS

Twenty patients were initially enrolled in this study: one patient was excluded because he needed additional chemoradiation therapy. Finally, 19 patients were included in the analysis. The demographics and ESD results of the 19 patients are summarized in Table 1. The mean age of the patients was 70.2 ± 5.6 years and 18 of them were men. The tumors were located in the upper thoracic esophagus in six patients, the middle thoracic esophagus in 12 patients, and the lower esophagus in 1 patient. The median circumferential mucosal defect ratio (range) and the median longitudinal mucosal defect size (range) were 50% (40%–100%) and 32 mm (16–72 mm), respectively. Histopathological results were squamous cell carcinoma in all of the cases. The invasion depth in 12 patients was epithelium and in the remaining seven

Table 1 Demographics and ESD results

Patients	
Total number	19
Male/female	18/1
Age, mean ± SD (year)	70.2 ± 5.6
ESD results	
Location (Ce/Ut/Mt/Lt/Ae)	0/6/12/1/0
The number of patients with circumferential ESD	5
Circumferential mucosal defect ratio, median (range) (%)	50 (40–100)
Longitudinal mucosal defect size (all), median (range) (mm)	32 (16–72)
In patients with circumferential ESD	52 (22–72)
In patients without circumferential ESD	32 (16–40)
Invasion depth, EP/LPM/MM	12/7/0
Histopathological result (SCC/Adenocarcinoma)	19/0
Number of patients with stricture preventions, n/N (%)	5/19 (26.3)
Number of patients with stricture resolutions, n/N (%)	2/19 (10.5)

ESD, endoscopic submucosal dissection; SCC, Squamous cell carcinoma.

Table 2 Frequency of dysphagia and results of HRM before and after ESD

	Before ESD	After ESD	*P*-value
Symptoms			
Number of patients with dysphagia, n/N (%)	1/19 (5.3)	6/19 (31.6)	0.131*
Five-point Likert scale, mean ± SD (range)	0.1 ± 0.5 (0–2)	1.0 ± 1.6 (0–4)	0.043**
The results of HRM			
DCI, median (range), (mmHg-s-cm)	1681.1 (430–6673.6)	1511.0 (587.8–5850.1)	0.091**
ΔDCI, median (range)	286 (−4861.2–1730.7)		
Frequency of weak, failed, or fragmented			
Weak, failed, or fragmented contractions in 10 swallows, mean ± SD (range)	2.1 ± 2.9 (0–10)	2.6 ± 3.0 (0–10)	0.287**

*McNemar's chi-square test; **Wilcoxon signed-rank test.
ΔDCI = (DCI after ESD) – (DCI before ESD)
DCI, distal contractile integral; ESD, endoscopic submucosal dissection.

patients was lamina propria muscularis. Five of 19 patients (26.3%) had circumferential ESD. Three of them underwent only stricture preventions, which successfully prevented post-operative stricture. In contrast, two of them developed postoperative stricture even after stricture preventions and then underwent stricture resolutions.

The frequency of dysphagia and HRM results before and after ESD is shown in Table 2. Only one patient (5.3%) complained of dysphagia before ESD and six patients (31.6%) complained of dysphagia after ESD. However, there was not a statistically significant difference in the emergence of dysphagia ($P = 0.131$). The mean five-point Likert scale score before and after ESD was 0.1 ± 0.5 and 1.0 ± 1.6, respectively, and there was a statistically significant difference between the scores ($P = 0.043$) (Fig. 2A). The DCI (range) before and after ESD was 1681.1 (430–6673.6) mmHg-s-cm and 1511.0 (587.8–5850.1) mmHg-s-cm, respectively (Fig. 2B). Although there was no statistically significant difference before and after ESD, the value of DCI tended to decrease after ESD ($P = 0.091$). The frequency of weak, failed, or fragmented contractions before and after ESD was 2.1 ± 2.9 and 2.6 ± 3.0 times, respectively, and there was no statistically significant difference between the frequencies ($P = 0.287$) (Fig. 2C). The median ΔDCI (range) was −286 (−4861.2–1730.7). Univariate regression analysis showed a relatively strong inverse correlation of ΔDCI with the circumferential mucosal defect ratio $\{P < 0.01$, standardized regression coefficient $(r) = -0.65\}$, the number of stricture preventions ($P < 0.01$, $r = -0.601$), and the number of stricture resolutions ($P < 0.01$, $r = -0.77$) (Fig. 3). Although longitudinal mucosal defect size tended to be related with ΔDCI, it was not statistically significant ($P = 0.054$, $r = -0.45$). The details of the five patients with circumferential ESD are shown in Table 3. Four of the patients developed dysphagia and their five-point Likert scale scores increased after ESD. The values of DCI decreased in all patients and the frequency of weak, failed, or fragmented contractions increased after ESD in four patients. Representative cases with circumferential ESD (case No. 4 and 1) are shown in Figures 4 and 5, respectively. Both cases showed impairment of esophageal peristalsis and developed pressurization in HRM after ESD.

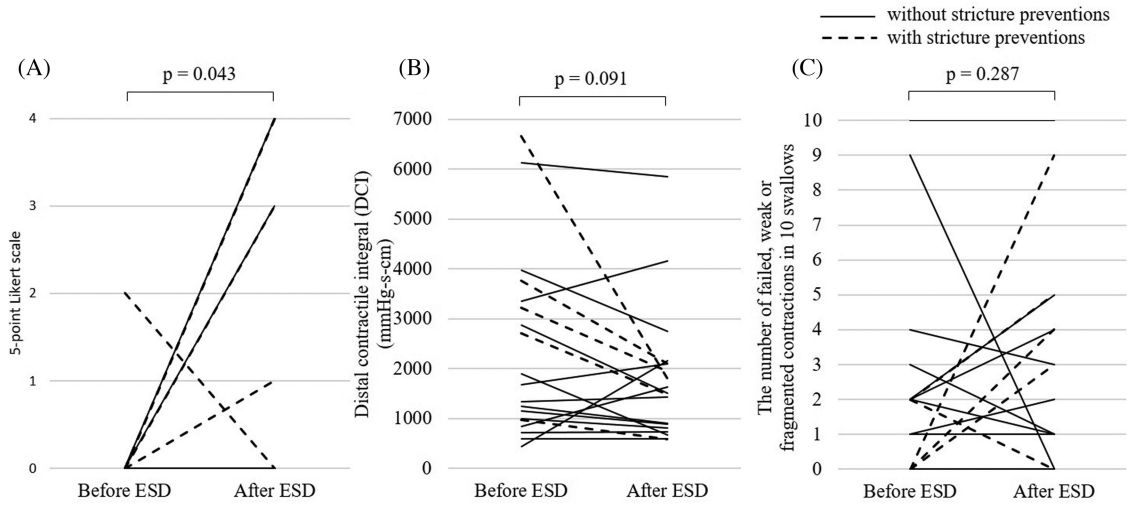

Fig. 2 Five-point Likert scale scores significantly increased after ESD (A). Although there was no statistically significant difference in the scores, DCI tended to decrease after ESD. In the five patients with circumferential ESD, DCI decreased remarkably (B). Regarding the number of failed, weak, or fragmented contractions, there were no definitive differences between before and after ESD. However, in four of the five patients with circumferential ESD, the frequency of these contractions increased (C). Several lines are overlapping in these graphs. *P*-values were calculated by the Wilcoxon signed-rank test.

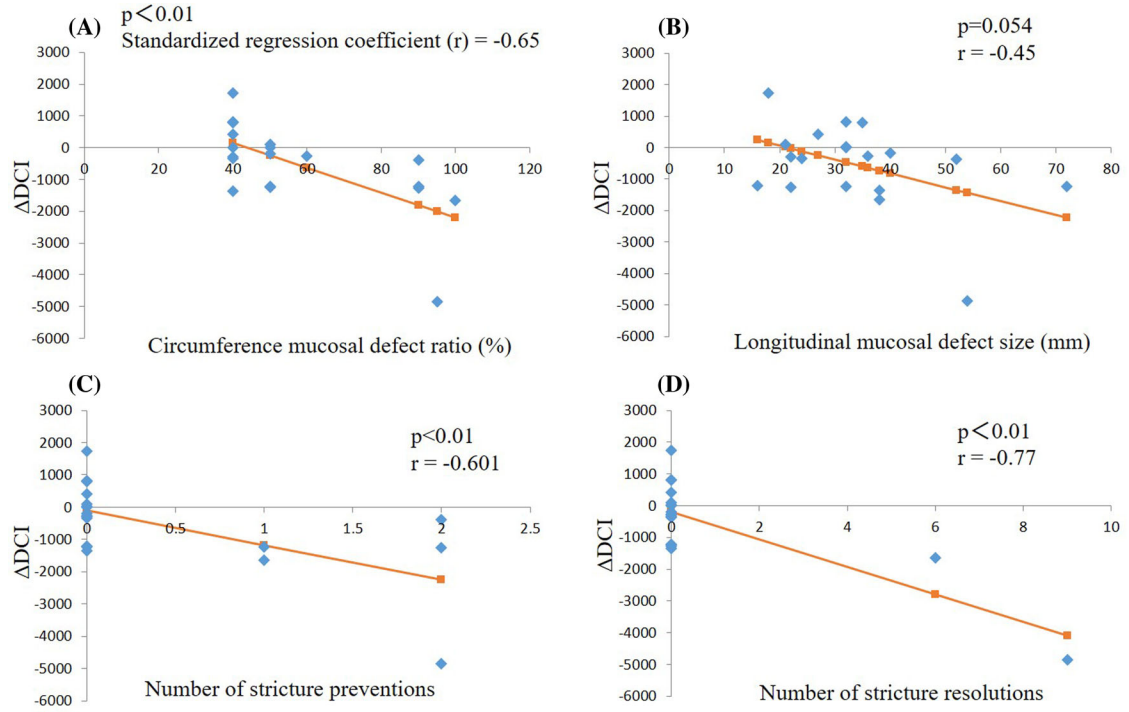

Fig. 3 Univariate regression analysis revealed a relatively strong inverse correlation of ΔDCI with circumferential mucosal defect ratio $\{P < 0.01$, standardized regression coefficient $(r) = -0.65\}$ (A), the number of stricture preventions ($P < 0.01$, $r = -0.601$), (C) and the number of stricture resolutions ($P < 0.01$, $r = -0.77$) (D). Although longitudinal mucosal defect size tended to be related with ΔDCI, it was not statistically significant ($p = 0.054$, $r = -0.45$) (D).

DISCUSSION

In this study, DCI tended to decrease and the frequency of weak, failed, or fragmented contractions tended to increase after ESD. These tendencies were remarkable, especially in the five patients who underwent circumferential ESD. In all patients, the DCI value decreased and in four patients, the number of weak, failed, or fragmented contractions increased after ESD. Furthermore, univariate regression analysis showed a significant inverse correlation of ΔDCI with the circumferential mucosal defect ratio, stricture preventions, and stricture resolutions, although longitudinal mucosal defect size was not significantly correlated with ΔDCI. These results indicate that circumferential ESD and subsequent stricture

Table 3 Details of the five patients with stricture preventions

Case	Age	Sex	Circumferential mucosal defect ratio (%)	Longitudinal mucosal defect size (mm)	Number of stricture preventions	Number of stricture resolutions
1	57	M	100	38	1	6
2	71	M	90	52	2	0
3	65	M	90	72	1	0
4	81	F	95	54	2	9
5	65	M	90	22	2	0

Five-point Likert scale	DCI	Frequency of weak, failed, or fragmented contractions
Before/after ESD	Before/after ESD	Before/after ESD
0/4	3763.0/2110.5	0/3
0/4	966.4/587.8	2/5
0/3	2710.0/1483.4	2/0
0/1	6673.6/1812.4	5/9
2/0	3220.0/1955.0	0/4

DCI, distal contractile integral; EBD, endoscopic balloon dilatation; ESD, endoscopic submucosal dissection; ETI, endoscopic triamcinolone injection.

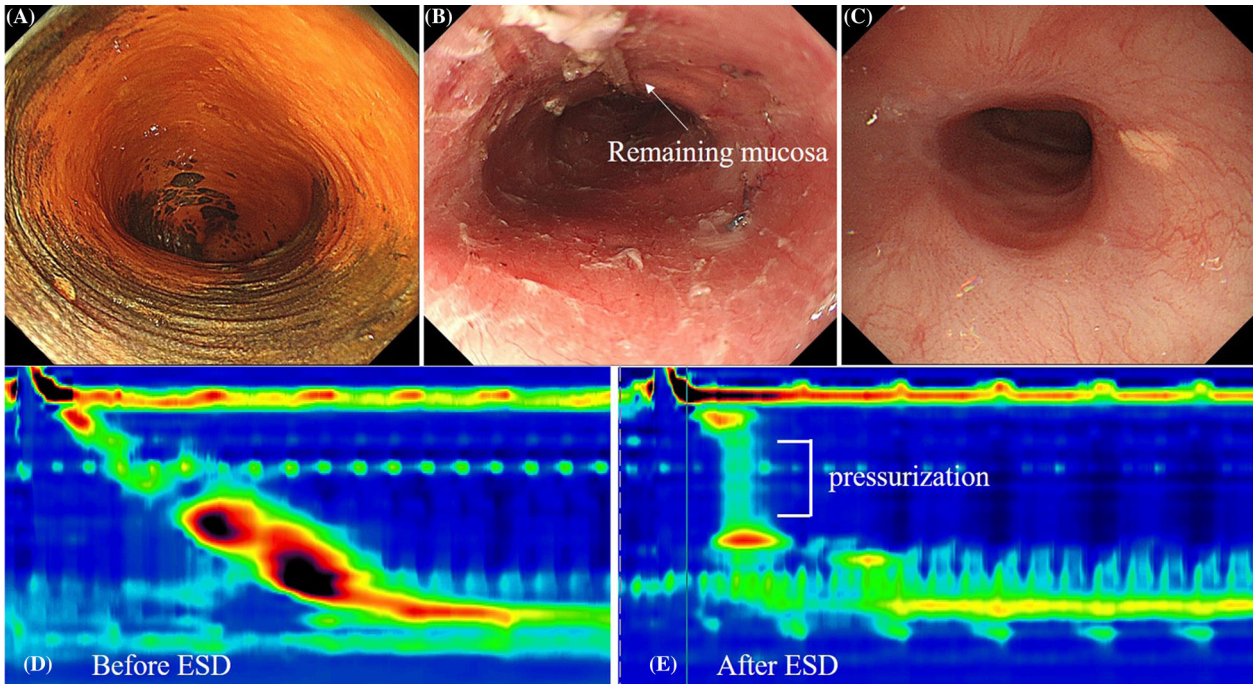

Fig. 4 An 81-year-old woman (No. 4 in Table 3) was diagnosed with superficial esophageal cancer that was spreading semi-circumferentially (A). She underwent ESD and only a tiny mucosa remained after the resection (B). She underwent stricture prevention twice and stricture resolution nine times. After these procedures, the endoscope could pass through the scar although a slight stricture remained (C). Before ESD, relatively strong contractions were observed (DCI: 6673.6 mmHg-s-cm) and the number of failed, weak, or fragmented contractions was 5 out of 10 swallows (D). After ESD, DCI decreased remarkably (DCI: 1812.4 mmHg-s-cm) and 9 of 10 contractions were failed, weak, or fragmented, indicating esophageal motility was impaired after ESD. Furthermore, pressurization appeared after ESD (E).

preventions and resolutions could impair esophageal motility. The reason the correlation of longitudinal mucosal defect size with ΔDCI was weaker than that with circumferential mucosal defect ratio remains unknown. Our previous report also showed that the circumferential mucosal defect ratio was more strongly correlated with impaired esophageal motility than longitudinal mucosal defect size.[8] There are Meissner's plexus in the submucosal layer and Auerbach's plexus in the proper muscle layer, which are responsible for esophageal peristalsis.[14] It is reasonable to consider Meissner's plexus is damaged by ESD because we resect submucosal layer during the procedure. Furthermore, Honda *et al.* reported that ESD could damage myenteric nerve plexus in animal models, which might also occur in humans.[15,16] Therefore, impaired esophageal motility after ESD might derive from damage to the nerve plexus, including Meissner's and Auerbach's plexus. Since the esophagus is columnar construction, the undamaged nerve plexus located in the same height of the esophagus where the nerve plexus was damaged by ESD might

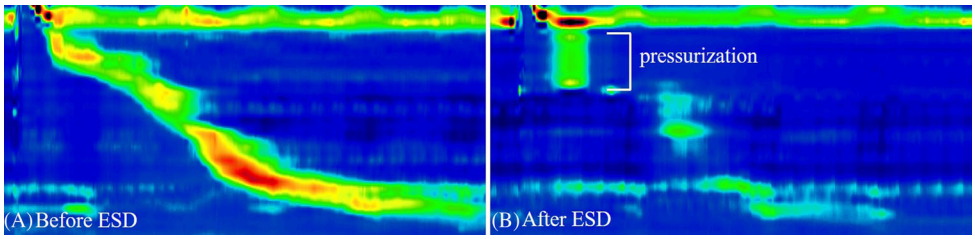

Fig. 5 This is another case of a patient with circumferential ESD and stricture resolutions (No. 1 in Table 3). Before ESD, esophageal peristalsis was within normal range. After ESD, DCI decreased and pressurization appeared just like in case No. 4. He developed frequent dysphagia even after postoperative stricture disappeared.

compensate for the damaged nerve plexus even when the damage to the nerve plexus is longitudinally extensive. However, if circumferential ESD is performed, most of the nerve plexus in the same height of the esophagus where ESD was performed could disappear, resulting in the disappearance of the continuity of the nerve plexus. As a result, compensation for the damaged nerve plexus could not occur, which might explain why the circumferential mucosal defect ratio was more strongly related with impaired esophageal motility than longitudinal mucosal defect size.

With regard to symptoms, the five-point Likert scale scores significantly increased after ESD, especially in patients who underwent circumferential ESD, indicating impaired esophageal motility resulted in dysphagia. These results are consistent with previous reports.[8,17] To the best of our knowledge, this is the first report to prospectively investigate esophageal motility before and after ESD.

Patients who have circumferential ESD usually have to undergo ETI and EBD to prevent or resolve postoperative strictures. We found that stricture preventions and resolutions were significantly correlated with the change in the DCI value; therefore, it is necessary to consider the mechanism of the effects of these procedures on esophageal motility. Since we injected triamcinolone into the remaining submucosal layer on the ulcer base, the direct effect of this procedure on the esophageal muscle layer would be slight. Furthermore, triamcinolone prevents the migration and activation of inflammatory cells and fibroblasts, which did not seem harmful to the muscular layer.[6,18] Although ETI does not theoretically seem to impair esophageal motility, our study revealed a significant correlation between ΔDCI and stricture preventions. Since ETI was mainly used for stricture preventions, the circumferential mucosal defect ratio was deeply related to ETI. Therefore, we assumed that our results were derived from the confounding factor between circumferential mucosal defect ratio and stricture preventions. In contrast, EBD could damage the esophageal muscle layer by making a deep laceration. In this study, two of the five patients who had circumferential ESD underwent EBD as stricture resolution and their decline in DCI values or increase in weak, failed, or fragmented contractions was conspicuous. Univariate regression analysis showed a strong inverse correlation between ΔDCI and stricture resolutions. Furthermore, HRM results of these two patients showed pressurization in the topography (Figs. 4,5), indicating that the distensibility of their esophagus was impaired due to the fibrosis by repeated stricture resolutions, and their esophageal wall turned stiff. We considered that not only the decline of esophageal peristalsis, but also the esophageal stiffness could result in dysphagia. The number of patients with stricture resolutions was small and should be considered a confounding factor with the circumferential mucosal defect ratio when interpreting the results. Nevertheless, considering the damage to the esophageal wall by EBD, it is reasonable to conclude that EBD is related to the esophageal motility impairment.

For now, it is difficult to treat patients who have dysphagia after ESD due to impaired esophageal motility. Regarding the treatment of dysmotility of the esophagus, there are several prokinetics available in Japan, including mosapride, baclofen, and acotiamide. Mosapride is reported to improve esophageal motility in patients with ineffective esophageal motility.[19,20] Baclofen, a GABA B agonist, also affects esophageal motility and improves symptoms in patients with gastroesophageal reflux diseases.[21] Furthermore, acotiamide normalizes impaired lower esophageal sphincter relaxation in patients with esophagogastric junction outflow obstruction although it does not affect esophageal motility in healthy subjects.[22,23] Although the effects of these drugs on esophageal motility were not striking according to previous reports,[19–23] they have the potential to improve esophageal motility in patients who undergo circumferential ESD and might be helpful for treatment.

There are several limitations in this study. First, the number of patients who underwent circumferential ESD was small. Although the motility of the esophagus in patients who underwent circumferential ESD tended to be impaired and dysphagia emerged in most patients, a larger sample size is needed in order to make definitive conclusions. Second, although we speculated that esophageal motility was impaired due to damage to the muscle layer or myenteric nerve plexus, it is difficult to confirm that these changes

actually occurred in the human body. Therefore, it remains unknown why impairment of esophageal motility occurs after ESD. Third, although one patient already had complained of dysphagia before ESD, it is difficult to elucidate the mechanism of this symptom. The invasion depth of his lesion was the epithelium. Therefore, it is unlikely that the tumor affected esophageal motility, which resulted in dysphagia. We speculate that the psychological effect due to the esophageal carcinoma might be related to this patient's dysphagia.

CONCLUSIONS

This HRM study showed that impairment of esophageal motility could be caused by ESD. The impairment of esophageal motility was conspicuous, especially in patients with circumferential ESD and subsequent procedures such as ETI and EBD. Impaired esophageal motility after ESD might explain dysphagia.

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