

[ORIGINAL ARTICLE]

Esophageal Diverticulum - Indications and Efficacy of Therapeutic Endoscopy

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Abstract:

Objective Esophageal diverticulum is rare, and the concomitance of esophageal motility disorders (EMDs) and the efficacy of novel endoscopic treatment have not been investigated in Japan.

Methods An examination including high-resolution manometry (HRM) was performed for patients with both EMDs and epiphrenic diverticulum. EMD-related epiphrenic diverticulum and Zenker's diverticulum were treated using salvage peroral endoscopic myotomy (s-POEM) and endoscopic diverticulotomy, respectively.

Results Six cases of epiphrenic diverticulum were diagnosed in this study. Among 125 patients with achalasia and spastic disorders, concomitant epiphrenic diverticulum was observed in 4 (3.2%). Of these, three showed a normal lower esophageal sphincter pressure on HRM, although gastroscopy and esophagography revealed typical findings of an impaired lower esophageal sphincter relaxation. These four patients were successfully treated with s-POEM, and the Eckardt score improved from 6.3 to 0.25 at 32.5 (range: 13-56) months of follow-up, with equivalent treatment efficacy to that observed for achalasia and spastic disorders without epiphrenic diverticulum. In contrast, the two remaining cases of epiphrenic diverticulum had normal esophageal motility. Six cases of Zenker's diverticulum were diagnosed, and endoscopic diverticulotomy was successfully performed in all. The dysphagia score decreased from 2.8 to 0.17 at 14.8 (range: 2-36) months of follow-up. Overall, 12 endoscopic treatments were performed for esophageal diverticulum; no adverse events were observed.

Conclusion In epiphrenic diverticulum patients, concomitant EMDs are not rare and should be carefully diagnosed. A normal lower esophageal sphincter pressure on HRM does not always mean a normal lower esophageal sphincter relaxation. S-POEM and endoscopic diverticulotomy are effective minimally invasive treatment options for EMD-related epiphrenic diverticulum and Zenker's diverticulum.

Key words: Zenker's diverticulum, epiphrenic diverticulum, peroral endoscopic myotomy, endoscopic diverticulotomy, high-resolution manometry

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Introduction

Esophageal diverticulum is benign but can be devastating to a patient's quality of life as it expands to cause esophageal symptoms, such as dysphagia and regurgitation (1, 2). Complications, such as aspiration pneumonia, are sometimes

critical. At present, esophageal diverticulum is categorized as epiphrenic diverticulum (ED) or Zenker's diverticulum (ZD), as Rokitansky diverticulum (RD), which is a traction-type diverticulum caused by severe infection such as pulmonary tuberculosis, is rarely observed. Furthermore RD is basically tracted upwards; retention of the food or liquid in the RD is rare and is generally non-symptomatic, so treatment is con-

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sidered unnecessary (3). Consequently, symptomatic ED and ZD are currently of concern in this field.

For many years, diverticulum-resection-based surgery has been developed as a standard treatment for ED and ZD. However, most of the esophagus is in the mediastinum, which increases the difficulty of ED surgery. In addition, the greatest concern for the cervical approach to ZD is complications, such as injury to the nerves that control swallowing and speaking, and a conspicuous cutaneous scar remains.

On the other hand, 43-100% of ED cases were reported to be related to esophageal motility disorders (EMDs) (1, 4), so peroral endoscopic myotomy (POEM) was developed as a minimally invasive treatment for EMDs such as achalasia and spastic disorders (5). In addition, flexible endoscopic diverticulotomy using the endoscopic submucosal dissection (ESD) technique was developed as a minimally invasive intervention for ZD (2, 6). The shift in perspective concerning the treatment endpoint from removing the diverticulum to being symptom-free and advances in endoscopic techniques, such as POEM and ESD, have led to breakthroughs in ED and ZD treatment.

However, reports regarding ED and EMDs based on high-resolution manometry (HRM) are scarce because both disorders are rare, and HRM was only recently developed (7). Furthermore, the efficacy of endoscopic treatment for ED and ZD has not been investigated in Japan.

The present study assessed the relationship between ED and EMDs using HRM and clarified the safety and long-term efficacy of endoscopic treatment for ED and ZD.

Materials and Methods

Patients with esophageal diverticulum from 2014 to 2020 were retrospectively analyzed. The study was approved by the ethics committee of our institution and was conducted according to the tenets set by the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out system on a website. The analysis of ZD and endoscopic diverticulotomy was also performed prospectively following the approval of the ethics committee.

All authors had access to the study data and reviewed and approved the final manuscript.

The analysis of ED and concomitant EMDs

Patients suspected of having EMDs due to the presence of esophageal symptoms without any organic disorders were subjected to an HRM examination. Patients with symptomatic ED also underwent HRM to investigate concomitant EMDs. The HRM diagnosis was based on the Chicago classification criteria v3 (8) and a comprehensive evaluation of gastroscopy and esophagography findings. The integrated relaxation pressure (IRP) is an established parameter for the lower esophageal sphincter (LES) pressure; it was measured within a 10-second timeframe and the subsequent 4 seconds during which the e-sleeve value is the lowest, with an IRP \geq 26 defined as an elevated pressure of the LES (9). Gas-

troscopy and esophagography were also performed to comprehensively evaluate the impaired relaxation of LES. In addition, secondary EMDs, such as eosinophilic esophagitis and reflux esophagitis were excluded. The Eckardt score was used to assess the symptom severity and treatment efficacy, being the sum of the four-point scores of dysphagia, regurgitation, chest pain, and weight loss. A higher score reflects more severe symptoms of EMDs (maximum: 12), while a lower score indicates milder symptoms (minimum: 0) (10).

Patients with EMD-related ED were subjected to s-POEM, which was performed as previously reported (11), with endoscopic myotomy on the different longitudinal lines of the ED to relax impaired LES. A pathologic thick LES bundles was completely dissected.

The ZD assessment and treatment

The diagnosis of ZD was based on gastroscopy and esophagography findings. The Dakkak/Bennett dysphagia score (DBDS) was used for the assessment of symptom severity and treatment efficacy; a higher DBDS reflects more severe symptoms of ZD (maximum: 4), while a lower score indicates milder symptoms (minimum: 0) (12).

Endoscopic diverticulotomy was performed as previously reported (13). Under general anesthesia, a diverticuloscope was inserted, and the edge of one flap was inserted into the true esophageal lumen, with the other flap inserted to the bottom of the ZD. Thereafter, septal wall myotomy was conducted. After successful direct diverticulotomy with a diverticuloscope, the Z-POEM technique was also used, and the exposed septum was dissected after the endoscope was inserted into the submucosal layer (14).

Statistical analyses

The Mann-Whitney U test was used to analyze the relationship between the patient characteristics and HRM findings. P values <0.05 were considered statistically significant for all statistical analyses. All such analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (15).

Results

Characteristics of ED insidious in achalasia, esophagogastric junction outflow obstruction, and spastic disorders

Six cases of ED were diagnosed between 2014 and 2020. A total of 125 patients were diagnosed with primary EMDs, including achalasia (n=105), and other esophageal motility disorders (n=20) including Esophagogastric junction outflow obstruction (EGJOO), Jackhammer esophagus, and distal

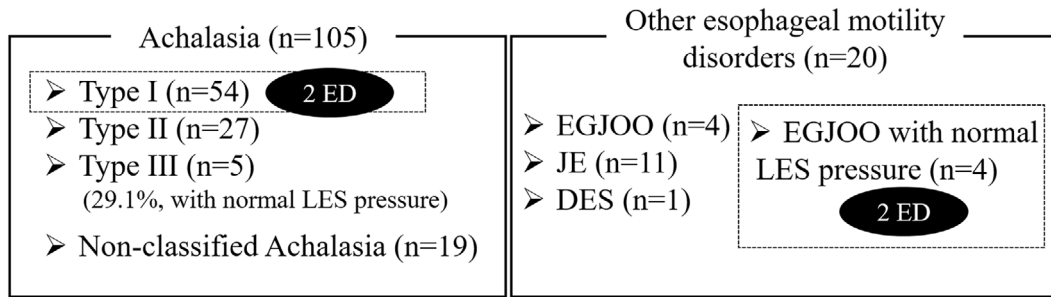


Figure 1. Epiphrenic diverticulum (ED) from the perspective of esophageal motility disorders. ED was observed in 4 (3.2%) out of 125 cases of achalasia, EGJOO, and spastic disorders.

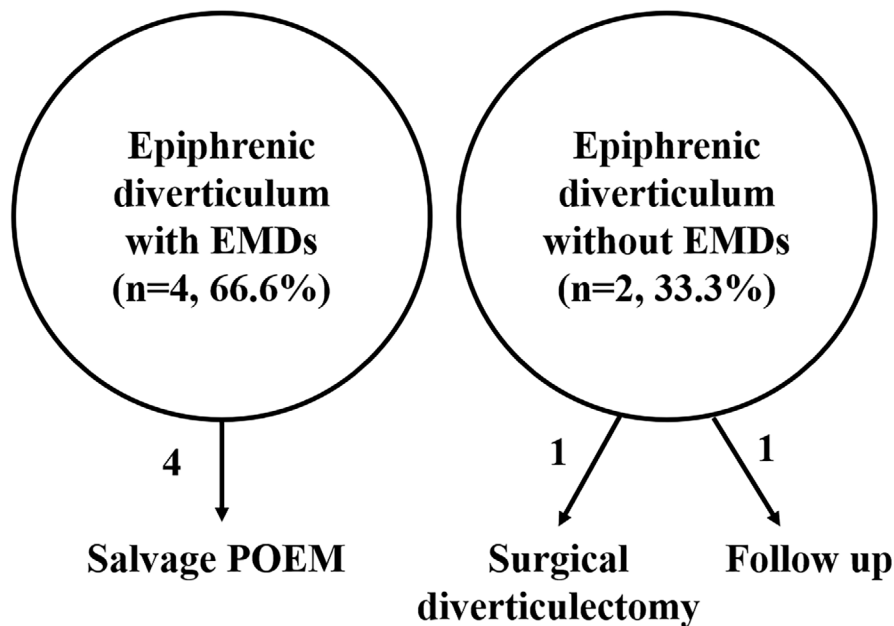


Figure 2. Esophageal motility disorders (EMDs) from the perspective of epiphrenic diverticulum (ED). EMDs were seen in 4 (66.6%) out of 6 EDs, which was treated with salvage peroral endoscopic myotomy to relax the impaired lower esophageal sphincter.

esophageal spasm. (Fig. 1). Type I, II, III, and typical endoscopic and esophagography findings of achalasia were present in 54, 27, 5, and 19 cases, respectively. Among 86 cases of Type I-III achalasia, excluding the 7 cases of prior intervention (Heller myotomy and balloon dilation), 29.1% (23 cases) had a normal IRP (<26). EGJOO, Jackhammer esophagus, and distal esophageal spasm were diagnosed in 4, 11, and 1 case, respectively. Furthermore, EGJOO with a normal IRP was diagnosed in two cases based on an impaired LES pattern on HRM. In these cases, on gastroscopy, the lower edge of the esophageal palisade vessels was not visible after deep inspiration, and the endoscope showed severe resistance through the LES. Esophagography revealed a bird-beak appearance, indicating impaired LES relaxation (Fig. 2) (Table 1).

In contrast, two cases of EDs were not related to EMDs. These ED cases had within-normal peristalsis with an IRP of <26, no bird-beak appearance visible on esophagography, and the lower edge of palisade vessels was clearly visible.

The Eckardt score was lower in these two patients than in those with EMD-related ED. One was treated with surgical resection with fundoplication, and the other was followed up due to mild symptoms (Fig. 2).

In summary, 4 cases of ED (Type I achalasia=2; EGJOO=2) were identified among 125 patients with primary EMDs (comorbidity rate of ED per EMDs: 3.2%). The concomitant rate of EMDs with ED was 66.6% (4 out of 6). Right-sided ED (n=4) was more common than left-sided ED (n=2).

Long-term efficacy of salvage POEM for EMD-related ED

Four patients with EMD-related ED received s-POEM, and the Eckardt score improved from 6.3 to 0.25 at an average of 32.5 (range: 13-56) months of follow-up (Fig. 3). The success rate (Eckardt score ≤ 3) was 100%. Recurrence of symptoms was not observed during the follow-up period.

Treatment efficacy of POEM was compared between achalasia and EGJOO patients with and without ED (control

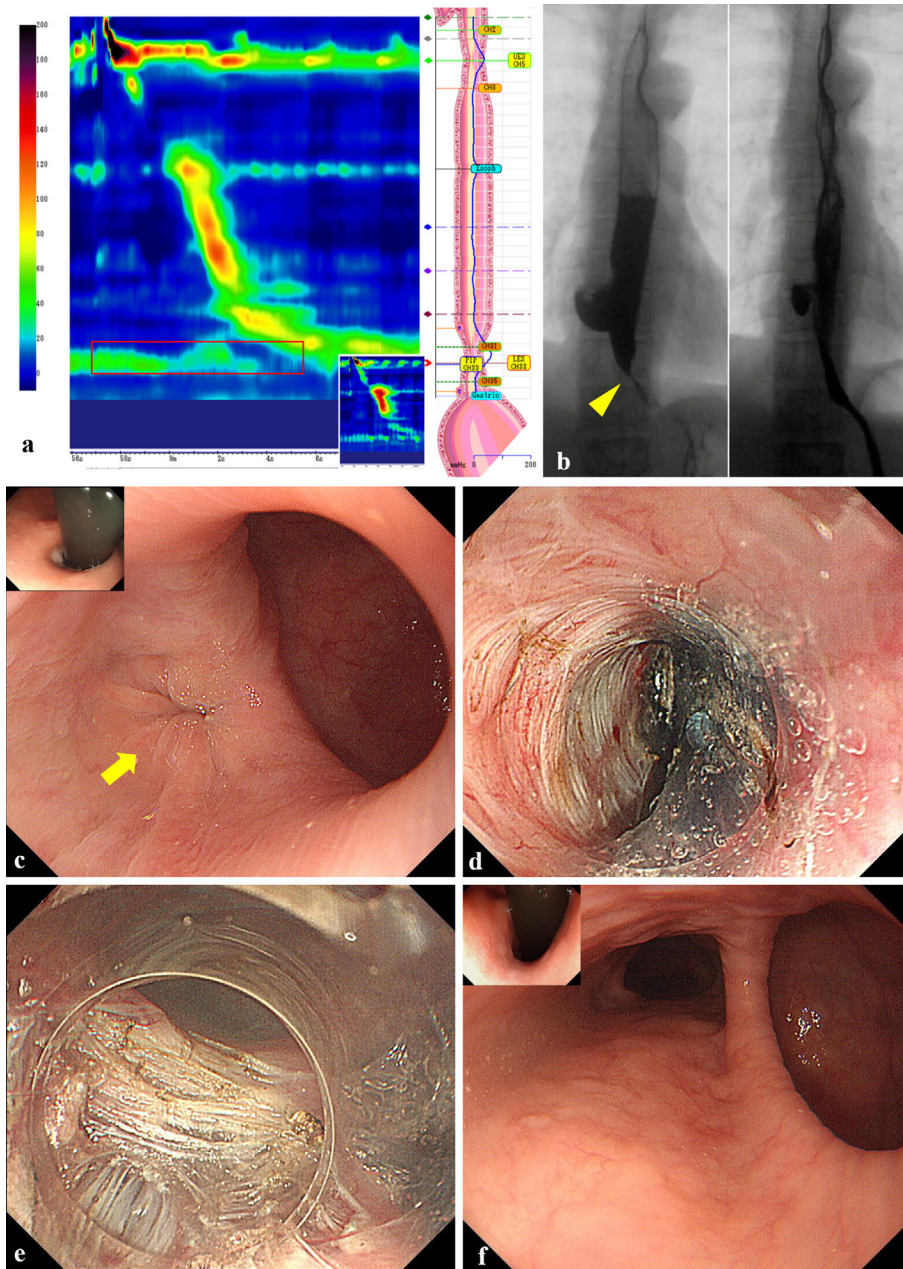


Figure 3. (a) A case of EGJOO on HRM (IRP: $15.7 < 26$, red box). The inset reveals the HRM findings after salvage peroral endoscopic myotomy (s-POEM). (b) Left: Esophagography showing a bird-beak appearance (yellow triangle) and remnant contrast medium in the esophagus. Right: After s-POEM, the flow through EGJ improved with the relaxation of the LES. (c) The lower edge of palisade vessels was not visible (yellow arrow) in the case of EGJOO with ED. The inset is an endoscopic view of the reversed position, revealing an impaired LES relaxation. (d) S-POEM was performed. (e) Myotomy was performed to relax the impaired LES. (f) After s-POEM, the released EGJ was visible (inset, an endoscopic view of the reversed position from the gastric side).

group). The Eckardt score in achalasia and EGJOO patients decreased to the same level at 0.25 and 0.45, respectively ($p = 0.49$), whereas the IRP decreased to approximately 9.27 and 9.53, respectively ($p = 0.91$) (Supplemental material).

Long-term efficacy of endoscopic diverticulectomy for ZD

Six patients were diagnosed with ZD (3 women, average 62.2 years old) based on esophagography and endoscopy

findings (Table 2). The long diameter and septum length of the ZD were calculated as 31.6 mm and 20.9 mm, respectively (Fig. 4) (13). All received endoscopic diverticulotomy, and the septum was completely dissected (Fig. 5). The average time of the procedure was 31.2 minutes, and the mean post-procedure hospital stay was 3.5 days with no adverse events observed. The DBDS improved from 2.8 to 0.17 at an average of 14.8 (range: 3-36) months of follow-up.

Table 1. Patients' Characteristics of Epiphrenic Diverticulum.

Case	M/F	Age (years)	Eckardt score ^a	HRM	IRP (on HRM)	Esophagography	Gastroscopy	Side of ED	Treatment
1	F	84	2/2/0/0	EGJOO	15.5	Bird-beak appearance	Esophageal palisade vessels: not visible	Right	s-POEM
2	M	87	3/2/0/3	Type I achalasia	24	Bird-beak appearance	Dilated esophagus, esophageal palisade vessels: not visible	Right	s-POEM
3	F	63	1/0/3/3	EGJOO	15.7	Bird-beak appearance	Esophageal palisade vessels: not visible	Right	s-POEM
4	F	66	3/1/0/2	Type I achalasia	35.3	Sigmoid esophagus, bird-beak appearance	Esophageal palisade vessels: not visible	Left	s-POEM
5	F	49	2/0/0/0	Within normal	13.8	Non-dilated	Esophageal palisade vessels: visible	Right	Surgical diverticulectomy, fundoplication
6	F	45	1/0/0/0	Within normal	23.2	Non-dilated	Esophageal palisade vessels: visible	Left	Follow-up

^a Eckardt score: dysphagia/regurgitation/chest pain/weight loss. M: male, F: female, HRM: high-resolution manometry, IRP: integrated relaxation pressure, EGJOO: esophagogastric junction outflow obstruction, ED: epiphrenic diverticulum, s-POEM: salvage peroral endoscopic myotomy: myotomy is performed for esophageal motility disorder while epiphrenic diverticulum remains.

Table 2. Patients' Characteristics of Zenker's Diverticulum and Clinical Course of Endoscopic Diverticulotomy.

Case	M/F	Age (years)	DBDS	Size of ZD, mm (long diameter, septum)	Procedure time of endoscopic diverticulotomy, min	Hospital stay after endoscopic diverticulotomy, days	DBDS after endoscopic diverticulotomy
1	F	39	3	24.1, 17.7	26	6	0
2	M	78	3	23.6, 18	27	3	0
3	M	78	2	39.1, 24.6	29	3	1
4	F	46	3	44.5, 22.8	23	3	0
5	F	53	3	19.6, 11	30	3	0
6	M	73	3	38.6, 31.5	52	3	0

M: male, F: female, DBDS: Dakkak/Bennett dysphagia score, ZD: Zenker's diverticulum

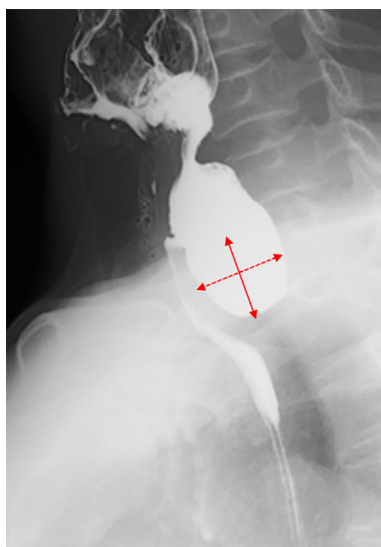


Figure 4. Zenker's diverticulum on esophagography (solid line: length of the septum, dotted line: width).

Discussion

This study revealed the characteristics of Japanese patients with concomitant ED and HRM-based EMDs and the long-term efficacy of endoscopic treatment for esophageal diverticulum including ZD. Four out of 6 ED cases (66.6%) were related to EMDs with achalasia (2 cases) and EGJOO (2 cases), and remarkably, 3 out of those 4 cases had within-normal IRP values. Therefore, a complementary diagnosis using gastroscopy and esophagography is necessary, particularly in cases where HRM shows a normal IRP.

In achalasia, a variant with a normal IRP was reported (16), and the groups with elevated and normal IRP values showed equal treatment efficacy. Therefore, they are considered to be in the same disease category (17). In our cohort, 29.1% of patients were categorized into this group with a normal IRP.

In pathophysiology, there are two populations of myenteric plexus neurons that cause a variant of achalasia: excitatory cholinergic neurons and inhibitory neurons using nitric

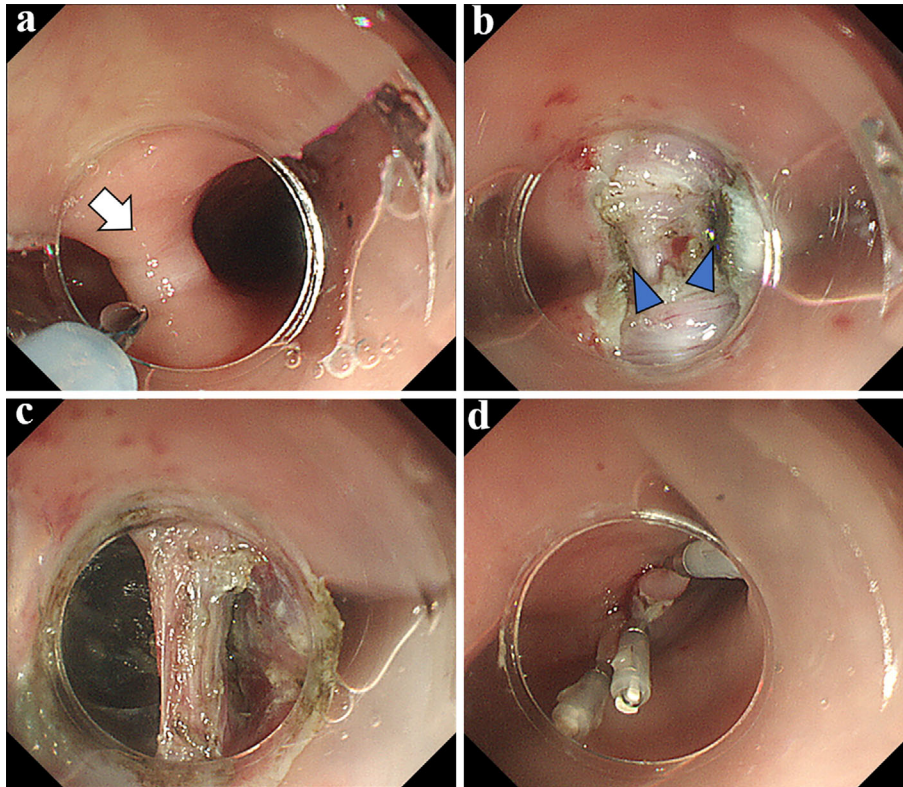


Figure 5. Endoscopic diverticulotomy for Zenker's diverticulum (Z-POEM). (a) Saline was injected into the mucosa of the septum. (b) A mucosal incision was performed under direct visualization; submucosal tunnels were then created at both the diverticulum and esophageal sides (blue triangles). (c) The exposed septum was dissected, extending until the longitudinal muscle bundles of the esophagus were observed. (d) Mucosal entry was closed using through-the-scope clips.

oxide and vasoactive intestinal polypeptide as neurotransmitters (18). Therefore, we may reasonably consider that there are two subgroups of EGJOO: an elevated IRP and normal IRP group. In achalasia, no normal peristalsis was observed on HRM; therefore, we may easily suspect achalasia even when the IRP is normal. In contrast, EGJOO patients occasionally show within-normal peristalsis with every swallow, similar to a healthy condition, which makes it difficult to suspect EGJOO. In such cases, the HRM patterns of impaired LES relaxation and findings on gastroscopy and esophagography should be carefully assessed to differentiate concomitant EGJOO when making treatment decisions, as diverticulectomy alone is considered insufficient for EDs concomitant with EMDs.

The Chicago classification criteria v4 (19) were recently published, also referencing the importance of supporting tests, such as esophagography, for the EGJOO diagnosis. The symptom score may be useful for the differential diagnosis; concomitant EMDs increase disease severity, and chest pain and weight loss may be rather specific for EMDs. Our study showed that s-POEM for EMDs with EDs had sufficient efficacy compared to POEM for EMDs, although EDs persisted in the ED group. This paradoxically means that EMD with a normal IRP also causes pulsion-type pseudo-diverticulum. However, POEM with diverticulotomy (D-POEM) for ED was also reported (20), although a fur-

ther discussion is necessary for the addition of diverticulotomy for ED. In most cases, the septum of ED is not sharp, like ZD, on endoscopy and esophagography; retained liquid or food can wash out after EMD treatment alone. Furthermore, ED occurs more often on the right side than on the left side (1), presumably because of adjacent mediastinal structures that prevent it from forming on the left side (21).

ZD is similarly a pulsion-type pseudo-diverticulum, and the anatomical weakness in Killian's triangle is considerably related to the etiology (2). At present, the European Society of Gastrointestinal Endoscopy recommends flexible endoscopic treatment over open surgical treatment as the first-line therapy for patients with symptomatic ZD of any size (22). In our cohort of Japanese patients, including elderly subjects, the long-term efficacy was sufficient, and no adverse events were reported. First, we used a diverticuloscope to perform diverticulotomy; thereafter, we performed flexible endoscopic intervention using the POEM technique, as recently reported (14, 23). Further studies are required to investigate the difference in the efficacy of these two methods. To generalize the procedure in Japan, multicenter studies are also necessary.

Several limitations associated with the present study warrant mention. In the starlet HRM system, the IRP cut-off value was only defined using healthy volunteers, and the validation study of the IRP threshold for achalasia and EG-

JOO was not sufficient (24). Therefore, a further study using a large sample size will be necessary to obtain a consensus concerning the definition of impaired LES relaxation, particularly in Japanese subjects.

In conclusion, concomitant EMDs are frequently observed in ED and should be carefully diagnosed using several complementary tests, including HRM. Impaired LES relaxation does not always show an elevated IRP on HRM. S-POEM and endoscopic diverticulotomy are minimally invasive and effective treatment options for EMD-related ED and ZD.

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and in adherence to the Declaration of Helsinki (1964 and later versions). Informed consent for participation or its equivalent was obtained from all patients included in this study.

The authors state that they have no Conflict of Interest (COI).

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