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ORIGINAL ARTICLE

Peroral endoscopic myotomy for advanced achalasia with megaesophagus

Chise Ueda[1] · Hirofumi Abe[1] · Shinwa Tanaka[1] · Fumiaki Kawara[1] · Takashi Toyonaga[2] · Ryusuke Ariyoshi[1] · Tomoya Sako[1] · Hiroya Sakaguchi[1] · Nobuaki Ikezawa[1] · Satoshi Urakami[1] · Tatsuya Nakai[1] · Yuzo Kodama[1]

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Abstract

Background The outcomes of peroral endoscopic myotomy for advanced achalasia are not well known. This study aimed to evaluate the outcomes of peroral endoscopic myotomy for achalasia with megaesophagus, which is one of the characteristics of advanced achalasia.

Methods In total, 234 patients with achalasia who underwent peroral endoscopic myotomy in our hospital from April 2015 to March 2019 were included in this retrospective observational study. Megaesophagus was defined as a maximum esophageal diameter of 6 cm or more. Outcomes, including clinical success (Eckardt score ≤ 3 without retreatment) at the 1-year follow-up, technical success, and perioperative complications, were investigated and compared between patients with and without megaesophagus.

Results Eleven patients (4.7%) were diagnosed with megaesophagus. The clinical success rate achieved was 63.6% in patients with megaesophagus, with a significant decrease in the Eckardt score (6 vs. 2, $p = 0.003$) and integrated relaxation pressure (28 mmHg vs. 9 mmHg, $p = 0.028$). The technical success rate was 100%. However, patients with megaesophagus had a significantly lower clinical success rate than those without megaesophagus (63.6% vs. 96.0%, $p = 0.002$). Furthermore, patients with megaesophagus had significantly higher rates of major adverse events than those without megaesophagus (18.2% vs. 2.7%, $p = 0.048$).

Conclusions Peroral endoscopic myotomy improved achalasia-related symptoms, and this was technically feasible in patients with megaesophagus. However, the clinical success rate was somewhat low, and the rate of major adverse events was high. Therefore, peroral endoscopic myotomy should be carefully performed for advanced achalasia with megaesophagus.

Keywords Esophageal achalasia · Peroral endoscopic myotomy · Advanced achalasia · End-stage achalasia

Introduction

Achalasia is a rare neurodegenerative disorder of the esophagus with an estimated prevalence of eight cases per 100,000 inhabitants and an incidence of one case per 100,000 inhabitants/year [1]. It is characterized by an impaired lower esophageal sphincter (LES) relaxation or abnormal contraction of the esophagus, resulting in dysphagia, an absence of feeding, and weight loss [2]. Treatments for achalasia include pharmacologic agents, endoscopic botulinum toxin injection, balloon dilation, and surgery. Recently, peroral endoscopic myotomy (POEM) is becoming a standard endoscopic treatment for achalasia [3].

Advanced achalasia is characterized by severe esophageal dilatation or loss of the straight esophageal axis (sigmoid-shaped esophagus) [4]. Esophagectomy is the only fundamental treatment for patients with advanced achalasia; however, it is associated with high mortality and severe complications. In addition, pneumatic dilation may be less effective in these patients. Thus, it might be reasonable to consider surgical myotomy before esophagectomy [5]. Besides, some studies have reported acceptable outcomes

✉ Hirofumi Abe
abe627@med.kobe-u.ac.jp

[1] Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan

[2] Division of Endoscopic Medicine, Kobe University Hospital, Kobe, Japan

of surgical myotomy for advanced achalasia, and the average clinical success rate was 79% (range 54–100%) [6–12].

Hu et al. reported excellent outcomes of POEM for advanced achalasia with sigmoid esophagus, resulting in long-term symptom relief in over 96% of the cases [13]. However, little is known about the outcome of POEM for advanced achalasia defined in terms of esophageal dilation. Therefore, the purpose of this study was to evaluate the outcomes of POEM in patients with megaesophagus.

Methods

Patients and characteristics

In this retrospective study, we reviewed the clinical data of consecutive patients who underwent POEM for achalasia in our hospital from April 2015 to March 2019. We excluded patients who had undergone POEM or who did not come for their 1-year follow-up.

Before POEM, all the patients were interviewed to determine their Eckardt score, and they underwent esophagogastroduodenoscopy (EGD), barium esophagram, and esophageal high-resolution manometry (HRM) to classify the achalasia subtype according to the Chicago classification (version 3.0). However, the esophagram and endoscopy in patients who failed to undergo HRM due to severe flexion or dilation of the esophagus were comprehensive enough for an appropriate diagnosis to be established.

Based on the esophagram and computed tomography (CT) findings, the severity of dilation was classified into grade I (diameter of maximum lumen < 3.5 cm), grade II (≥ 3.5 cm and < 6.0 cm), and grade III (≥ 6.0 cm). Megaesophagus was defined as a maximum esophageal diameter of 6 cm or more, that is grade III dilation. Patients with esophageal diverticula were excluded from the group of patients with megaesophagus. As mentioned in the classification by Inoue et al., sigmoid-type achalasia was subdivided into sigmoid-type 1 (S1) and sigmoid-type 2 (S2) according to the degree of tortuosity of the esophageal lumen observed on barium swallow and/or CT [14].

Opt-out methods of obtaining consent were used. Written informed consent was obtained from all the study participants. The study protocol was approved by the Ethics Committee at Kobe University Hospital (institutional review board no. B200073).

Outcome measurements

The primary endpoint was clinical success, defined as an Eckardt score of ≤ 3 without an indication for retreatment, at the 1-year follow-up. The secondary endpoints included technical success defined as completion of gastric and esophageal myotomy, perioperative complications according to the International Per Oral Endoscopic Myotomy Survey classification [15], Eckardt score, and manometric findings, such as integrated relaxation pressure (IRP).

Additionally, the time-to-event data analysis, in which an event was defined as either retreatment or postoperative Eckardt score of ≥ 4 during the observation period (till March 31, 2020), was used to assess the clinical outcomes at follow-up visits.

POEM and follow-up protocol

Patients were routinely administered general anesthetics with endotracheal intubation in the operating room. The standard protocol was as follows:

(1) Making the mucosal entry at the 5 o'clock or 2 o'clock position.
(2) Submucosal tunneling.
(3) Ensuring the submucosal tunnel adequately fitted into the cardia by detecting gastric-penetrating vessels or using the double-scope method.
(4) Myotomy, starting 1 cm distal to the mucosal entry and continuing 3 cm into the cardia.
(5) Closure of the mucosal entry.

All procedures were performed under carbon dioxide insufflation. Antibiotics were administered only on the day of surgery to prevent surgical site infection. On postoperative day 1, patients underwent an esophagram and EGD to check for a leak and the appropriate closure of the mucosal entry. The patients fasted for 1 day after POEM; a liquid diet was started on the second day after POEM. They were prescribed proton pump inhibitors (PPIs) for 1 month after discharge.

Follow-up visits were scheduled at approximately 3 months after POEM (2–6 months), 1 year after POEM, and once annually thereafter regardless of the presence of megaesophagus. During those follow-up visits, a clinical assessment was performed using EGD and the Eckardt score. The patients were evaluated for gastroesophageal reflux disease (GERD) symptoms and reflux esophagitis (> grade B, LA classification) at the 3-month follow-up visit, accompanied with a 2-month washout period of PPIs, unless PPIs were indispensable for the patients. The patients underwent HRM and barium esophagram at 3 months after POEM.

The measurements of the following parameters were analyzed on the barium esophagram images of the patients with megaesophagus: the maximum esophageal diameter (R), minimum diameter of the esophageal outflow (r), esophageal body angle (θ), and length of esophageal outflow (L) (Fig. 1). We measured the aforementioned parameters in the

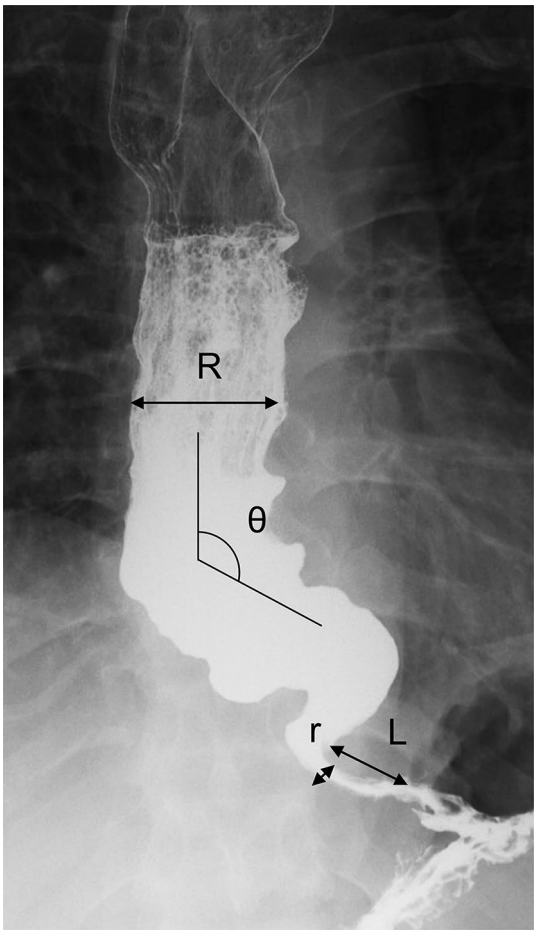

Fig. 1 The measurements of the following parameters were taken on the esophagram images: the maximum esophageal diameter (*R*), minimum diameter of the esophageal outflow (*r*), esophageal body angle (θ), and length of esophageal outflow (*L*)

Barium swallow views with the most esophagogastric junction outflow.

Statistical analysis

Clinical success, defined as an Eckardt score of ≤ 3 without retreatment, at the 1-year follow-up and technical success were compared using Fisher's exact test. Regarding clinical outcomes, Kaplan–Meier curves were used to assess the time-to-event analysis, where an event was defined as either retreatment or postoperative Eckardt score of ≥ 4 during the observation period. Patients were censored if they did not undergo an event during the observation period; event-free survivals were compared between groups using the log-rank test.

Fisher's exact tests were used to compare categorical variables between groups, and Student *t* tests and Mann–Whitney *U* tests (for skewed data) were used to continuous variables as appropriate. All *p* values less than 0.05 were considered statistically significant.

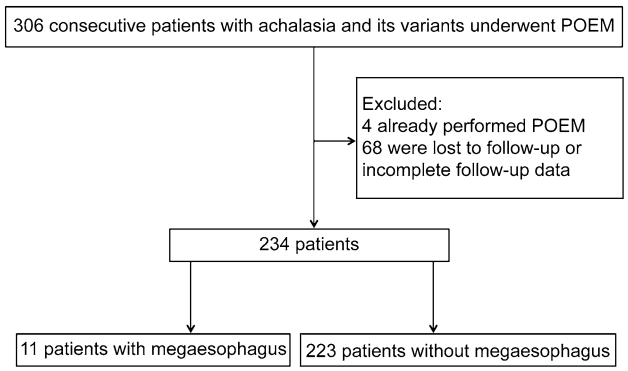

Fig. 2 Flow chart of patient selection

Results

Baseline characteristics

During the study period, 306 patients with achalasia underwent POEM. Four patients who had undergone POEM previously and 68 patients who were lost to follow-up or had incomplete follow-up data were excluded; thus, 234 patients were enrolled in this study (Fig. 2).

The baseline characteristics of these 234 patients are shown in Table 1. The median age was 49 (range, 5–88) years, and the median duration of symptoms was 5 (range, 0.2–61) years. The median pretreatment Eckardt score was 6 (range, 1–10), and 53 patients (22.6%) had a sigmoid esophagus.

There were 11 patients with megaesophagus (4.7%). Patients with megaesophagus had a significantly longer duration of symptoms than those without megaesophagus (15 [range 2–41] years vs. 5 [range 0.2–61] years, $p = 0.003$). Additionally, they had a higher incidence of sigmoid esophagus than the patients without megaesophagus (90% vs. 19.3%, $p < 0.001$) (Table 2).

Treatment outcomes of patients with megaesophagus

Clinical success was achieved in 7 of 11 (63.6%) patients with megaesophagus, and the rate of technical success was 100% (Table 3). Perioperative adverse events occurred in 2 of the 11 (18.2%) patients with megaesophagus; all were major adverse events. Two major complications occurred in patients with megaesophagus due to the mucosal entry incision, which required endoscopic intervention in all cases. It was difficult to close the mucosal incision using

Table 1 Baseline characteristics of 234 patients who underwent POEM

	Total ($n=234$)
Age, median (range), years	49 (5–88)
Sex (male), *n* (%)	104 (44.4)
Duration of symptoms, median (range), years	5 (0.2–61)
Anticoagulant, *n* (%)	16 (6.8)
Previous invasive treatment, *n* (%)	60 (25.4)
Endoscopic pneumatic dilation, *n* (%)	59 (25.2)
Surgical myotomy, *n* (%)	7 (3.0)
Disease type	
Straight type, *n* (%)	181 (77.4)
Sigmoid type, *n* (%)	53 (22.6)
Dilation grade	
Grade 1 (< 3.5 cm), *n* (%)	98 (41.9)
Grade 2 (≥ 3.5 cm and < 6.0 cm), *n* (%)	125 (53.4)
Grade 3 (≥ 6.0 cm) [megaesophagus] *n* (%)	11 (4.7)
Eckardt score, median (range)	6 (1–10)
Chicago classification	
Type 1, *n* (%)	161 (68.8)
Type 2, *n* (%)	53 (22.6)
Type 3, *n* (%)	20 (8.5)
Operator	
Expert, *n* (%)	41 (17.5)
Non-expert, *n* (%)	193 (82.5)

POEM peroral endoscopic myotomy

only endoclips due to the thickness of the mucosal layer. A case closure technique using a polyglycolic acid (PGA) sheet (Neoveil; Gunze Co., Kyoto, Japan) and fibrin glue and another using an endoloop (MAJ-254; Olympus Optical Co Ltd, Tokyo, Japan)/clips were performed for the entry incision in POEM (Fig. 3). The patients were discharged without undergoing additional treatments. The median Eckardt score of the patients with megaesophagus (excluding three patients who needed retreatment within 1 year after the first POEM) significantly decreased from 6 [range 2–10] to 2 [range 0–4] after POEM ($p=0.003$) (Fig. 4a). Five patients (45.5%) were eligible for HRM before and after POEM. The median IRP significantly decreased from 28 [range 11–34] mmHg to 9 [range 3–21] mmHg after POEM ($p=0.028$) (Fig. 4b). The median maximum esophageal diameter decreased from 71 mm [range 61–117] to 46 mm [range 33–76] after POEM ($p<0.001$) (Table 4). The esophageal angulation improved from 86° (range 68–144) to 118° (range 78–141) after POEM ($p=0.014$). Three patients (27.3%) required retreatments within 1 year after POEM, i.e. one of them underwent endoscopic balloon dilation, and two of them underwent a repeat POEM.

Comparison in treatment outcomes between patients with and without megaesophagus

Patients with megaesophagus had a significantly lower clinical success rate than those without megaesophagus (63.6% vs. 96.0%, $p=0.002$). Kaplan–Meier curves comparing

Table 2 Comparison of baseline characteristics between patients with and without megaesophagus

	Patients with megaesophagus $n=11$	Patients without megaesophagus $n=223$	*p* value
Age, median (range), years	52 (24–71)	49 (5–88)	0.967
Sex (male), *n* (%)	8 (72.7)	96 (43.0)	0.066
BMI, median (range), kg/m	21 (12–35)	22 (16–31)	0.508
Duration of symptom, median (range), years	15 (2–41)	5 (0.2–61)	0.003
Previous invasive treatment, *n* (%)	4 (36.4)	56 (25.1)	0.79
Endoscopic pneumatic dilation, *n* (%)	4 (36.4)	55 (24.7)	0.476
Surgical myotomy, *n* (%)	0 (0)	7 (3.1)	1.000
Anticoagulant, *n* (%)	0 (0)	16 (7.2)	0.451
Chicago classification			
Type 1, *n* (%)	10 (90.9)	151 (67.7)	0.180
Type 2, *n* (%)	1 (9.0)	52 (23.3)	0.464
Type 3, *n* (%)	0 (0)	20 (9.0)	0.605
Sigmoid type, *n* (%)	10 (90.9)	43 (19.3)	< 0.001
S1, *n* (%)	4 (36.4)	35 (15.7)	0.91
S2, *n* (%)	6 (54.5)	8 (3.6)	< 0.001
IRP, median (range), mmHg	23 (11–34)	29 (4–75)	0.053
Eckardt score, median (range)	6 (2–10)	6 (1–10)	0.823
Operator (expert), *n* (%)	2 (18.2)	39 (17.5)	1.000

BMI body mass index, *IRP* integrated relaxation pressure

Table 3 The comparison in treatment outcomes between patients with and without megaesophagus

	Patients with megaesophagus $n=11$	Patients without megaesophagus $n=223$	p value
Myotomy length, median (range), cm	9 (4–16)	13 (5–25)	<0.001
Procedure time, median (range), min	71 (39–100)	62 (29–182)	0.357
Postoperative IRP, median (range), mmHg	9 (3–21)	12 (0.1–40)	0.128
Postoperative Eckardt score-1 year, median (range)	2 (0–4)	0 (0–5)	0.003
Technical success, *n* (%)	11 (100)	223 (100)	1.000
Perioperative adverse events, cases (%)	2 (18.2)	22 (9.9)	0.314
Major adverse events, cases (%)	2 (18.2)	6 (2.7)	0.048
ICU stay, events (%)	0 (0)	1 (0.4)	1.000
Surgical/IR/other intervention, events (%)	2 (18.2)	0 (0)	0.002
Readmittion within 30 days, events (%)	0 (0)	2 (0.9)	1.000
Leak noted on post POEM imaging or endoscopy, events (%)	2 (18.2)	1 (0.4)	0.006
IV antiviotecs > 5 days, events (%)	0 (0)	3 (1.3)	1.000
Cardiac arrythmia, events (%)	0 (0)	1 (0.4)	1.000
Pneumonia/respiratory issue, events (%)	0 (0)	2 (0.9)	1.000
Minor adverse events, cases (%)	0 (0)	16 (7.2)	1.000
Capnoperitoneum requring intraprocedural venting, events (%)	0 (0)	9 (4.0)	1.000
Inadvertent mucosal perforation of mucosal flap, events (%)	0 (0)	9 (4.0)	1.000
Clinical success *n* (%)	7 (63.6)	214 (96.0)	0.002
Endoscopic reflux esophagitis findings, *n* (%)	0 (0)	46 (20.6)	0.128
GERD symptoms, *n* (%)	1 (9)	59 (26.5)	0.294

IRP integrated relaxation pressure, *ICU* intensive care unit, *IR* interventional radiology, *IV* intravenous, *POEM* peroral endoscopic myotomy, *GERD* gastroesophageal reflux disease

event-free survival in the two groups are shown in Fig. 5 (log-rank $p<0.001$).

Furthermore, the patients with megaesophagus had significantly higher rates of major adverse events than those without megaesophagus (18.2% vs. 2.7%, $p=0.048$) (Table 3). The myotomy lengths in patients with megaesophagus were significantly shorter than those in patients without megaesophagus (9 cm [range 4–16] vs. 13 cm [range 5–25], $p<0.001$). Similarly, they had higher 1-year postoperative Eckardt scores (2 [range 0–4] vs. 0 [range 0–5], $p=0.003$). There were no significant differences in procedure time, postoperative integrated relaxation pressure (IRP), rate of endoscopic reflux esophagitis findings, and GERD symptoms.

Clinical characteristics of treatment failure among patients with megaesophagus

Table 5 shows the differences in the clinical characteristics between the success group and failure group in patients with megaesophagus (Fig. 6). There was no significant difference between the success and failure groups in age, duration of symptoms, previous invasive treatment, sigmoid esophagus, preoperative Eckardt score, and myotomy length.

Table 6 shows the differences in the esophagram findings between the success group and failure group in patients with megaesophagus. There were no significant differences in the radiographic findings between the success group and the failure group, except for the postoperative caliber ratio (r/R), that is, the ratio of the minimum diameter of the esophageal outflow to the maximum esophageal diameter (0.275 [0.193–0.47] vs. 0.216 [0.122–0.244], $p=0.023$).

Discussion

From this study's findings, POEM significantly improved achalasia-related symptoms and manometric findings, even in patients with megaesophagus. However, the achieved clinical success rate (63.6%) was somewhat lower than that of patients without megaesophagus. Additionally, patients with megaesophagus had higher rates of major adverse events (18.2%). Radiographic findings indicated that a higher postoperative caliber ratio could be important for treatment success in patients with megaesophagus.

Achalasia occurs when the Meissner and Auerbach plexuses within the wall of the esophagus are destroyed. Patients with chronic achalasia may develop severe sigmoidization

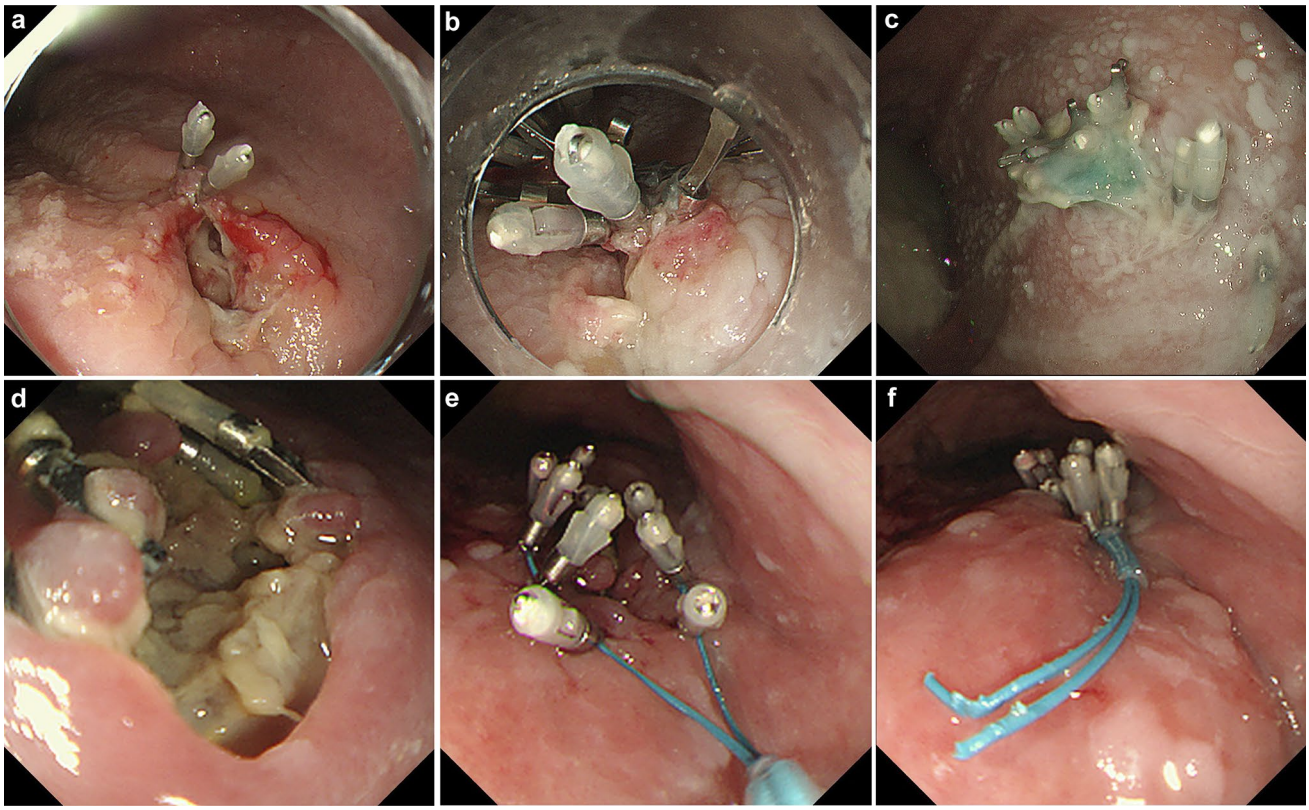

Fig. 3 A case closure technique using a polyglycolic acid (PGA) sheet and fibrin glue for the entry incision in peroral endoscopic myotomy (POEM). **a** The entry incision was opened 1 day after POEM. **b** It was difficult to close the mucosal incision with endoclips alone. **c** The mucosal defect was covered with PGA sheets and sprayed with Fibrin glue. A case closure technique using endoloop/clips for the entry incision in POEM. **d** With the occurrence of dysphagia, an endoscopy was performed 5 days after POEM. The entry incision was opened. **e** Because it was difficult to close the mucosal incision with endoclips alone, the endoloop/clips technique was used. **f** The entry incision was closed using endoclips and an endoloop

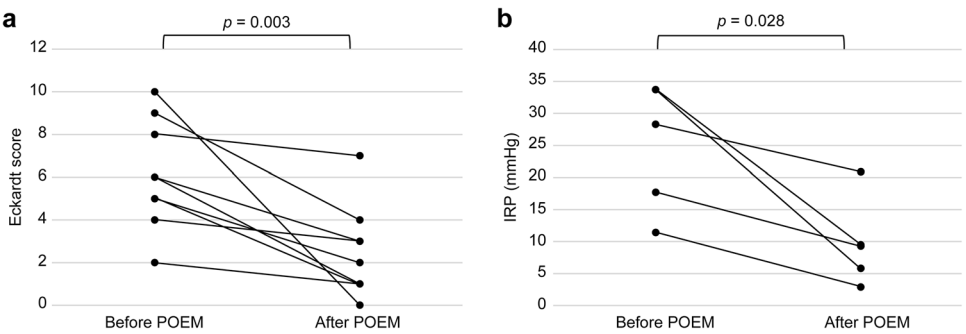

Fig. 4 Symptom relief and manometry outcomes before and after POEM for patients with megaesophagus. **a** Eckardt score. **b** Manometry outcomes

and megaesophagus. Evidence-based data of the optimal options for advanced achalasia are lacking, and the initial treatments for advanced achalasia remain controversial. Recently, POEM has been introduced as a new minimally invasive treatment for achalasia; however, its effectiveness is unclear. In a previous report, esophageal dilation and sigmoid esophagus were the independent factors for response to POEM [16]. However, little is known about the clinical outcomes of POEM for advanced achalasia with megaesophagus. To the best of our knowledge, this is the first report stating the outcomes of POEM in patients suffering from advanced achalasia with megaesophagus compared to those without megaesophagus.

There is no consensus on the threshold of the esophageal diameter to consider the status of achalasia as advanced. Regarding the anatomic cut-off for the definition of advanced achalasia in the diameter of the esophageal lumen, it varies as some authors adopt 6 [17], 7 [18], or 8 cm [19]. In Brazil

Table 4 Treatment outcomes of patients with megaesophagus

	Before POEM ($n=11$)	After POEM ($n=11$)	p value
Eckardt score, median (range)	6 (2–10)	2 (0–4)	0.003
IRP, median (range), mmHg	28 (11–34)	9 (3–21)	0.028
Esophagus maximum diameter, median (range), mm	71 (61–117)	44 (30–57)	< 0.001
Esophageal body angle, median (range), degree	86 (68–144)	118 (78–141)	0.014
Retreatments within 1-year after POEM, *n* (%)		3 (27.3)	
Endoscopic balloon dilation, *n* (%)		1 (9.0)	
Re-POEM, *n* (%)		2 (18.2)	

POEM peroral endoscopic myotomy

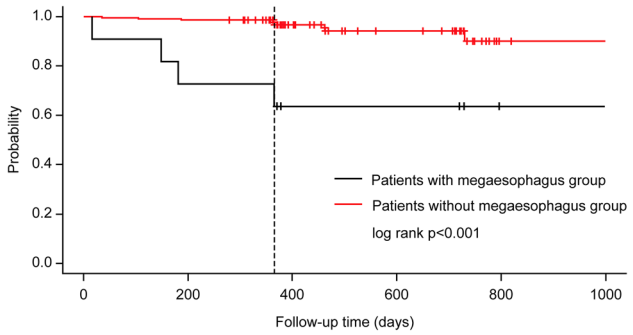

Fig. 5 Kaplan–Meier curves comparing the event-free survival for patients with and without megaesophagus using the log-rank test. An event was defined as either retreatment or postoperative Eckardt score of ≥ 4 during the observation period

where Chagas' disease is highly prevalent, megaesophagus is defined as an esophagus with a maximum esophageal diameter of ≥ 10 cm [20]. However, a maximum diameter of 6 cm was the most used threshold in previous studies focusing on idiopathic achalasia [7–9, 17, 21, 22]. In addition, in Japan, the degree of esophageal dilatation was classified into three grades; i.e., grade I (< 3.5 cm), grade II (3.5–6 cm), and grade III (> 6 cm), and a maximum esophageal diameter of 6 cm was considered the threshold for advanced disease. Thus, we selected a diameter of 6 cm as a criterion for megaesophagus.

A massively dilated esophagus is reported in no more than 5% of idiopathic achalasia series [6]. In our study, 4.7% (11 patients) of all patients with achalasia had megaesophagus, similar to previous reports. As the disease progresses, the esophagus may appear significantly dilated, angulated, and tortuous, giving it a sigmoid shape [22]. Our report shows that the patients with megaesophagus had a significantly longer duration of symptoms and a higher incidence of sigmoid esophagus than those without megaesophagus.

In this study, myotomy lengths were shorter in patients with megaesophagus than in those without megaesophagus. This difference may have resulted from the variation in the incidence of type 3 achalasia, which required a longer myotomy for treating spastic contraction in the esophageal body, and type 1 achalasia for which a shorter myotomy was sufficient to treat tight LES alone. Additionally, it may have been due to the surgeon pre-setting a shorter myotomy length in anticipation of severe fibrosis in the submucosa and the thick muscle layer of the megaesophagus. However, we emphasize that this difference was not due to a higher incidence of incomplete myotomy in patients with megaesophagus because we had ensured that the submucosal tunnel adequately fitted into the cardia in all patients using

Table 5 Comparison of characteristics between clinical success and failure in patients with megaesophagus

	Success ($n=7$)	Failure ($n=4$)
Age, median (range), years	55 (24–71)	45 (28–64)
Duration of symptom, median (range), years	15 (2–41)	20 (2–40)
Previous invasive treatment, *n* (%)	2 (28.6)	2 (50)
Endoscopic pneumatic dilation, *n* (%)	2 (28.6)	2 (50)
Surgical myotomy, *n* (%)	0 (0)	0 (0)
Sigmoid type, *n* (%)	7 (100)	3 (75)
S1, *n* (%)	4 (57.1)	1 (25)
S2, *n* (%)	3 (42.9)	2 (50)
Eckardt score, median (range)	5 (2–10)	7 (5–9)
Myotomy length, median (range), cm	9 (4–10)	12 (9–16)

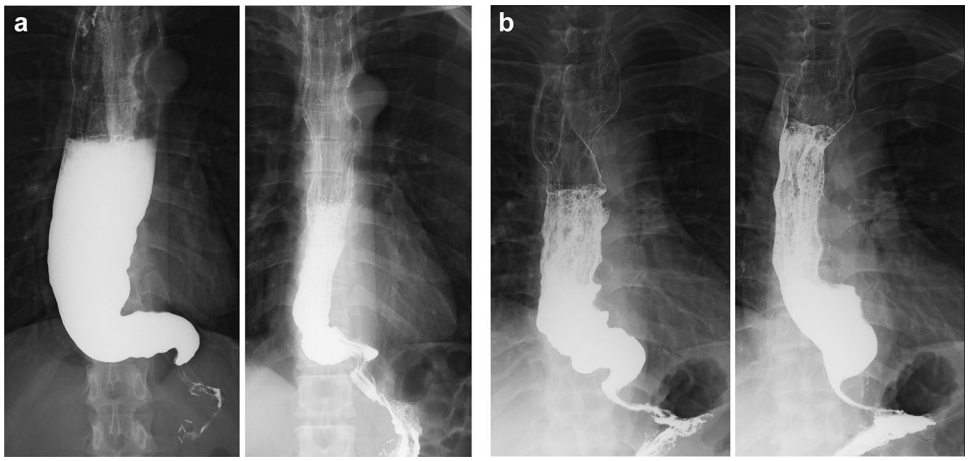

Fig. 6 Esophagram of patients with megaesophagus. **a** The esophagram of a treatment success case of patients with megaesophagus: before POEM (left), and at the 3-month follow-up (right), showing obvious opening of the esophagogastric junction and smooth passage of contrast. **b** The esophagram of a treatment failure case of patients with megaesophagus: before POEM (left), and at 3-month follow-up (right), showing a closed EGJ, esophageal dilation, and contrast retention

Table 6 Comparison of esophagrams between clinical success and failure in patients with megaesophagus

	Success ($n=7$)	Failure ($n=4$)	p value
Before POEM			
R: maximum diameter of the esophagus, median (range), mm	71 (66–82)	73(61–117)	0.817
r: minimum diameter of the esophageal outflow, median (range), mm	6.1 (3.4–7.5)	6.9 (4.3–8.5)	0.383
r/*R*: caliber ratio, median (range)	0.084 (0.048–0.112)	0.105 (0.059–0.0.116)	0.383
θ: esophageal body angle, median (range), degree	86 (68–126)	99.5 (69–144)	0.788
L: length of esophageal outflow, median (range), mm	20.5 (10.6–26.8)	12.9 (11.8–38.8)	0.833
After POEM			
R: maximum diameter of the esophagus, median (range), mm	41 (30–57)	49 (41–51)	0.491
r: minimum diameter of the esophageal outflow, median (range), mm	12 (10–14)	10 (6–11)	0.065
r/*R*: caliber ratio, median (range)	0.275 (0.193–0.47)	0.216 (0.122–0.244)	0.023
θ: esophageal body angle, median (range), degree	118 (78–132)	116 (107–141)	0.648
L: length of esophageal outflow, median (range), mm	19.5 (17.9–27.3)	15.7 (13.0–27.8)	0.517

POEM peroral endoscopic myotomy

double-scope methods or anatomical landmarks based on gastric-penetrating vessels.

As achalasia becomes advanced, the epithelium thickens, and the multilayered squamous epithelial structure increases [23]. It makes the mucosal entry friable, and there is a risk of failure of closure of the mucosal entry. In our study, the two major complications that occurred in patients with megaesophagus were both due to the mucosal entry incision, and the closure of the mucosal incision using endoclips was difficult due to the thickness of the mucosal layer. Therefore, attention should be paid when closing the entry of patients with megaesophagus, and alternative method for entry closure with the use of an endoloop, over-the-scope clip (OCTS) and polyglycolic acid (PGA) sheets may be desirable [24]. In addition, the dilated and tortuous esophageal lumen may make endoscopic dissection and separation of tissues more challenging and time-consuming, and in such a tortuous megaesophagus, it is easy to be lost in the tunnel [15]. Thus, POEM for patients with megaesophagus is generally considered to be technically difficult and unsafe. In our study, though the rate of technical success was 100%, patients with megaesophagus had significantly higher rates of major adverse events (18.2% vs. 2.7%, $p=0.048$). Therefore, detailed informed consent should be obtained preoperatively.

In our study, the Eckardt score and IRP improved significantly after POEM. These results are convincing because POEM is an endoscopic treatment, which is equivalent to Heller myotomy that is recommended in the American College of Gastroenterology guidelines as the initial treatment for patients with advanced achalasia [5]. However, patients with megaesophagus had a significantly lower clinical success rate than those without megaesophagus (63.6% vs. 96.0%, $p=0.002$). This may be because a dilated esophagus is one of the independent risk factors for a poor response to POEM. Additionally, the patients with megaesophagus have a high prevalence of sigmoid esophagus, which is one of the independent risk factors

[16]. Therefore, in patients with megaesophagus, POEM should be performed carefully. Considering the clinical success rate in this study, it is unclear whether POEM or surgical myotomy should be the initial treatment for advanced achalasia. However, considering less invasiveness, less adhesions [25, 26], and its technical feasibility, that is the capability of being accomplished till the end of the procedure, POEM could become an initial approach for advanced achalasia with megaesophagus before esophagectomy.

Among patients with megaesophagus, we assessed the baseline characteristics, including radiographic findings, to select patients who were likely to achieve clinical success. None of the clinical characteristics were associated with clinical success, except the postoperative caliber ratio, which is the ratio of the minimum diameter of the esophageal outflow to the maximum esophageal diameter. Certainly, it is difficult to ascertain whether the significant difference in the caliber ratio was a cause or result of clinical success. However, this result suggests that the width of esophageal outflow suitable for the width of the diameter of the esophagus rather than the mere width of esophageal outflow is required for clinical success in patients with megaesophagus. In other words, the optimal width of esophageal outflow might depend on the diameter of the esophagus.

This study had several limitations. Firstly, this was a retrospective observational study from a single-center, which potentially included selection bias and information bias. Second, the sample size was relatively small. Thus, its results are not generalizable enough to prove a significant difference in rare events between patients with and without megaesophagus. We intend to resolve these limitations through a future large multi-institutional prospective study.

In conclusion, POEM improved achalasia-related symptoms and manometric findings even in patients with megaesophagus. However, the clinical success rate in patients with megaesophagus is somewhat lower than that in patients without megaesophagus. Additionally, patients with megaesophagus had higher rates of major adverse events. Thus, POEM for advanced achalasia with megaesophagus should be carefully performed.

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Declarations

Ethical Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Conflict of interest The authors declare no conflict of interest for this article.

Informed consent Informed consent or substitute for it was obtained from all patients for being included in the study.

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