

Long-term clinical results of per-oral endoscopic myotomy (POEM) for achalasia: First report of more than 10-year patient experience as assessed with a questionnaire-based survey

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ABSTRACT

Background and study aims Since per-oral endoscopic myotomy (POEM) was introduced in 2010, it has become accepted as one of the standard treatments for esophageal achalasia worldwide. This study aimed to present long-term clinical results of POEM over 10 years and evaluate the technique and outcomes at the institution where it was first used in clinical settings.

Patients and methods Questionnaire-based surveys were sent to patients who received POEM in our institution from September 2008 to May 2010. Patient demographics and procedural outcomes and open-ended questions were posed about the postoperative courses, including symptom improvement and recurrence, additional treatments, and post-POEM gastroesophageal reflux disease (GERD) symptoms. Achalasia symptoms and post-POEM GERD symptoms were evaluated with Eckhardt scores and GerdQ systems, respectively.

Results Thirty-six consecutive POEMs were performed in that period and 10-year follow-up data were obtained from 15 patients (41.7%). Although four cases (26.7%) required additional pneumatic balloon dilatation (PBD), reduction in post-Eckardt scores were observed in 14 cases (93.3%). GerdQ score was positive in one patient (6.7%). Proton pump inhibitors (PPI) were taken by four patients (26.7%) and their symptoms were well-controlled.

Conclusions Clinical results of POEM over 10 years were favorable regardless of various factors. Symptoms improved even in patients who required additional treatments, suggesting that POEM plays a significant role in treatment of achalasia.

Introduction

Ten years after the first report of per-oral endoscopic myotomy (POEM) for esophageal achalasia by Inoue et al [1], POEM has been established as one of the standard treatments of esophageal achalasia worldwide [2, 3]. While evidence-based studies have proven POEM to be a safe and effective technique, [4, 5], concerns regarding gastroesophageal reflux (GERD) after

POEM have emerged in recent years [6, 7]. Along with this, the advantages and disadvantages of POEM still remain controversial; however, through an increasing number of reports and discussions, these have gradually become clearer in recent years. In addition, how to perform POEM more effectively and safely has been widely debated, and various evolutions of the indications and of techniques have been evaluated [8, 9].

Bearing in mind that available literature on POEM has been limited to short- or mid-term results of up to approximately 5 years [10, 11], assessing the long-term clinical results of POEM in the initial period since its introduction into clinical settings was deemed to be important.

In this study, as the earliest institution to develop POEM and the largest referral center for POEM in Japan, we present our long-term clinical results of POEM over 10 years. The initial technique and outcomes are also examined and discussed.

Patients and methods

Study design and patients

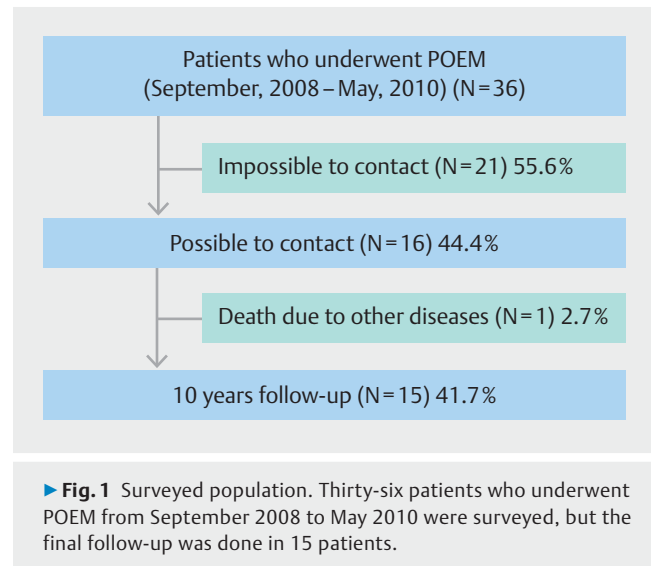
This was a single-center retrospective cohort study. A database of information from patients who received POEM at Showa University from September 2008 to May 2010 was reviewed using electronic charts. Clinical surveys of patient symptoms over 10 years were conducted via phone calls or mail questionnaires. There were no exclusion criteria in this follow-up study; however, patients under 18 years of age or those with advanced sigmoid type achalasia were excluded from the indications for POEM procedure over the study period.

Procedural technique of POEM

The POEM procedure was performed as previously described in our first report of 17 consecutive POEM patients [1]. Of them, seven cases (Cases 1–7) were also included in this study. The procedure was done with the patient under general anesthesia with positive pressure ventilation. A submucosal tunnel was created on the posterior (5 o'clock axis) or anterior (2 o'clock axis) side from the level of the mid- or lower esophagus downwards about 1 to 3 cm into the proximal stomach passing the esophagogastric junction (EGJ). In all cases, myotomy was also carried out with selective circular muscle cutting. An adequate myotomy on the gastric side was confirmed by the endoscopic appearance, such as the insertion length of the endoscopy, a prompt decrease in resistance when entering into the stomach side passing through EGJ, and recognition of the palisade vessels in the esophagus and submucosal spindle vessels in the stomach. Confirmation by double-scope [8] or other methods [9] was not performed at that time. All procedures were performed by one expert endoscopist who was the first in the world to pioneer POEM.

Follow-up measurements

The surveys conducted during this study consisted of open-ended questions regarding the postoperative course, such as symptom improvement and recurrence, additional treatment, and GERD symptoms after POEM. Achalasia symptoms and post-POEM GERD symptoms were evaluated with Eckardt score and GerdQ systems [12], respectively. Esophagogastroduodenoscopy (EGD), barium swallow, and 24-hour impedance-pH monitoring (MII-pH) were added in Case 11 (32nd experience with POEM for our team) because the patient answered that he had both insufficient results from POEM and a positive GerdQ score after POEM.



Definition of outcome measurements

The degree of esophageal dilatation and type were classified by barium esophagogram. According criteria from the Japan Society of Esophageal Diseases, the degree of esophageal dilatation was classified by the maximum diameter of the esophageal lumen into grade I (<3.5 cm), grade II (<3.5–6.0 cm), and grade III (>6 cm), and the type of achalasia was classified by the shape of the esophageal lumen as straight (St), sigmoid (Sg), and advanced sigmoid (aSg) [13].

The primary endpoint of this study was symptom improvement by obtaining a reduction in Eckardt score at 10 years after POEM. The secondary endpoint was GERD symptoms at 10 years after POEM. Positive GERD symptoms were defined as a post-POEM GerdQ score of 8 or more according to the previous report [12].

Ethical considerations

This study was approved by the Ethics Committee of Showa University Koto Toyosu Hospital (IRB Registration No:20T7022). Written informed consent was obtained from all participants.

Statistical analysis

Median (minimum-maximum range) was used to report continuous and categorical variables. All analyses were performed using JMP Pro 14.0.0 (SAS Institute Inc., North Carolina, United States).

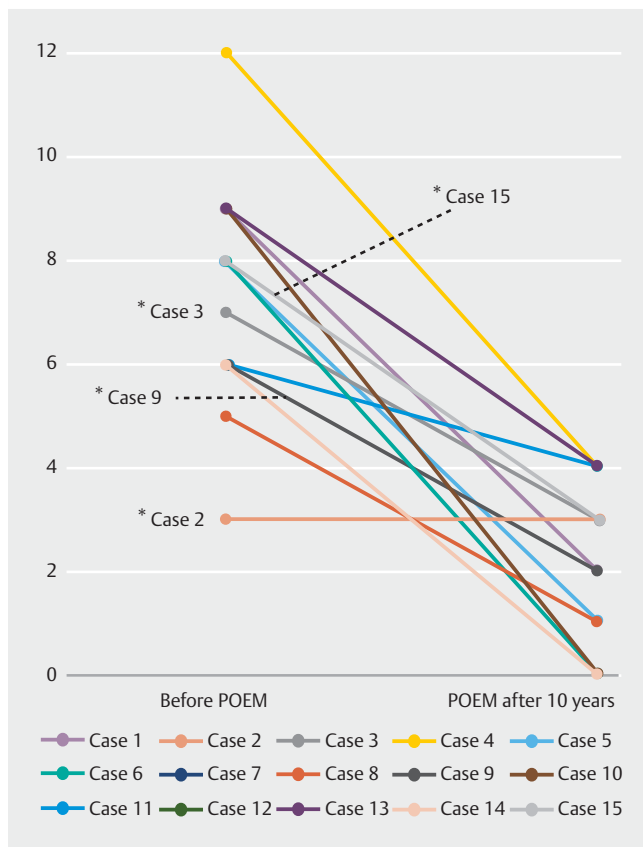
Results

Between September 2008 and May 2010, POEM was performed on 36 consecutive patients in our institution. We were able to follow up with 16 of them (44.4%) via phone calls or mail questionnaires. However, one of the 16 patients died from another disease 2 years after POEM. Therefore, 10 years of follow-up data from a total of 15 patients (41.7%) were analyzed in this study (► **Fig. 1**).

▶ **Table 1** Patient demographics and procedural data.

Case	Date	Rank in our experience	Age	Gender	Dilatation grade	Type	Previous treatment	Duration of symptoms (years)	Eckardt score (before POEM)	Procedure time (min)	Myotomy axis	Myotomy length on esophagus side (cm)	Myotomy length on gastric side (cm)	Adverse events
1	Sep/2008	1 st	37	M	II	St	PBD	2.2	9	110	Posterior	3	2	None
2	May/2009	4 th	37	F	II	St	None	20.4	3	120	Anterior	3	1	None
3	Jun/2009	5 th	18	F	II	St	PBD	2	7	150	Anterior	2	1	None
4	Nov/2009	14 th	41	M	III	Sg	PBD	4	12	135	Anterior	12	2	None
5	Dec/2009	15 th	53	M	II	St	None	1	8	100	Anterior	13	1	None
6	Dec/2009	16 th	39	M	III	Sg	PBD	3.1	8	100	Anterior	12	3	None
7	Dec/2009	17 th	38	F	I	St	None	2.5	8	130	Anterior	9	3	None
8	Jan/2010	19 th	59	M	III	Sg	PBD	20	5	240	Anterior	10	3	None
9	Feb/2010	21 st	59	M	I	St	None	2	6	90	Anterior	10	3	None
10	Feb/2010	25 th	75	F	II	St	None	2	9	95	Anterior	10	3	None
11	Mar/2010	27 th	51	M	I	St	None	25	6	100	Anterior	10	3	None
12	Mar/2010	29 th	68	F	I	St	PBD	10	8	110	Anterior	15	3	None
13	Apr/2010	32 nd	63	F	II	St	None	32	9	120	Anterior	13	1	None
14	Apr/2010	35 th	70	F	I	St	None	10	6	150	Anterior	13	2	None
15	May/2010	36 th	38	F	II	Sg	Additional PBD after transthoracic Heller Myotomy	10	8	175	Anterior	10	2	None

St, straight; Sg, sigmoid; PBD, pneumatic balloon dilation.



► **Fig. 2** Therapeutic effects of POEM after 10 years. Eckardt scores before and 10 years after POEM in each case. Please note that Cases 7, 12 and 15 all coincided in one line. All cases other than Case 14 showed a decrease in Eckardt scores after POEM. *Cases that required additional PBD.

Patient demographics and procedural data are shown in ► **Table 1**. In the initial period, POEM was indicated for all typical achalasia except in patients under 18 years old or who had advanced sigmoid type achalasia. The median age was 51 years (range 18–75) and the median duration of symptoms was 4 years (range 1–32). Seven patients (46.7%) were male, three (20.0%) had grade III dilation, and four (26.7%) had sigmoid type achalasia. Seven patients (46.7%) received previous treatment with pneumatic balloon dilatation (PBD). In one case (Case 15), previous PBD was done as an additional treatment after transthoracic Heller myotomy because of its insufficient effect. The median pre-POEM Eckardt score was 8 (range 3–12).

In the first case (Case 1), myotomy on the posterior side was selected, but in all the latter cases (Cases 2–15), myotomy was switched to the anterior side (2 o'clock). This is due to the presence of the spine behind the esophagus, which destabilized the appropriate motion of the endoscopic tips. In addition, anterior myotomy can avoid destroying the angle of His in the light of preventing the risk of post-POEM GERD. Furthermore, because the procedure at that time was focused on opening the EGJ and consensus about the appropriate length of myotomy had not yet been reached, the length of myotomy in the esophagus side varied from 2 to 15 cm, and a minimum of 1 cm on the

stomach side. Based on our experience with the first seven cases (Cases 1, 2, and 3 in this paper), the myotomy length on the esophageal side was relatively short. After subsequent reports that a 7-cm myotomy was generally recommended to achieve complete release of LES in surgical Heller myotomy, myotomy on the esophageal side was extended to over 8 cm in the latter cases [14]. The median procedural time was 120 minutes (range 90–240) and no adverse events occurred in this series.

Symptomatic results in each case are shown in ► **Fig. 2** and ► **Table 2**. As shown in ► **Fig. 2**, although four patients (Cases 2, 3, 9, and 15) required additional treatments (shown with asterisk in ► **Fig. 2**), symptom improvement was obtained in 14 of 15 patients (93.3%). ► **Table 2** shows the details of the clinical course in each case. Cases 4, 11, and 13 had a post-Eckardt score of 4, which was generally considered inadequate relief of achalasia symptoms. In case 13, the patient had a temporary feeling of symptom recurrence 1 month after POEM, but in Cases 4 and 13, they were satisfied with the results at present without further treatment. In Case 11, the patient was satisfied and achalasia symptom improvement was noted, but an uncomfortable feeling of GERD symptoms was reported. Additional PBD was required in Cases 2, 3, 9, and 15. The duration of the recurrence of symptoms was 1 to 5 years after POEM. Additional PBD was effective in Cases 2, 3, and 9, with relief of symptoms to some extent. Meanwhile, symptom recurrence at 5 years after POEM was noted in Case 15; however, due to the mildness of the symptoms, the patient did not seek any treatment. The patient's symptoms eventually worsened, prompting him to finally seek care and he subsequently received an additional PBD 9 years after POEM. Despite the additional PBD, no symptom improvement was noted, yet the patient was able to tolerate the symptoms afterwards.

Post-POEM GERD data are shown in ► **Table 2**. Four of 15 patients (26.7%) are taking proton pump inhibitors (PPIs). Of them, two patients (Cases 2 and 4) are taking PPIs at their request to prevent GERD symptoms despite being asymptomatic. The patient in Case 8 only takes PPIs when symptoms occur, whereas the patient in Case 12 takes PPIs daily. In both patients, the symptoms are well controlled.

Meanwhile, one patient (Case 11) (6.7%) had a positive GerdQ score without any PPI intake. As such, repeat evaluation was performed, which included EGD, barium swallow, and MII-pH. EGD findings revealed inadequate opening of the EGJ and large diverticulum just above the EGJ. Barium swallow also revealed retention of barium in the esophagus with a large diverticulum above the EGJ (► **Fig. 3**). MII-pH showed that percent time clearance pH was 0.0% and DeMeester composite score was 0.9, which indicated no GERD in this patient.

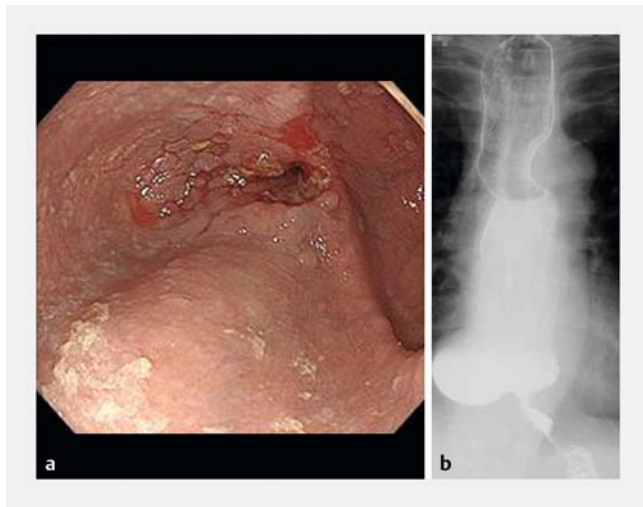
Discussion

In the present paper, the experience at the earliest institution to develop POEM and the largest referral center for the technique in Japan, including 10-year clinical results based on post-POEM GERD data, is presented. POEM has been reported to be a highly effective, minimally invasive treatment for achalasia and

▶ **Table 2** Symptomatic results before and 10 years after POEM.

Case	Dilatation grade	Type	Previous treatment	Period of symptoms (years)	Myotomy length on esophagegus side (cm)	Myotomy length on gastric side (cm)	Eckardt score (Before POEM)	Eckardt score (10 years after)	Date of symptom recurrence	Additional treatment	Date of additional treatment	Effect of additional treatment	GerDQ score	PPI intake	PPI effect
1	II	St	PBD	2.2	3	2	9	2					Negative	No	-
2	II	St	None	20.4	3	1	3	3	2 years after	PBD	2 years after	Effective	Negative	Yes	Unknown
3	II	St	PBD	2	2	1	7	3	1 year after	PBD	1 year after	Effective	Negative	No	-
4	III	Sg	PBD	4	12	2	12	4	None	None	-	-	Negative	Yes	Unknown
5	II	St	None	1	13	1	8	1					Negative	No	-
6	III	Sg	PBD	3.1	12	3	8	0					Negative	No	-
7	I	St	None	2.5	9	3	8	3					Negative	No	-
8	III	Sg	PBD	20	10	3	5	1					Negative	Yes (on demand)	Effective
9	I	St	None	2	10	3	6	2	5 years after	PBD	5 years after	Effective	Negative	No	-
10	II	St	None	2	10	3	9	0					Negative	No	-
11	I	St	None	25	10	3	6	4	none	None	-	-	Positive	No	-
12	I	St	PBD	10	15	3	8	3					Negative	Yes	Effective
13	II	St	None	32	13	1	9	4	1 month after	none	-	-	Negative	No	-
14	I	St	None	10	13	2	6	0					Negative	No	-
15	II	Sg	Additional PBD after transthoracic Heller Myotomy	10	10	2	8	3	5 years after	PBD	9 years after	No change but tolerable	Negative	No	-

St, straight; Sg, sigmoid; PBD, pneumatic balloon dilation.



► **Fig. 3** Findings from EGD and barium swallow in Case 11. **a** EGD showed inadequate opening of the EGJ, mild erosive GERD, and a large diverticulum just above the EGJ. **b** Barium swallow also revealed retention of barium in the esophagus with a large diverticulum above the EGJ.

related esophageal motility disorders with short-term follow-up [4, 15]; however, to our knowledge, this is the longest follow-up report and the first report of over 10 years of clinical results with POEM.

Since the introduction of POEM into clinical practice based on the evidence of an experimental report on the safety of endoscopic myotomy in a porcine model by Pasricha et al [16], indications initially were restricted for only typical achalasia; hence, POEM has been safely completed in all cases regardless of prior treatment. Based on primary reports regarding efficiency and safety associated with short-term results of POEM, indications for the procedure have been expanded [15, 17–19], and to date, modifications and discussions are still being done among endoscopists all over the world to achieve safer and better results [20, 21].

The majority of patients in this study obtained symptom improvement 10 years after POEM, suggesting that the clinical efficacy of POEM is favorable. On the other hand, four patients (Cases 2, 3, 9, and 15) required additional PBD treatment during their clinical courses. Based on previous literature, patient demographics factors associated with poor results of POEM were reported to be male gender, high pre-Eckardt score, longer duration of achalasia symptoms over 10 years, prior treatments, dilated esophagus, sigmoid type achalasia, and type III Chicago classification [22–25]. However, in the present study, tendencies toward these factors were not elucidated due to the small sample size. In addition, procedural factors such as myotomy length also were reported to have an effect on POEM results. According to clinical practice guidelines for POEM in Japan [2], to secure a complete LES incision, 1- to 2-cm myotomy into the gastric side is recommended. In our series, in four cases (Case 2, 3, 5 and 13), a shorter 1-cm myotomy was made in the stomach. In two of these patients (Case 2 and 3), additional PBD was required and one patient (Case 13) had a feeling of

symptom recurrence 1 month after POEM and had a post-POEM Eckardt score of 4. Our study could not draw concrete conclusions about the importance of the length of myotomy on the gastric side, but taking into account previous reports, we cannot totally rule out that these results may have been influenced by the shorter gastric myotomy length. Another interesting result was that in most of the cases with symptom recurrence, the recurrence occurred a short time after POEM, and additional PBD resulted in improvement in symptoms. This suggests that even if the myotomy length is insufficient, it is possible that this previous myotomy site can become the “starting point” for the dilatation since it has already been cut, hence, enhancing the effects of the additional PBD. To avoid compromising the effects of POEM due to insufficient myotomy length, a double-scope method has been used routinely in recent years in our center to intraoperatively confirm adequacy of myotomy length on the gastric side [8]. In Case 15, POEM was done as a “second myotomy” following the insufficient effect of the first transthoracic surgical Heller myotomy and PBD. Symptom improvement to some extent was noted. Although a slight exacerbation occurred after 5 years, symptoms were still tolerable for the patient. Nine years after POEM, additional PBD was carried out to improve her symptoms; however, it did not provide relief. Since this case had several factors such as sigmoid type, long duration of symptoms, and prior treatment, complete relief of symptoms might not be obtained only by making an opening in the LES. Still, POEM was considered to have a role in alleviating this patient’s symptoms to some extent.

Despite the high efficacy and safety rates for POEM, the onset of GERD after POEM has become a concern and it is now an important issue for discussion. Apart from Heller myotomy with antireflux surgery, adjacent structures surrounding the distal esophagus, which work as one of the major natural barriers to reflux, are potentially preserved in POEM; however, post-POEM GERD has been reported, ranging from 14% to 57% [5, 7, 26, 27]. In our cases, four patients (Cases 2, 4, 8, and 12) were prescribed PPIs. Of these, two patients (Cases 2 and 4) took PPIs for prophylaxis regardless of being asymptomatic, and in the other two patients (Cases 8 and 12), symptoms were controlled well with PPIs. Based on available reports, factors that may increase the risk of post-POEM GERD include the following: a myotomy length on the gastric side >2.5 cm, female sex, low pre-POEM LES pressure, full-thickness myotomy, and posterior myotomy [6, 27–30]. However, the present study did not reveal a tendency toward these factors affecting GERD symptoms. Only Case 11 had a positive GerdQ score. In this case, although the length of myotomy in the stomach was 3 cm, the therapeutic effect was not sufficient, and the patient still exhibited a post-POEM Eckardt symptom score of 4. Considering the emergence of a diverticulum just above the EGJ after POEM and a poor outflow of barium in the esophagogram, the positive GerdQ score might not represent acid reflux from the stomach caused by post-POEM GERD, but instead, reflux of esophageal residue due to an insufficient therapeutic effect of POEM. This consideration was also supported by the results of MII-pH. We believe that additional treatment, such as PBD or a second POEM, is required in such cases after detailed examinations, including

high-resolution manometry (HRM) and the indications must be carefully considered.

Certain limitations of this study must be acknowledged. Aside from its single-center retrospective nature, the sample size was relatively small. Contacting patients more than 10 years after treatment posed challenges, such as ascertaining their current whereabouts, which is why we were able to reach only 44.4% of them. Moreover, there is a lack of objective analysis. Our hospital was the only facility performing POEM 10 years ago, and most of the patients at that time came from far away to receive POEM. Because most of them were satisfied with their past results with POEM, unfortunately, we could not get consent from them to come all the way to our facility just for the follow-up examinations. Furthermore, the COVID-19 pandemic made it difficult to perform follow-up and provide usual examinations. Finally, POEM procedures in this series had not yet been standardized 10 years ago, and methods to stabilize the therapeutic effect and safety were not yet established. This consequently resulted in various biases in considering the clinical outcomes in this study. Therefore, a multicenter study with objective data is needed in the near future.

These are the longest-term clinical results with POEM to date. The clinical results of POEM were satisfying enough regardless of various patient and procedural factors. Even in cases for which additional treatment was required, symptoms scores improved to below their pre-POEM baselines, suggesting that the technique plays a significant role in treatment of achalasia.

Conclusion

In conclusion, this study showed satisfactory long-term clinical results with POEM over 10 years. We believe this study provides important information and lessons that can be applied to future POEM treatment.

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Competing interests

Dr. Inoue is an advisor for Olympus Corporation and Top Corporation. He has also received educational grants from Olympus Corp. and Takeda Pharmaceutical Co.

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