Comparison of the safety and efficacy of peroral endoscopic myotomy between octogenarians and non-octogenarians

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Comparison of the safety and efficacy of peroral endoscopic myotomy between octogenarians and non-octogenarians

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Author contributions: All authors have contributed to the content of the manuscript. HA, ST, FK, and YK conceived and designed the study. HA, ST, FK, TT, RA, HS, TS, and NI performed the experiments. HA and ST analyzed the data and wrote the initial draft of the manuscript. All other authors contributed to data interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

【Abstract】

Objectives:

This study compared the safety and efficacy of peroral endoscopic myotomy for esophageal motility disorders between octogenarians and non-octogenarians.

Methods:

This retrospective observational study recruited 321 patients (28 octogenarians and 293 non-octogenarians) who underwent peroral endoscopic myotomy from two institutions. Clinical success (postoperative Eckardt score≤3), technical success (completion of gastric and esophageal myotomy), and perioperative adverse events were compared between octogenarians and non-octogenarians. Perioperative adverse events were classified into major and minor adverse events based on the International Peroral Endoscopic Myotomy Survey criteria and were subdivided into technical and non-technical adverse events according to the presence of a direct causal relationship with the procedure.

Results:

There were no significant differences in the rates of clinical success 1-year after treatment (100% vs. 97.3%, p=0.64) and technical success (100% vs. 99.7%, p=0.91) between octogenarians and non-octogenarians. Octogenarians had a higher incidence of

perioperative adverse events (28.6% vs. 10.2%, p=0.00097), particularly major adverse events (25.0% vs. 3.0%, p<0.0001). There were no significant differences in the incidence of minor adverse events (7.1% vs. 7.9%, p=0.67). Although there was no difference in the incidence of technical adverse events (10.7% vs. 9.2%, p=0.74), octogenarians had a significantly higher incidence of non-technical adverse events (17.9% vs. 1.0%, p=0.0002).

Conclusions:

There were no significant differences in short-term clinical success and technical success between octogenarians and non-octogenarians. However, octogenarians showed a significantly higher incidence of perioperative adverse events, particularly in major adverse events and non-technical adverse events. Peroral endoscopic myotomy for octogenarians should be carefully applied.

【**Key words**】Aged, 80 and over; Esophageal Achalasia; Esophageal Motility Disorders; Myotomy; Retrospective Studies

【Introduction】

Esophageal motility disorders (EMD) such as achalasia or achalasia variants are diseases characterized by impaired relaxation of the lower esophageal sphincter (LES) or abnormal contraction of the esophageal body,[1] which often results in dysphagia, reduced food consumption, and weight loss.[2]

Over the years, pharmacological therapy, botulinum toxin therapy, endoscopic balloon dilation, and surgical myotomy have been the main treatments for EMD.[3] Recently, peroral endoscopic myotomy (POEM) developed by Inoue et al.[4] has become one of the main therapeutic options because it is less invasive and has a high response rate equivalent to that of conventional surgical myotomy.[5]

Recently, the increasing rate of the ageing population poses a global challenge. In particular, in Japan, where the aged population is rapidly increasing,[6] a minimally invasive and effective treatment is needed for elderly with EMD.

POEM is considered as one of the useful therapeutic options for the elderly with EMD because of its minimal invasiveness and effectiveness. The comparison of the safety and efficacy of POEM for EMD in adults aged 60 years and above and adults under 60 years has already been reported.[7] Studies on EMD in adults aged 80 years and above have

been limited to descriptive data collected in an international multicenter study about the safety and efficacy of POEM[8]. There is also a paucity of data on a comparison between octogenarians and non-octogenarians. It has not been clarified whether the safety and efficacy of POEM for EMD in adults aged 80 years and above are similar to those under 80 years old with EMD.

The aim of this study was therefore to evaluate the safety and efficacy of POEM for EMD in adults aged 80 years and above by comparing the clinical outcomes between patients aged 80 years and above and patients under 80 years.

【Methods】

Patient characteristics

A consecutive series of patients who underwent POEM in two specialized institutions for symptomatic EMD, with an Eckardt score of 3 and above, a tolerance to general anesthesia, and a preserved swallowing function, between April 2015 and March 2019, were included in this study. Patients who had undergone POEM previously and those who were younger than 18 years old were excluded. Opt-out methods of consent were used, and no patients declined to consent to the study. This retrospective multicenter study was approved by the ethics committee in the respective centers.

Baseline characteristics such as age, sex, duration of symptoms, presence of previous invasive treatments such as pneumatic dilation or surgical myotomy, body mass index (BMI), Charlson comorbidity index,[9] and Onodera's prognostic nutritional index (O-PNI)[10] were obtained from the electronic medical records of patients. EMD-related symptoms were evaluated using Eckardt score[2] before POEM, 3 months after POEM and one year after POEM. The morphology of the esophagus was classified into Straight type (St type: the measure of minimum angle at the inflection point in the esophageal body ≥135°) and Sigmoid type (Sg type: <135°). The severity of dilation was classified into grade 1 (diameter of maximum lumen <3.5 cm), grade 2 (≥3.5 cm, <6.0 cm) and grade 3 (≥6.0 cm) using an esophagram. EMD was diagnosed using a high-resolution manometry (HRM) and classified into achalasia or achalasia variants according to Chicago classification version 3.[1] However, patients who could not undergo the high-resolution manometry due to severe flexion or dilation of the esophagus, were comprehensively diagnosed using esophagram and endoscopic findings. Adults aged 80 years and above were defined as octogenarians, while adults less than 80 years old were defined as non-octogenarians. Patients with suspected swallowing dysfunction, such as octogenarians and patients with aspiration, were routinely evaluated for swallowing function by otolaryngologist before POEM.

POEM and follow-up protocol

Five surgeons performed POEM, and those who performed more than 100 POEM procedures as chief surgeons were defined as experts and the others, non-experts. According to the 2012 Japan Gastroenterological Endoscopy Society (JGES) guidelines for the management of antithrombotic drugs, antithrombotic drugs were withdrawn prior to POEM.

Patients routinely underwent general anesthesia with endotracheal intubation in the operating room. The standard protocol were as follows: 1) making the mucosal entry at 5 or 2 o'clock, 2) submucosal tunneling, 3) ensuring submucosal tunnel adequately into the cardia by detection of gastric penetrating vessels or double scope method, 4) myotomy, starting -1 cm distal to the mucosal entry and continuing 3 cm into the cardia, and 5) closure of the mucosal entry. All procedures were performed under carbon dioxide insufflation by using Flush knife BT3.0 (DK2618JB; Fujifilm Medical Co., Ltd., Tokyo, Japan) or Triangle-tip knife (KD-640L; Olympus Corp., Tokyo Japan). Antibiotics were administered on only the day of operation to prevent surgical-site infection. On post-op day (POD) 1, patients underwent an esophagram and esophagogastroduodenoscopy (EGD) to ensure that there was no leak and also to ensure that the mucosal entry was well closed. Patients ate no food after POEM for 1 day and started eating liquid diet on the

second day after POEM. They were put on proton pump inhibitors (PPI) for 1 month after discharge.

All patients were scheduled for follow-up visit at 3 months and 1 year after POEM for EGD and an evaluation of Eckardt score. HRM was performed at 3-months follow-up. Gastroesophageal reflux disease (GERD) symptoms and reflux esophagitis were evaluated at the 3-month follow-up visit accompanied by a 2-month withdrawal period of PPI to avoid obscuring abnormal acid reflux, unless PPI was indispensable for the patients.

Assessment of safety and efficacy

Postoperative Eckardt score, technical success, and clinical success were used as metrics to assess the efficacy of POEM. Postoperative Eckardt score was evaluated at 3 months and one year after POEM. Clinical success was defined as a postoperative Eckardt score less than or equal to 3. Technical success was defined as completion of esophageal and gastric myotomy.

Postoperative hospital stay, postoperative symptomatic reflux esophagitis, and perioperative adverse events which occurred from the beginning of procedure till POD 14 were used as metrics to assess the safety of POEM. Perioperative adverse events were subdivided into major adverse events and minor adverse events based on the international

peroral endoscopic myotomy survey (IPOEMS) [11] criteria (**Table S1**). Major adverse events were defined as follows: ICU stay, readmission within 30 days, intravenous antibiotics > 5 days, delayed bleeding, leak (i.e., a fistula between the submucosal tunnel and esophageal lumen identified after POEM by endoscopic and other imaging), pneumonia, surgical conversion, disability requiring a level of care higher after discharge than prior to POEM, and cardiac arrhythmia. In this study, however, prolonged hospitalization of >5 days was not regarded as major adverse events because patients were scheduled to stay in our hospitals for 5 days after POEM, in the absence of complications. Minor adverse events were capnoperitoneum requiring intra-procedural venting, inadvertent mucosal perforation requiring endoscopic repair, and premature perforation of muscle layer at the time of submucosal tunnel creation.

The most severe perioperative adverse events of each patient were classified into technical adverse events and non-technical adverse events. Technical adverse events were events with a direct causal relationship with the procedure such as technical failure, mucosal perforation, hydrothorax, bleeding, gas-related complications and leakages. Non-technical adverse events largely depended on the patient's inability to tolerate surgical stress rather than a direct causal relationship with the procedure. These were cardiac arrhythmia, pneumonia, and disuse syndrome. Some recent reports have indicated

that achalasia is associated with swallowing dysfunction[12] or frailty[13]. In this study, we defined “disuse syndrome” as extreme functional decline compared with the situation prior to POEM, such as swallowing dysfunction and inactivity during hospitalization requiring intensive rehabilitation. Intensive rehabilitation was referred for physiotherapy and swallowing rehabilitation with additional hospitalization for more than one week or with transfers to a specialized rehabilitation institution. These rehabilitations involved physical training or tongue and swallowing exercises for functional recovery delivered by physiotherapists or swallowing therapists.

Statistical analysis

Categorical parameters were expressed as counts (percentages) and continuous parameters are expressed as median (range) or mean (range). Univariate analysis was used to compare the baseline characteristics and the metrics of safety and efficacy between octogenarians and non-octogenarians. Continuous data were analyzed using T-test (normally distributed data) or Wilcoxon rank-sum test (skewed data), and categorical data were analyzed using Fisher's exact test.

【Results】

Baseline characteristics

During the study period, 331 symptomatic patients with EMD (322 from one institution, 9 from the other) underwent POEM. Five patients who were younger than 18 years old and five patients who had undergone POEM previously were excluded; thus, 321 patients were enrolled in this study (**Figure1**).

Baseline characteristics of these 321 patients are shown in **Table 1**. Out of this number, the proportion of octogenarians was 8.7%. Octogenarians had a higher proportion of comorbidities and antithrombotic drug use and showed a significantly lower BMI and O-PNI (**Table 2**). Experienced surgeons tended to perform POEM for octogenarians.

Efficacy-related outcomes

As shown in **Table 3**, there were no significant differences in clinical success at 3 months after POEM (100% vs. 97.1%, p=0.52), clinical success at 1 year after POEM (100% vs. 97.3%, p=0.64) and technical success (100% vs.99.7%, p=0.91) between octogenarians and non-octogenarians. Furthermore, there were no significant differences in myotomy length, duration of procedure, postoperative integrated relaxation pressure (IRP), and postoperative Eckardt score between the groups.

Safety-related outcomes

Octogenarians showed a significantly higher rate of perioperative adverse events than

non-octogenarians (28.6% vs.10.2%, p=0.00097) (**Table 4**). Major adverse events occurred in 16 patients (5.0%) and minor adverse events occurred in 25 patients (7.8%). There was no significant difference in the minor adverse events rate between the two groups (7.1% vs.7.9%, p=0.67); however, major adverse events occurred more frequently in octogenarians than in non-octogenarians (25.0% vs.3.1%, p<0.0001). The rate of leak (7.1% vs.0.7%, p=0.04), IV antibiotics >5 days (10.7% vs.1.0%, p=0.01), and disability requiring higher-level care (14.3% vs.0.3%, p=0.0002) were higher in octogenarians than in non-octogenarians. Details of each major adverse event are described in **Table S2**.

Although there was no difference in the rate of technical adverse events between groups (octogenarians 10.7% vs. non-octogenarians 9.2%, p=0.74), octogenarians had a significantly higher proportion of non-technical adverse events than non-octogenarians (17.9% vs.1.0%, p=0.0002).

Postoperative hospital stay was longer in octogenarians (9.8 days vs.5.4 days, p=0.0013). There was no difference in the rate of postoperative symptomatic GERD (13.0% vs.19.4%, p=0.59).

【Discussion】

To the best of our knowledge, this is the first study comparing the safety and efficacy of

POEM between octogenarians and non-octogenarians in the same medical region. There were no differences in short-term clinical success and technical success between octogenarians and non-octogenarians. However, octogenarians had a significantly higher incidence of perioperative adverse events and a higher incidence of non-technical adverse events.

The aging population of our country is increasing more rapidly than other countries[6]. The latest provisional estimate by government in 2018 reports that 28.1% of the Japanese population are over 65 years old[14]. With this percentage, it is expected that the need to select treatment for EMD among the aged population will increase.

POEM for EMD is minimally invasive and has a high success rate in elderly patients[7]. Thus, clinical practice guidelines for POEM from JGES[15] state that POEM is a safe and effective procedure for elderly patients as an answer to the clinical question regarding the effectiveness of POEM in treating elderly patients with esophageal achalasia. However, this statement is based on reports in which “elderly” was defined as either 60 years[7] or 65 years[16] and older; therefore, it is worth discussing whether it can be applied to octogenarians. An International multicenter study by Chen et al.,[8] which focused on octogenarians found that adverse events appeared to be slightly higher, although POEM is technically feasible and clinically effective in octogenarians. However,

the study could not statistically establish the high risk of adverse events of POEM for octogenarians because there was no comparison with non-octogenarians. Therefore, further studies comparing the rate of adverse events between octogenarians and non-octogenarians in the same medical region was necessary to establish that adverse events of POEM are statistically higher in octogenarians.

There were some significant differences in clinical presentations between octogenarians and non-octogenarians. Octogenarians showed not only higher proportions of comorbidity and antithrombotic drug use but also poorer nutritional status, which can most likely lead to poorer surgical stress tolerance. Thus, more expert surgeons perform POEM for octogenarians to compensate for the poor tolerance as a result of their age.

In terms of efficacy-related outcomes, there were no statistically significant differences in clinical success and technical success between the two groups and these successful rates were high in octogenarians. Therefore, it was concluded that POEM technically feasible and clinically effective in octogenarians. These findings were consistent with the result from Chen et al.[8]

Studies based on IPOEMS criteria[11] or modified IPOEMS criteria[17] have reported that the rate of minor and major adverse events were approximately 17% and 3%, respectively. Therefore, the rate of minor adverse events (7.8%) in this study was

acceptable, but the rate of major adverse events (5.0%) were higher than those from previous reports. The proportion of octogenarians in this study was 8.7% which was higher than that of IPOEMS[11] which was 1.7% (14 octogenarians out of 841 patients). The differences in the results of major adverse events between this study and previous studies[11,17] probably originates from the differences in age distribution among each population. Furthermore, major adverse events from this study in octogenarians (seven out of twenty-eight, 25%) occurred more frequently than severe adverse events (one out of sixty-four, 1.6%) from Chen et al.'s study[8]. However, it is worth noting that the grading system developed by the American Society for Gastrointestinal Endoscopy (ASGE) lexicon[18], used in Chen et al.'s study, reports a lower incidence of major adverse events than the grading system according to IPOEMS criteria[19]. Thus, the difference in the frequency of major adverse events among octogenarians between this study and Chen et al.'s study could be attributed to the discrepancy in the grading system between ASGE lexicon and IPOEMS (**Table S1**).

In terms of safety-related outcomes, octogenarians showed a significantly higher rate of perioperative adverse events, particularly in major adverse events. The rate of non-technical adverse events was significantly higher in octogenarians than non-octogenarians. This could not be fully explained; however, results could be attributed to

lower surgical stress tolerance in octogenarians and this could have led to higher rate of non-technical adverse events that could not be technically avoided by experienced surgeons. In the IPOEMS criteria[11], non-technical complications, such as arrhythmia, pneumonia, and disuse syndrome, tend to be classified as major adverse events. As a result, it can be inferred that the rate of both non-technical adverse events and major adverse events increased in octogenarians.

It is impossible to technically prevent non-technical adverse events, but some non-technical interventions (e.g., a nutritional or rehabilitative approach to prevent disuse syndrome) are possible. Therefore, in addition to the indications for POEM based on sufficient evaluations of general preoperative status and informed consent about the higher risk of perioperative adverse events, a comprehensive perioperative management program, including rehabilitation and nutritional support are important as the main strategies for preventing non-technical adverse events in octogenarians.

There were some limitations to this study. First, this study was a retrospective observational study, which potentially included selection bias and information bias. Second, the sample size was relatively small; therefore, it was impossible to identify independent risk factors for non-technical adverse events using multivariate logistic regression analysis. Third, the distinguishing technical adverse events from non-technical

adverse events depended on author's discretion to a certain extent. Fourth, there was a bias representation in the number of patients from each institution, resulting in the nearly single-center study. Finally, the proportion of experienced surgeons were significantly different between octogenarians and non-octogenarians, which might have some influenced clinical outcomes. Therefore, well-designed, large-scale prospective studies are needed to overcome these limitations.

In conclusion, there were no differences in short-term clinical success and technical success between octogenarians and non-octogenarians. However, octogenarians showed significantly higher perioperative adverse events, particularly in non-technical adverse events. Considering the higher perioperative adverse events, indications for POEM in octogenarians should be carefully judged.

【Acknowledgments】

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【Conflicts of Interest】

TT invented the Flush knife BT3.0 in conjunction with Fujifilm Medical, has a patent for

it, and receives royalties from its sale. Other authors have no conflicts of interest to disclose.

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【Figure legends】

Figure 1. Patient eligibility flowchart. POEM: peroral endoscopic myotomy

【Supplementary table legends】

Table S1. Differences in grading system between IPOEMS and ASGE lexicon.

Table S2. Details of major adverse events.

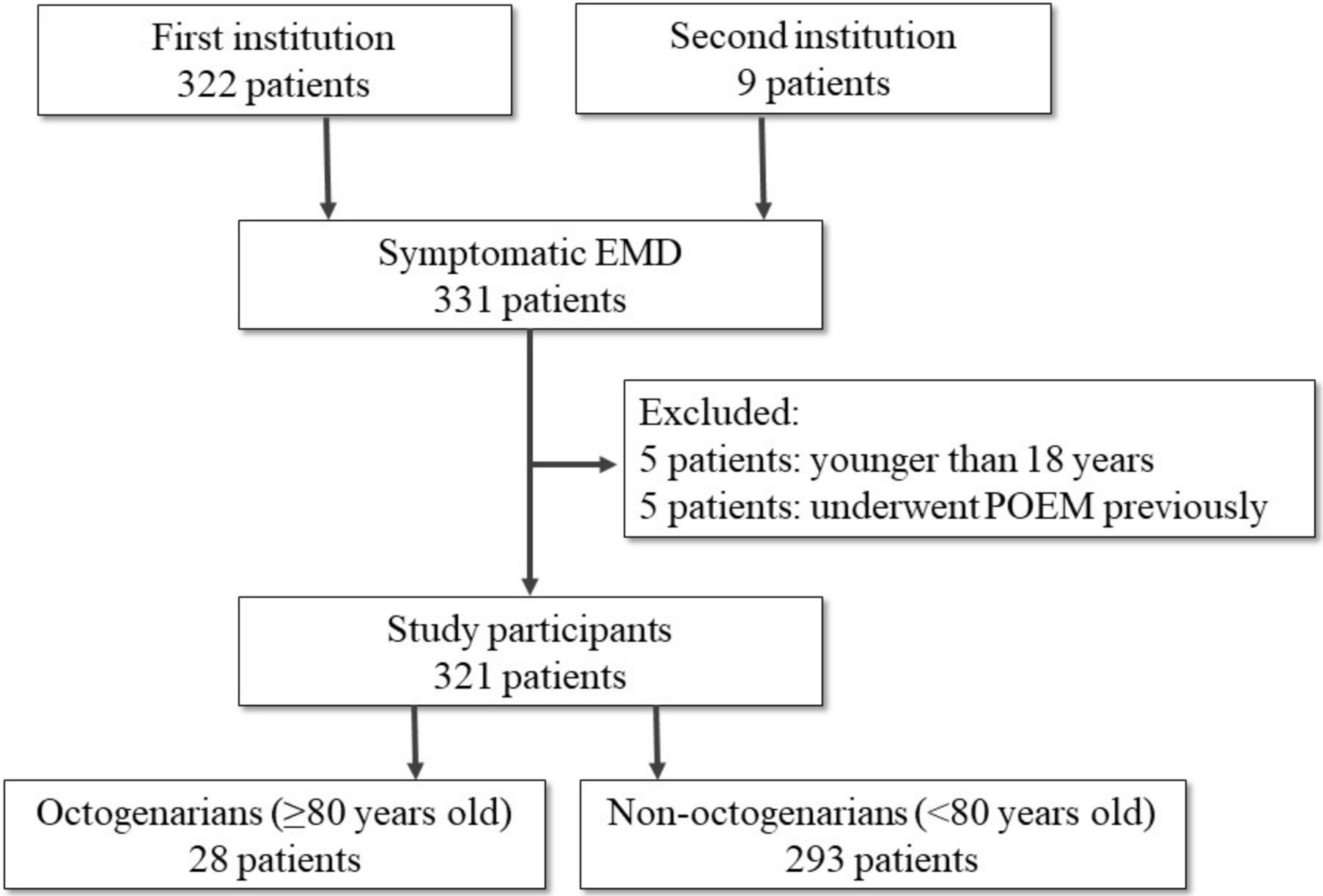
First institution
322 patients
Second institution
9 patients
Symptomatic EMD
331 patients
Excluded:
5 patients: younger than 18 years
5 patients: underwent POEM previously
Study participants
321 patients
Octogenarians (≥80 years old)
28 patients
Non-octogenarians (<80 years old)
293 patients

Table 1. Baseline characteristics of 321 patients who underwent POEM

Age, median (range), years	50 (19–88)
Octogenarians (≥ 80years), n (%)	28 (8.7)
Sex (male), n (%)	162 (50.5)
BMI, median (range), kg/m	21.1 (11.6–36.9)
Duration of symptom, median (range), years	5 (0.2–61)
Antithrombotic drugs, n (%)	29 (9.3)
Previous invasive treatment†, n (%)	82 (25.5)
Endoscopic pneumatic dilation, n (%)	80 (24.9)
Surgical myotomy, n (%)	10 (3.1)
Charlson comorbidity index ≥ 1, n (%)	47 (14.6)
Diagnosis	
Achalasia, n (%)	293 (91.3)
Achalasia variants, n (%)	28 (8.7)
IRP, median (range), mmHg	28.0 (2.3–66.9)
Disease type	
Straight type, n (%)	242 (75.4)

Sigmoid type, n (%)	79 (24.6)
Dilation grade	
grade 1, n (%)	142 (44.2)
grade 2, n (%)	170 (53.0)
grade 3, n (%)	9 (2.8)
Eckardt score, median (range)	6 (3-12)
O-PNI, median (range), mg/dL	49.6 (29.3–64.1)
Surgeons	
expert, n (%)	70 (21.8)
non-expert, n (%)	251 (78.2)

POEM: per-oral endoscopic myotomy, BMI: body mass index

IRP: integrated relaxation pressure, O-PNI: onodera's prognostic nutritional index

† pneumatic balloon dilation or surgical myotomy

Table 2. Comparison of clinical characteristics between octogenarians and non-octogenarians

	Octogenarians n = 28	Non-octogenarians n = 293	p value
Sex (male), n (%)	12 (42.9)	150 (51.2)	0.43
BMI, median, kg/m	19.5 (14.6–26.7)	21.3 (11.6–36.9)	0.0035***
Duration of symptom, median, years	5.5 (0.25–59)	4 (0.2–61)	0.37
Previous invasive treatment[†], n (%)	12 (42.9)	70 (23.9)	0.040*
Charlson comorbidity index ≥1, n (%)	14 (50.0)	33 (11.3)	< 0.0001****
Antithrombotic drugs, n (%)	10 (35.7)	19 (6.5)	< 0.0001****
Diagnosis (achalasia), n (%)	23 (82.1)	270 (92.2)	0.083
Straight type, n (%)	20 (71.4)	222 (75.8)	0.65
Dilation grade ≥ 2, n (%)	12 (42.9)	167 (57.0)	0.17
IRP, median, mmHg	21.1 (7.2–57.5)	28.4 (2.3–66.9)	0.048*
Eckardt score, median	5 (3–9)	6 (3–12)	0.073
O-PNI, median, mg/dL	40.7 (32.5–51.7)	50.3 (29.3–64.1)	< 0.0001****
Surgeons (expert), n (%)	17 (60.7)	53 (18.1)	< 0.0001****

*p < 0.05, ** p < 0.01, ***p < 0.005, ****p < 0.001

BMI: body mass index, IRP: integrated relaxation pressure, O-PNI: onodera's prognostic nutritional index

† pneumatic balloon dilation or surgical myotomy

Table 3. The efficacy-related outcomes

	Octogenarians	Non-octogenarians	p value
	n = 28	n = 293	
Myotomy length, median (range), cm	14.5 (4–26)	13 (5–27)	0.63
Procedure time, median (range), min	60.5 (36–124)	59 (29–184)	0.68
Technical success, n (%)	28 (100)	292 (99.7)	0.91
3 months after POEM	n = 23	n = 273	
Postoperative IRP-3 months, median (range), mmHg	7 (0.7–18.9)	11.1 (0–40.1)	0.061
Postoperative Eckardt score-3 months, median	0 (0–2)	0(0–9)	0.29
Clinical success-3 months (Eckardt score $\leq$ 3), n (%)	23 (100)	265 (97.1)	0.52

1 year after POEM	n = 17	n = 223	
Postoperative Eckardt score-1 year, median	0 (0–2)	1 (0–5)	0.39
Clinical success-1 year (Eckardt score $\leq$ 3), n (%)	17 (100)	217 (97.3)	0.64

*p < 0.05, ** p < 0.01, ***p < 0.005, ****p < 0.001

IRP: integrated relaxation pressure

Table 4. The safety-related outcomes

	Octogenarians n = 28	Non-octogenarians n = 293	p value	total
Perioperative adverse events, cases[†] (%)	8 (28.6)	30 (10.2)	0.0097**	38 (11.8)
Major adverse events[‡], cases with any of below (%)	7 (25.0)	9 (3.1)	< 0.0001****	16 (5.0)
ICU stay, cases (%)	1 (3.6)	1 (0.3)	0.17	
bleeding/hematoma requiring blood transfusion, cases (%)	1 (3.6)	0 (0)	0.087	
Surgical / IR / other intervention, cases (%)	2 (7.1)	3 (1.0)	0.062	
Readmission within 30 days, cases (%)	1 (3.6)	1 (0.3)	0.17	
Leak noted on post POEM imaging or endoscopy, cases (%)	2 (7.1)	2 (0.7)	0.040*	

Hydrothorax / hematothorax / pneumothorax, cases (%)	0 (0)	2 (0.7)	0.83	
IV antibiotics > 5 days, cases (%)	3 (10.7)	3 (1.0)	0.01*	
Cardiac arrythmia, cases (%)	1 (3.6)	0 (0)	0.087	
Pneumonia / respiratory issue, cases (%)	1 (3.6)	2 (0.7)	0.24	
Disability requiring higher level care, cases (%)	4 (14.3)	1 (0.3)	0.0002****	
Minor adverse events, cases with any of below (%)	2 (7.1)	23 (7.9)	0.67	25 (7.8)
Inadvertent mucosal perforation of mucosal flap, cases (%)	2 (7.1)	9 (3.1)	0.25	
Capnoperitoneum requiring intraprocedural venting, cases (%)	0 (0)	15 (4.8)	0.38	
Premature perforation of muscle layer, cases (%)	0 (0)	1 (3.4)	0.91	
The most serious perioperative adverse event per patients				
Technical adverse events, cases (%)	3 (10.7)	27 (9.2)	0.74	30 (9.3)

(technical failure, mucosal perforation, hydrothorax, bleeding, leak etc.)				
Non-technical adverse events, cases (%)	5 (17.9)	3 (1.0)	0.0002****	8 (2.5)
Cardiac arrythmia, cases (%)	1 (3.6)	0 (0)	0.087	
Disuse syndrome, cases (%)	3 (10.7)	1 (0.3)	0.0023***	
Pneumonia, cases (%)	1 (3.6)	2 (0.7)	0.24	
Postoperative hospital stay, mean (range), days	9.8 (4–51)	5.4 (3–78)	0.0013***	
	n = 23	n = 273		
Postoperative symptomatic RE-3 months, n (%)	3 (13.0)	53 (19.4)	0.59	56 (18.9)

*p < 0.05, ** p < 0.01, ***p < 0.005, ****p < 0.001

POEM: per-oral endoscopic myotomy, ICU: intensive care unit, IR: interventional radiology, IV: intravenous, RE reflux esophagitis

†Cases with either major or minor adverse events.

‡ Details are described in **Table S2.**

Table S1. Differences in grading system between IPOEMS and ASGE lexicon

Severity grade	IPOEMS[11]	Severity grade	ASGE lexicon[18]
Major	ICU stay	Fatal	Death
	Bleeding/hematoma requiring blood transfusion	Severe	Unplanned admission/prolongation of hospital stay for > 10 nights
	Surgical/IR/other intervention		ICU admission > 1 night
	Readmission within 30 days		Surgery for an adverse event
	Leak noted on post POEM imaging or endoscopy		Permanent disability
	Hydrothorax/hematothorax/pneumothorax		
	IV antibiotics > 5 days	Moderate	Unplanned anesthesia/ventilation support

	Cardiac arrythmia		Unplanned admission/prolongation of hospital stay for 4–10 nights
	Pneumonia/respiratory issue		ICU admission for 1 night
	Disability requiring higher-level care than prior to POEM		Transfusion
	Prolonged hospitalization events (> 5days)		Repeat endoscopy for an adverse event
			Interventional radiology for an adverse event
			Interventional treatment for integument injuries
Minor	Inadvertent mucosal perforation of mucosal flap	Minor	Unplanned hospital admission/prolongation of hospital stay for ≤ 3 nights
	Capnoperitoneum requiring intraprocedural venting		Post-procedure medical consultation
	Premature perforation of muscle layer		Procedure aborted (or not started) because of an adverse event

IPOEMS: international per oral endoscopic myotomy survey, ASGE: American Society for Gastrointestinal Endoscopy

POEM: per-oral endoscopic myotomy, ICU: intensive care unit, IR: interventional radiology, IV: intravenous

Table S2. Details of major adverse events

	Octogenarians n = 28	Non-octogenarians n = 293
Major adverse events, cases with any of below (%)	**7 (25.0)**	**9 (3.1)**
ICU stay, cases (%)	**1 (3.6)**	**1 (0.3)**
cases: details	1: hemodynamic instability due to ventricular fibrillation	1: hemodynamic instability due to systemic emphysema

Bleeding/hematoma requiring blood transfusion, cases (%)	**1 (3.6)**	**0 (0)**
cases: details	1: delayed bleeding with closure dehiscence	0: not applicable
Surgical/IR/other intervention, cases (%)	**2 (7.1)**	**3 (1.0)**
cases: details	1: endoscopic repair for mucosal perforation 1: endoscopic hemostasis for delayed bleeding and endoscopic repair for closure dehiscence	2: endoscopic repair for closure dehiscence 1: endoscopic repair for mucosal perforation and surgical intervention for the technical failure
Readmission within 30 days, cases (%)	**1 (3.6)**	**1 (0.3)**

cases: details	1: delayed bleeding with closure dehiscence	1: transient dysphagia due to esophageal edema
Leak, cases (%)	**2 (7.1)**	**2 (0.7)**
cases: details	1: mucosal perforation 1: delayed bleeding with closure dehiscence	1: mucosal perforation 1: closure dehiscence
Hydrothorax/hematothorax/pneumothorax, cases (%)	**0 (0)**	**2 (0.7)**
cases: details	0: not applicable	2: hydrothorax
IV antibiotics > 5 days, cases (%)	**3 (10.7)**	**3 (1.0)**
cases: details	1: pneumonia	2: closure dehiscence

	1: delayed bleeding with closure dehiscence 1: mucosal perforation	1: mucosal perforation
Cardiac arrythmia, cases (%)	**1 (3.6)**	**0 (0)**
cases: details	1: ventricular fibrillation	0: not applicable
Pneumonia/respiratory issue, cases (%)	**1 (3.6)**	**2 (0.7)**
cases: details	1: pneumonia	2: pneumonia
Disability requiring higher level care, cases (%)	**4 (14.3)**	**1 (0.3)**
cases: details	1: disuse syndrome (swallowing dysfunction and inactivity)	1: disuse syndrome (inactivity)

	1: disuse syndrome (swallowing dysfunction)
	2: disuse syndrome (inactivity)

ICU: intensive care unit, IR: interventional radiology, IV: intravenous