



Comparison of Zenker's per-oral endoscopic myotomy (Z-POEM) with standard flexible endoscopic septotomy for Zenker's diverticulum: a prospective study with 2-year follow-up

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Abstract

Background Flexible endoscopic therapy of Zenker's diverticulum using submucosal tunneling (Z-POEM) similar to esophageal Per-Oral Endoscopic Myotomy (POEM) is becoming increasingly common. However, data comparing Z-POEM with traditional flexible endoscopic septotomy (FES) are sparse. The aim of this study was to compare outcomes of Z-POEM with traditional FES over a medium-term follow-up period.

Methods This was a prospective study of patients who underwent Z-POEM for treatment of Zenker's diverticulum between 2018 and 2020 at a tertiary academic medical center compared to prior patients who had FES (between 2015 and 2018). Procedural characteristics and clinical outcomes (technical and clinical success, and adverse events) were compared between patients who underwent each treatment.

Results A total of 28 patients underwent ZD therapy during the study period. 13 patients (mean age 70 years; 77% male) underwent Z-POEM and 15 patients (mean age 72 years; 73% male) underwent traditional FES. The mean Zenker's diverticulum size was 2.4 ± 0.6 cm in the ZPOEM group vs 2.5 ± 0.8 cm in the FES group. The mean procedure time was similar between groups: 43.9 min (range 26–66) in the Z-POEM group and 60.2 min (range 25–92) in the traditional FES group ($t = 1.74$ $p = 0.19$). Overall technical success was seen in 100% of patients. There was one adverse event in the FES group (dehydration resulting in near-syncope) (1/28, 3.6%). Overall clinical success was seen in 92.8% (26/28) of patients and was not significantly different between groups (Z-POEM; 13/13, 100% vs FES; 13/15, 86.7%, $t = -1.36$ $p = 0.18$).

Conclusion This prospective study suggests that ZPOEM is an effective technique for the treatment of Zenker's diverticulum with no significant differences in clinical outcomes or adverse event rates when compared to traditional FES.

Over the past few years, Zenker's per-oral endoscopic myotomy (Z-POEM) has gained traction as a safe and effective treatment option for Zenker's diverticulum (ZD) [1–3], using a submucosal tunneling approach similar to esophageal POEM for achalasia. Traditional flexible endoscopic septotomy (FES), initially described in 1995 [4, 5], involves division of the septum containing the cricopharyngeus muscle between the Zenker's diverticulum and esophagus from the mucosa to the diverticular base. The main proposed advantage of Z-POEM over FES is the ability to visualize and completely cut the septum in the submucosal tunnel under the safety net of the overlying intact mucosa, theoretically

leading to lower rates of symptom recurrence. Data comparing Z-POEM to FES is still emerging, mainly consisting of retrospective comparison studies with short follow-up that have found no significant differences regarding rates of clinical success and symptom recurrence between these two treatment modalities and differing results with regard to rates of adverse events [2, 3, 5]. The aim of this study was to compare our prospective experience with Z-POEM versus FES over a medium-term follow-up period.

Methods

Patient selection and study design

All adult patients (≥ 18 years of age) undergoing Z-POEM for symptomatic Zenker's diverticulum at a single, tertiary academic medical center were enrolled in this study. The

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comparator group included patients who had undergone FES between 2015 and 2018, prior to the introduction of Z-POEM at our institution. Patients were included if they had a history of dysphagia and/or regurgitation, objective evidence of ZD demonstrated by esophagram and/or upper endoscopy, and underwent endoscopic myotomy. Patients were excluded if they were unable to consent or had any of the following medical conditions: portal hypertension, coagulopathy (INR > 1.5 and/or platelets < 50,000), a history of achalasia or other primary esophageal motility disorders, eosinophilic esophagitis, or other conditions that precluded the safe performance of endoscopy or anesthesia. The authors acknowledge that patients in the FES group have been included in a prior publication, [5] however a comparative study with these patients has not previously been done.

Description of endoscopic procedures

All patients underwent pre-procedure diagnostic upper endoscopy and barium esophagram to confirm the diagnosis and rule out alternate and coexisting conditions. Patients were asked to stay on a clear liquid diet for one day before the procedure to allow adequate clearance of food from the ZD for visualization and to minimize the risk of adverse events. Antibiotics were administered peri-procedurally, typically a semi-synthetic penicillin with beta-lactamase inhibitor (ampicillin-sulbactam), or a fluoroquinolone and metronidazole in the case of penicillin allergy.

All procedures (Z-POEM and FES) were performed in the interventional GI endoscopy unit by a single experienced endoscopist (MSW). Flexible endoscopic septotomy was performed under deep sedation (Monitored Anesthesia Care) or general anesthesia, as per assessment and recommendations by the attending anesthesiologist. Z-POEM

was performed under general anesthesia with endotracheal intubation. The technical steps of FES and Z-POEM have been previously described [4, 6, 7] and were performed as follows:

- (a) FES for ZD involves division of the muscle septum between the diverticulum and the esophageal lumen to create a common channel. This was accomplished by directly cutting the septum including the overlying mucosa, submucosa, and the muscle to the base or just above the base of the diverticulum with endoscopic knives (Fig. 1). Typical knives used were at the discretion of the endoscopist (Hook knife, Insulated Tip-2 knife (Olympus America, Central Valley, Pennsylvania), Hybrid Knife (ERBE, Marietta, GA), and Clutch-Cutter knife (Fujifilm Medical Systems USA, Lexington, MA)). The septotomy site was approximated with endoscopic clips (Quick Clip Pro, Olympus America, Center Valley, PA) at the discretion of the endoscopist.
- (b) Z-POEM was performed by submucosal injection and mucosal incision 1–2 cm proximal to the septum. The endoscope was advanced into the submucosal space and submucosal tunneling was performed by endoscopic submucosal dissection (ESD) and intermittent fluid injection with the Hybrid knife (ERBE, Marietta, GA). Tunneling was continued in the caudal direction toward the septum and on both sides of the septum. Myotomy of the exposed septum in the submucosal tunnel was then performed with the Hybrid Knife to the base, or just distal to the base, of the ZD (Fig. 2). As Z-POEM evolved, the technique was modified for the more recent procedures, where submucosal injection and incision was made directly on the septum rather than proximal to it. The submucosa was dissected directly under the incision, and ESD performed on the diverticular side and esophageal side of the septum to completely expose it. Myotomy was then completed as

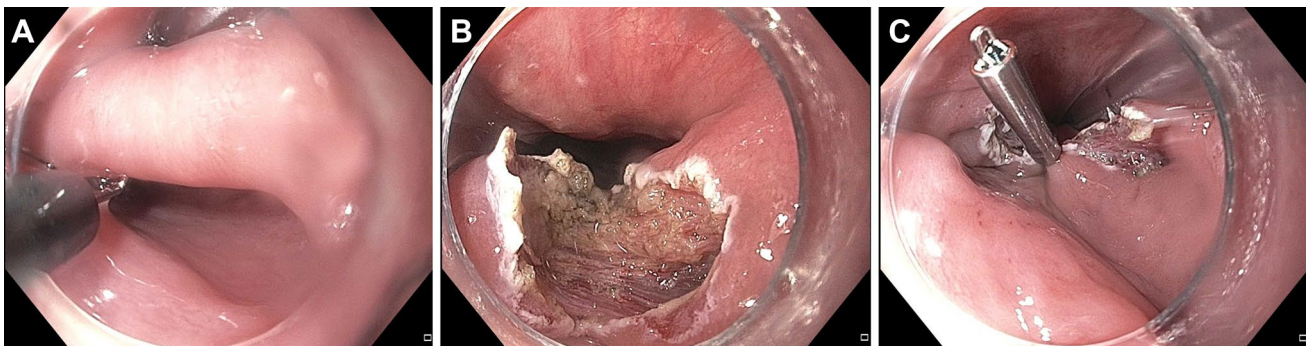
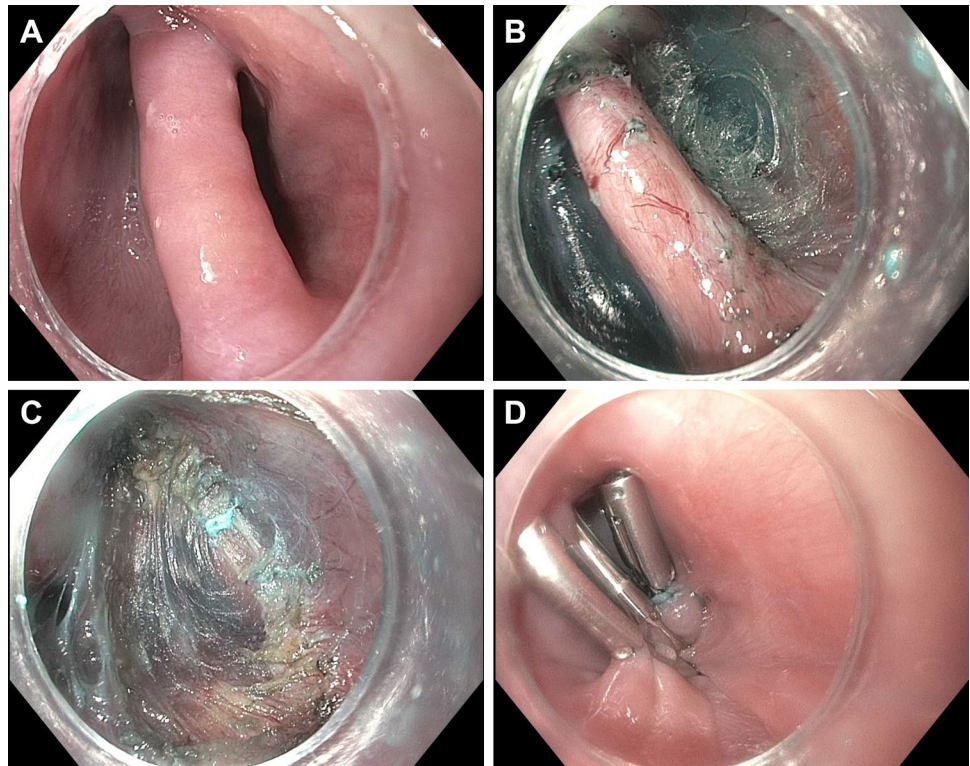


Fig. 1 Steps of Flexible Endoscopic Septotomy (FES) for Zenker's diverticulum: **A** A hook knife (Olympus Medical, Tokyo, Japan) is used to directly incise the septum. **B** The muscular septum is incised

to the base of the diverticulum **C** One endoscopic clip placed at the base of the incision. Images provided courtesy of Dr. Mihir Wagh

Fig. 2 Steps of endoscopic therapy of Zenker's Diverticulum using submucosal tunneling (Z-POEM): **A** A septum is visible between the Zenker's diverticulum to the left and esophageal lumen to the right of the photo. **B** The muscular septum is exposed via submucosal tunneling on the diverticular and esophageal sides. **C** Complete septotomy is performed inside the tunnel to the base or just beyond the base of the diverticulum. **D** The mucosal incision is closed with endoscopic clips. Images provided courtesy of Dr. Mihir Wagh



described above with the Hybrid knife. Exposed vessels or intraprocedural bleeding was treated with the dissection knife and/or Coagrasper (Olympus America, Center Valley, PA). The mucosal incision was closed with endoscopic clips (Quick Clip Pro, Olympus America, Center Valley, PA).

All patients were admitted for overnight observation and an esophagram was obtained the following morning to exclude leak after myotomy. Patients were discharged on a liquid diet and advanced to soft foods in 1 week. Oral antibiotics were continued for 7 days. Patients were seen for clinic follow-up and surveillance upper endoscopy.

Data collection and outcomes

Baseline information collected on patients included demographic information, symptom severity, measured by the pre-procedural Eckardt Score and individual components, dysphagia as measured by the pre-procedure Dakkak and Bennet Dysphagia score [8], and size of ZD as measured by barium esophagram. Peri-procedural characteristics were collected including the American Society of Anesthesiologists (ASA) class, device(s) used, length of the myotomy, number of clips used to close the myotomy, procedure time, and adverse events. Post-procedure variables included length of follow up, Eckardt score, and dysphagia score.

In addition, all patients were called at 24–72 h after their endoscopy per our endoscopy unit protocol to assess for adverse events. All patients underwent clinical follow-up and EGD at 3–6 months after Z-POEM per protocol to assess symptoms and treatment site. All data for 1 and 2 year outcomes were obtained via chart review and via patient phone call if these data were unavailable.

The primary outcome was comparison of the technical and clinical success of endoscopic ZD therapy between the two groups. The secondary outcome was assessment of adverse events in either group. For this study, technical success was defined as the ability to sever the septum between the ZD and esophagus and successfully complete the cricopharyngeal myotomy for Z-POEM or standard FES. Clinical success was defined as improvement in the Eckardt Score to ≤ 2 or the dysphagia score to ≤ 1 . Procedure related adverse events were recorded and categorized per published American Society for Gastrointestinal Endoscopy (ASGE) criteria [9]. Z-POEM time was calculated from the time of injection to the placement of the last clip, while FES time was calculated from the start of the septotomy to the end of septotomy or placement of the last clip (if clips were placed in the FES technique). This study was approved by the IRB and informed consent was obtained from all patients who participated in the study.

Statistical analysis

Descriptive variables are reported for all patients as mean \pm SD if normally distributed and median [IQR] if non-parametric. Minimum and maximum times are reported for all procedures. Group comparisons were performed using Student's t-test Mann–Whitney U testing as appropriate. All tests were two sided with significance defined as $\alpha < 0.05$. SAS version 9.4 was used for all analyses (SAS Institute, Cary, NC).

Results

Patient and procedure characteristics

A total of 28 patients (Z-POEM = 13, FES = 15) underwent ZD therapy (Table 1). The mean age of the cohort was 71 ± 10.16 and 21 (75%) of the patients were male. The mean pre-procedure ZD size was 2.48 ± 0.83 cm, median Eckardt score was 3 [2, 5], and the median dysphagia score was 1 [1, 3]. The two groups had no evidence of statistically significant differences in baseline characteristics (Table 1).

Regarding procedural characteristics, the mean procedure time was 43.9 ± 13.7 min in the Z-POEM group (range 26–66) and 60.2 ± 22.4 min (range 25–92) in the FES group (Table 2). This difference did not show evidence of statistical significance ($t = 1.74$ $p = 0.19$). However, notably in the Z-POEM group, the average procedure time decreased with successive procedures (33.2 ± 8.8 min for the last four procedures). The Hybrid Knife was used for the initial incision and tunneling in all patients undergoing Z-POEM ($n = 13$), and used for the myotomy in 10 patients. Three patients had the myotomy performed with the Clutch-Cutter knife inside the submucosal tunnel. Knife usage in patients undergoing

Table 2 One year outcomes of Z-POEM vs FES

	Overall ($n = 25$)	Z-POEM ($n = 13$)	Traditional FES ($n = 15$)
Eckardt score ^a	0 [0, 2]	0 [0, 1.5]	1 [0, 2]
Dysphagia score ^a	0.5 [0, 1]	0 [0, 1]	1 [1, 1.5]

^aReported as median [IQR]

traditional FES was as follows: hybrid knife = 2, hook knife = 5, Clutch-Cutter = 5, hook knife and insulated tip-2 knife = 2, hook knife and dual knife = 1. A median of 4 [4, 5] clips were placed during the procedure in the Z-POEM group and 1 clip at the base of the septotomy in one patient in the FES group.

Clinical outcomes

Overall technical success was seen in 100% (28/28) of patients. Overall clinical success was seen in 92.8% (26/28) of patients and was not significantly different between groups by either Eckardt score or dysphagia score (Z-POEM; 13/13, 100% vs FES; 13/15, 86.7%, $t = -1.36$ $p = 0.18$). The overall adverse event rate was 1/28 (3.6%)—1 patient in the traditional FES group experienced vertigo with near-syncope within 24 h of the procedure. The patient was admitted to the hospital and his symptoms resolved with administration of IV fluids. There were no AEs observed in the Z-POEM group.

One year follow-up data were available for 25 patients (Z-POEM = 12, FES = 13). The two groups did not significantly differ in terms of post-procedure Eckardt score (Z-POEM = 0 [0, 2], FES = 1 [0, 2], $z = -0.981$, $p = 0.34$),

Table 1 Patient demographics and procedural details

	Overall ($n = 28$)	Z-POEM ($n = 13$)	Traditional FES ($n = 15$)	p -value ^c
Age (years) ^a	71.1 ± 10.2	69.9 ± 11.5	72.2 ± 9.1	$p = 0.55$
Sex (n , male)	21, 75%	10, 77%	10, 73%	$p = 1.00$
Pre-procedural symptoms ^b				
Eckardt score ^b	4 [2, 6]	5 [3, 7]	3 [2, 5]	$p = 0.74$
Dysphagia score	1 [1, 3]	1 [1, 3]	2 [1, 2]	$p = 0.40$
ASA Class ^b	2 [2, 3]	2 [2, 3]	2 [2, 3]	$p = 0.82$
Zenker's diverticulum size (cm) ^a	2.4 ± 0.6	2.4 ± 0.6	2.5 ± 0.8	$p = 0.63$
Procedure time (min) ^a	51.8 ± 19.9	43.9 ± 13.7	60.2 ± 22.4	$p = 0.19$
Technical success (%)	100%	100%	100%	$p = 1.00$
Clinical success (n , %)	26 (92.8%)	13 (100%)	13 (86.7%)	$p = 0.18$

^aReported as mean \pm SD

^bReported as median [IQR]

^cCompared with Student's t-test, χ^2 test, or Mann–Whitney U test as appropriate

or dysphagia score (Z-POEM = 0 [0, 1], FES = 1 [1, 1.5], $z = 1.21$, $p = 0.24$). Two-year follow-up data were collected for 9 Z-POEM patients. The median 2-year Eckardt score was 1 [0, 1] and the median 2-year dysphagia score was 0 [0, 1]. None of the patients who had 2-year data required additional therapy following Z-POEM.

Discussion

Both Z-POEM and FES have come to prominence as viable and preferred alternatives to more-invasive surgical management of Zenker's diverticulum. In addition, when compared to transoral stapled diverticulotomy traditionally performed by otolaryngology, Z-POEM and FES do not require a bulky rigid esophagoscope or extreme neck extension, making these procedures more suitable for elderly patients with poor neck mobility, often the very population where ZD is more common, and for smaller ZD. The rigid stapling device can be difficult to maneuver and treat small ZD due to poor visualization and difficulty in isolating the septum, and may leave a residual pouch since the stapling device does not cut to the very end of the blades, accounting for the high risk of recurrence [7, 10, 11].

Although FES has previously been demonstrated as an effective and safe option for the treatment of ZD [12], the technique could leave a small remnant muscular septum that could theoretically cause recurrent dysphagia. [7] The recent Z-POEM technique solves this potential issue by allowing the endoscopist to dissect down to the base or just beyond the base of the septum and perform complete myotomy, but has been criticized as being time-consuming, more technically challenging and potentially associated with higher adverse events. Thus, comparison of both the long-term clinical outcomes and safety of these procedures is necessary.

In this study, we demonstrated that Z-POEM did not significantly differ from FES for the treatment of ZD in terms of clinical outcomes, and that both methods achieved a high degree of clinical success with a low rate of AEs. We further demonstrate that the beneficial effect of Z-POEM persisted to two years of follow up. Our findings are consistent with those of Al-Ghamdi et al. where 92.7% of patients had initial clinical success after the procedure, but our patients notably had less long-term recurrence of symptoms, with 0% recurrence at 2 years vs 14.7% at around 9 months. [3] Data so far, therefore suggests that Z-POEM is at least as effective as FES in the treatment of ZD.

The strengths of this study are that ZPOEM patients were prospectively enrolled, underwent endoscopy at 3–6 months to assess myotomy site, and had medium-term clinical follow-up of 2 years as opposed to other studies with shorter average follow-up time [13–15]. Furthermore, we demonstrate, that despite the increased complexity of the

Z-POEM procedure, requiring endoscopic submucosal dissection, overall procedure times in the hands of a trained endoscopist were similar for both procedures. The improvement in mean procedural time as more Z-POEM procedures were performed (48.7 ± 13.0 min for the first 11 procedures vs 33.2 ± 8.8 min for the last 4 procedures) shows that additional experience in the Z-POEM technique resulted in more time savings. These data, in addition to the similar technical success rates and adverse event rates between groups, support that Z-POEM can be considered as a primary treatment for ZD.

We acknowledge that our study has several limitations. Our study was performed at a single center with a limited number of patients, and recruitment was impacted by the COVID-19 pandemic. Patients who underwent Z-POEM were recruited consecutively (2018–2020) and compared to prior ZD patients who had FES (2015–2018), which may have introduced selection bias into the cohort owing to improvements in technology over the study periods, including availability of endoscopic equipment, accessories and refinements in technique developed over time that are not accounted for in the analysis. We also realize that since this study compared the two techniques over different time periods, with a finite number of patients in the FES control group, we were not able to perform sample size calculations. As a result, we may only be able to detect large differences between Z-POEM and FES groups and smaller differences may have been missed. Also, all procedures (Z-POEM and FES) were performed by a single endoscopist, and data analysis does not account for changes or improvement in procedural technique over time. In addition, follow-up data was collected via phone call if not available from clinical encounters, which may have introduced reporting bias. Our results differ from a recently published systemic review and meta-analysis that demonstrated that Z-POEM has higher clinical success than FES [13]. However, improvements in Z-POEM technique, and smaller numbers of patients with high clinical success may account for this differing result. Our study did not compare the utility of the two techniques for various ZD sizes and we are also unable to comment on the cost effectiveness of the two techniques.

Several other considerations should be noted when clinically comparing and choosing between the two treatment modalities. First is that Z-POEM requires advanced technical skills, an endoscopist trained in endoscopic submucosal dissection and may require the use of the more specialized knives, which may not be feasible at all centers, although notably we have previously demonstrated that the choice of knife used does not have significant impact on procedural outcomes [5]. Second, the Z-POEM procedure requires the use of multiple endoscopic clips, which may add to the cost of the procedure. Lastly, although general anesthesia was used for both procedures in our center as per anesthesia

recommendations, FES can be performed safely with moderate or deep sedation (Monitored Anesthesia Care), which depending on anesthesia availability may factor into the choice of procedure.

Conclusion

Z-POEM appears to be safe and comparable to FES in terms of procedural characteristics and clinical success at medium-term follow-up in the hands of an experienced endoscopist. Moving forward, larger prospective, longer-term, controlled studies are needed to fully compare the two techniques.

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Declarations

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