

Review

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Expanding the therapeutic options for Zenker's diverticulum: from open diverticulectomy to transoral septoplasty

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How to cite this article: Scardino A, Siboni S, Milito P, Bonavina L. Expanding the therapeutic options for Zenker's diverticulum: from open diverticulectomy to transoral septoplasty. *Mini-invasive Surg* 2022;6:57. <https://dx.doi.org/10.20517/2574-1225.2022.55>

Received: 13 Jul 2022 **First Decision:** 5 Aug 2022 **Revised:** 6 Sep 2022 **Accepted:** 30 Sep 2022 **Published:** 14 Nov 2022

Academic Editor: Giulio Belli **Copy Editor:** Jia-Xin Zhang **Production Editor:** Jia-Xin Zhang

Abstract

Significant technical changes and a shift toward a transoral approach have occurred in the management of Zenker's diverticulum over the past three decades. Transoral stapling is already an established and commonly performed procedure. Zenker peroral endoscopic myotomy (Z-POEM) and Zenker peroral endoscopy septotomy (Z-POES) are innovative techniques that are rapidly spreading and replacing more traditional therapeutic options. This review provides an overview of the current status of minimally invasive transoral management to assess whether a tailored approach is feasible and safe and may improve quality of life and reduce recurrence rates.

Keywords: Zenker diverticulum, cricopharyngeal myotomy, rigid endoscopy, flexible endoscopy, peroral endoscopic myotomy, Z-POEM, Z-POES

INTRODUCTION

Zenker diverticulum (ZD) is an acquired mucosal pouch protruding from the Killian's triangle. Pathogenetic factors include altered upper esophageal sphincter coordination, reduced hypopharyngeal wall compliance, and increased intrabolus pressure^[1,2]. It is considered a rare disease, with an estimated prevalence of 0.11% or 2 per 100,000 persons per year, but the incidence will likely increase with the



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progressive population aging^[3]. Common symptoms are dysphagia and regurgitation, and the most frequent complication is recurrent aspiration pneumonia^[4]. It has been estimated that the ZD annual average caseload is 8.7 patients per year^[5].

Historically, surgical treatment of ZD consisted of surgical resection of the pouch. Only during the last five decades has the crucial role of the cricopharyngeal muscle been recognized, and cricopharyngeal myotomy, performed either surgically or endoscopically, has become the main target of treatment. The developments of minimally invasive surgery and endoscopic technologies, including rigid and flexible endoscopy, have led to profound changes in management^[6,7]. Most importantly, the recent introduction of Zenker peroral endoscopic myotomy (Z-POEM) reflects a better understanding of the pathophysiology of the disease and the need to minimize recurrence rates and improve the quality of life in these patients. In this review, we analyze the current status of minimally invasive transoral management of ZD.

EVOLUTION OF TREATMENT (1): FROM OPEN TO TRANSORAL SURGERY

Zenker diverticulum was initially treated by open surgery or rigid endoscopy, respectively, with the aim to resect the pouch or divide the septum between the esophagus and the diverticulum. Surgical procedures for ZD have been refined and progressively standardized using a stapler to reduce the incidence of leaks. Over time, the importance of adding a cricopharyngeal myotomy to surgical resection of the pouch has been recognized as a critical component of the surgical procedure to minimize leaks and reduce anatomical and symptomatic recurrences^[8] [Table 1].

This has encouraged the development of minimally invasive transoral techniques to divide the common septum using mainly electrocautery or CO₂ laser^[9]. At the beginning of the laparoscopic era, transoral stapling revolutionized the therapeutic approach to ZD. The procedure, first proposed by Collard^[10], Martin-Hirsch^[11], and Narne^[12] in 1993, consisted of division of the septum by an endoscopic linear endostapler introduced through a rigid Weerda diverticuloscope under general anesthesia. This technique showed excellent clinical outcomes, especially in patients with large-sized (> 3 cm) diverticula [Table 2]. In addition, restoration of pharyngoesophageal physiology was shown by manometric and scintigraphic studies showing decreased hypopharyngeal intrabolus pressure and improved upper esophageal sphincter clearance^[13]. However, placement of the rigid diverticuloscope and actioning of the endostapler might be difficult in patients with neck stiffness or limited mouth opening^[14]. In addition, the procedure is not indicated in patients with small diverticula (< 3 cm) because of the inability to engage enough cricopharyngeal muscle tissue for stapling over the entire length of the septum^[15,16]. A multicenter study from the UK on 585 patients operated by otolaryngologists showed a conversion rate of 7.7%, an overall complication rate of 9.6%, and a recurrence rate of 12.8%^[17]. Over the years, a modified endostapling technique using a traction suture on the apex of the septum was proposed to add an average of 1 cm of septum length into the stapler jaws, thus enabling extended septal division^[18,19] [Figure 1]. In addition, various cutting and coagulation devices, including Harmonic scalpel and LigaSure, were introduced to provide complete septum division at least 1 cm distal to the uncut suture line. Soft overtubes have also been proposed to obviate the difficulties in positioning the rigid diverticuloscope^[20].

EVOLUTION OF TREATMENT (2): FROM STANDARD FLEXIBLE ENDOSCOPY TO THIRD-SPACE ENDOSCOPY

Although transoral stapling has been the preferred initial approach for ZD, lack of expertise with the rigid transoral approach, anatomic limitations of septum exposure such as reduced neck extension or inadequate mouth opening, and the requirement for narcosis have encouraged the development of flexible endoscopic techniques. Flexible endoscopic septotomy (FES) has quickly gained popularity since the first report by

Table 1. Outcomes of open surgical therapy for Zenker diverticulum

Author	Year	No. patients	Complications (%)	Mortality (%)	Satisfactory results (%)	Recurrence (%)
Bonafede et al. ^[38]	1997	87	24	3.5	78	NR
Zbären et al. ^[39]	1999	66	15	1.5	77	6
Leporrier et al. ^[40]	2001	40	17.5	0	92	0
Gutschowet al. ^[41]	2002	101	13	0	98	3.9
Colombo-Benkmann et al. ^[42]	2003	79	15	0	76	2.5
Bonavina et al. ^[8]	2007	116	3.4	0.8	84.2	1.7
Lerut et al. ^[43]	2008	289	8.5	0	94.2	0.03
Rizzetto et al. ^[44]	2008	77	13	0	95	5.2
Greene et al. ^[45]	2015	68	NR	0	69%	NR

Modified from Aiolfi et al.^[6]; NR: not reported.

Table 2. Outcomes of transoral stapling for Zenker diverticulum

Author	Year	No. patients	Complications (%)	Mortality (%)	Satisfactory results (%)	Recurrence (%)
Cook et al. ^[46]	2000	74	5	0	71	8.7
Jaramillo et al. ^[47]	2001	32	3.7	0	80	7.4
Stoeckli et al. ^[48]	2002	30	27	0	96	NR
Counter et al. ^[49]	2002	31	9.7	0	50	22
Chang et al. ^[50]	2003	150	12.7	0	73.3	11.8
Wasserzug et al. ^[51]	2010	55	4	0	90	10
Bonavina et al. ^[52]	2015	100	2	0	84	24

Modified from Aiolfi et al.^[6]; NR: not reported.

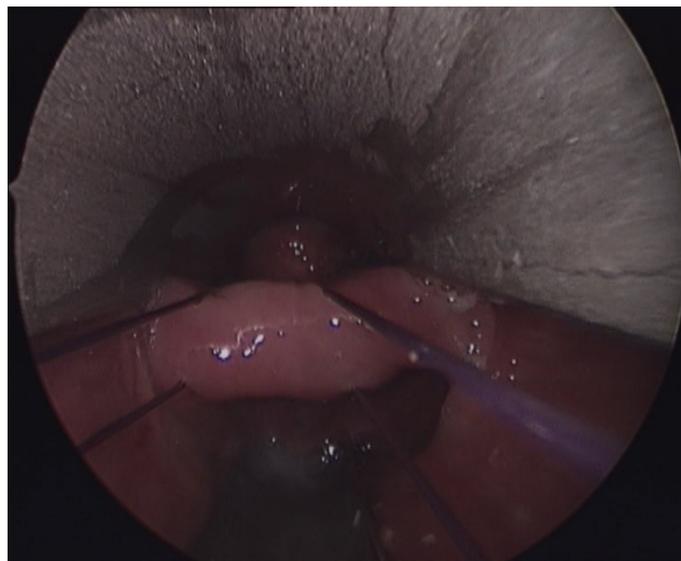


Figure 1. Transoral septum stapling: Traction sutures applied with Endostitch™ to enable extended septum division.

Ishioka et al. in 1995. Since then, this procedure has commonly been performed under deep sedation and in the outpatient setting, thus allowing the treatment of elderly patients with small (< 3 cm) pouches who may be unfit for general anesthesia^[21]. Over time, different devices, such as needle-knife, hook-knife, harmonic

scalpel, thulium laser, *etc.*, have been introduced to assist the FES with satisfactory outcomes. Additionally, the use of CO₂ insufflation and routine mucosal closure have consistently been recommended to minimize the risk of perforation. Regardless of the device used, FES has proven feasible and effective during short-term follow-up, with a recurrence rate of 29%^[22-25]. However, FES is repeatable, and multiple treatments can be done to complete septum division. A systematic review and network meta-analysis including nine cohort studies with a total of 903 patients and comparing endoscopic laser-assisted diverticulotomy, endoscopic stapler-assisted diverticulotomy, and transcervical diverticulectomy concluded that the open surgical approach has a decreased likelihood of persistent or recurrent symptoms compared with the endoscopic techniques^[26].

Experience with the use of POEM for esophageal achalasia^[27] helped translate the principles of third-space endoscopy to the pharyngoesophageal area, thereby pushing the boundaries of FES. The Z-POEM technique has quickly gained popularity and will be accepted as the gold standard flexible endoscopic technique. Z-POEM is an innovative technique that allows cricopharyngeal myotomy through submucosal tunneling. The majority of reports now differentiate between two different tunneling techniques based on the site of mucosal incision. In the conventional technique, originally described by Li *et al.*, the hypopharyngeal mucosa is opened 1.5-2 cm proximal to the septum and the submucosal tunneling is created to reach and divide the cricopharyngeal muscle^[28]. The mucosal entry site is then closed using endoscopic clips. Performing the incision proximal to the septum makes the procedure safer, given its distance from the mediastinum, but care must be taken to avoid tearing the thin hypopharyngeal mucosa during clip closure. A limitation of Z-POEM is that only the cricopharyngeal muscle is divided, not the proximal esophageal muscle, and that the defunctionalized remnant pouch may be responsible for residual symptoms.

An alternative third-space approach, called Zenker peroral endoscopic septotomy (Z-POES), was described by Mavrogenis *et al.* to overcome the technical challenges of the Z-POEM technique and to improve outcomes^[29]. Z-POES is a modified tunneling technique that consists in opening the mucosa alongside the long axis of the septum, directly on top of it, to gain direct access to the muscle. Then, the submucosal tunnel ahead and behind the cricopharyngeal muscle is created, and the proximal esophageal muscle fibers are also divided [Figure 2]. At the end of the myotomy, a remodeling V-shaped mucosal septal incision can be performed to widen the communication between the residual pouch and the esophagus, making this procedure particularly suitable for larger diverticula^[30].

A recent pilot study by Repici *et al.* on 20 patients advocated the use of Z-POES for ZD > 20 mm in size^[31]. The average procedural time was 13.8 min, and the technique was successful in 100% of patients. No symptomatic adverse events occurred, and the one-year clinical success rate was 95%. In a recent systematic review by Spadaccini *et al.*, which included nine studies with a total of 196 patients undergoing Z-POEM or Z-POES, the pooled rate of clinical success and the pooled rate of adverse events were 93.4% and 4.9%, respectively^[32]. No significant differences in terms of efficacy and safety were found between the two tunneling techniques. A recent meta-analysis of 11 studies^[33] that included a total of 357 patients undergoing Z-POEM showed a pooled technical success of 96.3% (95%CI: 93.6%-97.9%), a pooled incidence of adverse events of 12.4% (95%CI: 9.1%-16.7%), and a clinical success rate of 93% (95%CI: 89.4%-95.4%). The pooled clinical recurrence rate was 11.2% (95%CI: 7.6%-16.2%).

CLINICAL RESULTS OF Z-POEM AND Z-POES

A summary of the outcomes of Z-POEM and Z-POES reported in the literature, including our personal experience, is presented in Table 3.

Table 3. Literature review and personal experience with Z-POEM and Z-POES

Author	Study design	Technique	No. of patients	Technical success (%)	Clinical success (%)	Adverse events (%)	Follow-up range, months
Maydeo et al., 2019 ^[53]	Retrospective single-center	Z-POEM	20	100	86	No serious AE	0-12
Kamal et al., 2020 ^[54]	Meta-analysis	Z-POEM	233	95	NR	6	NR
Yang et al., 2020 ^[55]	Retrospective multicenter	Z-POEM	75	97.3	92	6.7 (1 bleeding, 4 perforations)	3.4-14.5
Sanaei et al., 2020 ^[56]	Retrospective multicenter	Z-POEM	32	93.8	96	12.5 (2 leaks)	NR
Al Ghamdi et al., 2020 ^[57]	Retrospective multicenter	Z-POEM	91	NR	95	6	3-7.5
Repici et al., 2020 ^[31]	Retrospective single-center	Z-POES	20	100	95	No serious AE	6-20
Klingler et al., 2020 ^[58]	Retrospective single-center	Z-POES	19	94.7	89.5	10.5 (2 perforations, 1 retropharyngeal abscess)	4.7-15.5
Spadaccini et al., 2021 ^[32]	Systematic review	Z-POEM, Z-POES	196	96.9	93.4	4.9	NR
Personal experience [University of Milan, IRCCS Policlinico San Donato]	Retrospective single-center	Z-POES	17	100	94.2	5.8 (1 leak)	3-41

AE: Adverse event; NR: not reported; Z-POEM: Zenker peroral endoscopic myotomy; Z-POES: Zenker peroral endoscopic septotomy.



Figure 2. Z-POES: Mucosal incision and exposure of the cricopharyngeus (left); and visualization of the buccopharyngeal fascia after myotomy (right).

Over the past two decades, a total of 271 patients have been treated for ZD at our esophageal center. Of these individuals, 20 (7.4%) underwent open surgery and 198 (73%) transoral stapling through rigid endoscopy. Overall, 53 (19.6%) patients underwent a flexible endoscopic procedure, 17 (32%) of whom were treated with Z-POES. The technical success rate of the procedure was 100%, and the clinical success rate was 94.2%. One patient developed a subclinical leak which was treated conservatively with antibiotics and naso-enteral nutrition.

DISCUSSION

The development of transoral techniques has allowed a minimally invasive and precise approach to treating ZD. However, anatomical characteristics of patients, small pouches, and lack of physician's expertise with

rigid endoscopy represent limitations of the transoral stapling technique^[34]. Both Z-POEM and Z-POES appear safe and effective and may prove superior to the standard flexible endoscopy technique because they provide direct exposure of the cricopharyngeal muscle and allow performing single-stage cricopharyngeal myotomy with pouch remodeling. This may translate into a reduction of anatomical and symptomatic recurrences and lower reintervention rates.

A complete cricopharyngeal myotomy is the cornerstone of both surgical and endoscopic approaches. From the flexible endoscopic perspective, the buccopharyngeal fascia represents an important safety landmark. This thin structure is displaced posteriorly by the diverticulum, and its preservation may guarantee a complete myotomy without risks. However, it must be kept in mind that the cricopharyngeus is a circular muscle lacking an external layer of longitudinal muscle and perforation of the buccopharyngeal fascia may result in mediastinitis^[35]. In real-world practice, it is challenging to identify a precise visual cue confirming that the myotomy is complete without breaking the fascia and entering the prevertebral space. Often, the trade-off to minimize the risk of perforation during standard FES is to plan a multi-stage procedure. With Z-POEM, identification of the buccopharyngeal fascia at the bottom of the pouch remains difficult during submucosal tunneling, but avoiding the posterior approach may further reduce the risk of perforation^[36].

Management of ZD requires an interdisciplinary and cooperative approach. Multiple specialists (surgeons, gastroenterologists, and otolaryngologists) may be involved in the decision-making process to deliver the best care to the patient. Nowadays, indications for an open surgical approach have become rare. In our opinion, large ZD (> 3 cm) can be safely treated with endostapling, while smaller ZD can be treated with FES or Z-POES. Recurrent ZD can be safely treated with either transoral or open approach^[37].

CONCLUSIONS

Peroral endoscopic myotomy techniques have opened a new era in the management of patients with ZD. However, appropriate training in advanced operative endoscopy remains critical, and high-quality studies with long-term and standardized patient-reported outcomes are necessary to validate these promising clinical findings.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Siboni S, Bonavina L

Performed data acquisition: Milito P, Scardino A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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