

World Journal of *Clinical Cases*

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REVIEW

- 2066 Tumor circulome in the liquid biopsies for digestive tract cancer diagnosis and prognosis
Chen L, Chen Y, Feng YL, Zhu Y, Wang LQ, Hu S, Cheng P
- 2081 Isoflavones and inflammatory bowel disease
Wu ZY, Sang LX, Chang B

MINIREVIEWS

- 2092 Cytapheresis for pyoderma gangrenosum associated with inflammatory bowel disease: A review of current status
Tominaga K, Kamimura K, Sato H, Ko M, Kawata Y, Mizusawa T, Yokoyama J, Terai S
- 2102 Altered physiology of mesenchymal stem cells in the pathogenesis of adolescent idiopathic scoliosis
Ko DS, Kim YH, Goh TS, Lee JS
- 2111 Association between liver targeted antiviral therapy in colorectal cancer and survival benefits: An appraisal
Wang Q, Yu CR
- 2116 Peroral endoscopic myotomy for management of gastrointestinal motility disorder
Feng Z, Liu ZM, Yuan XL, Ye LS, Wu CC, Tan QH, Hu B

ORIGINAL ARTICLE**Case Control Study**

- 2127 Clinical prediction of complicated appendicitis: A case-control study utilizing logistic regression
Sasaki Y, Komatsu F, Kashima N, Suzuki T, Takemoto I, Kijima S, Maeda T, Miyazaki T, Honda Y, Zai H, Shimada N, Funahashi K, Urita Y
- 2137 Clinical application of ultrasound-guided selective proximal and distal brachial plexus block in rapid rehabilitation surgery for hand trauma
Zhang J, Li M, Jia HB, Zhang L
- 2144 High flux hemodialysis in elderly patients with chronic kidney failure
Xue HY, Duan B, Li ZJ, Du P
- 2150 Determination of vitamin D and analysis of risk factors for osteoporosis in patients with chronic pain
Duan BL, Mao YR, Xue LQ, Yu QY, Liu MY

Retrospective Study

- 2162 Differences in parents of pediatric liver transplantation and chronic liver disease patients
Akbulut S, Gunes G, Saritas H, Aslan B, Karipkiz Y, Demyati K, Gungor S, Yilmaz S
- 2173 Epidemiological investigation of *Helicobacter pylori* infection in elderly people in Beijing
Zhu HM, Li BY, Tang Z, She J, Liang XY, Dong LK, Zhang M
- 2181 Application of a pre-filled tissue expander for preventing soft tissue incarceration during tibial distraction osteogenesis
Chen H, Teng X, Hu XH, Cheng L, Du WL, Shen YM
- 2190 Evaluation of clinical significance of claudin 7 and construction of prognostic grading system for stage II colorectal cancer
Quan JC, Peng J, Guan X, Liu Z, Jiang Z, Chen HP, Zhuang M, Wang S, Sun P, Wang HY, Zou SM, Wang XS
- 2201 Choice and management of negative pressure drainage in anterior cervical surgery
Su QH, Zhu K, Li YC, Chen T, Zhang Y, Tan J, Guo S
- 2210 Risk scores, prevention, and treatment of maternal venous thromboembolism
Zhang W, Shen J, Sun JL
- 2219 Role of Hiraoka's transurethral detachment of the prostate combined with biopsy of the peripheral zone during the same session in patients with repeated negative biopsies in the diagnosis of prostate cancer
Pan CY, Wu B, Yao ZC, Zhu XQ, Jiang YZ, Bai S
- 2227 Efficacy of thoracoscopic anatomical segmentectomy for small pulmonary nodules
Li H, Liu Y, Ling BC, Hu B

Observational Study

- 2235 Attitudes, awareness, and knowledge levels of the Turkish adult population toward organ donation: Study of a nationwide survey
Akbulut S, Ozer A, Gokce A, Demyati K, Saritas H, Yilmaz S
- 2246 Metabolic biomarkers and long-term blood pressure variability in military young male adults
Lin YK, Liu PY, Fan CH, Tsai KZ, Lin YP, Lee JM, Lee JT, Lin GM
- 2255 Cytokines predict virological response in chronic hepatitis B patients receiving peginterferon alfa-2a therapy
Fu WK, Cao J, Mi NN, Huang CF, Gao L, Zhang JD, Yue P, Bai B, Lin YY, Meng WB

SYSTEMATIC REVIEWS

- 2266 Utilising digital health to improve medication-related quality of care for hypertensive patients: An integrative literature review
Wechkunanukul K, Parajuli DR, Hamiduzzaman M

META-ANALYSIS

- 2280** Role of *IL-17* gene polymorphisms in osteoarthritis: A meta-analysis based on observational studies
Yang HY, Liu YZ, Zhou XD, Huang Y, Xu NW

CASE REPORT

- 2294** Various diagnostic possibilities for zygomatic arch pain: Seven case reports and review of literature
Park S, Park JW
- 2305** Extensive multifocal and pleomorphic pulmonary lesions in Waldenström macroglobulinemia: A case report
Zhao DF, Ning HY, Cen J, Liu Y, Qian LR, Han ZH, Shen JL
- 2312** Lung cancer from a focal bulla into thin-walled adenocarcinoma with ground glass opacity – an observation for more than 10 years: A case report
Meng SS, Wang SD, Zhang YY, Wang J
- 2318** Pyogenic discitis with an epidural abscess after cervical analgesic discography: A case report
Wu B, He X, Peng BG
- 2325** Clinical characteristics, diagnosis, and treatment of COVID-19: A case report
He YF, Lian SJ, Dong YC
- 2332** Paraplegia after transcatheter artery chemoembolization in a child with clear cell sarcoma of the kidney: A case report
Cai JB, He M, Wang FL, Xiong JN, Mao JQ, Guan ZH, Li LJ, Wang JH
- 2339** Macrophage activation syndrome as a complication of dermatomyositis: A case report
Zhu DX, Qiao JJ, Fang H
- 2345** Serial computed tomographic findings and specific clinical features of pediatric COVID-19 pneumonia: A case report
Chen X, Zou XJ, Xu Z
- 2350** Myxofibrosarcoma of the scalp with difficult preoperative diagnosis: A case report and review of the literature
Ke XT, Yu XF, Liu JY, Huang F, Chen MG, Lai QQ
- 2359** Endoscopic pedicle flap grafting in the treatment of esophageal fistulas: A case report
Zhang YH, Du J, Li CH, Hu B
- 2364** Hemophagocytic syndrome as a complication of acute pancreatitis: A case report
Han CQ, Xie XR, Zhang Q, Ding Z, Hou XH
- 2374** Reduced delay in diagnosis of odontogenic keratocysts with malignant transformation: A case report
Luo XJ, Cheng ML, Huang CM, Zhao XP

- 2380** Gastric pyloric gland adenoma resembling a submucosal tumor: A case report
Min CC, Wu J, Hou F, Mao T, Li XY, Ding XL, Liu H
- 2387** Ataxia-telangiectasia complicated with Hodgkin's lymphoma: A case report
Li XL, Wang YL
- 2392** Uterine incision dehiscence 3 mo after cesarean section causing massive bleeding: A case report
Zhang Y, Ma NY, Pang XA
- 2399** Optical coherence tomography guided treatment avoids stenting in an antiphospholipid syndrome patient:
A case report
Du BB, Wang XT, Tong YL, Liu K, Li PP, Li XD, Yang P, Wang Y

LETTER TO THE EDITOR

- 2406** Macrophage activation syndrome as an initial presentation of systemic lupus erythematosus
Shi LJ, Guo Q, Li SG

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Editorial Board Member of *World Journal of Clinical Cases*, Consolato M Sergi, FRCP (C), MD, PhD, Professor, Department of Lab. Medicine and Pathology, University of Alberta, Edmonton T6G 2B7, Canada

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Peroral endoscopic myotomy for management of gastrointestinal motility disorder

Zhe Feng, Zi-Ming Liu, Xiang-Lei Yuan, Lian-Song Ye, Chun-Cheng Wu, Qing-Hua Tan, Bing Hu

ORCID number: Zhe Feng (0000-0002-6545-6899); Zi-Ming Liu (0000-0001-6123-4466); Xiang-Lei Yuan (0000-0003-2281-5094); Lian-Song Ye (0000-0001-5542-2508); Chun-Cheng Wu (0000-0002-8390-4202); Qing-Hua Tan (0000-0001-5032-9849); Bing Hu (0000-0002-9898-8656).

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Zhe Feng, Zi-Ming Liu, Xiang-Lei Yuan, Lian-Song Ye, Chun-Cheng Wu, Qing-Hua Tan, Bing Hu, Department of Gastroenterology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Corresponding author: Bing Hu, MD, Chief Doctor, Professor, Department of Gastroenterology, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan Province, China. hubingnj@163.com

Abstract

Achalasia is a type of esophageal motility disorder, consisting of relaxation dysfunction of the lower esophagus and disturbed esophageal peristalsis. Related clinical symptoms include dysphagia, regurgitation, chest pain, and weight loss. Traditional treatment options include endoscopic botulinum toxin injection, endoscopic pneumatic dilation, and laparoscopic Heller's myotomy. These therapies mainly relieve symptoms by reducing the pressure on the lower esophageal sphincter and reducing blood flow resistance at the esophagogastric junction. Based on endoscopic submucosal dissection and natural orifice transluminal endoscopic surgery, peroral endoscopic myotomy (POEM) is a purely endoscopic method of myotomy with minimal invasiveness and a low rate of adverse events when performed by experienced operators. Since then, numerous studies have shown the significant clinical efficacy and safety of POEM. The purpose of this article is to introduce different modified POEMs, special indications for different POEMs, and their advantages as well as disadvantages.

Key words: Endoscopy; Achalasia; Peroral endoscopic myotomy; Esophageal diverticula; Gastroparesis; Pyloric stenosis

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Core tip: There are several articles in the literature introducing some specific peroral endoscopic myotomies (POEM). However, this is the first minireview to report most of the modified POEM and to compare the advantages and disadvantages of them as well as their special indications. In addition, this article not only focuses on the application of POEM in achalasia, but also includes the treatment of esophageal diverticulum, gastroparesis, and pyloric stenosis.

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INTRODUCTION

Over the last decade, peroral endoscopic myotomy (POEM) has been introduced as an alternative treatment option for patients with achalasia. POEM is an operation that is conducted to establish a tunnel between the esophageal mucosa and the muscularis propria through an endoscope. This operation is based on endoscopic submucosal dissection and natural orifice transluminal endoscopic surgery, and tunnel establishment and muscle incision are regarded as two essential elements. Compared with traditional treatments including medication, Botox injections, pneumatic dilation, and laparoscopic Heller myotomy (LHM), POEM has significant advantages of minimal invasiveness and a low rate of adverse events (AEs) when performed by experienced operators^[1]. POEM should be strongly recommended as the first-line and standard treatment option for patients with achalasia^[2,3]. Besides, POEM is a feasible and effective treatment for other gastroesophageal diseases such as gastroparesis (G-POEM) and esophageal diverticulum (D-POEM). Recent studies have showed promising results of POEM for these diseases. Till now, it has been the preferred treatment option in most of the centers, with excellent and similar long-term results as the conventional strategies.

CLASSICAL POEM

POEM is an alternative technique for patients with achalasia, and this was first introduced in 2010 for conducting myotomy under the guidance of an endoscope^[4,5]. Over the last decade, POEM has been considered an initial treatment option for patients with achalasia^[3]. The detailed procedure is as follows^[1]:

Establishment of mucosal entry

First, the site for anterior mucosal incision should be selected by correlating with high-resolution manometry (HRM) parameters. It is generally existing in the middle of the esophagus, *i.e.*, about 13 cm above the esophagogastric junction (EGJ). For type III achalasia, it is necessary to establish the entrance above all the stenotic loops that are caused by abnormal contraction (the stenotic loops can be seen under the endoscope, and the abnormal contraction sites can also be measured by HRM). All the stenotic loops should be cut open. The key point in this step is to judge the "EGJ" accurately to avoid a long tunnel, and the indigo carmine is injected into the submucosal layer.

Establishment of submucosal tunnel

A 1.5 cm to 2cm longitudinal or horizontal mucosal incision was made in the mid esophagus. Next, a blunt dissection was created followed by carbon dioxide insufflation, and the submucosal tunnel was extended towards the EGJ for about 2 cm to 3 cm onto the gastric cardia. The length of the tunnel, which is usually 5 cm to 15 cm^[6-9], depends on the choice of each surgeon according to the patients' conditions. Also, the basic principle is that the length of the tunnel allows enough space for a full muscularis incision.

Myotomy

This part of operation is highly controversial. Classically, the circular fibers, lower esophageal sphincter (LES), and stomach are divided, leaving the longitudinal layer intact. The length of myotomy is generally 8-10 cm, with at least 2 cm below the EGJ. The myotomy length of achalasia type III is determined according to the stenotic loops.

Closure of mucosectomy

Finally, after an adequate myotomy, the tunnel was checked for any blood exudation or electric injury on large vessels and washed several times. The mucosectomy site was then closed by using hemostatic clips or endoscopic sutures.

After LHM and pneumatic dilation (PD) as first-line treatments for achalasia,

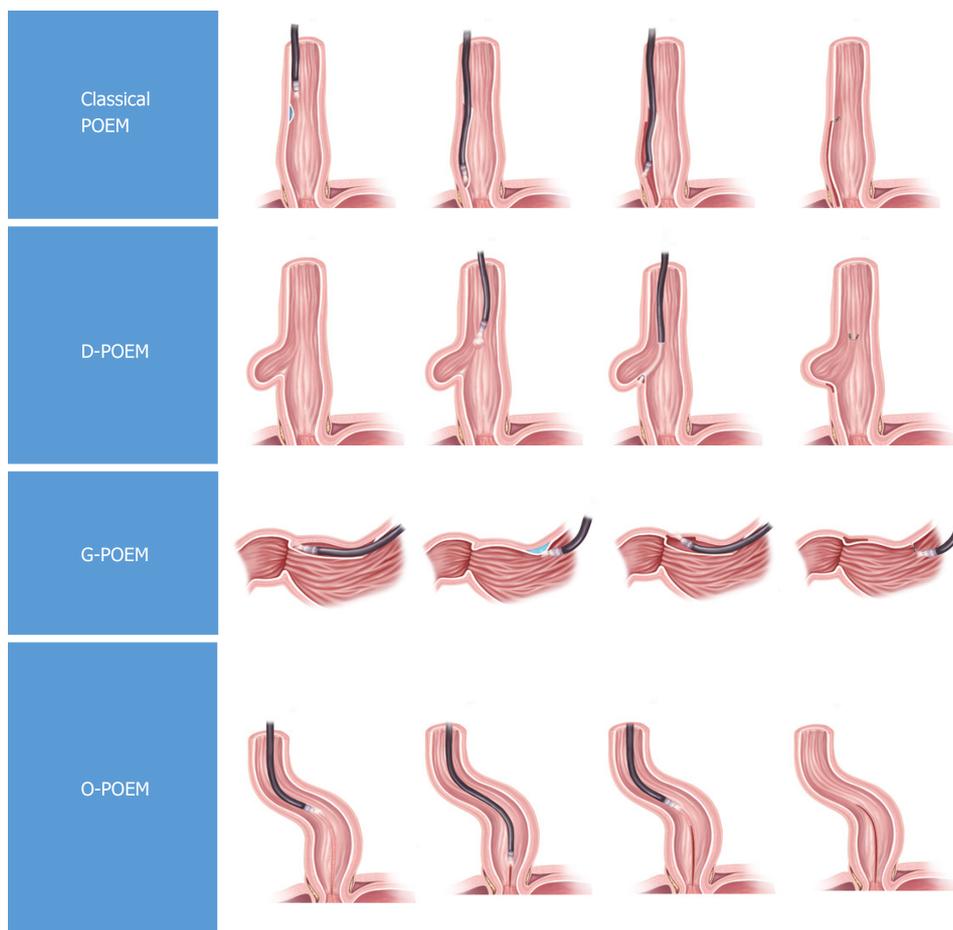


Figure 1 Schematic representation of peroral endoscopic myotomies. The procedures of classical peroral endoscopic myotomy (POEM), esophageal diverticulum POEM, gastroparesis POEM, and open POEM are shown in this figure. The blue part in the procedure represents the injection. POEM: Peroral endoscopic myotomy; D-POEM: Diverticulum peroral endoscopic myotomy; G-POEM: Gastroparesis peroral endoscopic myotomy; O-POEM: Open peroral endoscopic myotomy.

POEM has been the widespread and recognized technique. A systematic review and meta-analysis conducted by Schlottmann *et al*^[10] showed that POEM is more effective than LHM in improving the symptoms like dysphagia, but is associated with a higher incidence of gastroesophageal reflux according to short-term results. An analysis of more than 1300 patients by Shiwaku *et al*^[2] also confirmed that POEM is a safe and effective option, supporting it as a first-line and standard treatment for achalasia. A randomized clinical trial by Ponds *et al*^[3] have further demonstrated that for treatment-naïve patients with achalasia, POEM resulted in a higher treatment success rate at 2 years when compared to PD. In addition, for patients aged below 18 years^[11,12] or with gastric bypass^[13], POEM treatment was proved to be clinically effective and safe.

All these findings above suggest that POEM might be an initial and standard treatment option for achalasia.

OPEN POEM

Liu *et al*^[14] have described open POEM (O-POEM) without a submucosal tunnel for treating achalasia. Considering the most common potential complications of high technical requirements for tunnel construction and mucosal injury associated with O-POEM, the endoscopic myotomy by this technique is considered to be much safer and more feasible and effective under direct visualization and by leaving the postresection mucosal defect open^[15,16]. The O-POEM procedures are as follows^[16]: (1) Sterile saline solution was injected into the submucosa to perform mucosotomy (6-10 cm above the gastroesophageal junction at the 5-6 o'clock position) with at least 2 cm below the EGJ into the proximal stomach; (2) After mucosotomy, the submucosal fibers were extended from the proximal end to the distal end; (3) Next, selective myotomy of the circular muscle for at least 4-6 cm proximal to the EGJ and 2 cm distal to the EGJ was

performed. Much attention should be paid while conducting the procedure to avoid cutting the longitudinal muscle layer. However, the longitudinal muscle is so thin that it might play by itself; (4) After completing the incision, a smooth passage exists with minimal resistance through the EGJ; and (5) After that, a nasogastric tube was inserted into the gastric lumen under endoscopic guidance for gastric decompression, because acid secretion might affect the healing of injury. And the mucosal defect will close by itself.

According to a case series of 82 cases^[16], O-POEM seems to be an exceptionally effective treatment over others for achalasia due to a short-term success rate of more than 95%, significant improvement of symptoms and manometry outcomes, and decreased Eckardt score. In that study, the follow-up gastroscopy showed a wider cardia and the radiography displayed an easy passage of barium into the stomach. Moreover, this was comparable to classical POEM^[17], and the total clinical reflux complication rate of O-POEM was 15.9%. However, compared with classical POEM, the rates of minor and severe AEs are slightly higher after undergoing O-POEM^[18]. Nonetheless, most of the O-POEM-related AEs are usually self-limiting and do not require retreatment. Compared with classical POEM treatment, another major advantage of O-POEM is its simplicity and expeditiousness. In that case series, the average O-POEM treatment time was 20.0 min, which was remarkably lower than that of classical POEM treatment^[19]. Furthermore, the O-POEM treatment decreases the volume of gas to a certain extent within the working field, possibly lowering the risk of insufflation-related AEs. Considering the difficulty to define a clear separation of circular and longitudinal muscular layers, treatment with O-POEM might lead to potential infection-related AEs. Therefore, prophylactic antibiotics and postoperative gastrointestinal decompression should be routinely applied to prevent possible infection. Based on the indications of O-POEM, the preliminary results demonstrated that it could be a treatment option mainly for patients with severe submucosal fibrosis (such as sigmoid achalasia or patients after Heller myotomy), in which the submucosal tunnel would be technically demanding.

According to other short-term outcomes for achalasia with sigmoid-shaped esophagus or failed Heller myotomy, O-POEM could be a potential first-line treatment^[20-22].

DOUBLE O-POEM

An alternative O-POEM was recently described by Yuan *et al*^[23] in a patient with negative predictors of myotomy, namely, severe preoperative dysphagia and esophageal dilatation, and named double O-POEM (D-O-POEM).

The indigo carmine was injected into the submucosal layer, and the mucosal and submucosal layers were incised directly at 9 o'clock position.

After mucosectomy, the circular muscle was cut to 2 cm below the cardia and a full-thickness myotomy was performed at the LES level. During the single procedure, a second myotomy was performed in the same way at 3 o'clock position. The double mucosectomy and myotomy conducted should be of 10 cm and 9 cm in length, respectively.

Finally, instead of using endoscopic clips, the mucosal defects were left open.

According to some short-term outcomes in patients with achalasia in that study, the D-O-POEM might be regarded as a simple and quick treatment for patients with achalasia and negative predictors of myotomy, probably achieving absolute myotomy and averting retreatment.

PERORAL ENDOSCOPIC DUAL MYOTOMY

Yuan *et al*^[24] have described a peroral endoscopic dual myotomy (dual POEM) technique. To avoid repeated intervention for achalasia patients with negative predictors, dual myotomies were performed during a single procedure.

First, the mixture of saline and methylene blue was injected into the submucosa of the posterior esophageal wall.

Next, a hybrid knife was used to make a mucosal entry of about 7 cm above the EGJ, creating an at least half-esophageal-lumen wide submucosal tunnel. Usually, dual POEM is performed separately at 3 o'clock and 8 o'clock positions, and myotomy was extended to 2 cm below the cardia.

The mucosal entry is finally closed using the endoscopic clips.

SHORT TUNNEL POEM

Different from the standard tunnel in classical POEM, Li *et al*^[25] have decreased the length of the tunnel, which might reduce the surgical duration and the rates of post-POEM complications according to the short-term outcomes. The innovative short tunnel POEM procedure is as follows: (1) A 0.8 cm to 1.0 cm wide transverse incision was made at the proximal end of the EGJ, followed by making a 0.8 cm to 1.0 cm longitudinal incision from the middle of transversal incision to the anal side; (2) After that, a short submucosal tunnel was established. The length of the short tunnel was only 6 cm to 8 cm, while that of a standard tunnel was 10 cm to 14 cm; (3) For myotomy, only a part of the circular muscle at the starting point was cut, and the depth of the myotomy increased from the beginning to the cardia area where the full-thickness myotomy was operated; and (4) The entry was closed. Both the transversal and longitudinal incisions lengthwise were closed with titanium clips.

LIU POEM

Liu *et al*^[26] have put forwarded a modified endoscopic myotomy (Liu-POEM) in which the submucosal tunnel is replaced by a submucosal water column. This improvement makes POEM more simplified and less time-consuming. The specific steps are as follows^[26]: (1) The patient was placed on the left decubitus position with normal preparation; (2) Longitudinally, a submucosal water column was formed by injecting the saline into the submucosa from the bottom to the middle part of the esophagus; (3) The mucosal layer was cut open and then separated into the submucosal layer under the guidance of an endoscope to form a submucosal space about 2 cm deep; (4) The muscle layer was cut from the proximal esophagus to the bottom of the stomach through the cardia; and (5) The “water tunnel” was closed.

Compared with classical POEM, Liu-POEM demonstrated similar postoperative effects, hospitalization days, and post-POEM complications, such as fever, abnormal routine blood parameters, pleural effusion, and reflux esophagitis^[26]. However, after replacement of traditional submucosal tunnel, the duration of operation was significantly reduced, and the laborious steps were simplified. Moreover, the rate of gas-related complications associated with Liu-POEM was lower than that of classical POEM treatment. Furthermore, as the mucosa and muscularis are separated by a submucosal water column, the probability of subcutaneous emphysema and pneumomediastinum is also lower than that of classical POEM.

POEM FOR ESOPHAGEAL DIVERTICULA

In addition to the above modifications, POEM could also be used for treating more diseases, and esophageal diverticula might be one of the indications.

Yang *et al*^[27] have found the possibility of POEM treatment for esophageal diverticula, which was named D-POEM. This unique technique, as a consequence of creating a submucosal tunnel, assists in making septotomy under endoscopic view more methodically and completely. The procedure technique is as follows:

A mixture of 1% indigo carmine, diluted epinephrine, and 0.9% sterile saline was injected into the submucosa 1-2 cm from the diverticular septum to form a mucosal vesicle. A 1 cm incision was then created using a triangular tip knife as an entrance to the tunnel. The submucosal fibers were dissected by spray coagulation, followed by the entry of an endoscope into the submucosal space through the transparent cap. The spray coagulation was then used and indigo carmine solution was injected to form a submucosal tunnel until the diverticular septum was identified. The tunnel should be extended on both sides of the septum till the bottom of the diverticulum.

The septotomy was performed with an insulated tip knife. Under direct endoscopic view, the muscle fibers of the septum were completely dissected till the bottom of the diverticulum. To ensure a complete septotomy, myotomy should be extended to about 1 cm of the proximal esophagus.

Finally, after examination of the esophageal mucosa, the incision was closed with endoscopic clips.

According to a multicenter study^[27] and several case reports^[28-32], the D-POEM treatment is considered to be feasible, safe, and effective for esophageal diverticula, especially in elderly patients with coexisting diseases which make them unable to tolerate anesthesia, or those with failed previous laparotomy. D-POEM was considered to have a definitive advantage of complete septostomy. Larger multicenter studies are still warranted to confirm this.

G-POEM FOR GASTROPARESIS AND PYLORIC STENOSIS

G-POEM was first reported by Khashab *et al*^[33] in 2013, and could be another alternative treatment for gastroparesis and pyloric stenosis. This is a slightly invasive novel approach for gastroparesis and pyloric stenosis. The process of G-POEM was similar to that of classical POEM that is traditionally performed for achalasia.

Before G-POEM treatment, conventional preparation for endoscopic operation and a high-resolution endoscope with a transparent cap are necessary. Besides, carbon dioxide should be continuously pumped in throughout the whole procedure to keep the vision bright and clear. The particular procedures are shown as follows^[33,34]:

A mixture of glycerin fructose and methylene blue was injected into the mucosa approximately 5 cm from the pylorus. Most frequently, a 1.5-2 cm longitudinal incision was made with a triangular-tip knife as an entry into the submucosa.

After the endoscope enters the incision, the submucosal fibers should be isolated and then a submucosal tunnel is established. During this procedure, when the submucosal anatomical plane becomes difficult to define, repeated injection of glycerin fructose and methylene blue mixture strengthens the boundary between the submucosal layer and the muscularis propria. As the submucosal tunnel extends into the pylorus, the operation then should be performed close to the muscular layer to avoid any damage to the mucosal layer during the incision. When a blue mucosa is observed near the pylorus, it can extend 0.5-1.0 cm to the distal end of the tunnel.

The proximal end is returned. The medialis oblique and circular muscle bundles of the pylorus are incised from the proximal end, which was about 2-3 cm away from the pylorus to the end point of the submucosal tunnel.

The incision of the mucosa is closed with titanium clamp.

According to the single institution study^[34] and several case reports or case series^[35-37], the G-POEM treatment is considered a feasible, safe, and effective method for gastroparesis and pyloric stenosis, especially for medical refractory gastroparesis, in short term. It was also described that G-POEM demonstrates successful improvement in a patient with gastric stenosis post-laparoscopic sleeve gastrectomy^[38]. Long-term study for relief from gastroparesis and pyloric stenosis symptoms is still needed.

OTHER POEMS

Considering the time-consuming characteristics of POEM, there are still more improvements that need to be checked in the procedure of POEM. Philips *et al*^[39] have modified the procedure, in which a proximal-to-distal circular myotomy is operated after creating about half of the classical submucosal tunnel (4-6 cm in length). The myotomy continues while the submucosal tunnel extends. This half-tunnel POEM might be more efficient than the classical POEM and the outcome might be equivalent to that of short-term outcome follow-up. On the other hand, Hernandez Mondragón *et al*^[40] have used a new small-caliber endoscope in the POEM procedure in patients with achalasia, and named it thin-POEM. Other procedures are the same as those of classical POEM. With a short-term follow-up of 45 patients after thin-POEM, it might be considered a safe, effective, and feasible option for achalasia treatment. In Digestive Disease Week 2019 United States, Gutierrez *et al*^[41] and Bell *et al*^[42] have described a new POEM treatment combined with transoral incisionless fundoplication (TIF). During the POEM procedure, a flap valve was made after TIF over the cardiac entrance^[43]. According to the short-term outcomes of nine patients, the TIF procedure might be a safe and effective solution in treating gastroesophageal reflux disease (GERD) after POEM treatment. As for the length of the incision, Wellington *et al*^[44] have offered a possible solution for patients who need minimum myotomy length and showed improved symptoms best indeed. They studied five patients with spastic esophageal disorders and took the use of topography to figure out an optimal length of myotomy for each patient.

RELEVANT DATA

According to data analysis at eight facilities in Japan^[2], a total of 1346 patients, including the straight type in 1105 (82%) patients and the sigmoid type in 241 (18%), received POEM during the study period. The operation time was 99.6 min on an average and the mean length of myotomy was 10.8 cm in the esophageal body, extending a mean of 2.8 cm into the stomach. The response rates (Eckardt score ≤ 3) at 3 mo and 12 mo were 95.1% and 94.7%, respectively. During this study, 50 (3.7%) AEs

of Clavien-Dindo classification grade \leq IIIa were recorded and all were resolved during the follow-up treatment. In addition, there were no Clavien-Dindo classification grade \geq IIIb AEs. On the other hand, post-POEM gastroesophageal reflux was confirmed in 14.8% of patients, and responded well to treatment with a proton-pump inhibitor.

LIMITATIONS OF POEM

However, for some diseases, such as idiopathic achalasia, POEM showed no successful outcomes as before, with a significantly higher likelihood of postoperative gastroesophageal reflux than LHM. According to this research^[45], POEM was noninferior to LHM plus Dor's fundoplication in controlling the symptoms of idiopathic achalasia at 2 years. A total of 221 patients were randomly assigned to receive either POEM (112 patients) or LHM plus Dor's fundoplication (109 patients). During the 2-year follow-up period, 83.0% of the patients in the POEM group and 81.7% in the LHM group achieved clinical success. The incidence of serious AEs was 2.7% in the POEM group and 7.3% in the LHM group. For the postoperative gastroesophageal reflux, 57% of patients in the POEM group and 20% in the LHM group had reflux at 3 mo as assessed by endoscopy, and the corresponding percentages at 2 years were 44% and 29%, respectively.

DISCUSSION

Since its first introduction in 2010, POEM has already been considered an initial and standard treatment instead of LHM and PD^[2,3]. However, POEM has been especially challenging. For instance, submucosal fibrosis might be the most common cause of failed tunneling, and morphological changes in the esophagus such as curved esophageal lumen might cause out of direction. Only experienced endoscopists could perform this technique. Moreover, as for the problems of "time-consuming", "high technique-demanding", and "post-POEM complications", more modified POEM introduced above were created to solve these problems.

Liu *et al*^[14] have introduced the "open POEM", in which myotomy was directly performed without a submucosal tunnel to treat complex achalasia such as submucosal fibrosis and sigmoid esophagus. Compared with conventional POEM procedures, the O-POEM does not require submucosal tunneling. The procedure reduces high technique-requirement relatively. Based on the O-POEM, the D-O-POEM^[23] was created for patients with negative predictors of myotomy, despite the risk of perforation or leakage and similar potential infection-related AEs. On the other hand, another modified POEM (Liu-POEM)^[26] replaced the tunnel by a water column, which greatly reduced the duration and complexity of treatment. Besides, POEM with a shorter tunnel (short tunnel POEM) was described due to its association with high safety and low rates of AEs.

For other disadvantages associated with POEM treatment^[39-44], such as post-POEM gastroesophageal reflux, POEM with TIF showed unique superiority over other modifications. For the problem of "time-consuming", thin POEM and half tunnel POEM might be possible solutions. As POEM was applied in many centers, several other indications including esophageal diverticula (D-POEM) and gastroparesis and pyloric stenosis (G-POEM) have been developed. Relevant short-term studies^[27-38] confirmed improvements in symptoms with POEM treatment.

As for the potential complications, infection and perforation are main potential complications for O-POEM. Prophylactic antibiotics and postoperative gastrointestinal decompression could help with possible infection. The perforation is mainly related to the operator's technology. It is still recommended that doctors with rich traditional POEM surgery experience perform O-POEM operation. The main complication of Dual-POEM and double-O-POEM is the reflux problem. According to current experience, the reflux that occurs in these patients is relatively mild (the proportion of grade A esophagitis will be larger, and rarely grade C or above). And the incidence of esophagitis is equivalent to that of traditional POEM. PPI treatment can achieve good results, and no case requires additional fundoplication. Some scholars^[46] proposed adding fundoplication to the classical POEM procedure to reduce gastroesophageal reflux.

CONCLUSION

In summary, although short-term outcomes of various modifications in POEMs have proved them to be safe and effective, multiple large sample studies and randomized clinical trials are still warranted to discuss the relief from symptoms, post-POEM events, and long-term consequences.

Table 1 Comparison of advantages and disadvantages of different peroral endoscopic myotomies and specific indications

Modified POEM	Ref.	Special indications	Advantages	Disadvantages
Classical POEM	Ponds <i>et al</i> ^[3]	Children Patients after bypass Diffuse esophageal spasm Nutcracker esophagus	-	-
O-POEM	Liu <i>et al</i> ^[14]	Sigmoid-shaped esophagus Failed Heller myotomy Severe submucosal fibrosis	Time-saving Less technical-demanding	A little higher rate of AEs Potential infection-related AEs
D-O-POEM	Yuan <i>et al</i> ^[23]	Patients with negative predictors	Time-saving Less technical-demanding Avoid retreatment Less risk of adverse insufflation events	A little higher rate of AEs Potential infection-related AEs Risk of perforation and leakage
Dual-POEM	Yuan <i>et al</i> ^[24]	Patients with negative predictors	Avoiding retreatment	More time-consuming More technical-demanding
Short tunnel POEM	Li <i>et al</i> ^[25]	-	Higher safety Lower rate of AEs	More technical-demanding
Liu-poem	Liu <i>et al</i> ^[26]	-	Time-saving Less technical-demanding Less gas-related AEs	-
Half tunnel POEM	Philips <i>et al</i> ^[39]	-	Time-saving Less technical-demanding	-
Thin-POEM	Hernandez Mondragón <i>et al</i> ^[40]	-	Time-saving Higher safety	Operational limitations
TIF POEM	Gutierrez <i>et al</i> ^[41]	Pre- and post-POEM GERD	Treatment of GERD	Higher technical-demanding
Topography module POEM	Wellington <i>et al</i> ^[44]	-	Optimal length of myotomy	-
D-POEM	Yang <i>et al</i> ^[27]	Esophageal diverticula	-	-
G-POEM	Khashab <i>et al</i> ^[33]	Post-LSG gastric stenosis after a failed pneumatic dilation Refractory gastroparesis	-	-

POEM: Peroral endoscopic myotomy; O-POEM: Open peroral endoscopic myotomy; AEs: Adverse events; D-O-POEM: Double open peroral endoscopic myotomy; TIF: Transoral incisionless fundoplication; GERD: Gastroesophageal reflux disease; D-POEM: Diverticulum peroral endoscopic myotomy; G-POEM: Gastroparesis peroral endoscopic myotomy; LSG: Laparoscopic sleeve gastrectomy.

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