

Endoscopic Management of Reflux



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KEYWORDS

- Esophagitis • Fundoplication • Gastroesophageal reflux • Hiatal hernia • Humans
- Laparoscopy • Proton pump inhibitors

KEY POINTS

- The pathophysiology of GERD is complex and involves the integration of both the lower esophageal sphincter complex as well as the diaphragm crura.
- In patients with refractory GERD, or those concerned about long terms medical therapy, step up therapy should be considered via endoscopic or surgical approaches.
- The patient's anatomy, comorbidities, and surgical risk profile should all be considered by the clinician to inform the best treatment option.
- Improvements in both technique and devices have made endoscopic management a viable option for many patients.

INTRODUCTION

Gastroesophageal Reflux Disease (GERD) is the most prevalent GI disorder in the United States, resulting from a breakdown of the antireflux barrier and excessive retrograde movement of gastric content into the esophagus. The pathophysiology of GERD is complex, involving the integration of both the lower esophageal sphincter (LES) complex and the diaphragm crura. While medical and surgical treatments have been the mainstay of GERD therapy, there are currently several endoscopic treatment approaches that are used in clinical practice.^{1,2} The most common endoscopic approaches to manage GERD include: transoral incisionless fundoplication (TIF 2.0), endoscopic suturing, and endoscopic resection (ARMS) or ablation (ARMA), alone or in combination with suturing (resection and plication [RAP] and mucosal ablation and suturing of the GE junction [MASE]). In this article, these procedures will be reviewed, with special emphasis on the proposed mechanism of action, patient selection, clinical outcomes, safety, and technical considerations. It is important to highlight

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Abbreviations	
ARB	Antireflux barrier
ARMA	Antireflux mucosal ablation
ARM-C	Cap-assisted ARMS
ARM-L	Band-ligation ARMS
ARM-P/V	Antireflux mucosoplasty with valve
ARMS	Antireflux mucosectomy
cTIF	Consecutive transoral fundoplication
EGJ	Esophago-gastric junction
FDA	Food and Drug Administration
FLIP	Functional lumen imaging probe
GE	Gastroesophageal
GEFV	Gastroesophageal flap valve
GEJ	Gastroesophageal junction
GERD	Gastroesophageal reflux disease
LES	Lower esophageal sphincter
LHM	Laparoscopic Heller myotomy
MASE	Mucosal ablation and suturing of the GE junction
POEM	Per-oral endoscopic myotomy
PPI	Proton pump inhibitor
RAP	Resection and plication
TIF	Transoral incisionless fundoplication
TLESRs	Transient LES relaxations

at the onset that none of the endoscopic approaches can reduce a hiatal hernia nor repair a widened diaphragmatic hiatus. Therefore, endoscopic approaches to GERD should only be considered in patients who do not require or are deemed unsuitable for a laparoscopic or robotic hernia reduction and/or crural repair.

UNDERSTANDING ESOPHAGO-GASTRIC JUNCTION ANATOMY AND PHYSIOLOGY

In order to understand the role of endoscopic antireflux procedures, one first has to appreciate how each procedure may (or may not) reconstruct and/or augment the anatomy and physiology of the normal gastroesophageal junction (GEJ). Remarkably, only in recent years have we begun to understand the intricacies of the antireflux barrier (ARB) at the esophago-gastric junction (EGJ), which includes the diaphragmatic crura, the lower esophageal sphincter (LES), and the gastroesophageal flap valve (GEFV). The pressure gradients between the abdominal stomach and thoracic esophagus would promote the retrograde movement of gastric contents into the esophagus during most human activities were it not for these 3 components of the ARB. First, the crural diaphragm in normal individuals acts in synchrony with the LES to open during swallowing and then contract, acting as a sling, pulling the GEJ posterior, inferior, and toward the right.³ The LES complex is intrinsic to the esophagus and has 2 components—the proximal portion is made up of the intrinsic muscles of the distal esophagus, and the distal portion consists of the sling fibers of the proximal stomach⁴ (Fig. 1A), and physiologically contributes to the ARB. The GEFV, which includes the LES complex, is a musculo-mucosal structure, which anatomically contributes to the ARB by way of its flap-valve mechanism⁵ (Fig. 1B). The LES and GEFV function as the *internal* sphincter, whereas the crural diaphragm can be considered the *external sphincter*. The phreno-esophageal ligament attaches the distal esophagus to the crural diaphragm, thus coupling the internal and external sphincters.

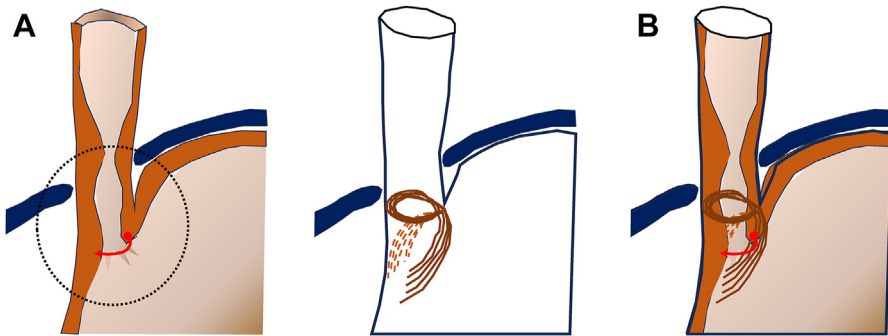


Fig. 1. Diagram of LES and GEJV shown separately (A) and together (B). (A) The dotted circle indicates the GEJV and the red arrow the direction of movement from the greater curve toward the lesser curve. On the right, the circular muscle fibers of the distal esophagus are continuous with the gastric sling fibers. (B) Both the LES and the GEJV act as one construct to both narrow the esophageal lumen and position the flap valve toward the lesser curve.

In patients who have a nearly intact crural sphincter (ie, absence of, or very limited hiatal hernia, Hill Grade 1 or 2, AFS Grade 2⁶), the potential for an endoscopic approach to restore the GEJV exists. Conceptually, this could include decreasing the distensibility of the entire LES (TIF 2.0) or just the gastric portion (ARMS, ARMA, MASE, RAP) to prevent shortening and loss of LES competence during gastric distention by increasing the resting pressure of the LES, and/or reinforcing the sling fibers at the GEJ. Ideally, the length of the GEJ is increased, the diameter is decreased, and the geometry of the GEJV is restored or augmented to its original design⁷ (TIF 2.0).

TRANSORAL INCISIONLESS FUNDOPLICATION 2.0

TIF was initially introduced in 2006 and has evolved over the years, with significant published research available to date. TIF creates a 3 cm length 270° omega-shaped GEJV, simulating the normal structure and function of the LES, including the gastric sling fibers, and the GEJV (Fig. 2A–C). Not only does it create valve length and luminal narrowing, but it also creates an anatomic valve that reflects the geometry and symmetry of the natural GEJV (Fig. 2D). TIF is a treatment option for GERD patients who have lost LES integrity and function, but retained an intact crura; whereas in patients requiring a hiatal hernia repair, TIF can be performed consecutively with a hiatal hernia repair during the same session (cTIF). The TIF procedural steps are repetitive sequences with a standardized protocol which optimizes efficiency, safety, and reproducibility. While previous endoscopic GERD treatment strategies involved injecting bulking agents, or delivering heat energy to the GEJ, the TIF procedure uses the EsophyX (Merit Medical, South Jordan, Utah) device which was designed to align with surgical and anatomic principles in restoring the ARB.^{5,8} The device obtained Food and Drug Administration (FDA) clearance early on, then major advancements to its design created an easier to use, more automated device to ensure consistent, and reproducible fundoplication by each user. The TIF technique has also evolved, with the latest version, TIF 2.0, incorporating a rotational wrap of the cardia and fundus around the circumference of the distal esophagus in addition to providing a 2 cm to 4 cm length of the wrap over the intraabdominal distal esophagus.⁹

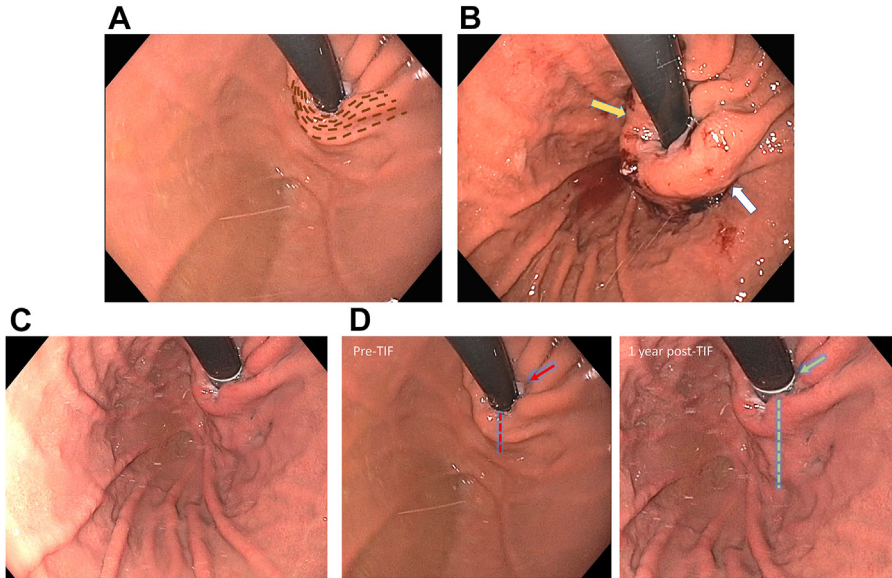


Fig. 2. The anatomic goal of the TIF valve includes augmenting and tightening the gastric sling fibers and optimizing the geometry of the GEJV. (A) At baseline, the GEJV is loose, and the gastric sling fibers (depicted in *brown dotted lines*) are played. (B) Immediately after the TIF procedure is completed, one can see the valve has been lengthened, and that there are 2 symmetric grooves formed, called the anterior (*white arrow*) and posterior (*yellow arrow*) grooves. (C) 1 year post-TIF, the immediate postprocedure swelling is gone and the valve appears geometrically similar to the natural valve. (D) Side-by-side comparison of the native valve and the augmented TIF valve 1 year later. The valve length has increased substantially (*red dotted vs blue dotted lines*) and the valve diameter has narrowed around the scope (*red arrow vs blue arrow*).

TRANSORAL INCISIONLESS FUNDOPLICATION 2.0 PROCEDURE

The Esophyx device (Fig. 3a–m) includes a handle with controls; an 18 mm diameter frame through which a standard gastroscope (9 mm) can be introduced; the tissue invaginator with side holes at the distal part of the frame to which external suction can be applied; the tissue mold which pushes tissue against the shaft of the device; a helical screw which retracts tissue; 2 stylets over which polypropylene H-shaped fasteners can be deployed; and a cartridge with 20 fasteners. In the TIF procedure,¹⁰ the device is introduced into the stomach and CO₂ is used for insufflation (Fig. 4). The endoscope within the device is positioned in retroflexion with the lesser curve located at the 12 o'clock position and the greater curve at 6 o'clock. The tissue mold is retroflexed, closed against the device, rotated to 11 o'clock posteriorly, and withdrawn to where the tip is located at the EGJ.¹⁰ The helical screw is advanced to engage tissue just below the squamocolumnar junction. Traction is then applied by suctioning of the gastric lumen to allow the gastric cardia and distal esophagus to slide downward into the tissue mold. Plication is then achieved by deploying multiple sets of H-shaped fasteners while rotating the tissue mold to allow the stomach to slide over the distal esophagus. This results in a circumferential tightening of the neo valve to $\geq 270^\circ$ using at least 20 fasteners over 10 plications to construct the valve (Fig. 5A–D). The fastener deployment process is mechanized such that 2 fasteners *fire* simultaneously with the depression of a handle. This

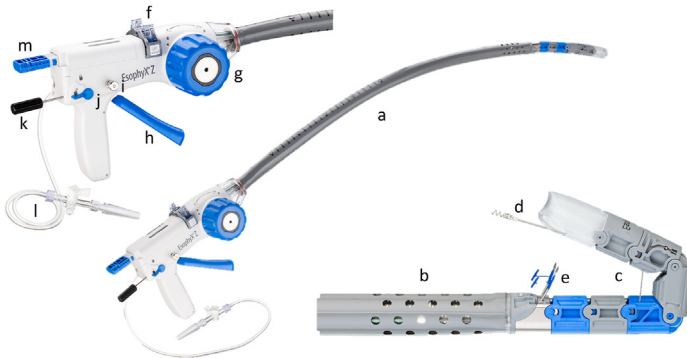


Fig. 3. Explaining the features of the EsophyX-Z+ device. (a) Flexible shaft with measurement markings. (b) Invaginator suction ports that *couple* the device shaft to the tubular esophagus to aid in reducing a small hernia and in ‘pushing off the diaphragm’. (c) Tissue mold that opens and closes to capture and rotate tissue for plication. (d) Helical retractor to retract tissue into the tissue mold to create valve length. (e) Stylets with H-shaped fasteners that are *fired* from the shaft through tissue and into the receiving clear plastic chamber at the distal tip of the device. (f) Fastener cartridge containing 20 polypropylene fasteners which load 2 at a time. (g) Tissue mold knob that opens and closes the tissue mold. This has a ratchet mechanism that precludes backward slippage of the wheel and a safety feature that precludes overtightening. (h) Fastener delivery trigger—this fires the stylets and fasteners across the tissue mold. (i) Fastener delivery trigger release that must be depressed in order to release the trigger handle (j) Helical retractor control lock—once in the lock position, this still allows the retractor to be pulled back, but does not allow slippage away from the device. (k) Helical retractor control—clockwise rotation into tissue and counterclockwise rotation to come off tissue. (l) Stop cock for invaginator—this connects suction to the invaginator ports. (m) Fastener pusher—this receives and pushes the fasteners down to the distal end of the device. (© Merit Medical, Reprinted by Permission.)

automated delivery mechanism facilitated standardization of the fundoplication procedure among patients.

The mechanism of action of the TIF procedure was evaluated using the functional lumen imaging probe (FLIP) to quantify EGJ distensibility, esophageal manometry to detail the EGJ high pressure zone, and impedance-pH monitoring to quantify acid reflux.¹¹ TIF resulted in a marked reduction of the number of transient LES relaxation and both the number and proximal extent of reflux episodes. EGJ distensibility was reduced after the procedure and basal LES pressure in the fasted state was increased. TIF creates a 3-cm high pressure zone at the distal esophagus in the configuration of a flap valve which decreases both upright and supine reflux. It is a 270° partial fundoplication with the luminal diameter controlled by the diameter of the Esophyx device, which minimizes the occurrence of postprocedure dysphagia.

Postoperative care is similar to that after traditional fundoplication techniques. Patients may experience substernal and shoulder discomfort which usually resolves within a week. Postoperative nausea may occur, but patients can vomit if needed. However, there is risk of fundoplication disruption with heavy retching. Intraoperative prophylactic intravenous antibiotics are usually given, along with 3 to 5 days of oral antibiotics postprocedure. Some practitioners perform TIF as an outpatient procedure, but many observe the patients overnight. Gradually advancing the diet over a period of 4 to 6 weeks is recommended in the postoperative period to minimize dysphagia during healing and to improve peristaltic coordination.

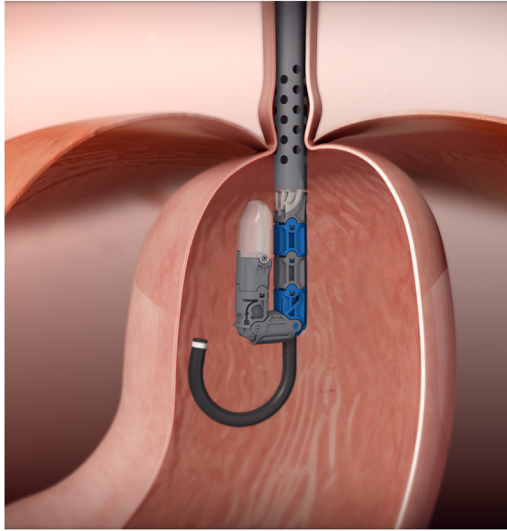


Fig. 4. Delivery of the TIF device over a standard gastroscope into the stomach. Once the distal working end of the device is in the stomach, the scope is withdrawn into the device, the tissue mold is then closed, and the scope exits a side port for full endoscopic visualization throughout the entire procedure.

TRANSORAL INCISIONLESS FUNDOPLICATION 2.0 EVIDENCE

To satisfy 5 major tenants of antireflux surgery, the TIF procedure evolved over time to address each of these requirements.¹²

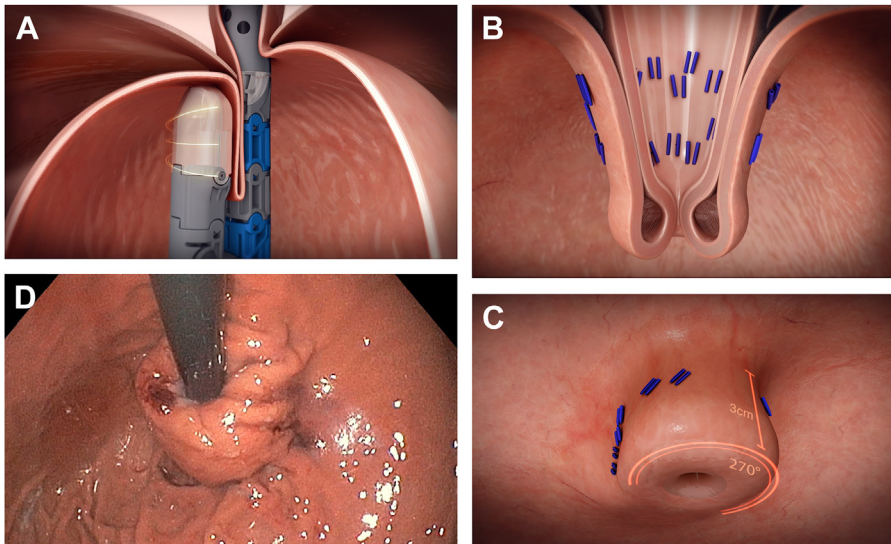


Fig. 5. Final appearance of the TIF 2.0 valve. (A) The TIF device is used to retract the gastroesophageal junction in order to create the valve length. (B) A total of 20 to 30 fasteners are used to secure the valve, with a length of 2 cm to 4 cm. (C) A typical valve is 3 cm in length and has a 270-degree wrap. (D) An actual image of the completed TIF valve, showing 3 cm of length and approximately 320-degree wrap.

1. The fundoplication must bring fundus over the esophagus and be secured to the esophagus.
2. Constructed without stricture.
3. Constructed to achieve 2 cm to 4 cm length.
4. The fundoplication must remain below the diaphragm.
5. The diaphragmatic crura must be approximated to the esophagus.

Bell inaugurated the TIF 2.0 era in 2011 with a procedure that fulfilled 4 of the 5 above criteria.¹³ Patients with a low LES basal pressure, no hiatal hernia but with a loose diaphragmatic hiatus, and both upright and supine reflux were ideally suited for TIF. In the initial RCT, the TEMPO trial, 63 patients were randomized to TIF (40 patients) versus high dose PPI (23 patients).¹⁴ At the 6-month follow-up, 97% of TIF patients had complete elimination of regurgitation compared to 50% of PPI cohort (RR= 1.9, $P=.006$). Esophagitis was healed in 100% of TIF patients and 82% were able to discontinue PPI use. Esophageal acid exposure was normalized in 54% of TIF patients. The authors concluded that TIF was more effective than maximum standard dose PPI therapy in eliminating troublesome regurgitation and extraesophageal symptoms of GERD at the 6-month follow-up. In a multi-center, open label trial with a crossover arm, TEMPO was carried out to 3 years and showed that 71% of the patients fully discontinued PPI therapy, and 86% of patients were without esophagitis.¹⁵ Atypical symptoms were controlled in 87%, and quality-of-life scores remained normalized. Outcome measures remained stable at 1-year, 2-year, and 3-year follow-ups and a final 5-year report demonstrating durability of TIF for 5 years.¹⁶ These TIF valves were created with serosa to serosa apposition with multiple points of adhesion due to passage of approximately 20 to 30 transmurals fasteners (Fig. 6A–F).

Another level-1 evidence clinical trial, the RESPECT trial, involved TIF 2.0 plus placebo versus a sham procedure plus PPI therapy.¹⁷ Eighty-seven patients with GERD and hiatal hernia less than or equal to 2 cm were randomly assigned to TIF (n=45) or sham (n=42). By intention-to-treat analysis, TIF achieved the primary endpoint of eliminating troublesome regurgitation in more patients than PPIs (67% vs 45%, $P=.023$).

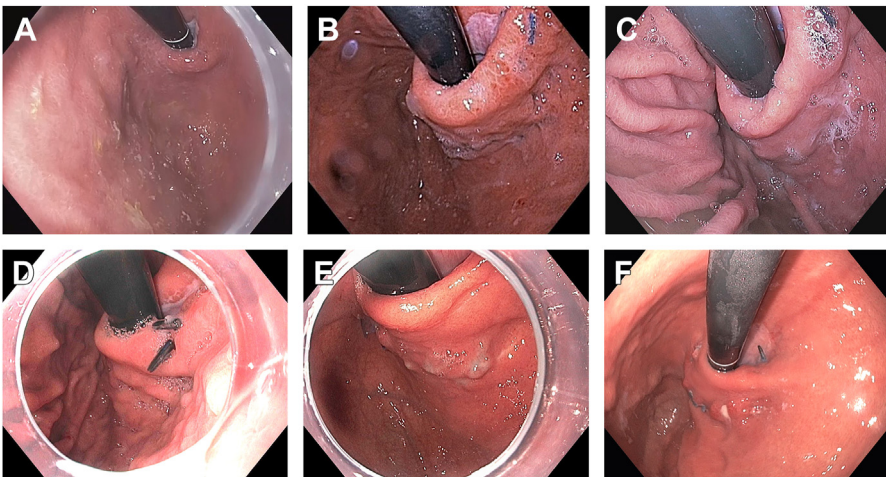


Fig. 6. Durability of a TIF valve illustrated in a single patient over 5 years. (A) GEFV at baseline is short and loose. (B) TIF valve at 1 month. (C) TIF valve at 1 year (D) TIF valve at 2 years (E) TIF valve at 3 years (F) TIF valve at 5 years.

Patients from both groups had similar reduction in GERD symptom scores. The authors concluded that TIF was an effective treatment for patients with GERD, particularly in those with persistent regurgitation despite PPI therapy. After crossover, at 12 months (76% of the sham patients elected to crossover to fundoplication) 72% had control of regurgitation and remained completely off PPI.

In a randomized sham-controlled trial from Europe, patients treated with TIF discontinued PPI 59% of the time (9% sham arm), with significant improvement in esophageal acid exposure.¹⁸

A meta-analysis of TIF 2.0 randomized controlled studies demonstrated that TIF 2.0 can reduce PPI use and control symptoms similarly to conventional antireflux procedures with a better side effect profile and greater safety.¹⁹ The durability of TIF was demonstrated at 10-years with nonsignificant changes in symptom control over time.²⁰ Another study confirmed durability out to 9 years.²¹ A literature review up to May 2020 of studies reporting greater than 3-year outcomes suggested that TIF offered a safe, long-term therapeutic option for patients with GERD who are opposed to life-long medical therapy or conventional surgery, are intolerant to PPIs, or are at increased surgical risk.²²

A prospective registry recently reported the 1-year outcomes of 85 patients following TIF 2.0.²³ Clinical success was achieved in 94%, Reflux Symptom Index score normalized in 85% of patients with elevated baseline, and GERD Health-Related Quality of Life scores improved in 89%. Patient satisfaction increased from 8% to 79% ($P < .0001$). At study entry, 81% were taking at least daily PPI, and after TIF 2.0, 80% were either completely off or only occasional taking PPI ($P < .0001$). Esophageal acid exposure time was normal in 72% of the cohort. Interestingly, among those patients who received an optimized TIF 2.0 valve (defined as >300 -degree circumference and >3 cm length), 94% normalized the esophageal acid exposure time as compared to 57% normalization if the optimized TIF 2.0 valve was not achieved ($P = .007$). There were no TIF 2.0-related serious adverse events. This study concluded that TIF 2.0 is a safe and effective outpatient endoscopic treatment for selected patients with GERD.

With experience, it has become apparent that when the diaphragmatic hiatus is dilated to greater than 2 cm in transverse diameter, outcomes for TIF can be negatively affected. Furthermore, this diameter is often underestimated.²⁴ Identifying and repairing a dilated hiatus fulfills the fifth major criteria for effective antireflux surgery. Hence, a hiatal hernia repair followed by a consecutive TIF procedure (cTIF) saw its first publication of safety and efficacy in 2011²⁵ and the FDA granted a modification in 2017, allowing TIF following hiatal repair under the same sedation session, that is, cTIF.

A number of recent studies have shown cTIF to be a promising alternative to anti-reflux surgery for managing refractory GERD with comparable short-term efficacy and safety profile along with a low side effect profile.^{26–31} A prospective randomized control trial comparing cTIF with laparoscopic Nissen fundoplication is near completion.

TRANSORAL INCISIONLESS FUNDOPLICATION SAFETY

Safety of TIF is at least equivalent to laparoscopic fundoplication in the literature and review of industry-gathered data indicates that the serious adverse event rate is lower than laparoscopic fundoplication at 0.41%,³² with 91 serious events being reported out of a total of approximately 22,000 procedures, as of July 2019. Major complications, including pleural effusion, mediastinitis, abscess, and esophageal perforation,

have been reported²⁵ and were more common in the first few years after introduction of TIF. Changes in technique, device design, and increased level of experience with the device reduced the incidence of these complication.

In the early years of EsophyX development, there was concern over esophageal injury as the gastric wall is thicker and a gastric leak is more manageable. The EsophyX device has the endoscope inside the tissue mold which tapers the end of the device and provides a safety feature to avoid esophageal injury. Also, shields in the device protect surrounding tissue from the advancing stylet. Further, a separate channel for the trailing leg of the fastener reduces the number of fasteners that would either not fully deploy or push fully through tissue.

TRANSORAL INCISIONLESS FUNDOPLICATION POST PER-ORAL ENDOSCOPIC MYOTOMY

In achalasia patients, the choice for therapy between per-oral endoscopic myotomy (POEM) and laparoscopic Heller myotomy (LHM) with partial fundoplication may be influenced by the incidence of post-POEM GERD. If this can be controlled either by PPI or TIF, then POEM often becomes the treatment of choice. In a multicenter retrospective study, post-POEM patients with GERD underwent TIF and changes in symptom scores, PPI use, and pH-metry were evaluated. The study concluded that TIF may be effective and safe in treating GERD after POEM.³³ While the durability of the myotomy with POEM and LHM should be very long, the durability of the surgical partial fundoplication may be more limited. Thus, when the fundoplication does loosen, a repeat TIF is much easier to perform than a revisional surgical fundoplication.

Our group retrospectively analyzed 132 consecutive POEM patients and found that only 12 (9%) developed post-POEM refractory GERD with this being least likely with type 2 achalasia at only 1.6%.³⁴ All 12 patients underwent TIF with satisfactory clinical outcomes; none required antireflux surgery. Thus, TIF is an excellent salvage for post-POEM GERD patients, especially since these patients seldomly have a hiatal hernia.

SUMMARY FOR TRANSORAL INCISIONLESS FUNDOPLICATION 2.0

With level 1 medical evidence, confirmed durability, and FDA approval, we now have an effective endoscopic treatment for GERD with TIF and cTIF, which significantly changes the spectrum of care. TIF is an alternative for patients who are refractory to medical therapy and/or wish to avoid the potential risks associated with prolonged PPI therapy. TIF is the only endoscopic procedure that can restore and augment both the LES and the GEFV, resulting in optimization of the geometry and symmetry of the anatomic ARB. The clinical impact on patients who are appropriate for TIF includes: control of reflux symptoms, healing of esophagitis, normalization of esophageal acid exposure on objective testing, and the opportunity to discontinue anti-acid medications. Early disease without dilation of the hiatus can be treated with the TIF procedure alone, and patients with more advanced anatomic alterations may have cTIF. TIF and cTIF offer great safety and side effect profiles, with good outcomes and durability. cTIF has fewer comprehensive studies to date, but appears to have similar outcomes in safety, symptom control, and normalization of esophageal pH-metry, while minimizing the side effects that deterred patients from definitive treatments in the past.

ANTIREFLUX MUCOSECTOMY (ARMS)

Antireflux mucosectomy (ARMS) is a novel endoscopic treatment for refractory GERD. The mechanism was originally proposed after observation that patients with Barrett's

esophagus undergoing mucosectomy of cardia neoplasms had improved reflux symptoms. The ARMS technique was then refined in a 2014 case series by Inoue and colleagues with patients undergoing either total circumferential or crescentic mucosectomy at the EGJ for GERD resulting in significant improvement in the key symptoms of heartburn and regurgitation.³⁵

The aim of ARMS is to rebuild the mucosal flap valve via mucosectomy at the EGJ, with the submucosal fibrosis and scarring resulting in anatomic narrowing of the gastric cardia opening while recreating the angle of His (Fig. 7A–D). Further refinement of the technique has restricted the crescentic mucosectomy to the lesser curvature of the EGJ, thereby allowing the non-scarred greater curvature flexibility to perform as a mucosal flap valve.

Multiple iterations of ARMS have been developed with the same overall physiologic ethos of causing subcircumferential fibrosis to tighten the EGJ, while varying the depth or technique of mucosectomy. Cap-assisted ARMS (ARM-C) and band-ligation ARMS (ARM-L) involve argon plasma coagulation demarcation of the resection site, followed by either suction cap technique or submucosal injection followed by band ligation, respectively, to perform the 270° mucosectomy.^{36–39}

ANTIREFLUX MUCOSAL ABLATION (ARMA)

Antireflux mucosal ablation (ARMA) uses a through-the-scope dissection knife in spray coagulation mode to perform mucosal ablation along the gastric cardia in a

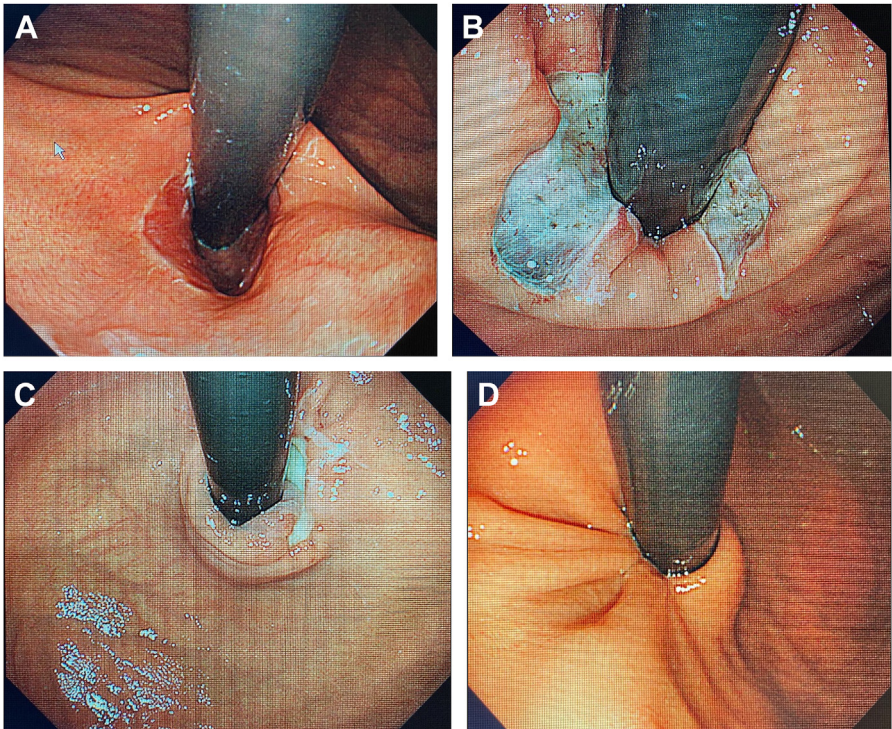


Fig. 7. ARMS. Retroflexed view showing the *butterfly* pattern of the mucosal resection. This sequence illustrates the healing process after ARMS. (A) Pre-ARMS. (B) Immediately after ARMS. (C) 12 days post-ARMS. (D) 1-month post-ARMS. (Photos courtesy of Dr Haruhiro Inoue.)

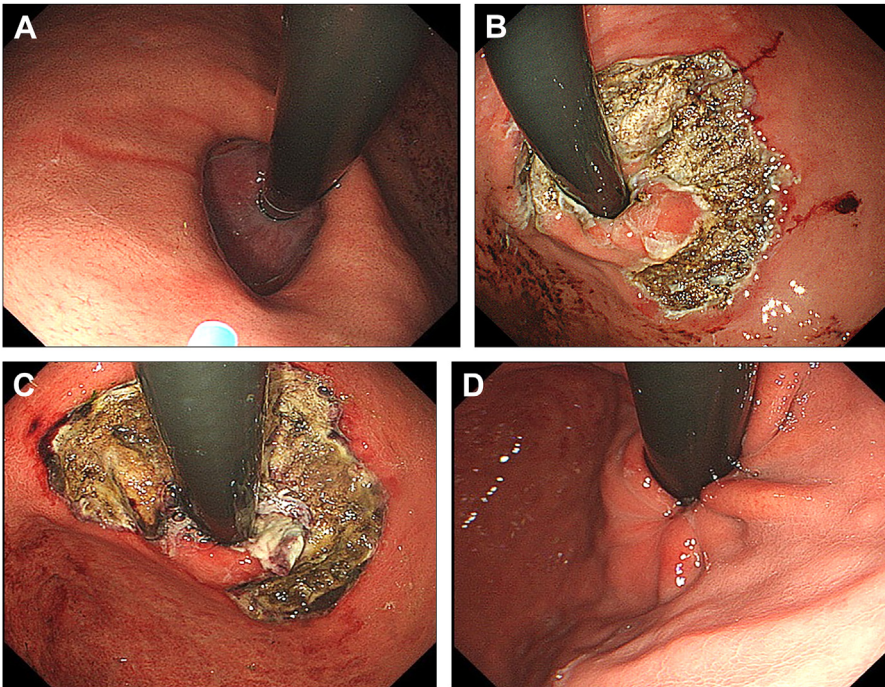


Fig. 8. ARMA. Retroflexed view showing the ablation pattern, which is similar to ARMS resection pattern. (A) Pre-ARMA. (B) Immediately after ARMA. (C) 4 days post-ARMA. (D) 1 months post-ARMA. (Photos courtesy of Dr Haruhiro Inoue.)

butterfly shape pattern, thus leaving 2 contralateral untouched mucosal areas to prevent stricturing^{40,41} (Fig. 8A–D). The additive benefit of ARMA is that this technique can be performed regardless of existing fibrosis from prior therapies.

The latest iteration is a combination of antireflux mucosoplasty with valve (ARM-P/V) performed in one patient with a sliding hiatal hernia.⁴² This technique involves initial cautery demarcation of only one-third of the mucosal circumference along the cardia lesser curvature, followed by mucosotomy and submucosal dissection along the cardia to create a *double flap with semi-free mucosa*. Endoscopic clips are then deployed to prevent flattening of the neo mucosal flap by securing the flap to the underlying muscle, followed by mucosal defect closure with a second layer of clips applied in a zig-zag manner. The proposed benefit of closing the mucosotomy was to mitigate the risk of bleeding and stricture formation.

A recent systematic review has focused on the ARM-C, ARM-L, and ARMA techniques.⁴³ The pooled clinical success rate over 7 ARMs studies were reported at 73.8% (95% CI=69%–78%) with pooled analysis suggesting that ARMA had a higher success rate compared to ARMs and ARM-L ($P<.001$). Pooled estimates were that 61.5% (95% CI=54.6%–67.9%) of patients could discontinue PPI therapy altogether and 87.8% (95% CI=81.8%–92.0%) could reduce PPI use at 6 months. When evaluating clinical success based on objective measures of esophageal pH-metry, all studies in the pooled analysis showed significant improvement in both the DeMeester scores and significant decreases in the mean esophageal acid exposure times following ARMs and ARMA. It should be noted that the study numbers were in general

small, with a follow-up period for pH-metry at only 3 months and, while scores improved, they did not normalize. Adverse events including bleeding, perforation, or dysphagia were noted in 6% to 100% of patients with most complications managed conservatively or endoscopically. The dysphagia rate was 6% to 16%. Currently of these studies are limited with follow-up periods of up to 2 years.

FULL THICKNESS SUTURING TECHNIQUES

The incorporation of endoscopic suturing of the EGJ to modulate the lower esophageal sphincter through tissue apposition has also recently developed as an alternative option for complex refractory GERD patients. This technique was first reported by our group in 2018 among 10 patients.⁴⁴ Using a double-channel gastroscope integrated to the endoscopic suturing platform, 2 running sutures were placed on the gastric side of the gastroesophageal junction in 2 layers in order to create a narrowed and elongated gastroesophageal junction. While technical success was achieved in all patients, including those with a history of previous antireflux procedures ($n=7$) and those with a hiatal hernia ($n=6$), and the GERD-HRQL score improved, the median duration of improvement was short lived at only 1 month. Therefore, similar to the paradigm experienced in the transoral outlet reduction procedure for patients with weight regain after gastric bypass, full thickness suturing is not durable by itself in these *high traffic* areas. Thus, analogous to our experience with transoral outlet reduction procedures, enhancements by way of mucosal ablation or resection prior to suturing were the logical options to explore. We next moved to MASE of the EGJ, by first ablating the cardia tissue via argon plasma coagulation prior to performing running endoscopic sutures from the 7 to 4 o'clock position along the posterior and lesser curvature similar to our initial study.⁴⁵ This technique allows for both narrowing and elongation of the EGJ, especially in patients with prior surgical anatomy (fundoplication, esophagectomy, sleeve gastrectomy, etc) where dissection or resection is not technically feasible (Fig. 9A–E). In our initial small series of 27

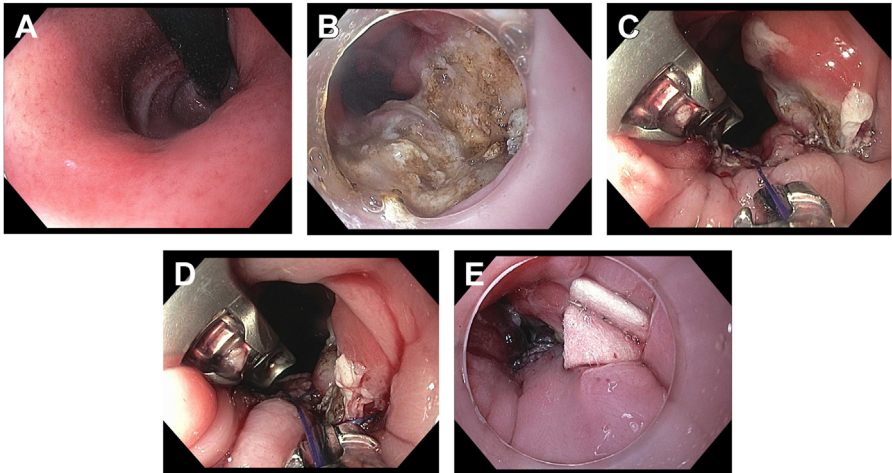


Fig. 9. MASE in a patient with GERD after gastric-bypass. (A) Retroflexed view showing baseline AFS hiatus grade 3. (B) Mucosal ablation along posterior lesser curve aspect from 7 o'clock to 3 o'clock position. (C) Beginning of the first suture in a pattern similar to RAP. (D) End of first suture placement. (E) Second suture placement similar to RAP, with needle suture anchor supported with white pledget.

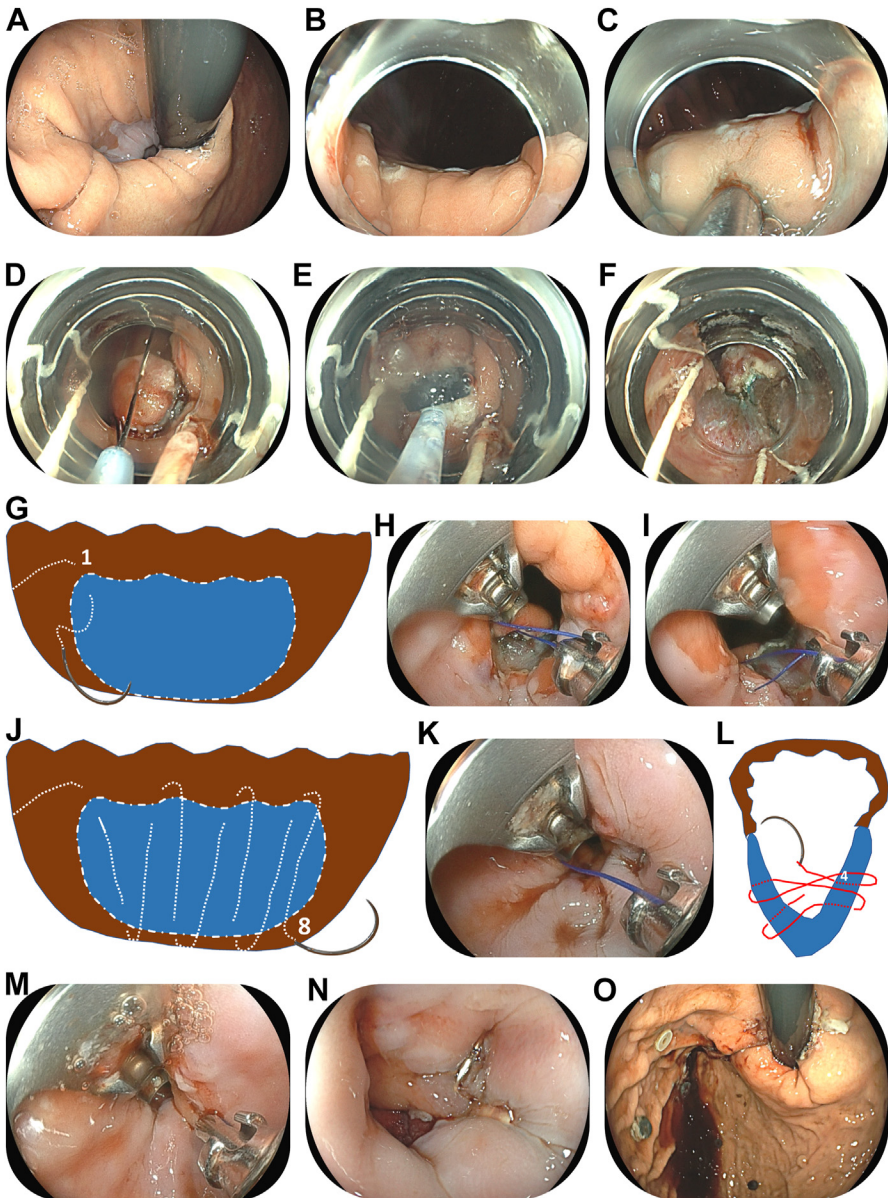


Fig. 10. RAP. (A) Retroflexed view showing baseline AFS grade 3 with gaping hiatus. (B) Marking of resection area, approximately 1.5 cm length, from 8 o'clock to 3 o'clock. (C) Submucosal injection to lift mucosa prior to band ligation (D) Banding of mucosa followed sequentially with snare ligation. (E) Snare ligation best performed beneath the band. (F) After 6 piecemeal contiguous band ligations, the muscle layer is exposed. (G) Diagram showing the suture pattern of the first suture begins with a bite at the most distal-left corner, then alternating between distal and proximal bites going from left to right, forming a "W" pattern. (H) Initial suture bite. (I) Second suture bite. (J) Diagram showing the final suture bite (8), which ends on the proximal right. (K) Releasing the needle anchor after the final bite, followed by cinching and cutting the suture. (L) Diagram showing the suture pattern

patients, 59% were able to discontinue PPI therapy and 14% were able to reduce PPI dose. This appeared more durable than suturing alone. The next iteration was the resection and plication (RAP) approach, first described by Benias and colleagues.⁴⁶ The RAP procedure is similar to a MASE procedure with the key difference of performing a semicircumferential mucosal resection using multi-band ligations in lieu of ablation prior to full-thickness plication at the level of the gastric cardia. In this initial series of 10 patients, all had significant improvement in their GERD-health related quality of life (HRQL) scores (absolute reduction of 22.3, $P < .001$) with 80% of patients discontinuing PPI use at 9 months. No significant intra-procedural adverse events occurred, although 2 patients reported dysphagia requiring endoscopic balloon dilation. Our group published our initial RAP experience in 26 patients showing 100% technical success.⁴⁷ Eighteen of these patients (70%) had altered anatomy: esophagectomy (4), roux-en Y gastric bypass (4), sleeve gastrectomy (1), prior failed Nissen fundoplication (5), prior failed TIF (2), endoscopic sleeve gastropasty (2). Mean follow-up was 6 months. Sixty percent of patients were able to discontinue or decrease PPI use. Reflux Disease Questionnaire score for symptom severity was 14.6 pre-RAP and 3.0 post-RAP ($P < .01$). Reflux Disease Questionnaire score for symptom frequency was 16.1 pre-RAP and 3.1 post-RAP ($P < .01$). GERD-HQRL was 25.7 pre-RAP and 3.7 post-RAP ($P < .01$). There were no adverse events in this series; 90% of patients were discharged the same day. The technique was slightly different from that of Benias and colleagues with the resection and plications performed more posterior and toward the lesser curve (Fig. 10A–O). In addition, most patients receive a second reinforcing suture (see Fig. 10L, M).

The RAP procedure has become our primary choice in patients with altered anatomy that precludes either laparoscopic approaches or TIF. We have performed 74 RAP procedures to date, including patients who are postesophagectomy with refractory GERD. The RAP procedure can be performed even within a hiatal hernia and does not require a retroflexed position, an advantage in patients postsleeve gastrectomy. The main advantages of RAP include short procedure time (approximately 30 minutes), outpatient procedure, and high utility in patients with altered anatomy or those that have failed surgical or endoscopic fundoplication.

Since the RAP procedure is an endoscopic gastro-gastric plication, we do not view it as the optimal method to augment and recreate the GEFV (as does TIF) and the durability in our experience is estimated only in the 2 to 5 year range. Hence, patients may need a future revision. In such cases, we offer MASE after previous RAP, since any attempt at resection is difficult over the previous scarred area.

CONCLUDING PERSPECTIVES

In refractory GERD patients or those concerned about long terms medical therapy, step up therapy should be considered via endoscopic or surgical approaches. The



of the second suture, taking 4 to 6 bites starting on the left side at the bottom of the "V", then alternating right and left and moving up the "V" until sufficient closure is accomplished. This second suture serves as a reinforcing suture as well as titrating the final aperture of the valve. (M) Final bite (6) on the right side. (N) Final forward view at the top of the new valve. (O) Final retroflexed view of the gastric side of the new valve, which created approximately 1.5 cm in length with obvious tightening around the scope.

Modality	GEFV Lengthening (cm)	GEFV Narrowing	Optimal GEFV Geometry	Causes Dysphagia	Durability of New Valve
TIF 2.0	2–4	Yes	Yes	Minimal	5–10 y
ARMS	<1.5	Yes	No	++	?
ARMA	< 1.5	Yes	No	+	?
RAP	< 1.5	Yes	No	Minimal	?
MASE	< 1.5	Yes	No	Minimal	?

patient's anatomy, comorbidities, and surgical risk profile should all be considered by the clinician to inform the best treatment option. Improvements in both technique and devices have made endoscopic management a viable option for many patients. Here are some key perspectives in considering the various endoscopic approaches to GERD.

1. If the patient is a surgical candidate, please perform a careful assessment of the hiatus grade (we prefer to use the AFS Hiatus Grade⁶) to confirm whether a hernia reduction or crural repair is required. If the hiatus grade is high or underestimated, any endoscopic approach will have less than optimal results.
2. Among the endoscopic options, the TIF 2.0 procedure stands above the others because of FDA approval for the treatment of GERD, level 1 medical evidence pertaining to clinical efficacy, objective improvement, and normalization of acid exposure time, long-term durability, minimal side effects, and being most aligned with current anatomic principles to optimally augment and restore the GEFV.
3. However, if TIF is not feasible (eg, altered anatomy) or unavailable, other endoscopic procedures for performing a gastro-gastric plication are appropriate options. Gastro-gastric plication antireflux procedures should decrease the compliance of the proximal stomach within 1 to 2 cm of the gastroesophageal junction. Without the ability to increase the intraabdominal length of the esophagus or create a lengthy flap-valve, the gastro-gastric plication can only plicate the sling fibers of the proximal stomach, which comprise the lower portion of the LES. While creating a lengthy flap-valve is not realistic, a short valve can be constructed by drawing tissue around the GEJ (see Fig. 100). In Table 1, we have summarized the attributes of the various procedures discussed.
4. For those endoscopic techniques that leverage submucosal fibrosis as the means to create luminal narrowing, there is a degree of unpredictability as to the final result after healing has occurred. There is risk that after healing, the lumen will still be either too loose (reflux persists) or too tight (dysphagia ensues). There is a trend now to close the defect, initially by using clips^{48,49} and subsequently by hand-suturing,⁵⁰ to mitigate these risks. This has been coined antireflux mucoplasty. Interestingly, if you combine ARMS with closure, you are essentially performing a RAP procedure, and if you combine ARMA with closure, you are essentially performing a MASE procedure. The only difference is in the depth of the closure (mucosal vs full-thickness). We feel the evolution of these techniques will likely converge on closure or plication after resection or ablation. More data are needed on all these gastro-gastric plication techniques to confirm objective impact on esophageal acid exposure with long term results.

CLINICS CARE POINTS

- After a careful endoscopic assessment of the GEJ and diaphragmatic hiatus, if a hernia reduction or crural repair is needed and the patient is a surgical candidate, we recommend a hiatal hernia repair plus fundoplication (which could be cTIF).
- Among the endoscopic options, TIF 2.0 stands above the others (FDA approval, Level 1 evidence, and most aligned with current understanding of anatomic principles to optimally augment and restore the GEFV).
- If TIF is not feasible (altered anatomy) or unavailable, other endoscopic procedures which perform a gastro-gastric plication are appropriate options.
- Endoscopic techniques that utilize resection or ablation may result in the lumen being still too loose (reflux persists) or too tight (dysphagia ensues). More predictable tightening can be achieved if resection or ablation is combined with closure or flap creation using sutures or possibly clips.

DISCLOSURE

Dr K.J. Chang has served as consultant for Apollo Endosurgery, Boston Scientific, Cook Medical, Erbe, Endogastric Solutions, Fujifilm, Medtronic, Olympus.

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