Chapter 17
Endoluminal Gastroesophageal Reflux Disease Therapies

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Introduction

Gastroesophageal reflux disease (GERD) is a potential precursor to esophageal adenocarcinoma, one of the fastest rising incidences of cancer in developed countries [1]. Other major complications of GERD include stricture and Barrett's esophagus, which lead to altered quality of life. Approximately 25% of patients living in North America are affected by GERD, leading to increased spending and substantial healthcare costs estimated around $18.1 billion annually [2]. Current first-line treatment efficacy, such as acid-suppressive medication and weight loss, has been ineffective in up to 40% of patients [3, 4]. Those patients who either fail medical therapy or lifestyle changes may wish to pursue more definitive treat-

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ment such as laparoscopic or endolumenal therapies. Patients undergoing surgical intervention have consistently demonstrated symptomatic relief and durability, as noted by long-term follow-up studies. Endoluminal therapies, which will be discussed in this section, offer a wide variety of benefits, including but not exclusively minimal IV sedation, decreased pain and recovery, limited incisions, as well as offering lower perioperative patient risks.

Diagnosis and Management

The extent of the work-up is directly associated with patient symptom characteristics, age, risk factors, and alarm features. Those who have typical GERD symptoms of regurgitation and heartburn should be given a trial of proton pump inhibitors along with lifestyle modifications [5]. Lifestyle modification and medication trials are usually the first-line treatment of gastroesophageal reflux disease. Surgical management may be offered to those who fail medical therapy, have persistent or progressive symptoms, noncompliance with medication, or are unwilling to commit to long-term medication therapy [6]. In contrast, any patient over the age of 50 with atypical symptoms such as anemia, vomiting, dysphagia, weight loss, or with alarm symptoms should be evaluated with esophagogastroduodenoscopy (EGD) (Fig. 17.1). The role of EGD is to rule out any neoplastic process, strictures, Barrett's esophagus, ulcerations, infections, or GEJ defects that may be contributing to GERD. Patients who undergo EGD frequently have normal studies and adjunct studies such as barium swallow, high-resolution manometry, pH impedance, and BRAVO studies are available to further delineate any abnormalities in patients' anatomy, the functionality of the LES, and acid exposure [5].

Surgical management can be divided into either laparoscopic, open repair, or natural orifice endoluminal surgery. The principal objective of surgical intervention is to restore the anatomy in order to achieve normal lower esophageal sphincter pressure and overall shorter sphincter length [7]. Laparoscopic Nissen fundoplication is proven, effective, and

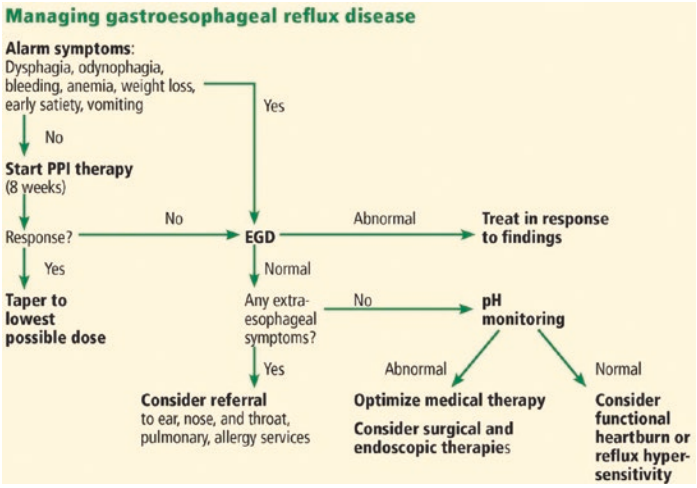

FIGURE 17.1 Practical algorithmic approach to managing patients with gastroesophageal reflux disease based on their initial symptoms, response to medical therapy, and EGD findings (Courtesy of: Young A, Kumar MA, Thota PN. GERD: A practical approach. Cleve Clin J Med. 2020 Apr;87(4):223–230)

durable. However side effects exist, including gas bloat, inability to belch, dysphagia, and inability to vomit. Natural orifice endoluminal techniques offer minimally invasive procedures for patients who are poor surgical candidates or prefer to avoid standard surgical procedures. It is associated with fewer adverse effects. However, its evaluation of efficacy and durability is still yet to be determined as research studies are currently evaluating its outcomes.

Specific Endoluminal Therapies

Several FDA-approved therapies will be discussed in this section. As of today, multiple FDA-approved GERD treatment devices are available in the USA, including EsophyX and Stretta®, both of which will be discussed at length below.

Esophyx and Transoral Incisionless Fundoplication

The EsophyX device was initially designed in 2006 to create an internal esophagogastric fundoplication by restoring the angle of His [8]. Since its inception, EsophyX (Fig. 17.2) has evolved to the EsophyX 2 and most recently EsophyX Z (Fig. 17.3). As the models improved over the years, the device became more user friendly with more consistent and reproducible results amongst different users. Figure 17.5 compares all three models. The device is introduced over a flexible

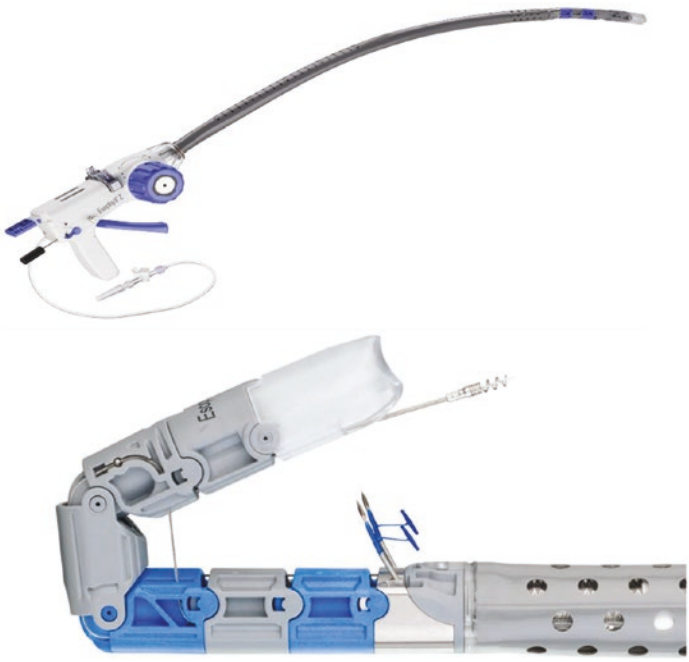

FIGURE 17.2 The EsophyX device illustrates the handle and shaft (*top*) and the distal end with tissue mold, helical retractor, tissue invaginator, and stylet with fastener (*bottom*) (courtesy of EndoGastric Solutions)

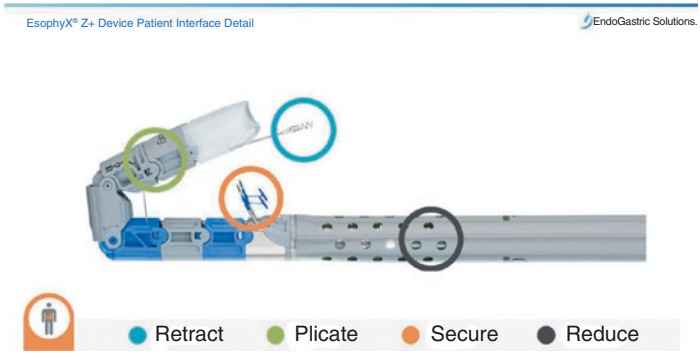

Figure 17.3 EsophyX Z+ device demonstrating the area of plication used to rotate tissue *(green)*, Helical retractor used to grasp tissue in order to create valve length *(blue)*, H-shaped polypropylene fasteners used to fire through tissue *(orange)*, and invaginator suction area of the shaft used to reduce small hiatal hernia's *(black)* (courtesy of EndoGastric Solutions)

endoscope with an over-tube with the patient under general endotracheal anesthesia. A helical screw on a cable is used to hold one tissue plane while the device's tip is folded on itself, creating tissue apposition and compression. A small "H"-shaped polypropylene suture fastener is then delivered across the apposed tissue to fix the plication. These full-thickness fasteners create a serosal fusion of the apposed tissues, and between the two legs has a length of 6.5 mm and is equivalent in strength to a 3-0 prolene suture [8] (Fig. 17.4). Providers demonstrated concern of excessive compression on the tissue which led to fastener pull-through. Thus the "H" fastener was widened to 7.5 mm, which is the current standard size used today with the EsophyX2 model. Not only did widening the fastener solve the pull-through issue, but it also improved the ease of deployment and overall delivery. The EsophyX Z device upgrades incorporated a change to the folding, which tubularized the tissue mold, streamlining the end of the device with the endoscope. This was a significant safety concern that was addressed to avoid injuring the esophagus. In addition, a separate channel for the second leg of the fastener

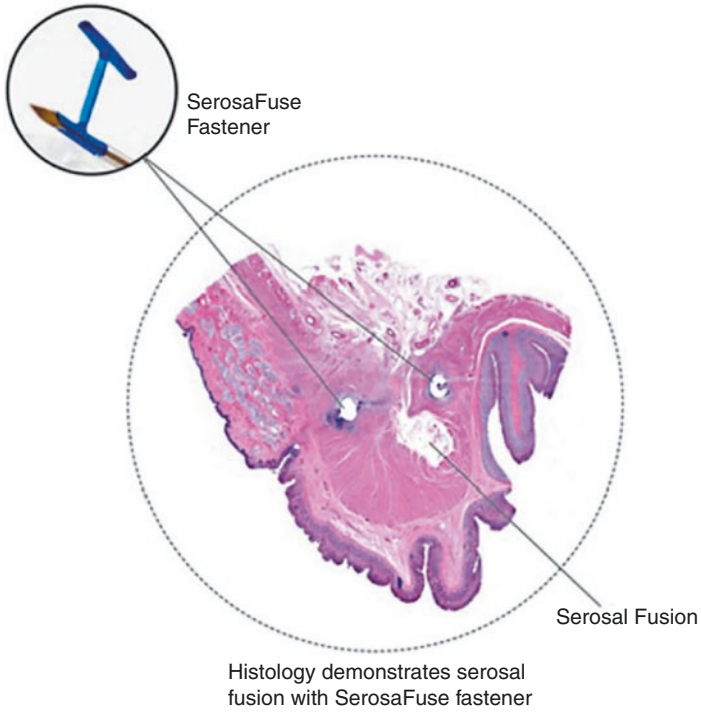

FIGURE 17.4 Porcine photomicrograph illustrating fusion of apposed serosa by the EsophyX fastener (courtesy of EndoGastric Solutions)

was created to allow for simultaneous advancement and deployment, making this automated delivery standardized and reproducible [8] (Fig. 17.5).

The EsophyX device is composed of:

1. A handle wherein the various controls are located.
2. A chassis of 18 mm diameter through which the endoscope is inserted and control channels run.
3. Side holes on the distal end of the chassis to which external suction can be applied (the tissue invaginator).
4. A tissue mold, which, when brought into retroflection, pushes tissue against the shaft of the device.

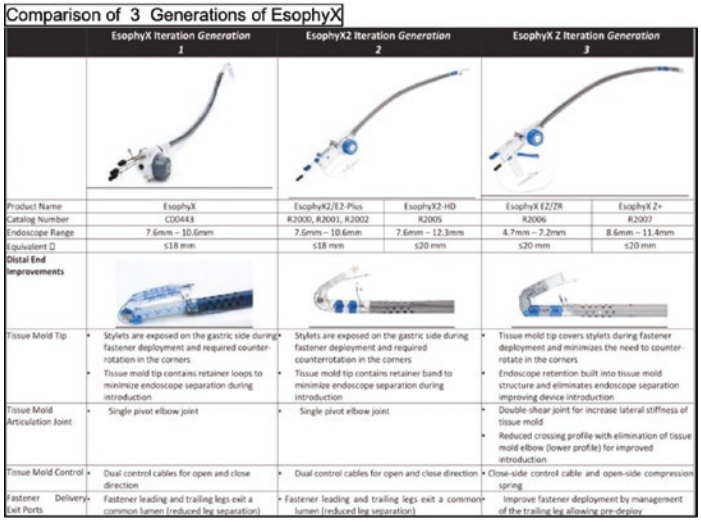

Figure 17.5 Comparison of 3 generations of EsophyX. EsophyX Generation 1 *(far left)* demonstrating the endoscope range, tissue mold tip and articulation joint as well as its control and delivery. EsophyX2 *(middle)* demonstrating wider endoscope range compared to the first generation, with similar mold tip, articulation joint as well as mold control and delivery as the first generation. EsophyX Z *(far right)* demonstrating its endoscope range as low as 4.7 mm, as well as double shear joint for increased lateral stiffness and improved scope introduction due to lower profile, and improved fastener deployment (courtesy of Ihde GM. The evolution of TIF: transoral incisionless fundoplication. Therap Adv Gastroenterol. 2020 May 21;13:1756284820924206)

5. A helical screw is advanced into the tissue to pull tissue caudally between the tissue mold and the shaft.
6. Two stylets, which advance from the shaft of the device through the plicated tissue and then through eyelets in the tissue mold.
7. A cartridge containing polypropylene H-shaped fasteners (or plicators), which are deployed over the stylets so that the trailing leg engages within the esophageal lumen and the leading leg engages within the gastric lumen.

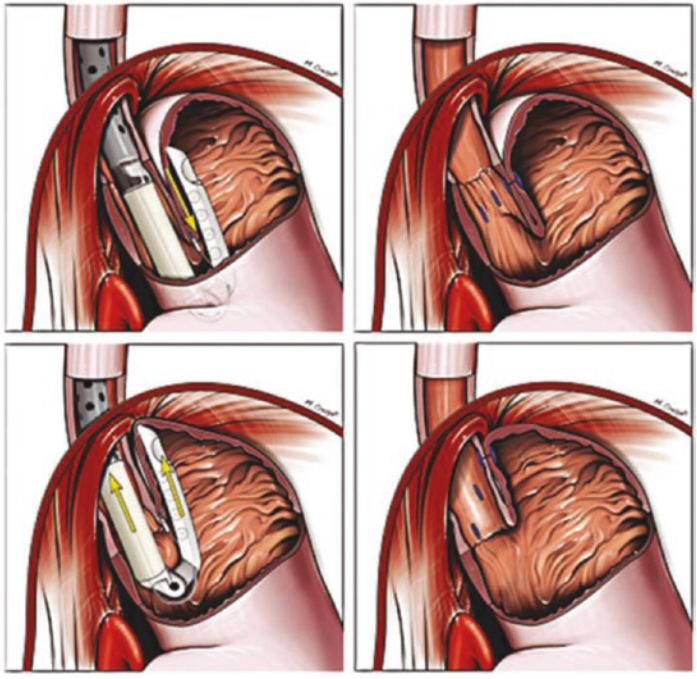

Figure 17.6 Illustration of use of EsophyX device create gastrogastric plication (*top*) or esophagogastric plication (*bottom*) (artist: Massimilano Crespi, info@max-medicalillustrator.com)

Multiple fasteners can be deployed in a circumferential fashion to create either a gastrogastric (original technique) or an esophagogastric (current technique) plication (Fig. 17.6). A rotational element was also developed to fold tissue around the esophagus. The techniques have been described in detail by Jobe [9] and Bell [10]. The TIF 2 is the procedure most commonly performed today using the EsophyX device. The final construct has an endoscopic appearance similar to a surgical fundoplication (Fig. 17.7).

Canine studies of a gastrogastric plication created with the EsophyX device demonstrated an increase in lower esophageal sphincter length and pressure, primarily due to pressure

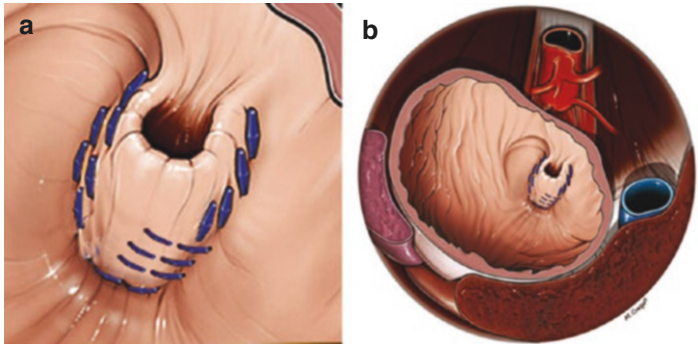

FIGURE 17.7 Completed TIF esophagogastric fundoplication with external structures in both panel **a** (zoomed in) and panel **b** (artist: Massimilano Crespi, info@max-medicalillustrator.com)

augmentation at the lower end of the LES. The TIF 2 esophagogastric plication resulted in a valve with sphincter vector–volume characteristics similar to a Nissen procedure [9]. Human studies using endoluminal functional imaging and impedance have demonstrated a decrease in EG junction distensibility immediately after the procedure and decreased liquid and mixed TLESR-related reflux events at six months post-TIF (16.8 ± 1.5 vs. 9.2 ± 1.3; $p < 0.01$). TIF also led to a decrease in the number and proximal extent of reflux episodes and improved acid exposure in the upright position [11]. The mechanism by which the TIF procedure keeps a hiatal hernia reduced has not been thoroughly investigated. Canine studies found that the TIF 2 procedure "captured" a loose phrenoesophageal membrane within the plication. In some cases, bulking the GE valve, or capturing the PE membrane at the edge of the hiatus during fastener delivery, may have a role in keeping the hiatal hernia reduced.

Similar criteria to other endoluminal therapies have been used for the TIF procedure. Patients with symptomatic GERD who have Hill grades I-II, hiatal hernia <2 cm, and those refusing medical therapy or surgery, are candidates for TIF as a safe and effective therapeutic option [12]. Contraindications have been severe esophagitis, Barrett's, gastroparesis, a hiatal her-

nia of >2 cm, and BMI >35. Additionally, a transverse hiatal dimension of >3 cm may be a limiting factor as the patient likely will require a crural closure [10]. Patients undergoing the TIF procedure should undergo the same preoperative objective documentation of GERD as a patient undergoing a laparoscopic fundoplication.

The TIF procedure is performed under general endotracheal anesthesia. Medication to decrease postoperative nausea, a proton pump inhibitor, and antibiotics are administered preoperatively. Proton pump inhibitors are continued postoperatively for two weeks to aid in healing the gastric portion of the plication. Before device introduction, endoscopic evaluation of the hiatus for hernia dimensions and measurement of the distance to the diaphragm is performed. The endoscope is placed through the EsophyX device and introduced into the esophagus, and then both are advanced carefully, especially as the elbow of the device passes through the cricopharyngeus. The device is visualized entering the stomach, and then the endoscope is pulled back and reintroduced so that it is outside the tissue mold. The tissue mold is retroflexed under direct visualization as the spleen lies outside the stomach on the greater curve.

With both the tissue mold and the endoscope in a retroflexed position, the helical retractor is engaged at the gastroesophageal junction (generally the Z-line) at the posterior corner of the anticipated fundoplication position. The tissue mold is partially opened and rotated out of this corner. The device is then pulled back (cranially) a predetermined amount, generally 1–3 cm. The tissue mold is then rotated back into the corner while tension is applied to the helical retractor and the stomach is desufflated. With the fundus so rotated, the tissue mold is closed and locked in place, the helix is locked, and the tissue invaginator is placed on suction. This set of maneuvers accomplishes the following: withdrawing the device moves the set point for the emergence of the stylets cranial to the GE junction so that an esophagogastric plication is created; rotation of the tissue mold with the device at this set distance then rotates the fundus around the

esophagus; tension on the helical retractor pulls the GE junction slightly caudally and stabilizes the tissue; desufflation of the stomach enables rotation of the gastric fundus.

With the tissue in position, the position of the plication in relation to the diaphragm is assessed so that the stylets and fasteners will not traverse the diaphragm. Understanding anatomic relations, palpating the diaphragm with the tissue mold before tissue positioning, and ensuring that the device is introduced beyond the depth of the diaphragm (as previously measured to the incisors) are essential. Advancing the device caudally with the tissue invaginator on suction enables caudal advancement of gastroesophageal junction below the diaphragm without displacing the device in relation to the esophagogastric junction. Concurrent laparoscopic visualization in humans has confirmed that 2–3 cm of additional separation between the esophagus and diaphragm can be obtained with this maneuver.

The stylet furthest away from the corner is advanced until visible beyond the tissue mold (e.g., the anterior stylet when in the rear corner). At times, counterrotation of the device is needed to reduce tension on the tissue mold aligning it with the stylet course. With stylet in view, the fastener is advanced gradually, allowing the trailing leg of the fastener to deploy within the esophageal lumen and the leading leg to deploy within the gastric lumen, creating a full-thickness "H" fixation. The fastener closest to the corner is then deployed, leaving two fasteners at the same depth, a "plication set." The device is reloaded, the tissue mold and helix unlocked, the tissue invaginator taken off suction, and the procedure repeated at a different location.

The precise positions of the plication sets are a matter of surgical judgment. The initial TIF 2 technique involved creating two plication sets 1 cm deep at the anterior and posterior corners (towards the lesser curve). Two plications were set 3 cm deep along the greater curve, with a helical deployment at each location with mild degrees of rotation. The evolution of the technique has included increasing the number of plication sets from 6 to 10 or more, decreasing the number of heli-

cal deployments, and increasing the rotational component compared with the longitudinal movement.

Once the fundoplication has been created, the tissue mold is straightened under direct vision, and the device is withdrawn. Positioning the endoscope at the very end of the chassis during final withdrawal enables careful inspection of the esophageal lumen during the retreat. A final endoscopy without the device is performed to evaluate for bleeding and to assess the final result. In a retrospective review in 2011, data suggested that TIF 2.0 may be improved if hiatal hernia repair was performed just prior to the fundoplication. In patients who had undergone TIF 2.0, at 6 months follow-up, endoscopy demonstrated a significantly dilated hiatus, thus bringing up the concern for symptom recurrence. Table 17.1 shows superiority in patient symptom score in the post-TIF with crural repair vs. TIF alone [8].

Table 17.1 Demonstrates comparison between patients who underwent TIF and those who underwent TIF with crural closure. Their respective follow-up GERD quality of life scores, reflux symptoms scores, reflux symptom index scores, regurgitation and satisfaction were compared (courtesy of Ihde GM. The evolution of TIF: transoral incisionless fundoplication. Therap Adv Gastroenterol)

Table 17.1 TIF 2.0 *versus* TIF 2.0 w/CC$_{\text{(median scores)}}$

Post TIF		**Post TIF w/CC**	
• GERD-HRQL	5	• GERD-HRQL	3
• RSI	5	• RSI	4
• GERSS	6	• GERSS	1
• Regurgitation	5	• Regurgitation	0
• Satisfaction	50%	• Satisfaction	83%

$p < 0.001$ for all changes

CC, crural closure; GERD, gastroesophageal reflux disease; GERSS, gastrocsophageal reflux symptom score; HRQL, health-related quality of life; RSI, reflux symptom index; TIF, transoral incisionless fundoplication

Most patients stay overnight to help with pain and nausea management and are discharged from the hospital the following day. A soft diet is prescribed as postoperative edema narrows the esophageal lumen. Regular diet will resume over the next couple of weeks. Direct procedure-related complications have been bleeding and infection. Bleeding during the advancement of a stylet will generally stop with fastener deployment. Pneumoperitoneum may be seen after TIF and in and of itself does not indicate a clinically significant complication. Full-thickness injury to the esophageal or gastric wall has been reported after the TIF procedure, generally developing a few days afterward. This is likely due to fasteners pulling through the wall of the viscera from excess tension, retching, or vomiting. Abdominal or mediastinal infection can result. Laparoscopy with mediastinal drainage and removal of offending fasteners has been performed successfully. Procedural technique predicated upon understanding external anatomic relations decreases the potential for these complications.

Major procedure-related complications were seen in 2.4% of 635 patients in the reported series, including perforation (0.7%) or bleeding requiring transfusion (1%). Technique modification to ensure that stylet and fastener deployment occurs below the diaphragm has reduced the perforation rate, and recent series have reported no perforations in 160 patients [13–15]. As of July 2019, a review of the safety data reveals a markedly lower SAE rate of 0.41% when compared to laparoscopic fundoplication out of a total of 22,000 procedures. Figure 17.8 demonstrates the events by type.

Multiple single-arm clinical studies have been published with 6–36-month follow-ups. A meta-analysis of 15 studies published through 2012 found that GERD-HRQL scores (21.9 vs. 5.9) and Reflux Symptom Index (RSI) scores (24.5 vs. 5.4) were significantly reduced after TIF ($p \leq 0.0001$). PPI discontinuation was 67% across all studies, with a mean follow-up of 8.3 months [16]. Recent long-term data on patients who were followed for ten years after TIF demonstrated a high rate of cessation or decrease in antisecretory medical

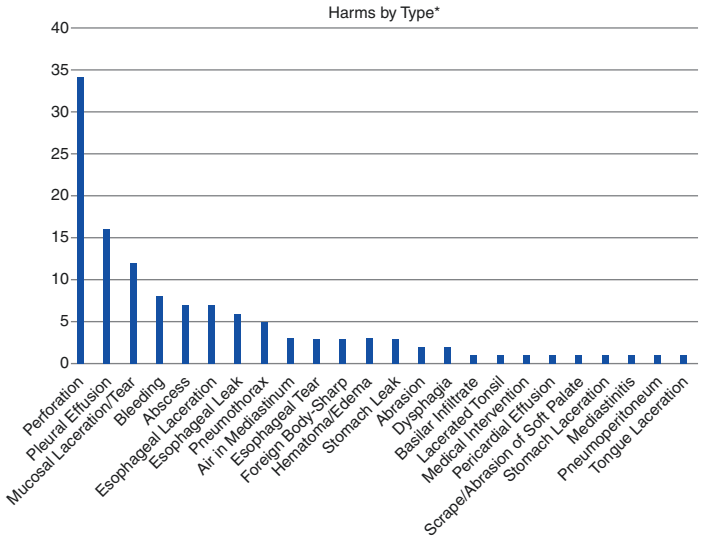

Figure 17.8 Figure demonstrating predominance of complication events from TIF. Perforation on the far left is the most predominant complication followed by pleural effusion, mucosal laceration or tear, bleeding, abscess, leak, and pneumothorax as most common (courtesy of Ihde GM. The evolution of TIF: transoral incisionless fundoplication. Therap Adv Gastroenterol)

therapy at 2 (86.7%), 3 (84.4%), 5 (73.5%), 7 (83.3%), and 10 (91.7%) years after the procedure [12].

Regurgitation symptoms respond very well to TIF. In a recent study of 63 patients at 6-month follow-up, troublesome regurgitation was eliminated in 97% of TIF patients vs. 50% of PPI patients, relative risk (RR) = 1.9, 95% confidence interval (CI) = 1.2–3.11 (p = 0.006) [17]. Patients with a history of esophagitis grade A and B, proven GERD on pH monitoring, and with typical symptoms of GERD underwent TIF using Esophyx demonstrating promising results. The specific symptoms of heartburn, regurgitation, and chest pain were eliminated in 57.1%, 88.2%, and 83.3%, respectively, at a median follow-up of 59 months [18].

A single sham-controlled study of the TIF 2 technique has been reported. Patients were assigned to groups that underwent TIF and then received 6 months of placebo ($n = 87$) or sham surgery (endoscopy and dilation for 45 min under general anesthesia) and six months of once or twice-daily omeprazole (controls, $n = 42$). Patients were blinded to therapy and reassessed at 2, 12, and 26 weeks. At six months, patients underwent 48-h esophageal pH monitoring and esophagogastroduodenoscopy. By intention-to-treat analysis, TF eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%) ($p = 0.023$). Control of esophageal pH improved following TF (mean 9.3% before and 6.3% after, $p < 0.001$), but not after sham surgery (mean 8.6% before and 8.9% after). Subjects from both groups who completed the protocol had similar reductions in GERD symptom scores. Severe complications were rare (3 subjects receiving TF and 1 receiving the sham surgery) [19].

Several studies of esophageal pH alterations after the TIF 2 technique have demonstrated statistically significant improvement in esophageal acid exposure measured by DeMeester score, % time pH less than 4, and a number of reflux episodes [20, 21], though some have not [9]. A recent open-label RCT comparing PPI treatment with TF demonstrated benefit for TF over PPI in control of troublesome GERD symptoms, with 54% of patients achieving normalization of intra-esophageal pH off PPI following TF [17]. A study of 15 patients before and six months after having TIF demonstrated a reduced number of postprandial TLESRs (16.8 ± 1.5 vs. 9.2 ± 1.3; $p < 0.01$) and the number of postprandial TLESRs associated with reflux (11.1 ± 1.6 vs. 5.6 ± 0.6; $p < 0.01$), but the proportion of TLESRs associated with reflux was unaltered (67.6 ± 6.9 vs. $69.9 \pm 6.3\%$). TIF also led to a decrease in the number and proximal extent of reflux episodes and improved acid exposure in the upright position. TIF did not affect gas reflux, which may be why TIF has not been associated with increased gas-related symptoms [11].

In a retrospective review by Ihde et al., where the investigators reviewed pH scores in hiatal hernia repair combined

with TIF demonstrated improvement in the mean pH score from 35.3 (SD, 2.27) to 10.9 (SD, 11.5), $p < .001$ with short-term follow-up data [22]. However, when comparing only TIF to PPI in a randomized controlled trial over 12 months, despite the improved quality of life in the TIF group, there was no improvement in esophageal acid exposure compared to baseline ($p = 0.171$) [23]. Normal pH levels were only accomplished in 29% of the population in the TIF group, with 61% having to restart the PPI's. More long-term studies and objective data are needed to evaluate TIF without any adjuncts further.

Only a few studies have reported longer-term follow-up. Two-year results of a US Multicenter study found that GERD health-related quality of life and regurgitation scores improved by ≥50% in 63 of 96 (66%) and 62 of 88 (70%) of patients who had elevated preoperative scores. The RSI score normalized in 53 of 82 (65%) patients. Daily PPI use decreased from 91 to 30% [24]. Muls reported a 3-year follow-up on 66 of 79 initial patients. GERD- HRQL improved to 4 (0–32) from 25 (13–38) off PPI, 9 (0–22) on PPI before TIF. By modified intention to treat, 61% of patients remained off daily PPIs (unpublished report, in review, by Testoni, 50 patients, 84% off or halved PPI therapy at 3 and 6 years post-TIF).

The TEMPO trial demonstrated TIF 2.0 durability, safety, and clinical outcomes evaluated at five years. Patients with chronic GERD and refractory to PPI with small or absent hiatal hernia and abnormal acid exposure were randomized to TIF or PPI groups. Resolution and elimination of regurgitation at 1, 3, and 5 years were 88%, 90%, and 86%, respectively, without any significant adverse events, concluding the safety and sustainability of providing long-term symptomatic relief in this cohort of patients [25].

Some patients seem to derive no benefit after a TIF procedure. Edema in the distal esophagus persists for some weeks after the TIF procedure, and some patients have a recurrence of their symptoms after this edema resolves. These are probably initial technical failures. The TIF procedure is technically

more demanding than other endoluminal GERD procedures; technique may play a role in these early failures.

Postoperative retching or coughing has been associated with disruption of the TIF fundoplication. Unrecognized or developing hiatal hernia may be the leading reason for technical failure of the TIF procedure, and studies have shown that any hernia is associated with a lower success rate than no hernia [13].

Two European studies have reported on 26 patients having laparoscopic fundoplication for recurrent reflux after TIF [26, 27] with complications of infection (2 patients). Although objective parameters improved, quality of life did not, and dysphagia was noted to be a problem. Two US studies [24, 28] reported on 33 patients having a laparoscopic revision of prior TIF. There were no perforations, and short-term follow-up indicated the improved quality of life and no issue with dysphagia. Long-term outcome has not been reported.

Ten to twenty percent of laparoscopic fundoplication failures are due to loosening of the fundoplication alone, without any evidence of hiatal failure. Results of utilizing the TIF procedure in 11 patients with failed laparoscopic fundoplication demonstrated resolution of primary symptom in 8 of 10 patients at a median 14-month follow-up, and reduction in esophageal acid exposure from 8.1% (21–4.8%) to 0.6% (13.4–0.01%) ($p = 0.008$) [29].

Compared to laparoscopic Nissen Fundoplication, a direct comparison of TIF was performed in a systematic review and meta-analysis of randomized control trials by Richter et al. in patients with GERD. Seven studies with compiled 1128 patients were analyzed for quality of life and physiologic parameters. Although TIF demonstrated the highest probability of increasing patients' health-related quality of life (0.96), compared to LNF (0.66), sham procedures (0.35), and PPIs (0.042), however, in terms of physiologic parameters, laparoscopic Nissen Fundoplication had the highest probability of decreasing percent time at pH <4 (0.99) and increased LES pressure (0.78) when compared to TIF (0.32) and (0.72) respectively [30].

In Summary, transoral incisionless fundoplication creates a valve that resembles a laparoscopic fundoplication endoscopically without restricting the ability to belch and vomit. Gas bloat has been a rare event. Clinical success at normalizing GERD quality of life and decreasing dependence on daily PPIs has been seen in 65–80% of patients, and this effect persists up to 3 years and beyond. Most esophageal pH studies have demonstrated improvement in esophageal acid exposure after TIF, with normalization of pH in about 50% of patients.

TIF has been demonstrated to be an effective option in patients with Hill grades I-II, small hiatal hernia <2 cm, or in those who do not wish to be on lifelong medical therapy and do not wish to undergo surgery [12]. Patients were able to significantly decrease or discontinue their medical treatment up to 10 years after the procedure.

Although TIF has produced the most significant increase in health-related quality of life in a systematic review meta-analysis in a study by Richter et al., it has yet to replace Laparoscopic Nissen Fundoplication as a long-term alternative treatment of GERD. Further studies need to be performed to evaluate the device further [30].

Stretta® Radiofrequency Treatment of the Gastroesophageal Junction

Introduction

Non-ablative radiofrequency (RF) treatment of the GE junction can be performed with an endoluminal catheter with an inflatable and flexible balloon- basket with four needle electrode sheaths [31] (Fig. 17.9). The electrodes are introduced into the esophageal wall in the LES region, and RF energy at 465 kHz is delivered to the electrodes. Cellular heating results in tissue remodeling. A thermocouple on the electrode enables control of the power delivered to reach but not exceed 50 °C. Irrigation of the overlying mucosa minimizes heat injury to the esophageal lining (Fig. 17.10) [32].

FIGURE 17.9 The Stretta® device illustrating the handle, catheter with balloon, and extruded radiofrequency needle (courtesy of Mederi Therapeutics)

Figure 17.10 The Stretta® device, illustrates the balloon in place, subsequent areas of ablation (*circles*), and proposed thickening of lower esophageal sphincter tissues (courtesy of Mederi Therapeutics)

Mechanism of Action

Radiofrequency energy produced by the Stretta® device induces collagen contraction in animal and human tissue. Animal models show that Stretta results in thickening of the LES decreased transient LES relaxations (TLESRs) and subsequent decrease in reflux events. Human studies have shown decreased gastric distention-induced TLESRs (3.5/h pretreatment vs. 1/h posttreatment) [33]. A double-blind, sham-controlled study showed that sildenafil, a smooth muscle relaxant, normalized GE junction compliance to pre-Stretta levels; the authors believe that this argues against fibrosis being a mechanism of action of Stretta® [13]. Esophageal motility studies after Stretta have not shown a consistent change in resting LES pressure, nor LES relaxation, compared to pretreatment parameters. Animal studies of RF energy applied to the intestine demonstrate an increase in smooth muscle fiber size, with more muscle fibers per muscle bundle that result in the lengthening and thickening of the sphincter [34].

Patient Selection

Clinical studies have excluded patients with a hiatal hernia of >2 cm, severe esophagitis (Grade C or D) despite medical therapy, and Barrett's esophagus. Patients with medically

responsive but refractory GERD have comprised the bulk of study subjects. Patients undergoing the Stretta® procedure should undergo the same preoperative objective evaluation as patients undergoing a laparoscopic fundoplication.

Stretta® Technique

Under deep sedation, endoscopy confirms eligibility criteria and measures the position of the squamocolumnar junction. A guidewire is introduced, the endoscope is withdrawn, and the RF delivery catheter is introduced orally over a guidewire. The balloon is inflated to 2.5 psi starting 2 cm proximal to the squamocolumnar junction, and the electrode needles (22 gauge, 5.5 mm length) are deployed into the esophageal wall. RF energy is delivered from a device-specific energy source from 60 to 90 s to reach a target temperature of 50 °C. The needles are pulled back, the balloon is deflated, the catheter is rotated 45°, and the procedure is repeated. This sequence is repeated serially every 0.5 cm to cover an area 2 cm above and 1.5 cm below the squamocolumnar junction. An average of 22 sets of needle deployments with RF energy delivery is performed. Additional sets are deployed below the cardia. During the procedure, the mucosa is cooled with water irrigation to prevent injury to the mucosa. The procedure takes 30–40 min to perform. Following the procedure, chest pain is relatively common, and patients are treated with analgesics as needed. Stretta is typically performed as a same-day procedure.

Complications and Safety

Temporary gastroparesis and erosive esophagitis have been the most commonly reported SAEs [35]. Double-dose Stretta® was associated with gastroparesis in 2 of 12 patients [36]. Stretta is performed under intravenous sedation, obviating the need for general anesthesia. Published reports of the

Stretta procedure indicate only mild complications, including minor GI bleeding, aspiration pneumonia, fever, leukocytosis, sedation-associated hypotension, or superficial mucosal injury. Immediate complications have been few and occurred primarily early in the overall learning curve for the device. There have been no reports of death, esophageal perforation, or other serious adverse events in these trials except for several patients who developed transient gastroparesis or esophagitis. Modifications to the Stretta® device employed in the current Mederi device, including more sensitive temperature regulation and prong redesign, have further increased the safety profile [37].

Clinical Results

Numerous studies show that patients treated with Stretta® have a significant improvement in quality of life. In the meta-analysis by Perry, 18 studies containing 1441 patients evaluated the effect of treatment on patient quality of life (QOL). The Velanovich GERD- HRQL scale was measured in 433 patients (9 studies) with an average follow-up interval of 19.8 months. The QOL scores improved from 26.11 ± 27.2 at baseline to 9.25 ± 23.7 after treatment ($p = 0.0001$). QOLRAD scores were collected from four studies comprising 250 patients and improved from 3.3 ± 5.9 to 4.97 ± 4.9 at a mean follow-up interval of 25.2 months ($p = 0.001$). SF-36 was utilized to assess the global QOL of the patient population in six studies. The SF-36 physical form evaluated in 299 patients with a mean follow-up period of 9.5 months demonstrated an improvement from 36.45 ± 51.6 at baseline to 46.12 ± 61.9 after the procedure ($p = 0.0001$). The SF-36 mental form was included in 5 of the six studies and 264 patients, with an improvement from 46.79 ± 20.5 to 55.16 ± 17.6 at 10-month follow-up ($p = 0.0015$) [35].

Stretta® has been compared to proton pump inhibitors in patients with non-erosive reflux disease with a six-month follow-up. Both groups demonstrated improved symptoms

and quality of life through the RDQ and SF-36 score, respectively; however, the Stretta® group revealed a statistically significant improvement in the RDQ score at six months follow-up compared to the PPI group alone [38]. At this time, the recommendation is that the Stretta® procedure is effective for patients with non-erosive reflux disease (NERD) [39].

Three sham-controlled studies of Stretta® have been published [36, 40, 41]. Objective data was variable. There was a statistically significant improvement in medication use, GERD-HRQL, and satisfaction scores in treatment groups but not sham procedure groups. At crossover, similar improvements occurred in the sham patients. No sham group patient was able to discontinue medical therapy, while 50–56% of treated patients had discontinued PPI therapy at one year in two of the three studies.

Stretta® has been compared to Laparoscopic repair with Toupet Fundoplication in a specific cohort of GERD patients with extra-esophageal symptoms, including pneumonia, bronchitis, asthma, and extra-esophageal symptoms globus, and chronic cough with three years of follow-up data. There was no significant difference regarding discontinuation of PPI as both groups achieved significant PPI independence (61.7% vs. 64.7%, $p = 0.835$). Despite the promising results demonstrating safety with Stretta®, effective GERD control of extra-esophageal symptoms, and reducing PPI use following a 3-year prospective study, patients in the laparoscopic repair group achieved better improvement in symptoms with higher patient satisfaction [42].

A recent report by Dughera et al. reported on 26 patients who had completed 4- and 8-year follow-up after Stretta® [43]. GERD-HRQL scores were significantly improved than baseline at both 4 and 8 years, as were QOL scores. At four years, 21 (80.7%) of patients and at eight years, 20 patients (76.9%) were entirely off PPIs. Interestingly, mean esophageal acid exposure was improved at four years but returned to baseline values at eight years. A second report by Noar et al. of 99 patients completing a 10-year follow-up (217

patients in the initial cohort) found that peak improvement in GERD-HRQL, patient satisfaction, and medication use occurred two years after Stretta. That significant improvement compared to baseline continued out to 10 years [44]. All patients were on double-dose PPI therapy before Stretta®; at ten years, 64% sustained at least a 50% reduction in PPI use, and 41% of patients remained off PPIs altogether. These results are echoed in the Stretta vs. PPI study by Suyu, Fei, et al., which demonstrated a statistically significant number of patients who were successfully weaned off PPI (60%) in a short time period six month follow-up [38].

Although few studies evaluating esophageal function by manometry have demonstrated no significant change in LES resting and nadir pressure and no change in esophageal body peristalsis in the past [33]. In the recent study by Suyu, Fei, et al., as mentioned earlier, the Stretta® group was able to demonstrate statistically significant higher LES resting pressure on six months follow-up when compared to the proton pump inhibitor group (14.2 ± 4.4 mm Hg vs. 10.1 ± 4.1 mm Hg, p = .002) [38].

The Stretta® procedure appears to decrease distal esophageal acid exposure. In the abovementioned meta-analysis by Perry and colleagues [35], seven studies with 267 patients reported DeMeester scores before Stretta® and at a mean of 13.1-month follow-up. The DeMeester score improved from 44.37 ± 93 before the procedure to 28.53 ± 33.4 post-procedure (p = 0.0074). Eleven studies comprising 364 patients demonstrated improvement in percent time esophageal acid exposure from 10.3 ± 17.8% to 6.5 ± 12.5% at a mean of 11.9-month follow-up (p = 0.0003). The improvement in pH at 1-year follow-up appeared to be better than the improvement reported at six months in other studies. The significance of improvement in pH control with time is not clear.

Some patients have undergone repeat Stretta® procedure after an initial failure or after a recurrence of symptoms, with some marginal benefit. Rates of conversion to laparoscopic

fundoplication lack in most published reports, but technically the conversion has been straightforward.

Safety and efficacy of Stretta® device have been studied in patients who previously underwent sleeve-gastrectomy with 6 months of follow-up data by Khidir et al. The data demonstrated that only 20% of patients were able to discontinue the PPI and that 66.7% of patients were not satisfied based on the HR-QoL questionnaire [45].

Although the mechanism by which RFA to the lower esophagus and cardia improves GERD symptoms is still not clear, studies indicate that postulated mechanisms such as fibrosis or sensory denervation probably are not the major mechanism. Reduction in TLESRs appears to have the most support [37]. Heartburn, daily PPI use, and standardized quality of life questionnaires have seen improvement following Stretta® in most studies, and 8–10 years' data indicate durable success at symptom control in the range of 40%. Objective data (esophageal acid exposure and lower esophageal sphincter measurements) have been conflicting. However, meta-analysis indicates that esophageal acid exposure does decrease in many patients after the procedure, and LES resting pressures are significantly elevated in the short-term follow-up [38]. The safety profile of Stretta® in its current configuration and use is excellent.

The Future of Endolumenal GERD Therapies

GERD is a chronic and progressive disease manifested primarily by symptoms that affect the quality of life. Strategies for treating chronic disease often involve management over cure. In this context, managing a GERD patient's quality of life may include multimodality therapy, including altering a medical treatment or repeating interventions. The need for reintervention with cardiac stents, or repeat arthroscopies, is not so much a failure of technique as it is the nature of a chronic illness. In this light, the ability of the endolumenal

procedures to normalize GERD-HRQL in patients with PPI-refractory symptoms, do so with minimal side effects, and achieve >65% elimination of PPI therapy in the process, is a significant success.

An increasing body of evidence exists that endoluminal therapies effectively manage GERD-related symptoms in patients who have incomplete control with medical treatment. Efficacy is in the 65–75% range and appears durable up to 3 years and beyond. The option of endoluminal therapy should be provided to patients with symptomatic medically refractory GERD or those wishing to reduce or eliminate dependence on intrusive lifestyle modification or medication. In light of increasing recognition that PPI therapy is effective at symptom control in only 60–80% of patients, endoluminal therapies have demonstrated similar efficacy and should be considered a maintenance option for patients wishing to decrease or eliminate dependence on PPIs.

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