ESOPHAGUS (MF VELA, SECTION EDITOR)

Update on Fundoplication for the Treatment of GERD

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Abstract Rudolph Nissen firstly implemented the idea of surgical treatment of gastroesophageal reflux more than 55 years ago. Today, laparoscopic fundoplication has become the surgical "golden standard" for the treatment of GERD. However, the initial enthusiasm and increasing number of performed procedures in the early 1990s declined dramatically between 2000 and 2006. Despite its excellent outcome, laparoscopic fundoplication is only offered to a minority of patients who are suffering from GERD. In this article we review the current indications for antireflux surgery, technical and intraoperative aspects of fundoplication, perioperative complications as well as short and long-term outcome. The focus is on the laparoscopic approach as the current surgical procedure of choice.

$$\label{eq:Keywords} \begin{split} \textbf{Keywords} & \ \, \text{GERD} \cdot \text{Gastro-esophageal reflux} \cdot \\ \text{Fundoplication} \cdot \text{Diagnostic} \cdot \text{Outcome} \cdot \text{Technique} \cdot \\ \text{Complications} \cdot \text{Morbidity} \end{split}$$

Introduction

More than 55 years ago, Rudolph Nissen began the evolution of surgical treatment of gastro-esophageal reflux disease (GERD). It began in an era of increasing interest in esophageal physiology and diagnostics. The first two

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patients treated surgically for reflux esophagitis by Nissen's "gastroplication" were published in 1956 [1]. Five years later, Nissen gave more detailed insight into "Gastropexy and 'fundoplication' for the surgical treatment of hiatal hernia" [2]. At that time, hiatal hernia repair was the primary focus of a surgical approach to treat reflux disease. In addition to Nissen's approach, Belsey in Great Britain and Hill in the US described alternative methods. As knowledge of esophageal physiology and the introduction of better diagnostic techniques, the trend shifted towards more physiologic reconstructive techniques by creation of an "artificial valve"—the fundoplication [3]. Soon, "reconstructive" surgery of the GE barrier was recognized as the most effective control for gastroesophageal reflux and it was widely recognized that this was most easily best accomplished with the Nissen fundoplication [4]. As such the Belsey and Hill procedures were slowly relegated to the minority of antireflux techniques over time.

Antireflux surgery was then and still is, limited to a select group of patients. Prior to 1990, the need for laparotomy or thoracotomy, limited application to those with the most severe manifestations of reflux and or major complications including refractory esophagitis, stricture, recurrent pneumonia or occasionally long segment Barrett's esophagus [5, 6]. Enthusiasm for antireflux surgery was rekindled with the introduction of laparoscopic fundoplication increasing its use and popularity for both patients and their referring physicians [7]. As such, the rates for antireflux surgery increased dramatically in the 1990s rising nearly threefold from 4.4 to 12 procedures per 100,000 population [8]. Estimates suggest that antireflux procedures peaked at approximately 33,000 procedures in the US in 2000. Via analysis of the National Impatient Sample (NIS) database, Wang and colleagues reported a steady decrease in antireflux



procedures performed in the US to approximately 19,700, per year, a 40% decrease between 2000 and 2006 [9]. Reasons for this include an efficacious pharmaceutical alternative (PPIs), surgery related side effects such as dysphagia, bloating and flatulence, as well as perioperative complications. Despite these facts, carefully performed laparoscopic fundoplication in properly selected patients remains an excellent treatment for gastroesophageal reflux disease, and an option this is almost certainly underutilized.

Indications for Antireflux Surgery and Patient Selection

Antireflux surgery should be considered an option in patients with objectively documented (positive pH study OFF medications, erosive esophagitis or Barrett's esophagus) moderate to severe gastroesophageal reflux disease. Persistent symptoms despite PPI therapy; often nocturnal regurgitation, chronic cough or respiratory symptoms, PPI dose escalation; young age and concern over long term PPI use are the most common "triggers" for referral to a surgeon.

Published guidelines including the 2008 medical position statement of the American Gastroenterological Association (AGA) state:

- When a patient with an esophageal GERD syndrome is responsive to, but intolerant of, acid suppressive therapy, antireflux surgery should be recommended as an alternative.
- 2) Antireflux surgery for patients with an esophageal GERD syndrome with persistent troublesome symptoms, especially troublesome regurgitation, despite PPI therapy. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and post-surgery bowel symptoms [10••].

Kahrilas et al. in an enlightening review have shown that the PPI treatment relieves regurgitation in the minority of patients [11•]. The increasing recognition of untoward effects of chronic PPI use including risk of hip fracture [12], interaction with antiplatelet agents [13], increased incidence of community acquired pneumonia [14], and c. difficile colitis [15] and hypomagnesaemia [16] raises concern for both patients and their primary care providers which historically was non-existent. The recognition of a lifelong need for medication intake and its expenses are also concerns. Finally, patients who already have complications of GERD (strictures, intestinal metaplasia) and failed medical response should be considered for surgery.

Consideration of antireflux surgery escalates the need for preoperative diagnostics allowing as complete an understanding of the patients underlying anatomic and physiologic abnormalities as possible. This helps assure a high probability of symptomatic relief following surgery as well as minimize untoward side effects including dysphagia. Patients should undergo an upper endoscopy (EGD), ideally by the operating surgeon with careful assessment of the grade of mucosal damage (LA grades A-D), the presence of columnar lined epithelium, strictures and size of any associated hiatal hernia [17].

Ambulatory pH monitoring is the most objective assessment whether or not the patient has GERD. In fact several studies have shown that an abnormal 24-h pH score is the best predictor of a successful surgical outcome [18]. Both transnasal catheter based (Sandhill Scientific, Highlands Ranch, CO) and wireless indwelling capsule (Given Imaging, Inc., Duluth, GA) systems are in current use. Prolonged pH monitoring (48 h or more) likely increases the sensitivity to detect pathological increased esophageal acid exposure [19, 20]. Each has advantages and disadvantages; wireless systems allow monitoring during normal daily activities that are not compromised by a transnasal catheter, while catheter based systems have the advantage of detection of both acid and non-acid reflux events by the use of multichannel intraluminal impedance (MII) sensors placed along the catheter. Furthermore, an additional proximal pH probe allows detecting proximal reflux events as well.

Preoperative esophageal motility assessment is an additional helpful tool to rule out any underlying motility disorder that might be responsible for patients' symptoms. Chest pain for instance can be caused by hypercontractile esophageal peristalsis and dysphagia by impaired LES relaxation (e.g. Achalasia) as well as spastic esophageal body contractions. Furthermore, patients with reduced circular muscle strength, frequent failed peristalsis and/or weak peristalsis with peristaltic defects might benefit from a partial fundoplication. More recently introduced were HRM-catheters combined with multiple impedance channels in between pressure channels, which enable to detect bolus movement along the esophageal contraction and to determine whether esophageal contractions are effective to clear the bolus.

An upper GI using barium swallows provides valuable anatomic and functional information such as relation of the GE junction to the diaphragmatic hiatus and the reducibility of hiatal hernias. Furthermore, barium swallows may reveal esophageal mucosa irregularities, as well as obstructive lesions such as strictures and tumors. Optimally, the esophagram is video recorded to review the dynamic of the study, especially with regard to esophageal peristalsis, bolus transport and reducibility of hiatal hernias. To detect GER, the barium-esophagography will only reveal 40% of patients with spontaneous reflux during the radiographic evaluation. The integrity of the GE barrier can be tested with provocative maneuvers such as Trendelenburg position and/or abdominal compression [21].



Technique of Laparoscopic Fundoplication

Partial or Complete Fundoplication

Debate continues regarding the use of a partial or complete fundoplication as the antireflux procedure of choice in uncomplicated patients. Although most experts favor a 360° Nissen fundoplication as the optimal procedure, the side effects of complete fundoplication coupled with long term studies showing similar clinical effectiveness of partial fundoplications fuels continued debate. Randomized trials of medical versus surgical treatment of GERD show a modest but clear increase in the prevalence of dysphagia (5% to 7% above PPI Rx) and flatulence (20% to 30% above PPI Rx) 12 to 24 months following Nissen fundoplication [22]. Mardani & Lundell recently reported the 20-year outcomes of a randomized trial of open total or posterior partial fundoplication in 137 patients with GERD [23•]. Outcomes were assessed via a validated self-reporting questionnaire. Successful control defined as no or minimal symptoms of heartburn (80% total vs. 87% partial) and regurgitation (82% vs. 90%) were similar despite the degree of fundoplication. Dysphagia scores were low (4.6 vs. 3.3) and similar as was the prevalence of flatulence and bloating. The authors concluded that both total and partial fundoplication "maintain a high level of reflux control after 2 decades of follow-up" and that the differences in mechanical side effects in favor of a partial wrap "seemed to disappear over time." In contrast several single center studies suggest a higher prevalence if persistent heartburn in patients with partial fundoplication. Sgromo et al. reported symptomatic relief, patient satisfaction and quality of life in 266 patients 6 years after either Nissen (n=99) or Toupet (n=62) procedures [24]. Eighty percent of Nissen patients were either reflux symptom free (51%) or improved (29%) compared to 90% of the Toupet patients either symptom free (37%) or improved (53%). Significantly more of the Toupet patients had either persistent heartburn (55% vs. 36%) or regurgitation (50% vs. 34%). Both groups had equivalent quality of life scores and both reported high levels of satisfaction (86% vs. 84%). Two meta-analyses of randomized controlled trials of Nissen vs. Toupet fundoplication have been published. Both suggested that total fundoplication has a higher incidence of postoperative dysphagia, bloating, flatulence and re-operation rate than partial. Importantly, patient satisfaction and symptom outcome was not different between the two procedures and it was acknowledged that the poor quality of the trials in the analyses warranted caution in interpretation of the data [25, 26]. Taken together these data suggest that partial fundoplication is certainly a very viable option as an antireflux procedure of choice, that it may decrease the prevalence of side effects and reoperation but may also result in higher chance of recurrent or persistent GERD symptoms.

Technical Elements

While far from truly standardized, the technique if laparoscopic fundoplication includes several key technical elements that most agree upon. These include:

- Crural dissection, identification and preservation of both vagi often including the hepatic branch of the anterior vagus
- 2. Circumferential dissection and mobilization of the esophagus
- 3. Crural closure
- 4. Fundic mobilization by division of short gastric vessels
- Creation of a short, loose fundoplication by enveloping the anterior and posterior wall of the fundus around the lower esophagus

In fact the lack of a standard technique has clouded the interpretation of many of the studies alluded to above and below. As such, investigators engaged in the design and implementation of the LOTUS trial, developed and required a consensus-standardized technique for laparoscopic Nissen fundoplication. The key elements, published in 2008, are identical to that described above, and were found to be highly reproducible, safe and efficacious [36].

The procedure begins with opening the pars flaccida or gastrohepatic ligament above and below the hepatic branch of the vagus nerve. This allows access the right crura and subsequent right and left crural dissection. The distal esophagus is mobilized circumferentially through the hiatus to allow 3–4 cm to be positioned within the abdominal cavity. The fundus is mobilized via division of the short gastric vessels. The hiatus is routinely closed using several 0 gauge non-absorbable sutures. The mobile fundus is brought posteriorly behind the distal esophagus and sutured together in front of the esophagus incorporating the anterior esophageal muscular wall. The length of the fundoplication should be 1–2 cm. Several excellent descriptions of the technique have been published [27].

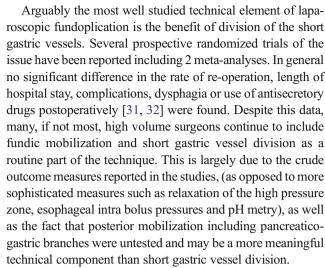
Although far from well-studied, published reports have investigated several of the technical elements of laparoscopic fundoplication. Two provocative papers address controversy over 2 key general issues namely; 1) the extent of dissection and 2) fixation of the fundoplication. St. Peter et al. randomized 177 pediatric patients to either minimal or extensive mobilization of the hiatal structures during laparoscopic fundoplication [28•]. Patients selected for minimal dissection had no violation of the phrenoesophageal ligament during dissection. Those in the extensive groups underwent circumferential division of the phrenoesophageal ligament attachments. The primary outcome variable was postoperative herniation of the wrap assessed by barium study 1 year later. Patients with known hiatal hernia before surgery were excluded from the study. Postoperative hiatal



hernia was present in 30% of the extensive groups compared to only 8% of the minimal dissection cohort. Reoperation rates were also significantly different; 18.4% following extensive mobilization and 3.3% with minimal dissection. The authors concluded that minimal esophageal mobilization during laparoscopic fundoplication decreases postoperative wrap herniation and the need for reoperation. Whether these data from the pediatric patient population, well known to include a high prevalence of patients with neurologic disorders which may predispose to wrap herniation (over 50% in both groups), can be translated to an adult population with GERD is unknown. The data are provocative however and raise awareness of the potential effect of extent of dissection on clinical outcomes.

Mucio et al. from Mexico City studied long term outcomes in 512 patients having one of 3 technical modifications; a) partial fundoplication (n=131), b) Nissen (n=133), or c) "fixed" fundoplication [29]. The later included several sutures to "fix" the fundoplication including from the posterior aspect of the wrap to the right crus, esophagus to crus superiorly, and left side of fundus to left crus. Outcome measures included clinical evaluation, pH & manometry study and SF-36 QOL 1, 5, 10 and 15 years post-op. Three hundred nineteen patients were followed for 15 years. Erosive esophagitis was significantly lower in the "fixed" group (7.2%) when compared to either the Nissen (21.5%) or partial (39.8%) groups. Recurrent reflux (symptoms and/or positive pH study) was present in 13/ 97 of the fixed, 41/102 Nissen and 98/103 partial fundoplication groups. Although the prevalence of both erosive esophagitis and recurrent reflux is high in the Nissen and partial fundoplication groups compared to the vast majority of other publications, the data raise provocative questions regarding the potential benefit of fixation of the fundoplication.

Transhiatal mobilization of the esophagus into the posterior mediastinum has emerged as an excellent mechanism to increase intraabdominal esophageal length. Bochkarev and Oleynikov evaluated the benefit of this technical maneuver in 106 patients operated between 2003 and 2006 [30]. All had suspected short esophagus based upon pre-operative barium swallow study and underwent extended transhiatal mediastinal dissection with the aim of achieving >3 cm of intraabdominal esophagus. Intraoperative esophageal length was routinely measured via both intraluminal endoscopy and laparoscopy. The majority of patients (80) had 3-8 cm of mediastinal esophageal dissection. Mobilization resulted in a mean of 2.6 cm of additional esophageal length for a mean of 3.15 cm total intraabdominal esophagus. None required a Collis procedure, preoperative symptom scores improved and all patients normalized pH scores postoperatively. While no comparative data exist for this technical maneuver, most experts have incorporated esophageal mobilization into the standard operative technique of laparoscopic fundoplication.



The importance of hiatal closure in all patients was discovered early in the experience of laparoscopic fundoplication [33]. Questions remain regarding the relationship of hiatal size to recurrent hernia and the relative benefits of using mesh as an adjunct to hiatal closure. Koch and Pointner have assessed the influence of hiatal size on the rate of reherniation after laparoscopic fundoplication in which mesh augmentation was used routinely. The average size of the hiatal opening after dissection in patients having a primary antireflux procedure was 8.2 cm and ranged from 5.6 to 16 cm. Despite the use of mesh, radiographic recurrence occurred in 5/24 patients (21%). Although not statistically significant, hiatal size was smaller in those without herniation (7.5 cm) compared to those who did (9.5 cm). The benefit of mesh was also found to be questionable in the long-term results of a large prospective study of mesh use in patients undergoing laparoscopic fundoplication for paraesophageal hernia repair. Hernia recurrence was detected in over 50% of both groups irrespective of the use of mesh or not [34, 35]. It is likely that the size of the hiatal defect is associated with the risk of hernia recurrence, and that the risks of mesh placement outweigh the benefits. As such mesh use to augment the hiatoplasty is not recommended by the vast majority of experts.

Mickevicuis et al. studied the effect of the length of the anterior segment of the fundoplication on outcome. The authors compared outcomes of 1.5 cm and 3 cm fundic lengths in both Nissen and Toupet fundoplication. Significant more patients had persistent reflux in the 1.5 cm Toupet group compared to 3 cm. More patients in the 1.5 cm Nissen group were considered to be treatment failures, although the difference did not reach statistical significance [36].

Early experience with robotic fundoplication has also been reported. At least in the short term, there seems to be no differences in outcome and quality of life scores when robotic and conventional laparoscopic approaches are compared. In contrast robotic procedures however are associated with higher procedure related costs [37–41].



One of the challenges of surgically creating an effective antireflux barrier is to do so without also creating postoperative dysphagia. A recent randomized controlled trial found an association with early dysphagia and surgeon-experience. The study also found less operating time and postoperative morbidity with increased experience, albeit no significant influence on short and long-term outcomes [42].

Perioperative Complications

Elective laparoscopic fundoplication, particularly in the setting of treatment for GERD, is among the safest major surgical procedures performed. Although intraoperative complications including gastro-esophageal perforations (0% to 2.2%), splenic or/hepatic injury (0% to 2.2%) and pneumothorax (0% to 3.5%) have been reported in randomized trials, recent data would suggest these are currently rare [42–46]. The conversion rate from laparoscopic to an open approach in high-volume centers is less than 2.4% [43, 44, 47, 48].

A recent analysis of the ACS NSQIP database from 2005 to 2009 showed a 30-day mortality of 0.19%. Mortality was as low as 0.05% in patients under 70 years. Complications occurred in 3.8% of patients. The mean length of surgical stay was 2.4 (±4.1) days [49]. Wang and colleagues recently reported an analysis of the US National Impatient Sample (NIS) database. They found an inpatient mortality of 0.26% to 0.54%. Further they pointed out that mortality was nearly 10 times lower (0.1%) in high volume centers (>40 fundoplications/year) when compared to those with low volumes (1.15%, <10 fundoplications/year). Similarly the overall complication rate was significantly lower in high volume centers (7.7% vs. 5%). In 2006, splenectomy was required in 0.7%, intraoperative transfusion in 2.3% and infection occurred in 0.3%. Low volume centers tend to have a higher transfusion and TPN rates (3.3% vs. 1.5% and 1.7% vs. 0.1% respectively). However, no difference in the prevalence of splenectomy (0.8% vs. 07%), infection (0.1% vs. 0.5%) or post-op esophageal dilation (1% vs. 1%) was found comparing high and low volume centers. The average length of hospital stay was 3.7 days, but significantly shorter in high volume centers (3.3 vs. 3.9 days) [9].

A nationwide cohort analysis of 1,019 cases used data from the North Carolina Hospital Association Patient Data System comparing low- (<10 fundoplication/year) and high-volume centers (>10/year) in North Carolina. In their analysis, no deaths occurred in either group, while the rate of accidental puncture and laceration was significantly higher in low-volume centers (3.3% vs. 0.9%), but the rate of atelectasis was higher in high-volume centers. The authors suggested that this may be due to a higher rate of pulmonary co-morbidities (COPD, cystic fibrosis) in high-volume centers in this study [50•].

Outcome

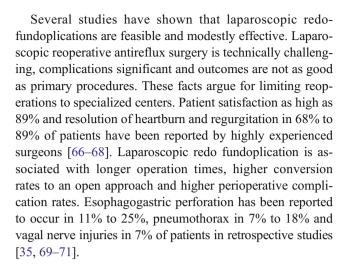
The fact that laparoscopic antireflux surgery results in excellent control of typical GERD symptoms (heartburn, regurgitation and dysphagia) has been documented in numerous case series, prospective studies, and controlled trials. Dallemagne has reported the 10-year clinical outcomes of laparoscopic fundoplication in 100 consecutive patients operated upon by a single surgeon in 1993 [51]. Two thirds (68) had a Nissen fundoplication and 32 a modified Toupet procedure. Outcome was assessed via a structured clinical questionnaire 5 and 10 years after surgery. Four required reoperation, 3 for recurrent reflux and one for dysphagia. A total of 93% were free of significant reflux symptoms at 5 years and 89.5% at 10 years. Ten year symptomatic control was better following the Nissen (93.3%) than a Toupet (81.8%). Similar long-term (median 11 years) outcomes were reported by Morgenthal, Hunter and Smith [52]. Overall symptom scores decreased from 7.5 at baseline to 2.6 postoperatively, 93% stated they would have the procedure again, and 70% were off daily antireflux medications. Gee and Ratner used the validated gastroesophageal reflux disease-health related quality of life instrument (GERD-HRQL) along with the prevalence of reoperation and PPI use to assess 405 consecutive patients undergoing laparoscopic Nissen from 1997 to 2006 at Massachusetts General Hospital [53]. Median follow-up was 5 years. Seventy one percent of patients were satisfied with the long-term results. The mean GERD-HRQL score was 5.7 (0 is no symptoms). As others have reported, 43% of patients took antireflux medication at some point following surgery although half had no diagnostic testing to assess recurrent GERD. Reoperation was uncommon (3/405, 1.2%).

Similar excellent long-term outcomes have been reported from around the world. Zaninotto reported 6 to 10 year outcomes of laparoscopic Nissen for both GERD and paraesophageal hernia in 145 consecutive patients seen at the University of Padova School of Medicine [54]. Surgical failure was defined broadly as any one of 1) recurrent GERD symptoms or post-operative positive 24 h pH study, 2) recurrent erosive esophagitis, recurrent hernia or slipped fundoplication on Barium study, post op dysphagia or new onset bloating. At a median follow-up of 8 years, 74% of the patients successfully met the rigorous criteria above given the primary antireflux procedure and 86% if adjunctive procedures were included such as reoperation (n=13) or endoscopic dilation (n=8). Kelly and Watson reported clinical outcomes at least 10 years following laparoscopic Nissen in 250 patients treated at the University of Adelaide Australia [55]. Eighty three percent were highly satisfied with the clinical outcome and 84% had good or excellent control of heartburn. A high preoperative heartburn score correlated with high patient's satisfaction and lower dysphagia score postoperatively.



Several recent randomized controlled trials comparing laparoscopic fundoplication to medical treatment have been published. The LOTUS trial, a large European multi-center trial comparing maintenance therapy of esomeprazole (PPI) to a standardized laparoscopic Nissen fundoplication reported 5-year outcomes of 372 patients in 2011. Relief of GERD symptoms at 5 years was higher in the PPI group (92% vs. 85%), however limited by the fact that the trial design required pre-enrollment symptomatic response to PPI use. Nearly a quarter (23%) of patients in the PPI group required an increase in their dosage to maintain symptom control. While heartburn and regurgitation improved in the surgery group, they remained stable in the PPI group over time with regurgitation being significantly worse in the PPI group. Balancing these symptomatic outcomes, the prevalence of dysphagia (11% vs. 5%), bloating (40% vs. 28%) and flatulence (57% vs. 40%) were higher in the surgery group. Perioperative mortality and morbidity was low, 0% and 3% respectively [56.]. Anvari reported the 3-year outcomes of 93 patients in a Canadian randomized controlled trial of laparoscopic Nissen versus PPI [57]. Outcome was assessed via a GERD symptom scale, visual analog scale (VAS) for overall symptom control and 24 h pH monitoring at baseline and 3 years. Primary treatment failure (redo fundoplication or PPI use) occurred in 12% of patients in the surgical arm and 16% in the PPI arm (inadequate reflux control despite maximal PPI dosage). Antireflux surgery was superior to PPI for heartburn-free days (mean -1.35 days per week, p=0.0077), overall VAS control of symptoms and quality of life. Gastro-esophageal reflux score was significantly improved in both groups after 3 years and although the percent time of pH <4 on 24-h pH study was less in the surgical group (mean 2.1% vs. 4.3%), although the difference did not reach statistical significance [57].

Control of atypical symptoms (cough, hoarseness, asthma) has proven to be significantly more difficult. This is almost certainly due to the diagnostic challenge of linking laryngeal and respiratory symptoms to GERD as the underlying cause. Recent data comparing pre- and postoperative symptom assessment of typical symptom, such as heartburn, regurgitation and dysphagia to atypical extra-esophageal symptoms such as cough, hoarseness and wheeze reinforce this fact. Typical symptoms improved in 87.4% to 95.7% of patients and atypical ones from 72.4 to 75% after Nissen fundoplication [58]. These findings are consistent with previously published longterm satisfaction rates for typical reflux symptoms between 80% and 96% [57, 59-63] and atypical ranging from 59% to 81% [64, 65]. Furthermore, Brown et al. correlated the symptom-outcome to manometry findings. Patients with atypical symptoms and hypomotile esophageal body function showed the least improvement compared to those with normal motility (21.7% vs. 72.4%). This again underlines the benefit of pre-operative manometry [58].



Conclusions

Laparoscopic Nissen fundoplication is the current "gold standard" to effectively restore the GE barrier, control GERD symptoms and improve patient satisfaction. Analysis of large national data samples show that it can be done with very low perioperative morbidity and mortality. Referring physicians and patients should be aware of surgery related side effects such as dysphagia and that these can be reduced by experienced surgeons in high-volume centers. A careful preoperative evaluation including EGD, pH monitoring, esophageal manometry and radiologic evaluation, as well as integration of other specialties (such as ENT to evaluate extra-esophageal reflux symptoms) are important factors in identifying the "right" patient for surgical treatment. Excellent outcomes, now extending to 20 years and beyond, have been amply documented.

Disclosure No potential conflicts of interest relevant to this article were reported.

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