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· The Center for Videoendoscopic Surgery
· The Center for Esophageal and Gastric Surgery

FUNDING

Byers Endowed Professorship in Esophageal Research
Dennis and Mary Wise Esophageal Research Fund
Society of American Gastrointestinal and Endoscopic Surgeons
Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR)
Covidien
Cook Surgical, Inc.
Synovis Surgical Innovations
Torax Medical, Inc.

I. GASTROESOPHAGEAL REFLUX DISEASE (GERD)

I.A. BROAD ASSESSMENT OF CLINICAL OUTCOMES AFTER LAPAROSCOPIC ANTIREFLUX SURGERY (LARS)

There is considerable discussion regarding "success" rates for laparoscopic anti-reflux surgery (LARS). Our experience with the long-term follow-up of these patients taught us that the success or failure of this operation is much more difficult to define. For example, there are patients who are extremely satisfied with the degree to which their symptoms have been controlled even though the esophageal acid exposure has not completely returned to normal. On the other hand, there are patients whose presenting symptoms have essentially disappeared but who have developed substantial side effects of the operation and for whom the quality of life has deteriorated. As our experience grew, we realized that instead of talking about "success" or "failure" of the operation, we ought to analyze the multiple domains affected by the operation and try to define the results in the context of each domain. We felt this type of comprehensive assessment would bring clarity that would allow physicians to understand how to best describe the expectations to patients in the different domains – the ultimate way to define a true informed consent.

Toward this end, we analyzed our extensive experience over a substantial number of years taking a broad view, attempting to document outcomes in what we thought were the major and most important domains, thereby allowing for a more thorough assessment of LARS. Thus, our work is not necessarily an endorsement of LARS, but instead a thorough analysis of all areas affected, positively and negatively, by the operation. This should provide the kind of data that would allow patients and physicians to decide for themselves whether the operation fits their needs.

We hypothesized that, in part, this was a reflection of the outcome variables used. We therefore defined 8 specific variables (within 3 categories) and assessed outcomes for each in a large cohort of patients (Table 1).

METHODS: Four hundred patients (208 females; median age 52y/o) who underwent LARS at the University of Washington from 1993 to 2008 were given a comprehensive questionnaire to assess various aspects of their outcomes from LARS. In addition, we analyzed all functional studies and all endoscopies performed in these patients in our institution, whether the patients had symptoms or not, and compared the findings to all available preoperative values.

RESULTS: The median follow-up was 92 (6–175) months.

A. SYMPTOMS:

1. *Effect on presenting symptoms:* Heartburn (n = 376) improved in 326 (87%), regurgitation (n = 365) improved in 331 (91%), and chest pain (n = 265) improved in 207 (78%), measured by patient's perception.
2. *Durability*: The percentage of patients with successful control of symptoms of gastroesophageal reflux disease (GERD): 88% at 1 year, 83% at 2 years, 77% at 5 years, and 74% after 10 years.
3. *Development of new symptoms (side effects):* The following side effects developed (were new) or worsened (present before surgery): dysphagia in 72 (18%) patients; bloating in 96 (24%) patients; diarrhea in 61 (15%) patients. The severity (0–10 scale) of these symptoms were: dysphagia 5.1 ± 2.6, bloating 6.5 ± 2.2, diarrhea 6.5 ± 2.9.
4. *Patient perception of overall success*: Currently, 279 (70%) patients rate their operation as a complete success, 86 (22%) as partially successful and 35 (8%) as unsuccessful. Those with partial or no success cited recurrent reflux (n = 70), a side-effect (n = 37), or both (n = 14) as the reason.

B. EFFECTS ON ESOPHAGEAL FUNCTION AND MUCOSAL INTEGRITY:

1. *Esophageal Acid Exposure*: The average pre-op DeMeester (DM) score was 56.8 ± 48.1 (n = 320), which decreased to 16.0 ± 31 in patients who underwent post-op testing between 1 month and 1 year (n = 149). Among 129 patients who had both pre-op and post-op values available, 92 (71%) had normalization of a previous abnormal DM score, while 114 (88%) had at least some improvement.

TABLE 1: Outcome domains of LARS

DEFINITIONS OF SUCCESS	SUCCESS RATE (%)
A. Symptoms (subjective)	
Improvement of the primary presenting symptom.	89
Full resolution of a GERD symptom (heartburn, regurgitation or chest pain)	54-76
Improvement of *any* GERD symptom.	87-91
Complete success of LARS by the patient's perception	70
Complete or partial success of LARS by the patient's perception	92
Complete or partial success of LARS by the patient's perception due solely to poor control of reflux symptoms	79
Absence of any side effect after LARS (dysphagia, bloating, diarrhea).	34
No newly developed or worsening side effects (dysphagia, bloating, and diarrhea) after LARS	62
B. Acid exposure and mucosal integrity	
Normalization of DeMeester score at post-op follow-up	71
Prevention of development of Barrett's esophagus	97%
Prevention of development of high grade dysplasia or cancer in patients with previous diagnosis of Barrett's esophagus	97%
C. Need for additional therapy	
Taking a lower dosage of anti-acid medication after LARS	77
Taking no anti-acid medication after LARS	59
Improvement of GERD symptoms accepting the use of anti-acid medication after LARS	98
No need for revisional operation	96.3

2. *Mucosal integrity*: *Progression of Barrett's esophagus (BE)*: Of the 58 patients with BE before LARS, 2 developed high grade dysplasia (HGD)/cancer (or 1 per 258 patient years). Out of 342 patients in our study without BE prior to LARS, 9 developed BE at a rate of 1 per 275 patient years (0.36% per year).

C. NEED FOR ADDITIONAL THERAPY:

1. *Medication use*: 236 (59%) patients remain completely off medications for GERD; 164 (41%) are using antireflux medications. Of these, 73 (45%) patients are taking less medication than before LARS. The most common reasons for continuing GERD medication after LARS were: heartburn (n = 100) 60%, regurgitation (n = 13) 8%, Barrett's esophagus (n = 13) 8%.
2. *Reoperations*: Fifteen (3.7%) patients required reoperations, 9 for recurrent reflux and 6 for side-effects.

Conclusion: The success or failure of LARS cannot be defined in a single domain. A comprehensive analysis of outcomes requires categorization that includes symptom response, side effects, patient's perception and objective measurement of acid exposure, mucosal integrity, and the need for additional medical or surgical treatment. Only then can patients and physicians better understand the role of LARS and make informed decisions.

I.B. Pepsin

I.B.i. IT IS NOT ABOUT ACID ANYMORE: THE ROLE OF WEAK ACID, IMPEDANCE, AND PEPSIN IN THE PATHOGENESIS OF GERD-RELATED LARYNGITIS

Gastroesophageal reflux disease (GERD) is the most common gastrointestinal disease in the United States. While most patients suffer from typical esophageal manifestations (e.g., heartburn and regurgitation), it is recognized that many patients experience laryngeal manifestations (e.g., cough, hoarseness, globus sensation) that are increasingly being linked to GERD. It is assumed that a common pathway for these manifestations is aspiration, whereby gastric material travels proximally and traverses the upper esophageal sphincter (UES) to enter the laryngopharynx. As a result, many now refer to this as laryngopharyngeal reflux or LPR. The clinical spectrum of LPR is wide and includes laryngeal injury (cough, hoarseness, subglottic stenosis, laryngeal cancer), dental erosion, asthma, and other respiratory tract disorders (e.g., chronic cough, sinusitis, and recurrent pneumonia).

It is estimated that 3–10% of the US population has significant LPR symptoms for which treatment is sought, costing over $1 billion per year. Most laryngeal diseases associated with LPR are thought to develop following direct contact of the laryngeal epithelium with gastric refluxate, potentially containing acid, pepsin and bile acids. To date, diagnosis and treatment have focused on the acid component of the refluxate. This is because the traditional focus of GERD was on acid, and also because it was thought that pepsin and bile acids would not cause injury at higher pH. Thus, patients with LPR are prescribed proton pump inhibitors (PPIs) to increase the pH of the refluxate.

This focus, however, appears misguided for several reasons. One, PPI therapy appears to have limited ability to protect these patients from LPR-induced damage. Two, more sophisticated testing methods such as multi-channel intraluminal impedance-pH monitoring (MII) has demonstrated a strong association of non-acidic reflux with laryngeal symptoms and injury. Three, we have also demonstrated in prior work a neutralizing effect on refluxate as it extends up the esophagus, so that by the time the refluxate can be aspirated, its pH is usually > 4. Four, our team of investigators have data which supports a role for pepsin in reflux-attributed laryngeal injury and disease, independent of the pH of the refluxate. Of most significance, we have recently demonstrated that pepsin is taken up by human laryngeal epithelial cells by receptor-mediated endocytosis in patients with a clinical diagnosis of LPR.

Medical therapy provides relief to some patients, but with less consistency than for those with typical symptoms of GERD. This may be due to persistent aspiration and injury components of the refluxate. Surgical therapy has been more successful in treating some of these disorders, although its effectiveness is inferior in this group of patients when compared with patients who have typical symptoms. Therefore, while patient selection is key in directing the treatment of GERD, patient selection is even more necessary for reflux-associated respiratory disorders such as LPR.

The problem is partly due to lack of a good diagnostic test. Typically, the diagnosis of GERD is made by a combination of thorough patient history plus several imaging and physiologic studies, with 24-hour ambulatory pH monitoring considered the "gold standard" for the diagnosis of GERD. While 24-hr pH monitoring can diagnose GERD, there is no specific test in patients with airway disease for linking respiratory symptoms with GERD. As a result, even effective treatment and resolution of GERD does not always result in the abatement of symptoms. There are two shortcomings of pH monitoring, especially in the pharynx. One is the sole reliance on pH, even though reflux that travels from

Natural Orifice Transluminal Endoscopic Surgery (NOTES) represents a paradigm shift that may significantly change the management of gastrointestinal and intra-abdominal diseases. It is an exciting time. Not since the adoption of laparoscopic surgery 20 years ago has there been such a radical change in the way surgery is viewed.

the stomach to the pharynx may no longer have a pH<4, and injury from aspiration may not be dependent on acid. The other is that the pharynx, unlike the esophagus, is a larger cavernous cavity that does not collapse. It constantly contains both liquid and gas and makes catheter-based methods of detecting reflux problematic. There are two new technologies that may combat these shortcomings.

The first is a newly designed pH probe. The Restech probe (24-hour pharyngeal pH measurement) is a new minimally invasive device used to measure acid exposure in the posterior oropharynx. This probe is able to detect aerosolized acid and does not required endoscopy or manometry for proper placement. Recently, a set of normal values and discriminating thresholds for pharyngeal acid exposure using the Restech probe was described in the literature. The 95th percentile values (normal) for the components and the composite score of pharyngeal Ph exposure at the discriminating pH thresholds are analyzed separately because the mean pharyngeal pH is lower during the supine period than in the upright period. This is because salivary flow is reduced during the night, resulting in a lower pharyngeal pH. The calculated threshold for the upright period is 5.5 and for the supine period 5.0. The components with normal values established are: % time pH below the threshold: 0.13 and 5.15 minutes; number of episodes: 1 and 4; longest episode: 0.71 and 18.97 minutes; and RYAN Score (composite pH score for pharyngeal acid exposure): 9.41 and 6.79 for upright and supine period, respectively.

The second technology is multichannel intraluminal impedance (MII), which has been introduced to measure bolus presence and transit and to detect reflux independent of its pH. MII permits not only identification of liquid, gaseous, or mixed intraesophageal/intrapharyngeal materials, but also the direction in which the elements travel. MII technology in conjunction with a pH sensor allows discrimination of acid (pH < 4.0) from non-acid (pH4 and above) reflux. Our group has recently demonstrated that the majority of the reflux episodes into the pharynx are in fact non-acidic. In addition, we have also shown that in patients with reflux-related laryngitis, the amount of non-acidic reflux in the distal esophagus, as well as in the pharynx, is greater than in controls. Thus, the traditional 24-hour pH monitoring system may underestimate the extent of reflux that may be playing a significant role in the pathogenesis of LPR.

Laryngoscopy is a common screening tool for patients with symptoms such as hoarseness, cough, and laryngitis. This often reveals erythema, nodularity, ulceration, granuloma, or leukoplakia, but to date no single finding seems to be pathognomonic of reflux-induced laryngeal reflux. We note that laryngoscopic findings have strengthened the case for a positive response to laparoscopic Nissen fundoplication (LNF), but have not been seen to have a strong predictive value.

Still, MII and Restech, even at the level of the pharynx, are indirect measurements. Pepsin may represent a more direct and accurate tool in the work-up of patients thought to have reflux-related laryngitis. We have reported the presence of pepsin in laryngeal biopsy specimens taken from patients with clinically diagnosed LPR, not detected in "normal" control subjects. Furthermore, we have recently discovered that pepsin is taken up by laryngeal epithelial cells by receptor mediated endocytosis, irrespective of its proteolytic activity. It was originally thought that pepsin would only cause injury in acidic refluxate. However, we have shown that pepsin, at pH 7, causes intracellular (mitochondrial) damage in laryngeal epithelial cells (unpublished data). Using electron microscopy, we have demonstrated the presence of pepsin in late endosomes and in the trans-reticular Golgi (TRG), which is approximately pH 5 (unpublished data). Thus, it is possible that inactive pepsin (in non-acidic reflux) is taken up by laryngeal epithelial cells and reactivated in either late endosomes or in the TRG, due to their lower pH, causing intracellular damage. Alternatively, binding/activation of the cell surface receptor may cause a cell

signaling event, ultimately having a detrimental effect on the cell. This novel mechanism of peptic injury could explain why many patients with reflux-attributed laryngeal injury have persistent symptoms despite acid suppression therapy. Ongoing studies to identify the receptor will help delineate the role of pepsin in reflux-attributed laryngeal injury. Pepsin inhibitors and receptor antagonists are being tested *in vitro* to investigate whether they prevent peptic uptake/injury and thus have therapeutic potential.

Currently, it is well known that LNF results in good short- and long-term relief of airway symptoms, even for patients with poor responses to medical therapy. However, the reported efficacy of LNF for airway symptoms (65-75%) is inferior to that reported for heartburn and regurgitation (90%). Failure to correctly identify the patients who will respond to LNF is the most likely reason for not reaching 90% to 100% success. This highlights the lack of a diagnostic test or algorithm with the necessary accuracy to link GERD and airway disease in all patients.

Therefore, we propose a prospective study of 20 patients with clinical LPR who are being considered for LNF, whereby each patient would have reflux measurements with Restech and MII, as well as have laryngeal pepsin checked before and after LNF. Our hypothesis is that LNF will result in the elimination of reflux from the esophagus and pharynx, and pepsin from the laryngeal epithelium. If this is confirmed with testing after LNF has been performed, we should be able to more fully understand the patho-physiology of LPR and assess the relative value of these tests to predict the response of LPR to LNF.

I.C. LINX™ Reflux Management System Clinical Study

Since there are so many patients with GERD and no perfect therapy, we are constantly looking for the perfect solution, or more likely, solutions to fit a subset of the GERD population that will address their specific problems. A possible solution for some patients is the LINX™ Reflux Management System. This device is designed to help people with GERD by reinforcing or strengthening the esophageal sphincter function.

Torax™ Medical, Inc. has designed a device to help facilitate the function of the lower esophageal sphincter (LES). The LES is a ring of muscle that forms a valve at the lower end of the esophagus, where it joins the stomach. A healthy LES opens when food is swallowed, allowing food to pass into the stomach, The LES then closes after the food has passed to prevent the stomach contents from going back into the esophagus (Figure 1).

The LES is considered an important part of preventing reflux, and can sometimes become weak, allowing gastric contents to "reflux" into the esophagus (Figure 2).

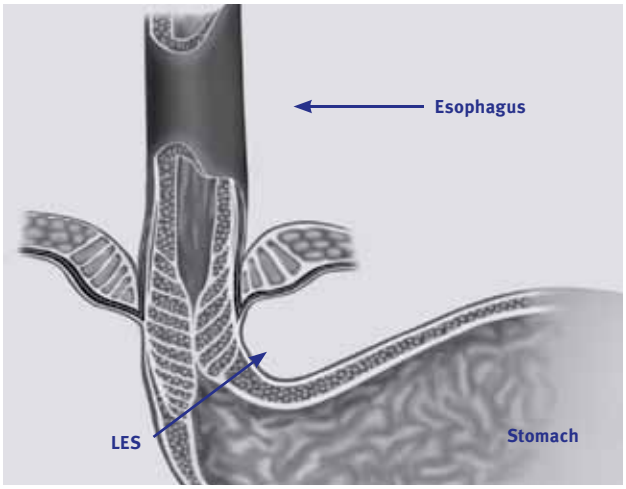

Figure 1. Normal, healthy lower esophageal sphincter

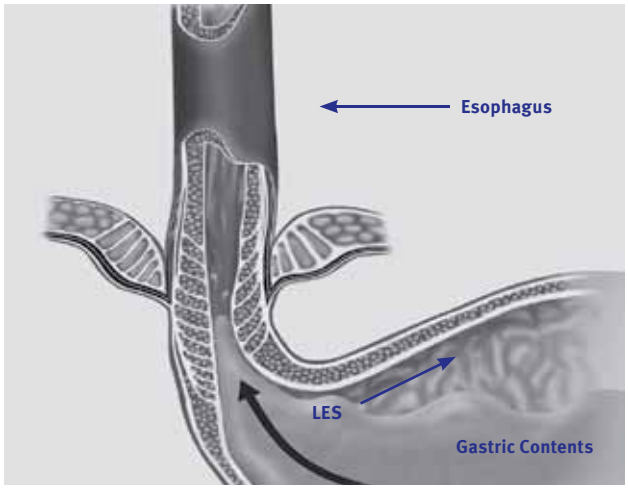

Figure 2. Weak LES allowing gastric contents to reflux into esophagus

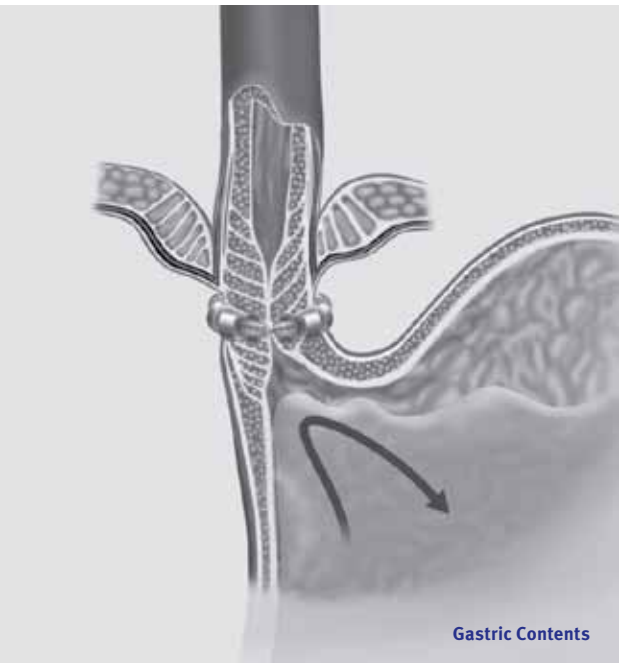

Figure 3. LINX™ device in place on esophagus

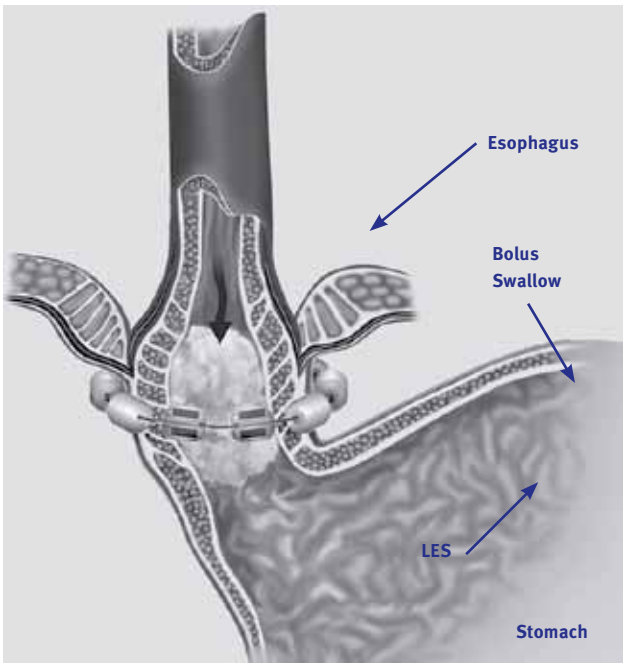

Figure 4. LINX™ device actuation during swallow

An implantable device consists of a series of magnetic beads that are attached with wires to create a ring shape. The device is placed on the external esophagus in the region of the LES. The attractive force of the magnetic beads provides additional strength to keep a weak LES closed (Figure 3).

As food is swallowed, the magnetic force decreases as the magnetic beads move away from each other on the wires. This allows the esophagus to stretch open, much like a good working esophagus, and allows the swallowed food to pass into the stomach (Figure 4).

The device is a permanent implant for the treatment of GERD. The procedure is reversible and can be surgically removed if necessary. Removal of the device does not likely have any harmful effects on other treatments for GERD.

The University of Washington, together with nine other clinical sites in the United States, participated in a multi-centered prospective trial to evaluate the safety and efficacy of this device in patients with moderate GERD. One hundred patients were implanted with the device. This fall we hope to complete the one-year follow-up on the first 100 patients and be able to evaluate what role this may play in the large population of patients with GERD.

II. Paraesophageal Hernia

II.A. Long-term outcomes of biologic prosthesis to prevent recurrence after laparoscopic paraesophageal hernia repair

Laparoscopic paraesophageal hernia repair (LPEHR) is associated with a high recurrence rate. Repair with synthetic mesh lowers recurrence, but can cause dysphagia and visceral erosions. In 2006 we reported at the American Surgical Association the results of a randomized trial showing that the use of a biologic prosthesis (small intestinal submucosa, SIS) decreased hiatal hernia recurrence from 24% (with primary repair, PR) to 9%, 6 months after LPEHR. Recently, we have completed the second phase of this trial, which was designed to determine the long-term durability of biologic mesh-reinforced repair at 5 years. We systematically searched for each of the 108 patients reported in the Phase I trial to assess clinical symptoms and quality of life (QOL) and to determine anatomy by follow-up upper gastrointestinal series (UGI) read by 2 radiologists blinded to the treatment received. From the original multi-center randomized cohort of 108 patients, 72 had completed clinical follow-up and 60 patients underwent a UGI to assess for the presence of recurrence.

TABLE 2. Change in symptom severity, QOL, hernia size, and recurrence from pre-op to long-term follow-up

	Heartburn*	Dysphagia*	QOL (SF-36/PCS)	Hiatal Hernia Vertical Ht (mm)	Recurrent Hernia (>2cm)
PR	1.5	1.7	43	21 ± 21	59%
SIS	2.0	1.3	44	24 ± 20	54%
***p*-value**	0.44	0.5	0.8	0.9	0.7

*Symptoms score: visual analog scale (0-10); PR: primary repair; SIS: small intestinal submucosa; PCS: physical component summary

Primary Outcome: At a median follow-up of 58 months, there was no significant difference in radiographic hiatal hernia recurrence between the PR group and the SIS group (Table 2). The greatest rate of recurrence in the SIS cohort was identified in the patients with at least 5 years elapsed since their surgery.

Secondary Outcomes: Clinical symptoms and QOL remained improved from the baseline and were largely similar to the results observed at 6 months. There were no significant differences between the PR and SIS cohorts with respect to severity of clinical symptoms or QOL (Table 2).

This trial has demonstrated that LPEHR produces long and durable relief of clinical symptoms and improvement in QOL. In addition, the benefit of biologic mesh seems to diminish after 5 years.

As part of this larger randomized trial, we also plan to gain more insight into the natural history of laparoscopic hernia repair. A subsequent study will be performed where we plan to determine the long-term anatomic results, QOL, and symptom severity outcomes for all patients undergoing LPEHR. In addition, we will determine whether the presence of a recurrent hiatal hernia detected on UGI correlates with worsening QOL and clinical symptoms. These are two big questions which remain yet to be answered in the surgical community. A well-designed study with long-term follow-up is expected to provide some answers.

II.B. SAFETY OF THE USE OF BIOLOGIC MESH IN THE REPAIR OF LARGE, COMPLICATED HIATAL HERNIA

Although it has been shown in the past that the use of biologic mesh can reduce the risk of recurrence at 6 months, there have been several case series reporting on complications associated with its use, such as erosion into the esophagus and dysphagia.

We therefore decided to analyze the safety of the use of biologic mesh for large, complicated hiatal hernia in our patients. All patients at the University of Washington who had an operation with the use of biologic mesh at the hiatus with a minimal follow-up of 1 year were contacted. The patients were asked to fill out a questionnaire on symptoms related to gastroesophageal reflux, hiatal hernia and complications of the mesh. When available, the post-operative upper-GI study and endoscopy reports were analyzed. The primary outcome measure was complication due to the mesh leading to intervention. Secondary outcome measures were post-operative dysphagia and satisfaction with the operation.

Outcomes: Of the 126 patients that were found to be eligible for the study, 71 (56%) patients returned the questionnaire. Four patients had died to causes unrelated to the operation, four refused to participate, and 47 were not able to be contacted. The majority of patients were female (71%) and obese (mean BMI 30.6 kg/m2). There were no peri-operative complications directly related to the use of mesh. Median follow-up for patients who returned the questionnaire was 45 months. One patient had a re-operation due to recurrent hernia and reflux. No complication directly related to the mesh was found. Post-operative dysphagia that was worse than before the operation was seen in six patients. In four of these patients, causes other than the mesh could explain their swallowing difficulty. In the other two patients, the cause of their dysphagia was unclear, and it therefore could be related to the use of mesh. Patients rated the overall result of the operation as good or excellent in 89% of cases.

This study shows that our use of biologic mesh for repair of large, complicated hiatal hernia is safe.

III. Esophageal Cancer And Diverticulum

III.A. ESOPHAGEAL CANCER

III.A.i. OUTCOMES OF LAPAROSCOPIC ASSISTED ESOPHAGECTOMY FOR ADENOCARCINOMA OF THE ESOPHAGUS

In the last decade, the incidence of esophageal adenocarcinoma has increased more rapidly than any other gastrointestinal malignancy. The prognosis of patients with esophageal cancer remains poor. Only 56% of patients who present with esophageal cancer have resectable disease, with an overall five-year survival rate of 10%. Esophageal resection remains the gold standard, not only in providing the optimal chance for cure, but also the best palliation for dysphagia. However, the conventional open operations are quite invasive, with a morbidity of 50% and a mortality of 5-10% in high-volume centers.

Laparoscopic procedures offer an advantageous alternative to conventional open operations, such as less operative trauma than experienced with thoracotomy or manual blind and blunt transhiatal esophagectomy; less perioperative blood loss; and shorter ICU stay. Furthermore, a minimally invasive procedure does appear to offer the potential for a more radical mediastinal resection, under direct vision, when compared with transhiatal esophagectomy. However, controversy still exists about what is the best approach to and extent of the dissection. At the University of Washington, we started performing laparoscopic-assisted esophagectomy in 1995 for tumors of the distal esophagus and gastroesophageal junction. We conducted this study to determine the short-term (complications, length of stay, pathologic staging, lymph node harvest, blood loss) and long-term (cancer free survival, overall survival) outcomes with this approach.

Since 1995, 72 patients with esophageal adenocarcinoma underwent laparoscopic-assisted transhiatal esophagectomy at the University of Washington using the aforementioned technique. The mean operative time was 321 ± 73 minutes and the blood loss 318 ± 239 ml. The median ICU stay was one day (range, 1-35), whereas the hospital stay was nine days (range, 7-58). One patient (1.4%) died within 30 days postoperatively.

The most common complications were: anastomotic leak in 14 patients (all but one were managed non-operatively), pneumothorax in 18 patients (only six patients required drainage), pleural effusion in nine patients, atrial fibrillation in eight, wound infection in seven (all managed in the outpatient setting), transient recurrent nerve paralysis in six, deep vein thrombosis in four, and pulmonary embolism in three patients. In the long-term follow-up, 13 patients reported anastomotic stricture requiring dilation. The overall long-term survival was 85% at one year, 68% at three years, and 63% at five years.

Our results support the performance of laparoscopic-assisted transhiatal esophagectomy as a safe and feasible procedure with decreased morbidity and mortality and with good survival rate. Therefore, this approach should be included in the armamentarium for the treatment of esophageal adenocarcinoma.

III.B. EPIPHRENIC DIVERTICULUM

III.B.i. MINIMALLY INVASIVE TREATMENT OF EPIPHRENIC DIVERTICULUM

Epiphrenic diverticula are those that occur in the distal esophagus. They represent herniation of the superficial layers of the esophageal wall through the muscular layer as a result of increased intraluminal pressure. This is a very rare entity for which the cause is not well known. In the majority of cases an underlying neuromuscular disorder is present, causing increased intraluminal pressure.

There are controversies regarding the ideal surgical treatment and approach of epiphrenic diverticula. Historically, the standard operation for the treatment of epiphrenic diverticula has been thoracotomy (big incision in the chest), resection of the diverticula, and myotomy (cutting the distal sphincter of the esophagus to decrease the intraluminal pressure). Since the introduction of minimally invasive surgery for the treatment of gastroesophageal reflux disease in 1991, a variety of esophageal diseases have been approached using this technique. Although epiphrenic diverticula is rarely seen in most clinical practices,

these patients are now being referred and repaired with increased frequency in those centers performing minimally invasive esophageal surgery. Several authors have reported in the literature their modest experience with treating epiphrenic diverticula using a minimally invasive approach. We began treating epiphrenic diverticula using a minimally invasive approach 11 years ago. Based on our vast experience using this technique and our high volume of patients, we are reviewing our treatment outcomes with minimally invasive surgery for epiphrenic diverticula.

Material and Methods: From 1997 to 2008, 23 patients underwent surgery for epiphrenic diverticula at the University of Washington. Our initial approach was laparoscopy in 19 patients, video-assisted thoracic surgery (VATS) in two and open thoracotomy in two. Details of the operation and postoperative course were recorded in our database. In June 2008 the patients were contacted by one of the investigators regarding current symptoms.

Results: The median age was 57 years (range, 23-83). The medium follow-up was 45 months. Eighteen patients had esophageal manometry in our institution; 12 of them were abnormal (66.67%). The median diameter of diverticula was 4 cm (range, 2-10). From the 19 patients approached by laparoscopy, there was one conversion to open thoracotomy, in a patient with an associated leiomyoma. Both patients approached by VATS were converted to thoracotomy. Considering just the patients approached by laparoscopy, the median length of stay was 3 days. There was one contained esophageal leak. The 30-day mortality was 5% (n = 1), from a port site hernia leading to small bowel obstruction and sepsis. Of the contacted patients, 92% had improvement of their dysphagia, and 77% obtained relief from regurgitation. None of the patients developed recurrent diverticula. Eighty-five percent of the patients rated the results of the operation as good or excellent.

Conclusion: Most epiphrenic diverticula can be treated successfully using a laparoscopic approach with low morbidity, low conversion rates and good symptom control. As a result of this work, we are now approaching nearly all of these diverticulae laparoscopically, resulting in a positive impact on patient recovery and outcomes.

IV. Surgical Treatment Of Achalasia

IV.A. IMPROVEMENT OF RESPIRATORY SYMPTOMS FOLLOWING HELLER MYOTOMY FOR ACHALASIA

Recently, our group reported the high prevalence of respiratory symptoms in patients who suffer from achalasia, a motor disorder of the esophagus. The University of Washington's long-term experience with the diagnosis and surgical management of this disease led to the clinical question of what happens to these respiratory symptoms in such patients after they undergo surgical treatment with Heller myotomy.

To address this question, we studied the course of 111 patients who underwent Heller myotomy at the University of Washington between 1994–2008. Study participants were given questionnaires post-operatively that assessed their preoperative and postoperative symptoms. The median follow-up time after surgical myotomy was 71 months.

Patients were asked to indicate both preoperative and postoperative frequency and severity of respiratory symptoms, including dyspnea (shortness of breath), hoarseness, cough, wheezing, pneumonia, and/or sore throat, as well as more typical esophageal symptoms such as dysphagia, regurgitation, chest pain, and heartburn on a 5-point scale (0 = never, 1 = once a month, 2 = once a week, 3 = once a day, 4 = several times daily). Severity of symptoms was rated on a 10-point visual analog scale ranging from 0 (absent) to 10 (worst). Patients reporting respiratory symptoms (dyspnea, hoarseness, cough, wheezing, or sore throat) occurring at least once per week prior to myotomy and/or a history of asthma or pneumonia were considered to have respiratory symptoms or diseases and included in our analysis.

Our results were compelling. The high prevalence of respiratory symptoms was again confirmed. Of the 111 patients who participated in this study, 63 (57%) reported at least one clinically significant baseline respiratory symptom or respiratory disease prior to undergoing Heller myotomy. There were no significant demographic or clinical differences between those patients with and those without respiratory manifestations. Of the sixty-three patients who did report respiratory symptoms, 55 (87%) patients experienced

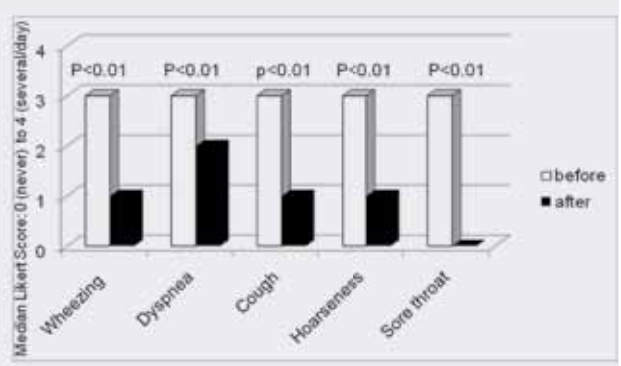

Figure 5. **Comparison of preoperative and postoperative frequency (0-4) of respiratory symptoms**

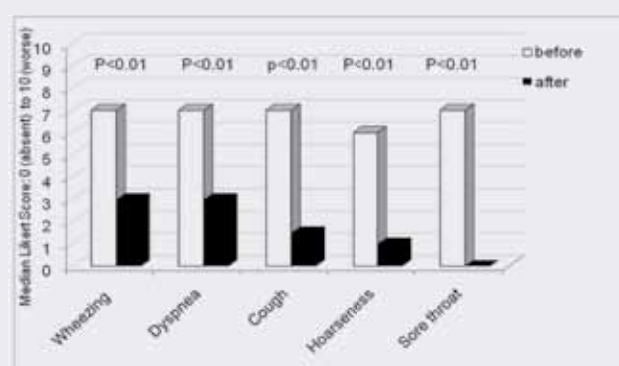

Figure 6. **Comparison of preoperative and postoperative severity (0-10) of respiratory symptoms**

durable improvement in their dysphagia, confirming the efficacy of surgical myotomy. The frequency and severity of all respiratory symptoms decreased significantly following surgery (Figures 5 and 6). Twenty-four of the 29 patients (82%) who reported a history of pneumonia prior to surgery did not experience recurrent episodes for up to 5 years following Heller myotomy.

In our group's previous study, we found a high prevalence of pulmonary symptoms/disease in patients with achalasia. In this study we demonstrated significant improvement in these symptoms following successful surgical treatment of achalasia with Heller myotomy, and these improvements parallel improvements in dysphagia. The most logical causal link between esophageal obstruction and the presence of respiratory symptoms in the setting of achalasia is esophageal non-emptying and aspiration of retained food and secretions from the esophagus into the upper and lower respiratory tracts.

These findings present a strong case that highlights the presence of and explains the pathophysiology of respiratory disease in patients with achalasia. Delayed esophageal emptying is certainly the most likely reason for these respiratory symptoms, and the improvement after performance of Heller myotomy strengthens the likelihood of this association. Moreover, the substantial improvement in respiratory symptoms and disease after Heller myotomy, which was heretofore not appreciated, is yet another benefit of surgical therapy for this disease.

IV.B. DOR VS. TOUPET FUNDOPLICATION: A MULTI-CENTER RANDOMIZED TRIAL

The development of gastroesophageal reflux is essentially guaranteed after a well done Heller myotomy. Our experience has shown that there is no way to maximally relieve the dysphagia of achalasia and at the same time prevent GERD. For this reason, most surgeons add a partial fundoplication to this procedure. The most common fundoplications are a Dor (anterior) and Toupet (posterior) fundoplication. The theoretical advantage of the Toupet is that it holds the edges of the myotomy open (possibly better relief of dysphagia) and is considered a better antireflux procedure, while the Dor fundoplication is placed over the exposed mucosa of the esophagus, thus buttressing a microperforation, should it occur.

A group of four major esophageal surgical centers have organized a multi-center randomized trial to answer whether one of these fundoplications is superior to the other in this situation. They are performed fairly equally around the world at this time, and we hope to definitively determine whether there is a difference.

IV. C. LONG-TERM OUTCOMES OF HELLER MYOTOMY FOR ACHALASIA

At the University of Washington from 1994 to 2010, we have performed over 400 Heller myotomies for the treatment of achalasia. This year we plan to complete our long-term assessment of both postoperative clinical symptoms and physiologic outcomes, including manometry and 24 hour pH study results. We have been prospectively collecting a standardized questionnaire using visual analog scales to determine the frequency and severity of a wide range of clinical symptoms both before and after surgery. In addition, we have been collecting manometry and 24 hour pH study data prospectively on all patients at 6 months following surgery since 1997. The primary objective of this study will be to determine our overall success rate in alleviating dysphagia. We also plan to identify preoperative predictors of favorable long term outcome to further guide optimization of patient selection criteria.

V. Esophageal Motility

V.A. FACTORS RESPONSIBLE FOR FUNDOPLICATION FAILURE AS ASSESSED BY HIGH-RESOLUTION ESOPHAGEAL MANOMETRY (HRM)

HRM is a recently developed tool in the evaluation of esophageal motility. It utilizes many closely spaced pressure-recording sites along a manometry catheter in order to display a relatively continuous profile of esophageal motor activity from the upper esophageal sphincter, along the length of the esophageal body, and across the lower esophageal sphincter. A recording device produces a color-contour plot, with time on x-axis, esophageal length on y-axis, and pressure represented by a color scale. Data between recording sites is interpolated to demonstrate pattern and pressure gradients. The result is a more complete and detailed picture of esophageal motility, with potentially better and more accurate characterization of esophageal function than standard manometry. We have been using HRM in the evaluation of all patients referred to the University of Washington Center for Esophageal and Gastric Surgery for esophageal motility testing in the last 2 years; to date, we have performed more than 1,200 HRM studies.

With this new technology, we suspected that we would be able to identify detailed physiologic abnormalities in patients with esophageal symptoms. One group of particular interest to our center is that of patients who present with recurrent symptoms after antireflux surgery. It has been estimated that 10 to 25% of patients undergoing antireflux procedures eventually redevelop symptoms resulting from anatomic failure of the hiatal repair or the fundoplication. Because HRM allows for reliable evaluation of the lower esophageal sphincter (LES) in detail, including subtle evidence of a hiatus hernia that may be difficult to detect using other methods, we sought to characterize the dynamics and function of the LES postoperatively using this technique in order to determine which elements may contribute to recurrent symptoms after antireflux surgery.

Thirty-four patients who had a Nissen fundoplication – 23 with recurrent symptoms and/or abnormal 24h pH monitoring (Unsuccessful group) and 11 asymptomatic patients who were tested as part of routine follow-up (Successful group) – were evaluated using HRM. HRM tracings were analyzed for percentage of peristaltic contractions, LES pressure (LESP), length of the high pressure zone (HPZ), residual pressure during LES relaxation, and the presence of a dual HPZ (indicating a recurrent hiatus hernia – see Figure 7). Results were compared between the two groups, and HRM findings in the symptomatic patients were also compared to findings on upper GI and endoscopic examinations.

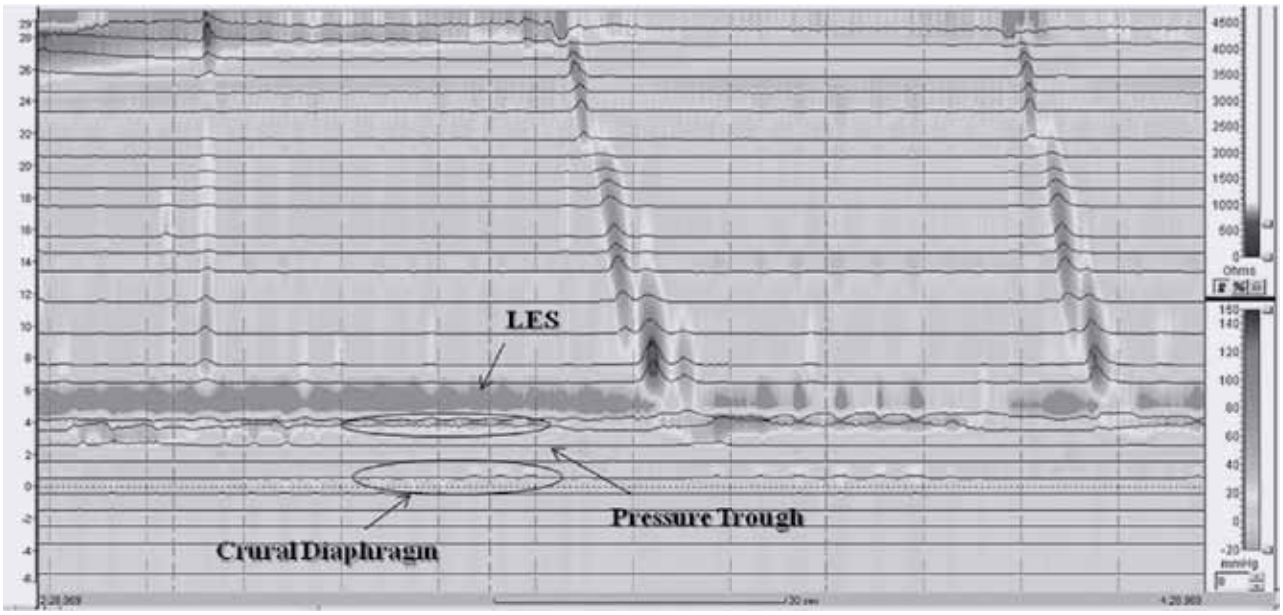

Figure 7. HRM tracing in a patient with recurrent hiatus hernia demonstrating a dual HPZ

Mean LESP tended to be greater in the Successful group compared with the Unsuccessful group ($p = 0.068$). There were no differences when comparing both groups on length of the HPZ, pressure profiles, residual pressures, and rates of peristalsis. A dual HPZ was identified in 13 patients in the Unsuccessful group (56%), and 1 (9%) of the Successful patients ($p < 0.05$). An abnormal DeMeester score was observed in 79% of patients with a dual HPZ, compared with only 35% of patients without a dual HPZ ($p < 0.05$). In contrast, the DeMeester score was abnormal in 70% of patients with a recurrent hiatus hernia on either UGI or esophagogastroduodenoscopy (EGD) ($p = 0.16$).

From these results, we concluded that the presence of a dual HPZ on HRM in patients who have had a fundoplication appears to be a strong predictor of recurrent GERD, and it may be useful as an initial test to guide further workup. In patients with recurrent symptoms after antireflux surgery, HRM also provides valuable information regarding peristalsis and LES characteristics that help plan appropriate patient management.

The results of this study were presented in December 2009 at the Annual Meeting of the Southern Surgical Association and published in the *Journal of the American College of Surgeons* in May 2010.

V.B. THE PREVALENCE OF RESPIRATORY SYMPTOMS IN PATIENTS WITH ACHALASIA

Achalasia is a primary esophageal motor disorder that results in poor clearance of the esophagus. Although an esophagus filled with debris and undigested food should put these patients at risk for aspiration, the frequency with which the latter occurs has never been documented. Therefore, we sought to determine the incidence of respiratory symptoms and complaints in patients with achalasia.

A comprehensive symptom questionnaire was administered to 110 patients with achalasia presenting to the Swallowing Center at the University of Washington between 1994–2008 as part of their preoperative work-up. These questionnaires were analyzed for the frequency of respiratory complaints in addition to the more typical symptoms of dysphagia, regurgitation, and chest pain.

Ninety-five patients (86%) complained of at least daily dysphagia. Fifty-one patients (40%) reported the occurrence of at least one respiratory symptom daily, including cough in 41 patients (37%), aspiration (the sensation of inhaling regurgitated esophagogastric material) in 34 patients (31%), hoarseness in 23 patients (21%), wheezing in 17 patients (15%), shortness of breath in 11 patients (10%) and sore throat in 13 patients (12%). Neither age, gender, nor manometric findings differed between those with and those without respiratory symptoms.

We concluded that patients with achalasia experience respiratory symptoms with much greater frequency than the approximately 10% which was previously believed. Awareness of this association may be important in the workup and ultimate treatment of patients with this uncommon esophageal disorder. The results of this work have recently been accepted for publication in the journal *Diseases of the Esophagus*.

V.C. SUBTYPES OF INEFFECTIVE ESOPHAGEAL MOTILITY—IMPLICATIONS FOR DIAGNOSIS AND MANAGEMENT

Ineffective Esophageal Motility (IEM) is a motility pattern diagnosed on esophageal manometry which is characterized by >30% of swallows being other than normal peristaltic sequences. Subgroups within this classification can be identified based on the predominant type of failed swallowing sequence, including hypocontractile swallows, those that fail to propagate in the distal esophagus, and simultaneous, low amplitude contractions. The clinical significance of IEM subgroups remains unclear, however. We sought to combine high resolution esophageal manometry (HRM) data in patients experiencing IEM with information obtained from ambulatory pH monitoring and patient symptom questionnaires in order to investigate the correlation between IEM subtype and esophageal acid exposure, bolus transit, and patient symptoms, and to determine if this might have an impact on further workup and management in these patients.

HRM tracings, pH data, clinic notes and symptom questionnaires in 84 patients with IEM and 50 control subjects with normal esophageal manometry and a diagnosis of GERD are being reviewed. We will compare esophageal acid exposure (% time pH <4 in the distal esophagus, DeMeester scores), bolus transit and patient symptoms between IEM subtypes and control subjects using analysis of variance. Through this study, we expect to be able to better determine which patients with IEM are more likely to have either increased acid exposure, more severe symptoms, or both, and to make suggestions as to how patients with such findings might warrant more aggressive treatment for associated problems, in particular GERD.

VI. Natural Orifice Translumenal Endoscopic Surgery

Natural Orifice Transluminal Endoscopic Surgery (NOTES) represents a paradigm shift that may significantly change the management of gastrointestinal and intra-abdominal diseases. The idea, as the name implies, is to access and perform procedures in the abdominal cavity via a natural orifice (e.g., mouth or anus) using an endoscope. The theoretical advantages of NOTES include reducing operative pain and morbidity, as well as avoiding wound infections, hernias, and adhesions. Furthermore, NOTES might offer advantages for patients in whom conventional transabdominal or laparoscopic procedures are unattractive, e.g., morbidly obese patients and patients with extensive scars, burns, or infections in the abdominal wall. The first animal experience with NOTES was published in 2004 by Kalloo et al., who demonstrated the feasibility and safety of a peroral transgastric endoscopic approach to the peritoneal cavity with long-term survival in a porcine model.

Our main goal for NOTES research at the UW is to assess the feasibility and safety of new devices and tools as well as different surgical procedures, most of which are currently being done via traditional surgical methods, but instead using a translumenal approach. We have developed relationships with our gastroenterology and bioengineering colleagues to form a NOTES research group. This group's goal is to develop and test the next generation of instruments that will make more advanced flexible endoscopic and NOTES procedures not only possible, but safe and effective. It is an exciting time. Not since the adoption of laparoscopic surgery 20 years ago has there been such a radical change in the way surgery is viewed.

VI.A. A Segmented Balloon-tip Overtube for Peritoneal Access in NOTES

NOTES applications often require repeated insertion and withdrawal of endoscopes and accessories into the peritoneal cavity after achieving initial access to the peritoneum. To achieve this, an extended overtube can be advanced across the luminal wall at the time of initial peritoneal access. However, the length of overtube required restricts the working length of the endoscope (length of endoscope minus the length of the overtube). We have developed a segmented overtube system that allows for maximal working length once peritoneal access has been achieved.

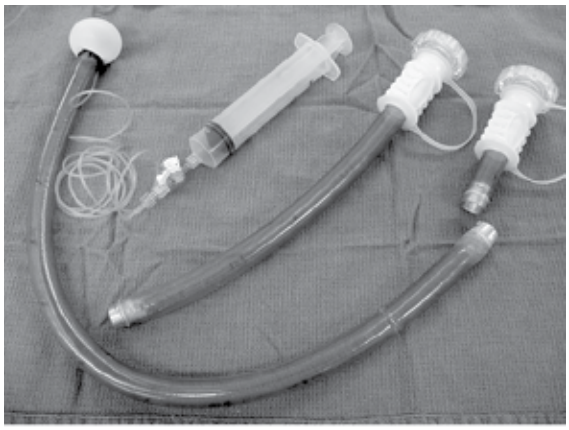

Figure 8. Overtube used in NOTES

The overtube (Figure 8) consists of the following components, modified from the Guardus® overtube (US Endoscopy): 1. A single distal overtube section (60 cm) with an inflatable balloon on the distal end used to secure the tip of the overtube after peritoneal access. A threaded connector is attached to the proximal end; 2. Two proximal sections of two lengths (30 cm and 5 cm) which are interchangeable via a threaded connector; 3. A single inner tube (90 cm) used for peritoneal access only. The 30 cm proximal section is attached to the distal section (total length of 90 cm), and the inner tube is inserted along with the endoscope. The endoscope is then advanced along with the tip of the overtube into the peritoneum using the standard needle knife/balloon dilation technique. The overtube balloon is then inflated, securing the tip within the peritoneum. The entire overtube can then be reduced. The endoscope and inner tube are withdrawn and the longer proximal section of the overtube is detached and replaced with the shorter proximal segment (5 cm). The operator now has approximately 40 cm of working length with the endoscope and has direct access into the peritoneum via the overtube.

Results: Preliminary *in vivo* studies using this overtube system have been performed resulting in stable access to the peritoneal cavity for NOTES procedures. The overtube system allows for rapid insertion and withdrawal of the endoscope and the ability to deliver accessories and materials into the peritoneum without sacrificing the working length of the endoscope.

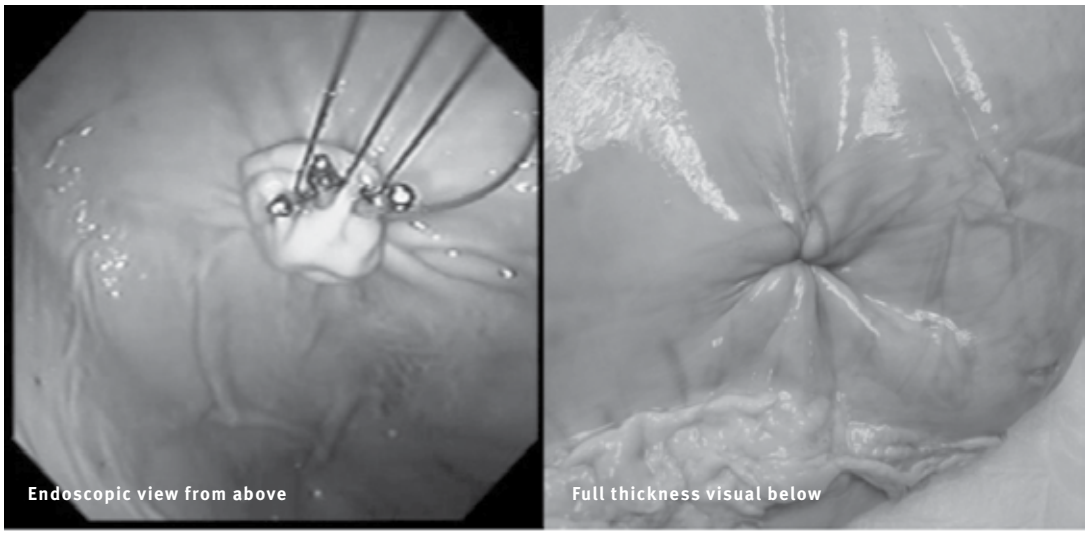

Figure 9. Image of closure in NOTES gastrotomy

This overtube system is relatively simple to build using existing commercially available components, and can potentially be modified for human anatomy to maintain a sterile conduit into the peritoneum.

VI.B. Retracted Clip-assisted Loop Closure for Gastrotomy in NOTES

A reliable method for gastrotomy closure will be essential for NOTES to become viable clinically. Several methods have been reported; however, simple methods using existing endoscopic accessories have been ineffective. Specialized devices are in development but are not widely available. We have developed a novel, simple method for gastric closure that uses existing endoscopic accessories with very minor modifications. We report preliminary data on a new method of gastrotomy closure using modified clips and endoloops.

A standard NOTES gastrotomy with needle-knife incision followed by balloon-dilation with a 20 mm diameter balloon was performed in 12 *ex vivo* pig stomachs. Gastrotomies were closed using the conventional hand-sewn technique in 6 specimens and using the new retracted clip-assisted loop closure technique in 6 specimens. The retracted clip-assisted loop closure technique involves deploying 3-4 Resolution® clips (modified by attaching a 90 cm length of suture string to the end of each clip) along the margin of the gastrotomy with one jaw on the serosal surface and the other jaw on the mucosal surface. The attached strings are exteriorized through an overtube. With the endoscope external to the subject, an endoloop is then passed through the endoscope channel, opened, and the strings are threaded through the open loop and advanced into the stomach. Retraction is then applied to the strings, causing the gastric wall to tent. The endoloop is then secured below the tips of the clips, completing a full thickness gastrotomy closure. An air leak test was performed via insufflation with the endoscope. Fluid leak pressure was then measured for each specimen.

The retracted clip-assisted method achieved an air-tight seal in 100% of the specimens. Endoscopic image of the appearance of the closure is provided (Figure 9, left image). On visual inspection, 2/6 appeared to achieve a full thickness closure (Figure 9, right image). The leak pressure ranged from 16-88 mmHg (mean, 37 mmHg). Results improved as the investigators gained experience with the technique. In comparison, the leak pressure for the hand-sewn technique ranged from 67-103 mmHg (mean, 81 mmHg).

The retracted clip-assisted gastrotomy closure technique is a promising new technique for NOTES gastrotomy closure that uses existing endoscopic accessories with minor modifications and warrants further investigation.

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