

The Impact of Minimally Invasive Esophageal Surgery



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KEYWORDS

• Esophagectomy • Minimally invasive esophagectomy • Esophageal cancer

KEY POINTS

- Esophagectomy is one of the larger more complex surgeries commonly performed on the human body.
- Esophageal cancer is the 18th most common malignancy and accounts for less than 1% of all cancer cases in the United States annually.
- The National Institutes of Health estimates that of the 16,910 new cases diagnosed in the United States in 20,016 there will be 15,690 deaths and only 18.4% of patients will survive 5 years. This is partly attributable to the late presentation of the disease.

INTRODUCTION

To most Americans, esophageal cancer remains a fairly unknown malignancy. According to the National Institutes of Health (NIH) esophageal cancer is the 18th most common malignancy and accounts for less than 1% of all cancer cases in the United States annually. This is despite that adenocarcinomas of the esophagus are increasing at a faster rate than any other malignancies. The annual incidence of esophageal cancer in the United States is 4.3 cases per 100,000. Yet, for physicians caring for these patients, the relative infrequency of the disease provides little solace and even less if the disease has a personal effect.

The NIH estimates that of the 16,910 new cases diagnosed in the United States in 20,016 there will be 15,690 deaths and only 18.4% of patients will survive 5 years. This is attributable in part to the late presentation of the disease. It is estimated by the Surveillance, Epidemiology, and End Results (SEER) database that 30% of tumors are limited to the primary site and nearly three-fourths of patients have regional (31%) and distant (38%) disease. Poor long-term survival is not surprising in advanced

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disease cases but survival among patients with localized disease should be considerably better and perhaps comparable to other malignancies. Regrettably, this is not the case. Again, based on the SEER database, 5-year survival for localized tumor is 41%. This is considerably lower than lung cancer for example (70%).

There are several axioms that are frequently referred to regarding esophageal malignancies. Often it is stated that the tumor is more aggressive, implying worse outcome as a result of disease. Certainly, from an anatomic perspective, it is more likely to spread to lymphatics at an earlier depth of invasion than in other malignancies for the gastrointestinal tract. For example, tumor stage T1b tumors involving the submucosa have a 5% risk of lymph node metastasis and T2 tumors invading the muscularis propria have a 20% risk of metastatic lymphatic involvement. Another perceived adverse predictor of risk is age. The median age at diagnosis is 67 years old (NIH) and nearly 40% of patients diagnosed are less than 65 years old. Others point to lower health care dollars spent on esophageal cancer research. The amount of money spent on esophageal cancer per death is \$1542 per patient, which is similar to other less funded diseases, such as lung cancer \$1553. These numbers pale in comparison to other malignancies, such as cervical cancer, \$18,870; breast cancer, \$14,095; and lymphoma, \$12,791. These issues may lead to treatment bias, lack of optimism in treatment, and frequently undertreatment of the tumor. This negative outlook is further exacerbated by realistic and unrealistic morbidity and mortality associated with esophagectomy. In fact, many patients who are potentially resectable are either not offered surgery or decline surgery, and are, therefore, less likely cured of their disease. Dubecz and colleagues¹ analyzed multiple databases to review care and outcomes of more than 25,000 esophageal subjects with cancer. This large study found only 44% of subjects with potentially resectable disease underwent surgery in the state of New York. In other words, 56% of subjects with resectable disease were undertreated for their malignancy. This pervasive undertreatment likely plays a role in the poor long-term survival of esophageal patients with cancer.

Surgeons who care for these patients have been eager to see real change in short-term and long-term outcomes. Advances in diagnosis, screening, referral, and treatment of this cancer have been slow in coming and, while waiting for those changes, work continues toward improving surgical outcomes, techniques, and expanding the reach of esophagectomy to deserving patients. To many, these advances have been dramatic and profound. Leading the way to new innovation has been the use of minimally invasive techniques in esophagectomy. This article discusses the surgical innovations that have occurred in the last decade and their impact on patients with esophageal cancer.

THE EVOLUTION OF MINIMALLY INVASIVE ESOPHAGECTOMY

Surgical resection of esophageal malignancy is not novel or unique, and remains a mainstay of the treatment of this malignancy. However, as it relates to morbidity and mortality, it can be argued that esophagectomy is one of the larger more complex surgeries commonly performed on the human body. When comparing esophagectomy mortality to that of other major elective surgery, others may pale in comparison. The mortality in the twenty-first century has been reported as 13% nationwide and as high as 23% at low-volume institutions.² The disparity is equally compelling in terms of morbidity. Studies routinely demonstrate morbidity rates in esophagectomy series are above 50%.³⁻⁶ Long-term morbidity, as it relates to dysphagia, weight loss, and quality of life (QoL), can be disappointing.

To the point, it is no surprise that more than 60% of patients who need an esophagectomy are not offered or refuse one.¹ Undertreatment, by not offering surgery, is a major factor in the poor outcomes of this disease. In attempts to improve overall outcomes of esophageal cancer, surgeons were challenged to improve surgical outcomes. Some surgeons embraced minimally invasive techniques, resulting in the evolution of the minimally invasive esophagectomy (MIE). Leading the way was the University of Pittsburgh Medical Center (UPMC). In a seminal paper, Luketich and colleagues³ published the outcomes of 222 consecutive subjects who underwent MIE. The mortality rate of 1.4% and length of stay of 7 days were remarkable compared with any previously published open series. In addition, this paper demonstrated QOL scores similar to preoperative scores. Although, clearly a landmark paper that opened the eyes of many to MIE, there were many who contributed to the development of this procedure. The first to report thoracoscopic esophagectomy was Cuschieri and colleagues⁷ in 1992. In 1994, Cuschieri⁸ described reported thoracoscopic mobilization in the prone position. The esophagus was mobilized in the chest and later a cervical anastomosis was created after laparotomy. As minimally invasive surgical techniques evolved, thoracoscopic mobilization was performed more frequently via lateral decubitus position.³ The appeal of the lateral decubitus approach was easy to understand because it allowed similar orientation to open surgery and simplified conversion to open surgery if necessary. Several studies have demonstrated advantages of prone thoracoscopic mobilization in terms of diminished operative times and reduced blood loss.⁹ A recently published meta-analysis demonstrated superiority of the prone position in terms of reduced pulmonary complications, reduced estimated blood loss, and increased lymph node procurement.¹⁰ Despite these results, left lateral decubitus position remains the preferred approach at most institutions.

Laparoscopic mobilization of the neoesophagus was the next advancement in the mid-1990s when surgeons began to report smaller series.^{11,12} At that time, the overwhelming approach was cervical anastomosis and either totally laparoscopic or a modified Ivor Lewis, frequently referred to as a McKeown, esophagectomy.

In 2002, Luketich and colleagues³ reported on several modifications made during the series in the hopes of minimizing morbidity. One of these concerned conduit width. Initially, a narrow gastric conduit was used but, according to the investigators, this resulted in higher than expected anastomotic leaks. The technique was modified by moving toward a wider conduit and the investigators concluded this resulted in an 11.7% decrease in anastomotic leaks. In a different study, 220 subjects undergoing transhiatal or transthoracic esophagectomy were compared. The anastomotic leak rate in the neck was 14% and 16%, respectively,¹³ and risk of vocal cord paralysis was 14% and 24%, respectively. These complications are often cited as the driving force in the evolution of minimally invasive Ivor Lewis esophagectomy with intrathoracic anastomosis. Watson and colleagues¹⁴ were the first to report a modified Ivor Lewis approach in 1999 but it was Bizekis and colleagues¹⁵ at the University of Pittsburgh who published the first large series of intrathoracic anastomosis in 50 subjects in 2006. Risk of anastomotic leaks vary greatly in the literature but, again, are generally considered higher in the cervical anastomosis at 15%¹³ than in the intrathoracic anastomosis at 6%.¹⁵ These issues have collectively led to more frequent use of the Ivor Lewis MIE. In 2012, Luketich and colleagues¹⁶ published a series of 1033 consecutive MIE subjects with more than half receiving intrathoracic anastomosis. Total operative mortality was now reported as even lower at 1.68%. The Ivor Lewis approach also resulted in a reduction of incidence of recurrent laryngeal nerve injury, which was statistically significant. It should be noted that recurrent laryngeal nerve injuries can occur

during intrathoracic anastomosis but the risk is generally considered much lower than in the neck.

Esophageal anastomotic techniques vary widely. For many experienced surgeons, creation of the anastomosis remains a challenge. Even open esophageal anastomosis can be challenging. Creation of the anastomosis seems to be variable based on surgeon preference. The Pittsburgh group prefers an end-to-side circular stapled anastomosis,^{3,15} whereas others use side-to-side totally stapled anastomosis.⁴ Currently, even robotic handsewn anastomosis exists.¹⁷ In 2016, Harustiak and colleagues¹⁸ looked at 415 esophageal anastomosis at a single institution and reported that stapled anastomosis resulted in fewer leaks, 10% versus 21%, and fewer strictures, 6% versus 20%, when compared with handsewn.

A critique of the Harustiak and colleagues¹⁸ publication is that it was a single surgical center outcome and perhaps not all handsewn anastomosis are similar. Another criticism is of the significant variables that come into play. These include width of conduit, handling of the neoesophagus, technique of handsewn anastomosis, and countless others making surgical technique comparisons difficult. Speaking from the authors' own experiences on creation of an anastomosis, we believe that we have performed virtually every type of anastomosis described and are confident that all anastomosis can fail. The authors' advice is that all techniques have advantages and pitfalls, and likely the best choice is the one that the surgeon feels most comfortable with until data demonstrate otherwise.

Surgical simulation may be used in the future to improve anastomotic techniques. The authors published our experience using a bovine tissue block and creating a simulated intrathoracic thoracoscopic anastomosis.¹⁹ The model allows for recreation of virtually any anastomosis. The study demonstrated that, with repetition, residents could improve their technical skills rapidly and create increasingly successful thoracoscopic anastomosis.

Gastric emptying following esophagectomy remains a critical issue as it relates to short-term morbidity and long-term QoL. Delayed gastric emptying is associated with increased aspiration, increased perioperative morbidity, decreased patient satisfaction, and prolonged hospital stay.²⁰

Delayed gastric emptying occurs in 15% to 30%^{21,22} of cases and can result from several factors, which can cause problems separately or in conjunction with one another. Causes include rotation of gastric conduit, obstruction at the hiatus, hypertonic pylorus, transection of vagal nerves, or any combination of these. It should be noted that there are likely still other factors that might cause delays in emptying that are less well-defined. Frequently, it is stated that narrow gastric conduits are associated with improved emptying but there are little to no data to support this. If in fact, as some argue, the neoesophagus serves as a passive gravity-dependent conduit and, in physics, a wider tube has less resistance and should empty better. It does seem plausible that the idea of a narrow conduit is a conceptualized surrogate for what is actually redundant intrathoracic stomach, which certainly can be a significant problem.

Pyloric obstruction is considered by most physicians a major cause of delayed gastric emptying, and pyloromyotomy and pyloroplasty have been used to reduce delayed gastric emptying. However, randomized trials evaluating these procedures have shown little benefit.^{23,24} In one study, Zieren and colleagues²⁴ stated that in most circumstances no emptying procedure should be done. A meta-analysis in 2002 by Urshel and colleagues²⁵ shows that early complications from delayed gastric emptying can be reduced when a pyloroplasty is performed. However, no long-term difference was observed. Generally, there is a lack of significant data to support an emptying procedure in the setting of esophagectomy. However, the difficulties with

delayed emptying are so severe that they continue to be performed frequently. Unfortunately, pyloroplasty and pyloromyotomy cannot be done with impunity. These procedures can lead to stricture, leak, and death.²⁶ As some surgeons chose to forgo this procedure in open esophagectomy (OE) and MIE, others looked for alternatives. In 2007, Kent and colleagues²⁷ (including the senior author of this article) published a pilot study looking at the use of Botox injection of the pylorus. In 2009, this was followed with a larger study²⁸ that demonstrated 91% of subjects showed no significant delay on esophagram or clinically. Four (9%) subjects in the study group had significant delay on the esophagram but only 2 (4.5%) had clinically relevant delayed emptying. Botox injection seems a reasonable alternative and seems durable. Three (7%) subjects who were doing well developed delayed emptying at approximately 3.5 months. All responded to retreatment. Only 1 of 48 (2%) patients had an aspiration event postoperatively. More recently, other investigators have suggested balloon dilation.²⁹ Bakhos and colleagues³⁰ published a multi-institutional study of 220 esophagectomy subjects and found the omission of a pyloric procedure was directly linked to postoperative pneumonia. Most pyloric procedures in that series included Botox injection.

Oncologic principles of esophagectomy are yet another critical issue in the treatment of esophageal cancer. Any modification in technique must not compromise adequacy of oncologic resection. Complete resection (R0) can be used to define oncologic effectiveness of a surgical technique but may not represent the entire picture. Most MIE series demonstrate high R0 resection rates exceeding 95%³⁻⁵ but most of these studies are published at highly specialized centers. The Eastern Cooperative Oncology Group (ECOG) 2202 study was a multicenter feasibility trial of MIE.³¹ R0 was achieved in 96% of subjects and the 30-day mortality was 2.1%. The median follow-up was 35 months and 3-year survival was 58.4%. Another frequently used surrogate for oncologic completeness is lymph node procurement. Although the number of lymph nodes harvested has never shown survival benefit, it is clear that lack of adequate procurement can result in under staging, undertreatment, and worse oncologic outcomes. Several series have shown comparable or superior levels of lymph node procurement between MIE and OE.^{4,5} One of the most consistent differences between OE and MIE is intraoperative blood loss.⁴ As a surrogate this may be relevant. Blood loss is equated to physiologic strain, although it has not been directly linked to oncologic outcomes. Blood transfusions have been shown to negatively affect survival independent of tumor stage in malignancies.³²

Some data exist supporting better long-term oncologic survival with MIE versus OE. Palazzo and colleagues³³ reported data of 5-year survival as being statistically superior with MIE 64% versus OE 35%. At the same time, the investigators correctly conceded that several biases may have influenced the results. Despite this, the results are intriguing.

Multiple studies have demonstrated the feasibility of MIE at both academic centers and community settings,⁴ as well as improved outcomes of patients undergoing esophagectomy at institutions adopting MIE.^{4,5} Data have also demonstrated that the technique is applicable to virtually all patients, including patients following neoadjuvant chemoradiation.¹⁹

Proponents of MIE argue that it confers advantages for patients by reducing morbidity and mortality. Opponents often point to the lack of data supporting that concept or criticize the source. In the case of retrospective studies, subject selection and selection biases can frequently be cited. Certainly, there are limited data comparing MIE to OE; there is only a single prospective randomized trial.³⁴ In this study, 5 centers in 3 countries randomized subjects between MIE and OE. This study showed less intraoperative blood loss, less postoperative pneumonia, shorter

postoperative length of stay, and improved QoL at 6 weeks. These findings were comparable to what was reported in retrospective comparisons nearly a decade earlier.^{4,5} However, not all studies have demonstrated benefits with MIE. A retrospective study comparing OE to MIE using the Society of Thoracic Surgeons database showed little difference between the techniques.³⁵ Notable publications and advancements in MIE techniques are demonstrated in Fig. 1.

Regardless of how reported outcomes of MIE and OE are interpreted, MIE is gaining market share and will likely continue to do so, either as some incarnation described by Luketich or, perhaps, using robotic techniques. By reducing morbidity and mortality through clinically oriented research, the opportunity exists to significantly affect survival with this increasingly common malignancy.

As the techniques have advanced in MIE surgery, so has the expertise of thoracic surgeons using minimally invasive techniques and intraabdominal laparoscopy. Advances have allowed foregut surgeons to reassert their expertise. Foregut surgeons are not limited to the thoracic cavity but are also experts in intraabdominal minimally invasive surgery. Laparoscopic approaches to intrathoracic stomach, shortened esophagus, achalasia, and epiphrenic diverticulum have all evolved during this same time. No better evidence of this assertion exists than the more than 50 publications by Dr. James Luketich at UPMC regarding laparoscopic surgical conditions in these 4 areas. There is no reluctance by thoracic surgeons to enter the chest and there are clearly times when this is appropriate but now there is the realization that the ideal approach to these pathologic conditions is via the abdomen. Not only have these advances helped patients but also helped thoracic surgeons broaden the profession as surgeons of the complete foregut.

Advanced laparoscopic and/or robotic surgeons, at this time, prefer to be in the abdomen reducing the giant hiatal hernia, avoiding a Collis gastroplasty, or enjoying the visualization of muscle fibers of the gastroesophageal junction as they complete the ideal myotomy.

Surgeons stand on the shoulders of those who came before: Ivor Lewis, Belsey, Orringer, and Luketich, who each left an everlasting legacy yet were unable to predict the future of surgical techniques or care. For now that is minimally invasive abdominal and thoracic surgery. However, thoracic surgery has always evolved and will continue

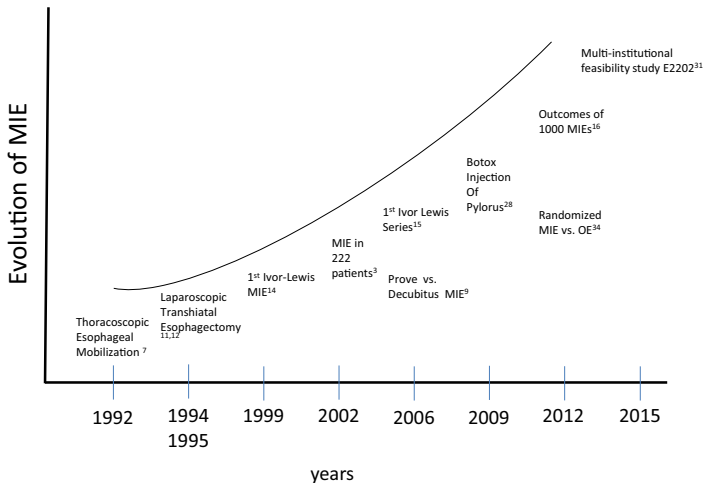


Fig. 1. Technical and notable advancements in MIE. (Data from Refs. 3,7,9,11,12,14–16,28,31,34)

on to meet somewhere near the intersection of technology, patient pathologic conditions, and enthusiasm.

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