Review Article

Future directions—minimally invasive approaches to esophageal resection: a narrative review

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Abstract: From the time of the first transthoracic esophagectomy to the present day, techniques for esophageal resection have evolved considerably. While open surgical techniques are still often employed, minimally invasive esophagectomy (MIE) has seen a tremendous rise in adoption in many centers worldwide and has in fact surpassed open esophagectomy. Robotic assisted minimally invasive esophagectomy (RAMIE) continues to increase steadily in recent years as well. Along with improved care algorithms including neoadjuvant and adjuvant treatments, minimally invasive approaches to esophageal resection have also contributed to a contemporaneous decrease in perioperative morbidity and mortality, as well as improvements in overall survival in esophageal cancer. Regardless of techniques or technologies employed, a continued reduction in complications such as anastomotic leak rate and pulmonary complications will be imperative in order to truly advance the field of esophageal resection. Importantly, endoscopic therapies such as endoscopic mucosal and submucosal resections (EMR/ESR) have garnered a substantial role in the treatment of early stage esophageal cancer. Novel robotic endoscopic platforms are in early development as well. The future of esophagectomy will no doubt continue to involve applications of new technology, including robotics and other novel developments.

Keywords: Minimally invasive esophagectomy (MIE); endoscopic; robotic

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Introduction

In 2020 it is estimated that esophageal cancer will be newly diagnosed in 18,440 people and will be responsible for 16,170 deaths in the United States. It is the 7th most common cause of cancer deaths among men, with an overall 5-year survival of 19%, up from 5% in the 1960s and 70s. The 5-year survival rate is 45% for localized (T1-T3N0) disease, 24% for regional nodal disease (N1–N3), and 5% for Stage IV disease (1). Subset analysis by a number of centers have shown that very early T1N0 cases have cure rates approaching 90% in selected centers (2). From the 1970s to the 2000s, the proportion of patients with esophageal adenocarcinoma in the United States nearly doubled. Throughout this time period, surgery was performed for localized disease in 89% of patients with esophageal cancer, which represented a significant increase. There was a concomitant increase in the overall median survival (6 *vs.* 10 months, P<0.001) and 5-year survival rate (9% to 22%, P<0.001), likely related to a combination of earlier diagnosis and increased use of surgical treatment (3). To date, esophageal resection remains the cornerstone of therapy for localized cancers of the esophagus. The following will include a brief review of the history of esophagectomy, a review of the current data, and a discussion on future directions in minimally invasive esophageal surgery.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aoe-2019-08).

History of esophagectomy

The first successful transthoracic esophageal resection was performed in 1913 by Franz Torek for squamous cell carcinoma. Sixteen years later, Tohru Osawa performed the world's second successful esophagectomy; he was the first to perform gastric reconstruction of the resected esophagus and to create an intrathoracic esophagogastric anastomosis (4). In 1933, the first transhiatal esophagectomy was performed by Turner. This approach was popularized in the late 1970s by Orringer. In 2007, Orringer reported his overall experience with transhiatal esophagectomies [group 1: n=1,063 (1976 to 1998); group 2: n=944 (1998 to 2006)], with an overall leak rate of 12% (14% in group 1, 9% in group 2) and hospital mortality rate of 3% (4% for group 1, 1% for group 2) (5).

In 1946, Ivor Lewis introduced a staged transthoracic esophagectomy. The first stage of the operation involved laparotomy and gastric mobilization, and the second stage (performed 2 weeks later) involved esophageal resection and reconstruction via right thoracotomy. In 1976, McKeown introduced an alternative technique involving a right thoracotomy, followed by laparotomy and left cervical incision with creation of a cervical esophagogastric anastomosis.

Traditional open two-hole (Ivor Lewis) or three-hole (McKeown) esophagectomy both carry significant morbidity and mortality, with mortality rates quoted at 5–8% at high-volume centers and morbidity as high as 60%. While transhiatal approaches may carry less surgical morbidity, there is significant debate and concern regarding the relatively diminished extent of lymphadenectomy and oncologic quality of this approach compared to transthoracic operations. With the evolving trend in minimally invasive surgery and the clear need for reduced morbidity of open transthoracic esophagectomy, minimally invasive esophageal resection was developed to decrease surgical complications while maintaining the oncologic advantages of these operations.

Minimally invasive esophagectomy (MIE)

MIE was introduced in 1992 by Cuschieri who performed the first thoracoscopic esophagectomy. The initial variations of minimally invasive esophageal surgery included many hybrid approaches, such as laparoscopy with thoracotomy or thoracoscopy with laparotomy.

Luketich performed one of the first totally minimally invasive esophagectomies in 1996 and reported this in 1998 (6). This initial MIE was performed totally laparoscopically, but his technique soon evolved to include a videothoracoscopic and laparoscopic modification of the McKeown approach (7). Using this new McKeown MIE approach, Luketich subsequently reported on 77 MIEs with a thirty-day operative mortality rate of zero (8). In 2003, Luketich *et al.* reported their MIE series of 222 cases, of which 206 underwent successful MIE without requiring conversion to open. The predominant approach in this cohort was a modified McKeown technique with thoracoscopic mobilization and cervical anastomosis. Operative mortality rate in this series was 1.4%, which was equal to or better than that in most open series (9). In 2012, Luketich *et al.* published a follow-up institutional series of over 1,000 patients who underwent MIE with either the McKeown (n=481) or Ivor Lewis (n=530) approach from 1996 to 2011. The total 30-day operative mortality rate in this series was 1.68% (Ivor Lewis 0.9%, McKeown 2.5%). McKeown was associated with higher rates of recurrent laryngeal nerve injury (8% *vs.* 1%, P<0.001) and ARDS (4% *vs.* 2%, P=0.3). This study demonstrated that MIE could be performed with low morbidity and mortality using either approach. While the Ivor Lewis approach was shown to have significantly lower mortality, this may have been related to the learning curve as the institution transitioned from the early McKeown operations to the currently predominant and preferred Ivor Lewis operations, in part in response to the increasing incidence of lower third esophageal adenocarcinomas (10).

Following our single institution studies, our group worked with a number of other pioneers in MIE, and The Eastern Cooperative Oncology Group E2202 study was developed. This was a prospective multicenter intergroup phase II trial in which 95 patients from 17 institutions underwent McKeown or Ivor Lewis MIE. R0 resection was performed in 96% of patients, and at a median follow-up of 40 months, local-regional recurrence occurred in only 6.7% of patients. This study demonstrated the feasibility and safety of performing MIE across multiple institutions, with 30-day mortality of 2.1%, anastomotic leak rate of 8.6%, and 3-year overall survival of 58.4% (11). Basically, ECOG 2202 proved that the MIE was not a "Pittsburgh operation."

The TIME trial [2012] was the first multicenter randomized controlled trial comparing MIE *vs.* open esophagectomy. This multi-national European study randomized patients with esophageal cancer across 5 centers between 2009 and 2011 to either minimally invasive transthoracic esophagectomy (n=59) or open transthoracic esophagectomy (n=56). MIE demonstrated lower pulmonary infection rates (9% *vs.* 29%) and reduced length of stay (11 *vs.* 14 days) when compared with open (12). The combined 30-day and in-hospital mortality for all patients was 2.6% and did not differ between groups. The overall anastomotic leak rate was 9.6% and did not differ between groups.

As demonstrated by these studies, the development of MIE significantly advanced the care of patients with esophageal cancer by offering equivalent oncologic outcomes and reduced morbidity (and potentially mortality) when compared with traditional esophagectomy. Length of hospital stay and pulmonary complications in particular decreased significantly. As such, use of MIE has currently surpassed that of open esophagectomy (13).

Robotic assisted minimally invasive esophagectomy (RAMIE)

Over the past decade, RAMIE has increasingly come into practice, offering the added appeal of magnified stereoscopic and central optics, enhanced motion with extra degrees of freedom, and increased operator control over the conduct of operations with less reliance on an assistant (14). The first total thoracolaparoscopic robotic MIE was a three-hole esophagectomy reported by Kernstine *et al.* in 2004 (15). Sarkaria *et al.* described the first total robotic minimally invasive Ivor Lewis approach in a cohort of 17 patients in 2013 from Memorial Sloan Kettering Cancer Center (4 additional patients underwent total RAMIE with a three-hole approach) (16). Three patients developed anastomotic leaks in this early series, and three developed airway fistulas (1 early and 2 delayed at 2 and 3 months post-operatively). The authors expressed caution and attention in the use of thermal dissection along the airway in these cases. With modifications to the technique addressing these pitfalls, a follow-up study of 100 RAMIE cases demonstrated a leak rate of 6% with zero complications of airway fistulization, 0% 30-day mortality, and 1% 90-day mortality (17).

Endoscopic esophageal resection

Injection-assisted endoscopic mucosal resection was introduced in the setting of rigid sigmoidoscopy in 1955 and then for flexible colonoscopy in 1973 for the removal of suspicious mucosal lesions (18). Today, endoscopic therapy is widely used for the staging, diagnosis, and treatment of early esophageal cancer (high-grade intraepithelial neoplasia or esophageal cancer which is limited to the mucosa). Unlike ablative therapies such as photodynamic therapy or argon plasma coagulation, endoscopic resection as a treatment method for early stage disease has the added benefit of allowing for histological assessment of the resected specimen in order to determine depth of tumor infiltration and freedom from neoplasia at the lateral and basal margins. Historically, intramucosal cancer was an indication for esophagectomy, but with the advent of endoscopic resection and the knowledge that disease limited to the mucosal layer has a low risk of lymph node metastasis, there is now a curative alternative with significantly lower morbidity and mortality.

The 2007 study by Ell *et al.* was the first prospective study to demonstrate the efficacy of endoscopic resection in treating early stage disease with favorable morbidity and mortality when compared with esophagectomy. Out of 144 resections, there were no major complications, and complete local remission was achieved in 99% of patients after 1.9 months. On 3-year follow up, recurrent or metachronous carcinomas were found in 11% of patients, but successful repeat treatment with endoscopic resection was possible in all of these cases. An important aspect of this study was that over 500 patients were evaluated and excluded from EMR due to high risk criteria such as multifocal, lymphovascular invasion, longer segments of nodular Barrett's, etc. The calculated 5-year survival rate in this highly selected group was 98%. The advent of endoscopic resection is especially critical in the treatment of patients with early stage disease whose surgical risk may prohibit esophagectomy (19).

Present and future of minimally invasive esophageal surgery: outcomes, unanswered questions, and emerging platforms

There have been several large series on MIE, including a recent analysis from the Japanese National Clinical Database of 24,233 esophagectomies performed between 2012 and 2016. This study demonstrated equivalence or superiority of MIE over open esophagectomy in most postoperative morbidities and in surgery-related mortality (overall surgery-related mortality 1.7% for MIE, 2.4% for open) ($P<0.001$) (20). The 3-year follow up results of the TIME trial comparing MIE with open esophagectomy were published in 2017. Overall 3-year survival in the open group was 40.4% *vs.* 50.5% in the minimally invasive group (P=0.207), and disease-free 3-year survival was 35.9% in the open group *vs.* 40.2% in the minimally invasive group [HR 0.691 (0.389 to 1.239)] (21). A prospective non-randomized trial of well-matched RAMIE (n=65) and open (n=108) transthoracic esophagectomy at Memorial Sloan Kettering Cancer Center reported improved short term quality of life and rates of infectious and pulmonary complications with RAMIE, and equivalent morbidity and mortality between the groups (22). The ROBOT trial, the first randomized control trial comparing open esophagectomy (n=55) with robot-assisted thoracolaparoscopic esophagectomy (n=54), was published in 2019. This study demonstrated significantly lower pulmonary, cardiac, and overall complications in the RAMIE group when compared to open, with no difference in oncologic outcomes, median disease-free survival, or overall survival (23). Additional randomized control trials comparing MIE with open esophagectomy and comparing RAMIE with MIE are currently in progress [the ROMIO (24) and RAMIE trials, respectively (25)]. Early institutional series have demonstrated that RAMIE can yield similar oncologic and operative outcomes as MIE or open approaches when performed at high volume centers (14).

There remain several unanswered questions regarding optimal technique and necessity of certain portions of the procedure. The necessity of a gastric emptying procedure, for example, remains in question. While some surgeons may prefer pyloroplasty or pyloromyotomy, others advocate for botulinum toxin injection, while still others will not perform a gastric emptying procedure at all. Pyloric drainage procedures have been associated with significant morbidity, particularly when resulting in leakage from the pyloroplasty or pyloromyotomy site. A meta-analysis of randomized control trials investigating the necessity of pyloric drainage after esophagectomy found that performing a pyloric drainage procedure reduces early postoperative gastric outlet obstruction but has little impact on patient outcomes otherwise. Notably, the studies included in the analysis differed in technique of esophagectomy, size of conduit, and several other factors that may influence potential benefits of a pyloric draining procedure. Furthermore, these studies predated the advent of MIE (26). Due to the lack of current randomized data regarding the necessity of a pyloric drainage procedure in the setting of a narrow gastric conduit, our institution is currently conducting a randomized control trial on pyloroplasty *vs.* no pyloric drainage procedure in patients undergoing MIE.

Optimal conduit size, anastomotic technique, and even patient positioning have also remained controversial topics among esophageal surgeons. Some surgeons performing MIE or RAMIE advocate for a conduit that is 4 centimeters in diameter, but data regarding the optimal size for gastric tube is lacking. Recently, our institution has begun to shift to a narrower conduit of 2.5 to 3 centimeters. Similarly, recommendations regarding optimal anastomotic technique are not well defined. Some perform the anastomosis in an end-to-side fashion with the EEA stapler utilizing various techniques for anvil insertion. Others perform the anastomosis in a hybrid partial linear stapled and partially sewn technique. While we have employed the end-to-side anastomosis with the EEA routinely in our Ivor Lewis MIEs, our institution may also utilize a completely hand-sewn end-to-end technique as well. A 2014 meta-analysis of randomized control trials comparing stapled *vs.* hand-sewn anastomosis in patients undergoing esophagectomy with reconstruction for esophageal cancer demonstrated increased anastomotic stricture rates, pulmonary complication rates, and mortality rates with the stapled technique, with no difference in anastomotic leak rates between the two techniques (27). Alternatively, a more recent systematic review and meta-analysis found linear stapled/hybrid and circular stapled techniques to be associated with decreased leak rates compared to completely hand-sewn or triangulating stapled anastomoses, and decreased stricture rates compared to hand-sewn techniques (28).

The need for routine feeding jejunostomy in esophagectomy patients is also an area of active investigation. Recent studies have demonstrated that post esophagectomy weight loss occurred at termination of tube feeds independent of duration of feeds and that discharge with home-tube feeds did not reduce length of hospital stay, number of hospital readmissions, or weight loss overall (29). Such results challenge the utility of routine jejunostomy placement, especially given the associated complications that may arise, such as occlusion, dislodgement, insertion site infection, and even need for reoperation.

The future of minimally invasive esophageal surgery will likely include use of advanced technologies such as near-infrared fluorescence imaging (NIFI) with indocyanine green or other tissue and/or cancer specific imaging agents. These technologies may aid in identification of sentinel lymph nodes or accurate real-time assessment of conduit perfusion to reduce anastomotic leak rates (30). The robotic platform will likely continue to grow and offer new enhancements in minimally invasive esophageal surgery. In an effort to advance minimally invasive esophageal surgery even further, uniportal esophagectomy is being investigated at various centers. Uniportal thoracoscopic surgery was initially introduced to the thoracic surgical community by Marello Migliore in the late 1990s (31) and has predominantly been used in pulmonary surgery. Uniportal esophagectomy has been described by Dmitrii *et al.* (32) and by Batirel (33). Guo *et al.* recently reported the first series of uniportal MIE. Forty-one patients were included in the study; the first 29 underwent four-port VATS and the remaining 12 underwent single-utility incision VATS. There were no mortalities in either group (34). These experiences suggest the potential of uniportal esophagectomy as a future direction in esophageal surgery, however additional studies with larger sample sizes will be necessary to elucidate its feasibility and safety (35).

Several innovative minimally invasive therapies are also emerging in the treatment of benign esophageal disease. Endoscopic stapled diverticulectomy has been used for treatment of Zenker's diverticulum; however this approach has been complicated by persistent diverticulum and recurrent dysphagia in up to 20% of cases. This has been attributed to a larger diverticulum common wall after stapled as compared to open diverticulectomy. A novel technique of endoscopic plication has been proposed for reduction of the common wall size by using the stapler to fold the wall of the residual diverticulum (36). For medically refractory gastroesophageal reflux disease (GERD), laparoscopic surgical fundoplication was historically the sole alternative therapy. In the past two decades, there have been numerous advancements in endoscopic GERD therapy aimed at either lower esophageal sphincter (LES) augmentation or gastroesophageal junction reconstruction. Available LES augmenting therapies include the Stretta procedure, which uses radiofrequency ablation to provide thermal energy to the LES, and the LINX procedure, which involves placement of a magnetic string of compliant titanium beads around the LES. Gastroesophageal junction reconstructive therapies include the transoral incisionless fundoplication (TIF), mucosal ablation and suturing of the gastroesophageal junction, the resection and plication procedure, and the Medigus Ultrasonic Surgical Endostapler procedure (MUSE). In TIF, the gastric fundus is folded up around the distal esophagus and anchored with polypropylene fasteners. This is an increasingly favorable option in patients with medically refractory GERD and Hill Grade II who will not require surgery for a large hiatal hernia (37). C-BLART (clip band ligation anti-reflux therapy) has been recently presented as a new treatment method for refractory GERD. This endoscopic procedure involves constricting the mucosa of the esophagogastric junction and inducing scar formation to create an anti-reflux barrier utilizing only band ligation and clips (38).

The amalgamation of robotics with endoscopy will play a key role in advancing the field of minimally invasive esophageal surgery even further. Endoscopy has already provided alternative approaches to many esophageal procedures as discussed above, but it is mainly limited by reduced instrument dexterity and confined workspace. Applying robotics to the advent of endoscopic surgery may allow for performance of more complex procedures. Several such platforms already exist including the MASTER system, which utilizes two robotic arms in addition to a standard endoscope, as well as the STRASS system. These platforms allow use of instruments with 5 degrees of freedom, enabling performance of more complex procedures. A recently proposed system, the i2 Snake robotic platform, consists of a snake-like robot with a supporting arm, a light source, a camera, and two robotic instruments. It was designed for performance of procedures such as endoscopic submucosal dissection and peroral endoscopic myotomy (POEM) (39).

Conclusions

The field of minimally invasive esophageal surgery has flourished over the past few decades, revolutionizing the treatment of both benign and malignant esophageal disease. There are still several areas within the field that require further research. Randomized control trials regarding pyloric drainage procedures, optimal conduit size and anastomotic technique, and optimal methods of feeding after esophagectomy are needed, as are further trials comparing RAMIE with MIE. Furthermore, several novel robotic platforms and endoscopic therapies are emerging with a wide array of application in the treatment of esophageal disease.

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