Review Article (Management of Foregut Malignancies and Hepatobiliary Tract and Pancreas Malignancies)

Esophagectomy from then to now

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Abstract: We have come a long way from the onset of surgery for esophageal cancer. Surgical resection is pivotal for the long-term survival in patients with locally advanced esophageal cancer. Moreover, advancements in post-operative care and surgical techniques have contributed to reductions in morbidity. More recently minimally invasive esophagectomy has been increasingly used in patients undergoing esophageal cancer resection. Potential advantages of MIE include: the decreased pulmonary complications, lower post-operative wound infection, decreased post-operative pain, and decreased length of hospitalization. The application of robotics to esophageal surgery is becoming more widespread. Robotic esophageal surgery has potential advantages over the known limitations of laparoscopic and thoracoscopic approaches to esophagectomy while adhering to the benefits of the minimally invasive approach. This paper is a review of the evolution from open esophagectomy to the most recent robotic approach.

Keywords: Transhiatal esophagectomy; transthoracic esophagectomy; robotic esophagectomy

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Introduction

Esophageal cancer is increasing in incidence worldwide. In 2018, it is estimated there will be 17,290 new cases of esophageal cancer with 15,850 dying from the disease in the USA (1). The overall survival for patients with esophageal cancer remains poor despite improvements in multidisciplinary care. The current approach to locally advanced esophageal cancer includes neoadjuvant chemoradiation followed by surgical resection (2). This multi-modality approach has demonstrated an improvement in survival for patients with advanced non-metastatic disease (3,4).

Esophageal resection is crucial for improving the overall survival in patients with esophageal cancer. While survival for patients with resected esophageal cancer has improved with the institution of multidisciplinary treatment, the morbidity from esophagectomy remains high at 30–60% (5-12). Traditionally, esophagectomy is performed via 2–3 large incisions via trans-abdominal [transhiatal (TH)], transthoracic [Ivor Lewis (ILE)] or three-field (McKeown approach) (13-18). The transhiatal approach is performed with an abdominal and left neck incision and esophageal to gastric anastomosis is performed in the left neck. Whereas ILE is performed using an abdominal incision and a right posterolateral thoracotomy incision with anastomosis performed within the right chest. The McKeown approach begins in the right chest, then progresses to the abdomen with anastomosis performed in the left neck.

The utilization of minimally invasive techniques for esophageal resection (MIE) offers some potential advantages over the conventional open esophagectomy. Some authors

have demonstrated faster recovery times, decrease in blood loss, decrease in post-operative morbidities and shorter length or hospitalization, with comparable oncologic outcomes (19). Retrospective reviews have demonstrated MIE does not compromise oncologic principles and is safe compared to traditional open esophagectomy for esophageal cancer (20-24). Moreover, the Ivor Lewis approach when performed via a minimally invasive approach has the potential to substantially reduce pulmonary complications, a significant morbidity associated with the open approach.

The evolution of surgery to include robotics has expanded the capabilities of performing complex operations via minimally invasive techniques. The application of robotic technology to esophagectomy is proving to have some advantages over conventional minimally invasive techniques such as an increase accuracy in dissection through improved visualization via 3-dimensional camera and improved maneuverability through articulation of instruments (25). The utilization of thoracoscopic, laparoscopic, and robotic approaches to esophagectomy have shown to result in equivalent oncologic outcomes compared to open techniques (26-29) with some authors demonstrating reductions in post-operative morbidity (30,31).

Methods

This study was approved by the institutional review board at Sarasota Memorial Hospital and deemed as exempt (IRB#15-onc-23). A query was performed utilizing PubMed with keywords "open esophagectomy, minimally invasive esophagectomy, robotic esophagectomy, Ivor Lewis esophagectomy, trans-hiatal esophagectomy and trans-thoracic esophagectomy" to identify existing peer reviewed manuscripts reporting outcomes associated with open, minimally invasive and robotic esophagectomy. One-hundred and fifty-seven manuscripts were identified and fifty-one were included in this review.

Transthoracic *vs.* transhiatal approach

In the 1990s, research was conflicted on whether the transhiatal esophagectomy or the transthoracic (Ivor Lewis) esophagectomy was superior. Bolton *et al.* investigated 55 patients between 1981 to 1990 who underwent trans-thoracic or trans-hiatal esophagectomy. They found the transhiatal approach had significantly lower operative mortality, lower cardiopulmonary complications and a shorter ICU stay (32). However, Jauch *et al.* in their series of 49 patients between 1982 to 1989 found no significant difference in mortality or overall survival rates between trans-hiatal *vs.* trans-thoracic esophagectomy but they did demonstrate an increase in anastomotic leak in the trans-hiatal group (33). Several additional studies published between 1993 and 1996 corroborated these findings that trans-hiatal and trans-thoracic approach are very similar in terms of postoperative complications, hospital mortality, and overall survival rates (34,35).

More recently it has been suggested that transhiatal approaches have a statistically significant increase in rates of anastomotic leak. Homesh *et al.* in 84 patients, 43 receiving a transhiatal esophagectomy and 41 receiving a transthoracic esophagectomy for esophageal cancer; They reported no significant difference in ICU stay, blood transfusions and mean hospital stay. However the transhiatal approach had a much higher rate of anastomotic leak compared to transthoracic esophagectomy; 21% *vs.* 12%, P=0.001 (36). Klink *et al.* specifically investigated patients with cancer of the middle and lower third of the esophagus with transhiatal versus transthoracic esophagectomy. They also discovered lower rate of anastomotic leak in the transthoracic group, along with decreased incidence of wound infections, recurrent laryngeal nerve injury and hospital stay (37). In addition, patients with T3 N1 tumors, Kutup *et al.* demonstrated that TTE achieved a higher rate of R0 resections, a higher lymph node yield, and resulted in a prolonged survival than THE (38). The best approach to esophagectomy continues to be up for debate.

Open versus MIE

A propensity score matched analysis performed on 1,727 patients who underwent open or minimally invasive esophagectomy for esophageal cancer demonstrated an increase in surgical re-intervention and anastomotic leaks in the MIE group (39). This study however had significantly higher complications in both groups compared to historical data (19,20,35,40). Most studies since then have found no significant difference or decrease in post-operative outcomes with the minimally invasive approaches. The E2202 study showed feasibility and safety of performing MIE, with 30-day mortality of 2.1%, anastomotic leaks 8.6%, and 3-year overall survival of 58.4% (19). Maas *et al.* also demonstrated feasibility with no difference between open verses MIE with regards to post-operative morbidity, oncological outcome or 5-year survival. The MIE group did

have a statistically significant shorter hospital stay than the open esophagectomy group (41).

Bierre *et al.* conducted one of the first randomized trials of MIE versus open esophagectomy (42). In the TIME trial, 59 patients were randomized to the MIE group and 56 patients were randomized to the open esophagectomy group. Open esophagectomy demonstrated higher pulmonary infection rates; 29% *vs.* 9%; [relative risk (RR) 0.30, 95% CI: 0.12–0.76; P=0.005]. Length of hospital stay was also lower in MIE patients (11 *vs.* 14 days; P=0.044). With regards to in-hospital mortality, two patients in the minimally invasive group died from aspiration and mediastinitis after anastomotic leakage and a single patient in the open esophagectomy group died from anastomotic leakage. In a 3-year follow up of Biere's TIME trial participants' quality of life, MIE demonstrated superiority for global health, physical component, and pain (43). A small randomized controlled trial by Schoppmann *et al.* of 62 patients corroborated these results by demonstrating improved post-operative morbidity, transfusion rates and pulmonary complications in the MIE group versus the open cohort (44). Guo *et al.* has also confirmed decrease length of hospital stay and fewer pulmonary infections in MIE (45).

In 2016, Sihag *et al.* queried the Society of Thoracic Surgeons National Database to determine outcomes of MIE versus open esophagectomy (46). The analysis compared both open transthoracic (n=1,291) and transhiatal (n=214) against minimally invasive Ivor Lewis esophagectomy (n=600) patients. Morbidity and mortality were similar between open and MIE. However, MIE was associated with longer median operative times (443.0 *vs.* 312.0 minutes; P<0.001), shorter length of hospitalization (9.0 *vs.* 10.0 days; P<0.001). Patients who underwent MIE had increased rates of empyema (4.1% *vs.* 1.8%; P<0.001) and re-operation (9.9% *vs.* 4.4%; P<0.001). Patients undergoing open esophagectomy had increased rates of post-operative transfusions (18.7% *vs.* 14.1%; P=0.002), ileus (4.5% *vs.* 2.2%; P=0.002) and wound infections (6.3% *vs.* 2.3%; P<0.001). Propensity score-matched analysis corroborated these findings. Yerokun *et al.* confirmed these results in an analysis of the National Cancer Database (47). They identified 4,266 patients and 1,308 (30.6%) underwent minimally invasive esophagectomy. Minimally invasive approaches were more often performed at academic centers or cancer centers. Additionally, MIE patients had shorter hospital stays (10 *vs.* 11 days; P=0.046) and more lymph nodes retrieved (15 *vs.* 13; P=0.016). There were equivalent R0 resections, 30-day mortality, and readmissions. There were no differences in survival between the matched groups at 3 years.

A meta-analysis of 48 studies by Zhou *et al.* comparing 14,311 patients undergoing MIE and open esophagectomy demonstrated that compared to open patients, MIE patients experienced less pulmonary complications, pulmonary embolism, in-hospital mortality, and arrhythmias, with no differences in leakage from the anastomosis (48). The evidence has resulted in a push toward using a minimally invasive approach as the standard of care for esophagectomy.

Hybrid approach

There have been few studies on a hybrid approach to esophagectomy. Woodard *et al.* investigated the feasibility and safety of hybrid esophagectomy in 131 patients, demonstrating 30- and 90-day mortality rates of 0.8% and 2.3% respectively, and overall survival at 1, 3 and 5 years of 85.9%, 65.3% and 53.9% (49). Briez *et al.* further investigated the implication of a hybrid approach to esophagectomy on pulmonary complications. They discovered that post-operative pulmonary complications were much less in hybrid approach than open, 15.7% *vs.* 42.9%, P<0.01 (50). The hybrid approach is feasible with better outcomes than open esophagectomy but has not proven to be superior to MIE in hospital mortality or morbidity.

Esophagectomy volume and outcome

While the type of operation performed can dictate patient outcomes, equally as important is the experience and number of esophagectomies performed by the surgeon. The previously discussed TIME trial by Bierre *et al.*, reported that patients who underwent esophagectomy had an improvement in morbidity and mortality if they had operations performed by high volume surgeons regardless of open or minimally invasive technique. Derogar *et al.* in a population-based cohort study of 1,335 patients with esophageal cancer undergoing esophagectomy from 1987 to 2005 confirmed these findings. They found a 23% reduction in mortality when esophagectomy was performed by high volume surgeons which was independent of hospital volume (51).

Robotic approaches to esophagectomy

The application of robotics in surgery has shown the

potential to increase accuracy in dissection through improved maneuverability and visualization while minimizing post-operative recovery time and blood loss. Robotic assisted Ivor Lewis esophagectomy is a technique with some potential advantages over conventional laparoscopic and thoracoscopic approach to esophagectomy. Robotic arms have the ability to articulate more than even a surgeon's capability. Resultantly, these movements closely mirror open surgical techniques. It is these potential benefits that has led to a significant increase in the utilization of robotics for esophageal resection over the last 5 years. Although there is the implication of significant increase in cost of utilizing the robotic for esophageal resection, these costs may be offset from decreased blood loss, morbidity, and length of hospitalization (52).

Outcomes with robotic approaches to esophagectomy

Robotic approach to esophagectomy has proven safe and feasible since its beginning. Dunn *et al.* investigated outcomes of 40 patients who underwent transhiatal robotic esophagectomy demonstrating practicality of robotic esophagectomy. Median operative time and blood loss were 311 minutes and 97 mL and the median length of hospital stay was 9 days. R0 resection achieved was 94.7% and 30-day mortality was 2.5% (25). Moreover, Puntambekar displayed feasibility in utilizing robotics for the transthoracic approach, with mean operative time of 204.94 minutes, mean hospital stay of 10 days, and 19.28% of postoperative complications (52). In a series of 147 robotic assisted Ivor Lewis esophagectomies (RAIL) by Meredith *et al.* RAIL had similar operative times to esophagectomies performed via other minimally invasive approaches; median time of 346 minutes versus median time of 320 minutes respectively (53,54). Meredith *et al.* also achieved 100% R0 resection with median nodal harvest of 20.4. The median length of stay in the ICU and hospital stay were 2 days and 9 days respectively and the complication rate was 25.2% (53).

Coker *et al.* reported that RAIL had overall fewer complications (cardiovascular, wound, pulmonary, and overall) compared to open Ivor Lewis esophagectomies (55). Additionally, length of hospitalization was significantly lower in the RAIL versus open. However, in a series by Mori *et al.* comparing robotically-assisted transhiatal esophagectomy (RATE), a transthoracic approach resulted in increased pulmonary complications (56). Unfortunately, there were only 22 patients in the robotic transhiatal group and these were compared to conventional transthoracic not robotic esophagectomies. Additionally, aspiration events, which are known to be higher in the TH approach, were not reported in this series.

As the length of operation for RAIL continues to decrease, the rates of pulmonary complications also are reduced as demonstrated by Hernandez *et al.* who reported decreasing rates of pneumonias as operative times decreased (57). Conversely, robotic assisted transhiatal esophagectomy has increased rates of major complications compared to robotic Ivor Lewis approach. These include increased wound complications, a higher incidence of recurrent laryngeal nerve injuries, aspiration, and anastomotic leaks (25,56,58,59). Other authors have confirmed anastomotic leaks, pneumonias, wound complications, and any complication were all decreased in the cohort of patients who had robotic Ivor Lewis esophagectomy (56).

While the R0 resection rates for RATE and RAIL may be comparable, the ability to perform an extended lymphadenectomy of the mediastinal lymph nodes which may have staging and survival implications are benefited by patients undergoing RAIL (31,52,55,58). Lymph node dissection in RATE is limited by the robot's ability to fit through the diaphragmatic hiatus and resultant limited view into the thoracic cavity from the abdomen. Therefore, the superior extent of lymph node dissection and subsequent lymph node harvest in RATE is inferior compared to RAIL. In comparison of our own data with minimally invasive esophagectomy, RAIL was superior to other techniques with median lymph node retrieval for open IL, RAIL, MIE IL, and MIE transhiatal being 10, 20, 14, and 9, P=0.001 (40).

Conclusions

There have been significant improvements made in the surgical resection of esophageal cancer from the highly morbid open esophagectomy. The advancements in MIE have improved post-operative outcomes significantly to result in shortened length of hospitalization, fewer pulmonary complications, and improved quality of life. Most importantly, there is no compromise in oncologic outcomes such as nodal harvests, margin status, and survival compared to open approaches. There is still some debate on the benefits of transthoracic versus transhiatal approaches, with most recent evidence demonstrating transthoracic to

be superior. With the added benefits of robotic surgery, esophagectomies have evolved even further. The robotic assisted Ivor Lewis esophagectomy demonstrates similar outcomes compared to other MIE techniques. While there is a significant learning curve associated with robotic assisted Ivor Lewis esophagectomy, as the number of cases performed increases, the post-operative complications and length of operation and is decreased. More data is needed to compare robotic assisted techniques to existing minimally invasive techniques in order to determine the best approach for esophageal resection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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