SM Vascular Medicine

Review Article

From Open Surgery to Robotics: The Evolution of Esophageal Cancer Treatment and Its Impact on Patient Outcomes

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Abstract

Esophageal cancer, the seventh most common cancer in the world, exhibits massive geographical variation. Its incidence is highest in China, while Central America and Africa have the world's lowest rates. The two histological subtypes have different distributions. Squamous Cell Carcinoma (SCC) is the dominant form in the high-burden areas, while Adenocarcinoma (AC), is more evenly distributed in the Western world. Despite the multidisciplinary progress made in treating this disease, the morbidity that follows esophagectomy remains staggeringly high. Estimates place the figure at the high end of the 30-60% range. Meanwhile, the surgery itself has undergone a revolution from old, traditional methods (like the trans hiatal esophagectomy and Ivor Lewis esophagectomy) to a combination of minimally invasive techniques and surgical robots that reduce trauma, improve recovery time, and cut down the complication rate.

Keywords: Esophageal Cancer; Minimally Invasive Surgery; Robotic Surgery; ERAS Protocols; Endoscopic Surgery; Open Surgery.

INTRODUCTION

Esophageal cancer is ranked as the seventh cancer with one of the highest incidences, with China having the highest incidence and Central America, Middle and Western Africa the lowest incidence. Mortality rates have the same epidemiology as well and have placed Esophageal cancer as the sixth in the overall mortality [1]. There are two main histological subtypes of esophageal cancers such as Squamous Cell Carcinoma (SCC) and Adenocarcinoma (AC). It has been observed that areas with higher epidemiological burden mainly consist of the SCC subtype. Adenocarcinoma is mainly encountered in the esophageal gastric junction tumors [2]. The overall survival depends on the resection of the esophagus. The current treatment strategy involves many different modalities surrounding the perioperative period. Adequate nutrition, chemoradiation for locally advanced diseases, symptomatic treatment, as well as physiotherapy, consists of some of the main aspects of standard care. It is important to note, however, that even though the introduction of multidisciplinary treatment has significantly improved the survival rates for patients with resected esophageal cancer, the morbidity after esophagectomy still remains as high as 30-60% [3,4].

Evolution of Surgical Techniques

Traditionally, Trans Hiatal Esophagectomy (THE) is a two – incisional surgical procedure involving the removal of the esophagus through an abdominal and cervical incision, avoiding thoracic access. The technique typically consists of a "blind" dissection of the mid-esophagus followed by an esophago-gastric anastomosis in the left cervical area and mediastinal lymphadenectomy [5]. It has been proven highly beneficial, especially in patients with early-stage disease or severe comorbidities where more invasive thoracic procedures may not be tolerated. However, the technique can lead to increased blood loss, and therefore tracheal and azygous injuries, due to its "blind" dissection of the mid-esophagus [6]. Ivor Lewis Esophagectomy (ILE) is a two – incisional surgical technique consisting of an abdominal incision and a right posterolateral thoracotomy. Unlike THE, anastomosis in this case is performed in the right chest area and this increases the likelihood of intrathoracic complications. It is a procedure of choice, especially for middle or lower esophageal cancer, followed by two – field lymphadenectomy [7]. McKeown esophagectomy is a three – field surgical approach. It begins with a right thoracotomy, moving to an abdominal incision, and ending with an anastomosis in the left cervical area, Due to the highly invasive nature, this procedure has a high risk of complications, and a high mortality rate compared to the other techniques [8,9]. The evolution towards Minimally Invasive Surgery (MIS) began as a response to the limitations of traditional approaches. MIS techniques aim to reduce surgical trauma, leading to decreased blood loss, decreased inflammatory response, shorter recovery times, and lower rates of postoperative complications, especially respiratory infections and post-operative deep vein thrombosis. Moreover, through the endoscopic resection, lymphadenectomy is significantly improved, fewer cases of positive margins have been documented, and the visualization of the operating field is more accurate [10,11]. The main limitation of the minimally invasive technique is the limitations of the view of the surgical field dure to its own dimensional view and narrow space of the movement inside the mediastinal zone. Moreover, there is a risk of liver damage, puncture of the great intrathoracic vessels, azygos vein and the recurrent laryngeal nerve or lung parenchyma mainly due to the introduction of the first trocar into the abdominal space. Most of these incidents take place during the "stomach mobilization" part of the operation and frequently correspond to the "learning curve" of the procedure [11]. Appropriate patient selection is essential for Minimally Invasive Isophagectomy (MIE), thereby it is of great importance to highlight its indications in the case of esophageal cancer: <5 cm lesion diameter or >5 cm lesion diameter but confined within the esophageal lumen, absence of pleural adhesions, early-stage esophageal cancer or later stage cancer that does not invade the full thickness of the esophagus or tumors with good response to neoadjuvant chemoradiation, absence of local lymph node invasion or distant metastasis [12]. Additionally, a few contraindications can be mentioned, such as patients unable to bear the stressful peri-operative environment, inadequate pre-operative evaluation and management,

Submitted: 21 March 2025 | **Accepted:** 09 May 2025 | **Published:** 10 May 2025

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Citation: Hamza N, Ana-Elena Zaharia J, Fadi AV, Zsoldos MR, Zoghieb (2025) From Open Surgery to Robotics: The Evolution of Esophageal Cancer Treatment and Its Impact on Patient Outcomes. SM Vasc Med 5: 6.

personal history of thoracic surgery, and patients with the following risk factors: old age, decreased functional status, impaired general health, hepatic or renal dysfunction, diabetes mellitus, advanced tumor stage. Robot assisted esophagectomy provides a three-dimensional view and the freedom of the surgical instrument maneuvers, and reduction of the learning curve of MIE. Due to the novelty of the technique and the lack of clinical research data in the robotic esophagectomy there are limited data regarding the efficacy over the long-standing traditional approaches. However, it has been shown to offer increased precision in dissection, a shorter surgical duration, minimal blood loss, and a significantly reduced hospitalization stay [13].

Perioperative and Enhanced Recovery Strategies

The perioperative and enhanced recovery strategies are imperative in patients with esophageal surgeries. Malnutrition is common in esophageal cancer patients. A systematic review of the literature showed that the rate of malnutrition was between 30-40%, with total variation being between11.9% to 88% [14]. The efficacy between the enteral and parenteral nutrition have been tested and researched and based on evidence it's been proven that the enteral nutrition is more beneficial and efficacy than parenteral. The main factors that were analyzed to test the efficacy were the albumin values, duration of the hospital stays, the duration of the systemic inflammatory response, patient complications, and the time to the first fecal passage. The results showed with clinical significance ($p<0.05$) that the enteral nutrition group passed fecal matter earlier, required a smaller dose of albumin infusion, and the duration of the systematic inflammatory response and hospitalization duration were shorter than the parenteral group [15]. There have been studies which evaluated the hospital stay and how fluid and electrolyte disorders and discharge disposition different between the enteral and parenteral nutrition. Patients undergoing enteral nutrition stayed 3.07 days longer in the hospital with high significance ($p=0.001$), while parenteral patients stayed 9.07 days longer with high significance ($p<0.001$). As for fluid and electrolyte disorders, it was found that parenteral nutrition patients (53.77%) were at a higher risk than enteral (43.07%) with a $p<0.001$. For discharge disposition, it was found that none (0%) of the enteral patients went to a skilled nursing facility, while 55 patients (5.19%) of the parenteral patients went ($p<0.001$) [16].

The CROSS Trial, which primarily included patients with adenocarcinoma (75%), demonstrated a 5-year overall survival rate of 47% when treated with a combination of paclitaxel, carboplatin, and radiotherapy (41.4 Gy/23 fractions). In contrast, the MAGIC Trial, focusing mainly on gastric adenocarcinoma with 11% junctional and 14% lower esophageal adenocarcinoma, reported a 5-year overall survival rate of 36% for patients receiving combined therapy (epirubicin, cisplatin, and 5-FU before and after surgery) compared to 23% for surgery alone. Similarly, the ACCORD Trial, which included 64% junctional adenocarcinoma and 11% lower esophageal adenocarcinoma, showed a 5-year overall survival rate of 38% for patients treated with cisplatin and 5-FU (2 cycles preoperatively and 4 postoperatively) compared to 24% for surgery alone. Lastly, the OEO2 Trial, with 66% adenocarcinoma, reported a 5-year overall survival rate of 23% for patients receiving cisplatin and 5-FU (2 cycles preoperatively) compared to 17% for surgery alone. These trials collectively highlight the survival benefits of combined chemoradiotherapy or chemotherapy over surgery alone in the treatment of esophageal and gastric adenocarcinomas [14]. Risk assessment for esophageal cancer patients can be conducted using several methods such as the Charlson Comorbidity Index, the American Society of Anesthesiologists Score, and Cardiopulmonary exercise testing.

The Charleson comorbidity index revealed that parenteral nutrition leads to a higher Charleson comorbidity score compared to enteral. There is a significant difference between $p<0.001$ with 22.63% of enteral nutrition patients having a score of 2 while parenteral patients made up 21.23%, and 77.37% of enteral nutrition patients had a score of 3+ while parenteral patients had 78.77% [16].

A study compared the Anesthesiologist's Score for patients undergoing transthoracic and trans hiatal esophagectomy. It was found that 34.6% of high-risk transthoracic esophagectomy patients had an ASA 3 score and 0.4% had ASA 4, while 40.1% of high-risk trans hiatal esophagectomy patients had ASA 3 and 2.6% had ASA 4. There is a high statistical significance $p<0.001$. Higher-risk patients had higher rates of higher ASA scores [17]. Cardiopulmonary exercise testing is a crucial tool to assess risk since cardiovascular illness is a common complication of esophageal cancer. Based on a prospective cohort study it was found that the most reliable predictor for major cardiovascular complications is an anaerobic threshold under 9.5 ml/kg/min and <11 ml/kg/min for minor cardiovascular complications [18] (Table 1).

Many factors are taken into consideration in ERAS protocols which is detailed in the Mayo Clinic MERIT protocols such as cardiac blood analysis (if risk for atrial fibrillation is present), discontinuing chest drainage, activity goals (8+ hours out of bed, head at over 30 degrees,

Table 1: The Association between Structures and Important Factors

Factors	Studies found	Odds Ratio	95%Confidence Interval	Association: yes, or no?
Anastomotic leakage	7	0.78	0.62-0.97	No
Cardiovascular disease	7	1.62	1.22-2.16	Yes
Diabetes	7	1.62	1.20-2.19	Yes
Wide Gastric Conduit	4	0.98	0.37-2.56	No
Mechanical anastomosis	4	0.84	0.47-1.48	No
Colonic Interposition	3	0.20	0.12-0.35	No
Trans hiatal approach	3	1.16	0.81-1.64	No

ambulation 4-5 times a day, enteral nutrition, and dietary consultations [19]. The protocols were supported by a meta-analysis that looked at 2042 patients. It was demonstrated that the ERAS group had fewer non-surgical and pulmonary complications than the standard care group, with an RR of 0.71, 95% CI 0.62-0.80, p<0.00001 for ERAS compared to an RR of 0.75, CI 0.60-0.94, p<0.01 for standard care. There were no significant differences in surgical complications [20]. Further findings showed that there is less postoperative pain, less operative trauma, and shorter hospital stays for patients that undergo minimally invasive procedures. These findings align with the ERAS protocol goals that aim to reduce morbidity and improve patient recovery. It was also found that patients that underwent minimally invasive esophagectomy compared to open esophagectomy had fewer pulmonary complications. 17.1% from the minimally invasive esophagectomy group compared to 22.6% from the open esophagectomy group [21]. For pain management NSAIDs and COX-2 selective inhibitors should be used over other COX inhibitors and opioids. As for post-operative pain, there was no difference found between the use of systemic and epidural analgesia when looking at pain scores [22].

Complications found for post-esophageal cancer surgery are anastomotic leaks, strictures, and pulmonary complications. Anastomotic leaks have been associated with several comorbidities and lifestyle choices and the statistical significance between anastomotic leaks and BMI (p<0.047), congestive heart failure (p<0.001), coronary artery disease (p<0.002), peripheral artery disease (p<0.001), hypertension (p<0.001), preoperative chemotherapy (0.02), history of diabetes (p<0.001), renal insufficiency (p<0.001), and smoking (p<0.001) [23].

The studies analyzed various factors and their associations with outcomes, reporting Odds Ratios (OR) and 95% Confidence Intervals (CI). Anastomotic leakage showed no significant association (OR 0.78, 95% CI 0.62–0.97), while cardiovascular disease (OR 1.62, 95% CI 1.22–2.16), and diabetes (OR 1.62, 95% CI 1.20–2.19), were significantly associated with adverse outcomes. Factors such as wide gastric conduit (OR 0.98, 95% CI 0.37–2.56), mechanical anastomosis (OR 0.84, 95% CI 0.47–1.48), colonic interposition (OR 0.20, 95% CI 0.12–0.35), and the trans hiatal approach (OR 1.16, 95% CI 0.81–1.64), did not show significant associations. These findings suggest that while cardiovascular disease and diabetes are linked to poorer outcomes, the other factors examined do not demonstrate a significant impact [24].

There were several comorbidities identified, some of which being cardiovascular disease, COPD, and diabetes. Conversely, there is no statistically significant link between gender, preoperative stay, tumor-specific variables, blood values like hemoglobin and albumin, respiratory values like FEV1, FEV1%, FEV/FVC, MVV was found [23].

Advances in Surgical Outcomes and Reconstruction

Throughout the years, reconstruction techniques have been developing, but the main two for esophageal cancer remain the gastric conduit and the colonic interposition. Gastric conduit has a shorter operating time with a lower risk of anastomotic leakage, which in this case only requires one anastomosis. It also has a better blood supply (the gastroepiploic artery), can be used in most patients, has a lower risk of graft failure, and has fewer post-operative complications in general. However, it still showed other post-operative complications such as the occurrence of anastomotic strictures, gastric tube stenosis, hemorrhages, and fistula formation [25].

Colonic interposition has a lower reflux and dumping syndromes, has a really good long-term functionality, it could be used in patients that do not have a viable stomach, and it provides an adequate length for reconstruction. On the other hand, it needs a longer operative time, results in greater blood loss, a higher incidence of anastomotic leakage, and an increased morbidity risk [26].

Recently tissue engineering has been used to reduce the usage of materials from the patients, which reduces the post-operative morbidity and mortality rates.

As for the scaffolds, there are two types, a single-layer scaffold and a multi-layer scaffold.

There are two main categories of scaffold materials that can be used: Acellular matrix (small intestinal submucosa, urinary bladder submucosa, and esophageal mucosa), and polymer materials (poly (3-hydroxybutyrate-co-3-hydroxyvalerate), poly (l-lactide-co-ε-caprolactone), polylactide-poly (ε-caprolactone), polyurethane, polylactide). Another technique that showed good results in the scaffolds was the introduction of cells such as ECs, SMCs, and stem cells into the biomimetic single-layer scaffolds. Although a promising technology it still has its faults and needs to be further studied and improved to be able to use it in the treatment of esophageal cancer patients [30] (Table 2).

Future Directions in Esophageal Cancer Surgery

The future of surgery for esophageal cancer is evolving rapidly, with significant emphasis on recent advances in surgical techniques and perioperative management. Recent developments in thoracoscopic surgery and imaging systems have significantly improved the invasive nature of these procedures. Advances in 3D imaging with 4K UHD cameras and 2D systems with 8K cameras have enhanced the understanding of thoracic anatomy, allowing for more precise surgeries. Another advancement for esophageal cancer treatment is robot-assisted thoracoscopic esophagectomy, their only downfault is expense and training. Technological innovations such as preoperative 3D computed tomographic angiography and intraoperative real-time navigation systems are aiding in safer surgeries which increase surgical outcome efficacy. Other advancements include MRI-guided systems, virtual reality simulators, sentinel node navigation, are all techniques that will lead to better surgical patient outcomes [31].

A case study was analyzed as a new way to treat esophageal cancer in a patient with a Right Aortic Arch (RAA), which is a rare congenital defect. The patient received neoadjuvant immunotherapy using sintilimab, a PD-1 inhibitor, which reduced the tumor size to help aid in the outcome of minimally invasive esophagectomy. In addition to the neoadjuvant, 3D reconstruction technology was used to aid in preoperative planning. This case demonstrated how combining immunotherapy with advanced imaging can help manage esophageal cancer in patients anatomically challenging cases and suggests that this should be further researched in future studies as a superior method for managing esophageal cancer [32].

Artificial Intelligence (AI) is enhancing the diagnostic accuracy, procedural and screening efficacy of the gastrointestinal endoscopy which results in better clinical outcomes. Each AI system works differently but for example in endoscopy, it has three key areas: Computer-Aided Detection (CADe) for identifying abnormalities, Computer-Aided Diagnosis (CADx) for lesion classification and Computer-Aided Quality assessment (CADq) for procedural precision. It is used clinically in various organs, and helps detect metaplasia and neoplasia in the esophagus, stomach, small and large bowel. More specifically, in the esophagus AI detects Barrett's esophagus and esophageal squamous carcinoma with precise sensitivity. Artificial intelligence also significantly improves polyp detection and histologic analysis, boosting adenoma detection rate. AI has improved early diagnostic accuracy which positively impacts the course of management by avoiding invasive cancer removal procedures. Artificial intelligence's future will continue to evolve in everyday routine clinical practice, because of its superior performance [33].

Chemotherapy drugs like Trastuzumab have demonstrated clinical efficacy, for HER2-positive cancers, others like pertuzumab and trastuzumab emtansine require further investigation to determine their potential benefits. This article also goes into detail about other promising

Table 2: Clinical Trials and Studies Comparing Different Surgical Techniques

Technique	Study	Method	Results	Conclusion	Reference
Intrathoracic anastomosis	ICAN trial	Patients were randomly assigned (1:1) to transthoracic MIE with intrathoracic or cervical anastomosis.	Among the 122 patients studied, 15 experienced anastomotic leakage. The treatment approach was associated with fewer severe complications, a lower incidence of recurrent laryngeal nerve palsy, and an overall better quality of life for the patients. These findings suggest that the intervention may offer improved safety and patient outcomes compared to alternative methods.	Intrathoracic anastomosis showed better results than when using the cervical anastomosis technique.	[27]
Cervical anastomosis	ICAN trial	Patients were randomly assigned (1:1) to transthoracic MIE with intrathoracic or cervical anastomosis.	Anastomotic leakage necessitating reintervention occurred in 39 of 123 patients with cervical anastomosis.	Although a valid technique but it showed worse results than the intrathoracic anastomosis technique.	[28]
Reinforcement of esophageal anastomosis with a Biologic, Degradable, Extracellular Matrix	A Phase II Trial Evaluating Esophageal Anastomotic Reinforcement with a Biologic, Degradable, Extracellular Matrix after Total Gastrectomy and Esophagectomy.	ECM wassurgically wrapped circumferentially around the anastomosis, for selected patients that underwent total gastrectomy and esophagectomy.	In the study, anastomotic leaks wereobserved in 6 out of 66 patients, while stenosis requiring invasive treatment occurred in 8 out of 66 patients. Additionally, 10 out of 66 patients reported issues with their ability to eat. Notably, the use of extracellular matrix (ECM) did not result in any reported side effects. These findings highlight the occurrence of postoperative complications such as leaks, stenosis, and eating difficulties, while underscoring the safety of ECM usage in this context.	It is a feasible and safe technique but did not show a statistically significant decreasein anastomotic leak.	[29]

future targeting therapies such EGFR-, VEGF-, c-Met-, and mTOR. Studies show that these clinical investigations for improved treatment approaches are key for managing esophageal and gastric cancers. New and improved clinical trials such as The Cancer Genome Atlas (TCGA) project are working to classify gastric malignancies into subtypes based on mutation profiles, may lead to more specific and personalized treatment approaches. New clinical trials and research on biomarkers and immunotherapies tailors to better patient selection, optimizing combination therapies, and exploring molecular targets to improve therapeutic outcome [34].

DISCUSSION

The way we manage esophageal cancer has really evolved over the last few decades, especially when it comes to surgical techniques and the care we provide around surgery. While traditional methods like trans hiatal and Ivor Lewis esophagectomy have been effective, they often come with significant risks and complications. Thankfully, the move towards minimally invasive and robot-assisted surgeries has helped tackle many of these issues, leading to less surgical trauma, better visualization, and quicker recovery times. Still, we face challenges like anastomotic leaks, strictures, and pulmonary complications, which means we need to keep refining our surgical techniques and perioperative care strategies. Speaking of perioperative care, things like nutritional support and Enhanced Recovery After Surgery (ERAS) protocols have been crucial in boosting patient outcomes. Research shows that enteral nutrition is more effective than parenteral nutrition, leading to shorter hospital stays, less systemic inflammation, and fewer complications. Plus, enhanced recovery protocols that focus on early mobilization and effective pain management have made a real difference in reducing complications and improving patients' quality of life. Clinical trials such as CROSS, MAGIC, ACCORD, and OEO2 have consistently shown that combining chemoradiotherapy with surgery offers better survival rates than surgery alone, highlighting the need for a team-based approach. Innovations in reconstruction techniques, like gastric conduit and colonic interposition, have also improved functional outcomes, although each method has its own drawbacks. Looking ahead, emerging technologies like 3D imaging, robotic surgery, and artificial intelligence are set to transform diagnostics and surgical accuracy, bringing new hope for personalized treatment options.

CONCLUSION

Esophageal cancer is still a tough battle, with high rates of illness and death, even though we've made some real strides in treatment. The way we perform surgeries has come a long way, shifting from traditional open methods to more advanced minimally invasive and robot-assisted techniques, which have led to better outcomes for patients. However, challenges like anastomotic leaks and strictures are still around. On the care side, focusing on things like enteral nutrition and ERAS protocols has really helped speed up recovery and cut down on complications. Clinical

trials have highlighted how crucial combined chemoradiotherapy is for boosting survival rates. Plus, new technologies like 3D imaging, robotic surgery, and artificial intelligence are showing a lot of promise for the future, potentially allowing for more tailored and precise treatments. As research keeps pushing the envelope with new therapies and fine-tuning existing methods, bringing these innovations into everyday clinical practice will be key to improving outcomes and enhancing the quality of life for those facing esophageal cancer.

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