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Review

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Comparison of conventional and robotic-assisted minimally invasive esophagectomy for esophageal cancer

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Abstract

Conventional minimally invasive esophagectomy (MIE) and robotic-assisted MIE (RAMIE) have increased in prevalence across the world for the management of esophageal cancer. Both minimally invasive modalities have demonstrated decreased morbidity, with preservation of oncologic outcomes, when compared to open esophagectomy. A limitation of conventional MIE is the use of rigid instruments with 2D visualization leading to a prolonged learning curve and extended operative times. RAMIE offers both improved visualization with 3D video capable of magnification and full dexterity with wristed instruments. To date, retrospective and randomized controlled trials demonstrate overall higher harvest during lymphadenectomy by RAMIE compared to MIE, though more studies are needed to determine definitive impact on oncologic outcomes and long-term survival. RAMIE showed superiority for lymphadenectomy after neoadjuvant therapy and for bilateral recurrent laryngeal nerve (RLN) lymphadenectomy with decreased rates of RLN paralysis. Current data suggests no overall cost difference between the two modalities. Ongoing studies will further clarify the role for RAMIE in esophageal adenocarcinoma (EA) and the outcomes of robotic/MIE hybrid techniques.

Keywords: Esophageal cancer, robotic-assisted minimally invasive esophagectomy, minimally invasive esophagectomy, esophageal cancer surgery

INTRODUCTION

An estimated 500,000 people die each year from esophageal cancer with another 600,000 new cases diagnosed each year, according to the Global Cancer Observatory[1]. Esophageal cancer remains challenging to treat with a 5-year survival of 21% in the United States and only a 5% increase in survival over the last 20 years[1,2]. There is geographic variation in the histological subtype of esophageal cancer, with esophageal squamous cell carcinoma (ESCC) more common in Eastern societies and esophageal adenocarcinoma (EA) more prevalent in Western societies. Treatment for esophageal cancer remains reliant on upfront resection for early-stage cancer and neoadjuvant chemoradiation followed by resection for resectable, locoregionally advanced cancer (cT2-4aN0-3M0 and T0-1 N+ M0)[3,4]. Esophagectomy remains the mainstay of surgical management and is commonly performed by a transthoracic technique, the Ivor Lewis Esophagectomy or modified McKeown Esophagectomy, due to improved feasibility of mediastinal lymphadenectomy[5]. The Ivor Lewis esophagectomy, commonly performed in Western countries due to the higher incidence of distal EA, consists of a two-field thoracic and abdominal lymphadenectomy with an intra-thoracic esophagogastric anastomosis. The modified McKeown Esophagectomy, commonly performed in eastern countries due to the higher incidence of more proximally located ESCC, is a three-field lymphadenectomy procedure that adds a neck dissection, and the anastomosis is performed in the left neck.

Across all surgical subspecialties, minimally invasive techniques have been increasing to improve perioperative outcomes and reduce morbidity associated with resection. A recent Society of Thoracic Surgery database study analyzed the incidence and 5-year trends of esophagectomy in the United States. Of the 10,607 patients included, 54.3% underwent open esophagectomy, 33.2% underwent conventional minimally invasive esophagectomy (MIE), and 12.4% underwent robotic-assisted MIE (RAMIE). During the 5-year study period, there was a declining trend of open cases ($P < 0.0001$) and an increase of conventional MIE and RAMIE ($P < 0.0001$)[6]. When considering outcomes, the traditional invasive *vs.* minimally invasive esophagectomy (TIME) trial demonstrated that conventional MIE reduced the risk of perioperative complications compared to open esophagectomy and achieved satisfactory long-term oncologic outcomes[7,8]. However, conventional MIE is technically challenging, with potential for long learning curves that could put patients at risk of high morbidity complications[9]. Potential technological limitations include the two-dimensional view or the restriction of movement with laparoscopic and thoracoscopic instruments, particularly with straight instruments rotating on a fulcrum at the body wall. In contrast, the potential advantages of the robotic platform are a three-dimensional view with full dexterity and flexibility of the wrist joints. Similar to conventional MIE, RAMIE has demonstrated decreased perioperative complications compared to open esophagectomy, while preserving oncologic outcomes[10]. As conventional MIE and RAMIE increase in prevalence for the management of esophageal carcinoma, new evidence comparing the two modalities continues to emerge. We aim to review the current literature comparing RAMIE to conventional MIE and discuss future trials that will continue to shape the landscape of MIE.

CURRENT LANDSCAPE OF CONVENTIONAL MIE COMPARED TO RAMIE

Retrospective data

Numerous retrospective studies worldwide have compared conventional MIE and RAMIE outcomes[11-14]. However, most studies are limited by small sample size and retrospective data. The largest retrospective study to date is a single institution study from a high-volume academic center in the United States (University of Pittsburgh), conducted over a 7-year period[15]. The study included 246 propensity score-matched patients with RAMIE ($n = 65$) *vs.* conventional MIE ($n = 181$). All operations were completed using the Ivor Lewis esophagectomy technique. The study concluded there was no significant difference in the primary endpoints of overall survival and disease-free survival. The authors also found no significant

difference in perioperative outcomes including blood loss, operative time, anastomotic leak, complete resection rates, or postoperative complications. There was also no difference in readmission or mortality within 90 days. Notably, the only significant difference was in the oncologic resection, with more lymph nodes harvested in the RAMIE group (32 *vs.* 29, $P = 0.02$)[15].

A recent meta-analysis identified 18 studies comparing RAMIE and conventional MIE, with 17 retrospective studies and one randomized control trial (the RAMIE trial). The RAMIE trial will be covered in full detail later in this review as the only published randomized control trial comparing conventional MIE to RAMIE. The meta-analysis contained 2,932 patients with resectable esophageal cancer (92.88% squamous cell carcinoma, 29.83% neo- adjuvant therapy, 15.07% adjuvant therapy, and 38.93% stage III-IV). Studies included both the Ivor Lewis Esophagectomy and the modified McKeown Esophagectomy, along with hybrid approaches. A total of 1,418 underwent RAMIE and 1,514 underwent conventional MIE, with no significant difference in histology, stage, the use of neoadjuvant treatment, and the use of adjuvant treatment between the two groups. The meta-analysis also found no significant difference in perioperative outcomes between RAMIE and conventional MIE including no difference in blood loss, operative time, length of stay, or mortality within 90 days. In the postoperative outcomes, the two groups had similar outcomes except that RAMIE had a significantly decreased incidence of pneumonia[16]. This result was in accordance with recent studies suggesting a reduced risk of pneumonia with RAMIE due to the improved visualization, which may reduce injury of the lung parenchyma and pulmonary vagal nerves[17-21]. In terms of oncologic resection, RAMIE had a significant increase in total harvested lymph nodes [mean difference (MD) = 1.18; 95% confidence interval (CI): 0.06-2.30; $P = 0.04$), left recurrent laryngeal nodes (MD = 0.22; 5%CI: 0.09-0.35; $P < 0.001$) and abdominal lymph nodes (MD = 1.04; 95%CI: 0.19-1.89; $P = 0.02$)]. The findings of this meta-analysis highlight not only the increased number of total lymph nodes, but additionally, more lymph nodes along the recurrent laryngeal nerve (RLN) which are considered to be the most challenging with high morbidity. To date, this is the only meta-analysis comparing long-term outcomes including disease-free survival and long-term survival. Notably, this study found improved 3-year disease-free survival in the RAMIE group [odds ratio (OR) = 1.42; 95%CI: 1.11-1.83; $P = 0.006$)], which could be hypothesized to be related to the increased lymph node resection, but additional long-term oncology data will be needed to clarify this[16].

When examining long-term oncology data more closely, studies are limited. Single-center studies have found RAMIE to deliver similar long-term survival outcomes compared to other modalities[22]. When comparing outcomes between modalities, a National Cancer Database (NCDB) study found RAMIE to be superior[23]. The authors analyzed the overall survival of 5,170 patients who underwent esophagectomy from 2010-2017, with 428 undergoing RAMIE, 1,417 MIE, and 3,325 open esophagectomy. There were no significant differences between demographics or baseline characteristics between the three groups. When compared to RAMIE, there was an increased risk of death for those that underwent either MIE [hazard ratio (HR) = 1.19; 95%CI: > 1.00 to 1.41; $P < 0.047$)] or open esophagectomy (HR = 1.22; 95%CI: 1.04 to 1.43; $P < 0.017$). Findings suggest potential increased survival for patients undergoing RAMIE, though findings are limited by retrospective nature and lack of disease-specific mortality.

Upper GI International Robotic Association

Across the world, robotic esophagogastric surgery has been increasing, leading to the founding of Upper GI International Robotic Association (UGIRA) in 2017. UGIRA is a multicontinental group of robotic surgeons, striving to facilitate the worldwide implementation and advancement of robotic esophagogastric surgery. To provide quality control and gain deeper insights into outcomes, UGIRA established a comprehensive international registry for RAMIE. Using data from this registry, UGIRA provided a snapshot on transthoracic RAMIE for cancer between 2016 and 2019. During this period, 856 RAMIE

procedures were performed in centers worldwide (682 from Europe, 95 from Asia, 56 from North America, and 23 from South America). Most RAMIEs were performed as a 2-stage Ivor Lewis (n = 622, 73%) and a smaller percentage via a 3-stage McKeown approach (n = 234, 27%). The increased utilization of the 2-stage Ivor Lewis esophagectomy is likely reflective of the large number of European and American centers represented in the UGIRA consortium. Overall, robotic surgery was used in variable phases of the esophagectomies: in both the thoracic and abdominal phase (n = 386, 45%), only the thoracic phase (n = 415, 49%), or only the abdominal phase (n = 55, 6%)[24]. Moving forward, the URGIRA registry promises to provide real-time data on RAMIE to ensure appropriate implementation in diverse settings.

Completed randomized control trials comparing conventional MIE to RAMIE

RAMIE trial

The RAMIE trial represents the first randomized control trial comparing conventional MIE and RAMIE for esophageal squamous cell cancer. The trial was conducted across six centers in China over a 2-year period (2017-2019). Given the increased incidence of esophageal squamous cell cancer in Asia with primary tumors located in the proximal or mid esophagus, all cases were completed using a completely minimally invasive modified McKeown esophagectomy technique. A total of 358 patients were randomized to either RAMIE (n = 181) or conventional MIE (n = 177). There was no significant difference in demographics or illness severity between the two groups. RAMIE resulted in a shorter total operation time, with RAMIE taking 203.8 *vs.* 244.9 min for conventional MIE (P < 0.001). When broken down to the thoracic and abdominal portions, both portions of conventional MIE were longer [Thoracic: 84.2 *vs.* 111.6 min for conventional MIE (P < 0.001); Abdomen: 38.0 *vs.* 53.3 min for conventional MIE (P < 0.001)]. There was no significant difference in other perioperative outcomes including blood loss, conversion rate, postoperative complications, readmission, or mortality within 90 days. In terms of oncologic resection, there was no significant difference in R0 resection, pathologic disease severity, or lymph nodes resected. However, on post-hoc analysis when the groups were stratified by neoadjuvant therapy, the median number of retrieved thoracic lymph nodes and bilateral (right and left) RLN lymph nodes was significantly higher in patients who underwent RAMIE after neoadjuvant therapy (15 *vs.* 12, P = 0.016; 3 *vs.* 2, P = 0.033; 2 *vs.* 1, P = 0.041, respectively). RAMIE also demonstrated higher rates of achievement in resection of left RLN lymph nodes in neoadjuvant patients (79.5% *vs.* 67.6%, P = 0.001)[25]. The significant difference in lymph node resection after stratification by neoadjuvant therapy could once again highlight the benefit of the robotic platform with improved dexterity and three-dimensional visualization that could circumvent the scarring and friability associated with neoadjuvant therapy, leading to improved oncologic resection.

Robotic-assisted esophagectomy vs. video-assisted thoracoscopic esophagectomy trial

The robotic-assisted esophagectomy *vs.* video-assisted thoracoscopic esophagectomy (REVATE) trial is a multicenter randomized control trial comparing robotic esophagectomy to conventional thoracoscopic MIE for left RLN lymphadenectomy in ESCC[26]. The primary endpoint of this study focused on the left RLN lymph nodes given they are often the most difficult lymph node basin resulting in low resection rates and high morbidity associated with RLN palsy. The secondary endpoints of the trial included right RLN lymphadenectomy, total lymph nodes collected, and perioperative outcomes. The trial was completed and the results were presented at the UGIRA clinical congress in 2023. The REVATE trial demonstrated increased resection of left RLN lymph nodes in the RAMIE group (88%) compared to conventional thoracoscopic MIE (66%) (P < 0.001). Despite the great lymph node yield, the RAMIE cohort had a decreased incidence in left RLN palsy immediately post op (21% to 34%, P = 0.03) and at 6 months (5% to 17%, P = 0.007). In terms of their secondary perioperative outcomes, the RAMIE group also had a higher mediastinal lymph node harvest (16 [12-22] *vs.* 14 [10-20], P = 0.04). There was a significant increase in the thoracic operative time with conventional MIE (124 [103.5-154] *vs.* 110 [89-137] P = 0.004) and there was earlier chest tube removal (4 [3-7] *vs.* 6 [4-9] days, P = 0.007). All other outcomes were similar, including R0

resection, postoperative complications, length of stay, or 90-day mortality[27]. The results of the REVATE trial provide further evidence showing benefit of RAMIE over conventional MIE in performing lymphadenectomy, particularly in the more challenging nodal basins.

Future directions and actively enrolling randomized control trials

Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy vs. MIE (ROBOT-2)

The ROBOT-1 trial compared open esophagectomy to RAMIE and will now be followed by the ROBOT-2 trial comparing conventional MIE to RAMIE in resectable EA[10,28]. The ROBOT-2 trial is the first randomized control trial comparing conventional MIE to RAMIE to be conducted outside of Asia (in Europe) and the first to focus on EA. The primary outcome of this study is the total number of resected abdominal and mediastinal lymph nodes specified per lymph node station. Secondary outcomes include perioperative parameters and oncologic outcomes. The study will also include quality-of-life metrics and up to 5-year survival[28]. The results of the ROBOT-2 trial may clarify if prior findings are specific to squamous cell carcinoma and the McKeown esophagectomy, or if outcomes are consistent across both histologies and techniques. Finally, the protocol includes a cost analysis between the two modalities, a topic that requires further examination. Though robotic surgery has been found to be less cost-effective in other types of surgery, limited data exists on RAMIE as discussed at the end of this review. The ROBOT-2 trial has accrued 85% of its participants and is expected to close in 2024.

Overall morbidity after total minimally invasive keyhole oesophagectomy vs. hybrid oesophagectomy (MICkey trial)

The MICkey will also be conducted in Germany and the Netherlands, but is not specific to EA. Patients will be enrolled in either hybrid esophagectomy (HYBRID-E) via laparoscopic or robotic abdominal phase and open thoracic surgery or MIE including laparoscopic or robotic esophagectomy. The primary outcome will be postoperative morbidity within 30 days. The secondary outcomes will include perioperative parameters and patient-reported and oncologic outcomes[29]. The MICkey trial could provide insight into outcomes of hybrid robotic techniques compared to conventional MIE.

RAMIE vs. MIE in patients with esophageal cancer after neoadjuvant therapy (RAMIE-2)

The authors of the RAMIE trial are now actively enrolling for a second trial comparing RAMIE to conventional MIE in patients who have received neoadjuvant therapy. The trial will occur in China and only include squamous cell esophageal carcinoma. Neoadjuvant therapy will include chemoradiotherapy, chemotherapy and immunotherapy. The primary endpoints will include surgical and oncological results in patients with locally advanced ESCC after neoadjuvant therapy[30]. The RAMIE-2 trial will further explore the post-hoc analysis of the RAMIE trial, which demonstrated superiority of RAMIE for lymphadenectomy in patients who underwent neoadjuvant therapy. Given current recommendations of neoadjuvant therapy for locoregionally advanced cancer (cT2-4aN0-3M0 and T0-1 N+ M0), this study aims to provide valuable insight for operative planning.

Summary

The results of the discussed published randomized control trials and the ongoing trials are included in Table 1. This review included randomized control trials comparing RAMIE to MIE, but additional randomized control trials studying RAMIE were excluded. Additional information on active clinical trials can be found at clinicaltrials.gov[31].

Cost comparison

Limited data exists surrounding the cost comparison between RAMIE and conventional MIE, with no cost analysis reported in the completed randomized control trials previously mentioned. Currently there is only

Table 1. Completed and ongoing randomized controlled trials for RAMIE

Study name	Year	Number of patients	Location	Surgical procedures	Histology	Primary endpoint	Key findings
RAMIE trial	2022	358	China	RAMIE Conventional total MIE	ESCC	Efficacy and safety of RAMIE to MIE	RAMIE associated with greater lymph node harvest and shorter operation time with similar complications
REVATE trial[1]	2022	212	China and Taiwan	RAMIE Conventional total MIE	ESCC	Left RLN lymphadenectomy	RAMIE associated with increased left RLN node harvest, decreased left RLN palsy, increased mediastinal lymph nodes, early chest tube removal, and shorter operation time
ROBOT-2 trial	Ongoing	Enrolling	Europe	RAMIE Conventional total MIE	EA	Total number of lymph nodes resected	Enrollment ongoing
MICkey trial	Ongoing	Enrolling	Germany and the Netherlands	Hybrid esophagectomy (laparoscopic/robotic abdominal and open thoracic surgery) to total MIE (robotic/laparoscopic)	EA	Postoperative morbidity within 30 days	Enrollment ongoing
RAMIE-2	Ongoing	Enrolling	China	RAMIE Conventional total MIE	ESCC	Surgical and oncological results in patients with locally advanced ESCC after neoadjuvant therapy	Enrollment ongoing

[1]REVATE trial preliminary results with abstract presented at UGIRA Conference 2024 with manuscript submission pending. RAMIE: Robotic-assisted minimally invasive esophagectomy; MIE: minimally invasive esophagectomy; ESCC: esophageal squamous cell carcinoma; REVATE: robotic-assisted esophagectomy *vs.* video-assisted thoracoscopic esophagectomy; RLN: recurrent laryngeal nerve; EA: esophageal adenocarcinoma.

one single institution study from Germany comparing costs in RAMIE and conventional MIE. This study determined surgical costs, including expenses for disposable instruments and sterilization of reusable instruments, were higher for RAMIE (€12,370 *vs.* €10,059, $P < 0.001$). However, the total costs of care that includes the postoperative hospitalization were comparable between the two modalities (E€30,510 *vs.* €29,180, $P = 0.460$). The authors suggested the equalization of cost could be attributed to RAMIE resulting in a lower incidence of postoperative pneumonia (8% *vs.* 25%, $P = 0.029$) and a trend towards shorter hospital stays (15 *vs.* 17 days, $P = 0.205$)[32]. Therefore, the greatest determinant of cost was not necessarily surgical modality, but complications resulting in longer hospital stays.

Though not directly comparing conventional MIE to RAMIE, previous trials can provide insight into the cost of minimally invasive techniques compared to open esophagectomy. The ROBOT-1 trial published a follow-up study comparing cost of RAMIE to open esophagectomy. The authors found mean total hospital costs were comparable between RAMIE (€40,211) and open esophagectomy (€39,495), with a range of € -14,831 to 14,783 ($P = 0.932$). The ROBOT-1 group similarly concluded that postoperative complications were the greatest predictors of cost[33]. When comparing MIE to open esophagectomy, a randomized control trial with 5,000 cases found overall treatment cost per capita for MIE was significantly higher than that for open esophagectomy (median: $9,600 *vs.* $8,200, $P < 0.001$)[34]. Notably, these studies were all completed in different hospital systems across the world, making comparison difficult. It does not appear at this time that RAMIE has significantly different total cost of care compared to conventional MIE. The results of the ROBOT-2 trial will hopefully

provide further evidence on the cost comparison between the two modalities as part of their secondary outcomes.

CONCLUSION

Both conventional MIE and RAMIE are increasing in frequency for the management of esophageal cancer. The TIME and ROBOT-1 trials demonstrated that minimally invasive surgery decreased morbidity while preserving oncologic outcomes, when compared to open esophagectomy. When comparing minimally invasive techniques, thoracoscopic/laparoscopic *vs.* robotic, the current literature consistently demonstrates a superior lymphadenectomy with RAMIE. The RAMIE trial also provided evidence for the superiority of RAMIE in lymphadenectomy in patients following neoadjuvant therapy. The REVATE trial demonstrated RAMIE offered higher success of total lymphadenectomy and RLN lymphadenectomy with decreased RLN palsy. Another benefit of RAMIE included decreased operative times compared to conventional MIE. Finally, some studies support decreased postoperative risk of pneumonia and decreased ICU stay in patients undergoing RAMIE, but the causality of this requires further investigation[16-20,35]. A common hypothesis for this finding is the superiority of robotic platforms including a magnified three-dimensional view of the operative field, tremor filtration that enables precise dissection, and improved dexterity due to the flexibility of the wristed surgical instruments[12]. However, neither modality has consistently demonstrated superiority in reducing postoperative outcomes, with most studies showing no significant difference. Additionally, the impact on quality of life remains unclear, though the ROBOT-2 study aims to provide further insight on this topic. The overall cost difference between the two modalities appears minimal with primary predictors of cost being complications or hospital stay, not surgical modality. Therefore, RAMIE may offer improved oncologic resection with decreased perioperative complications compared to conventional MIE, with an overall net neutral total cost of care. Currently, published randomized control trials have limited long-term survival with only 90-day outcomes reported. Future trials will continue to define the role for RAMIE and conventional MIE in the management of esophageal cancer, including long-term oncologic outcomes such as locoregional recurrence and survival.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study: Oh, DS
Performed data acquisition, analysis and interpretation: Murillo A, Brian R

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Oh DS is an Associate Medical Officer at Intuitive Surgical. Murillo A and Brian R receive funding as participants in the Intuitive Surgical University of California San Francisco (UCSF) Simulation-Based Surgical Education Research Fellowship.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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