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Review

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A comparative review of minimally invasive approaches to esophagectomy: technical considerations, variations, and outcomes

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Abstract
Esophageal cancer continues to rise as a public health issue, and esophagectomy remains a mainstay therapy for the disease. Surgical approaches to esophagectomy have evolved over the past few decades with the advent of laparoscopic, thoracoscopic, and robotic technologies. The aim of this review is to identify original articles and perform a comprehensive literature search to provide updates on surgical approaches and technical considerations for esophagectomy. Articles describing the surgical technique specific to robotic-assisted minimally invasive esophagectomy (RAMIE) were reviewed and included. Technical considerations reviewed were comprised of patient positioning, optimal trocar placement, dissection, indocyanine green use, kocherization, pyloric interventions, anastomotic techniques, jejunostomy tube placement, and gastric ischemic conditioning, discussing relevant outcomes for each consideration and approach. Clinical outcomes were also evaluated by comparing RAMIE to open esophagectomy and minimally invasive esophagectomy. Outcomes reviewed included lymph node harvest, intra-operative blood loss, operative times, 30-day readmission, mortality, length of stay, pulmonary complications, recurrent laryngeal nerve injury, anastomotic leak, long-term survival, and disease-free survival.

Keywords: Esophagectomy, robotic esophagectomy, minimally invasive esophagectomy, open esophagectomy, clinical outcomes, technical variations, review

INTRODUCTION

Esophageal cancer is a highly morbid and prevalent disease, with 604,100 new cases of esophageal cancer recorded globally and 544,076 cancer-related deaths documented for 2020. In the United States alone, population-based cancer incidence data has proposed an estimated 20,640 adults diagnosed with the disease in 2022, with 16,410 subsequent cancer-related deaths[1,2]. Surgical treatment remains the core fundamental therapy for the management of esophageal cancer in early-stage and locally advanced esophageal cancer[3]. However, with rapid technological advancements and the increasing use of minimally invasive medical tools, the approach to esophagectomy shows trends towards increasing use of minimally invasive esophagectomy (MIE) since its initial report in 1992 and, more recently, the robotic-assisted minimally invasive esophagectomy (RAMIE) approach[4]. In fact, from 2010-2015, the annual number of open esophagectomies (OE) decreased from 63.6% to 44.1% of all esophagectomies performed, whereas MIEs and RAMIEs saw a rapid increase[5]. Despite the increased adoption of these minimally invasive approaches and their associated benefits, the post-operative course remains challenging, with multiple complications and high morbidity. Thus, it is integral to evaluate the short-term and long-term outcomes, comparing the varying operative techniques to identify differences and optimize outcomes. Over the past decade, there have been a multitude of studies, including meta-analyses and randomized controlled trials (RCT), such as the TIME trial, identifying differences between OE and MIE with pooled, reviewed data[6-16]. The aim of this study is to perform a comprehensive review of existing literature evaluating the updated techniques and nuances of esophagectomy and surgical outcomes of RAMIE in comparison to MIE and OE.

METHODS

A comprehensive literature search was performed on PubMed from 1984 to 2022. Studies that described surgical techniques of RAMIE and its approaches and studies evaluating the clinical outcomes of OE, MIE, and RAMIE were included. A further review was also performed on the references of each study. Studies that were not published in English were excluded from the review. No specific study formats were excluded from the study.

Surgical technique

The described approaches to esophagectomy are variable based on surgeon preferences. The fundamentals of esophagectomy have been identified and generally involve both the abdominal and thoracic mobilization of the esophagus, the creation of a neo-esophageal conduit, and the performance of an anastomosis, either thoracic or cervical. The varying approaches include a “two-incision” (abdominal and thoracic) Ivor-Lewis esophagectomy, a three-incision McKeown (abdominal, thoracic, and cervical) esophagectomy, and a “two-incision” (abdominal and cervical) transhiatal esophagectomy.

Within the 21st century, with the advancement of surgical technology, the paradigm has shifted to approach esophageal malignancies once treated with laparotomy and thoracotomy with less invasive modalities to complete the aforementioned fundamental aspects of the procedure[17]. During this transition, hybrid approaches have been described and utilized in clinical practice, combining a laparoscopic approach with open thoracotomy or an open abdominal approach with thoracoscopy[18,19]. Likewise, completely minimally-invasive approaches have also been practiced and studied, with a combined laparoscopic and thoracoscopic approach or a completely transhiatal approach with a cervical anastomosis. Nevertheless, the goal of developing such techniques has been to optimize patient outcomes, surgeon ergonomics, and earlier post-operative recovery[17]. Totally robotic-assisted procedures have been proposed to provide such advantages and, thus, have had an increase in adoption globally[18]. Thus, we will describe accepted approaches and their variances for the RAMIE.

RAMIE patient positioning and trocar placement

Abdomen

The initial positioning for the abdominal portion of the procedure is generally supine in the reverse Trendelenburg position[17]. Although we do not routinely employ a rightward rotation in our practice, a mild degree of rotation can be useful in some instances[17,20]. Five trocars are generally placed, with one accommodating the laparoscope, three for the robotic instruments, and one port to be used by an assistant. Although it has been frequently described to place the camera port supra-umbilically or infra umbilically at the midline, an off-midline position may provide some benefit in reducing trocar site hernias[17,20,21]. In our practice, we make an additional subxiphoid incision for a Nathanson liver retractor to assist with exposure, although suture suspension with clips has also been described in the literature[20,22,23]. Two examples of abdominal trocar placements can be noted in [Figure 1]. Figure 1A reveals a left-sided assistant port orientation, which provides significant benefits if a liver retractor is omitted, as the assistant can elevate the liver. This is also preferred if the patient has a pre-operative jejunostomy feeding tube present in the left abdomen that limits the location for trocar placement. Figure 1B orientation reveals a right-sided assistant port orientation. This orientation is often used when a pre-operative jejunostomy is not present and can serve as the jejunostomy site for the abdominal portion of the case. It also provides excellent access to the upper abdomen and hiatus for assistance with conduit creation and transhiatal mobilization of the distal esophagus.

Thoracic

There are several options for the trocar placements for RAMIE described and utilized globally. Ninomiya *et al.* have described two arrangements that establish an optimized approach for patients in the lateral decubitus position, which has been illustrated in Figure 2A and B[24]. These approaches utilize a 6-port technique, with four 8 mm robotic trocars and two 12 mm assistant ports[24]. Similarly, 5-port site arrangements have been described, such as the trocar variant noted in Figure 2C or the arrangement illustrated by Shen *et al.* [Figure 2D][17]. There are many factors that should be considered when choosing the optimal trocar arrangement. These variables include tumor location, anastomotic site, transhiatal mobilization, patient anatomic variations, prone *vs.* left lateral decubitus positioning, and use of single lung ventilation. In our practice, if an appropriate transhiatal mobilization of the distal esophagus was able to be performed in the abdominal phase of the procedure, we opt for a 5-port approach with three robotic trocars and a 12 mm assistant port positioned in the 7th intercostal space and the robotic arm 4 trocars in the 4th intercostal space at the anterior axillary line [Figure 2D]. This approach has provided acceptable visualization and accessibility to the proximal and middle thoracic esophagus, and in the case of a conversion from RAMIE to open, the trocar sites may simply be connected to complete the posterolateral thoracotomy incision.

Cervical

If a cervical anastomosis is planned, as in a McKeown or transhiatal esophagectomy, the patient is repositioned supine, or they are maintained in a supine position, respectively. Although this portion of the procedure is not performed using robotic technology, it is a key portion of the noted approaches. A standard incision is made at the medial border of the left sternocleidomastoid muscle; the omohyoid muscle, along with other strap muscles, if necessary, can be divided as dissection proceeds towards the esophagus. Bilateral recurrent laryngeal nerves (RLN) must be identified and preserved, often traversing the tracheoesophageal groove. The esophagus is encircled and mobilized distally, meeting the dissection plane performed transhiatal or transthoracic. The esophagus, along with the neo-esophagus (generally gastric conduit), is pulled through resected, and a cervical anastomosis is created.

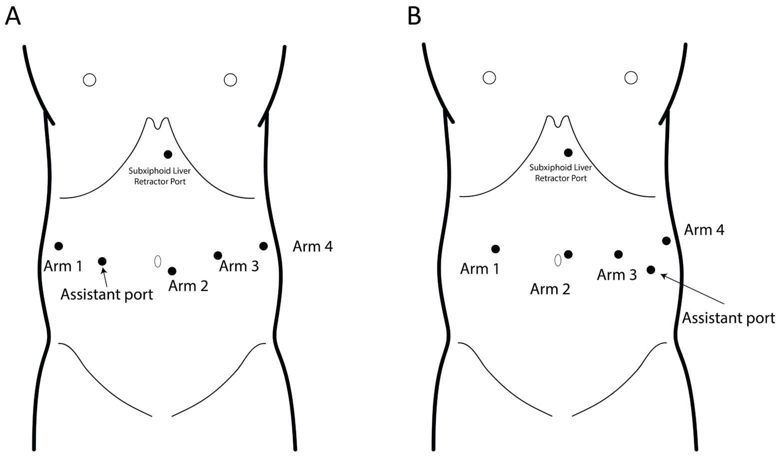

Figure 1. Two examples of abdominal trocar placement for RAMIE. (A) Assistant port in the right abdomen; (B) Assistant port in the left abdomen. RAMIE: Robotic-assisted minimally invasive esophagectomy.

Technical approaches and considerations

Abdominal dissection, indocyanine green (ICG), and duodenal mobilization

The abdominal and thoracic portion of esophagectomy contains critical steps to ensure a complete dissection and operation. However, there are variances in approach and considerations that have been incorporated and studied that may provide benefit to the overall procedure and patient outcomes. For instance, a transhiatal mobilization of the distal esophagus is often performed after the mobilization of the lesser curvature and dissection of the phrenoesophageal ligament[20]. This dissection can be carried proximally to the level of the inferior pulmonary vein circumferentially if visualization is sufficient. Though this clinical approach has not been studied for patient outcomes, it has been reported to assist with the thoracic dissection of the esophagus[20].

With regard to gastric conduit creation, there are multiple technical considerations and tools that can be utilized. The conduit is generally created, measuring approximately 4-5 cm along the greater curvature from the pyloric antrum to the fundus using serial loads of a 45 mm tissue cutting stapler. A 45 mm stapler is used instead of a 60 mm stapler in order to navigate the curvature of the stomach when making the conduit. Indocyanine green (ICG) can be used to evaluate the conduit, confirming clinical findings of perfusion, and has been associated with a decreased risk of anastomotic leaks[17,20,25]. Kocherization of the duodenum is another adjunct and technical consideration described. Kocherization is used to mobilize the gastric conduit to allow for a tension-free thoracic anastomosis by increasing the length and mobility of the conduit. A single-center, retrospective cohort study compared 43 total patients undergoing Kocherization (n = 29) *vs.* no routine Kocherization (n = 14). The study suggests that decreased anastomotic leak rates may be correlated with routine performance of kocherization (3.4% *vs.* 35.7%, P = 0.01). However, it should be noted that high-quality, randomized trials have not been performed to reproduce these findings[26].

Pyloric interventions

Prophylactic intra-operative pyloric interventions have been a concept holding controversy in clinical practice over the last 20 years. It is classically performed surgically via pyloromyotomy or pyloroplasty as an adjunct procedure at the time of the esophagectomy to prevent delayed gastric emptying (DGE) and acute gastric conduit distention. However, studies have failed to show improvement in clinical outcomes or a decreased need for post-operative development of DGE. For instance, a single-center retrospective study evaluating 31 patients undergoing prophylactic pyloroplasty to 109 patients without pyloroplasty noted no significant difference in leak rates (9.7% *vs.* 9.6%). Instead, there were notably increased operative times in the pyloroplasty group (360 *vs.* 222 min, $P < 0.01$)[27]. However, more recently, there has been rising interest

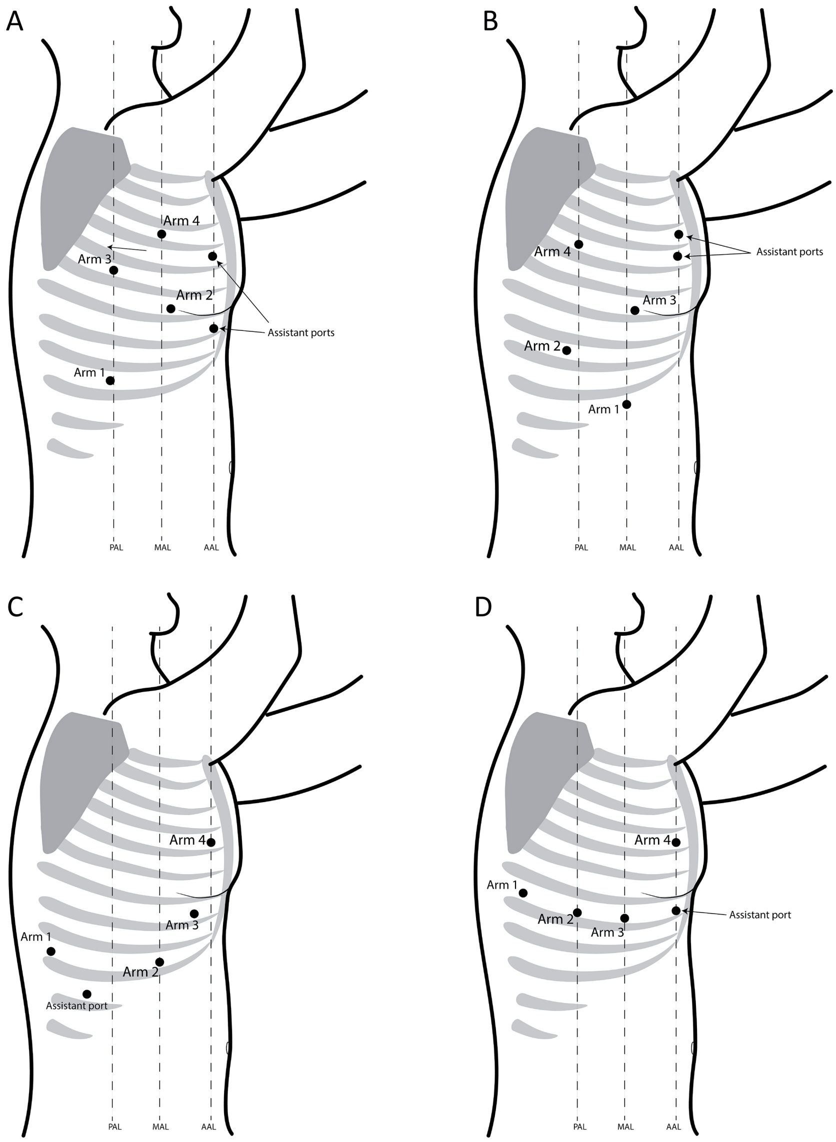

Figure 2. Several variations for the thoracic trocar placement during the thoracic portion of RAMIE. The variations illustrated are for patients positioned in the left lateral decubitus position. (A) and (B) both describe two assistant port arrangements, which are both 12-mm trocars, with Arm 1-4 as 8-mm robotic trocars. The camera is placed in Arm 2 (A) or Arm 3 (B); (C) illustrates a single assistant port set-up with a 12-mm assistant trocar. Arm 2 is designated for the camera through an 8-mm robotic trocar, Arm 3 as a 12-mm robotic trocar, and Arm 1 and 4 through 8-mm robotic trocars; (D) notes a linear trocar assekmbly by Shen *et al.*,with Arm 3 as a 12-mm trocar designated for the camera, a 12-mm assistant port, and the remaining arms are docked to 8-mm robotic trocars[17]. RAMIE: Robotic-assisted minimally invasive esophagectomy.

in performing chemical pyloroplasty using botulinum toxin injection with or without pneumatic dilation of the pylorus.

Giugliano *et al.* evaluated pyloroplasty, pyloromyotomy, botulinum toxin injection, and no intervention for the six-month need for post-operative endoscopic interventions, with 31.7% of the botox group, 28.8% of the pyloroplasty group, and 18.4% of the pyloromyotomy group requiring interventions. Interestingly, the no-intervention group had the lowest percentage of six-month endoscopic intervention at 12.5%[28]. Conversely, in a small comparative retrospective cohort analysis comparing botox injection (n = 14) to no intervention (n = 27) by Fuchs *et al.*, there was an increased risk of developing pyloric dysfunction in the no-intervention group requiring endoscopic therapy post-operatively (0% *vs.* 30%, P < 0.05). However, no significant difference in anastomotic strictures or leaks was noted[29].

A more recent study by Bolger *et al.* evaluated 171 patients who underwent MIE without pyloric intervention, revealing that 25% required endoscopic pyloric dilation. Endoscopic pyloric dilation was also associated greatly with the American Society of Anesthesiologists (ASA) status (OR 10.8, $P = 0.03$). Endoscopic pyloric dilation was not associated with re-operation for pyloric procedure and overall survival (OS) or the need for jejunostomy tube placement[30].

Overall, there is still no consensus regarding the need or use for routine pyloric interventions, as there are no high-quality comparative prospective, randomized trials evaluating clinical outcomes in MIE or RAMIE with or without pyloric interventions.

Anastomotic techniques

There are multiple accepted approaches, with the circular-stapled anastomosis (CS) being reported as the most frequently employed technique[17]. The circular stapler anvil is inserted either transorally or transthoracically into the esophagus. A gastrotomy is then created, generally at the staple line of the gastric conduit. The handle of the circular stapling device is inserted, and the spike is pierced through the gastric wall. The anvil and spike are connected and then deployed to complete the anastomosis. The gastrotomy created is then closed either with a suture or simply with a linear stapling device[31,32].

A linear-stapled anastomosis (LS) can also be performed by creating an esophagotomy at the staple line and a gastrotomy approximately 3-6 cm distal from the transected staple line of the gastric conduit. A 30-mm to 60-mm robotic stapler is then inserted into both the esophagotomy and gastrotomy and fired to create a side-to-side linear stapled anastomosis. The common enterotomy is then closed in two layers with absorbable sutures[33]. A hand-sewn anastomosis (HS) can also be performed in two layers between the esophagus and gastric conduit. This is performed with a single running suture or interrupted suture technique for both layers[34,35].

These three techniques have all been reported to be safe approaches with acceptable anastomotic leaks and stricture rates[33,35-39]. Unfortunately, there are no head-to-head randomized prospective trials evaluating the techniques for short-term and long-term outcomes. Recent meta-analyses have attempted to compare the techniques for complications and post-operative morbidities. One such study has revealed a slight advantage of CS over HS and LS, with anastomotic leak rates reported to be 6% compared to 9% and 10%, respectively[40]. However, there has been increasing data favoring LS. In another recent meta-analysis, LS was shown to have reduced relative risk for both anastomotic leak (RR 0.70, 95%CI 0.54-0.91; $P < 0.01$) and anastomotic stricture (RR 0.32, 95%CI 0.20-0.51; $P < 0.0001$) when compared to CS[38]. Compared to HS, LS has again been shown to have decreased anastomotic leak rates and anastomotic stricture rates in a large volume, single-center retrospective cohort study[41].

The anastomosis can also be reinforced with the omental tongue, which has been shown to protect against anastomotic micro-leaks[22,31,33].

Routine use of jejunostomy tubes for enteric nutrition

Routine placement of jejunostomy tubes has also been evaluated for their efficacy and operative considerations. A recent retrospective cohort study has illustrated no significant improvement in nutritional outcomes with routine jejunostomy use and, in fact, revealed increased esophagogastric anastomotic leak rates[42]. A subsequent meta-analysis by Li *et al.* did not reproduce a statistically significant increased risk of anastomotic leak but demonstrated a shorter length of stay (LOS) and post-operative pneumonia in the jejunostomy tube group, in addition to an increased risk of bowel obstruction[43]. There remains no consensus on the practice of placing a jejunostomy tube, and more high-quality studies are needed evaluating the efficacy of routine jejunostomy placement *vs.* no enteric tube placement in the esophagectomy population.

Gastric ischemic conditioning

Ischemic conditioning (IC) has been performed since the 1990s preoperatively to allow for maturation of the gastroepiploic arcade and augmentation of vascular flow to the gastric conduit[44]. It can be performed weeks in advance prior to initiation of neoadjuvant therapy at the time of staging laparoscopy and placement of feeding jejunostomy tubes[25]. However, this may cause unnecessary surgical dissection with the understanding that some malignancies progress despite neoadjuvant therapies. Thus, routine gastric IC should be performed with caution, as disease progression and its unresectability at the time of restaging after neoadjuvant treatment will effectively result in unnecessary surgical dissection performed preemptively. Nonetheless, IC has shown benefit in increasing neovascularization of the gastric conduit and decreasing anastomotic strictures and complications[25,45,46].

OUTCOMES

Short-term outcomes

Despite early criticism for the MIE and RAMIE, the efficiency of thoracic oncology surgeons has improved significantly over the past decade, resulting in safe and feasible surgical treatment of esophageal cancer when compared to OE[32,47-49]. There have been multiple studies that have evaluated the short-term outcomes of MIE and RAMIE compared to conventional OE.

Lymph node harvest

Both RAMIE and MIE have shown superiority in lymph node (LN) yield when compared to OE. For instance, with matched cohorts, Espinoza-Mercado *et al.* revealed an increased LN yield with MIE *vs.* OE (16 *vs.* 13, $P = 0.002$) and RAMIE *vs.* OE (17 *vs.* 13, $P < 0.001$)[5]. This was reproduced in a large observational study by Meredith *et al.*, with RAMIE (20 ± 9 LNs) and MIE (14 ± 7 LNs) producing an increased yield compared to OE (10 ± 6 LNs) ($P < 0.001$)[50].

RAMIE has similarly produced a greater LN harvest when compared to MIE alone. Deng *et al.* initially noted this increased LN yield in RAMIE *vs.* MIE in 2019 in their single-center cohort study (20 *vs.* 17, $P = 0.048$)[51]. Most recently, Khaitan *et al.* reproduced the improved LN harvest of RAMIE in their observational study utilizing the Society of Thoracic Surgeons Database (STS Database) when compared to MIE and OE (19 *vs.* 16 *vs.* 17, $P < 0.0001$)[52]. Similar trends were shown by Mederos *et al.* in a meta-analysis. However, statistical significance was unable to be reproduced (mean difference -1.10 favoring RAMIE, 95%CI, -2.45 to 0.25). It is worth noting that this study preceded the STS Database analysis by Khaitan *et al.*[52,53].

Intra-operative blood loss

With regards to intra-operative blood loss, RAMIE has shown decreased volumes of blood loss when compared to OE. In their RCT, van der Sluis *et al.* reported improved blood loss in RAMIE compared to OE for thoracic blood loss (120 *vs.* 200 mL, $P < 0.001$) and total blood loss (400 *vs.* 568 mL, $P < 0.001$)[54]. Meredith *et al.* redemonstrated such findings in an observational study favoring RAMIE compared to OE techniques (156 ± 107 mL in RAMIE *vs.* 289 ± 354 mL for open Ivor-Lewis and 275 ± 226 mL for open transhiatal, $P < 0.001$)[50]. Biere *et al.* revealed similar benefits of MIE when compared to OE in their multicenter RCT, with a mean estimated blood loss (EBL) of 475 *vs.* 200 mL, respectively ($P < 0.001$)[15]. RAMIE has been compared to MIE for EBL in multiple observational studies. Even a pooled analysis in a recent meta-analysis and systematic review by Angeramo *et al.* revealed favor towards RAMIE with statistical significance (MIE 213.6 mL *vs.* RAMIE 144.3 mL, $P = 0.006$)[48,50,51,53,55-59].

Operative times

Operative times have been consistently shown to be greater in RAMIE groups when compared to other surgical approaches. For instance, van der Sluis *et al.* revealed this increased operative time in RAMIE *vs.* OE (349 ± 56.9 *vs.* 296 ± 33.9 min, $P < 0.001$)[54]. Similar findings were noted in prior observational studies, and a recent meta-analysis redemonstrated this significance, with heterogeneity noted among the studies with nonoverlapping 95%CIs [5,50,52,53,60,61].

30-day readmission

There does not appear to be a difference among the surgical approaches regarding 30-day readmission rates. Espinoza-Mercado *et al.* evaluated 30-day readmission in MIE (4.9%), RAMIE (6.1%), and OE (6.2), and even with matched cohort analysis, revealed no significant difference when comparing MIE *vs.* OE ($P = 0.057$), MIE *vs.* RAMIE ($P = 0.110$), and RAMIE *vs.* OE ($P = 0.746$)[5].

Mortality

Both 30- and 90-day mortality have been studied as outcomes, yet, once again, no differences among the technical approaches have been revealed in the literature. Mederos *et al.* compared RAMIE to MIE in their meta-analysis, revealing near identical rates in their pooled analysis of 30- and 90-day mortality combined; nevertheless, this was without statistical significance (risk difference -0.01, 95%CI -0.02 to 0.00)[53]. When comparing RAMIE to OE, multiple studies, including an RCT by van der Sluis *et al.*, did not reveal any short-term mortality advantages of one group *vs.* the other, even with propensity matching[6-9,11,13,48,50,51,53-58,62,63].

With regards to MIE compared to OE, Yibulayin *et al.*, in their 2016 meta-analysis, revealed a decreased mortality risk for MIE compared to OE (3.8% *vs.* 4.5%, OR = 0.668, 95%CI 0.539 to 0.827, $P < 0.05$). However, it is important to note that their meta-analysis only contained one RCT at the time[10]. A more recent multicenter RCT by Mariette *et al.* from 2019 did not reveal a significant difference between the two groups for 30-day mortality[64].

LOS

Hospital LOS (HLOS) was comparable in all groups in four observational studies evaluating this parameter for RAMIE, MIE, and OE, with Espinoza-Mercado *et al.* illustrating statistical significance between RAMIE and OE (9 *vs.* 10 days, $P = 0.016$)[5,50,60,61]. A meta-analysis evaluating these studies, in addition to nine non-United States studies, did not reveal any difference among the groups with a mean or median LOS reported at ten days[53]. The short-term outcomes of the MIRO trial did not reveal a difference, either, comparing MIE to OE[64].

Pulmonary complication

Pulmonary complications evaluated included pneumonia, pneumothorax, pulmonary emboli, and ARDS. van der Sluis *et al.*, in their RCT, revealed a significantly higher risk for OE in overall pulmonary complications (58% *vs.* 32%, $P = 0.005$) and an increase in pneumonia in subgroup analyses (55% *vs.* 28%, $P = 0.005$) when compared to RAMIE[54]. Meredith *et al.* again revealed the lowest rates of pulmonary complications in the RAMIE group compared to MIE and OE (9.7% *vs.* 18.9% *vs.* 17.1%, $P = 0.001$), with

RAMIE showing the lowest rates of pneumonia in subset analysis followed by MIE, when compared to OE (6.9% *vs.* 8.4% *vs.* 15.2%, $P = 0.001$)[50]. Similarly, Mederos *et al.*, in their meta-analysis of pooled data, revealed a 6% risk difference favoring RAMIE when compared to MIE for all pulmonary complications with statistical significance (RD -0.06, 95%CI -0.11 to -0.01)[53]. Similar findings were revealed by Angeramo *et al.* favoring RAMIE compared to MIE (OR 0.46, 95%CI 0.35-0.61, $P < 0.001$)[59].

Yabulayin *et al.*, in their meta-analysis, also identified a significant decrease in pulmonary complications comparing MIE to OE (OR 0.527, 95%CI = 0.431 to 0.645, $P < 0.05$)[10]. The subsequent MIRO trial revealed a lower incidence of major pulmonary complications between MIE and OE (18% *vs.* 30%) but did not reveal any statistical significance ($P = 0.89$)[64].

Recurrent laryngeal nerve injury

RLN injury and palsy have been evaluated for RAMIE to OE in multiple observational studies and one RCT. However, pooled analysis by Mederos *et al.*, in their meta-analysis, did not reveal any statistically significant benefit of one technique over another[53]. When comparing RAMIE to MIE, Yang *et al.* revealed a significant favor towards MIE compared to RAMIE (RD 0.14, 95%CI 0.07 to 0.21, $P < 0.001$), whereas Chen *et al.* in their observational study favored RAMIE (RD -0.19, 95%CI -0.34 to -0.03, $P = 0.02$)[58,65]. These findings have not been reproduced in any other study to date, and pooled meta-analysis of all studies has not revealed any significant difference among the techniques[53].

MIE, similarly, has not revealed any significant difference in RLN injury when compared to OE in a pooled meta-analysis (OR 1.108, 95%CI 0.917 to 1.339, $P = 0.289$)[10].

Anastomotic leak

In 2020, Meredith *et al.* revealed lower anastomotic leak rates in their RAMIE group compared to MIE and OE (2.8% *vs.* 4.2% *vs.* 4.8%, $P = 0.03$)[50]. In a meta-analysis and systematic review, Angeramo *et al.* evaluated RAMIE to MIE, noting similar anastomotic leak rates without statistical significance (7% *vs.* 7%, $P = 0.23$)[59]. However, in a recent observational study utilizing reported outcomes through the STS Database, Khaitan *et al.* revealed improved anastomotic leak rates in OE compared to MIE and RAMIE (11.49% *vs.* 12.51% *vs.* 16.66%, $P < 0.0001$)[52].

Long-term outcomes

There has been an increase in reports of long-term outcomes regarding RAMIE as the technical approach continues to gain popularity with surgeon practice nationally and globally. We will evaluate reports for OS and disease-free survival (DFS) below for RAMIE, MIE, and OE.

Overall survival

There have been multiple studies showing trends toward favoring RAMIE compared to the other modalities regarding length of survival and five-year OS in the literature. In their unmatched cohort data, Espinoza-Mercado *et al.* noted overall median survival favoring RAMIE compared to OE (58.8 *vs.* 43.6 months, $P = 0.007$). However, with propensity-matching, there was no difference between the groups (58.8 *vs.* 53.8 months, $P = 0.306$)[5]. No difference was found with RAMIE *vs.* MIE (58.8 *vs.* 45.9 months, $P = 0.604$) or RAMIE *vs.* MIE (58.8 *vs.* 45.9 months, $P = 0.603$)[5].

RAMIE revealed an increased five-year OS compared to OE by Na *et al.* in their propensity-matched study at 75.1% survival compared to 57.9% survival ($P = 0.02$)[66]. For RAMIE *vs.* MIE, Mangriasso *et al.* evaluated reported five-year OS in their meta-analysis and revealed no significant difference between the groups (OR

1.035, 95%CI 0.720 to 1.487, *P* = 0.855)[62].

Straatman *et al.* revealed no difference in three-year OS comparing MIE to OE (40.4% *vs.* 50.5%, *P* = 0.207)[67]. These findings were reproduced by the MIRO trial RCT evaluating five-year OS, noting a trend favoring MIE compared to OE (59% *vs.* 47%) again, though unable to reveal a significant difference among the groups (*P* = 0.09)[68]. However, in their study, they revealed major overall intra-operative and post-operative complications, defined as Clavien-Dindo classification > II, along with major pulmonary complications, were associated with worse OS (HR 2.21, *P* < 0.001 and HR 1.94, *P* = 0.005, respectively)[68].

Disease-free survival

Mederos *et al.* evaluated DFS within their meta-analysis by pooling an RCT and an observation prospective cohort study for RAMIE *vs.* MIE and favored RAMIE (15 *vs.* 9 months, *P* = 0.04)[53]. When comparing RAMIE to OE for DFS, the meta-analysis and the individual studies it pooled found no significant difference[53,54,63]. Locoregional or distant recurrence was also evaluated by Yun *et al.* and did not reveal any significant difference between RAMIE and OE[63]. However, Na *et al.* recently evaluated five-year freedom from regional nodal recurrence and favored RAMIE compared to OE (81.4% *vs.* 62.7%, *P* = 0.03)[66].

In their three-year follow-up to the TIME trial, Straatman *et al.* note a DFS rate of 37.3% *vs.* 42.9% in comparing MIE to OE, favoring MIE; however, their results were not statistically significant (*P* = 0.602)[67]. Similarly, five-year DFS was evaluated in the MIRO trial comparing MIE to OE, also noting a trend towards improved DFS in MIE compared to OE (52% *vs.* 44%), yet there also lacked statistical significance (*P* = 0.26)[68]. Similar to OS, Nuytens *et al.* revealed major intra-operative and post-operative complications and major pulmonary complications as risk factors for five-year DFS for MIE and OE (HR 1.93, *P* = 0.002 and HR 1.85, *P* = 0.006, respectively)[68].

Healthcare cost

Although RAMIE may provide potential advantages, the use of technology and increased operative times may translate to higher healthcare costs associated with RAMIE. Van der Sluis *et al.*, in their ROBOT trial, identified this increased cost burden of the RAMIE when compared to OE[69]. These findings were clarified in a subsequent follow-up analysis of the ROBOT trial by Goense *et al.*, where a decrease in surgical cost was identified for RAMIE compared to OE (€8601 *vs.* €5937, *P* = 0.004)[70]. However, there was no significance in total costs comparing RAMIE to OE (€40,211 *vs.* €39,495, *P* = 0.932)[70]. Additionally, their multivariable analysis noted that any complication was a significant predictor for increasing healthcare costs for any patient undergoing esophagectomy[70].

Higher costs have been revealed by RAMIE, nonetheless, often accredited the cost of robotic devices and their disposable parts, with one particular study by Clark *et al.* suggesting the highest cost with RAMIE, followed by MIE and then OE[71,72]. Liu *et al.* also revealed a decreased total cost of OE compared to MIE ($12,643 *vs.* $14,890, *P* = 0.027). However, they noted that surgical costs were higher in the MIE group compared to OE ($9923 *vs.* $6267, *P* < 0.001), although MIE did have improved post-operative hospitalization costs compared to OE ($3891 *vs.* $5807, *P* = 0.001)[73].

Nonetheless, the total cost-effective nature favoring OE over MIE and RAMIE has been reproduced in the literature even when accounting for increased LOS associated with the open technique[10,74].

DISCUSSION

RAMIE has seen a notable rise in popularity over the last 20 years in thoracic surgery and, recently, has revealed some advantages over both MIE and OE in short-term and long-term clinical outcomes. RAMIE has shown significant benefits in short-term outcomes, including shorter HLOS, increased LN yield, decreased EBL, and decreased rates of overall pulmonary complications and pneumonia. These short-term outcome benefits can be interpreted to potentially justify the increased operative times and increased surgical costs identified in the literature for RAMIE when compared to MIE and OE. However, as thoracic surgeons continue to employ this approach increasingly and as technology advances, operative times may decline and healthcare costs may reduce, respectively. In fact, as identified in the follow-up to the ROBOT trial, focusing on techniques that reduce overall morbidity and complication rates, such as RAMIE, may show some cost benefit in overall healthcare spending[70].

Interestingly, the recent STS Database study revealed OE correlated with decreased anastomotic leak rates compared to MIE and RAMIE[52]. This does not account for anastomotic techniques, and further studies standardizing anastomotic techniques in a randomized control trial comparing RAMIE, MIE, and OE may provide additional insight into the benefits of the techniques with regards to this short-term outcome and for understanding the cost-benefit of each approach with regards to short-term outcomes.

RAMIE additionally provides technical advantages for esophagectomy, with improved dexterity, dissection, and visualization that may be the predisposing factors leading to notable findings such as decreased EBL and increased LN yield. The latter finding likely results in increased accuracy in surgical staging, thus leading to improved long-term outcomes, such as decreased rates of LN recurrences that have been noted in the recent propensity-matched study by Na *et al.*[66]. Furthermore, the improved LN yield with RAMIE results in increased accuracy in pathologic staging of patients, which more appropriately offers patients adjunct therapies. Nonetheless, the long-term clinical outcomes remain a challenge, and management is varied due to consistent reproducibility of the differing management options in the literature.

Managing esophageal cancer and performing esophagectomy remains a clinical challenge, with high peri-operative morbidity and complications. The practice of the RAMIE as an approach has shown promise to improve some of these outcomes when compared to its counterparts, MIE and OE. Although MIE and OE show no significant difference in certain peri-operative parameters such as OS, DFS, 30-day mortality, or RLN injury, as surgeons grow increasingly facile with the robotic approach, it is possible that these advantage gaps will become narrowed or may even favor RAMIE. Likewise, the current benefits of RAMIE may continue to show improving benefits as the technique continues to become widely adopted by thoracic surgeons. However, additional studies will be integral in evaluating OS and DFS within the setting of higher accuracy in pathologic staging that is offered by RAMIE with its increased LN yields. This, coupled with ongoing innovations in the realm of adjunct therapies for oncologic disease, may improve morbidity and mortality further for esophageal cancer and esophageal surgery.

The ergonomic and surgeon longevity benefits that may be associated with robot utilization are unclear for RAMIE due to the paucity of studies evaluating RAMIE, MIE, and OE in these parameters. These benefits are often made by extrapolating data from studies evaluating robot utilization in other surgical procedures. Therefore, well-designed studies that evaluate esophagectomy approaches with regard to surgeon-specific parameters are still needed to fully understand if RAMIE provides such benefits in ergonomics and improves surgeon career longevity.

DECLARATIONS

Author's contributions

Research (conception and design, data interpretation), Manuscript development (writing the manuscript, critical revision), Approval (approval of manuscript), Accountability (agreement to be accountable): Erol HA, Imai TA, Murayama KM

Availability of data and materials

The data acquired and reported to support the findings of this study are openly available in PubMed at https://pubmed.ncbi.nlm.nih.gov/.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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