Robot-assisted Surgery for Esophageal Cancer: Analysis of Short- and Long-term Outcomes

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Mark Wilson, MD, PhD and William Gunnar, MD, JD, FACHE for the purpose of understanding the potential benefits and costs for robot-assisted surgery. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge Sachi Yagyu and Zhaoping Li for their contributions to this project.

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

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Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

TABLE OF CONTENTS

EXECUTIVE SUMMARY **1**
Abbreviations Table 6
INTRODUCTION **7**
Topic Development 7
Search Strategy 8
Study Selection 8
Quality Assessment 9
Data Synthesis 9
Rating the Body of Evidence 9
Peer Review 10
RESULTS **11**
Description of Evidence 11
Key Question 1 – What is the clinical effectiveness of robot-assisted esophagectomy compared to thoracoscopic/laparoscopic or open esophagectomy for cancer? 14
Certainty of Evidence for Key Question 1 21
Key Question 2 – What is the cost-effectiveness of robot-assisted esophagectomy compared to thoracoscopic/ laparoscopic or open esophagectomy for cancer? 24
Summary of Findings 26
Limitations 26
Publication Bias 26
Study Quality 26
Heterogeneity 26
Applicability of Findings to the VA Population 27
Research Gaps/Future Research 27
Conclusions 29
REFERENCES **30**

FIGURES

Figure 1. Literature Flow Chart 19
Figure 2. Intra-Operative Outcomes 21
Figure 3. Short-Term Post-Operative Outcomes 25
Figure 4. Long-Term Outcomes 27

TABLES

Table 1. Certainty of Evidence for Key Question 1…………………………………………..…30

Table 2. Evidence Table for Cost Studies……………………………………………….…….33

APPENDIX A. SEARCH STRATEGIES 34

APPRENDIX B. PEER REVIEWER COMMENTS AND AUTHOR RESPONSES 37

APPENDIX C. COCHRANE RISK OF BIAS TOOL 41

APPENDIX D. RISK OF BIAS IN NON-RANDOMISED STUDIES – OF INTERVENTIONS (ROBINS-I) 43

APPENDIX E. QUALITY ASSESSMENT FOR INCLUDED RCT STUDIES 44

APPENDIX F. QUALITY ASSESSMENT FOR INCLUDED OBSERVATIONAL STUDIES 45

APPENDIX G. EVIDENCE TABLES 49

APPENDIX H. OPERATIVE TECHNIQUES OF INCLUDED STUDIES 88

APPENDIX I. CITATIONS FOR EXCLUDED PUBLICATIONS 91

ABBREVIATIONS TABLE

ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CFS	Cancer-Free Survival
EBL	Estimated Blood Loss
GRADE	Grading of Recommendations Assessment, Development and Evaluation
LN	Lymph Node
LOS	Length of Stay
LR	Local Recurrence
MIE	Minimally Invasive Esophagectomy
NACT	Neoadjuvant Chemotherapy
NIS	National Inpatient Samples
NSQIP	National Surgical Quality Improvement Program
OE	Open Esophagectomy
OR	Operating Room
OS	Overall Survival
RLN	Recurrent Laryngeal Nerve
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
RAMIE	Robot-Assisted Minimally Invasive Esophagectomy
RCT	Randomized Clinical Trial
ROBINS-I	Risk of Bias in Non-Randomized Studies-of Interventions
VAMIE	Video-Assisted Minimally Invasive Esophagectomy

EVIDENCE REPORT

INTRODUCTION

Worldwide adoption of robot-assisted surgery continues to increase, particularly for cancer and thoracic operations. Esophageal cancer is the seventh most common cancer diagnosis globally each year, with an estimated 572,000 new cases in 2018.[1] Esophagectomy is an important component of esophageal cancer treatment and is performed using open, conventional minimally invasive techniques (thoracoscopic and laparoscopic), or robot-assisted approaches. In 2016, there were over 1,800 robotic esophagectomies performed worldwide, a 9-fold increase from those performed in 2009.[2]

Historically, open esophagectomy (OE) is the standard surgical approach for esophageal cancer and is often combined with perioperative chemotherapy or chemoradiation for more advanced disease.[3,4] However, OE is a technically difficult operation with an associated morbidity and mortality of nearly 50% and 5%, respectively.[5] Minimally invasive approaches have been adopted, combining laparoscopic and thoracoscopic techniques with a handful of trials demonstrating fewer post-operative complications and similar oncologic outcomes.[6-8]

Robot-assisted minimally invasive esophagectomy (RAMIE) offers additional benefits to standard minimally invasive approaches due to the 540 degrees of wrist articulation, three-dimensional perspective, and greater magnification which may allow for a more meticulous dissection.[9,10] Despite the rapid adoption of RAMIE, several questions remain about its utility compared to OE and other minimally invasive approaches, especially with regard to long-term oncologic outcomes. Another important consideration is the economics of the robotic platform, which requires an upfront investment and costs for annual maintenance, instruments, staff and training, and infrastructure upgrade.

Individual studies and systematic reviews comparing RAMIE to MIE or OE have methodological variations and inconsistent reporting of oncologic and surgery-related outcomes. This is complicated further by the multiple approaches for esophagectomy (Ivor-Lewis, McKeown, and transhiatal) as well as determining if the benefit of the robot lies in the abdominal or thoracic phase of a multi-field esophagectomy.

Robot-assisted surgery for esophageal cancer is being increasingly used, and it is imperative to examine how it compares to open and other minimally invasive approaches, with an emphasis on long-term oncologic outcomes. We have conducted a systematic review to help clinicians, patients, and policymakers weigh these approaches in patients undergoing esophagectomy for cancer.

TOPIC DEVELOPMENT

This topic was developed in response to a nomination by Dr. Mark Wilson, National Director of Surgery, and Dr. William Gunnar, Director, National Center for Patient Safety, Veterans Health Administration. Key questions were then developed with input from the topic nominator, the ESP coordinating center, the review team, and the technical expert panel (TEP).

The Key Questions were:

KQ1: What is the clinical effectiveness of robot-assisted esophagectomy compared to thoracoscopic/laparoscopic or open esophagectomy for cancer?

KQ2: What is the cost-effectiveness of robot-assisted esophagectomy compared to thoracoscopic/laparoscopic or open esophagectomy for cancer?

The review was registered in PROSPERO: CRD42020198907.

SEARCH STRATEGY

We conducted broad searches using terms relating to "robotic surgery" or "esophagectomy" or "cancer." We searched PubMed (1/1/13-5/5/20), Cochrane (1/1/13-5/11/20), Ovid Medline (1/1/13-5/5/20), and Embase (1/1/13-5/6/20). Prior to 2013, robot-assisted procedures for esophagectomy were not widely being performed and many surgeons were still in the early so-called "learning curve". As such, our technical expert panel considered evidence from studies published prior to the year 2013 to be insufficiently relevant to modern practice. See Appendix A for complete search strategy.

STUDY SELECTION

Three team members working in pairs (MM/MG and MM/RS) independently screened the titles of retrieved citations. For titles deemed relevant by at least 1 person, abstracts were then screened independently in duplicate by 5 team members working in pairs (MM/MG; MM/MMG; MM/PT; and MM/RS). All disagreements were reconciled through group discussion. Full-text review was conducted in duplicate by 2 independent team members (MM and MD) with any disagreements resolved through discussion.

Studies were included at either the abstract or the full-text level if they were randomized clinical trials (RCTs) or observational studies comparing robot-assisted surgery with either thoracoscopic/laparoscopic or open surgical approaches for the included surgical procedure. The approach in the robotic arm (*eg*, Ivor-Lewis, McKeown, transthoracic, transhiatal) needed to be similar to the comparison arm to be included. We included all RCTs regardless of outcomes studied or sample size. Observational studies were subjected to additional selection criteria. Observational studies with less than 10 subjects in either arm of the study were excluded. Additionally, observational studies from the same data source, either large databases or single institutional databases, were considered to have a large overlap if >50% of the same subjects were included in multiple studies or if there was >50% overlap in the enrollment period. In this instance, the publication with the most recent data and the most outcomes of interest was included. We also included publications of cost-effectiveness models that compared robot-assisted surgery with thoracoscopic/laparoscopic or open surgical approaches.

DATA ABSTRACTION

Data extraction was completed in duplicate (MM/MD; MM/MMG; and MM/MG). Data from a non-English study was extracted by 1 member of the research team (MMG) with assistance from an English-speaking physician with extensive experience in systematic reviews whose native language is the non-English language of interest. All discrepancies were resolved with full group discussion. We abstracted data on study design and pre-operative patient and tumor characteristics, intra-operative outcomes, short-term outcomes, long-term clinical/oncologic outcomes, and data needed for the Cochrane Risk of Bias tool or Cochrane Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I).

Intra-operative outcomes of interest included the duration of the operation (OR time), estimated blood loss (EBL), and number of lymph nodes (LN) harvested. The short-term outcomes of interest included anastomotic leak, recurrent laryngeal nerve (RLN) palsy and/or hoarseness, pulmonary complications (*ie*, pneumonia, pleural effusion), duration of hospitalization (length of stay [LOS]), total post-operative complications, and mortality within 90 days. Long-term oncologic outcomes of interest were cancer recurrence and cancer-free survival. Of note, we used total OR time when reported. For LOS, since non-US studies have notably longer LOS (more than a week typically), we decided to only plot US-based studies in our analysis figures. For total post-operative complications, we reported this outcome if it was specifically provided or, if not, we reported major complications if available. Continuous outcomes were analyzed using the mean or median along with a measure of dispersion (standard deviation, inter-quartile range) to calculate the difference and 95% confidence interval between arms. For binary outcomes, the number of subjects with the outcome was collected and a risk difference was derived with its 95% confidence interval.

QUALITY ASSESSMENT

RCTs were assessed for quality (risk of bias) with the Cochrane Risk of Bias tool.[11] This tool requires an assessment of whether a study is at high or low (or unknown) risk of bias in 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other (See Appendix C for tool; Appendix E for table). We used the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) for observational studies.[12] This tool requires an assessment of whether a study is at critical, serious, moderate, or low risk of bias (or no information) in 7 domains: confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result (see Appendix D for tool; Appendix F for table). Since observational studies are not required to have published an *a priori* protocol, we operationalized the last domain (bias in selection of the reported result) as requiring that studies report the most common variables.

DATA SYNTHESIS

Because there was a paucity of RCTs, we did not conduct a meta-analysis of trials. The observational studies were too clinically heterogeneous to support meta-analysis; hence, our synthesis is narrative.

RATING THE BODY OF EVIDENCE

We used the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[13] GRADE assesses the certainty of the evidence based on the assessment of the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. This results in categories as follows:

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low/Insufficient: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

PEER REVIEW

A draft version of the report was reviewed by technical experts and clinical leadership. Reviewer comments and our responses are documented in Appendix B.

RESULTS

We identified 390 potentially relevant citations, of which 146 were included at the abstract screening level. From these, a total of 101 abstracts were excluded: Wrong comparison (n=66), wrong intervention (n=1), review/editorial (n=19), systematic review (n=7), and protocol (n=8). This left 45 publications for full-text review, of which 23 publications were excluded for the following reasons: wrong intervention (n=6), wrong comparison (n=3), small sample size (n=1), not original research (n=1), duplicate or studies with a large overlap of patients from the same data source (n=11), and unavailable (n=1). A full list of excluded studies from the full-text review is included in Appendix I. A total of 22 publications were identified at full-text review as meeting initial inclusion criteria: 20 publications with clinical outcomes, 1 publication with both clinical and cost outcomes, and 1 publication with only cost outcomes. See Figure 1 for literature flow. Descriptions of included publications are available in the Evidence Table (Appendix G).

DESCRIPTION OF EVIDENCE

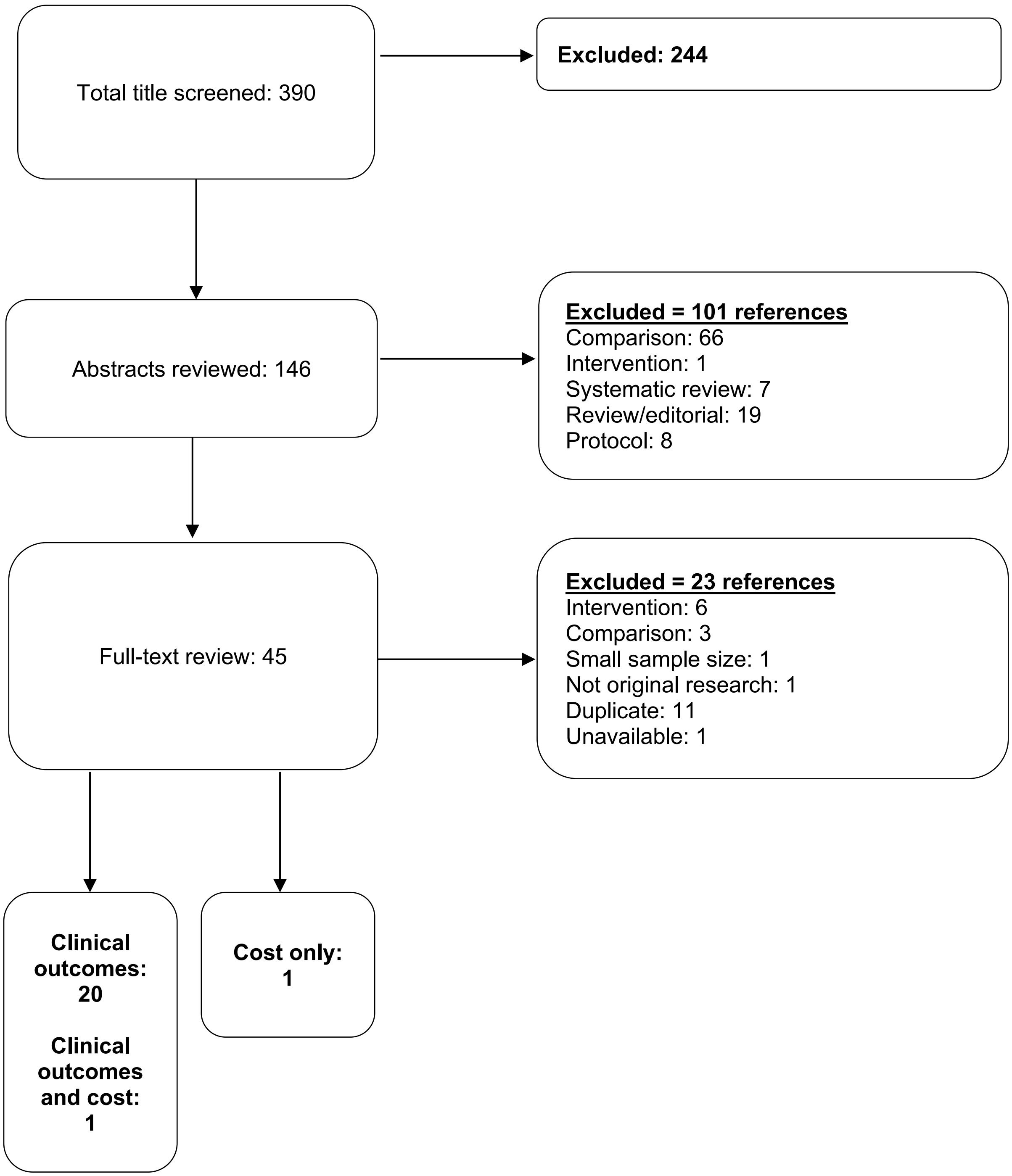
We identified 22 publications that met the inclusion criteria, of which 1 only reported cost data. As such, 21 studies reported clinical outcomes. Of these, 2 were RCTs,[14,15] and the remaining were observational studies. One RCT from the Netherlands randomized 109 patients with esophageal cancer to RAMIE (robot-assisted thoracic portion and laparotomy) or open esophagectomy (thoracotomy and laparotomy).[14] The other RCT from China randomized 192 patients with esophageal squamous cell carcinoma to RAMIE (robot-assisted thoracic and abdominal portions) or total thoracolaparoscopic MIE.[15] Both RCTs reported intra-operative, short-term, and long-term, cancer-specific outcomes.

Of the 19 observational studies, 11 were propensity matched for patient characteristics and pre-operative factors, such as age, sex, BMI, certain comorbidities, receipt of neoadjuvant treatment, and clinical cancer staging.[16-26] The majority of the observational studies were from East Asia, with only 5 studies coming from the US. [19,22,27-29] The robot and non-robot cohorts of each study had comparable surgical approaches and varied in size from 36 to 5,553 patients. Ten observational studies compared transthoracic RAMIE with MIE.[16-18,20,22-24,26,30,31] Four studies compared transthoracic RAMIE with open esophagectomy.[21,25,28,32] One study utilized the robot for the abdominal portion only.[33] Three studies compared MIE, RAMIE, and open esophagectomy,[19,27,34] and 1 study compared transhiatal MIE with transhiatal RAMIE.[29] Two studies were from large national databases.[19,22] The study from the National Surgical Quality Improvement Program (NSQIP) database compared open esophagectomy with all minimally invasive esophagectomies (RAMIE and MIE combined) for the primary analysis but performed a secondary analysis comparing MIE and RAMIE with 2:1 propensity matching.[22] Only data from the secondary analysis was abstracted for this review. The other database study analyzed patients from the National Cancer Database and compared RAMIE, MIE, and open esophagectomy.[19]

All observational studies reported intra-operative and short-term outcomes, but only one-third reported long-term, cancer-specific outcomes. The majority of studies described tumor location and histologic type of cancer. Due to epidemiologic differences in esophageal cancer subtype, patients in the studies from East Asia primarily had squamous cell carcinoma, and the patients in the US studies predominantly had adenocarcinoma. Certain pre-operative factors, such as tumor location, stage, receipt of neoadjuvant therapy, and location of the anastomosis are known to correlate with perioperative outcomes and are shown for each study in Appendix G. The surgical approach (*eg*, McKeown, Ivor-Lewis), operative technique for the thoracic and abdominal portions, and location and method of creating the anastomosis are provided in more detail in Appendix H (Operative Techniques of Included Studies).

For clarity, we elected to refer to robot-assisted study arms as robot-assisted minimally invasive esophagectomy (RAMIE) for the remainder of our report. Likewise, we refer to all video-assisted arms as video-assisted minimally invasive esophagectomy (VAMIE), which includes the different varieties and combinations of thoracoscopic/laparoscopic approaches.

Figure 1. Literature Flow Chart



KEY QUESTION 1 – What is the clinical effectiveness of robot-assisted esophagectomy compared to thoracoscopic/laparoscopic or open esophagectomy for cancer?

Intra-operative Outcomes

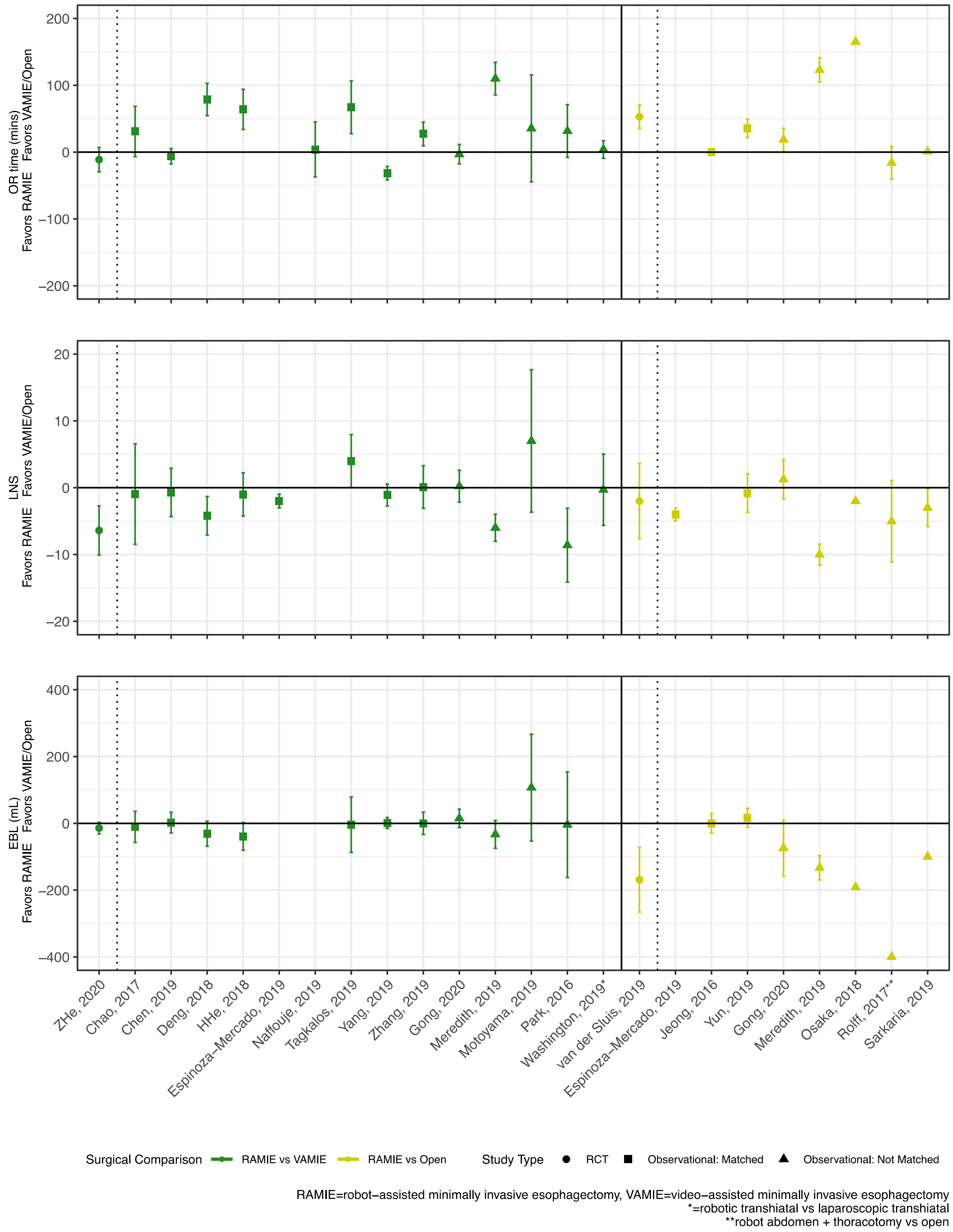
Intra-operative: RAMIE compared with VAMIE

Figure 2 presents 3 intra-operative outcomes: OR time, LN harvest, and EBL. For the RCT,[15] OR time was not longer for RAMIE as compared to VAMIE. The number of LNs harvested was greater for RAMIE, and EBL was not different. For the observational studies, OR time was reported as longer for RAMIE in 4 of the matched studies[18,20,23,26] and as no difference in 3 of the other matched studies.[16,17,22] One matched study reported shorter OR time[24] for RAMIE. For the unmatched observational studies, 1 reported longer OR time with RAMIE[27] and 4 reported no difference.[29-31,34] Two of the matched studies reported a greater number of LNs harvested for RAMIE,[18,19] whereas 6 reported no difference.[16,17,20,23,24,26] For unmatched observational studies, 2 reported greater number of LNs harvested with RAMIE,[27,31] and 3 reported no difference.[29,30,34] None of the matched or unmatched observational studies reported differences in EBL for RAMIE as compared to VAMIE.[16-18,20,23,24,26,27,30,31,34]

Intra-operative: RAMIE compared with Open Esophagectomy

For the RCT,[14] OR time was significantly longer for RAMIE compared to the open approach. The number of lymph nodes harvested was not different in the RAMIE arm. EBL was less for RAMIE. For the observational studies, there was a signal of longer OR time for RAMIE (4 reported significantly longer;[25,27,32,34] 3 no difference[21,28,33]). Seven studies reported on the number of LNs harvested and of these, 3 reported higher numbers removed by the RAMIE approach.[19,27,32] More than half of the observational studies reported less EBL with RAMIE[27,28,32,33] whereas 3 reported no difference.[21,25,34]

Figure 2. Intra-operative Outcomes



[1]Dotted line separates RCT from the observational studies
[2]Solid line separates the studies comparing RAMIE with VAMIE or RAMIE with open esophagectomy

Short-term Post-operative Outcomes

Figure 3 presents 6 short-term post-operative outcomes: anastomotic leak, recurrent laryngeal nerve palsy/hoarseness, pulmonary complications, duration of hospitalization, total complications, and mortality. Twelve studies compared RAMIE vs VAMIE,[15-18,20,22-24,26,29-31] 6 studies compared RAMIE with open esophagectomy,[14,21,25,28,32,33] and 3 studies compared RAMIE with both VAMIE and open esophagectomy.[19,27,34]

Short-Term: RAMIE compared with VAMIE

Of the studies comparing RAMIE with VAMIE, 14 assessed anastomotic leak, and there was no significant difference between study arms or trend favoring RAMIE or VAMIE in either the RCT or the 8 matched and 5 unmatched observational studies.[15-18,20,22-24,26,27,29-31,34] Cervical anastomoses were used in 9 studies, including 8 studies primarily or exclusively utilizing the McKeown approach[15-18,20,24,31,34] and 1 utilizing a transhiatal approach.[29] Three studies directly compared intrathoracic anastomoses with an Ivor-Lewis approach in both study arms.[22,23,26] One study was from a large database and compared robot-assisted Ivor-Lewis with an unspecified "transthoracic" MIE, suggesting at least 1 study arm had an intrathoracic anastomosis.[27] Another study reported a transthoracic approach for both study arms but did not specify whether an intrathoracic or cervical anastomosis was performed.[30] There was no clear difference favoring RAMIE or VAMIE when evaluating studies with a cervical or intrathoracic anastomosis separately.

The RCT found no difference in recurrent laryngeal nerve (RLN) palsy between study arms.[15] Of the 6 matched observational studies assessing RLN injury, 1 reported lower RLN palsy with RAMIE,[17] 1 reported lower RLN palsy with VAMIE,[24] and 4 reported no difference.[16,19,20,26] For the 3 unmatched studies, 1 reported lower rate of RLN palsy as compared to RAMIE,[30] and 2 reported no difference.[31,34]

The RCT[15] did not report a difference in pulmonary complications for RAMIE as compared to VAMIE. One propensity matched study reported fewer pulmonary complications[24]; however, the other 7 studies did not.[16-18,20,22,23,26] None of the 4 unmatched observational studies reported a difference between RAMIE and VAMIE approaches.[27,30,31,34] Most of the studies had a point estimate of effect falling within the 95% confidence interval of the RCT, which may suggest a possible signal that there may be fewer pulmonary complications in RAMIE compared with VAMIE.

None of the 4 US observational studies assessing LOS found a significant difference between RAMIE as compared to VAMIE; 2 were matched and 2 were unmatched studies.[19,22,27,29] One of these studies compared robot-assisted and laparoscopic transhiatal esophagectomy, which had no difference in LOS.[29] Nine non-US studies evaluated LOS, of which none demonstrated differences between RAMIE and VAMIE (see Appendix G. Evidence table).[15-18,20,23,24,26,34] All but 1 of the 9 non-US studies had a LOS with a central tendency (mean or median) greater than 10 days in both study arms,[26] whereas all US studies had a measure of central tendency of 10 days or less.

Ten studies assessed outcomes for total complications.[15,18,20,22,24,26,27,29,31,34] One study compared robot-assisted transhiatal and laparoscopic transhiatal esophagectomy.[29] The remaining studies compared a robot-assisted transthoracic approach to a thoracoscopic approach. Neither the RCT nor the matched and unmatched observational studies found a difference in complications.

Mortality was assessed in 14 studies.[15-20,22-24,26,27,29,31,34] Mortality was not different in the RCT or the matched and unmatched observational studies. In general, mortality rate was low across all studies.

Short-Term: RAMIE compared with Open Esophagectomy

Eight studies comparing RAMIE and open esophagectomy assessed anastomotic leak rate.[14,21,25,27,28,32-34] The RCT, 2 matched observational studies, and 5 unmatched observational studies reported no difference in leak rate. One observational study utilized the robot for the abdominal portion combined with thoracotomy, which did not demonstrate a difference in anastomotic leak rates, as the technique for creating the anastomosis was the same in both arms of the study.[33]

Of the 2 matched[21,25] and 3 unmatched observational studies[28,32,34] assessing RLN palsy, none found a difference between RAMIE and open esophagectomy.

Eight studies assessed pulmonary complications.[14,21,25,27,28,32-34] The rate of pulmonary complications was lower for RAMIE and open esophagectomy in the RCT.[14] One matched observation study and 2 unmatched observational studies also reported a lower rate for RAMIE.[25,27,28] The largest difference was seen in the RCT[14] but significance was also achieved in the 1 matched observational study[25] and 2 unmatched observational studies.[27,28] One matched observational study and 3 unmatched observational studies did not report a difference in pulmonary complications.[21,32-34]

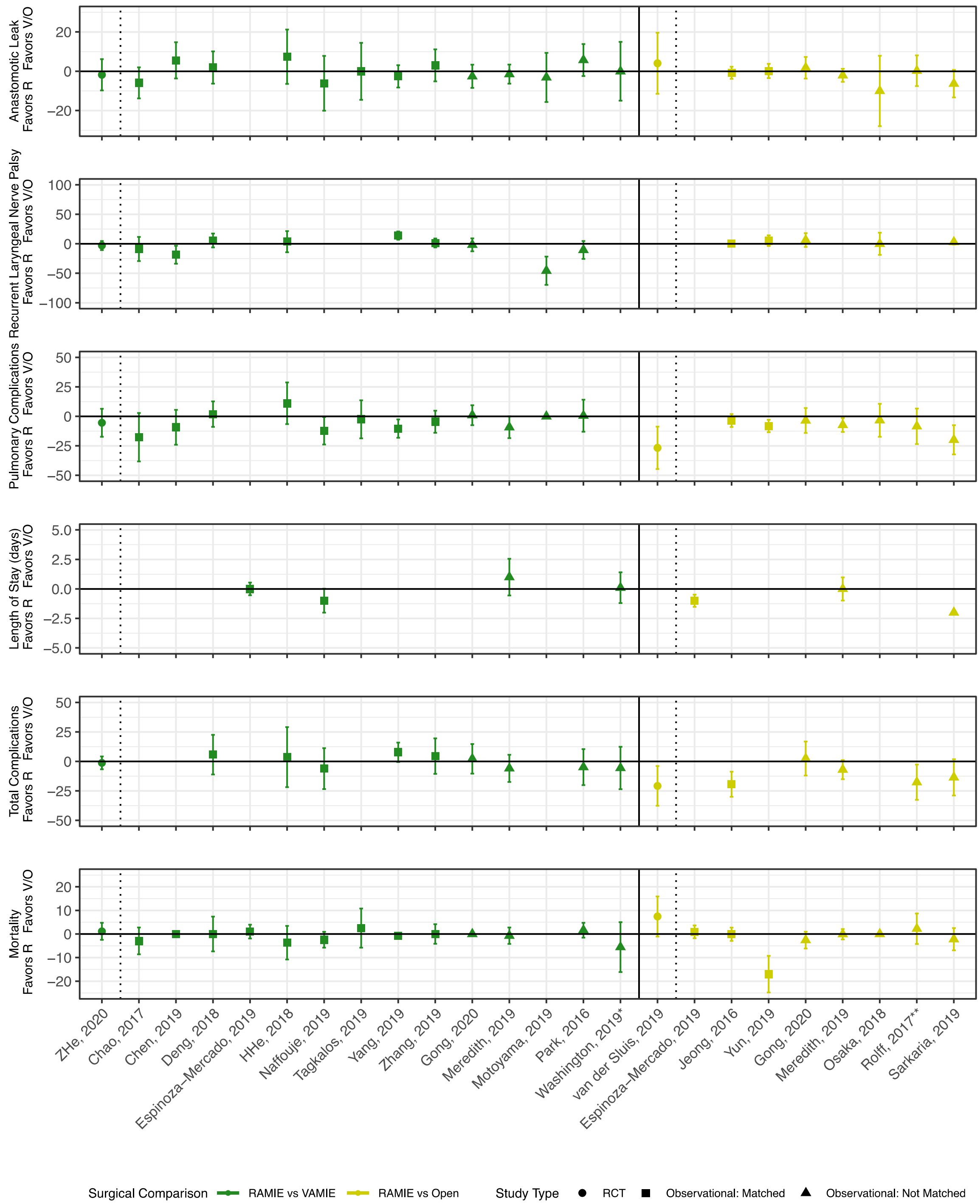
Three US studies evaluated LOS.[19,27,28] One matched observational study[19] and an unmatched observational study[28] demonstrated a shorter time to discharge with RAMIE. The third study (unmatched observational) did not find any differences in LOS between the study arms.[27] Of the 6 non-US studies that assessed LOS,[14,21,25,32-34] 2 demonstrated a shorter hospital stay for RAMIE compared with open esophagectomy (see Appendix G. Evidence Table).[32,33] The central tendency for LOS was greater than 10 days in both arms of the non-US studies except for one.[33] One out of the 3 US studies had LOS with a central tendency greater than 10 days.[28]

Six studies assessed total complication rate.[14,21,27,28,33,34] The RCT demonstrated a lower total complication rate with RAMIE.[14] Additionally, 1 matched observational study[21] and 1 unmatched study[33] showed reduced rates of total complications with RAMIE. Of note, the unmatched study compared the utilization of the robot for the abdominal portion with laparotomy (thoracic portion was performed via thoracotomy in both study arms). Three additional unmatched studies reported no difference total complications with RAMIE as compared to open esophagectomy.[27,28,34]

Mortality was assessed in 9 studies.[14,19,21,25,27,28,32-34] The RCT reported no different in mortality for RAMIE compared with open esophagectomy.[14] One matched observational study found that

RAMIE was associated with a lower mortality compared with open esophagectomy.[25] The remaining studies did not show a difference in mortality between study arms.

Figure 3. Short-term Post-operative Outcomes



RAMIE(R)=RAMIE=robot–assisted minimally invasive esophagectomy, VAMIE(V)=video–assisted minimally invasive esophagectomy, O=Open
*=robotic transhiatal vs laparoscopic transhiatal
**robot abdomen + thoracotomy vs open

[1]Dotted line separates RCT from the observational studies
[2]Solid line separates the studies comparing RAMIE with VAMIE or RAMIE with open esophagectomy

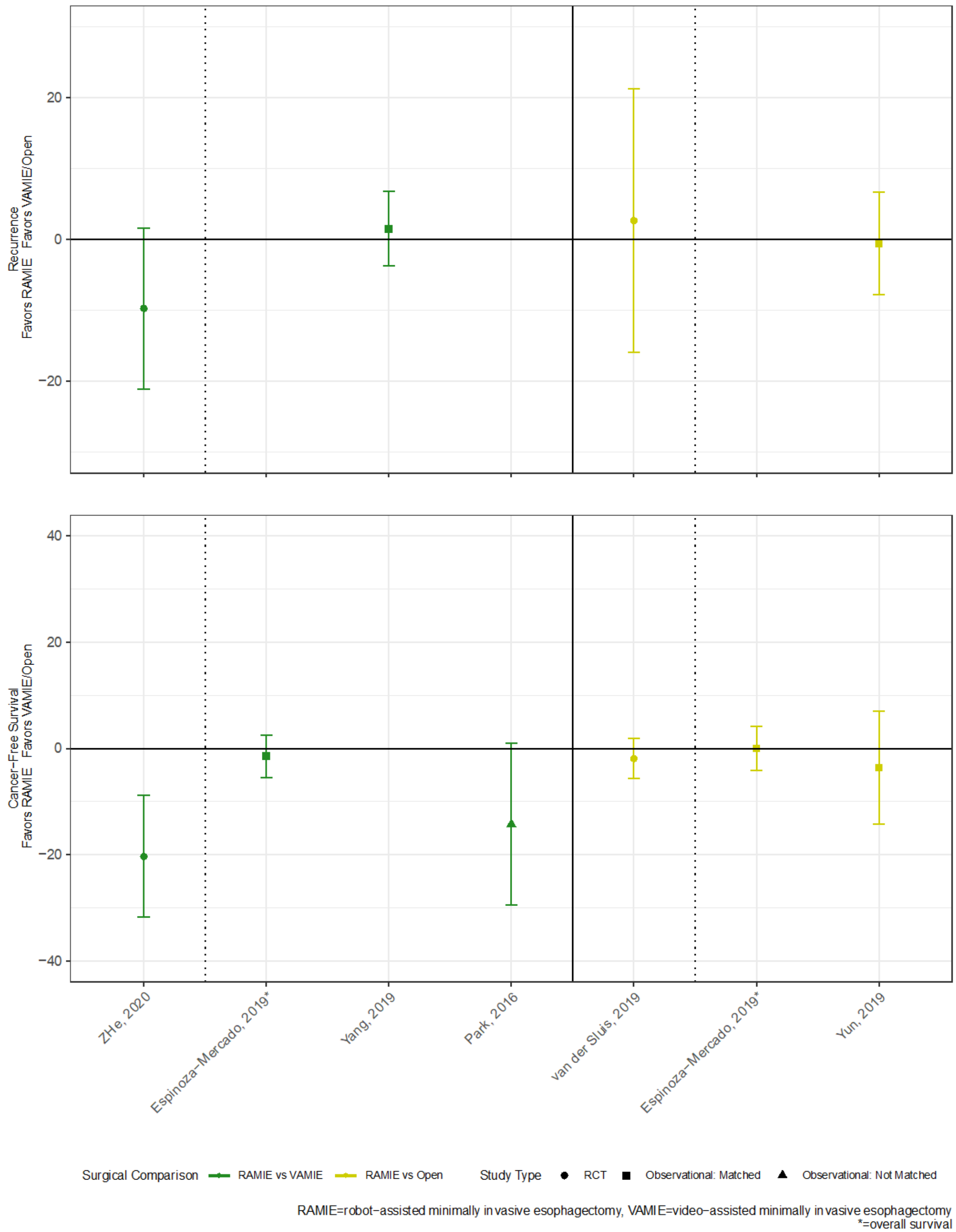
Long-term Outcomes

Long-term: RAMIE compared with VAMIE or Open Esophagectomy

Figure 4 presents graphically the results of long-term outcomes for recurrence and cancer-free survival. These outcomes were less frequently reported than the intra-operative and short-term post-operative outcomes. These were evaluated in 2 RCTs[14,15] and 3 observational studies.[24,25,31] One study reported overall survival instead of cancer-free survival.[19]

The RCT reported no difference in recurrence rate for RAMIE as compared to VAMIE, but a better cancer-free survival.[15] Recurrence rate was not different in the 1 matched observational study that reported on RAMIE as compared to VAMIE.[24] For the matched observational study that only reported overall survival, there was no difference between RAMIE and VAMIE.[19] Cancer-free survival was not different between RAMIE and VAMIE for 1 unmatched observational study.[31] The one RCT and 2 matched observational studies comparing RAMIE to open esophagectomy did not report differences in either of these long-term outcomes.[14,19,25]

Figure 4. Long-term Outcomes



[1]Dotted line separates RCT from the observational studies
[2]Solid line separates the studies comparing RAMIE with VAMIE or RAMIE with open esophagectomy

Summary of Findings

In general, OR time for RAMIE was longer than VAMIE and open esophagectomy. Although the RCT comparing RAMIE and VAMIE demonstrated OR times that were not different between study arms, several propensity-matched observational and unmatched observational studies concluded OR times were longer for RAMIE. The majority of studies demonstrated a signal of greater LN harvest with RAMIE compared with VAMIE and open esophagectomy. RAMIE may be associated with less EBL compared with VAMIE, but none of the findings reached statistical significance. Alternatively, RAMIE was associated with less EBL compared with open esophagectomy across the majority of studies.

Regarding short-term post-operative outcomes, the rate of anastomotic leak and RLN palsy did not appear to be different between RAMIE compared with either VAMIE or with open esophagectomy approaches. A difference in outcomes for different approaches (*ie*, McKeown and Ivor-Lewis esophagectomy) was not identified, and none of the studies reached statistical significance. RAMIE may be associated with slightly fewer pulmonary complications compared with VAMIE based on consistent findings across the majority of studies. The benefit of RAMIE on the rate of pulmonary complications was more apparent compared with open esophagectomy. It is unclear if LOS in the US was shorter with RAMIE compared with VAMIE, as there were too few studies with mixed results to draw a conclusion. In contrast, RAMIE was likely associated with decreased LOS compared with open esophagectomy based on 2 studies,[14,28] including 1 RCT. RAMIE had similar rates of total complications compared with VAMIE but was associated with decreased total complications when compared with open esophagectomy. Short-term mortality (within 90 days) was similar between RAMIE and VAMIE. Short-term mortality between RAMIE and open esophagectomy was less clear due to differences between studies, but RAMIE likely did not have worse mortality.

With regard to oncologic outcomes, RAMIE may be associated with better cancer-free survival compared with VAMIE. However, this conclusion was based primarily on 1 RCT.[15] There was no difference between RAMIE and VAMIE for recurrence rate. There was no difference in recurrence rate and disease-free survival between RAMIE and open esophagectomy.

Certainty of Evidence for Key Question 1

RAMIE compared with VAMIE

We judged the certainty of evidence for the outcome of longer OR time and improved lymph node harvest for RAMIE compared with VAMIE as low due to inconsistency and imprecision. We judged the certainty of evidence that there are no differences in EBL and anastomotic leak between RAMIE and VAMIE as moderate due to inconsistency. RLN palsy was determined to be not different with low certainty of evidence based on inconsistency. The certainty of evidence for the outcome of fewer pulmonary complications in RAMIE compared with VAMIE was deemed low due to inconsistency and relatively small estimated effect. The certainty of evidence that there are no differences in LOS or total complications between RAMIE and VAMIE is moderate due to some inconsistency and imprecision due to limited data. We judged the certainty of evidence that there is no difference in mortality between RAMIE and VAMIE as moderate due to some imprecision. Regarding long-term outcomes, we deemed the certainty of evidence that recurrence is not different between RAMIE and VAMIE as very low due to inconsistency, imprecision due to a paucity of studies, and serious study limitations due to large attrition rates in 1 study.[24] The certainty of evidence that cancer-free survival is longer for RAMIE compared with VAMIE is very low for the same reasons.

RAMIE compared with Open Esophagectomy

We judged the certainty of evidence for the outcome of longer OR time for RAMIE compared with open esophagectomy as high. The certainty of evidence of improved lymph node harvest favoring RAMIE was judged to be moderate due to imprecision. We judged the certainty of evidence that EBL is less for RAMIE as high. The certainty of evidence that anastomotic leak is not different between RAMIE and open esophagectomy is moderate due to imprecision. We deemed the certainty of evidence that RLN palsy is not different between RAMIE and open esophagectomy as moderate due to study limitations. The certainty of evidence that RAMIE is associated with a lower rate of pulmonary complications compared with open esophagectomy is deemed to be moderate due to imprecision. We judged the certainty of evidence that LOS is shorter for RAMIE compared with open esophagectomy as very low due to inconsistency and imprecision due to sparsity of data. The certainty of evidence that there are fewer total complications with RAMIE compared with open esophagectomy is moderate due to some imprecision. The certainty of evidence that short-term mortality is not different between RAMIE and open esophagectomy is deemed to be very low due to inconsistency and imprecision. The certainty of evidence that recurrence and cancer-free survival are similar for RAMIE compared with open esophagectomy is very low due to imprecision, paucity of studies, and study limitations.

Table 1. Certainty of Evidence for Key Question 1

Outcome	Study Limitations	Consistency	Directness	Precision	Certainty of Evidence
Intra-operative					
Operating Room Time	RCT: Low				
RAMIE > VAMIE	Matched observational studies: Moderate	Inconsistent	Direct	Imprecise	Low
RAMIE > Open	Unmatched observational studies: High	Consistent	Direct	Precise	High
Lymph Node Harvest	RCT: Low				
RAMIE >VAMIE	Matched observational studies: Moderate	Inconsistent	Direct	Imprecise	Low
RAMIE > Open	Unmatched observational studies: High	Consistent	Direct	Imprecise	Moderate
Estimated Blood Loss	RCT: Low				
RAMIE = VAMIE	Matched observational studies: Moderate	Inconsistent	Direct	Precise	Moderate
RAMIE < Open	Unmatched observational studies: High	Inconsistent	Direct	Precise	High
Short-term Post-operative					
Anastomotic Leak	RCT: Low				
RAMIE = VAMIE	Matched observational studies: Moderate	Inconsistent	Direct	Precise	Moderate
RAMIE = Open	Unmatched observational studies: High	Consistent	Direct	Imprecise	Moderate
Recurrent Laryngeal Nerve Palsy	RCT: Low				
RAMIE = VAMIE	Matched observational studies: Low	Inconsistent	Direct	Precise	Low
RAMIE = Open	Unmatched observational studies: Moderate	Consistent	Direct	Precise	Moderate
Pulmonary Complications	RCT: Low				
RAMIE < VAMIE	Matched observational studies: Moderate	Inconsistent	Direct	Precise	Low
RAMIE < Open	Unmatched observational studies: High	Consistent	Direct	Imprecise	Moderate
LOS					
RAMIE = VAMIE	Matched observational studies: Moderate	Inconsistent	Direct	Imprecise	Moderate
RAMIE < Open		Inconsistent	Direct	Imprecise	Very Low

Outcome	Study Limitations	Consistency	Directness	Precision	Certainty of Evidence
	Unmatched observational studies: High				
Total Complications RAMIE = VAMIE RAMIE < Open	RCT: Low Matched observational studies: Moderate Unmatched observational studies: High	 Inconsistent Consistent	 Direct Direct	 Imprecise Imprecise	 Moderate Moderate
Mortality RAMIE = VAMIE RAMIE = Open	RCT: Low Matched observational studies: Moderate Unmatched observational studies: High	 Consistent Inconsistent	 Direct Direct	 Imprecise Imprecise	 Moderate Very Low
Long-term/Oncologic					
Recurrence RAMIE < VAMIE RAMIE = Open	RCT: Low Matched observational studies: Moderate Unmatched observational studies: High	 Inconsistent Inconsistent	 Direct Direct	 Imprecise Imprecise	 Very Low Very Low
Cancer-Free Survival RAMIE > VAMIE RAMIE = Open	RCT: Low Matched observational studies: High Unmatched observational studies: High	 Inconsistent Consistent	 Direct Direct	 Imprecise Imprecise	 Very Low Very Low

KEY QUESTION 2 – What is the cost-effectiveness of robot-assisted esophagectomy compared to thoracoscopic/ laparoscopic or open esophagectomy for cancer?

No studies evaluated the cost-effectiveness of robot-assisted surgery compared with open or thoracoscopic/laparoscopic surgery for esophagectomy for cancer. Two publications included in their analysis some measure of cost (see Table 2).[17,35] One was a retrospective cohort study from a single institution in China comparing transthoracic RAMIE with transthoracic VAMIE. The second was an RCT from a single institution in the Netherlands comparing transthoracic RAMIE with open thoracotomy. The RCT was an abstract[35] published ahead of the full manuscript.[14] The abstract contains cost data that was not included in the final publication. Both were small studies including approximately 50 patients in the robotic arm.

Table 2. Evidence Table for Cost Studies

Author Year	Study Design, Number of Institutions, Country	Comparison(s)	Number of surgeons	Sample size	Source of cost data	Cost data	Misc Outcomes
Chen, 2019[17]	Retrospective cohort (propensity matched) Single institution China	Robot-assisted McKeown esophagectomy vs thoracolaparoscopic McKeown	Single surgical team	**Matched** Robot: 54 Lap: 54	Not stated	**Matched** **Total expenses (USD):** Robot: \$25,300±9,000 Lap: \$20,800±9,000 (p = 0.009) **Expenses/day (USD):** RAMIE: \$1,700±700 TLMIE: \$1,500±400 (p = 0.028)	**Matched** Duration: 187 min (robot) vs 193 min (lap), p=0.30 ICU stay 4.0 days (robot) vs 2.5 days (lap), p=0.14 Total LOS 17.1 days (robot) vs 15.2 days (lap), p=0.33
Van der Sluis, 2018[35]	RCT Single institution Netherlands	Robot-assisted thoracolaparoscopic esophagectomy vs open transthoracic esophagectomy	Two surgeons	Robot: 54 Open: 55	Not stated	**Mean costs:** Robot: €34,892 Open: €39,463 (p = 0.07)	Total OR time 349 min (robot) vs 296 min (open), p<0.001 ICU stay 1 day (robot) vs 1 day (open), p=0.45 Total LOS 14 days (robot) vs 16 days (open), p=0.33

Summary of Findings

The RCT found no statistical difference in total expenses or cost, while the observational study found the robot-assisted approach was more expensive. There are serious limitations to both of these studies. Neither study included any description of how costs were derived; there is no mention of the time horizon, the financial "perspective" (costs vs charges vs payments), or the methods used to obtain estimates. In particular, with respect to the cost of the robot, it is unclear whether or not these studies included relevant costs such as instrument, maintenance, or depreciation expenses. It is unclear how to compare cost estimates from China to the Netherlands or how these might compare to costs in the US.

Given the paucity of evidence and significant limitations of the available evidence, we are unable to draw any conclusion about the cost-effectiveness of RAMIE compared with VAMIE or open esophagectomy.

LIMITATIONS

Publication Bias

We were not able to test for publication bias and can make no conclusions about its possible existence. However, we feel it is extremely unlikely that there exists a high-quality randomized trial of robot-assisted surgery versus other surgical approaches that we did not identify and has similarly escaped detection by all other experts in this field. There is probably a plentitude of observational experiences about robot-assisted therapies from individual institutions that have never been published, and the available literature likely represents only a small fraction of what could be known using observational studies.

Study Quality

The RCTs were judged to have low risk of bias for short-term outcomes, such as intra-operative and short-term post-operative outcomes, and long-term oncologic outcomes. The observational studies were judged to have moderate risk of bias due to their non-random assignment of treatments for short-term outcomes and high risk of bias for longer-term outcomes. Many of the observational studies did not state how robotic esophagectomy was decided or offered for each patient, causing a risk of selection bias. However, of these studies, 11 were propensity matched, which mitigates the risk of selection bias, reducing the risk from serious to moderate. In terms of long-term outcomes, the high risk of bias is due to the fact that most of the studies calculated survival despite a high attrition rate, with some studies with an attrition rate over 50%.

Heterogeneity

The 2 general comparisons of the studies were RAMIE compared with VAMIE and RAMIE compared with open esophagectomy. We evaluated these 2 comparison groups separately to account for methodologic heterogeneity. Despite this, there was still significant heterogeneity between the studies. For example, the majority of studies compared transthoracic robot-assisted surgery to open or other minimally invasive approaches, but there are several transthoracic methods (*eg*, Ivor-Lewis and McKeown esophagectomies) and several hybrid combinations, such as utilizing the robot for the transthoracic portion combined with laparotomy or laparoscopy for the abdominal portion. Further, there are differences between studies with regard to certain techniques, such as creation of the anastomosis, patient positioning, and port placement, that may have an impact on outcomes.

In addition to the variety of procedures performed, certain outcomes were also measured differently across studies. For example, with regard to lymph node harvest, some studies performed a 2-field or 3-field lymphadenectomy. Similarly, some studies reported lymph nodes harvested from specific sites (*eg*, right and left RLN lymph nodes). RAMIE may have some benefit in terms of lymph node harvest in these particular areas, but it was not reported consistently across studies. Another outcome that was heterogeneous across studies is total complications. While many studies used validated tools such as the Clavien-Dindo classification to define severity of complications, many did not. There was even variability within studies that used the Clavien-Dindo classification because select studies reported grade ≥3 complications while others reported complications that were ≥2. Moreover, many studies classified the post-operative complications into categories and listed the specific complications and frequencies within these categories; however, a handful of studies grouped all complications into one measurement without defining which complications were included. Furthermore, studies did not give specifics, in general, on how complications were treated, like how anastomotic leaks were managed for the different approaches.

Applicability of Findings to the VA Population

None of the included studies were specific to VA populations. The applicability of these results to VA populations may depend on both the similarity of the patients studied to VA patients and the experience of the surgical teams using the robot to VA surgical team experience. However, the benefits for the robot-assisted approach may still be realized despite patient-level differences (VA patient population has greater burden of comorbidities than the general population), which will need to be confirmed in future studies. Robot-assisted procedures are gaining popularity in thoracic surgery, and the adoption of this platform for esophagectomy will likely translate well into the VA setting. Our group, in conjunction with another VA research team, is in the early stages of utilizing VA NSQIP data to assess the frequency and trends of robot-assisted surgery for esophagectomy in Veterans as well as analyze its association to clinical outcomes.

Research Gaps/Future Research

Several research gaps are apparent. First, there are numerous surgical techniques for performing an esophagectomy (*ie*, Ivor-Lewis, McKeown, transhiatal, thoracoabdominal); any combination of robot-assisted, open, or minimally invasive approaches can be utilized. Often, tumor characteristics, such as size and location (upper, mid-, or lower esophagus), dictate which approach or combination is used. We focused on comparing robot-assisted surgery for the thoracic portion of the procedure. However, even when grouping studies that performed a transthoracic esophagectomy, certain outcomes like anastomotic leak might not be generalizable depending on where the anastomosis was located (*eg*, intrathoracic anastomosis for Ivor-Lewis esophagectomy or cervical anastomosis for McKeown esophagectomy). Therefore, determining the influence of the robot-assisted approach in comparison to other techniques is difficult to disentangle when RCTs or well-designed, matched studies are few.

Additionally, the robotic platform can be used in various stages of an esophagectomy (thoracic or abdominal portions). Na et al,[36] which was not included in our review, performed a propensity-matched analysis comparing hybrid RAMIE (robot for the thoracic portion combined with laparotomy) with total RAMIE (*ie*, thoracic and abdominal portions performed with robot). There were no differences in clinical outcomes between approaches; however, the small sample size limited the comparisons. Ideally, studies like this, but with a larger number of patients, could help elucidate differences between specific robotic uses within techniques, such as the abdominal portion in this example. In fact, the Society of Thoracic Surgeons (STS) National Database has worked to expand patient follow-up to 5 years and to include specifics on the various types of approaches, which will allow for more detailed comparisons in the future.

Second, regional variations of surgical practice and esophageal cancer epidemiology exist. The predominant histologic type of esophageal cancer in East Asian countries is squamous cell carcinoma while adenocarcinoma predominates in the US.[37-39] The 5-year survival is less than 25% between the 2 subtypes, but the risk factors differ and underscore important clinical variation in patient populations.[38,39] For example, gastroesophageal reflux disease and obesity are risk factors for adenocarcinoma, while smoking, alcohol consumption, and nutritional deficiencies are risk factors for squamous cell carcinoma.[37-39] Further, East Asian countries in general have a higher incidence of esophageal cancer and thus higher surgical volume.[37-39]

Third, in addition to understanding the relationship of clinical outcomes for patients, the surgeon's physical experience is relevant. The robotic platform has demonstrated improved ergonomics and less musculoskeletal complaints from surgeons compared with open and other minimally invasive surgical techniques, but this has not been universally observed.[40] There is evidence that a prolonged time sitting at the robot-assisted console may add physical challenges. The physical impact of minimally invasive versus open surgery on the surgeon is still debated. Physical discomfort and symptoms of poor posture have been reported with minimally invasive surgery as compared to open surgery.[41,42] However, objective intraoperative measurement of surgeon posture suggests open surgery is more demanding for the neck and trunk.[43] Research is needed to assess detailed quality of life, assessment of chronic physical injuries, and longevity of operating compared across these approaches.

Fourth, the learning curve likely has an impact on certain outcomes like OR time, blood loss, and intra-operative complications. Its influence on reported outcomes in the literature is hard to discern, as the majority of studies fail to comment on the previous robotic experience or if a learning curve was specifically present. This learning curve is typically present with most evolving surgical technology;. However, the influence of the learning curve should lessen with time and experience.[44] Therefore, the learning curve may be a potential factor in our findings.

Fifth, there is a lack of high-quality evidence demonstrating the long-term and oncologic benefits, or risks, of RAMIE. The majority of studies comparing RAMIE focus on intra-operative and post-operative outcomes. Intra-operative events have a direct impact on short-term outcomes and potentially an indirect influence on long-term functional status and cancer control. However, new data suggests anastomotic leak does not compromise long-term outcomes or oncological control.[45] Two RCTs, 1 comparing RAMIE to VAMIE[15] and another comparing RAMIE to open esophagectomy,[14] evaluated recurrence and disease-free survival with adequate follow-up. However, these were relatively small studies (n=192 and n=99, respectively). Several observational studies that assessed long-term oncologic outcomes were small and had large attrition. To that end, RAMIE is gaining popularity and more cases are being performed each year, so within several years there may be large studies with adequate follow-up that become available.

Sixth, there is a paucity of studies directly comparing cost between RAMIE and other comparable approaches. Only 2 studies had some measure of cost, but both came from different countries and practice settings and do not generalize well to cost in the US. There is a need for standardized methods to assess cost – which applies to all robot-assisted operations, (*ie*, analytics, consistent definitions of cost, how upfront capital was accounted for, how to adjust for training staff, *etc*). Along these lines, formal cost-effectiveness studies that weigh the benefits and risks along with cost are needed.

Further, the recent Laparoscopic Approach to Cervical Cancer trial compared minimally invasive surgery, including laparoscopic and robotic, to open surgery in early-stage cervical cancer and found *worse* survival in the minimally invasive group.[46] In response, the FDA issued a warning: "The relative benefits and risks of surgery using robotically-assisted surgical devices compared with conventional surgical approaches in cancer treatment have not been established." The FDA encouraged research on robotic surgery, emphasizing impact on long-term clinical and oncologic outcomes. Careful analysis is warranted.

CONCLUSIONS

In summary, esophagectomy is a complex procedure with a high rate of morbidity, and while the robot-assisted approach has the potential to provide beneficial outcomes, current data is too limited to provide definitive conclusions. Future research should include RCTs or well-designed prospective matched studies with adequate power and follow-up to assess long-term as well as oncologic outcomes in patients undergoing robot-assisted surgery for esophageal cancer, including determination of risks. Additional work should also weigh the financial differences of the robot-assisted esophagectomy relative to the clinical advantages and disadvantages.

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