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

December 2020

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence Synthesis Program (ESP) Center
West Los Angeles VA Medical Center
Los Angeles, CA
Paul G. Shekelle, MD, PhD, Director

Authors:
Principal Investigators:
Melinda Maggard-Gibbons, MD
Paul G. Shekelle, MD, PhD

Co-Investigators:
Mark D. Girgis, MD
Paul Toste, MD
Michael A. Mederos, MD
Michael J. de Virgilio, BS
Christopher P. Childers, MD, PhD
Linda Ye, MD
Rivfka Shenoy, MD

Research Associates:
Selene S. Mak, PhD, MPH
Meron Begashaw, MPH
Marika S. Booth, MS

VA | U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

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.

Recommended citation: Mederos MA, de Virgilio MJ, Girgis MD, Toste P, Childers CP, Ye L, Shenoy R, Mak SS, Begashaw M, Booth MS, Maggard-Gibbons M, Shekelle PG, Robot-Assisted Surgery for Esophageal Cancer: Analysis of Short and Long-Term Outcomes. Los Angeles: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #05-226; 2020. Available at: https://www.hsrd.research.va.gov/publications/esp/reports.cfm.

This report is based on research conducted by the Evidence Synthesis Program (ESP) Center located at the **West Los Angeles VA Medical Center, Los Angeles, CA**, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*e.g.*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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.

Mark Wilson, MD, PhD
National Director of Surgery
Department of Veterans Affairs

William Gunnar, MD, JD, FACHE
Director, National Center for Patient Safety
VA Ann Arbor Healthcare System
Associate Professor of Surgery, University of Michigan Medical School

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:

Rajeev Dhupar, MD, MBA, FACS
Assistant Professor of Cardiothoracic Surgery
Chief, Thoracic Surgery
VAMC of Pittsburgh Department of Cardiothoracic Surgery

Nir N. Hoftman, MD
Clinical Professor, Anesthesiologist
Director, Thoracic Anesthesia
UCLA Department of Anesthesiology

James D. Maloney, MD
Chief of Surgical Services at William S. Middleton Memorial Veterans Hospital
Chief, Section of Thoracic Surgery
University of Wisconsin Health System

Daniel C. Wiener, MD
Chief, Thoracic Surgery, VA Boston Healthcare System, West Roxbury
Assistant Professor of Surgery, Thoracic Surgery
Harvard Medical School

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.

EXECUTIVE SUMMARY

INTRODUCTION

Worldwide adoption of robot-assisted surgery continues to increase and has been applied to esophagectomy for esophageal cancer. Since 2009, there has been a more than 9-fold increase in robot-assisted minimally invasive esophagectomy (RAMIE) operations performed. Despite the rapid adoption of RAMIE, several questions about its utility compared to open esophagectomy and other video-assisted minimally invasive esophagectomy (VAMIE) approaches remain, 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. We conducted a systematic review to help clinicians, patients, and policymakers weigh these approaches in patients undergoing esophagectomy for cancer.

METHODS

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?

Data Sources and Searches

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).

Study Selection

Studies were included if they were randomized clinical trials (RCTs) or observational studies comparing robot-assisted surgery with either thoracoscopic/laparoscopic and/or open surgical approaches for esophagectomy for cancer. We also included publications of cost-effectiveness models that compared robot-assisted surgery with thoracoscopic/laparoscopic or open surgical approaches. We included all RCTs regardless of outcomes and sample size. Observational studies were subjected to additional selection criteria. Observational studies with fewer 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 potentially 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. For clarity, we elected to refer to

robot study arms as RAMIE. We refer to all non-robotic video-assisted arms as VAMIE, which includes the different varieties of thoracoscopic/laparoscopic approaches.

Data Abstraction and Quality Assessment

We abstracted data on the following: study design, patient characteristics, sample size, intra-operative outcomes (operating room [OR] time, lymph nodes [LN] harvested, estimated blood loss [EBL]), short-term post-operative outcomes (anastomotic leak, recurrent laryngeal nerve [RLN] palsy, pulmonary complications, length of stay [LOS], total complications, and mortality), long-term oncologic outcomes (recurrence and cancer-free survival), and data needed for the Cochrane Risk of Bias tool or Cochrane Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I).

Data Synthesis and Analysis

Because only 2 RCTs were identified, each comparing RAMIE to a different approach (one compared to VAMIE and the other to open esophagectomy), we did not conduct a meta-analysis of trials. The observational studies were too clinically heterogeneous to support a meta-analysis; hence, our synthesis is narrative. We used the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group to assess the certainty of evidence across studies.

RESULTS

Results of Literature Search

We identified 390 potentially relevant citations, of which 146 were included at the abstract screening level. From these, a total of 23 abstracts were excluded. Twenty-two 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 (therefore 21 in total had clinical outcomes), and 1 publication with only cost outcomes. See Figure 1 for literature flow.

Summary of Results for Key Questions

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

In general, OR time for RAMIE was longer than VAMIE and open esophagectomy. Although the RCT comparing RAMIE and VAMIE demonstrated near-equivalent OR times 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 consistently had less blood loss than VAMIE, but in no study was this difference statistically significant. Alternatively, RAMIE was associated with less blood loss compared to open esophagectomy across the majority of studies.

Regarding short-term post-operative outcomes, there was no evidence of a difference in anastomotic leak or RLN palsy rates between RAMIE compared with either VAMIE or with open esophagectomy. 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. There were few studies that had mixed results. In contrast, RAMIE was likely associated with decreased LOS compared with open esophagectomy based on 2 of 3 studies, 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. However, 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, 1 RCT found statistically significantly longer cancer-free survival in patients treated with RAMIE as compared to those treated with VAMIE. There was no difference between RAMIE and VAMIE for recurrence rate. There was no difference in recurrence rate and cancer-free survival between RAMIE and open esophagectomy.

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

The total expenses or cost of RAMIE compared with open esophagectomy in the RCT found no difference between study arms, while the observational study comparing RAMIE with VAMIE found the robot-assisted approach was more expensive. There were 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 also 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 strong conclusions about the cost-effectiveness of RAMIE compared to VAMIE or open esophagectomy.

DISCUSSION

Key Findings and Certainty of Evidence

RAMIE is associated with longer OR times compared with VAMIE and open esophagectomy. The certainty of evidence was low for the comparison of RAMIE and VAMIE and high for RAMIE compared with open esophagectomy based on consistency. There was greater lymph node harvest with RAMIE compared with VAMIE and open esophagectomy with low and moderate strength of evidence, respectively. There was moderate certainty of evidence that there were no differences in EBL between RAMIE and VAMIE. Conversely, there was high certainty of evidence that RAMIE was associated with less EBL compared with open esophagectomy. There was moderate certainty of evidence that the rate of anastomotic leak or RLN palsy were not different between RAMIE and VAMIE. The certainty of evidence was low for the slightly fewer pulmonary complications with RAMIE compared with VAMIE. There was moderate certainty of evidence that this benefit was more apparent comparing RAMIE with open

esophagectomy. There was moderate certainty of evidence that there were no differences with LOS or total complications between RAMIE and VAMIE. There was very low certainty of evidence that RAMIE was associated with a shorter LOS compared with open esophagectomy, due to limited data. On the other hand, there was moderate certainty of evidence that RAMIE had fewer total complications compared with open esophagectomy. There was moderate and very low certainty of evidence that there were no differences in short-term mortality (within 90 days) for RAMIE compared with VAMIE or open esophagectomy, respectively. Regarding long-term outcomes, there was very low certainty of evidence that cancer recurrence is not different between RAMIE and VAMIE or open esophagectomy due to a paucity of studies evaluating this outcome. Cancer-free survival is similar between RAMIE and open esophagectomy but improved when compared with VAMIE. The certainty of evidence is again very low due to limited studies assessing this outcome.

Formal cost-effectiveness studies comparing RAMIE with other approaches were not identified. The total expenses or cost of RAMIE compared with open esophagectomy based on 1 RCT from the Netherlands suggests there is no difference between study arms. Alternatively, RAMIE was more expensive than VAMIE based on a single observational study from China. Definitive conclusions regarding the balance between the benefits, risks, and cost cannot be made based on these 2 studies due to several methodologic differences, paucity of additional studies addressing some measure of cost, and the lack of a formal cost-effective analysis.

Applicability

No 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 the 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 operations are becoming prominent in thoracic surgery, so the experience 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, numerous techniques are used to perform an esophagectomy: combinations of robot-assisted, open, or minimally invasive approaches. We focused on comparing robot-assisted surgery for the thoracic portion of the procedure; however, outcomes like anastomotic leak might not be comparable depending on the tumor location and location of the anastomosis. Several other outcomes related to esophagectomy correlate with pre-operative variables, such as receipt of neoadjuvant therapy, tumor stage, and comorbid status. Although several studies in this review match for these characteristics, there are inconsistencies with reporting these variables across studies. It is difficult to determine the influence of the robot-assisted approach when there are few RCTs or well-designed, matched studies.

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. Risk factors differ and underscore important clinical variation in patient populations. Further, East Asian countries have a higher incidence of esophageal cancer and thus higher surgical volume.

Third, the surgeon's physical experience using robot-assisted techniques is important to assess. The robotic platform has demonstrated improved ergonomics and less musculoskeletal complaints from surgeons compared to open and other minimally invasive surgical techniques, but this has not been universally observed. Research is needed to assess quality of life, chronic physical injuries, and longevity across approaches.

Fourth, the learning curve likely has an impact on certain outcomes like OR time, blood loss, and intra-operative complications. This learning curve is typically present with most evolving surgical technology; however, its influence should lessen with time and experience. Therefore, the learning curve may be considered as a potential factor in our findings.

Fifth, there is a lack of high-quality evidence on long-term and oncologic benefits, or risks, of RAMIE. Most studies comparing RAMIE focus on intra-operative and post-operative outcomes. 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 larger studies with adequate follow-up may be available.

Sixth, there is a paucity of studies directly comparing cost between RAMIE and other comparable approaches. There is a need for standardized methods to assess cost (*ie*, analytics, consistent definitions of cost, how upfront capital was accounted for, how to adjust for training staff, *etc*). Formal cost-effectiveness studies are needed.

Further, there has been evidence in other cancer types, mainly in gynecologic oncology that *worse* survival may occur with minimally invasive surgery. This finding supports the ongoing need for rigorous investigation into the comparative benefits and risks of robotic surgery across specialties and cancer types.

CONCLUSIONS

In summary, esophagectomy is a complex procedure with a high rate of morbidity, and while the robot-assisted approach has the potential to improve several important patient outcomes, current data are 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 the determination of risks as well. Additional work should weigh the financial differences of the robot-assisted esophagectomy relative to the clinical advantages and disadvantages.