



Patient reported outcomes (PROs) after minimally invasive and open esophagectomy

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Abstract: Esophagectomy for esophageal malignancies remains an operation with significant potential morbidity and mortality. However, surgical outcomes continue to improve over time and focus has shifted toward not just good outcomes, but quality of life post operatively. Patient reported outcomes (PROs) focus on quality of life measures via validated patient surveys has increasingly become a significant focus. While PROs do have their limitations, they represent a glimpse into the symptomatology, quality of life, and well-being of a patient undergoing a procedure with inherent morbidity. Working to improve outcomes from the perspective of the patient is not a new concept, but has become increasingly relevant as surgical quality for all procedures improves. The optimal approach to esophagectomy is controversial. Minimally invasive approaches attempt to avoid laparotomy and thoracotomy with the thought of improving post-operative quality of life by mitigating complications related to those open surgical approaches. The data in favor of laparoscopy and thoracoscopy is quite strong and multiple randomized controlled trials exist in this realm supporting minimally invasive approaches with regards to quality of life outcomes and more rapid return to patient's preoperative baseline. The data in favor of a robotic approach for esophagectomy is not quite as robust, but more studies show that these approaches mirror the benefits of the laparoscopic and thoracoscopic approaches without robotic assistance.

Keywords: Esophagectomy; minimally invasive esophagectomy (MIE); esophageal cancer; robotic esophagectomy; patient reported outcomes (PROs)

Submitted Feb 25, 2020. Accepted for publication May 13, 2020.

doi: 10.21037/jtd-2019-pro-09

View this article at: <http://dx.doi.org/10.21037/jtd-2019-pro-09>

Introduction

As surgical morbidity and mortality continues to decrease, and surgeons are embarking on increasingly complex procedures, outcomes and other quality metrics are continually monitored and critiqued. As health care systems continue to evolve, emphasis on the reporting of these outcomes has undergone a paradigm shift, from one of physician reported outcomes alone, to one that includes patient reported outcomes (PROs). PROs assess certain

interventions, and their effect on multiple reportable metrics, all from the perspective of the patient undergoing that specific intervention (1). As patient advocates from a surgical perspective, surgeons may use these data to select the most appropriate approach to surgery to help improve outcomes from the patient's point of view, although utilization of PROs to make meaningful conclusions does remain an area of controversy (1,2).

An esophagectomy remains a procedure with a significant amount of inherent morbidity, and techniques

and approaches that improve patient's overall well-being and quality of life are advantageous. While the immediate goal of an esophagectomy for malignancy is an appropriate oncologic outcome, an equal goal is good quality of life postoperatively, but often the latter is erroneously overlooked. Patients with esophageal cancer who undergo treatments with curative intent have a significant number of quality of life altering symptoms (3). Improved quality of life after esophagectomy also can be a predictor of long term survival outcomes, and may predict improved outcomes to a better degree than functional status scoring systems (4-6).

Functional recovery, immediate and chronic pain, and physical, social, and emotional well-being are all facets of complete perioperative recovery and represent targets for potential improvement after esophagectomy. Several instruments, primarily in the form of questionnaires, can be used to monitor these facets postoperatively from the patient's perspective. The most extensively utilized ones for post esophagectomy patients are the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-OES18, and Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaires coupled with patient reported pain scoring systems. These instruments contain quality of life measurements for general oncology issues, as well as esophageal components specific to esophageal quality of life concerns.

Minimally invasive approaches, whether laparoscopic and thoracoscopic alone or robotic assisted, seem to improve quality of life after esophagectomy when compared to similar open approaches. Analysis of the comparison of minimally invasive versus open esophagectomy (OE), from a quality of life perspective, will help to apply operative approaches to maximize PROs. For the purposes of this review, the focus will be on the randomized controlled trials available and higher quality large series, if applicable. Also, for the purposes of this review, MIE is defined as those approaches utilizing a complete laparoscopic and thoracoscopic approach, and hybrid approaches will not be discussed. Data for minimally invasive and robotic esophagectomies will be looked at separately in comparison to open, although robotic approaches represent a subset of the minimally invasive approach.

Minimally invasive esophagectomy (MIE) versus OE

The TIME trial was a randomized controlled trial comparing minimally invasive Ivor Lewis esophagectomy with thoracoscopy and laparoscopy with standard open approaches, and PROs were reported as secondary outcomes at 6 week patient follow up (7). In the MIE arm, short term quality of life outcomes were improved in SF-36 physical health component summary score, which primarily represents physical functioning, physical capabilities, pain, and general health ($P=0.007$), with the mental component summary scores statistically similar ($P=0.806$). By the EORTC-C30, global patient health was improved with MIE ($P=0.020$) and by EORTC-OES18, talking and pain scores were improved in MIE ($P=0.008$, $P=0.002$) (7). All of these short term quality of life outcomes differences persisted at one year follow up, with the exception of talking scores becoming statistically similar (8).

In another randomized trial, Hong *et al.* randomized patients to minimally invasive or OE (9). Using the EORTC QLQ-30 and OES-18, both groups had global quality of life and physical functioning declines, not unexpectedly. However, the MIE arm had improved global quality of life scores at 2 and 4 weeks, ($P<0.001$), improved physical functioning scores at 2, 4, and 8 weeks ($P<0.001$), and improved fatigue and pain symptom scores at 2, 4, 8, and 12 weeks. ($P<0.001$). Also, the MIE global quality of life scores nearly matched the preoperative levels (82.5 ± 11.4 baseline *vs.* 82.1 ± 10.5 at 12 weeks), while the OE cohort failed to return near baseline (83.3 ± 10.9 baseline *vs.* 71.3 ± 11.9). Also, pain and fatigue symptom scores at 12 weeks exceeded their baseline in the OE arm.

In the largest propensity matched cohort study of MIE *vs.* OE in the literature, Wang *et al.* compared 444 MIE patients to 444 OE and included analysis on quality of life using the EORTC QLQ-30 and OES-18 questionnaires (10). Analysis included measurements to 24 months post operatively. MIE patients had improved global quality of life at 1, 3, 6, and 12 months ($P<0.001$), improved physical function at 1, 3, 6, and 12 months ($P<0.001$), less fatigue symptoms at 1, 3, 6, and 12 months ($P<0.001$), less pain symptoms at 1, 3, and 6 months ($P<0.001$) and less dyspnea symptoms at 1, 3, and 6 months ($P<0.001$). Beyond those time periods noted, there

was no statistically significant difference in scores up to 24 months. Also, type of surgical approach, whether minimally invasive or open, independently had a positive impact of patients post-operative quality of life scores, with age and neoadjuvant therapy having a negative impact.

It is important to note, that nearly all minimally invasive techniques for esophagectomy use the Ivor Lewis or McKeown approach. Minimally invasive, or laparoscopic, transhiatal esophagectomy has been attempted by some surgeons with varying opinions. Some have advocated its use in distal esophageal cancers (11), while others have reported poor results leading to inadequate lymph node dissection and difficulty with hemostasis (12). Overall, laparoscopic transhiatal esophagectomy is associated with fewer complications and shorter hospital stays (13). Nevertheless, there are currently no known randomized studies strictly comparing a minimally invasive transhiatal esophagectomy to conventional OE in the setting of esophageal cancer. In a randomized study by Fontan and colleagues, minimally invasive laparoscopic esophagectomy was compared to open transhiatal esophagectomy in patients with megaesophagus in the setting of achalasia (14). A total of 30 patients were included, with 15 in each group. Dysphagia, overall pain, and in-hospital complications were analyzed, and with a mean follow-up time of 33 months, no statistically significant difference was identified. One death was reported in each group. Also, although there have been numerous studies comparing open transhiatal esophagectomy to other open approaches that include a transthoracic component, no randomized studies comparing minimally invasive transhiatal esophagectomies to other minimally invasive approaches have been reported.

Robotic assisted minimally invasive esophagectomy (RAMIE) versus open

While robotic assisted surgery is essentially a subset of minimally invasive surgery, its comparison as a unique surgical approach in comparison to open should be evaluated as well. While high quality data for robotic approaches compared to open remains less robust in comparison with minimally invasive approaches, data is maturing in favor of the robotic assisted approaches. However, it is important to note that robotic assisted techniques and approaches vary in the literature, with the only completely robotic approach published by Sarkaria and colleagues (15-17).

In the only randomized control trial in this arena,

the recently published ROBOT trial compared robotic esophagectomy versus open, and in the trial, PROs were evaluated, but it was not a primary endpoint of the trial (18). Mean overall postoperative pain scores were less in RAMIE vs. OE ($P < 0.001$) and in 11 of 14 days, daily mean pain scores were statistically significantly less in the RAMIE arm. Using the EORTC-QLQC30, both discharge and 6-week health related quality of life and physical functioning were both statistically improved after RAMIE compared to OE ($P = 0.02$ to 0.049)

Sarkaria *et al.* evaluated quality of life outcomes for RAMIE or OE utilizing the FACT-E questionnaire in a prospective fashion (19). This includes a total score and subset scores for physical, social, emotional, and functional, and esophageal-specific well-being. Overall, there was no difference in the total FACT-E scores between RAMIE or OE ($P = 0.84$), or in any specific subset ($P = 0.49$ to $P > 0.95$). Both approaches to surgery yielded lower physical well-being scores at 1 month ($P < 0.001$), with improvement at 4 months ($P \leq 0.001$), but without returning to baseline ($P = 0.011$); findings for emotional well-being scores were similar. Importantly, RAMIE compared to OE had lower pain scores ($P = 0.005$) and pain interfering with daily activity scores ($P = 0.002$) in the early post-operative period. For both RAMIE and OE, pain scores significantly improved at each measured period to 4 months.

Sugawara *et al.* also analyzed quality of life outcomes up to 24 months post operatively (20). RAMIE patients had higher physical and emotional function scores at 3, 6, and 18 months and 6, 18, and 24 months, respectively, compared to the open cohort. Generalized pain scores were lower in the RAMIE group at 3, 6, 12, and 24 months post-operatively, and esophageal specific pain scores were less at 3 and 18 months as well. Fatigue and insomnia at 24 months were less frequently reported in the RAMIE group. Importantly, this study is associated with significant bias due to the comparison of a robotic transhiatal approach with an open Ivor Lewis approach.

Similarly, as in traditional minimally invasive approaches, robotic assisted techniques for esophagectomy more commonly involve a transthoracic component as well. The studies regarding RAMIE above all include a transthoracic component during the esophagectomy, unless otherwise stated. There are currently a limited number of studies evaluating robotic transhiatal esophagectomies, none of which are randomized. Although some authors have reported similar oncologic results in robotic transhiatal resections compared to open (21,22), no study has reported

PROs. Overall, further randomized perspective studies need to be performed to provide any definitive conclusions.

Conclusions

Based on the aforementioned studies, it appears that both minimally invasive esophagectomies, whether laparoscopic and thoracoscopic or robotic assisted approaches, offer significant benefits with regards to PROs in comparison to its open counterpart. These primarily represent improved functional recovery, quality of life, and improved pain, all facets which minimally invasive surgeons have emphasized as benefits of the approach. Overall, the weight of data supports the use of MIE from the perspective of improved post-operative quality of life, and more rapid return to preoperative baseline.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Peter Kneuert) for the series “Patient reported Outcomes in Thoracic Surgery: A new Frontier” published in *Journal of Thoracic Disease*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-2019-pro-09>). The series “Patient reported Outcomes in Thoracic Surgery: A new Frontier” was commissioned by the editorial office without any funding or sponsorship. Dr. JDL reports and owns stock in: Intuitive Surgical, Inc., Cigna Corp, and Proctor and Gamble. ISS serves as an unpaid editorial board member of *Journal of Thoracic Disease* from Sept 2018 to Aug 2020. Dr. ISS reports honoraria and/or grants for research/education/training, and/or consulting for Intuitive Surgical, Inc., On Target Laboratories, Cambridge Medical Robotics, and Auris Medical, all outside the scope of the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work are

appropriately investigated and resolved.

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Cite this article as: Brady JJ, Witek TD, Luketich JD, Sarkaria IS. Patient reported outcomes (PROs) after minimally invasive and open esophagectomy. *J Thorac Dis* 2020;12(11):6920-6924. doi: 10.21037/jtd-2019-pro-09