



# Outcomes of robotic esophagectomy

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**Abstract:** Esophagectomy has long been considered the standard of care for early-stage ( $\leq$  T2N0) esophageal cancer. Minimally invasive esophagectomy (MIE), using a combined laparoscopic and thoracoscopic approach, was first performed in the 1990s and showed significant improvements over open approaches. Refinement of MIE arrived in the form of robotic-assisted minimally invasive esophagectomy (RAMIE) in 2004. MIE is a challenging procedure for which consensus on optimal technique is still elusive. Although nonrobotic MIE confers significant advantages over open approaches, MIE remains associated with stubbornly high rates of complications, including pneumonia, aspiration, arrhythmia, anastomotic leakage, surgical site infection, and vocal cord palsy. RAMIE was envisioned to improve operative-associated morbidity while achieving equivalent or superior oncologic outcomes to nonrobotic MIE. However, owing to RAMIE's significant upfront costs, steep learning curve, and other requirements, adoption remains less than widespread and convincing evidence supporting its use from well-designed studies is lacking. In this review, we compare operative, oncologic, and quality-of-life outcomes between open esophagectomy, nonrobotic MIE, and RAMIE. Although RAMIE remains a relatively new and underexplored modality, several studies in the literature show that it is feasible and results in similar outcomes to other MIE approaches. Moreover, RAMIE has been associated with favorable patient satisfaction and quality of life.

**Keywords:** Esophageal cancer; esophagectomy; open thoracotomy; minimally invasive esophagectomy (MIE); robotic-assisted esophagectomy

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## Introduction

Esophageal cancer is the eighth most common malignancy worldwide, with an annual incidence of 572,034 cases, according to the GLOBOCAN database (1). The role of esophagectomy in early-stage ( $\leq$  T2N0) esophageal cancer is well established, and the procedure is considered the cornerstone of curative treatment for patients with this disease (2).

Although surgery in general has undergone an evolution

toward minimally invasive techniques during the last several decades, the safety of minimally invasive esophagectomy (MIE) and its routine use have taken longer to establish. However, several recent randomized controlled trials have shown that MIE results in lower morbidity and better short-term quality of life, compared with open esophagectomy (3,4).

Esophagectomy is a complex procedure, and controversy remains regarding the optimal technique for this operation. A thoracic approach is mandatory for optimal resection

**Table 1** Meta-analyses comparing outcomes of minimally invasive versus open esophagectomy

Study	Year	MIE/OE, No.	Overall complications	Pulmonary complications	Anastomotic leak	EBL, WMD	Days in hospital, WMD	R0 resection	Harvested lymph nodes, WMD	5-year survival
Sgourakis et al. (9)	2010	203/805	1.98 (1.08–3.43) <sup>a</sup>	1.31 (0.52–3.31) <sup>a</sup>	1.63 (0.68–3.87) <sup>a</sup>	NA	NA	NA	-1.51, P=0.10	NA
Nagpal et al. (10)	2010	152/326	0.52 (0.32–0.84) <sup>a</sup>	0.58 (0.35–0.98) <sup>a</sup>	0.58 (0.28–1.20) <sup>a</sup>	-268, P<0.01	-2.75, P=0.004	NA	1.02 (0.84–2.88) <sup>a</sup>	NA
Dantoc et al. (11)	2012	494/1,212	NA	NA	NA	NA	NA	NA	0.33, P=0.04	0.88 (0.65–21) <sup>c</sup>
Guo et al. (12)	2016	765/784	1.20 (1.08–1.34) <sup>b</sup>	1.42 (1.03–1.97) <sup>b</sup>	1.08 (0.78–1.48) <sup>b</sup>	345.2, P<0.001	NA	NA	NA	0.92 (0.72–1.18) <sup>c</sup> , P=0.5
Lv et al. (13)	2016	2,091/3,934	NA	0.74 (0.58–0.94) <sup>b</sup>	NS	44.4, P<0.01	NA	1.03 (0.98–1.08) <sup>b</sup>	-0.80, P=0.68	NA
Yibulayin et al. (14)	2016	5,235/10,555	0.7 (0.62–0.78) <sup>a</sup>	0.527 (0.43–0.64) <sup>a</sup>	NS	-196, P<0.05	-3.60, P<0.05	NA	-1.27, P=0.58	NA
Xiong et al. (15)	2017	256/229	NA	Shorter in MIE, P<0.01	NS	-0.9, P<0.01	Shorter in MIE, P<0.01	NA	0.07, P=0.4	NA

<sup>a</sup>, odds ratio (confidence interval); <sup>b</sup>, relative risk (confidence interval); <sup>c</sup>, hazard ratio (confidence interval). MIE, minimally invasive esophagectomy; OE, open esophagectomy; EBL, estimated blood loss; WMD, weighted mean difference; NA, not available; NS, not significant.

of the tumor and surrounding lymph nodes (5). However, even with refinement of the approach, and even when it is performed by surgeons with considerable expertise with the technique, high complication rates persist for esophagectomy. In the Western world, surgical morbidity has been reported to be as high as 23% to 50%, with surgical mortality of 2% to 8% (6). Hence, there is a constant drive among surgeons to identify innovations and refinements that can improve outcomes for these patients.

To minimize the morbidity associated with open esophagectomy, MIE was developed in the 1990s. The current definition of MIE includes the use of a laparoscopic and/or thoracoscopic approach (6), and more recently robotic assistance has been included. Robotic esophagectomy was first described by Kernstine and colleagues in 2004 (7). Over the past 15 years, robotic-assisted minimally invasive esophagectomy (RAMIE) has begun to grow in popularity, as the use of the DaVinci system has become more widespread and training programs have adopted this technique. Robotic surgery offers the advantages of enhanced visualization and freedom of motion. Whereas robotic approaches are routinely used for a range of oncologic procedures, including radical prostatectomy and hysterectomy, the technique is still being investigated for esophagectomy.

Candidates for MIE are also candidates for RAMIE. The indications for MIE include Barrett's esophagus with high-grade dysplasia, end-stage achalasia, esophageal strictures, and esophageal cancer (8). The specific steps and details of the procedure are beyond the scope of this article. In this chapter, we will compare operative, oncologic, and quality-of-life outcomes between RAMIE, nonrobotic MIE, and open esophagectomy.

### Operative outcomes

The benefits of MIE over open surgery have been established in several retrospective studies and were summarized in a recently published meta-analysis (9-15) (Table 1). These studies reported that perioperative total complications and intraoperative estimated blood loss (EBL) were lower for MIE than for open esophagectomy. Overall, the most common postoperative complications following MIE are respiratory complications (pneumonia, aspiration), followed by arrhythmia, anastomotic leakage, surgical site infection, and vocal cord palsy. These complications have varying effects on outcomes, and early accurate diagnosis is required to avoid life-threatening issues. Although it is not

yet the state of the practice, it is hoped that, in the future, such complications could be largely avoided through the optimization of the surgical techniques used for MIE.

To prevent pneumonia in esophagectomy patients, adequate breathing, early mobilization, and effective postoperative pain management are key. Accordingly, MIE, which achieves improvements in breathing, mobilization, and pain over open esophagectomy, has been shown to reduce the incidence of pulmonary infection during the postoperative course (3,8,12-15). Biere *et al.* reported the results of a randomized controlled trial comparing outcomes between MIE and open esophagectomy (3). They found that only 9% of MIE patients developed pulmonary infection within the first 2 postoperative weeks, compared with 29% of open esophagectomy patients ( $P=0.005$ ). Moreover, mirroring the findings from the meta-analysis, they observed significantly less vocal-cord paralysis (2% *vs.* 14%;  $P=0.01$ ) and EBL [median [range], 200 [20-1,200] *vs.* 475 [50-3,000] mL;  $P<0.001$ ] in patients undergoing MIE versus open esophagectomy.

The reduced morbidity associated with minimally invasive techniques results in a decrease in hospital and ICU stay, compared with open approaches (19.6 and 7.6 days *vs.* 14.9 and 4.5 days) (16). The results of the ECOG 2202 trial—a multicenter phase II prospective trial designed to evaluate the feasibility of MIE for patients with high-grade dysplasia or esophageal cancer—observed 30-day mortality of 2.1% in patients who underwent MIE. ICU stay was 2 days for MIE patients, with an overall hospital stay of 9 days (17).

Although thoroscopic MIE has been shown to be superior to open esophagectomy in operative outcomes, some limitations have been noted—for instance, the two-dimensional visualization of the MIE approach and the limited freedom of instrumental movements due to the positioning of the fulcrum at the intercostal space. RAMIE was developed to address some of these limitations. The robotic platform provides three-dimensional vision of the surgical field and 10-fold magnification and includes an EndoWrist instrument with 7 degrees of freedom, which can translate the surgeon's natural movements. Of importance, Gergadus reported that patients who underwent RAMIE experienced less pain than patients who underwent other MIE techniques. The authors suggested this finding was attributable to the longer instruments of the robotic platform, which carry the advantage of placing the fulcrum inside the thoracic cavity instead of at the intercostal space (18).

In addition, RAMIE has been noted to include other

potential intraoperative and postoperative advantages. The robot is especially useful in operating fields where locations are hard to reach. Bodner *et al.* suggested that the esophagus is an ideal organ for the use of RAMIE, as the operative area is relatively small and difficult to maneuver around. Hence, RAMIE allows a meticulous dissection, with the magnified field enhancing the ability to operate on moving structures caused by breathing and pulsatile movements of the heart and the aorta (19).

Another benefit of the RAMIE technique is the decreased volume of EBL, which is secondary to the detailed and magnified dissection capabilities of the robotic platform. In a retrospective study by Cerfolio *et al.*, no patients who underwent RAMIE required blood transfusion (20). A meta-analysis by Jin *et al.* confirmed that RAMIE definitively reduced EBL, compared with other MIE approaches [mean difference (MD), -33.2268;  $P=0.0075$ ]. Perioperative complication rates were similar between RAMIE and other MIE approaches, with no statistically significant differences in the incidence of anastomotic leak, pneumonia, arrhythmia, or chylothorax. In its favor, RAMIE did result in fewer cases of vocal cord palsy [odds ratio (OR), 0.5696;  $P=0.0447$ ] (21). This severe complication is secondary to intraoperative recurrent laryngeal nerve injury. Although, at present, there are too few analyses of RAMIE versus MIE to make definitive conclusions, the better visualization afforded by the robotic platform during lymph node dissection gives hope that wider use of RAMIE will eventually lead to lower rates of vocal cord paralysis and aspiration.

Postoperative mortality and length of hospital stay were also found to be similar between RAMIE and MIE. In a meta-analysis, 30-day mortality (OR, 0.8341;  $P=0.7696$ ), 90-day mortality (OR, 0.3224;  $P=0.3329$ ), in-hospital mortality (OR, 0.3733;  $P=0.3895$ ), and length of hospital stay (MD, -5.0228 days;  $P=0.1342$ ) did not differ between techniques (21).

A common perceived shortcoming of any MIE technique, especially RAMIE, is that it requires increased intraoperative time. However, Jin *et al.* described no significant difference in operation time between conventional approaches and MIE (MD, 24.3655 min;  $P=0.2402$ ) (21). Furthermore, Weksler *et al.* observed homologous operative time between RAMIE and any other MIE [449 min (RAMIE) *vs.* 510 min;  $P=0.07$ ], including the time required to dock and prepare the robot (22).

In conclusion, MIE results in better operative outcomes than open esophagectomy. RAMIE results in lower incidence of EBL, pain, and vocal-cord paralysis than nonrobotic MIE. The adoption of RAMIE does include

increased costs, a complex learning curve, and specific requirements for room layout and robot docking. For these reasons, many remain skeptical that RAMIE is superior to MIE.

### Oncologic outcomes

Overall and disease-free survival have been shown to be similar between MIE and open esophagectomy (3). Straatman *et al.* observed similar overall 3-year survival between MIE and open esophagectomy among patients with esophageal cancer of any stage [41.2% (MIE) *vs.* 42.9% (open);  $P=0.633$ ]. Furthermore, in this study, disease-free survival was not significantly different between MIE and open esophagectomy (37.3% *vs.* 42.9%;  $P=0.602$ ) (8). In addition, in a recent national population study, matched overall survival was not significantly different between MIE or RAMIE versus open esophagectomy ( $P=0.306$ ) (23).

Lymph node harvest plays a crucial role in staging and stratification of esophageal cancer. Patients with esophageal cancer have a high rate of cancer metastasis, especially on the recurrent laryngeal nerve area in cases of squamous cell histologic type. Extended lymphadenectomy is associated with improved overall survival (24). Rizk *et al.* demonstrated that staging was most accurate when at least 18 lymph nodes were harvested between the thoracic and abdominal areas during esophagectomy (25). The National Comprehensive Cancer Network (NCCN) guidelines recommend harvesting at least 15 nodes (26). Therefore, because of the staging and prognostic importance of adequate lymphadenectomy, it is critical that the surgical approach used for esophagectomy allows optimal lymph node exposure and dissection. Patients undergoing nonrobotic MIE or RAMIE had more lymph nodes harvested than patients undergoing open surgery (23,27). Experience suggests that surgeons find it easier to reach the upper mediastinal nodes and achieve complete oncological resection during MIE—and, in particular, RAMIE—than by conventional thoracotomy. Van Der Horst *et al.* reported an average lymph node yield of 24 using RAMIE, which is well above the NCCN recommendation (28). In a pooled data analysis from a meta-analysis, the number of lymph nodes harvested did not differ significantly between MIE and RAMIE (MD, 0.82;  $P=0.20$ ) (21).

The ability to obtain a complete microscopic R0 resection is another important predictor of long-term survival in patients with esophageal cancer (29). In a 2-year single-center study, Cerfolio *et al.* reported that

R0 resection was achieved in all patients who underwent RAMIE (20). The authors suggested that the robotic approach was a defining factor in attaining R0 resection, as it allowed better visualization and mobility during surgery. However, in a meta-analysis from Jin *et al.*, the R0 resection rate was not statistically different between RAMIE and nonrobotic MIE (OR, 1.11;  $P=0.8647$ ) (21).

### Quality-of-life measures

An important consideration for the validation of a new technique is its impact on quality of life. Luketich *et al.* showed that, following MIE, patients return to their baseline quality-of-life scores and that such scores were similar to those for the mean overall population (29). Following open surgery, patients often report protracted pain in the thoracotomy scar and dysfunction in the right shoulder. Postoperative thoracotomy syndrome, which has been reported to occur in up to one-third of patients, has a negative influence on performance of daily activities (30).

In a study from Parameswaran *et al.*, fatigue scores were similar between open esophagectomy and MIE at 3 months but were better at 6 months among patients who had undergone MIE. Similarly, ability to perform daily living activities was similar between the two groups immediately after surgery but was better at 3 months in the MIE group (31). Furthermore, in a recently published randomized controlled study, RAMIE was associated with better short-term quality of life and short-term postoperative functional recovery, compared with open esophagectomy (4).

Sugawara *et al.* investigated quality of life between nonrobotic MIE and RAMIE. They reported that, at 24 months after surgery, global quality of life ( $P=0.01$ ) and emotional function ( $P=0.01$ ) were significantly higher in the RAMIE group than in the nonrobotic MIE group. Moreover, they observed less fatigue ( $P=0.04$ ), pain ( $P=0.04$ ), and insomnia ( $P=0.04$ ) in patients who had undergone RAMIE (32).

A Japanese study examining patients who had undergone transmediastinal esophagectomy found that global health stats, physical functional scale scores, and cognitive functional scale scores were significantly higher in patients who had undergone robotic procedures, compared with those who had undergone laparoscopic transthoracic esophagectomy. In addition to the above quality-of-life measures, the authors investigated several subjective endpoints that correlate with patient wellness. They found that fatigue ( $P=0.003$ ), nausea ( $P=0.032$ ), pain ( $P=0.025$ ),

appetite loss ( $P=0.018$ ), reflux ( $P=0.001$ ), and taste score ( $P=0.041$ ) were all significantly better after RAMIE than laparoscopic transthoracic esophagectomy (33). Hence, MIE—and, in particular, RAMIE—results in superior quality of life outcomes.

## Conclusions

Although RAMIE remains a relatively new and underexplored modality, several studies have demonstrated that the robotic approach is feasible and results in similar outcomes to other MIE approaches. Moreover, RAMIE has been associated with favorable results for patient satisfaction and quality of life, compared with other MIE techniques (30-33). However, RAMIE requires increased costs and a steep learning curve, and data from large randomized controlled trials investigating its use are currently lacking.

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