Review Article

Narrative review of worldwide data on outcomes of robotic esophagectomy

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Objective: Within the last decade, robotic esophagectomy has been adopted in many centers worldwide. Here we present the most relevant and recent publications regarding the various important aspects of robotic-assisted minimally invasive esophagectomy (RAMIE) including complications, mortality, operative and short-term outcomes as well as long-term oncologic results.

Background: Since the introduction of robotic-assisted approaches to thoracic surgery, the adoption rate of RAMIE has grown exponentially. As such, critical analysis of outcomes following RAMIE should follow the same accepted standards as its minimally invasive esophagectomy (MIE) predecessor. Furthermore, in considering the technological improvements associated with the Da Vinci™ platform, proponents of RAMIE have advertised it as a superior surgical technique compared to MIE and open approaches. Therefore, we report the most relevant and recent publications regarding the various important aspects of RAMIE including postoperative complications, mortality, operative and short-term outcomes, and long-term oncologic results.

Methods: All the publications under "robotic esophagectomy" and "robot-assisted esophagectomy" from PubMed and Embase databases were reviewed, the selection was based on case reports and group experiences, the analysis was limited to studies with the largest number of cases.

Conclusions: Reported outcomes for robotic esophagectomies are comparable to the historic data for MIE. Robotic esophagectomy seems to be superior to MIE in the number of harvested lymph nodes (LNs) around the recurrent laryngeal nerve (RLN) with a lower incidence of RLN injury but higher quality data is required.

Keywords: Robotic esophagectomy; robotic-assisted esophagectomy (RAE); esophageal cancer

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Introduction

Esophagectomy is considered standard of care for esophageal cancer. This procedure is associated with significant morbidity and mortality. Since the introduction of minimally invasive approaches to esophagectomy, there has been improvement in postoperative outcomes, less postoperative respiratory complications, shorter hospital stay and improved short-term quality of life (QOL). More importantly, these improved outcomes are achieved while maintaining similar oncological outcomes compared to open esophagectomy (OE) (1-3).

Minimally invasive esophagectomy (MIE) has become

the preferred approach to esophagectomy over the open approach. The TIME trial (1) was a multi-center randomized controlled trial (RCT) in which 56 patients underwent OE and 59 patients underwent MIE. The minimally invasive surgery group experienced significantly lower pulmonary infections, blood loss and better short-term QOL. Furthermore, there was a trend towards shorter length of stay (LOS) in the MIE groups. No differences were found in the incidence of postoperative anastomotic leaks, return to the operating room, and 30-day mortality. A follow up study to the TIME trial (2) revealed similar 3-year disease-free survival (DFS) and 3-year overall survival (OS) among the two groups. Significant experience has accumulated regarding surgical outcomes for MIE which has led to the creation of an international consensus (4) providing guidance in data collection for complications and mortality associated with esophagectomy by system and the creation of standardized definitions and classifications for the following procedure-specific complications: anastomotic leak, conduit necrosis, chyle leak and vocal cord injury/palsy. Efforts to define and establish best possible outcomes for esophagectomy have been undertaken and published (5,6). Robotic trans hiatal esophagectomy was initially reported by Horgan *et al.* (7) in 2003, Kernstine *et al.* (8) reported Mckeown robot-assisted MIE (RAMIE) in 2004 and the first series was published by van Hillegersberg *et al.* (9). Within the last decade the number of reported robotic-assisted esophagectomy (RAE) cases has increased exponentially and multiple resources are available for education and training. Recently, the upper gastrointestinal international robotic association (UGIRA) presented the Da Vinci Ivor-Lewis Esophagectomy Procedure Guide, in this document the procedure is described step-by-step with thoughtful recommendations and technical comments and abundance of images. There is also an international consensus statement on RAMIE (10), this was a global initiative grouping 23 experts reviewed the available evidence and added their professional experience to publish a consensus statement on robotic esophagectomy to provide guidance for shortening the learning curve and improved outcomes. There is an emphasis in perioperative care as well which should help improve postoperative care and therefore outcomes, guidelines for perioperative care after esophagectomy have been recently published (11). Therefore, the objective of this study is to identify the current literature regarding RAE and to report its outcomes in comparison to the standard surgical techniques. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-56/rc).

Methods

Search under "robotic esophagectomy" and "robotic-assisted esophagectomy" was performed on PubMed and Embase in May 2021, publications were screened to series of cases with outcomes to reflect surgical groups particular experience, given large number of publications the results of the search was later limited to studies with the largest number of patients. In some publications comparing RAMIE with MIE, data were extracted to reflect RAMIE outcomes. Studies comparing RAMIE with MIE were selected as well, given MIE established role in the treatment of esophageal cancer with accepted short-term benefits compared to OE. Information was also presented according to institutional series, analyses of large national databases, literature reviews and metanalyses and ongoing related randomized trials to offer a general view of state-of-the-art in robotic esophagectomy.

Institutional series

Most of the current literature regarding RAMIE are contributions from institutional experiences (*Table 1*). In the largest multicenter study to date, Kingma *et al.* (12) reported the outcomes following RAMIE in 20 centers spanning across Europe, Asia, North and South America from 2016 to 2019. In their study of 856 patients undergoing RAMIE, the reported mortality (3%), morbidity (60%) and R0 (94%) and harvested lymph nodes (LNs) (median 28) were in accordance with international benchmarking studies. This study offers an insight of the status of RAMIE in the world. The largest single center experience on RAMIE was presented by Pointer *et al.* (13), 350 patients underwent RAMIE from 2010 to 2016, morbidity of 74%, mortality of 2.6%, R0 95%; outcomes similar to those reported by Kingma.

Cerfolio *et al.* (14) presented their experience on a single center retrospective review of 85 RAMIEs performed between 2011 and 2015. While this study is identified as one of the earlier single institutional studies, this manuscript is of particular interest due to the details provided regarding complications associated with the robotic surgical technique as an attempt to improve outcomes through a root-cause analysis. It is also one of the few reports with conduit ischemia listed as a complication in two patients where

Table 1 Data from large institutional series

Study [year]	N	Mortality (%)	Rate of R0 resection (%)	No. of LNs harvested*	Morbidity (%)	Conversion rate (%)	LOS (d)*	ICU stay (d)*	PNA/ pulmonary (%)	Conduit ischemia (%)	Anastomotic leak rate (%)	Anastomotic stricture rate (%)	RLN injury (%)	Chyle leak (%)	Airway injury/ fistula (%)
Puntambekar *et al.* [2015]	83	0	97.60	18.3 [13–24]	19.20	0	10.3 [10–13]	1 [1–3]	4.80	NR	3.60	NR	2.40	1.20	NR
Park *et al.* [2016]	114	2.60	97.40	43.5±1.4	NR	0.80	16 [7–350]	1 [0–117]	9.60	NR	14.90	NR	26.30	1.80	0.80
Park *et al.* [2016]	62	1.60	98	37±17	NR	1.60			14.50	NR	NR	NR	13%	NR	NR
Cerfolio *et al.* [2016]	85	3.5	99	22	36.40	2.40	8 [5–46]		7.10	2.20	4.30	NR	NR	5.90	NR
Sarkaria *et al.* [2019]	64	1.60	97	25	NR		9 [5–17]	8 [5–34]	14	NR	2	4.70	3.10	0	NR
Chen *et al.* [2019]	68	0.00	100	24.7±7.5	NR	NR	15.1±9.3	3.8±5.8	18	NR	9	NR	NR	2.90	NR
van der Sluis *et al.* [2019]	56	4	93	27 [17–33]	59	5	14 [11–25]	1–2	28	NR	22	NR	9		NR
Xu *et al.* [2021]	310	0.60	96.20	22.4±8.1	31.60	NR		NR	8.70	NR	7.40	NR	9.70	1.30	NR
Yang *et al.* [2020]	271	0	93.90	20.3±9.5	45	–	11 [6–81]	2 [0–15]	8.90	0.40	11.80	NR	29.20	1.50	NR
Meredith *et al.* [2020]	144	1.40	100	20±9	23.60	NR	9 [4–66]	NR	6.90	NR	2.80	7.60	NR	NR	NR
Kingma *et al.* [2020]	856	3	94	28 [0–89]	60	NR	NR	NR	NR	NR	6–33	NR	IL: 0–2%, Mckeown: 7–11%	NR	NR
Pointer *et al.* [2020]	350	2.6	95.7	21 [4–63]	74	NR	9 [4–65]	NR	15	NR	15.7	NR	NR	1.7	NR
van der Sluis *et al.* [2021]	100	1	92	29 [8–65]	30	2	11 [7–92]	1 [0–84]	17	NR	8	NR	3%	4	1

*, data are presented as median [range] or mean ± SD. LN, lymph node; LOS, length of stay; ICU, intensive care unit; PNA, pneumonia; RLN, recurrent laryngeal nerve; NR, not reported; SD, standard deviation.

Table 2 Reviews of national databases

Study [year]	N (RAMIE)	Mortality (%)	Rate of R0 resection (%)	Rate of R1 resection (%)	No. of LNs harvested	Conversion rate (%)	LOS (days)	Comments
Yerokun *et al.* [2016]	231	3.70	NR	6.50	16	11.60	10	NCDB, 2010–2012
Weksler *et al.* [2017]	581	5.40	95.20	NR	10–23	6.70	NR	NCDB, 2010–2013
Harbison *et al.* [2019]	100	3	NR	6	NR	11	10	ACS-NSQIP, 2016–2017
Ali *et al.* [2021]	1,543	7.8	NR	3.9	16	5.4	12	NCDB, 2010–2016

RAMIE, robotic-assisted minimally invasive esophagectomy; LN, lymph node; LOS, length of stay; NR, not reported; NCDB, National Cancer Database; ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program.

conversion to an open approach was necessary.

Park *et al.* (15) reported their single center experience on 114 patients who underwent RAMIE McKeown between 2006 to 2014. In their cohort, Park *et al.* identified that 73% of their patients had the abdominal phase completed laparoscopically while only 1 patient required a conversion to thoracotomy for the chest portion. The authors performed extended lymphadenectomy which shows the largest number of harvested LNs (43.5±1.4) within all the studies analyzed in this article, the recurrent laryngeal nerve (RLN) injury was 26.3%. One event of tracheal fistula was reported as well and was adequately treated with stent insertion.

Puntambekar *et al.* (16) presented a single center, retrospective review of 83 patients that underwent RAMIE between 2009 and 2012. In their McKeown approach, while the abdominal portion was performed laparoscopically, the conduit was created extracorporeally. Furthermore, the esophageal mobilization was all performed robotically, and a lymphadenectomy was performed in an *en-bloc* fashion with preservation of the azygous vein. No conversions reported and anastomotic leak, chyle leak and RLN injury of 3.6%, 1.2% and 2.4 % respectively.

Sarkaria *et al.* (17) reported differences in QOL measure in 106 patients undergoing OE and 64 undergoing RAMIE between 2012 and 2014 at their institution. In their study, QOL was assessed using the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) and the Brief Pain Inventory (BPI) at 1 and 4 months after esophagectomy, the authors found similar FACT-E scores but significant lower BPI scores for RAMIE patients compared to OE. A follow up study at 2-year post esophagectomy (18) revealed higher FACT-E and lower BPI scores for RAMIE patients. The European experience was recently reported by van der Sluis *et al.* (19), results on 100 patients that underwent RAMIE with intrathoracic anastomosis, end-to-end anastomosis (EEA) 25 or 28 mm was used for anastomosis, 30% morbidity, 8% anastomotic leakage, 2 conversions of thoracic part, one due to technical issues with the gastric conduit and the other for adhesions. Thirty- and 90-day mortality were 1% and 3%.

Analyses of large national databases

Reviews of large nationally collected databases are valuable for they allow for the analysis in outcomes for large number of patients. They offer a glimpse of the status of current clinical practice. However, there are some shortcomings with this type of analysis; there is great variability in clinical practice, adherence to protocols, and in general a lack of standardization across different centers. Furthermore, reporting is not specific for the procedure and therefore data granularity and information pertinent to esophagectomy such as standardized definitions of postoperative complications are typically not provided (*Table 2*).

The National Cancer Database (NCDB)

Yerokun *et al.* (20) published a retrospective review of the NCDB, the authors compared open *vs.* minimally invasive approaches to esophagectomy. From 2010–2012, in the United States, out of a total of 4,266 esophagectomies performed for esophageal cancer, 2,958 underwent OE and 1,308 underwent MIE. A further analysis of the MIE group identified that 17.5% [231] underwent RAMIE. While there a higher number of LNs harvested in the MIE group, there was no difference in R0 resection, mortality, or their primary endpoint of 3-year survival between the MIE and OE group. In a similar comparison utilizing the NCDB, Weksler and Sullivan (21) compared and reported surgical approaches in 9,217 esophagectomies performed between

Table 3 Meta-analyses and systematic reviews

Author [study period]	Type	Studies included	Patients	Comments
Ruurda *et al.* [2007–2014]	Systematic review	16	432	High conversion rates 0–21% as well as anastomotic leakage 4–38%
Bongiolatti *et al.* [2009–2019]	Literature review	14	3,104	Improved conversion rate 6.7–12.1%, still high anastomotic leak 3.1–37%
Jin *et al.* [up to 2018]	Meta-analysis	8	931 RAMIE	No differences in R0, conversion, mortality, postoperative complications
Zheng *et al.* [1980–2020]	Meta-analysis	14	1,435 RAMIE, 1,452 MIE	Overall similar outcomes but RAMIE longer operative time and lower incidence of pneumonia
Manigrasso *et al.* [up to 2021]	Meta-analysis	23	3,832 RAMIE, 7,947 MIE	Overall similar outcomes but higher number of LNs retrieved and trend toward less pneumonia in the RAMIE patients
Angeramo *et al.* [2000–2020]	Meta-analysis	16 RAMIE, 46 MIE	974 RAMIE, 5,275 MIE	Only Ivor-Lewis esophagectomy, RAMIE with higher rate of R0

RAMIE, robotic-assisted minimally invasive esophagectomy; MIE, minimally invasive esophagectomy; LN, lymph node.

2010 and 2013. In this cohort, 581 patients underwent RAMIE, 2,379 MIE, and 6,257 OE. Important differences to note in the analysis was that RAMIEs were more likely to be performed at the highest volume centers per year. Despite reporting no differences in median survival among the three groups, unmatched analysis showed patients that underwent RAMIE or MIE had more LNs harvested than OE patients did. However, when comparing MIE and RAMIE, there were no differences between harvested LNs. While 30-day mortality was higher for the RAMIE group, there was no difference in 90-day mortality. Similarly, the propensity matched analysis showed no difference in number of LNs harvested or R0 resection, higher 30-day mortality in RAMIE persisted. Ali *et al.* (22) queried the NCDB from 2010 to 2016, on 6,661 patients, 1,543 RAMIE and 5,118 MIE, multivariable analysis showed lower risk of conversion to open, lower rate of R1 and higher LN yield in RAMIE patients. Ninety-day mortality was similar.

American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP)

Harbison *et al.* (23) conducted a retrospective analysis querying the ACS-NSQIP 2016–2017 database. The authors compared post-operative mortality and overall morbidity rates in patients undergoing RAMIE *vs.* MIE. Over this 2-year study period, a total of 725 patients underwent esophagectomy across a small number of NSQIP participating hospitals, 100 of which underwent RAMIE and 625 MIE. There were no significant differences in mortality or surgical complications between the two groups. Anastomotic leak in 14% and pneumonia in 11% were among reported complications.

Literature reviews and meta-analyses

Ruurda *et al.* (24) performed a literature search between 2007 and 2014 identifying 432 patients who underwent robotic esophagectomy across 16 studies. One hundred and eighteen of these RAMIE patients underwent a trans hiatal approach. Reported mortality ranged from 0% to 6%. Rates of R0 varied from 81–100% with 18 to 38 LNs harvested. Bongiolatti *et al.* (25) carried on a literature review on surgical and oncological outcomes in RAMIE in 14 studies published between 2009 and 2019. In an analysis of 3,104 patients, based on their qualitative assessment the authors concluded that RAMIE has similar outcomes to MIE (*Table 3*).

A meta-analysis by Jin *et al.* (26) identified 8 studies published to September of 2018 comparing 931 RAMIE and 931 MIE patients. While the authors did not find major significant differences between the two techniques, they found that RAMIE has long operative times, lower blood loss and trend towards less incidence of RLN injury. Despite these differences, there was no difference in the rate of R0 resection, number of harvested LNs and mortality.

Recently published by Zheng *et al.* (27), a meta-analysis on short-term clinical outcomes between RAMIE and MIE.

The final selection consisted of 14 studies, 1,435 patients in RAMIE group and 1,452 in the MIE group. While RAMIE again was found to have longer operative time, the RAMIE group had a lower incidence of pneumonia and RLN injury while experiencing similar mortality or OS when compared to the MIE group.

In their meta-analysis of clinical outcomes, Manigrasso *et al.* (28) reported on 35 studies comparing outcomes between RAMIE and Mie and between RAMIE and OE. A total of 3,832 RAMIE and 7,947 MIE patients were compared and there was no difference in mortality, R0, incidence of chylothorax, blood loss and conversion to open. RAMIE had higher number of harvested LNs and lower incidence of pneumonia. A total of 1,919 RAMIE and 2,566 OE patients were compared as well. RAMIE was superior to OE in many aspects, decreased blood loss, decreased incidence of postoperative pneumonia and surgical site infection, shorter LOS, and higher number of harvested LNs and R0. There were no differences in anastomotic leakage, RLN injury and chyle leak.

Angeramo *et al.* (29) conducted a meta-analysis comparing RAMIE with MIE in patients undergoing Ivor-Lewis esophagectomy, 60 studies were included of which 16 were RAMIE and 34 were MIE; 5,275 patients were in the MIE group and 974 patients were in the RAMIE group. Similar mortality, anastomotic leak and LN yield were found, RAMIE group had lower rate of pneumonia, higher rates of R0 and lower morbidity.

Studies comparing RAMIE *vs.* MIE

Robotic surgery is considered technologically superior to laparoscopic/thoracoscopic, multiple studies have been published comparing RAMIE to MIE, two ongoing randomized trial will offer stronger evidence for this comparison (*Table 4*).

In a retrospective single center, Chen *et al.* (30) performed a propensity score match analysis on 108 patients, 54 underwent RAMIE and 54 MIE for thoracic esophageal squamous cell carcinoma (SCC). The two approaches were similar in most of the short-term outcomes analyzed except for injury to the RLN. The incidence of RLN injury was significantly higher in the MIE group, 31.5% *vs.* 13%.

Meredith *et al.* (31), on a single center analysis of a prospective database of a total of 302 patients, 144 underwent RAMIE, 95 MIE-Ivor Lewis (MIE-IL) and 63 MIE-transhiatal esophagectomy (MIE-THE). RAMIE took longer, with higher retrieval of LNs, and lower pulmonary complications. Mortality was similar for all three groups.

Deng *et al.* (32) presented their single center retrospective review of 84 patients who had McKeown esophagectomy, 42 underwent RAMIE and 42 MIE. Overall short-term outcomes were similar but the number of harvested LNs around RLN was significantly higher for RAMIE patients. Duan *et al.* (33) reported similar results with lower in RLN injury in RAMIE. Gong *et al.* (34) found similar rate of RLN injury with higher LN retrieval in the RAMIE group. Tsunoda *et al.* (35) reported lower RLN injury in RAMIE group with significant lower incidence of postoperative pneumonia.

In one of the largest studies to date, Yang *et al.* (36), published a single center retrospective review on 650 patients who underwent McKeown esophagectomy between 2015 and 2018, 280 underwent RAMIE and 372 MIE, after propensity matching 271 patients per group were compared. Short-term outcomes were similar with only significant higher incidence in RLN injury in the RAMIE group. They also reported similar incidence and pattern of recurrence, 11.8% for RAMIE and 10.2% for MIE. No difference was noted for OS and DFS among the two groups for a median time of follow up of 20.2 months.

Park *et al.* (37) reported a single center experience between 2006 and 2014, early postoperative outcomes and long-term survival were compared between two groups, 62 patients underwent RAMIE and 43 MIE. To note, within the RAMIE group 42% of the patients had the abdominal part performed laparoscopically. Medians follow up 22 months. The 5-year survival rate was similar, 69% in the RAMIE group and 59% in the MIE group.

Xu *et al.* (38) presented a propensity score-matched study comparing the long-term outcomes of RAMIE *vs.* MIE McKeown. Between 2015 and 2019 a total of 721 patients underwent esophagectomy, 310 RAMIE and 411 MIE. A total of 292 patients from each group formed the cohorts after propensity matching, follow-up ranged 1 to 56 months with a median of 39.2 months. Five-year OS and DFS were similar for the two groups.

Shirakawa *et al.* (39) detailed their outcomes on 75 RAMIE and compared to MIE after pairing 51 cases using a propensity score. No significant differences were found between the two techniques. Similar results were reported by Tagkalos *et al.* (40) and Zhang *et al.* (41) and He *et al.* (42).

Randomized clinical trials

To date, there has been one completed randomized

Table 4 Series comparing RAMIE with MIE

Study [year]	Study group	N	Mortality (%)	Rate of R0 resection (%)	No. of LNs harvested*	Anastomotic leak rate (%)	RLN injury (%)	Chyle leak (%)	Pneumonia (%)	Conversion (%)	ICU stay (days)*	Hospital stay (days)*	Conduit necrosis (%)
He *et al.* [2018]	RAMIE	27	0	NR	20±7	11.10	14.80	0	18.50	NR	NR	13.8±2	NR
	MIE	88	2.30	NR	18±6	10.20	15.90	1.10	18.20	NR	NR	14.1±4.2	NR
Deng *et al.* [2018]	RAMIE	42	0	NR	21.9±9.9	4.80	9.50	2.40	7.10	NR	NR	NR	NR
	MIE	42	2.40	NR	17.8±8.3	2.40	14.30	2.40	4.80	NR	NR	NR	NR
Park *et al.* [2016]	RAMIE	62	1.60	98	37±17	8.10	13	NR	14.50	1.60	NR	NR	NR
	MIE	43	0	98	28.7±11.8	2.30	24	NR	14	2.30	NR	NR	NR
Zhang *et al.* [2019]	RAMIE	76	1.30	100	19.7±9.8	9.20	6.60	1.30	6.60	NR	NR	9 [8–12]	NR
	MIE	108	1.90	99.10	20.3±9.7	5.60	6.50	2.80	9.30	NR	NR	9 [8–12.3]	NR
Chen *et al.* [2019]	RAMIE	54	0	100	25.4 ±7.5	9.30	13	1.90	14.80	0	4±6.3	17.1±10.1	NR
	MIE	54	0	100	24.7±11.2	3.70	31.50	3.70	24	0	2.5±3.7	15.2±9.8	NR
Meredith *et al.* [2020]	RAMIE	144	1.40	NR	20±9	2.80	NR	NR	6.90	NR	NR	NR	NR
	MIE	95	2.10	NR	14±7	4.20	NR	NR	13.70	NR	NR	NR	NR
Yang *et al.* [2020]	RAMIE	271	0	94.10	20.3±9.9	11.80	29.20	1.50	8.90	0.70	2 [0–15]	11 [6–54]	0.40
	MIE	271	0.70	93.70	19.2±9.6	14.40	15.10	0.70	12.50	5.90	1 [0–61]	11 [4–94]	1.10
Tsunoda *et al.* [2021]	RAMIE	45	0.00	96	60 [32–124]	NR	7	NR	18.00	NR	NR	NR	NR
	MIE	45	0	100	54 [26–123]	NR	20	NR	44	NR	NR	NR	NR
Gong *et al.* [2020]	RAMIE	91	0.00	100	22.8±8.4	4.40	22	1.10	9.89	NR	NR	NR	NR
	MIE	144	0	100	23.1±10.2	6.90	24	0.07	10.40	NR	NR	NR	NR
Xu *et al.* [2021]	RAMIE	292	6.80	96.20	22.4±8.1	7.20	8.20	1	8.60	NR	NR	NR	NR
	MIE	292	1	95.50	21.7±5.9	8.20	9.20	1.40	9.90	NR	NR	NR	NR
Shirakawa *et al.* [2021]	RAMIE	51	0	NR	NR	9.80	17.70	NR	17.70	0	5 [5–6]	25 [21–36]	NR
	MIE	51	0	NR	NR	13.70	15.70	NR	19.60	0	6 [5–6]	23 [18–33]	NR
Tagkalos *et al.* [2021]	RAMIE	50	0	NR	27 [13–84]	12	NR	NR	12	NR	1 [1–43]	12 [7–59]	NR
	MIE	50	2.50	NR	23 [11–48]	18	NR	NR	18	NR	2.5 [1–25]	19 [9–55]	NR
Duan *et al.* [2021]	RAMIE	109	0	100	24.8±8	5.50	14.70	0.90	6.40	NR	6 [4–21]	NR	NR
	MIE	75	0	98.70	22.2±8.6	5.30	14.70	1.30	12	NR	7 [3–20]	NR	NR

*, data are presented as median [range] or mean ± SD. RAMIE, robotic-assisted minimally invasive esophagectomy; MIE, minimally invasive esophagectomy; LN, lymph node; RLN, recurrent laryngeal nerve; ICU, intensive care unit; NR, not reported; SD, standard deviation.

Table 5 Randomized control trials analyzing outcomes following RAMIE

Trial name	Study period	Center type	Goal of study
ROBOT	2019	Single-center	112 patients (56 RAMIE, 56 OE), no difference in postoperative complications and mortality with similar oncological outcomes. RAMIE patients had fewer cardiopulmonary complications, less blood loss and better functional recovery
RAMIE	Up to 2017	Multi-center	360 patients with SCC, RAMIE vs. MIE with primary endpoint 5-year survival. Short-term outcomes, QOL are secondary endpoints
REVATE	Up to 2018	Multi-center	To compare RAMIE with MIE for LN dissection along RLN in esophageal SCC
ROBOT-2	Up to 2021	Multi-center	To compare RAMIE with MIE, primary endpoint is number of LNs retrieved in esophageal adenocarcinoma

RAMIE, robotic-assisted minimally invasive esophagectomy; OE, open esophagectomy; SCC, squamous cell carcinoma; MIE, minimally invasive esophagectomy; QOL, quality of life; LN, lymph node; RLN, recurrent laryngeal nerve.

controlled trial (RCT) comparing RAMIE to other surgical approaches to esophagectomy. The ROBOT trial (43) was a single-center RCT of 112 patients, of which 56 underwent RAMIE and 56 OE. In this study, there was no significant difference in postoperative complications and mortality with comparable oncological outcomes. However, in the immediate postoperative period, the ROBOT trial identified a decreased incidence of cardiopulmonary complications, less blood loss and better functional recovery associated with the RAMIE group. Long-term follow up results were published by de Groot *et al.* (44) with comparable 5-year OS (41% RAMIE and 40% OE) and 5-year DFS rate (42% RAMIE and 43% OE), the recurrence pattern and incidence were similar as well.

Currently, there are three ongoing RCTs studying RAMIE. The RAMIE trial (45) is a multicenter, prospective, randomized non-inferiority trial initiated in 2017. A total of 360 patients with SCC from four high-volume centers in China will be assigned to either RAE or MIE. The primary endpoint of the RAMIE trial will be 5-year survival. Short-term outcomes, QOL, 5-year DFS and 3-year OS will be included as secondary endpoints. The REVATE trial (46) is a RCT designed to compare RAE with video-assisted thoracoscopic esophagectomy for LN dissection along the RLN in patients with esophageal SCC. It is a multicenter, open-label, RCT with patient recruitment started in 2018. The ROBOT-2 trial is a European, multicenter study started in 2021 aims to compare RAMIE with MIE for esophageal adenocarcinoma, the primary endpoint is number of LNs retrieved. Among secondary outcomes are complications, mortality, survival, QOL, and cost analysis (47) (*Table 5*).

Discussion

There is no doubt that the introduction of the Da Vinci™ platform has revolutionized the way we perform various surgical procedures in thoracic surgery. However, while this platform has augmented our abilities due to technology innovation, we must critically analyze outcomes to improve the way how we implement this technology. Efforts to define and establish best possible outcomes for esophagectomy have been undertaken and published (5,6). Thirteen surgical departments from Europe and US performing more than 20 esophagectomy per year, collected prospectively data from minimally invasive transthoracic esophagectomies within a period of 5 years (2011 to 2016) and out of 1,057 patients selected 334 patients that met low surgical risk criteria, surgical outcomes on this group of low-risk patients were considered the benchmark to be used as standard to meet or exceed. Several areas that continue further analysis include conversion from robotic to open techniques as well as several procedure specific postoperative complications.

Conversion to an open approach

During the widespread adoption of the MIE, conversion rates were reported frequently. Within the RAMIE literature, Cerfolio (14) reported conversion to an open approach in two patients. One patient required a conversion to laparotomy due to a dehiscence in the staple line during gastric conduit creation while the second patient required a conversion to thoracotomy due to the identification of tumor invasion into the airway. Sarkaria *et al.* (48) in a series of 21 patient reporting initial experiences with

RAMIE disclosed 5 conversions due to excessive operative time, questionable anastomotic integrity, dense adhesions and positive margin. Park (15) presented one conversion due to uncontrolled bleeding from a segmental branch of left inferior pulmonary vein. van der Sluis (19) reported two conversions out of 100 patients, one due to technical issues with creation of gastric conduit and another due to adhesions. The opening of this discussion may help programs who want to adopt the RAMIE approach to set reasonable standards and practice goals when starting off.

RLN LN dissection

The need for LN dissection near the RLN dissection is dependent on several factors including but not limited to tumor location, tumor histology, and preoperative imaging. Proponents of RAMIE have indicated potential superiority over MIE and OE approaches due to the improved visualization and therefore precise dissection. With the robotic platform, several authors have reported significantly higher number of LN harvested around the RLN (36,38). However, multiple studies have also reported higher incidence of RLN injury in the RAMIE group with reported RLN palsy rates of 26.3% (unilateral in 23.7% and bilateral in 2.6%) (15,36,38). While this may be alarming and may increase morbidity and mortality following esophagectomy, Yang and colleagues reported all RLN injuries they experienced were reversible and disclosed complete recovery during follow-up (36). Duan *et al.* (33) found increased number of LNs retrieved around the left RLN and similar or lower incidence of injury when compared with MIE and after the learning curve. The incidence of injury has also been associated with the learning curve with reports showing significant decrease in injury as experience grows (33).

Anastomotic leakage and conduit complications

Cerfolio (14) reported a 16.6% 30-day mortality and 33.3% 90-day mortality for patients with anastomotic leak or conduit ischemia. Yang *et al.* (36) reported 4 patients with conduit necrosis, 1 from RAMIE and 3 from MIE groups. Kingma *et al.* (12) on their series of 856 patients described in the detail site of the anastomosis and technique of creation with incidence of leak for each one. Hand-sewn anastomoses both neck or intrathoracic had the highest incidence of leak: 27% and 33%. Circular-stapled anastomoses had lower incidence of leak, 6% in the neck and 17% for intrathoracic. In their meta-analysis, Manigrasso *et al.* (28) looked into this, over 18 studies and 1,471 RAMIE and 2,011 MIE with no statistical difference between the two approaches. In summary, no big differences have been noted in the anastomotic leak rate between RAMIE and MIE and with very few reported cases of conduit ischemia and necrosis. It is unclear if this is due to the improved optics and use of indocyanine green (ICG) to assess conduit perfusion or reporting bias. With the improved suturing in the robotic platform, dedicated studies should be undertaken to assess anastomotic techniques and outcomes.

Chyle leak

Dezube *et al.* (49) addressed this issue in particular, on 347 esophagectomies, 70 RAMIE and 277 MIE. Chyle leak rate was 12.9% for RAMIE and 3.6% for MIE. Chyle leak was more likely in three-hole compared to Ivor-Lewis esophagectomy, also surgeon robotic experience made a difference and chyle leak was also more frequent on cases with prophylactic thoracic duct ligation. A meta-analysis (28) found no differences between RAMIE and MIE on 2,433 cases, 1,207 RAMIE and 1,226 MIE. In summary, the incidence of chyle leak does not seem to be different within the two approaches.

Airway fistula

Sarkaria *et al.* (48) on initial experience at MSKCC with RAMIE reported two patients with tracheobronchial fistula and anastomotic leak, the authors warned about potential for thermal injury during dissection close to the airway. Park (15) reported one tracheal fistula treated with stent, no additional details were provided. van der Sluis (19) reported an intraoperative airway injury which was repaired robotically with pericardial patch. Duen *et al.* (33) reported three tracheoesophageal fistulae but no details were given. As with conduit ischemia, airway fistula is rarely reported in the most recent publications likely due to increase in expertise and experience with the robotic technique.

QOL

It is expected that with minimally invasive techniques, short-term outcomes and QOL to be superior to open approach, the group from MSKCC reported early and 2-year QOL after RAMIE and OE (17,18) similar short-

term functional assessment but improved QOL at 2-year was found in patients that underwent RAMIE. In a propensity score-matched study (50) long-term health-related QOL was superior for RAMIE patients when compared to OE. The University of Michigan group recently published (51) no difference in QOL at 1-year when comparing conventional trans hiatal and robotic trans hiatal esophagectomy. Additional studies are warranted to assess this very important topic.

Oncological outcomes

With mastering of the robotic techniques, increased number of harvested LN around the RLN, long-term outcomes are expected to improve particularly for SCC of the esophagus, to date short-term and mid-term oncological outcomes are similar between RAMIE and MIE. Motoyama *et al.* (52) reported lower local recurrence in mediastinal nodes for patients undergoing RAMIE when compared to MIE, the authors suggested that the ability to retrieve higher number of LNs around RLN with RAMIE could be the reason. The currently ongoing randomized RAMIE and REVATE trials will address this issue.

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Footnote

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