

Systematic Review

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# Robot-assisted minimally invasive esophagectomy: systematic review on surgical and oncological outcomes

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## Abstract

**Aim:** Esophagectomy is associated with several post-operative complications (50%-70%) due to surgical trauma. Minimally invasive techniques have therefore been applied to decrease mortality and morbidity. Robot-assisted minimally-invasive esophagectomy (RAMIE) was developed to overcome the drawbacks of the thoraco-laparoscopic approach. The objective of this systematic review is to report some recent experiences and to compare RAMIE with other approaches to esophagectomy, focusing on technical and oncological aspects.

**Methods:** Pubmed, Embase and Scopus databases were searched for “robot-assisted esophagectomy”, “minimally invasive esophagectomy” and “robotic esophagectomy” in January 2020. The study was focused on original papers on totally endoscopic RAMIE in the English language. No statistical procedures (meta-analysis) were performed.

**Results:** Three hundred and twenty studies were identified across the database and after screening and reviewing, 14 were included for final analysis. The overall 90-day post-operative mortality after trans-thoracic esophagectomy ranged from 0% to 9% and did not differ between approaches. Post-operative complications ranged between 24% and 60.9%: respiratory (6.25% to 65%), cardiac (0.8% to 32%), anastomotic leak (3.1% and



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37.5%) and vocal cord palsy (9.1%-35%) were the most frequent. The evidence for long-term outcomes is weak, with no significant differences in overall survival, disease-free survival and recurrence identified in comparison with other approaches. The selected papers showed that RAMIE had comparable outcomes between the open and thoraco-laparoscopic approaches within a multimodal treatment pathway.

**Conclusion:** RAMIE also seems to be associated with better lymph node dissection, nerve sparing and quality of life, but larger studies are needed to obtain more evidence.

**Keywords:** Robot-assisted minimally invasive esophagectomy, esophageal cancer, robotic surgery

## INTRODUCTION

In the multimodal treatment pathway for esophageal carcinoma (EC), esophagectomy still remains an important component for curative and radical treatment. Current international guidelines<sup>[1-5]</sup> recommend combined treatment for patients with localized esophageal or esophagogastric cancer and support the use of minimally invasive surgery such as minimally-invasive thoraco-laparoscopic esophagectomy (MIE) and also RAMIE. Esophagectomy is still associated with several post-operative complications<sup>[5]</sup> due to surgical trauma and pre-operative clinical condition of the patient (advanced age, malnutrition, weight loss, chemoradiation). To reduce the consequent mortality and morbidity rates, surgeons have developed minimally invasive techniques also for a complex procedure such as esophagectomy<sup>[6-9]</sup>.

Furthermore, post-operative and oncological outcomes after esophagectomy are influenced by surgical volume and optimized by referral to specialized centers<sup>[10]</sup>. Several concerns have limited acceptance of MIE such as its technical complexity and doubts about its oncological value. The robotic platform (DaVinci system® Intuitive Surgical Inc, Sunnyvale, CA) has several advantages that could overcome the drawbacks typical of MIE such as a magnified and three-dimensional endoscopic view, and articulated instruments with digitally filtered movements<sup>[11]</sup>. From the innovative and pioneering experiences of Giulianotti *et al.*<sup>[12]</sup> and Kernstine *et al.*<sup>[13]</sup>, RAMIE has gained popularity amongst surgeons because it seems to ensure adequate oncological outcomes with lower surgical trauma, and fewer post-operative complications in a stable and comfortable environment<sup>[14]</sup>. A recent randomized controlled trial (RCT)<sup>[14]</sup>, a meta-analysis<sup>[15]</sup> and some multicenter retrospective studies<sup>[16,17]</sup> have demonstrated the safety and oncological adequacy of RAMIE, but other well-designed comparative long-term studies are needed to validate and establish the role of RAMIE.

The objective of this systematic review is to report some recent experiences and to compare RAMIE and other approaches for esophagectomy, with a focus on the technical and oncological aspects.

### Technical aspects of RAMIE

#### *Indications*

The selection criteria and indications for RAMIE are the same as standard trans-thoracic open or MIE<sup>[8-10]</sup> and nowadays, some centers perform it after neo-adjuvant chemotherapy or radiation therapy<sup>[14,15,17]</sup>. Relative contraindications to MIE include: poor performance status, impaired lung function to tolerate one-lung ventilation, previous mediastinal surgery or extensive radiation therapy to the mediastinum<sup>[18]</sup>. Some types of esophagectomy are available, principally due to localization of the tumor, surgeon preference and the reconstructive options, but the most used are the trans-hiatal and trans-thoracic approaches with reconstruction of the digestive tract in the neck (McKeown esophagogastrostomy) or chest (Ivor Lewis esophagogastrostomy)<sup>[18-22]</sup>.

### *Trans-hiatal RAMIE*

In this approach, the robotic platform is used only for gastrolisis, abdominal lymph node dissection, esophageal and mediastinal dissection and gastric tube reconstruction<sup>[19]</sup>. The anastomosis is performed in the neck<sup>[23,24]</sup>. The absence of thoracic incisions seems to be associated with lower post-operative respiratory complications and thus, this procedure could be proposed to patients with comorbidities such as chronic obstructive pulmonary disease and impaired lung function<sup>[19]</sup>. The mediastinal lymph node dissection includes only the para-esophageal and subcarinal stations<sup>[19]</sup>.

### *Trans-thoracic RAMIE with intrathoracic anastomosis (Ivor-Lewis procedure -ILE-)*

With the patient supine, the first abdominal step includes complete mobilization of the stomach, preserving the blood supply from the right gastro-epiploic artery, celiac and splenic lymphadenectomy, hiatal and low mediastinal dissections and finally, gastric tube tailoring. Next, the thoracic phase is frequently performed in a full-lateral left decubitus, semi-prone or prone position with or without single-lung ventilation<sup>[24-27]</sup>. The prone position is associated with low pressure capnothorax that could decrease the incidence of post-operative respiratory complications, but some concerns could arise in the event of conversion. Nowadays, the preferred patient position is semi-prone<sup>[14,18,28]</sup>. Usually, four or five access ports are used anteriorly to the latissimus dorsi muscle<sup>[14,18,28,29]</sup>. The surgical steps are: complete intrathoracic mobilization of the esophagus; para-esophageal, subcarinal and para-tracheal lymph node dissection; and lastly, esophago-gastric anastomosis above or at the level of the azygos vein<sup>[25-29]</sup>. Several types of anastomosis can be constructed in the chest and the choice depends on the surgeon's experience, skills and preference. Hand-sewn anastomosis can be performed with the robotic platform, but it did not show clear advantages in terms of reduced incidence of anastomotic leak or stricture, and is associated with longer operative times<sup>[20]</sup>. The last Xi DaVinci® platform is armed with robotic staplers and some surgeons have shifted from hand-sewn to mechanical anastomosis<sup>[30]</sup>.

### *Trans-thoracic RAMIE with cervical anastomosis (McKeown procedure -MKE-)*

Three-field esophagectomy starts with complete mediastinal mobilization, radical thoracic lymphadenectomy and esophageal dissection in the upper region of the chest<sup>[31]</sup>. As for the Ivor Lewis procedure, the McKeown's thoracic phase could be performed through the left lateral decubitus or prone position<sup>[21,27,29,30]</sup>. After the thoracic phase, gastrolisis, celiac lymph node dissection and gastric conduit construction can be performed in the abdomen<sup>[21,29,30]</sup>. The gastric conduit is then pulled-up through the posterior mediastinum and the esophago-gastric anastomosis is performed in the neck<sup>[14,21]</sup>. The robotic platform ensures greater exposure for dissection of the upper region of the chest, reducing potential injury to vascular, respiratory (trachea and main bronchi) or nervous structures (vagus and recurrent laryngeal nerves)<sup>[14,32]</sup>.

## **Technical aspects of anastomosis**

After three-field and trans-hiatal esophagectomy, the preferred techniques of cervical anastomosis are hand-sewn end-to-side and linear-stapled side-to-side anastomosis (modified Collard, Orringer)<sup>[33,34]</sup>.

According to the literature, esophagogastric anastomosis using the modified Collard method has lower rates of anastomotic leakage (0%-18.4% vs. 0%-27%) and stricture (0%-65.1% vs. 0%-89.9%)<sup>[35]</sup>.

The minimally-invasive intrathoracic anastomosis is considered a more challenging technique due to the reduced degree of freedom and less space for instrument handling and staplers. However, with the development of new equipment and the evolution of robotic platforms, some intrathoracic anastomosis techniques are now available: hand-sewn<sup>[25,26,36,37]</sup>, circular-stapled<sup>[28]</sup>, linear-stapled and trans-oral circular-stapled<sup>[38]</sup>.

**Table 1. Summary of selected papers on robot-assisted minimally-invasive esophagectomy-RAMIE**

Author	Year of publication	Type of study	LOE	GOR	Number of patients	Comments
Boone <i>et al.</i> <sup>[18]</sup>	2009	Retrospective study	3b	C	47	One of the largest series of RAMIE for EC published before 2010 with some technical pitfalls and details
Puntambekar <i>et al.</i> <sup>[27]</sup>	2011	Retrospective study	4	D	32	Retrospective study of RAMIE in prone position
Dunn <i>et al.</i> <sup>[19]</sup>	2012	Retrospective study	3b	D	40	The largest series of RAMIE with the trans-hiatal approach, focusing on post-operative and mid-term oncological outcomes
Sarkaria <i>et al.</i> <sup>[21]</sup>	2012	Retrospective study	4	D	21	Retrospective study of patients enrolled over one year in a tertiary center
Suda <i>et al.</i> <sup>[32]</sup>	2012	Retrospective study	3b	C	36	Technical report on RAMIE for SCC focusing on lymph node dissection
de la Fuente <i>et al.</i> <sup>[36]</sup>	2013	Retrospective study	3b	C	50	Retrospective study on Ivor-Lewis RAMIE in a referral center
Yerokun <i>et al.</i> <sup>[39]</sup>	2016	Retrospective propensity matched study on NCDB	3b	C	231	Population-based analysis of RAMIE using a national database; comparison between OE and MIE with regard to post-operative outcomes and 3-year survival
Weksler <i>et al.</i> <sup>[17]</sup>	2017	Retrospective propensity matched study on NCDB	3b	C	581	Population-based analysis of RAMIE using a national database; comparison between OE, MIE and RAMIE on survival
van der Sluis <i>et al.</i> <sup>[14]</sup>	2018	Randomized controlled trial	1b	A	112	The only RCT published which compared OE and RAMIE on post-operative and oncological long term outcomes
Harbison <i>et al.</i> <sup>[16]</sup>	2019	Retrospective study on ACS-NSQIP database	3b	C	725	Retrospective analysis of a national database comparing RAMIE with MIE on morbidity and mortality
Yang <i>et al.</i> <sup>[22]</sup>	2019	Retrospective propensity matched study	3b	C	652	Large retrospective study which compared MIE and MKE-RAMIE on post-operative results and mid-term oncological outcomes
Tagkalos <i>et al.</i> <sup>[28]</sup>	2019	Retrospective study propensity matched study	3b	C	100	Comparison between ILE-RAMIE and ILE-MIE on post-operative outcomes
Sarkaria <i>et al.</i> <sup>[31]</sup>	2019	Prospective, non-randomized trial	2b	B	106	Prospective trial which compared OE and RAMIE focusing in particular on post-operative outcomes, functional assessment and quality of life
Yun <i>et al.</i> <sup>[29]</sup>	2019	Retrospective study propensity matched study	3b	C	371	Large retrospective analysis of the comparison between RAMIE and OE for SCC on post-operative outcomes and mid-term survival

RAMIE: robot-assisted minimally-invasive esophagectomy; LOE: level of evidence; GOR: grade of recommendation; EC esophageal cancer; SCC: squamous cell carcinoma; NCDB: National Cancer Data Base; ACS-NSQIP: American College of Surgeons-National Surgical Quality Improvement Program; OE: open esophagectomy; MIE: minimally-invasive esophagectomy; RCT: randomized controlled trial; MKE: McKeown esophagectomy; ILE: Ivor-Lewis esophagectomy

Large studies are needed to determine which technique is associated with less anastomotic complications, even if a group reported the shift from hand-sewn end-to-side intrathoracic anastomosis to linear-stapled, reducing the post-operative leak rates<sup>[30]</sup>.

## METHODS

### Literature search

Pubmed, Embase and Scopus databases were searched for “robot-assisted esophagectomy”, “minimally invasive esophagectomy” and “robotic esophagectomy” in January 2020. This search was focused on original papers on totally endoscopic RAMIE (systematic reviews and papers about hybrid procedures were excluded) in the English language. Articles were screened for the type and year of publication, first author, number of patients, pre- and post-operative characteristics, post-operative complications and oncological outcomes by the authors Bongiolatti S and Farronato A. Baseline characteristics for all included studies

**Table 2. Study type, year of publication and main characteristics of the included studies**

Author	Type of esophagectomy	Conversions	EBL (mL)	Type of anastomosis
Boone <i>et al.</i> <sup>[18]</sup>	TT MKE	7 (15%)	625	Cervical handsewn end-to-side
Puntambekar <i>et al.</i> <sup>[27]</sup>	TT MKE	0	80	NA
Dunn <i>et al.</i> <sup>[19]</sup>	TH	5 (12.5%)	97.2	Cervical mechanical end-to-end
Sarkaria <i>et al.</i> <sup>[21]</sup>	TT ILE+MKE	10 (48%)	307 cm <sup>3</sup>	Mechanical circular endo-to-end (ILE) Cervical handsewn end-to-side (MKE)
Suda <i>et al.</i> <sup>[32]</sup>	TT MKE	NA	144	Cervical handsewn end-to-side or cervical handsewn end-to-end
de la Fuente <i>et al.</i> <sup>[36]</sup>	TT ILE	NA	146	NA
Yerokun <i>et al.</i> <sup>[39]</sup>	NA	28 (12.1%)	NA	NA
Weksler <i>et al.</i> <sup>[17]</sup>	NA	6.7%	NA	NA
van der Sluis <i>et al.</i> <sup>[14]</sup>	TT MKE	3 (5%)	120	Cervical handsewn end to side
Harbison <i>et al.</i> <sup>[16]</sup>	TT	11 (11%)	NA	NA
Yang <i>et al.</i> <sup>[22]</sup>	TT MKE	2 (0.7%)	211	Cervical mechanical end-to-end
Tagkalos <i>et al.</i> <sup>[28]</sup>	TT ILE	NA	NA	Cervical mechanical end to side
Sarkaria <i>et al.</i> <sup>[31]</sup>	TT ILE+MKE	NA	250	NA
Yun <i>et al.</i> <sup>[29]</sup>	TT MKE+ILE	3 (2.3%)	110	Mechanical circular

EBL: estimated blood loss; TT: trans-thoracic; MKE: McKeown esophagectomy; ILE: Ivor-Lewis esophagectomy; NA: not available; TH: trans-hiatal

are summarized in Table 1. No formal statistical procedure (meta-analysis) was performed. One study was a RCT<sup>[14]</sup>, and the other 13 were observational studies including one prospective<sup>[31]</sup> and 12 retrospective studies published from 2009 to 2019. In addition, four papers had propensity-matched analysis<sup>[22,28,29,39]</sup> and three were multi-center studies<sup>[16,17,39]</sup>.

## RESULTS

Three-hundred and twenty studies were initially identified from the electronic databases and after screening and reviewing, 14 were included for final analysis. Table 2 shows the main characteristics of the included studies.

### Intra and post-operative outcomes

Conversion rates were reported in ten papers and were much different from the early experience to the latest study [Table 2]. The largest multi-center studies, published in 2016 and 2017, showed a conversion rate ranging from 6.7% to 12.1%; in the RCT, the rate is lower (5%), probably due to the large experience gained by the Dutch group<sup>[14]</sup>. Operative time is significantly longer for RAMIE in comparison with open esophagectomy (OE)<sup>[14,29,31]</sup> and MIE<sup>[16,22,29]</sup>.

Dunn *et al.*<sup>[19]</sup> in 2012 demonstrated the feasibility of the trans-hiatal approach in a cohort of 40 patients with 2.5% mortality at 30 days, but there was quite a high incidence of overall post-operative complications: anastomotic leaks without the need for re-operation ( $n = 10$ , 25%); recurrent laryngeal nerve injuries ( $n = 14$ , 35%) and pneumonia ( $n = 8$ , 20%) [Table 3]. The use of this approach has gradually decreased in favor of trans-thoracic esophagectomy because the lymph node dissection is more extensive with trans-thoracic esophagectomy and more accurate surgical and pathological staging could be obtained. Trans-hiatal MIE or RAMIE could be useful approaches in patients with severe lung function impairment or other relevant co-morbid conditions because one-lung ventilation and thoracic incisions are not required<sup>[9]</sup>.

The overall 90-day post-operative mortality rate after trans-thoracic esophagectomy was reported in ten papers and ranged between 0% to 9% without any difference between two or three field esophagectomy<sup>[14,16-19,22,28,29,31]</sup>. The RCT published by van der Sluis *et al.*<sup>[14]</sup> reported comparable in-hospital mortality rates between patients who underwent RAMIE (2%) and OE (4%) ( $P = 0.62$ ). The 90-day mortality rate was not significantly higher for RAMIE patients (2% vs. 9%;  $P = 0.11$ ). Multicenter analysis by Harbison *et al.*<sup>[16]</sup>

**Table 3. Post-operative outcomes of RAMIE**

Author	Post-operative mortality 90day	Complications				
		Overall	Respiratory	Anastomotic	Cardiac	VCP
Boone <i>et al.</i> <sup>[18]</sup>	3 (4.05%)	NA	21 (44.7%)	10 (21.3%)	6 (12.7%)	9 (19.1%)
Puntambekar <i>et al.</i> <sup>[27]</sup>	NA	NA	2 (6.25%)	3 (9%)	NA	NA
Dunn <i>et al.</i> <sup>[19]</sup>	1( 2.5%)	NA	26 (65%)	10 (25%)	NA	14 (35%)
Sarkaria <i>et al.</i> <sup>[21]</sup>	1 (5%)	5 (24%)	NA	3 (14%)	NA	3 (14%)
Suda <i>et al.</i> <sup>[32]</sup>	0	8 (50%)	1 (6.25%)	6 (37.5%)	1 (6.25%)	6 (37.5%)
de la Fuente <i>et al.</i> <sup>[36]</sup>	NA	14 (28%)	5 (10%)	2 (4%)	5 (10%)	NA
Yerokun <i>et al.</i> <sup>[39]</sup>	NA	NA	NA	NA	NA	NA
Weksler <i>et al.</i> <sup>[17]</sup>	7.8%	NA	NA	NA	NA	NA
van der Sluis <i>et al.</i> <sup>[14]</sup>	5 (9%)	32 (59%)	17( 32%)	13 (24%)	17 (32%)	5 (9.1%)
Harbison <i>et al.</i> <sup>[16]</sup>	3 (3%)	31 (31%)	11 (11%)	14 (14%)	NA	NA
Yang <i>et al.</i> <sup>[22]</sup>	0	122 (45%)	71 (25.3%)	32 (11.8%)	9 (3.3%)	79 (29%)
Tagkalos <i>et al.</i> <sup>[28]</sup>	(5%)	NA	(12%)	(12%)	NA	NA
Sarkaria <i>et al.</i> <sup>[31]</sup>	1 (1.56%)	39 (60.9%)	NA	2 (3.1%)	5 (7.8%)	2 (3.1%)
Yun <i>et al.</i> <sup>[29]</sup>	0	49 (37.7%)	NA	4 (3.1%)	1 (0.8%)	33 (25.4%)

VCP: vocal cord palsy; NA: not available

showed similar mortality between RAMIE and MIE (3% *vs.* 2.24%); other large retrospective studies have demonstrated that RAMIE had similar mortality rates when compared with MIE and OE<sup>[22]</sup>.

Post-operative complications were reported in eight studies and ranged between 24% and 60.9%<sup>[14,16,21,22,29,31,32]</sup>. Although it can now be performed through a minimally invasive approach, esophagectomy is still associated with a high incidence of overall complications. In the RCT, the overall complication rate was assessed at 59%<sup>[14]</sup>; Harbison *et al.*<sup>[16]</sup> reported an overall morbidity rate of 31%, while other large single-institution studies reported variable rates from 45%<sup>[22]</sup> to 37.7%<sup>[29]</sup>.

The absence of thoracotomy did not avoid respiratory complications, which were reported in 6.25% to 65% of cases<sup>[14,16,18,22,27,39]</sup>. Some possible mechanisms could be involved: prolonged one-lung ventilation, reduced cough reflex due to vagus nerve injury, alteration of swallowing and consequent aspiration, and the presence of comorbidities such as advanced age and chronic obstructive pulmonary disease<sup>[14,16,18,22,27,39]</sup>. Cardiac arrhythmias were frequent and reported in 0.8% to 32% of cases<sup>[18,22,29]</sup>.

Anastomotic complications are still the Achilles' heel of MIE and RAMIE. No subtype (mechanical *vs.* hand-sewn, end-to-end *vs.* end-to-side) nor location (cervical or intrathoracic) of esophagogastric anastomosis have shown to be more reliable and safer than others and even after RAMIE, the anastomotic complication rate is still significant and ranges between 3.1% and 37.5%. Although data about anastomotic leak rates are available in most studies, anastomotic stricture is less frequently reported even if it has a negative impact on the quality of life. The RCT<sup>[14]</sup> described the need of anastomotic dilatation in 52% of patients who underwent RAMIE, while other single institutional reports showed lower rates of stricture or anastomotic dilatation (4.7%) and the majority of these patients underwent intrathoracic anastomosis<sup>[21]</sup>.

Although the robot-assisted platform has a magnified three-dimensional view, recurrent laryngeal nerve palsy was described in eight papers and it was frequently reported after cervical anastomosis (9.1%-35%), probably due to extensive lymph node dissection. Chylothorax is another frequent complication and assessed from 0% to 17%<sup>[14,21,22,29]</sup>; in the RCT, 4% of patients needed re-intervention for chylothorax<sup>[14]</sup>. Some centers perform a prophylactic thoracic duct ligation just above the diaphragm between the descending aorta and esophagus<sup>[14,27]</sup>.

Only two studies have focused their attention on quality of life after RAMIE, reporting controversial results: Sarkaria *et al.*<sup>[31]</sup> evaluated the quality of life using the Functional Assessment of Cancer Therapy-

**Table 4. Post-operative and long-term oncological outcomes.**

Author	Induction therapy	Tumor type	Mean n dissected lymph nodes	Radicality	3yOS	5yOS	DFS
Boone <i>et al.</i> <sup>[18]</sup>	3 (4%)	ADC 29 (61.7%) SCC 18 (38.3%)	29	36 (76.6%)	NA	NA	NA
Puntambekar <i>et al.</i> <sup>[27]</sup>	NA	NA	NA		NA	NA	NA
Dunn <i>et al.</i> <sup>[19]</sup>	17 (42,5%)	ADC 36 (90%) SCC 2 (5%)	20	94.7%	NA	NA	NA
Sarkaria <i>et al.</i> <sup>[21]</sup>	16 (76%)	ADC 18 (85%) SCC 3 (14%)	20	17 (85%)	NA	NA	NA
Suda <i>et al.</i> <sup>[32]</sup>	NA	SCC 100%	37.5	14 (87.5%)	NA	NA	NA
de la Fuente <i>et al.</i> <sup>[36]</sup>	35(70%)	ADC 46 (92%) SCC 3 (6%)	20	100%	NA	NA	NA
Yerokun <i>et al.</i> <sup>[39]</sup>	120 (70.6%)	ADC 186 (80.5%) SCC 45 (19.5%)	16	NA	NA	NA	NA
Weksler <i>et al.</i> <sup>[17]</sup>	412 (70,9%)	ADC (78.3%) SCC (21.7%)	16	553 (95.2%)	48 months	48 months	NA
van der Sluis <i>et al.</i> <sup>[14]</sup>	49 (94%)	ADC 41 (76%) SCC 13 (24%)	27	50 (93%)	50%	50%	26m
Harbison <i>et al.</i> <sup>[16]</sup>		ADC 68 (68%) SCC 8 (8%)	NA	NA	NA	NA	NA
Yang <i>et al.</i> <sup>[22]</sup>	30 (10.7%)	NA	19.3	263 (93.9%)	NA	NA	NA
Tagkalos <i>et al.</i> <sup>[28]</sup>	NA	NA	27	NA	NA	NA	NA
Sarkaria <i>et al.</i> <sup>[31]</sup>	48 (75%)	ADC 59 (93.7%) SCC 4 (6.3%)	25	62 (96.9%)	81.7%	NA	NA
Yun <i>et al.</i> <sup>[29]</sup>	21 (16.2%)	SCC 130 (100%)	39	127 (97.7%)	81.7%	NA	49.2%

3yOS: three years overall survival; 5yOS: five years overall survival; DFS: disease-free survival; ADC: adenocarcinoma; SCC: squamous cell carcinoma; NA: not available

Esophageal (FACT-E) and Functional Assessment of Cancer Therapy-General (FACT-G) scores, demonstrating a return to pre-operative values only after four months, without difference between OE or RAMIE. van der Sluis *et al.*<sup>[14]</sup> administered some validated questionnaires (Short Form-36, EORTC-European Organisation for Research and Treatment of Cancer-Quality-of-life Questionnaire Core 30, EORTC QLQ-OES18-Quality of Life Questionnaire Oesophageal Cancer Module-and EQ-5D-EuroQoL-5-Dimension) at discharge and six weeks after esophagectomy, demonstrating that functional recovery after RAMIE was better and faster than after OE.

### Oncological outcomes

Long-term outcomes after RAMIE are still scarce, but data from a large multi-center study<sup>[17]</sup> and from the only RCT<sup>[14]</sup> showed encouraging results [Table 4]. Trans-thoracic esophagectomy seems to ensure more extensive lymph node dissection than the trans-hiatal approach and in particular, the mean number of retrieved lymph nodes was reported between 5 and 39. Furthermore, trans-thoracic esophagectomy was associated with a complete resection rate between 76.6% and 100%. On the other hand, few papers have reported long-term oncological results: the only RCT<sup>[12]</sup> showed that there were no statistically significant differences between OE and RAMIE in overall survival (OS) (log rank  $P = 0.427$ ) at 40 months of follow-up. Moreover, the authors demonstrated no statistical differences regarding disease-free survival (DFS) (26 for RAMIE vs. 28 months for OE) and recurrence pattern.

In their analysis of the National Cancer Data Base (NCDB), Weksler *et al.*<sup>[17]</sup> showed 48 months of overall survival after RAMIE, this outcome was not different in comparison with the oncological results obtained by OE and MIE also after the propensity-matched analysis ( $P = 0.121$  and  $P = 0.53$ ). With the magnified view and extreme precision of the articulated instruments, RAMIE is increasingly being used after induction treatments: in the RCT, 79% of patients were previously treated with chemo-radiation and in other studies, a large portion of patients were treated before surgery with chemotherapy alone (70.9%-75%)<sup>[16,17]</sup> or combined treatments (68%-75%)<sup>[17,21,39]</sup>.

Dunn *et al.*<sup>[19]</sup> in 2012 achieved 94.7% of radical resection with a median of 20 lymph nodes retrieved and a median overall survival of 20 months after trans-hiatal RAMIE. Another paper regarding laparoscopic trans-hiatal esophagectomy showed a median overall survival of 28 months with 3.7% of local recurrence, 22% regional and 37% distant recurrence<sup>[23]</sup>.

## DISCUSSION

RAMIE has gained popularity in the past decade due to increased experience in Western countries and the availability of the robotic platform through Eastern countries, where the incidence of esophageal carcinoma is higher. Large multi-center studies and RCTs have demonstrated that minimally-invasive esophagectomy is safe and oncologically adequate, but it is a technically demanding procedure due to drawbacks from thoracoscopy and laparoscopy<sup>[1,5-9]</sup>.

The robot-assisted approach has some advantages over the thoraco-laparoscopic one: first, the magnified and three-dimensional intra-corporeal view; secondly, better dexterity due to the articulated instruments with tremor filtering, which allows fine dissection of mediastinal and abdominal structures; and finally, longer instruments with the fulcrum inside the body instead of the abdominal or chest wall, which could decrease post-operative pain. On the other hand, the lack of tactile feedback, longer operative time and costs are the main reported disadvantages of RAMIE. The latest version of the available robotic platform (DaVinci Xi), has four arms that work in a more parallel way than the previous version and with longer instruments, that facilitates meticulous dissection in narrow fields such as the esophageal hiatus and the upper region of the thorax<sup>[10,14,40]</sup>. The visceral and lymph node dissections in the cervico-mediastinal outlet could be more accurate and ergonomic with the RAMIE approach, avoiding injuries to other nervous, vascular or respiratory structures. Furthermore, these characteristics have a significant impact on lymph node dissection such that it can be performed in a safe manner due to the magnified view of the operating field and the small instrument tips. Some studies have demonstrated that lymph node dissection in the celiac area, subcarinal and paratracheal is safe and oncologically adequate with reduced nerve injury with RAMIE<sup>[32]</sup>.

Moreover, for tumors of the esophagogastric junction or lower thoracic esophagus, the robotic platform permits easy handling of instruments to perform hand-sewn or mechanical intrathoracic anastomosis<sup>[20,21,25,26,36]</sup>. Anastomotic leak is still the Achilles' heel of esophagectomy and no anastomotic subtype was superior in terms of leakage or stricture. Some factors are associated with anastomotic leaks and a poorly perfused conduit is a well-known risk factor for anastomotic dehiscence. This issue could be reduced with the use of NRF (Near InfraRed Fluorescence) associated with the intravenous administration of indocyanine green. With NRF, the surgeon could obtain a real-time gastric conduit perfusion, identifying inadequately perfused or ischemic areas and then the surgeon could construct the esophagogastric anastomosis on a well-perfused conduit<sup>[30,41]</sup>. Moreover, the latest robotic platform is armed with robotic staplers and the surgeon can create a mechanical end-to-side esophagogastric anastomosis with easier handling.

Although evidence about RAMIE are still weak, data from large institutional studies and from the only published RCT supported the application of RAMIE in the treatment of EC in a multimodal treatment pathway<sup>[3,4,10,42]</sup>. Some recent papers reported a variable, but high use of induction chemotherapy and chemoradiation therapy with potentially improved long-term results. Long-term OS and DFS were evaluated in few papers, but RAMIE was demonstrated not to be inferior to MIE or OE<sup>[14,17,22,31]</sup>.

The main issue of robot-assisted surgery remains the high costs to buy the platform and instruments, to start a program and for periodical technical assistance. The actual monopoly of Intuitive Surgical is

undesirable, but competitors are now present on the market and could improve developments, diffusion of ideas and decreasing the costs of robot-assisted surgery.

In conclusion, although possible with a minimally-invasive approach, trans-thoracic esophagectomy is still associated with significant post-operative complications. It has demonstrated acceptable oncological outcomes in terms of radicality, lymph node dissection, overall and disease-free survival. The robotic platform has shown some advantages in lymph node dissection, nerve sparing, improved intra-thoracic anastomosis and faster recovery after surgery, but large studies are necessary to understand the actual role of RAMIE in the multimodal treatment of EC.

## DECLARATIONS

### Authors' contributions

Conceptualization: Bongiolatti S

Data collection: Bongiolatti S, Farronato A

Formal Analysis, investigation, methodology, project administration, resources and software: Bongiolatti S

Supervision: Bongiolatti S, Voltolini L

Validation and visualization: all authors

Writing-original draft and writing-review and editing: Bongiolatti S

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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