

Review

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# Trends in the evolution to robot-assisted minimally invasive thoracoscopic esophagectomy

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## Abstract

Much effort has been made to improve outcomes and/or minimize the invasiveness of esophagectomy for thoracic esophageal cancer. This has led to the evolution from open esophagectomy to thoracoscopic minimally invasive esophagectomy (MIE), and from MIE to robot-assisted minimally invasive esophagectomy (RAMIE). RAMIE is being applied clinically to overcome the limitations of MIE. In this article, we review the trends in the evolution from thoracoscopic MIE to RAMIE. It has now been demonstrated that RAMIE is both safe and feasible, and may decrease morbidity and mortality rates associated with esophagectomy and improve oncological outcomes. On the other hand, there are still many problems that need to be solved.

**Keywords:** Esophagectomy, esophageal cancer, robot-assisted esophagectomy, thoracoscopic esophagectomy

## INTRODUCTION

Esophageal cancer is the 6th highest cause of cancer mortality worldwide due, in large part, to its high potential for metastasis<sup>[1]</sup>. The most reliable curative treatment is surgery entailing radical resection of the esophagus with extended lymphadenectomy in the mediastinum, abdomen, and neck. However, esophagectomy is associated with high postoperative morbidity (about 40%) and mortality (about 3.4%)<sup>[2,3]</sup>. To improve outcomes, patients are often treated with multimodal treatments such as neoadjuvant



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**Table 1. RAMIE history**

Year	
1960s	Start of development of a remote operation system
1998	DVSS enters clinical trials, first commercial sale
2000	DVSS obtains Food and Drug Administration clearance
2001	Performance of the first transatlantic surgery (robotic cholecystectomy)
2003	The first transhiatal RAMIE
2004	The first transthoracic RAMIE

DVSS: Da Vinci Surgical System; RAMIE: robot-assisted minimally invasive esophagectomy

chemotherapy or chemoradiotherapy, and there is much surgical effort towards improving operative techniques<sup>[4,5]</sup>. This has led to the evolution from open esophagectomy (OE) to thoracoscopic minimally invasive esophagectomy (MIE)<sup>[6]</sup>, and from MIE to robot-assisted minimally invasive esophagectomy (RAMIE)<sup>[7]</sup>. Despite the many advantages of MIE, there are several associated limitations. RAMIE, which has advantages in terms of an enhanced three-dimensional magnified view, tremorless action, and articulated instruments, is being applied clinically to overcome the limitations of MIE<sup>[8]</sup>. In this article, we review the trends in the evolution from thoracoscopic esophagectomy to MIE and RAMIE.

## HISTORY OF RAMIE

In the 1960s, the US Army and NASA began research on surgical robots with the aim of developing a remote operative system. It took nearly 30 years to complete the first fully functional surgical robot system. Called the Da Vinci Surgical System (DVSS), it has been clinically applied in the USA since 1997. In 1998, DVSS entered clinical trials and became commercially available in the USA. In 2000, DVSS was approved by the USA Food and Drug Administration. In 2001, a French surgeon, Jacques Marescaux, successfully performed the first transatlantic robotic-assisted cholecystectomy while working in the USA<sup>[9]</sup>. In 2003, Talamini *et al.*<sup>[10]</sup> reported the first series of transhiatal RAMIE. This was 8 years after the first transhiatal conventional MIE was reported by DePaula *et al.*<sup>[11]</sup> in 1995. In 2004, Kernstine *et al.*<sup>[12]</sup> reported the first series of transthoracic RAMIEs, which was 12 years after the first transthoracic conventional MIE was reported by Cuschieri *et al.*<sup>[6]</sup> in 1992. Since then, RAMIE has been performed worldwide in many institutions. Moreover, given its many unique advantages, further clinical application of RAMIE is now being widely investigated. The history of RAMIE is summarized in [Table 1](#).

## CHARACTERISTICS OF THE OPERATIVE APPROACHES TO ESOPHAGECTOMY

MIE was introduced to improve outcomes and/or reduce the invasiveness of OE, and it has produced satisfactory results. In 2003, Luketich *et al.*<sup>[13]</sup> reported the first large series of total MIEs and reported impressively low incidence of morbidity and mortality among 222 patients. Total MIE is performed by starting with a transthoracic MIE, followed by laparoscopic surgery to mobilize the stomach and perform upper abdominal lymphadenectomy. Transthoracic MIE provides improved magnified vision, less chest wall injury and relatively easy access to the upper thoracic structures, while laparoscopic surgery has less abdominal wall injury and less blood loss due to the pneumonic pressure. The first published randomized control trial in 2012, the TIME trial, is considered to be the cornerstone of MIE studies<sup>[14]</sup>. Between 2009 and 2017, eight meta-analyses were published, comparing postoperative and oncologic outcomes of MIE and OE<sup>[15]</sup>. MIE was generally found to be superior to OE in terms of intraoperative blood loss, acute immunological response, postoperative pulmonary infections, length of hospital stay, postoperative pain scores, and quality of life. Furthermore, the lymph node dissection (LND) yield and 3-year survival were equivalent<sup>[14,16,17]</sup>. However, the two-dimension view, reduced eye-hand coordination, narrow operative field, restricted freedom of movement of operative instruments, moving targets, and nearby vital structures are all limitations such that MIE remains a highly complex procedure to be mastered by the surgeon<sup>[8,18]</sup>. For example, the learning curve for an intrathoracic anastomosis was 119 cases when the incidence of

**Table 2. Characteristics of each approach to esophagectomy**

	OE	MIE	RAMIE
Difficulty level of technique	Relatively easy	Highly complex	Easier than MIE
Special points	Conventional operative method with a lot of history Gold standard method	Better vision A two-dimensional view Reduced eye-hand coordination Restricted range of movement	Zoomed-in enhanced three-dimensional vision Better overview Increased range of movement Tremorless actions Flexible endo-wrists
Ergonomic conditions	Normal	Worst	Best
Blood loss	More	Less	Least
Operative time	Shorter	Longer	Longer
Postoperative pain score	High	Lower	Lower
Postoperative respiratory complications	More	Less	Less
Difficulty and exactness of upper mediastinum lymph node dissection	Difficult to access	More challenging maneuver than OE	Easier than MIE
Postoperative recurrent laryngeal nerve paralysis	Equivalent	Equivalent	More exact Reduced
Intrathoracic hand-sewn anastomosis	Difficult	The most difficult	Easy compared to MIE
Acute immunological response	More	Less	Same as total MIE
Functional recovery	Slowest	Fast	Same as total MIE
Length of hospital stay	Longest	Short	Same as total MIE
Mortality	Equivalent	Equivalent	Equivalent
Cost	Equivalent	Equivalent	Highest
Survival	Equivalent	Equivalent	Equivalent

OE: open esophagectomy; MIE: minimum invasive esophagectomy; RAMIE: robot-assisted minimally invasive esophagectomy

anastomotic leakage was the determining parameter (the anastomotic leakage rate dropped from 18.8% to 4.5%)<sup>[18]</sup>. The learning phase of MIE was also considered to be a likely explanation for the higher re-operation rates as compared to OE in multiple population-based studies<sup>[19-22]</sup>. This may explain the findings from a survey amongst esophageal surgeons in 2014, which showed that only 43% of the respondents reported MIE as their preferred approach<sup>[23]</sup>. Indeed, due to its high technical complexity, MIE has not been adopted as the standard approach for esophageal cancer. These issues are summarized in [Table 2](#).

A hybrid MIE (HMIE), which combines laparoscopy with a conventional thoracotomy, or combines a thoracoscopy with a conventional laparotomy, has been suggested as an alternative to total MIE<sup>[24]</sup>. Messager *et al.*<sup>[25]</sup> reported that patients undergoing HMIE showed less mortality at both 30 (3.3% vs. 5.7%) and 90 days (6.9% vs. 10%) when compared to OE. In addition, Mariette *et al.*<sup>[26]</sup> reported a randomized phase III trial (MIRO trial), which found that HMIE had a lower incidence of perioperative complications (36% vs. 64%), especially pulmonary complications (18% vs. 30%), with equivalent 3-year survival (67% vs. 55%) when compared to OE. Studies comparing HMIE with total MIE are scarce. In one study, however, Bonavina *et al.*<sup>[27]</sup> compared a series of 80 total MIE versus 80 HMIE patients and found no differences in early postoperative complications or mortality. In addition, Grimminger *et al.*<sup>[28]</sup> reported a series of 75 patients (HMIE 25, total MIE 25, RAMIE 25), which showed comparable morbidity and short-term outcomes in the three groups, although the total minimally invasive approaches appear to be associated with a lower incidence of complications such as pneumonia and wound infections. Those studies showed that although HMIE is a transitional operative method between OE and total MIE, because of its relatively lower difficulty level, somewhat reduced invasiveness and satisfactory clinical outcomes, it is a valuable operative method worth being performed.

To overcome the disadvantages of total MIE and HMIE, a robotic surgical system was developed and applied clinically. Transhiatal RAMIE was first introduced in 2003<sup>[11]</sup>, and transthoracic RAMIE

was introduced a year later<sup>[12]</sup>. Although RAMIE is still under development, it is now described as a promising minimally invasive operative method with short-term and long-term clinical outcomes that are equivalent to (or perhaps better than) those achieved with OE and MIE [Table 2]<sup>[29]</sup>. In a US report, 32.1% of esophageal cancer patients were treated with MIE. Of these, 19.6% were RAMIE<sup>[30]</sup>. In that report, no differences in postoperative mortality or disease-free survival was noted between MIE and RAMIE<sup>[30]</sup>. Nevertheless, given the many unique advantages of the robot, it is expected to decrease the morbidity and mortality rates of surgery for esophageal cancer and to improve oncological outcomes. Results of the recently published ROBOT trial showed improved clinical outcomes with reduced surgical and cardiopulmonary complication rates, reduced pain and improved functional outcomes with RAMIE as compared to OE<sup>[31]</sup>. Moreover, RAMIE was associated with less intraoperative blood loss, lower postoperative pain scores, faster functional recovery, and better quality of life when compared to OE<sup>[31]</sup>. Lymph node yield and overall survival did not differ between the two approaches, indicating that RAMIE offers short-term benefits while maintaining the high oncological standards. Needless to say, evidence remains weak due to limited RCT results, and more RCT studies are still needed.

Additionally, Yun *et al.*<sup>[32]</sup> showed that RAMIE is also safe and feasible for use with patients who have received neoadjuvant chemoradiotherapy for locally advanced esophageal cancer, with postoperative mortality and morbidity rates comparable to that in OE. Another recently published study compared the clinical benefits of RAMIE with conventional OE. They showed that RAMIE could be a better surgical option for selected esophageal squamous cell carcinoma patients, offering both short-term and long-term benefits<sup>[33]</sup>. Although both the short-term and long-term outcomes of RAMIE appear equivalent to MIE in most studies, one paper showed that RAMIE for esophageal cancer patients with node-positive disease in the superior mediastinum is associated with increased mortality (7.5%) and morbidity<sup>[34]</sup>.

## LYMPH NODE DISSECTION IN RAMIE

The number of lymph nodes removed is a key factor contributing to the improved survival of esophageal cancer patients<sup>[35]</sup>. LND along the recurrent laryngeal nerve (RLN) is considered beneficial; however, RLN LND is frequently complicated by RLN palsy (20%-80%), which is especially common on the left side. Early meta-analysis studies showed that, unfortunately, MIE does not reduce the rates of postoperative RLN palsy following RLN LND<sup>[36-38]</sup>. On the other hand, RAMIE has several advantages for LND, especially RLN LND [Table 2]. The ROBOT trial showed that a mean of 27 and 25 lymph nodes were harvested in RAMIE and OE, respectively (not significantly different)<sup>[31]</sup>, which demonstrated that robotic surgery is at least comparable to open surgery for retrieving a sufficient number of lymph nodes. Although most early studies have found that the lymph node yield with RAMIE and MIE are similar<sup>[39-41]</sup>, in two recent series in which RAMIE and MIE were applied to upper mediastinal LND, markedly larger numbers of lymph nodes were harvested with RAMIE (median 37-49 *vs.* 19-21)<sup>[42,43]</sup>. In addition, when Motoyama *et al.*<sup>[44]</sup> compared the number of lymph nodes dissected from around the left RLN, they found that significantly more lymph nodes were dissected with RAMIE than MIE (median 6 *vs.* 4). This indicates that a robot-assisted surgical system may enable more extensive dissection of lymph nodes around the left RLN. Similarly, Park *et al.*<sup>[42]</sup> demonstrated that the total number of dissected lymph nodes was significantly greater in the RAMIE group (37.3 ± 17.1 *vs.* 28.7 ± 11.8; *P* = 0.003), and intergroup differences were significant for the number of lymph nodes dissected from both the upper mediastinum (RAMIE: 10.7 ± 9.7 *vs.* MIE: 6.3 ± 9.3, *P* = 0.032) and abdomen (RAMIE: 12.2 ± 8.7 *vs.* MIE: 7.8 ± 7.1, *P* = 0.007). The five-year overall survival did not differ between the two groups (RAMIE: 69% *vs.* MIE: 59%, *P* = 0.737). Deng *et al.*<sup>[45]</sup> showed that RAMIE may have an advantage for lymphadenectomy (mean: 20.6 ± 8.8 *vs.* 17.9 ± 7.7; *P* = 0.048) over MIE without increasing the risk of major postoperative complications. A recent propensity-matched analysis of patients undergoing modified Ivor Lewis esophagectomy also showed that the median total lymph node yield was 27 (range 13-84) in the RAMIE group compared to 23 in the MIE group (range 11-48). With a *P*-value of 0.053, their results suggest a trend towards improved lymphadenectomy with RAMIE<sup>[46]</sup>. These studies

**Table 3. Intrathoracic anastomosis in RAMIE**

Intrathoracic anastomosis methods	Merits	Limitations
Hand-sewn	Can take full advantage of robot-assisted hand-sewing. Can be performed when the length is insufficient for staple anastomosis	Operative field is not satisfactory in the posterior wall anastomosis
Overlap (linear stapler × 1) + Hand-sewn	No need for additional mini-thoracotomy. Lower occurrence of stenosis. Can save stapler. Can take full advantage of robot-assisted hand-sewing	Cannot completely remove tissue poorly supplied with blood. Need a longer tubular stomach and esophageal end than circular stapler
Function (linear stapler × 2)	No need for additional mini-thoracotomy	Need a longer tubular stomach and esophageal end. Cannot completely remove tissue poorly supplied with blood
Triangular stapling (linear stapler × 3)	A reportedly lower rate of anastomotic complications. Lower occurrence of stenosis	The need to intrathoracically staple three times in three directions is a technical challenge
Circular stapler	Relatively easy to perform. Can completely remove tissue poorly supplied with blood	Need an additional mini-thoracotomy. Need an extra circular stapler. Higher occurrence of stenosis

RAMIE: robot-assisted minimally invasive esophagectomy

demonstrate that RAMIE may be more effective for extensive LND than MIE or OE. Recurrent nerve palsy is a complication that is especially associated with lymph node dissection in the superior mediastinum. In the ROBOT trial, the recurrent nerve palsy rate was 9%<sup>[31]</sup>. However, Park *et al.*<sup>[47]</sup> showed a significant learning curve on RLN palsy rates, which dropped from 55% to 0% after performing 20 cases in their study. The length of the learning curve for RAMIE has been reported to be 20-70 cases<sup>[8,18]</sup>.

### ROBOTIC INTRATHORACIC ANASTOMOSIS

The robotic intrathoracic anastomosis can be hand-sewn or performed with linear or circular staplers. Although complete hand-sewing takes full advantage of robot assistance, it appears posterior wall anastomoses are technically challenging because of the deep and narrow operative field<sup>[48]</sup>. Wang *et al.*<sup>[49]</sup> showed side-to-side anastomosis to be a promising approach with the advantages of there being no need for additional mini-thoracotomy and a lower incidence of stenosis. In their report, the authors also emphasized the usefulness of the barbed knotless suture. Another recent study reported similar satisfactory outcomes with end-to-side anastomosis<sup>[50]</sup>. Those authors concluded that end-to-side anastomosis requires a shorter length of the esophageal end, and section with poor blood supply was removed by a second stapler, which may ensure a good blood supply to the anastomosis. Triangular stapling is another anastomotic technique, which is reportedly associated with a lower rate of anastomotic complications<sup>[51]</sup>. However, stapling three times in three directions would seem to present a great technical challenge intrathoracically. Recently, Han *et al.*<sup>[52]</sup> reviewed diverse ways of intrathoracic anastomosis. Among these anastomotic methods, mortality was equivalent, but the anastomotic leak rates differed. Further large clinical trials are still needed. In general, each method has its merits and demerits. Surgeons should determine the anastomotic method of every single case with the final aim of maximizing patient benefits. The methods used for anastomosis in RAMIE are summarized in [Table 3](#).

### TRANSTHORACIC VS. TRANSHIATAL RAMIE

As with MIE, different variations of RAMIE have been established. Transthoracic RAMIE is one of the most commonly used approaches. It has a wide operative field, and after posterior and middle mediastinal LND, superior mediastinal LND can be performed in this operative field. However, destruction of the thoracic wall and pleura are unavoidable and differential lung ventilation is still needed. In 2003, Talamini *et al.*<sup>[10]</sup> reported the first series of transhiatal RAMIE. Conventional transhiatal MIE has been proven as a less

**Table 4. Transthoracic vs. transhiatal route in RAMIE**

RAMIE	Merits	Limitations
Transthoracic	Wide operative field. Superior mediastinum lymph node dissection can be performed in the same operative field	Thoracic wall and pleura destruction are unavoidable. Differential lung ventilation is still needed in most case
Transhiatal	No need for thoracic wall destruction. No pleurotomy. No need of differential lung ventilation. No need for a change in body position. Almost no postoperative respiratory complications	Narrow operative field. Need a decent experience for mediastinum lymph node dissection under mediastinoscopy

RAMIE: robot-assisted minimally invasive esophagectomy

invasive operative method but oncologically inferior to radical esophagectomy<sup>[53]</sup>. Although lymph node dissection of the lower mediastinal field is considered to be equivalent to radical esophagectomy, when it comes to the middle mediastinal field, it shows shortages because conventional endoscopic devices suffer from the paralleled right- and left-hand in the deep narrow operative fields. Meanwhile, the robot has articulated instruments and enhanced three-dimensional magnified view, which can move freely in the deep narrow cavity. It has been proven that RAMIE can overcome the limitations of the conventional transhiatal MIE and can dissect lymph nodes equivalent to radical esophagectomy<sup>[54]</sup>. Yoshimura *et al.*<sup>[55]</sup> showed that transhiatal RAMIE is associated with fewer pulmonary complications (0%) and better postoperative quality of life. However, it requires two LND steps. Posterior and middle mediastinal LND is performed using transhiatal RAMIE, followed by cervical mediastinoscopy for superior mediastinal LND. Mori *et al.*<sup>[56]</sup> showed that the radicality of transmediastinal esophagectomy is equivalent to that of transthoracic esophagectomy in terms of the number of harvested lymph nodes and the pathology of surgical margins. Similarly, postoperative pneumonia did not occur in the transhiatal group. Although short-term and long-term outcomes were reported to not be inferior, due to the narrow operative field with the transhiatal procedure and mediastinoscopy, transhiatal RAMIE appears to be a more complex procedure. RAMIE operative routes are summarized in [Table 4](#).

### OPERATIVE POSITIONS IN RAMIE

Acute lung injury occurs in 25%-30% of patients after transthoracic esophagectomy, and single lung ventilation has been implicated in its pathogenesis<sup>[57]</sup>. Until recently, RAMIE has been performed with the patient in the left lateral decubitus position in a setting of single-lung ventilation. Full lateral decubitus position with a cephalic parallel approach was reported to save some operative time ( $381 \pm 57.7$  min)<sup>[58]</sup>. However, this approach requires total lung collapse and is therefore, often accompanied by serious pulmonary complications. To overcome the disadvantages of differential ventilation, Palanivelu *et al.*<sup>[59]</sup> performed MIE with patents in a prone position. With their large patient cohort, they found that the prone position takes advantage of gravity to displace the lung from the dorsal thoracic structures and the esophagus, and that it has lower respiratory complications and shorter operative times due to the excellent exposure of the operative field and the better ergonomics for the surgeon. Sometimes, the vertebral column may obstruct the view of the operative field. Ruurda *et al.*<sup>[60]</sup> reviewed the application of the prone position in RAMIE, with the patient cart of the robot system standing on the patient's side and extending its arms in a direction crossing the longitudinal axis of the patient. In the subsequent abdominal phase, the patient cart must be repositioned in front of the patient's head. This patient cart repositioning is time-consuming<sup>[58]</sup>. On the other hand, urgent conversion to a classic thoracotomy, if needed, is probably more difficult with the prone position<sup>[61]</sup>. As a solution to overcome this problem, whilst retaining the benefits of the prone position, a relatively complicated position, a modified semi-prone position has been adopted by surgeons around the world<sup>[62]</sup>. Operative positions are summarized in [Table 5](#).

**Table 5. Operative positions in RAMIE**

	Merits	Limitations
Left lateral decubitus position	Similar to open resection and does not require repositioning in the case of a conversion to open surgery	Need single-lung ventilation with more postoperative pulmonary complications.
Prone position	Takes advantage of gravity to displace the lung from the dorsal thoracic structures and the esophagus. Excellent exposure of the operative field. Allows for double-lung ventilation with less postoperative pulmonary complications	Need repositioning in the case of a conversion to open surgery
Semi-prone position	Has benefits of both the prone position and left lateral decubitus position	Relatively complicated

RAMIE: robot-assisted minimally invasive esophagectomy

**Table 6. Prospects of RAMIE**

1	Tactile function
2	Forceps tip shape change function
3	Automatic forceps switch function
4	Flexible camera
5	Artificial intelligence
6	Miniaturized operating robot body and wrist
7	Break the monopoly of the Da Vinci system

RAMIE: robot-assisted minimally invasive esophagectomy

## PROSPECTS FOR RAMIE

Although RAMIE has a number of advantages that can overcome the shortcomings of MIE, there are still many problems that need to be resolved [Table 6]. For example, to perform surgery more safely, if possible we would like to add tactile function to the robot. To shorten the operative time, a forceps tip with shape changing function, automatic forceps switching function, and flexible camera are expected. Artificial intelligence is another exciting feature that is being developed. To reduce interference, we are looking forward to the development and manufacture of an operating robot with a miniaturized body and wrists. In addition, to break the monopoly of the Da Vinci system, many surgical robot companies worldwide are working on the development and manufacture of new robot surgery systems, which could bring lower costs.

## DECLARATIONS

### Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Liu J, Motoyama S

Performed data acquisition, as well as provided administrative, technical, and material support: Sato Y, Wakita A, Kawakita Y, Nagaki Y, Fujita H, Imai K, Minamiya Y

### 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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