



Robotic-assisted minimally invasive esophagectomy: past, present and future

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Abstract: Esophagectomy for cancer of the esophagus is increasingly performed using minimally invasive techniques. After the introduction of minimally invasive esophagectomy (MIE) in the early 1990's, robotic-assisted techniques followed after the turn of the millennium. The advent of robotic platforms has allowed the development of robotic-assisted minimally invasive esophagectomy (RAMIE) over the past 15 years. Although recent trials have shown superior peri-operative morbidity and quality of life compared to open esophagectomy, no randomized trials have compared RAMIE to conventional MIE. This paper summarizes the current literature on RAMIE and provides an overview of expected future developments in robotic surgery.

Keywords: Esophageal cancer; minimally invasive esophagectomy (MIE); robotic-assisted minimally invasive esophagectomy (RAMIE); robotic surgery

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Introduction

Esophageal cancer presents a significant oncological burden; it is the 7th most common cancer and the 6th most fatal globally (1). Esophageal resection is the mainstay of curative management, achieving a 5-year survival rate that approaches 50% when preceded by neoadjuvant chemo(radio)therapy (2,3).

The surgical approach to the esophagus, especially in the context of esophageal cancer, is challenging due to several factors. Firstly, the esophagus spans both the chest and the abdomen, which typically means that both compartments are accessed to perform an esophagectomy with two-field lymphadenectomy (i.e., dissection of both abdominal and thoracic lymph node stations). This surgical approach is widely preferred worldwide, as it has been shown to increase disease free survival in patients with proven nodal

involvement (4,5). Secondly, the esophagus is nestled between vital structures which are not readily resectable; the aorta, atrium, main airways and pulmonary vessels. The need to access the thorax has fuelled a desire to perform esophagectomy by less invasive ways in an attempt to reduce morbidity associated with thoracotomy. The requirement to perform delicate yet thorough dissection around vital thoracic structures without compromising resection margins can be challenging when using standard minimally invasive tools. By offering technical advantages such as enhanced three-dimensional vision and full dexterity, robotic assistance can be useful during complex surgical procedures. This article reviews the origins of minimally invasive esophagectomy (MIE) and robotic-assisted minimally invasive esophagectomy (RAMIE). The available evidence for MIE and RAMIE will be reviewed and future developments will be discussed.

The past

The history and development of MIE are important in order to understand the roots of RAMIE. MIE was first described in 1992 (6) and has seen a steady increase in uptake over the past decades (5,7,8). The first step toward MIE was by means of a laparoscopic transhiatal approach (9). Subsequently true minimally invasive Ivor Lewis or McKeown procedures were developed involving a laparoscopic abdominal phase combined with a thorascopic chest phase. Concerns about the thorascopic component with regards to its safety, standardisation and reproducibility across centres led to the development of the “hybrid” esophagectomy consisting of an open chest phase whilst maintaining a laparoscopic abdominal phase.

To date, only one multi-centre randomised trial has compared total MIE to open esophagectomy for distal esophageal tumors; the TIME trial (10). Four nations participated in this seven-centre study randomising a total of 115 patients. MIE consisted of a laparoscopic abdominal phase followed by a right thorascopic phase in the prone position. Comparison was made to open esophagectomy, which could involve either a two-stage (i.e., Ivor Lewis) or three-stage (i.e., McKeown) procedure. The primary outcome was pulmonary complications, although definitions, particularly of pneumonia, were not standardised and the relatively high rates of reported pulmonary complication, particularly in the open group (36%) were questioned (11,12). Our group developed and validated the Universal Pneumonia Score in an attempt to standardise post esophagectomy hospital-acquired pneumonia (13). Although controversial with regard to its primary endpoint, the TIME trial showed that MIE was superior to open esophagectomy in terms of postoperative pulmonary infections (relative risk 0.30, 95% CI: 0.12–0.76; $P=0.005$). In addition, MIE was associated with less intraoperative blood loss, a better preserved acute immunological response, lower postoperative pain scores, shorter length of hospital stay, and improved quality of life. Long term oncological outcomes have since been reported and show equivalence to open esophagectomy in terms of disease free and overall survival (14).

Multiple systematic reviews comparing MIE to open esophagectomy have been performed over the years, which largely mirror the findings of the TIME trail (15,16). Moreover, several trails are currently recruiting comparing MIE to open esophagectomy to further assess safety, peri-operative morbidity and long-term outcomes.

A multicentre, prospective, randomised, open and parallel controlled trial in China aims to compare the effectiveness of MIE to open McKeown esophagectomy for resectable esophageal cancer. It is expecting to recruit 324 patients to each arm over a 3-year period (17).

The MIRO trial was the first to compare open two-stage esophagectomy (laparotomy and right thoracotomy) with hybrid two-stage esophagectomy (laparoscopic abdominal phase and open thoracic phase) (18). The primary end point was 30-day morbidity [grade II–IV on the Clavien-Dindo system (19)]. This trial recruited 207 patients from 12 centres and showed a reduction in major post-operative morbidity (OR 0.31, 95% CI: 0.18–0.55; $P<0.001$) with equivalent 3-year oncological outcomes (20). In the UK, the ROMIO study is currently recruiting (21). Originally intended to be a three-arm trial comparing open esophagectomy, hybrid esophagectomy (laparoscopic abdomen and open thoracotomy) and total MIE, a lack of standardisation for MIE across centres ultimately resulted in the trial comparing hybrid esophagectomy to open alone.

Whilst the results of MIE are promising, population-based studies in the United Kingdom, Japan, the United States of America, and the Netherlands demonstrated increased re-intervention rates (22–25) after MIE. Some authors postulated that this was possibly an effect of the learning curve that was experienced by surgeons and centres during the early national adaptation phase. This may be a plausible explanation, as the MIE learning curve can be associated with additional morbidity (26) and takes 50–119 cases, depending on the chosen parameters of proficiency. Regardless, these data represent the outcomes in the countries of inclusion and should therefore be carefully considered. As such, follow-up studies are warranted to investigate whether the re-intervention rate has normalized in the more recent years (26–28).

The early evidence that MIE was safe and at least equivalent to open esophagectomy drove the development of RAMIE, aiming to overcome some of the inherent technical difficulties commonly experienced during MIE, particularly the thorascopic phase. The relatively rigid chest cavity, with limited access due to the proximity of the ribs, scapula and vertebral column, proved a challenging environment for standard minimally invasive tools. The first RAMIE was performed in 2003 (29) and case series were published in 2006 (30).

RAMIE has become an established technique for performing esophagectomy for resectable esophageal cancer, with groups reporting their experiences all over the

world [for example (31-33)]. The term “RAMIE” should be treated with some caution as it is used interchangeably to describe totally robotic esophagectomy (34) or a laparoscopic abdominal phase combined with a robotic thoracic phase (35). Alternative terms such as robotic assisted Ivor Lewis esophagectomy (RAILE), robotic assisted transhiatal esophagectomy (RATE), robotic assisted mini invasive McKeown esophagectomy (RAMIME) and robotic Ivor-Lewis esophagectomy (RILE) are also used in the literature. Equally the location and method of performing the oesophagogastric anastomosis varies between centres which has resulted in heterogeneous groups making interpretation and comparisons of case series difficult. A systematic review of all 16 available case series showed that a majority of patients had a cervical anastomosis, although nearly half of the studies did not specify the type of construction used to form the join (36). At this stage the literature consisted entirely of case series but proved the initial feasibility and safety of RAMIE with good short-term oncologic results compared to both MIE and open esophagectomy.

The present

Current evidence

To date >600 RAMIE procedures have been performed in the University Medical Centre Utrecht for esophageal cancer. We have recently published a single centre, superiority, controlled, parallel-group, randomized controlled trial comparing RAMIE to open McKeown esophagectomy; the ROBOT trial (35). This was the first trial to compare open esophagectomy to RAMIE and showed a lower percentage of overall surgery-related and cardiopulmonary complications in the RAMIE group with lower postoperative pain, better short-term quality of life, and a better short-term postoperative functional recovery without compromising oncological outcomes (37).

Sarkaria *et al.* recently published the results of a single centre comparative study (34). Here, open esophagectomy (either Ivor Lewis or left thoracoabdominal procedures) was compared to RAMIE (robotic thoracic and abdominal phases, almost exclusively Ivor Lewis) with the primary outcome being Quality of Life (QoL) as assessed by the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) subset and the Brief Pain Inventory (BPI). This was a non-randomized comparative study where allocation to treatment was determined by which surgeon

the patient presented to. Although the cohorts were not propensity matched, the baseline characteristics were not statistically different. The results showed that short-term QoL was better following RAMIE. The study also assessed oncological outcomes and peri-operative morbidity as secondary outcomes. As was described in the ROBOT trial, the authors showed that pulmonary complications were lower in the RAMIE group. Beyond this, they reported a reduction in infective complications, a reduction in re-admission to ICU and an increase in lymph node yield in the RAMIE group.

Both van der Sluis *et al.* (35) and Sarkaria *et al.* (34) have shown that RAMIE is safe and results in reduced peri-operative morbidity, improved early QoL, with equivalent oncological outcomes compared to open esophagectomy. To date, only one study has compared MIE to RAMIE (robotic abdomen and thorax) (32). In this single surgeon, propensity matched study 66 patients were paired to compare MIE with RAMIE. The authors found that, apart from a longer operative time for RAMIE, the outcomes, both oncological and in terms of complications, were equal. A commentary (38) on the study commended the clinical relevance of this study, but raised the issue that in a cohort of total of 76 patients (from which 66 were propensity matched) the learning-curve effect, which takes 20–70 cases for RAMIE, may have affected this study. The REVATE study will be the first multi-centre, open-label, randomized controlled trial to prospectively compare RAMIE to MIE (39). This trial is based on a single surgeon experience (40), which showed reduced recurrent laryngeal nerve neuropraxia in the RAMIE group with a minimal learning curve effect of 12 procedures for experienced thoracoscopic surgeons. Although the primary outcome will be recurrent laryngeal nerve neuropraxia, secondary outcomes will include complication rates and oncological outcomes.

Precision surgery

The current robotic platforms allow 10-fold magnification and a stable, three-dimensional endoscopic view. As a result of this, we were able to identify anatomy not previously recognised or documented. For example, our group collaborated to first describe a distinct fascial layer surrounding the esophageal blood supply and lymphatics in essence forming a “meso-esophagus” (41,42). We also identified that the branches contributing to the thoracic duct join approximately 7 cm superior to the esophageal

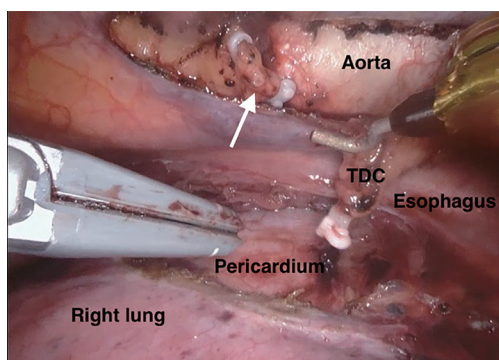


Figure 1 Transected thoracic duct (white arrow). The distal, transected thoracic duct compartment (TDC) has been labelled.

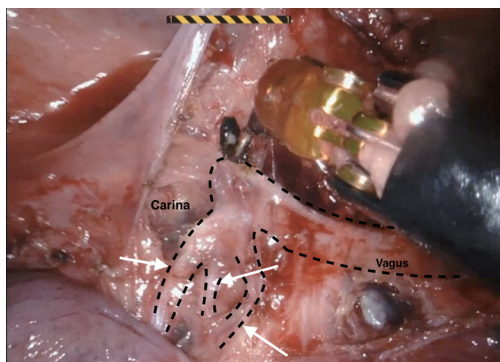


Figure 2 Sparing of bronchial vagal branches (white arrows).

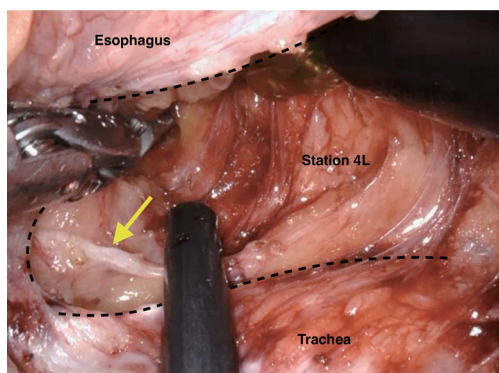


Figure 3 Sparing of left recurrent laryngeal nerve (yellow arrow) during dissection of thoracic lymph node stations 4 and 2.

diaphragmatic hiatus (43). The magnified, stable, view during RAMIE routinely allows us to clip the thoracic duct *en bloc* and visualise a single transected lumen (Figure 1). A further anatomical detail, that is more readily

appreciated and preserved during RAMIE, are the vagal branches supplying the right and left main bronchus (44,45) (Figure 2). The fact that several studies have now shown reduced pulmonary complications in RAMIE is likely to be multifactorial. One of these factors may be related to the ability to preserve the parasympathetic innervation of the lungs by sparing vagal branches which has been associated with reduced pulmonary complications (46).

We routinely perform upper mediastinal lymphadenectomy (nodal stations 4 and 2, bilaterally) in the thorax as previously described (47) (Figure 3). Studies have shown that even in the context of distal esophageal cancers (Siewert Type I) these stations contain nodal metastases in 11% of cases (48). Again, the use of the robot has given greater access in terms of operating in both the aperture of the chest whilst maintaining the ability to reach the hiatus (this is a limitation in thoracoscopic surgery), as well as the ability to visual and spare the recurrent laryngeal nerves whilst dissecting paratracheal lymph node stations.

With the developments in robotic technology, multi-quadrant work has become more attainable. This is of particular relevance in the abdomen, where the required dissection spans a relatively large field from the apex of the greater curve, to the duodenum, to the splenic hilum and the diaphragmatic hiatus. The use of the da Vinci Xi in particular has aided uptake in upper GI robotic surgery, which is reflected by the recent increase of reported total robotic-assisted gastrectomies. Beyond this, advances in energy dissecting tools now make the dissection in the abdomen, particularly along the greater curve and pylorus of the stomach, safer, faster and more haemostatic. As a result, several centres, amongst these our own centre, have started to routinely perform fully robotic esophagectomies (31,34).

The future

The concept of sentinel lymph node identification and sampling is well established in oncological surgery (49-51). In esophageal cancer, however, this has proved challenging with the initial use of blue dyes (52,53). Advances in radio-guided techniques using peritumoral injection of ^{99m}Tc antimony colloid by upper endoscopy prior to the operation has proven to have a high sensitivity and specificity in identifying sentinel nodes in early esophageal cancer (54), although similar techniques have been less useful in advanced cancers (55). In the context of a 23% complete response rate in adenocarcinomas following neo-

adjuvant treatment with CROSS (3) or radical endoscopic resections for T1 tumors, this technology could be crucial in avoiding the significant morbidity associated with esophagectomy and 2-field lymphadenectomy; in patients with cT1N0M0 middle or lower esophageal cancer, if sentinel nodes are detected in the mediastinum or abdominal but are all histopathologically negative for cancer metastasis, lymphadenectomy may potentially be omitted. We are currently recruiting to the SNAP study (Sentinel node Navigation surgery in early Adenocarcinoma Patient) (56) which uses a combination of ICG and Tc99 which is injected in the tumor the day prior to surgery in an attempt to identify sentinel nodes in the context of cT1N0M0. The ability for the operating surgeon to readily switch between fluorescence and plain light modes whilst maintaining a stable magnified view and permitting selective nodal dissection is greatly aided by robotic systems.

Oncological treatments are becoming increasingly progressive in treating oligometastatic disease and previously deemed irresectable tumors. There are reports of locally advanced tumors invading the aorta, atrium, pulmonary vessels, or the airways (i.e., T4b disease) being successfully treated by means of down staging through radical chemoradiotherapy followed by RAMIE (57,58).

The future of RAMIE is closely related to the developments in robotic platforms. In terms of the available hardware, multiple new systems are expected over the next couple of years (59,60). Recently, improvements in robotic tri-stapling devices, energy dissection instruments and Firefly integration have streamlined RAMIE. In the near future, the greatest future advances in robotic surgery, however, are likely related to software developments. The use of artificial intelligence, data and imaging integration and connectivity will open up new possibilities in terms of precision surgery, but also permit big data collection and machine learning (61).

Training in complex minimally invasive surgical techniques such as 2-stage esophagectomy is a long process with learning curves from 50 to 119 cases described (26,28). A recent meta-analysis suggested as many as 36 anastomotic leaks in a series of 646 should be directly attributed to the learning curve (26). Equally, early series in MIE have reported higher rates of acute gastric conduit necrosis (28), which in some cases were attributed to technique and put down to the learning curve effect. Interestingly, the learning curve of RAMIE is reported to be 20–70 (57). The observation that this may indeed be lower is not simply a reflection of the fact that these surgeons progressed from

MIE to RAMIE, since some of the reported series went straight from open esophagectomy to RAMIE. However, it should be noted that the parameters of proficiency and chosen methods to visualize the learning curve varied in previous studies, which makes it impossible to draw any firm conclusions regarding the length of the learning curve for RAMIE in relation to MIE. The key is likely to be the implementation of a structured training programme which has proven benefits in significantly lowering the learning curve of a procedure irrespective of the parameters of proficiency selected. The availability of dual console systems has further enhanced the teaching and training opportunity in the context of RAMIE; in our unit we have divided the thoracic and abdominal phases into their constituent parts and use a global assessment scale ranging from 1–6 (where 1 is “step done by trainer” and 6 is “masterful performance by trainee”) to grade the performance and required proctoring of the trainee surgeon. Advances in digital connectivity, particularly through 5G networks, have allowed the realistic developments in telesurgery—remote operating, where the console surgeon and patient are not within the same vicinity. Although not a new phenomenon, the first tele-surgical cholecystectomy was performed in 2001 (62), the increasingly accepted concept of remote operating will potentially play a significant part in the proctoring process.

The advent of single port robotic systems (e.g., da Vinci SP system, Intuitive Surgical Inc, SPORT surgical system, Titan Medical Inc) will inevitably see developments in single port stages of either the abdominal or thoracic (or both) phase(s) of esophagectomy. The single port robotic systems can be of particular significance in the cervical approach for the upper mediastinum. To date, most surgeons perform the transcervical approach of the transhiatal esophagectomy by blunt dissection. This potentially limits the quality of the lymph node dissection. The single port mediastinoscopic cervical approach has been described in order to improve esophageal dissection and lymph node harvesting of the upper mediastinum in transhiatal esophagectomies (63,64). However, dissecting with straight, conventional, non-articulating instruments within the narrow deep mediastinal working place around the aortic arch and tracheal bifurcation is challenging. The single site robotic platform can overcome these challenges. The wristed 3D camera and fully wristed elbowed instruments allow surgeons to increase surgical quality and thus expand its applications in the mediastinum. A preclinical study has demonstrated the feasibility of a transcervical esophagectomy with the da Vinci SP (65). This study described excellent visibility

and handling of the mediastinal organs located along the esophagus. Several groups have already reported on single incision thoracic phases, although these were not performed robotically (66-68). The current single port robotic systems are still limited with the absence of a vessel sealing device or robotic staplers. Until the single port robotic systems are embedded and standardized, it is difficult to consider the additional value in the transthoracic phase compared to the multiport robotic systems.

Concluding remarks

To date, esophagectomy and lymphadenectomy remains a cornerstone in the treatment of esophageal malignancy in combination with chemo(radio)therapy. Minimally invasive methods for the oncological resection of the esophagus have equivalent long-term oncological outcomes, but reduced peri-operative morbidity and improved QoL compared to open surgery. Several studies have now shown that RAMIE is safe, feasible and results in reduced complications compared to open surgery. Evidence from randomized prospective trials comparing MIE and RAMIE is awaited. The expected influx of new robotic platforms including the use of artificial intelligence will impact robotic surgery through even less invasive surgery, big data sharing, augmented reality, and adjunctive technology such as the use of ICG to routinely assess perfusion, localise lymphatics or identify sentinel nodes.

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Footnote

Conflicts of Interest: JP Ruurda, R van Hillegerberg are both proctors for Intuitive Surgical. The other authors have no conflicts of interest to declare.

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

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