Outcomes and complications after robot-assisted minimally invasive esophagectomy

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Abstract: Esophagectomy is the mainstay treatment for cancer of the esophagus. Over the past 15 years uptake in minimally invasive surgery, and in particular robotic techniques, have become increasingly popular in esophageal surgery. The team in University Medical Centre Utrecht were among the earliest to pioneer robotic-assisted minimally invasive esophagectomy (RAMIE) and have now performed in excess of 450 RAMIE procedures. We have recently published the first randomized controlled trial to assess the value of RAMIE over open McKeown esophagectomy. This paper reports on our unit's outcomes, complications and technical development of the procedure in the world's largest RAMIE cohort, but also incorporates available evidence from other units. Common and important complications such as anastomotic leak, pulmonary complications, chyle leak, recurrent laryngeal nerve palsy, delayed gastric emptying, diaphragmatic herniation and stricturing are all discussed. The specific value that the robot brings to our esophagectomy practice will be highlighted. This article is accompanied by several videos to illustrate the developments of specific elements of RAMIE including dissection and ligation of the thoracic duct and the robotic handsewn end-to-side sutured intrathoracic anastomosis.

Keywords: Robotic-assisted minimally invasive esophagectomy (RAMIE); robotic esophagectomy; outcomes; complications

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Introduction

Oesophageal cancer is the 8th most prevalent cancer worldwide. The prognosis remains relatively poor with an overall 5-year survival rate of 36–50% for those undergoing surgical resection (1,2), making it the 6th most lethal cancer globally (3).

Esophagectomy is the mainstay curative option for cancer of this part of the gastrointestinal (GI) tract. Historically this operation has been associated with significant morbidity and mortality. This is predominantly due to the anatomical position of the oesophagus and its associated lymph drainage with the subsequent need for two operative fields; the chest and abdomen.

Consequently, there has been a great drive to reduce the surgical insult of this operation resulting in a wide variety of operative approaches to the chest and the abdomen. The common open procedures described are fourfold: (I) the Ivor Lewis esophagectomy; a laparotomy (either high midline or rooftop incision) and a right thoracotomy; (II) a McKeown approach, which consist of an abdominal and thoracic phase but with an extra incision in the neck to form a cervical anastomosis; (III) the left thoracoabdominal approach; a continues incision from superior to the umbilicus to the tip of the left scapula, and (IV) a transhiatal approach; a laparotomy with dissection in the chest through the hiatus. Each operation has benefits and short-comings, but, in general, a right-sided chest approach (i.e., 1 or 2) is favoured by most units as it permits good access to the oesophagus and the surrounding lymph tissue throughout the chest. Advances in minimally invasive surgery have seen further variation in terms of how esophagectomy can be performed. Broadly speaking minimally invasive methods have utilized a right thoracic approach either with neck or chest anastomosis, although there are cohorts of transhiatal (4) and case reports of left-sided approaches (5,6). Minimally invasive esophagectomy (MIE) can be performed in a hybrid manner where the abdominal phase is performed laparoscopically and the chest open, or truly minimally invasive using laparoscopy followed by thoracoscopic chest dissection. Although some studies have shown benefit in MIE (7-9) there is still ongoing debate regarding the exact benefits of MIE (10). Developments in robotic assisted surgery have allowed some groups to start robotic-assisted MIE (RAMIE) over the past 20 years. Our unit in Utrecht was one of the pioneers of RAMIE and first described our methods and initial experience in 2006 (11). Since then several groups have published case series of their RAMIE experience (12-15), although the total number is still only a few thousand world-wide. van der Sluis *et al.* (16) published the first randomized trial of RAMIE versus open esophagectomy in 2018. It showed an overall reduction in cardiopulmonary complications, reduced intra-operative blood loss, a lower mean post-operative pain, reduced ICU length of stay, earlier functional recovery with better quality of life scores at discharge. Nonetheless, even in this study esophagectomy continues to be an extensive procedure with an overall complication rate of 59% and a 30-day mortality of 2%. These numbers were not significantly different compared to the open group.

Here we review the common complications associated with esophagectomy in the context of our extensive experience in RAMIE and how we have used the robot to reduce the rate of these. In particular, we will focus on anastomotic leak, pulmonary complications, chylothorax, recurrent laryngeal nerve (RLN) palsy, delayed gastric emptying (DGE), diaphragmatic herniation and stricturing. Our methods have been continuously revised and optimised based on our rigorous prospective data analysis. This article is accompanied by up-to-date videos of specific parts of the operation to illustrate how we utilise the da Vinci Xi robot to minimise some of the potential complications described.

Oncological outcomes

The primary objective of esophagectomy for cancer of the esophagus is to perform a radical resection with margins clear of tumour and an adequate lymphadenectomy in both the abdomen and chest offering the optimal chance of disease-free survival in the long term. Any advances or changes in established surgical approach need to ensure this primary objective is met. Several publications have reported on the oncological outcomes of RAMIE compared to open or hybrid esophagectomy and have shown no difference in disease free survival between the groups (2,17). Lymph node yield, particularly in the upper mediastinum has been shown to be higher in RAMIE by Park *et al.* (18). In our own recently published randomised control trial between RAMIE and open McKeown esophagectomy (ROBOT Trail) there was no statistical difference in resection margins, overall or disease-free survival, or the lymph node yield (16) The same trial did, however, show a statistically significant reduction in cardiopulmonary complications, intensive care stay and recovery times.

Anastomotic leak

Anastomotic leak is arguably the most revered complication of esophagectomy. Although not the most common, a recent large Dutch cohort study of 4,096 patients using population attributable fraction (PAF) methodology has shown this complication to be the greatest contributor to re-operation and re-admission to hospital following discharge (19). One of the inherent difficulties, however, in assessing anastomotic complications in esophageal surgery is the great variety in the location and method of constructing the anastomosis following resection of the esophagus. This join can be formed in the chest or in the neck, hand sewn, stapled or combination of both, end to end, end to side or side to side. In the context of RAMIE, all these varieties exist, but the greatest cohorts are cervical hand sewn anastomoses.

In our unit we almost exclusively performed RAMIE with cervical esophagogastric anastomosis (McKeown) until 2017. Recent studies, however show that cervical anastomoses are associated with a higher incidence of anastomotic leak compared to an intrathoracic anastomosis (20-22). A separate Dutch cohort study of 3,348 patients also showed a significant reduction in RLN palsy and length of stay for patients with an intrathoracic anastomosis

Figure 1 Formation of a robotic handsewn end-to-side intrathoracic anastomosis (24).
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compared to a cervical join (23). Based on this evidence, we have moved to handsewn intrathoracic anastomosis using the robot and Stratafix (Ethicon) continuous full thickness sutures followed by 3 or 4 tension reduction sutures (*Figure 1*): This anastomosis was performed using the Intuitive Surgical da Vinci Xi. We routinely use ICG prior to making the anastomosis to ensure adequate perfusion of the gastric conduit. An enterotomy is made in the gastric conduit and an end-to-side (ETS) anastomosis with the native esophagus is formed using 2 Stratafix sutures to form a single layer continues anastomosis. Tension release sutures are subsequently placed using 4/0 vicryl. The entire join is wrapped in omentum which is secured with the ends of the Stratafix*)*. The RAMIE cohort reported in the ROBOT trial had a 22% anastomotic leak rate (non-significant compared to 20% in the open group). This is within the expected range based on the literature which generally cites 6–41% as an expected anastomotic leak rate (25-29). In the ROBOT trial, all clinical or nonclinical signs of anastomotic leak were scored prospectively, which is likely to have contributed in the relatively higher leak rates in both trial arms. Anastomotic leakage with any sign of mediastinal involvement (mediastinitis) was treated with antibiotic treatment and surgical drainage of the mediastinum through the cervical incision. These interventions were scored as type III anastomotic leakage (re-operation) according to the Esophagectomy Complications Consensus Group (ECCG) definitions (30), which again is a reflection of our standard early and aggressive management of suspected anastomotic failure.

More recently we have routinely started to use indocyanine green (ICG) to assess the vascularity of the gastric conduit perfusion. Although assessment of its potential reduction in anastomotic leak is ongoing, and a randomized controlled trial (RCT) is desirable, a recent meta-analysis (31) certainly showed promise in this technique. The ease with which this technique has been incorporated within are day to day practice is in part due to the Firefly fluorescence camera on the da Vinci Xi which is readily operated by the console surgeon. We have also started to perform the abdominal phase robotically; the fourth arm of the Xi and the wristed 60-mm Intuitive Tri-Stapler have made this transition possible.

Chyle leak

Chylothorax is characterized by the build-up of lymphatic fluid in the thorax commonly associated with a leak from the main thoracic duct or its branches. It has a reported incidence of 1–9% in transthoracic esophagectomy (32-34), but carries a significant morbidity and even mortality often related to associated pulmonary compromise. Debate continues to surround the need and location of ligation of the thoracic duct during esophagectomy, although prophylactic ligation was recently shown to reduce chyle leak in a meta-analysis (35).

The thoracic duct is most readily identified in the right chest due to its relation to the azygous vein and the descending thoracic aorta. The RAMIE group in the recent ROBOT trial had an incidence of chyle leak of 17% (compared to 11% in the open group; P=0.69). The vast majority of these were type I leaks and could therefore be managed successfully by dietary modification. Only two patients required operative intervention to manage their chylothorax which consisted of right-sided video-assisted thoracoscopic surgery (VATS) with additional clipping of chylous tributaries. Our relatively high incidence of chylothorax (both in RAMIE and open groups) reflects the radical *en-bloc* esophagolymphadenectomy including a thoracic duct resection which we routinely perform for all cases. We recently studied the anatomy of the thoracic duct in more detail and found that it consists of multiple tributaries at the level of the diaphragm and fuses to form a single duct, from a median of 3 tributaries, 1.8 cm above the oesophageal diaphragmatic hiatus (36). This leads to a solid rationale to perform a mass ligature of the thoracic duct and surrounding tissue or clip it at a slightly more cranial level.

A recent systematic review and meta-analysis has shown that the number of lymph nodes removed to be and independent factor in survival (37). A recent study by

Figure 2 Isolation of the thoracic duct and ligation (39).
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Schurink *et al.* (38) has carefully identified the thoracic duct and proven it has associated lymph nodes ranging between 1–6. In our unit we routinely dissect the thoracic duct and ligate it (using hem-o-lok clips) supra-diaphragmatically (*Figure 2*): This dissection was performed using the Intuitive Surgical da Vinci Xi. The lymphatic tissue bundle containing the thoracic duct was dissected between the aorta and the esophagus. It was ligated using hem-o-lok clips proximally and distally and divided. Further inspection revealed a further small branch which was clipped using a further hem-o-lok clip).

Pulmonary complications

Pulmonary complications are the most common following esophagectomy (19) and occur in approximately one third of all patients. The exact nature of the "pulmonary complication" can be difficult to ascertain from the literature as they are often grouped under this single heading which makes precise assessment of these complications, incidence and severity complex. The esophagogastric community has relatively recently addressed this by generating an international consensus on standardization of data collection for complications associated with esophagectomy (30). These specify pneumonia (as defined by the American Thoracic Society and Infectious Diseases Society of America), pleural effusion requiring additional drainage procedure, pneumothorax requiring treatment, atelectasis mucous plugging requiring bronchoscopy, respiratory failure requiring reintubation, acute respiratory distress syndrome (ARDS) [as per the Berlin definition (40)], acute aspiration, tracheobronchial injury, chest tube maintenance for air leak for >10 days postoperatively. Prehabilitation, pulmonary vagal nerve sparing (41,42), administration of intra-operative corticosteroids during the thoracic phase to reduce the risk of ARDS (43) and aggressive chest physio on the day of surgery on the Intensive Care Unit are routine practice in our centre for all RAMIE patients. We place bilateral Jackson Pratt drains at each lung base and an apical drain in the right chest. The apical drain is typically removed day 1 post-operatively following a chest X-ray and no persistent pneumothorax. Basal drains are removed if 24 h production is <200 mL, unless the fluid is high in amylase or suggestive of a leak. Our most recent study (16) showed that an incidence of pulmonary complication of 32% in the RAMIE group, compared to 50% in the open group. Of the pulmonary complications, pneumonia was by far the commonest pulmonary complication (88% in RAMIE and 94% in the open group) and was defined by the uniform pneumonia score (UPS) that was developed in recent years (44,45)

RLN palsy

Both RLN are at risk during oesophageal resection. Typically, neuropraxias are caused by high right thoracic lymphadenectomy or, more commonly, during the left paratracheal lymphadenectomy around the aortic arch (station 4L). Where a cervical anastomosis is fashioned, the recurrent nerve can be damaged in the neck. The reported incidence of RLN palsy following esophagectomy in the most recent Dutch multicenter study reports in incidence of 4.9% (19) Most RLN palsies are not due to transection of the nerve, instead being a result of blunt trauma or lateral heat spread during lymphadenectomy. The da Vinci robot uses either the monopolar diathermy hook or, more recently, a wristed vessel sealer which relies on bipolar diathermy followed be a bladed division of the sealed tissue. In our trial the incidence of RLN palsy was 9% (compared to 10% in the open group); all of these were type I palsies and patients made a full recovery in terms of their speech. We routinely resect station 4L and visualise the left RLN; the robot permits incredibly close-up vision and precise dissection of the lymph nodes around the RLN. Manufacturers of robotic surgical equipment are developing wristed ultrasonic energy devices, which are expected to market imminently. Interestingly, a recent study in Japan compared the thermal spread of ultrasonic devices and diathermy devices and found that the ultrasonic device reached far higher temperatures and had greater heat spread to the surrounding tissues (46) As a point of reference, when using a diathermy vessel sealant (in this particular study the LigaSure), tissue 2 mm from the edge of the blade will, on average, experience an increase in temperature of 6.4 degrees Celsius. This compares to 19.6 degrees for the ultrasonic device at a similar distance.

DGE

DGE is a major problem following esophagectomy; denervation of the pylorus through division of the vagal nerve is thought to be the main reason for this phenomenon. It is described in 10–50% of patients who have a gastric interposition to reconstitute the GI tract following esophagectomy (47). Definitions of DGE varies across studies, between symptoms of gastric stasis combined with a delay on a barium swallow, gastric conduit dilatation on radiography, or only symptoms of gastric stasis (postprandial fullness, vomiting, regurgitation). Neither is there is a consensus in how to best manage DGE, which came out in a recent meta-analysis (48). Although many centres chose to do prophylactic balloon dilatations of the gastric pylorus, pyloroplasty or injection of botulinum toxin intraoperatively, there is no convincing evidence that this results in a long-term difference. As a matter of fact, Marchese *et al.* (49) report the best outcomes in the non-treated pylorus group.

In our RAMIE practice we do not routinely treat the pylorus intra-operatively. Of course, apparent DGE can be result of a restriction at the hiatus which may be apparent on a contrast swallow study, but can be difficult to appreciate. In this instance laparoscopy and release of the crural suture(s) is often the most successful treatment.

Diaphragmatic herniation post resection

Symptomatic post-operative diaphragmatic herniation (PODH) following esophagectomy is reported to be 0–19% (22). The numbers of asymptomatic diaphragmatic hernias will be significantly higher, but more difficult to establish. There is evidence that the risk of PODH is greater following MIE (50,51), although other studies have found comparable rates to open (52). Consequently, practice varies widely between units and even within units with regards to routine closure of the diaphragmatic defect caused by removal of the esophagus (and in certain cases fibres of the crus to achieve clear, circumferential, margins). Brenkman *et al.* (52) published a series of MIE showing an incidence of symptomatic diaphragmatic herniation of 7% if the defect was left open. In our own experience of RAMIE, we equally used to leave the hiatus open, but since the publication by Brenkman *et al.* have started to assess the hiatus even more critically and commonly place a suture at the anterior apex from within the thorax using the robot. At this level, the dexterity of the robot helps us to carefully close the diaphragm. In conventional thoracoscopy, the angle required to close the hiatus is very acute and it can therefore be extremely difficult to assess and close the hiatus once the gastric conduit has been pulled through.

Stricture

Anastomotic stricture is a potential feature of all GI anastomoses. In the context of esophagectomy benign structuring is reported in 9–46% of patients (53-55). The underlying aetiology is complex and poorly understood, but is thought to be associated with ischaemia or following anastomotic leak (55-57). Stricturing can have serious effect on quality of life (58) and may result in nutritional deficit. Most strictures respond to endoscopic balloon dilatation, but occasionally re-operation is required. Multiple studies have investigated the risk factors for anastomotic stricture, predominantly focusing on anastomotic technique (linear stapled, circular stapled, handsewn), anastomotic configuration [end-to-end (ETE), ETS, side-to-side] and anastomotic location (cervical, intra-thoracic). In our most recent series (16), 52% of RAMIE patients underwent anastomotic balloon dilatation (compared to 50% of the open group). We analysed the stricture rate in our unit from 1991 to 2011; a period during which we changed from and ETE to an ETS anastomosis in 2004 reflecting our uptake of RAMIE (59). The ETS cohort included 278 patients, 152 of which were performed by means of minimally invasive techniques, the majority of which would have been RAMIE. In this particular cohort, the stricture rate was 32% and there was no direct association with anastomotic leak. The median number of dilatations required for the ETS cohort was 4 (range, 2–8), which compared favourable to a mean of 11 (range, 7–17) in the ETE cohort.

Concluding remarks

This review focusses on the outcomes and complications experienced in one of the early adopters and pioneers of RAMIE. The evidence suggests that RAMIE is oncologically equivalent to open esophagectomy, but with reduced complications, shorter length of stay and faster functional recovery and improved early quality of life.

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Footnote

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