The evolution of surgical approach for esophageal cancer

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Esophageal surgery for esophageal cancer has been performed for over a century now. Minimally invasive esophagectomy (MIE) was first described in 1992, and it is now a standard approach in many countries. However, MIE is technically difficult and requires a long learning curve. It takes >100 cases to train for MIE with gastric tube reconstruction with an intrathoracic anastomosis. A possible option to overcome several challenges of MIE might be the use of a robotic system. A robot-assisted MIE was first described in 2005, and long-term results have shown its feasibility and safety. Over the years, different approaches for esophagectomy have been established. Our review discusses these developments and recent literature on open, minimally invasive and robotic esophageal surgery.

Keywords: esophageal cancer; esophageal resection; robotic esophagectomy; gastric tube reconstruction; minimally invasive esophagectomy; transthoracic esophagectomy

Introduction

Esophageal cancer (EC) is one of the most common cancers in the world, especially in male patients, with an estimated worldwide incidence of 455,800 patients and 400,200 EC-related deaths in 2012.1 Traditionally, surgery is the only curative treatment, with a 5-year overall survival rate of 29–39%.2 Although the median overall survival rate of EC patients has increased to almost 50 months following the introduction of neoadjuvant therapy, esophageal surgery remains the cornerstone of EC treatment.3–5 In recent years, minimally invasive esophagectomy (MIE) has become the standard approach for EC surgery in some countries, such as the Netherlands, where 82% of patients are operated via a minimally invasive approach.6 The advantages of MIE are that patients will experience less postoperative pain, mobilize faster, develop less pulmonary complications, be discharged earlier, and have a better quality of life accordingly, as was demonstrated in a randomized controlled trial (RCT).7

However, nationwide studies could not demonstrate the same results, showing a higher percentages of reoperations.8–11 This could partially be due to the proficiency gain curve for MIE. To reach a low incidence (<8%) of anastomotic leakage, >100 cases need to be operated to gain proficiency for MIE with gastric tube reconstruction of intrathoracic anastomosis.12 Therefore, high-quality training and proctoring programs are essential to reduce the learning-associated morbidity. In robot-assisted esophagectomy, these same advantages have been found, with possible favorable ergonomics for the surgeon.13

To date, different approaches for an esophagectomy are available and each comes with specific advantages and challenges. Our concise review will describe the developments and recent literature on open, minimally invasive and robotic esophageal surgery.
Open esophagectomy

The first successful transthoracic resection for EC was performed by Franz John A. Torek in 1913. He performed a transthoracic esophageal resection in a 67-year-old female patient with typical signs of a malignant stricture in the esophagus and used an external rubber tube for reconstruction, reaching from the proximal esophagus to the stomach. The patient survived this procedure for 12 years.14

Ivor Lewis described a two-stage transthoracic esophagectomy in 1946.15 He started with gastric mobilization and performed the esophageal resection and reconstruction through a right thoracotomy two weeks after the initial laparotomy. Historically, all other techniques are measured against this standard procedure. Left thoracotomy and laparotomy or left thoracophrenicolaparotomy provides an adequate exposure to the distal esophagus but presents greater difficulty to access the upper and middle thirds, and to perform an anastomosis high in the chest. An alternative three-incision approach was introduced by McKeown in 1976, in which a right thoracotomy is the initial stage of the procedure, followed by repositioning of the patient in the supine position for abdominal and, usually left, cervical incision, to perform a cervical esophagogastic anastomosis.16

The first transhiatal esophagectomy for esophageal carcinoma was performed by Turner in 1933.17 In 1978, Orringer and Sloan described the initial series of blunt transhiatal esophagectomy.18 This operation could be suitable to those patients who are in no condition to undergo thoracotomy. The possible advantages of this transhiatal approach are that by avoiding thoracotomy, the patient’s pain is minimized and certain postoperative complications, such as pneumonia and mediastinitis, may be prevented.18

The largest randomized controlled trial that compared a transthoracic with a transhiatal esophageal resection is the the Transhiatal Versus Extended Esophagectomy (HIVEX) trial published in 2002.2 This trial compared an open three-stage esophagectomy16 with an open transhiatal esophagectomy.18 The results show a nonsignificant trend toward an improved survival for patients following a transthoracic approach. In a subgroup analysis for patients with a distal esophageal carcinoma and in patients with 18 positive lymph nodes, these results were statistically significant. Staging in this trial was performed with an abdominal ultrasound and a conventional chest X ray. Since then, staging has improved enormously with the use of high-resolution computed tomography (CT) and positron emission tomography-CT scans. In addition, this trial was performed before the implementation of neoadjuvant chemoradiotherapy. Therefore, the results could probably not be applicable to current practice.

To date, these procedures are increasingly performed using minimally invasive techniques. However, in the anatomically difficult situations (e.g., a T4b tumor with suspected tracheal or aortic infiltration, or suspected enlarged paratracheal or subaortic lymph nodes), adhesions due to previous diseases, radiotherapy, or operations, or for complex salvage procedures, open resections will always be important in the armamentarium of the esophageal surgeon.

Minimally invasive esophagectomy

MIE was first described in 1992, with the report on thoracoscopic esophagectomy by Cuschieri et al.19,20 Since then, many new minimally invasive techniques have been developed and experience has been gained with this demanding technique. Sadanaga et al. introduced the laparoscopic transhiatal approach, which was later fine-tuned by Scheepers et al.21,22 The thoraco-laparoscopic McKeown and Ivor Lewis esophagectomies have both been extensively described in many series since the nineties.23–27 In the Netherlands, MIE was introduced by Miguel Cuesta. In 2001, he started with a laparoscopic transhiatal resection, followed by a transthoracic resection in the left lateral decubitus position with the robot in 2006, and in prone position (nonrobotic) in 2007. Since then, proctoring programs have been developed, and many Dutch centers have adapted this technique and gradually gained experience in MIE. The Dutch Upper Gastrointestinal Cancer Audit (DUCA) has shown that in 2016, 82% of all oncologic esophagectomies were performed by a minimally invasive procedure.6

With respect to the current evidence for MIE versus open procedures, so far two RCTs have been performed. Earlier international reports on MIE were promising, but the real breakthrough came with the publication of the Traditional
Invasive vs. Minimally Invasive Esophagectomy (TIME) trial in the *Lancet* in 2012.7 This was the first RCT comparing MIE with open esophagectomy. The five European centers participated in the trial that randomized 115 patients. The primary endpoint was the in-hospital pulmonary infection within 2 weeks. Both Ivor Lewis and McKeown procedures were included in the trial, and the majority was operated with the three-incision McKeown approach (66% in open esophagectomy and 64% in the MIE group). The results showed significantly less pulmonary infectious complications within 2 weeks (9% versus 29%; P = 0.005) and in-hospital (12% versus 34%; P = 0.005) following MIE compared with open esophagectomy. In addition, MIE resulted in less blood loss, a shorter hospital stay, a better quality of life, and comparable results concerning the quality of the surgical resection specimen (no residual tumor (R0) resection rate and retrieved lymph nodes). In the open group, the operation time was shorter, and there were more vocal cord paralyses. Pneumatic dissection by CO₂ from the thoracic phase along the cervical esophagus may have simplified the cervical dissection and reduce recurrent nerve lesions.28 In addition, the double lumen tube used in the open group could have caused some of the vocal cord paralyses.29,30 All other complications were comparable, including a 30-day in-hospital mortality. After a 1-year follow-up, the quality of life remained superior in the MIE group, and after 3 years, the survival rates were comparable.31,32 The median 3-year survival rate following open esophagectomy was 24 months (range 14.6–33.3) and 27 months (range 11.2–42.8) following MIE (P = 0.633). The open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III (MIRO) trial from the FREGAT group has not been published yet although the results were presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting and the European Society for Medical Oncology 2017 Congress (NCT00937456). Herein, 219 patients were randomized to either open or hybrid (laparoscopic/right thoracotomy) Ivor Lewis procedures (HMIE). The primary endpoint of this trial was 30 days peri- and postoperative morbidity grades II–IV according to the Clavien-Dindo classification. At 30 days, a major postoperative morbidity occurred in significantly fewer patients in the HMIE compared with the open group (35.9% versus 64.4%, OR 0.31, 95%CI: 0.18–0.55; P < 0.001). At three years, there was also a trend in the HMIE group toward improved overall survival and disease-free survival (67.0% versus 55%, P = 0.05 and 57% versus 48%, P = 0.15).

The results of the TIME and MIRO trials could not be reached in larger cohort studies from the UK, United States, and Japan, and in a population-based cohort study with the Dutch National Audit data.8–11 In the propensity score-matched study, postoperative pulmonary complications were comparable between the open and MIE groups: 34.2% (open) versus 35.6% (MIE; P = 0.669). This concerns all pulmonary complications and not just the infectious complications.8 Furthermore, anastomotic leakage rates were higher in the MIE group. This may be explained by the long proficiency gain curve for MIE, especially for intrathoracic anastomosis.12 The proficiency gain curve for Ivor Lewis total MIE (TMIE) is 119 cases in the high-volume centers that already have vast experience in McKeown TMIE, before the level of a <8% anastomotic leakage rate is achieved.12 Learning-associated anastomotic leakage is observed in 36 esophagectomy patients (10% of all patients operated on during the proficiency gain curve). The incidence of textbook outcome increases from 28% to 53% and the mean operative time decreases from 344 to 270 min after completion of the proficiency gain curve.12

The propensity score-matched population-based study includes the earlier years of MIE in the Netherlands.8 The MIE rate went up from 38% in 2011 to 82% in 2016.5,33 None of the centers performed >100 Ivor Lewis TMIE at that time. The lymph node yield was significantly higher in the MIE group (20 versus 18; P = 0.001) and R0 resection rates were comparable.8 To overcome the difficulties of a TMIE with an intrathoracic anastomosis, an alternative approach was proposed in the MIRO trial, in which a hybrid procedure was chosen in the MIE arm.34,35 The learning curve in HMIE as compared with TMIE has been described as clearly shorter, and transition from open esophagectomy to HMIE does not result in an increase of anastomotic complications.36,37 The Randomized Open or Minimally Invasive Oesophagectomy (ROMIO) trial is a three-arm trial that is still recruiting patients.
This trial randomizes between open esophagectomy, HMIE, and TMIE, and will hopefully clarify what the preferred approach is for patients with a resectable EC.35

Given the current evidence, MIE as either HMIE or TMIE could become the new standard. Of course, in difficult cases (salvage, high tumor burden, and high-dose radiotherapy) of open esophagectomy, it is still the preferred strategy as described above. Moreover, it is important to follow some rules, such as a minimum of 40 esophagectomies per year and the registration of fundamental items in a prospective database, when changing from the open to MIE procedures, as recently recommended by a Delphi consensus study in Europe.38

In summary, there is a vast implementation of MIE in Europe, and especially in the Netherlands, and the evidence-based advantages from the two RCTs are less pulmonary complications, less blood loss, a shorter hospital stay, and a better quality of life. The quality of the surgical resection specimens, including lymph node yield, and a 3-year survival is comparable or even better following MIE. In the cohort studies, the complication rate is higher than in the TIME and MIRO trials, which demonstrates that TMIE is a difficult procedure with a long learning curve. Most experts believe this is due to the technical difficulty of TMIE. The esophagus is in close contact with the aorta, heart, airway, and other essential structures; therefore, the dissection is very delicate. Moreover, creating the intrathoracic anastomosis is a technically challenging maneuver.

**Robotic esophagectomy**

An option to overcome several challenges of TMIE is the use of a robot system. A robot-assisted MIE (RAMIE) was first described in 2005, and the long-term results have shown its feasibility and safety.39,40 Robotic surgery is usually performed with the aid of the da Vinci® system (Intuitive Surgical, Sunnyvale, CA).13 But other robotic systems are being developed and will be discussed later. The robotic system offers technical advantages over standard minimally invasive surgery, both in the fields of visualization and manipulation. A full 3D image of the operative field is provided, projected in line with the surgeon’s normal working axis, in a console. From this console, the surgeon manipulates two joysticks, whose movements are translated to the robotic arms. The robotic instruments offer additional degrees of freedom of motion (wrists) and augment the surgeon’s movements through scaling and tremor filtration.

With the use of RAMIE, some groups have described extensive paratracheal lymph node dissections.41 Especially in the areas difficult to reach with conventional instruments, the robot may offer a better access.13,42 For instance, the upper thoracic aperture can be reached without any problems, offering clear sights on the recurrent laryngeal nerves (Fig. 1). These advantages are difficult to compare with standard MIE, but recently the Robot-assisted Thoracolaparoscopic Esophagectomy vs. Open Transthoracic Esophagectomy (ROBOT) trial was closed.43 This trial compared open esophagectomy with RAMIE and the results were presented.
at the Congress of the European Society for Diseases of the Esophagus 2017 and the 2018 ASCO Annual Meeting; they are expected to be published soon. A previous retrospective study from the same group showed that RAMIE can be performed with a high percentage of R0 radical resections, an adequate lymphadenectomy, an acceptable morbidity rate, and a low percentage (6%) of local recurrence after 5 years. 40 On the contrary, the robot might also have some disadvantages, such as higher costs, more time-consuming procedures, and the lack of tactile feedback. 44 The proficiency gain curve might be even longer than for MIE although no large studies have been completed to support this assumption. 45 In addition, these systems are unavailable for surgeons in all countries.

The prospect for RAMIE extends further than just offering the current benefits. The newest robotic systems offer technological improvements that will further enhance the surgeon’s capabilities. Fluorescence cameras are now standard features on these systems and will allow visualization of the vascularization of the gastric conduit but possibly also help us to improve lymph node dissection and target sentinel nodes. 46,47 Furthermore, a robotic 45-mm stapler (EndoWrist® Stapler System, Intuitive Surgical, Sunnyvale, CA) was recently developed for use with the da Vinci Xi® Surgical System. This stapler offers extended articulation (108° total side-to-side and 54° total up and down), and is equipped with force feedback. This feedback system detects whether the stapler is adequately closed on tissue or when excessive tissue is present within the stapler. This robotic stapler will make stapling more standardized and reproducible. 48

The newest development in a robotic surgery is that the Intuitive Surgical’s competitors are finally emerging in this market. The new robotic systems are brought to the market (e.g., by Titan MedicalTM, CMR Surgical, TransEnterixTM, Verb Surgical, Medtronic, and avateramedical® GmbH), which will possibly reduce costs. Technological developments in these new robotic devices focus not only on specific features of the robotic arms, instruments, console, and video technology, but also on using artificial intelligence and image recognition to enhance the surgeon’s capabilities. Whether the technical developments of robot-assisted surgery will result in better outcomes for our patients has to be answered in the upcoming years. 49

**Future perspectives**

In the near future, it is expected that the new technical applications will be developed for robotic as well as “traditional” thoraco-laparoscopic systems, and for an open surgery, such as new instruments that will make dissection easier, and novel optical techniques that will enhance the surgeons’ vision, and will make perfusion and lymph node dissemination routes visible.

Although MIE and robotic esophagectomies will be increasingly practiced, open surgery will never be abandoned as an approach for EC. The most important feature of the operation is to radically remove the esophageal carcinoma and locoregional lymph node stations, and open surgery is an excellent way to do so.

**Competing interests**

The authors declare no competing interests.

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