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Applications and prospects of robotic surgery in esophageal cancer

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Abstract Esophageal cancer (EC) is among the most common malignances and one of the leading causes of cancer-related death worldwide. Surgery plays a significant role in the multidisciplinary treatment for esophageal cancer. Recent advances in minimally invasive esophagectomy (MIE), including conventional thoracoscopic surgery and more recent robotic surgery, has been shown to improve short-term outcomes compared to open surgery. Robot-assisted minimally invasive esophagectomy (RAMIE) was first performed in 2003 and has been increasingly utilized in tertiary medical centers. Compared to conventional video-assisted minimally esophagectomy (VAMIE), RAMIE provides certain advantages such as increased magnification, three-dimensional visual clarity and better lymphadenectomy, with superior short-term outcome and at least equivalent oncological results. This review focuses on the techniques, benefits and obstacles in applications of robotic esophagectomy for treating EC, meanwhile discussing the future of robotic esophageal surgery.

Key words Esophageal cancer; Minimally invasive esophagectomy (MIE); Robotic-assisted minimally invasive esophagectomy (RAMIE), Robotic surgery

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Esophageal cancer is the ninth most common cancer and the sixth leading cause of cancer-related death worldwide[1]. In the Asia-Pacific region, the vast majority of esophageal cancers are squamous cell carcinomas (SCC), while in western countries most EC are adenocarcinoma. Although pathological and biologic features differ between SCC and adenocarcinoma, esophagectomy remains the cornerstone of curative treatment for both types of esophageal carcinoma. Conventional surgery for esophageal cancer consists of open esophagectomy, two-field or three-field lymphadenectomy and

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reconstruction of digestive tract using remnant stomach. Common surgical approach for esophagectomy includes left thoracotomy approach (Sweet), right thoracotomy and epigastric midline incision approach (Ivor-Lewis) and right thoracotomy-abdominal midline-neck triple incision approach (Mc-Keown). Transhiatal esophagectomy (THE) without thoracotomy is also performed for preserving pulmonary function and reducing pulmonary complications, but is possibly associated with poor long-term survival[2]. However, such highly invasive open surgery leads to severe postoperative complications, such as pulmonary complications, anastomotic leak, conduit necrosis, chyle leak, and recurrent nerve injury[3]. Recently, minimally invasive esophagectomy (MIE) was first developed in 1992 and has been increasingly adopted for up to 45% of resectable esophageal cancer worldwide. MIE has been shown to be superior compared to open esophagectomy regarding perioperative outcome[4–6] without compromising oncologic results[7–8].

The evidence that MIE was safe and at least oncological equivalent to open esophagectomy drove the development of RAMIE, which overcomes some of the intrinsic technical disadvantages commonly experienced during MIE, particularly the thoracoscopic phase. The relatively rigid chest cavity, with limited access due to the proximity of the ribs, scapula and vertebral column, as well as the use of rigid surgical instruments and a two-dimensional view, increased the operation difficulty for standard minimally invasive tools. The first RAMIE was performed in 2003[9] and has been increasingly utilized in tertiary medical centers, with the first case series published in 2006[10]. By offering technical advantages such as an enhanced 10–fold magnification stable, three-dimensional endoscopic view and robotic arms with full dexterity, robotic assistance can be useful during complex surgical procedures, even allowing surgeons to identify anatomy not previously recognized or documented. For example, a distinct fascial layer surrounding the esophageal blood supply and lymphatics in essence forming a "meso-esophagus" was first described with help from robotic system[11].

As RAMIE established as a technique for performing esophagectomy for resectable esophageal cancer and increasingly utilized worldwide, terms and meaning extended from "RAMIE" appear from time to time. For instance, the term "RAMIE" may cause ambiguity as it's used interchangeably to describe totally robotic esophagectomy[12] or a laparoscopic abdominal phase combined with a robotic thoracic phase. Extended 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. Even though, the location and method of performing the esophagogastric anastomosis varies between centers even during the same "RAILE" or "RAMIME" process, which has brought difficulties in collecting and comparing data from heterogeneous case groups and series.

1 Procedure and Techniques of RAMIE Surgery

1.1 Robotic Assisted Ivor Lewis Esophagectomy (RAILE)

RAILE procedures are performed using Da

Vinci Surgical System. A four-arm approach are mostly often performed in both the abdominal and thoracic phases. First, the patient was supine in a reverse Trendelenburg position. The camera is inserted into a 5-mm port and the abdomen is entered via an optiview technique. If there' s no evidence of metastatic disease, additional 8-mm ports are placed in the right lateral and left lateral positions. A robotic stapling port is placed in the right paramedian location. An assistant port is placed in the left paramedian location. Then the camera port is upsized to an 8 mm (Da Vinci Xi), or 10 mm (Da Vinci Si) [13]. The core procedure of the abdominal phase included mobilization of the stomach with abdominal lymphadenectomy, intracorporal creation of a gastric conduit, and laparoscopic-feeding jejunostomy. The celiac lymphadenectomy is performed by exposing the left gastric and dissecting it to the celiac, and a formal lymphadenectomy including lymph nodes surrounding the celiac trunk and the left gastric, common hepatic, and splenic arteries (stations 1-4, 7-9, and 11 with or without station 12) is routinely performed. The gastric conduit is usually created with several green loads of the robotic stapler, and then it is sutured to the gastric remnant. For the thoracic phase, the patient was positioned in the left-lateral decubitus position with single-lung ventilation. Thoracic procedures are started with an 8-mm incision in the 7th intercostal space. After confirming no evidence of metastatic deposits, the robotic ports are placed including an 8-mm port in the posterior 10th interspace and an additional 8-mm port in the 3rd interspace. The extraction incision (5 cm) is made in the 9th interspace[13]. The lymph node dissection was initiated along the right recurrent laryngeal nerve (RLN). Then, the esophagus is completely mobilized, and the conduit is pulled up through the hiatus. The lymph nodes in the periesophageal, bronchial and subcarinal areas (stations 107-111) and along the left RLN are dissected carefully[14]. The proximal esophagus is then disconnected with conduit stomach. For the intrathoracic gastroesophageal reconstruction, a circular stapler is introduced and passed into the chest for an end-to-end intracorporeal anastomosis, or a completely robot-assisted hand-sewn anastomosis technique was used. Finally, a single chest drainage tube is placed in the posterior location and goes out through the 10th interspace port site.

1.2 Robotic Assisted Mini Invasive McKeown Esophagectomy (RAMIME)

In the case of malignancies of the upper third esophageal, a three-field robotic McKeown esophagectomy is usually performed. The abdominal and thoracic phase are generally the same from RAILE procedure, only the thoracoscopic esophageal dissection is performed first. Thoracic esophageal is brought to the thoracic inlet until full mobilization, then mobilized from the thoracic inlet to the diaphragmatic crura. The azygos vein is routinely transected, and lymph nodes at paratracheal, subcarinal, and paraesophageal stations were dissected as described above. After the thoracic phase, the patients were then turned to reverse Trendelenburg. Before the abdominal procedure, the cervical esophagus was transected through a 5-cm incision along the left sternocleidomastoid muscle. After cervical procedure, abdominal phase is completed basically the same as RAILE. Finally, the gastric tube was delivered to the neck, and the

3-leaf clipper-assisted manual end-to-side layered anastomosis was performed at the cervical region, then an endoscopic linear stapler was used to transect the excessive portion of tubular stomach[15].

1.3 Robotic Assisted Transhiatal Esophagectomy (RATE)

Difficulties in thoracic access and the risk of pulmonary complications are major problems in esophageal surgery, thus transhiatal techniques are theoretically superior than transthoracic esophagectomy in terms of pulmonary compilations, because it avoids the thoracic approach. Moreover, RATE procedure has been found to have similar perioperative oncologic results compared to laparoscopic THE[16]. However, minimally invasive THE' s oncological radicality and lymph nodes yielding ability continues to be questioned compared to transthoracic approach, even their survival data seems equivalent[17-19]. Details of the standardized RATE procedure are roughly the same as laparoscopic THE, including dividing the short gastric vessels followed by periesophageal mediastinal dissection, ligation of the left gastric artery, performance of an upper midline mini-laparotomy with the creation of a stapled nontubularized gastric conduit, pyloroplasty, placement of feeding jejunostomy. The mobilized esophagus with the attached cardia of the stomach is then brought up through the cervical incision into the operative field in the neck, and a cervical gastroesophageal anastomosis is performed using a stapled technique[20]. Subsequently, the hiatus was examined and closed tightly around the gastric pull-up without compromising blood supply of the gastric tube[21].

2 Current Evidence of Robotic Esophagectomy

Since the first case series reported in 2006[10], increasing number of studies have provided evidence for RAMIE. Hereby we'll provide the latest published reports comparing RAMIE with other surgical approach, meanwhile discussing its relevance with the adaption and learning curve of RAMIE.

University Medical Centre Utrecht recently published their results of a single center, superiority, controlled, parallel-group, randomized controlled trial comparing RAMIE to open McKeown esophagectomy (the ROBOT trail) [22]. 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 compared to open transthoracic esophagectomy (OTE), bringing lower postoperative pain, better short-term quality of life, and a better short-term postoperative functional recovery without compromising oncological outcomes which was in concordance with the highest standards nowadays[23]. Similarly, a single center non-randomized comparative study compared open esophagectomy (either Ivor Lewis or left thoracoabdominal procedures) with RAMIE (almost exclusively RAILE procedures) regarding Quality of Life (QoL) assessed by the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) subset and the Brief Pain Inventory (BPI) [24]. The results showed that short-term QoL was better in RAMIE group as RAMIE was associated with lower immediate postoperative pain severity and interference and decreased pulmonary and infectious complications. Although the allocation in this study were not randomized and cohorts were not propensity matched, the baseline characteristics were not statistically different between groups. J.K.Yun and colleagues[25] reported that RAMIE is superior than open esophagectomy in not only short-term outcomes such as reducing incidence of pneumonia, requirement for vasopressors and wound problems, but long-term all-cause mortality and disease-free survival in 371 patients with esophageal SCC. These studies have shown that RAMIE is safe and improves short-term outcome by reducing peri-operative morbidity, improved early QoL, with equivalent oncological outcomes compared to open esophagectomy.

Since 2015, more than 100 RAMIE procedures have been performed in the Department of Thoracic Surgery, Ruijin Hospital. We have recently published a single center, propensity score-matched retrospective analysis comparing RAILE and conventional thoracoscopic-assisted Ivor Lewis esophagectomy (TAILE) [26]. After propensity match 66 patients were paired to compare MIE with RAMIE. We found that apart from a longer operative time for RAMIE, both the oncological outcome and short-term outcomes in terms of complications were equal. However, the learning-curve effect, which takes 20–70 RAMIE cases to enter experienced phase for surgeons, may have affected our study' s clinical relevance. An analysis of RAILE' s learning curve using cumulative sum (CUSUM) method is currently ongoing in our center, and we preliminarily found that a proficiency phase was achieved at approximately 50 of RAILE cases. In contrast, Zhang H[27] reported that 26 cases are required to gain an early proficiency of robot-assisted McKeown esophagectomy. Newest experience from a single surgeon[28] during transition from VATE to RAMIE, showed reduced recurrent laryngeal nerve neuropraxia and other perioperative complications in the RAMIE group with a minimal learning curve effect of 12 cases for experienced thoracoscopic surgeons. Thus, apart from intrinsic features of RAMIE, different surgical approach also affects the adaption process of robotic esophagectomy by surgeons, which consequently alters the comparative outcomes between RAMIE and MIE.

Besides, the first multi-center, open-label, randomized controlled prospective clinical trial involving robotic esophagectomy, The REVATE study, which compares RAMIE to MIE, is currently on recruitment of patients. This study focuses on whether RE could facilitate radical lymph node dissection (LND) along the left RLN, which remains difficult to perform with video-assisted thoracoscopic esophagectomy (VATE) and associated with a significant burden of morbidity[29].

3 What Shall We Expect in Future

The future of RAMIE depends on the developments in robotic platforms to a great extent. With advances in hardware, multiple new systems are expected over the next decade, such as surgeon consoles with 3D HD display technology, advanced collaborative robotics that allow surgical teams to move arms while the surgeon is operating, etc[30]. Recently, improvements in robotic tri-stapling devices, energy dissection instruments have simplified RAMIE. Nevertheless, in the nearest future, the greatest future advances in robotic surgery are likely to be in software developments. The use of artificial intelligence, data and imaging integration and connectivity will open up new possibilities in terms precision surgery, but also permit big data collection and machine learning[31–32]. Besides, the advent of single port robotic systems (e.g., da Vinci SP system, Intuitive Surgical Inc, SPORT surgical system, Titan Medical Inc) will inevitably witness developments in single port stages of both the abdominal and thoracic phases of esophagectomy. The single port robotic systems can make a significant difference in the cervical approach for the upper mediastinum field, mainly improving the esophageal dissection and lymphadenectomy of the upper mediastinum in transhiatal esophagectomies[33–34].

4 Concluding Remarks

Over the past two decades, robotic esophageal surgery has become more and more important overtime, as esophagectomy and lymphadenectomy remains a cornerstone in the treatment of esophageal malignancy in combination with neoadjuvant and (or) adjuvant therapy. Several studies have now shown that RAMIE is safe, feasible and results in reduced complications compared to open surgery. However, we still need more high quality prospective evidence to prove that RAMIE is equal or even superior than conventional MIE in terms of perioperative and long-term outcomes. Future influx of new robotic platforms including the artificial intelligence software, next-generation tri-stapling and energy dissection instruments and sentinel node mapping technology will impact robotic surgery through even less invasive surgery, big data sharing, precision surgery, and cooperation of surgical team.

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