Robot-assisted minimally invasive esophagectomy for esophageal cancer: Meticulous surgery minimizing postoperative complications

Kei Hosoda | Masahiro Niihara | Hiroki Harada | Keishi Yamashita

Naoki Hiki

Abstract
Minimally invasive esophagectomy (MIE) has been reported to reduce postoperative complications especially pulmonary complications and have equivalent long-term survival outcomes as compared to open esophagectomy. Robot-assisted minimally invasive esophagectomy (RAMIE) using da Vinci surgical system (Intuitive Surgical, Sunnyvale, USA) is rapidly gaining attention because it helps surgeons to perform meticulous surgical procedures. McKeown RAMIE has been preferably performed in East Asia where squamous cell carcinoma which lies in more proximal esophagus than adenocarcinoma is a predominant histological type of esophageal cancer. On the other hand, Ivor Lewis RAMIE has been preferably performed in the Western countries where adenocarcinoma including Barrett esophageal cancer is the most frequent histology. Average rates of postoperative complications have been reported to be lower in Ivor Lewis RAMIE than those in McKeown RAMIE. Ivor Lewis RAMIE may get more attention for thoracic esophageal cancer. The studies comparing RAMIE and MIE where recurrent nerve lymphadenectomy was thoroughly performed reported that the rate of recurrent nerve injury is lower in RAMIE than in MIE. Recurrent nerve injury leads to serious complications such as aspiration pneumonia. It seems highly probable that RAMIE is beneficial in performing recurrent nerve lymphadenectomy. Surgery for esophageal cancer will probably be more centralized in hospitals with surgical robots, which enable accurate lymph node dissection with less complications, leading to improved outcomes for patients with esophageal cancer. RAMIE might occupy an important position in surgery for esophageal cancer.

KEYWORDS
complication, esophagus, minimally invasive esophagectomy, RAMIE, robotic surgery
INTRODUCTION

Worldwide, 445,800 new esophageal cancer cases occurred, while 400,200 deaths occurred in 2012.¹ Curative treatment for intrathoracic esophageal cancer comprises preoperative chemotherapy²,³ or chemoradiotherapy⁴,⁵ followed by surgical resection, which is the most invasive procedure in gastroenterological surgery resulting in 40% of the morbidity rate with a mortality rate of 3%, according to the National Clinical Database in Japan.⁶ Subtotal esophagectomy with extensive mediastinal lymphadenectomy remains a critical element in the treatment of esophageal cancer. Minimally invasive esophagectomy (MIE), which uses thoracoscope or laparoscope to minimize the surgical trauma to the thoracic or abdominal wall, has been introduced to reduce the operative stress in the area of esophageal surgery especially in high-volume centers. Randomized controlled trials and meta-analyses have revealed that MIE reduces postoperative complications, especially pulmonary complications, and has equivalent long-term survival outcomes as compared to open esophagectomy.⁷⁻⁹ However, traditional thoracoscopic esophagectomy requires such high skill that only limited expert surgeons can perform this surgery. Some of the reasons that make this surgery so difficult are: limited range of movement of the instrument tip caused by narrow intercostal space; proximity of important organs such as trachea, main bronchi, and thoracic aorta, lymph node dissection around the recurrent nerves; and narrow upper mediastinum surgical space.

In 2000, da Vinci was approved in the Food and Drug Administration (FDA) as the first computerized telesurgical device in the United States.¹⁰ Initially, robot-assisted surgery was widespread in the field of pelvic surgery, including prostate surgery and gynecological surgery. The da Vinci surgical system provides surgeons with a three-dimensional camera, instruments with 7° freedom of movement, tremor filtration, and motion scaling, which enable surgeons to overcome the difficulty encountered in conventional MIE and to perform extremely delicate procedures needed for esophageal cancer surgery more easily and precisely.

In this article, we aim to highlight the development and current status of robot-assisted minimally invasive esophagectomy (RAMIE) and compare it with conventional MIE, reviewing the pertinent literature.

STUDY SELECTION

A manual search using PubMed and Embase was conducted for references related to studies on RAMIE published until 30 March 2020. The following search terms were used: “Esophagus” and “robot.” A total of 49 out of 815 studies were selected that: (a) included more than 10 patients; (b) in which the RAMIE technique used was clearly described;
and (c) in which the complications were adequately described. For manuscripts from the same institution, new reports were adopted if they were considered to contain the same cases (Figure 1).

3 | CLASSIFICATION OF RAMIE

RAMIE is thought to be classified into three categories: transthoracic thoracoscopic esophagectomy with cervical anastomosis (McKeown RAMIE), transthoracic thoracoscopic esophagectomy with intrathoracic anastomosis (Ivor Lewis RAMIE), and transhiatal esophagectomy (transhiatal RAMIE).

4 | MCKEOWN RAMIE

In the transthoracic RAMIE, McKeown procedure has been preferably performed for the ease of reconstruction, especially for middle or upper-third thoracic esophageal cancer. The case of McKeown RAMIE with three-field procedure was first reported by Kernstine and colleagues in 2004.11 The patient had T3N0 adenocarcinoma in the lower thoracic esophagus area and had undergone preoperative chemoradiotherapy of paclitaxel, carboplatin, and 40 Gy of radiation therapy. Robotic surgery was applied for both the thoracic and the abdominal procedures with the total surgical console time of 260 minutes and estimated blood loss (EBL) of 900 mL. They concluded that transthoracic RAMIE could potentially provide an oncologically superior resection with reduction of the burden to the patient. After this report, McKeown RAMIE has been favorably performed especially in East Asia where squamous cell carcinoma, which lies in more proximal esophagus than adenocarcinoma, is a predominant histological type of esophageal cancer.12–14

Table 1 lists case series studies of McKeown RAMIE including 10 cases or more.12,13,15–26 In most studies, squamous cell carcinoma was the predominant histological type. Median or average EBL was 100 mL or more in all studies reporting EBL with maximum median EBL of 950 mL. Median or average numbers of harvested lymph nodes were more than 20 in nine of the 13 studies. The average rates of postoperative complications were as follows: pneumonia 19.6%, anastomotic leak 15.1%, chyle leak 9.2%, recurrent nerve injury 15.9%. The average mortality rate was 4.0%.

We started McKeown RAMIE in November 2018 and experienced 20 cases until January 2020. The number of 20 cases might not have completed the learning curve period. However, the short-term outcomes were comparable to those in the other studies of McKeown RAMIE with median operative time of 490 minutes, median EBL of 151 mL, and median number of harvested recurrent nerve lymph nodes of 7.4. The rate of postoperative complications was also acceptable with pneumonia of 10% and recurrent nerve injury of 10%. RAMIE certainly offers advantages over MIE even in the introductory period.18

In 2019, Utrecht group reported the results of the first randomized controlled trial comparing McKeown RAMIE and open transsthoracic esophagectomy (ROBOT trial).27 In this study, they compared 54 patients allocated to RAMIE and 55 patients allocated to open transthoracic esophagectomy and reported that RAMIE was better than open transthoracic esophagectomy in postoperative complication rate (59% vs 80%, P = .02) and functional recovery at postoperative day 14. The long-term oncological outcome was comparable with each other. This trial provided evidence for the use of McKeown RAMIE to improve short-term postoperative outcomes.

5 | IVOR LEWIS RAMIE

On the other hand, Ivor Lewis RAMIE, which was first reported by Melvin et al in 2002,29–30 has been preferably performed in the United States where the adenocarcinoma, including Barrett esophageal cancer, is the most frequent histology in patients with esophageal cancer. Ivor Lewis esophagectomy requires intrathoracic anastomosis, which is relatively difficult, either by hand-sewn or mechanical anastomosis when performed thoracoscopically. Surgical robot may help surgeons perform intrathoracic hand-sewn anastomosis more proficiently as compared with that in conventional thoracoscopic MIE.

Recurrent nerve injury is reported to be significantly less in Ivor Lewis MIE than in McKeown MIE.29–30 Table 2 shows case series studies of Ivor Lewis RAMIE including more than 10 cases.31–42 Only four studies reported recurrent nerve injury with the average rate of 4.2%.31,33,37,39 On the other hand, recurrent nerve injury rates in the case series of McKeown RAMIE were reported to be 2.9%–29% with the average rate of 15.9%.12,13,15–26 However, it should be considered that McKeown and Ivor Lewis procedures have different operative indications and the attitudes toward upper mediastinal dissection would be different, which could affect the rate of recurrent nerve palsy and other complications.

In most studies, adenocarcinoma was the predominant histological type. Median or average EBL was <100 mL in three of the 10 studies reporting EBL with maximum average EBL of 311 mL. Median or average numbers of harvested lymph nodes were more than 20 in only three of the 11 studies. The average rates of postoperative complications were lower than McKeown RAMIE, as follows: pneumonia 8.5%; anastomotic leak 5.6%; chyle leak 3.7%; recurrent nerve injury 4.2%. The average mortality rate was 1.5% and was also lower than McKeown RAMIE. For the patients in whom the rate of lymph node metastasis in the superior mediastinum is suspected to be very low, or when the advanced MIE (RAMIE) can realize radical superior mediastinal lymph node dissection easily, Ivor Lewis RAMIE may get more attention for thoracic esophageal cancer.

6 | TRANSHIATAL RAMIE

Another robotic esophagectomy, transhiatal RAMIE, was first reported by Horgan et al in 2003.43 One of the greatest advantages of this operation is that it can be performed without separate
| Author               | Year | n  | Country     | Pathology (%) | Complications (%) | Abbreviations | Complications (%) | Abbreviations | Complications (%) | Abbreviations | Complications (%) | Abbreviations | Complications (%) | Abbreviations | Mortality |
|----------------------|------|----|-------------|---------------|-------------------|---------------|-------------------|---------------|-------------------|---------------|-------------------|---------------|-------------------|---------------|-----------|
| van Hillegersberg   | 2006 | 21 | Netherland  | SCC 52, Adeno 48, Other 0 | Op time 450, EBL 950, HLN 20 | SCC 48, Adeno 14, Other 14, Pneumonia 14, Anast leak 14, Chyle leak 5.0 | Anast leak 14, Chyle leak 5.0, RN injury 5.0, Mortality 4.0 |
| Kernstine           | 2007 | 14 | USA         | SCC 29, Adeno 57, Other 14 | Op time 672, EBL 275, HLN 18 | SCC 21, Adeno 14, Other 7.0, Pneumonia 14, Anast leak 7.1, Chyle leak 4.8, RN injury 29, Mortality 0 |
| Boone               | 2009 | 47 | Netherlands | SCC 38, Adeno 62, Other 14 | Op time 450, EBL 625, HLN 29 | SCC 45, Adeno 21, Other 13, Pneumonia 19, Anast leak 19, Chyle leak 6.4, RN injury 0, Mortality 1.8 |
| Kim                 | 2010 | 21 | Korea       | SCC 95, Adeno 5, Other 0 | Op time 410, EBL 150, HLN 40 | SCC 0, Adeno 19, Other 7.1, Pneumonia 4.8, Anast leak 19, Chyle leak 29, RN injury 0, Mortality 0 |
| Puntambekar         | 2011 | 32 | India       | NA, NA, NA | Op time 210, EBL NA, HLN NA | SCC 6.3, Adeno 9.3, Other 9.3, Pneumonia 6.2, Anast leak 2.5, Chyle leak 5.0, RN injury NA |
| Kim                 | 2014 | 40 | Korea       | SCC 100, Adeno 0, Other 0 | Op time 429, EBL 158, HLN 43 | SCC 13, Adeno 10, Other 5.0, Pneumonia 20, Anast leak 20, Chyle leak 2.5, RN injury 2.5, Mortality 0 |
| van der Sluis       | 2015 | 108| Netherlands | SCC 19, Adeno 72, Other 9 | Op time 381, EBL 340, HLN 26 | SCC 33, Adeno 19, Other 18, Pneumonia 9.3, Anast leak 9.3, Chyle leak 5.0, RN injury 5.0, Mortality 5.0 |
| Park                | 2016 | 114| Korea       | SCC 96, Adeno 4, Other 0 | Op time 420, EBL 209, HLN 44 | SCC 9.6, Adeno 15, Other 1.8, Pneumonia 26, Anast leak 2.6, Chyle leak 5.0, RN injury 5.0, Mortality 5.0 |
| Chu                 | 2017 | 20 | Hong Kong   | SCC 85, Adeno 15, Other 0 | Op time 500, EBL 356, HLN 18 | SCC 5, Adeno 15, Other 5.0, Pneumonia 25, Anast leak 25, Chyle leak 5.0, RN injury 0, Mortality 5.0 |
| Somashekhar         | 2017 | 35 | India       | SCC 74, Adeno 26, Other 0 | Op time NA, EBL NA, HLN 32 | SCC 2.9, Adeno 0, Other 0, Pneumonia 2.9, Anast leak 0, Chyle leak 0, RN injury 0, Mortality 0 |
| van der Horst       | 2017 | 31 | Netherlands | SCC 61, Adeno 39, Other 0 | Op time 435, EBL 350, HLN 22 | SCC 32, Adeno 19, Other 29, Pneumonia 13, Anast leak 13, Chyle leak 0, RN injury 0, Mortality 0 |
| Goel                | 2018 | 27 | India       | SCC 96, Adeno 4, Other 0 | Op time 343, EBL 208, HLN 18 | SCC 7.4, Adeno 11, Other 3.7, Pneumonia 7.4, Anast leak 7.4, Chyle leak 3.7, RN injury 3.7, Mortality 3.7 |
| Zhu                 | 2019 | 10 | China       | SCC 100, Adeno 0, Other 0 | Op time 374, EBL 100, HLN 22 | SCC NA, Adeno NA, Other 0, Pneumonia 0, Anast leak 20, Chyle leak 0, RN injury 20, Mortality 0 |
| Hosoda              | 2020 | 20 | Japan       | SCC 90, Adeno 10, Other 0 | Op time 490, EBL 151, HLN 44 | SCC 10, Adeno 25, Other 5.0, Pneumonia 10, Anast leak 0, Chyle leak 0, RN injury 0, Mortality 0 |

Abbreviations: Adeno, Adenocarcinoma; Anast leak, Anastomotic leak; EBL, Estimated blood loss; HLN, Harvested lymph nodes in total; Op time, Operative time; RN injury, Recurrent nerve injury; SCC, Squamous cell carcinoma. 

aIn hospital or 90-d mortality. 
bAverage otherwise median.
| Author       | Year | n   | Country | SCC | Adeno | Other | Op time | EBL  | HLN  | Pneumonia | RN injury | Anast leak | Chyle leak | Mortality |
|--------------|------|-----|---------|-----|-------|-------|---------|------|------|-----------|-----------|------------|-----------|-----------|
| Cerfolio^39  | 2013 | 16  | USA     | 19  | 81    | 0     | 367^b   | 60^b | 18^b | 0         | 0         | 0          | 0         | 0         |
| de la Fuente^38| 2013 | 50  | USA     | 6   | 92    | 2     | 445     | 146  | 20   | 10        | NA        | 2.0        | 4.0       | 0         |
| Hernandez^34 | 2013 | 52  | USA     | 6   | 88    | 6     | 442     | NA   | 19   | 9.6       | NA        | 1.9        | 3.8       | 0         |
| Trugeda^37   | 2014 | 14  | Spain   | 36  | 64    | 0     | 222^b   | 75^b | 18^b | 0         | 0         | 7.1        | 14        | 0         |
| Hodari^36    | 2015 | 54  | USA     | 6   | 85    | 9     | 362     | 74   | 16   | 14        | NA        | 5.5        | 2.3       | 1.9       |
| Wee^45       | 2016 | 20  | USA     | 10  | 75    | 15    | 455^b   | 275^b| 23   | 10        | NA        | 0          | 10        | 0         |
| Egberts^32   | 2017 | 75  | Germany | 0   | 96    | 4     | 392^b   | 172^b| 29   | NA        | NA        | 9.6        | NA        | 3.9       |
| Zhang^31     | 2018 | 61  | China   | 95  | 0     | 5     | 316     | 189  | 19   | 6.6       | 8.2       | 9.8        | 1.6       | 0         |
| Meredith^40  | 2018 | 147 | USA     | 10  | 86    | 4     | 415     | 158  | 20   | 6.8       | NA        | 2.7        | 3.4       | 1.4       |
| Pötscher^41  | 2019 | 11  | Austria | NA  | NA    | NA    | 389^b   | NA   | NA   | NA        | NA        | 18         | NA        | NA        |
| Wang^42      | 2019 | 31  | China   | 71  | 26    | 3     | 387     | 110^b| 17   | 3.2       | NA        | 6.5        | NA        | 0         |
| var der Sluis^33| 2020 | 100 | Germany | 19  | 79    | 2     | 415     | 311  | 29   | 12        | 3.0       | 8.0        | 4.0       | 3.0       |

Average: 8.5 4.2 5.6 3.7 1.5

Abbreviations: Adeno, Adenocarcinoma; Anast leak, Anastomotic leak; EBL, Estimated blood loss; HLN, Harvested lymph nodes in total; Op time, Operative time; RN injury, Recurrent nerve injury; SCC, Squamous cell carcinoma.

^aIn hospital or 90-d mortality.

^bMedian otherwise average.
pulmonary ventilation or artificial pneumothorax, which enables esophagectomy even in patients with possible intrathoracic adhesion or low respiratory function.

Transhiatal RAMIE in combination with transcervical upper mediastinal dissection is quite different from transhiatal RAMIE in Western countries. Mori et al claimed that surgical robot with articulating instrument enables the same extent of lymph node dissection as that achieved in open transthoracic esophagectomy. It has been reported that transhiatal RAMIE had less postoperative pneumonia with improved postoperative quality of life than open transthoracic esophagectomy. Although this surgery has a possibility to become widespread, mediastinoscopic anatomical knowledge is not widely known, which may lead to life-threatening organ damage such as damage of bronchi which lie at the deepest point from both the abdomen and the neck.

Robotic transcervical recurrent nerve lymph node dissection in combination with transhiatal RAMIE using da Vinci Xi has recently been reported as an innovative treatment. This transcervical method enables recurrent nerve lymph node dissection by robotic approach. The rate of recurrent nerve injury is currently reported to be relatively high (25%-33%), but this might be because of an incomplete learning curve. More recently, though using a cadaveric model, a preclinical study demonstrated that transcervical esophagectomy is technically feasible with the novel da Vinci SP Surgical System without additional ports or assistance. In this cadaveric study, all the thoracic procedures including the dissection of subcarinal lymph nodes and lower mediastinal lymph nodes were successfully performed from the neck. Although clinical trials are needed to prove the feasibility in clinical setting, this transcervical RAMIE might become the ultimate minimally invasive esophagectomy with radical mediastinal lymph node dissection for esophageal cancer.

7 | COMPARISON OF SHORT-TERM OUTCOMES BETWEEN RAMIE AND MIE

One systematic review with meta-analysis of retrospective studies comparing short-term outcomes between RAMIE and MIE has been reported. However, no prospective randomized controlled trial comparing RAMIE and MIE has been reported yet. Table 3 shows 12 retrospective studies comparing short-term outcomes of RAMIE and MIE. In seven of these studies, propensity score matching was conducted to balance confounding factors to reduce possible bias.

Most of the studies reported that operative time was longer in RAMIE. Robotic surgery includes docking and undocking of the patient cart, replacement of the instruments, etc. In this respect, robotic surgery tended to take longer time than conventional minimally invasive surgery. Six studies reported that EBL was lower in RAMIE than MIE, while five did not. The only systematic review with meta-analysis reported that EBL was significantly lower in RAMIE than MIE. However, in a report by Yang et al, who analyzed the largest number of cases in RAMIE and MIE using propensity score matching, EBL was similar between the groups. If the learning curve of robotic surgery was completed, operative time would become shorter and EBL would become lower in RAMIE than in conventional MIE because of improved dexterity of the instruments.

In terms of lymph node dissection, six studies reported that RAMIE yielded a higher number of total harvested lymph nodes, whereas two reported that RAMIE yielded a lower number of total harvested lymph nodes. The number of harvested lymph nodes is recognized as one of the markers of surgical quality. The tendency of RAMIE to harvest a larger number of lymph nodes might indicate the higher surgical quality of RAMIE.

Regarding postoperative complications, pneumonia is an important life-threatening complication with the incidence rate of postoperative pneumonia reported in almost all studies. None of these studies showed significant difference in the incidence rate of postoperative pneumonia. However, two studies which included 100 or more cases undergoing RAMIE reported a relatively lower rate of postoperative pneumonia. On the other hand, no consistent trend was found regarding another important life-threatening complication of anastomotic leak. Anastomotic methods for RAMIE and MIE were similar within the same study, though varied from study to study. RAMIE did not affect the anastomotic leakage rate.

8 | DISSECTION OF RECURRENT NERVE LYMPH NODES

The extent and quality of recurrent nerve lymph node dissection substantially vary among different regions. In the Western countries, where predominant histological type of esophageal cancer is adenocarcinoma and preoperative chemoradiotherapy followed by surgical resection is the standard of care for esophageal cancer, recurrent nerve lymph node dissection may be quite different from that performed in Japan. Therefore, comparison of recurrent nerve injury rate between the studies does not directly translate into the comparison of the quality of esophageal surgery. There have been four studies which compared RAMIE and MIE where the methods of recurrent nerve dissection were described in detail and the number of harvested recurrent nerve lymph nodes was five or more. All these studies reported that the rate of recurrent nerve injury is lower in RAMIE than in MIE. Recurrent laryngeal nerve injury leads to serious complications such as aspiration pneumonia. It is highly probable that RAMIE is beneficial in performing extended upper mediastinal lymph node dissection.

One of the keys to successful lymph node dissection around the recurrent nerves is how to avoid tractive damage to the nerves. The surgical robot can help surgeons perform the lymph node dissection with minimum tractive damage with intuitive and meticulous manipulations. Hiki demonstrated that minimally invasiveness in laparoscopic gastrectomy derives from less manipulation, such as intestinal manipulation and pancreatic compression, which he calls ‘organ-touchless surgery’. We think that this concept is in line...
| Author   | Year | Country   | Matching | Method   | n   | Op time | EBL  | HLN | Complications (%) | Total | Thoracic | Pneumonia | RN injury | Anast leak | Chyle leak | Mortality |
|----------|------|-----------|----------|----------|-----|---------|------|-----|-------------------|-------|----------|-----------|-----------|------------|------------|-----------|
| Suda     | 2012 | Japan     | Non      | RAMIE    | 16  | 682     | 144  | 37  | 18                | 6.0   | 38       | 38        | 0         | 0          |            |           |
|          |      |           |          | MIE      | 20  | 649     | 139  | 39  | 22                | 20    | 75       | 10        | 10        | 0          |            |           |
| Weksler  | 2012 | USA       | Non      | RAMIE    | 11  | 439     | 200  | 23  | NA                | 9.1   | 9.1      | 9.1       | NA        | 0          |            |           |
|          |      |           |          | MIE      | 26  | 484     | 226  | 23  | NA                | 15    | 3.8      | 15        | NA        | 7.6        |            |           |
| Park     | 2016 | Korea     | Non      | RAMIE    | 62  | 490     | 463  | 37  | NA                | 15    | 13       | 8.1       | NA        | 1.6        |            |           |
|          |      |           |          | MIE      | 43  | 458     | 467  | 29  | NA                | 14    | 24       | 2.3       | NA        | 0          |            |           |
| He       | 2018 | China     | PS       | RAMIE    | 27  | 349     | 119  | 20  | NA                | 19    | 15       | 11        | 0         | 0          |            |           |
|          |      |           |          | MIE      | 27  | 285     | 158  | 19  | NA                | 7.4   | 11       | 3.7       | 3.7       | 3.7        |            |           |
| Chao     | 2018 | Taiwan    | PS       | RAMIE    | 34  | 231     | 92   | 37  | 18                | 5.9   | 21       | 0         | NA        | 0          |            |           |
|          |      |           |          | MIE      | 34  | 200     | 103  | 36  | 19                | 18    | 29       | 5.9       | NA        | 2.9        |            |           |
| Deng     | 2019 | China     | PS       | RAMIE    | 52  | 353     | 96   | 22  | 12                | 9.6   | 14       | 5.8       | 0         | 3.8        |            |           |
|          |      |           |          | MIE      | 52  | 274     | 128  | 17  | 10                | 7.7   | 7.7      | 3.8       | 1.9       | 3.8        |            |           |
| Tagkalos | 2019 | Germany   | PS       | RAMIE    | 40  | 388     | 339  | 27  | NA                | 15    | NA       | 13        | NA        | 5.0        |            |           |
|          |      |           |          | MIE      | 40  | 321     | 343  | 23  | NA                | 18    | NA       | 13        | NA        | 2.5        |            |           |
| Zhang    | 2019 | China     | PS       | RAMIE    | 66  | 302     | 200  | 19  | 10                | 6.1   | 6.1      | 7.6       | 0         | 1.5        |            |           |
|          |      |           |          | MIE      | 66  | 275     | 200  | 19  | 12                | 7.6   | 4.5      | 4.5       | 1.5       | 1.5        |            |           |
| Chen     | 2019 | China     | PS       | RAMIE    | 54  | 187     | 119  | 25  | NA                | 15    | 13       | 9.3       | NA        | 1.9        |            |           |
|          |      |           |          | MIE      | 54  | 193     | 117  | 25  | NA                | 24    | 32       | 3.7       | 3.7       | NA         |            |           |
| Motoyama | 2019 | Japan     | Non      | RAMIE    | 21  | 634     | 492  | 52  | 23                | 0     | 24        | 5.0       | 5.0       | NA         |            |           |
|          |      |           |          | MIE      | 28  | 598     | 385  | 59  | 20                | 0     | 47        | 8.0       | 3.0       | NA         |            |           |
| Yang     | 2019 | China     | PS       | RAMIE    | 271 | 244     | 211  | 20  | 12                | 8.9   | 29       | 12        | 1.5       | NA         |            |           |
|          |      |           |          | MIE      | 271 | 276     | 210  | 19  | 12                | 13    | 15       | 14        | 0.7       | 0.7        |            |           |
| Harbison | 2019 | USA       | Non      | RAMIE    | 100 | 445     | NA   | NA  | NA                | 11    | NA       | 14        | NA        | 3.0        |            |           |
|          |      |           |          | MIE      | 625 | 418     | NA   | NA  | NA                | 19    | NA       | 15        | NA        | 2.2        |            |           |

Abbreviations: Anast leak, Anastomotic leak; EBL, Estimated blood loss; HLN, Harvested lymph nodes; Op time, Operative time; PS, propensity score matching; RN injury, Recurrent nerve injury.

*a*Median otherwise average.

*b*Thoracic operative time.

*c*Left recurrent nerve injury.

*d*In-hospital or 90-d mortality.
with that in the successful recurrent nerve lymph node dissection in RAMIE.

9 | FUTURE DIRECTION

In April 2018, robot-assisted thoracoscopic esophagectomy was covered by the national insurance in Japan. Subsequently, robot-assisted mediastinoscopic esophagectomy was also covered by the national insurance in Japan in April 2020. Japan has been far behind Europe, the US, Korea, and China in the field of robotic surgery partly because RAMIE had not been covered by medical insurance until recently and Japanese national insurance prohibits mixed medical care. Therefore, once a patient hopes to undergo RAMIE, he or she had to pay the large medical expenses related to the disease without insurance. However, due to the potential benefit provided by the surgical robot, RAMIE is rapidly prevailing, especially in advanced medical institutes in Japan. Compared with conventional MIE, the maneuverability is improved, the physical burden on the operator is reduced. The significance of robot-assisted thoracoscopic esophagectomy seems overwhelming.

On the other hand, there are numerous reports showing that surgical outcomes, including postoperative morbidity and mortality, were better in high-volume centers than those in low-volume centers.63–65 Though not as many as in other countries, surgical robots have been installed in the majority of leading high-volume centers in Japan but might not be installed in many other centers. This may be because only high-volume centers can afford to buy and maintain running these robots, as there is a large financial burden associated with the da Vinci surgical system. Surgery for esophageal cancer will probably be more centralized in hospitals with surgical robots, leading to improved outcomes for esophageal cancer surgery.

There are two ongoing multicenter prospective randomized controlled trials comparing RAMIE and MIE which are called “REVATE” trial66 and “RAMIE” trial.67 “REVATE” trial is designed to demonstrate the superiority of RAMIE regarding recurrent nerve lymph node dissection. The primary endpoint is set to be the rate of unsuccessful recurrent nerve lymph node dissection defined as failure to remove lymph nodes along the left recurrent nerve or occurrence of permanent left recurrent nerve injury. “RAMIE” trial is designed to demonstrate non-inferiority of RAMIE in overall survival. These trials will provide important evidence of usefulness of RAMIE compared to MIE.

10 | CONCLUSION

RAMIE is one of the operations that can maximize the advantages of surgical robots. Most of the studies reported so far dealt with the initial experience of RAMIE. According to these results, the safety and feasibility of RAMIE during the learning period were confirmed. In the surgical resection for esophageal squamous carcinoma, which is a predominant histological type of esophageal cancer in East Asia including Japan, lymph node dissection around recurrent nerve is the most important point. This recurrent nerve lymph node dissection is where the robotic surgery can be most beneficial through precise movement of robotic instrument. Esophageal cancer surgery including RAMIE will be centralized more and more. Although the entire field of RAMIE is still so immature that further studies are needed to demonstrate the superiority of RAMIE to the other surgical methods, RAMIE might occupy an important position in surgery for esophageal cancer.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87–108.
2. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29:1715–21.
3. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (UCOG9907). Ann Surg Oncol. 2012;19:68–74.
4. Van Hagen P, Hulshof MCCM, Van Lanschot JJB, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BPL, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–84.
5. Shapiro J, Van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. Lancet Oncol. 2015;16:1090–8.
6. Takeuchi H, Miyata H, Gotoh M, Kitagawa Y, Baba H, Kimura W, et al. A risk model for esophagectomy using data of 5534 patients included in a Japanese nationwide web-based database. Ann Surg. 2014;260:259–66.
7. Bierie SSAY, Van Berge Henegouwen MI, Maas KW, Maas KW, Bonavina L, Rosman C, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicentre, open-label, randomised controlled trial. Lancet. 2012;379:1887–92.
8. Straatman J, Van Der Wielen N, Cuesta MA, Daams F, Roig Garcia J, Bonavina L, et al. Minimally invasive versus open esophageal resection. Ann Surg. 2017;266:232–6.
9. Shannugasundaram R, Hopkins R, Neeman T, Beenen E, Ferguson J, Gananadha S. Minimally invasive McKeown’s vs open oesophagectomy for cancer: A meta-analysis. Eur J Surg Oncol. 2019;45:941–9.
10. Melvin WS, Needelman BJ, Krause KR, Schneider C, Wolf RK, Michler RE, et al. Computer-enhanced robotic telesurgery: Initial experience in foregut surgery. Surg Endosc Other Interv Tech. 2002;16:1790–2.
11. Kerstine KH, DeArmond DT, Karimi M, Van Natta TL, Campos JC, Yoder MR, et al. The robotic, 2-stage, 3-field esophagolymphadenectomy. J Thorac Cardiovasc Surg. 2004;127:1847–9.
12. Kim DJ, Hyung WJ, Lee CY, Lee J-G, Haam SJ, Park I-K, et al. Thoracoscopic esophagectomy for esophageal cancer: Feasibility and safety of robotic assistance in the prone position. J Thorac Cardiovasc Surg. 2010;139(1):53–9.

13. Kim DJ, Park SY, Lee S, Il KH, Hyung WJ. Feasibility of a robot-assisted thoracoscopic lymphadenectomy along the recurrent laryngeal nerves in radical esophagectomy for esophageal squamous carcinoma. Surg Endosc. 2014;28:1866–73.

14. Suda K, Ishida Y, Kawamura Y, Inaba K, Kanaya S, Teramukai S, et al. Robot-assisted thoracoscopic lymphadenectomy along the recurrent laryngeal nerve for esophageal squamous cell carcinoma in the prone position: Technical report and short-term outcomes. World J Surg. 2012;36:1608–16.

15. van der Horst S, Weijts TJ, Ruurda JP, Mohammad NH, Mook S, Brosens LAA, et al. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy for esophageal cancer in the upper mediastinum. J Thorac Dis. 2017;9:S834–842.

16. Goel A, Shah SH, Selvakumar VPP, Garg S, Kumar K. Robot-assisted mckeown esophagectomy is feasible after neoadjuvant chemoradiation. Our Initial Experience. Indian J Surg. 2018;80:24–9.

17. Zhu Y, Ma L, Liu L, Lin Y. Application of full lateral decubitus position with cephalic parallel approach in robotic-assisted minimally invasive esophagectomy. J Thorac Dis. 2019;11:3250–6.

18. Hosoda K, Niihara M, Ushiku H, Harada H, Sakuraya M, Washio M, et al. Prevention of intra-thoracic recurrent laryngeal nerve injury with robot-assisted esophagectomy. Langenbeck's Arch Surg. 2020;405:533–40.

19. Van Hillegersberg R, Boone J, Draaisma WA, Broeders IAMJ, Giezeman MJMM, Rinkes IHMB. First experience with robot-assisted thoracoscopic esophagolympadenectomy for esophageal cancer. Surg Endosc Other Interv Tech. 2006;20:1435–9.

20. Kernstine KH, DeArmond DT, Shamoun DM, Campos JH. The first series of completely robotic esophagectomies with three-field lymphadenectomy: initial experience. Surg Endosc. 2007;21:2285–92.

21. Boone J, Schipper MEI, Moojen WA, Borel Rinkes IHM, Cromheecke GJE, Van Hillegersberg R. Robot-assisted thoracoscopic oesophagectomy for cancer. Br J Surg. 2009;96:878–85.

22. Puntambekar SP, Rayate N, Joshi S, Agarwal G. Robotic trans-thoracic esophagectomy in the prone position: Experience with 32 patients with esophageal cancer. J Thorac Cardiovasc Surg. 2011;142:1283–1284.

23. van der Sluis PC, Ruurda JP, Verhage RJJ, van der Horst S, Havercamp L, Siersma PD, et al. Oncologic long-term results of robot-assisted minimally invasive thoraco-laparoscopic esophagectomy with two-field lymphadenectomy for esophageal cancer. Ann Surg Oncol. 2015;22:1350–6.

24. Park SY, Kim DJ, Yu WS, Jung HS. Robot-assisted thoracoscopic esophagectomy with extensive mediastinal lymphadenectomy: experience with 114 consecutive patients with intrathoracic esophageal cancer. Dis Esophagus. 2016;29:326–32.

25. Chiu PW, Teoh AW, Wong VW, et al. Robot-assisted minimally invasive esophagectomy for treatment of esophageal carcinoma. J Robot Surg. 2017;11:193–9.

26. Somashekhar SP, Jaka RC. Total (Transhioracic and Transabdominal) robotic radical three-stage esophagectomy—Initial Indian Experience. Indian J Surg. 2017;79:412–7.

27. van der Sluis PC, van der Horst S, May AM, Schippers C, Brosens LAA, Joore HCA, et al. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: A randomized controlled trial. Ann Surg. 2019;269:621–30.

28. van Workum F, van der Maas J, van den Wildenberg FJH, Polat F, Kouwenhoven EA, van Det MJ, et al. Improved functional results after minimally invasive esophagectomy: Intrathoracic versus cervico-anastomosis. Ann Thorac Surg. 2017;103:267–73.

29. Luketich JD, Pennathur A, Awais O, Levy RM, Keeley S, Shende M, et al. Outcomes after minimally invasive esophagectomy: Review of over 1000 patients. Ann Surg. 2012;256:95–103.

30. Zhai C, Liu Y, Li W, Tongzhen X, Yang G, Hengxiao L, et al. A comparison of short-term outcomes between Ivor-Lewis and McKeown minimally invasive esophagectomy. J Thorac Dis. 2015;7:2352–8.

31. Zhang Y, Xiang J, Han Y, Huang M, Hang J, Abbas AE, et al. Initial experience of robot-assisted Ivor-Lewis esophagectomy: 61 consecutive cases from a single Chinese institution. Dis Esophagus. 2018;31.

32. Egberts JH, Stein H, Aselmann H, Jan-Hendrik A, Becker T. Fully robotic da Vinci Ivor-Lewis esophagectomy in four-arm technique—problems and solutions. Dis Esophagus. 2017;30:1–9.

33. Van Der Sluis PC, Schizas D, Liakakos T, Van Hillegersberg R. Minimally invasive esophagectomy. Dig Surg, 2020;37:93–100.

34. Hernandez JM, Dimou F, Weber J, Almanna H, Hoffer S, Shridhar R, et al. Defining the learning curve for robotic-assisted esophagogastrectomy. J Gastrointest Surg. 2013;17:1346–51.

35. Wee JO, Bravo-Iñiguez CE, Jaklitsch MT. Early experience of robot-assisted esophagectomy with circular end-to-end stapled anastomosis. Ann Thorac Surg. 2016;102:253–9.

36. Hodari A, Park KU, Lace B, Tsiouris A, Hammoud Z. Robot-assisted minimally invasive ivor lewis esophagectomy with real-time perfusion assessment. Ann Thorac Surg. 2015;100:947–52.

37. Trugeda S, Fernández-Díaz MJ, Rodríguez-Sanjuán JC, Palazuelos CM, Fernández-Escalante C, Gómez-Fleitas M. Initial results of robot-assisted Ivor-Lewis oesophagectomy with intrathoracic hand-sewn anastomosis in the prone position. Int J Med Robot Comput Assist Surg. 2014;10:397–403.

38. de la Fuente SG, Weber J, Hoffer SF, Shridhar R, Karl R, Meredith KL. Initial experience from a large referral center with robotic-assisted Ivor Lewis esophagogastrectomy for oncologic purposes. Surg Endosc. 2013;27:3339–47.

39. Cerfolio RJ, Bryant AS, Hawn MT. Technical aspects and early results of robotic esophagectomy with chest anastomosis. J Thorac Cardiovasc Surg. 2013;145:90–6.

40. Meredith K, Huston J, Andacoglu O, Shridhar R. Safety and feasibility of robotic-assisted Ivor-Lewis esophagectomy. Dis Esophagus. 2018;31.

41. Pöttscher A, Bittermann C, Längle F. Robot-assisted esophageal surgery using the da Vinci® Xi system: operative technique and initial experiences. J Robot Surg. 2019;13:469–74.

42. Wang WP, Chen LQ, Zhang HL, Yang Y-S, He S-L, Yuan Y, et al. Modified intrathoracic esophagogastrectomy with minimally invasive robot-assisted Ivor-Lewis esophagectomy for cancer. Dig Surg. 2019;36:218–25.

43. Horgan S, Berger RA, Elii EF, Espat NJ. Robotic-assisted minimally invasive transthiatal esophagectomy. Am Surg. 2003;69:624–6.

44. Mori K, Yamagata Y, Aikou S, Nishida M, Kiyokawa T, Yagi K, et al. Short-term outcomes of robotic radical esophagectomy for esophageal cancer by a nontransthoracic approach compared with conventional transthoracic surgery. Dis Esophagus. 2016;29:429–34.

45. Yoshimura S, Mori K, Yamagata Y, Aikou S, Yagi K, Nishida M, et al. Quality of life after robot-assisted transmediastinal radical surgery for esophageal cancer. Surg Endosc. 2018;32:2249–54.

46. Nakachi M, Uyama I, Suda K, Shibasaki K, Kikuchi K, Kadoya S, et al. Robot-assisted mediastinoscopic esophagectomy for esophageal cancer: the first clinical series. Esophagus. 2019;16:85–92.

47. Egberts JH, Schlemmering M, Hauser C, Beckmann JH, Becker T. Robot-assisted cervical esophagectomy (RACE procedure) using a single port combined with a transthiatal approach in a rendezvous technique: a case series. Langenbeck's Arch Surg. 2019;404:353–8.
48. Chiu PWY, Ng SSM, Au SKW. Transcervical minimally invasive esophagectomy using da Vinci® SPTM Surgical System: a feasibility study in cadaveric model. Surg Endosc. 2019;33:1683–6.

49. Jin D, Yao L, Yu J, Liu R, Guo T, Yang K, et al. Robotic-assisted minimally invasive esophagectomy versus the conventional minimally invasive one: A meta-analysis and systematic review. Int J Med Robot Comput Assist Surg. 2019;15:1–11.

50. Weksler B, Sharma P, Moudgil N, Chojnacki KA, Rosato EL. Robot-assisted minimally invasive esophagectomy is equivalent to thoracoscopic minimally invasive esophagectomy. Dis Esophagus. 2012;25:403–9.

51. Yang Y, Zhang X, Li B, Hua R, Yang Y, He Y, et al. Short- and mid-term outcomes ofrobotic versus thoraco-laparoscopic McKeown esophagectomy for squamous cell esophageal cancer: A propensity score-matched study. Dis Esophagus. 2020;33(6):doz080.

52. Harbison GJ, Vossler JD, Yim NH, Murayama KM. Outcomes ofrobotic versus non-robotic minimally-invasive esophagectomy for esophageal cancer: An American College of Surgeons NSQIP database analysis. Am J Surg. 2019;218:1223–8.

53. Park S, Hwang Y, Lee HJ, Park IK, Kim YT, Kang CH. Comparison ofrobot-assisted esophagectomy and thoracoscopic esophagectomy in esophageal squamous cell carcinoma. J Thorac Dis. 2016;8:2853–61.

54. He H, Wu Q, Wang Z, Zhang Y, Chen N, Fu J, et al. Short-term outcomes of robot-assisted minimally invasive esophagectomy for esophageal cancer: A propensity score matched analysis. J Cardiothorac Surg. 2018;13:52.

55. Chao YK, Hsieh MJ, Liu YH, Liu HP. Lymph node evaluation in robot-assisted versus video-assisted thoracoscopic esophagectomy for esophageal squamous cell carcinoma. Ann Surg. 2018;366:73–80.

56. Deng Y, Luo J, Li S-X, Li G, Alai G, Wang Y, et al. Does robot-assisted minimally invasive esophagectomy really have the advantage of lymphadenectomy over video-assisted minimally invasive esophagectomy in treating esophageal squamous cell carcinoma? A propensity score matched analysis based on short-term. Dis Esophagus. 2019;32:1–8.

57. Tagkalos E, Goense L, Hoppe-Lotichius M, Ruurda JP, Babic B, Hadzijusufovic E, et al. Robot-assisted minimally invasive esophagectomy (RAMIE) compared to conventional minimally invasive esophagectomy (MIE) for esophageal cancer: A propensity-matched analysis. Dis Esophagus. 2019;33(4):doz060.

58. Zhang Y, Han Y, Gan Q, Xiang J, Jin R, Chen K, et al. Early outcomes of robot-assisted versus thoraco-laparoscopic-assisted Ivor Lewis esophagectomy for esophageal cancer: A propensity score-matched study. Ann Surg Oncol. 2019;26:1284–91.

59. Chen J, Liu Q, Zhang X, Yang H, Tan Z, Lin Y, et al. Comparisons of short-term outcomes between robot-assisted and thoraco-laparoscopic esophagectomy with extended two-field lymph node dissection for resectable thoracic esophageal squamous cell carcinoma. J Thorac Dis. 2019;11:3874–80.

60. Motoyama S, Sato Y, Wakisaka Y, Nagaki Y, Imai K, et al. Extensive lymph node dissection around the left laryngeal nerve achieved with robot-assisted thoracoscopic esophagectomy. Anticancer Res. 2019;39:1337–42.

61. Hiki N. Why minimally invasive surgery for esophageal cancer is minimally invasive? Ann Gastroenterol Surg. 2020;4:188–9.

62. Schlottmann F, Strassel PD, Charles AG, Patti MG. Esophageal cancer surgery: Spontaneous Centralization in the US contributed to reduce mortality without causing health disparities. Ann Surg Oncol. 2018;25:1580–7.

63. Kauppila JH, Wahlin K, Lagergren P, Lagergren J. University hospital status and surgeon volume and risk of reoperation following surgery for esophageal cancer. Eur J Surg Oncol. 2018;44:632–7.

64. Nishigori T, Miyata H, Okabe H, Toh Y, Matsubara H, Konno H, et al. Impact of hospital volume on risk-adjusted mortality following esophagectomy in Japan. BJES (British J Surgery). 2016;103:1880–6.

65. Chao Y-K, Li Z-G, Wen Y-W, Kim D-J, Park S-Y, Chang Y-L, et al. Robotic-assisted esophagectomy vs video-assisted thoracoscopic esophagectomy (REVATE): Study protocol for a randomized controlled trial. Trials. 2019;20:346.

66. Yang Y, Zhang X, Li H, Sun Y, Mao T, et al. Robot-assisted esophagectomy (RAE) versus conventional minimally invasive esophagectomy (MIE) for resectable esophageal squamous cell carcinoma: Protocol for a multicenter prospective randomized controlled trial (RAMIE trial, robot-assisted minimal invasive Esophagectomy). BMC Cancer. 2019;19:608.

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