# Long-term outcomes after robotic minimally invasive esophagectomy for esophageal squamous cell carcinoma

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## Abstract

**Background:** The use of the minimally invasive surgery robotic esophagectomy (RE) for esophageal cancer (EC) has been increasing over the past decade, as it reduces morbidity and mortality compared with other surgical approaches. However, although the technical feasibility and safety of RE for EC have been reported, few studies have evaluated oncological outcomes. This retrospective cohort study aimed to determine the long-term outcomes of RE for EC.
**Methods:** Twenty-four consecutive patients who underwent RE with total mediastinal lymph node dissection for EC between 2009 and 2013 were enrolled in this study. The short- and long- term outcomes, including the 5-year overall survival (5yOS) and 5-year recurrence-free survival (5yRFS) rates, were examined retrospectively.
**Results:** With a median follow-up of 37 months, the 5yOS was 70.8% and the 5yRFS was 62.5%. Tumor recurrence was found in nine (37.5%) patients, and liver metastasis, the most common site of recurrence, was seen in five (20.8%) patients. Multivariate analysis demonstrated that pathological tumor stage ($pT \geq 2$) and certain late complications of surgery as measured by the Clavien–Dindo (CD) classification (pneumonia CD grade II and stenosis CD grade III) were significantly associated with 5yOS, while $pT \geq 2$ and $pN \geq 1$ were significantly associated with 5yRFS. Anastomotic leakage was the most common complication, observed in seven (29.2%) patients. The median number of harvested lymph nodes was 41 and 13 patients (54.2%) had node-positive disease.
**Conclusions:** We have shown that RE for EC is not only safe and feasible but also has encouraging oncological outcomes. We also demonstrated that late complications are significantly associated with long-term survival. Confirmation in a prospective study would assure the place of RE in the management of EC with curative intent.

**Keywords:** Esophagectomy, minimally invasive surgery, robotic surgical procedures, recurrence and survival.

## Introduction:

Esophageal cancer (EC) is the eighth most common malignancy and the sixth most common cause of cancer-related death[1]. EC is a relatively common type of cancer in Japan[2], with overall death rates from EC reported as 15.7 per 100,000 males and 2.6 per 100,000 females. Despite the modest improvement in the 5-year overall survival rates (5yOS) from 5% between 1975 and 1977 to 19% between 2002 and 2008, the outlook for patients with EC is considered relatively poor compared with that for patients with other types of malignancies, especially gastrointestinal malignancies[2].

Radical open esophagectomy with complete lymph node (LN) dissection, including total mediastinal nodal dissection, is the cornerstone of the multimodality treatment with curative intent for EC[3, 4]. However, surgery for EC is frequently associated with considerable rates of cardiopulmonary morbidity and mortality[5, 6]. Minimally invasive surgery (MIS) for the treatment of gastrointestinal and thoracic diseases was introduced in the late 1980s and helped, to a great extent, in reducing surgical trauma, resulting in lower rates of morbidity and mortality[7]. More recently, surgical robots with impressive dexterity and precise dissection skills have been developed to help surgeons perform these complex operations. The robotic system known as the da Vinci surgical system (DVSS; Intuitive Surgical, Inc., Sunnyvale, CA, USA), has tenfold magnified 3-dimensional vision and great maneuverability of its seven articulating instruments, thereby overcoming some limitations of conventional MIS for a more precise surgical dissection and the performance of manual anastomosis[8, 9].

## Patients and Methods:

We conducted a single-institution retrospective cohort study at Fujita Health University, Japan, between February 2009 and April 2013. The study was approved by the Institutional Review Board of Fujita Health University. All patients who underwent RE for squamous cell carcinoma between February 2009 and April 2013 were included. The exclusion criteria were as follows: adenocarcinoma, systemically metastatic EC, other previous surgical modalities, palliative resection, and any medical contraindication to single lung ventilation (Figure 1).

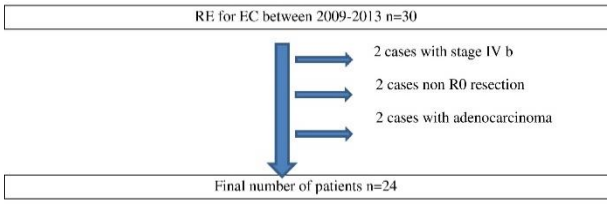


Figure 1

All details of the operation and possible complications were explained to the patients and all patients provided signed informed consent.

The indications for esophagectomy, perioperative management, the extent of resection and LN dissection have been previously discussed[10]. All the operations were performed by I.U. The patients were observed for at least three years following surgical resection, with follow-up appointments every three months following the operation and a CT scan and upper endoscopy were routinely performed every six months.

### *Outcome measures and other assessments*

The following long-term outcomes were assessed: 5-year overall survival rates (5yOS); 5-year recurrence-free survival rates (5yRFS); sites of recurrence and late complications. In addition, the short-term surgical outcomes were assessed, including clinicopathological characteristics (measured using the TNM staging system), operation time, estimated blood loss, early complications within 30 days after surgery, length of postoperative hospital stay, and the number of harvested LNs. Complications from surgery were measured using the Clavien–Dindo (CD) classification[11, 12].

The primary endpoint was the 5yOS and was estimated from the date of the initial diagnosis of EC. Short-term outcomes were re-examined in the same manner as reported previously.

### *Procedures*

*Routine diagnostic workup*

A detailed history and thorough clinical examination of each patient was conducted. In addition, the following were performed at diagnosis: a chest X-ray, ECG and UCG; esophagogastrography; upper endoscopy and biopsy; endoscopic ultra-sonography (EUS); and computed tomography (CT). Positron emission tomography (PET) was performed in patients with advanced EC and other investigations for fitness for surgery and respiratory function tests were done as needed.

*RE technique*

The setting and operative procedures of RE were performed at our hospital in the same manner as previously reported[13].

In brief, the patient cart was placed near the left shoulder, 45° counter clockwise to the craniocaudal axis of the patient, all the surgical assistants were on the right side of the patient's chest, and the monitor was on the left[10, 13] (Figures 2&3).

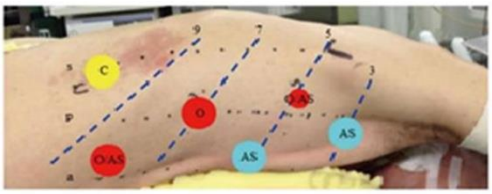


Figure 2

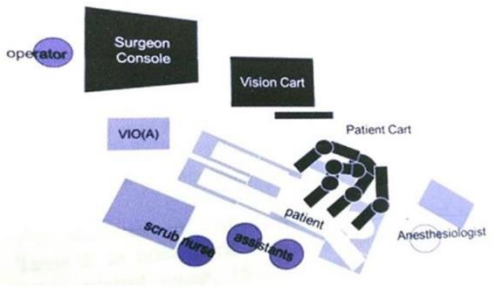


Figure 3

A 12 mm camera trocar was inserted in the 7th intercostal space at the level of the post-axillary line, and four other trocars were inserted under thoracoscopic guidance: an 8 mm trocar was placed in the 3rd space along the post-axillary line for the 3rd arm, an 8 mm trocar was placed in the 5th space below the scapular angel for the 1st arm, a 12 mm trocar was placed in the 5th space along the mid-axillary line for the assistant, and finally, an 8 mm trocar was placed in the 9$^{th}$ space along the post-axillary line for the second arm[10, 13].

The operative steps were as follows: we started by opening the mediastinal pleura overlying the anterior aspect of the esophagus, and the azygos arch that divides the right bronchial artery was dissected and divided. Whole mediastinal LNs were dissected en bloc with the specimen, including the recurrent laryngeal LNs. The thoracic duct was preserved unless it had been infiltrated by the tumor. The upper part of the esophagus was then divided at the level of the aortic arch to facilitate the LNs on the left [10].

Reconstruction was performed from the left cervical incision between the cervical esophagus and the reconstruction organ in all patients. The first choice of reconstruction organ was the gastric conduit, but the colon was acceptable if the gastric conduit could not be

used, such as postgastrectomy. Reconstruction technique depended on the surgeon's preference for that patient. The approaches used for anastomosis were: functional end-to-end anastomosis, circular stapler, triangular anastomosis or hand sewn.

*Post-operative management*

The patients were admitted to the intensive care unit immediately post-operation, until extubation and the stabilization of vital signs. All the patients were nil by mouth for at least the first 5 days post- operation. An examination of the vocal fold mobility was routinely performed in the second week post- operation for all patients, even those who were non-symptomatic. Neoadjuvant or induction chemotherapy (cisplatin 80 mg/m2 on days 1 and 29 + 5- fluorouracil 800 mg/m2 on days 1–5 and 29–33) was administered to patients with T3, any N, M0 cancer or T≤2, N ≥2, M0 cancers. Neoadjuvant chemoradiation therapy (cisplatin 70 mg/m2 on days 1 and 29 + 5-fluorouracil 700 mg/m2 on days 1–4 and 29–32 + irradiation 2 Gy/day 20 times for a total of 40 Gy) was administered to those with T ≥4a, any N, M0 cancers.

Patients with T ≤4a, any N, and M0 cancers were determined to be resectable. The pathological stage (pStage 0-IV) was determined based on the pathological investigations of the resected esophagus and LNs as described previously [13].

CT examination for abdomen and pelvis is performed routinely every 6 months for all patients. When LN or systemic metastasis was suspected, positron emission tomography scanning was performed.

***Statistical analysis***

All the statistical analyses were conducted using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY). The continuous variables were shown in median and range. Independent continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the $\chi 2$ (chi-square) test or Fisher's exact test. Long-term outcomes were analyzed using the Kaplan–Meier method with the log-rank test and Cox regression analyses.

Univariate analyses were performed for all the potential confounding variables and effect modifiers. Considering the relatively small sample size, all the variables with a significance level of $P < 0.200$ in the univariate analysis were included as independent variables in the following multivariate analysis. The data were expressed as the median (range) or the odds/hazard ratio (OR/HR; 95% confidence interval (CI)) unless otherwise stated. P values of <0.05 (two-tailed) were considered statistically significant

## Results:

***Patient's characteristics:***

Twenty four patients who underwent RE were enrolled in this study (Figure 1). Of the 24 patients, 21 were male (87.5%). The age and body mass index (BMI) were 64 (50-75) and 21.8 (17-30), respectively. Fifteen patients (62.5%) had an American Society of Anesthesiologists Physical Status (ASA- PS) class 1[14]. Seven patients (29.2%) had obstruction in spirometric function. The tumors were located in the upper, middle and lower third of the esophagus in 3, 12, and 9 patients respectively. Three patients (12.5%) received neoadjuvant chemotherapy, and 14 patients (58.3%) received adjuvant chemotherapy. No patients received preoperative radiotherapy in this study. According to Japanese clinical guidelines for EC, most patients (18 of 24) had stage I or II disease.

Table 1: Baseline patient and tumor characteristics

| ***Baseline characteristics*** | ***RE n=24*** |
|---|---|
| Gender (M:F) | 21:3 |
| Age (years; range) | 64 [50-75] |
| Body mass index (kg/m$^2$; range) | 21.8 [17-30] |
| ASA-PS > class 1, n (%) | 15 (62.5) |
| Obstruction of respiratory function, n (%) | 7 (29.2) |
| Main tumor location (Ut:Mt:Lt) | 3:12:9 |
| Neoadjuvant chemotherapy, n (%) | 3 (12.5) |
| Adjuvant chemotherapy, n (%) | 14 (58.3) |
| Clinical Japanese guideline stage (0:I:II:III) | 1:10:8:5 |
| Clinical T (1a:1b:2:3) | 2:10:8:4 |
| Clinical N (0:1:2:3) | 19:3:2 |

M:F= Male:Female, ASA-PS= American Society of Anesthesia – Performance status, Ut:Mt:Lt= Upper third: Middle third: Lower Third

***Surgical outcomes***

The total operation time, the time in thoracic approach, and the console time were 731 (560- 1087), 372 (277-618), and 331.5 (245-480) min, respectively (Table 2). The estimated blood loss was 201 (52-983) mL. The thoracic duct was preserved in 19 (79.2%) patients. The numbers of dissected LNs in the neck, chest and abdomen were 0.5 (0-25), 23 (12-40) and 18 (4-44). The most common organ for reconstruction was the gastric conduit, in 22 patients (91.6%), with colon reconstruction in only two patients. The duration of postoperative intubation was 0 (0-129) hours. The median ICU stay was 1 (0-7) day, while the median hospital stay was 32 (9-114) days.

There was no conversion to other procedures and only one patient needed reoperation. No in- hospital mortality occurred in this series.

Table 2: Short-term surgical outcomes

| ***Surgical outcomes*** | ***RE n= 24*** |
|---|---|
| Operation time (min; range) | 731 [560-1087] |
| Chest time (min; range) | 372 [277-618] |
| Console time (min; range) | 331.5 [245-480] |
| Estimated blood loss (g; range) | 201 [52-983] |
| Preservation of thoracic duct, n (%) | 19 (79.2) |
| Total no. of dissected LNs (n, range) | 41.5[16-75] |
| Neck nodes | 0.5 [0-25] |
| Chest nodes | 23 [12-40] |
| Abdominal nodes | 18 [4-44] |
| Reconstruction passage (retrosternal : posterior mediastinum) | 23:1 |
| Organ for reconstruction (gastric conduit:colon) | 22:2 |
| Anastomotic procedure (FEEA:Triangle:Handsewn:Circular) | 9:9:5:1 |
| Conversion to other procedures, n (%) | 0 |
| Hospital stay (days, range) | 32 [9-114] |
| Duration of postoperative intubation (hours, range) | 0 [0-129] |
| ICU stay (days, range) | 1 [0-7] |
| Reoperation, n (%) | 1 (4.2) |
| In-hospital mortality, n (%) | 0 |

FEEA= Functional end-to-end anastomosis

***Post-operative Complications***

According to the CD classification, the total number of patients with early post-operative complications ≥ CD grade III was 10 (41.7%)[11, 12](Table 3). Anastomotic leakage occurred in 7(29.2%) patients, and intrathoracic abscess, anastomotic stenosis and pancreatic fistula were observed in one (3.3%) patient each. Chylothorax and intrathoracic bleeding were not seen in the present series. Hoarseness of voice was reported in 10 (41.7%) patients. Recurrent laryngeal nerve paralysis (≥ CD grade II) occurred in 5 (20.8%) patients. Post-operative pneumonia occurred in 3 (12.5%) patients. However, no cases of pleural effusion (≥ CD grade II) were observed.

With regard to late complications which usually occur after 30 days post-operative, two (8.3%) patients developed pneumonia (≥ CD grade II) and three (12.5%) patients developed anastomotic stenosis (≥ CD grade III) (Table 3).

Table 3: Early and late postoperative complications (Clavien–Dindo (CD) classification)

| ***Complications*** | ***RE n= 24*** |
|---|---|
| *Early complications (Postoperative day < 30)* | |
| Total, n (%) | 10 (41.7) |
| Anastomotic leakage, n (%) | 7 (29.2) |
| Anastomotic stenosis, n (%) | 1 (4.2) |
| Intrathoracic abscesses, n (%) | 1 (4.2) |
| Pancreatic fistula, n (%) | 1(4.2) |
| Pleural effusion, n (%) | 0(0) |
| Intrathoracic bleeding, n (%) | 0(0) |
| Chylothorax, n (%) | 0 (0) |
| Pneumonia, n (%) CDII | 6 (25) |
| CDIII | 3 (12.5) |
| Recurrent laryngeal nerve paralysis, n (%) | |
| CDII | 3(12.5%) |
| CDIII | 2(8.3%) |
| Right: left :bilateral (n) | 0:11:1 |
| Hoarseness | 10 (41.7) |
| *Late complications (Postoperative day ≥ 30)* | |
| Anastomotic stenosis (CDIII), n (%) | 3(12.5) |
| Pneumonia (CDII), n (%) | 2 (8.3) |

***Pathological findings***

The median tumor size was 40 (10-80) mm (Table 4). The numbers of metastatic LNs in the chest, abdomen and neck were 0 (0-8), 0 (0-4) and 0 (0-3), respectively.

The number of patients with postoperative pathological stage 0, I, II, III, and IV was 3 (12.5%), 8 (33.3%), 5 (20.8%), 6 (25%) and 2 (8.3%), respectively.

***Recurrence***

Nine (37.5%) patients experienced tumor recurrence within 5 years of surgical resection. Only two of these patients had received neoadjuvant chemotherapy. Two (8.3%) patients presented with local neck LN recurrence, and four (16.7%) patients developed hepatic metastasis. Lung metastasis and pleural metastasis were each reported in one (4.2%) patient.

Table 4: Pathological investigations

| | ***RE n=24*** |
|---|---|
| Tumor size (mm; range) | 40 [10-80] |
| Metastatic LNs (n; range) | 0 [0-13] |
| Neck | 0 [0-3] |
| Chest | 0 [0-8] |
| Abdomen | 0 [0-4] |
| Pathological JCECa stage (0:I:II:III:IV), n | 3:8:5:6:2 |
| Pathological T factor (0:1a:1b:2:3:4), n | 1:7:8:1:6:1 |
| Pathological N factor (0:1:2:3), n | 11:5:5:3 |

JCECa= Japanese classification of esophageal cancer

Table 5: Recurrence sites

| | ***RE n=24*** |
|---|---|
| LN station 101* | 2 |
| Liver | 4 |
| Lung | 1 |
| Pleura | 1 |
| LN station 104*+liver | 1 |

LN 101 = Cervical para-esophageal LN, LN 104= Supraclavicular LN

*according to Japanese classification of esophageal cancer – 11th edition

***Long-term outcomes***

The follow-up period was 37 months (range, 1–82 months). The cumulative 5yOS was 70.8% (Figure 4). One patient died during follow-up due to pneumonia, which was not considered related to cancer recurrence. The cumulative 5yRFS was 62.5% (Figure 5). The median OS was 37 months and the median RFS was 36.5 months.

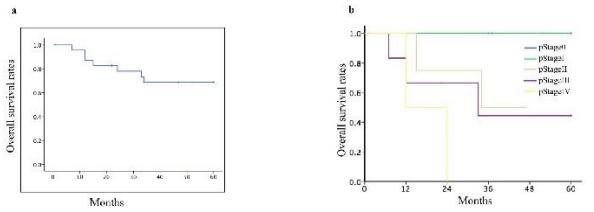


Figure 4

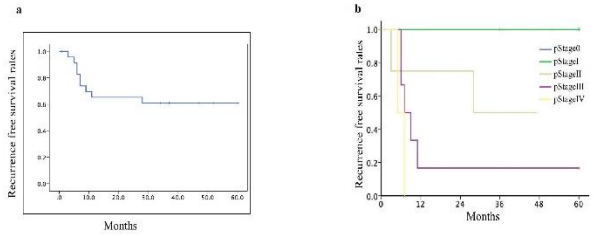


Figure 5

The 5yOS stratified according to the pathological JCEC stage (p0, pI, pII, pIII, and pIVa)[15] was 100%, 100%, 60%, 50% and 0%, respectively. The 5yRFS

stratified according to the pathological JCEC stage (p0, pI, pII, pIII, and pIVa) was 100.0%, 100%, 60%, 16%, and 0%, respectively.

***Factors associated with the 5-year long-term outcomes:***

To investigate the factors determining the long-term outcomes, univariate and multivariate analyses were conducted. The univariate analyses revealed that the following were associated with 5yOS: pT 2 or higher ($p < 0.007$), the late complications pneumonia CD grade II and anastomotic stenosis CD grade III ($p < 0.043$), and the postoperative intubation period (< 12 h; $p < 0.024$). Multivariate analysis was conducted by adding the factors with $p < 0.200$, that is: age ≥65 years old ($p < 0.082$), ≥cT2 ($p < 0.189$), and ICU stay ≥2 days ($p < 0.102$). The multivariate analysis demonstrated that ≥ pT2 (HR 7.091; 95% CI 1.118-44.962; $p < 0.038$) and late complications (HR 2.643; 95% CI 1.084–6.44; $p = 0.032$) were significantly associated with 5yOS.

Univariate analyses revealed that age (≥65y; $p < 0.045$), ≥pT2 ($p < 0.005$) and postoperative intubation period (<12 h; $p < 0.018$) were associated with 5yRFS. By adding the factors with $p < 0.200$, which were: ASA-PS ≥class II ($p < 0.138$); ≥cT2 ($p < 0.193$); ≥pN1 ($p < 0.102$), ICU stay (≥2 days; $p < 0.089$), and late complications (pneumonia CD grade II and anastomotic stenosis CD grade III; $p < 0.162$), the multivariate analysis demonstrated that ≥pT2 (HR 13.531; 95% CI 2.293-79.858; $p < 0.004$) and ≥ pN1 (HR 8.217; 95% CI 1.272–53.069; $p = 0.027$) were significantly associated with 5yRFS.

## Discussion:

Although we have reported the technical aspects and short-term outcomes of RE previously[10,13], few studies have evaluated longer term oncological outcomes. In this study we show that the5-year oncological outcomes with RE and total mediastinal lymphadenectomy in our patient series were comparable to those reported for open surgery[16, 17]. We also confirm the feasibility and short-term safety of with the robotic approach and demonstrate the long-term safety of the approach.

Only a few reports demonstrating acceptable oncological feasibility of the long-term outcomes of robotic esophagectomy have been published. As a relatively new technology, da Vinci Surgical System has not been in use long enough for the oncological outcomes of robotic esophagectomy to be evaluated correctly[18]. The study with the longest follow-up period, a median of 58 months, was reported by van der Sluis et al. The 5-year OS rate was 42%, median recurrence-free survival was 21 months, and median OS was 29 months. Locoregional tumor recurrence occurredin only six patients (6%)[19].

Other relevant studies have reported that patients undergoing surgery only have median survival rates between 13 and 19 months, 2-year survival rates between 35% and 42%, and 5-year survival rates of 15% to 24% [16, 17]. In the present study, which included a considerable number of cases with advanced disease, the median OS was 37 months, and the median RFS was 36.5 months.

Previously published studies have reported an incidence of anastomotic leakage varying from 8% to 15% in general esophagectomies, compared with 29.2% in this series. The study by D'Journo et al. and other studies reported a relation between post-operative complications, especially for respiratory complications, and OS rates [20, 21]. In our study, we found that late pneumonia (≥CD grade II) and anastomotic stenosis (CD grade III) were significantly associated with the long-term survival rates ($p<0.032$), and this may be explained by the effect of late complications on oral intake and tolerance for chemotherapy, which in turn affected the general condition of the patient and their long-term survival.

Node-positive disease (pN1-3) was observed in 54% of patients. The total mediastinal lymphadenectomy performed, including bilateral removal of recurrent laryngeal LNs and tracheobronchial LNs, is evidenced by the median of 41 dissected LNs per patient. This number of dissected LNs is higher than that in other published reports of outcomes after minimally invasive esophagectomy[19, 22, 23]. Peyre et al. reported a survival benefit for patients with 23 LNs or more resected compared with patients who had fewer than 23 LNs resected[24, 25].

With regard to recurrence, no recurrent mediastinal LNs were found in our series, which suggests thorough mediastinal LN dissection. Other studies have reported a mediastinal LN recurrence rate of 4%[26] and 6%[19]. Late metastases were observed in 20.8% of patients in our series. The relatively high 5yRFS of 62.5% indicates the oncologic efficacy of robotic surgery in esophagectomy[27]. Our RFS data are similar to other reports [26, 28]. A possible explanation for the high RFS achieved with RE is that the magnified 3D vision and free articulation afforded by robotic surgery facilitates more meticulous LN dissection and better tumor clearance.

With regard to short-term surgical outcomes, in this study the estimated blood loss was 201 (52 - 983) mL, which is comparable with blood loss reported previously during RE[29, 30]. The longer operation time (median 731 min), compared with that reported previously, may have been due to the wide extent of nodal dissection performed, including the cervical, thoracic, and abdominal regions. Moreover, the present series represents our early experience of performing RE, and so, while the operative safety and feasibility were clearly demonstrated, the long operative time may reflect the learning curve required to attain proficiency. For surgeons proficient in performing minimally invasive esophagectomy, the learning curve for a robotic-assisted procedure to achieve near proficiency is considered to be about 20 cases[31].

One limitation of our study is that it was conducted at a single institution in a retrospective manner. The sample size was small and the follow-up period was relatively short. Consequently, the data may be biased, and the overall results should be interpreted with caution. Nevertheless, the positive outcomes we report are

encouraging and should now be evaluated in prospective multi-institution studies with a larger number of patients.

In conclusion, our study confirmed that RE for EC is feasible and safe, up to a follow-up duration of 37 months. Furthermore, we have shown that RE is oncologically effective and extends overall survival, and that there is a significant association between late complications of pneumonia and anastomotic stenosis with long-term survival.

**List of abbreviations:**
Robotic esophagectomy (RE)
Esophageal cancer (EC)
5-year overall survival (5yOS)
5-year recurrence-free survival (5yRFS)
Clavien–Dindo (CD)
Minimally invasive surgery (MIS)
Endoscopic ultra-sonography (EUS)
Positron emission tomography (PET)

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