Original Article

Comparison of robot-assisted esophagectomy and thoracoscopic esophagectomy in esophageal squamous cell carcinoma

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Background: The aim of the study was to compare robot-assisted esophagectomy (RE) with thoracoscopic esophagectomy (TE) for the treatment of esophageal squamous cell carcinoma (ESCC).

Methods: A total of 105 patients who underwent RE (n=62) or TE (n=43) due to ESCC were included in this study. Early postoperative outcomes and long-term survivals between the two groups were compared.

Results: The RE and TE groups were comparable in preoperative clinical characteristics. Total operation times were not significantly different between the two groups (490 minutes in RE *vs*. 458 minutes in TE; P=0.118). The total number of dissected lymph nodes was significantly greater in the RE group (37.3±17.1 *vs*. 28.7±11.8; P=0.003), and intergroup differences were significant for numbers of lymph nodes dissected from the upper mediastinum (10.7±9.7 in RE *vs*. 6.3±9.3 in TE; P=0.032) and the abdomen (12.2±8.7 in RE *vs*. 7.8±7.1 in TE; P=0.007). Five-year overall survival was not different between the two groups (69% in RE and 59% in TE; P=0.737).

Conclusions: Better quality lymphadenectomy could be achieved in RE although survival benefit was not clear. Prospective randomized studies comparing the RE and TE are necessary.

Keywords: Esophageal neoplasms; thoracoscopy; robotic surgical procedures

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Introduction

Surgical resection remains a standard treatment for esophageal squamous cell carcinoma (ESCC), based on the principles of complete primary tumor removal and radical lymphadenectomy. However, the invasiveness of surgery involving the chest and abdomen and a relatively high postoperative complication rate are major concerns for esophagectomy. To improve outcomes, minimally invasive esophagectomy (MIE) has been gradually accepted as a reliable surgical procedure for esophageal cancer (1,2). Although the procedure is technically demanding it has been suggested that MIE can be performed with low pulmonary complication rates (1,3) and comparable long-term oncological outcomes (4,5).

Most MIEs have been performed using endoscopic techniques utilizing thoracoscopy and laparoscopy. However, recent developments in robotic technology have made robot-assisted esophagectomy (RE) as another surgical option for MIE (6,7). Robotic technology has several technical advantages over the thoracoscopic technique, such as, the free articulation of robotic arms and superior imaging quality, including three-dimensional vision, which are regarded as optimal technologies for radical oncologic surgery. However, the advantages of RE over thoracoscopic esophagectomy (TE) have not been clearly defined, and

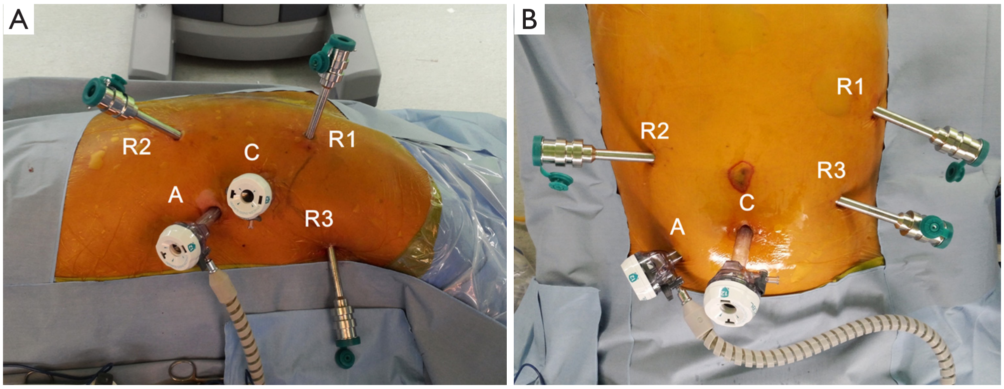

Figure 1 Positions of robotic ports in thoracic and abdominal procedure. (A) Photograph of the robot port insertion sites used for the thoracic procedure; (B) photograph of robot port insertion sites used for the abdominal procedure. A, assistant port; C, camera port; R1, port for robot arm 1; R2, port for robot arm 2; R3, port for robot arm 3.

perhaps as a result, RE has not been widely applied for the treatment of ESCC. The aim of this study was to compare the short-term and long-term outcomes of RE and TE and to identify any clinical or oncological benefits of RE as compared with TE in ESCC.

Methods

Patients

This study was approved by the institutional review board of our hospital and the patients' consent was waived (approval number: 1407-137-597). The inclusion criterion was the patients who underwent RE or TE between 2006 Jan and 2014 Jun for the treatment of ESCC. The exclusion criteria applied were; (I) the patients who underwent three field lymphadenectomy; (II) the receipt of laparoscopic transhiatal esophagectomy; and (III) the use of the colon as a substitute graft.

During the study period 435 patients underwent esophagectomy in our institute. MIE was performed in 136 patients (31%) during the same period. After applying the above-mentioned criteria, 105 patients (62 in the RE group and 43 in the TE group) were enrolled in the study. Initially the indication for MIE at our institute was limited to early esophageal cancer, but indications were gradually expanded to advanced esophageal cancer. Currently multi-station lymph node metastasis, invasion to adjuvant organs, and severe pleural adhesion are regarded as contraindications for MIE at our institute. The same indications for MIE were applied to both the TE and RE groups.

Surgical technique of RE

Surgeries were conducted using four-arm technique for thoracic and abdominal procedures and one additional assistant port was made (*Figure 1*). With a patient positioned in the prone or lateral decubitus position (the prone position was favored for cervical anastomosis and the lateral decubitus for thoracic anastomosis) a camera port was made in the 7th intercostal space just below the scapula tip. Number 1 robotic port was made at the 5th intercostal space at the medial border of scapula, number 2 robotic port was placed at the intersection between the vertical line from number 1 port and the 10th intercostal space. Number 3 robotic port was made in the posterior axillary line in the 3rd intercostal space, and the assistant port was made in the 8th intercostal space at posterior axillary line. Cadiere forceps and robotic scissors were used interchangeably between number 1 and number 3 arms (right arms). Lymph node dissection was performed in whole mediastinal nodal stations. Right and left recurrent laryngeal nerve (RLN) dissections were performed precisely by completely exposing nerves and removing whole lymphatic tissues up to the thoracic inlet and contralateral hilum (*Figure 2*).

Preoperative evaluation and postoperative follow-up

All patients underwent an intensive preoperative evaluation. Endoscopy, endoscopic ultrasound, chest CT, abdominal CT, PET-CT, cervical ultrasonography, and pulmonary function and blood testing were performed routinely. Bronchoscopy was performed if indicated. For the

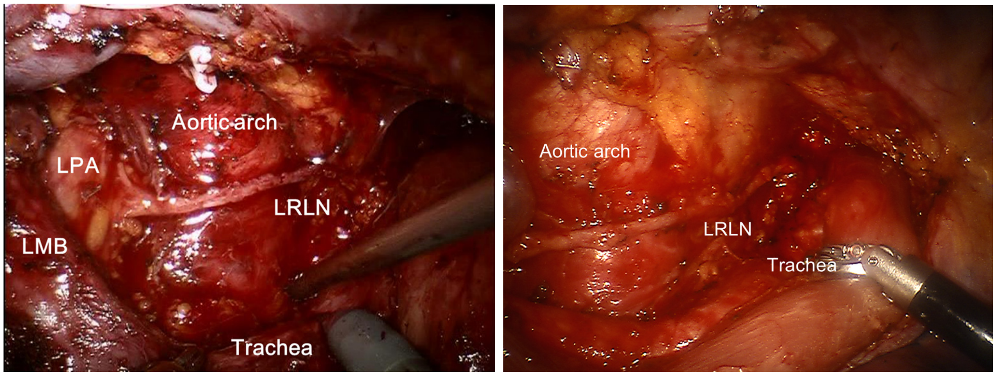

Figure 2 Photograph of left upper mediastinum after robot-assisted dissection along the left recurrent laryngeal nerve. Lymph nodes along the left recurrent laryngeal nerve and aortopulmonary lymph nodes were completely removed. LMB, left main bronchus; LPA, left pulmonary artery; LRLN, left recurrent laryngeal nerve.

assessment of RLN injury, vocal cord function was assessed by nasal laryngoscopy on the 3rd postoperative day in all patients. Postoperative surveillance of recurrence was conducted intensively. A PET-CT scan was performed at 1st, 2nd, and 5th years postoperatively and a chest CT scan was performed at 6th months, 18th months, 3rd years, and 4th years postoperatively. Endoscopic examinations were performed annually.

Definition of assessment parameters

Grade of dysphagia was scored from 0 to 4 using the scoring system proposed by Mellow and Pinkas (8). Performance status was graded from 0 to 5 according to the European clinical oncology group performance status scoring system (9). Dissected lymph node locations were classified using three mediastinal groups. Upper mediastinal lymph nodes were defined as 2R (right upper paratracheal nodes), 4R (right lower paratracheal nodes), 2L (left upper paratracheal nodes), 4L (left lower paratracheal nodes), 3P (posterior mediastinal nodes), 5 (aortopulmonary nodes) and lymph nodes along right RLN. Middle mediastinal lymph nodes were defined as 7 (subcarinal nodes), 8M (middle paraesophageal lymph nodes), 10L (left tracheobronchial nodes), and 10R (right tracheobronchial nodes), and lower mediastinal lymph nodes as 8L (lower paraesophageal lymph nodes), 9 (pulmonary ligament nodes), and 15 (diaphragmatic nodes). Postoperative morbidity was prospectively recorded during bi-monthly morbidity conferences and severities of complications were graded using the Clavien-Dindo classification (10).

Statistical methods

The student's *t*-test or Wilcoxon's rank-sum test were used to compare continuous group variables, depending on normality of distribution. The Chi-square test or Fishers' exact test were used to compare categorical variables. Survival was estimated using the Kaplan-Meier method and the significances of differences were determined using the log-rank test. All statistical tests were two-sided and SPSS software (version 21, IBM, Armonk, NY, USA) was used throughout. Statistical significance was accepted for P values <0.05.

Results

Preoperative characteristics

Demographic and preoperative features were comparable in the RE and TE groups (*Table 1*). Asymptomatic patients in whom ESCC was incidentally detected during endoscopic screening constitute 66% in the RE group and 67% in the TE group. The co-morbidity rate was significantly high in both groups and 66% of the RE group and 74% of the TE group had an American Society of Anesthesiologists (ASA) class of more than II.

Operation

For thoracic procedures, robotic and thoracoscopic surgery were performed in all 105 patients. For abdominal procedures, robot-assisted surgery was performed in 36 patients (58%) in the RE group and laparoscopic procedures were performed in 21 patients (49%) in

Table 1 Patient characteristics

Variables	RE group (n=62, %)	TE group (n=43, %)	P value
Gender (male:female)	57:5	40:3	0.836
Age (years, mean ± SD)	64.3±8.0	66.2±7.4	0.231
Smoking status			0.940
Never smoker	13 (21.0)	8 (18.6)	
Ex-smoker	22 (35.5)	15 (34.9)	
Current smoker	27 (43.5)	20 (46.5)	
BMI (kg/m^2, mean ± SD)	23.5±2.8	23.3±3.1	0.214
Weight loss >5%	9 (14.5)	3 (7.0)	0.352
Grade of dysphagia			0.582
Grade 0	41 (66.1)	29 (67.4)	
Grade 1	18 (29.0)	10 (23.3)	
Grade 2	3 (4.1)	4 (9.3)	
Performance status			0.652
Grade 0	26 (41.9)	20 (46.5)	
Grade 1	35 (56.5)	23 (53.5)	
Grade 2	1 (1.6)	0 (0.0)	
Co-morbidity			
Hypertension	26 (41.9)	22 (51.2)	0.351
Diabetes mellitus	9 (14.5)	11 (25.6)	0.156
COPD	7 (11.3)	4 (9.3)	1.000
History of tuberculosis	2 (3.2)	4 (9.3)	0.224
Chronic hepatitis	3 (4.8)	1 (2.3)	0.643
Liver cirrhosis	2 (3.2)	2 (4.7)	1.000
Ischemic heart disease	6 (9.7)	2 (4.7)	0.467
Atrial fibrillation	3 (4.8)	0 (0.0)	0.268
Renal disease	0 (0.0)	2 (4.7)	0.165
Cerebrovascular disease	7 (11.3)	1 (2.3)	0.137
Other vascular disease	4 (6.5)	0 (0.0)	0.143
History of previous cancer	6 (9.7)	5 (11.6)	0.756
Other disease	1 (1.6)	2 (4.7)	0.566
ASA classification			0.123
I	21 (33.9)	11 (25.6)	
II	37 (59.7)	32 (74.4)	
III	4 (6.5)	0 (0.0)	
Tumor location			0.852
Upper thoracic	8 (12.9)	7 (16.3)	
Mid thoracic	15 (24.2)	9 (20.9)	
Lower thoracic	39 (62.9)	27 (62.8)	
FEV_1 (pred%, mean ± SD)	101.6±17.1	106.7±13.8	0.107
Clinical stages			0.467
I	23 (37.1)	21 (48.8)	
II	28 (45.2)	15 (34.9)	
III	11 (17.7)	7 (16.3)	
Clinical T stages			0.306
cT1	31 (50.0)	25 (58.1)	
cT2	21 (33.9)	13 (30.2)	
cT3	10 (16.1)	5 (11.6)	
Clinical N stages			0.355
cN0	42 (67.7)	27 (64.3)	
cN+	20 (32.3)	15 (35.7)	
Neoadjuvant chemoradiation	8 (12.9)	4 (9.3)	0.757

Table 1 (*continued*)

RE, robot-assisted esophagectomy; TE, thoracoscopic esophagectomy; SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; FEV_1, forced expiratory volume in 1 second.

the TE group and the proportion of laparotomy was comparable in the two groups. Cervical anastomosis was performed in 56 patients (90%) in the RE group and in 35 patients (81%) in the TE group (P=0.186). The posterior mediastinal route was employed in all patients. Conversion to thoracotomy was necessary in one patient in each group. Total operation time was not different between the two groups (490.3±84.0 minutes in the RE group *vs.* 458.4±111.9 minutes in the TE group; P=0.118). However, one-lung ventilation time, which represent the time required for the main thoracic procedure was significantly greater in the RE group (185.2±67.4 minutes *vs.* 120. ±68.5 minutes; P<0.001). Intraoperative blood loss amounts were not different between the two groups (462.9±493.9 mL in the RE group *vs.* 466.8±333.0 mL in the TE group; P=0.965) (*Table 2*). Complete resection

Table 2 Intraoperative data

Variables	RE group (n=62)	TE group (n=43)	P value
Operation time (min)			
Overall	490.3±84.0	458.4±111.9	0.118
Thoracic procedure	185.2±67.4	120.1±68.5	<0.001
Abdominal procedure	305.1±66.6	338.4±105.4	0.072
Intraoperative blood loss (mL)	462.9±493.9	466.8±333.0	0.965
Route of reconstruction			
Posterior mediastinal route	62 (100%)	43 (100%)	1.000

RE, robot-assisted esophagectomy; TE, thoracoscopic esophagectomy.

rates were also comparable (98% in the RE group *vs*. 98% in the TE group; P=1.000).

Pathology and lymph node yields

The distributions of pathologic stages in the two groups were comparable (*Table 3*). The mean number of dissected lymph nodes was significantly greater in the RE group (37.3±17.1 in the RE group *vs*. 28.7±11.8 in the TE group; P=0.003). To examine this difference in further detail, we classified lymph node stations into four categories, that is, upper mediastinum, middle mediastinum, lower mediastinum, and abdomen. A significant intergroup difference was evident in upper mediastinum (10.7±9.7 in the RE group *vs*. 6.3±9.3 in the TE group; P=0.032). For abdominal lymph node dissection, the mean number of lymph nodes dissected by the robot was greater than that by laparoscopy (10.9±8.3 in the RE group *vs*. 5.4±6.0 in the TE group; P=0.010). Numbers of dissected lymph nodes per station are plotted in *Figure 3*. The difference was evident in lymph nodes of both RLNs and number 5.

Early outcomes (Table 4)

One 30-day mortality occurred in the RE group (1.6%), but no 30-day mortality occurred in the TE group. The incidences of respiratory complications and anastomosis leakages were not different. The incidence of vocal cord paralysis was lower in the RE group, however the difference was not statistically significant (13% *vs*. 24%; P=0.149). The incidence of major complication more than grade IIIa according to Clavien-Dindo classification was not different between the two groups (16% *vs*. 21%; P=0.233).

Table 3 Pathologic data

Variables	RE group (n=62, %)	TE group (n=43, %)	P value
Pathologic stages			0.577
IA	10 (16.1)	13 (30.2)	
IB	24 (38.7)	14 (32.6)	
IIA	4 (6.5)	2 (4.7)	
IIB	15 (24.2)	6 (14.0)	
IIIA	6 (9.7)	6 (14.0)	
IIIB	2 (3.2)	1 (2.3)	
IIIIC	1 (1.6)	0 (0.0)	
IV	0 (0.0)	1 (2.3)	
Pathologic T stages			0.184
0	2 (6.9)	3 (9.7)	
1	21 (72.4)	15 (48.4)	
2	2 (6.9)	5 (16.1)	
3	4 (13.8)	8 (25.8)	
Pathologic N stages			0.750
0	42 (67.7)	31 (72.1)	
1	14 (22.6)	10 (23.3)	
2	5 (8.1)	2 (4.7)	
3	1 (1.6)	0 (0.0)	
No. of harvested lymph nodes			
Total	37.3±17.1	28.7±11.8	0.003
Location of lymph node stations			
Upper mediastinum	10.7±9.7	6.3±9.3	0.032
Mid mediastinum	10.5±6.2	9.8±4.8	0.552
Lower mediastinum	3.7±3.5	2.3±3.0	0.057
Abdomen	12.2±8.7	7.8±7.1	0.007
Laparotomy	14.0±9.1	10.2±7.4	0.119
Robot *vs*. laparoscopy	10.9±8.3	5.4±6.0	0.010

Stages were designated according to the 7th edition of the AJCC staging system. RE, robot-assisted esophagectomy; TE, thoracoscopic esophagectomy.

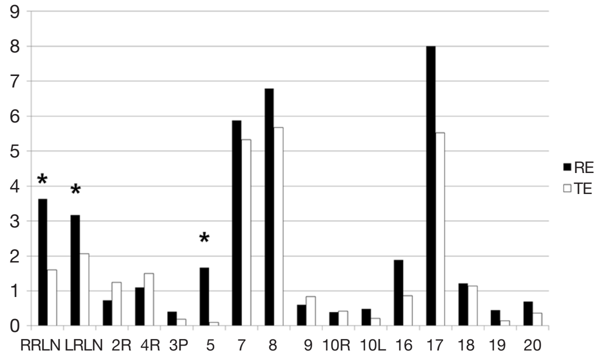

Figure 3 Numbers of dissected lymph nodes according to the nodal map. *, represents stations at which nodal number yields were significantly higher in the RE group than in the TE group. RE, robot-assisted esophagectomy; TE, thoracoscopic esophagectomy; RRLN, right recurrent laryngeal nerve lymph node; LRLN, left recurrent laryngeal nerve lymph node.

Table 4 Postoperative mortality and morbidities

Variables	RE group (n=62, %)	TE group (n=43, %)	P value
30-day mortality	1 (1.6)	0 (0)	0.344
Respiratory complication	9 (14.5)	6 (14.0)	0.935
Leakage	5 (8.1)	1 (2.3)	0.213
Vocal cord paralysis	8 (12.9)	10 (23.8)	0.149
Complication ≥ grade IIIa	10 (16.1)	9 (20.9)	0.233

RE, robot-assisted esophagectomy; TE, thoracoscopic esophagectomy.

Long-term outcomes

The median follow-up duration was 22 months (17 months in RE group and 26 months in TE group). The 5-year overall survivals were not different between the two groups (69% in the RE group *vs.* 59% in the TE group; P=0.737; *Figure 4*). The 5-year freedom from locoregional recurrence was 88% in the RE group and 74% in the TE group. However the difference was not statistically significant (P=0.100, *Figure 5*). The 5-year freedom from distant recurrence was not different between the two groups (72% in the RE group and 71% in the TE group; P=0.594).

Discussion

In the present study, the short-term and long-term surgical outcomes achieved by RE and TE in ESCC were compared. The two study groups were comparable in terms of preoperative clinical characteristics and clinical stages. In this study, the RE group was found to have an advantage over the TE group in terms of numbers of lymph nodes dissected, especially in the upper mediastinum. But on

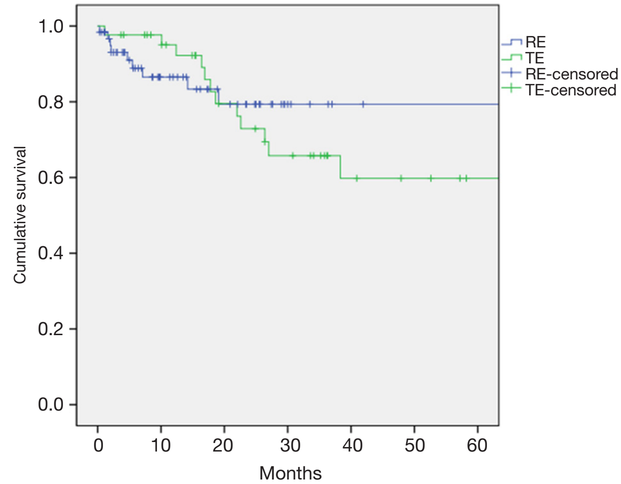

Figure 4 The 5-year overall survival. Overall survival was 69% in the RE group and 59% in the TE group. However the difference was not statistically significant (P=0.737). RE, robot-assisted esophagectomy; TE, thoracoscopic esophagectomy.

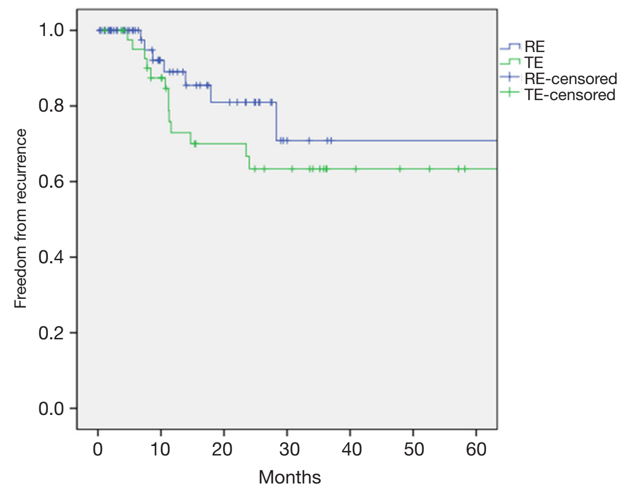

Figure 5 The 5-year freedom from locoregional recurrence. Freedom from locoregional recurrence was 88% in the RE group and 74% in the TE group. However the difference was not statistically significant (P=0.100). RE, robot-assisted esophagectomy; TE, thoracoscopic esophagectomy.

the other hand, the RE group also required significantly longer one-lung ventilation time. Other clinical outcomes including mortality and morbidities were comparable. In terms of long-term oncologic outcomes, overall survival and freedom from recurrence were not different between two groups. Although lower locoregional recurrence was identified in the RE group, the difference was not statistically significant.

Lymphadenectomy in esophageal cancer is technically challenging, and this is especially true in ESCC. The most common location of mediastinal nodal metastasis in ESCC is in the lymph nodes along RLNs (11,12). Many authors have emphasized that the extent of mediastinal lymphadenectomy in ESCC should include lymph nodes along bilateral RLNs (13,14). Furthermore, bilateral RLN dissection requires a meticulous technique to achieve the complete removal of lymphatic chains and the safe preservation of nerves. However, it remains debatable whether thoracoscopic surgery can achieve comparable quality of lymphadenectomy to that of thoracotomy. Because of the steep learning curve, lower dissected lymph node yields in thoracoscopic surgery have been reported as compared to open surgery (15,16). The other issue regarding RLN dissection is the incidence of vocal cord paralysis which has been reported to range from 6% to 40% after thoracoscopic RLN dissection (17,18). Whether thoracoscopic RLN lymph node dissection can achieve comparable incidence of vocal cord paralysis is still questionable. Therefore better surgical technique to improve the quality of lymphadenectomy in MIE is necessary.

Thoracoscopic instruments have their limitations with respect to dissection in a small and narrow space, and thus, thoracoscopic dissection along a deeply located RLN in the thoracic inlet area is technically challenging. Instead robotic surgery has several technological advantages over thoracoscopic surgery in this respect, as it provides a three-dimensional view, ten times magnification, and freely articulated movement of the robotic arms, which enables more meticulous dissection, and thus, reduces the risk of damaging nearby nerves. However, the actual benefits of robotic surgery remain controversial. Kim *et al.* concluded that robot-assisted surgery could improve the quality of lymphadenectomy. They compared conventional upper mediastinal lymphadenectomy in 18 patients and extended upper mediastinal lymphadenectomy in 22 patients, and found that extensive dissection around the RLN increased numbers of retrieved lymph nodes from 35 to 48 (19). However, other studies failed to demonstrate increased yields of dissected lymph nodes during robotic surgery (17,20). In the present study, a greater number of lymph nodes was dissected in the RE group, and this advantage was more obvious in the upper mediastinum around both the RLN and aortopulmonary window lymph nodes where thoracoscopic dissection is technically difficult and dangerous. Although no statistical significance was found, the incidence of vocal cord paralysis was also lower in the RE group, which concurs with the findings of Suda *et al.* (17). In our opinion, these findings represent advantages of robot-assisted surgery over thoracoscopic surgery.

However, early postoperative outcomes were comparable between the RE and TE groups. Overall complication rates and severities of complications were not different in the two groups. Both groups had relatively low pulmonary complication and anastomosis leakage rates, which agree with previous studies (17,20). These comparable early results were expected because the invasiveness of both surgical methods is not greatly different. Instead, we believe that the advantages of RE over TE are better oncologic surgery and improved long-term survival. We have already indicated RE is superior in terms of quality of lymphadenectomy, but we were not able to demonstrate improved survival in the RE group. We did find that 5-year overall survival and freedom from locoregional recurrence rates were higher in the RE group by 10% and 14%, respectively. However these differences were not large enough to show significance, presumably because of the relatively small number of patients recruited. Furthermore, as several studies have reported correlations between dissected lymph node numbers and long-term survival (21,22), we recommend that a larger scale comparative study should be conducted on RE and TE.

Several disadvantages of robotic surgery were identified in this study. The first disadvantage was its longer operation time, especially one-lung ventilation time, which has the potential to increase postoperative respiratory complications (23). Although no significant increase in the risk of respiratory complications was identified in the RE group, this increase in operation time could adversely affect postoperative outcomes. The second disadvantage is the cost of robotic surgery. In our country robotic surgery is not reimbursed by national medical insurance system, and thus, additional charges should be paid by patients. This is the undoubtedly the most important obstacle to the widespread use of robotic surgery in our country. Accordingly, more evidence on the superiority of robotic surgery as compared with conventional MIE is required to justify the cost of robotic surgery.

Several limitations of the present study warrant consideration. The first concern is the relatively small number of patients enrolled. Importantly, several outcome variables were improved in the RE group but these improvements were not significant despite large differences. The vocal cord paralysis rate was decreased by 11% and 5-year freedom from locoregional recurrence was increased by 14%. However, the difference was not statistically significant. The second limitation stems from the retrospective nature of this study, for example, although preoperative parameters were comparable in the two groups, unidentified, uncontrolled selection bias might have existed.

Conclusions

In the present study, we compared RE and TE and found RE enabled more radical lymphadenectomy, especially in the upper mediastinum. On the other hand, RE was associated with longer operation times. Considering that balance between radicality and safety is an important goal of minimally invasive surgery, however unfortunately, we were not able to determine whether robotic surgery is a better proposition for esophagectomy. However, the better quality lymphadenectomy offered by robotic surgery has the potential to improve oncologic outcomes in the long-term follow-up. Well-designed large scale studies are required to compare RE and TE to define the role of robotic surgery in ESCC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was reviewed by the Institutional Review Board and was approved as a minimal risk retrospective study (approval number: 1407-137-597), which did not require individual consent based on the institutional guidelines for waiving consent.

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