The Oncologic Outcome of Esophageal Squamous Cell Carcinoma Patients After Robot-Assisted Thoracoscopic Esophagectomy With Total Mediastinal Lymphadenectomy

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Background. The oncologic outcome of esophageal squamous cell carcinoma (ESCC) patients after robot-assisted thoracoscopic esophagectomy (RATE) with total mediastinal lymphadenectomy (ML) has not been reported. This study was performed to determine the oncologic outcome of RATE and the effectiveness of total ML for ESCC.

Methods. The 115 patients who underwent RATE without neoadjuvant therapy from 2006 to 2014 were reviewed. The efficacy index (EI) was calculated by multiplying the incidence of metastasis by the 3-year survival rate of the patients for each node station.

Results. The majority of patients were male (92.2%), and the mean age was 63.2 ± 0.8 years. Tumor location was the upper esophagus in 12 patients (10.4%), the middle esophagus in 59 patients (51.3%), and the lower esophagus in 44 patients (38.3%). R0 resection was achieved in 110 (95.7%) patients; the mean number of dissected nodes was 49.0 ± 1.9. Operative mortalities were 4 (3.5%) cases; in the remaining 111 patients, the mean follow-up time was 32.4 ± 2.2 months. Overall survival (OS) and recurrence-free interval (RFI) at 3 years were 85.0% and 79.4%, respectively. The 3-year OS and RFI were 94.4% and 96.2% in patients with stage I disease, 86.2% and 80.1% in stage II disease, and 77.8% and 79.5% in stage IIIA disease, respectively. High EI values were determined in the bilateral recurrent laryngeal nerve (RLN) nodes in upper and middle ESCC, and in the left gastric and paracardial nodes in lower ESCC.

Conclusions. The oncologic outcome of RATE was acceptable. Total ML, including dissection of the RLN nodes, is recommended especially in upper or middle ESCC.

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Radical esophagectomy with adequate lymph node clearance is a mainstay of treatment for patients with localized esophageal cancer [1]. In East Asia, where esophageal squamous cell carcinoma (ESCC) accounts for more than 90% of esophageal cancers, total mediastinal lymphadenectomy (ML), including the bilateral dissection of recurrent laryngeal nerve (RLN) chains, is considered mandatory to achieve long-term survival [2]. However, because this aggressive procedure carries significant morbidity and mortality, various forms of minimally invasive esophagectomy (MIE) have been used [3]. Recent developments in robotic technology have enabled the introduction of robotic surgical procedures in patients with esophageal cancer, and early studies have demonstrated their technical feasibility and safety [4]. In 2006, we introduced robot-assisted thoracoscopic esophagectomy (RATE) to overcome the difficulties encountered in the bilateral dissection of the RLN chains. An assessment of RATE showed that it enabled the dissection of a large number of lymph nodes in esophageal cancer patients and that the level of associated morbidity was acceptable [5, 6]. However, we are aware of only one report on the oncologic outcome associated with the use of RATE: a study from The Netherlands in which long-term survival was evaluated [7]. The authors reported a 5-year overall survival of 42% and a median disease-free survival of 21 months, but only 19% of the study population had ESCC. Thus, the oncologic outcome achieved by the use of RATE with total ML for the treatment of ESCC is unknown.

To measure the efficacy of lymph node dissection using RATE with total ML, we adopted the modified efficacy index (EI), defined as the incidence of metastasis to a specific lymph node station multiplied by the 3-year

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survival rate of patients with metastasis to that station, divided by 100 [8]. Theoretically, to achieve long-term survival, adequate lymph node dissection should include lymph node stations with a high EI. If the EI of the bilateral RLN chains is high, and if use of the robotic system enables more meticulous dissection, then RATE would be a useful tool to achieve long-term survival and better locoregional control, given its advantages in restricted anatomic spaces and complex procedures (three-dimensional [3D] view, articulation of the instruments, and tremor filtering) [5, 9, 10]. Therefore, in this study, we determined the oncologic outcome associated with RATE and investigated the effectiveness of total ML in patients with ESCC.

Patients and Methods

Patients

From July 2006 to December 2014, 140 consecutive patients with esophageal cancer underwent RATE with total ML at our institute. Five patients with esophageal adenocarcinoma, 3 with concomitant gastric cancer, and 5 who underwent salvage esophagectomy were excluded from the analysis. Twelve patients who received preoperative neoadjuvant therapy were also excluded. Thus, the final study population consisted of 115 patients who underwent RATE with total ML for ESCC with curative intent. This retrospective study was approved by the Institutional Review Board (IRB approval no. 2016-0179-001). The patients' demographic, surgical, and pathologic data were recorded prospectively.

Preoperative endoscopic biopsy was performed to confirm the histologic diagnosis. The staging workup consisted of endoscopic ultrasonography, chest computed tomography (CT), abdominopelvic CT, and positron emission tomography (PET). The operative technique used in RATE with total ML has been described previously [11]. Briefly, four trocars were placed with the patient in the semiprone position, and a da Vinci robotic cart (Intuitive Surgical, Mountain View, CA) was introduced from the left cranial side of the patient. After division of the azygos vein, en bloc resection of the middle and lower esophagus was done. The thoracic duct, mediastinal pleura, and lymph nodes at the paraesophageal, subcarinal, and peribronchial stations were dissected to remain en bloc with the esophagus. Then, the mediastinal pleura overlying the right vagus nerve was incised, and the right RLN was identified at the lower margin of the right subclavian artery. Lymph nodes along the right RLN were removed with the articulating forceps and scissors under the magnified view. Then, the trachea was retracted, and the left RLN was identified. Lymph nodes and fatty tissue between the left RLN and the trachea were dissected carefully. Small vessels were controlled by the application of metal clips, and care was taken to avoid the traction or thermal injury to the nerve at this point. The dissection of lymph nodes along the left RLN was done up to the level of the lower pole of the thyroid gland. Bilateral neck node dissection was performed in patients with upper ESCC and in those with middle or lower ESCC in whom clinically evident metastasis at the upper mediastinum or cervical area was confirmed. Neck node dissection was performed under the collar incision, and it included the deep internal cervical lymph nodes (cervical recurrent laryngeal nerve nodes), deep lateral cervical lymph nodes (lateral side of jugular vein), and external cervical lymph nodes (medial side of spinal accessory nerve) [11].

The lymph node station was classified according to the Japanese Guidelines for Clinical Pathologic Studies on Carcinoma of the Esophagus [12]. Pathologic staging was reported according to the 7th edition of the TNM classification of the Union for International Cancer Control / American Joint Committee on Cancer (UICC/AJCC) [13]. Postoperatively, chest and abdominopelvic CT scans were obtained at 6-month intervals in patients with stage I disease and at 4-month intervals in those with stage II or higher disease.

Esophagogastroduodenoscopy was performed every 2 years in all patients. Locoregional recurrence was defined as disease occurring at the anastomosis site or at sites in the mediastinum and abdomen where lymph node dissection had been performed. Distant recurrences were those developing in tissues outside the operative field, such as the lung, brain, liver, adrenal glands, and bone. Recurrence was diagnosed based on the results of imaging studies, including a PET scan; a tissue biopsy was obtained if clinically indicated.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows statistical software (version 20.0; SPSS Inc., Chicago, IL). Clinical and pathologic indicators are given as means $\pm$ standard error of the mean for continuous variables and as frequencies (%) for categoric variables. Overall survival (OS) was measured from the date of operation to the date of death of any cause. Recurrence-free interval (RFI) was measured from the date of operation to the date of the initial recurrence of ESCC (locoregional or distant), and death of other causes was censored. The Kaplan-Meier method and log-rank test were used to calculate and compare the survival rates. The EI was obtained by multiplying the incidence of metastasis by the 3-year patient survival rate for each node station. All p values were two-sided. A p value < 0.05 was considered to indicate statistical significance.

Results

Patient Demographics and Pathologic Data

The demographic data of the patients are listed in Table 1. The majority (89.6%) of the patients had middle or lower ESCC, and 66.0% presented with clinical stage I disease. R0 resection was achieved in 110 (95.7%) patients; the mean number of dissected lymph nodes was 49.0 $\pm$ 1.9. The pathologic data were analyzed after the data of the 4 patients who died postoperatively were excluded (Table 2). The majority of patients had a pT1 lesion

Table 1. Patient Demographics (n = 115)

Variable	n (%)
Age, y	63.2 ± 0.8
Sex	
Male	106 (92.2)
Female	9 (7.8)
Tumor location	
Upper	12 (10.4)
Middle	59 (51.3)
Lower	44 (38.3)
Clinical stage at presentation	
I	76 (66.0)
II	29 (25.2)
III	10 (8.7)
Neck dissection	22 (18.3)
Resection status	
R0	110 (95.7)
R1	3 (2.6)
R2	2 (1.7)
Number of dissected LNs	
Total	49.0 ± 1.9
Mediastinal	25.7 ± 1.0
Abdominal	18.7 ± 0.8
Cervical (in 22 patients)	23.1 ± 3.3
Major morbidities	
Pneumonia	13 (11.3)
Recurrent laryngeal nerve palsy	34 (29.6)
Operative mortality	4 (3.5)
Postoperative pneumonia	3 (2.6)
Conduit necrosis	1 (0.9)

LNs = lymph nodes.

Table 2. Pathologic Data in the Surviving Patients (n = 111)

Variable	n (%)
pT stage	
T1	84 (75.7)
T2	7 (6.3)
T3	18 (16.2)
T4	11 (9.9)
Differentiation	
G1	19 (17.1)
G2	76 (68.5)
G3	15 (13.5)
Tumor length (cm)	2.9 ± 0.1
Lymphovascular invasion	31 (27.9)
Perineural invasion	11 (9.9)
pN stage	
N0	60 (54.1)
N1	28 (25.2)
N2	20 (18.0)
N3	3 (2.7)
Preoperative nodal staging	
Up / Accurate / Down	43 (38.7)
Accurate	62 (55.9)
Down	6 (5.4)
Pathologic stage	
I	56 (50.5)
II	28 (25.2)
IIIA	13 (11.7)
IIIB + C	14 (12.6)
Adjuvant therapy	
None	74 (66.7)
Chemotherapy	19 (17.1)
Radiotherapy	5 (4.5)
Chemoradiotherapy	13 (11.7)

(84, 75.7%) and the mean tumor length was 2.9 ± 0.1 cm. In 38.7% of the patients, the nodal stage migrated to a higher N stage after operation. Thus, the number of patients with stage I disease after operation decreased from 76 (66.0%) to 56 (50.5%), and the number of patients with stage III disease after operation increased from 10 (8.7%) to 27 (24.3%).

Recurrences and Survival Analysis

Follow-up was complete in all patients; the mean follow-up time was 32.4 ± 2.2 months. During follow-up, 19 (17.1%) patients experienced disease recurrence, including local recurrence in 7 (6.3%) patients. Within this group, disease was detected in the upper mediastinum in 1 patient, in the subcarinal area in 3 patients, in the left supraclavicular fossa in 2 patients, and in the paraaortic area in 1 patient. Distant metastasis developed in 5 (4.5%) patients, in the lungs in 2 patients, in the bones in 2 patients, and in the adrenal gland in 1 patient. Combined recurrence (simultaneous local and distant recurrence) was present in 7 (6.3%) patients. Among the 14 (12.6%) patients who died during follow-up, 11 (9.9%) died of cancer and 3 (2.7%) of intercurrent disease.

The 3-year OS and RFI in all patients were 85.0% and 79.4%, respectively (Fig 1). The 3-year OS was 94.4% in patients with stage I disease, 86.2% in patients with stage II disease, 77.8% in patients with stage IIIA disease, and 37.5% in patients with stage IIIB/C disease (Fig 2A). The 3-year RFI was 96.2% in patients with stage I disease, 80.1% in patients with stage II disease, and 79.5% in patients with stage IIIA disease (Fig 2B). Tumor recurrence within 2 years after operation developed in more than 80% of patients with stage IIIB/C disease. The difference in RFI was marginal between patients with stage I and II disease ($p = 0.061$) and between patients with stage I and IIIA disease ($p = 0.069$).

The OS and RFI according to pathologic N stage are shown in Figure 3. The 3-year OS in patients with pathologic N0, N1, and N2 disease was 84.4%, 80.7%, and 51.6% (pN0 vs pN2, $p = 0.024$; pN0 vs pN3, $p = 0.018$), respectively. The 3-year RFI in patients with pathologic N0, N1, and N2 disease was 92.4%, 84.8%, and 49.4% (pN0 vs pN2, $p < 0.001$; pN1 vs pN2, $p = 0.007$), respectively. All patients with N3 disease died within 3 years after operation.

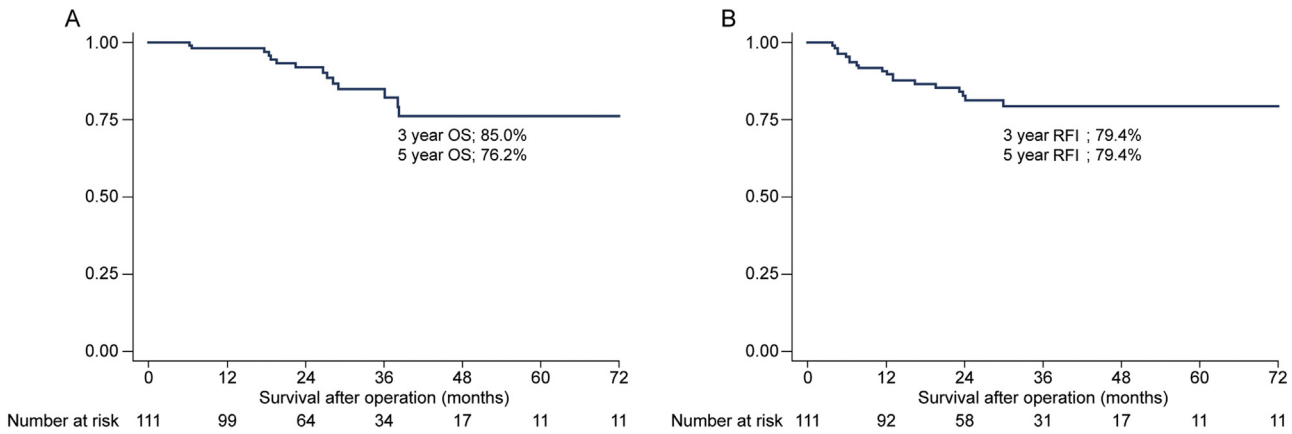

Fig 1. Survival curves. (A) Overall survival (OS) in 111 patients. (B) Recurrence-free interval (RFI) in 111 patients.

Efficacy Index

The EI of each lymph node station was calculated; the results are shown in Table 3. Overall, the right RLN and left gastric lymph nodes had the highest EI (14.4 and 11.8, respectively.) In upper and middle esophageal cancer, the highest EIs were those of the right and left RLN (41.7 and 16.7 in upper esophageal cancer and 15.8 and 5.3 in middle esophageal cancer), whereas in lower esophageal cancer the left gastric lymph nodes (20.8) and paracardial lymph nodes (16.6) had the highest EIs. The distribution of the EI values for each lymph node station according to the location of the primary tumor is summarized in Table 3.

Comment

To the best of our knowledge, this is the first report of the oncologic outcome in ESCC patients after RATE. Our study showed acceptable long-term survival rates as well as good locoregional control. The 3-year and 5-year OS were 85.0% and 76.2%, respectively, and locoregional recurrence was observed in 14 (12.6%) patients. The favorable oncologic outcome may have been due to the high rate of R0 resection (95.7%) and the large number of dissected lymph nodes (49.0 ± 1.9). The rate of R0 resection is one of the most powerful parameters influencing locoregional control and long-term survival [14], and most studies report a dismal prognosis in patients with R1 or R2 resection regardless of the surgical approach. The rate of R0 resection achieved in this study by the use of RATE was similar to that in open esophagectomy (86% to 100%) and thoracoscopic esophagectomy (91% to 97%) [15]. In addition, the acceptable oncologic outcome may have been the result of adequate lymph node clearance, inasmuch as the number of dissected lymph nodes was higher than in previous

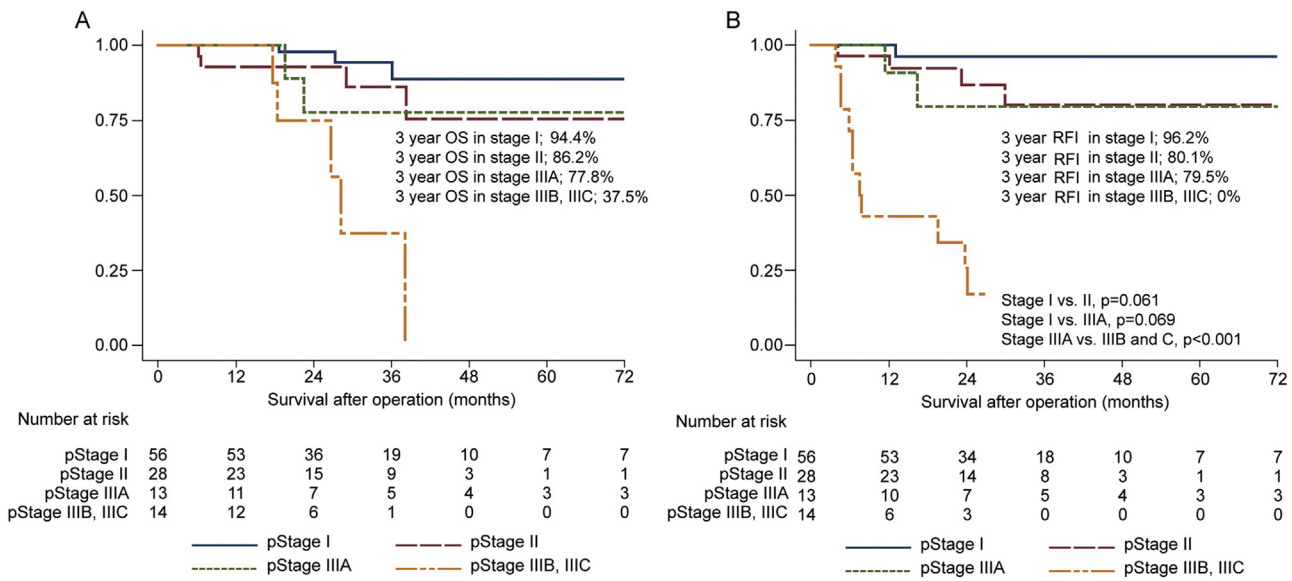

Fig 2. Survival curves according to pathologic stage. (A) Overall survival (OS). (B) Recurrence-free interval (RFI).

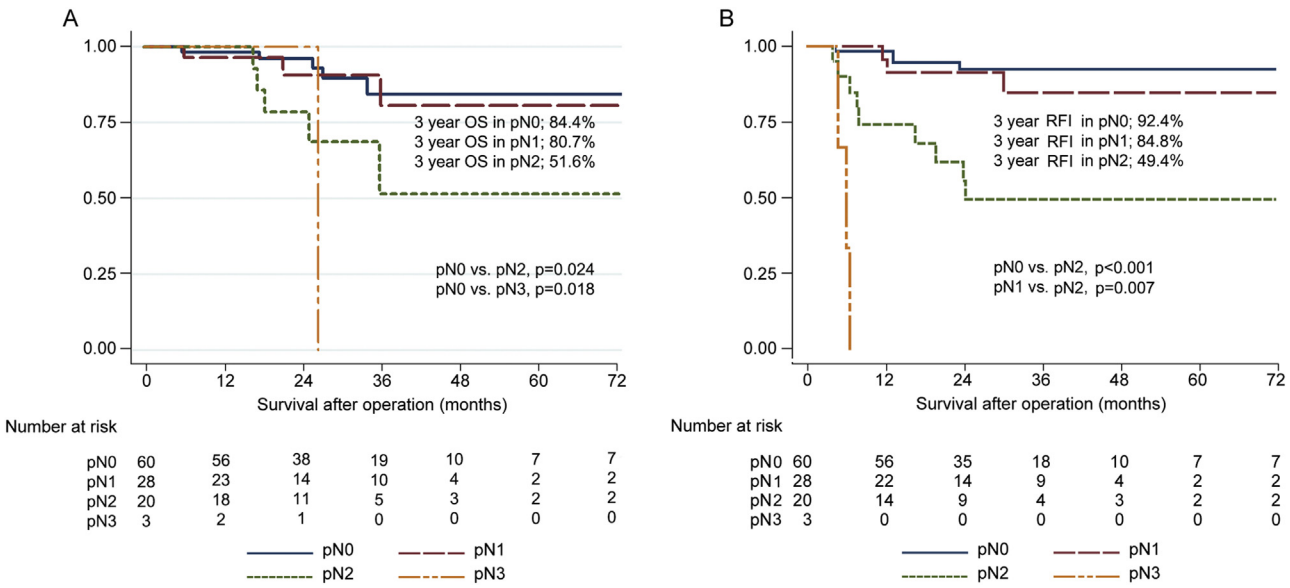

Fig 3. Survival curve showing (A) overall survival (OS) and (B) recurrence-free interval (RFI) according to pathologic N stage.

reports. Rizk and colleagues [16] suggested that the dissection of more than 30 lymph nodes could maximize survival after esophagectomy; in our study, the mean number of dissected lymph nodes (49.0 ± 1.9) was even higher. Furthermore, with its 3D magnified view, the robotic system provides a better perspective around the esophagus. It also enables fine meticulous dissection along the RLN chains bilaterally because of the articulation of the instruments and the tremor-filtering effect. These benefits contributed to both the high rate of R0 resection and the relatively large number of dissected lymph nodes in our series. One notable finding was the favorable survival rate in patients with stage I to IIIA disease. The 3-year OS was 94.4% in patients with stage I disease and 86.2% and 77.8% in those with stage II and IIIA disease, respectively. Despite the small number of patients in this study, it can be speculated that radical esophagectomy with total ML can cure ESCC until a

Table 3. Efficacy Index

Station	3-Year Survival Rate (%)	All (n = 111)		Upper (n = 12)		Middle (n = 57)		Lower (n = 42)	
		Metastasis (%)	EI	Metastasis (%)	EI	Metastasis (%)	EI	Metastasis (%)	EI
Deep internal cervical	50	3.6	1.8	16.7	8.4	0	0	4.8	2.4
Other cervical lymph nodes	100	2.7	2.7	8.3	8.3	1.8	1.8	2.4	2.4
RLN, right	100	14.4	14.4	41.7	41.7	15.8	15.8	4.8	4.8
RLN, left	100	4.5	4.5	16.7	16.7	5.3	5.3	0	0
Right tracheobronchial	…	0	…	0	…	0	…	0	…
Left tracheobronchial and infraaortic	NA	7.2	…	16.7	…	8.8	…	2.4	…
Hilar	…	0	…	0	…	0	…	0	…
Paraesophageal	60.6	11.7	7.1	8.3	5.0	8.8	5.3	16.7	10.1
IPL	…	0	…	0	…	0	…	0	…
Subcarinal	NA	3.6	…	0	…	5.3	…	2.4	…
Diaphragmatic	…	0	…	0	…	0	…	0	…
Paracardial	77.8	9.9	7.7	0	0	3.5	2.7	21.4	16.6
Left gastric	87.5	13.5	11.8	8.3	7.3	7.0	6.1	23.8	20.8
Common hepatic and celiac	0	3.6	0	0	0	1.8	0	7.1	0
Splenic	66.7	2.7	1.8	0	0	0	0	7.1	4.7

EI = efficacy index; IPL = intrapulmonary ligament; NA = not applicable; RLN = recurrent laryngeal nerve.

certain disease stage. However, upfront radical esophagectomy is likely to have a very limited role in patients with stage IIIB/C disease because of the high likelihood of early recurrence and poor long-term survival. Accordingly, the use of the robotic interface in this subset of patients will probably have no added value because of the significantly high tumor burden. Thus, surgical candidates who have undergone neoadjuvant treatment or definitive concurrent chemoradiation should be carefully selected to identify those most likely to benefit from RATE.

The number of metastatic lymph nodes is one of the most important prognostic factors in esophageal cancer, as reflected in the 7th edition of the TNM classification (UICC/AJCC) [13]. In patients undergoing curative operations, the number of dissected lymph closely correlates with improved survival [16, 17]. However, whether all lymph nodes around the esophagus are of the same importance in terms of oncologic outcome is unclear. For example, lymph nodes such as the right RLN nodes have a high frequency of metastasis, whereas metastasis is rare in lymph nodes such as the pretracheal or diaphragmatic nodes. In addition, the complete dissection of some lymph nodes may allow a favorable prognosis, whereas metastasis in other specific lymph nodes may be strongly associated with a poor prognosis. The EI was initially proposed by Sasako and colleagues [8] as a means to evaluate the significance of lymph node metastases in patients with gastric adenocarcinoma. It is defined as the incidence of metastasis to a region (%), multiplied by the 5-year survival rate (%) of patients with metastasis to that region, divided by 100 [8]. Thus, the EI numerically expresses the possible effect of the dissection of a certain lymph node region in terms of the 5-year survival rate of patients with similar metastases. In this report, we modified the definition of EI by the incidence of metastasis to a region (%), multiplied by the 3-year survival rate (%) of patients with metastasis to that region, divided by 100, because relatively short follow-up periods and most recurrences usually developed within 3 years. Because the pattern of lymphatic drainage in esophageal cancer depends on the location of the primary lesion, we calculated the EI for upper, middle, and lower ESCC separately. In upper and middle ESCC, the EI was highest for the right and left RLN nodes, whereas in lower ESCC the highest EI was that of the left gastric and paracardial lymph nodes (Table 3). This result correlates well with a previous report by Udagawa and colleagues [18], who evaluated 906 patients with thoracic esophageal cancer (mostly ESCC). In those with upper esophageal cancer, the EI was high in the right and left RLN nodes (41.7 and 16.7, respectively), whereas in patients with lower esophageal cancer, the highest EIs were those of the paracardial and left gastric nodes (16.6 and 20.8, respectively). These data suggest that the original location of the dissected lymph nodes is more important than the number of dissected lymph nodes. Considering that robotic operations offer several advantages in the dissection of the upper mediastinum [5], RATE will be most useful to surgeons whose surgical policy is a radical esophagectomy with total ML. Nonetheless, RATE also has several as yet unsolved problems. First, there is the high cost of the initial installation and subsequent maintenance of the equipment for robotic surgical procedures. Studies on the cost-effectiveness of RATE have to be done in the future. Second, despite the acceptable postoperative outcomes achieved with RATE [6], the learning curve has not yet been rigorously assessed.

This study has several limitations. First, because it used a retrospective design and was conducted in a single institution, comparisons with other series were not possible. To demonstrate that the oncologic outcome achieved with RATE is comparable to that achieved with open esophagectomy or conventional thoracoscopic esophagectomy requires prospective, randomized clinical trials. Second, the number of patients was relatively small, even though we based our study on patients with ESCC, the group most often treated with RATE; however, a larger number of patients is required to confirm our results. Third, it was difficult to evaluate the therapeutic value of the cervical lymph nodes because bilateral dissection of the neck nodes was performed in selected patients. In our institute, three-field lymph node dissection is not a routine procedure because the lymph nodes are instead dissected along the bilateral RLNs, up to the inferior margin of the thyroid gland. Bilateral neck dissection is added only in patients with upper ESCC or in those with lymph node metastasis to the cervical or RLN nodes, as determined by preoperative imaging studies. Therefore, we may have underestimated the EI of the cervical lymph nodes in comparison with the values reported from Japan [18]. Last, we used adjuvant therapy after the operation on the basis of pathologic stage. Even though the role and efficacy of adjuvant therapy in ESCC has not been established, the potential bias could exist in the survival after RATE.

In conclusion, our study demonstrated that RATE may be a useful and effective tool to achieve the long-term survival of ESCC patients. The acceptable oncologic outcomes of RATE may be related to the meticulous dissection of the upper mediastinum, especially including the bilateral RLN chains, using the advantages of robotic system. Total ML including dissection along the bilateral RLN chains should be carried out, especially in patients with upper or middle ESCC. A prospective randomized trial with longer follow-up times is necessary to validate the true efficacy of RATE for ESCC.

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