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Comparison of Open and Thoracoscopic Esophagectomy in Patients With Locally Advanced Esophageal Squamous Cell Carcinoma After Neoadjuvant Therapy

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Abstract. *Background/Aim: The safety and effectiveness of thoracoscopic compared with open esophagectomy remain uncertain. We aimed to clarify the differences between these surgical modalities in patients with esophageal squamous cell carcinoma (ESCC) who underwent neoadjuvant therapy. Patients and Methods: We reviewed surgical outcomes among 133 patients with locally advanced ESCC who underwent neoadjuvant therapy followed by esophagectomy. We compared the operative outcomes, postoperative complications and survival rates between 65 and 68 patients who were respectively treated by open and thoracoscopic esophagectomy. Results: The surgical duration was longer, but blood loss was lower during thoracoscopic, compared with open esophagectomy. The numbers of dissected mediastinal lymph nodes and rates of postoperative complications did not significantly differ between open and thoracoscopic esophagectomy. However, the rates of postoperative pneumonia and recurrent laryngeal nerve paralysis were significantly lower and higher, respectively, after thoracoscopic, compared with open esophagectomy. Overall survival did not significantly differ between the groups. Conclusion: Thoracoscopic esophagectomy is feasible for patients with locally advanced ESCC who undergo neoadjuvant therapy.*

Neoadjuvant therapy followed by surgery is generally conducted for local control and to improve the survival of patients with locally advanced esophageal cancer. Neoadjuvant chemotherapy or chemoradiotherapy (NCT and NCRT, respectively) are frequently administered for locally advanced esophageal squamous cell carcinoma (ESCC) (1-3). We have also reported the results of NCT or NCRT followed by surgery for resectable locally advanced ESCC (4-7).

Although intensive neoadjuvant therapy might cause toxicity and postoperative morbidity, the incidence of postoperative morbidity and mortality has not recently increased among patients given neoadjuvant therapy compared with surgery alone (2, 3, 8-10). However, esophageal surgery is highly invasive and still associated with a higher likelihood of postoperative morbidity and mortality than other types of gastroenterological surgery (8, 11). Furthermore, postoperative complications are significantly associated with prognosis after surgery for esophageal cancer (12-14). Therefore, invasiveness and postoperative complications of esophageal surgery should be further minimized.

The incidence of thoracoscopic esophagectomy is increasing, even though whether it improves short- and long-term outcomes is supported by limited evidence (15, 16). Furthermore, the safety and effectiveness of thoracoscopic, compared with open esophagectomy remain uncertain especially as treatment for advanced ESCC after neoadjuvant therapy. The present study compares the outcomes of these surgical modalities between patients with locally advanced ESCC who underwent NCT or NCRT at our institute.

Patients and Methods

Patients. We reviewed 133 consecutive patients with SCC in the thoracic esophagus and esophagogastric junction (EGJ) who underwent NCT or NCRT followed by esophagectomy *via* thoracotomy or a thoracoscopic approach at our institution between January 2012 and December 2018. Patients who were treated by salvage surgery after definitive CRT were excluded.

Patients with performance status (PS) 0 or 1 according to the Eastern Cooperative Oncology Group criteria underwent NCT or NCRT and surgery if cancer of the esophagus or gastroesophageal junction was resectable, and if tumor invasion was worse than cT2,

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positive for lymph node (LN) metastasis (cN+) or supraclavicular LN metastasis was resectable (cM1 LYM). We basically adopted NCRT as the first choice of preoperative therapy especially for patients with bulky cT3 tumors associated with dysphagia, and selected NCT when patients had cT1 or cT2 disease with clinical LN metastasis and without dysphagia.

The clinicopathologic profiles of the tumors were based on the TNM Classification of Malignant Tumors, 7th edition (17). The Institutional Review Board of Hiroshima University approved this study (approval no. E-1756).

Neoadjuvant therapy. NCT comprised cisplatin/5-fluorouracil, nedaplatin/5-fluorouracil or docetaxel/cisplatin/5-fluorouracil regimens, as described (4). NCRT comprised concurrent radiotherapy (40 Gy in 20 fractions) and chemotherapy with 5-fluorouracil and either docetaxel or cisplatin or a combination of both, as described (5-7, 10, 12, 13). Patients with elevated serum creatinine were treated with nedaplatin instead of cisplatin.

Surgical procedures. All patients were treated by transthoracic or thoracoscopic esophagectomy approached from the right side of the chest 4 to 8 weeks after completing neoadjuvant therapy. Open esophagectomy proceeded *via* a ~15-cm skin incision in the 4th intercostal thoracotomy, and under one-lung ventilation with patients in the left decubitus position. Thoracoscopic esophagectomy proceeded using five trocars for pneumothorax and maintained CO_2 insufflation (10 mm Hg) under two-lung ventilation in prone patients. We dissected LNs in at least the thoracic and abdominal regions (two-field LN dissection). Esophageal cancer in the upper and middle third of the thoracic esophagus, and LN metastasis in the superior mediastinum was essentially treated by lymphadenectomy in the cervical, thoracic and abdominal regions (three–field LN dissection). Abdominal procedures comprised open or laparoscopic surgery, and the gastric tube or pedicled jejunum were subsequently lifted *via* posterior mediastinal, retrosternal or subcutaneous routes for cervical anastomosis with the esophagus.

LNs were postoperatively separated from esophageal specimens and periesophageal tissues, and assigned specific numbers indicating LN stations that were numbered and named according to the guidelines of the Japan Esophageal Society (18).

We graded postoperative morbidity from 0-5 based on the Clavien–Dindo classification of surgical complications (19). The highest grades of postoperative complications during hospitalization after surgery were compared between open and thoracoscopic surgery.

Statistical analysis. Categorical variables were analyzed using χ^2 tests, and continuous variables were analyzed using unpaired *t*-tests for comparison of each thoracic approach. Potential preoperative and surgical factors for pneumonia and recurrent laryngeal nerve (RLN) paralysis were analyzed by univariate analysis, and independent predictors of these postoperative complications were determined by multivariate logistic regression analysis using forward selection.

Survival data were analyzed using Kaplan–Meier curves and results were compared using log rank tests. Potential preoperative, surgical and pathological factors for overall survival (OS) were evaluated by univariate analysis, and independent predictors of OS were determined by multivariate Cox proportional hazards analysis using forward selection. Values with $p<0.05$ were considered statistically significant. All data were statistically analyzed using SPSS software (version 20.0, IBM Corp., Armonk, NY, USA).

Results

Patient characteristics. The distribution of age, gender, PS, various preoperative comorbidities, neoadjuvant therapy, and clinical and pathological stages did not differ between the patients who underwent open or thoracoscopic surgery (Table I).

Comparison of operative factors between open and thoracoscopic esophagectomy. Table II shows that the fields of LN dissection, organ for reconstruction, and curability did not differ between operative procedures. More patients underwent thoracoscopic than open esophagectomy *via* the abdominal laparoscopic approach and the retrosternal reconstruction route (p=0.01 and 0.003, respectively). The rate of R2 resection tended to be higher during open than thoracoscopic esophagectomy, but it did not reach significance (p=0.08).

The thoracic surgical duration was significantly longer in thoracoscopic than open surgery (269 *vs.* 201 min, $p<0.0001$). Total surgical duration was also significantly longer in thoracoscopic than open surgery (527 *vs.* 466 min, p=0.02). The amount of blood loss was significantly lower in thoracoscopic, than open surgery (261 *vs.* 450 ml, p=0.0004). Therefore, significantly fewer patients required blood transfusions after thoracoscopic, than open surgery (7 *vs.* 19 patients, p=0.006).

Comparison of dissected lymph nodes between open and thoracoscopic esophagectomy. Table III shows that the numbers of all dissected LNs and of mediastinal LNs did not significantly differ between the groups (p=0.71 and 0.31, respectively). More LNs were dissected in left tracheobronchial (No.106tbL) and lower thoracic paraesophageal regions (No.110) during thoracoscopic than open surgery (p=0.03 for both). The numbers of dissected LNs in other mediastinal LN stations did not significantly differ between the groups.

Comparison of postoperative complications between open and thoracoscopic esophagectomy. Table IV shows postoperative complications. The severity of complications based on the Clavien–Dindo classification (19) did not differ between the groups (p=0.64). The rate of pneumonia was significantly higher during open compared to thoracoscopic surgery (21.5% *vs.* 7.4%, p=0.02). The rate of RLN paralysis was significantly lower in open, than thoracoscopic surgery (9.2% *vs.* 22.0%, p=0.04).

Tables V and VI respectively show preoperative and surgical factors associated with postoperative pneumonia and RLN paralysis. Univariate analysis of preoperative and surgical factors significantly associated PS [odds ratio (OR)=3.92; 95% confidence interval (CI)=1.26-12.23; p=0.02] and open surgery (OR=3.46; 95%CI=1.17-10.24; p=0.03) with postoperative pneumonia. Multivariable analysis subsequently selected PS (OR=4.65; 95%CI=1.39-15.56; p=0.01) and open surgery

Table I. *Patient characteristics*.

Parameters	Open surgery (n=65)	Thoracoscopic surgery (n=68)	*p*-Value
Mean age (y)	64.0±8.8	65.2±9.0	0.43
Gender			
Male	56 (86.2)	50 (73.5)	0.07
Female	9 (13.8)	18 (26.5)	
Performance status[1]			
0	57 (87.7)	58 (85.3)	0.69
1	8 (12.3)	10 (14.7)	
Primary tumor location			
Upper third	14 (21.5)	11 (26.2)	0.70
Middle third	29 (44.6)	34 (50.0)	
Lower third and esophagogastric junction	22 (33.8)	23 (33.8)	
cT[2]			
1	3 (4.6)	6 (8.8)	0.23
2	11 (16.9)	14 (20.6)	
3	48 (73.8)	48 (70.6)	
4	3 (4.7)	0 (0)	
cN[2]			
0	16 (24.6)	14 (20.1)	0.71
1	37 (56.9)	36 (52.9)	
2	11 (16.9)	17 (25.0)	
3	1 (1.5)	1 (1.5)	
cM2 (Supraclavicular LN metastasis)			
0	58 (89.2)	56 (82.4)	0.26
1	7 (10.8)	12 (17.6)	
cStage[2]			
IB	6 (9.2)	8 (11.8)	0.60
II	16 (24.6)	13 (19.1)	
III	36 (55.4)	35 (51.5)	
IV	7 (10.8)	12 (17.6)	
Neoadjuvant therapy			
Chemotherapy	28 (43.1)	34 (50.0)	0.42
Chemoradiotherapy	37 (56.9)	34 (50.0)	
ypT3			
0	15 (23.1)	19 (27.9)	0.77
1	11 (16.9)	15 (22.1)	
2	13 (20.0)	12 (17.6)	
3	23 (35.4)	18 (26.5)	
4	3 (4.6)	4 (5.9)	
ypN3			
0	30 (46.2)	31 (45.6)	0.91
1	20 (30.8)	24 (35.3)	
2	12 (18.5)	11 (16.2)	
3	3 (4.6)	2 (2.9)	
ypM[3] (Supraclavicular LN metastasis)			
0	59 (90.8)	61 (89.7)	0.84
1	6 (9.2)	7 (10.3)	
ypStage[3]			
0	11 (16.9)	15 (22.1)	0.98
I	12 (18.5)	11 (16.2)	
II	13 (20.0)	13 (19.1)	
III	19 (29.2)	18 (26.5)	
IV	6 (9.2)	7 (10.3)	
T0N+	4 (6.2)	4 (5.9)	

SD: Standard deviation. Values are shown as n (%) or as means±SD. [1]According to Eastern Cooperative Oncology Group. [2]Pretherapeutic and [3]pathological staging according to TNM Classification, 7th edition (17).

Table II. *Comparison of operative factors between open and thoracoscopic surgery.*

Operative factors	Open surgery (n=65)	Thoracoscopic surgery (n=68)	*p*-Value
Fields of lymph node dissection			
Thoracic and abdominal	19 (29.2)	25 (36.8)	0.36
Thorax, abdominal, and cervical	46 (70.8)	43 (63.2)	
Abdominal procedure			
Open	64 (98.5)	59 (86.8)	0.01
Laparoscopy	1 (1.5)	9 (13.2)	
Reconstructed organ			
Stomach	61 (93.8)	67 (98.5)	0.16
Others	4 (6.2)	1 (1.5)	
Reconstruction route			
Posterior mediastinal	14 (21.5)	3 (4.4)	0.003
Retrosternal	47 (72.3)	64 (94.1)	
Subcutaneous	4 (6.2)	1 (1.5)	
Curability[1]			
R0/1	60 (92.3)	67 (98.5)	0.08
R2	5 (7.7)	1 (1.5)	
Thoracic surgical duration (median, min)	201 (135-431)	269 (144-453)	<0.0001
Total surgical duration (median, min)	466 (329-1,003)	527 (350-747)	0.02
Blood loss (median, g)	450 (195-2,030)	261 (57-1,912)	0.0004
Blood transfusion			
−	46 (70.8)	61 (89.7)	0.006
+	19 (29.2)	7 (10.3)	

[1]Defined based on TNM Classification of Malignant Tumors, 7th edition (17).

Table III. *Comparison of the numbers of dissected lymph nodes between open and thoracoscopic surgery.*

	Open surgery No. of LN	Thoracoscopic surgery No. of LN	*p*-Value
All dissected LNs	43.8±16.7	44.8±16.8	0.71
All dissected mediastinal LNs	18.6±9.7	20.0±8.5	0.31
Stations of mediastinal LN[1]			
105: Upper thoracic (paraesophageal)	1.6±1.7	1.8±2.0	0.49
106recR: Right recurrent nerve	3.1±3.5	3.2±2.4	0.92
106recL: Left recurrent nerve	2.2±2.5	2.4±2.3	0.64
106tbL: Left tracheobronchial	0.6±1.1	1.2±1.7	0.03
107: Subcarinal	2.6±2.1	2.3±2.4	0.43
108: Middle thoracic (paraesophageal)	1.5±1.7	2.1±1.9	0.09
109R: Right main bronchus	2.0±1.6	1.7±1.5	0.31
109L: Left main bronchus	2.3±2.0	2.0±1.5	0.10
110: Lower thoracic (paraesophageal)	1.7±1.7	2.5±2.5	0.03
111: Supradiaphragmatic	0.3±0.9	0.2±0.6	0.59
112: Posterior mediastinal	0.2±0.5	0.4±1.0	0.09

LN: Lymph node; SD: standard deviation. Data are shown as means±SD. [1]According to Japanese Society for Esophageal Diseases guidelines (18).

(OR=3.93; 95%CI=1.27-12.19; *p*=0.02) as independent covariates for postoperative pneumonia.

Univariate analysis of preoperative and surgical factors significantly associated thoracoscopic surgery (OR=2.78; 95%CI=1.01-7.69; *p*=0.049) and three-field LN dissection (OR=5.70; 95%CI=1.26-25.71; *p*=0.02) with RLN paralysis. Multivariable analysis subsequently selected thoracoscopic surgery (OR=3.26; 95%CI=1.15-9.27; *p*=0.03) and three-field LN dissection (OR=6.58; 95%CI=1.43-30.28; *p*=0.02) as independent covariates for RLN paralysis.

Comparison of survival between open and thoracoscopic esophagectomy and predictive factors associated with survival. Figure 1 shows the overall survival (OS) and disease-

Table IV. *Comparison of postoperative complications between open and thoracoscopic surgery.*

Clavien–Dindo classification[1]	Open surgery (n=65)	Thoracoscopic surgery (n=68)	*p*-Value
Grade 0	26 (40.0)	20 (29.4)	0.64
Grade 1	2 (3.1)	3 (4.4)	
Grade 2	10 (15.4)	16 (23.5)	
Grade 3	25 (38.5)	26 (38.2)	
Grade 4	2 (3.1)	3 (4.4)	
Grade 5	0 (0)	0 (0)	
Morbidity and mortality			
Anastomotic leak	12 (18.5)	13 (19.1)	0.90
Pneumonia	14 (21.5)	5 (7.4)	0.02
Recurrent nerve palsy	6 (9.2)	15 (22.0)	0.04
Arrhythmia	6 (9.2)	4 (5.9)	0.46
Pleural effusion	5 (7.7)	3 (4.4)	0.43
Wound infection	4 (6.2)	4 (5.9)	0.95
Atelectasis	5 (7.7)	3 (4.4)	0.43
Pneumothorax	4 (6.2)	2 (7.4)	0.38
Empyema	4 (6.2)	5 (7.4)	0.78
Chylothorax	2 (3.1)	6 (8.8)	0.16
Respiratory failure	2 (3.1)	3 (4.4)	0.69
Graft necrosis	0 (0)	2 (2.9)	0.16
Bleeding	1 (1.5)	2 (2.9)	0.59
Re-operation	3 (4.6)	6 (8.8)	0.33
30-day Mortality	0 (0)	0 (0)	–
Hospital mortality	1 (1.5)[2]	0	0.30

Data are shown as n (%). [1]Highest grade of postoperative complication during hospitalization. [2]Due to rapid cancer recurrence without hospital discharge.

specific survival (DSS) curves of patients treated with open and thoracoscopic surgery. The 5-year OS and DSS rates of patients after open and thoracoscopic surgery were 48.9% *vs*. 51.9% (p=0.46) and 58.8% *vs*. 59.4% (p=0.59), respectively and did not significantly differ between these groups.

Table VII shows the preoperative, surgical and pathological factors associated with OS. Univariate and multivariate analyses showed that gender [female *vs*. male: hazard ratio (HR)=4.40; 95%CI=1.72-11.24; p=0.002], PS (0 *vs*. 1: HR=3.18; 95%CI=1.65-6.13; p=0.001), neoadjuvant therapy (NCT *vs*. NCRT: HR=3.02; 95%CI=1.74-5.24; $p<0.001$) and ypT (0/1 *vs*. 2/3/4: HR=3.91; 95%CI=2.18-7.01; $p<0.001$) significantly correlated with OS as independent covariates. However, thoracic procedures were unrelated to OS.

Discussion

The outcomes of open and thoracoscopic esophagectomy after neoadjuvant therapy have never been fully evaluated in patients with advanced ESCC. We therefore compared these surgical outcomes between patients with locally advanced ESCC who had received neoadjuvant therapy. The surgical duration was significantly longer, but blood loss was significantly lower during thoracoscopic than open esophagectomy. The number of dissected mediastinal LNs did not significantly differ between them. Although overall postoperative complications were essentially equivalent between the two approaches, rates of RLN paralysis and pneumonia were significantly higher and lower after thoracoscopic than open surgery, respectively. Survival rates were similar after both approaches.

Thoracoscopic surgery under direct vision offers many advantages, such as good lighting, magnification effect, wide field of view, fewer incisions, and less pain, compared with open surgery. Esophagectomy requires fine manipulation within a deep and narrow space. Thus, the thoracoscopic approach is suitable for esophagectomy (20). Minimally invasive surgery in general is longer, whereas operative blood loss is decreased, compared with open approaches (21-27). We also found that although thoracoscopic esophagectomy was prolonged, less blood was lost compared with open esophagectomy for ESCC after neoadjuvant therapy.

LN metastasis is one of the most negative prognostic factors (5, 7, 12, 13), and an adequate extent of LN dissection is particularly important for staging and improving long-term survival after thoracic ESCC (28). During open surgery, *en-bloc* resection of the thoracic paratracheal and cervical paraesophageal LNs through a transthoracic approach is quite difficult because of a narrow space at the cervicothoracic junction and poor illumination. However, during thoracoscopic surgery, a thoracoscope can provide better illumination and exposure of this space (28), and paracervical esophageal LNs can be effectively dissected from the thoracic cavity (29).

Furthermore, thoracoscopic surgery of prone patients afforded a good operative field from the mid-to-lower mediastinum without retraction of the right lung compared with the lateral decubitus position (11, 30). The prone position also provides better visualization of the subaortic arch and subcarinal and supraphrenic regions (11, 28). We found that although the total number of dissected mediastinal LNs did not significantly differ between open and thoracoscopic surgery, more LNs at the left tracheobronchial (No.106tbL) and lower thoracic paraesophageal (No.110) regions were dissected during thoracoscopic, than open surgery. A narrow mediastinal area containing important structures, namely the bilateral main bronchus, left RLN, aortic arch, and pulmonary artery has anatomically impeded 106tbL LN dissection under direct vision by open surgery. Therefore, thoracoscopic surgery might benefit LN dissection especially at the left tracheobronchial station (No.106tbL) of the subaortic arch region and at the lower thoracic paraesophageal station (No.110) in the supraphrenic region due to better visualization.

Table V. *Preoperative and surgical factors associated with postoperative pneumonia.*

Variables (preoperative factors)	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (continuous)	0.99	0.94-1.04	0.65	–	–	–
Gender						
Female (reference)	1			–	–	–
Male	2.39	0.52-10.99	0.27	–	–	–
Performance status[1]						
0 (reference)	1			1		
1	3.92	1.26-12.23	0.02	4.65	1.39-15.56	0.01
Primary tumor location						
Ut/Mt	1			–	–	–
Lt/EGJ	0.51	0.19-1.37	0.18	–	–	–
cT[2]						
1/2 (reference)	1			–	–	–
3/4	7.33	0.94-57.19	0.06	–	–	–
cN[2]						
0/1 (reference)	1			–	–	–
2/3	1.11	0.34-3.63	0.87	–	–	–
cM[2]						
0 (reference)	1			–	–	–
1	3.38	0.42-26.90	0.25	–	–	–
Neoadjuvant therapy						
Chemotherapy	1			–	–	–
Chemoradiotherapy	1.60	0.59-4.35	0.36	–	–	–
Thoracic procedure						
Thoracoscopic	1			1		
Open	3.46	1.17-10.24	0.03	3.93	1.27–12.19	0.02
Abdominal procedure						
Open	1			–	–	–
Laparoscopy	0.54	0.08-3.93	0.54	–	–	–
Organ for reconstruction						
Stomach	1			–	–	–
Others	4.35	0.68-27.98	0.12	–	–	–
Reconstruction route						
Posterior mediastinal	1			–	–	–
Retrosternal	0.09	0.01-1.39	0.09	–	–	–
Subcutaneous	0.15	0.04-1.63	0.25	–	–	–
Lymph node dissection[2]						
Two-fields	1			–	–	–
Three-fields	1.08	0.38-3.08	0.88	–	–	–
Curability[2]						
R0/1	1			–	–	–
R2	4.35	0.68-27.78	0.12	–	–	–
Thoracic surgical duration (continuous)	0.99	0.99-1.00	0.19	–	–	–
Total surgical duration (continuous)	1.00	0.99-1.01	0.61	–	–	–
Blood loss (continuous)	1.00	1.00-1.00	0.09	–	–	–

CI: Confidence interval; EGJ: esophagogastric junction; Lt: lower third; Mt: middle third; OR: odds ratio; Ut: upper third. [1]According to Eastern Cooperative Oncology Group. [2]According to TNM Classification, 7th edition (17).

Radical mediastinal LN dissection could result in a high incidence of vocal cord paralysis related to RLN injury, which is challenging for esophageal surgeons especially when precise LN dissection is required around the RLN. The causes of RLN injury include thermal, clamping, traction, compression, transection, suction, and energy devices (31). The RLN paralysis rates for thoracoscopic surgery range from 0% to 41.9% (11, 16, 24, 26, 27, 29-31). RLN paralysis was significantly more prevalent in patients after thoracoscopic, compared with open surgery in the present study. Apparently, 30-60 procedures on prone patients are needed to reach a plateau in the thoracoscopic esophagectomy learning curve

Table VI. *Preoperative and surgical factors associated with recurrent laryngeal nerve paralysis.*

Variables (preoperative factors)	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
Age (continuous)	1.02	0.96-1.07	0.61	–	–	–
Gender						
Female (reference)	1			–	–	–
Male	1.28	0.42-3.87	0.66	–	–	–
Performance status[1]						
0 (reference)	1			–	–	–
1	2.38	0.75-7.58	0.14	–	–	–
Primary tumor location						
Ut/Mt	1			–	–	–
Lt/EGJ	0.56	0.19-1.65	0.30	–	–	–
cT[2]						
1/2 (reference)	1			–	–	–
3/4	1.56	0.48-4.99	0.46	–	–	–
cN[2]						
0/1 (reference)	1			–	–	–
2/3	1.47	0.51-4.19	0.47	–	–	–
cM[2]						
0 (reference)	1			–	–	–
1	1.52	0.45-5.13	0.50	–	–	–
Neoadjuvant therapy						
Chemotherapy	1			–	–	–
Chemoradiotherapy	1.93	0.72-5.14	0.19	–	–	–
Thoracic procedure						
Open	1			1		
Thoracoscopic	2.78	1.01-7.69	0.049	3.26	1.15-9.27	0.03
Abdominal procedure						
Open	1			–	–	–
Laparoscopy	1.75	0.21-14.57	0.61	–	–	–
Organ for reconstruction						
Stomach	1			–	–	–
Others	1.93	0.13-29.81	0.64	–	–	–
Reconstruction route						
Posterior mediastinal	1			–	–	–
Retrosternal	1.27	0.06-25.96	0.88	–	–	–
Subcutaneous	2.06	0.13-31.92	0.61	–	–	–
Lymph node dissection[2]						
Two fields	1			1		
Three fields	5.70	1.26-25.71	0.02	6.58	1.43-30.28	0.02
Curability[2]						
R0/1	1					
R2	1.93	0.13-29.82	0.64	–	–	–
Thoracic surgical duration (continuous)	1.00	0.99-1.01	0.78	–	–	–
Total surgical duration (continuous)	1.00	0.99-1.01	0.81	–	–	–
Blood loss (continuous)	1.00	0.99-1.00	0.89	–	–	–

CI: Confidence interval; EGJ: esophagogastric junction; Lt: lower third; Mt: middle third; OR: odds ratio; Ut: upper third. [1]According to Eastern Cooperative Oncology Group. [2]According to TNM Classification, 7th edition (17).

and to reduce morbidity rates by decreasing the surgical duration, retrieving more chest nodes, and decreasing rates of RLN paralysis (32, 33). The present study might include procedures that have not yet reached a plateau in the learning curve. We need to improve the surgical techniques for LN dissections around RLN.

Furthermore, most patients developed pneumonia after open than thoracoscopic surgery. A randomized control study also found a significantly lower rate of postoperative pneumonia after minimally invasive, than open esophagectomy (12% *vs*. 34%) (23). Furthermore, minimally invasive surgery reduces the rate of postoperative pulmonary

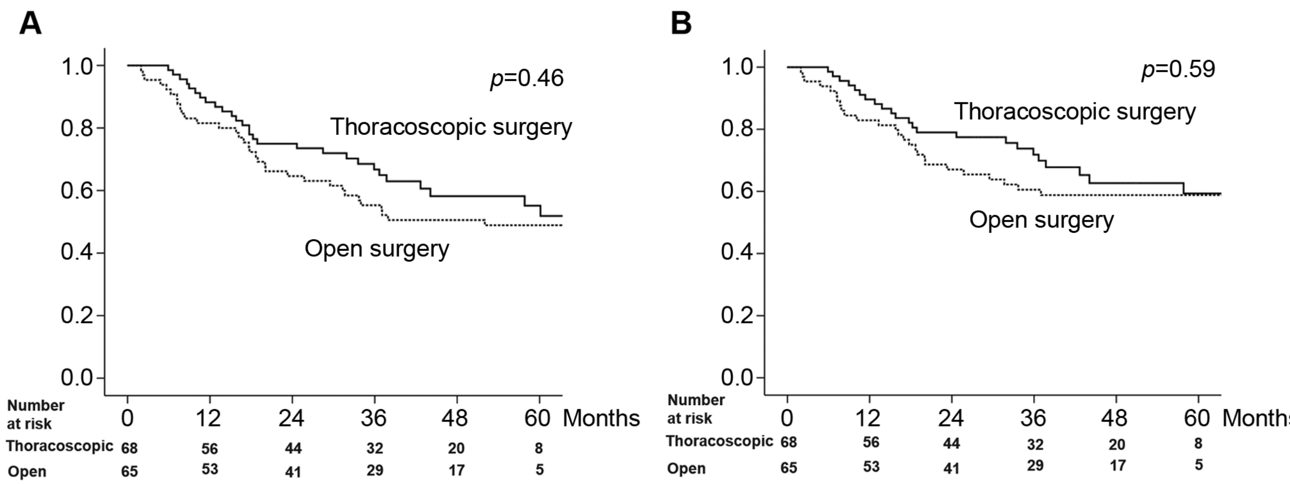

Figure 1. *Survival rates. Five-year overall survival (A) and disease-specific survival(B) rates of patients after open and thoracoscopic surgery are 48.9% vs. 51.9% (p=0.46), and 58.8% vs. 59.4% (p=0.59), respectively.*

complications (16, 22, 25, 34). The smaller incision for thoracoscopic esophagectomy probably helped to preserve lung function, as well as the ability to expectorate sputum and reduce pulmonary complications (26).

The survival of patients after thoracoscopic and open esophagectomy has been compared, but the results remain controversial (16). Some studies found no significant differences in survival between the two approaches (26, 34, 35), whereas others indicated significantly better survival after thoracoscopic, than open surgery esophagectomy (22, 27). The recent TIME trial also found that disease-free and 3-year OS did not significantly differ between minimally invasive and open esophagectomy (36). Furthermore, a systematic review and meta-analysis found equivalent long-term oncological outcomes of minimally invasive esophagectomy and open esophagectomy (37). The Japan Clinical Oncology Group is conducting a randomized phase III study to compare OS between thoracoscopic and open surgery for stage I-III esophageal cancer (15). This study is ongoing and should define the impact of each method on short- and long-term outcomes.

This retrospective study included inherent selection bias. Abdominal procedures and reconstruction routes varied between open and thoracoscopic surgery in actual clinical practice. However, we applied multivariate analysis to evaluate risk factors before, during and after surgery that might have influenced the occurrence of postoperative pneumonia, RLN paralysis, and survival. Furthermore, the outcomes of patients with locally advanced ESCC who undergo neoadjuvant therapy followed by surgery have not been assessed as far as we can ascertain. Therefore, our findings are important for evaluating thoracoscopic surgery for patients with locally advanced ESCC who receive neoadjuvant therapy.

In conclusion, although the surgical procedure was longer, blood loss was significantly lower during thoracoscopic, than open esophagectomy. Postoperative complications and survival were almost equivalent between thoracoscopic and open esophagectomy. Thus, thoracoscopic esophagectomy is feasible for patients with locally advanced esophageal cancer who have received neoadjuvant therapy.

Conflicts of Interest

The Authors have no commercial support or conflicts of interest to disclose in relation to this study.

Authors' Contributions

YH drafted the article. ME, YI, TK, TY, RH, MO and NK contributed to patient care. YH performed the literature search. ME, YI, and MO participated in the critical revision of the article. All the Authors read and approved the final article.

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Table VII. *Predictive factors associated with overall survival*.

Variables (preoperative factors)	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age (continuous)	1.01	0.98-1.04	0.53	–	–	–
Gender						
Female (reference)	1			1		
Male	3.59	1.44-8.97	0.01	4.40	1.72-11.24	0.002
Performance status[1]						
0 (reference)	1			1		
1	2.46	1.33-4.56	0.004	3.18	1.65-6.13	0.001
Primary tumor location						
Ut/Mt	1			–	–	–
Lt/EGJ	1.33	0.77-2.30	0.31	–	–	–
cT[2]						
1/2 (reference)	1			–	–	–
3/4	3.15	1.50-6.62	0.003	–	–	–
cN[2]						
0/1 (reference)	1			–	–	–
2/3	1.62	0.92-2.83	0.09	–	–	–
cM[2]						
0 (reference)	1			–	–	–
1	1.82	0.98-3.36	0.06	–	–	–
Neoadjuvant therapy						
Chemotherapy	1			1		
Chemoradiotherapy	2.26	1.33-3.85	0.003	3.02	1.74-5.24	<0.001
Thoracic procedure						
Open	1			–	–	–
Thoracoscopic	0.83	0.50-1.37	0.46	–	–	–
Abdominal procedure						
Open	1			–	–	–
Laparoscopy	0.60	0.19-1.92	0.39	–	–	–
Organ for reconstruction						
Stomach	1			–	–	–
Others	1.52	0.48-4.96	0.48	–	–	–
Reconstruction route						
Posterior mediastinal	1			–	–	–
Retrosternal	0.48	0.12-1.85	0.28	–	–	–
Subcutaneous	0.69	0.22-2.22	0.54	–	–	–
Lymph node dissection[3]						
Two-fields	1			–	–	–
Three-fields	1.09	0.63-1.87	0.76	–	–	–
Curability[2]						
R0/1	1			–	–	–
R2	3.91	1.41-10.79	0.01	–	–	–
Thoracic surgical duration (continuous)	1.00	1.00-1.01	0.08	–	–	–
Total surgical duration (continuous)	1.00	0.99-1.00	0.25	–	–	–
Blood loss (continuous)	1.00	1.00-1.00	0.01	–	–	–
ypT[2]						
0/1 (reference)	1			1		
2/3/4	3.62	2.04-6.42	0.01	3.91	2.18-7.01	<0.001
ypN[2]						
0 (reference)	1					
1/2/3	2.09	1.23-3.55	0.01	–	–	–
ypM[2]						
0 (reference)	1			–	–	–
1	2.07	1.02-4.21	0.04	–	–	–

CI: Confidence interval; EGJ: esophagogastric junction; HR: hazard ratio; Lt: lower third; Mt: middle third; Ut: upper third. [1]According to Eastern Cooperative Oncology Group. [2]According to TNM Classification, 7th edition (17). [3]Two-field LN dissection: thoracic and abdominal regions; Three–field LN dissection: cervical, thoracic and abdominal regions.

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