The Impact of Combined Thoracoscopic and Laparoscopic Surgery on Pulmonary Complications After Radical Esophagectomy in Patients With Resectable Esophageal Cancer

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Abstract. *Background: Pulmonary complications (PCs) after esophagectomy for patients with esophageal cancer have been correlated with prolonged hospital stays and in-hospital mortality. Previous studies have shown that minimally-invasive esophagectomy (MIE) is associated with a lower rate of PCs compared to conventional open surgery. Although PCs were reportedly associated with many factors, including surgical approaches, patients' demographics, and perioperative variables, the predictive factors for PCs including MIE, have not been fully evaluated. Patients and Methods: A total of 209 patients with resectable esophageal cancer who underwent three types of esophagectomy were included in the present study; (i) 93 cases who underwent the combined thoracoscopic MIE and laparoscopic MIE; (ii) 42 cases who underwent the combined open thoracotomy and laparoscopic MIE; (iii) 74 cases who underwent the combined open thoracotomy and open laparotomy, which were defined as the total MIE group, hybrid MIE group, and total open group, respectively. We compared clinical outcomes of the three groups and identified postoperative predictive factors of PCs using multivariate analysis. Results: The incidence of PCs was significantly reduced (p=0.015) in the total-MIE group (8/93: 8.5%) compared with the total-open group (16/74: 21.6%), but it was not significantly reduced in the hybrid MIE group (5/42: 11.9%) compared with the total open group (p=0.19). The multivariate analysis showed that the presence of cardiac comorbidity [odds ratio (OR)=5.90; p=0.013], lung comorbidity (OR=3.95; p=0.031), and anastomotic leakage (OR=6.00; p<0.01) were independent risk factors for PCs after esophagectomy. In contrast, total MIE reduced the risk of PCs (OR=0.328; p=0.036). Conclusion: The combination of thoracoscopic and laparoscopic MIE presents as an excellent surgical procedure for the reduction of PCs after esophagectomy.*

Esophagectomy accompanied by radical lymphadenectomy is a potential curative treatment for resectable esophageal cancer. Despite recent advancements in surgical procedures and perioperative management, esophagectomy is reportedly associated with high rates of morbidity and mortality (1, 2). Among various complications after esophagectomy, pulmonary complications (PCs) have been reportedly correlated with prolonged hospital stay and in-hospital mortality (1, 3, 4), and some previous studies have identified risk factors for PCs, which included advanced age, history of smoking, respiratory comorbidities, impairment of respiratory function, poor general condition and poor nutrition (4-6).

Minimally-invasive esophagectomy (MIE) has recently received a great deal of attention because of reduced surgical trauma. Some case–control studies have shown that MIE is associated with a lower rate of PCs in comparison to conventional open surgery (7, 8), whereas other reports have shown MIE is not particularly useful in the prevention of PCs after esophagectomy (9, 10). In addition, predictive factors for PCs including surgical approaches have not been completely investigated using multivariate analysis. Although many advantages of MIE have been reported, various types of MIE were included in the previous reports, such as a combination of thoracoscopic MIE and open laparotomy, combination of laparoscopic MIE and open thoracotomy, and

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combination of thoracoscopic and laparoscopic MIE. Therefore, the aim of the present study was to evaluate predictive risk factors for PCs after esophagectomy, and determine whether not only the combination of thoracoscopic and laparoscopic MIE, but also the combination of open thoracotomy and laparoscopic MIE reduces the risk of PCs using univariate and multivariate analyses.

Patients and Methods

Between April 2002 and April 2012, 349 patients with esophageal cancer were treated *via* surgical intervention at the Department of Surgical Oncology, Osaka City University Hospital, Japan. The following inclusion criteria were used in the present study: (i) patients with intra-thoracic esophageal cancer who underwent subtotal esophagectomy with radical lymphadenectomy; (ii) those who underwent esophageal replacement using a gastric conduit. The exclusion criteria were: (i) patients with esophageal cancer and another concomitant active cancer; (ii) those who received preoperative chemoradiotherapy for esophageal cancer; (iii) those with a history of laparotomy or thoracotomy; and (iv) those with clinical and pathological T4 or stage IV esophageal cancer. We excluded patients who received chemoradiotherapy because most of the patients who received chemoradiotherapy underwent open esophagectomy instead of MIE. Subsequently, we analyzed the postoperative predictive factors of PCs in the remaining 209 patients with esophageal cancer. The three types of approach included total MIE, which was the combination of video-assisted thoracoscopic surgery (VATS) and hand-assisted laparoscopic surgery (HALS), hybrid MIE which was HALS together with open thoracotomy, and the total open group which was open thoracotomy combined with open laparotomy.

Surgical procedures. In our institution, MIE procedures were introduced in April 2000. Superficial tumors without clinical lymph node metastasis (T1N0M0) during that time and more recently, advanced esophageal cancer (T2-3N0-3), have been treated *via* MIE. Regarding the patient's position during thoracoscopy, VATS was performed with 67 patients in the left lateral position between April 2000 and April 2010, and 26 patients in the prone position between May 2010 and April 2012. The MIE procedure in our institution was previously reported (11). Regarding the lymphadenectomy in the thorax, periesophageal, postmediastinal, and supradiaphragmal lymph nodes were completely dissected. Moreover, the lymph nodes around the left and right recurrent nerves in the upper thorax were then carefully dissected to preserve the nerves. Following thoracoscopy, gastric mobilization was performed *via* HALS. The thoracic and abdominal phases of open conventional esophagectomy were performed through approximately 20-cm posterolateral thoracotomy and midline laparotomy. The alimentary tract was reconstructed *via* a gastric conduit, which was extracorporeally created using an automatic linear suturing instrument. The conduit was pulled up to the neck *via* retrosternal or posterior mediastinal routes. The open and MIE procedures were standardized and performed by three general surgeons (MO, YY, and NK). Epidural analgesia was primarily administered to all patients. If the epidural analgesia was unsuccessful, patient-controlled analgesia with intravenous opioids was administered. Intraoperative anesthesiologic protocol including fluid and agents administration did not change during this period.

PCs and evaluated parameters. PCs included postoperative pneumonia, respiratory failure, and adult respiratory distress syndrome (ARDS). Respiratory failure was defined as prolonged (>3 days) ventilator management or re-intubation. Postoperative pneumonia was determined *via* radiographic evidence accompanied by fever more than 38°C. ARDS was defined according to the American–European consensus conference on ARDS (12). The level of serum C-reactive protein (CRP) from postoperative day 1 to 4 was compared between the three groups as a postoperative inflammatory marker. Histopathological staging was based on the sixth edition of the Union Internationale Contre le Cancer tumor–lymph node–metastasis (TNM) classification system (13).

Preoperative risk factors for PCs were evaluated, which included age, gender, preoperative comorbidity, respiratory function, body mass index, weight loss, use of adjuvant chemotherapy, tumor location, pathological tumor stage, concentrations of serum albumin, lymphocytes, and CRP. Intra- and postoperative variables included estimated intraoperative blood loss, surgical duration, perioperative transfusions, reconstruction route, 2- or 3-field esophagectomy, use of total or hybrid MIE. Postoperative variables included anastomotic and chyle leakage and vocal cord palsy. With regard to comorbidity, lung comorbidity included chronic obstructive pulmonary disease (COPD) and bronchial asthma, while cardiac comorbidity included coronary artery disease and congestive heart failure. All data were obtained from medical records and operative charts. Informed consent from all patients was obtained.

Statistical analysis. Continuous data are presented as means and standard deviation. The Fisher exact and Chi-square tests were used for categorical variables, whereas Student's *t*-test was used for continuous variables. A *p*-value of less than 0.05 was considered statistically significant. Variables with a *p*-value of less than 0.1 in univariate analysis were assessed *via* multivariate analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics of patients undergoing esophagectomies at our Institution. The 209 patients in this study included 173 males and 36 females. We located 22, 105, 72 and 10 tumors in the upper third, the middle third, the lower third of the thorax and the multiple areas, respectively. Regarding microscopic findings, 190, 7 and 12 patients had squamous cell carcinoma, adenocarcinoma and other types, respectively. Pathological staging of the esophageal cancers was categorized as follows: 63, 49, 39, and 58 patients were designated as stage I, IIA, IIB, and III, respectively. With regard to the surgical procedures, the total open group, hybrid MIE, and total MIE were performed in 74, 42 and 93 patients, respectively. The demographics and clinical outcomes of patients with esophageal cancer who underwent the three types of surgical procedures are listed in Tables I and II. Age, gender, performance status, the rate of patients with various comorbidities, and the placement of epidural analgesia were comparable among the three surgical groups, whereas significant differences were found in pT, pN and

Table I. *Demographics of patients undergoing three types of esophagectomy.*

Clinical variables	Total MIE (n=93)	Hybrid MIE (n=42)	Total open (n=74)
Age	64.1±8.2	65.4±9.0	62.2±7.2
Gender (male/female)	77/16	34/8	60/14
PS (0/1)	90/3	40/2	72/2
Lung comorbidity (+/−)	5/88	4/38	7/67
Cardiac comorbidity(+/−)	8/85	4/38	3/71
Tumor location (Upper/middle/lower)	12/49/27	8/21/13	3/36/34
pT1/T2/T3	67/13/13*,**	18/7/17	25/5/44
pN0/N1	46/47*	19/23	26/48
pStage I/IIA/IIB/III	38/25/21/9*,**	11/12/5/14	14/12/15/33
Pre-operative chemotherapy (+/−)	14/79*	8/34	4/70
Epidural analgesia (+/−)	85/8	40/2	70/4

MIE: Minimally invasive esophagectomy; PS: performance status; N.S.: not significant. *p<0.05 compared to the total-open group; **p<0.05 compared to the hybrid group.

Table II. *Clinical outcomes of patients undergoing three types of esophagectomy.*

	Total MIE (n=93)	Hybrid MIE (n=42)	Total open (n=74)
Operative time (min.)	579±89	556±126	557±125
Bleeding (ml)	493±394*	644±355*	1005±672
CRP value (mg/dl)			
POD1	8.3±3.4*	8.5±2.3*	10.4±4.4
POD2	15.4±6.3	16.6±6.3	16.9±6.3
POD3	11.3±6.2*	12.5±6.3	13.5±6.5
POD4	8.1±6.4*	8.8±6.8	10.4±6.5
Overall complication rate (%)	40 (46.2)	17 (40.4)	35 (47.2)
PCs (%)	8 (8.6)*	5 (11.9)	16 (21.6)
Vocal cord palsy (%)	32 (34.0)*,**	5 (11.9)	14 (22.9)
Wound complication (%)	2 (2.1)*	4 (9.5)	14 (18.9)
Anastomotic leakage (%)	6 (6.4)	4 (9.5)	7 (9.4)
Chyle leakage (%)	8 (8.6)	4 (9.5)	5 (6.7)
Conduit necrosis (%)	2 (2.1)	0	0
SIRS condition (days)	2.3±3.2*,**	3.4±3.4	3.6±3.4
ICU stay (days)	3.4±3.8	2.9±1.5	3.2±2.5
Hospital stay (days)	32.3±23*	33.0±16	40.2±23
Postoperative death (90 days) (%)	2 (2.1)	0	2 (2.7)
No. of retrieved LN in chest	30.9±14	26±13	26.7±16

CRP: C-Reactive protein; POD: postoperative day; PCs: pulmonary complications; SIRS: systematic inflammatory respiratory syndrome; ICU: intensive care unit; LN: lymph nodes; N.S.: not significant. *p<0.05 as compared to total open group; **p<0.05 compared to the hybrid group.

pStage between the total MIE and total open groups. With regard to perioperative outcomes, the volume of intraoperative blood loss was significantly reduced (p<0.01) in the total and hybrid MIE groups (493±394 ml and 644±355 ml, respectively) compared to that in the total open group (1,005±672 ml). The incidence of PCs was significantly reduced (p=0.015) in the total MIE group (8/93: 8.5%) than in the total open group (16/74: 21.6%), but it was not significantly reduced in hybrid MIE (5/42: 11.9%) compared to the total open group (p=0.19). In addition, the rate of wound complication was significantly lower (p<0.01) in the total MIE group (2/93: 2.2%) than in total open groups (14/74: 18.9%). However, the rate of postoperative vocal cord paralysis was significantly higher (p=0.019) in the total MIE group (32/94: 34%) than the total open group (14/74: 18.9%). The rate of anastomotic and chyle leakage were

Table III. *Preoperative variables stratified by pulmonary complication using univariate analysis.*

Evaluated variable	Available number	Pulmonary complication		*p*-Value
		Present (n=33)	Absent (n=176)	
Age (mean±SD)	209	66.2±8.1	62.9±8.0	0.038
Gender; n (%)				
Male	209	28 (16.2)	144	0.72
Female		5 (13.8)	31	
Body mass index	209	21.2±2.0	21.4±3.1	0.70
Body weight loss; n (%)				
Present	209	13 (22.0)	46	0.12
Absent		20 (13.3)	130	
Serum albumin (g/dl)	209	3.88±0.3	4.01±0.3	0.033
Lymphocyte count	209	1703±512	1819±675	0.35
Preopoerative CRP (mg/dl)	209	0.67±1.3	0.43±1.2	0.30
% Forced expiratory volume in 1 second				
<70	196	11 (15.2)	61	0.87
≥70		20 (16.1)	104	
Current nicotine use; n (%)				
Yes	198	27 (16.6)	135	0.30
No		4 (11.1)	32	
Lung comorbidity; n (%)				
Present	208	6 (37.5)	10	0.014
Absent		27 (14.0)	165	
Cardiac comorbidity; n (%)				
Present	208	6 (42.8)	8	<0.01
Absent		27 (13.9)	167	
Diabetes mellitus; n (%)				
Present	209	2 (13.3)	13	0.78
Absent		31 (15.9)	163	
Prior treatment; n (%)				
None	209	31(16.9)	152	0.23
Chemotherapy		2 (7.6)	24	
Tumor location; n (%)				
Upper	199	2 (9.0)	20	0.31
Middle		20 (19.0)	85	
Lower		11 (15.2)	61	
Pathological stage; n (%)				
I	209	10 (15.3)	55	0.80
IIA, IIB		13 (16.8)	77	
III		10 (18.5)	44	

Table IV. *Peri- and postoperative variables stratified by pulmonary complication using univariate analysis.*

Evaluated variable	Available number	Pulmonary complication		*p*-Value
		Present (n=33)	Absent (176)	
Type of Surgery; n (%)				
Total MIE	167	8 (8.5)	85	0.015
Total open		16 (21.6)	58	
HybridMIE	116	5 (11.9)	37	0.19
Total open		16 (21.6)	58	
Site of anastomosis; n (%)				
Neck	209	30 (16.5)	151	0.42
Intrathorax		3 (10.7)	25	
Route of reconstruction; n (%)				
Posterior mediastinum	209	30 (15.2)	167	0.36
Retrosternal		3 (25.0)	9	
Operative blood loss (ml)	209	961±779	653±485	<0.01
Operative time (minutes)	209	579±90	563±113	0.37
Transfusion; n (%)				
Yes	209	11 (35.4)	26	0.01
No		22 (14.1)	150	
Anastomotic leak; n (%)				
Yes	209	7 (50)	8	<0.01
No		26 (15.8)	168	
Chyle leak; n (%)				
Yes	209	6 (42.1)	11	0.021
No		27 (16.4)	165	
Vocal cord palsy; n (%)				
Yes	209	5 (10.2)	46	0.17
No		28 (20.7)	130	
Postoperative in-hospital death; n (%)	209	3 (8.5)	1 (0.5)	<0.01

VATS: Video-assisted thoracoscopic surgery; HALS: hand-assisted laparoscopic surgery; MIE: minimally invasive esophagectomy.

equivalent among the three surgical groups. Moreover, the incidences of overall complications and in hospital mortality were comparable among the three surgical groups. Serum CRP levels were significantly reduced in the total MIE group compared to those in the total open group on postoperative days 1, 3, and 4. The hospital stay duration was significantly shorter (p=0.035) in the total MIE group (32.3±23 days) than in the total-open group (40.2±23 days). The SIRS duration was significantly lower (p=0.03) in the total-MIE group (2.3.±3.2 days) than in the total-open group (3.6±3.4 days). Four patients (two in the total MIE and two in the total-open group) died postoperatively. Two patients died of conduit necrosis, while another two patients died of pneumonia and heart disease, respectively.

Correlations between the incidence of PCs and patients' clinicopathological features are listed in Table III. As shown in Table III, advanced age (p=0.038), low serum albumin level (p=0.033), lung comorbidity (p=0.014), and cardiac comorbidity (p<0.01) were risk factors for PCs, as determined by univariate analysis. However, clinical stage was not significantly associated (p=0.80) with the occurrence rate of PCs. Correlations between PCs and intra- or postoperative variables are shown in Table IV. The rate of PCs was significantly lower in the total MIE group than in the total open group (p=0.015). However, no significant differences in the rate of PCs were found between the hybrid MIE group and the total open group (p=0.19). Use of perioperative transfusions (p=0.01) and anastomotic and chyle leakage

Table V. *Multivariate analysis of pulmonary complication after esophagectomy.*

Evaluated variable	Odds ratio	95% CI	*p*-Value
Age (years)			
<75	1.0	0.55-7.48	0.28
≥75	2.03		
Serum albumin (g/dl)			
≥3.5	1.0	0.63-8.23	0.21
<3.5	2.28		
Lung comorbidity			
Yes	3.95	1.13-13.7	0.031
No	1.0		
Cardiac comorbidity			
Yes	5.90	1.45-23.9	0.013
No	1.0		
Type of surgery			
Total MIE	0.328	0.11-0.92	0.036
Total open, hybrid MIE	1.0		
Blood loss (ml)			
≥1000	1.70	0.59-4.89	0.32
<1000	1.0		
Transfusion			
Yes	1.51	0.53-4.29	0.43
No	1.0		
Anastomotic leakage			
Yes	6.00	1.65-21.7	<0.01
No	1.0		
Chyle leakage			
Yes	3.32	0.93-11.7	0.063
No	1.0		

VATS: Video-assisted thoracoscopic surgery; HALS: hand-assisted laparoscopic surgery; MIE: minimally invasive esophagectomy; CI: confidence interval.

($p<0.01$ and $p=0.021$, respectively) was a predictive risk factor for PCs, as determined *via* univariate analysis.

The results of stepwise logistic regression and multivariate analysis are shown in Table V. The presence of cardiac comorbidity [odds ratio (OR)=5.90; 95% confidence interval (CI)=1.45-23.9; $p=0.013$], presence of lung comorbidity (OR=3.95; 95% CI=1.13-13.7; $p=0.031$), and anastomotic leakage (OR=6.00; 95% CI=1.65-21.7; $p<0.01$) were independent risk factors for PCs. In contrast, total MIE reduced the risk of PCs (OR=0.328; 95% CI=0.11-0.92; $p=0.036$).

Discussion

MIE is considered a useful surgical modality because it is associated with a decrease in postoperative respiratory complications, less intraoperative blood loss and surgical stress, and shorter hospital stay in comparison to open procedures (14, 15). In the present study, the incidence of PCs and wound complication was significantly reduced in the total MIE group compared to the total open group. The volume of intraoperative blood loss and serum CRP level on postoperative days 1, 3, and 4 were significantly reduced in the total MIE group compared with the total open group. The duration of SIRS and hospital stay was significantly shorter in the total MIE group than that in the total open group. These findings suggested that total MIE seemed to potentially be a less invasive procedure and had a lower rate of PCs after esophagectomy in comparison to the total open procedure. Subsequently, we evaluated predictive risk factors for PCs after esophagectomy by various surgical approaches including MIE using multivariate analysis. The analysis demonstrated that the total MIE was an independent inverse predictive factor for PCs after esophagectomy. Although to the best of our knowledge, three previous reports have used multivariate analysis to assess risk factors for PCs among patients who underwent esophagectomy by the open and MIE approach, the results of these reports were controversial. Two reports (6, 16) showed that MIE did not reduce the overall risk for PCs, whereas the other report demonstrated that MIE reduced the risk for PCs (17). One explanation for the discrepancy of the results between these studies may be correlated with the definition of MIE. In the two reports that showed no significant correlation between MIE and the reduction of PCs, MIE included both hybrid and total MIE, while our study and the report by Kinjo *et al*. (17) that showed a significant correlation between MIE and the reduction of PCs included only total MIE. In the present study, hybrid MIE had no significant impact on the reduction of PCs after esophagectomy, whereas total MIE significantly reduced the risk of PCs ($p=0.036$). Recently, the first randomized trial that compared open and minimally-invasive esophagectomy in patients with esophageal cancer, including combined prone thoracoscopy and laparoscopic esophagectomy, was published (18). The rate of PCs in the present report was significantly lower in the MIE group than in the open esophagectomy group. This result also supported the hypothesis that a combined VATS and HALS procedure may reduce the rate of PCs.

Our present multivariate analysis showed that the presence of lung and cardiac comorbidity were independent risk factors for PCs. Previous studies demonstrated lung and cardiac comorbidity were closely associated with high mortality and morbidity after esophagectomy (5, 19, 20). Therefore, total MIE should be conducted for patients with these risk factors to reduce the risk for PCs after esophagectomy. Moreover, these patients may require more intensive postoperative care. Anastomotic leakage was also closely associated with the incidence of PCs in the present study. Anastomotic leakage could result in extended SIRS duration and attenuation of immune defenses after esophagectomy, subsequently resulting in the incidence of respiratory failure and ARDS (1, 21). Therefore, prevention of anastomotic leakage presents a useful strategy to reduce the incidence of PCs after esophagectomy.

However, our study had some limitations. This was a retrospective and non-randomized study at a single Institution. In addition, heterogeneity of the disease stage was observed in the population of patients who underwent MIE and the total open group. At our Institution, MIE was performed in 2000, during which patients with early-stage esophageal cancer were chosen as candidates for MIE. Recently, patients with more advanced diseases have also been indicated for MIE. In the present study, univariate and multivariate analyses revealed that the total MIE significantly reduced the incidence of PCs, although the stage of esophageal cancer was not a significant risk factor for PCs. These findings suggested that multivariate analysis may have overcome the population bias of patients with different stages of diseases.

In conclusion, the presence of lung and cardiac comorbidities, and anastomotic leakage were independent risk factors for PCs after esophagectomy, as determined using multivariate analysis. In contrast, combined VATS and HALS reduced the risk for PCs after esophagectomy. Therefore, total MIE is a potentially excellent surgical method to reduce the incidence of postoperative PCs.

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