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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Long-Term Outcomes of Thoracoscopic Esophagectomy in the Prone versus Lateral Position: A Propensity Score-Matched Analysis

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ABSTRACT

Background. Several studies have suggested that thoracoscopic esophagectomy (TE) in the prone position (TEP) may be more feasible than TE in the lateral position (TEL); however, few studies have compared long-term survival between the two procedures. We evaluated whether TEP is oncologically equivalent to TEL.

Methods. Surgical outcomes of TEs performed from January 2006 to December 2013 at our hospital were retrospectively analyzed. Propensity score matching was used to control for confounding factors.

Results. TE was performed in 200 patients diagnosed with esophageal squamous cell carcinoma; 78 patients were matched in two procedures. The mean thoracic operative time in TEL was shorter than in TEP (228.9 min vs. 299.1 min; $p < 0.001$); however, the mean thoracic blood loss in TEL was higher than in TEP (186.9 ml vs. 76.5 ml; $p < 0.001$). The mean number of thoracic lymph nodes harvested in TEL was lower than in TEP (23.5 vs. 26.9; $p < 0.05$), and the pulmonary complication rate in TEL was higher than in TEP (30.8% vs. 15.4%; $p < 0.05$). The 5-year overall survival rates in pathological stage I (81.2% vs. 81.6%; $p = 0.82$), stage II (65.3% vs. 80.9%; $p = 0.21$), stage III (26.7% vs. 24.2%; $p = 0.86$) and all stages (63.6% vs. 62.3%; $p = 0.88$), and the 5-year progression-free survival rates in pathological stage I (78.0% vs. 81.8%; $p = 0.54$), stage II (53.5% vs. 77.6%; $p = 0.13$), stage III (10.5% vs. 12.8%; $p = 0.81$) and all stages (53.6% vs. 57.9%; $p = 0.50$) were not significantly different between the two procedures.

Conclusion. TEP and TEL provide equal oncological efficiency.

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BACKGROUND

Patients can be placed in several positions during minimally invasive esophagectomy (MIE) for esophageal cancer. Currently, thoracoscopic esophagectomy (TE) in the left lateral decubitus position (TEL)[1–5] and TE in the prone position (TEP)[6–11] are frequently used. However, large-scale studies and meta-analyses that compare conventional open esophagectomy and MIE for esophageal cancer do not distinguish between TEL and TEP.[12–17] TEL and TEP differ not only in patient position during surgery but they are also based on different surgical concepts. Whether these two procedures have equivalent surgical outcomes requires evaluation.

TEL for esophageal cancer was first reported in 1992.[1] The rate of pulmonary complications with TEL was reported to be similar or lower than the rate with open esophagectomy. Long-term survival of open esophagectomy and TEL were reported to be equivalent.[2–5] TEP was first reported in 1994,[6] and was reported to result in a lower incidence of pulmonary infection and equivalent or better long-term survival than open esophagectomy.[7–11]

Several studies have suggested that TEP might be a more practical and promising procedure than TEL, with less blood loss, fewer pulmonary complications, and increased lymph node harvest.[18–24] Therefore, for thoracic esophageal cancer, we have shifted from conventional open esophagectomy to TEL, and then from TEL to TEP. We previously reported that TEP improves postoperative oxygenation compared with TEL;[25] however, there are few reports comparing the long-term survival of TEL versus TEP.[26,27] In this study, we evaluated whether TEP is oncologically equivalent to TEL, comparing the long-term survival of patients who have undergone either of these two procedures.

METHODS

Surgical outcomes, including long-term survival, in patients who underwent MIE from January 2006 to December 2013 at Kobe University Hospital were retrospectively analyzed using a prospectively constructed database. Patients were classified according to the TNM classification of malignant tumors (7th edition).[28] We introduced TEL during 2007–2012 and TEP in 2010. From January 2006 to December 2013, 263 patients underwent esophagectomy at our hospital, of whom 248 underwent MIE. Of these 248 patients, using the database we identified 200 patients who were diagnosed with squamous cell carcinoma in the thoracic esophagus with clinical T1–3, N0–3, M0 disease.

The primary endpoints were the 5-year overall survival (OS) and progression-free survival (PFS) rates, while the secondary endpoints were operative time for the thoracic part of the procedure, blood loss during the thoracic part of the procedure, number of lymph nodes harvested during the thoracic part of the procedure, postoperative mortality, and postoperative morbidity.

Propensity score matching was used to control for confounding factors (age, sex, clinical T stage, clinical N stage, and neoadjuvant chemotherapy status). Clinical TNM staging was performed before treatment with computed tomography (CT), positron emission tomography/CT, and esophagogastroduodenoscopy (EGD).

In general, surgery was considered for patients with resectable esophageal cancer.[29] Patients diagnosed with clinical stage IB–III disease underwent neoadjuvant chemotherapy consisting of two courses of fluorouracil and cisplatin, the standard treatment in Japan.[30] Patients diagnosed with clinical stage IA disease before surgery but diagnosed with pathological stage IB–III disease after surgery underwent adjuvant chemotherapy (two courses of fluorouracil and cisplatin).[31] Informed consent was obtained from all patients. This retrospective study was approved by the Ethics Committee of Kobe University Hospital, and the experimental protocols met the guidelines for clinical research at Kobe University.

Surgical Procedures

For TEL, general anesthesia was initiated in the supine position with a double-lumen endotracheal tube. Patients were then placed in the left lateral decubitus position. The thoracic procedure was performed under one-lung ventilation without carbon dioxide insufflation. Access ports were inserted at the posterior axillary line in the fourth, sixth, and ninth intercostal spaces, and at the midaxillary line in the fourth, fifth, and ninth intercostal spaces.

For TEP, general anesthesia was performed in the supine position with a single-lumen endotracheal tube and balloon blocker. Patients were then placed in the prone position. The thoracic procedure was performed under one-lung ventilation with the balloon blocker insufflated with carbon dioxide at 8 mmHg to collapse the right lung. Access ports were inserted at the posterior axillary line in the third, fifth, seventh, and ninth intercostal spaces, and at the midaxillary line in the sixth and eighth intercostal spaces.

Esophagectomy and lymph node dissection were performed during the thoracic procedure. Lymphadenectomy along the recurrent laryngeal nerves in TEP was performed as previously described.[32–35] After the thoracic procedure, double-lung ventilation was resumed and patients were placed in the supine position. The gastric conduit was constructed with laparoscopic-assisted surgery during the abdominal procedure. The gastric conduit was pulled up via the retromediastinal, retrosternal, or subcutaneous route, and the anastomosis was created in the cervix (McKeown esophagectomy).[36] Reconstruction of the esophagus was performed with a pedicled jejunal flap or ileocolic conduit if the stomach was unavailable for reconstruction.

These 200 cases of esophagectomy were performed by four surgeons. Two surgeons experienced the open esophagectomy, TEL and TEP, but the other two surgeons experienced almost TEP only. All cases were supervised by two experienced surgeons.

Postoperative Treatment

All patients were admitted to an intensive care unit after surgery for 4 days. Extubation was performed on postoperative day (POD) 1. Oral food intake was resumed around

POD 7, after evaluation of swallowing and recurrent laryngeal nerve function with laryngoscopy. Mortality was defined as postoperative death within 90 days after surgery, and morbidity was defined as a postoperative complication with Clavien–Dindo (CD) grade II or higher.[37] Assessment of disease recurrence was performed with CT every 6 months and EGD annually for 5 years after surgery. Recurrence patterns were classified as lymphatic, hematogenous, or disseminated. Patients with recurrence underwent additional treatment based on the location of the recurrence.

Statistical Analysis

JMP version 10 (SAS Institute Inc., Cary, NC, USA) and R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. Propensity scores were calculated using logistic regression, with procedure (TEL or TEP) as the dependent variable and five variables (age, sex, clinical T stage, clinical N stage, and neoadjuvant chemotherapy) as the covariates. Patients were matched based on propensity scores using the 1:1 nearest neighbor algorithm. Differences between the two groups were compared using the *t* test, Wilcoxon signed-rank test, or Fisher's exact test. Long-term survival of the two groups was assessed using the Kaplan–Meier method and compared using the log-rank test. Statistical significance was set at 0.05.

RESULTS

From January 2006 to December 2013, 200 patients diagnosed with squamous cell carcinoma in the thoracic esophagus (upper thoracic, mid thoracic, and lower thoracic regions) with clinical T1–3, N0–3, M0 disease underwent MIE at Kobe University Hospital. TEL was performed in 80 patients (lateral group), while the remaining 120 patients underwent TEP (prone group). Propensity score matching resulted in 78 pairs of patients.

Table 1 shows the clinical characteristics of the two groups before and after matching. There were no significant differences in age, sex, tumor location, clinical T stage, clinical N stage, clinical stage, and neoadjuvant chemotherapy status before matching. The covariates in the two groups were adjusted after matching.

Table 2 shows the surgical outcomes of the two groups before and after matching. The mean operative time of the thoracic procedure in the lateral group was shorter than in the prone group after matching (lateral group vs. prone group: 228.9 min vs. 299.1 min; $p < 0.001$); however, mean blood loss during the thoracic procedure in the lateral group was higher than in the prone group after matching (186.9 ml vs. 76.5 ml; $p < 0.001$). The mean number of lymph nodes harvested during the thoracic procedure in the lateral group was lower than in the prone group after matching (23.5 vs. 26.9; $p < 0.05$). The two groups had a similar number of open conversions ($p = 0.37$). Four patients in the lateral group underwent open conversion because of massive adhesions, and one patient in the prone group underwent open conversion because of bleeding.

The mortality rate was similar in the two groups. In the lateral group, two patients died from pneumonia and one patient died from gastric conduit necrosis, while in the prone group, one patient each died from cerebral infarction and anastomosis leakage. The postoperative pulmonary complication rate (pneumonia and atelectasis with antibiotics) was higher in the lateral group than in the prone group after matching (30.8% vs. 15.4%; $p < 0.05$). The rates for other complications and reoperation were not significantly different between the two groups ($p = 0.68$). In the lateral group, one patient each underwent reoperation due to gastric conduit necrosis and anastomosis leakage, while six patients in the prone group underwent reoperation. Three patients underwent reoperation due to anastomosis leakage. The other reasons for reoperation were ileus, chylothorax, and hiatal hernia. Postoperative stay and pathological staging were not significantly different between the two groups.

Figure 1 shows long-term survival before and after matching. The median length of follow-up for all patients was 74.3 months (range 1.2–122.3) in the lateral group and 56.6 months (range 1.9–102.5) in the prone group. The 5-year OS rates of the two groups were similar after matching (lateral group vs. prone group: 63.6% vs. 62.3%; $p = 0.88$). Figure 2 shows OS in pathological stages I, II, and III. The 5-year OS rates of the two groups in pathological stages I, II, and III were similar after matching (Table 2), as were the 5-year PFS rates of the two groups (53.6% vs. 57.9%; $p = 0.50$). Figure 3 shows PFS in pathological stages I, II, and III. The 5-year PFS rates of the two groups in pathological stages I, II, and III were similar after matching (Table 2). The pattern of recurrence was not significantly different between the two groups (Table 2).

DISCUSSION

In this study, we compared surgical outcomes, including long-term survival, between TEL and TEP. We used a propensity score-matched analysis to control for confounding factors, unlike previous studies.[26,27]

Reduced blood loss in the prone group may have been due to suppression of venous flow and capillary oozing with carbon dioxide insufflation, while the lower rate of

TABLE 1 Clinical characteristics

	Before matching		p value	After matching		p value
	Lateral group (n = 80)	Prone group (n = 120)		Lateral group (n = 78)	Prone group (n = 78)	
Age, years[a]	65.6	65.9	0.83	65.7	65.9	0.86
Sex[a]						
Male	61	103	0.09	61	62	1.0
Female	19	17		17	16	
Body mass index, kg/m^2	21.1	21.0	0.87	21.0	20.6	0.62
Serum albumin, g/dl	3.88	3.97	0.21	3.87	3.95	0.27
Hypertension						
Yes	24	52	0.07	24	37	0.07
No						
Diabetes						
Yes	10	18	0.68	10	11	1.0
No						
Smoking history						
Yes	58	100	0.08	58	62	0.56
No						
Tumor location						
Ut	13	25	0.26	13	13	0.49
Mt	43	50		42	35	
Lt	24	45		23	30	
Clinical T stage[a]						
T1	37	48	0.49	36	36	0.88
T2	10	22		10	8	
T3	33	50		32	34	
Clinical N stage[a]						
N0	42	53	0.40	41	38	0.89
N1	30	57		30	32	
N2	8	10		7	8	
Clinical stage						
IA	31	34	0.54	30	30	0.96
IB	6	10		6	3	
IIA	5	9		5	5	
IIB	10	25		10	11	
IIIA	20	33		20	21	
IIIB	8	9		7	8	
IIIC	0	0		0	0	
Neoadjuvant chemotherapy[a]						
Yes	41	78	0.06	41	42	1.0
No	39	42		37	36	

Ut upper thoracic, *Mt* mid thoracic, *Lt* lower thoracic

[a]Covariates used for propensity score matching analysis

TABLE 2 Surgical outcomes

	Before matching		*p* value	After matching		*p* value
	Lateral group (n = 80)	Prone group (n = 120)		Lateral group (n = 78)	Prone group (n = 78)	
Operative time (min)						
Total	604.2	695.7	< 0.001	605.7	703.7	< 0.001
Chest part	227.8	295.5	< 0.001	228.9	299.1	< 0.001
Blood loss, ml						
Total	574.3	436.2	0.03	580.4	471	0.28
Chest part	188.1	74.5	< 0.001	186.9	76.5	< 0.001
Open conversion	4	1	0.08	4	1	0.37
Lymph node harvest						
Chest and abdominal part	38.6	44.6	0.009	38.1	44.2	0.014
Chest part	23.7	26.7	0.048	23.5	26.9	0.039
Upper mediastinum	10.5	11.0	0.59	10.3	10.8	0.50
Middle mediastinum	9.9	11.4	0.13	9.9	11.4	0.14
Lower mediastinum	3.3	4.3	0.12	3.3	4.7	0.10
Abdominal procedure						
Open	25	37	1.0	25	28	0.61
Laparoscopic assist	55	83		53	49	
Reconstruction						
Gastric conduit	74	109	0.80	72	67	0.61
Others	6	11		6	11	
Postoperative stay, days	44.0	51.4	0.21	44.5	52.6	0.22
Mortality	2	2	1.0	2	1	1.0
Morbidity						
Pulmonary complications	24	20	0.036	24	12	0.036
Recurrent nerve paralysis	10	22	0.33	10	13	0.65
Anastomosis leak	6	11	0.80	6	5	1.0
Reoperation	2	5	0.70	2	4	0.68
Pathological stage						
0	1	3	0.28	1	0	0.90
IA	29	36		29	26	
IB	3	3		3	2	
IIA	13	11		12	8	
IIB	14	31		13	15	
IIIA	7	12		7	7	
IIIB	4	9		4	7	
IIIC	8	13		8	12	
IV	1	2		1	1	
R0 resection	76	113	1.0	74	73	1.0
Adjuvant chemotherapy	4	8	0.77	3	7	0.33
OS at 5 years, %						
All stages	64.5	62.7	0.81	63.6	62.3	0.88
pStage I	81.2	78.9	0.95	81.2	81.6	0.82
pStage II	67.8	77.3	0.29	65.3	80.7	0.21
pStage III	26.7	27.2	0.72	26.7	24.2	0.86

TABLE 2 continued

	Before matching		*p* value	After matching		*p* value
	Lateral group (*n* = 80)	Prone group (*n* = 120)		Lateral group (*n* = 78)	Prone group (*n* = 78)	
PFS at 5 years, %						
All stages	54.7	57.6	0.55	53.6	57.9	0.50
pStage I	78.0	79.5	0.59	78.0	81.8	0.54
pStage II	56.6	70.8	0.28	53.5	77.6	0.13
pStage III	10.5	16.0	0.84	10.5	12.8	0.81
Recurrence						
Local	3	2	0.39	3	1	0.62
Lymphatic	12	17	1.0	11	12	1.0
Hematogenous	13	13	0.29	13	10	0.65
Dissemination	0	3	0.28	0	2	0.49

OS overall survival, *PFS* progression-free survival

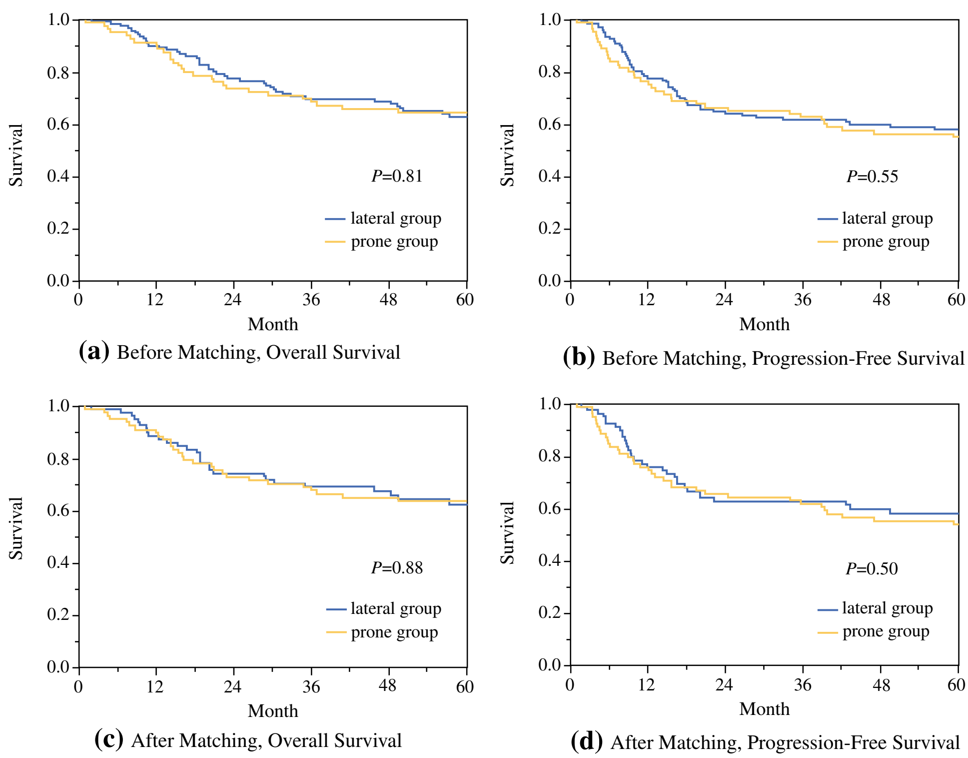

FIG. 1 Kaplan–Meier **a** OS and **b** PFS curves for the lateral and prone groups before matching. Kaplan–Meier **c** OS and **d** PFS curves for the lateral and prone groups after matching. *OS* overall survival, *PFS* progression-free survival

postoperative pulmonary complications in the prone group might have been due to improved oxygenation in the prone position, resulting from increased functional residual capacity and uniformly distributed lung perfusion. In addition, there was less atelectasis in the prone position due to postural drainage. Lung maneuvering was not necessary because of carbon dioxide insufflation.[25,38–41]

Regarding the increased number of dissected lymph nodes in the prone group, lymphadenectomy could be performed with a good operative view in the prone position. There were three reasons for the good operative view. First, the esophagus and other structures in the posterior mediastinum fell and the mediastinum was extended due to gravity, while the right lung fell due to carbon dioxide insufflation. Second, intraoperative bleeding and exudate

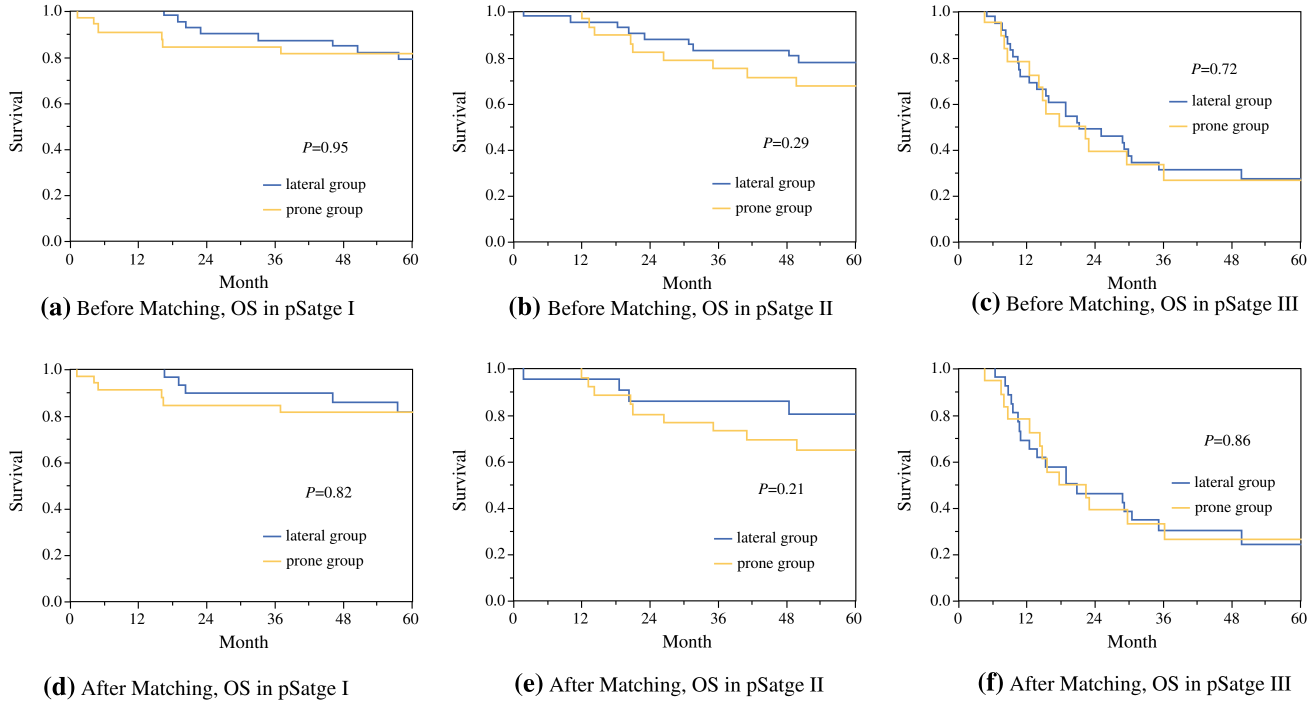

FIG. 2 **a** Kaplan–Meier OS curves in **a** pathological stage I, **b** pathological stage II, and **c** pathological stage III for the lateral and prone groups before matching. Kaplan–Meier OS curves in **d** pathological stage I, **e** pathological stage II, and **f** pathological stage III for the lateral and prone groups after matching. *OS* overall survival

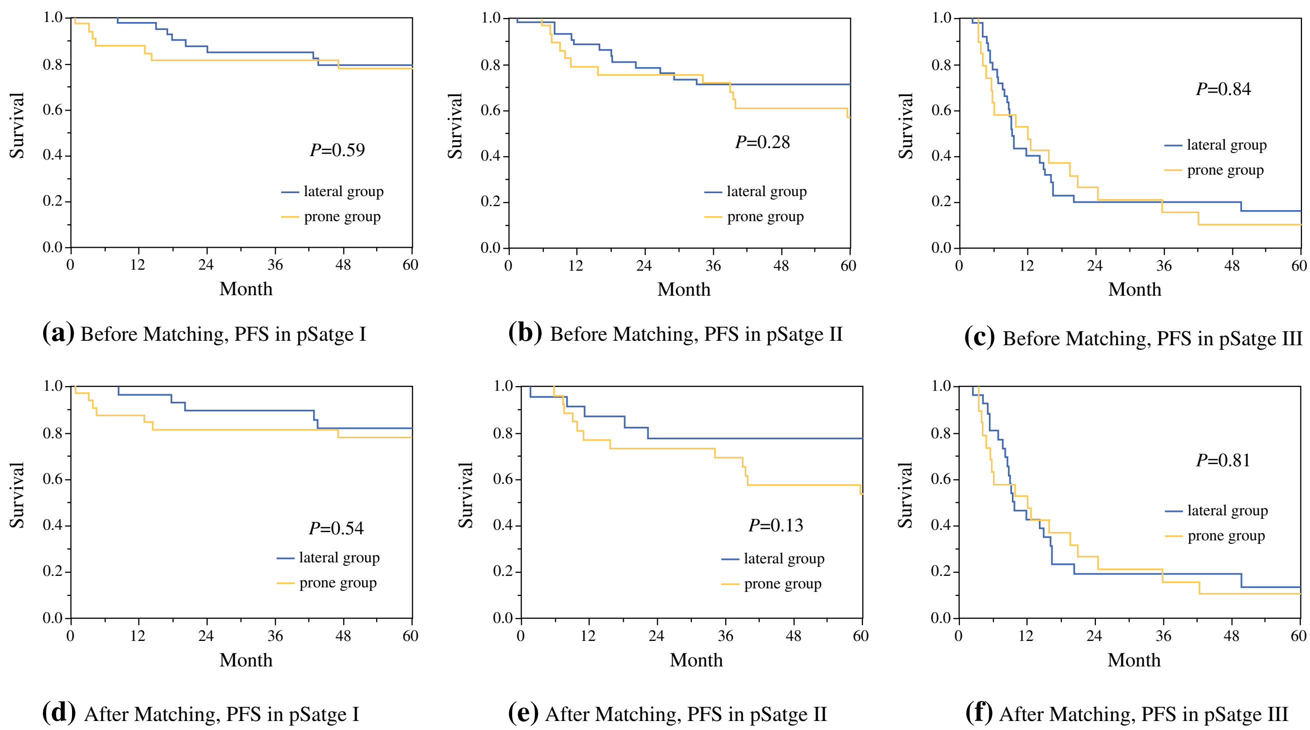

FIG. 3 Kaplan–Meier PFS curves in **a** pathological stage I, **b** pathological stage II, and **c** pathological stage III for the lateral and prone groups before matching. Kaplan–Meier PFS curves in **a** pathological stage I, **e** pathological stage II, and **f** pathological stage III for the lateral and prone groups after matching. *PFS* progression-free survival

did not pool in the mediastinum in the prone position, and, third, bleeding was suppressed by carbon dioxide insufflation.

Nonetheless, in this study, operative time was higher for the prone group. Some previous studies have reported a shorter operative time for TEP than for TEL;[18,20,22] however, there were fewer dissected lymph nodes in those studies. One study reported that more than 20 lymph nodes were dissected during the thoracic procedure, which was similar to the number in the present study;[19] that study reported a longer operative time for TEP versus TEL. Radical lymph node dissection in the mediastinum with TEP may currently require more operative time;[19] reducing TEP operative time is part of the agenda for the future. It took a long time to standardize procedures during TEP[27,42] because the operative view in the prone position is different from the operative view in conventional open esophagectomy.

The short-term surgical outcome results in this study were almost similar to the results of a meta-analysis published in 2015,[24] however, TEP is oncologically equivalent to TEL. Some possible reasons for this are that there was a sufficient number of dissected lymph nodes (more than 30) in each group,[43] and neoadjuvant or adjuvant chemotherapy was performed in almost all patients with advanced esophageal cancer.[30,31] In studies evaluating the long-term survival of MIE including TEL and TEP, it was not necessary to distinguish between TEL and TEP; however, it is necessary to distinguish between TEL and TEP in order to evaluate the short-term surgical outcomes of MIE.

This study had several limitations. First, this was not a prospective study and further studies are necessary. Second, we analyzed McKeown esophagectomy for esophageal squamous cell carcinoma; this study did not include Ivor–Lewis esophagectomy or transhiatal esophagectomy for esophageal adenocarcinoma.[44,45] Third, it was difficult to evaluate the influence of the learning curve because each surgeon had a different experience of surgery.

CONCLUSIONS

TEP extended operation time but reduced blood loss and pulmonary complication and increased lymph node harvest compared with TEL. In addition, TEP provides equal oncological efficiency compared with TEL.

DISCLOSURES Susumu Miura, Tetsu Nakamura, Yukiko Miura, Gosuke Takiguchi, Nobuhisa Takase, Hiroshi Hasegawa, Masashi Yamamoto, Shingo Kanaji, Yoshiko Matsuda, Kimihiro Yamashita, Takeru Matsuda, Taro Oshikiri, Satoshi Suzuki, and Yoshihiro Kakeji have no commercial interests in the study subject to disclose.

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