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Low invasiveness of thoracoscopic esophagectomy in the prone position for esophageal cancer: a propensity score-matched comparison of operative approaches between thoracoscopic and open esophagectomy

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Abstract

Background In this study, cytokine levels, outcome, and survival rates after esophagectomy for esophageal cancer were retrospectively investigated in a propensity score-matched comparison of operative approaches between the thoracoscopic esophagectomy (TE) in the prone position and open esophagectomy (OE).

Patients and Methods Between 2005 and 2014, TE was performed on a group of 85 patients, which was compared with a group of 104 OE cases. Eventually, 65 paired cases were matched using propensity score matching.

Results Although the TE group underwent a significantly longer operation time than the OE group ($P<0.001$), the TE group exhibited less blood loss ($P<0.001$) and had a shorter postoperative hospital stay ($P=0.038$) than the OE group. The serum interleukin-6 levels on ICU admission ($P<0.001$) and on POD 1 ($P<0.001$) were significantly lower in the TE group. The interleukin-10 levels on ICU admission ($P<0.001$), POD 1 ($P=0.016$), and POD 3 ($P<0.001$) were also significantly lower in the TE group. Pulmonary complication was significantly lower in the TE group ($P=0.043$). The 5-year PFS rates in the TE and OE groups were 70.6 and 58.7% ($P=0.328$), respectively, and OS rates were 64.9 and 50.2% ($P=0.101$), respectively.

Conclusion TE compared to OE is a less invasive procedure with lower surgical stress and less pulmonary complication for the treatment of esophageal squamous cell carcinoma.

Keywords Esophageal cancer · Minimally invasive surgery · Cytokines · Surgical stress · Prone position

The incidence of esophageal cancer has been increasing in Japan; there were 23,119 new cases diagnosed in the year 2011, and 11,543 secondary deaths in 2013, which accounted for 3.2% of all cancer deaths in that year [1].

Surgery is a common treatment modality for esophageal cancer, but it can be one of the most invasive procedures among digestive disease surgeries. It is also associated with a high morbidity/mortality rate, along with a poor prognosis [2, 3].

The thoracoscopic esophagectomy (TE) in the prone position has been investigated as a morbidity-reducing strategy [4]. Randomized control trials demonstrated lower morbidity with TE than with open esophagectomy (OE) [5–7]. Two additional randomized control trials are currently in progress [8, 9] to elucidate the potential advantages of TE over OE, such as a decrease in major postoperative complications, an increase in quality of life, and the cost-effectiveness of the procedure. Retrospective and meta-analysis studies have revealed clear advantages of TE in terms of clinical outcomes such as shorter hospital stays, lower incidence of respiratory complications, and lower overall morbidity [10, 11].

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Theoretically, TE offers advantages over conventional OE, and preliminarily studies have shown it to provide benefits with regard to perioperative outcomes. Nevertheless, the long-term outcomes and surgical stress associated with TE, in comparison to OE, have not been appropriately studied, especially for esophageal squamous cell carcinoma (ESCC).

In the present study, outcomes, IL-6 and IL-10 levels, and survival rates following esophagectomy for esophageal squamous cell carcinoma were investigated, retrospectively, by a propensity score-matched comparison of operative approaches.

Materials and methods

Patients

Between 2005 and 2014, TE was performed on a group of 85 patients, which was compared with a group of 104 cases of OE. All patients underwent esophagogastroduodenoscopy and were given a diagnosis of pathologic disease. All patients had squamous cell carcinoma. Imaging examinations, thoracoabdominal-enhanced computed tomography, upper gastrointestinal series, and positron emission tomography were used to determine the clinical stage. For patients with a diagnosis of clinical stage II or more advanced disease, neoadjuvant chemotherapy was performed. The treatment was determined by a multidisciplinary team. Before 2008, all cases underwent OE. We started TE in a prone position in 2008 for patients with clinically UICC Stage 0–I esophageal cancer. From 2010, TE was expanded for patients with advanced cancer such as UICC Stage II–IV. During the observation period, little change was seen in perioperative management such as nutritional control, use of antibiotics and steroids, rehabilitation, and regimens of chemotherapy.

The study protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. This study protocol was approved by the Institutional Review Board for the Use of Human Subjects at the Yamaguchi University School of Medicine, and written informed consent was obtained from all patients prior to their entry into this study.

Preoperative management

Patients were admitted 1 week prior to surgery and were instructed to stop smoking. IMPACT® (AJINOMOTO, Tokyo, Japan) was administered for preoperative oral immunonutrition, and preoperative respiratory muscle training was performed with Souffle® (POLA Pharma, Tokyo, Japan) for 1 week prior to surgery.

Operative technique

Two thoracic epidural catheters were placed at the T4–T5 and T8–T9 levels prior to the administration of general anesthesia.

We performed a three-field esophagectomy with an anastomosis in the neck, and started with the thoracic component. During the thoracic component, one-lung ventilation was performed with a double-lumen endotracheal tube. An open esophagectomy was performed through an antero-lateral right thoracotomy preserving the latissimus dorsi muscle in the left decubitus position with the help of thoracoscopy, and mobilization of the esophagus and a mediastinal lymphadenectomy were then carried out. TE was performed in a similar manner to that reported by Noshiro et al. [12] Right thoracoscopic access was obtained and four trocars were placed using a transitory CO_2 pneumothorax (6 mmHg) in the prone position. Esophageal mobilization and a mediastinal lymphadenectomy were then performed.

Once the thoracic component of the esophagectomy was completed, the double-lumen endotracheal tube was replaced with a single-lumen endotracheal tube for normal ventilation. A gastric conduit was constructed, and a perigastric lymphadenectomy was performed in the supine position. Hand-assisted laparoscopic surgery was usually used in TE.

A cervical end-to-side anastomosis was then performed using a circular stapler. A hand-sewn anastomosis was carried out unless a stapled anastomosis was considered to be safer, e.g., if the cervical esophagus was too small or too short to insert the anvil head. In the case of upper thoracic esophageal cancer, or the right or left recurrent nerve lymph node being diagnosed as metastatic in intraoperative consultation, a cervical lymphadenectomy was also performed.

Perioperative management

The extubation criteria were as follows: partial pressure of arterial oxygen (PaO_2) > 100 mmHg, with the fraction of inspired oxygen (FiO_2) at 0.4, and no radiographic or bronchoscopic findings. As a prophylactic, 1 g of cefazolin was given 30 min prior to surgery, followed by 1 g every 3 h during surgery, and every 12 h postoperatively for 3–5 days. Gabexate mesilate was administrated routinely for 3–5 days, and no steroids were used during the perioperative period to protect against systemic inflammatory response syndrome. Epidural anesthesia was used for 5–7 days. Continuous enteral feeding through a jejunostomy was started 6 h after the operation at a rate of 10 kcal/h (1 kcal/ml), and the dose was escalated by 10 kcal every day up to a maximum of 2000 kcal.

Postoperative complications

Postoperative respiratory failure, pneumonia, acute respiratory distress syndrome (ARDS), and atelectasis were all classified simply as postoperative pulmonary complications. These pulmonary complications were diagnosed based on rhonchus, lung radiographic findings, deterioration of neutrophil count, C-reactive protein (CRP), PaO_2/FiO_2 ratio, positive active surveillance culture, and/or sputum on bronchoscopic findings. Surgical site infection (SSI) included any superficial incisional, deep incisional, or organ/space site infection according to the CDC definition [13]. Anastomotic leakage was diagnosed by saliva leakage through the neck wound or upper gastrointestinal series. In every case of anastomotic leakage, a diagnosis of SSI was made. We regarded postoperative hoarseness as indicative of recurrent laryngeal nerve paralysis. Gastric conduit necrosis was diagnosed by esophagogastroduodenoscopy. Chylothorax was diagnosed by milky drainage. Cerebral infarction was diagnosed by a neurosurgeon, and any associated arrhythmia was diagnosed by a cardiologist.

Blood samples

White blood cell (WBC) count, neutrophil count, CRP, platelets, Serum IL-6, and Serum IL-10 were analyzed on ICU admission, POD 1 and POD 3. Blood samples for measuring cytokine levels were collected in tubes with EDTA, separated by centrifugation (3000 rpm for 10 min at room temperature), aliquoted into microtubes, and stored at − 80 °C until the cytokine assay. Serum levels of IL-6 and IL-10 were measured using ELISA kits (Invitrogen, CA, USA) according to the manufacturer's instructions.

Data collection and statistical analysis

Clinical data for all cases were collected from the prospectively maintained database at our institution. The pathologic classification was made according to the Union for International Cancer Control esophageal cancer TNM (tumor-node metastasis) staging system (7th edition). Postoperative follow-up comprised physical examination, blood examination, and computed tomography every 3 months. Forty of the 130 patients (30.8%) achieved 5 years of follow-up. Fifty-eight of the 130 patients (44.6%) received adjuvant treatment and no discrepancies in adjuvant treatment were seen between groups.

Statistical analyses were performed according to the intent-to-treat principle. To compensate for potential differences in the characteristics of patients between the 2 groups, the method of propensity score matching was used. By using a logistic regression model, which included variables such as age, gender, ASA-PS, pTNM (pathologic), propensity scores were computed as the conditional probability of receiving cases, via either TE or OE. Using the nearest neighbor matching algorithm, we created propensity score-matched pairs without replacement (a 1:1 match). The caliper definition was set at 0.02. Eventually, 65 paired cases were matched from the cohort, and the 2 groups were comparable in patient characteristics (Table 1). There were no significant differences in body mass index and pulmonary function between two groups after propensity score matching. No significant differences in the subgroups of the TE and OE groups that underwent neoadjuvant treatment were evident after matching ($P=0.500$).

Nonparametric continuous variables were reported as the median and interquartile range (IQR). The Mann–Whitney U test was used to compare the median values of two independent parametric continuous variables. Pearson's chi-squared or Fisher's exact test was used to compare categorical variables. All statistical analyses were performed using the JMP® 11.0.0 (SAS Institute Inc., Cary, NC, USA) software and $P<0.05$ was considered statistically significant.

Results

Surgical findings

Although the operation time was significantly longer for TE than for OE (536 vs. 491 min; $P<0.001$), blood loss was significantly lower for TE (250 vs. 599 ml; $P<0.001$). Hand-assisted laparoscopic surgery was used significantly more frequently for TE. The number of dissected mediastinal lymph nodes was significantly higher for TE than for OE (25 vs. 21; $P=0.03$), indicating that the accuracy of lymphadenectomy for TE was equal to that for OE. Postoperative hospital stay (POD 29 vs. POD 35; $P=0.038$) was significantly shorter for TE (Table 2).

Clinical data

The PaO_2/FiO_2 ratio was significantly higher for TE than for OE on POD 1 [387 (351–433) vs. 351 (277–392); $P<0.001$]. CRP levels for TE were significantly lower than for OE on POD 1 and POD 3 [6.68 mg/dl (5.32–7.25) vs. 8.07 mg/dl (6.93–10.63); $P<0.001$, 10.79 mg/dl (7.19–14.88) vs. 15.31 mg/dl (11.78–21.47); $P<0.001$, respectively]. The neutrophil/lymphocyte ratio was significantly lower for TE than for OE on POD 3 [9, 12 (5–22) vs. 12 (1–42); $P<0.05$]. The WBC count showed no differences (Fig. 1).

Table 1 Patient demographics before and after propensity matching

Variables	Before matching		*P* values	After matching		*P* values
	TE (n = 85)	OE (n = 104)		TE (n = 65)	OE (n = 65)	
Age, median [year (IQR)]	66 (62–71)	67 (60–70)	0.904[a]	66 (62–70)	66 (61–70)	0.972[a]
Gender			0.242[b]			0.790[b]
Male	74	83		56	58	
Female	11	21		9	7	
ASA-PS			0.114[b]			0.915[b]
1	22	15		16	14	
2	58	79		45	47	
3	5	10		4	4	
p-Stage (UICC 7th)			0.001[b]			1.000[b]
0, I	42	27		24	24	
II, III, IV	43	77		41	41	
BMI [median (IQR)]				20.6 (18.4–23.3)	21.1 (18.3–23.4)	0.659[a]
%VC						0.619[b]
<80%				3	1	
≥80%				62	64	
FEV1.0%						0.144[b]
<70%				28	19	
≥70%				37	45	
NAC						0.430[b]
Absence				28	30	
Presence				37	35	

TE thoracoscopic esophagectomy in the prone position, *OE* open esophagectomy, *IQR* inter quartile range, *BMI* body mass index, *VC* vital capacity, *FEV* forced expiratory volume, *NAC* neo adjuvant chemotherapy

[a]Wilcoxon rank sum test

[b]Fisher's exact test

Table 2 Surgical findings

Variables	TE (n = 65)	OE (n = 65)	*P* values
Operation time [min (IQR)]	536 (501–593)	491 (415–575)	< 0.001[a]
Bleeding [ml (IQR)]	250 (160–503)	599 (360–875)	< 0.001[a]
Lymphadenectomy fields			0.082[b]
2	41	51	
3	24	14	
HALS	49	7	< 0.001[b]
Number of dissected mediastinal lymph nodes (IQR)	25 [20–30]	21 (16.25–28)	0.030[a]
Postoperative Hospital Stay (Day)	29 [22–41]	35 [25–66]	0.038[a]

TE thoracoscopic esophagectomy in the prone position, *OE* open esophagectomy, *2 fields* mediastinal and perigastric lymphadenectomy, *3 fields* 2 fields + cervical lymphadenectomy, *HALS* hand-assisted laparoscopic surgery

[a]Wilcoxon rank sum test

[b]Fisher's exact test

Perioperative cytokine levels

For both TE and OE, IL-6 levels showed a maximum on ICU admission and IL-10 levels showed a maximum on POD 1. IL-6 levels for TE were significantly lower than those for OE on ICU admission [671 pg/ml (23–6201) vs. 1450 pg/ml (222–6201); $P < 0.001$] and POD 3 [497 pg/ml (1–2058) vs. 976 pg/ml (128–5034); $P < 0.001$]. IL-10 levels for TE were also significantly lower than those for OE on ICU admission [2.54 pg/ml (0.62–26.36) vs.

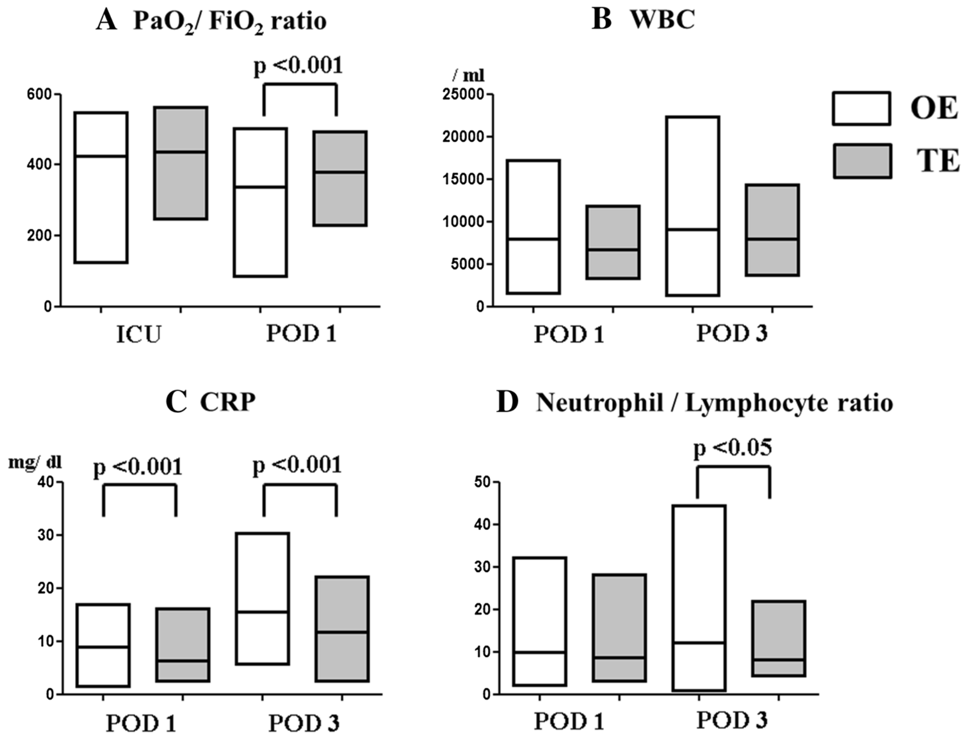

Fig. 1 Clinical data change over time. **A** *P*/F ratio was significantly higher following TE than that following OE on POD 1 [387 (351–433) vs. 351 (277–392); $P<0.001$]. **B** WBC showed no differences over time. **C** CRP following TE was significantly lower than that following OE on POD 1 and POD 3 [6.68 mg/dl (5.32–7.25) vs. 8.07 mg/dl (6.93–10.63); $P<0.001$, 10.79 mg/dl (7.19–14.88) vs. 15.31 mg/dl (11.78–21.47); $P<0.001$, respectively]. **D** N/L ratio was significantly lower following TE than that following OE on POD 3 [9, 12 (5–22) vs. 12 (1–42); $P<0.05$]

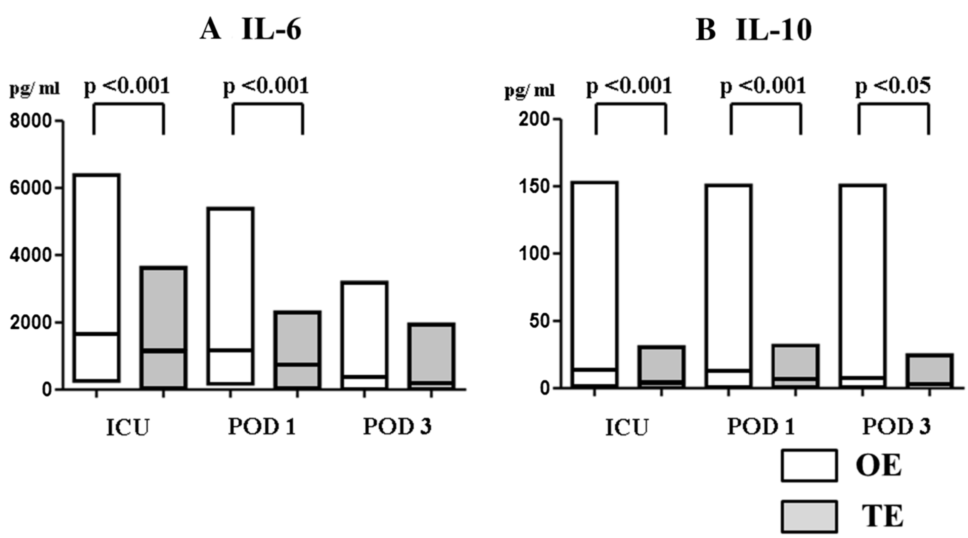

Fig. 2 Perioperative cytokine changes over time. **A** For both TE and OE, IL-6 levels showed a maximum on ICU admission and IL-10 levels showed a maximum on POD 1. The IL-6 level for TE was significantly lower than that for OE on ICU admission [671 pg/ml (23–6201) vs. 1450 pg/ml (222–6201); $P<0.001$] and POD 3 [497 pg/ml (1–2058) vs. 976 pg/ml (128–5034); $P<0.001$]. **B** The IL-10 level for TE was significantly lower than that for OE on ICU admission [2.54 pg/ml (0.62–26.36) vs. 7.66 pg/ml (0.07–150); $P<0.001$], POD 1 [3.97 pg/ml (0.00–18.60) vs. 10.18 pg/ml (0.56–148); $P<0.001$] and POD 3 [1.63 pg/ml (0.00–13.88) vs. 3.08 pg/ml (0.02–148); $P<0.05$]

7.66 pg/ml (0.07–150); $P<0.001$], POD 1 [3.97 pg/ml (0.00–18.60) vs. 10.18 pg/ml (0.56–148); $P<0.001$] and POD 3 [1.63 pg/ml (0.00–13.88) vs. 3.08 pg/ml (0.02–148); $P<0.05$] (Fig. 2).

Morbidity and mortality

Pulmonary complication was significantly lower in the TE group than in the OE group (16.9 vs. 33.9%; $P=0.043$). Other postoperative morbidity was similar between the two

Table 3 Morbidity

	TE (n = 65)	OE (n = 65)	*P* values
Pulmonary complications (pneumonia, ARDS)	16.9% (11)	33.9% (22)	0.043[a]
SSI	15.4% (10)	21.5% (14)	0.498[a]
Anastomotic leakage	10.8% (7)	12.3% (8)	1.000[a]
Recurrent laryngeal nerve paralysis	23.1% (15)	29.3% (19)	0.550[a]
Arrhythmia	9.2% (6)	15.4% (10)	0.424[a]

Data are given as % (numbers)

TE thoracoscopic esophagectomy in the prone position, *OE* open esophagectomy, *ARDS* acute respiratory distress syndrome, *SSI* surgical site infection

[a]Fisher's exact test

groups (Table 3). There were no deaths through POD 30 in either group.

Survival

The 5-year progression free survival (PFS) and overall survival (OS) rates for the TE and OE groups were 70.6 vs. 58.7% and 64.9 vs. 50.2%, respectively. No statistical difference was found in the survival curves between the two groups ($P = 0.328$ and $P = 0.101$, respectively) (Fig. 3).

Further, the relation between pulmonary complication and survival was investigated. The 5-year PFS and OS rates for the pulmonary complication absence and the pulmonary complication presence groups were 58.6 vs. 70.6% and 34.1 vs. 64.1%, respectively. Although no statistical difference

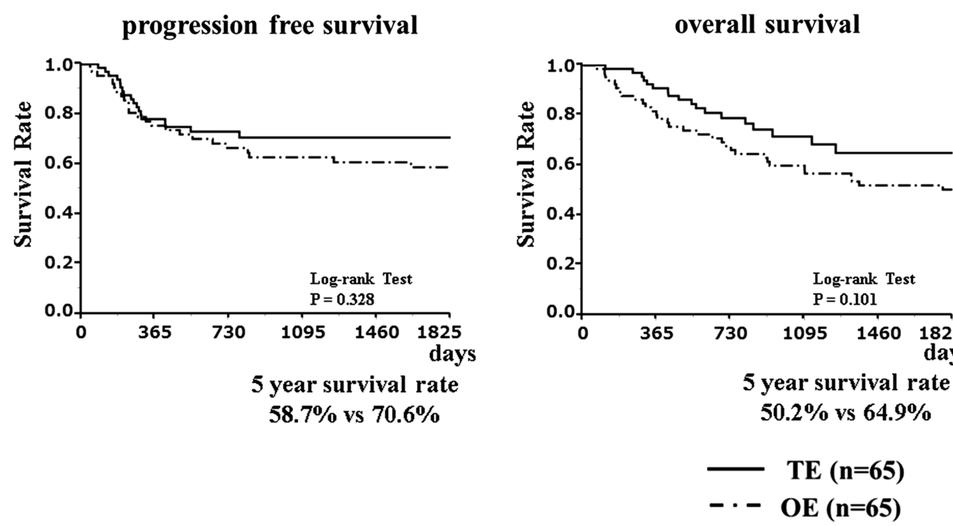

Fig. 3 Survival curve. The 5-year progression free survival and overall survival rates for the TE and OE groups were 70.6 vs. 58.7% and 64.9 vs. 50.2%, respectively. No statistical difference was found between the survival curves for the two groups ($P = 0.328$ and $P = 0.101$, respectively)

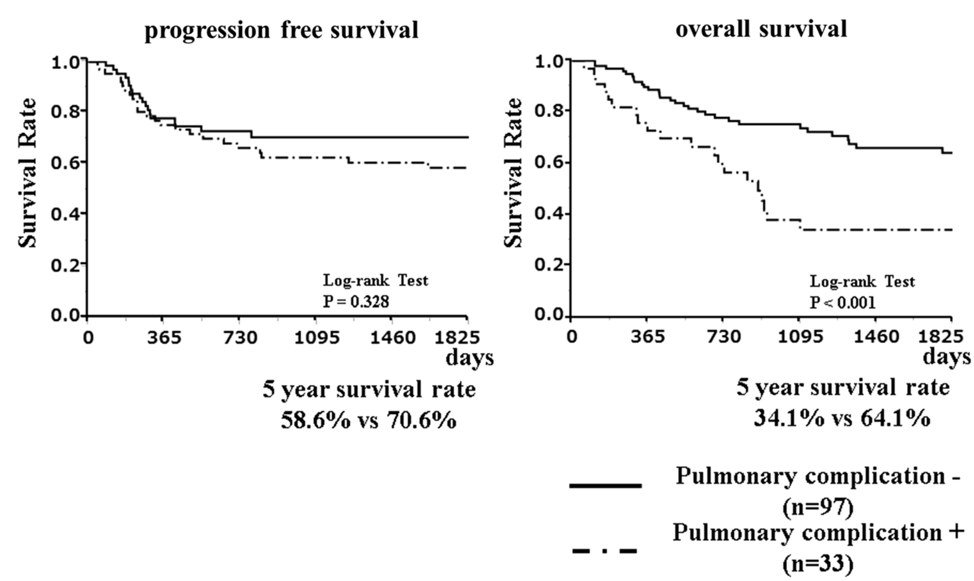

Fig. 4 The relation between pulmonary complication and survival. The 5-year PFS and OS rates for the pulmonary complication absence and the pulmonary complication presence groups were 64.7 vs. 59.5% and 61.6 vs. 39.2%, respectively. Although no statistical difference was found in PFS between the two groups ($P = 0.777$), OS was significantly better in the pulmonary complication absence group than in the pulmonary complication presence group ($P = 0.011$)

was found in PFS between the two groups ($P=0.328$), OS was significantly better in the pulmonary complication absence group than in the pulmonary complication presence group ($P<0.001$) (Fig. 4).

Discussion

Although esophagectomy plays an important role in curative treatment of esophageal cancer, perioperative morbidity and mortality rates are high [2]. By reducing surgical stress, it should be possible to reduce the rates of perioperative morbidity and mortality.

In this study, we demonstrated that TE results in reduced inflammatory responses in terms of CRP, IL-6, and IL-10 levels despite a longer operation time. The TE group had less blood loss, better oxygenation after surgery, less pulmonary complication, and shorter postoperative hospital stay than the OE group.

IL-6 is a pro-inflammatory cytokine frequently used to assess surgical stress [14], and IL-10 is commonly examined as an anti-inflammatory cytokine [15–17]. In the present study, IL-6 levels were significantly lower for TE than for OE, which is indicative of a reduced inflammatory response associated with TE. This finding is consistent with those of Fukunaga et al. [18] and Tsujimoto et al. [19], but differs from that of Takemura et al. [20] For three reasons, this discrepancy may depend upon whether the thoracic component employs thoracotomy. First, pleural oxygen exposure leads to an increased level of serum IL-6 [14]. During a thoracoscopic esophagectomy, CO_2 is used for the transitory pneumothorax. Therefore, the pleura is not exposed to oxygen, which could reduce IL-6 levels. Second, the local response of lung tissue is one source of increased serum IL-6 levels [21], and thus, manipulation of the lung can elevate these levels [22]. In a prone thoracoscopic esophagectomy, the lung and trachea are retracted by gravity and CO_2 pressure, whereas in a thoracoscope-assisted esophagectomy or an open esophagectomy, they are retracted using a spatula. Reduced manipulation in TE may be a reason for the lower IL-6 level. Finally, a shorter incision length has been reported to lead to reduced IL-6 levels in an animal model [23]. The advantages of no oxygen exposure, reduced manipulation of the lung and trachea, and a shorter incision length may outweigh the effects of the longer operation time. This would explain why IL-6 levels were lower for TE with complete thoracoscopic surgery.

There seems to be bias with respect to the gastric portion of the procedure in this study. The majority of TE underwent hand-assisted laparoscopic approaches to the abdominal portion of the procedure while the OE group underwent laparotomy. TE and HALS were induced at almost the same time and sets of surgical procedures in this study, so we could not discuss them separately. In this sense, this article is about minimally invasive esophagectomy used in combination with thoracoscopic and hand-assisted laparoscopic surgery. In fact, several reports have recognized that HALS significantly attenuates surgical stress and is useful for patients with esophageal cancer [24, 25]. However, surgical stress is reportedly larger with thoracotomy than with laparotomy [26] and promotes tumor growth [27, 28]. The low invasiveness of thoracoscopic esophagectomy was thus considered to be the most important facet in this study.

The TE group had better oxygenation after surgery, less pulmonary complication, and shorter postoperative stay in the present study. Although recent accumulating data suggest that there are perioperative advantages to the use of TE, there has only been a single randomized control trial, which showed a lower incidence of pulmonary infections during hospital stay, a shorter hospital stay, and better short-term quality of life following TE [5]. Furthermore, a meta-analysis showed that TE was associated with a shorter hospital stay, and reduced respiratory complications and morbidity [29], while there was no difference in the 30-day or overall survival rate between TE and OE [30]. Our data are compatible to the above findings.

Cytokines are useful objective indicators of surgical stress [15–17], and can also act as biomarkers for predicting complications and prognoses [31–34]. Hirai et al. [35] recognized that excessive surgical stress and postoperative complications cause a storm of perioperative cytokine release, enhance tumor metastasis, and result in a poor prognosis. In fact, OS was significantly better in the pulmonary complication absence group than in the pulmonary complication presence group in our study. If it is assumed that TE is less invasive and had less morbidity than OE, it may be possible to improve the survival curve using TE. Although there was no statistically significant difference, the survival curve for TE in Fig. 3 appears better than that for OE in our study. This is a small-scale study and might be underpowered. If a larger study will be conducted, significant differences may be demonstrated between the two groups.

Although we demonstrated a lower inflammatory response with TE through a detailed cytokine analysis, this study has some limitations. The treatment with TE was not based on random assignment, and the results thus may have been confounded by other variables. Although we used rigorous statistical methods to adjust for baseline differences between patients, including propensity score matching and stratification, the retrospective nature of the study means that our ability to control for differences was limited to variables for which data were available. A further prospective study including a quality-of-life questionnaire will be needed in order to verify the improved relief as a clinical advantage.

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Compliance with ethical standards

Disclosures Shoichi Hazama received research funding from NEC Corporation and Toyo Kohan Corporation. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication. Drs. Kanekiyo, Drs. Takeda, Drs. Tsutsui, Drs. Nishiyama, Drs. Kitahara, Drs. Shindo, Drs. Tokumitsu, Drs. Tomochika, Drs. Tokuhisa, Drs. Iida, Drs. Sakamoto, Drs. Suzuki, Drs. Yamamoto, Drs. Yoshino, Drs. Ueno, Drs. Nagano have no conflicts of interest or financial ties to disclose.

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