Title: Effectiveness of combined thoracoscopic-laparoscopic esophagectomy: comparison of postoperative complications and midterm oncological outcomes in patients with esophageal cancer.

Running head: Thoracoscopic-laparoscopic esophagectomy

Authors: Yousuke Kinjo[1], MD, Noriaki Kurita[2], MD, Fumiaki Nakamura[2], MD, Hiroshi Okabe[1], MD, PhD, Eiji Tanaka[1], MD, PhD, Yoshiki Kataoka[1], MD, Atsushi Itami[1], MD, PhD, Yoshiharu Sakai[1], MD, PhD, and Shunichi Fukuhara[2], MD, DMSc, FACP

Affiliations: [1] Department of Surgery, Graduate School of Medicine, Kyoto University and [2]Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Public Health, Kyoto University

Corresponding author: Shunichi Fukuhara, MD, DMSc, FACP, Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Public Health, Kyoto University, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan, E-mail: <fukuhara.shunichi.6m@kyoto-u.ac.jp>, phone: +81-75-753-4646, fax: +81-75-753-4646

Abstract

Background: During esophagectomy, laparoscopy can be used together with thoracoscopy, but it is not known whether a combined thoracoscopic-laparoscopic procedure is associated with fewer postoperative complications than open esophagectomy, and without compromising oncological outcome.

Methods: This was a longitudinal cohort study that included 185 esophageal-cancer patients: 72 who underwent combined thoracoscopic-laparoscopic esophagectomy (TLE), 34 who underwent thoracoscopic esophagectomy (TE), and 79 who underwent open esophagectomy (OE), between January 2002 and May 2010. The main outcome measures were postoperative respiratory and overall complications. The secondary outcome was 2-year relapse-free survival (RFS).

Results: Respiratory complications occurred in 9 patients who underwent TLE, 13 who underwent TE, and 31 who underwent OE. TLE was associated with fewer respiratory complications (TLE vs OE: odds ratio [OR], 0.22; 95% confidence interval [CI], 0.09-0.53 and TE vs OE: OR, 0.71; 95%CI, 0.29-1.76). Overall complications occurred in 34 patients who underwent TLE, 20 who underwent TE, and 54 who underwent OE. TLE was associated with fewer overall complications (TLE vs OE: OR, 0.47; 95%CI, 0.23-0.94 and TE vs OE: OR, 0.51; 95%CI, 0.21-1.25). The 2-year RFS percentages were similar among the three groups: 71.6% for TLE, 57.7% for TE, and 58.3% for OE (TLE vs OE: hazard ratio, 0.65; 95%CI, 0.35-1.20 and TE vs OE: hazard ratio, 0.91; 95%CI, 0.45-1.82, respectively).

Conclusions: Unlike TE, TLE was associated with fewer postoperative complications than was OE, with no compromise of 2-year RFS. A randomized controlled trial with longer follow-up is needed.

Key words:

Esophagectomy, thoracoscopy, minimally invasive surgery, esophageal cancer, laparoscopy

Abbreviations:

ASA-PS: American Society of Anesthesiology Physical Status Classification

CI: Confidence interval

CTCAE: Common Terminology Criteria for Adverse Events

$FEV_1\%$: Forced expired volume in the first second, as a percentage of the forced vital capacity

MIE: Minimally invasive esophagectomy

OE: Open esophagectomy

OR: Odds ratio

RFS: Relapse-free survival

TNM: Tumor Node Metastasis classification

Introduction

In patients with esophageal cancer, minimally invasive esophagectomy (MIE) can be used to reduce surgical invasiveness, gain a better operative field, and lessen perioperative complications. MIE is believed to entail less blood loss and shorter hospital stays than conventional open esophagectomy (OE). The superiority of MIE over OE with regard to postoperative complications has been suggested by several meta-analyses [1-3] and comparative studies [4-7]. However, it is not clear whether MIE provides these benefits without compromising oncological outcome.

Furthermore, there is no consensus regarding the optimal method for MIE. The techniques used can be thoracoscopic, laparoscopic, or both, and the combined technique has been directly compared with the others only rarely [6, 8, 9]. Specifically, the additional benefit of laparoscopy is unclear.

We therefore studied whether incorporating laparoscopy into MIE for esophageal cancer could reduce the postoperative respiratory and overall complications without compromising 2-year relapse-free survival.

Patients and Methods

Preoperative patient assessment and definition of procedures

This longitudinal cohort study was done at the Department of Surgery, Kyoto University Hospital, with data collected over more than 8 years. It was approved by the ethics committee at Kyoto University. All patients had detailed preoperative risk assessments based on clinical presentation, chest radiography, electrocardiography, and pulmonary function tests. Preoperative tumor staging was based on physical examination, radiologic examination (computed

tomography and/or magnetic resonance imaging), upper gastrointestinal series, ultrasonography, and endoscopy.

We used three procedures: combined thoracoscopic-laparoscopic esophagectomy (TLE), thoracoscopic esophagectomy (TE), and open esophagectomy (OE). Through August 2005, all esophagectomies at our hospital were done with an open transthoracic approach (OE). In September 2005, we started using thoracoscopic procedures (TLE or TE), and have continued using these techniques. The indications for OE changed with the introduction of thoracoscopic procedures, and they differ from the indications for TLE or TE. Before thoracoscopic procedures were introduced, OE was indicated in patients with T1 to T3 (TNM classification (sixth edition)) and technically resectable T4 tumors (those with invasion of adjacent structures) irrespective of lymph node metastasis, previous chemoradiation therapy, or previous esophageal resection. Starting in September 2005, TLE or TE was indicated only in those with T1 to T3 tumors. OE was indicated only in the remaining patients: those with previous chemoradiation therapy, previous esophageal resection, or T4 tumor. Irrespective of the type of thoracic procedure, the surgeon's preference determined whether a patient underwent laparotomy or laparoscopy.

Eligible patients for the analyses

We reviewed the records of 243 patients who had histologically proven primary esophageal cancer and who underwent first esophagectomy between January 2002 and May 2010. To reduce imbalances in patient's clinical characteristics between procedures, only data from patients with T1 to T3 tumors, which is also the indication for TLE or TE, were eligible for the analyses. By that criterion 195 patients were eligible, and the remaining 48 were excluded. Ten patients who underwent thoracotomy-laparoscopy were also excluded, and thus the remaining

total was 185. The TLE group comprised 72 patients, the TE group 34, and the OE group 79 (Figure 1).

The data were analyzed by intention-to-treat. That is, any patients who required conversion from TLE to OE or TE because of intraoperative trauma were considered to belong to the TLE group.

Surgical procedure

The thoracoscopic approach was defined as thoracoscopic mobilization of the esophagus and regional lymphadenectomy without use of mini-thoracotomy, as reported previously [10, 11]. For thoracoscopic mobilization, patients were placed in the left lateral decubitus position or the prone position. The regional lymph nodes removed were the mediastinal (paraesophageal, paratracheal, subcarinal, supradiaphragmatic, and para–recurrent-laryngeal-nerve) and perigastric nodes. In patients with an upper esophageal tumor or metastases to the para–recurrent-laryngeal-nerve lymph nodes, the cervical lymph nodes were also removed.

Subsequently, patients were placed in the supine position for the gastric mobilization to obtain complete en bloc resection with upper abdominal lymph nodes. The abdominal procedure was done either by laparoscopic (endoscopic or hand-assisted endoscopic) surgery, or by open laparotomy. In the laparoscopic approach, after the first port was inserted through the umbilicus and CO_2 pneumoperitoneum at 8 mmHg was established, four operating ports were placed. The greater omentum, gastrosplenic ligament, and short gastric vessels were cut. The esophagus was dissected all around at the level of the hiatus, and mobilized with preservation of the right gastroepiploic vessels. Then, laparotomy within 5 cm was done to remove the specimen. In the open approach, an upper abdominal midline incision was made. An incision was made on the left

side of the neck, and then the prepared stomach was pulled up via the posterior mediastinal route, an intrathoracic route, or a retrosternal route, and a colon conduit was created through the antethoracic or retrosternal route.

The thoracotomy approach comprised open transthoracic esophageal mobilization using a three-incision technique as previously reported [12]. A right posterolateral thoracotomy was done, followed by laparoscopy or laparotomy for esophageal dissection and abdominal lymphadenectomy. Reconstruction was similar to that done with the thoracoscopic approach.

No patients underwent pyloroplasty, and no feeding jejunostomy tubes were placed.

Perioperative management

The procedures were done under a combination of epidural and general anesthesia. A double-lumen endotracheal tube was used for single-lung ventilation. At the beginning of the operation, 125 mg of methylprednisolone was administered intravenously to attenuate intraoperative surgical stress responses and to prevent postoperative complications [13]. Immediately after the operation, all patients were routinely admitted to the ICU and placed on mechanical ventilation overnight. The management of all the patients was in the same environment using intensive care, and the same principles of care were applied. After extubation on the next day, patients received respiratory physiotherapy to aid expectoration of any retained secretions. Bronchoscopic suction was done when necessary. For postoperative analgesia, epidural analgesia was preferred.

Histopathologic assessment

The pathological classifications of the primary tumor, the degree of lymph node involvement, and the presence of organ metastases were defined according to the TNM classification (sixth edition), and R classification was used to describe the extent of residual disease after esophagectomy (R0: no residual tumor, R1: microscopic residual tumor, R2: macroscopic residual tumor) [14].

Outcomes

The main outcomes of interest were respiratory and overall complications that occurred within 30 days of the operation. The secondary outcome was 2-year relapse-free survival (RFS). Respiratory complications were selected from complications higher than grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 (adult respiratory distress syndrome, pneumonia, pleural effusion, atelectasis, bronchopulmonary hemorrhage, cough, hiccups, aspiration, pneumothorax, and respiratory tract fistulae [supplementary material 1]) because these were considered to be clinically important. Cases of pleural effusion and pneumothorax were included only if they appeared after withdrawal of the thoracic drainage tube. Cases of atelectasis were included only if they were confirmed by chest radiography or bronchoscopy.

Overall complications were, in addition to the respiratory complications described above, cardiac or liver dysfunction or failure, stroke, intestinal fistulae, anastomotic leakage, chylothorax, perforation of the conduit, anastomotic stenosis, ileus, wound infection, intraoperative trauma, intraoperative bleeding, and palsy of the recurrent laryngeal nerve (supplementary material 1). Information on these complications, and on death within 30 days of

the operation, was extracted from medical records by two reviewers who worked independently and were blinded to the surgical procedures (Y. Kinjo and Y. Kataoka).

Two-year RFS was ascertained only for the patients with R0. The duration used was the duration from the date of the surgery until the date of either death (due to any cause) or of the first recurrence confirmed by diagnostic imaging.

Statistics and survival analysis

Continuous variables were expressed as mean $\pm$ SD when normally distributed or as median and range when non-normally distributed. The three groups were compared with one-way ANOVA, Kruskal-Wallis test, or chi-square test, as appropriate. Logistic-regression models were used to compare the occurrence of postoperative complications between the groups. RFS curves were estimated by the Kaplan–Meier method, and differences between them were compared with the log-rank test. The Cox proportional-hazard model was used to compare the RFS among the three groups. Variables with a p value less than 0.20 in the bivariate analyses were included in the multivariate analyses. All p values less than 0.05 were considered statistically significant. All analyses were done with STATA statistical software, version 11.0 (Stata, College Station, TX, USA).

Results

Patient characteristics and surgical outcomes

The clinical and pathologic characteristics of the patients are shown in Table 1. There were no significant differences in age, sex, body mass index, smoking history, or FEV_1%. The prevalence of a history of neoadjuvant chemotherapy varied between groups: TLE > TE > OE.

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The mean preoperative serum albumin and the proportion of patients with squamous cell carcinoma were higher in the TLE group. There was no significant difference in pathological TNM staging between the groups.

The details of the surgical procedures are shown in Table 2. There was no significant difference in the field of lymphadenectomy. No patient in the TLE or the TE group had intrathoracic anastomosis. Use of stomach conduit and use of hand-sewing were more common in the TLE group. For the thoracoscopic procedure, the prone position was used in 16 patients; 13 (18%) in the TLE group and 3 (9%) in the TE group.

The intraoperative and postoperative surgical outcomes are shown in Table 3. The thoracic procedure took more time in the TLE group than in the TE and OE groups (308 vs 264 vs 268 minutes, $p < 0.001$), but TLE was done with less loss of blood (320 vs 536 vs 680 g, $p < 0.001$). The postoperative hospital stay, duration of epidural anesthesia, and length of oxygen therapy were shorter in the TLE group. There were no difference in residual tumor or in the duration of ICU stay.

Respiratory and overall complications

Respiratory complications occurred in nine patients (13%) in TLE group, 13 patients (38%) in TE group, and 31 patients (39%) in OE group (Table 3). Overall complications occurred in 34 patients (47%), 20 patients (58%), and 54 patients (68%), respectively. The proportions of patients who required reoperation were similar. One patient in the TLE group, three in the TE group, and three in the OE group had reoperations due to anastomotic leakage, and one patient in the TLE group had a reoperation due to a chylothorax. All patients in all groups survived longer than 30 days after the operation.

The details of postoperative complications within 30 days are shown in Table 4. A total of 14 respiratory adverse events occurred in the TLE group, 21 occurred in the TE group, and 36 occurred in the OE group. For overall adverse events, the totals were 50, 42, and 81, respectively.

In the bivariate analyses, having respiratory complications was associated with age, ASA-PS, history of smoking, pathological T stage, colon conduit, and with having undergone OE rather than TLE (Table 5). Having respiratory complications was not associated with having undergone OE rather than TE. In the multivariate analyses, having respiratory complications was associated with having undergone OE rather than TLE (adjusted odds ratio [AOR] = 0.22; 95% confidence interval [CI] 0.09-0.53; $p = 0.001$).

In the bivariate analyses, having at least one of the overall complications was associated with ASA-PS, history of smoking, pathological T stage, colon conduit, and with having undergone OE rather than TLE (Table 6). In the multivariate analyses, having undergone TLE was associated with a lower adjusted odds of having one or more of the overall complications (AOR = 0.47; 95% CI 0.23-0.94; p = 0.034).

Relapse-free survival

The median follow-up time was 26 months (range: 3 to 63) in the TLE group, 24 months (4 to 51) in the TE group, and 50 months (3 to 95) in the OE group. The 2-year RFS percentages were 71.6%, 57.7%, and 58.3%, respectively. The RFS curve for TLE group was slightly higher than the curves for the other groups (Figure 2; TLE vs OE: $p = 0.079$; TE vs OE: $p = 0.845$ by log-rank test). When compared with OE, neither TLE nor TE was associated with longer RFS (Table 7).

Discussion

Both TE and TLE were associated with acceptable mid-term oncological outcomes, but only the TLE group had lower odds of postoperative respiratory and overall complications than the OE group. In comparison to OE, laparoscopy might result in more rapid recovery of bowel function, easier postoperative ambulation, and thus also easier expectoration of respiratory secretions. This is consistent with post-gastrectomy findings that laparoscopy results in less impaired pulmonary function [15] and fewer pulmonary complications [16] than do open procedures. In addition, thoracoscopic surgery can minimize damage to the chest wall, which will preserve lung and chest-wall compliance. It can also provide a better operative field and easier identification of the mediastinal structures, for more precise dissection.

Use of the prone position during thoracoscopy may promote hemostasis [10] and decrease lung injury. The mediastinum is exposed because bloody exudate flows out from the chest cavity by gravity, and thus does not conceal the operative field. The lung collapses because of the positive pressure pneumothorax, so lung retraction is not necessary. The overall result is less blood loss and fewer respiratory complications. The finding that TE alone was not associated with fewer postoperative complications indicates that the combination of laparoscopic and thoracoscopic surgery may synergistically reduce postoperative pain and restriction to breathing, resulting in fewer respiratory complications.

Three previous studies have compared the results of TLE, TE, and OE. The present results are consistent with the report in which the percentage of patients with postoperative pulmonary complications was significantly lower in the TLE group (6.7%) than in the other two groups (20% for TE, 30% for OE) [8]. The other two studies did not show such a benefit of TLE [6, 9]. This inconsistency between studies may be related to study designs: First, we used a

relatively broad definition of "respiratory complication." Second, the previous reports did not give details of the clinicopathological characteristics of the patients who underwent the three procedures, and likely confounders for respiratory complication such as age, history of smoking, and ASA-PS were not considered [17-19]. In contrast, our analyses included adjustments for likely confounders, which should provide stronger evidence of the superiority of TLE in terms of postoperative complications.

The patients who underwent TLE were less likely to have overall complications (Table 6) than were those who underwent OE (both bivariate and multivariate analyses). The only exception was palsy of the recurrent laryngeal nerve, which was more common in the TLE group than in the other groups. All cases of this complication were CTCAE grade 2, which required testing and follow-up but were not aggravated. In this context we note that the prone position was more frequently used during TLE than during TE. The prone position provides better visual control than does the left decubitus position. When patients are in the prone position the lymph nodes are more clearly seen, and therefore the nodes might have been more aggressively dissected from the recurrent nerve, which could account for the higher incidence of recurrent laryngeal nerve palsy in TLE group. This does not mitigate the advantage of TLE, but of course more attention should be given to the dissection of lymph nodes around the recurrent laryngeal nerve to minimize the risk of injury.

The advantages of TLE were not accompanied by any compromise in 2-year RFS. The Kaplan-Meier curve for RFS after TLE was the best of the three curves, although that might have been due to there being slightly more patients with N0-stage tumors in the TLE group. The survival advantage for TLE that was seen in the bivariate analysis was attenuated after adjustment for likely confounders. Thus, with regard to oncological outcome we consider TLE

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and OE to be comparable, and we note that decisions to use the newer technique (TLE) therefore do not require any compromise with regard to that outcome. We are aware of no previous comparative studies in which RFS was evaluated. In two previous studies there were no differences in overall survival between TLE and OE [8, 9], although the numbers of patients in the TLE groups of those studies were relatively small (19 and 30 patients), so reasonable comparisons between techniques are difficult. The next question is whether TLE affects long-term survival, and this question requires further follow-up.

There are several limitations in our study. First, the 30-day mortality and in-hospital mortality were zero in this study and could not be used as main outcomes. We presume that the major reason was the fact that patients were not included if they had undergone chemoradiation therapy, or had a T4 tumor. Second, there were several imbalances in important clinical characteristics between the groups. For example, no patients in the TLE group underwent reconstruction with a colon conduit, which might have resulted in confounding. We tried to adjust for these imbalances by using multivariate analyses, but there could be residual confounding. However, in previous studies the type of reconstruction conduit (colon vs stomach) did not affect the safety of esophagectomy [20, 21]. Third, our main outcomes are susceptible to bias. To minimize bias regarding the ascertainment of the main outcomes, the data reviewers were blinded to the surgical procedures. Finally, the duration of follow-up was limited. Still, the majority of recurrences develop within one year, and more than 90% of them develop by the third year after surgery [22, 23]. Thus, we believe that our follow-up period was long enough for comparing RFS among the groups.

We conclude that in patients with esophageal cancer TLE, but not TE, was associated with fewer postoperative complications than OE, with no compromise of mid-term RFS. These

findings support the hypothesis that the combination of thoracoscopy with laparoscopy has a benefit greater than that of thoracoscopy alone. A randomized controlled trial with longer follow-up is needed.

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Legends for figures

Figure 1

Numbers of patients who underwent each surgical procedure each calendar year. TLE: combination of thoracoscopy and laparoscopy, TE: thoracoscopy and laparotomy, OE: open esophagectomy.

Figure 2

Kaplan-Meier curves for relapse-free survival in the three groups: TLE (combination of thoracoscopy and laparoscopy), TE (thoracoscopy and laparotomy), and OE (open esophagectomy); TLE vs OE: $p = 0.079$; TE vs OE: $p = 0.845$ by log-rank test.

Table 1. Clinical and pathological characteristics

Variable	TLE (n = 72)	TE (n = 34)	OE (n = 79)	p
Age	62.7 ± 7.4	64.2 ± 8.8	63.3 ± 8.6	0.700[a]
Sex (male : female)	58 : 14	29 : 5	70 : 9	0.385[b]
Body mass index	20.0 ± 3.0	19.5 ± 2.8	20.6 ± 3.0	0.180[a]
ASA-PS				0.846[c]
I	35 (48%)	15 (44%)	36 (46%)	
II	37 (52%)	19 (53%)	41 (51%)	
III	0 (0%)	0 (0%)	2 (3%)	
History of smoking	57 (79%)	31 (91%)	64 (81%)	0.302[b]
$FEV_1\%$ (%)	75.2 ± 7.4	74.7 ± 10.2	77.1 ± 10.3	0.325[a]
Mean serum albumin (mg/dL)	4.1 ± 0.3	3.9 ± 0.4	4.1 ± 0.4	0.021[a]
Neoadjuvant chemotherapy	41 (57%)	13 (38%)	11 (14%)	< 0.001[b]
Tumor site				0.769[b]
Upper	13 (18%)	8 (24%)	12 (15%)	
Middle	35 (49%)	15 (44%)	35 (44%)	
Lower	24 (33%)	11 (32%)	32 (41%)	
Histologic diagnosis				0.037[b]
Squamous cell carcinoma	71 (99%)	31 (91%)	71 (90%)	
Adenocarcinoma	0 (0%)	3 (9%)	3 (4%)	
Other	1 (1%)	0 (0%)	5 (6%)	
Pathological T stage				0.528[b]
T1, 2	41 (57%)	16 (47%)	46 (58%)	
T3, 4	31 (43%)	18 (53%)	33 (42%)	
Pathological N stage				0.242[b]
N0	35 (49%)	13 (38%)	28 (35%)	
N1	37 (51%)	21 (62%)	51 (65%)	
Pathological M stage				0.511[b]
M0	63 (88%)	27 (79%)	65 (82%)	
M1a, 1b	9 (12%)	7 (21%)	14 (18%)	
Pathological stage				0.487[c]
I	21 (29%)	11 (32%)	18 (23%)	
IIA, B	26 (36%)	7 (21%)	27 (34%)	
III	16 (22%)	9 (26%)	20 (25%)	
IVA, B	9 (13%)	7 (21%)	14 (18%)	

Continuous variables are reported as mean ± SD. Abbreviations: ASA: American Society of Anesthesiology Classification, $FEV_1\%$: forced expiratory volume in 1 second as a percentage of the forced vital capacity. [a]One-way ANOVA. [b]Chi-square test. [c]Kruskal-Wallis test.

Table 2. Surgical procedures

Variable	TLE (n = 72)	TE (n = 34)	OE (n = 79)	p
Conduit				0.001[a]
Stomach	72 (100%)	27 (79%)	66 (84%)	
Colon	0 (0%)	7 (21%)	13 (16%)	
Field of lymphadenectomy				0.093[a]
Two fields	57 (79%)	25 (74%)	50 (63%)	
Three fields	15 (21%)	9 (26%)	29 (37%)	
Site of anastomosis				< 0.001[a]
Neck	73 (100%)	34 (100%)	63 (80%)	
Thoracic cavity	0 (0%)	0 (0%)	16 (20%)	
Method of anastomosis				< 0.001[a]
Hand-sewing	66 (92%)	22 (65%)	9 (11%)	
Stapling	6 (8%)	12 (35%)	70 (89%)	

[a]Chi-square test.

Table 3. Surgical outcomes

	TLE (n = 72)	TE (n = 34)	OE (n = 79)	*p*
Procedure-related variable				
Operative blood loss (g)	320 (25 - 1930)	536 (75 - 1530)	680 (190 – 4040)	< 0.001[a]
Duration of thoracic procedure (min)	308 ± 73	264 ± 46	268 ± 80	< 0.001[b]
Lymph nodes removed (intrathoracic)	28 (2 - 50)	24 (3 - 64)	18 (1 - 56)	0.002[a]
Residual tumor				0.499[c]
R0	66 (92%)	31 (91%)	68 (86%)	
R1-R2	6 (8%)	3 (9%)	11 (14%)	
Conversion during thoracic procedure	2 (3%)	1 (3%)	-	
Postoperative course				
Duration of ICU stay (days)	1 (1 – 3)	1 (1 – 8)	1 (1 – 8)	0.114[a]
Duration of epidural analgesia (days)	4.4 ± 1.4	4.7 ± 1.3	6.2 ± 1.8	< 0.001[b]
Duration of oxygen therapy (days)	9.2 ± 4.1	10.6 ± 3.7	17.3 ± 8.8	< 0.001[b]
Duration of hospital stay (days)	23 (13 - 100)	32 (17 - 147)	53 (22 - 412)	< 0.001[a]
Complications within 30 days				
Respiratory complication	9 (13%)	13 (38%)	31 (39%)	0.001[c]
Overall complication	34 (47%)	20 (58%)	54 (68%)	0.031[c]
Reoperation	2 (3%)	3 (9%)	3 (4%)	0.344[c]
Mortality within 30 days	0	0	0	

Operative blood loss, lymph nodes removed, and durations of ICU stay and hospital stay are reported as median and range; other continuous variables are reported as mean ± SD.

[a]Kruskal-Wallis test. [b]One-way ANOVA. [c]Chi-square test.

Table 4. Details of postoperative complications within 30 days

	TLE (n = 72)				TE (n = 34)				OE (n = 79)			
	Number of events	Grade (CTCAE)			Number of events	Grade (CTCAE)			Number of events	Grade (CTCAE)		
		2	3	4		2	3	4		2	3	4
Respiratory complications												
ARDS	0 (0%)	0	0	0	1 (3%)	0	0	1	0 (0%)	0	0	0
Atelectasis	3 (4%)	2	0	1	7 (21%)	6	0	1	16 (20%)	16	0	0
Pneumonia	5 (7%)	5	0	0	10 (29%)	8	2	0	7 (9%)	7	0	0
Pleural effusion	0 (0%)	0	0	0	1 (3%)	1	0	0	9 (11%)	9	0	0
Bronchopulmonary hemorrhage	0 (0%)	0	0	0	0 (0%)	0	0	0	0 (0%)	0	0	0
Pneumothorax	0 (0%)	0	0	0	0 (0%)	0	0	0	2 (3%)	1	1	0
Respiratory tract fistula	1 (1%)	1	0	0	0 (0%)	0	0	0	0 (0%)	0	0	0
Cough	2 (3%)	2	0	0	0 (0%)	0	0	0	1 (1%)	1	0	0
Hiccups	0 (0%)	0	0	0	0 (0%)	0	0	0	0 (0%)	0	0	0
Aspiration	3 (4%)	2	1	0	2 (6%)	2	0	0	1 (1%)	1	0	0
Other complications												
Arrhythmia	7 (10%)	7	0	0	3 (9%)	3	0	0	5 (6%)	4	1	0
Chylothorax	1 (1%)	0	1	0	0 (0%)	0	0	0	0 (0%)	0	0	0
Diarrhea	0 (0%)	0	0	0	1 (3%)	1	0	0	3 (4%)	3	0	0
Ileus	1 (1%)	0	1	0	0 (0%)	0	0	0	2 (3%)	1	1	0
Anastomotic leakage	3 (4%)	2	1	0	8 (24%)	5	3	0	13 (17%)	10	3	0
Anastomotic stenosis	4 (6%)	4	0	0	2 (6%)	2	0	0	3 (4%)	3	0	0
Liver dysfunction	2 (3%)	2	0	0	1 (3%)	1	0	0	1 (1%)	1	0	0
Wound infection	1 (1%)	1	0	0	2 (6%)	2	0	0	8 (10%)	8	0	0
Palsy of the recurrent laryngeal nerve	17 (23%)	17	0	0	4 (12%)	4	0	0	10 (13%)	10	0	0

Abbreviations: ARDS: adult respiratory distress syndrome, CTCAE: Common terminology criteria for adverse events.

Table 5. Bivariate and multivariate analyses of respiratory complications (n = 185)

Variable	Categories or units	Bivariate OR (95%CI)	p	Multivariate AOR (95%CI)	p
Procedure					
TE	TE vs OE	0.96 (0.42-2.19)	0.920	0.71 (0.29-1.76)	0.464
TLE	TLE vs OE	0.22 (0.10-0.51)	< 0.001	0.22 (0.09-0.53)	0.001
Age	per year	1.05 (1.01-1.09)	0.020	1.03 (0.99-1.08)	0.174
Sex	female vs male	0.64 (0.24-1.68)	0.362		
Body mass index	per kg/m^2	1.02 (0.91-1.14)	0.708		
ASA-PS	II, III vs 1	2.07 (1.06-4.01)	0.032	1.58 (0.73-3.42)	0.244
Serum albumin	per g/dL	0.63 (0.26-1.51)	0.298		
FEV$_1$%	per percent	0.97 (0.93-1.00)	0.088	0.98 (0.94-1.02)	0.336
History of smoking	yes vs no	3.45 (1.15-10.4)	0.027	3.10 (0.94-10.3)	0.066
History of neoadjuvant chemotherapy	yes vs no	0.65 (0.32-1.30)	0.219		
Pathological T stage	T3, 4 vs T1, 2	2.01 (1.05-3.83)	0.035	1.83 (0.86-3.91)	0.119
Pathological N stage	N1 vs N0	1.93 (0.98-3.80)	0.058	1.32 (0.60-2.90)	0.492
Conduit	colon vs stomach	2.84 (1.11-7.28)	0.030	1.69 (0.59-4.88)	0.332
Site of anastomosis	neck vs thoracic cavity	1.56 (0.54-4.53)	0.416		

Abbreviations: OR: odds ratio, AOR: adjusted odds ratio, CI: confidence interval, ASA: American Society of Anesthesiology

Classification, FEV$_1$%: forced expiratory volume in 1 second as a percent of forced vital capacity.

Table 6. Bivariate and multivariate analyses of overall complications (n = 185)

Variable	Categories or units	Bivariate		Multivariate	
		OR (95%CI)	*p*	AOR (95%CI)	*p*
Procedure					
TE	TE vs OE	0.66 (0.29-1.52)	0.330	0.51 (0.21-1.25)	0.143
TLE	TLE vs OE	0.41 (0.21-0.80)	0.009	0.47 (0.23-0.94)	0.034
Age	per year	1.02 (0.98-1.06)	0.296		
Sex	female vs male	0.67 (0.30-1.50)	0.331		
Body mass index	per kg/m^2	1.04 (0.94-1.16)	0.399		
ASA-PS	II, III vs 1	2.10 (1.16-3.80)	0.015	1.97 (1.05-3.71)	0.034
Serum albumin	Per g/dL	0.65 (0.29-1.49)	0.310		
FEV$_1$%	per percent	0.99 (0.95-1.02)	0.376		
History of smoking	yes vs no	2.20 (1.02-4.72)	0.043	1.87 (0.83-4.21)	0.130
History of neoadjuvant chemotherapy	yes vs no	0.91 (0.49-1.68)	0.768		
Pathological T stage	T3, 4 vs T1, 2	1.92 (1.05-3.50)	0.033	2.08 (1.10-3.93)	0.025
Pathological N stage	N1 vs N0	1.24 (0.69-2.25)	0.473		
Conduit	colon vs stomach	4.61 (1.30-16.3)	0.018	3.51 (0.92-13.3)	0.065
Site of anastomosis	neck vs thoracic cavity	0.91 (0.32-2.56)	0.857		

Abbreviations: OR: odds ratio, AOR: adjusted odds ratio, CI: confidence interval, ASA: American Society of Anesthesiology

Classification, FEV$_1$%: forced expiratory volume in 1 second as a percent of forced vital capacity.

Table 7. Bivariate and multivariate analyses of relapse-free survival (n = 165)

Variable	Categories or units	Bivariate		Multivariate	
		HR (95%CI)	*p*	Adjusted HR (95%CI)	*p*
Procedure					
TE	TE vs OE	1.07 (0.56-2.07)	0.834	0.91 (0.45-1.82)	0.781
TLE	TLE vs OE	0.58 (0.32-1.06)	0.079	0.65 (0.35-1.20)	0.176
Age	per year	1.00 (0.97-1.03)	0.994		
Sex	female vs male	1.03 (0.52-2.02)	0.941		
ASA-PS	II, III vs 1	0.62 (0.37-1.04)	0.068	0.57 (0.33-0.96)	0.036
Serum albumin	per g/dL	0.56 (0.28-1.10)	0.094	0.81 (0.40-1.63)	0.553
History of neoadjuvant chemotherapy	yes vs no	0.69 (0.38-1.25)	0.219		
Field of lymphadenectomy	3 fields vs 2 fields	1.43 (0.84-2.44)	0.192	0.98 (0.56-1.69)	0.933
Pathological T stage	T3, 4 vs T1, 2	2.24 (1.33-3.76)	0.002	1.59 (0.91-2.79)	0.106
Pathological N stage	N1 vs N0	4.53 (2.35-8.76)	< 0.001	3.91 (1.98-7.74)	< 0.001

Patients with R0 were included in this analysis. Abbreviations: HR: hazard ratio, CI: confidence interval, ASA: American Society of
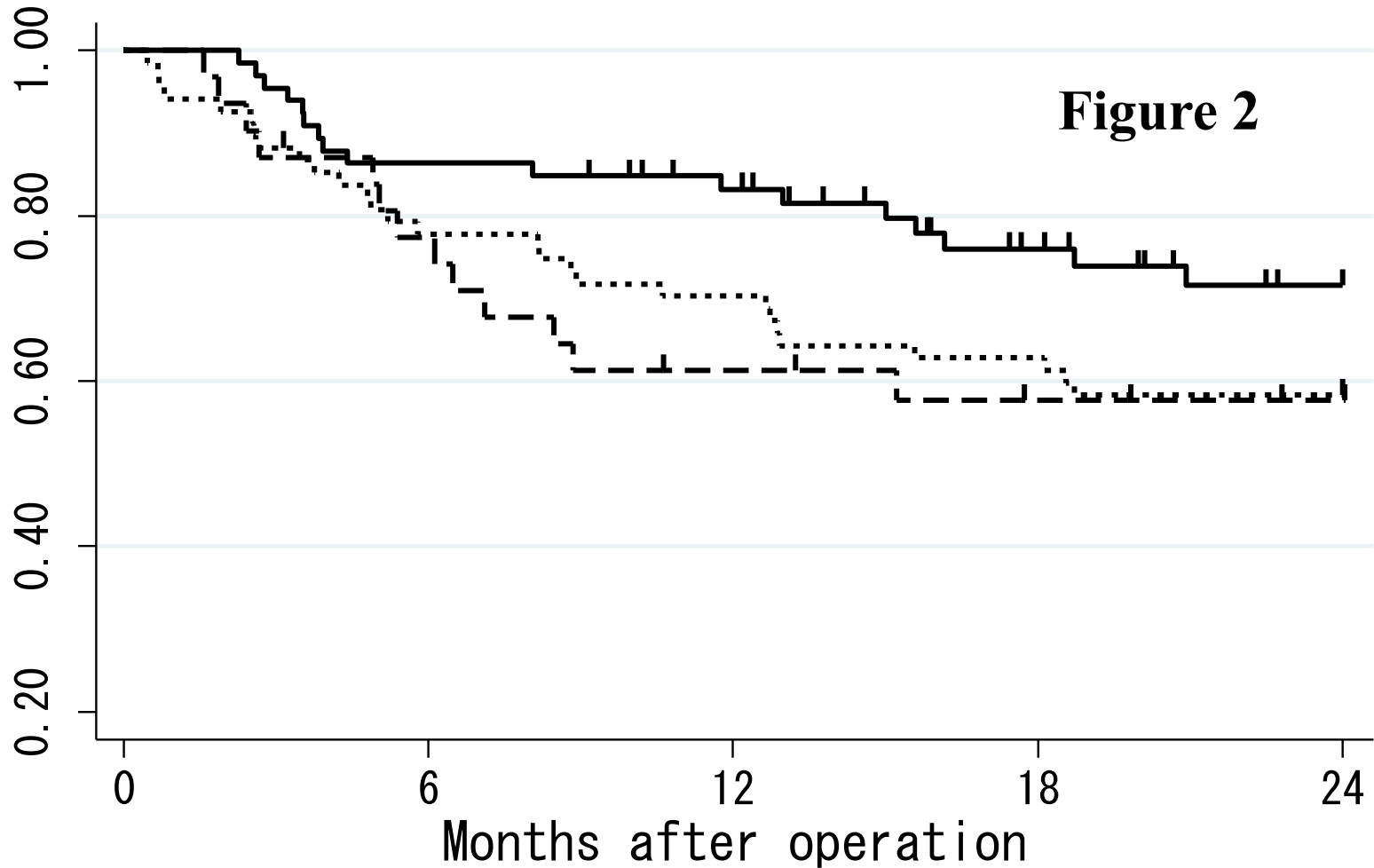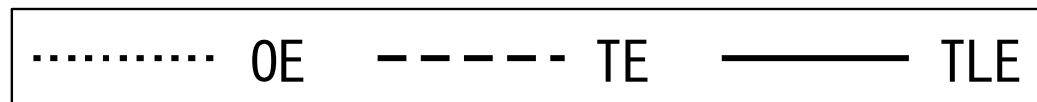
Anesthesiology Classification.

Figure 1
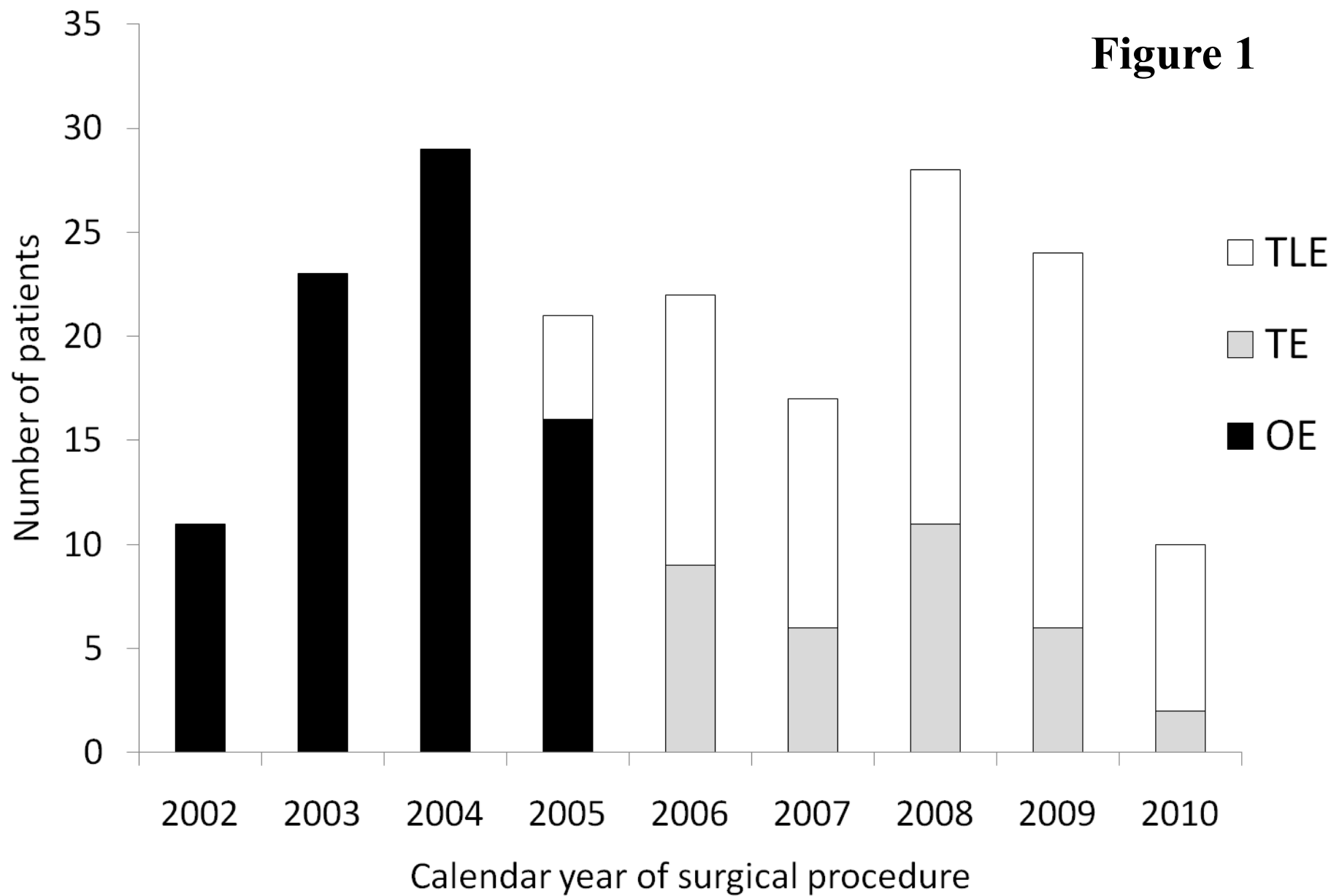
Figure 2

Number at risk

OE	68	52	47	42	39
TE	31	24	18	15	13
TLE	66	57	51	38	29

.... OE ----- TE ——— TLE

Supplementary material 1. List of postoperative complications and CTCAE grade

	Grade (CTCAE)		
	2	3	4
Respiratory complication			
ARDS	-	Present, intubation not indicated	Present, intubation indicated
Atelectasis	Symptomatic, medical intervention indicated	Operative intervention indicated	Life-threatening respiratory compromise
Pneumonia	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated
Pleural effusion	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening
Bronchopulmonary hemorrhage	Symptomatic and medical intervention indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated ; radiation therapy	Life-threatening consequences; major urgent intervention indicated
Pneumothorax	Symptomatic; intervention indicated	Sclerosis and/or operative intervention indicated	Life-threatening, causing hemodynamic instability; ventilatory support indicated
Respiratory tract Fistula	Symptomatic, tube thoracostomy or medical management indicated; associated with altered respiratory function but not interfering with ADL	Symptomatic and associated with altered respiratory function interfering with ADL; or endoscopic or primary closure by operative intervention indicated	Life-threatening consequences; operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated
Cough	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	-
Hiccups	-	Symptomatic, intervention indicated	Symptomatic, significantly interfering with sleep or ADL
Aspiration	Symptomatic ; medical intervention indicated	Clinical or radiographic signs of pneumonia or pneumonitis; unable to aliment orally	Life-threatening

Other complication

Arrhythmia	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device	Life-threatening
Chylothorax	Symptomatic; thoracentesis or tube drainage indicated	Operative intervention indicated	Life-threatening
Diarrhea	Increase of 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; hospitalization; interfering with ADL	Life-threatening
Ileus	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences
Anastomotic Leakage	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening
Anastomotic Stenosis	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening; Operative intervention requiring complete organ resection
Liver dysfunction	Jaundice	Asterixis	Encephalopathy or coma
Wound infection	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening
Palsy of the recurrent laryngeal nerve	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated	Life-threatening; tracheostomy indicated

Abbreviations: CTCAE: Common terminology criteria for adverse events, ARDS: adult respiratory distress syndrome, IV: intravenous,

GI: gastrointestinal, TPN: total parenteral nutrition.