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Original Article

Case-matched analysis of combined thoracoscopic-laparoscopic versus open esophagectomy for esophageal squamous cell carcinoma

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Abstract: The aim of this study is to evaluate surgical results and long-term survival of combined thoracoscopic-laparoscopic esophagectomy (TLE) performed for esophageal squamous cell carcinoma. Data of 59 patients with esophageal squamous cell carcinoma, undergoing TLE from January 2007 to January 2015, were compared to a control group of 59 patients who underwent open esophagectomy (OE) during the same period. The two groups were matched in terms of age, sex, American Society of Anesthesiology (ASA) score and clinical TNM stage. Laparoscopic approach resulted in longer operating time (P=0.003) and lower blood loss (P=0.000). There was no difference in perioperative morbidity and mortality rate; TLE approach was associated with a shorter hospital stay (P=0.000). After a mean follow up of 38 months, 5-year disease free survival and 5-year overall survival were 38% and 50% for TLE group, and 36% and 45% for OE group (P>0.05). TLE for esophageal squamous cell carcinoma is feasible and safe in selected patients and can result in good surgical results, with similar outcomes in terms of long-term outcomes.

Keywords: Esophageal squamous cell carcinoma, esophagectomy, minimally invasive surgery, prognosis

Introduction

Esophageal squamous cell carcinoma is one of the most common neoplasms in the Eastern Asia countries, such as China, Japan and Korea [1-5]. Radical esophagectomy is considered a crucial treatment for patients with esophageal squamous cell carcinoma [1-5]. Minimally invasive esophagectomy was first described in 1990s [6-8], and since then, the availability of new surgical instruments, modern anaesthesiological techniques and intensive care ideas allowed the diffusion of combined thoracoscopic-laparoscopic approach for resection of esophageal carcinoma [9-14]. Nevertheless, the real benefits of combined thoracoscopic-laparoscopic approach for esophagectomy are still under controversial, as well as the potential risks of postoperative complications and inadequate radicality of tumor resection [15-18]. The aim of this study is to compare the results of combined thoracoscopic-laparoscopic and open esophagectomy performed for esophageal squamous cell carcinoma using a case matched analysis for age, sex, American Society of Anesthesiology (ASA) score and clinical TNM stage.

Patients and methods

This study complied with the Declaration of Helsinki. This retrospective research was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. Written informed consent was obtained from all patients and their families before esophagectomy.

On January 2007, a clinical program of combined thoracoscopic-laparoscopic esophagectomy (TLE) was started. Since then, data concerning all cases have been collected. Patients who were potential candidates for liver resec-

Table 1. Characteristics features

	TLE (*n*=59)	OE (*n*=59)	*P* value
Age (years)	57 (41-72)	56 (48-71)	0.381
Sex			0.689
Male	42	40	
Female	17	19	
ASA score			0.536
I	41	38	
II	16	18	
III	2	3	
Comorbidity			0.605
Hypertension	3	4	
Stable angina	1	1	
Diabetes Mellitus	2	3	
Interstitial lung disease	1	0	
Arrhythmia	3	1	
Clinical TNM stage (7th AJCC-UICC)			0.635
IB	17	15	
IIA	37	38	
IIB	5	6	
Tumor location			0.575
Middle thoracic esophagus	23	26	
Lower thoracic esophagus	36	33	

TLE: combined thoracoscopic-laparoscopic esophagectomy; OE: open esophagectomy.

tion were systematically evaluated for combined thoracoscopic-laparoscopic approach at routine multidisciplinary meetings. The combined thoracoscopic-laparoscopic approach was considered on the basis of the patient status and tumor status: it was proposed for lesion located in the middle and lower thoracic esophagus, with clinical T1-3N0M0 stage and without neoadjuvant therapy. Patients with resection of other organs were not suitable for TLE because of higher risk of positive surgical margin. Patients with previous upper abdominal or thoracic surgery, cardiac or respiratory impairments were not suitable for TLE.

We searched our prospectively maintained database starting from the January 2007 for patients who underwent TLE for respectable esophageal squamous cell carcinoma. Fifty-nine patients from January 2007 to January 2015 underwent TLE for respectable esophageal squamous cell carcinomas are considered the study group.

Preoperative assessment included s upper gastrointestinal endoscopy, endoscopic ultrasonography, computed tomographic scans of brain, chest, and upper abdomen and ultrasonography of neck. Positron emission tomography-computerized tomography (PET-CT), mediastinoscopy and bone scanning were selectively used. The clinical stage of esophageal carcinoma was based on the 7th edition of the TNM classification of esophageal carcinoma which was proposed by Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) [19]. For those of the patients operated before 2010, their TNM staging was recalculated to match the 7th TNM esophageal carcinoma classification by UICC and AJCC [19]. The lymph nodes map was based on the tenth edition of Japanese Classification of Esophageal Cancer [20].

In a case-matched analysis, data from patients undergoing combined thoracoscopic-laparoscopic approach (TLE group) were compared with data of patients who underwent esophagectomy for esophageal squamous cell carcinoma by open thoracotomy-laparotomy approach (OE group) during the same period. The following criteria were matched for each patient: age, sex, ASA score and clinical TNM stage. Fifty-nine patients fulfilled all selection criteria and formed the control group.

The surgical technique of TLE has been described elsewhere [21]. Briefly, thoracoscopic was performed through thoracoscopic mobilization of the esophagus and resection of the mediastinal lymph nodes; laparoscopic was performed through laparoscopic resection of abdominal lymph nodes.

Postoperative complications, morbidity occurring within 30 postoperative days or hospital stay, were classified using Clavien-Dindo classification [22]. Major complications were defined as grades 3, 4 and 5. Minor complications were classified as 1 and 2. After the discharge, all patients were followed with a protocol of surveillance that included abdominal and chest computed tomography scan and ultraso-

Table 2. Surgical results

	TLE (*n*=59)	OE (*n*=59)	*P* value
Operative time (min)	250 (210-320)	200 (170-250)	0.003
Blood loss (ml)	190 (150-420)	420 (250-550)	0.000
Blood transfusion (patients)	5 (3-6)	6 (4-9)	0.000
Postoperative stay (d)	9 (7-19)	15 (10-28)	0.000
Overall complications *n* (%)	14 (23.7)	19 (32.2)	0.305
Major complications *n* (%)	3 (5.0)	5 (8.5)	0.714
Pulmonary embolism	1	2	
Anastomosis leakage	2	3	
Minor complications *n* (%)	11 (18.6)	14 (23.7)	0.499
Recurrent laryngeal nerve injury	4	5	
Pneumonia	2	4	
Urinary tract infection	1	1	
Atelectasis	2	1	
Heart failure	2	3	

TLE: combined thoracoscopic-laparoscopic esophagectomy; OE: open esophagectomy.

Table 3. Pathological results

	TLE (*n*=59)	OE (*n*=59)	*P* value
Retrieved lymph nodes	15 (13-28)	16 (14-27)	0.582
Pathological TNM stage (7th AJCC-UICC)			0.877
IB	12	11	
IIA	26	27	
IIB	18	17	
IIIA	1	3	
IIIB	2	1	
IIIC	2	1	
Resection margin			1.000
R0	59	59	
R1	0	0	
R2	0	0	

TLE: combined thoracoscopic-laparoscopic esophagectomy; OE: open esophagectomy.

nography of neck at 3 months after resection. Upper gastrointestinal endoscopy is suggested every once a year for after surgery. The follow-up was closed in February 2015.

Data were presented as mean and standard deviations for variables following normal distribution and were analyzed by *t* test. For data following non-normal distribution, results were expressed as median and range and were compared by nonparametric test. Differences of semi-quantitative results were analyzed by Mann-Whitney *U*-test. Differences of qualitative results were analyzed by chi-square tests or Fisher exact test as appropriate. The overall survival was assessed from the date of esophagectomy by OE or TLE until the last follow up or death of any cause. The disease-free survival was calculated from the date of esophagectomy until the date of cancer recurrence or death of any cause. Univariate analyses were performed to identify prognostic variables related to overall survival and disease-free survival. Univariate variables with probability values less than 0.10 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted odds ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics features are summarized in **Table 1**. Patient characteristics, such as age, sex, ASA score, comorbidities and clinical TNM stage were similar between the TLE and OE groups.

Surgical and pathological results are summarized in **Tables 2** and **3**. All surgical resections were performed by the same surgical team with proven expertise in esophageal carcinoma. The combined thoracoscopic-laparoscopic procedure was successfully completed in all patients without conversion to open resection. The median operative time was 250 min in the TLE group and 200 min in the OE group (*P*=0.003). Intra-operative blood loss was 190 ml in the TLE group and 420 ml in the OE group (*P*=0.000). No death within 30 postoperative days or in hospital stay was recorded in both groups. Postoperative complications occurred in fourteen patients in the TLE group (23.7%) and nineteen patients in the control group (32.2%) (*P*=0.305). Median postopera-

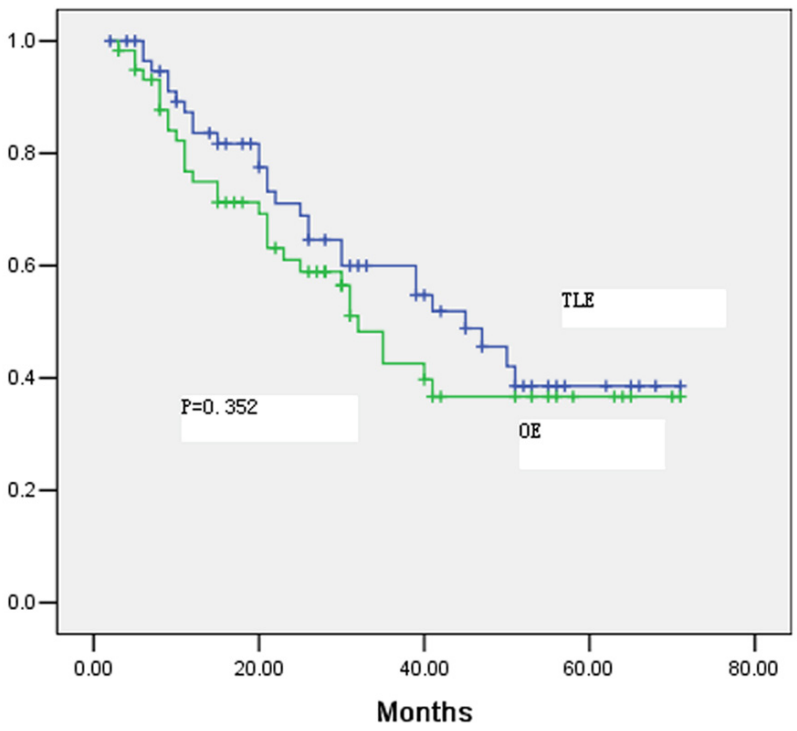

Figure 1. Disease-free survival curve by type of resection was shown. Analysis showed no significant difference between TLE and OE (*P*=0.352). TLE: combined thoracoscopic-laparoscopic esophagectomy; OE: open esophagectomy.

Table 4. Multivariate Cox regression analyses of disease-free survival

Regression variables	Adjusted hazard ratio	95% CI	*P* value
Pathological T stage			
T_1/T_2	1.00		
T_3/T_4	4.52	2.01-7.02	0.020
Pathological N stage			
N_0/N_1	1.00		
N_2/N_3	3.85	3.01-8.02	0.021
Angiolymphatic invasion			
Yes	1.00		
No	3.21	2.05-5.28	0.030

tive hospital stay was 9 days in the TLE group and 15 days in the OE group (*P*=0.000).

In all patients of TLE and OE group the final histology showed clear margins (R0 resection, **Table 3**).

The median follow-up was 38 months. No patients developed port-site metastases in the TLE group. The 5-year disease-free survival was 38% in the TLE group and 36% in the OE group (**Figure 1**, *P*=0.352). Multivariate Cox regression analysis of disease-free survival of all patients was performed. Significant predictors of worse disease-free survival were advanced pathologic T3 or T4 stage, pathologic N2 or N3 disease, and pathologic angiolymphatic invasion (**Table 4**). Surgical approach by combined thoracoscopic-laparoscopic approach was not found to be a significant predictor for disease-free survival by univariate analysis and multivariate analysis.

Five-year overall survival was 50% and 45%, respectively, in the TLE group and the OE group (**Figure 2**, *P*=0.504). In TLE group, twenty patients died for tumor recurrence, two for stroke and one for accident. In OE group, twenty-six deaths were recorded during the follow-up period: twenty-one patients died for tumor recurrence, and five for unrelated causes. Multivariate Cox regression analysis of overall survival of all patients in the whole cohort was also performed. Significant predictors of worse overall survival were advanced pathologic T3 or T4 stage, pathologic N2 or N3 disease, and poor differentiation of esophageal squamous cell carcinoma (**Table 5**). Surgical approach by TLE was not found to be a significant predictor for overall survival by univariate analysis.

Discussion

Minimally invasive esophagectomy for esophageal carcinoma is still a developing field [23-25]. Even though more than 20 years have already elapsed since the first minimally invasive esophagectomy was performed, only in the recent years this surgical procedure is gaining progressive acceptance [26-30]. Our series showed that TLE for esophageal squamous cell carcinoma is safe and feasible, without compromising overall and disease-free survival.

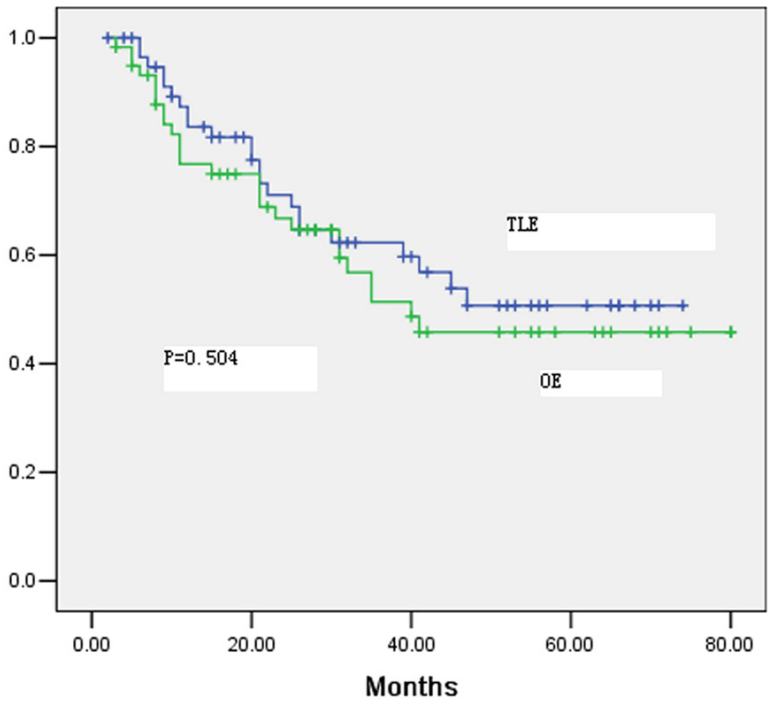

Figure 2. Overall survival curve by type of resection was shown. Analysis showed no significant difference between TLE and OE (*P*=0.504). TLE: combined thoracoscopic-laparoscopic esophagectomy; OE: open esophagectomy.

Table 5. Multivariate Cox regression analyses of overall survival

Regression variables	Adjusted hazard ratio	95% CI	*P* value
Pathological T stage			
T_1/T_2	1.00		
T_3/T_4	4.58	2.87-10.87	0.008
Pathological N stage			
N_0/N_1	1.00		
N_2/N_3	5.84	2.05-7.89	0.019
Differentiation grade			
Good/Moderate	1.00		
Poor	4.20	1.89-8.21	0.013

Open esophagectomy requires incisions through the rectus abdominis and ribs which are painful and leaves large, asymmetric scars. On the other hand, minimally invasive esophagectomy is associated with decreased need for narcotic pain relief, less blood loss, shorter hospital stay, faster recovery, better cosmetic results and evidence of decreased physiologic stress [31-33].

Our paper uses a case-matched analysis to compare short- and long-term outcome variables between patients undergoing TLE versus OE for esophageal squamous cell carcinoma. Case-matched study is ideal in small studies, because a single case can be matched with multiple controls in order to increase the power of the study. In addition, subjects can be matched according to known risk factors affecting overall survival and cancer recurrence.

Technical advances have allowed for minimally invasive esophagectomy to be performed safely, but radical esophagectomy for esophageal squamous cell carcinoma must demonstrate equivalent long-term outcomes before minimally invasive esophagectomy can be considered a suitable alternative to open resection [26-30]. Currently, the surgical literature on the subject has relatively few papers dedicated exclusively to malignant lesions. Furthermore, there is a lack of studies using sound statistical methods to compare oncological outcomes or TLE versus OE in matched patients.

This case-matched analysis demonstrates that combined thoracoscopic-laparoscopic approach to esophagectomy for esophageal squamous cell carcinoma offers significant advantages over the traditional open resection. Blood losses have been reduced in the TLE group than in the OE group. TLE patients were discharged significantly sooner than open resection patients, after a postoperative course with a reduced complication rate, though without statistical evidence. The combined thoracoscopic-laparoscopic approach might reduce postoperative complications in patients because the chest and abdominal wall is preserved. By decreasing surgical stress, minimally invasive surgery results in reduced postoperative pain and need for analgesic drugs,

earlier ambulation and oral food intake, better fluid balance. These results are confirmed also by studies concerning the application of minimally invasive surgery to other thoracic surgeries [26-38].

The main concern about the use of combined thoracoscopic-laparoscopic technique for malignancies is the risk of inadequate tumor resection; obtaining a negative margin (R1 or R2 resection) is a well known prognostic factor in resection for esophageal squamous cell carcinoma [38]. In our series no laparoscopic patient had a R1 resection, and the width of free margin did not differ between the two groups (data not shown). Another concern about combined thoracoscopic-laparoscopic resection of malignancies is the risk of port site tumor recurrence, which was not recorded in our series.

Upon analysis, neither margin status, nor overall survival, nor recurrence was significantly different between the two cohorts. This suggests that use of laparoscopic surgery does not compromise oncologic outcomes. Our findings corroborate other studies with the same conclusion [26-34].

It is becoming increasingly well recognized that minimally invasive esophagectomy can be performed safely in skilled thoracic surgeons with proven expertise in esophageal carcinoma. However, minimally invasive esophagectomy for esophageal neoplasm carries a heavier burden of proof: it must also demonstrate equivalent prognosis. A head-to-head comparison with a large, multi-center, prospective, randomized trial would be the best way to definitively compare minimally invasive esophagectomy versus open resection for esophageal squamous cell carcinoma, however, due to the technically difficult; such a trial with large sample size is unlikely to be performed nearly. Performing case-matched analysis with multiple controls can optimize smaller series, such as this one.

Every study had limitations. The main limitation of this study remains not prospective, randomized study. Imbalance between patient characteristics that were not recorded could bias the results. This limitation should be taken into account when interpreting the results. In addition, the follow-up period was relatively shorter, so tumor recurrence or death related to cancer may not have been observed during the time of analysis.

In conclusion, the present study shows that combined thoracoscopic-laparoscopic approach for esophagectomy is feasible and safe for the treatment of esophageal squamous cell carcinoma. It can drive to clinical advantages in recovery, cosmetic results, intraoperative blood losses and postoperative hospital stay without jeopardizing the oncological outcome, since long-term results concerning disease-free survival and overall survival are comparable to open resection. However, this procedure should be performed for selected patients and by an expert thoracicl team. These favorable findings in minimally invasive resection for respectable esophageal squamous cell carcinoma need further investigation in larger group of patients.

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Discourse of conflict of interest

None.

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