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ORIGINAL ARTICLE

Survival following video-assisted thoracoscopic versus open esophagectomy for esophageal carcinoma

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Summary

Purpose: *This study aimed to compare the overall and disease-free survival of patients who under-went video-assisted thoracoscopic esophagectomy (VATE) or open esophagectomy for esophageal carcinoma.*

Methods: *Patients who underwent radical esophagectomy via VATE (VATE group, N=89) for esophageal carcinoma between January 2008 and De-cember 2012 were retrospectively enrolled in this study. Patients subjected to open radical esophagectomy (open group) were retrospectively included at a ratio of 1:1, matching the VATE group in sex, age, clinical TNM stage, location of the primary tumor and ASA (American Society of Anesthesiologists) score.*

Results: *All the video-assisted thoraco-scopic procedures were successfully completed, without conversion to open procedure. The age, gender, clinical TNM stage, location of the primary tumor and ASA score were similar in the two groups. VATE group was associated with significantly less blood loss and shorter hospital stay. The operative morbidity and mortality were similar between the two groups. The quality of the specimens in terms of resection margin and the number of lymph nodes examined were not inferior in the VATE group. With the median follow-up of 52 months, the 5-year overall survival and disease-free survival were similar between the two groups. The operative approach was not an independent prognostic factor in the overall and disease-free survival in univariate and multivariate analysis.*

Conclusions: *VATE for esophageal carcinoma is associated with more favorable short-term outcomes and comparable long-term prognosis when compared with open esophagectomy.*

Key words: *esophageal carcinoma, esophagectomy, prognosis, video-assisted thoracoscopic surgery*

Introduction

Esophageal carcinoma is one of the most common malignancies around the world and its incidence has risen in Eastern Asian countries [1-5]. Currently it is the third most common cancer and second leading cause of cancer death in China [6,7]. Surgical resection with radical intent has remained the mainstay treatment for operable esophageal carcinoma. However, the operation is a major undertaking and is associated with significant morbidity and mortality, especially in elderly patients with concomitant medical conditions [6-8]. VATE has been reported to improve the short-term outcomes in terms of less blood loss and analgesic requirements, quicker recovery and a shorter hospital stay [9]. However, the survival outcomes of VATE for esophageal carcinoma remain a matter of debate. The current study aimed to evaluate the outcomes including survival of consecutive patients who underwent VATE for esophageal carcinoma in a high volume

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Table 1. Patient characteristics of the two groups

	VATE (N=89)	*Open (N=89)*	*p value*
Age (years), median (range)	63 (42-75)	62 (45-72)	0.450
Gender (Male: Female)	61: 28	58: 31	0.633
Comorbidities			
Hypertension	8	5	0.969
Type 2 diabetes mellitus	4	3	
Arrhythmia	2	2	
Stable angina	2	1	
Clinical TNM stage (7th AJCC-UICC)			
IB	21	20	0.670
IIA	33	31	
IIB	30	32	
IIIA	5	6	
Location of the primary tumor			
Upper thoracic esophagus	12	14	0.527
Middle thoracic esophagus	33	35	
Lower thoracic esophagus	44	40	
ASA score			
I	73	78	0.297
II	10	7	
III	6	4	

VATE: video-assisted thoracoscopic esophagectomy, Open: open esophagectomy, ASA: American Society of Anesthesiologists, UICC: Union Internationale Contre le Cancer, AJCC: American Joint Committee on Cancer

tertiary center. Comparison of the outcomes with those patients who underwent open resection performed during the same period of time was performed.

Methods

This study complied with the Declaration of Helsinki rules. This retrospective research was approved by the Ethics Committee of the University of Shanghai for Science and Technology. The need for informed consent from all patients was waived be-cause of the study's retrospective nature.

A total of 89 patients were hospitalized for elective radical esophagectomy via VATE approach for esophageal carcinoma between January 2008 and December 2012. The eligibility criteria for VATE were as follows: clinical T1-3N0-1M0 esophageal squamous cell carcinoma, without clinical cervical metastasis, without neoadjuvant therapy, without need for other organ resection, and with no evidence of metastasis. Any patient would be excluded if he/she was complicated with serious cardiopulmonary insufficiency or any other contraindication for receiving radical resection. The patients undergoing open esophagectomy with radical intent (open group) who matched the VATE group in sex, age, clinical TNM stage, location of the primary tumor and ASA score were prospectively selected at a ratio of 1:1 for outcome comparisons during the same period.

All patients were subjected to preoperative evaluation, consisting of an upper gastrointestinal endoscopy with a biopsy, a barium-swallow study, computed tomography (CT) scans of the brain, chest, and abdomen, and upper abdominal ultrasonography. Positron emission tomography-computerized tomography (PET-CT), staging thoracoscopy and bone scanning were selectively used. The stage of esophageal carcinoma was based on the 7th edition of the TNM classification of esophageal carcinoma proposed by Union Internationale Contre le Cancer (UICC), and the American Joint Committee on Cancer (AJCC). For those of the patients operated before 2010, their staging was recalculated to match the 7th TNM classification. This VATE surgical procedure is described elsewhere [10]. The surgical techniques for lymph node dissection are principally the same in open esophagectomy [11].

Patients received routine postoperative care and monitoring. Postoperative mortality (defined as death within 30 days after the operation), and postoperative morbidity (defined as complications occurring within 30 postoperative days) were reviewed. Morbidity was graded according to the Clavien-Dindo classification [12]. Major complications were defined as grades 3b, 4a, 4b and 5. Minor complications were classified as 1, 2 and 3a.

Routine outpatient follow-up visits were scheduled at 3-month intervals in the first 3 years after sur-

Table 2. Operative data and postoperative course of the two groups

Data	*VATE (N=89)*	*Open (N=89)*	*p value*
Operative time (min), median (range)	230 (200-340)	200 (160-310)	0.020
Blood loss (ml), median (range)	300 (260-620)	390 (240-800)	0.012
Postoperative hospital stay (days), median (range)	10 (7-24)	13 (10-36)	0.002
Overall complications	24	31	0.256
Major complications	4	7	0.350
Respiratory failure	1	3	
Anastomosis leakage	1	2	
Recurrent laryngeal nerve injury	2	2	
Minor complications	20	24	0.487
Anastomotic leakage	8	9	
Pneumonia	3	5	
Chylothorax	3	3	
Atelectasis	1	3	
Delayed gastric emptying	3	2	
Pleural effusion	2	2	
30-day mortality	0	0	-

VATE: video-assisted thoracoscopic esophagectomy, Open: open esophagectomy

gery, and annually thereafter. The follow-up examinations consisted of tumor marker estimation (squamous cell carcinoma antigen and CEA), upper abdominal ultrasonography, and chest x-ray. Upper gastrointestinal endoscopy was performed annually during the first 5 years. Disease recurrence was defined as locoregional or distant metastasis proven radiologically or bioptically where appropriate [13-15]. The last follow up was January 2015. Overall survival was assessed from the date of surgery until the last follow up or death of any cause and disease-free survival was calculated from the date of surgery until the date of cancer recurrence or death of any cause.

Statistics

For statistical analysis, the SPSS software 14.0 for Windows (SPSS Ill, Chicago, IL, USA) was used. Data were presented as mean and standard deviations for variables following normal distribution and were analyzed by Student's *t*-test. For variables following non-normal distribution, results were expressed as median and range and were compared by Wilcoxon nonparametric test. Differences of semiquantitative results were analyzed by Mann–Whitney *U* test. Differences of qualitative results were analyzed by x^2 test or Fisher's exact test where appropriate. Survival rates were analyzed using the Kaplan-Meier method and differences between the two groups were analyzed with the log-rank test. Univariate analysis was performed to identify prognostic variables related to overall survival and disease-free survival. Univariate variables with probability values <0.05 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted hazard ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. A two-sided p value <0.05 was considered statistically significant.

Results

The two groups had comparable demographic data (Table 1).

The operative results are summarized in Table 2. No operation in the VATE group was converted to an open procedure. The blood loss and postoperative hospital stay were significantly less in the VATE group (p<0.05). The median operative time was 30 min longer in VATE than in open surgery (p<0.05). No 30-day death occurred. There was a similar incidence between the open and VATE groups with respect to complications.

Pathological examination data are listed in Table 3. Involvement of the surgical margin and the number of resected lymph nodes were not significantly different between the 2 groups. Histologically, the disease was squamous cell carcinoma in 93% of the patients.

The median duration of follow-up was 52 months for the whole cohort (range 3-91). Tumor recurrence rate, type of recurrence and median time to first cancer recurrence were similar between groups (Table 4). There were no incision or port sites recurrences. The overall 5-year survival rate was 50% in the open group and 56% in the VATE group (p=0.461) (Figure 1). The 5-year dis-

Table 3. Pathological data of the two groups

Data	*VATE (N=89)*	*Open (N=89)*	*p value*
Retrieved lymph nodes, median (range)	18 (16-23)	17 (15-25)	0.358
Pathological stage			0.478
IB	6	7	
IIA	23	25	
IIB	39	40	
IIIA	12	10	
IIIB	4	3	
IIIC	5	4	
Residual tumor			
R0	88	88	1.000
R1	1	1	
R2	0	0	
Differentiation grade			
G1 (good)	46	44	0.921
G2 (moderate)	28	32	
G3 (poor)	15	13	
Histology			
Adenocarcinoma	6	5	0.756
Squamous cell carcinoma	83	84	

VATE: video-assisted thoracoscopic esophagectomy, Open: open esophagectomy

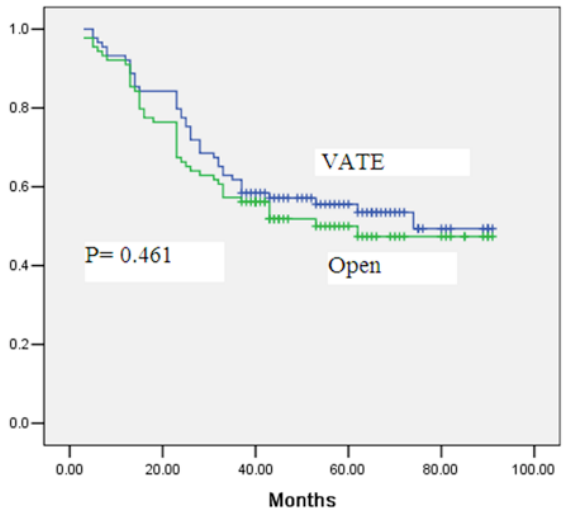

Figure 1. Overall survival in relation to VATE vs open esophagectomy (p=0.461).

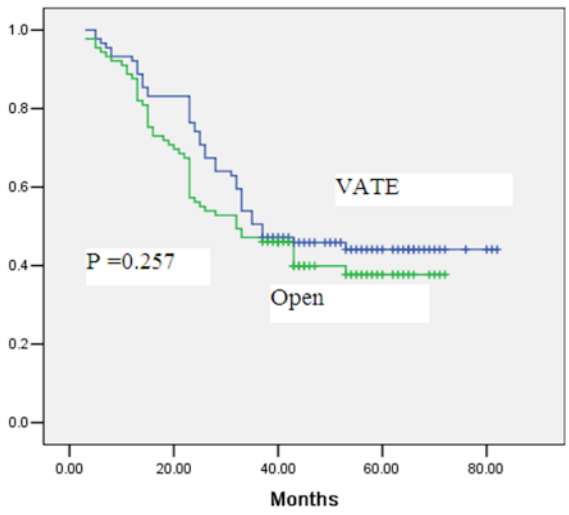

Figure 2. Disease-free survival in relation to VATE vs open esophagectomy (p=0.257).

ease-free rate was 38% in the open group and 44% in the VATE group (p=0.257) (Figure 2).

The results of multivariate analyses for independent predictive factors of overall survival in the whole patient cohort are shown in Table 5. Multivariate analysis identified age > 70 years, advanced pathological T stage, and more metastatic lymph nodes as factors with independent impact on overall survival. The results of multivariate analysis for predictive factors of disease-free patient survival are shown in Table 6. Multivariate analysis identified advanced pathological T stage, advanced pathological N stage and grade 3 tumors as factors with independent impact on disease-free survival. The type of operative approach (VATE vs open) did not influence the overall and disease-free survival in univariate and multivariate analyses.

Table 4. Recurrence after radical resection of the two groups

Recurrence	*VATE N*	*Open N*	*p value*
Overall recurrence	49	53	0.544
Locoregional	36	42	
Cervical lymph nodes	3	4	
Mediastinal lymph nodes	16	10	0.264
Abdominal lymph nodes	9	16	
Anastomosis	8	12	
Distant	13	11	
Brain	2	2	0.661
Lung	8	6	
Liver	3	3	
Time to recurrence, months (median)	15	12	0.120

VATE: video-assisted thoracoscopic esophagectomy, Open: open esophagectomy

Table 5. Multivariate Cox regression analysis of overall survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
Age, years			
<70	1.00		
≥70	2.33	1.80-4.02	0.032
Pathological T stage			
T_1/T_2	1.00		
T_3/T_4	3.35	2.88-6.20	0.021
Pathological N stage			
N_0/N_1	1.00		
N_2/N_3	3.88	3.11-6.89	0.008

Table 6. Multivariate Cox regression analysis 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	1.88	1.20-3.58	0.035
Pathological N stage			
N_0/N_1	1.00		
N_2/N_3	2.77	1.65-5.02	0.012
Differentiation grade			
Good	1.00		
Moderate	1.59	0.70-2.00	0.325
Poor	3.02	1.80-5.87	0.023

Discussion

This study suggests that VATE was associated with less blood loss, and shorter postoperative hospital stay, without compromizing the oncological outcome compared with open resection for esophageal carcinoma. Notably, the rates of cancer recurrence, overall survival and disease-free survival were similar between the two groups during long-term follow-up.

Since the first report of VATE for esophageal carcinoma in 1990s [16], an increasing number of small retrospective studies have been published [17-19]. These studies have reported encouraging results for the feasibility and safety of this procedure. VATE has been more frequently proposed as a curative treatment for esophageal carcinoma.

One of the advantages of VATE for esophageal carcinoma is the less blood loss compared with the open method. Osugi and colleagues [17] reported that the VATE approach resulted in less blood loss compared with open resection for esophageal carcinoma. Additionally, Hsu and colleagues reported a retrospective analysis of a prospectively maintained database of 129 radical resections for esophageal carcinoma [19]. They showed less blood loss with VATE vs open resection. These results are comparable with the results of the pres-

ent study.

The main concern with using the VATE for esophageal carcinoma is the risk of inadequate tumor resection. However, no difference has been observed in marginfree resections between VATE and open resection in many comparative studies [17-19]. In our series, one case in each group had positive margin (R1 resection). Another concern about VATE for esophageal carcinoma is the risk for a portsite tumor recurrence, which was not recorded in our series. With more than 2000 cases of minimally invasive esophagectomy in the literature, no incidence of portsite recurrence or tumor seeding has been reported [20-30]. Thus, this concern should not prevent surgeons from conducting a laparoscopic approach.

No prospective, randomized controlled trial has been reported comparing VATE with open resection for esophageal carcinoma. However, several studies have provided outcomes of comparisons between VATE and open resection for operable esophageal carcinoma. Thomson and colleagues [18] provided the largest comparison of VATE (N=165) with open esophagectomy (N=56) in patients with esophageal carcinoma. The 5-year overall survival and disease-free survival were not significantly different between the VATE and open groups. Operative approach (VATE or open resection) was not a prognostic factor for recurrence or mortality. Independent prognostic factors associated with locoregional recurrence were positive surgical margins (R1 resection) and lymph node metastasis. Distant recurrence was associated with advanced T stage, poor differentiation, tumor length larger than 6 cm, and lymph node metastasis. Our results are comparable with the results of other studies and confirmed the feasibility, safety, and benefits of VATE for esophageal carcinoma.

Limitations of our study include the non-randomized retrospective design and the small number of cases. So we cannot exclude bias in the selection of patients and of surgical approach. In the absence of a randomized phase 3 study it is difficult to eliminate the thoracic surgeon's selection bias for the VATE approach. Other clinical factors that may affect long-term survival are not completely accounted for by this case-matched analysis. These limitations should be taken into account when interpreting the results.

In conclusion, the present study showed that VATE for operable esophageal carcinoma is feasible and safe in selected patients and can lead to acceptable surgical results with a shorter postoperative hospital stay, less intraoperative bleeding, and similar survival outcomes in terms of overall and disease-free survival when compared with open resection.

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