Video-assisted thoracic surgery versus open thoracotomy for non-small-cell lung cancer: a propensity score analysis based on a multi-institutional registry

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INTRODUCTION

Video-assisted thoracoscopic surgery (VATS) has made a strong impact in thoracic oncology in recent years. A standardized technique of VATS lobectomy in the treatment of early-stage non-small-cell lung cancer (NSCLC) was demonstrated to be feasible and safe for selected patients in the Cancer and Leukemia Group B (CALGB) 39802 trial [1]. Despite encouraging institutional reports and meta-analyses suggesting superior perioperative outcomes, widespread adoption of the VATS technique has been limited internationally [2, 3]. This observation is likely to reflect the uncertain oncological efficacy of VATS, which may influence survival outcomes.

Historical randomized controlled trials that compared VATS lobectomy to conventional thoracotomy were limited by their study design and lack of long-term data [4, 5]. A recent meta-analysis of the current literature did not identify any differences in

< 0.001), female gender (P = 0.013) and pathological staging (P < 0.001). Patients who underwent VATS vs open lobectomy had similar long-term survival (P = 0.07).

CONCLUSIONS: The current propensity score analysis suggests that well-matched patients with NSCLC who underwent standardized VATS lobectomy had similar long-term survival outcomes when compared with those who underwent open lobectomy.

Keywords: Video-assisted thoracic surgery • Thoracotomy • Non-small-cell lung cancer • Propensity score analysis
Two or three ports without rib spreading using 100% monitor vision. Currently, there remains doubt as to whether VATS lobectomy is able to achieve similar long-term survival outcomes when compared with conventional thoracotomy [7, 8]. In view of the difficulties associated with performing randomized controlled trials to answer this question [2, 3, 9], we conducted a multi-institutional propensity-matched study comparing VATS lobectomy to conventional open lobectomy for patients with NSCLC in an attempt to stratify any potential differences in long-term survival outcomes between the two procedures. The secondary aims of this study were to examine a number of potential prognostic factors and their impact on overall survival, including pathological staging based on the new TNM staging system, which assesses the tumor size, nodal involvement and metastasis status [10].

METHODS

We established a multi-institutional registry for patients with NSCLC who underwent lobectomy between January 2001 and December 2008 in eight institutions from the People’s Republic of China. Ethics approval was obtained from participating institutions through their respective institutional review boards or the chairperson of the ethics committee, who waived the need for patient consent for the study as individual patients were not identified. The inclusion criteria were patients diagnosed with NSCLC who were considered for VATS or open lobectomy and systematic lymph node dissection or sampling. Exclusion criteria included patients who underwent lobectomy for pulmonary metastases or small cell lung cancer and patients who underwent sublobar resections. Patients with Stage IIIb and Stage IV NSCLC and those that did not meet the criteria of the CALGB definition [1] for VATS lobectomy were also excluded from analysis. Standardized clinical data for consecutive patients treated in each of the eight institutions were entered into an independent central database at the Collaborative Research (CORE) Group in Sydney, Australia. The collected data were analysed by an independent biostatistician. The follow-up data of all patients were obtained from their most recent medical review, which consisted of clinical examination and removing limits of chest X-rays or computed tomography scans.

VATS lobectomy was performed according to the definition proposed by the CALGB 39 802 prospective, multi-institutional study [1]. Specifically, each VATS procedure was performed through two or three ports without rib spreading using 100% monitor vision.

Standardized data form

A blinded standardized data form was created to retrieve all relevant information on clinical data (age, sex and date of surgery); pathological data (histological type, pathological tumour (T), node (N) and metastasis (M) status); treatment-related data (VATS vs open lobectomy) and perioperative outcomes. Pathological staging was performed according to the seventh edition of the TNM Classification of Malignant Tumours by the International Union Against Cancer (UICC) [10]. Perioperative mortality was defined as deaths that occurred during the same hospital admission or within 30 days of surgery. Perioperative mortality was included in the overall survival analysis.

Multi-institutional registry data

Between 2001 and 2008, a total of 4312 patients with NSCLC who underwent lobectomy via VATS or open thoracotomy were entered into the current multi-institutional registry. The follow-up data were available in 99.9% of patients. Two thousand nine hundred and eighty-six patients (69%) were alive at the time of the latest follow-up. The median follow-up period was 30.7 months (range 0–130 months). Mean age at the time of surgery was 59 (standard deviation (SD) = 11) years. There were 2908 male patients (69%). One thousand seven hundred patients (39%) underwent VATS lobectomy and 2612 patients (61%) underwent open lobectomy. Of the patients who attempted to undergo VATS lobectomy, 65 were converted to assisted-VATS (a-VATS) and 49 patients were converted to open lobectomy, with an overall conversion rate of 7.8%.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences for Windows (Version 18; SPSS GmbH, Munich, Germany). A significant difference was defined as P < 0.05. Overall survival was chosen as the primary endpoint, which was calculated from the time of surgery. Survival analysis was performed using the Kaplan–Meier method and compared using the log-rank test. Age (<60 vs ≥60 years), gender (male vs female), smoking history (yes vs no), percentage predicted forced expiratory volume in 1 s (<50% vs ≥50%), histological type (adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma and bronchioloalveolar carcinoma vs large cell tumour), pathological stage (seventh edition of TNM staging) and type of procedure (VATS vs open lobectomy) were entered into a Cox proportional hazards model with forward stepwise selection of covariates and with entering and removing limits of P < 0.10 and P > 0.05 in order to identify independent prognostic factors for survival.

In this cohort of 4312 patients, age (P = 0.004), gender (P < 0.001), histological type (P < 0.001) and pathological TNM stage (P < 0.001) were found to be independently associated with survival outcomes. There were significant differences across all the baseline characteristics between the two surgical groups (Table 1). Therefore, a propensity score analysis was performed to match the two comparative groups.

Propensity score analysis

In the present study, age, gender, histological type and pathological TNM staging were entered into a non-parsimonious multivariable logistic regression model. The predicted probability derived from the logistic equation was used as the propensity score for each individual. An independent biostatistician, blinded from the survival data, used SPSS macro to match each patient who underwent VATS lobectomy to a corresponding patient who underwent open lobectomy according to their propensity scores measured in five, four, three, two and one decimal places in five repeated steps. The paired patients were extracted from the central database. Using this method, 1458 of 1700 patients who underwent VATS lobectomy were matched with 1458 of 2612 patients who underwent open lobectomy with similar propensity scores (Table 1).
RESULTS

Clinical data

The mean age of the 2916 matched patients was 59 (SD = 11) years. Two thousand one hundred and sixty-six patients (67%) were males. Before matching, there were significant differences in the distribution of baseline characteristics between VATS and open groups (Table 1). After propensity-matching, VATS and open lobectomy patients were similar in regards to age, gender, histological type and pathological TNM staging (Table 1).

Survival outcome

After selecting the propensity-matched patients, overall median survival was 99.4 months (range 0–130 months), with 1-, 3- and 5-year survival of 92, 74 and 62%, respectively. The perioperative mortality rate was 1.1% for the open group and 0.8% for the VATS group. Bivariate analysis identified seven significant prognostic variables associated with improved survival (Table 2): age <60 (P < 0.001), female gender (P = 0.006), histopathology (P = 0.008), low T staging (P < 0.001), low N staging (P < 0.001) and pathological TNM staging (P < 0.001).

Four prognostic factors were independently associated with improved survival outcome in multivariate analysis: age <60 (P < 0.001), gender (P = 0.001), histological type (P < 0.001) and pathological TNM staging (P < 0.001). When analysing the two propensity-matched populations, patients who underwent VATS lobectomy did not demonstrate any statistically significant differences in long-term survival compared with patients who underwent conventional thoracotomy (P = 0.07, Fig. 1). When subgroup analyses were performed according to TNM staging, the two treatment groups also had similar outcomes for patients with Stage I (P = 0.22) or Stage II/IIIa (P = 0.58) disease.

DISCUSSION

Since the introduction of VATS lobectomy 20 years ago, there has been growing evidence to suggest improved perioperative outcomes for this minimally invasive technique compared to conventional open thoracotomy [11, 12]. Retrospective studies have reported reduced incidences of arrhythmias [13], pneumonia [14], pain [15] and diminished inflammatory markers [13, 15]. Standardized techniques developed over the past two decades include a posterior approach popularized by William Walker and an anterior approach by Hansen and Petersen [16, 17]. The 20th Anniversary VATS Lobectomy Meeting held in Edinburgh, UK in November 2012 reported favourable outcomes for VATS lobectomy from a number of institutions in North America, Europe and Asia. In addition, with technological improvements and specialized experience, more complicated procedures such as extrapleural pneumonectomy have been performed through the VATS approach [18]. However, despite encouraging results for patients with NSCLC who undergo VATS lobectomy, there is still a lack of robust clinical data on long-term survival. Ultimately, the highest level of clinical evidence may be derived from large randomized controlled trials. However, logistical challenges and a ‘lack of equipoise’ amongst the thoracic community have thus far prevented such a study from being conducted [2, 3, 9].

To clarify the definition of ‘true’ VATS lobectomy in the clinical setting, Swanson and colleagues described a standardized procedure that mandated the use of videoscopic guidance with anatomical hilar dissection without the use of rib spreaders through a 4–8 cm incision site and two port incisions. Results of 111 patients who successfully underwent a VATS lobectomy in this study demonstrated the feasibility of a ‘complete’ VATS procedure, with a relatively low complication rate and short chest tube duration. Although this study provided a much needed definition for a standardized form of VATS lobectomy, many institutions reported variations of VATS lobectomy procedures, and the practice of a-VATS...
is particularly common in developing countries, where the cost of performing a-VATS is significantly lower than c-VATS [5, 19].

To date, two small randomized controlled trials have compared patients with NSCLC who underwent VATS lobectomy vs open thoracotomy [4, 5]. The first was conducted by Kirby et al. [4], in 1995, who randomized 61 patients with clinical stage I NSCLC to undergo muscle-sparing thoracotomy (n = 30) or VATS lobectomy (n = 31). Long-term survival was not assessed due to limited mean follow-up of 13 months. Results of this study found that VATS lobectomy was associated with significantly fewer postoperative complications (6% vs 16%), but not a significant decrease in blood loss, duration of chest tube drainage, length of hospital stay or postoperative pain. In 2000, Sugi et al. [5] randomized 100 patients with clinical stage IA NSCLC to undergo VATS lobectomy (n = 48) or open lobectomy (n = 52). This trial found no significant differences in recurrence or survival rates between the two treatment groups. In addition, several non-randomized studies have attempted to directly compare the short- and long-term outcomes of VATS vs open procedures [14, 20]. However, observed and unobserved systematic differences can exist between treatment groups, resulting in bias. One method of minimizing this potential bias in a non-randomized setting is to analyse the data from two treatment groups using propensity score-based matching [21–23]. Two recent propensity-matched analyses have indicated that VATS procedures can be associated with improved perioperative outcomes when compared with open procedures for selected patients with NSCLC [7, 9]. Scott et al. [9] extracted data from the American College of Surgeons Oncology Group Z0030 trial to construct propensity scores for a relatively small number of patients who underwent VATS (n = 66) vs open (n = 686) procedures, based on age, gender, performance status, histology, tumour location and T1 vs T2 staging. This analysis concluded that VATS was associated with fewer respiratory complications and a shorter duration of hospital stay. However, the median follow-up period was not clearly stated and the authors acknowledged that 82% of all VATS cases were performed by a single surgeon, whose individual skill and postoperative management represented a potential confounding factor. Another study by Paul et al. [7] matched 1281 patients with NSCLC in both the VATS and open groups using data from the Society of Thoracic Surgeons General Thoracic Database. This report concluded that

### Table 2: Univariate analysis of clinicopathological factors affecting overall survival for propensity-matched patients who underwent lobectomy by VATS or open thoracotomy for non-small-cell lung cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>Median survival (months)</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>2916</td>
<td>99.4</td>
<td>(89.3–109.5)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Age at the time of surgery</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>&lt;60 years</td>
<td>1445</td>
<td>111.3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>≥60 years</td>
<td>1471</td>
<td>85.2</td>
<td>(72.6–97.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1897</td>
<td>97.7</td>
<td>(85.6–109.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1019</td>
<td>99.4</td>
<td>(84.0–114.8)</td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
<td>0.008</td>
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<tr>
<td>Adenocarcinoma</td>
<td>648</td>
<td>129.3</td>
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<td>Squamous cell carcinoma</td>
<td>1852</td>
<td>97.7</td>
<td>(85.9–109.5)</td>
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<td>Adenosquamous carcinoma</td>
<td>152</td>
<td>72.1</td>
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<td>Bronchioalveolar carcinoma</td>
<td>55</td>
<td>46.2</td>
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<td>Large cell carcinoma</td>
<td>102</td>
<td>105.5</td>
<td>(85.3–125.7)</td>
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<tr>
<td>Sarcoma</td>
<td>33</td>
<td>44.4</td>
<td>(10.6–78.2)</td>
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<tr>
<td>Others</td>
<td>70</td>
<td>103.6</td>
<td>(32.3–175.0)</td>
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<tr>
<td>Pathological TNM</td>
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<td>&lt; 0.001</td>
</tr>
<tr>
<td>1a</td>
<td>631</td>
<td>105.5</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>1016</td>
<td>111.3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>486</td>
<td>68.0</td>
<td>(54.9–81.2)</td>
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<tr>
<td>2b</td>
<td>118</td>
<td>57.0</td>
<td>(27.1–86.9)</td>
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<tr>
<td>3a</td>
<td>665</td>
<td>32.9</td>
<td>(28.6–37.2)</td>
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<tr>
<td>VATS</td>
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<td>102.9</td>
<td>–</td>
<td></td>
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<tr>
<td>Conventional open surgery</td>
<td>1458</td>
<td>99.4</td>
<td>(85.8–113.0)</td>
<td></td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in 1 s.

Figure 1: Overall survival stratified by open thoracotomy lobectomy vs VATS lobectomy for patients with non-small-cell lung cancer.
patients who underwent VATS procedures had significantly improved perioperative morbidity but similar perioperative mortality compared with patients who underwent open thoracotomy. A recent meta-analysis of propensity score matched patients demonstrated superior outcomes for VATS compared with open thoracotomy with significantly lower incidences of overall complications, pneumonia, atrial arrhythmia and a shorter duration of hospitalization [24].

The propensity score is the conditional probability of receiving an intervention given the individual’s measured covariates, which can be assigned values from 0 to 1. The patients from two groups are then blindly matched by similar propensity scores and where there is no match, they are excluded from further analyses. Propensity score matching is considered to strengthen observational studies in a number of ways [21–23]. Most importantly, it enables investigators to retrospectively assemble a study cohort in which patients are balanced in all significant covariates. This makes the assessment of the intervention more accurate by minimizing potential bias between the comparative groups. In addition, the process of propensity score matching can be achieved in a blind fashion without the investigator having access to outcome data.

For the present study, 4312 patients who underwent VATS or conventional thoracotomy for NSCLC were identified from our registry. This collaborative effort represents the largest study to date to evaluate the long-term oncological efficacy of VATS when compared with open thoracotomy. After matching patients from the two treatment groups according to propensity score analysis, 1458 patients were assigned to each treatment group. Data from these propensity-matched patients reported perioperative outcomes that are comparable with other studies [3, 6]. A number of limitations apply to the present study and interpretations should be made with caution. Firstly, despite the utilization of propensity score matching, intrinsic biases may remain, as patients between the two treatment arms were not randomized. Secondly, the patient selection process differed between institutions and inevitably there were some variability in the experience and skill of individual surgeons. Nonetheless, this may be more representative of the ‘real world’ scenario rather than the outcomes from a single surgeon [9]. Finally, the results of our study were based on predominately male patients of Chinese ethnicity, thus limiting generalizability.

In conclusion, the present multi-institutional study represents the largest dataset evaluating surgical outcomes of patients who underwent VATS for NSCLC. To minimize potential biases inherent in the non-randomized setting, we presented the data using the technique of propensity score analysis based on a number of identified significant prognostic factors. The study found that VATS lobectomy for NSCLC was not associated with inferior long-term survival compared with conventional thoracotomy.

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