Pleural Recurrence and Long-Term Survival After Thoracotomy and Thoracoscopic Lobectomy

Sung Hwan Kim, MD, Hong Kwan Kim, MD, PhD, Yong Soo Choi, MD, PhD, Kwhannien Kim, MD, PhD, Jhingook Kim, MD, PhD, and Young Mog Shim, MD, PhD

Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, and Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea

Background. There are concerns over procedure-related pleural dissemination during video-assisted thoracic surgery (VATS) lobectomy. We compared the incidence of pleural recurrence and long-term survival between patients undergoing thoracotomy and VATS lobectomy for non-small cell lung cancer (NSCLC) with visceral pleural invasion.

Methods. From 2004 to 2009, 2,774 patients underwent curative-intent pulmonary resection for NSCLC at our institution. Of those, 478 patients were pathologically confirmed to have visceral pleural invasion by primary tumor. Among these, 239 patients (50%) underwent VATS lobectomy and 239 (50%) underwent thoracotomy lobectomy. Their medical records were retrospectively reviewed and a propensity score-matched analysis was performed.

Results. Matching based on propensity scores produced 167 patients in each group. There were no significant differences between two groups in age, sex, histologic type, tumor size, and pathologic N stage. The median follow-up duration was 52 months. During follow-up, 14 patients (8.4%) from the VATS group and 12 (7.2%) from the thoracotomy group had ipsilateral pleural recurrence ($p = 0.735$). There was no significant difference in the recurrence pattern between the two groups. Overall survival at 5 years was 83% and 74% in the VATS and thoracotomy groups, respectively ($p = 0.16$). Disease-free survival at 5 years was 65% and 62% in the VATS and thoracotomy groups, respectively ($p = 0.45$).

Conclusions. Compared with thoracotomy, VATS lobectomy does not seem to increase the risk of procedure-related pleural dissemination in patients with NSCLC with visceral pleural invasion. Long-term survival and pattern of recurrence were similar between the two groups.

Accepted for publication May 13, 2013.


Address correspondence to Dr Hong Kwan Kim, Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, 50 Ilwon-dong, Gangnam-gu, Seoul 135-710, Republic of Korea; e-mail: hkt6@skku.edu.

© 2013 by The Society of Thoracic Surgeons

Video-assisted thoracic surgery (VATS) lobectomy is a preferred surgical option for patients with early stage non-small cell lung cancer (NSCLC), and many thoracic surgeons agree that this minimally invasive procedure is feasible and safe. However, it is still controversial whether VATS lobectomy is oncologically effective in patients with NSCLC. Two recent metaanalyses demonstrated that VATS lobectomy was associated with improved survival, but some surgeons are still concerned about the potential violation of oncologic principles during this approach. These concerns arise from the possibility of procedure-dependent recurrence during VATS manipulation, the risk of leaving residual tumors at the surgical margin, and the apprehension about performing an insufficient lymph node dissection.

In particular, regarding the procedure-dependent recurrence, it cannot be ignored that tumor may be disseminated into the pleural cavity during VATS manipulation. This concern would heighten especially when the tumor is peripherally located abutting the pleural surface, compared with the tumor located deep in the parenchyma. However, few investigators have addressed this issue in the literature before. Therefore, in this study, we aimed to assess whether VATS manipulation increases the risk of procedure-related tumor dissemination into the pleural cavity by comparing the incidence of pleural recurrence, the pattern of recurrence, and long-term survival outcomes between patients undergoing VATS lobectomy and patients undergoing thoracotomy lobectomy for NSCLC with visceral pleural invasion.

Patients and Methods

Between January 2004 and December 2009, 2,774 consecutive patients underwent curative-intent surgery for NSCLC at our institution. Among these, 478 patients were found to have visceral pleural invasion on pathologic examination. Patients were excluded from the study if they underwent a lesser resection (wedge or segmentectomy) or a more extensive operation (pneumonectomy,

© 2013 by The Society of Thoracic Surgeons
bilateral lobectomy, sleeve resection, chest wall resection, or major vessel resection), they received neoadjuvant treatment or prior pulmonary resection, and the primary tumor invaded both visceral and parietal pleura. Of these, 239 patients (50%) underwent thoracotomy lobectomy and 239 (50%), VATS lobectomy. Their medical records were retrospectively reviewed to assess clinical characteristics, early postoperative outcomes, recurrence pattern, and survival. The Institutional Review Board of Samsung Medical Center approved this study and waived consent.

The routine preoperative workup included pulmonary function tests, computed tomography (CT) scans of the chest and upper abdomen, positron emission tomography/CT scans, flexible bronchoscopy, and brain magnetic resonance imaging (MRI). For patients with preoperatively proven NSCLC, cervical mediastinoscopy was routinely performed regardless of the findings of CT or positron emission tomography/CT scans. In general, candidates for VATS lobectomy were patients with clinical stage I disease, peripherally located lesions (no endobronchial lesions), and a tumor of 6 cm in diameter or smaller. Patients were required to be able to tolerate single-lung ventilation, as determined by preoperative pulmonary function tests.

The VATS lobectomy was performed as previously described [6]. Briefly, all patients underwent standard anesthesia care with the use of double-lumen endotracheal tubes. Two ports and a utility incision were made without rib spreading. A 15-mm trocar for the 10-mm, 30-degree thoracoscope was placed through the seventh or eighth intercostal space in the posterior axillary line. A 4-cm utility incision was made through the fourth or fifth intercostal space in the anterior axillary line. An additional 5-mm trocar was placed through the sixth or seventh intercostal space in the posterior scapular line. The vessels and bronchi of the target lobe were individually dissected. All specimens were placed into an impermeable bag and removed through the utility incision. Thoracotomy lobectomy was performed through a posterolateral thoracotomy incision. The chest was entered through the fourth or fifth intercostal space and a rib spreader was used to obtain exposure. Otherwise, the procedure of lobectomy was done in the same manner as VATS lobectomy. Systematic lymph node dissection was mandatory at thoracotomy and thoracoscopic approach. Mediastinal lymph node dissection consisted of en bloc resections of all nodes at stations 2R, 4R, 7, 8, 9, and 10R for right-sided tumors and nodes at stations 4L, 5, 6, 7, 8, 9 and 10L for left-sided tumors.

Postoperatively, patients were managed based on the same treatment strategy, irrespective of whether the procedure was done through thoracotomy or VATS. Adjuvant chemotherapy, radiotherapy, or concurrent chemoradiation was administered to patients who were eligible and able to tolerate additional treatments. Patients were regularly evaluated by CT every 3 to 4 months for the first 2 years after surgery, and then every 6 months thereafter. Patients were annually evaluated by positron emission tomography/CT scans. Locoregional recurrence was defined as that occurring within the ipsilateral hemithorax, including the pleura and mediastinal lymph nodes. Distant recurrence was defined as that developing within the contralateral hemithorax or a distant solid organ. Whenever recurrence was suspected, we tried to obtain histologic or unequivocal radiologic proof. In cases lost to follow-up, a telephone interview was conducted to determine late outcomes.

Descriptive statistics were used to assess patient demographic characteristics and outcomes. Normally distributed continuous data were expressed as mean ± SD. Categorical data were expressed as counts and proportions. Student’s t tests or the Wilcoxon rank sum test, depending on the normality of distribution, and the χ² test or Fisher’s exact test were used to compare continuous and categorical variables, respectively. One-way analysis of variance or the Kruskal-Wallis test, depending on the normality of distribution, was used to compare the continuous variables among three groups. Overall survival was defined as the time from the date of surgery until the last date of follow-up for patients who remained alive or until death. Disease-free survival (DFS) was defined as the time from the date of surgery to recurrence or death. Survival curves were prepared using the Kaplan-Meier method and were compared univariately using the log rank test. All statistical tests were two-sided with a significance level set at 0.05 and were performed using Stata software version 10.0 (Stata, College Station, TX).

A propensity score-matched analysis was performed. Propensity scores were generated using a logistic regression model, in which lobectomy through VATS or thoracotomy was the dependent variable and age, sex, tumor size, pathologic N stage, and histologic subtype were the independent variables. Patients who underwent VATS lobectomy or thoracotomy lobectomy were then matched on the basis of their propensity score using a genetic matching algorithm. The balance in the covariates between the two groups was assessed by standardized differences.

Results

Clinicopathologic Features

The patients’ characteristics of the initial study population are summarized in Table 1. There were more female patients with adenocarcinoma in the VATS group than in the thoracotomy group. Furthermore, patients in the VATS group had smaller primary tumor with lower maximum standardized uptake value (SUVmax) than patients in the thoracotomy group. In this context, patients in the VATS group showed better overall survival (85% versus 71% at 5 years, p = 0.0018; Fig 1) and DFS (85% versus 70% at 5 years, p = 0.0006; Fig 2) than patients in the thoracotomy group, although there was no significant difference in the incidence of pleural recurrence between the two groups. Therefore, we decided to perform the propensity-matching approach to make the two groups comparable in terms of the clinicopathologic features.
Matching based on propensity scores produced 167 patients in each group. The baseline characteristics of the patients in each group are shown in Table 2. As designed, there was no statistically significant difference between the two groups in terms of age, sex, and histologic subtype. There were no cases of incomplete resection. There were no statistically significant differences between the two groups in the size of primary tumor and pathologic T stage. The median number of metastatic and dissected lymph nodes were 0 (range, 0 to 14) and 15 (range, 14 to 50), respectively. There was no significant difference between the two groups in terms of the numbers of metastatic and dissected lymph nodes and thus pathologic N stage. Postoperatively, 162 patients (48.5%) underwent adjuvant chemotherapy (n = 109), radiotherapy (n = 24), or chemoradiation (n = 29). There was no significant difference in the frequency of adjuvant treatment between the two groups (p = 0.51).
Early Postoperative Outcomes

There were 4 in-hospital deaths (2.4%) in the VATS group and 6 in-hospital deaths (3.6%) in the thoracotomy group. All the patients died of acute respiratory distress syndrome. Ninety-six patients (28.7%) had postoperative complications. The most common complication was prolonged air leak (47 patients). There were 16 episodes of acute lung injury or acute respiratory distress syndrome, 18 episodes of atrial fibrillation, 13 episodes of pneumonia, 5 episodes of chylothorax, and 1 episode of postoperative bleeding. There was no significant difference in the incidence of in-hospital mortality and postoperative morbidity between the two groups ($p = 0.75$ and 0.47, respectively).

Table 2. Characteristics of the Study Population After Propensity Score-Based Matching ($n = 334$)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n = 334)</th>
<th>VATS (n = 167)</th>
<th>Thoracotomy (n = 167)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td>60.2 (31–82)</td>
<td>59.9 (31–81)</td>
<td>60.7 (36–82)</td>
<td>0.411</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.276</td>
</tr>
<tr>
<td>Male</td>
<td>184 (55.1)</td>
<td>87 (52.1)</td>
<td>97 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>150 (44.9)</td>
<td>80 (47.9)</td>
<td>70 (41.9)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>Yes</td>
<td>113 (33.8)</td>
<td>53 (31.7)</td>
<td>60 (35.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>221 (66.2)</td>
<td>114 (68.3)</td>
<td>107 (64.1)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td>0.827</td>
</tr>
<tr>
<td>Yes</td>
<td>173 (51.8)</td>
<td>80 (47.9)</td>
<td>93 (55.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>161 (48.2)</td>
<td>87 (52.1)</td>
<td>74 (44.3)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td>0.978</td>
</tr>
<tr>
<td>ADC</td>
<td>281 (84.1)</td>
<td>140 (83.8)</td>
<td>141 (84.4)</td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>28 (8.4)</td>
<td>14 (8.4)</td>
<td>14 (8.4)</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>25 (7.5)</td>
<td>13 (7.8)</td>
<td>12 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Tumor size, cm, mean</td>
<td>3.04</td>
<td>3.05</td>
<td>3.04</td>
<td>0.628</td>
</tr>
<tr>
<td>SUVmax of tumor, mean</td>
<td>8.15</td>
<td>7.58</td>
<td>8.7</td>
<td>0.143</td>
</tr>
<tr>
<td>Total dissected LN, median</td>
<td>15</td>
<td>13</td>
<td>17</td>
<td>0.077</td>
</tr>
<tr>
<td>Positive LN, median</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.981</td>
</tr>
</tbody>
</table>

*Includes large cell neuroendocrine carcinoma or mucoepidermoid carcinoma.

ADC = adenocarcinoma; LN = lymph node; SCC = squamous cell carcinoma; SUVmax = maximum standardized uptake value; VATS = video-assisted thoracic surgery.

PLEURAL RECURRENCE AFTER VATS LOBECTOMY

Pleural Recurrence, Recurrence Pattern, and Survival

The median follow-up duration was 52 months (range, 0.2 to 99.6). Follow-up was complete for all patients. At the end of follow-up, there were 261 surviving patients (78.1%). Overall survival at 5 years was 83% and 74% in the VATS and thoracotomy groups, respectively (Fig 3). There was no significant difference in overall survival at 5 years between the two groups ($p = 0.16$).

During follow-up, 83 patients (24.9%) had recurrence. Fourteen patients (8.4%) from the VATS group and 12 (7.2%) from the thoracotomy group had ipsilateral pleural recurrence ($p = 0.735$). Eighteen patients (10.8%) and 16 (9.6%) had locoregional recurrence in the VATS and thoracotomy groups, respectively ($p = 0.717$). Thirty-two patients (19.2%) and 37 patients (22.2%) had distant metastasis in the VATS and thoracotomy groups, respectively ($p = 0.499$). The pattern of recurrence was listed in Table 3. There was no significant difference in the pattern of recurrence between the two groups. Disease-free survival at 5 years was 65% and 62% in the VATS and thoracotomy groups, respectively (Fig 4). There was no significant difference in DFS at 5 years between the two groups ($p = 0.45$).
Over the past 2 decades, VATS lobectomies have been performed with increasing frequency, and many researchers have demonstrated that VATS lobectomy is a feasible and safe procedure [1–6]. However, questions still remain about whether VATS lobectomy is oncologically effective for patients with NSCLC. Although recent metaanalyses showed that VATS lobectomy was associated with improved survival [7, 8], some thoracic surgeons are still reluctant to adopt VATS lobectomy for patients with NSCLC, because they are concerned about the potential violation of oncologic principles during this approach. These concerns arise from the possibility of procedure-dependent recurrence during VATS manipulation, the risk of leaving residual tumors at the surgical margin, and the apprehension over performing an insufficient lymph node dissection [8–11].

Although it is basically difficult to scientifically measure and compare the performance of surgical techniques, several investigators attempted to determine whether mediastinal lymph node dissection can be performed as effectively in VATS as in open thoracotomy. Sagawa and colleagues [12] performed VATS lobectomy and lymph node dissection followed by immediate thoracotomy to look for “remnant” lymph nodes. They found that remnant lymph nodes missed by VATS were only 2% to 3% [12]. Scott and associates [13] showed that the median total number of lymph nodes retrieved was similar for both VATS lobectomy (15 nodes) and open lobectomy (19 nodes). More recently, Boffa and coworkers [14] demonstrated that mediastinal nodal evaluation by VATS and thoracotomy resulted in equivalent upstaging from N0 to N2 (5.0% open and 4.9% VATS; p = 0.52), suggesting that both approaches achieve similarly complete nodal evaluations of the mediastinum during lobectomy. With regard to the complete resection rate, Swanson and coworkers [4] showed that complete resection was possible in all patients. In addition, many other series have shown no difficulty in achieving complete resection with thoracoscopic lobectomy [1, 2].

However, few studies have reported on the incidence of procedure-related tumor dissemination during VATS procedure. In the present study, we investigated the incidence of pleural recurrence in patients who underwent VATS or thoracotomy lobectomy for non-small cell lung cancer and then compared them between the two groups, based on the notion that the pleural recurrence might result from procedure-related pleural dissemination. Among the whole study population, there were 26 cases (7.8%) of ipsilateral pleural recurrence during follow-up. Fourteen patients (8.4%) from the VATS group and 12 (7.2%) from the thoracotomy group had pleural recurrence. The overall incidence of pleural recurrence after surgical treatment for patients with visceral pleural invading NSCLC appears to be low, and there was no significant difference between the two groups.

The concerns over the possibility of procedure-related tumor dissemination by VATS lobectomy could be ultimately relieved by the findings that its long-term survival outcomes are comparable to that of conventional thoracotomy. Whitson and coworkers [7] performed a systematic review of 39 studies comparing VATS with open lobectomy. In their report, patients who underwent VATS lobectomy had improved 4-year survival versus patients with open lobectomy (88.4% versus 71%, p = 0.003). More recently, a meta-analysis by Yan and colleagues [8] demonstrated that 5-year survival was significantly improved for patients undergoing VATS lobectomy for early-stage NSCLC [8]. In our series, 5-year overall survival and DFS were similar between patients who underwent VATS and thoracotomy lobectomy. These findings suggest that VATS lobectomy is oncologically equivalent to thoracotomy lobectomy, which seems to be in line with those from previous reports [15–18].

**Table 3. Summary of Recurrence in Study Population After Propensity Score-Based Matching**

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>All Patients (n = 334)</th>
<th>VATS Group (n = 167)</th>
<th>Thoracotomy Group (n = 167)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall recurrence</td>
<td>129 (38.6)</td>
<td>64 (38.3)</td>
<td>65 (38.9)</td>
<td>0.704</td>
</tr>
<tr>
<td>Ipsilateral pleura*</td>
<td>26 (7.8)</td>
<td>14 (8.4)</td>
<td>12 (7.2)</td>
<td>0.735</td>
</tr>
<tr>
<td>Locoregional</td>
<td>34 (10.2)</td>
<td>18 (10.8)</td>
<td>16 (9.6)</td>
<td>0.717</td>
</tr>
<tr>
<td>Distant</td>
<td>69 (20.7)</td>
<td>32 (19.2)</td>
<td>37 (22.2)</td>
<td>0.499</td>
</tr>
</tbody>
</table>

*a Ipsilateral pleural recurrence was counted separately from locoregional recurrence.

VATS = video-assisted thoracic surgery.

**Comment**

Fig 4. Disease-free survival of the study population after propensity score-based matching: video-assisted thoracic surgery (VATS [solid line]) versus thoracotomy (dotted line).
The main limitation of this study is that the determination as to whether the pleural tumor dissemination truly occurred during procedures was only based on whether patients had pleural recurrence during follow-up. That is, we did not evaluate the microscopic presence of malignant cells by means of pleural fluid cytology. Possibly, this suggests that we might have missed the presence of occult microscopic pleural dissemination that developed even before the operation. This also means that the pleural recurrence might not have been related to the procedure per se. This likelihood can be even increased by the fact that we narrowed down the study population into patients with visceral pleural invasion. To overcome this limitation, we should have done pleural fluid cytology in every case. Nonetheless, it should be noted that the probability of pleural recurrence seems to be similar irrespective of whether patients underwent VATS or thoracotomy lobectomy.

This study has several other limitations. Because our data were retrospectively collected and reviewed, unknown confounding factors and inherent selection biases could exist. For the initial study population before the propensity-matching method, there was no significant difference in the incidence of pleural recurrence between the VATS and thoracotomy groups. However, in terms of the survival outcomes, both overall survival and DFS in the VATS group were significantly better than in the thoracotomy group. These results were related to patients in the VATS group having more favorable clinicopathologic features such as female adenocarcinoma with small size and lower SUVmax. That also implies that there might have been a tendency to select candidates for VATS lobectomy among patients in whom the procedure can be done more easily, although no surgeons of our institution preferentially perform VATS or thoracotomy lobectomy for early stage NSCLC. Indeed, the reason we conducted this study was that we aimed to demonstrate that VATS is at least not inferior to conventional thoracotomy when avoiding the risk of procedure-related tumor dissemination into the pleural cavity. However, it does not seem to be persuasive if we argue that VATS is superior to thoracotomy merely based on the outcomes of the initial study population, in which the patients characteristics were unevenly distributed between the two groups. A prospective randomized trial would ideally confirm the equivalence of VATS and thoracotomy lobectomy in avoiding the risk of procedure-related pleural dissemination, but it may be neither ethical nor practical to actually complete the trial comparing surgical techniques. Therefore, we decided to perform the propensity-matching approach to allow for comparative analysis of patients with similar characteristics. Nonetheless, it should be noted that the propensity-matching approach still has inherent limitations regarding the selection bias, because it essentially selected the study population from the initial population, which may not be free from the selection bias.

In summary, we compared the incidence of pleural recurrence and long-term survival between patients undergoing thoracotomy and VATS lobectomy for NSCLC with visceral pleural invasion. There were no significant differences between the two groups in terms of clinical and pathological characteristics including age, sex, histologic type, tumor size, and pathologic N stage. There were no significant difference in the incidence of pleural recurrence, overall survival, and DFS between the two groups. Therefore, compared with thoracotomy, VATS lobectomy does not seem to increase the risk of procedure-related pleural dissemination in patients with NSCLC with visceral pleural invasion.

References

INVITED COMMENTARY

Kim and associates [1] have described their series of lobectomy patients with visceral pleural invasion and demonstrated that thoracoscopic lobectomy patients have no increased risk of pleural dissemination compared with open lobectomy patients. In addition, no differences were demonstrated between the groups in terms of locoregional recurrence, distant recurrence, and survival. The strengths of this study include the propensity matching to attempt to eliminate selection bias and also the excellent follow-up of the patients. The main weakness of the study is the relatively high rate of morbidity and mortality (nearly 3% mortality and 14% prolonged air leak rate), although these were not significantly different between the two groups.

Although the risk of pleural spread should be a minor concern with either a minimally invasive or open approach if care is taken not to manipulate the tumor itself, debates continue regarding the overall oncologic efficacy of minimally invasive lobectomy. Although the results of the present study point to no difference in oncologic efficacy with thoracoscopy, some concern persists. First, although propensity matching is laudable to address selection bias, it may lead to a study underpowered to detect small differences. Indeed, no significant difference was seen in preoperative morbidity and mortality (nearly 3% mortality and 14% prolonged air leak rate), although these were not significantly different between the two groups.

As surgeons adopt minimally invasive approaches, oncologic outcomes must remain paramount. Assessment of lymph nodes is extremely important, given the efficacy of adjuvant therapy for N1 disease. The good news is that efficacy of minimally invasive hilar lymph node analysis and subsequent upstaging improves with surgeon experience [1]. We must continue to perform procedures with as little morbidity as possible with complete lymph node assessment. Otherwise, we will lose resectable patients to the radiation oncologists.

Mark Onaitis, MD
Thoracic Surgery
Duke University
DUMC Box 3055
Durham, NC 27710
e-mail: mwo@duke.edu

References