Long-term survival in video-assisted thoracoscopic lobectomy vs open lobectomy in lung-cancer patients: a meta-analysis

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INTRODUCTION

Thoracoscopy is a useful adjunct in the thoracic surgeon’s arsenal. The diagnostic role of video-assisted thoracic surgery (VATS) wedge resection in non-small-cell lung cancer (NSCLC) is well acknowledged. However, in the past two decades there has been less agreement on the role of VATS lobectomy in the treatment of lung cancer. The majority of lobectomies are still approached via a thoracotomy. Critics of the VATS technique cite concerns in regard to intraoperative safety [1] and inferior oncological technique. Proponents of VATS lobectomy argue that patients have better cosmesis, less postoperative pain, shorter length of stay and lower overall cost.

Cholecystectomies underwent a similar revolution with the advent of laparoscopy. However, the key difference here is that the aetiology is primarily a benign inflammatory process. As oncological surgeons, the driving impetus is performing the optimal surgical oncological procedure. The superiority of either the VATS or thoracotomy approach is not clear-cut as data from large randomized trials are scarce. The two most significant randomized clinical trials [2, 3] involving a total of 155 patients were conducted more than 10 years ago. One of the trials reported data on long-term outcomes and concluded that there were no differences in 5-year recurrence and survival between the two approaches [3]; the other trial showed that there were lower postoperative complications with VATS [2]. Most individual observational studies comparing VATS lobectomy with open lobectomy include small numbers of patients and are thus underpowered to detect a difference, if one exists. There have been three reviews published in the last 5 years on this topic [4-6], but none of them focused on long-term survival. Therefore, we reviewed the current literature in order to better illustrate the long-term outcomes of VATS lobectomy and how this compares with open lobectomy.

METHODS

Original research studies that evaluated long-term outcomes of VATS vs thoracotomy were identified by searching the National Library of Medicine and National Institutes of Health PubMed database and Embase. The search strategy included the following keyword search terms: ‘thoracic surgery’, video-assisted’, ‘thoracotomy’ and spanned from January 1990 to December 2011. In addition, references included in two previously published meta-analyses [4, 6] and a systematic review [5] on short- and long-term outcomes of VATS were reviewed. Reference lists from all retrieved articles were also reviewed in search of additional eligible articles.

Eligibility

Studies were considered eligible according to the following a priori criteria: (1) be written in English; (2) be observational; (3) have the presence of a control group and (4) have the availability...
<table>
<thead>
<tr>
<th>Study, year [ref]</th>
<th>Year</th>
<th>Design</th>
<th>V (N)</th>
<th>T (N)</th>
<th>Inclusion criteria</th>
<th>Histology</th>
<th>Outcome</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landreneau et al., 1997 [57]</td>
<td>1997</td>
<td>RC</td>
<td>60</td>
<td>117</td>
<td>PathT1N0 NSC (CT)</td>
<td>NA</td>
<td>5-year survival, recurrence</td>
<td>Survival: T: 70%; V: 65% Local/systemic recurrence: T: 19%; V: 26% V: 97%; T: 78.5%</td>
<td>Patients old, with comorbidities</td>
</tr>
<tr>
<td>Kaseda et al., 2000 [58]</td>
<td>2000</td>
<td>RC</td>
<td>44</td>
<td>77</td>
<td>50 patients were path Stage I (not known how many VATS)</td>
<td>NA</td>
<td>5-year survival</td>
<td>V: 62.8%; T: 62.9% Stage IA: 64.9%; 79.7% Thoracotomy survival is from 1976 to 1990</td>
<td></td>
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<tr>
<td>Thomas et al., 2002 [38] and Giudicelli et al., 1994 [39]</td>
<td>1990-1999</td>
<td>RC</td>
<td>110</td>
<td>405</td>
<td>Path Stage I (NSC)</td>
<td>AD, SCC, other</td>
<td>5-year survival</td>
<td>V: 62.8%; T: 62.9% Stage IA: 64.9%; 79.7%</td>
<td>V more frequent in AD, females. V offered to Stage ID, &lt;5 cm, no adhesions Patients &gt;65 years. V more frequent in patients with CV diseases</td>
</tr>
<tr>
<td>Koizumi et al., 2002 [59]</td>
<td>1990-2000</td>
<td>RC</td>
<td>52 (Stage IA: 25)</td>
<td>35 (Stage IA: 9)</td>
<td>TI, TII</td>
<td>AD, SCC, small, Large, AD + SCC, carcinoma</td>
<td>5-year survival</td>
<td>V: 56.6%; T: 38.3% Stage IA: V: 83.9%; T: 60%</td>
<td></td>
</tr>
<tr>
<td>Tatsumi and Ueda, 2003 [60]</td>
<td>1995-2003 for VATS; 1993-1998 for T</td>
<td>RC</td>
<td>118</td>
<td>121</td>
<td>Clinical Stage I and II NSC (CT)</td>
<td>AD, SCC</td>
<td>5-year survival</td>
<td>V: 91.9%; T: 89.3% Stage IA AD: V 92.4%; T: 86.5%</td>
<td></td>
</tr>
<tr>
<td>Watanabe et al., 2005 [61]</td>
<td>1997-2004</td>
<td>RC</td>
<td>221</td>
<td>190</td>
<td>Clinical Stage I NSC</td>
<td>AD, SCC, other</td>
<td>5-year survival, recurrence</td>
<td>Survival: V: 88.6%; T: 92.4% Recurrence: V: 92.9%; T: 86.5%</td>
<td>V more frequent in AD and less advanced cases</td>
</tr>
<tr>
<td>Tashima et al., 2005 [62]</td>
<td>1996-2000</td>
<td>RC</td>
<td>67</td>
<td>173</td>
<td>Clinical Stage I</td>
<td>AD, SCC, large</td>
<td>5-year survival</td>
<td>Clinical Stage IA: V: 98%, T: 90% V: 72%; T: 63%</td>
<td>V more frequent in Stage IA; results derived from figure</td>
</tr>
<tr>
<td>Ng et al., 2005 [40] and Garzon et al., 2006 [41]</td>
<td>1999</td>
<td>RC</td>
<td>11</td>
<td>10</td>
<td>15 path Stage I</td>
<td>7 AD; 2 SCC; 1 large</td>
<td>5-year disease-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigemura et al., 2006 [63]</td>
<td>1999-2004</td>
<td>RC</td>
<td>81</td>
<td>55</td>
<td>Clinical Stage I NSC (CT, ultrasound, scintigraphy)</td>
<td>AD, SCC, BAC, large</td>
<td>5-year survival</td>
<td>Stage IA</td>
<td>V: 96%; T: 97.2%</td>
</tr>
<tr>
<td>Shiraishi et al., 2006 [44]</td>
<td>1994-2005</td>
<td>RC</td>
<td>81</td>
<td>79</td>
<td>Clinical Stage I NSC (CT, MRI)</td>
<td>NA</td>
<td>5-year survival, recurrence</td>
<td>Survival: V: 89.1%; T: 77.7% Recurrence: V: 80%; T: 76.2%</td>
<td>AD more frequent in V; recurrence associated to lung side and lymph node involvement (multivariate analysis)</td>
</tr>
<tr>
<td>De L Stanbridge et al., 2007 [50]</td>
<td>1998-2005</td>
<td>RC</td>
<td>137</td>
<td>30</td>
<td>Mixed stage, higher stages among T</td>
<td>AD, SCC, large, others</td>
<td>5-year survival</td>
<td>V: 64%; T: 59%</td>
<td>AD more frequent in V; SCC in T; patients selection changed over time</td>
</tr>
<tr>
<td>Sawada et al., 2007, 2008 [64, 65]</td>
<td>1993-2002</td>
<td>RC</td>
<td>165</td>
<td>123</td>
<td>Clinical Stage I NSC</td>
<td>BAC, BAC + AD, other AD, SCC, large</td>
<td>5-year survival</td>
<td>V: 94.9%; T: 81.5%</td>
<td>V includes more AD, smaller lesions, better lung function</td>
</tr>
<tr>
<td>Sakuraba et al., 2007 [66]</td>
<td>1997-2004</td>
<td>RC</td>
<td>84</td>
<td>56</td>
<td>Clinical Stage I NSC (CT, scintigraphy, MRI)</td>
<td>AD, others</td>
<td>5-year survival, disease-free</td>
<td>V: 82%; T: 72% Disease free: V: 80; T: 68%</td>
<td></td>
</tr>
<tr>
<td>Whitson et al., 2007 [67]</td>
<td>1998-2005</td>
<td>RC</td>
<td>59</td>
<td>88</td>
<td>Clinical Stage I NSC</td>
<td>AD, SCC, other</td>
<td>4-year survival</td>
<td>V: 72%; T: 64%</td>
<td></td>
</tr>
<tr>
<td>Seder et al., 2009 [51]</td>
<td>2003-2008</td>
<td>RC</td>
<td>89</td>
<td>160</td>
<td>Stage I NSC (CT, PET)</td>
<td>NA</td>
<td>30-month survival</td>
<td>Total recurrence; 40-month survival</td>
<td>V: 84%; T: 86%</td>
</tr>
</tbody>
</table>
of information on 3- to 5-year mortality for both intervention and control groups.

**Video-assisted thoracic surgery**

The search resulted in 53 eligible papers. Further detailed review of the 53 papers excluded: 24 papers due to missing long-term follow-up data [7–30], 4 due to lack of survival overall [31–33] or for the control group [34], 1 paper did not have a control group [35], 1 was written in Japanese [36] and 1 paper only reported 2 years of survival data [37]. Twenty-two articles were included on VATS vs thoracotomy. Of the 22, 4 [38–41] overlapped and relied on the same source populations and were therefore considered as 2 distinct data sets, bringing the overall number of data sets on VATS to 20 (Table 1).

**Quality of the studies**

Two studies [42, 43] used propensity score matching in order to make other covariates and possible confounding similar in the two groups. Four studies [42–45] adjusted the results for possible confounders with a multivariate analysis.

**Statistical methods**

For each study, the standard error of the 5-year mortality rate (expressed as a percentage) was calculated according to the formula:

\[ SE = \frac{\sqrt{(a \times (100 - a))}}{\sqrt{n}}, \]

where \( a \) = 5 year mortality rate expressed as a percentage and \( n \) = sample size.

The percent difference in 5-year mortality between the two surgical methods was calculated for each study; the standard error of the difference was calculated as

\[ SE (\text{diff}) = \sqrt{(SE1)^2 + (SE2)^2}), \]

where \( SE1 \) is the SE of the 5-year mortality in Group 1 and \( SE2 \) is the SE of the 5-year mortality in Group 2 [46].

In order to carry out the meta-analysis computations, the ‘metan’ command in Stata (Stata Version 10, StataCorp. LP, College Station, TX, USA) was used. This command applies meta-analytic techniques to calculate the combined percent difference in mortality between the two groups. Fixed effect models were used if no heterogeneity among studies was observed; otherwise, random effect models with inverse-variance weighting were applied. The Q statistics were used to test for heterogeneity between the studies included in the meta-analyses. The proportion of total variability attributed to between-studies heterogeneity was assessed with the \( I^2 \) statistic, a confirmatory test for heterogeneity [47, 48], with \( I^2 < 25 \), 25–50 and >50% representing low, moderate and high degree of heterogeneity, respectively. The possibility of publication bias was
determined by performing Begg funnel plots and the Egger’s bias test [49].
Stratified analyses were performed according to the geographical area of origin of the study (Asia, USA/Europe).

RESULTS
Published papers included 2106 patients who underwent VATS and 2661 patients who underwent thoracotomy (Table 1). The size of the studies ranged from 21 [40] to 515 patients [38]. All studies but two [45, 50] reported on early-stage NSCLC. All studies were observational and retrospective in nature. The assignment to one surgical treatment or the other was made on the basis of clinical judgment.

Five-year survival ranged from 62 to 97% for VATS and from 58 to 97% for thoracotomy. The summary estimates for 5-year survival are presented in Fig. 1. There was an advantage in 5-year mortality for patients who underwent VATS vs patients who underwent thoracotomy (meta difference in survival: 5%; 95% CI: 3–6%) with large heterogeneity among studies (Q = 42.6; P-value: 0.001; \(I^2 = 55.7\%) ). There was no evidence of publication bias (Fig. 2).

Data were stratified according to the geographical area where the study was conducted (Table 2). Average difference in survival between lung-cancer patients who underwent VATS and those who underwent thoracotomy was large in studies conducted in Asia in comparison with studies conducted in the USA/Europe (5.5 vs 0.5%). However, a large heterogeneity was observed among Asian studies. Three studies conducted in the USA/Europe reported follow-ups between 30 and 40 months [43, 51–53]. When those studies were excluded, the difference in 5-year mortality between VATS studies and thoracotomy studies conducted in western countries was 3.2%. No heterogeneity was observed in the US/European studies.

DISCUSSION
Our meta-analysis suggests that VATS lobectomy is an acceptable alternative to open thoracotomy. The short-term benefits of the VATS approach have been previously documented in the
literature. Patients undergoing VATS lobectomy tend to have fewer complications, shorter chest tube duration and shorter length of stay [42, 54]. The relative slow adoption of this technique is likely attributed to concerns regarding presumed procedure-dependent recurrence and long-term survival. Our meta-analysis of long-term outcomes reveals a 5-year survival advantage with VATS lobectomy in comparison with classic thoracotomy. It is not completely clear why this would be the case, but it may be related to the reduced number of cytokines released and the resultant reduction in perioperative immunosupression seen in VATS patients [13, 14, 20, 26, 40, 55] or patient selection bias.

Original studies examining long-term outcomes are predominately limited to case and case–control series and are included in the present meta-analysis. The size of the studies is variable, but always limited to a few hundred patients. The largest of these studies [42] showed a trend towards improved 5-year survival with VATS lobectomy vs thoracotomy; however, the difference in survival between the two techniques was not statistically significant. There are two randomized control trials (RCTs) on this topic that were conducted more than 10 years ago [2, 3], and only one reported results on long-term outcome. It is likely that techniques have changed over the last 10 years and that surgeon expertise in performing VATS has greatly improved over time, thus making the results of the RCTs somewhat obsolete. Unfortunately, it is unlikely that a large prospective randomized trial will be performed as noted by the inability to open the CALGB 140501: VATS lobectomy vs open lobectomy trial due to funding limitations [5]. Therefore, we will have to rely on summary estimates from observational studies to make a decision about the efficacy of VATS on long-term outcomes in lung-cancer patients.

Three meta-analyses and systematic reviews have been performed in attempts to extract a more legitimate result [4–6]. These showed a trend towards improved 5-year survival with VATS lobectomy. One of the summary estimates was not statistically significant [4] while two were statistically significant [5, 6]. None suggested the inferiority of VATS lobectomy in regard to long-term survival. However, the present meta-analysis reports summary estimates from 20 studies and is thus more inclusive than previous publications that calculated 5-year mortality rates on 7 studies [4, 6], or included studies on VATS that had no comparison group [5]. In addition, previous meta-analyses rely on the use of relative risk as a point estimate—therefore not taking full advantage of the original design of the individual studies included, which reported and calculated incidence and mortality over time using survival techniques. In the present analysis, we refrained from accepting this approximation, and instead used the percent difference in mortality rates between the two surgical techniques.

Limitations of the present study include non-uniformity of VATS techniques across institutions and moderate heterogeneity, probably due to patient selection bias. As previously observed, any meta-analysis of observational studies is affected by the same biases present in the original studies contained in it [56]. Two randomized clinical trials, which should represent the gold standard, have been published; however, they do not report long-term mortality but only short- and long-term morbidities. There are selection biases that are easily identifiable in the present meta-analysis. Patients who underwent VATS lobectomy were more likely to have earlier-stage disease and often there was no intention-to-treat analysis. More technically challenging cases and conversions were placed in the thoracotomy group. Several studies also included sub-lobar resections in their analyses. The appropriateness of this technique is currently being addressed in the ongoing CALGB 140503: lobectomy vs sublobar resection trial. In addition, several studies had only 3- or 4-year survival data, from which 5-year results were extrapolated. Such biases could have artificially increased the benefits observed with VATS vs open lobectomy.

Despite this, over 4500 patients were involved over a timespan beginning in the late 1980s (when VATS was in its infancy) to 2009—one of the largest pool of patients analyzed. The present meta-analysis conducted on over 2000 patients in each group suggests that long-term outcomes with VATS are at least similar, if not better, than outcomes observed with classic thoracotomy. Therefore, this study lends credence to the literature and provides more evidence in support of the VATS approach to lung cancer. Consequently, when approached judiciously, we advocate VATS lobectomy for the treatment of early-stage NSCLC.

Conflict of interest: none declared.

REFERENCES


Shiraishi T, Shirakusa T, Miyoshi T, Hiratsuka M, Yamamoto S, Iwasaki A.


