Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer

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CRD summary
The review found the safety and efficacy of video-assisted thoracic surgery lobectomy for early stage non-small cell lung cancer was similar to open surgery and found a significant benefit for systemic recurrence and five-year mortality rates. The authors’ conclusions should be treated with caution due to the modest quality of the included studies and the potential for heterogeneity.

Authors’ objectives
To evaluate the safety and efficacy of video-assisted thoracic surgery lobectomy for early stage non-small cell lung cancer.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, and DARE were searched from inception to December 2007 for publications in English, including abstracts and conference proceedings. Search terms were reported. Bibliographies of each retrieved article were handsearched.

Study selection
Randomised and non-randomised comparative studies of video-assisted thoracic surgery lobectomy compared with open lobectomy for early stage non-small cell lung cancer were eligible for inclusion. Studies not directly relevant to lobectomy surgery, such as video-assisted thoracic surgery wedge resection or segmentectomy, or those focusing on patients undergoing lobectomy for pulmonary metastases, were excluded. Studies where the outcomes were biochemical markers or where video-assisted thoracic surgery was compared with assisted video-assisted thoracic surgery lobectomy were also excluded. For studies publishing trial updates, the most recent or complete reports were included.

The review assessed morbidity, mortality, recurrence and all cause five-year mortality.

In included studies, the median length of the incision was 7cm (maximum 10cm); most included studies used posterolateral thoracotomy for open access; and most studies did not use a rib spreader. Where recorded, surgery time ranged from 1.3 to 4.9 hours, blood loss ranged from 72 to 443mL, chest drain duration ranged from 1.2 to 10 days, and hospital stay ranged from 4.1 to 24.9 days. Most included patients were clinical stage cIA and/or cIB and had relatively good pulmonary function. Most studies were conducted in Asia.

It was not clear how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed by two reviewers independently using the method for randomised and non-randomised comparative studies developed by Downs and Black, which used 27 criteria on external and internal validity. Discrepancies were resolved by discussion and consensus with a senior investigator; the final results were reviewed by two senior investigators.

Data extraction
The number of events for each outcome was extracted in order to calculate relative risk (RR) and 95% confidence intervals (CI).

Data extraction was performed by two reviewers independently, with discrepancies resolved by discussion and consensus with a senior investigator; final results were reviewed by two senior investigators.
Methods of synthesis
Relative risks were pooled using a fixed-effect and a random-effects model (DerSimonian and Laird). Between study heterogeneity was determined using $X^2$ and $I^2$ tests, where $I^2$ of 50% or more indicated substantial heterogeneity. Results of random-effects meta-analysis were reported for most outcomes as there was substantial heterogeneity. Publication bias was assessed visually using funnel plots. Some of the included studies did not provide sufficient data to contribute to pooled analyses. Subgroup analyses were performed for the studies where no rib spreader was used and for studies where individual hilar ligation was performed for both video-assisted thoracic surgery and open lobectomy.

Results of the review
Twenty one relevant studies were identified (n=2,641 patients), including two randomised controlled trials (RCTs, n=161 patients, range 61 to 100) and 19 observational cohort studies (n=2,480 patients, range 22 to 292). The mean Downs and Black quality score was 14 out of a maximum of 33 (standard deviation 2.3).

Morbidity and mortality: There were no statistically significant differences between video-assisted thoracic surgery and open lobectomy for postoperative prolonged air leak (eight studies; $I^2=0\%$), arrhythmia (seven studies; $I^2=35.1\%$), pneumonia (five studies; $I^2=28.3\%$), or perioperative mortality (three studies; $I^2=29.8\%$). The pooled estimates for some outcomes were associated with severe heterogeneity ($I^2$ over 90%): blood loss (14 studies), chest drain duration (11 studies), and length of hospital stay (13 studies). The median conversion rate for video-assisted thoracic surgery to open lobectomy was 8.1% (range 0 to 15.7%; 14 studies) due to technical difficulties, extent of tumour, hilar lymph node metastasis, uncontrollable bleeding, completely fused fissure or other reasons.

Recurrence and survival: There was no statistically significant difference between video-assisted thoracic surgery and open lobectomy in locoregional recurrence (six studies; $I^2=30.2\%$), but video-assisted thoracic surgery was associated with a significantly reduced systemic recurrence rate (RR 0.57, 95% CI 0.34 to 0.95; five studies; $I^2=0\%$) and a significantly reduced all-cause five-year mortality rate (RR 0.66, 95% CI 0.45 to 0.97; seven studies; $I^2=0\%$).

The subgroup analyses for studies not using a rib spreader found similar non-significant results for postoperative prolonged air leak, arrhythmia, pneumonia, and locoregional recurrence, but the results for both systemic recurrence rate (three studies; $I^2=0\%$) and all-cause five-year mortality rate (four studies; $I^2=0\%$) did not show a statistically significant benefit for video-assisted thoracic surgery.

Authors' conclusions
Both randomised and nonrandomised trials suggested that video-assisted thoracic surgery lobectomy was an appropriate procedure for selected patients with early stage non-small cell lung cancer when compared with open surgery in terms of safety, survival and local control of cancer.

CRD commentary
The review addressed a well-defined question in terms of participants, interventions and study design, but relevant outcomes were less clear. Relevant databases were searched and unpublished studies were included. Only studies published in English were included, so some relevant studies may have been missed. Validity assessment and data extraction were carried out with efforts to reduce error and bias, but it was not clearly reported whether this process applied to study selection.

Study quality was assessed using suitable criteria and quality scores were reported, but little other relevant detail was given, which made it difficult to judge the quality of the evidence. Some relevant study details were reported, but there were no details of length of follow-up or loss to follow-up, the age and sex of patients, or the procedures used in the comparison groups. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The authors adopted a relatively high threshold for significant heterogeneity. The statistical methods used for the meta-analysis seemed appropriate. The results of all the subgroup analyses were not significant, implying that the reliability of the significant results for all studies should be treated with caution. More than half of the included studies had less than 100 participants.
In view of the modest quality of the included studies and the potential for heterogeneity, the extent to which the authors' conclusions are reliable is unclear.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors identified a need for a well-designed prospective multi-institutional RCT, with a clearly designed protocol for concealment allocation, eligibility criteria, interventions and endpoints.

**Funding**
Funded by one of the authors.

**Bibliographic details**

**PubMedID**
19289625

**DOI**
10.1200/JCO.2008.18.2733

**Original Paper URL**
http://jco.ascopubs.org/cgi/content/abstract/27/15/2553

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Carcinoma, Non-Small-Cell Lung /mortality /surgery; Clinical Trials as Topic; Humans; Lung Neoplasms /mortality /surgery; Neoplasm Recurrence, Local /epidemiology; Pneumonectomy /methods; Video-Assisted Surgery

**AccessionNumber**
12009106026

**Date bibliographic record published**
19/08/2009

**Date abstract record published**
16/06/2010

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.