
DATE: 02 February 2009

CONTEXT AND POLICY ISSUES:

In Canada, lung cancer is the most common type of cancer affecting men and women; it is also the leading cause of death due to cancer in both men and women.\(^1\) It was estimated that 23,900 Canadians would be diagnosed with lung cancer in 2008, and another 20,200 Canadians would die of this disease.\(^2\) The majority of all lung cancers (80%) are non-small cell lung cancer (NSCLC).\(^1\) Surgical resection is recommended for patients with stage I or II NSCLC who have no medical contraindications (such as comorbid disease) and adequate lung function.\(^3\) Surgeons may perform a lobectomy (removing one lobe of the affected lung), a pneumonectomy (removal of an entire lung) or a sublobar resection (removing a portion of one lobe). This has been carried out through a thoracotomy, which involves opening the chest cavity with a skin incision of 15 to 25 cm long, dividing certain muscles and cutting/spreading the ribs.\(^4,5\)

Since 1990s, surgeons began using video-assisted thoracic surgery (VATS) to perform lobectomies.\(^6\) Within the literature, VATS lobectomy is a term used to describe a spectrum of operations, from a mini-thoracotomy with rib-spreading and direct visualization through the wound, to a completely minimally invasive approach with no rib-spreading and use of only thoracoscopic instruments.\(^7\) In the former, a skin incision measuring from 5 to 10 cm in length is required besides the access ports, while the thoracoscope serves only as a light source.\(^8,9\) “Completely thoracoscopic lobectomy” does not require the skin incision but only a few access ports approximately 2 cm in length,\(^4\) therefore maximizes the benefits of this procedure’s decreased invasiveness.\(^8\) Compared to thoracotomy, VATS, especially the completely thoracoscopic lobectomy, produces a strikingly smaller incision resulting in less surgical trauma to the chest wall, which can minimize postoperative inflammatory reactions and pain, and result in earlier return to preoperative functional status.\(^10,11\) Lobectomy was performed via VATS in 20% of all lobectomies.\(^12\) Minimally invasive surgical techniques, like VATS, have been gaining increased interest within the medical community.

Disclaimer: The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

Links: This report may contain links to other information on available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.
Despite the potential benefit associated with minimally invasive lobectomy, uncertainty exists for its use over the conventional open surgery for patients with lung cancer, such as adequacy of the operation, cancer cell dissemination around the trocar insertion, higher/lower cost, the use of special instruments, and appropriate patient selection.\textsuperscript{7,13}

The purpose of the current report is to evaluate the evidence for the clinical and cost-effectiveness of minimal access lobectomy for treatment of patients with lung cancer as compared to open lobectomy.

**RESEARCH QUESTIONS:**

1. What is the clinical effectiveness of minimal access lobectomy compared to open lobectomy for treatment of patients with lung cancer?

2. What is the cost-effectiveness of minimal access lobectomy for treatment of patients with lung cancer?

**METHODS:**

A limited literature search was conducted on key health technology assessment (HTA) resources, including PubMed, OVID’s Embase, the Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2004 and January 2009, and are limited to English language publications only. Filters were applied to limit the retrieval to HTAs, systematic reviews, meta-analyses, economic studies, randomized controlled trials (RCTs), controlled clinical trials, and observational studies.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, HTA reports, systematic reviews, and meta-analyses are presented first. These are followed by economic evaluations, RCTs, observational studies, and evidence-based guidelines.

**SUMMARY OF FINDINGS:**

Three systematic reviews and three observational studies were identified examining the clinical effectiveness of treatment of minimal access lobectomy for patients with lung cancer. There were no economic reports identified.

**Health technology assessments**

No HTAs were identified.

**Systematic reviews and meta-analyses**

Whitson et al. performed a systematic review to determine the potential superiority of the VATS approach compared with thoracotomy on short-term morbidity and long-term survival, for patients with stage I NSCLC.\textsuperscript{6} The authors searched articles published in English only, from January 1992 through April 2007. Thirty-nine studies, of which only one was an RCT, met the selection criteria of the review. The two groups were not significantly different with regards to patient characteristics, tumor histology and cancer stage. Compared to thoracotomy, VATS lobectomy was associated with lower overall complication rate, shorter chest tube duration, shorter hospital length of stay, and higher survival four years after the procedure.
Nonsignificantly lower rates of atrial fibrillation, pneumonia and persistent air leak after VATS compared with thoracotomy were observed. Limitations of this review were that most of the included primary studies were case series or small observational studies, only English-language studies were examined, literature search was performed in a single electronic database (MEDLINE), a concern of publication bias, and the evolutions of practical patterns in thoracic surgery during the 15-year search time frame also influenced the results of this review. The authors concluded that compared with open surgery, VATS lobectomy for patients with early stage NSCLC appears to experience lower morbidity and improved survival rates.

A meta-analysis conducted by Cheng et al. determined whether VATS improves clinical and resource outcomes compared with thoracotomy in adults undergoing lobectomy for NSCLC.\(^5\) Multiple databases were searched from the earliest available date to April 2007. There was no restriction on language. The average quality for the RCTs was low to moderate (assessment tool was not mentioned). Publication bias was not evident. Baseline characteristics were similar for RCTs; in non-RCTs, baseline prognosis was more favorable for VATS (smaller tumor size, earlier cancer stage and tumor more likely to be peripheral) as compared to the open surgery group. Patients in VATS group had fewer postoperative complications, reduced blood loss, less pain, greater postoperative vital capacity, shorter hospital stay, fewer chemotherapy delays and better survival, when compared to the open surgery group. Even though the authors comprehensively reviewed the available evidence, limitations of this report were that the majority of the data was counted on non-RCTs which were subject to selection bias; the small sample size in RCTs precluded adequate power to rule out potential differences, and the important clinical outcomes such as long-term survival rates were not assessed in RCTs either. This meta-analysis suggested that there may be some short-term and possibly even long-term advantages on performing lung resections with VATS techniques rather than through conventional thoracotomy.

Alam et al. conducted a systematic review on VATS lobectomy to assess the safety of the surgery and its adequacy as a cancer operation in patients with early stage NSCLC.\(^7\) The literature was searched from 1966 through June 2005. Practice guidelines, systematic reviews, meta-analyses, RCTs, phase III clinical trials, and major clinical studies published in English were evaluated. Twenty-five primary studies were included. Among the four RCTs, three compared VATS lobectomy with open thoracotomy, while the forth compared complete VATS (a nonrib-spreading approach) to assisted VATS (a mini-thoracotomy approach with rib-spreading). Results from RCTs showed lower postoperative complications, shorter length of hospital stay, less blood loss but longer operating time in the less invasive procedure group; however, the differences between groups were not always statistically significant. All the RCTs were with small sample size. In case-control studies, VATS was associated with less pain, less blood loss during the surgery, shorter chest tube duration, shorter length of stay and longer survival. Majority of the included case-control series enrolled small number of patients, and the two groups were not comparable with respect to cancer stage and severity of symptoms. Selection of controls was problematic in some trials. A number of case series were included as well. The rib-spreading and nonrib-spreading techniques of VATS were evaluated. In summary, a variety of VATS techniques were examined, making generalization of results difficult. It suggested that VATS lobectomy can be safely performed and was an adequate cancer operation for early stage NSCLC.

Details of these reviews are presented in Table 1.
Table 1: Systematic Reviews Examining the Effectiveness of Minimal Access Lobectomy

<table>
<thead>
<tr>
<th>Authors, # of primary studies</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitson et al., 2008&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Pts with stage I NSCLC</td>
<td>VATS lobectomy</td>
<td>Thoracotomy lobectomy</td>
<td>Overall complication rate after surgery: VATS: 16.4% Thoracotomy: 31.2%, p=0.018; Chest tube duration: VATS: 4.2d Thoracotomy: 5.7d, p=0.025; Hospital length of stay: VATS: 8.3d Thoracotomy: 13.3d, p=0.016 4y survival rates: VATS: 88.4% Thoracotomy: 71.4%, p=0.003 Nonsignificant but lower rates for atrial fibrillation, pneumonia and persistent air leak after between groups in VATS vs. thoracotomy, p &gt;0.05</td>
</tr>
<tr>
<td>Cheng et al., 2007&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Pts with NSCLC</td>
<td>VATS (defined by the authors of primary studies, with or without use of rib spreader)</td>
<td>Open lobectomy</td>
<td>VATS vs. Open: Postoperative complications: OR 0.48, 95% CI 0.32 to 0.70 Blood loss: WMD -80ml, 95%CI -110 to -50ml Postoperative vital capacity: WMD 20, 95%CI 15 to 25 Reduced incidence of severe postoperative pain: OR 0.03, 95%CI 0 to 0.3 Hospital stay: WMD -2.6d, 95%CI -5 to -1 Reduced chemotherapy delays: OR 0.15, 95%CI 0.06 to 0.38 Cancer recurrence rates: OR 0.78, 95%CI 0.58 to 1.04 Death rates at 1-5ys: OR 0.72, 95%CI 0.55 to 0.94</td>
</tr>
</tbody>
</table>

Minimal Access Lobectomy for Lung Cancer Patients
<table>
<thead>
<tr>
<th>Authors, # of primary studies</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alam et al., 2007(^7)</td>
<td>Pts with early stage NSCLC</td>
<td>VATS lobectomy</td>
<td>Open lobectomy</td>
<td>RCTs Postoperative complications rate: VATS vs. Open: 6 vs. 16%, p value NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant difference for length of hospital stay, blood loss, operating time, and recurrence rates or survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Case-control studies Less pain, less blood loss, shorter chest tube duration, shorter hospital stay and quick return to activity was reported in VATS group. P values NR.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Case-series 5y survival rates for stage I disease: ranged from 77.9% to 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5y survival rates for stage II disease: ranged from 51.3% to 70.3%</td>
</tr>
</tbody>
</table>

CI – confidence intervals; d – day; NR – not reported; NSCLC – non-small-cell lung cancer; OR – odds ratio; pt – patient; RCT – randomized controlled trial; VATS – video-assisted thoracic surgery; WMD – weighted mean difference; y – year

**Randomized controlled trials**
No RCTs were identified.

**Observational studies**
Three observational studies were identified. They were not addressed within the systematic reviews that were described previously.

Aoki *et al.* compared health-related quality of life (QOL) in patients with NSCLC after VATS lobectomy or thoracotomy, at time points of 3, 12 and 36 months after the surgery.\(^{14}\) Choice of surgical techniques was left to the discretion of the participating surgeons. Medical Outcomes Short Form 36-Item questionnaire (SF-36) was used, in that higher scores indicate a more favorable outcome. Patients in the VATS group were significantly younger than in the thoracotomy group, while other patient characteristics (i.e. sex ratio, pulmonary function, and cancer stage) were similar between groups. Over time, improved QOL was reported for patients in VATS group. At 3 months post surgery, QOL scores for all 8 domains were lower in the VATS group, but no significant difference between groups at 3 or 12 months after surgery. At 36 months post surgery, QOL scores for 6 domains were significantly higher in the VATS group compared to the thoracotomy group, and the difference was significant in two domains. The authors concluded that recovery was quicker in patients with VATS than in those with thoracotomy. Several limitations exist in this study. The authors did not collect patients’ QOL data prior to the surgery, therefore unable to determine whether patients in the two groups had comparable baseline QOL. On the other hand, patients in the VATS group were seven years younger in average than those in the open surgery group given that in the authors’ institution VATS was not used for older patients with lung cancer. Age would be a major confounder when examining the relationship between various surgical techniques and QOL.
The study by Sakuraba and colleagues compared VATS lobectomy with thoracotomy lobectomy in 140 patients with clinical stage IA lung cancer. Seven patients converted from the study group to the comparison group, and were included in the open thoracotomy group, due to firm adhesion in the thoracic space or positive lymph node sample. There were no statistically significant differences across baseline patient characteristics such as age, tumor size, histology types and cancer stages. No significant differences were observed for overall survival, disease-free survival and disease recurrence. The authors considered VATS lobectomy to be one of the therapeutic options in patients with clinical stage IA NSCLC.

Sawada et al. conducted a retrospective review of medical records in 288 patients with stage I NSCLC, to evaluate the relationship between patient characteristics and prognosis after VATS and open lobectomy. There were significantly more patients with stage IA disease, smaller tumor size and lower level of serum carcinoembryonic antigen in the VATS group than in the open surgery group. The 5-year survival rate in VATS group was significantly higher than that in the open surgery group in the univariate analysis. After adjusting for the patient characteristics of the two groups in multivariate analysis, the estimated survival curves were identical. The major limitation of this study was patient bias, which might have great influence on survival. The authors concluded that prognosis after VATS lobectomy was equal to that after open surgery, and that VATS lobectomy is ontologically feasible.

Details of these trials are presented in Table 2.

**Table 2: Observational Studies Examining the Effectiveness of Minimal Access Lobectomy**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Intervention</th>
<th>comparison</th>
<th>Results</th>
</tr>
</thead>
</table>
| Aoki et al., 2007 | 33 pts with NSCLC           | 17 pts VATS lobectomy: 5cm skin incision for utility thoracotomy, and additional 2 access ports | 16 pts Thoracotomy: 20-25cm skin incision, with rib resection | 3 months after surgery: VATS: QOL related to all 8 domains in SF-36 was decreased in VATS group vs. thoracotomy group, differences not significant (p values NR) 
12 months after surgery: no significant differences in QOL between groups (p values NR) 
36 months after surgery: QOL scores for PF, SF, RP, RE, BP and GH were higher in VATS group, difference was significant for RP and RE (p values NR) |
| Sakuraba et al., 2007 | 140 pts with clinical stage IA NSCLC | 84 pts VATS lobectomy: 5cm main access portion and additional 1 or 2 access ports | 56 pts Lobectomy via open thoracotomy: 20cm incision without rib resection | Overall 5y survival: VATS: 82% Open: 72%, p=0.933 
Disease free 5y survival: VATS: 80% Open: 68%, p=0.654 
Operative death and death within 30d of surgery: VATS: 0 |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Intervention</th>
<th>comparison</th>
<th>Results</th>
</tr>
</thead>
</table>
| Sawada et al., 2007 | Pts with stage I NSCLC | 165 pts VATS lobectomy: 6-8cm access thoracotomy plus 2 or 3 trocars placed | 123 pts Open lobectomy: 1 or 2 ribs resected | Open: 0  
Recurrence:  
VATS: 7pts  
Open: 6pts, p=0.209  
5y survival rates:  
VATS: 94.5%  
Open: 81.5%, p=0.002 |

BP – bodily pain; GH – general health; NR – not reported; NSCLC – non-small-cell lung cancer; PF – physical functioning; pt – patient; QOL – quality of life; RE – role emotional; RP – role physical; SF-36 – Medical Outcomes Short Form 36-Item questionnaire; SF – social functioning; y – year

**Economic evaluations**

No economic evaluations were identified.

**Limitations**

- Limited evidence was identified evaluating the effectiveness of minimal access lobectomy for patients with lung cancer; a small number of RCTs were included in the systematic reviews, while no economic studies were identified in the search time frame;
- In the systematic reviews, the majority of primary studies were non-RCTs and case series, in that patients’ baseline characteristics were not comparable between groups;
- Quality of the included studies varied and some were of low quality due to significant selection bias in non-RCTs;
- Various techniques from mini-thoracotomy to complete minimally invasive lobectomy were reported, make it difficult to draw conclusions;
- Most of the studies examined VATS in patients with early stage NSCLC, and the generalizability of our results to patients with advanced stage disease is uncertain.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

The evidence for effectiveness of minimal access lobectomy for patients with lung cancer is limited. There were few RCTs and no economic studies identified during the period of last five years. The majority of included studies in existing systematic reviews were non-RCTs and case series, and were primarily focused on early stage NSCLC. A challenging aspect of examining the literature for consistencies or generalizability was that a variety of VATS techniques were evaluated making it difficult to make broad comparisons.

However, the available evidence does suggest that VATS procedures appear to be associated with lower morbidity, less pain and greater lung function after surgery, less blood loss, shorter hospital stay, higher quality of life, and higher survival rates than conventional open thoracotomy, for patients with early stage lung cancer. VATS was found in one study reported in Cheng’s review to improve the delivery of adjuvant chemotherapy as well. However, differences between groups were not consistently significant across all trials. A major limitation of our report is that patients’ characteristics were not well matched in comparison groups: in most of the included non-RCTs, more patients in VATS group had less invasive disease and...
better prognosis. To eliminate this patient bias in studies, it would be preferable to conduct an RCT comparing prognosis between VATS lobectomy versus open lobectomy; however, this may not be feasible or ethical in certain cases.

In a consensus statement developed by professionals from multiple countries, VATS was recommended in patients with clinical stage I and II NSCLC, to reduce overall postoperative complications, to reduce pain and overall functionality over the short term, and to improve delivery of adjuvant chemotherapy. In the clinical practice, the choice of surgical technique should be left to the discretion of surgeons and patients.

In the future, more well-designed randomized (where appropriate) or non-randomized trials, preferably with standardization of VATS techniques, are warranted to provide more compelling evidence to estimate safety and clinical effectiveness of minimally access lobectomy for patients with lung cancer. Patients with advanced disease may be investigated when there are no contradictions. Cost-effectiveness analyses will be required to inform future policies in this area.

PREPARED BY:
Stella Chen, MD, MSc, Research Officer
Emmanuel Nkansah, MLS, MA, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


