Surgery for non-small cell lung cancer: Systematic review and meta-analysis of randomised controlled trials

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Key words: Systematic review, meta-analysis, non-small cell lung cancer, lobectomy, surgery

Word count: (excluding tables, figures and references): 3131
Abstract
Background: Surgery is considered the treatment of choice for patients with resectable stage I and II (and some patients with stage IIIA) non-small cell lung cancer (NSCLC) but there are no previous published systematic reviews.

Methods: A systematic review and meta-analysis of randomised-controlled trials was conducted to determine whether surgical resection of NSCLC improves disease-specific mortality in patients with stages I to IIIA, compared with non-surgical therapy and to compare the efficacy of different surgical approaches.

Results: Eleven trials were included. No studies had untreated control groups. In pooled analysis of three trials, 4-year survival was superior in patients undergoing resection with stage I to IIIA NSCLC who had complete mediastinal lymph node dissection compared with lymph node sampling; the hazard ratio estimated at 0.78 (95% CI: 0.65-0.93). Another trial reported an increased rate of local recurrence in patients with stage I NSCLC treated with limited resection compared with lobectomy. One small study reported a survival advantage among patients with stage IIIA NSCLC treated with chemotherapy then surgery compared with those treated with chemotherapy then radiotherapy. No other trials reported significant improvements in survival after surgery compared with non-surgical therapy.

Conclusion: Conclusions about the efficacy of surgery for loco-regional NSCLC are limited by the small number of participants studied and methodological weaknesses of trials. However current evidence suggests that complete mediastinal lymph node dissection is associated with improved survival compared with node sampling in patients with stage I to IIIA NSCLC undergoing resection.
INTRODUCTION

Complete surgical resection is considered the treatment of choice for individuals with stage I-II non-small cell lung cancer (NSCLC) and has a role in the multi-modality therapy of resectable stage III A disease (NSCLC).[1][2][3] Much of the evidence supporting surgical therapy is observational.[4][5] Lederle and Niewoehner have argued that these studies cannot be relied on because of the biases inherent in observational data. They also suggest that the negative results of previous lung cancer screening trials have provided indirect evidence against a benefit from surgery.[6] To our knowledge, there have been no prior systematic reviews of randomised controlled trials (RCTs) of surgery for NSCLC.[1] [3] [6] [7] The purpose of this review is to determine the efficacy of surgery for local and loco-regional NSCLC. RCTs comparing surgical resection for early stage lung cancer with no intervention, radiotherapy or chemotherapy were considered. Trials comparing different surgical approaches were also considered. These trials might provide indirect evidence about the efficacy of surgery. The review does not address the efficacy of neo-adjuvant or adjuvant therapy.
METHODS

Searching
A search of electronic databases including MEDLINE (1966 to December 2003), EMBASE (1974 to December 2003) and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Plus, Issue 4, 2003) was undertaken. Full details of the search strategy are outlined elsewhere.[8] The journal Lung Cancer was hand searched from 1995 to March 2004. Abstracts from the annual scientific meetings of the American Association for Thoracic Surgery for 2002 and European Association for Cardio-thoracic Surgery for 1999 to 2003 were hand searched. Bibliographies were also searched and authors of primary studies and experts in the field were contacted.

Selection
RCTs comparing surgical resection with no treatment or non-surgical therapy in patients with stage I to IIIA NSCLC were considered. Studies comparing different types of surgery, for example lobectomy versus limited resection were also considered. Trials were considered eligible if they included individuals with histopathologically or cytologically proven stages I to IIIA NSCLC and reported overall or disease specific survival at 2, 3, 4 or 5 years. Trials comparing surgery alone with surgery plus chemotherapy or radiotherapy were excluded.

Two reviewers (RM & DH) independently assessed titles and abstracts from electronic searches and relevant articles were selected for full text review. Studies were selected for inclusion in the review after 2 reviewers (RM & GW) assessed the full text articles. When assessing the eligibility and quality of studies, the reviewers were aware of the authorship and source of publication of the studies.

Validity assessment
Two reviewers (RM & GW) evaluated study quality independently with disagreements resolved by consensus. Using the Cochrane approach to allocation concealment, trials were described as having adequate, unclear or inadequate concealment.[9] The adequacy of the method of randomisation was also assessed as described by Jadad et al.[10] The reviewers assessed whether there was blinding of outcome assessment and adequate description of withdrawals.[10] Finally, an assessment was made as to whether the trial results used intention to treat analysis.[11] [12] The authors of included studies were asked to verify assessments of study methodology where possible.

Data extraction
Data extracted by one of the reviewers (RM) was entered in the Cochrane Collaboration software (Review Manager Version 4.2).[13] Authors of included studies were asked to confirm the data extracted where possible. A second reviewer (GW) extracted data from graphs, where necessary, for main study outcomes.

Outcome measures
The main outcomes were overall or disease-specific survival at 2, 3, 4 or 5 years. Secondary outcomes included progression free survival or recurrence rates (local, distant or both), post-operative mortality or treatment related death, and tests of respiratory function.

Quantitative data synthesis
Outcomes were pooled using the Review Manager and a pooled relative risk was calculated with 95% confidence intervals.[13] Homogeneity of effect sizes among pooled studies was tested using the chi-squared statistic for homogeneity, with p < 0.1 as the level for significance. In the
absence of significant statistical heterogeneity a fixed effects model was used for the pooled analysis.

Because of the broad inclusion criteria it was inappropriate to pool results for all studies. A pooled analysis was conducted on three trials comparing complete mediastinal lymph node dissection (CMLND) with systematic sampling (SS) of nodes[14][15][16] A separate pooled analysis was planned on trials comparing chemotherapy plus surgery with sequential chemotherapy plus radiotherapy in patients with stage IIIA NSCLC.[17][18] For the meta-analysis of survival data, the pooled log hazard ratio was calculated as a weighted average of the individual trial log hazard ratios, with weights inversely proportional to the variance of the log hazard ratio of each trial using the Review Manager software.[13][19][20] None of these studies reported a hazard ratio and variance that would be suitable for meta-analysis. The methods described by Parmar et al were used to estimate the hazard ratios and variance indirectly from confidence intervals or p-values for the log rank test.[19] For one study the hazard ratio was extracted from the survival curves using the methods of Parmar et al.[15][19] Briefly, in this case the time axis of the survival curve was split into equal non-overlapping time periods and the log hazard ratio was estimated for each equal time period and then combined in a stratified way across intervals to obtain an overall log hazard ratio. For a further study the authors[16] provided original data enabling hazard ratio and variance calculation using the Cox proportional hazards model.[21] For the meta-analysis of studies comparing complete mediastinal lymph node dissection with systematic sampling of mediastinal lymph nodes, follow up for 2 of the trials was restricted to 4 years so that the time periods of follow up would be comparable between pooled studies.[15][16]

For the remaining studies, where possible, a hazard ratio was calculated, otherwise survival at 2, 3, 4 or 5 years (depending on the data reported for the primary studies) was described by entering the number of participants surviving in Review Manager, but a pooled analysis was not conducted.[13]

Where possible, the statistical analysis was conducted in accordance with intention to treat principles. The level of agreement between reviewers evaluating studies for inclusion was assessed using simple Kappa statistics.
RESULTS

Search for trials
There were 1181 citations identified by the MEDLINE search, 70 citations identified by the search of the Cochrane Central Register of Controlled Trials and approximately 430 citations identified by the EMBASE search. After review of abstracts selected from the search of electronic databases, bibliographies and hand searches, 27 papers were selected for full text review. Eleven trials (some with multiple citations) were selected for inclusion in the review.[14][15][16][17][18][22][23][24][25][26][27][28][29][30] One of these controlled trials was not described as randomised in the report, however the primary author confirmed that the study was randomised.[17] There were no trials identified that included an untreated control group. Ongoing trials were also identified but results are not available as yet.[31][32][33] Two reviewers (RM & GW) agreed on the studies to be included in all but 1 case (Kappa statistic 0.93). The results of the search are outlined in figure 1. There were no additional studies identified by contacting authors of primary studies or experts.

Study characteristics
Trials comparing surgery (± other therapy) with non-surgical treatment arm
Several trials with diverse study designs were included in this category as shown in Table 1. There were 2 trials that compared chemotherapy then surgery with chemotherapy then radiotherapy in patients with stage IIIA NSCLC. In one study the inclusion criteria included the demonstration of pathological N2 disease,[18] but the TNM status of participants was not well described in the other study.[17]

Studies comparing different surgical approaches for lung cancer
Mediastinal lymphadenectomy (3 studies)
Three studies compared CMLND with SS in patients with resectable NSCLC.[14][15][16] Two of these were conducted in patients with resectable stages I-IIIA.[14][16] One was limited to patients with peripheral NSCLC less than 2 cm in diameter and without evidence of metastasis.[15] For this review the terminology recommended by Keller has been used.[32] SS refers to the routine biopsy of lymph nodes at the levels specified by the authors and CMLND refers to the routine removal of all ipsilateral lymph node bearing tissue. Further details are shown in Table 2. One reviewer (GW) determined that SS was performed in similar fashion in the three studies, and CMLND was performed according to the techniques of Naruke et al and Martini et al.[34][35] In these studies patients with involvement of N2 nodes were offered adjuvant radiotherapy to the mediastinum post-operatively, however in one study patient uptake in those with N2 disease in both arms was only about 30% according to the author.[16]
<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Control</th>
<th>Number Randomised</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Research Council trial, [27] England (1954 to 1958)</td>
<td>Histologically confirmed, clinically loco-regional lung cancer*</td>
<td>Thoracotomy &amp; radical resection of tumour with hilar &amp; mediastinal nodes</td>
<td>Radiotherapy (45 Gy to primary and mediastinum)</td>
<td>58</td>
<td>Overall 4-year survival</td>
</tr>
<tr>
<td>National Cancer Institute trial, [29] USA (1963 to 1966)</td>
<td>Histologically confirmed inoperable, locally advanced lung cancer, potentially operable after radiotherapy</td>
<td>Radiotherapy (40 Gy to primary and mediastinum) followed by surgery</td>
<td>Radiotherapy only (40 Gy to primary and mediastinum)</td>
<td>425 inoperable patients given radiotherapy, 152 randomised</td>
<td>Overall and disease free 5-year survival</td>
</tr>
<tr>
<td>National Cancer Institute of Canada Clinical Trials Group, [28] (prior to 1997) ‡</td>
<td>Stage IIIA NSCLC (pN2), fit for surgery, ECOG† £ ≤ 2</td>
<td>Induction chemotherapy followed by surgical resection</td>
<td>Radiotherapy (60 Gy total, 50Gy to primary tumour and mediastinum, plus 10 Gy to reduced target volume)</td>
<td>31</td>
<td>Overall 2-year survival</td>
</tr>
<tr>
<td>RTOG§ 89-01 trial, [18] USA (1990 to 1994) ‡</td>
<td>T1-T3 pN2 M0 NSCLC</td>
<td>Induction cisplatin-based chemotherapy followed by surgical resection</td>
<td>Induction cisplatin-based chemotherapy followed by radiotherapy (64 Gy)</td>
<td>73 given induction chemotherapy, 61 randomised</td>
<td>Overall 4-year survival</td>
</tr>
<tr>
<td>University of Athens, [17] Greece (1998 to 1991) ‡</td>
<td>Stage IIIA NSCLC (exact TNM not stated) Karnofsky performance status 70-90</td>
<td>4 cycles cisplatin-based chemotherapy followed by surgical resection</td>
<td>6 cycles of cisplatin-based chemotherapy followed by radiotherapy (50 Gy)</td>
<td>40</td>
<td>Overall 5-year survival</td>
</tr>
<tr>
<td>North American Intergroup trial 0139 (RTOG 93-09), [22] (1994 to 2001)</td>
<td>T1-3 pN2 M0 NSCLC, surgical resection technically feasible at randomisation</td>
<td>Concurrent cisplatin and etoposide and radiotherapy (45 Gy) followed by surgical resection</td>
<td>Concurrent cisplatin and etoposide and radiotherapy (61 Gy)</td>
<td>429</td>
<td>Progression free and overall 3-year survival</td>
</tr>
</tbody>
</table>

* Includes some cases of small cell lung cancer
† Eastern Co-operative Oncology Group performance status (0 = asymptomatic, 1 = capable of light work, 2 = less then half daylight hours in bed)
‡ Trial closed prematurely
§ Radiation Therapy Oncology Group
**Table 2. Trials comparing different surgical approaches for lung cancer**

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Control</th>
<th>Number randomised</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamaguchi University, [26] Japan (1993 to 1994)</td>
<td>Clinical stage IA NSCLC. No mediastinoscopy</td>
<td>Video-assisted thoracoscopic lobectomy</td>
<td>Thoracotomy and conventional lobectomy</td>
<td>100</td>
<td>Overall 5-year survival</td>
</tr>
<tr>
<td>Lung Cancer Study Group Trial, [24] North America (1982-1988)</td>
<td>T1 N0 M0 peripheral NSCLC, fit for lobectomy</td>
<td>Limited resection (wedge resection or segmentectomy, i.e. less than lobectomy)</td>
<td>Conventional lobectomy</td>
<td>276</td>
<td>Overall 5-year survival, local recurrence rate, death with cancer rate, pulmonary function</td>
</tr>
<tr>
<td>University of Munich &amp; Central Hospital, Gauting, [14] Germany (1989 to 1991)</td>
<td>Resectable NSCLC (stages I to IIIA)</td>
<td>Thoracotomy, surgical resection, complete mediastinal lymph node dissection</td>
<td>Thoracotomy, surgical resection, systematic sampling of mediastinal lymph nodes</td>
<td>201</td>
<td>Overall and progression free survival (median follow up 47 months)</td>
</tr>
<tr>
<td>Yamaguchi University, [15] Japan (1985 to 1992)</td>
<td>Peripheral NSCLC &lt; 2cm diameter, mediastinal and hilar lymph nodes &lt; 1cm on CT. (No mediastinoscopy)</td>
<td>Thoracotomy, surgical resection, complete mediastinal lymph node dissection</td>
<td>Thoracotomy, surgical resection, systematic sampling of mediastinal lymph nodes</td>
<td>115</td>
<td>Overall 5-year survival</td>
</tr>
<tr>
<td>Sun Yat-Sen University of Medical Sciences, Guangzhou, [16] China (1989 to 1995)</td>
<td>Pathologically confirmed NSCLC, clinical stages I-IIIA, age &lt; 71 years</td>
<td>Thoracotomy, surgical resection, complete mediastinal lymph node dissection</td>
<td>Thoracotomy, surgical resection, systematic sampling of mediastinal lymph nodes</td>
<td>532</td>
<td>Overall 5-year survival</td>
</tr>
</tbody>
</table>
**Limited resection (wedge excision or segmentectomy) versus lobectomy**

In a multi-institutional North American study, individuals with proven or suspected T1 N0 peripheral NSCLC were randomised to either limited resection (thoracotomy with wedge resection or segmentectomy) or lobectomy.[24] All patients were able to tolerate a lobectomy as assessed by cardiopulmonary function. Sublobar resections of up to 3 segments or wedge resections encompassing the tumour and 2 cm of lung were allowed, at the surgeon’s discretion. Pathological stage was confirmed prior to randomisation at the time of surgery by frozen section. After resection, the completeness of resection was assessed by frozen section and clinically and if the resection was incomplete or the tumour was found to be of a higher stage, the surgeon was required to complete the lobectomy. 276 were randomised at the time of surgery but there were 29 exclusions after randomisation.[24]

**Video-assisted thoracoscopic surgery (VATS) lobectomy versus conventional lobectomy**

One study compared 5-year survival in patients randomised to VATS lobectomy versus conventional lobectomy in patients with clinical stage IA NSCLC.[26]

**Quality of included trials**

In the three studies of CMLND versus SS, in some cases after contact with the authors, allocation concealment and method of randomisation were found to be adequate.[14][15][16] Further quality details of trials are shown in Table 3. None of the included studies contained a clear statement that they had conducted an intention to treat analysis. However this information was inferred from information provided about analysis and results for some of the trials. For 2 trials, there were no crossovers after randomisation but there were a number of exclusions after randomisation, not strictly adhering to intention to treat analysis.[12] [14] [16]
**Table 3. Methodological quality of included trials.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation concealment</th>
<th>Method of randomisation</th>
<th>Blinded assessment of outcome</th>
<th>Description of withdrawals</th>
<th>Intention to treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Research Council trial, [27] UK</td>
<td>Adequate</td>
<td>Not reported</td>
<td>None described</td>
<td>No description</td>
<td>Yes†</td>
</tr>
<tr>
<td>National Cancer Institute trial, (29) USA</td>
<td>Adequate</td>
<td>Not reported</td>
<td>None described</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>National Cancer Institute of Canada trial, [28] North America</td>
<td>Adequate†</td>
<td>Adequate†</td>
<td>No</td>
<td>No losses†</td>
<td>Yes†</td>
</tr>
<tr>
<td>RTOG‡ 89-01, [18]</td>
<td>Not reported</td>
<td>Not reported</td>
<td>None described</td>
<td>Incomplete description</td>
<td>No</td>
</tr>
<tr>
<td>University of Athens, [17] Greece</td>
<td>Not reported</td>
<td>Not reported</td>
<td>None described</td>
<td>No description</td>
<td>No</td>
</tr>
<tr>
<td>Intergroup 0139 trial, (RTOG‡ 93-09), [22] North America</td>
<td>Not reported</td>
<td>Not reported</td>
<td>None described</td>
<td>Incomplete description</td>
<td>No</td>
</tr>
<tr>
<td>Yamaguchi University (VATS vs. Open), [26]</td>
<td>Inadequate</td>
<td>Inadequate</td>
<td>None described</td>
<td>No losses†</td>
<td>No</td>
</tr>
<tr>
<td>Lung Cancer Study Group trial, [24], North America</td>
<td>Adequate</td>
<td>Not reported</td>
<td>None described</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(N.B. 18% loss in each group)</td>
<td></td>
</tr>
<tr>
<td>University of Munich, [14]</td>
<td>Adequate†</td>
<td>Adequate</td>
<td>Yes§</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Institution</td>
<td>Adequate</td>
<td>Adequate</td>
<td>None described</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------------</td>
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</tr>
<tr>
<td>Yamaguchi University, [15]</td>
<td>Adequate†</td>
<td>Adequate</td>
<td>None described</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sun Yat-Sen University of Medical Sciences, [16] Guangzhou</td>
<td>Adequate†</td>
<td>Adequate†</td>
<td>None described</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Unclear if losses to follow up
† Confirmed by contacting authors
‡ Radiation Therapy Oncology Group
§ Investigators undertaking follow up blinded from treatment group
**Data synthesis**

Trials comparing surgery (± other therapy) with non-surgical treatment arm

The results of 4 trials included in this category are shown in Table 4,[22] [27][28][29] These trials were diverse in terms of the interventions and populations and therefore not suitable for pooled analysis. In none of the studies was the surgical treatment arm found to be significantly superior to the non-surgical group in terms of overall survival. The authors intended to conduct a pooled analysis of the 2 studies comparing chemotherapy then surgery with chemotherapy then radiotherapy however, there was significant statistical heterogeneity between these studies (chi-squared statistic for homogeneity was 3.65, p=0.06) and therefore a pooled analysis was not performed. The results of these individual studies are displayed in figure 2. In one study there were two treatment related deaths in the chemotherapy/surgery group and one in the chemotherapy/radiotherapy group, RR = 2.21 (95% CI: 0.21 - 23.08; p=0.51).[18] Treatment related deaths were not described in the other trial.[17]
Table 4. Overall survival and progression free survival for trials comparing surgery (± other therapy) with non-surgical treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Relative risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Research Council trial, [27] UK</td>
<td>Surgery</td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-year OS* 23%</td>
<td>4-year OS* 7%</td>
<td>3.27 [0.74-14.42], p=0.12</td>
</tr>
<tr>
<td></td>
<td>Squamous cell subgroup analysis 30%</td>
<td>Squamous cell subgroup analysis 6%</td>
<td>5.10 [0.68-38.29], p=0.11</td>
</tr>
<tr>
<td>National Cancer Institute trial, [29] USA</td>
<td>Initially inoperable, radiotherapy</td>
<td>Initially inoperable, radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>No surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-year OS* 8%</td>
<td>5-year OS* 6%</td>
<td>1.42 [0.42-4.81], p=0.57</td>
</tr>
<tr>
<td></td>
<td>5-year PFS\† 6%</td>
<td>5-year PFS\† 4%</td>
<td>1.58 [0.39-6.38], p=0.52</td>
</tr>
<tr>
<td>National Cancer Institute of Canada trial, [28] North America</td>
<td>Chemotherapy then surgery</td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-year OS* 44%</td>
<td>2-year OS* 40%</td>
<td>1.09 [0.48-2.51]</td>
</tr>
<tr>
<td>Intergroup 0139 trial (RTOG\‡ 93-09), [22] North America</td>
<td>Concurrent chemotherapy &amp; radiotherapy then surgery</td>
<td>Concurrent chemotherapy and radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment deaths 14</td>
<td>Treatment deaths 3</td>
<td>4.43 [1.29-15.19], p=0.02</td>
</tr>
<tr>
<td></td>
<td>3-year PFS\† 29%</td>
<td>3-year PFS\† 19%</td>
<td>1.53 [1.06-2.21], p=0.02</td>
</tr>
<tr>
<td></td>
<td>3-year OS* 38%</td>
<td>3-year OS* 33%</td>
<td>1.16 [0.89-1.52], p=0.27</td>
</tr>
</tbody>
</table>

\*OS= overall survival  
\†PFS= progression free survival  
\‡Radiation Therapy Oncology Group
Studies comparing different surgical approaches for lung cancer

**Mediastinal lymphadenectomy**

A pooled analysis (fixed effects model) was conducted comparing hazards (or mortality rate) over the first 4 years post randomisation for the 3 studies included in this category. There was a significant reduction in the risk of death in the group undergoing CMLND (see figure 3); the pooled hazard ratio estimated at 0.78 (95%CI: 0.65-0.93; p=0.005). There was no significant statistical heterogeneity between studies being pooled (Chi-squared statistic=0.13; p=0.94). A subgroup analysis by stage was not conducted due to the possibility of stage migration in the CMLND group (Will Rogers phenomenon).[36] In one trial there was a non-significant trend to improved disease free survival in the CMLND group with a median follow up of 47.5 months, the hazard ratio was reported to be 0.82 (95% CI: 0.54-1.27).[14] The remaining trials did not report time to event data for disease recurrence so meta-analysis was not possible.

None of the trials individually found a significant difference between the groups in terms of 30-day operative mortality. In the pooled analysis, the relative risk was 0.86 ([95% CI: 0.19-3.77], p=0.84) without significant statistical heterogeneity between studies being pooled (p=0.39).

**Limited resection versus lobectomy**

In the study that compared limited resection with lobectomy in patients with peripheral stage I NSCLC, limited resection was associated with an increased risk of loco-regional recurrence (RR 2.84, [95% CI: 1.32-6.1], p=0.007).[24][25] There was also a trend to improved overall survival; the 5-year survival was 74% in the lobectomy group and 55% in the limited resection group.[25] The hazard ratio was 0.67 (95% CI: 0.44 - 1.02; p=0.062). There was a trend to an increased rate of deaths with cancer in the limited resection group compared with the lobectomy group (RR 1.46, [95% CI: 0.87-2.45]; p=0.15). It is not clear if the results presented above were based on an intention to treat analysis, however the investigators involved in the Lung Cancer Study Group trial also conducted an analysis that included all patients randomised, but actual results were not provided in the published report.[24][25] In the limited resection group there was less reduction (from preoperative level) in FEV1 at 12-18 months (mean % difference) compared with the lobectomy group. The mean difference between groups was 5.91 (95% CI: 0.29-11.53; p=0.04). However this difference is of doubtful clinical significance and furthermore less than 67% of participants had lung function results available at 12-18 months. There were 2 postoperative deaths in the lobectomy group and 1 in the limited resection group but these figures were for all 276 individuals randomised and it was not clear what the denominator was for each group from the report.[24]

**VATS lobectomy versus conventional lobectomy**

In the one study in this category the 5-year survival rate was 85% in the open group and 90% in the VATS group (RR= 1.09, [95% CI: 0.91 - 1.23], p=0.46).[26]
DISCUSSION

Eleven trials with a total of 1910 patients were included in this review. There were no studies comparing surgery alone with a no treatment arm identified. There was only one study that included patients with local and loco-regional NSCLC and compared surgery alone with radiotherapy alone.[27] However, although there was a trend to improved survival in the subgroup with squamous cell carcinoma in this study, this did not reach statistical significance in our analysis.[27] The review also highlights that the role of surgery in combined modality treatment for stage IIIA NSCLC is unclear. One study comparing chemotherapy then surgery with sequential chemotherapy and radiotherapy was inconclusive because of small numbers.[18] A similar study found in favour of chemotherapy plus surgery compared with sequential chemotherapy and radiotherapy in stage IIIA disease. However the results were not based on intention to treat analysis and it is possible that in this small study imbalance between unknown prognostic factors could have occurred.[17]

Although the Lung Cancer Study Group trial showed that there was a significant increase in local recurrence in the limited resection group, the trend to a reduction in the rate of death with cancer and death from all causes in the lobectomy group did not reach statistical significance at the conventional 5% level.[24] The study was designed to show equivalence between the 2 groups and therefore a more conservative p value of p>0.1 was used as acceptable evidence of equivalence. However the 95% confidence intervals for the hazard ratio for 5-year overall survival are wide, [0.44-1.02] and encompass equivalence. Likewise, they do not exclude a clinically important difference between the 2 groups.

The results of studies comparing CMLND with SS are of particular interest with respect to the efficacy of surgery in general and to future surgical practice. In the pooled analysis of the three studies there was a significant reduction in death from all causes in the group undergoing CMLND. These results suggest that the CMLND group have 78% (95% CI: 65%-93%) of the risk of dying on any given day, given survival to that point, compared to the SS group.

The results of this review should be interpreted taking into account the quality of the primary studies. Several studies in this review have some methodological weaknesses that represent serious threats to the validity of the findings. [24] [26] In particular, the Lung Cancer Study Group trial reported high rates of losses to follow up in both groups and did not clearly state whether patients were analysed according to treatment received or treatment assigned.[24] In addition, blinded assessment of outcome was not undertaken in this study and the high local recurrence rate in the limited resection group could, to some extent, reflect a detection bias. Furthermore, several trials excluded participants after randomisation in a manner that would not strictly fulfil the criteria for an intention to treat analysis.[12] [14] [16] It is difficult to draw any conclusions about the role of VATs versus conventional lobectomy because the only study included in this review was small and the analysis was not by intention to treat. [26]

Few trials included in this review have described the experience of the surgeons involved in performing surgery. The efficacy of the intervention may be influenced by the experience of the surgeons.[37] This information is required when making judgements about the generalisability of any findings.

In summary, the current evidence from RCTs neither supports nor discounts the survival benefit of surgery for NSCLC. However, as more extensive (complete) surgery appears superior to less, by inference some surgery might be better than no surgery. In particular lobectomy as compared with limited resection was shown to reduce the rate of local recurrence in individuals with stage I NSCLC in one study. CMLND appears to improve survival compared with SS in individuals with resected NSCLC. The results of the American College of Surgeons Oncology Group Z30 trial will be important to further clarify this issue.[32] Similarly, the results of ongoing trials should help to clarify the role of surgery following induction chemotherapy plus or minus radiotherapy for patients
with stage IIIA (N2) NSCLC. Further details of ongoing trials identified by this review are outlined elsewhere. If ongoing trials show that surgery does not significantly improve survival after induction chemotherapy plus or minus radiotherapy in patients with stage IIIA (N2) NSCLC then it may be reasonable to conduct further RCTs comparing surgery with radiotherapy or chemoradiation in selected groups of patients with earlier stage NSCLC. For example, in older patients in whom the peri-operative mortality of surgery is on average 6% for patients aged 70 to 79 years, and 8% for those 80 years and older, or in patients with reduced respiratory reserve.
ACKNOWLEDGEMENTS
We wish to thank the Iberoamerican Cochrane Center for assistance with database searches, and Dr Sera Tort, Dr Marta Roque and Dr Elinor Thompson (Co-ordinators of the Cochrane Lung Cancer Group) for assistance with protocol development and editing of the review. We would like to acknowledge the help provided by authors of primary studies who have responded to our correspondence and provided additional information. Some of the narrative in the text, tables 1, 2 and 3 and figures 2 and 3 of the present article also appear in the Cochrane Review (Copyright Cochrane Library, reproduced with permission).

Funding
Renee Manser is supported by an Australian National Health and Medical Research Council postgraduate scholarship (scholarship number 201713).

Competing Interests
All authors have no competing interests to declare.

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Figure 1

Figure 2

Figure 3
REFERENCES

1681 citations identified and screened for potentially relevant randomised controlled trials

1646 abstracts/trials excluded as not relevant

27 studies (35 citations) selected for full text review

16 studies/randomised controlled trials excluded (18 citations)
- Not randomised controlled trial (n=11)
- Review article (n=1)
- Randomised controlled trial in patients with small cell carcinoma only (n=1)
- Randomised controlled trial but no survival data reported (n=1)
- Ongoing randomised controlled trials awaiting survival results (n=2)

11 randomised controlled trials selected for inclusion (17 citations)

Randomised controlled trials withdrawn by outcome (n=0)

Randomised controlled trials with useable information by outcome:
- Survival (n=11)
- Progression or disease free survival (n=3)
- Local recurrence rate (n=1)
- Pulmonary function (FEV₁, FVC, MVV) (n=1)
- Postoperative mortality or treatment related deaths (n=9)

Figure 1: Results of search for trials and reasons for excluding trials
Figure 2: Hazard ratio (4-year survival) for studies comparing chemotherapy plus radiotherapy with chemotherapy plus surgery in patients with resectable stage IIIA non-small cell lung cancer. The square represents the hazard ratio for the individual trials and the line represents the corresponding 95% confidence intervals.

Test for heterogeneity: $\chi^2 = 3.65, \text{df} = 1 (P = 0.06), I^2 = 72.6\%$

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>log[Hazard ratio] (SE)</th>
<th>Hazard ratio (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stathopoulos</td>
<td>17</td>
<td>1.0950 (0.3592)</td>
<td>2.99 [1.48, 6.04]</td>
</tr>
<tr>
<td>Johnstone</td>
<td>18</td>
<td>0.2150 (0.2886)</td>
<td>1.24 [0.70, 2.18]</td>
</tr>
<tr>
<td>Study</td>
<td>Reference</td>
<td>log[Hazard ratio] (SE)</td>
<td>Hazard ratio (fixed) 95% CI</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Izbicki</td>
<td>14</td>
<td>-0.2485 (0.2475)</td>
<td></td>
</tr>
<tr>
<td>Sugi</td>
<td>15</td>
<td>-0.0577 (0.5526)</td>
<td></td>
</tr>
<tr>
<td>Wu</td>
<td>16</td>
<td>-0.2611 (0.0989)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100.00</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 0.13, df = 2 (P = 0.94), I² = 0%
Test for overall effect: Z = 2.80 (P = 0.005)

Figure 3: Hazard ratio (4-year survival) for studies comparing complete mediastinal lymph node dissection with mediastinal node sampling. For the individual trials the square represents the hazard ratio and the line represents the 95% confidence intervals. The diamond represents the results of the pooled analysis using the fixed effect model.