Is there a role for the use of radical lymph node dissection in the surgical management of resectable non-small cell lung cancer?

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Summary

A best evidence topic in cardiothoracic surgery was written according to a structured protocol. The question addressed was whether there is any survival benefit to the employment of the technique of radical lymph node dissection in the management of operable non-small cell lung cancer (NSCLC). Altogether 305 papers were found using the reported search, of which eight presented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results, and study weaknesses of these papers are tabulated. We conclude that extensive lymph node sampling is of benefit in accurately staging NSCLC; however, the design of studies in the literature has failed to account for the staging effect of extensive lymph node dissection on upstaging cancer patients when trying to determine a survival advantage.

Keywords: Evidence-based medicine; Thoracic surgery; Lymph node excision; Lung neoplasms

1. Introduction

A Best Evidence Topic was constructed according to a structured protocol. This protocol is fully described in Ref. [1].

2. Clinical scenario

You are a Specialist Registrar in Cardiothoracic surgery. You meet a senior trainee from Japan who is an enthusiastic proponent of radical lymph node dissection in early lung cancer. Your boss is an exponent of VATS lobectomy and you are aware that the application of radical lymph node dissection in near impossible with this technique. You wonder whether in general conducting a simpler staging technique, such as sampling, impacts on the accuracy of staging and the overall survival?

3. Three-part question

In [patients with Non-Small Cell Lung Cancer] can [radical lymph node dissection] improve [survival]?

4. Search strategy


5. Search outcome

Out of the 305 papers found 20 were deemed to be relevant. Eleven were out of scope and one was rejected on the basis of poor methodology. Eight papers were reviewed in full. These are listed in Table 1. A second table documenting the particular lymph node dissection strategies used in the papers is also given (Table 2).
Table 1
Table of best evidence papers

<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
<th>Patient group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Izbicki et al. (1995), <em>Ann Thorac Surg</em>, Germany [2]</td>
<td>201 patients with operable NSCLC. 100 patients with radical systematic mediastinal lymph node dissection (LA). 82 patients with mediastinal lymph node exploration and removal of suspicious nodes only (LS). After randomisation 19 patients (LS ( n = 1 ); LA ( n = 18 )) were excluded from analysis due to residual tumour or classification as small cell lung cancer.</td>
<td>Controlled prospective, randomised clinical trial (level 2b)</td>
<td>Effect of radical lymphadenectomy on nodal staging of NSCLC</td>
<td>Procedure - LS ( n = 1 ) N0 55%, N1 20%, N2 23%, N3 2% LA ( n = 82 ) N0 58.5%, N1 10.9%, N2 26.8%, N3 3.7%</td>
<td>Disproportionately high number excluded from the LA group. Small patient numbers in each subgroup. Median follow-up period was only 26.8 months. LS involved extensive sampling. Nodes from stations 4, 5 and 7 were excised in all patients, nodes in regions 2–9 were explored and removed if suspicious.</td>
</tr>
<tr>
<td>Izbicki et al. (1998), <em>Ann Surg</em>, Germany [3]</td>
<td>201 patients with operable NSCLC. 32 patients excluded from analysis. LA ( n = 76 ) LS ( n = 93 ) Same patient population as Izbicki et al. (1995). Median follow-up 47.5 months (range 25–67).</td>
<td>Controlled prospective, randomised clinical trial (level 2b)</td>
<td>Survival</td>
<td>LA 5 year survival 70.6%* LS 5 year survival 47.9%* LA prolonged relapse free survival ( P = 0.037 ) with a borderline effect on overall survival ( (P = 0.058) ) in patients with limited lymph node involvement (^*)pN1 disease or pN2 disease with involvement of only one lymph node level</td>
<td>Median follow-up 47.5 months (25–67 months). Small numbers within subgroups reducing statistical power. More squamous cell carcinomas in the LA group than in the LS group (52.7 vs. 31.6%). Study was powered to detect a 20% survival benefit of LA over LS only if there were 100 patients in each group. Stage migration.</td>
</tr>
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Morbidity
Postoperative course was more or less the same in the two groups

Higher need for postop transfusion and higher incidence of prolonged air leakage in patients with systematic lymph node dissection

No difference in hospital or ICU stay

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### Table 1 (continued)

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<td>Passlick et al. (2002), <em>Eur J Cardiothorac Surg</em>, Germany [4]</td>
<td>94 patients with pathological stage I–IIIA NSCLC.  Stage I NSCLC ( n = 73 ). Radical systematic en-bloc mediastinal lymphadenectomy (LA) ( n = 42 ). Mediastinal lymph node sampling (LS) ( n = 31 ). Samples were screened by immunohistochemistry for disseminated tumour cells using antibody Ber-Ep4.</td>
<td>Prospective randomised trial (level 2b)</td>
<td>Survival</td>
<td>Overall survival was 54.7% 5-year survival in the LA group and 41% in the LS group ( P = 0.27 )</td>
<td>Small numbers involved in the stage II–IV group (only 21 patients in total).</td>
</tr>
</tbody>
</table>
| Wu et al. (2002), *Lung Cancer*, China [5] | Resectable clinical stage I–IIIA NSCLC. 268 patients assigned to lung cancer resection combined with systematic lymph node dissection (SND). 264 patients were assigned to lung cancer combined with mediastinal lymph node sampling (MLS). 471 patients were eligible for follow-up. | Prospective randomised trial (level 1b) | Survival | Stage I \( n = 156 \)  
SND 82.2% 5-year survival  
MLS 57.5% 5-year survival  
\( P = 0.0104 \)  
Stage II \( n = 136 \)  
SND 50% 5-year survival  
MLS 34.1% 5-year survival  
\( P = 0.052 \)  
Stage III \( n = 179 \)  
SND 27% 5-year survival  
MLS 6.2% 5-year survival  
\( P = 0.284 \) | More stage I and less stage IIIA patients in those undergoing MLS, suggesting that MLS is less accurate in staging the disease and that stage migration may influence survival in this trial! Unequal follow-up between groups. |
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<td>Keller et al. (2000), Ann Thorac Surg, USA [6]</td>
<td>373 patients with NSCLC. 186 patients underwent systematic sampling (SS) of the mediastinal lymph nodes. 187 patients underwent complete mediastinal lymph node dissection (MLND).</td>
<td>Non-randomised controlled study (level 2b)</td>
<td>Survival</td>
<td>N1 disease SS 5-year survival 57% MLND 5 year survival 48% $P = 0.04$. N2 disease SS 5-year survival 41% MLND 5-year survival 35% $P = 0.035$</td>
<td>Not randomised. 192 surgeons involved in the study, some exclusively performed one technique or the other. 131 surgeons entered only one patient.</td>
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<tr>
<td>Garja et al. (2003), J Clin Oncol, USA [7]</td>
<td>442 patients with stage I NSCLC. 246 patients had random sampling. 115 patients had systematic sampling (SS). 81 patients had complete mediastinal lymphadenectomy (MLND).</td>
<td>Retrospective cohort study (level 4)</td>
<td>Overall survival</td>
<td>56, 83 and 86% ($P &lt; 0.0001$) for random sampling, SS and MLND, respectively Disease free survival</td>
<td>Retrospective data. Spurious downstaging of patients with inadequate sampling. Large number of patients excluded from the original cohort due to inadequate follow-up and incomplete data.</td>
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<tr>
<td>Sagi et al. (1998), World J Surg, Japan [8]</td>
<td>115 patients with peripheral NSCLC ≤2 cm diameter. 59 patients had lymph node sampling. 56 patients had radical lymph node dissection.</td>
<td>Randomised controlled trial (level 2b)</td>
<td>Survival</td>
<td>Lymph node sampling group 83.9% 5 year survival Lymph node dissection group 81.4% 5 year survival</td>
<td>Small numbers in each group. Study limited to 2 cm diameter tumours, therefore excluding some stage I tumours. No statistically significant difference Morbidity</td>
</tr>
<tr>
<td>Wu et al. (2003), Eur J Cardiothorac Surg [9]</td>
<td>321 patients undergoing surgery for stage I NSCLC.</td>
<td>Retrospective cohort study (level 2b)</td>
<td>Survival</td>
<td>Removed no. of lymph nodes &gt;15 5-year survival 57.1% 10-year survival 46.3% Removed no. of lymph nodes &lt;15 5-year survival 45.5% 10-year survival 31.5% $P &lt; 0.01$</td>
<td>13 patients with inadequate pulmonary reserve had sublobar resections. 18 patients lost to follow-up. Retrospective study. Spurious downstaging of patients with inadequate sampling.</td>
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</table>
6. Results

Izbicki et al. [2,3], Passlick et al. [4], Wu et al. [5] and Keller et al. [6] found a survival benefit to the use of radical lymph node dissection. Gargi et al. [7] and Sugi et al. [8] could not identify a survival benefit. Izbicki et al. [2,3] and Passlick et al. [4] describe outcomes regarding the same cohort of patients. These papers in common with Wu et al. [5] were prospective randomised controlled trials. Sugi et al. [8] is a randomised controlled trial, however, the findings are limited to a small subset of stage I lung cancer in which tumours are peripheral and less than 2 cm in diameter. Gargi et al. [7] conducted a retrospective case note review and acknowledged the potential for spurious downstaging of patients with inadequate sampling, a large number of patients from the original cohort were excluded due to inadequate follow-up and incomplete data.

In a number of patients in whom only a limited lymphadenectomy is performed, the true N stage remains unrecognised because the relevant lymph nodes are not removed and consequently not examined by a histopathologist. In the Izbicki cohort 5.5% of patients in the LA group had N2 disease that was detected only at lymph node levels that would not have been routinely included in the lymph node sampling group. Consequently the hypothetical benefit of LA in patients with limited mediastinal lymph node involvement might be due at least to an imbalance within the groups with respect to the number of patients with lymph node involvement at multiple levels of the N2 region. The phenomenon of stage migration as a source of misleading statistics for survival in cancer has been called the Will Rogers phenomenon [10].

Of note, the British Thoracic Society guidelines [11] with regard to lymph node management are based on the interim work of Izbicki et al. in 1994. At this juncture the results had not shown a statistical significance between their two groups of patients. According to the BTS guidelines lymph node dissection is essential at the time of lung resection to achieve accurate staging, however, extensive lymph node resection is not advised for its therapeutic value.

Assessment of a greater number of lymph nodes correlates with improved survival in patients with colorectal, breast and bladder cancer. Wu et al. [5] found that the number of lymph node metastases was an independent
predictor of survival. Vansteenkiste et al. [12] analysed 18 articles published between 1980 and 1995 and also concluded that N status is the most important prognostic factor. Hypothetically there exists a cohort of patients with metastatic disease that is truly limited to the regional lymph nodes. These are the patients who would benefit from the aggressive resection of the intrathoracic lymph nodes.

Proponents of the radical approach claim better staging of the tumour and improved prognosis. Opponents of radical lymph node dissection have claimed higher morbidity and mortality rates owing to the extent of the operation and even a negative effect on the long-term prognosis because of an impaired local immune response. Both Izbicki et al. [3] and Sugi et al. [8] found increased morbidity in the lymphadenectomy groups, however, neither found any increase in hospital or ICU stay.

7. Clinical bottom line

The small numbers of patients involved in these studies and the problems with study design have not yielded a clear cut answer as to the survival benefit of mediastinal lymphadenectomy. If a cohort does exist where metastatic disease is limited to the regional nodes then these are the patients who would benefit in terms of survival. This group of patients may be very small requiring a highly powered study to detect them.

References