In patients undergoing lung resection for non-small cell lung cancer, is lymph node dissection or sampling superior?

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Summary

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was ‘In patients undergoing lung resection for non-small cell lung cancer, is lymph node dissection or sampling superior?’ Altogether 845 papers were found using the reported search, of which 14 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. We conclude that in stage I tumours there is little difference in survival when performing either mediastinal lymph node dissection (MLND) or lymph node sampling. However, survival is increased when performing MLND in stage II to IIIa tumours. Increased accuracy in staging is not observed with MLND. However, MLND reliably identifies more positive N2 nodes which may offer advantages in postoperative adjuvant treatment in more advanced disease.

Key words: Lymphadenectomy; Lymph node sampling; Non-small cell lung cancer

1. Introduction

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

2. Three-part question

In [patients with non-small cell lung cancer] is [radical lymph node dissection or lymph node sampling] superior in terms of [survival and staging]?

3. Clinical scenario

You are about to undertake a right upper lobectomy for a stage Ia non-small cell lung cancer (NSCLC). You are deciding whether to undertake a complete mediastinal lymphadenectomy or lymph node sampling (LNS).

4. Search strategy

Medline 1966–March 2011 using the OVID interface


5. Search outcome

Eight hundred and forty-five papers were found using the reported search. Of these 14 papers were selected following appraisal as they represented the highest level of evidence and the most recent updates of the subject. These are presented in Table 1.

6. Results

This subject has previously been investigated by Barnard et al. [16] and this article represents an update of this previous work in light of significant recent development.

6.1. Survival

Wright et al. [2] performed a meta-analysis assessing the survival of patients undergoing lung resection for NSCLC combined with either mediastinal lymph node dissection (MLND) or LNS. In a pooled analysis of the three main randomised controlled trials (RCTs) at the time, the chance of survival over a four-year period was superior in patients who had MLND compared with LNS as the overall hazard ratio was 0.78 (95% CI 0.65–0.93; P=0.005). In a Cochrane review, Manser et al. [3] performed a further meta-analysis on the same three trials and noted reduced recurrence rates in the MLND group (RR 0.79, 95% CI 0.66–0.95; P=0.01). Furthermore, recent guidelines published by the British Thoracic Society [4] based on two RCTs advocate...
Table 1. Best evidence papers

<table>
<thead>
<tr>
<th>Author, date and country</th>
<th>Patient group</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al., (2006), Thorax, Australia, [2]</td>
<td>Three RCTs assessing patients undergoing lobectomy with either MLND or LNS</td>
<td>Four-year survival</td>
<td>There was a significant reduction in postoperative death at the four-year point. Hazard ratio estimated at 0.78 (95% CI 0.65–0.93)</td>
<td>Meta-analysis but only three RCTs Randomisation and concealment deemed as adequate (after contact with authors) in all three RCTs</td>
</tr>
<tr>
<td>Manser et al., (2005), Cochrane Database Syst Rev, Australia, [3]</td>
<td>Three RCTs assessing patients undergoing lung resection with either MLND or LNS</td>
<td>Overall survival (pooled analysis of three RCTS)</td>
<td>Risk of death in the MLND group was reduced (pooled hazard ratio was estimated to be 0.63 (95% CI 0.51–0.78; P=0.0001)</td>
<td>Meta-analyses carried out of the three RCTS Same RCTs as above Methodological quality summary performed</td>
</tr>
<tr>
<td>Lim et al., (2010), Thorax, UK, [4]</td>
<td>Two RCTS assessing patients undergoing lung resection and either MLND or LNS</td>
<td>Survival</td>
<td>Improved survival reported by both RCTs in those who underwent lung resection with MLND compared with LNS</td>
<td>Two RCTs however the RCTs used do not differentiate between stage of tumour at the time of resection</td>
</tr>
<tr>
<td>Darling et al., (2011), J Thorac Cardiovasc Surg, USA, [5]</td>
<td>N0 or N1 NSCLC with no metastatic spread underwent MLND (n=525) and LNS (n=498)</td>
<td>Histological staging</td>
<td>21 (4%) of patients were found to have occult N2 disease</td>
<td>Largest RCT assessing long term outcomes Rigorous staging procedure including sampling of station 10 at thoracotomy/ VATS prior to randomisation Good homogeneity between treatment arms Surgical technique between surgeons standardised Adequate randomisation</td>
</tr>
<tr>
<td>Wu et al., (2002), Lung Cancer, China, [6]</td>
<td>Patients with stage I–IIa NSCLC. Two hundred and sixty-eight randomised to lung resection with MLND (n=268) and LNS (n=264)</td>
<td>Five-year survival</td>
<td>Five-year survival was 82.16% vs. 57.49% at stage I (P=0.0104), 50.42% vs. 34.05% for stage II (P=0.0284) and 26.98% vs. 6.18% for stage III (P=0.0243) NSCLC for MLND and LNS, respectively</td>
<td>RCT of good size and follow-up period of five years. No difference between stratification factors Randomisation method unexplained</td>
</tr>
<tr>
<td>Izbicki et al., (1998), Ann Surg, Germany, [7]</td>
<td>In NSCLC stage I to IIa. LNS (n=93) MLND (n=76)</td>
<td>Disease-free survival</td>
<td>Median disease-free survival was 48 (2–54) months in the MLND group and 24 (3–53) months in the LNS group</td>
<td>Good-sized RCT. Detailed analysis of sub groups Excluded cases explained. Due to patient drop out, type 1 and 2 errors unable to be excluded</td>
</tr>
</tbody>
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Prospective randomised trial (level 2)

Patients with stage I NSCLC undergoing MLND (n=53) and LNS (n=41)

Five-year survival
MLND=56.8%; LNS=54.8% after median follow-up of 47.5 months (P=0.256)

Small data set
Higher percentage of squamous cell carcinoma in LNS group
Subgroup analysis added retrospectively
No differentiation between stages of tumour

RCT (level 2)

In NSCLC of <2 cm diameter. LNS, (n=56) or MLND (n=59)

Five-year survival and recurrence
The overall five-year survival was 81% in the dissection group and 84% in the sampling group. No significant differences in the recurrence rate or survival was seen between the groups

RCT, smaller in size. Good follow-up period

Retrospective cohort (level 3)

Patients with stage I NSCLC undergoing MLND (n=258) and LNS (n=207)

Five-year survival
LNS=59.1% alive after five years. MLND=64.7% alive after five years. (P=0.11) MLND a favourable indicator following multivariate analysis (Hazard risk: 1.43; 95% CI 1.00–2.4; P=0.048)

Retrospective analysis, non-randomised
However database collected prospectively and homogeneity noted between groups

Controlled, non-randomised trial (level 3)

In stage I NSCLC LNS (n=377) MLND (n=358)

Five-year survival
At 60 months the disease-free survival was 76.4 for LNS and 73.4 for MLND (P=0.376). Overall survival at 60 months was 83.2% for LNS and 79.7% for MLND (P=0.060)

Good study size with appropriate control. No randomisation and retrospective in nature. No significant difference between groups and low drop out rate

Gajra et al., (2003), J Clin Oncol, USA, [12]
Retrospective cohort (level 3)

Patients with stage I NSCLC undergoing MLND (n=81), LNS (n=115) and random sampling (n=246)

Five-year disease-free survival
LNS=83.3% and MLND=85.9% Random sampling=56.4%

Retrospective analysis without randomisation
Smaller sample size of MLND and LNS groups

Prospective cohort (level 3)

Two hundred and nineteen patients with stage III NSCLC followed up over five years. LNS (n=109) MLND (n=110)

One-, three- and five-year survival
The median survival was 23.5 months in the MLND group and 20 months for the LNS group (P<0.05). MLND was also a significant predictor of survival in the multivariate analysis

Prospective trial, not randomised or controlled. Adequate follow-up period

Non-randomised comparison (level 3)

In stage II and III NSCLC, LNS (n=187); MLND (n=186)

Overall survival, N1 and N2 disease identified and difference in staging
MLND median survival was 57.5 months and 29.2 months for LNS (P=0.004). N1 disease was identified in 40% and N2 identified in 60% of LNS. N1 disease was identified in 41% and N2 was identified in 59% of MLND (P=0.001). Among the 222 patients with N2 metastases, multiple levels of N2

Good sample size. No randomisation
Similar characteristics between groups
Potential differences in surgical and postoperative management described

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the performance of MLND and the removal of at least three nodal stations including subcarinal.

However, in the largest RCT of this population, Darling et al. [5] assessed patients with early stage NSCLC and rigorously staged them for nodal metastases. This process included mediastinoscopic sampling and intraoperative sampling including station 10. Following frozen section confirmation of N0 status, randomisation to MLND (n=525) and LNS (n=498) occurred. No significant difference was noted between the two groups in terms of survival (LNS=8.1 years, MLND=8.5 years; P=0.25) and five-year disease-free survival [LNS=68% (95% CI 64–73), MLND=67% (95% CI 62–71); P=0.89].

The overall survival may therefore be affected by the stage of the tumour at the time of either LNS or MLND. Indeed only one RCT in the meta-analysis, Wu et al. [6], showed a significant improvement in five-year survival for MLND over LNS for all stages of disease.

Izbicki et al. [7] did not observe a significant difference in survival when assessing resection of tumours of stages I to III combined. Also Passlick et al. [8] performed a prospective randomised trial of patients with stage I-IIa undergoing MLND (n=53) and LNS (n=41) and found that there was no overall survival difference at five years between the two groups (P=0.27).

Several studies assessed less advanced disease. Sugi et al. [9] failed to observe a significant difference in five-year survival rate in 115 patients with NSCLCs of <2 cm in diameter undergoing MLND and LNS (81% and 84%, respectively). Similarly, Doddali et al. [10] performed a retrospective analysis of patients who underwent LNS (n=207) and MLND (n=258) for stage I NSCLC. They observed no significant difference in five-year survival (59.1% for LNS and 64.7% for MLND, P=0.11). MLND was, however, a significant favourable prognostic indicator following the multivariate analysis (hazard ratio 1.429; P=0.048).

Furthermore, Okada et al. [11] also reviewed patients with stage I NSCLC. The five-year overall survival for the LNS group (n=377) and the MLND (n=358) group was 83.2% and 79.7%, respectively. In the multivariate analysis, the type of dissection performed did not significantly affect either the disease-free survival (P=0.636) or the overall survival (P=0.119). Also, Gajra et al. [12] retrospectively analysed 442 patients undergoing lung resection for stage I disease. There was no significant difference between MLND and systematic LNS in terms of survival (85.9% and 83.3%, respectively).

When assessing more advanced disease, Zhang et al. [13] followed up 219 patients with stage III NSCLC over five years. The median survival was 23.5 months in the MLND group and 20 months for the LNS group (P<0.05). MLND was also a significant predictor of survival in the multivariate analysis.

Keller et al. [14] in a non-randomised comparison study observed patients with stage II and IIa NSCLC. Median survival was 57.5 months for those patients who had undergone complete MLND (n=186) and 29.2 months for those patients who had LNS (n=187; P=0.004).

6.2. Staging

When assessing staging accuracy, Keller et al. [14] observed that of the 186 who underwent complete MLND, 41% had N1 disease compared with 40% who underwent LNS (P=0.92). N2 disease observed was also similar between MLND (N2=20%, N1 and N2=39%) and LNS (N2 only=21%, N1 and N2=39%). However, among the 222 patients with N2 metastases, multiple levels of N2 disease were documented in 30% of patients who underwent complete MLND and in 12% of patients who had LNS (P=0.001).

Izbicki et al. [15] conducted a RCT of 182 patients and showed a significant difference in the number of levels of lymph nodes involved. In those undergoing LNS 17.4% with N2 disease had multi-level nodal disease. This was compared to the MLND group with N2 disease where 57.2% were observed to have multi-level involvement (P=0.007).

7. Clinical bottom line

We conclude that in stage I tumours there is little difference in survival when performing either MLND or LNS.
Survival is increased when performing MLND in stage II to IIIa tumours. Increased accuracy in staging is not observed with MLND. However, MLND reliably identifies more positive N2 nodes which may offer advantages in postoperative adjuvant treatment in more advanced disease.

References


eComment: Lymph node dissection or sampling in patients with non-small cell lung cancer?

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We have read with great interest the paper of Hughes et al. [1]. Lymph-node staging during pulmonary resection for non small-cell lung cancer (NSCLC) has been greatly debated for some time. The present best evidence topic identifies a light advantage of mediastinal lymph-node dissection (MLND) compared to lymph node sampling (LNS) in respect of the rates of survival in stage II-IIIa. In addition, MLND is able to identify more multiple levels of N2 disease. It is possible to derive some practical suggestions from the Hughes’ study. Considering that the majority of patients requiring surgery for NSCLC lie in clinical stage I but some of them are shown to be understaged at pathological examination even in the ‘PET era’, it seems advisable to offer the advantages of MLND to all patients needing surgery. A second point arises from everyday experience where a node judged negative at surgery may be shown to be metastatic at pathological examination and, conversely, a node considered positive during dissection may be shown to be negative at pathological examination. In this scenario, we believe that MLND is more effective in determining the real node staging in practical surgery. Finally, it should be considered that research is progressing in molecular lymph-node staging and molecular technology could overtake the traditional hematoxylin-eosin in the near future [2–4]. Once again, MLND seems to be the only way to accurately collect the material for advanced lymph-node staging.

In conclusion, we thank Hughes and co-workers for highlighting the thin but important superiority of MLND compared to LNS. We hope that through MLND and precise detection of metastases (molecular staging), we may reach the definitive and correct stage for all patients affected by NSCLC. Considering that the majority of patients requiring surgery for NSCLC lie in clinical stage I but some of them are shown to be understaged at pathological examination even in the ‘PET era’, it seems advisable to offer the advantages of MLND to all patients needing surgery. A second point arises from everyday experience where a node judged negative at surgery may be shown to be metastatic at pathological examination and, conversely, a node considered positive during dissection may be shown to be negative at pathological examination. In this scenario, we believe that MLND is more effective in determining the real node staging in practical surgery. Finally, it should be considered that research is progressing in molecular lymph-node staging and molecular technology could overtake the traditional hematoxylin-eosin in the near future [2–4]. Once again, MLND seems to be the only way to accurately collect the material for advanced lymph-node staging.

References


