Invited discussant

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Belgium
30- and 90-day mortality after major lung resections in 2242 patients

A.E. Frick, H. Lüders, G. Leschber, ELK Berlin Chest Hospital, Berlin, Germany
What is known?

• Operative mortality after resection of NSCLC is reduced
• Difference in 30- versus 90-day mortality
• Relationship mortality-volume
Operative mortality has been improved

<table>
<thead>
<tr>
<th></th>
<th>Period</th>
<th>No of pts</th>
<th>† Lob</th>
<th>† Pneum</th>
<th>Pneum rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer Study Group (1)</td>
<td>1979-1981</td>
<td>2.200</td>
<td>2.9%</td>
<td>6.2%</td>
<td>25.6%</td>
</tr>
<tr>
<td>ACOSOG Z003O (2)</td>
<td>1999-2004</td>
<td>1.203</td>
<td>1.3%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>National Cancer Center (Tokyo, Japan) (3)</td>
<td>1997-2002</td>
<td>1.655</td>
<td>0.5%</td>
<td>5.2%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

1. Modern thirty-day operative mortality for surgical resections in lung cancer
Ginsberg et al., J Thorac Cardiovasc Surg 1983; 86:654-8


3. Recent results of postoperative mortality for surgical resections in lung cancer
Watanabe et al., Ann Thorac Surg 2004;78:999-1003
Perioperative mortality after neoadjuvant therapy and pneumonectomy for NSCLC

- Meta-analysis (1990-2010)
- Postoperative mortality after neoadjuvant therapy and pneumonectomy
- N = 27 studies (includes intergroup trial)
- 30-day mortality 7%
- 90-day mortality 12%

Kim et al., J Thorac Cardiovasc Surg 2012;143:55-63
Perioperative mortality after neoadjuvant therapy and pneumonectomy for NSCLC

FIGURE 3. Perioperative mortality. Perioperative mortality represented according to overall, right, and left pneumonectomies for all 27 studies.
Influence of hospital volume on survival after resection for lung cancer

Postoperative complications and survival in 76 hospitals in United States


<table>
<thead>
<tr>
<th></th>
<th>1-8 (n=34)</th>
<th>9-14 (n=14)</th>
<th>15-19 (n=10)</th>
<th>20-66 (n=16)</th>
<th>67-100 (n=2)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of all hospitals</td>
<td>45%</td>
<td>18%</td>
<td>13%</td>
<td>21%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>44%</td>
<td>28%</td>
<td>35%</td>
<td>32%</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall 5-Yr survival</td>
<td>33%</td>
<td>36%</td>
<td>39%</td>
<td>40%</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

High procedure volume is strongly associated with improved survival after lung cancer surgery

- 12,862 (9.6%) surgical resection
- Analysis of relation between hospital volume and survival
High procedure volume is strongly associated with improved survival after lung cancer surgery

<table>
<thead>
<tr>
<th>Hospital Volume (No. of procedures per year)</th>
<th>0 to 30 Days</th>
<th>31 to 365 Days</th>
<th>&gt; 365 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 70</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>70 to 99</td>
<td>0.81</td>
<td>0.82</td>
<td>0.95</td>
</tr>
<tr>
<td>100 to 129</td>
<td>0.75</td>
<td>0.92</td>
<td>0.94</td>
</tr>
<tr>
<td>130 to 149</td>
<td>0.91</td>
<td>0.78</td>
<td>0.97</td>
</tr>
<tr>
<td>≥ 150</td>
<td>0.58</td>
<td>0.80</td>
<td>0.84</td>
</tr>
</tbody>
</table>

χ² = 3.24, P = .07
χ² = 5.93, P = .01
χ² = 2.67, P = .10

NOTE. Based on shared-frailty model adjusted for age, sex, socioeconomic deprivation, Charlson comorbidity score, resection quintile, and hospital (random effect). Abbreviations: HR, hazard ratio; NSCLC, non-small-cell lung cancer.

*1 df.
All major lung cancer resections over time periods

<table>
<thead>
<tr>
<th>Period</th>
<th>Total</th>
<th>90 day mortality</th>
<th>30 day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998-2000</td>
<td>469</td>
<td>28 (6.0%)</td>
<td>13 (2.8%)</td>
</tr>
<tr>
<td>2001-2003</td>
<td>342</td>
<td>14 (4.1%)</td>
<td>8 (2.3%)</td>
</tr>
<tr>
<td>2004-2006</td>
<td>496</td>
<td>15 (3.0%)</td>
<td>6 (1.2%)</td>
</tr>
<tr>
<td>2007-2009</td>
<td>433</td>
<td>12 (2.8%)</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>2010-2013</td>
<td>473</td>
<td>7 (1.5%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

Dr. med. A. E. Frick, ELCC 2015, 16.04.2015
30- and 90-day mortality

Overall mortality:
- 1638 (76, 3.4%)
- 312 (15, 0.6%)

30-day mortality:
- 106 (2, 1.9%)
- 48 (2, 1.2%)
- 20 (1, 0.8%)
- 15 (1, 0.6%)
- 43 (2, 2.3%)
- 10 (1, 4.2%)
- 6 (1, 2.3%)

90-day mortality:
- 2242 (76, 3.4%)
- 34 (1, 1.5%)

Gesamt (Overall):
- 2242

Segmente (Surgical Procedure):
- Lobectomy
- Sleeve
- Pneumone
- Extended
Very large and nice study that illustrates importance to report 90-day mortality and importance of volume

Excellent results. Low mortality. Last period: 30-day 0.2%, 90-day 1.5%

What is definition of extended pneumonectomy?

What is the mortality after induction therapy?
Is routine sampling of the inferior mediastinal lymph node stations a necessity for pre-operative mediastinal staging in lung cancer?

- Dr Matthew Evison
- Consultant in Respiratory Medicine (Thoracic Oncology)
- Manchester Thoracic Oncology Centre
- University Hospital of South Manchester
- United Kingdom
Study

• Retrospective
• All NSCLC resections 2011-2014
• Pathological datasets
Conclusion 1

• A lack of combined EBUS-EUS procedures in our network may “miss” multi-station N2 disease in 2-3% of patients undergoing surgical resection for lung cancer

• Limitations: clinical staging unknown (bulky N2 vs occult N2), unknown how many had EBUS, EUS not just about stations 8&9
Conclusion 2

• Is routine pre-operative sampling of inferior mediastinal stations needed?

• .... probably not in our network
Invasive mediastinal staging

Cervical mediastinoscopy
EBUS-TBNA

EUS-FNA
Prospective, multicenter randomised study

Ghent, Leiden, Leuven, Papworth

Inclusion: NSCLC with indication for invasive staging, based on ESTS guidelines 2007
- PET positive N1-N2 nodes
- CT N2 nodes ≥ 1 cm
- Central tumors

Endpoints: sensitivity to detect N2/N3; rate of futile thoracotomies

Annema et al; JAMA 2010;304:2245-32
Invasive mediastinal staging?
ASTER

Inclusion: NSCLC with indication for invasive staging, based on ESTS guidelines 2007

- PET positive N1-N2 nodes
- CT N2 nodes ≥ 1 cm
- Central tumors

Surgical staging
N=118

Endoscopic ultrasonography staging (EBUS/EUS-FNA), if negative followed by surgical staging
N=123

Annema et al; JAMA 2010;304:2245-32
**Invasive mediastinal staging?**

**ASTER**

<table>
<thead>
<tr>
<th></th>
<th>Surgical staging (n=118)</th>
<th>Endoscopic staging and if negative surgical staging (n=123)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop detection N2/N3</td>
<td>35% (n=41)</td>
<td>50% (n=62)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sensitivity for N2-N3</td>
<td>80%</td>
<td>94%</td>
<td>0.04</td>
</tr>
<tr>
<td>(preoperative)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>85%</td>
<td>92%</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Annema et al; JAMA 2010;304:2245-32
In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered.

Depending on local expertise to adhere to minimal requirements for staging, endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available.

Due to its higher NPV, in case of PET positive or CT enlarged mediastinal LN's, videoassisted mediastinoscopy (VAM) with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy.
EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial

**Table 2** Diagnostic values of procedures in the detection of mediastinal metastasis

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Group A: EBUS-centred (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic accuracy, % (n/n)</td>
<td>93.2 (69/74) (87.5 to 99.0)</td>
</tr>
<tr>
<td>Accuracy of first procedure*, % (n/n)</td>
<td>91.9 (68/74) (85.7 to 98.1)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.754</td>
</tr>
<tr>
<td><strong>Sensitivity, % (n/n)</strong></td>
<td><strong>85.3 (29/34) (68.9 to 95.0)</strong></td>
</tr>
<tr>
<td><strong>Sensitivity of first procedure, % (n/n)</strong></td>
<td><strong>82.4 (28/34) (65.5 to 93.2)</strong></td>
</tr>
<tr>
<td>p Value</td>
<td>0.742</td>
</tr>
<tr>
<td>NPV, % (n/n)</td>
<td>88.9 (40/45) (75.9 to 96.3)</td>
</tr>
<tr>
<td>NPV of first procedure, % (n/n)</td>
<td>87.0 (40/46) (73.7 to 95.1)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.777</td>
</tr>
</tbody>
</table>

Stage shift adding EUS 7% (single level N2 → multilevel N2 by EUS, N2 by EBUS → N3 by EUS)

Adequacy of LN sampling - IASLC

• At least 3 mediastinal lymph node stations
• Station 7 sampled in all cases
• Station 5/6 in cases of a left upper lobe tumour
• Station 9 in cases of a lower lobe tumour

• (At least 3 hilar lymph node stations)
Systematic nodal dissection

Right side: mediastinal LNs: 2R, 4R, 7, 8, 9
hilar 10 (if lobect or segmentect: 11, 12, 13)

Left side: mediastinal LNs: 4L, 5, 6, 7, 8, 9
hilar 10 (if lobect or segmentect: 11, 12, 13)
Systematic nodal dissection

(% of) unforeseen nodal disease

• Depends on accuracy on preoperative invasive staging (EBS/EUS/mediastinoscopy)
• Depends on accuracy of intraoperative systematic nodal dissection
• After proper preoperative mediastinal staging, unforeseen N2 disease is often resectable with acceptable longterm survival
Potentially resectable NSCLC (or suspected) staged with CT and PET/CT (2171 pts)

If central T and/or SUV max > 8

Clinically staged I NSCLC (721 pts)

Med, EUS and/or EBUS 146 pts

140 pts were N0

715 pts proceeded to resection

Benign (101 pts)

p Stage 1 (405 pts)

p Stage II N=70 (47 pts N1 = 5.7%)

p Stage III N=106 (69 pts N2 = 9.6%)

p Stage IV N=17

Metastasis N=16

Clinically staged stage II, III or IV (1450 pts)

Cerfolio et al., Ann Thorac Surg 2009;88:917-23
100% PET-CT
24.6% EBUS/EUS and/or Mediastinoscopy

**dBase Bronchial carcinoma**
2007 - 2013
n = 1077

**Exclusions:**
- Induction therapy: 210
- cM1a/b: 36
- Previous lung surgery: 62
- SCLC: 12
- Carcinoid: 64
- Previous LN disease: 7
- Wedge: 6

**STUDY POPULATION**
n = 680

**Clinical Staging**
STAGE I
n = 334

- N0: 281 (84.1%)
- N1: 32 (9.6%)
- N2: 21 (6.3%)

**N2 disease:** 6.3%
Single level N2: 4.2%
Multilevel N2: 2.1%
Comments

- Retrospective surgical series
- No data on indication or percentage of patients who had preoperative invasive staging
- Intra-operative staging far from optimal
- 58% of patients with lower lobe tumours had station 9 removed. How were they selected?
- High percentage of resected multistation N2 (underscored due to less optimal intraoperative nodal dissection)
<table>
<thead>
<tr>
<th></th>
<th>2011 n=173</th>
<th>2012 n=333</th>
<th>2013 n=464</th>
<th>2014 n=437</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall proportion of adequate nodal sampling</strong></td>
<td>13%</td>
<td>22%</td>
<td>38%</td>
<td>51%</td>
</tr>
<tr>
<td></td>
<td>23/173</td>
<td>73/333</td>
<td>174/464</td>
<td>224/437</td>
</tr>
<tr>
<td><strong>≥3 mediastinal LN stations sampled</strong></td>
<td>17%</td>
<td>31%</td>
<td>47%</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>30/173</td>
<td>103/333</td>
<td>220/464</td>
<td>262/437</td>
</tr>
<tr>
<td><strong>Station 7 sampled</strong></td>
<td>36%</td>
<td>46%</td>
<td>63%</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>63/173</td>
<td>154/333</td>
<td>290/464</td>
<td>244/437</td>
</tr>
<tr>
<td><strong>Station 5/6 in LUL tumours</strong></td>
<td>72%</td>
<td>73%</td>
<td>76%</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>42/58</td>
<td>72/98</td>
<td>104/137</td>
<td>95/113</td>
</tr>
<tr>
<td><strong>Station 9 in lower lobe tumours</strong></td>
<td>49%</td>
<td>52%</td>
<td>60%</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>37/75</td>
<td>66/128</td>
<td>124/208</td>
<td>114/173</td>
</tr>
<tr>
<td><strong>Proportion of multi-station N2 resections</strong></td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>8/173</td>
<td>12/333</td>
<td>25/464</td>
<td>17/437</td>
</tr>
</tbody>
</table>
Comments

Carefull to draw any conclusions on importance of preoperative staging of lower mediastinal LN’s based on this study