Physiological assessment of patients with resectable NSCLC
Kris Nackaerts, MD, PhD

Speaker Information and Disclosure

• No relevant financial relationships with any commercial interests to declare.
Physiological assessment of patients with resectable NSCLC

- Case
- Risks of lung cancer surgery
- Important factors in lung cancer surgery
- Criteria of (in)operability
- Guidelines
- Summary

Case

- Woman, 72 yrs
- Chronic cardiac failure
- 07/08: RT coin lesion RUL, 60Gy/30
- cT1aN0M0
- Candidate for resection?

LF
- FEV1 76%pred
- DL,CO 47%pred
### Risks of lung cancer surgery

- Postoperative morbidity/mortality

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 1546)</th>
<th>1986–1989 (n = 103)</th>
<th>1990–1994 (n = 251)</th>
<th>2000–2004 (n = 373)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative mortality</td>
<td>65 (4.2%)</td>
<td>35 (3.4%)</td>
<td>28 (11.2%)</td>
<td>54 (14.5%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nonoperative mortality</td>
<td>85 (5.5%)</td>
<td>38 (3.7%)</td>
<td>27 (10.7%)</td>
<td>48 (12.8%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Postoperative hospital days</td>
<td>9.3 ± 6.9</td>
<td>13.2 ± 10.7</td>
<td>5.4 ± 4.3</td>
<td>8.8 ± 6.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- Short-term or perioperative risk
- Long-term risk
  - Physical performance
  - Quality of life

Ferguson MK et al, EJCTS 2008:33:496-500

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## Important factors in lung cancer surgery

- Different patient characteristics
  - Age, gender, co-morbidity (COPD), smoking
- Different tumor stages
  - Stage I-III A,B?
- Different surgical procedures
  - (bi-)lobectomy, pneumonectomy
  - Minimally invasive surgery, VATS
- Pretreatment (chemo-radiotherapy)?

### Table: Important factors in lung cancer surgery

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 1046)</th>
<th>1980–1989 (n = 320)</th>
<th>1990–1999 (n = 351)</th>
<th>2000–2006 (n = 375)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.0 (15.4)</td>
<td>65.5 (14.9)</td>
<td>63.1 (15.2)</td>
<td>66.5 (14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>577 (55.1%)</td>
<td>198 (61.9%)</td>
<td>184 (52.4%)</td>
<td>195 (51.9%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>469 (44.9%)</td>
<td>122 (38.1%)</td>
<td>167 (47.6%)</td>
<td>180 (48.1%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>577 (55.1%)</td>
<td>198 (61.9%)</td>
<td>184 (52.4%)</td>
<td>195 (51.9%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>469 (44.9%)</td>
<td>122 (38.1%)</td>
<td>167 (47.6%)</td>
<td>180 (48.1%)</td>
<td></td>
</tr>
<tr>
<td>Charlson index</td>
<td>3.6 (4.8)</td>
<td>4.0 (5.2)</td>
<td>3.2 (4.0)</td>
<td>3.7 (4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR-SSA</td>
<td>19.4 (11.1)</td>
<td>20.1 (11.5)</td>
<td>19.4 (11.1)</td>
<td>19.8 (11.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>83.1 (22.3)</td>
<td>81.2 (22.3)</td>
<td>83.2 (22.4)</td>
<td>81.9 (21.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>79.0 ± 19.7</td>
<td>79.7 ± 20.8</td>
<td>81.0 ± 20.4</td>
<td>82.9 ± 18.0</td>
<td>0.13</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>84.7 ± 29.9</td>
<td>84.4 ± 24.8</td>
<td>88.8 ± 22.7</td>
<td>81.3 ± 21.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLCO/VA</td>
<td>63.6 ± 18.6</td>
<td>65.6 ± 17.7</td>
<td>66.6 ± 19.7</td>
<td>62.4 ± 18.0</td>
<td>0.025</td>
</tr>
<tr>
<td>ENZ score</td>
<td>6.9 ± 2.7</td>
<td>6.5 ± 2.5</td>
<td>6.6 ± 2.5</td>
<td>7.4 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PS ≥ 2</td>
<td>116 (10.9)</td>
<td>74 (23.1)</td>
<td>58 (16.8)</td>
<td>24 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Induction therapy</td>
<td>74 (15.8)</td>
<td>55 (17.2)</td>
<td>18 (5.1)</td>
<td>26 (7.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Current smoker: any cigarette use within 6 weeks of operation; obesity: body mass index (>30 kg/m²); FEV1: forced expiratory volume in 1 s expressed as a percent of predicted; FVC/FEV1: predicted postoperative and preoperative FEV1; DLCO: single breath diffusing capacity for carbon monoxide expressed as a percent of predicted; DLCO/VA: predicted postoperative DLCO/VA; ENZ: risk score based on weighted scores for FEV1, DLCO, and age (see NM. 1035); PS: Eastern Cooperative Oncology Group performance status; Induction therapy: preoperative chemotherapy and/or radiation therapy.
Criteria for (in)operability

- Cardiac function
  - Revised Cardiac Risk Index (RCRI)

<table>
<thead>
<tr>
<th>Cardiac Risk Index</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. High-risk type of surgery</td>
<td>2.8 (0.6, 4.9)</td>
<td>2.6 (0.3, 3.9)</td>
</tr>
<tr>
<td>2. Ischemic heart disease</td>
<td>2.4 (0.3, 3.2)</td>
<td>2.5 (0.3, 3.9)</td>
</tr>
<tr>
<td>3. History of congestive heart failure</td>
<td>1.9 (0.1, 3.5)</td>
<td>1.5 (0.1, 4.1)</td>
</tr>
<tr>
<td>4. History of cerebrovascular disease</td>
<td>3.2 (0.8, 5.0)</td>
<td>3.2 (0.9, 5.9)</td>
</tr>
<tr>
<td>5. Insulin therapy for diabetes</td>
<td>3.0 (0.3, 7.1)</td>
<td>3.0 (0.2, 3.9)</td>
</tr>
<tr>
<td>6. Preoperative serum creatinine &gt;25 mg/dl</td>
<td>3.0 (0.4, 6.6)</td>
<td>3.0 (0.2, 3.3)</td>
</tr>
</tbody>
</table>

*Based on logistic regression models including these 6 variables.

Lee TH et al, Circulation 1999;100:1043-49
Auerbach A et al, Circulation 2006;113:1263-76
Criteria for (in)operability – cardiac 2

- Cardiac function
  - RCRI - risk on major cardiologic complications

[Graph showing criteria for operability]

Lee TH et al, Circulation 1999;100:1043-49

Influence of resection on pulmonary function

<table>
<thead>
<tr>
<th></th>
<th>PNEUMONECTOMY</th>
<th>LOBECTOMY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC, RV, TLC</td>
<td>-30 ± 45%</td>
<td>-10 ± 20%</td>
</tr>
<tr>
<td>FEV₁, PEF</td>
<td>-30 ± 45%</td>
<td>-10 ± 20%</td>
</tr>
<tr>
<td>Gas exchange</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL, CO</td>
<td>-15 ± 25%</td>
<td>-5 ± 10%</td>
</tr>
<tr>
<td>PaO₂</td>
<td>+5 ± 10%</td>
<td>+5 ± 5%</td>
</tr>
<tr>
<td>Mechanics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw</td>
<td>+45%</td>
<td>+30%</td>
</tr>
<tr>
<td>CL, Jet</td>
<td>-50 ± 70%</td>
<td>-20 ± 30%</td>
</tr>
</tbody>
</table>


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Criteria for (in)operability

- Influence of resection on pulmonary function
  - N segments: 19
  - R lung: 10
  - L lung: 9

Criteria for (in)operability - FEV₁

- FEV₁
  - ppoFEV₁ is crucial in all guidelines*
  - Predicted postoperative (ppo) FEV₁
    - Based on calculation of (non-obstructed) resected segments
    - Based on (Tc-99m) lung perfusion scintigraphy (pneumonectomy)
    - Based on imaging (MDCT,...)

* BTS Guidelines, Thorax 2001;56:89-108
  * ACCP Guidelines, Chest 2007;132: Suppl; 161S–177S
  * ERS/ESTS Guidelines, ERJ 2009:34:17-41
  * Bolliger CT et al, Respiration 2002:69:482-9
Criteria for (in)operability - FEV$_1$

• FEV$_1$
  – Predicting postop morbidity/mortality?
  – Preop absolute FEV$_1$ >1.5L (lobectomy)
  >2L (pneumonectomy)
  – Lowest ppoFEV$_1$ >40% → >30%
  (high risk threshold)

* BTS Guidelines, Thorax 2001;56:89-108
* ACCP Guidelines, Chest 2007;132:Suppl3,1615-1775
* ERS/ESTS Guidelines, ERJ 2009:34:17-41

Criteria for (in)operability - FEV$_1$

• FEV$_1$
  – ppoFEV$_1$ = predictor for postoperative complications risk
  – Prospective study
  – N=331 pts
  – ppoFEV$_1$ - Juhl Frost formula
    ppoFEV$_1$ = preopFEV$_1$ x [1-(Sx5.26)/100]

<1% mortality rate
17% complication rate

Criteria for (in)operability - FEV\textsubscript{1} 4

- **FEV\textsubscript{1}**
  - **ppoFEV\textsubscript{1}** is NOT a reliable predictor of complications
- Observed FEV\textsubscript{1}
  - Discharge, 1 & 3m
- Prospective study
- N=253 pts
- Results for lobectomy/ (pneumonectomy)


Criteria for (in)operability - FEV\textsubscript{1} 5

- **FEV\textsubscript{1}**
  - **ppoFEV\textsubscript{1}** in COPD pts
  - Lobectomy
  - Calculated ppoFEV\textsubscript{1}
  - Measured FEV\textsubscript{1}, (3-12m)
  - Retrospective study

Baldi S et al, JTCVS;130:1616

Figure 1. Observed postoperative/predicted postoperative FEV\textsubscript{1} ratio according to FEV\textsubscript{1}%.
**Criteria for (in)operability - FEV₁ 6**

- **FEV₁**
  - FEV₁ measured at Day 1 postop is better predictor of complications than ppoFEV₁.
  - Prospective study
  - N=272 pts
  - Lobectomy (242)
  - Pneumonectomy (30)
  - **MODEL** to predict Day1FEV₁

*Brunelli A et al, EJCTS 2007;32:783-6

**Criteria for (in)operability - DL,CO 1**

- **DL,CO**
  - Alveolar oxygen exchange
  - ppoDL,CO ≥ 40% → ≥ 30% (high risk threshold)
  - Predictor of postop mortality/morbidity*
  - ...even in pts with normal spirometry!
  - Routine measurement needed, regardless of spirometric findings

*Ferguson MK et al, Ann Thor Surg 2008;85:1158-65
Criteria for (in)operability -DL,CO 2

- DL,CO
  - Predictor of postop mortality/morbidity*
  ...even in pts with normal spirometry!

Predictors of postoperative cardiopulmonary morbidity in patients with FEV1 > 80% (508 cases)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Estimates</th>
<th>SE</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-3.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.01</td>
<td>1.03</td>
<td>1.01-1.05</td>
<td>0.007</td>
</tr>
<tr>
<td>ppoDLCO &lt; 40%</td>
<td>1.1</td>
<td>0.4</td>
<td>3</td>
<td>1.4-6.3</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Brunelli A et al, EJCTS 2006;29:567-70

Criteria for (in)operability -DL,CO 3

- Postop changes in
  FEV1, DL,CO
- Observations
  - Preop, Discharge, 1 & 3m
  - Prospective study
- N=200 pts (single center)

Brunelli A et al, Chest 2007;131:141-7
Criteria for (in)operability -DL,CO

- DL,CO
  - ppoDL,CO
  - Observed DL,CO
    - Discharge, 1 & 3m
    - Prospective study
    - N=253 pts
  - Results for lobectomy/pneumonectomy

Criteria for (in)operability -VO₂max

- VO₂max
  - When?
    - preop FEV₁ and DL,CO < 80%pred
  - How?
    - Cardiopulmonary exercise testing (CPET)
    - Stair climbing test
    - 6-min walking test (no)
    - Shuttle walk test (screening test)

References:
- ERS/ESTS Guidelines, ERJ 2009;34:17-41
Criteria for (in)operability - VO$_2$_max 2

- Postop changes in (FEV$_1$, DL, CO), VO$_2$_max
- Observations
  - Preop, Discharge, 1 & 3m
  - Prospective study
  - N=200 pts (single center)
  - Stair climbing test

Criteria for (in)operability - VO$_2$_max 3

- VO$_2$_max
  - Correlated to surgical outcome
    - VO$_2$_max > 20 ml/kg/min or >75% pred
    - VO$_2$_max < 10 ml/kg/min or <40% pred (high risk)
    - VO$_2$_max > 10 <20 ml/kg/min
  - ppoVO$_2$_max > 35%
ERS 1998 Guidelines -3
CALGB study
• Prospective study
• 403 patients
• 58 pts had surgery, but were “inoperable” on ERS 1998 algorithm!

**TABLE A** Outcomes for Patient Groups Categorized by the CALGB 9380 Algorithm

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Risk</th>
<th>High Risk</th>
<th>Very High Risk</th>
<th>No Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>227</td>
<td>51</td>
<td>68</td>
<td>37</td>
</tr>
<tr>
<td>D/C (mean ± SE)</td>
<td>80.9 ± 3.3</td>
<td>80.9 ± 3.7</td>
<td>66.0 ± 1.6</td>
<td>66.0 ± 1.3</td>
</tr>
<tr>
<td>1/3 (mean ± SE)</td>
<td>79.8 ± 1.4</td>
<td>79.8 ± 2.4</td>
<td>76.0 ± 2.0</td>
<td>76.0 ± 1.4</td>
</tr>
<tr>
<td>VEC (mean ± SE)</td>
<td>17.8 (0.49)</td>
<td>17.8 (0.48)</td>
<td>13.0 (0.24)</td>
<td>14.4 (0.71)</td>
</tr>
<tr>
<td>PVE (mean ± SE)</td>
<td>16.9 ± 1.3</td>
<td>16.9 ± 2.2</td>
<td>15.7 ± 1.8</td>
<td>16.9 ± 2.2</td>
</tr>
<tr>
<td>% Enrollment (95% CI)</td>
<td>76%</td>
<td>76%</td>
<td>76%</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ERS/ESTS 2009 Guidelines -1
Cardiac assessment

- History
- Physical examination
- Baseline ECG
- Consider ROSI
ERS/ESTS 2009 Guidelines -2

Lung function tests and Exercise tests

Prospective validation needed!

Smoking cessation preop.: yes!
Pre- and postoperative rehabilitation?
Combined cancer surgery/LVRS
Anatomical segmentectomy?
Neo-adjuvant chemoradiotherapy

Brunelli A et al, ERJ 2009:34:17-41

ERS/ESTS 2009 Guidelines -3

Cardiac assessment low risk or treated patient (fig. 1)

Either one <60%

<25% or <10 mL kg⁻¹ min⁻¹

Exercise testing Peak VO₂

>75% or >20 mL kg⁻¹ min⁻¹

Split function IPPV/PEEP ≥0.5 cmH₂O

At least one <30%

<25% or <10 mL kg⁻¹ min⁻¹

EPOETIN <500

Rejection up to calculated extent

EPOETIN <500

Rejection up to pneumonectomy

Lobectomy or pneumonectomy are usually not recommended. Consider other options.

Brunelli A et al, ERJ 2009:34:17-41
Summary

Cardiac and Lung Function evaluation tests are essential in the guidelines on functional evaluation before lung cancer resection.

1/ Cardiac and Lung Function evaluation tests are essential in the guidelines on functional evaluation before lung cancer resection.

2/ In patients with normal preop FEV\textsubscript{1} and DL\textsubscript{CO} (>80\%pred), no additional tests are needed.

3/ Exercise tests/split function studies should be indicated in pts with preop FEV\textsubscript{1} and DL\textsubscript{CO} values <80\% of normal.

4/ In case of (ppo)VO\textsubscript{2}max < 35\% or <10 ml/kg/min, lobectomy and pneumonectomy are not recommended, other treatment options need to be considered.
Thank you for your attention!