7th Annual Spring Oncology Symposium
Staging, Patient Assessment and Surgical Options for Non-Small Cell Lung Cancer

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Financial Disclosure

I receive no commercial support from any company for any activities
Objectives

- To understand the role of surgery in pre-operative tumor assessment and staging
- To understand the surgical perspective on who is a 'marginal' candidate for pulmonary resection
- To review operative strategies and techniques in pulmonary resection
- To discuss alternatives to pulmonary resection
Outline

• Surgical staging for NSCLC
• Assessment of the "marginal" patient
• Options for pulmonary resection
Female, 45%
Comorbid conditions, 76% (only 1: 25%; ≥2: 75%)
Previous cancer: 26% (head/neck, 19%, lung, 12%)

Diagnostic Evaluation - Initial

- H&P
- Pathology Review
- CT chest/upper abdomen
- Laboratory evaluation
- Smoking cessation
Diagnostic Evaluation

• Goals
  – Determine histology and stage
  – Identify treatment intent
  – Predict oncologic outcomes

• Factors
  – Clinical
  – Radiographic
  – Molecular
Pathologic stage
15,952 subjects

6th edition
Overall survival

Revised TNM
(7th edition)
Overall survival

2007;2:706-714
# Revisions AJCC/UICC Staging

<table>
<thead>
<tr>
<th>6th Edition T/M Descriptor</th>
<th>7th ed. T/M</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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</thead>
<tbody>
<tr>
<td><strong>T1</strong> (≤2cm)</td>
<td>T1a</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>T1</strong> (&gt;2–3cm)</td>
<td>T1b</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>T2</strong> (≤5cm)</td>
<td>T2a</td>
<td>IB</td>
<td>IIA (↓)</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>T2</strong> (&gt;5–7cm)</td>
<td>T2b</td>
<td>IIA (↑)</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>T2</strong> (&gt;7cm)</td>
<td>T3</td>
<td>IIB (↑)</td>
<td>IIIA (↑)</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>T3</strong> invasion</td>
<td>T3</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>T4</strong> (same_lobe_nodules)</td>
<td>T3</td>
<td>IIB (↓)</td>
<td>IIIA (↓)</td>
<td>IIIA (↓)</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>T4</strong> (extension)</td>
<td>T4</td>
<td>IIIA (↓)</td>
<td>IIIA (↓)</td>
<td>IIIA (↓)</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>M1</strong> (ipsilateral_lung)</td>
<td>T4</td>
<td>IIIA (↓)</td>
<td>IIIA (↓)</td>
<td>IIIA (↓)</td>
<td>IIIB</td>
</tr>
<tr>
<td><strong>M1</strong> (contralateral_lung)</td>
<td>M1a</td>
<td>IV (↑)</td>
<td>IV (↑)</td>
<td>IV (↑)</td>
<td>IV (↑)</td>
</tr>
<tr>
<td><strong>M1</strong> (pleural_effusion)</td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td><strong>M1</strong> (distant)</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

Goldstraw P, et al. *J Thorac Oncol* 2007;2:706-714; Stage increase(↑) or decrease (↓)
Prognostic factors
Evaluation for operability

- Tumor stage
- Medical fitness
Mediastinal evaluation

- Mediastinoscopy
  - Likely not beneficial in peripheral T1 nor small T2 NSCLC
    - Assuming low rate of occult N2 (<10%)  
    - Assuming benefit of induction therapy

- Endobronchial ultrasound-FNA
  - Appears superior to standard transbronchial technique

Meyers BF et al. *J Thorac Cardiovasc Surg* 2006;131:822-829
Wallace MB et al. *JAMA* 2008;299:540-546
Patterns of surgical care – 2001
Mediastinal evaluation

LN biopsy at med’scopy (evaluated in 27.1%)  

Frequency (95% CI)

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8

Teaching/Research  Comm CC  Comp Comm CC

p < .05

LN biopsy at resection (57.8% submitted separately)

Frequency (95% CI)

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8

Teaching/Research  Comm CC  Comp Comm CC

p < .01

Submitted tissue in 46.6%

**Prognostic factors**

**Evaluation for operability**

- Staging
- Patient factors
  - Age
  - Cardiovascular fitness
  - Pulmonary function
Prognostic factors
Pulmonary function testing

- Forced vital capacity (FVC)
- Forced expiratory volume, 1 sec (FEV₁)
- Diffusion capacity (DₗCO)

Current guidelines
- Pneumonectomy: FEV₁>2L
- Lobectomy: FEV₁>1.5L
- Obtain DₗCO for FEV₁<1.5-2L

### Pulmonary resection and FEV\textsubscript{1}

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>FEV\textsubscript{1}</th>
<th>Mort.</th>
<th>Morb.</th>
<th>New O2</th>
<th>Air leak</th>
<th>Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerfolio 1996</td>
<td>85</td>
<td>44</td>
<td>2.4</td>
<td>49</td>
<td>8</td>
<td>21</td>
<td>3.5</td>
</tr>
<tr>
<td>Temeck 1992</td>
<td>73</td>
<td>42</td>
<td>1.4</td>
<td>4.1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Miller 1997</td>
<td>32</td>
<td>1.2 Lpm</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>16</td>
<td>NA</td>
</tr>
<tr>
<td>Linden 2005</td>
<td>100</td>
<td>26</td>
<td>1</td>
<td>36</td>
<td>11</td>
<td>22</td>
<td>4</td>
</tr>
</tbody>
</table>

How good are PFTs?

110 pts
PPX: 36
Lobe: 65
Bilobe: 4
Wedge: 4

Pre-operative %predicted FEV\textsubscript{1}, FVC, D\textsubscript{L}CO, ppoFEV\textsubscript{1} Threshold: FEV\textsubscript{1}(%) 47% and D\textsubscript{L}CO(%) 45%

Prognostic factors
Pulmonary function testing

- Forced vital capacity (FVC)
- Forced expiratory volume, 1 sec (FEV\textsubscript{1})
- Diffusion capacity (D\textsubscript{L}CO)

- % predicted
  >30-40% FVC, FEV\textsubscript{1}, D\textsubscript{L}CO

- % predicted post-operative
  - Quantitative ventilation/perfusion (V/Q)
  - Estimated number of resected segments
Prognostic factors
“Marginal” patient

- Forced vital capacity (FVC)
- Forced expiratory volume, 1 sec (FEV₁)
- Diffusion capacity (D₇CO)
- % predicted
  >30-40% FVC, FEV₁, D₇CO
- % predicted post-operative
  - Quantitative ventilation/perfusion (V/Q)
  - Estimated number of resected segments

- Arterial blood gas testing, room air
- Cardiopulmonary exercise testing (maxVO₂)
Smoking Cessation

- Impaired wound healing
- Lower DLCO and total dose $\geq 60$ pk-yrs portend worse outcomes

- Ask, Advise, Assess, Assist, Arrange – the five “A”s
  - “Treating Tobacco Use and Dependence”
    - JAMA 2000; 283:3244-3254
  - Nicotine replacement therapy
    - Silagy C, et al. Cochrane Reviews 2004
  - Nicotine receptor partial agonists (varenicline, cytisine)
Prognostic factors
Evaluation for operability

- Tumor stage
- Medical fitness
  - Thoracotomy/thoracoscopy
    - Lobectomy/Pneumonectomy
    - Sublobar (anatomic segmentectomy/wedge)
  - Stereotactic body radiation therapy
  - Radiofrequency ablation
  - Cryoablation
Thoracotomy

- Division of latissimus dorsi, serratus anterior and intercostal muscles (4th or 5th ICS)
- Maximum inspiratory/expiratory pressure (MIP/MEP)
  - Decreased chest wall and lung compliance
  - Diaphragmatic dysfunction
- Slower recovery of MIP/MEP
- Longer duration of postoperative pain
Video-assisted thoracic surgery

- VATS
- Thoracoscopy
  1. Video assisted mini-thoracotomy
  2. Video assisted simultaneously stapled
  3. Video assisted non-rib spreading
Utilization of VATS lobectomy

Society of Thoracic Surgeons GT Database

![Chart showing the utilization of VATS lobectomy over years from 2002 to 2007]

Relative contraindications

- Single lung ventilation intolerance
- Tumor size > 6cm
- Sleeve resection
- Hilar lymphadenopathy or calcification
- Chest wall or mediastinal involvement
- Neoadjuvant radiation or chemotherapy
VATS Lobectomy

• Postoperative complications
  – Atrial dysrhythmia
  – Pneumonia
  – Air leak
  – Respiratory failure

• Port site recurrence, 0.2% (3/1321)
**VATs Lobectomy**

- Conversion rates: 0.9-13%
  - Inflammation/adhesions
  - Dense hilar lymphadenopathy
  - Bleeding

- Median lengths of stay: 3-6 days
- Morbidity: 2.3-22%
- Mortality: 0.5-3.6%

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VATS Lobectomy: Quality of Life

• **Walker, 1996**
  – 83 VATS, 110 Thoracotomy
  – Less morphine in VATS (mean 57mg vs 83mg)

• **Landreneau, 1998**
  – 178 VATS, 165 Muscle Sparing Thoracotomy
  – Compared narcotic use, LOS, & visual scale pain
  – Less pain and greater shoulder strength at 6mo

• **Kaseda, 2000**
  – VATS patients had better FEV1 and FVC at 3mo
VATS vs. Thoracotomy:

**Immunologic**

- Decreased suppression of circulating $T_h$ and NK cells
  - Better preserved lymphocyte oxidation
- Diminished acute phase response
  - C-reactive protein, IL6

VATS Lobectomy

• CON
  – Unsafe
  – Incomplete oncologic operation
  – No advantage over thoracotomy
  – Difficult to teach

• PRO
  – Decreased blood loss
  – Decreased pain
  – Shortened LOS
  – Preserved pulmonary function
  – Equivalent oncologic outcomes
  – Decreased inflammatory response
VATS Lobectomy

Outcomes appear to be at least equivalent to those of patients undergoing thoracotomy, particularly for patients with early stage lung cancer.
Extent of resection

- Lobectomy
- Segmentectomy
  - Upper lobes: apicalposterior, lingula
  - Lower lobes: superior, basilar
- Non-anatomic/"wedge"
Survival – extent of resection

N=3211, 1993-2002, Norway

## Postoperative survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mortality HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.41 (1.28-1.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 60-69</td>
<td>1.45 (1.20-1.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1.95 (1.62-2.36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.23 (2.38-4.40)</td>
<td></td>
</tr>
<tr>
<td>Upper lobectomy</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Lower lobectomy</td>
<td>1.16 (1.02-1.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>1.25 (1.05-1.49)</td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>1.57 (1.39-1.78)</td>
<td></td>
</tr>
<tr>
<td>Sublobar</td>
<td>1.41 (1.15-1.74)</td>
<td></td>
</tr>
<tr>
<td>Right side</td>
<td>1.11 (1.01-1.22)</td>
<td>0.028</td>
</tr>
<tr>
<td>Adenoca</td>
<td>1.44 (1.30-1.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>0.19 (0.11-0.32)</td>
<td></td>
</tr>
</tbody>
</table>

## Survival – early mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>N</th>
<th>30d Mortality, %</th>
<th>30d PPX, %</th>
<th>30d Lobe, %</th>
<th>30d Sublobar, %</th>
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</thead>
<tbody>
<tr>
<td>Weiss, 1974</td>
<td>1961-1965</td>
<td>364</td>
<td>14.0</td>
<td>17.0</td>
<td>10.1</td>
<td>0</td>
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<tr>
<td>Ginsberg, 1983</td>
<td>1979-1981</td>
<td>2200</td>
<td>3.7</td>
<td>6.2</td>
<td>2.9</td>
<td>1.4</td>
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<td>Romano, 1992</td>
<td>1983-1986</td>
<td>12439</td>
<td>4.1</td>
<td>11.6</td>
<td>4.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Deslauriers, 1994</td>
<td>1988-1989</td>
<td>783</td>
<td>3.8</td>
<td></td>
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<tr>
<td>Wada, 1998</td>
<td>1994</td>
<td>7099</td>
<td>1.3</td>
<td>3.2</td>
<td>1.2</td>
<td>0.8</td>
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<td>Harpole, 1999</td>
<td>1991-1995</td>
<td>3516</td>
<td>5.2</td>
<td>11.5</td>
<td>4.0</td>
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<tr>
<td>Watanabe, 2004</td>
<td>1987-2002</td>
<td>3270</td>
<td>0.6</td>
<td>3.1</td>
<td>0.3</td>
<td>0.3</td>
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</table>

Non-randomized Multi-center trial
567 subjects
cT1a

## Extent of resection

*a non-randomized multicenter trial*

<table>
<thead>
<tr>
<th>Location</th>
<th>Sublobar</th>
<th>Lobar</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUL</td>
<td>101 (33%)</td>
<td>112 (43%)</td>
</tr>
<tr>
<td>RLL</td>
<td>54 (18%)</td>
<td>54 (21%)</td>
</tr>
<tr>
<td>LUL</td>
<td>106 (35%)</td>
<td>63 (24%)</td>
</tr>
<tr>
<td>LLL</td>
<td>44 (14%)</td>
<td>33 (13%)</td>
</tr>
</tbody>
</table>

Disease-free survival

Entire Cohort (cT1a)

pT1N0M0

## Extent of resection

### 5-year survival

<table>
<thead>
<tr>
<th>Author</th>
<th>Sublobar resection</th>
<th>Lobar resection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>5-year survival (%)</td>
</tr>
<tr>
<td>Read et al., 1990(^{18})</td>
<td>113</td>
<td>84</td>
</tr>
<tr>
<td>LCSG 1995(^{1})</td>
<td>122</td>
<td>44*</td>
</tr>
<tr>
<td>Kodama et al., 1997(^{8})</td>
<td>46</td>
<td>93</td>
</tr>
<tr>
<td>Landreneau et al., 1997(^{19})</td>
<td>102</td>
<td>62</td>
</tr>
<tr>
<td>Okada et al., 2001(^{12})</td>
<td>68</td>
<td>87</td>
</tr>
<tr>
<td>Koike et al., 2003(^{9})</td>
<td>74</td>
<td>89</td>
</tr>
<tr>
<td>The present study</td>
<td>305</td>
<td>89.6</td>
</tr>
</tbody>
</table>

\(^{1}\) NSCLC, non–small cell lung cancer. *statistically significant.
Extent of resection
Post-resection PFT

Sublobar resection

- UVirginia (n=61, 43 w/ bronchogenic CA)
  - Median FEV₁ (% predicted): 55 (34-90)
  - Median ppo FEV₁: 42 (26-63)
  - DLCO (%): 55 (34-111)
  - Median F/U 28 months (range: 1-89 mo)

- In-hospital mortality, 3%

- Complications, 39%
  - Atelectasis, 16%
  - Pneumonia, 14%
  - SVT, prolonged air leak

- No locoregional recurrences
Kaplan-Meier survival, segmentectomy, UVA

<table>
<thead>
<tr>
<th></th>
<th>Total (25)</th>
<th>Limited (12)</th>
<th>Lobe (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁ (L)</strong></td>
<td>0.82</td>
<td>0.75</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>FEV₁ (%)</strong></td>
<td>46</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>8 (32%)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td><strong>Recurrences</strong></td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metastases</strong></td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Overall 2-yr mortality</strong></td>
<td>31%</td>
<td>56%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Sublobar resection and PORT

- **CALGB9335**
  - 65 patients enrolled (1995-1999)
  - VATS wedge, Stage IA NSCLC
    - 28 received PORT
      - 56 Gy if complete resection
      - 66 Gy if incomplete resection

Sublobar resection/brachytherapy

Brachytherapy reduced local recurrence from 17% to 3% (p=0.012) among the 124 subjects undergoing sublobar resection.

Sublobar resection/brachytherapy

Brachytherapy (n=60) reduced local recurrence from 17% to 3% (p=0.012) among the 124 subjects undergoing sublobar resection.

Sublobar Resection

• Brachytherapy
  – ACOSOG Z4032 (cT1N0-1)

• Lobectomy
  – CALGB 140503
ACOSOG Z0030

- Randomized mediastinal lymph node sampling (MLNS) and lymphadenectomy (MLND)
  - N0/1, T1/2 NSCLC
  - 1023 subjects
    - right upper lobe
    - adenocarcinoma
ACOSOG Z0030

- MLND: Occult N2 in 20 subjects (3.8%)
- No differences in survival

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MLNS</th>
<th>MLND</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival (years)</td>
<td>8.1</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Time to Recurrence (years)</td>
<td>5.7</td>
<td>6.1</td>
<td>NS</td>
</tr>
</tbody>
</table>
Darling GE, et al. Abstract #1; AATS 2010, Toronto ON
Non-operative treatment

- Radiofrequency ablation
  - ACOSOG Z4033
- Stereotactic Body Radiation Therapy
  - RTOG 0813 (inoperable central NSCLC)
  - STARS (Accuray)
  - RTOG 0618 (operable NSCLC)
- Cryoablation
**Who decides?**

- **Patient/family**
- **Multidisciplinary group**
  - Medical/radiation oncology
  - Pulmonary medicine
  - Thoracic surgery (oncology)
  - Radiology
  - Pathology
- “Medically unresectable”
Quality assurance/assessment

• Prospective database
  – Proper risk stratification
  – Outcomes

• Operative technique
  – Surgical approach
  – Mediastinal nodal evaluation
References


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Spring Kong, MD PhD