Sublobar Resection for T1a Non-Small Cell Lung Cancer

David Rice
Sublobar Resection for T1a Non-Small Cell Lung Cancer
Disclosure

- Olympus America, Inc - consultant
Introduction
Introduction

- Is sublobar resection adequate treatment for small, peripheral, early-stage NSCLC in ‘low risk’ patients?

- Is sublobar resection better than non-surgical ablation (especially SBRT) for small, peripheral NSCLC in ‘high risk’ patients?
Bronchial Anatomy – late 1800’s
Historical Perspective

- Bronchial Anatomy – late 1800’s
- Bronchopulmonary segment, 1932

Kramer R & Glass A. Ann Otol Rhinol Laryngol, 1932
Anatomy: Lateral Aspect
Anatomy

1. Single Unit (Segment)
   - Bronchus
   - Artery
   - Subpleural V.
   - Segmental V.

2. Compound Unit (Segment)
   - Bronchus
   - Subpleural Vein
   - Intersegmental Veins
   - Pleura

Historical Perspective

- Bronchial Anatomy, late 1800’s
- Bronchopulmonary segment, 1932
- Segmentectomy, 1939
LeRoux, 1972
- Segmentectomy in 17 patients with lung cancer
  - Presumed TB
  - Anatomically complete intersegmental fissures
  - Poor pulmonary function
- 5 patients survived longer than 5 years
Historical Perspective

From the small number of segmental resections undertaken it can only be said that this operation, undertaken in the management of bronchial carcinoma, is followed by long survival in a proportion of patients not noticeably different from that which follows resection of greater extent for tumours of the same relatively small size.
Jensik, 1973

- 123 segmentectomies over 15 years
- Mortality 5%
- 5-year survival 56% in 69 patients treated with curative intent
<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Surgery</th>
<th>Diameter</th>
<th>5-yr survival</th>
<th>Local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensik, 1979</td>
<td>168</td>
<td>Seg 168</td>
<td>NR</td>
<td>53%</td>
<td>10%</td>
</tr>
<tr>
<td>Read, 1990</td>
<td>113</td>
<td>Seg 107; wedge 6</td>
<td>2cm</td>
<td>51%</td>
<td>4%</td>
</tr>
<tr>
<td>Weisberg, 1993</td>
<td>170</td>
<td>Seg 58; wedge 97; NOS 15</td>
<td>3cm</td>
<td>55% (DFS)</td>
<td>14%</td>
</tr>
<tr>
<td>Warren, 1994</td>
<td>66</td>
<td>Seg 66</td>
<td>2.2 cm</td>
<td>43%</td>
<td>23%</td>
</tr>
<tr>
<td>Martini, 1995</td>
<td>62</td>
<td>Seg 13, wedge 49</td>
<td>3cm (max)</td>
<td>59%</td>
<td>23%</td>
</tr>
</tbody>
</table>
Randomized Trial of Lobectomy Versus Limited Resection for T1 N0 Non–Small Cell Lung Cancer

Lung Cancer Study Group (Prepared by Robert J. Ginsberg, MD, and Lawrence V. Rubinstein, PhD)

Background. It has been reported that limited resection (segment or wedge) is equivalent to lobectomy in the management of early stage (T1–2 N0) non–small cell lung cancer.

Methods. A prospective, multiinstitutional randomized trial was instituted comparing limited resection with lobectomy for patients with peripheral T1 N0 non–small cell lung cancer documented at operation. Analysis included locoregional and distant recurrence rates, 5-year survival rates, perioperative morbidity and mortality, and late pulmonary function assessment.

Results. There were 276 patients randomized, with 247 patients eligible for analysis. There were no significant differences for all stratification variables, selected prognostic factors, perioperative morbidity, mortality, or late pulmonary function. In patients undergoing limited resection, there was an observed 75% increase in recurrence rates ($p = 0.02$, one-sided) attributable to an observed tripling of the local recurrence rate ($p = 0.008$ two-sided), an observed 30% increase in overall death rate ($p = 0.08$, one-sided), and an observed 50% increase in death with cancer rate ($p = 0.09$, one-sided) compared to patients undergoing lobectomy ($p = 0.10$, one-sided was the predefined threshold for statistical significance for this equivalency study).

Conclusions. Compared with lobectomy, limited pulmonary resection does not confer improved perioperative morbidity, mortality, or late postoperative pulmonary function. Because of the higher death rate and locoregional recurrence rate associated with limited resection, lobectomy still must be considered the surgical procedure of choice for patients with peripheral T1 N0 non–small cell lung cancer.

Prospective, randomized trial
Accrue from 1982 to 1988
c-Stage Ia NSCLC
Intraoperative confirmation of N0
Randomization: Lobar vs. sublobar resection
Minimum 4.5 years of follow-up

Ginsberg R, Ann Thorac Surg, 1995; 60: 615
Lung Cancer Study Group

- 774 patients registered
- 276 patients randomized
  - Protocol violations (n=29)
  - Sublobar group (n=122)
    - Wedge 40 (33%)
    - Segmentectomy 82 (67%)
  - Lobectomy group (n=125)

Ginsberg R, Ann Thorac Surg, 1995; 60: 615
Lung Cancer Study Group

OS

Log-rank p = 0.088 (one tailed)

Months

0 12 24 36 48 60 72 84 96

DFS

Log-rank p = 0.016 (one tailed)

Months

0 12 24 36 48 60 72 84 96

Lobectomy

Sublobar resection

Ginsberg R, Ann Thorac Surg, 1995; 60: 615
Lung Cancer Study Group

Recurrence

- Lobectomy
- Segmentectomy x 2
- Wedge x 3.9

Ginsberg R, Ann Thorac Surg, 1995; 60: 615
Considerations

- 3cm or less by CXR. CT only required in the case of suspected metastatic disease
- CT scans not used for follow-up detection of recurrence
- Trial powered to 90% using one-sided log-rank tests with \( p \leq 0.10 \)
- Subset analyses used 2-sided tests and \( p \leq 0.05 \)

Ginsberg R, Ann Thorac Surg, 1995; 60: 615
SEER Data

- Mery, 2005
- SEER 1992-1997
- 14,555 pts with stage I & II NSCLC

![Graphs showing cumulative survival for different age groups: <65 years, 65–74 years, >75 years.](Mery C, Chest, 2005;128:237)
SEER Data

A ≤ 71 years

B > 71 years

Mery C, Chest, 2005;128:237
Influence of Tumor Size

- Okada, 2005
- 1,272 resections

![Graphs showing survival rates for different tumor sizes and surgical procedures.](Okada_M_J_Thorac_Cardiovasc_Surg_2005;129:87)
Influence of Tumor Size

- Koike, 2003
- Retrospectively reviewed 74 non-compromised patients undergoing sublobar resection for peripheral NSCLC
- 92% adenocarcinomas
- Tumors > 2cm, pleural invasion & positive nodes excluded
- Compared to 154 patients who had lobectomy

Koike T, J Thorac Cardiovasc Surg, 2003;125: 924
Influence of Tumor Size

Figure 1. Postoperative survival curve. There was no significant difference in the survivals of patients treated with limited resection and those treated with lobectomy ($P = .91$). Figures given in parentheses indicate censored cases.

Figure 2. Postoperative disease-free survival curve. There was no significant difference in disease-free survivals of patients treated with limited resection and those treated with lobectomy ($P = .93$).
Influence of Tumor Size

- Fernando, 2005
- Retrospective, multicenter review
- 124 patients with stage IA NSCLC underwent sublobar resection
- 47% adenocarcinomas
- Compared to 167 patients who had lobectomy

Fernando H, J Thorac Cardiovasc Surg, 2005; 129: 261
Influence of Tumor Size

Sublobar Resection vs. Lobectomy

< 2cm
NS
p = 0.003

2 - 3cm

Survival

Follow-up (months)

Fernando H, J Thorac Cardiovasc Surg, 2005; 129: 261
Influence of Tumor Size

- Bando, 2008
- 91 patients underwent ‘PA guided’ segmentectomy
- pT1N0M0
- 52% intentional (non-compromised)
- 75% adenocarcinoma
  - 91% of intentional group (p<0.01)
Influence of Tumor Size

Locoregional Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intentional</td>
<td>6%</td>
<td>18%</td>
<td>0.08</td>
</tr>
<tr>
<td>2cm or less</td>
<td>6%</td>
<td>30%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Bando T, Lung Cancer, 2009;63:58
## Contemporary Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Adenocarcinoma</th>
<th>Diameter (mean)</th>
<th>5-yr Survival</th>
<th>Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keenan, 2004</td>
<td>54</td>
<td>NR</td>
<td>NR</td>
<td>62%</td>
<td>11%</td>
</tr>
<tr>
<td>Martin-Uncar, 2005</td>
<td>17</td>
<td>59%</td>
<td>3.2cm</td>
<td>70%</td>
<td>0%</td>
</tr>
<tr>
<td>Fernando, 2005</td>
<td>124</td>
<td>NR (BAC 7%)</td>
<td>3cm (max)</td>
<td>47%</td>
<td>10%</td>
</tr>
<tr>
<td>El Sherif, 2006</td>
<td>207</td>
<td>36% (BAC 13%)</td>
<td>1.8cm</td>
<td>40%</td>
<td>14%</td>
</tr>
<tr>
<td>Schuchert, 2007</td>
<td>182</td>
<td>57% (BAC 1%)</td>
<td>2.3cm</td>
<td>83%</td>
<td>8%</td>
</tr>
<tr>
<td>Sienel, 2008</td>
<td>87</td>
<td>44%</td>
<td>2cm</td>
<td>63%</td>
<td>26%</td>
</tr>
<tr>
<td>Wolf, 2011</td>
<td>154</td>
<td>79%</td>
<td>1.5cm</td>
<td>59%</td>
<td>16%</td>
</tr>
<tr>
<td>Schuchert, 2011</td>
<td>75</td>
<td>65%</td>
<td>0.8cm</td>
<td>89%</td>
<td>3%</td>
</tr>
<tr>
<td>Taylor, 2012</td>
<td>169</td>
<td>NR</td>
<td>NR</td>
<td>49%</td>
<td>NR</td>
</tr>
<tr>
<td>Schuchert, 2012</td>
<td>325</td>
<td>NR (BAC 2%)</td>
<td>3cm (max)</td>
<td>77%</td>
<td>5%</td>
</tr>
</tbody>
</table>
## Contemporary Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Adenocarcinoma</th>
<th>Diameter (mean)</th>
<th>5-yr Survival</th>
<th>Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koike, 2003</td>
<td>74</td>
<td>92%</td>
<td>1.5cm</td>
<td>92%</td>
<td>3%</td>
</tr>
<tr>
<td>Okada, 2006</td>
<td>305</td>
<td>91%</td>
<td>1.6cm</td>
<td>90%</td>
<td>5%</td>
</tr>
<tr>
<td>Nakayama, 2007</td>
<td>63</td>
<td>100% (BAC 60%)</td>
<td>2cm (max)</td>
<td>69 – 95%</td>
<td>4%</td>
</tr>
<tr>
<td>Okada, 2012</td>
<td>102</td>
<td>89% (BAC 64%)</td>
<td>1.8cm</td>
<td>90%</td>
<td>5%</td>
</tr>
<tr>
<td>Koike, 2012</td>
<td>223</td>
<td>92%</td>
<td>2cm (max)</td>
<td>90%</td>
<td>4%</td>
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</table>
**CALGB 140503**

**ClinicalTrials.gov**
A service of the U.S. National Institutes of Health

<table>
<thead>
<tr>
<th>Trial record 1 of 1 for: 140503</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Study</td>
</tr>
</tbody>
</table>

**Comparison of Different Types of Surgery in Treating Patients With Stage IA Non-Small Cell Lung Cancer**

- **This study is currently recruiting participants.**
  
  *Verified February 2013 by National Cancer Institute (NCI)*

- **Sponsor:**
  Cancer and Leukemia Group B

- **Collaborators:**
  - National Cancer Institute (NCI)
  - Radiation Therapy Oncology Group
  - American College of Surgeons
  - Southwest Oncology Group

**ClinicalTrials.gov Identifier:**
NCT00499330

- First received: July 10, 2007
- Last updated: February 15, 2013
- Last verified: February 2013

**History of Changes**

- ▪ cStage I NSCLC, 2cm, intraop .nodes neg.
- ▪ Segmentectomy/wedge vs. lobectomy

Margins & Adjuvant Radiation

- Sawabata, 2004
- 118 NSCLC, wedge resection
  - Wedge only (41)
  - Comp. lobectomy (77)
- Positive margin:
  - Distance from tumor (HR 1.1)
  - Tumor diameter (HR 0.85)
Margins & Adjuvant Radiation

- El-Sherif, 2007
- 81 sublobar resections
  - 26 segmentectomies (27% margin < 1cm)
  - 55 wedges (62% margin <1cm)

<table>
<thead>
<tr>
<th></th>
<th>Margin &lt;1cm</th>
<th>Margin ≥1cm</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>15%</td>
<td>8%</td>
<td>0.04</td>
</tr>
<tr>
<td>Regional</td>
<td>10%</td>
<td>5%</td>
<td>NS</td>
</tr>
<tr>
<td>Distant</td>
<td>15%</td>
<td>13%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Limited Resection of Bronchogenic Carcinoma in the Patient with Marked Impairment of Pulmonary Function

Joseph I. Miller, M.D., and Charles R. Hatcher, Jr., M.D.

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Margins & Adjuvant Radiation

- D’Amato, 1998
- 14 patients, sublobar resection
- $^{125}$I Vicryl mesh
  - 10,000 Gy at 1cm
- 7 month follow up

$19\% \rightarrow 2\%$

Figure 3. Mesh with radioactive seeds is introduced through the intercostal access site.
Fernando, 2005
- 124 patients, T1a NSCLC
- Sublobar resection + $^{125}$I mesh
- Local recurrence 17% $\rightarrow$ 3%

Birdas, 2006
- 41 patients, T1b NSCLC (mean diam 3.3cm)
- Sublobar resection + $^{125}$I mesh
- Local recurrence 4.8%
- Phase III (ACOSOG Z4032)
  - Sublobar resection +/- $^{125}\text{I}$ brachytherapy
  - Completed accrual of 222 pts
  - Endpoint: local recurrence

- Phase II
  - Sublobar resection + $^{131}\text{Ce}$ brachytherapy
  - Tumors < 7cm diameter
  - 40 patients, accrual expected 2014
Sublobar Resection vs. SBRT
### SBRT: Single Arm Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Follow-up (median)</th>
<th>Locoregional Failure</th>
<th>OS 3-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fakaris, 2009</td>
<td>70</td>
<td>50</td>
<td>11%</td>
<td>43%</td>
</tr>
<tr>
<td>Timmerman (RTOG), 2010</td>
<td>55</td>
<td>34</td>
<td>11%</td>
<td>50%</td>
</tr>
<tr>
<td>Onishi, 2011</td>
<td>87*</td>
<td>55</td>
<td>22%</td>
<td>62%-73%</td>
</tr>
<tr>
<td>Lagerwaard, 2012</td>
<td>177*</td>
<td>32</td>
<td>≤14%</td>
<td>51%</td>
</tr>
<tr>
<td>Grills, 2012</td>
<td>505</td>
<td>16</td>
<td>&lt;23%</td>
<td>60% (2-yr)</td>
</tr>
</tbody>
</table>

* Potentially operable patients
Sublobar Resection vs. SBRT

- Grills, 2010
  - Sublobar (n=69) vs. SBRT (n=58), T1-3, No NSCLC
  - Local recurrence rate: SBRT 4%; Sublobar 20%

Grills IS, J Clin Oncol, 2010; 28:928
Lobectomy vs. SBRT

- Robinson, 2013
  - Lobectomy (n=260) vs. SBRT (n=78)
  - Stage I NSCLC
  - 4-yr local recurrence rate: SBRT 6%; Lobectomy 2% (p=0.015)
  - Cancer specific survival 75% vs 81% (p=NS)
Sublobar Resection vs. SBRT

- RTOG/ACOSOG Z4099
  - Sublobar +/- brachy vs. SBRT (High risk stage I NSCLC)
  - Survival

- POSTLIV (RTOG & Industry sponsored)
  - SBRT vs. surgery (operable stage I NSCLC)
  - 2-yr locoregional recurrence

- STARS (Industry sponsored)
  - SBRT vs. surgery (operable stage I NSCLC)
  - Disease free survival at 3 years
Technical Aspects
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Technical Aspects
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Technical Aspects
THANK YOU