Intentional Limited Resection for Lung Cancer should be Abandoned

Ashok Babu
University of Colorado
Lung Cancer is Bad

- Leading cause of cancer mortality worldwide
  - 1.2 million deaths per year
- 5-year survival <15% with modern therapies
  - Most present late

Stage Survival (clinical) Survival (pathologic)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>61</td>
<td>67</td>
</tr>
<tr>
<td>IB</td>
<td>38</td>
<td>57</td>
</tr>
<tr>
<td>IIA</td>
<td>34</td>
<td>55</td>
</tr>
<tr>
<td>IIB</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>IIIA</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>IIIB</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
How can we cure lung cancer?
• Radiation?
• Chemotherapy?
• Targeted therapies?
How can we cure lung cancer?

- Pick it up early
- Cut it out the right way
Early lung cancer is rare.

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-7 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**T1**
- (T2a 3-5 cm; T2b 5-7 cm)
- Atelectasis (part of lung)
- Invasion: Visceral pleura, main bronchus >2 cm from carina

**Lymph node**
- **N0**: No lymph nodes involvement
- **N1**: Ipsilateral bronchopulmonary hilar
- **N2**: Ipsilateral mediastinal/subcarinal
- **N3**: Contralateral hilar/contralateral mediastinal/supraclavicular

<table>
<thead>
<tr>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult Carcinoma</td>
</tr>
<tr>
<td>Stage 0</td>
</tr>
<tr>
<td>Stage IA</td>
</tr>
<tr>
<td>T1a</td>
</tr>
<tr>
<td>T1b</td>
</tr>
<tr>
<td>TX</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>MO</td>
</tr>
<tr>
<td>MO</td>
</tr>
<tr>
<td>MO</td>
</tr>
</tbody>
</table>

Invasion mediastinal organs/vertebral bodies/cardinal nodule in different ipsilateral lobe
CT screening is beneficial

- National Lung Screening Trial
  - 53,500 pts, enrolled 2002-2005
  - >30 pk yrs aged 55-74
  - Randomized to 3x/yr CT or CXR
- 20% fewer lung cancer related deaths in CT group

Right way to cut them out?

• 1930’s → pneumonectomy was the only way
  – Resection of entire organ with lymphatic basin
  – Oschner and DeBakey strong proponents
  – Despite 40% mortality

• 1950’s → lobectomy accepted as optimal
  – 70-80% 5 year cancer specific survival for Stage Ia cancers

• 1970’s → Jensik and Faber publish on segmentectomy

Oschner, DeBakey. SGO. 1939.
Thomas et.al. LCSG. ATS. 1990.
Jensik, Faber et.al. JTCVS. 1973.
Why not?

• Margins closer on segmentectomy
  – Intrapulmonary spread less likely to be cleared
• Less complete lymphadenectomy
• All translates to higher risk of local and distant recurrence
Why even consider it?

• For patients who cannot tolerate the best resection
• Decrease peri-operative morbidity
• Preserve long term pulmonary function
  – ONLY if recurrence rate not higher
  – TRADING mild FEV1 improvement for recurrence does not make sense
• 1982-1988
• Lung cancer <3cm detected by CXR (cT1N0)
• All pts fit to tolerate lobectomy
• Thoracotomy
  • NSCLC confirmed
  • Frozen sample of segmental, lobar, hilar, and med. nodes → confirmed N0
  • RML excluded
  • Surgeon determined resection would be adequate by lobectomy AND by a wedge/segmentectomy (2cm margin)
• THEN randomized

LCSG randomized trial

- 771 pts registered
  - 495 ineligible
    - 25% not amenable to limited resection
    - 25% >T1N0
    - 40% benign
  - 276 randomized
    - 29 eliminated (>T1N0, benign, RML, mets)
  - 247 left
    - 122 limited resection
    - 125 lobectomy

More recurrence with limited resection

All cause survival

LCSG randomized trial

• Post-op morbidity
  – No difference

• Extent of limited resection
  – 33% wedge
  – 67% segmentectomy
  – Doubling of recurrence rate applied in both

• Size
  – Stratified to 3, 9, and 27 cm$^3$
  – No difference in local recurrence rate

# LCSG loss of FEV1

<table>
<thead>
<tr>
<th></th>
<th>Limited</th>
<th>Lobectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>-1.76%</td>
<td>-9.1%</td>
</tr>
<tr>
<td>12-18 months</td>
<td>-5.18%</td>
<td>-11.1%</td>
</tr>
</tbody>
</table>

Why is recurrence rate so high?
Predictors of Lymph Node and Intrapulmonary Metastasis in Clinical Stage Ia Non–Small Cell Lung Carcinoma

Kenji Suzuki, MD, Kanji Nagai, MD, Junji Yoshida, MD, Mitsuyo Nishimura, MD, and Yutaka Nishiwaki, MD
Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

- July 1987 to April 1988—1142 NSCLC resected
- 389 Stage Ia
- Lobectomy with lymphadenectomy
- 5mm slice, H&E staining
- 23% had intrapulmonary mets, interlobar, or lobar nodes positive
- For tumors 2-3cm, mod or poor diff., >40% had spread

Conclusions. Limited surgical resection is not feasible for clinical stage IA non–small cell lung cancer, especially when the tumor shows moderate or poor differentiation, or pleural involvement.

Molecular margin analysis predicts local recurrence after sublobar resection of lung cancer

Brett G. Masasyesva¹, Betty C. Tong², Malcolm V. Brock², Thomas Pilkington¹, David Goldenberg¹, David Sidransky¹, Susan Harden¹, William H. Westra¹,³ and Joseph Califano¹*

¹Department of Otolaryngology, Head and Neck Cancer Research Division, Johns Hopkins Medical Institutions, Baltimore, MD, USA
²Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD, USA
³Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD, USA

• Negative margins by light microscopy may not actually be so...

• 44 pts sublobar resection
  – 13 had k-ras mutation at codon 12.1
  – Fluorescence based assay used to detect mutant DNA as low as 1/5,000 copies

• 9/13 had detectable mutant DNA at margin

• 67% of these had local recurrence

Weakness of retrospective studies

- Not comparing the same patients or cancers
- Propensity for bigger, more central tumors to fall in lobectomy group
- More severe comorbidities in sublobar patients
  - Worse non-cancer survival
  - May subsequently underestimate recurrence and cancer related mortality
Segmentectomy afflicted with same problems as wedge
• T1N0 and T2N0
• 5 yr follow-up
• 68 segmentectomy
  – Local recurrence 23%
• 105 lobectomy
  – Local recurrence 4.9%

T1 and T2

Size matters

- 2.1 to 3 cm – 38% lymphatic spread
- 1.1 to 2 cm – 17% lymphatic spread
- <1 cm – 7% lymphatic spread

1. Ishida et al. ATS. 1990.
• 1980-1999 → 1417 T1 lesions resected
  – 7% → 100pts <1cm tumor
• 75 pts bilobectomy / lobectomy
• 25 sublobar
  – 13 wedge
  – 12 segment
• 6 N1 in lobectomy, 1 in wedge

Miller et al. ATS. 2002.
Morbidity similar

Can’t the boys at the Mayo do a wedge with less than 4% operative mortality??!!

Miller et.al. ATS. 2002.
Cancer specific survival dissimilar

Miller et al. ATS. 2002.
Local Recurrence

• Local recurrence
  – Lobectomy 13%
  – Segmentectomy 8%
  – Wedge 31%

Miller et.al. ATS. 2002.
• 784 stage I (Ia and Ib) patients
  – 577 lobectomy
  – 207 sublobar
• Median f/u 31 months
• Lobectomy had 50% Ib vs. only 27% in sublobar
• Lobectomy tumor size 2.8cm vs. 1.8cm

El-Sherif et.al. ATS. 2006.
Recurrence rate no different?

<table>
<thead>
<tr>
<th></th>
<th>Lobar</th>
<th>Sublobar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Free</td>
<td>72%</td>
<td>71%</td>
</tr>
<tr>
<td>Local</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Regional</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Distant</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Total recurrence</strong></td>
<td><strong>28%</strong></td>
<td><strong>29%</strong></td>
</tr>
</tbody>
</table>

El-Sherif et.al. ATS. 2006.
The Elderly
Similar Long-term Survival of Elderly Patients With Non-small Cell Lung Cancer Treated With Lobectomy or Wedge Resection Within the Surveillance, Epidemiology, and End Results Database*

Carlos M. Mery, MD, MPH; Anastasia N. Pappas, MSW, MPH; Raphael Bueno, MD, FCCP; Yolonda L. Colson, MD, PhD; Philip Linden, MD; David J. Sugarbaker, MD, FCCP; and Michael T. Jaklitsch, MD, FCCP

- SEER database: 15000 pts stage I or II
- Age stratified comparison of lobar vs. sublobar
- Overall survival endpoint

Age < 65

Age 65 to 74

![Cumulative Survival Graph](image)

- **Lobectomies**
- **Limited rsct**

$p = 0.0009$

Age > 75

The Elderly

• No local recurrence data
  – Bound to be higher with sublobar

• No morbidity / QOL data
  – Is there any advantage to sublobar?

• Not every 75 year old is the same
  – Some will live to be 90+

• Those with poor expected lifespan may be better served with SBRT or RFA
Is local recurrence bad?

- More diagnostic imaging studies
- More percutaneous procedures
- More surgery
- More chemo
- More cost
- More worry
- Less Survival?
Who can do segmentectomy?

- Failure of regionalization in US
- 5% of lobes in US done via VATS (2006)
- Not enough expertise at small centers
- Main goal is to cure cancer
  - Do what we know works, and what can be achieved by current system
Future Trials

• CALBG trial ongoing
  – <2cm lesions
  – Wedge or segment vs. lobe

• Japanese study JCOG0802 ongoing
  – 1100 pts with <2cm NSCLC
  – Segmentectomy vs. lobectomy
  – Expected to complete enrollment 2012

• ACSOG Z4032 ongoing
  – Brachytherapy at surgical margins of limited resection
Summary

• Local recurrence rate is higher after sublobar resection
• Survival is poorer after sublobar resection
• Retrospective studies arguing the contrary are inherently flawed
• Until more advanced techniques of detecting tumor spread are available, lobectomy is the gold standard