RESECTION FOR STAGE I LUNG CANCER: BIGGER IS NOT BETTER

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May 23, 2011
But first, a recap...

- We have debated many times. Here are the topics, and a recap of the last few...
  - Pre-operative nutrition
    - Babu pro; Damle con
  - Utility of ECMO
    - Babu pro; Damle con
  - Transplant vs. LVAD
    - Babu Transplant; Damle VAD
  - Thoracic Aneurysm: Open vs. Endovascular
    - Babu Open; Damle Endovascular
  - And the winner was…
Dr. Babu will argue that...
Lung Cancer

- Most common cause of cancer mortality...worldwide
  - 1.2 million deaths worldwide yearly
  - >220,000 deaths in US annually
  - Death in men decreasing, in women stable

- Risk factors
  - Smoking
  - Radiation Therapy
Lung Cancer

Most common cause of cancer mortality... worldwide
- 1.2 million deaths worldwide yearly
- >220,000 deaths in US annually
- Death in men decreasing, in women stable

Risk factors:
- Smoking
- Radiation Therapy

Annual age-adjusted cancer death rates among males for selected cancers, United States, 1930-2005

Annual age-adjusted cancer death rates* among females for selected cancers, United States, 1930-2005
Dx and Staging

- Typical workup: CT Chest, MRI Brain, PET scan
  - Mediastinal staging (PET, EBUS, Mediastinoscopy)
### T Staging

<table>
<thead>
<tr>
<th>Diam</th>
<th>Scopy</th>
<th>Atelectasis</th>
<th>Invasion</th>
<th>Nodules</th>
</tr>
</thead>
</table>
| **T1** | T1a ≤ 2cm  
         T1b > 2-3cm | No invasion lobar bronchus                       |                            |                              |
| **T2** | T2a: >3-5cm  
         T2b: >5-7cm or | main bronchus > 2cm to carina  
 Atelectasis or obstructive pneumonia to hilus not entire lung | visceral pleura            |                              |
| **T3** | > 7cm or  
         < 2cm to carina | Whole lung                                      | Chest wall  
 diafragm phrenic nerve  
 mediast pleura parietal pericard | Nodules in same lobe       |
| **T4** | Tumor in carina                    | Tumor in carina                                 | Heart great vessels  
 trachea esophagus spine | Nodules in other ipsilateral lobes |
# N Staging

## Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>N1</th>
<th>In ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2</td>
<td>In ipsilateral mediastinal and/or subcarinal lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>In contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes</td>
</tr>
<tr>
<td></td>
<td>T1a</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>N0</td>
<td>IA</td>
</tr>
<tr>
<td>N1</td>
<td>IIA</td>
</tr>
<tr>
<td>N2</td>
<td>IIIA</td>
</tr>
<tr>
<td>N3</td>
<td>IIIB</td>
</tr>
</tbody>
</table>
We will focus on stage Ia tumors

Which equals:

- T1 (Tumors < 3 cm in size without involvement of pleura)
  - T1a: <2cm
  - T1b: 2-3cm
- N0 (No positive nodes)
- M0 (No distant mets)

Why is this important?
- Widespread use of CT
- Implementation of screening programs.
Why *might* lobectomy be better?

- Wider resection margin
  - ? Improved clearance
  - ? Improved local recurrence
- More nodes sampled
  - ? Impact on survival
- Minimal added cost and hospital stay
Patients with lung CA also typically have COPD/emphysema
  - Limited resection better for long-term pulm function

Smaller operation with quicker recovery

Most NSCLC are peripheral and amenable to limited resection
In the next slides, I will prove:

1) Short-term: Periop Issues favor Wedge/Limited Resection
   1) Cost and LOS
   2) Pulmonary function
   3) Perioperative morbidity & mortality

2) Long-term: Survival advantage for limited resection (and no significant difference in recurrence)
   1) All comers
   2) Segmentectomy vs lobectomy
   3) Specific histologies
Cost Analysis for Thoracoscopy: Thoracoscopic Wedge Resection and Lobectomy

- Retrospective review 80 patients, early 90s
- Primary focus was VATS vs open
- Results:

<table>
<thead>
<tr>
<th></th>
<th>VATS Wedge (30)</th>
<th>VATS Lobe (10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS</td>
<td>10 d</td>
<td>25 d</td>
</tr>
<tr>
<td>OR Time</td>
<td>1 h</td>
<td>5 h</td>
</tr>
<tr>
<td>Chest Tube Duration</td>
<td>2 d</td>
<td>7 d</td>
</tr>
<tr>
<td>Total Hospital Charges</td>
<td>$6,100</td>
<td>$18,000</td>
</tr>
</tbody>
</table>

Surg Today
## Pulmonary Function

<table>
<thead>
<tr>
<th>Test</th>
<th>Limited (Mean % Diff)</th>
<th>Lobe (Mean % Diff)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Month FEV1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Month FVC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Month FEV1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*LCSG (ATS 1995)*

- 6 Month FEV1: -1.76% (-9.10%); p = 0.008
- 6 Month FVC: 1.93% (-5.93%); p = 0.007
- 12 Month FEV1: -5.18% (-11.09%); p = 0.041
Compared VATS Wedge vs open wedge vs open lobectomy

<table>
<thead>
<tr>
<th></th>
<th>Open WR</th>
<th>VATS WR</th>
<th>vs Lobectomy</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>68</td>
<td>71</td>
<td>vs 63</td>
<td>0.0002</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>64</td>
<td>69</td>
<td>vs 14</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>69</td>
<td>61</td>
<td>vs 88</td>
<td>0.0001</td>
</tr>
<tr>
<td>DLCO (% predicted)</td>
<td>73</td>
<td>51</td>
<td>vs 81</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Better Outcome

Sicker Patients

Operative mortality (%)  | 0 | 0 | vs 3.3 | 0.20
Postop. stay (days)     | 7.7 | 6.3 | vs 10.6 | 0.0002
## Perioperative Morbidity and Mortality

**SUB-LOBAR LUNG RESECTION OF PERIPHERAL T1N0M0 NSCLC DOES NOT AFFECT LOCAL RECURRENT RATE**

Rome, Italy

*Scandinavian Journal of Surgery 98: 225–228, 2009*

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<table>
<thead>
<tr>
<th>Characteristics of patients of the two groups.</th>
<th>Lobectomy 116 patients</th>
<th>Sub-lobar resection 36 patients</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>99 (85%)</td>
<td>31 (86%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Female</td>
<td>17 (15%)</td>
<td>5 (14%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Age</td>
<td>64.8 ± 8.7</td>
<td>68.7±8.4</td>
<td></td>
</tr>
<tr>
<td>FEV1</td>
<td>84,9% ± 18,5</td>
<td>71% ± 25,6</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>57 (49%)</td>
<td>26 (72%)</td>
<td>0.01</td>
</tr>
<tr>
<td>T1 NO M0</td>
<td>29 (25%)</td>
<td>22 (61%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>50 (43,1%)</td>
<td>13 (36,1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>45 (38,8%)</td>
<td>10 (27,8%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Bronchoalveolar</td>
<td>10 (8,6%)</td>
<td>10 (27,8%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Indifferentiated</td>
<td>11 (9,5%)</td>
<td>3 (8,3%)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0,9</td>
</tr>
</tbody>
</table>
This should come as no surprise. Lobe is a bigger operation that is more dangerous and most costly compared to a limited operation.
IS THERE A SURVIVAL ADVANTAGE?
LCSG: The Trial That Confused Us All

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)

1982-1988

247 patients with:

- <3 cm tumor in all dimensions
- No evidence of met dz (by labs)
- Ability to undergo a lobectomy

“Limited Resection” (122 pts)

- Wedge with 2 cm margin
- Segment with anatomical division of vessels and bronchus
- All patient had lymph node sampling
LCSG ATS 1995

- Mortality Outcome

![Graph showing mortality outcomes with time in months, comparing Lobectomy and Limited Resection, with logrank p=0.088 (one-tailed).]

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Lobectomy:</th>
<th>Limited Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>93</td>
<td>47</td>
</tr>
<tr>
<td>47</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>22</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Time in Months
Mortality Outcome
- No significant difference

Local Recurrence
- Higher in wedge resection…BUT
- If you count secondary tumors…
  - Then, there is NO difference

Overall, we should conclude: NO difference
Problems with LCSG

- Few patients
  - 60+% of patient screened were excluded
- Dx by CXR!!!
- Lumped wedges and segmentectomies
- Tumor volume/size in each group not specified.

- Lets jump ahead almost 10 years…
Prospective trial, 1992-2000
- Patient able to undergo lobectomy, asked to undergo wedge/segment instead
- NSCLC < 2 cm in size

Results
- 74 limited resection (60 segment, 14 wedge), 159 lobes
- Lymph node dissection variable
- Primary outcomes: Survival and recurrence
Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer

Survival: IDENTICAL
Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer

Recurrence: Same

% Disease-free survival

Lobectomy

Limited resection

Months
Conclusion:

- Limited resection is an equivalent alternative in patients with T1 tumors < 2 cm in size.
Run by NCI
Geographic cancer registry of ~ 28% of population
2 papers based on this database
SEER Review

- Ann Surg 2010
  - 1165 patients (Older)
    - 17% limited resection
  - Outcome
    - Mortality the SAME for lesion ≤ 2 cm

- Chest 2011
  - ~2100 patients
    - 33% limited resection
  - Outcome
    - Mortality the SAME for lesion ≤ 1 cm
Meta-analysis of 14 publications
## Anyone else?

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giacomo TD. Scand J of Surg 2009. Italy</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Sugi K. EJCTS 2010. Japan.</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Kraev K. Chest 2007. OR</td>
<td>Same (all comers)</td>
<td></td>
</tr>
</tbody>
</table>
No mortality or significant recurrence benefit to lobectomy in all comers

- But, a criticism of many of these papers has been mixed bag of wedge and segmentectomy and a mixed bag of histologies.

- Is there any benefit to segmentectomy vs lobectomy?
UK. EJCTS 2005
Case-matched study for high-risk stage I
Segmentectomy / Lobe with LND
17 patients in each arm
Average size of tumor 3.2 cm
Mean FEV1 ~ 43%

Results

Postoperative results

<table>
<thead>
<tr>
<th></th>
<th>Lobectomy</th>
<th>Segmentectomy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>1 (5.9%)</td>
<td>1 (5.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Complications</td>
<td>3 (18%)</td>
<td>3 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>6 (3-30)</td>
<td>8 (4-31)</td>
<td>NS</td>
</tr>
<tr>
<td>Drainage time</td>
<td>4 (2-13)</td>
<td>3 (1-30)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Expressed as median (range) or number (%).

Long-term results

<table>
<thead>
<tr>
<th></th>
<th>Lobectomy</th>
<th>Segmentectomy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recurrence</td>
<td>3 (18%)</td>
<td>3 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Loco-regional recurrence</td>
<td>2 (12%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Actuarial 3-year survival</td>
<td>69%</td>
<td>94%</td>
<td>NS</td>
</tr>
<tr>
<td>Actuarial 5-year survival</td>
<td>64%</td>
<td>70%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Role of adjuvant therapy
- Some data to support wedge + XRT
- In most data, wedge resection patient lot sicker than lobectomy patients
  - Skews mortality results
- Outcome results are small so need large populations to show significant differences
- Not all NSCLCs are the same (BAC vs SCC)
In Summary...

- Lobectomy is a risky operation for potential for disaster
  - Longer LOS, more pain, etc
- Lobectomy offers NO mortality advantage for these early stage tumors
- Recurrence rates are essentially the same
  - And, prior wedge offers ability for re-resection
Lobectomy offers NO advantage over limited resection in the treatment of stage I lung cancer. Therefore, bigger is not always better.
He will try to sell you this as a reliable old car that has proven data...

But, if you look a little closer, you’ll find there is nothing there to support it!
My opponent, the “classy” salesman.

- His arguments:
  - Only 1 “Great” RCT
    - Long time ago
    - No statistical mortality difference
    - Can’t effectively do new RCTs
  - Recurrence worse after limited resection
    - Modern studies show no difference
    - Some data suggests that recurrence s/p sublobar resection can be re-resected with good results.
Segmentectomy vs Lobectomy In Patients With Stage I Pulmonary Carcinoma

- Retrospective review 1980-1988
- Segment vs lobe for T1N0 or T2No
- Excluded wedge resection
- No evaluation of pre-op variables.

Results
- 169 pts (66 segmentectomy, 103 lobectomies)
- No difference.
- But, recurrences were higher.
Outcomes of Recurrence

- **Segmental Resection with recurrence**
  - 4 patients underwent further resection with 50% survival @ 5 yrs **AFTER** second resection
  - Remainder had adjuvant tx (not surgical candidates) with median survival 10 mo

- **Lobectomy with recurrence**
  - NONE could have further surgical therapy
  - Remainder had adjuvant tx with median survival 11 mo
Lobectomy offers NO periop benefit.
Lobectomy offers NO survival benefit.
Limited resection is better tolerated and does not prevent further surgical therapy for recurrence.

There should be a paradigm shift to treat small tumors with limited resection.
THANK YOU.

RESECTION FOR STAGE I LUNG CANCER: BIGGER IS NOT BETTER

Sagar Damle, MD
University of Colorado Denver
May 23, 2011
THANK YOU
Future Direction

- Wedge + adjuvant therapy
  - Radioactive seeds
  - XRT
  - Low-dose chemotherapy
- 2 large trials ongoing for segment vs lobe
  - US and Japan
Biggest criticism of limited resection = RECURRENCE

But, if you look at the data, recurrences are either the same or only somewhat elevated in sublobar.

What is the consequence of a recurrence?
Table II. Distribution of carcinomas according to diameter

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th>Group I (segmentectomy) %</th>
<th>Group II (lobectomy) %</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.0</td>
<td>58</td>
<td>33</td>
<td>72</td>
</tr>
<tr>
<td>2.1-3.0</td>
<td>20</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>23</td>
<td>57</td>
<td>74</td>
</tr>
</tbody>
</table>
But, survival better in lobectomy patients. Warren

![Graph showing survival probability over time with two groups: Group I (66 pts) and Group II (103 pts).](image-url)
Meta-analysis of 14 publications

- 12 retrospective
- 1 case-matched
- 1 RCT (LCSG)

Results

- Survival differences @ 1, 3 and 5 years: