Development of a Nomogram for Predicting Outcomes after Sublobar Resection for Lung Cancer

*An Analysis of ACOSOG Z4032*

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on behalf of the ACOSOG Z4032 Investigators

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Disclosures

None
**Introduction**

**ACOSOG Z4032**

- **Z4032** was a randomized, prospective trial
- Compared sublobar resection to sublobar resection with brachytherapy
- Accrual 2006-2010 (n=224)
- Included 41 centers and 48 surgeons
Introduction

Z4032

• Biopsy-proven, clinical stage I tumors 3cm or less

• Considered high-risk on the basis of cardiopulmonary disease

• Wedge or segmentectomy

• VATS or open
Z4032
Entry Criteria

**Major Criteria**
- FEV$_1$ < 50%
- DLCO < 50%

**Minor Criteria**
- Age $\geq$ 75 yrs
- FEV$_1$ 51-60%
- DLCO 51-60%
- Pulmonary HTN
- Poor LVEF
- pO$_2$ $\leq$ 55%
- pCO$_2$ $\geq$ 45mmHg
- Dyspnea score $\geq$ 3

*One major or two minor criteria required*
No difference in OS, DFS or local recurrence rates

Any recurrence: 26%

5-yr OS: 59%

40% of deaths were due to cancer

Fernando, J Clin Oncol 2015
Purpose

To develop a nomogram to predict:

- Overall survival
- Local recurrence-free survival
- Any recurrence-free survival
- Using data from ACOSOG Z4032
Methods

Data Source

• Secondary analysis of Z4032

• Data from both groups were combined

• 17 clinical variables were evaluated to construct survival and recurrence models

• Only patients with all variables were included (n=173)
Methods

Statistical Methodology

• Factors significant in the univariate model ($p \leq .10$) were included in the multivariate model

• Final model used factors significant at the .05 level

• Concordance index and calibration plots obtained using internal validation
## Clinical Variables

<table>
<thead>
<tr>
<th>Baseline Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm: SRB vs SR</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Baseline Performance Status</td>
</tr>
<tr>
<td>Race: White vs. Others</td>
</tr>
<tr>
<td>Method of payment: Uninsured/Medicaid vs. Others</td>
</tr>
<tr>
<td>ASA class: III/IV vs. I/II</td>
</tr>
<tr>
<td>Baseline DLCO%</td>
</tr>
<tr>
<td>Baseline FEV1%</td>
</tr>
</tbody>
</table>
Clinical Variables

<table>
<thead>
<tr>
<th>Surgical and Tumor Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery Approach: VATS vs. Thoracotomy</td>
</tr>
<tr>
<td>Type of Resection: Wedge vs. Segmentectomy</td>
</tr>
<tr>
<td>Clinical Nodule Size: &gt;2 cm vs. ≤ 2 cm</td>
</tr>
<tr>
<td>Actual Margin Size (cm)</td>
</tr>
<tr>
<td>Margin Tumor Ratio</td>
</tr>
<tr>
<td>Maximum Tumor Diameter (cm)</td>
</tr>
<tr>
<td>Lymph Node Evaluation: MLND/Sampling vs. None</td>
</tr>
<tr>
<td>Histology Type</td>
</tr>
</tbody>
</table>
CONSORT Diagram

Randomization (N=224)

115 Surgery (SR)
   1 Excluded
     [No IRB Approval]
   114 Surgery (SR)
     6 Ineligible
       [1 had lobectomy
        1 had no cancer
        2 had no NSCLC
        1 had T3N0
        1 CT scan outside 60 days of pre-registration]
     108 Eligible for Primary Endpoint Analysis in SR arm
     19 Incomplete Data on One or More Baseline Factors
     173 Complete Data on 17 Clinical Factors at Baseline

109 Surgery + Brachytherapy (SRB)
   1 Excluded
     [No Surgery]
   108 Surgery + Brachytherapy (SRB)
     4 Ineligible
       [1 had no cancer
        1 had no NSCLC
        1 had clinical T3
        1 CT scan outside 60 days of pre-registration]
     104 Eligible for Primary Endpoint Analysis in SRB arm
     20 Incomplete Data on One or More Baseline Factors

n=173
Results

Baseline Demographics

• Median age: 70
• Median F/U: 4.4 years
• Mean DLCO: 46% predicted
• Wedge resection: $n=129$ (74.6%)
• No LN sampling: $n=61$ (35.3%)
Results

Baseline Demographics

• Tumor diameter: 1.8 cm (0.4-6.5 cm)
• Margin size: 1.0 cm (0.0-3.6 cm)
• SCCA and AC equal
• Overall 5-year survival: 58.4%
Overall Survival

Univariate Analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.00, 1.06)</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline DLCO%</td>
<td>0.97 (0.96, 0.99)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Margin Tumor Ratio</td>
<td>0.66 (0.44, 0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Maximum Tumor Diameter</td>
<td>1.37 (1.06, 1.78)</td>
<td>0.02</td>
</tr>
<tr>
<td>Histology Type</td>
<td>1.63 (1.02, 2.60)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
# Overall Survival

## Multivariate Analysis

<table>
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<td>Baseline DLCO%</td>
<td>0.97 (0.95,0.99)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Margin Tumor Ratio</td>
<td>0.83 (0.53,1.28)</td>
<td>0.39</td>
</tr>
<tr>
<td>Maximum Tumor Diameter</td>
<td>1.29 (1.00,1.68)</td>
<td>0.05</td>
</tr>
<tr>
<td>Histology Type</td>
<td>1.24 (0.76,2.02)</td>
<td>0.39</td>
</tr>
</tbody>
</table>
Overall Survival

Nomogram

Points

Age (years)

Baseline DLCO %

Maximum Tumor Diameter (cm)

Total Points

5-Year OS Probability

C-index: 0.622
Overall Survival

Calibration Plot

Fraction Surviving 5 Years

Predicted 5 Year OS

n=173 d=72 p=3, 30 subjects per group
Gray: ideal
X - resampling optimism added, B=100
Based on observed-predicted
Recurrence-Free Survival Nomogram

- Nomograms also constructed for local recurrence, and any recurrence-free survival

- Age, DLCO and tumor diameter remained the three significant factors on multivariate analysis

- $C$-index for LRFS: 0.606

- $C$-index for RFS: 0.591
Summary

- Using data from ACOSOG Z4032, OS, LRFS and RFS were predicted by:
  - Age
  - Diffusion capacity
  - Tumor diameter

- Parenchymal margin, LN sampling and anatomic resection were not predictive
Limitations

- Unique patient population
- Many of the deaths were not due to cancer
- Not all relevant datapoints available (e.g. \( \text{SUV}_{\text{max}} \))
- Small data set and no external validation
Applicability

- May not be valid in lobectomy (standard-risk) population
- May not be valid in patients treated with other modalities (e.g. SBRT)
- The current nomograms are therefore considered exploratory
Strengths

• Multicenter, prospective database
• Central review of all operative and pathology reports
• Important cohort of patients in whom there is no consensus on treatment
Future Directions

- Plan to validate in an upcoming study comparing SRS to surgery in high-risk patients (*Stablemates study*, formerly ACOSOG Z4099)

- Consider use of nomogram to stratify patient groups in future studies