THERE IS A ROLE FOR SURGERY IN THE TREATMENT OF STAGE IIIA (N2) NSCLC

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Lung Cancer Survival

Figure 1: Overall survival by pathologic stage for lung cancer using the IASLC TNM staging system, seventh edition (Goldstraw P 2007)
Controversy in Management

- Stage IIIA: groups patients with significant heterogeneity in presentation and prognosis
- Limited, small, randomized studies
- Limited evidence as basis for recommendations
Heterogeneity within the Stage IIIA N2 Lymph Node-Positive Population

N = 702

Andre, JCO 18: 2981-9, 2000
Subtle Metastasis

Proven Stage IIIA by mediastinoscopy
Locally Advanced NSCLC (Bulky Stage IIIA)
Subsets of Stage IIIA (N2)

III\(A_1\)  Incidental nodal metastases on final pathology

III\(A_2\)  Nodal (single station) metastases recognized intraoperatively

III\(A_3\)  Nodal metastases recognized by prethoracotmy staging

III\(A_4\)  Bulky or fixed multistation N2 disease

J.C. Ruckdeschel *Semin Oncol* 1997
Incidental N2 Disease

III A\textsubscript{1} Incidental nodal metastases on final pathology
- Adjuvant therapy - \textbf{YES}

III A\textsubscript{2} Single station nodal metastases discovered in OR
- Resect - \textbf{YES}
- Adjuvant therapy - \textbf{YES}
Resection of Unsuspected N2 (IIIA) NSCLC

- 148 pts; all cN0-1 by PET
- R0 resection, thoracic lymphadenectomy
- 93% adjuvant chemo; 13% adjuvant XRT
- 5 yr OS 35%

Unexpected Single vs Multistation N2 (IIIA) NSCLC Survival After Resection

- Single station 5 yr OS – 40%
- Multistation 5 yr OS – 25%

ANITA: Overall Survival for N2 Disease with Adjuvant Chemotherapy

Douillard J, Lancet Oncology 2006 7:719-727

HR 0.60 (0.44-0.82)
N2 Disease Discovered on Pre-Thoracotomy Staging

Is there a role for induction therapy followed by surgery?
• Induction therapy
  – 5 yr OS 36%

• Surgery alone
  – 5 yr OS 15%

• Critiques
  – Small numbers
  – Postop stage imbalance
    (more IIIB/IV in surgery arm)

Roth R. *Lung Cancer* 1998
Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial

Rafael Rosell a,*, José Gómez-Codina b, Carlos Camps c, José Javier Sánchez d, José Maestre e, José Padilla f, Antonio Cantó g, Albert Abad a, Jordi Roig h

- Induction therapy
  - 5 yr OS 17%

- Surgery alone
  - 5 yr OS 0%

- Critiques
  - Small numbers
  - Poor survival in surgery arm

Rosell R. Lung Cancer 1999  p=0.005
INT 0139: Definitive CT/RT vs Induction CT/RT → Surgery for Stage IIIA N2

Stage IIIA (T1-3, pN2, M0) NSCLC N = 429 (396 eligible)

Cis/etop x 2 cycles w/concurrent XRT 45Gy

Surgery

Cis/etop x 2 cycles

Cis/etop x 2 cycles w/concurrent XRT 45Gy

Continue RT to 61GY

Cis/etop x 2 cycles

Albain *Proc ASCO* 2005
INT 0139: Treatment Delivered

Arm 1 (n=202)

- Eligible for thoracotomy: 177 (88%)
- Thoracotomy performed: 164 (81%)
  - Complete resection: 144 (71%)
  - Incomplete resection: 11 (5.5%)
  - No resection: 9 (4.5%)

Arm 2 (n=194)

- Eligible for consolidation CT/RT: 179 (92%)
- Commenced consolidation CT/RT: 155 (80%)
Intergroup 0139/RTOG 9309
Progression-Free Survival by Treatment Arms

Percent Alive

CT+RT+Surgery (n=201)

CT+RT (n=191)

Logrank $p = 0.02$
Intergroup 0139/RTOG 9309
Survival by Treatment Arms

Logrank \( p = 0.51 \)

- CT+RT+Surgery (n=201)
- CT+RT (n=191)
## INT 0139 Treatment-Related Deaths on CT/RT/S (n=14)

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>N</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>(L) Lobectomy</td>
<td>1</td>
<td>PE</td>
</tr>
<tr>
<td>(R) Bilobectomy</td>
<td>1</td>
<td>ARDS</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>12</td>
<td>ARDS/respiratory, 8; miscellaneous, 4</td>
</tr>
<tr>
<td>(R) simple</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>(R) complex</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>(L) complex</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
INT 0139 Exploratory Survival Analysis

- All but 2 post-op deaths followed pneumonectomy
- Hypothesis:
  - Advantage for CT/RT/S arm if lobectomy performed
  - Advantage for CT/RT if pneumonectomy done
- Pts in CT/RT/S arm were matched with those in CT/RT arm (KPS, age, gender, T stage)
- Match feasible for 51/54 pneumonectomies & 90/98 lobectomies
INT 0139: Results In “Lobectomy” and “Pneumonectomy” Patients

<table>
<thead>
<tr>
<th>Pneumonectomy “Matched”</th>
<th>Surgery</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Overall Survival</td>
<td>19 mo</td>
<td>29 mo</td>
</tr>
<tr>
<td>3-yr survival</td>
<td>36%</td>
<td>45%</td>
</tr>
<tr>
<td>5-yr survival</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td># Dead</td>
<td>38</td>
<td>42</td>
</tr>
</tbody>
</table>

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<tr>
<th>Lobectomy “Matched”</th>
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<th>RT</th>
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<tbody>
<tr>
<td>Median Overall Survival</td>
<td>34 mo</td>
<td>22 mo</td>
</tr>
<tr>
<td>5-yr survival</td>
<td>36%</td>
<td>18%</td>
</tr>
<tr>
<td># Dead</td>
<td>57</td>
<td>74</td>
</tr>
</tbody>
</table>

Albain *Proc ASCO* 2005
Trimodality Therapy vs. Chemo/RT for Stage IIIA N2 NSCLC: Lobectomy vs. Pneumonectomy Patients

Lobectomy/Matched Pts.

Pneumonectomy/Matched Pts.

Albain, Lancet 2009
Fox Chase Cancer Center – Stage IIIA NSCLC

- Induction chemoXRT (n = 155) followed by surgery vs definitive chemoXRT (n = 103)

Fig 4. — Overall survival curves of patients undergoing lobectomy (dashed line) vs CRT (solid line; \(P = .038\)). Median overall survival was 39 months for the lobectomy group vs 22 months for the CRT group. CRT = concurrent chemoradiation therapy.

STAGE IIIa(N2) NSCLC
Results of Induction Therapy + Surgery

• Combined modality therapy (chemo ± RT ± surgery) feasible, with acceptable morbidity and mortality

• Pneumonectomy should be avoided whenever possible
SWOG 8805
Importance of Nodal Downstaging

- Mediastinal lymph nodes downstaged – 3 yr OS 44%
- Mediastinal lymph nodes positive – 3 yr OS 18%

Albain K.S. J Clin Oncol 1995

p=0.0005
Higher Doses of Induction Radiation

- 40 patients with IIIA or IIIB NSCLC
- Per-op XRT to 59 Gy
- 83% mediastinal clearance
- 46% 5 yr OS
Favorable Prognostic Variables

• Radiographically occult disease

• Metastases to single lymph node stations

• Downstaging from N2 to N0-1

• T stage: 1-2 vs. 3

• LUL tumors with N2 nodes in subaortic station (level 5)
MY OPINION, RIGHT OR WRONG!
Medical Oncologists Believe there is a Role for Surgery for IIIA N2 NSCLC

- 406 American medical oncologists surveyed

- **92%** include surgery in treatment plan for single station N2 disease in fit patient with disease resectable by lobectomy

- Up to **50%** would use surgery in treatment plan for multistation N2 disease if offered by surgeon

Management of Stage IIIA Non-Small Cell Lung Cancer by Thoracic Surgeons in North America


<table>
<thead>
<tr>
<th>Surgery Only</th>
<th>Neoadjuvant Therapy and Surgery</th>
<th>Surgery and Adjuvant therapy</th>
<th>Chemotherapy and Radiation Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6% (3)</td>
<td>84% (430)</td>
<td>11% (58)</td>
<td>4% (22)</td>
</tr>
</tbody>
</table>
Single Station Macroscopic N2

Neoadjuvant Therapy and Surgery
+ N2 downstaging
↓
62% (318)

+/- N2 downstaging
↓
19% (98)*

Surgery Only
0%

Surgery and Adjuvant therapy
1% (7)

Chemotherapy and Radiation Only
18% (90)

* Thoracic surgeons > Cardiothoracic surgeons
Right Pneumonectomy with adequate PFT

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<th>Surgery Only</th>
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<th>Chemotherapy and Radiation Only</th>
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</thead>
<tbody>
<tr>
<td>n/a</td>
<td>+ N2 downstaging</td>
<td>4% (18)</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right Pneumonectomy: 30% (159)</td>
<td></td>
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<td></td>
<td>Lobectomy instead of</td>
<td></td>
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<tr>
<td></td>
<td>pneumonectomy if technically</td>
<td></td>
</tr>
<tr>
<td></td>
<td>possible: 32% (163)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/‐ N2 downstaging</td>
<td>22% (114)</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right Pneumonectomy: 5% (26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lobectomy instead of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pneumonectomy if technically</td>
<td></td>
</tr>
<tr>
<td></td>
<td>possible: 7% (34)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• Ideal patient T1-2 with single station microscopic N2 disease

• Next, multistation microscopic or single station gross N2 disease
  – Performance status
  – Extent of resection required (< pneumonectomy)

• Patients with bulky, multistation N2 generally poor candidates – consider definitive chemoradiation
Surgical Therapy Does Have a Role in the Treatment of Stage IIIA (N2) NSCLC