The Role of Surgery in Stage IIIA NSCLC

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Learning Objectives

• Define Stage IIIA NSCLC
  – Evidence based staging modalities
  – Understanding heterogeneity
• Review data regarding surgery alone for stage IIIA NSCLC
• Review data regarding post-operative therapy (adjuvant) for Stage IIIA NSCLC
• Review data regarding pre-operative therapy (neo-adjuvant) for Stage IIIA NSCLC

IIIB

• N3, T4 or T3N2
• Many trials have a smattering of IIIB
• Generally considered non-surgical
• New IASLC staging system will
  – Keep nodes as is
  – Malignant pleural effusion becomes M
  – Ipsilateral difft lobe goes from M to T4
• Not going to address

NSCLC Staging

Current Treatment and Survival Rates

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>5-Year Survival, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Surgery</td>
<td>60-70</td>
</tr>
<tr>
<td>II</td>
<td>Surgery</td>
<td>30-50</td>
</tr>
<tr>
<td>IIIA</td>
<td>Surgery/ Multimodality Regimen</td>
<td>10-30</td>
</tr>
<tr>
<td>IIIB</td>
<td>Chemotherapy/ Radiation</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>Chemotherapy</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Overall 5-year survival is 14%.

Fundamental Issues

- How do you define Stage III: imaging vs tissue?
- If satisfied with stage, form of Tx: surgery alone, neoadjuvant, adjuvant, definitive chemorads
- If neoadjuvant, do you restage prior to surgery, how extensive?
How Do You Define Stage IIIA?

1. CT
2. PET
3. PET/CT
4. Mediastinoscopy (2, 4 and 7)
5. Chamberlain/VATS (5, 6)
6. Transbronchial Bx (2, 4, 7, 10)
7. Endoscopic US (2, 4, 7, 8, 9)

Heterogeneity of Stage III NSCLC

- Microscopic vs. Bulky
- Fixed vs. Mobile
- Single vs. Multistation
Case

- 81 YO male with cough
- CXR showed RUL mass
- CT guided FNA demonstrated NSCLC
- Good performance status
- PFTs
  - FEV1 1.5 L (50%)
  - DLCO 60%
  - ABG 7.47/35/83
What is stage of this tumor?
1. IA
2. IB
3. IIA
4. IIB
5. IIIA
6. IIIB
7. Not known

Carefully Staged
- CT with IV contrast
- PET/CT
- FOB/Med (separate procedure)
- Thoughtful evaluation and conversation with pt. and family
Mediastinoscopy

- 2R, 4R, 7 and 4L nodes negative
- Tumor not adherent to airway
Resected Specimen

RUL Endobronchial Tumor

Final Pathology

- 7 cm poorly differentiated squamous cell carcinoma
- Nodal stations 4, 7, 8, 9, 10,11 neg
- Pathologic stage T3N0-IIB
Role of CT, PET in Stage III NSCLC

- ACOSOG Z0050 Trial
  - 303 pts from 22 institutions underwent PET after routine staging (CT, bone scan and brain imaging)
  - Deemed resectable, went to surgery
  - Preop staging compared to path

Accuracy of PET for Mediastinal Nodes

<table>
<thead>
<tr>
<th>Path</th>
<th>CT</th>
<th>PET</th>
<th>CT + PET</th>
<th>P value CT vs PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>147/168 (88%)</td>
<td>128/168 (76%)</td>
<td>132/168 (89%)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>N1</td>
<td>4/31 (13%)</td>
<td>13/31 (42%)</td>
<td>14/31 (45%)</td>
<td>0.0177</td>
</tr>
<tr>
<td>N2/N3</td>
<td>18/57 (32%)</td>
<td>33/57 (58%)</td>
<td>30/57 (53%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Adapted from Reed et al., JTCVS 2003;126:1943

Role of PET in Staging of NSCLC Results of ACOSOG Z0050

"Use of PET for mediastinal staging should not be relied on as a sole staging modality and positive findings should be confirmed by mediastinoscopy."

Reed et al., JTCVS 2003;126:1943
Approaches in Stage IIIA NSCLC

- Surgery Alone
- Adjuvant (Postoperative)
  - Chemotherapy, Radiotherapy, or Chemoradiotherapy
- Neoadjuvant (Preoperative)
  - Chemotherapy or Chemoradiotherapy
- Non-operative
  - Definitive Chemoradiotherapy

Multidisciplinary Team

- Primary Care
- Radiology
- Pathology
- Pulmonary
- Thoracic Surgery
- Medical Oncology
- Radiation Oncology

Typical Multimodality Tumor Board?

Lessons from non-Randomized Data in Surgery for Stage IIIA
Heterogeneity of Stage IIIA and Role of Surgery

N= 702

Andre, JCO 18: 2981-9, 2000

Surgery vs. Multimodality Tx
MD Anderson Experience

• 353 pts pathologically Stage IIIA
• Retrospective Analysis, 1986-2001
• 87% RO resection
• Surgery Alone 33%
• Surgery + XRT 44%
• Surgery + CT +/- XRT 23%


Survival Relative to Nodal Dz

Survival Relative to Extent of Resection

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Surgery vs. Multimodality Tx
MD Anderson Experience

<table>
<thead>
<tr>
<th></th>
<th>3 yr Survival</th>
<th>5 yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>30%</td>
<td>17%</td>
</tr>
<tr>
<td>Surgery +</td>
<td>38%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Median survival: Surgery-15.9 mos, Multimodality-25.3 mos


Survival not affected by type of resection
- 89 pneumonectomies (25%)
- 9% mortality
- 1 death in 13 with periop Tx (7.7%)

Neoadjuvant Tx for Stage III
Memorial Sloan-Kettering Experience

- Retrospective review, 1993-99
- 470 pts had neoadjuvant therapy
- Platinum based in 70%
- 316 (70.8%) were stage III
- R0 resection in 77.4%
- Operative mortality 4%

Martin, J et al. JCO, 2002;20:1989

Pathologic CR 4.5%
- Downstaged in 33%
- Pneumonectomy in 95 pts (21%)
- Pneumonectomy was associated with increased risk of death

Martin, J et al. JCO, 2002;20:1989
Neoadjuvant Tx for Stage III
Memorial Sloan-Kettering Experience

- 198 pts with residual N2 disease
- RO resection in 144

<table>
<thead>
<tr>
<th></th>
<th>Median mos</th>
<th>3 yr</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>20.7</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>R1</td>
<td>17.2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>R2</td>
<td>9.2</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Martin, J et al. JCO, 2002;20:1989

Neoadjuvant Tx for Stage III
Memorial Sloan-Kettering Experience

- “it may be appropriate to proceed with resection in patients who have residual N2 disease when the resection is likely to be complete”

Martin, J et al. JCO, 2002;20:1989

Survival of Patients With Unsuspected N2 (Stage IIIA) Non-small-Cell Lung Cancer

- Retrospective review 1998-2007
- 148 pts clinically Stage I or II
- Neg PET/CT for Stage III
- Lobectomy via thoracotomy with lymph node dissection
- 93% received adjuvant CT
- 13% received PORT

Cerfolio and Bryant, Ann Thorac Surg, 2008;86: 362-367

Survival Relative to Nodal Status

Cerfolio and Bryant, Ann Thorac Surg, 2008;86: 362-367
Trials to Support Multimodality Tx for Stage IIIA NSCLC

Adjuvant Trials Including Stage IIIA Patients

| Trial | Regimen | Stage | Overall Survival (CT vs. Observed) | No. of Pts (CT vs. Observed) | No. of Pts Receiving RT (%)
|-------|---------|------|-----------------------------------|-----------------------------|-----------------------------
| IALT  | CT vs. observation (CT: cisplatin/vindesine, mitomycin/ifosfamide/cisplatin, mitomycin/vinblastine/cisplatin or vincristine/cisplatin) | I–IIIA | 2-year survival rate: 70.3% vs. 66.7% (P=0.03) | 932 / 935 | 475 (25.4%) |
| BLT   | CT vs. observation (CT: cisplatin/vindesine, mitomycin/ifosfamide/cisplatin, mitomycin/vinblastine/cisplatin or vincristine/cisplatin) | I–IIIA | 2-year survival rate: 60% vs. 56% | 192 / 189 | 52 (14%) |
| ALPI  | Mitomycin/ Vindesine/cisplatin vs. observation | I–IIIA | Median: 55.2 mo vs. 48 mo | 548 / 540 | 470 (43.2%) |
| ANITA | vinorelbine/cisplatin vs. observation | I–IIIA | Median: 65.8 mo vs. 43.3 mo (P=0.013) | 433 / 407 | NR |

ALPI=Adjuvant Lung Project Italy; ANITA=Adjuvant Novelbine International Trialist Association; BLT=Big Lung Trial; CT=chemotherapy; IALT=International Adjuvant Lung Cancer Trial; NR=not reported; RT=radiation therapy.

ANITA Trial

- Patients in the chemotherapy group with stage II or IIIA NSCLC derived a significant survival advantage from treatment.
- There was no apparent benefit for stage IB patients.
- Median follow-up time was 70 months.
Lung Adjuvant Cisplatin Evaluation (LACE)

- Meta analysis of ALPI, ANITA, BLT, IALT and JBR10
- Median f/u 5.1 yrs
- 5 yr absolute benefit of 4.2% with CT
- Favors Stage II and III (HR 0.83)

Problems with Adjuvant Tx

- Overall poor compliance (50-66%)
- Smattering of RT
- Is there a better way?

Neoadjuvant Therapy for Stage III

Induction Chemotherapy for Stage IIIA NSCLC

<table>
<thead>
<tr>
<th>Trial, Arm</th>
<th>N</th>
<th>Med Surv</th>
<th>3-Year Surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosell, 1994 Surgery</td>
<td>30</td>
<td>8 m</td>
<td>0%</td>
</tr>
<tr>
<td>CT → Surgery</td>
<td>30</td>
<td>26 m</td>
<td>23%</td>
</tr>
<tr>
<td>Roth, 1994 Surgery</td>
<td>32</td>
<td>11 m</td>
<td>15%</td>
</tr>
<tr>
<td>CT → Surgery</td>
<td>28</td>
<td>64 m</td>
<td>56%</td>
</tr>
</tbody>
</table>

From Rosell, 1994

Rosell, NEJM 330: 153, 1994
Roth, JNCI 86: 673: 1994
Preoperative Chemotherapy vs Surgery alone in Stage III NSCLC: Phase III Trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Chemo Regimen</th>
<th>RT post</th>
<th>Stge</th>
<th>Patient s</th>
<th>MST (Month)</th>
<th>5 Yrs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass (1992)</td>
<td>DDP-VP16</td>
<td>54-60</td>
<td>cN2</td>
<td>14 13</td>
<td>16 29</td>
<td></td>
</tr>
<tr>
<td>Rosell (1994)</td>
<td>MIP</td>
<td>50</td>
<td>IIa</td>
<td>30 30</td>
<td>8 26*</td>
<td>0 17</td>
</tr>
<tr>
<td>Roth (1994)</td>
<td>DDP-VP16</td>
<td>66</td>
<td>IIa</td>
<td>32 28</td>
<td>14 21*</td>
<td>15 36</td>
</tr>
<tr>
<td>Deperie (2002)</td>
<td>MIP</td>
<td>66</td>
<td>I-IIIA</td>
<td>176 179</td>
<td>26 37</td>
<td>41 52</td>
</tr>
<tr>
<td>Tsucha (2003)</td>
<td>DDP-VDS</td>
<td>-</td>
<td>IIa</td>
<td>31 31</td>
<td>17 16</td>
<td>10 22</td>
</tr>
</tbody>
</table>

*p<0.05

SWOG 8805: Chemoradiation Followed by Surgery for Stage IIIA/IIIB NSCLC

N=126, Path-staged N2 or N3 IIIA/IIIB NSCLC

- Cisplatin/VP-16 x2 w/concurrent XRT 45 Gy
- (if no PD)
- Surgery
- (if R1/R2 or residual N2+)
- Cis/VP-16 x2, RT to 60 Gy

INT 0139: Definitive CT/RT vs. Induction CT/RT → Surgery for Stage IIA NSCLC

<table>
<thead>
<tr>
<th>IIA pN2</th>
<th>N = 439</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Residual N2+</td>
<td>39</td>
</tr>
<tr>
<td>Residual N2+</td>
<td>35</td>
</tr>
</tbody>
</table>

(p = 0.002)

Hypothesis:
Is CT/RT doing the work, and is surgery more prognostic than therapeutic?

SWOG 8805: Encouraging and Provocative Results

- Resection rate of 85% for IIA, 80% for IIIB
- 13 treatment-related deaths (10%)
- Median survival 15 months; 3-year survival 26%
- Restaging CT poorly predictive of pathologic response
- 26 of 65 relapses were CNS, including 19 brain only

Albain, IASLC 2003, Lung Cancer 41 (Suppl 2): A#PL-4
**Intergroup 0139/RTOG 9309**

**Progression-Free Survival by Treatment Arms**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Failed/Total</th>
<th>Logrank p</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/RT/S</td>
<td>159/202</td>
<td>0.017</td>
<td>0.77 (0.62, 0.96)</td>
</tr>
<tr>
<td>CT/RT</td>
<td>172/194</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**% Alive without Progression**

- Months from Randomization: 0 12 24 36 48 60
- Failed/Total:
  - CT/RT/S: 159/202
  - CT/RT: 172/194

**Overall Survival by Treatment Arms**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Failed/Total</th>
<th>Logrank p</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/RT/S</td>
<td>145/202</td>
<td>0.24</td>
<td>0.87 (0.70, 1.10)</td>
</tr>
<tr>
<td>CT/RT</td>
<td>155/194</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**% Alive**

- Months from Randomization: 0 12 24 36 48 60

**INT 0139 Treatment-Related Deaths on CT/RT/S Arm (n=16)**

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Total (of n=202)</th>
<th>Deaths n (% total)</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>38</td>
<td>1 (3%) Pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Exploration only</td>
<td>9</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Wedge</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>98</td>
<td>1 (1%) ARDS</td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>54</td>
<td>14 (26%) ARDS/respiratory 11; miscellaneous, 3</td>
<td></td>
</tr>
<tr>
<td>(R) simple</td>
<td>17</td>
<td>5 (29%)</td>
<td></td>
</tr>
<tr>
<td>(R) complex</td>
<td>12</td>
<td>6 (50%)</td>
<td></td>
</tr>
<tr>
<td>(L) simple</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(L) complex</td>
<td>19</td>
<td>3 (16%)</td>
<td></td>
</tr>
</tbody>
</table>

**Lung INT 0139: Patterns of Failure**

<table>
<thead>
<tr>
<th>Site of First Progression</th>
<th>Arm 1  (CT/RT/S)</th>
<th>Arm 2  (CT/RT)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local relapse only</td>
<td>10%</td>
<td>22%</td>
<td>0.002</td>
</tr>
<tr>
<td>primary</td>
<td>2%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>nodes</td>
<td>7%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>both</td>
<td>1%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Brain only</td>
<td>11%</td>
<td>15%</td>
<td>0.29</td>
</tr>
<tr>
<td>All distant metastases</td>
<td>37%</td>
<td>42%</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Summary

- Stage IIIA NSCLC is a heterogenous disease and must be treated as such- tailored Tx's
- Pts with IIIA need a multidisciplinary approach (Thor Surgeon, Onc, Rad Onc)
- CT, PET and CT/PET are not adequate to rule in mediastinal disease
- Mediastinoscopy remains gold standard for pathologic confirmation of mediastinal nodes

Summary

- Surgery continues to have a role in stage IIIA NSCLC
- Neoadjuvant Tx can achieve downstaging
- Downstaging is associated with survival benefit
- RO resection is associated with survival benefit
Summary

- Surgery (RO) should be considered in pts after neoadjuvant Tx if no evidence of PD
- The possibility of pneumonectomy should be considered but not used as an absolute criteria to decline surgery
- Encourage participation in trials