Persistent N2 Disease
after
Induction Therapy for Stage IIIA NSCLC: What Next?

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* No conflicts to disclose
Q53. At surgical exploration after induction therapy for Stage IIIa NSCLC, biopsies of the mediastinal lymph nodes show persistent viable tumor. Appropriate treatment options include:

a. Close without resection, plan postoperative radiation
b. Proceed with surgery if R0 resection of the nodes and primary tumor is feasible
c. Wedge out the primary tumor, plan chemoradiotherapy postoperatively
d. Do mediastinal node dissection, treat the primary with SBRT
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Professor Emeritus, Thoracic Surgery
Rush University Medical Center

Originator of “Chemo beamo”
Persistent N2 Disease

**Issues**

- Prognostic factors after induction therapy
- Diagnosis of persistent N2 disease
- Management options
Multimodality Therapy: Stage IIIA NSCLC

Therapeutic approaches

- Chemotherapy + surgery
- ChemoRT + surgery
- (Definitive chemoRT, no surgery)
Analysis of 18 Trials in 913 Patients
Induction: Chemo (8) vs Chemo-RT (10)
Median of Results From Each Trial

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Chemo-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>71%</td>
<td>62%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Resection Rate</td>
<td>58%</td>
<td>62%</td>
</tr>
<tr>
<td>Path CR Rate</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Median Survival</td>
<td>21 months</td>
<td>16 months</td>
</tr>
<tr>
<td>3 Year Survival</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>5 Year Survival</td>
<td>26%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Persistent N2 Disease

Issues

- Prognostic factors after induction therapy
- Diagnosis of persistent N2 disease
- Management options
MSKCC INDUCTION THERAPY TRIAL (Stage IIIa N2) - Treatment Plan – (n = 136)

2-3 cycles of MVP Chemotherapy

↓

SURGERY

↓

2 cycles of Chemotherapy

↓

Mediastinal RT

If tumor in resected N2 nodes

SURVIVAL BY RESPONSE TO CHEMOTHERAPY

- Major Response (105)
- No Major Response (31)

- Median = 21 mos
- Median = 12 mos

- p = 0.02
PATHOLOGIC COMPLETE RESPONSE (T0N0M0)
N = 19

Percent Survival

Years from Diagnosis

95%
71%
61%
Median = 64 mos
SURVIVAL BY TUMOR SIZE (CLINICAL)

- T1 (14)
- T2 (83)
- T3 (39)

p = 0.02 for (T1-2) vs T3

Percent Survival vs Years from Diagnosis
SURVIVAL BY RESECTION

Complete resection (89)
Incomplete or no resection (47)

Median = 27 mos
p < 0.00002

Median = 12 mos

Years from Diagnosis

Percent Survival

0.0 0.2 0.4 0.6 0.8 1.0
0 1 2 3 4 5 6
Overall Survival by Extent of Resection: R0 v R1, p=.001; R1 v R2/NR, p=.3
INT 0139: Definitive CT/RT vs Induction CT/RT → Surgery for Stage IIIA NSCLC

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

Randomize

Cis/VP16 x 2 cycles w/concurrent XRT 45Gy

Cis/VP16 x 2 cycles w/concurrent XRT 45Gy

Continue RT to 61GY

Surgery

Cis/VP16 x 2 cycles

Intergroup 0139/RTOG 9309
Survival by Treatment Arms

Percent Alive

Months

CT+RT+Surgery
(n=201)

CT+RT
(n=191)

Logrank  p = 0.51
INT 0139/RTOG 9309: Lobectomy subset from Arm 1 vs. matched cohort in Arm 2, overall survival (intent to treat)

Logrank p=0.0020
Figure 3: Overall survival in group 1 by pathological nodal substage determined after thoracotomy.

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological N0 (n=76)</td>
<td>66</td>
<td>44</td>
<td>19</td>
<td>14</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pathological N1-3, unknown (n=88)</td>
<td>61</td>
<td>44</td>
<td>33</td>
<td>20</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>No surgery (n=38)</td>
<td>61</td>
<td>47</td>
<td>34</td>
<td>24</td>
<td>19</td>
<td>15</td>
</tr>
</tbody>
</table>

Albain et al. 
*Lancet* 2009; 374:379-86
### INT 0139 Trimodality Arm (n=202)

**Survival by Pathologic Status at Surgery**

<table>
<thead>
<tr>
<th>T/N Subset</th>
<th>Median Survival (months)</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tany N0*</td>
<td>34</td>
<td>41%</td>
</tr>
<tr>
<td>Tany N1-3 or unknown</td>
<td>26</td>
<td>24%</td>
</tr>
<tr>
<td>No surgery</td>
<td>8</td>
<td>8%</td>
</tr>
</tbody>
</table>

*29 of these = T0N0 (pCR): MS, 40 months; 5-year, 42%. p<0.001 across all 3 groups.*
Stage IIIA N2 NSCLC
Considered unresectable

Platinum-based chemotherapy* x 3 cycles

if CR, PR, or SD

RANDOMIZE

XRT 60 Gy

Surgery

* Cisplatin $\geq 80 \text{ mg/m}^2$
  OR
  Carboplatin $\geq \text{AUC 5}$
  PLUS
  1 other agent

Surgery arm (n=154)

- 47% underwent pneumonectomy; 38% (bi-) lobectomy
- 50% complete resection rate (R0)
- Pathological nodal downstaging in 42%
- 30-day post-op mortality 4%

<table>
<thead>
<tr>
<th>Exploratory Subset</th>
<th>N</th>
<th>OS, median</th>
<th>5-yr OS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>58</td>
<td>25.4 mo</td>
<td>27%</td>
<td>.009</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>72</td>
<td>13.4 mo</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>ypN0/N1</td>
<td>64</td>
<td>22.7 mo</td>
<td>29%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ypN2</td>
<td>86</td>
<td>14.9 mo</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

Induction ChemoRT + Surgery for IIIA NSCLC
Survival and Prognostic Factors

- 1989-2008: 233 patients
- Overall 5 year survival: 43%
  - 90 day mortality 8%
- Prognostic factors:
  - Response to induction Rx
  - T status (T0=50%, T3-4=28%)
  - N status (N0=51%, N2=32%)
  - Lobe vs. pneumonectomy (51% vs. 33%)

Kim, Faber et al (Rush) Ann Thorac Surg 2011
Prognostic factors after induction therapy

- Response to chemotherapy
  - "Downstaging" in the mediastinum
- R0 vs. R1/2 resection
- Primary tumor T stage
- Lobe vs. pneumonectomy
Mediastinal restaging after induction therapy?

- Redo mediastinoscopy technically challenging
- PET (after chemo, not chemoRT) can help stratify patient prognosis
- Role of EBUS undefined
- Small but still significant chance of cure after R0 resection, even with persistent N2 (15-20%)
PET after induction therapy for Stage IIIA NSCLC \( (n=54) \)

\textbf{Disease free survival stratified by \% change in SUV}

\begin{itemize}
\item \textbf{>57\% decrease SUV:}
  \textbf{Median DFI - not reached}
\item \textbf{< 57\% decrease in SUV}
  \textbf{Median DFI - 17 mos}
\end{itemize}

\[ p = 0.026 \]
Prognostic Stratification

PET Pre and Post Induction ChemoRx ($n = 30$)

- 1995-2002: PET pre and post induction chemoRx, and complete resection

- Primary parameter: SUVmax in primary tumor

- 5 year survival:
  - $pN0$ or “minor $pN2$” * and >60% decrease: 62%
  - $pN0$ or “minor $pN2$” and < 60% decrease: 13%
  - > “minor $pN2$” and <60% decrease: 0%

  *10% or less viable cells

### INDUCTION THERAPY FOR NSCLC

Resection Mortality (18/470)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploration</td>
<td>0/58 (0)</td>
</tr>
<tr>
<td>Lesser resection</td>
<td>0/18 (0)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>7/297 (2.4%)</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>11/97 (11.3%)</td>
</tr>
<tr>
<td>Right</td>
<td>11/46 (23.9%)</td>
</tr>
<tr>
<td>Left</td>
<td>0/51 (0)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>18/470 (3.8%)</strong></td>
</tr>
</tbody>
</table>

Pneumonectomy after induction Rx

Contemporary outcomes


• Operative mortality 3%

• 5 yr. OS 38%

Weder et al. JThCvS 2010;139:1424-30
Resection NSCLC after induction therapy
Contemporary MSKCC experience
(2000-06: n=549)

- Median length of stay: 6 days
- Mortality: 1.8% (n=10), all pulmonary in origin
  - Pneumonectomy 4.3% (right 3.3%, left 5%)
- Grade 3 or greater AE: 23% (n=126)

Barnett, Rusch et al. JTO 2011;6(9):1530-1536
Morbidity (multivariate analysis) related to:

- Preop %pred. DLCO* (cutoff 58%)
- PPO DLCO* (cutoff 43%)
- PPO product* [PPO FEV1 x PPO DLCO] (cutoff 22%)

*Barnett, Rusch et al. *JTO* 2011;6(9):1530-1536*
Resection after induction therapy
Assessing feasibility of resection

- **Mediastinal lymph nodes resectable?**
  - for right-sided tumors divide azygous vein to achieve complete MLND
  - extent of residual N2 disease?

- **Primary tumor completely resectable?**
  - liberal use of frozen section to determine whether viable tumor present
  - extent of resection needed (lobe vs pneumonectomy)?
Surgery after Induction Therapy: Summary thoughts

- Combined modality therapy (chemo ± RT ± surgery) feasible, and improves OS (Meta-analysis of 13 trials. Song et al. JTO 2010;5:510-516)
- Pneumonectomy should be avoided whenever possible
- Surgery, especially lobectomy excellent option if RO resection achievable
- Meticulous preop assessment of pulmonary function critical and should include DLCO and quant. V/Q scanning
- Resection with residual N2 disease appropriate but requires nuanced pre- and intraoperative decisions