Loco-regional treatment for single station N2 NSCLC: Radiotherapy

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Disclosures

- I am not a radiation oncologist
Outline

1. N2: classification and prognosis
2. Adjuvant radiotherapy in single station pN2
3. Induction (chemo-)radiotherapy in single station cN2
4. Conclusions
Mediastinal lymph node stations

A lymph node or lymph gland is an oval-shaped organ of the lymphatic system, distributed widely throughout the body and linked by lymphatic vessels. Lymph nodes are garrisons of B, T, and other immunity cells. (Wikipedia)
1. **Infiltrative** N2/N3 involvement

2. **Discrete** clinically evident N2 involvement [by (PET-) CT-scan]

3. **Occult** N2 node involvement despite thorough preoperative staging

*Ramnath, CHEST, 2013*
Thorough mediastinal staging

For patients with extensive mediastinal infiltration of tumor and no distant metastases, it is suggested that radiographic (CT) assessment of the mediastinal stage is usually sufficient without invasive confirmation (Grade 2C).

In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (endobronchial ultrasound [EBUS]-needle aspiration [NA], EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test (Grade 1B).

For patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), a needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is suggested over surgical staging as a best first test (Grade 2B).

For patients with a peripheral clinical stage IA tumor (negative nodal involvement by CT and PET), it is suggested that invasive preoperative evaluation of the mediastinal nodes is not required (Grade 2B).

Silvestri, CHEST 2013
Is clinical single station N2 a fallacy?

<table>
<thead>
<tr>
<th>CN2 Status</th>
<th>pN2 Single</th>
<th>pN2 Multiple</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN2 Single</td>
<td>15 (35%)</td>
<td>28 (65%)</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>CN2 Multiple</td>
<td>6 (18%)</td>
<td>27 (82%)</td>
<td>33 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>21 (28%)</td>
<td>55 (72%)</td>
<td>76 (100%)</td>
</tr>
</tbody>
</table>

Sensitivity: 71%
Specificity: 49%
Positive predictive value: 35%

No conflict

Matsunaga, EJCTS 2013
### Is single N2 involvement prognostic?

<table>
<thead>
<tr>
<th>Series</th>
<th>Clin/pathol</th>
<th>Station/zone</th>
<th>Single/multiple</th>
<th>N</th>
<th>Median OS (m)</th>
<th>P value</th>
<th>Median PFS (m)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betticher 2003 (SAKK)</td>
<td>Clin</td>
<td>Station</td>
<td>Single</td>
<td>62</td>
<td>NR</td>
<td>0.013</td>
<td>16</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multiple</td>
<td>20</td>
<td>22</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Lorent 2004</td>
<td>Clin</td>
<td>Single center</td>
<td>Single</td>
<td>93</td>
<td>26</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multiple</td>
<td>38</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matsuguma 2008</td>
<td>Clin</td>
<td>Path station</td>
<td>Single</td>
<td>153</td>
<td>49</td>
<td>0.001</td>
<td>20.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multiple</td>
<td>64</td>
<td>33</td>
<td></td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Albain 2010 (IG)</td>
<td>Clin</td>
<td>Station</td>
<td>Single*</td>
<td>299</td>
<td>-</td>
<td>0.024</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multiple</td>
<td>86</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim 2010</td>
<td>Clin</td>
<td>Single center</td>
<td>Single</td>
<td>122</td>
<td>-</td>
<td>0.8</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multiple</td>
<td>31</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matsunaga 2013</td>
<td>Clin</td>
<td>Single center</td>
<td>Single</td>
<td>45</td>
<td>&lt; 0.001</td>
<td>5 y 23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multiple</td>
<td>33</td>
<td>5 y 20%</td>
<td></td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions (1)

• **Clinical** ‘single station N2’
  – Is a prognostic factor which is only moderately identifiable preoperatively
Caveats!

• A prognostic factor is not necessarily predictive
  – (although it is attractive to imply it)

• Association is not causation
  – Patients with good prognostic factors are selected for a certain treatment
  – This good prognosis is not attributable to the fact they underwent this treatment

• Introduction of routine PET-CT and/or EBUS changes the \textit{a priori} prevalence of cN2
2. Adjuvant radiotherapy in single station pN2

*PORT Meta-analysis Trialists Group, Cochrane Database System Rev 2005*
*NSCLC Meta-analyses Collaborative Group, Lancet 2008*

2232 pts meta-analysis; 50% PORT

8847 pts meta-analysis
2013 ACCP guidelines

- In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging
  - adjuvant platinum-based chemotherapy is recommended when they have a good performance status (Grade 1A)
  - sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high (Grade 2C)

Ramnath, CHEST, 2013
PORT in pN2

330 pN2 pts from ANITA
52% PORT

1987 pN2 pts from SEER
62% PORT

<table>
<thead>
<tr>
<th>5 y OS (%)</th>
<th>N</th>
<th>PORT -</th>
<th>PORT +</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>174</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>S-CT</td>
<td>156</td>
<td>34%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Douillard IJROBP 2008
Lally, J Clin Oncol 2006
Okawara, Lung Cancer 2004
Lymph node ratio = n_{p+} pN2/N_{pLN}

**TABLE 3.** Multivariate Analysis of Postoperative Radiotherapy Benefit for Overall Survival, Stratified by N-stage and LNR

<table>
<thead>
<tr>
<th>N2</th>
<th>Hazard Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2</td>
<td>0.86 (0.79–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>LNR &lt; 12.5% (n = 528)</td>
<td>0.94 (0.71–1.23)</td>
<td>0.632</td>
</tr>
<tr>
<td>LNR 12.5–24.9% (n = 829)</td>
<td>0.94 (0.77–1.15)</td>
<td>0.55</td>
</tr>
<tr>
<td>LNR 25–49.9% (n = 1042)</td>
<td>0.90 (0.76–1.06)</td>
<td>0.212</td>
</tr>
<tr>
<td>LNR ≥ 50% (n = 1197)</td>
<td>0.78 (0.67–0.90)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Urban, JTO 2013

26-29 March 2014, Geneva, Switzerland
Effect of number of pN2 involved

- 91 pN2 CR NSCLC
  - 50 single station pN2
  - PORT in 45: 21 single station pN2
  - OS in PORT and non-PORT group by single and multiple station N2 involvement
LUNGART

pN2: (Pre-operative chemotherapy)

- Complete resection
  - Randomisation
    - If pre-op chemo
      - No TRT
      - TRT
  - No chemo planned
    - Randomisation
      - No TRT
      - TRT
  - Post-operative chemo
    - Randomisation
      - No TRT
      - TRT
Conclusions (2)

• Clinical ‘single station N2’
  – Is a prognostic factor which is only moderately identifiable preoperatively
  – Is not predictive for a benefit of PORT
3. Induction (chemo-)radiotherapy in single station cN2

Documentation of the status of one single node station was sufficient for enrollment; the true number with multistation involvement is likely higher.

Ramnath, CHEST, 2013
2013 ACCP guidelines

- In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A)

Ramnath, CHEST, 2013
Long-term survival of stage T4N0-1 and single station IIIA-N2 NSCLC patients treated with definitive chemo-radiotherapy using individualised isotoxic accelerated radiotherapy (HNDAR)

Bart Reymen,*, Angela van Baardwijk, Gerben Bootsma, Cordula Pitz, Radiotherapy and Oncology

Median follow up: 50 m
Median OS: 26 m (15.6-36.4)
3 y OS: 37%
5 y OS 24% (estimated)
Median PFS 24 m (9.4-38.5)

Single station N2 involvement pathologically proven in 78%
## Outcome in c single station N2

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>PET staging</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betticher, 2003, multicenter</td>
<td>62</td>
<td>None</td>
<td>43</td>
</tr>
<tr>
<td>Lorent, 2004, single center</td>
<td>93</td>
<td>Some</td>
<td>26, 24%</td>
</tr>
<tr>
<td>Albain, 2009, intergroup- CT-RT-S</td>
<td>&lt;152</td>
<td>None</td>
<td>23.6, 27%</td>
</tr>
<tr>
<td>Albain, 2009, intergroup- CT-RT</td>
<td>&lt;146</td>
<td>None</td>
<td>22.2, 20%</td>
</tr>
<tr>
<td>Reymen, 2014, multicenter</td>
<td>41</td>
<td>All</td>
<td>26, 24%</td>
</tr>
</tbody>
</table>
Conclusions (3)

• Clinical ‘single station N2’
  – Is a prognostic factor which is only moderately identifiable preoperatively
  – Is not predictive for a benefit of PORT

• In thoroughly staged patients with clinical ‘single station N2’ involvement, modern definitive chemoradiation therapy results in at least equivalent outcome as retrospective series using induction therapy followed by resection
**Subgroups of cIIIA-N2 favouring resection?**

*Ramnath, CHEST, 2013*

Data taken from a group of resected patients are applied to a different group of clinically staged patients. Positive predictive value of c single node N2 on CT scan = 35%

No data define whether the inclusion of surgery in the treatment strategy further improves outcome.

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**Table: Selection criteria for trimodality therapy with surgery in patients with stage III (N2) lung cancer.**

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Pre-operatively identifiable?</th>
<th>Prognostic value?</th>
<th>Potential Flaw</th>
<th>Defines treatment value?</th>
<th>Summary: Justification for Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Minimal” N2</td>
<td>Moderate</td>
<td>Probably</td>
<td>Out-of-context</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Single station</td>
<td>Moderate</td>
<td>Yes</td>
<td>Out-of-context</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>cN0,1</td>
<td>Yes</td>
<td>Yes</td>
<td>Out-of-context</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Non-bulky nodes</td>
<td>Yes</td>
<td>Probably</td>
<td>Out-of-context</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Good surgical risk</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Downstaged</td>
<td>Limited</td>
<td>Yes</td>
<td>Landmark</td>
<td>Unclear</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
26-29 March 2014, Geneva, Switzerland

Organisers

European Lung
SECOND OPINION

BY ROB ROGERS

50 YEARS AGO THE SURGEON GENERAL WARNED THE WORLD ABOUT SMOKING... IT'S A MIRACLE I'VE SURVIVED THIS LONG!
ARE YOU A HEAVY SMOKER?