Surgery for single zone N2 NSCLC

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No disclosures to declare
• Establish your line in the sand
• Why surgery is not considered for N2 disease?
• Why there may be a role for primary surgery in N2 disease?
• What is necessary before primary surgery for N2?
• The N2 paradox
• Establish your line in the sand
• Why surgery is not considered for N2 disease?
• Why there may be a role for primary surgery in N2 disease?
• What is necessary before primary surgery for N2?
• The N2 paradox
• Can you cross the line in the sand?
Why surgery is not considered for N2 disease?
Against surgery

• “the outcome of INT 0139 and EORTC 08941 mean that evaluating the role of surgery is not a clinical priority”
• “using neoadjuvant therapy followed by surgery for known IIIA is not supported by current evidence”
• “combination chemoradiotherapy (concurrent) is the preferred treatment for known IIIA”
• “medical oncologists can be persuaded that non-surgical treatments result in fitter patients who can tolerate more consolidation regimes and biological agents”
Where is your line in the sand?

Chemoradiotherapy

ALL N2

Primary surgery

N0 or N1

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Why there may be a role for primary surgery in N2 disease?
L upper lobe tumour + single station 5 metastasis

Keller SM, ECOG 3950 trial. JTCVS 2004;128:130
LUL single level N2 : 49 mo v LUL N1 51 mo .
LUL N2 but no N1 : 59 mo
• **Inoue, JTCVS 2004;127:1100.**
  Any upper lobe single N2 : 53.5% 5 yr survival
Surgery / adjuvant chemotherapy may still be preferable to radiotherapy when large tumour volume and radical chemoradiation not possible
• **Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data.**

• “application of the overall hazard ratio to survival in the control group by stage suggests absolute improvements in 5-year survival of 5% (3–8) for stage III disease (from 30% to 35%)”
• Single zone N2a disease has similar prognosis to multistation N1b disease
• These results are based on postoperative pathological staging
• Which are based on intraoperative lymph node dissection
• Thus this needs to be simulated preoperatively
• Mediastinoscopy + lymph node dissection
What is necessary before primary surgery for N2?
Primary resection is indicated in single-zone N2 disease

• Single zone N2 may be suspected by low to moderate PET uptake in remaining N2 zones
• The need is to *exclude* nodal involvement rather than prove it
• EBUS/EUS is validated in confirming the positive usually in high prevalence states
• **VAMLA** is best at confirming the negative
• sensitivity of 93.8%, a specificity of 100%, and a false-negative rate of 0.9%.

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What should we achieve by mediastinoscopy?

VAMLA

- Video assisted mediastinoscopic lymphadenectomy
  - guided by anatomical landmarks, similar to open lymphadenectomy. 
    **en bloc resection of the right and central compartments** and lymphadenectomy of the left-side
  - average number of 20.7 (5-60) nodes were obtained
The N2 paradox
• In patients who have incidental (occult) N2 disease found at surgical resection despite thorough preoperative staging and in whom complete resection of the lymph nodes and primary tumour is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is suggested.
• In patients who have incidental (occult) N2 disease found at surgical resection despite thorough preoperative staging and in whom complete resection of the lymph nodes and primary tumour is technically possible, completion of the planned lung resection and mediastinal lymphadenectomy is suggested BUT

• In patients with discrete N2 involvement identified preoperatively, primary surgical resection followed by adjuvant therapy is not recommended
The N2 paradox: similar outcomes of pre and postoperatively identified single-zone N2a NSCLC
Tsitsias T et al, Eur J Cardiothorac Surg 2013

1131 NSCLC resections

pN2 = 68 (6%)

30 PET-CT N2a positive

38 PET-CT negative

14 mediastinoscopy

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Similar clinical data

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PET N2 +</th>
<th>PET N2 -</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>68</td>
<td>30</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>65 (± 9.4)</td>
<td>64 (± 9.6)</td>
<td>66 (± 9.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>33/35</td>
<td>11/19</td>
<td>22/16</td>
<td>0.09</td>
</tr>
<tr>
<td>PreFEV1 (median)</td>
<td>71%</td>
<td>69%</td>
<td>71%</td>
<td>0.73</td>
</tr>
<tr>
<td>Cardiac co-morbidities</td>
<td>14 (21%)</td>
<td>5</td>
<td>9</td>
<td>0.55</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>13</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Intrapericardial pneumonectomy</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>29</td>
<td>11</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sleeve Lobectomy</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Neo-adjuvant Chemotherapy</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>0.73</td>
</tr>
</tbody>
</table>
## Similar pathological data

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>PET N2 +</th>
<th>PET N2 -</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour size- mm (median)</strong></td>
<td>45 (130)</td>
<td>41 (110)</td>
<td>50 (120)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Cell type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AdenoCa</td>
<td>41</td>
<td>18</td>
<td>23</td>
<td>0.45</td>
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<tr>
<td>Squamous CC</td>
<td>23</td>
<td>9</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Resection margin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>45</td>
<td>20</td>
<td>25</td>
<td>0.95</td>
</tr>
<tr>
<td>R1</td>
<td>15</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rx</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loco-regional</td>
<td>32%</td>
<td>40%</td>
<td>26%</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>11.7%</td>
<td>16.6%</td>
<td>7.8%</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>19.1%</td>
<td>20%</td>
<td>18.4%</td>
<td>0.86</td>
</tr>
<tr>
<td>Distant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant chemotherapy</strong></td>
<td>43%</td>
<td>51%</td>
<td>37%</td>
<td>0.30</td>
</tr>
</tbody>
</table>

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Survival was significantly better in single level pN2a than multiple level pN2b

<table>
<thead>
<tr>
<th></th>
<th>Median OS (months)</th>
<th>95% CI</th>
<th>S.E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple level N2 (n=13)</td>
<td>5.4</td>
<td>0 – 22.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Single level N2 (n=55)</td>
<td>26.5</td>
<td>20.6 – 32.4</td>
<td>2.9</td>
</tr>
</tbody>
</table>

p=0.005
There was no difference in overall survival if resected N2 was PET positive or negative

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET N2 Negative (38)</td>
<td>18</td>
<td>15</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>PET N2 Positive (30)</td>
<td>14</td>
<td>13</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

PET N2 positive 22.2 months (95%CI 10.9 – 37.1)
PET N2 negative 24 months (95%CI 10.9 – 33.9)

p = 0.33
• Survival after resection of pN2 disease is adversely affected by the need for pneumonectomy, multizone pN2b involvement and by non-compliance with adjuvant chemotherapy
• Survival after resection of pN2 disease is adversely affected by the need for pneumonectomy, multizone pN2b involvement and by non-compliance with adjuvant chemotherapy.

• Long-term survival is no different between those patients who have a negative preop PET-CT and are found to have pN2 after resection, and those who are single-zone cN2a positive before resection on PET-CT (HR 1.37, P = 0.335).
• Survival after resection of pN2 disease is adversely affected by the need for pneumonectomy, multizone pN2b involvement and by non-compliance with adjuvant chemotherapy.

• Long-term survival is no different between those patients who have a negative preop PET-CT and are found to have pN2 after resection, and those who are single-zone cN2a positive before resection on PET-CT (HR 1.37, P = 0.335).

• Our results support a policy of intentionally resecting single-zone N2a NSCLC identified preoperatively as part of a multimodality therapy.
Where is your line in the sand?

- Chemoradiotherapy
- ALL N2
- Primary surgery
- N0 or N1

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Where is your line in the sand now?

Primary surgery

Chemoradiotherapy

N2b

N0, N1 and N2b
Can you cross the line?
• Albain, Lancet 2009. Intergroup 0139/RTOG 9309
• Progression free survival @ 2 years doubled by surgery
  11% v 22%, p=0.017
• Subset analysis :
  • 12 month median survival benefit from lobectomy :
    34 v 22 mo, p=0.002
  • Surgery added to chemoradiotherapy doubles 5 year survival
    18% to 36% if pneumonectomy is avoided
Decaluwe H, EJCTS 2009;36:433

ypN category (ypN0-1 and ypN2-single level vs multilevel-ypN2 and ypN3) independent prognostic factors after induction chemo.
Multizone N2 disease should be restaged after induction therapy

- There is no role for primary surgery in multizone N2 disease
- Initial histological confirmation by multizone EBUS/EUS
- For extensive mediastinal disease, mediastinoscopy can be avoided or spared for restaging after neoadjuvant therapy
  Restaging after PET to exclude N2 by VAMLA

- But _exclusion of mediastinal involvement_ requires mediastinoscopy or open lymphadenectomy

How realistic is downstaging?

- Only 37% of patients with favorable, nonbulky, biopsy-proven N2 disease actually complete their neoadjuvant therapy, undergo restaging, and then return for attempted resection. Only 28% undergo complete resection.

This idea has support
Guidelines on the radical management of patients with lung cancer.
Staging CT = cN2

Unresectable N2

Resectable N2

CTPET

Multi Zone N2

EBUS/EUS

positive

negative

VAMLA

Downstaging

Restaging

Single Zone N2

RESECTION

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**Surgical principles in N2**

1. Identify unresectable N2 from initial CT
2. Confirm single-zone N2 by mediastinoscopy
3. Resection in single-zone N2 followed by adjuvant chemotherapy
4. Identify multi-zone N2 by EBUS/EUS
5. Induction chemo/radiotherapy in multi-zone N2
6. Restage by mediastinoscopy
7. Resect in downstaged NO by lobectomy

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