Is there a place for neoadjuvant chemotherapy?

Enriqueta Felip
Vall d’Hebron Hospital, Barcelona, Spain

ESMO Preceptorship on NSCLC,
Copenhagen, Denmark, July 07-08 2015
Is there a place for neoadjuvant chemotherapy?

Outline

• NEO CT in early-stage disease

• NEO CT in resectable stage III disease

• Systemic therapy in non-metastatic NSCLC: latest findings and new perspectives
NEO CT in early-stage disease
Early-stage NSCLC

- Stage I/II disease ~ 25% of NSCLC cases
- Recurrence in up to 50% p, despite surgery
  - High incidence of distant relapse
The European Thoracic Oncology Platform Lungscape project: A way to bridge NSCLC molecular characteristics and clinical data


Logrank Test: p-value < 0.001

N=2130; median follow-up 58 months
5-yr OS by stage

Note: Number of patients and 5-year OS by stage, depicted in the figure
Results with NEO CT: randomized trials

- French Thoracic Cooperative Group: no OS differences, DFS longer with NEO and maintained with long-term follow-up (Depierre JCO 02, Westeel ASCO 10)

- MRC22/NVALT 2/EORTC 08012: no improvement in OS (Gilligan Lancet 07)

- NEO CT vs SUR trials that closed prematurely: survival benefit trend for NEO CT (Sorensen ASCO 05, Pisters JCO 10, Scagliotti JCO 11)

- NATCHE trial: NEO CT a NS trend towards improved DFS, absolute 6.5% improvement in 3-yr DFS, 4.2% in 5-yr DFS (Felip JCO 10)
NATCH trial: study design

Stratify by:
- Tumor size: (<3, 3-5 or > 5 cm)
- Age: (≤ 60 or >60 y)

Clinical stage
IA(>2cm), IB, II, T3N1

- Paclitaxel 200 mg/m²/3h + Carboplatin AUC=6 q3wk for a total of 3 cycles
- Post-op thoracic RT allowed for p-N2 disease
NATCH: disease-free survival by arm

**PREOP CT Arm vs Surgery Arm**

**ADJ CT Arm vs Surgery Arm**

<table>
<thead>
<tr>
<th></th>
<th>Surgery (N=210)</th>
<th>PREOP CT (N=199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>132</td>
<td>117</td>
</tr>
<tr>
<td>Median DFS (mo)</td>
<td>25.1</td>
<td>31.5</td>
</tr>
<tr>
<td>3-year DFS</td>
<td>41.9%</td>
<td>48.4%</td>
</tr>
<tr>
<td>5-year DFS</td>
<td>34.1%</td>
<td>38.3%</td>
</tr>
</tbody>
</table>

HR = 0.92; 95% CI (0.81 to 1.04); P = 0.176

<table>
<thead>
<tr>
<th></th>
<th>Surgery (N=210)</th>
<th>ADJ CT (N=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>132</td>
<td>125</td>
</tr>
<tr>
<td>Median DFS (mo)</td>
<td>25.1</td>
<td>26.0</td>
</tr>
<tr>
<td>3-year DFS</td>
<td>41.9%</td>
<td>44.9%</td>
</tr>
<tr>
<td>5-year DFS</td>
<td>34.1%</td>
<td>36.6%</td>
</tr>
</tbody>
</table>

HR = 0.96; 95% CI (0.75 to 1.22); P = 0.73
NATCH trial: findings

• More patients able to receive the NEO (96%) than ADJ treatment (66%)

• NEO CT, no negative impact on post-operative mortality

• Patients with RR and pCR to NEO CT, better outcomes (5-yr DFS 51% in responding patients, 59% in patients with pCR)

• Clinical stage II-T3N1 patients, greater benefit from NEO CT
  – 5-yr DFS 25% surgery vs 36.6% NEO
  – 5-yr OS 34.5% surgery vs 41.3% NEO
DFS in PR/CR to preop CT vs adj CT vs surgery

<table>
<thead>
<tr>
<th></th>
<th>Surgery (N=210)</th>
<th>Adj CT (N=210)</th>
<th>PR/CR to Preop CT (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year DFS</td>
<td>42%</td>
<td>45%</td>
<td>59%</td>
</tr>
<tr>
<td>5-year EFS</td>
<td>34%</td>
<td>37%</td>
<td>51%</td>
</tr>
</tbody>
</table>

At risk:

<table>
<thead>
<tr>
<th></th>
<th>Preop CT</th>
<th>Adj CT</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>131</td>
<td>130</td>
</tr>
<tr>
<td>1</td>
<td>68</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>25</td>
<td>23</td>
</tr>
</tbody>
</table>

years
DFS in clinical stage II-T3N1

5 year DFS 36.6% in PREOP CT vs 25% in Surgery alone
HR=0.81 (0.64-1.02); P=0.07

5 year DFS 31% in ADJ CT vs 25% in Surgery alone
HR=0.87 (0.54-1.38); P=0.54
Pre-operative CT improves survival and reduces recurrence in operable NSCLC: results of a systematic review and meta-analysis of individual patient data from 15 randomised trials

**Overall survival: 15 trials, 2385 patients, 1427 deaths**

<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative chemotherapy</th>
<th>Control</th>
<th>O-E</th>
<th>Variance</th>
<th>HR (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>France 1990</td>
<td>8/13</td>
<td>8/13</td>
<td>0.32</td>
<td>3.97</td>
<td></td>
</tr>
<tr>
<td>MD Anderson 1994</td>
<td>19/28</td>
<td>27/32</td>
<td>-6.40</td>
<td>11.19</td>
<td></td>
</tr>
<tr>
<td>Spain 1994</td>
<td>19/29</td>
<td>27/30</td>
<td>-8.88</td>
<td>9.65</td>
<td></td>
</tr>
<tr>
<td>MIP-91</td>
<td>137/179</td>
<td>146/176</td>
<td>-12.99</td>
<td>70.22</td>
<td></td>
</tr>
<tr>
<td>SWOG S9015</td>
<td>3/5</td>
<td>12/16</td>
<td>-1.04</td>
<td>2.94</td>
<td></td>
</tr>
<tr>
<td>JCOG 9209</td>
<td>28/31</td>
<td>25/31</td>
<td>2.25</td>
<td>12.97</td>
<td></td>
</tr>
<tr>
<td>Finland 2003</td>
<td>19/30</td>
<td>19/32</td>
<td>-0.50</td>
<td>9.48</td>
<td></td>
</tr>
<tr>
<td>MRC BLT</td>
<td>4/5</td>
<td>3/5</td>
<td>1.26</td>
<td>1.60</td>
<td></td>
</tr>
<tr>
<td>MRC LU22</td>
<td>151/258</td>
<td>158/261</td>
<td>-2.92</td>
<td>77.01</td>
<td></td>
</tr>
<tr>
<td>SWOG S9900</td>
<td>93/180</td>
<td>103/174</td>
<td>-9.31</td>
<td>48.84</td>
<td></td>
</tr>
<tr>
<td>China 2002</td>
<td>26/32</td>
<td>18/23</td>
<td>1.42</td>
<td>10.78</td>
<td></td>
</tr>
<tr>
<td>China 2005</td>
<td>8/19</td>
<td>14/21</td>
<td>-3.31</td>
<td>5.44</td>
<td></td>
</tr>
<tr>
<td>CHEST</td>
<td>45/129</td>
<td>61/141</td>
<td>-10.27</td>
<td>26.39</td>
<td></td>
</tr>
<tr>
<td>NATCH</td>
<td>99/201</td>
<td>109/212</td>
<td>-4.11</td>
<td>51.95</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>682/1178</td>
<td>745/1207</td>
<td>-50.62</td>
<td>351.78</td>
<td></td>
</tr>
</tbody>
</table>

**Overall effect**

HR=0.87 (95% CI 0.78-0.96), p=0.007

Heterogeneity: chi-square=18.75, df=14, p=0.175, I²=25.35

*Burdett Lancet 14*
Overall survival
15 trials, 2385 patients, 1427 deaths

HR=0.87, p=0.007
Absolute improvement of 5% at 5 years
Overall survival: pre-specified trial groups

- No evidence of difference in impact on survival by
  - Number of pre-operative CT cycles ($p=0.68$)
  - CT regimen ($p=0.95$)
  - Number of CT agents ($p=0.84$)
  - Cis or carbo regimen ($p=0.48$)
  - Use of planned post-operative RT ($p=0.57$)
Post-operative mortality

- Defined as proportion of patients who died within 30 days of surgery
- 10/15 trials could not provide appropriate data
- Results based on 5/15 trials
  - 1467 patients
  - 52 deaths
- No evidence of an effect of pre-operative CT on post-operative mortality ($p=0.17$)
  - Based on few events ($n=52$)
ADJ or NEO in early-stage disease?

- ADJ / NEO CT administration similar impact on survival benefit
- More conclusive evidence available favoring ADJ strategies
- A subset of p may benefit from a NEO strategy; yet to be defined
- Should NEO CT be considered in certain early-stage p?
  - P with $\geq 1$ N1 station involved (in IASLC database, p with multiple N1 disease same prognosis as p with N2)
  - P with T3N1 (based on NATCH sub-analysis)
In view of the equivalence of NEO and ADJ CT for overall survival, the consistent results and broad evidence base support ADJ CT as the timing of choice [I, A]
NEO CT in resectable stage III
2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

W. E. E. Eberhardt¹, D. De Ruysscher², W. Weder³, C. Le Péchoux⁴, P. De Leyn⁵, H. Hoffmann⁶, V. Westeel⁷, R. Stahel⁸, E. Felip⁹ & S. Peters¹⁰ Panel Members†

Table 2. Patient subsets and sub-stages included into stage III non-small-cell lung cancer

<table>
<thead>
<tr>
<th>IASLC/UICC 7</th>
<th>Definition</th>
<th>TNM subsets</th>
<th>Description</th>
<th>Robinson classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>Incidental N2 (unforeseen N2)</td>
<td>T1–3 N2</td>
<td>N2 found at surgery</td>
<td>IIIA1</td>
</tr>
<tr>
<td>IIIA</td>
<td>Potentially resectable N2</td>
<td>T1–3 N2</td>
<td>Microscopic N2 (final pathology)</td>
<td>IIIA2</td>
</tr>
<tr>
<td>IIIA</td>
<td>Potentially resectable N2</td>
<td>T1–3 N2</td>
<td>Microscopic/macrosopic N2 (frozen section)</td>
<td>IIIA3</td>
</tr>
<tr>
<td>IIIA</td>
<td>But: risk of incomplete resection</td>
<td></td>
<td>Minimal N2/single station at staging</td>
<td>IIIA3</td>
</tr>
<tr>
<td>IIIA</td>
<td>Unresectable N2</td>
<td>T1–3 N2</td>
<td>Pancoast tumour subsets, T3-4 N1, T3 N2 selective</td>
<td>IIIA3</td>
</tr>
<tr>
<td>IIIA</td>
<td>Unresectable T4</td>
<td>T4 N0–1</td>
<td>Bulky and/or multilevel N2 at staging</td>
<td>IIIA4</td>
</tr>
<tr>
<td>IIIA</td>
<td>But: risk of incomplete resection</td>
<td></td>
<td>Pulmonary artery, carina, spine, trachea, vena cava, right atrium</td>
<td>–</td>
</tr>
<tr>
<td>IIIB</td>
<td>Unresectable T4</td>
<td>T4 N0–1</td>
<td>Oesophagus, heart, aorta, pulmonary veins</td>
<td>–</td>
</tr>
<tr>
<td>IIIB</td>
<td>Unresectable N3</td>
<td>T1–4 N3</td>
<td>N3 nodes at staging</td>
<td>–</td>
</tr>
</tbody>
</table>
## Randomized studies
### NEO CT vs surgery alone

<table>
<thead>
<tr>
<th>Author</th>
<th>Tto</th>
<th>Stage</th>
<th>Nº patients</th>
<th>MS (months)</th>
<th>% 5-yr Survival</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass 1992</td>
<td>S CT+S</td>
<td>IIIA</td>
<td>14</td>
<td>16</td>
<td>12</td>
<td>.80</td>
<td>NS</td>
</tr>
<tr>
<td>Roth 1994</td>
<td>S CT+S</td>
<td>IIIA</td>
<td>32</td>
<td>11</td>
<td>14</td>
<td>.78</td>
<td>P&lt;.05</td>
</tr>
<tr>
<td>Rosell 1994</td>
<td>S CT+S</td>
<td>IIIA</td>
<td>30</td>
<td>8</td>
<td>0</td>
<td>.75</td>
<td>P&lt;.05</td>
</tr>
</tbody>
</table>
Stage IIIAN2: NEO phase II trials using 3rd generation drugs

<table>
<thead>
<tr>
<th>Author</th>
<th>CT Combination</th>
<th>N</th>
<th>RR</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Zandwijk</td>
<td>Cis/gem</td>
<td>47</td>
<td>70%</td>
<td>18.9 mo</td>
</tr>
<tr>
<td><em>JCO 2000</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’ Brien</td>
<td>Carbo/pac</td>
<td>52</td>
<td>64%</td>
<td>20.5 mo</td>
</tr>
<tr>
<td><em>Eur J Cancer 03</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betticher</td>
<td>Cis/doc</td>
<td>90</td>
<td>66%</td>
<td>28 mo</td>
</tr>
<tr>
<td><em>JCO 2003</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5-yr follow-up of cis/doc phase II study

• 75 p who underwent SUR:
  – Complete resection 55%; pCR: 19%
  – Postop mortality: 3%
  – Local relapse: 60%
  – 5-year DFS in resected p: 36%

Betticher Br J Cancer 2006
SLCG NEO trial 9901

- Resectable stage IIIAN2 / T4N0-1
- 3 cycles of neoadjuvant cisplatin / gemcitabine / docetaxel
- 136 patients included / 129 evaluable (Dec 99-March 03)
- Response rate: 59%
- 90 patients (70%) underwent surgery:
  - complete resection 69%; 71% in IIIA; 66% in IIIB
  - pCR 9%
  - surgical mortality 8% (all pneumonectomies; 6 right / 1 left)
- OS 15.9 months; EFS 11.4 months

Garrido JCO 07
## SLCG 9901: survival by subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N ° pts</th>
<th>MST (month)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>69</td>
<td>15.6</td>
<td>0.32</td>
</tr>
<tr>
<td>IIIB</td>
<td>67</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>(bi-)lobectomies</td>
<td>33(38)</td>
<td>36.9</td>
<td>0.5</td>
</tr>
<tr>
<td>pneumonectomies</td>
<td>37</td>
<td>42.3</td>
<td></td>
</tr>
<tr>
<td>Complete resection</td>
<td>62</td>
<td>45.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Incomplete resection</td>
<td>13</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>No resection</td>
<td>15</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>35</td>
<td>NR</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pN1-3/unknown</td>
<td>55</td>
<td>22.8</td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>46</td>
<td>7.34</td>
<td></td>
</tr>
</tbody>
</table>

**Garrido JCO 2007**
Which CT combination in the NEO setting?

• Cis is the cornerstone of the doublet combination; Cisca Meta-Analysis (*Ardizzoni JNCI 2007*)

• Carbo is an alternative when cis not suitable

• Cis in combination with doc, pac, vin, gem (SCC), or pem (non-SCC)
NEO platin-based CT in stage III

- Response rate: 40-60%
- Complete resection: 50-60%
- pCR: 5-10%
- Median survival: ~18 months
- Survival significantly influenced by complete resection and pathologic stage \( (Garrido\ JCO\ 07,\ Betticher\ JCO\ 03) \)
- Long term results: 29% 5-year survival; 22% 10-year survival \( (Burkes\ Lung\ Cancer\ 05) \)
Stage III, controversies in the last decade

- Role of surgery

- Preoperative CT vs CT/RT?
Role of surgery: phase III trials

**Int 0139**

- *Cp/Et x 2/Rt 45* → *No PROG* → Subgroup 396 → Subgroup 45
- *Cp/Et x 2* → Subgroup 332 → Subgroup 45

**EORTC 08941**

- *Qt ‘ddp x 3* → *>RPm* → Subgroup 332
- *Rt 60* → Subgroup 60
- *SUR* → Subgroup 61
Role of surgery: phase III trials

Int 0139

- No differences in median survival
- Unplanned exploratory analyses: survival advantage with surgery in patients requiring lobectomy

EORTC 08941

Chemoradiotherapy is to remain the standard treatment for future EORTC studies in stage IIIA-N2 NSCLC
Role of surgery: phase III trials; methodologic problems

Int 0139

- High post-operative mortality
- Preoperative RT?

EORTC 08941

Unresectable disease at diagnosis
1195O: Final results of the SAKK 16/00 trial: A randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC) – Pless M et al

- **Study objective**
  - To determine if the addition of neoadjuvant radiotherapy (RT) improves outcomes in patients with stage IIIA/N2 NSCLC receiving neoadjuvant chemotherapy (CT) + surgery

**Key patient inclusion criteria**
- Resectable stage IIIA/N2 NSCLC
- PS 0–1
- Adequate organ function
  
(n=232)

**Chemoradiation (CRT):**
- Three cycles of neoadjuvant CT, followed by accelerated concomitant boost, then surgery
  
(n=117)

**Neoadjuvant CT alone, then surgery**
  
(n=115)

**Stratification**
- Mediastinal bulk (≥5 cm vs. <5 cm), weight loss (≥5% vs. <5%), centre

**Primary endpoint**
- Event-free survival (EFS)

**Secondary endpoints**
- OS, post-operative 30-day mortality, ORR, failure pattern, rate of complete resection, operability

CT, cisplatin 100 mg/m² and docetaxel 85 mg/m² D1, q3w
RT, with 44 Gy in 22 fractions in 3 weeks

1195O: Final results of the SAKK 16/00 trial: a randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC) – Pless M et al

• Key results
  – Neither EFS nor OS were significantly longer with CRT

EFS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median EFS (95% CI)</th>
<th>HR 1.1 (95% CI 0.8, 1.4)</th>
<th>p=0.665</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>13.1 (9.9, 23.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RT</td>
<td>11.8 (8.4, 15.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
<th>HR 1.0 (95% CI 0.7, 1.4)</th>
<th>p=0.938</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>37.1 (22.6, 50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No RT</td>
<td>26.2 (19.9, 52.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1195O: Final results of the SAKK 16/00 trial: a randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC) – Pless M et al

- **Key results (cont.)**

<table>
<thead>
<tr>
<th></th>
<th>CRT (n=117)</th>
<th>CT (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate, %</td>
<td>61</td>
<td>44</td>
</tr>
<tr>
<td>Complete resection, %</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>pCR, %</td>
<td>16</td>
<td>12</td>
</tr>
</tbody>
</table>

- CT was associated with substantial toxicity (febrile neutropenia was especially common), but RT was well tolerated

- **Conclusion**
  - While the addition of RT to CT in patients with stage IIIA/N2 NSCLC improved ORR, complete resection and pCR, these benefits did not translate into improved EFS or OS

pCR, pathological complete remission

Phase III trials in stage III disease: conclusions

• Unresectable stage III, induction CT followed by surgery does not improve survival

• Resectable stage III, preoperative CT/RT improves DFS not OS

• Preoperative CT/RT is not standard of care

• Resectable stage III, standard of care:
  – NEO CT followed by surgery
  – Definitive CT/RT
**Figure 1.** Suggested algorithm for treatment in patients with logoregional non-small-cell lung cancer, based on imaging, invasive lymph node staging tests and multidisciplinary assessment. Reproduced from [17], by permission of Oxford University Press, on behalf of ESMO.
• An individualised decision must be made within a multidisciplinary team

• Due to the complexity of most stage III disease presentations that require multidisciplinary treatment, management should be carried out in high-volume centres

• Recommendation: All patients planned for definitive stage III NSCLC treatment should undergo a diagnostic high-resolution CT followed by a PET or a combined PET-CT with a CT technique with adequately high resolution for initial staging purposes [I, A]. Single PET-positive distant lesions need pathological confirmation [V, B].
Recommendation: PET-positive mediastinal findings should be pathologically assessed [I, A]. Invasive mediastinal staging may still be indicated despite PET negativity in case of suspicious lesions (primary tumour of >3 cm large axis, central tumours, cN1, CT-enlarged lymph nodes with small axis >1 cm) [III, B].

- Endoscopic methods should be preferred as the initial interventional procedure whenever feasible [I, A]. In case of negative endoscopic findings, and high suspicion of mediastinal node involvement, surgical staging is indicated [I, A].

Recommendation: Comorbidities are of paramount importance since the potential risk of toxicity/morbidity/mortality has to be balanced with the potential benefit of any aggressive curative-intent treatment strategy [III, A]
Potentially resectable IIIA(N2) disease

• Possible strategies include several options: induction CT followed by surgery, induction CT/RT followed by surgery, or concurrent definitive CT/RT [I, A]. No recommendation can yet be made; however, an experienced multidisciplinary team is of paramount importance in any complex multi-modality treatment strategy decision

• **Recommendation:** In potentially resectable superior sulcus tumours, concurrent CT/RT induction followed by definitive surgery is the treatment of choice [III, A]. The same strategy may be applied for potentially resectable T3 or T4 central tumours in highly selected cases and experienced centres [III, B]
Potentially resectable IIIA(N2) disease

**Recommendation:** The optimal surgical management aims at complete resection preferably carried out by lobectomy/ sleeve resection [I, A]. Complete resection necessarily includes systematic mediastinal nodal exploration. In selected patients, pneumonectomy must be carried out, but should be adequately selected and the procedure restricted to experienced centres [III, B]

**Recommendation:** Post-lobectomy and pneumonectomy mortality rates should not exceed 2%–3% and 3%–5%, respectively [IV, B]
Potentially resectable IIIA(N2) disease

- **Recommendation:** Thoracic and upper abdominal CT scan should be carried out every 6 mo for 2 years, and yearly thereafter [III, C] for 3 years. No routine PET-CT is recommended.

- **Recommendation:** Patients treated for stage III disease should be strongly encouraged to quit smoking and/or participate in smoking cessation programmes [I, A]
Systemic therapy in non-metastatic NSCLC: latest findings and new perspectives
7514: Trimodality therapy in the treatment of stage IIIA non-small cell lung cancer (NSCLC): Analysis of the National Cancer Database – Behera M et al

• **Study objective**
  – To examine outcomes and predictors of response in patients with stage IIIA NSCLC who received trimodality therapy

• **Study design**
  – A retrospective analysis was performed with data from the National Cancer Database on patients diagnosed with stage IIIA-N2 NSCLC who had been treated with chemotherapy and radiation (CRT) between 2003 and 2011
  – Three patient groups were identified:
    • CRT only/no surgery (NS)
    • CRT + lobectomy (L)
    • CRT + pneumonectomy (P)
  – Cox proportional hazards model and log rank tests were used to perform univariate and multivariable analyses

• **Key results**
  – The analysis included 29,584 patients: 91.7% treated with NS, 7% received L and 1.5% received P
7514: Trimodality therapy in the treatment of stage IIIA non-small cell lung cancer (NSCLC): Analysis of the National Cancer Database – Behera M et al

Key results (cont.)

Treatment factors

– Younger patients (those aged <60 years) were more likely to receive trimodality therapy: L 47%, P 60% vs. NS 29% (p<0.001)
– Patients who were treated in academic centres were more likely to get trimodality therapy (42%) than NS (25%)

Survival outcomes

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>P</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95%CI) for survival vs. NS</td>
<td>0.43 (0.38, 0.48)</td>
<td>0.57 (0.46, 0.71)</td>
<td>–</td>
</tr>
<tr>
<td>Median survival, months</td>
<td>44.5</td>
<td>25.6</td>
<td>15.7</td>
</tr>
<tr>
<td>5-year survival rates, %</td>
<td>44</td>
<td>33</td>
<td>14</td>
</tr>
</tbody>
</table>

– 30-day mortality was higher with P (7%) than with L (2.6%; OR 0.26, 95%CI 0.16, 0.45; p<0.001)
**Key results (cont.)**

*Survival outcomes*

– In the L group, survival was better in patients with <2 lymph nodes than patients with >2 lymph nodes (50% vs. 37%; 60 vs. 38.8 months), conversely, in the NS group survival was worse in patients with <2 lymph nodes compared with those with >2 lymph nodes (13.8% vs. 16.4%; 15.3 vs. 18.5 months)

– Survival rates for L and P were better than NS across all ages

<table>
<thead>
<tr>
<th>Age category</th>
<th>Survival rates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L</td>
</tr>
<tr>
<td>≤60 years</td>
<td>48</td>
</tr>
<tr>
<td>61–70 years</td>
<td>42</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>36</td>
</tr>
</tbody>
</table>

**Conclusions**

– Trimodality therapy appears to be used in highly selected patients with stage IIIA-N2 NSCLC

– In these patients, relative to CRT alone, trimodality therapy is associated with favourable outcomes
Phase II biomarker-guided NEO treatment strategy for IIIAN2 NSCLC based on EGFR mutation status

- 24 patients with resectable stage IIIAN2 NSCLC assigned to a NEO erlotinib arm or a gem/carbo (GC) arm based on EGFR mutation status

- RR, 58.3 % (7/12) for erlotinib arm with mutant EGFR and 25.0 % (3/12) for GC arm with wt-EGFR (P = 0.18)

- Median PFS, 6.9 mo vs 9.0 mo, respectively (P = 0.071)

- Median OS, 14.5 mo for erlotinib arm and 28.1 mo for GC arm (P = 0.201)

Zhong et al, Journal of Hemathology & Oncology 2015
Stage III: anti-PD1 & anti-PDL1 strategies

• A reality in the management of stage IV disease

• Ongoing trials in the ADJ setting and in stage III after radical CT/RT treatment

• NEO strategies?
Clinical case

- Man, 53 years old
- No family history
- Smoker 40 pack/year
- Diabetes mellitus with oral anti-diabetic treatment
Clinical case

- **Symptoms:** Right hemi-thorax pain - 15 days’ evolution

- **Physical exam:** ECOG PS 1, no abnormalities

- **Blood analysis:** normal

- **Chest x-ray:** Lesion in upper right lobe
Clinical case: work-up

**Thorax and abdomen CT-scan**
- 4 x 5 cm lesion in upper right lobe
- 1.5 cm lymph node in ipsilateral mediastinum

**Spirometry:**
- FEV1: 2180 cc (93%); FVC: 2940 cc; FEV1/FVC: 74

**Bronchoscopy**
- No endobronchial abnormalities

**Pathologic findings**
Bronchoaspirate, positive for ADC

**Brain CT**
- No evidence of brain metastases found
Clinical case: baseline PET-scan
Clinical case

• EBUS performed with FNA and showed invasion single station N2 positive for ADC

• The patient staged as stage T2pN2
  ✔ Is there a place for NEO treatment?
Thanks!!

efelip@vhebron.net