Combined chemotherapy and radiotherapy for NSCLC

P. Van Houtte

Department of Radiation Oncology

Institut Jules Bordet
RADIOTHERAPY for NSCLC
Results from « old » selected trials

<table>
<thead>
<tr>
<th>Stage I-IIIb</th>
<th>3 Y</th>
<th>5 Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dillman</td>
<td>3 %</td>
<td>1 %</td>
</tr>
<tr>
<td>LeChevalier</td>
<td>14 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Mattson</td>
<td>17 %</td>
<td>13 %</td>
</tr>
<tr>
<td>Perez</td>
<td>15 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Shaake Koning</td>
<td>13 %</td>
<td>2 %</td>
</tr>
</tbody>
</table>

- The basic principles of radiation oncology
- Relation between tumor size and local control
- Poor total radiation dose (60 Gy or less) for tumor > 3 cm

Poor survival & local control ➔ new strategies
LUNG CA: RADIATION
How to improve the results

- Improving the quality of the radiation procedure
- Higher biological doses
  fractionation chemotherapy
- Higher physical doses
  conformal radiotherapy to 4 D radiotherapy
  endoluminal brachytherapy
  particle beams (protons, carbon…)
- Decreasing the toxicity: radioprotectors
- A multimodal approach including chemotherapy and surgery
« Benzene could be combined with radiation in treating leukemia because both are myelotoxins »

F. Billings in 1905 published in 1922

- Nitrogen mustard in lung cancer
  Roswit & Kaplan 1951

- Are we still in the dark ?
RADIOTHERAPY & CHEMOTHERAPY
INDUCTION CT

⇒ ADVANTAGES

Drugs are less effective after RT (vascular access)
Systemic treatment is not delayed
Assessment of drug efficacy (maintenance CT)
Tumor shrinkage: better oxygenation RT efficacy
 volume reduction tissue protection

⇒ PROBLEMS

Delayed local treatment
Problem of drug resistance
<table>
<thead>
<tr>
<th>Authors</th>
<th>CT</th>
<th>RT</th>
<th>No Pts</th>
<th>Stage</th>
<th>Median Surv (m)</th>
<th>2 Y S %</th>
<th>2 Y S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matson</td>
<td>CAP</td>
<td>55 S</td>
<td>252</td>
<td>I-III</td>
<td>10</td>
<td>17</td>
<td>No dif</td>
</tr>
<tr>
<td>Brodin</td>
<td>DDP-VP16</td>
<td>56 C</td>
<td>302</td>
<td>I-III</td>
<td>11</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>56</td>
<td></td>
<td></td>
<td>10.5</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Jett</td>
<td>MACC</td>
<td>60 C</td>
<td>121</td>
<td>III</td>
<td>10</td>
<td>21</td>
<td>No dif</td>
</tr>
<tr>
<td>Arriagada</td>
<td>VCPC</td>
<td>65 C</td>
<td>353</td>
<td>I-III</td>
<td>12</td>
<td>21</td>
<td>Ben.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65 C</td>
<td></td>
<td></td>
<td>10</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Dillman</td>
<td>DDP, Vinbl</td>
<td>60 C</td>
<td>180</td>
<td>III</td>
<td>13.8</td>
<td>26</td>
<td>Ben.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 C</td>
<td></td>
<td></td>
<td>9.7</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Sause</td>
<td>DDP, Vinbl</td>
<td>60 C</td>
<td>490</td>
<td>III</td>
<td>13.6</td>
<td>31</td>
<td>Ben.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 C</td>
<td></td>
<td></td>
<td>11.6</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>
LUNG CANCER
IMPACT of INDUCTION CHEMOTHERAPY
Arriagada et al 1991

A = RT 64 Gy  B = CT---RT--CT

DISTANT META.

LOCAL CONTROL
INTERACTIONS BETWEEN DRUGS & RT
POSSIBLE MECHANISMS

• Spatial co-operation : sequential treatment

• Simple addition of anti-tumor effect : implies to have different type of toxicity

• Protection of normal tissues : induction treatment ?

• Enhancement of tumor response : our dream
RADIO-CHEMOTHERAPY
CONCURRENT APPROACH

**Benefits**
both the local and metastatic disease may be treated
possibility to obtain a “*radiosensitizing*” effect

**Drawbacks**
increase acute and late toxicity
radiation and drugs dosage to be adapted
logistic problems
EORTC TRIAL
DDP & RT LUNG CA
Schaake-Koning et al

Local control is an important matter
NSC LUNG CANCER: RADIOCHEMOTHERAPY QUESTIONS

• Can we use safely the new drugs?
• Is concurrent superior to sequential approach?
• What is the best sequence?
  Induction followed by concurrent chemoradiotherapy
  Concurrent chemoradiotherapy followed by adjuvant CT
• What is the place of maintenance chemotherapy?
• Is there a role for the new biological modifiers?
NSC LUNG CANCER: RADIOCHEMOTHERAPY
The so-called new drugs

Docetaxel
Paclitaxel
Vinorelbine
Tirapzamine
Gemcitabine

Are very good radiosensitizers
Protocol B9E-MC-JHDP(a)
Gemcitabine in Combination with Radiotherapy in Stage III Non-Small Cell Lung Cancer.
Scalliet, Alberts, Groen

<table>
<thead>
<tr>
<th></th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper gastrointestinal</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

GEM : 1 gr/m2 weekly concurrent with RT 60 Gy, 2 Gy/fr, 6 w., large field

3 toxic deaths
No concurrent RT-GEM in France
Key message

The extrapolation between lab (cell culture), animal models and humans is very difficult and must be considered with high precautions.

Do not make your own recipe out of a trial.
RADIOCHEMOTHERAPY FOR NSCLC
CALGB TRIAL   E. Vokes JCO 2002

DDP (80 mg/m²) + New drug  DDP + 66 Gy New drug

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>Paclitaxel</th>
<th>Vinorelbine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses (mg/m²)</td>
<td>1250</td>
<td>225</td>
<td>25</td>
</tr>
<tr>
<td>Induction</td>
<td>600</td>
<td>135</td>
<td>15</td>
</tr>
<tr>
<td>Concurrent with RT</td>
<td>62</td>
<td>58</td>
<td>55</td>
</tr>
<tr>
<td>Number patients</td>
<td>40</td>
<td>33</td>
<td>44</td>
</tr>
<tr>
<td>CR + PR</td>
<td>18.3</td>
<td>14.8</td>
<td>17.7</td>
</tr>
<tr>
<td>MS (months)</td>
<td>37 %</td>
<td>29 %</td>
<td>40 %</td>
</tr>
<tr>
<td>2 Year survival</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Phase II CALGB trial NSCLC E. Vokes JCO 2003

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel</th>
<th>Vinorelbine</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. pat.</td>
<td>58</td>
<td>55</td>
<td>62</td>
</tr>
<tr>
<td>Neutropenia G4 (%)</td>
<td>24</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Platelets G4 (%)</td>
<td>4</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Esophagitis G3/4 (%)</td>
<td>35 / 4</td>
<td>13 / 12</td>
<td>35 / 17</td>
</tr>
<tr>
<td>Dyspnea 3 &amp; 4 (%)</td>
<td>20</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting 3 &amp; 4 (%)</td>
<td>16</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>ARDS (%)</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>
Lung Cancer: RT and Gemcitabine
Blackstock et al JTO 2006

○ = lung toxicity
● = no lung toxicity

From phase Ia and Ib
STUDY DESIGN

Chemotherapy
Cisplatin 60 mg/m² D1-22
Vinorelbine 25 mg/m² D1-8-22-29
Gemcitabine 1 g/m² D1-8-22-29

Radiochemotherapy
RT 66 Gy, 2Gy/fx
Cisplatin 60 mg/m² D1-22
Vinorelbine 15 mg/m² D1-22
Gemcitabine 200 mg/m² D8-29
INITIAL RADIATION FIELDS

3 cases
# RADIATION TOXICITY & LUNG DOSE

<table>
<thead>
<tr>
<th>$V_{20}$ Gy</th>
<th>Number Patients</th>
<th>Clinical Symptoms</th>
<th>Required steroids</th>
<th>Required surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 – 30</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>31 – 40</td>
<td>6</td>
<td>3</td>
<td></td>
<td>1*</td>
</tr>
<tr>
<td>41 - 50</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* = lung necrosis within the tumor
Sequential or Concurrent Radio-chemotherapy

Efficacy
Easy

Toxicity
Complexity
RADIOCHEMOTHERAPY LUNG CA.
Sequential vs Concurrent trials

Median S  2 Y Surv  gr.3 esophagitis

Seq  Conc  Seq  Conc  Seq  Conc

Furuse  RTOG  GLOT  Petruzela

IMRT
Amifostine?
RADIO-CHEMOTHERAPY FOR NSCLC

Metaanalysis data

• Sequential CT-RT is superior to RT alone (Br. Med. J. 1995)

• Concurrent chemoRT is superior to RT?

  Cochrane review 14 trials 2393 patients
  2 Y death rate RR 0.93 (p = 0.1)
  2 Y locoregional progr. free survival RR 0.4 (p = 0.03)
## CONCURRENT vs SEQUENTIAL CHEMORADIOTherapy IN NSCLC

*The Cochrane Database of Systematic Reviews.*

<table>
<thead>
<tr>
<th>Study</th>
<th>Concurrent n/N</th>
<th>Sequential n/N</th>
<th>Relative Risk 95% CI</th>
<th>Relative Risk 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curran 2003</td>
<td>127/201</td>
<td>139/201</td>
<td>0.91 (0.79,1.05)</td>
<td></td>
</tr>
<tr>
<td>Fourmel 2001</td>
<td>67/103</td>
<td>80/104</td>
<td>0.85 (0.71,1.01)</td>
<td></td>
</tr>
<tr>
<td>Zatloukal 2003</td>
<td>34/52</td>
<td>43/50</td>
<td>0.76 (0.61,0.95)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>356</strong></td>
<td><strong>355</strong></td>
<td><strong>0.86 (0.78,0.95)</strong></td>
<td></td>
</tr>
</tbody>
</table>

*P=0.003*

- **favours concurrent**
- **favours sequential**
RADIO-CHEMOTHERAPY FOR NSCLC

Metaanalysis data

• Sequential CT-RT is superior to RT alone (Br. Med. J. 1995)
• Concurrent chemoRT is superior to RT?

**Cochrane review** 14 trials 2393 patients

2 Y death rate RR 0.93 (p = 0.1)
2 Y locoregional progr. free survival RR 0.4 (p = 0.03)

**Auperin Ann. Oncol.**

1764 patients 7 trials with platin compounds
4% absolute 2 Y benefit

**But the data are insufficient to define the size of the benefit and the optimal schedule**
**RADIOCHEMOTHERAPY LUNG CA.**
Sequential vs Concurrent trials
Problems of treatment compliance

<table>
<thead>
<tr>
<th>Trials</th>
<th>Treatment</th>
<th>Sequential</th>
<th>Concurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furuse</td>
<td>3 cycles CT</td>
<td>75 %</td>
<td>59 %</td>
</tr>
<tr>
<td></td>
<td>RT given</td>
<td>59 %</td>
<td>88 %</td>
</tr>
<tr>
<td></td>
<td>CT given</td>
<td>77 % 3 cycles</td>
<td>100 % 2 cycles</td>
</tr>
<tr>
<td>Fournel</td>
<td>CT 4 cycles</td>
<td>58 %</td>
<td>83 %</td>
</tr>
<tr>
<td></td>
<td>RT given</td>
<td>64 %</td>
<td>94 %</td>
</tr>
<tr>
<td>Zatloukal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
How to combine RT & CT for NSCLC

**Advantages**

**CT → CT/RT**
- Potential smaller RT ports
- Full dose CT sterilize
- micro-metastatic disease

**CT/RT → CT**
- Max. anti-tumor effect
- Potential synergy CT/RT
- Better tolerance

**Disadvantages**

- Chemo-insensitive disease continues to grow pre RT
- Enhanced toxicity
- No RT due toxicity
- Repopulation
- Enhanced toxicity
- Problem of adjuvant CT

Potential synergy with CT/RT

Potential synergy CT/RT

Repopulation issue
## Concurrent vs Induction for NSCLC

E. Vokes ASCO 2004

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Concurrent RT+CT</th>
<th>Induction followed by concurrent RT-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Patients</td>
<td>182</td>
<td>184</td>
</tr>
<tr>
<td>Median survival</td>
<td>11.4 months</td>
<td>14 months</td>
</tr>
<tr>
<td>1 Y Surv.</td>
<td>48 %</td>
<td>54 %</td>
</tr>
</tbody>
</table>

**Induction**: carbo AUC 6 + paclitaxel 200 mg/m²

**Concurrent**: carbo AUC 2 + paclitaxel 50 mg/m² weekly and 66 Gy/33 fr.
## NSC LUNG CANCER: CT & RT

### The Learning Process

**RTOG trial 9106 & 9204**


<table>
<thead>
<tr>
<th>Number of patients per institution</th>
<th>4 patients or less</th>
<th>&gt; 4 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival Months</td>
<td>13.4</td>
<td>20.5</td>
</tr>
<tr>
<td>2 Y S</td>
<td>20 %</td>
<td>45 %</td>
</tr>
<tr>
<td>3 Y S</td>
<td>13 %</td>
<td>31 %</td>
</tr>
</tbody>
</table>

*Concurrent radio-chemotherapy with twice per day irradiation*
NSC LUNG CANCER : CT & RT

Even in a combined approach, a precise radiation technique remains mandatory to take the full benefit from a chemotherapeutic program.

Drugs should not be used to compensate a poor technique.
INDUCTION CT for NSC LUNG CANCER
Dillman publication

- **Major deviations** from radiation protocol:
  
  - 34/151 patients 22.5%
  
- 12 patients: the tumor was not completely included in the large and small fields

- 21 patients the tumor was not encompassed in the small field

- 1 patient: the dose was less than the 90% prescribed dose

- 6 patients survived more than 2 years (5 had received CT+RT)

= incomplete resection
From 2 D to 4 D radiotherapy

Image guided radiotherapy

and

From RT to CHEMO RT

- 3 DCRT
- IMRT
- 4 D RT

⇨ Require a precise imaging not only for the treatment planning but also for the treatment delivery.
Technical evolution in the RT of early lung ca
EGFR & Erbitux + RT

Human squamous cell carcinoma cell line

Head & Neck Ca
STAGE III NSC LUNG CANCER

A very heterogeneous group

- According to *D. Grunenwald*: 3 groups
  a) T3N1, T1-T3 mN2  Surgery
  b) T4₁ N0-2, T1-3 cN2  Subgroup induction
  c) T4₂ N0-3, T1-4 N3  Subgroup No surgery
      Radiotherapy or no RT
      chemotherapy only? palliation

- T4₁ = sattelite nodule, vertebra, superior vena cava, trachea..
- T4₂ = oesophagus, aorta, ventricule…
- Pleural or pericardial effusion even positive
## INDUCTION RT+CT for LUNG CANCER
### Selected phase II trials

<table>
<thead>
<tr>
<th></th>
<th>Rush</th>
<th>Brown</th>
<th>LCSG</th>
<th>SWOG</th>
<th>N Israel</th>
<th>Padova</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>P-E</td>
<td>P-E</td>
<td>P-5FU</td>
<td>P-E</td>
<td>P-E</td>
<td>P-E</td>
</tr>
<tr>
<td>RT Gy</td>
<td>40</td>
<td>55.8</td>
<td>30</td>
<td>45</td>
<td>50.4</td>
<td>51.2</td>
</tr>
<tr>
<td>N°Pat</td>
<td>130</td>
<td>53</td>
<td>85</td>
<td>75</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>Stage IIIb (%)</td>
<td>6</td>
<td>0</td>
<td>13</td>
<td>37</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>CR %</td>
<td>65</td>
<td>89</td>
<td>56</td>
<td>69</td>
<td>61</td>
<td>16</td>
</tr>
<tr>
<td>Resect. %</td>
<td>46</td>
<td>51</td>
<td>57</td>
<td>73</td>
<td>56</td>
<td>51</td>
</tr>
<tr>
<td>Path CR %</td>
<td>13</td>
<td>23</td>
<td>9</td>
<td>15</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Postop mort.</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>2 YS %</td>
<td>50</td>
<td>50</td>
<td>22</td>
<td>40</td>
<td>39</td>
<td>27</td>
</tr>
</tbody>
</table>
• T3-4, No-1 after mediastinoscopy
• DDP-VP16 x 2 + 45 Gy
• additional course postoperatively
• 111 patients, 95 patients eligible for surgery
• 83 patients had a thoracotomy
• 76 patients had a complete resection, 2 postoperative deaths
• 44 patients had a pathological CR or minimal microscopic disease
• 2 Y Survival : 55 % for all eligible patients and 70 % after a complete resection
<table>
<thead>
<tr>
<th>Radiological Pathological</th>
<th>PR</th>
<th>Stable</th>
<th>No Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>17</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>pR1</td>
<td>14</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>pR2</td>
<td>12</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>40</td>
<td>5</td>
</tr>
</tbody>
</table>
SURGERY or RADIOTHERAPY for STAGE III NSCLCA?
RANDOMIZED TRIALS PATHOL. STAGE IIIa «Radiotherapy versus Surgery»

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Pat.</th>
<th>Median S. Months</th>
<th>5 Y S %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intergroup</td>
<td>R+C → S → C C</td>
<td>202</td>
<td>23.6</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>R+C → C C</td>
<td>194</td>
<td>22.2</td>
<td>20.3</td>
</tr>
<tr>
<td>EORTC</td>
<td>C → Resp → R S</td>
<td>165</td>
<td>17.5</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>167</td>
<td>16.4</td>
<td>15.7</td>
</tr>
<tr>
<td>RTOG</td>
<td>C → R S</td>
<td>45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_No statistical difference in survival_
EXPLORATORY ANALYSIS
Intergroup trial Surgery vs Radio-chemotherapy

OVERALL SURVIVAL OF PNEUMONECTOMY SUBSET VS MATCHED CT/RT SUBSET

- CT/RT/S: 38/51
- CT/RT: 42/51

Logrank P=NS

OVERALL SURVIVAL OF LOBECTOMY SUBSET VS MATCHED CT/RT SUBSET

- CT/RT/S: 57/90
- CT/RT: 74/90

Logrank P=0.002

Albain et al Proc ASCO 2005 Abstract 7014
STAGE IIIa-b RT or SURGERY Requirements:

- **Surgery**
  - The tumor should be *resectable*
  - A RO resection
  - No place for an incomplete resection
  - The patient should be *medically operable*
  - T4 potentially resectable
    - highly selected patients

- **Radiotherapy**
  - The tumor should be treated to a dose > 65 Gy or biological equivalent
  - Patient should have a good PS
  - Candidate for a combined approach
- The treatment of locally advanced NSCLC is more and more a *multimodal approach* including a local treatment, radiotherapy or/and surgery, and a systemic treatment.
- The treatment of stage IIIa/b disease should combine drug and radiation probably with a *concurrent* approach and the new tools of radiotherapy.
- The optimal sequence and drugs must still be defined.
- An *adequate selection* of patients to avoid an excessive toxicity.
- The current TNM staging (*a toy to evaluate the surgeon’s skill*) is not the best tool to select the locoregional treatment.
- There is a new IASLC staging project ongoing.
Two cases of stage IIIb

Patient treated only with Chemotherapy and a endobronchial prothesis

Patient with a small tumor treated with radiotherapy external and endobronchial
A basic radiation principle: **Relation dose-T volume** or number of tumoral cells
Thank you