State-of-the-art time/dose and fractionation for radio(chemo)therapy of lung cancer

José Belderbos
ELCC 14 april 2016
Disclosures

None
Introduction

• After CCRT local control ≈ 70% at 3-5 years (Auperin JCO 2010)

• RT dose conventional 60 Gy in 2 Gy +/- concurrent chemotherapy

• Dose escalation is limited by normal tissue tolerances
Variation in the use of concurrent chemoradiation (CCRT)

<table>
<thead>
<tr>
<th>Country</th>
<th>% CCRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands¹</td>
<td>~70%</td>
</tr>
<tr>
<td>England²</td>
<td>~54%</td>
</tr>
<tr>
<td>Italy³</td>
<td>~17%</td>
</tr>
<tr>
<td>Canada⁴</td>
<td>~18%</td>
</tr>
<tr>
<td>Australia⁵</td>
<td>~37%</td>
</tr>
<tr>
<td>USA⁶</td>
<td>~35%</td>
</tr>
</tbody>
</table>

¹ van Reij E. Act. Onc. 2014  
² Prewett S. Clin Onc 2012  
³ Ramella S. Tumori 2012  
⁴ Vinod S. JTO 2012  
⁵ Pramana A. AP JCO 2014  
⁶ Harris J. Int J Radiat Oncol Biol Phys 2014
Options to improve locoregional control

- RT dose escalation
- Enhance RT response by targeted radiosensitization
- *Improve treatment accuracy* → Image-guided adaptive RT
- Reduce overall treatment time and Accelerated cell repopulation
- Hypo- or Hyperfractionation or Acceleration
RT dose and fractionation

- Split course RT: with a several-day break
- Hyperfractionation: multiple smaller daily doses
- Acceleration: same dose in shorter period
- Hypofractionation: fewer larger fractions

BED = biological effective dose
Influence Local Control on survival
CHART trial:

60 Gy / 30 fx  40 days

54 Gy/ 36 fx  12 days

- 563 NSCLC patients
- 2 year OS benefit for hyperfractionation 9%
  (from 20 to 29%)
- For SCC 25% improved local control and a
  24% reduction in risk distant metastases
- Improved LC reduced the incidence of
  metastases and improved survival!

Saunders R&O 1999
Meta-analysis
Hyperfractionated / accelerated RT

- 10 trials, 2,000 NSCLC patients
- Modified fractionation improved OS as compared to conventional schedules
  \( (\text{HR} = 0.88, \text{95\% CI}, 0.80 - 0.97; p = 0.009) \)
- Resulting in an absolute OS benefit of 2.5%
  (8.3\% to 10.8\%) at 5 years
- Similar benefit in SCLC
Dose-response relation in NSCLC

The probability of sterilizing a tumor increases with increasing radiation dose to the tumor
Dose-response relationship in SABR for NSCLC

2-year 94%
3-year 91%

\[ \text{BED}_{10} < 105 \text{ Gy} \]
\[ \text{BED}_{10} \geq 105 \text{ Gy} \]

\( p < 0.001 \)
RTOG 0617: Trial design

Stratify:
- RT Technique (IMRT vs 3D)
- Perf Status (0 vs 1)
- Histology (squam vs other)
- PET staging (yes vs no)

RT: 60 Gy
Paclitaxel
Carboplatin +/- Cetuximab

RT: 74 Gy
Paclitaxel
Carboplatin +/- Cetuximab

Paclitaxel
Carboplatin X 2 +/- Cetuximab

Bradley et al  Lancet Oncology 2015
RTOG 0617
Survival by RT dose

Survival Rate (%)

18-Month Survival Rate
66.9%
53.9%

Standard (60 Gy) 90 213
High dose (74 Gy) 117 206

HR=1.56 (1.19, 2.06) p=0.0007

Patients at Risk
Standard 213 207 190 177 161 141 108
High dose 206 197 178 159 135 112 87

Months since Randomization
RTOG 0617
Local failure and RT dose

Local Progression Rate (%)

0 25 50 75 100

Months since Randomization

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Standard (60 Gy)</th>
<th>High dose (74 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fail</td>
<td>65</td>
<td>81</td>
</tr>
<tr>
<td>Total</td>
<td>213</td>
<td>206</td>
</tr>
</tbody>
</table>

HR=1.37 (0.99, 1.89)  p=0.0319

18-Month Local Progression Rate

25.1% Standard

34.3% High dose

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since Randomization</td>
<td>213</td>
<td>206</td>
</tr>
<tr>
<td>0</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>113</td>
<td>113</td>
</tr>
<tr>
<td>6</td>
<td>137</td>
<td>137</td>
</tr>
<tr>
<td>9</td>
<td>165</td>
<td>165</td>
</tr>
<tr>
<td>12</td>
<td>187</td>
<td>187</td>
</tr>
<tr>
<td>15</td>
<td>205</td>
<td>205</td>
</tr>
<tr>
<td>18</td>
<td>213</td>
<td>213</td>
</tr>
</tbody>
</table>
## RTOG 0617

Multivariate Cox Model

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison (RL)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation dose</td>
<td>60 Gy v 74 Gy</td>
<td>1.51 (1.12, 2.04)</td>
<td>0.007</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-squam v Squam</td>
<td>1.31 (0.99, 1.75)</td>
<td>0.061</td>
</tr>
<tr>
<td>Max esophagitis grade</td>
<td>&lt;3 vs ≥3</td>
<td>1.52 (1.06, 2.20)</td>
<td>0.024</td>
</tr>
<tr>
<td>Heart Contour</td>
<td>Per Protocol vs. Not per protocol</td>
<td>0.67 (0.47, 0.96)</td>
<td>0.029</td>
</tr>
<tr>
<td>GTV</td>
<td>Continuous</td>
<td>1.001 (1.000, 1.002)</td>
<td>0.038</td>
</tr>
<tr>
<td>Heart V50(%)</td>
<td>Continuous</td>
<td>1.017 (1.004, 1.030)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Backwards Selection: Exit criteria p>0.10  
Two-sided p-values  
Removed from model: Age (continuous), overall RT review (per protocol vs. not per protocol), and lung V5 (continuous)
Dose escalation using hypofractionation (CCRT)

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Fraction</th>
<th>Dose/fx</th>
<th>Acute BED</th>
<th>Late BED</th>
<th>3 Year OS (%)</th>
<th>1 Year OS (%)</th>
<th>AE (%)</th>
<th>AP (%)</th>
<th>LE (%)</th>
<th>LP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Machtay (2005)</td>
<td>60</td>
<td>20</td>
<td>3</td>
<td>78.0</td>
<td>120.0</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Belderbos (2007)</td>
<td>66</td>
<td>24</td>
<td>2.75</td>
<td>84.2</td>
<td>126.5</td>
<td>29</td>
<td>56</td>
<td>17</td>
<td>9</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Uitterhoeve (2007)</td>
<td>66</td>
<td>24</td>
<td>2.75</td>
<td>84.2</td>
<td>126.5</td>
<td>31</td>
<td>57</td>
<td>NR</td>
<td>NR</td>
<td>5a</td>
<td>18a</td>
</tr>
<tr>
<td>Tsoutsou (2008)</td>
<td>52.5</td>
<td>15</td>
<td>3.5</td>
<td>70.9</td>
<td>113.8</td>
<td></td>
<td></td>
<td>28</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bral (2010)</td>
<td>67.2</td>
<td>30</td>
<td>2.24</td>
<td>82.3</td>
<td>117.4</td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Matsuura (2009)</td>
<td>65</td>
<td>26</td>
<td>2.5</td>
<td>81.3</td>
<td>119.2</td>
<td>44</td>
<td>90</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Casas (2011)</td>
<td>61.6</td>
<td>23</td>
<td>2.68</td>
<td>78.2</td>
<td>116.7</td>
<td>34</td>
<td>59</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carruthers (2011)</td>
<td>55</td>
<td>20</td>
<td>2.75</td>
<td>70.1</td>
<td>105.4</td>
<td>38</td>
<td>73</td>
<td>13</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Maguire (2012)</td>
<td>55</td>
<td>20</td>
<td>2.75</td>
<td>70.1</td>
<td>105.4</td>
<td>38</td>
<td>73</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lin (2013)</td>
<td>69</td>
<td>22-24</td>
<td>3</td>
<td>85.8</td>
<td>132.0</td>
<td>34</td>
<td>59</td>
<td>15</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Liu (2013)</td>
<td>75</td>
<td>25</td>
<td>3</td>
<td>78.0</td>
<td>120.0</td>
<td>61</td>
<td>61</td>
<td>8</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chen (2013)</td>
<td>55</td>
<td>20</td>
<td>2.75</td>
<td>70.1</td>
<td>105.4</td>
<td>69</td>
<td>22</td>
<td>NR</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Donato (2013)</td>
<td>68.4</td>
<td>30</td>
<td>2.28</td>
<td>82.7</td>
<td>118.1</td>
<td>77a</td>
<td>77a</td>
<td>10a</td>
<td>5a</td>
<td>0a</td>
<td>5a</td>
</tr>
<tr>
<td>van Den Heuvel (2013)</td>
<td>66</td>
<td>24</td>
<td>2.75</td>
<td>84.2</td>
<td>126.5</td>
<td>80</td>
<td>80</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bearz (2013)</td>
<td>60</td>
<td>25</td>
<td>2.4</td>
<td>74.4</td>
<td>108.0</td>
<td>24</td>
<td>80</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Dose escalation using hypofractionation

- Prolonged overall treatment time proven disappointing
  → accelerated repopulation

- Dose escalation using hypofractionation:
  - **EORTC phase I/II study 08912^2**:  
    50 Gy/20 fx → 66 Gy /24 fx with daily cDDP was feasible

  - **EORTC phase III 08972-22973^3**: concurrent vs sequential;  
    66 Gy /24 fx with daily cDDP  
    2-year OS 39% (concurrent) and 34% (sequential)

  - **Dutch Raditux trial phase II^4**  
    66 Gy /24 fx with daily cDDP, +/- Cetuximab

Long-term FU of NSCLC pts receiving concurrent hypofractionated CCRT +/- cetuximab

- Median FU 60 months
- Median OS= 33 and 30 months
- p-value 0.722

Walraven et al., Radiother Oncol, Feb 2016
Raditux trial phase II
n=102

Median FU 60 months
Median OS = 32 months

5 year OS 37%
## Overall survival Raditux vs RTOG 0617

<table>
<thead>
<tr>
<th></th>
<th>Raditux trial</th>
<th>RTOG 0617 60 Gy</th>
<th>RTOG 0617 74 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>64%*</td>
<td>58%a</td>
<td>67%a</td>
</tr>
<tr>
<td>1-year OS (%)</td>
<td>75%</td>
<td>78%</td>
<td>69%</td>
</tr>
<tr>
<td>2-year OS (%)</td>
<td>60%</td>
<td>53%</td>
<td>42%</td>
</tr>
<tr>
<td>5-year OS (%)</td>
<td>37%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>32 months</td>
<td>29 months</td>
<td>20 months</td>
</tr>
</tbody>
</table>

*based on 5-years of follow-up

a based on 2-years of follow-up
## Baseline characteristics

### Raditux vs RTOG 0617

<table>
<thead>
<tr>
<th></th>
<th>Raditux trial 66 Gy</th>
<th>RTOG 0617 60 Gy</th>
<th>RTOG 0617 74 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>62 years</td>
<td>64 years</td>
<td>64 years</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>8%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Stage IIIA</strong></td>
<td>52%</td>
<td>66%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>Stage IIIB</strong></td>
<td>40%</td>
<td>34%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>GTV</strong></td>
<td>119 cc</td>
<td>93 cc</td>
<td>110 cc</td>
</tr>
<tr>
<td><strong>PTV</strong></td>
<td>499 cc</td>
<td>481 cc</td>
<td>478 cc</td>
</tr>
<tr>
<td><strong>PET staged</strong></td>
<td>92%</td>
<td>90%</td>
<td>90%</td>
</tr>
</tbody>
</table>
## Treatment characteristics

### Raditux vs RTOG 0617

<table>
<thead>
<tr>
<th></th>
<th>Raditux trial 66 Gy</th>
<th>RTOG 0617 60 Gy</th>
<th>RTOG 0617 74 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT OTT</strong></td>
<td>32</td>
<td>40</td>
<td>51</td>
</tr>
<tr>
<td><strong>Total treatment duration</strong></td>
<td>32</td>
<td>82</td>
<td>93</td>
</tr>
<tr>
<td><strong>IMRT</strong></td>
<td>76%</td>
<td>46%</td>
<td>47%</td>
</tr>
<tr>
<td><strong>EQD2T (time corrected equivalent RT dose)</strong></td>
<td><strong>59.6 Gy</strong></td>
<td><strong>49.7 Gy</strong></td>
<td><strong>58.8 Gy</strong></td>
</tr>
<tr>
<td><strong>Chemotherapy concurrent</strong></td>
<td><strong>cisplatin</strong></td>
<td><strong>paclitaxel and carboplatin</strong></td>
<td><strong>paclitaxel and carboplatin</strong></td>
</tr>
<tr>
<td><strong>Consolidation CT</strong></td>
<td>_</td>
<td><strong>paclitaxel and carboplatin</strong></td>
<td><strong>paclitaxel and carboplatin</strong></td>
</tr>
<tr>
<td><strong>Protocol adherence</strong></td>
<td>86%</td>
<td>83%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Low-volume centers (&lt; 4 pts per year)</strong></td>
<td>_</td>
<td>2/3</td>
<td>2/3</td>
</tr>
</tbody>
</table>
Improve accuracy: Intensity Modulated RT
Reduce Heart dose
Radiobiological Optimization of External-Beam RT

Nahum AE.
Improve accuracy:
Image-guided RT: Linear accelerator with Cone beam CT
Repeat 4D Cone Beam CT: Tumor regression during RT

Shows respiration, tumor shrinkage and baseline position variation
Image-guided adaptive RT Using Cone-Beam CT
e.g. dissolving of atelectases
Image-guided adaptive RT: Dose distribution before and after replanning
Current-Future developments

Combining high precision RT with targeted agents in a preclinical setting
Novel PET tracers (proliferation-hypoxia)
Evolving role of Radio-immunotherapy
Possibilities to predict RT response in serum
Proton therapy/Heavy Ions
Image-guided radiotherapy for small animals (μIGRT)
Image-guided radiotherapy for small animals (μIGRT) - mimicking clinical RT protocols -
Radio-Immunoonotherapy

• RT complements the effects of Immunotherapy
• RT can sensitize unresponsive tumors to anti CTLA-4
• Antitumor responses of RT and blocking of PD1 or PD-L1

NKI Trials RT + immunotherapy NSCLC
• RT + Selectikine (NHS-IL2LT) Phase Ib Completed*
• SABR+ Pembrolizumab vs. Pembrolizumab Phase I-II Recruiting

γ-H2AX assay to detect DSB secondary to ionising radiation

- Increased signal shortly after RT, lymphocytes with multiple foci
- Back to baseline levels at 24-hours and beyond

Courtesy of Shankar Siva
Take home messages

• The optimum dose and fractionation for NSCLC remains uncertain.
• The RT dose-response relationship remains a sound basis for further randomized studies making use of Image-guided adaptive RT
• Dose escalation: avoid long overall treatment time: hypofractionation or hyperfractionation
• Use of high precision RT: more personalized prescription
Meet NKI RT team ......