What is the optimal radiotherapy combined with chemotherapy for stage III non-small cell lung cancer (NSCLC)?

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Definition of “optimal”

A condition, degree, amount or compromise that produces *the best possible* result
Phase III trials

- Concurrent chemo-radiotherapy is superior to sequential chemo-radiation
- No benefit for surgery after concurrent chemo-radiation over definitive concurrent chemo-radiation
Better survival with concurrent chemoradiotherapy vs. sequential

Aupérin et al. J Clin Oncol 2010
The overall survival benefit is associated with improved local control

Local tumour control better still 30-40 % local progression

Same incidence of distant metastases

Aupérin et al. J Clin Oncol 2010
Most series used

- 60-66 Gy in 2 Gy/day fractions, 5 times per week
- Concurrently with
  - cisplatin-etoposide
  - cisplatin-vinorelbine
  - carboplatin-paclitaxel

➔ Much improvement is needed for systemic and local control
“Radioresistance does not exist”

Progression-free Survival of patients at 30 months (Martel et al. 1999)

TP = 3 days
Tk = 28 days
γ = 0.66 Gy/d

Influence of overall treatment time of radiotherapy on survival in stage I-III NSCLC without concurrent chemo-radiotherapy


<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>964/1056</td>
<td>0.88</td>
<td>[0.80;0.97], p=0.009</td>
</tr>
<tr>
<td>Test for heterogeneity: $X^2 = 9.74$, p = 0.37, $\hat{\phi} = 8%$</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for interaction: $X^2 = 0.17$, p = 0.98</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial</th>
<th>Exp. RT</th>
<th>Conv. RT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
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</thead>
<tbody>
<tr>
<td>Very accelerated RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMCI 88C091 CT</td>
<td>51/51</td>
<td>58/56</td>
<td>6.0</td>
<td>26.6</td>
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</tr>
<tr>
<td>CHART</td>
<td>316/338</td>
<td>217/225</td>
<td>-29.4</td>
<td>120.7</td>
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<tr>
<td>ECOG 2597</td>
<td>51/60</td>
<td>55/59</td>
<td>-7.4</td>
<td>25.8</td>
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<td></td>
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<tr>
<td>CHARTWEL</td>
<td>132/150</td>
<td>132/150</td>
<td>0.2</td>
<td>65.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHARTWELCT</td>
<td>40/53</td>
<td>47/53</td>
<td>-6.4</td>
<td>21.2</td>
<td></td>
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<tr>
<td>Subtotal</td>
<td>638/700</td>
<td>559/596</td>
<td>-37.8</td>
<td>283.4</td>
<td>0.88</td>
<td>[0.78;0.98]</td>
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<tr>
<td>Moderately accelerated RT</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gliwice 2001</td>
<td>26/29</td>
<td>27/29</td>
<td>-1.4</td>
<td>13.2</td>
<td></td>
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</tr>
<tr>
<td>Subtotal</td>
<td>26/29</td>
<td>27/29</td>
<td>-1.4</td>
<td>13.2</td>
<td>0.90</td>
<td>[0.52;1.54]</td>
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<tr>
<td>Hyperfractionated RT - identical total dose</td>
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<tr>
<td>NCCTG 902451</td>
<td>34/39</td>
<td>35/35</td>
<td>-7.0</td>
<td>15.7</td>
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<tr>
<td>NCCTG 942452</td>
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<td>108/121</td>
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<td>54.6</td>
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<tr>
<td>Subtotal</td>
<td>145/164</td>
<td>143/156</td>
<td>-9.6</td>
<td>70.3</td>
<td>0.87</td>
<td>[0.69;1.10]</td>
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<tr>
<td>Hyperfractionated RT - increased total dose</td>
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<tr>
<td>RTOG 8808</td>
<td>155/163</td>
<td>156/163</td>
<td>-6.4</td>
<td>76.9</td>
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<tr>
<td>Subtotal</td>
<td>155/163</td>
<td>156/163</td>
<td>-6.4</td>
<td>76.9</td>
<td>0.92</td>
<td>[0.74;1.16]</td>
</tr>
</tbody>
</table>
Radiation dose escalation with concurrent chemotherapy and prolongation of the overall treatment time

RTOG 0617, NCCTG N0628, CALGB 30609
Conventional vs. High Dose RT

- **RT: 60 Gy**
  - Paclitaxel
  - Carboplatin +/− Cetuximab

- **RT: 74 Gy**
  - Paclitaxel
  - Carboplatin +/− Cetuximab

- Paclitaxel
  - Carboplatin x 2
  - +/− Cetuximab
## Overall Survival – RT Comparison

<table>
<thead>
<tr>
<th>Months</th>
<th>Standard Dose: 60 Gy</th>
<th>High Dose: 74 Gy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>% Alive</td>
<td># at Risk</td>
</tr>
<tr>
<td>0</td>
<td>100.0%</td>
<td>213</td>
</tr>
<tr>
<td>3</td>
<td>98.5%</td>
<td>190</td>
</tr>
<tr>
<td>6</td>
<td>91.2%</td>
<td>149</td>
</tr>
<tr>
<td>9</td>
<td>84.7%</td>
<td>124</td>
</tr>
<tr>
<td>12</td>
<td>81.0%</td>
<td>104</td>
</tr>
<tr>
<td>Dead/Total</td>
<td>58/213</td>
<td></td>
</tr>
</tbody>
</table>

Median Sv: 21.7 mos vs. 20.7 mos

p = 0.02 (one-sided p-value, left tail)

(RTOG 9410 CON-QD one-year survival = 62.1%, MST = 17.0 months)
Why did RTOG0617 “fail”?

• Unknown
  – Preliminary results
  – No subgroup analysis yet of cetuximab subgroup
  – Interaction between 74 Gy and cetuximab?
  – Added toxicity of adjuvant chemotherapy and 74 Gy radiotherapy?
  – Technical factors (e.g. inhomogeneity 120 %, no delineation of mediastinal OARs …)
  – …
Many ongoing dose-intensification trials

- **Biological** dose escalation → dose intensification
  - Standard total doses, shorter overall time
- **Individualisation**
  - **Physical**
  - Biological, including molecular imaging
Examples

- IDEAL-RT
- I-START
- Isotoxic IMRT
- CHART-ED
- BIG Lung Trial (consisting of the CARSoN and ASCaN trials) in the UK.
- European PET-boost trial: Radiation dose redistribution within the tumour using an INDAR schedule: max Gy/ 24 fractions/ 5 weeks
- PET-plan trial in Germany randomises dose escalation based on the omission of elective nodal irradiation on FDG-PET scan. No acceleration component.
- ESPATÜ: 65 Gy/ 5.5 weeks
- RTOG 1106/ ACRIN 6697 is a randomised study looking at individualised dose escalation based on FDG-PET response with in the experimental arm a dose up to 85.5 Gy given in 30 daily fractions in 6 weeks.
But,... RTOG0617 shows

- That the OS with “current 60 Gy” is better than in the past (patient selection, staging, imaging integration in radiotherapy planning, planning and delivery ...)
- ... which leads to “reasonable” median survival rates of 21 months

➔ Dummy run shows that many centres could improve their results by emphasising the quality of the whole treatment chain!
Conclusions

- Radiotherapy to a dose of 60-66 Gy in 2 Gy per day, 5 days per weeks remains the standard when delivered concurrently with chemotherapy (*arguments in favour of high-dose, accelerated radiotherapy in non-concurrent schedules*)
- Individualised (accelerated, isotoxic) radiotherapy schedules are being investigated in many clinical trials and are still of much importance
- Improvement the quality of the *whole* diagnostic and treatment chain most probably improves overall survival