Optimal radiotherapy for stage III NSCLC in 2014: What dose/fractionation for concurrent and sequential schedules?

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Disclosure

None to declare
Dose and time influence local control

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

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

Total dose in 2 Gy fractions (= NTD)

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></td>
<td>Exp. RT</td>
<td>Conv. RT</td>
<td>O-E</td>
</tr>
<tr>
<td>Very accelerated RT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMCI 88C091</td>
<td>48/48</td>
<td>52/53</td>
<td>-0.8</td>
</tr>
<tr>
<td>PMCI 88C091 CT</td>
<td>51/51</td>
<td>56/56</td>
<td>6.0</td>
</tr>
<tr>
<td>CHART</td>
<td>316/338</td>
<td>217/225</td>
<td>-29.4</td>
</tr>
<tr>
<td>ECOG 2597</td>
<td>51/60</td>
<td>55/59</td>
<td>-7.4</td>
</tr>
<tr>
<td>CHARTWEL</td>
<td>132/150</td>
<td>132/150</td>
<td>0.2</td>
</tr>
<tr>
<td>CHARTWEL CT</td>
<td>40/53</td>
<td>47/53</td>
<td>-6.4</td>
</tr>
<tr>
<td>Subtotal</td>
<td>638/700</td>
<td>559/596</td>
<td>-37.8</td>
</tr>
<tr>
<td>Moderately accelerated RT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glivice 2001</td>
<td>26/29</td>
<td>27/29</td>
<td>-1.4</td>
</tr>
<tr>
<td>Subtotal</td>
<td>26/29</td>
<td>27/29</td>
<td>-1.4</td>
</tr>
<tr>
<td>Hyperfractionated RT - identical total dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCCTG 902451</td>
<td>34/39</td>
<td>35/35</td>
<td>-7.0</td>
</tr>
<tr>
<td>NCCTG 942452</td>
<td>111/125</td>
<td>108/121</td>
<td>-2.6</td>
</tr>
<tr>
<td>Subtotal</td>
<td>145/164</td>
<td>143/156</td>
<td>-9.6</td>
</tr>
<tr>
<td>Hyperfractionated RT - increased total dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 8808</td>
<td>155/163</td>
<td>156/163</td>
<td>-6.4</td>
</tr>
<tr>
<td>Subtotal</td>
<td>155/163</td>
<td>156/163</td>
<td>-6.4</td>
</tr>
<tr>
<td>Total</td>
<td>964/1056</td>
<td>885/944</td>
<td>-55.2</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 9.74$, p = 0.37, $I = 8\%$

Test for interaction: $\chi^2 = 0.17$, p = 0.98

Experimental RT better | Conventional RT better
Influence of induction chemotherapy

<table>
<thead>
<tr>
<th>Ctx</th>
<th>CF</th>
<th>CHARTWEL</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>103/150</td>
<td>96/150</td>
<td>0.97</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.69; 1.37)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>38/53</td>
<td>36/53</td>
<td>0.48</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.26; 0.89)</td>
<td></td>
</tr>
</tbody>
</table>

CF: Conventional fractionation (66 Gy/ 33 fr/ 6.6 weeks)
CHARTWEL: 60 Gy/ 40 fractions/ 2.5 weeks; 3 x 1.5 Gy/day

Baumann et al. Radiother Oncol 2011
Tumour volume and survival

Soliman et al. Radiother Oncol 2013
Tumour volume and survival (50 Gy/20 fractions)

- Black line: < 19 cc
- Red line: 19 to 48 cc
- Green line: 48 to 110 cc
- Blue line: 110 cc +

Statistical significance:
- P(global) = 0.041
- P(trend) = 0.017

Table of Number at Risk:

<table>
<thead>
<tr>
<th>Volume Range</th>
<th>Number at Risk</th>
<th>Years from Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 19 cc</td>
<td>123</td>
<td>95</td>
</tr>
<tr>
<td>19 to 48 cc</td>
<td>131</td>
<td>91</td>
</tr>
<tr>
<td>48 to 110 cc</td>
<td>128</td>
<td>92</td>
</tr>
<tr>
<td>110 cc +</td>
<td>127</td>
<td>72</td>
</tr>
</tbody>
</table>

Ball et al. Radiother Oncol 2013
Concurrent chemotherapy and radiotherapy

- Level I evidence: Concurrent chemo-radiotherapy is superior to sequential chemo-radiation
- Same radiotherapy schedule in both arms: Methodologically sound, biologically?
- Patient selection?
Why is concurrent chemo-RT better? Improved local tumour control

Local tumour control better still 30-40 % local progression

Same incidence of distant metastases

Aupérin et al. J Clin Oncol 2010
Phase III trials:
- 60-66 Gy in 2 Gy/day fractions, 5 times per week over 6-7 weeks or
- 66 Gy in 24 fractions over 5 weeks (2 trials)
- Concurrently with
  - cisplatin-etoposide
  - cisplatin-vinorelbine
  - cisplatin daily (2 trials)

Overall, all schedules seem to have similar efficacy
<table>
<thead>
<tr>
<th>RT Technique</th>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-CRT</td>
<td>Arm A: Concurrent chemotherapy* RT to 60 Gy, 5 x per wk for 6 wks</td>
<td>Arm A: Consolidation chemotherapy*</td>
</tr>
<tr>
<td>IMRT</td>
<td>Arm B: Concurrent chemotherapy* RT to 74 Gy, 5 x per wk for 7.5 wks</td>
<td>Arm B: Consolidation chemotherapy*</td>
</tr>
<tr>
<td>Zubrod</td>
<td>Arm C: Concurrent chemotherapy* and Cetuximab RT to 60 Gy, 5 x per wk for 6 wks</td>
<td>Arm C: Consolidation chemotherapy* and Cetuximab</td>
</tr>
<tr>
<td>PET Staging</td>
<td>Arm D: Concurrent chemotherapy* and Cetuximab RT to 74 Gy, 5 x per wk for 7.5 wks</td>
<td>Arm D: Consolidation chemotherapy* and Cetuximab</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Squamous</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Carboplatin and paclitaxel
Overall Survival

- Median survival time:
  - Standard (60 Gy): 28.7 months
  - High dose (74 Gy): 19.5 months

- Survival rates at 18 months:
  - Standard: 66.9%
  - High dose: 53.9%

- Hazard ratio (HR): 1.56 (1.19, 2.06)
  - p-value: 0.0007

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

18-Month Local Progression Rate

HR = 1.37 (0.99, 1.89)  \( p = 0.0319 \)

Patients at Risk

- Standard (60 Gy): 213, 206, 205, 197, 187, 165, 137, 113, 85
- High dose (74 Gy): 206, 197, 170, 134, 105, 80, 62

Local Progression Rate (%)

- Standard (60 Gy): 65, 81, fail, fail
- High dose (74 Gy): 81, 206, fail, fail

Months since Randomization

- 0, 3, 6, 9, 12, 15, 18

Fail

Total

- Standard (60 Gy): 213
- High dose (74 Gy): 206

0

20

40

60

80

100

0

3

6

9

12

15

18
Distant Failure

Distant Failure Rate (%)

Months since Randomization

Patients at Risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Standard (60 Gy)</th>
<th>High dose (74 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>213</td>
<td>206</td>
</tr>
<tr>
<td>3</td>
<td>205</td>
<td>193</td>
</tr>
<tr>
<td>6</td>
<td>175</td>
<td>161</td>
</tr>
<tr>
<td>9</td>
<td>145</td>
<td>126</td>
</tr>
<tr>
<td>12</td>
<td>115</td>
<td>93</td>
</tr>
<tr>
<td>15</td>
<td>97</td>
<td>73</td>
</tr>
<tr>
<td>18</td>
<td>213</td>
<td>206</td>
</tr>
</tbody>
</table>

Fail  Total

<table>
<thead>
<tr>
<th>Standard</th>
<th>97</th>
<th>213</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>104</td>
<td>206</td>
</tr>
</tbody>
</table>

HR=1.15 (0.87, 1.51)
p=0.1576

18-Month Failure Rate

- Standard (60 Gy): 47.8%
- High dose (74 Gy): 42.4%
Optimal dose/ fractionation

- **Non-concurrent**
  - High-dose accelerated, e.g. 66 Gy/ 24 QD fractions

- **Concurrent**
  - Standard is 60-66 Gy in 2 Gy QD fractions (RTOG0617)
  - Shortening overall treatment time with concurrent chemotherapy
    - Not studied in depth
    - Not beneficial in squamous cell cancer head and neck
Issues to be solved

• Same dose and fractionation for all histologies, molecular characteristics ...?
• Influence of the patient?
Individual image-based tissue characterization:
Possible prognostic and predictive use

Tumor
- Tumor cells:
  e.g., genetic instability, mutation status, resistance
- Microenvironment:
  e.g., hypoxia
- Malignant potential:
  e.g., undetermined pulmonary nodules
  At screening or staging

Normal tissues (e.g., lungs, heart)
- e.g., ventilation and perfusion heterogeneity

Selection of systemic treatment
Most appropriate drugs, dose, and sequence

Selection of local therapy
Determination of best radiation dose:
eScalation or deescalation
Selective avoidance of most susceptible parts of healthy organs

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CCR Translations

De Ruysscher D. Clin Cancer Cancer Res 2013
Changes in Hounsfield Units (HU) per Gy for each individual patient

$\Delta$HU/Gy and dyspnoea $\geq$ G2

$<$ median, 16/48 (33.3 %)
$>$ median, 17/47 (36.1 %)

(p=0.77)

De Ruysscher et al. Acta Oncol 2013
Great future ...