Thoracic Radiotherapy for Extensive Disease

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Small cell lung cancer

1980s: survival benefit of 5% at 3 years

Thoracic RT in LS

1990s: survival benefit of 5% at 3 years

PCI in LS

2000s: survival benefit of 14% at 1 year

Thoracic RT in ES

Does Thoracic Radiotherapy have a role in ES-SCLC as well?
ES-SCLC, KPS ≥70, 18-70 yrs

Complete evaluation

CR outside thorax

RANDOMIZE

TRT (36x1.5Gy) + daily carbo/etop

PCI

2 x PE

2 x PE

2 x PE

2 x PE

PR outside thorax

TRT (36x1.5Gy) + daily carbo/etop

PCI

Jeremic et al., JCO 1999
Overall survival

1 = DCR TRT
2 = DCR no TRT
3 = DPR/TCR TRT
4 = DPR/TPR TRT
5 = SD/PD

Jeremic et al., JCO 1999
Thoracic Radiation Therapy Improves the Overall Survival of Patients With Extensive-Stage Small Cell Lung Cancer With Distant Metastasis

Hui Zhu, PhD, MD; Zongmei Zhou, PhD, MD; Yan Wang, PhD, MD; Nan Bi, PhD, MD; Qinfu Feng, MD; Junling Li, MD; Jima Lv, MD; Dongfu Chen, MD; Yuankai Shi, PhD, MD; and Luhua Wang, MD

Table 4. Multivariate Analysis of the Prognostic Factors for Survival in Patients With M1 Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR</th>
<th>95% CI</th>
<th>Chi-Square Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (&lt;65 vs ≥65)</td>
<td>1.284</td>
<td>0.719-2.292</td>
<td>0.713</td>
<td>.398</td>
</tr>
<tr>
<td>Sex (women vs men)</td>
<td>1.103</td>
<td>0.624-1.950</td>
<td>0.114</td>
<td>.735</td>
</tr>
<tr>
<td>KPS score (&lt;80 vs ≥80)</td>
<td>1.281</td>
<td>0.718-2.288</td>
<td>0.702</td>
<td>.402</td>
</tr>
<tr>
<td>Brain metastasis (yes vs no)</td>
<td>1.307</td>
<td>0.797-2.144</td>
<td>1.124</td>
<td>.289</td>
</tr>
<tr>
<td>No. of metastatic organs (≥2 vs 1)</td>
<td>1.313</td>
<td>0.853-2.020</td>
<td>1.531</td>
<td>.216</td>
</tr>
<tr>
<td>Weight loss (≥5% vs &lt;5%)</td>
<td>1.449</td>
<td>0.854-2.459</td>
<td>1.886</td>
<td>.170</td>
</tr>
<tr>
<td>Smoking status (yes vs no)</td>
<td>1.328</td>
<td>0.891-1.979</td>
<td>1.935</td>
<td>.164</td>
</tr>
<tr>
<td>No. of ChT cycles (≥4 vs &lt;4)</td>
<td>0.532</td>
<td>0.342-0.830</td>
<td>7.758</td>
<td>.005</td>
</tr>
<tr>
<td>Treatment (ChT/TRT vs ChT alone)</td>
<td>0.658</td>
<td>0.449-0.965</td>
<td>4.594</td>
<td>.032</td>
</tr>
</tbody>
</table>

Abbreviations: ChT, chemotherapy; ChT/TRT, chemotherapy combined with thoracic radiation therapy; CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status.
Chest Radiotherapy Extensive Stage Trial
We thank the patients and clinicians in the following centers for their participation in this study:

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UMCU Utrecht (SY El Sharouni)
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VUmc Amsterdam (S Senan)

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Bristol Hematology & Oncology Center (P Wilson)
Castle Hill Hospital (R Barton)
Clatterbridge Hospital (P Jain)
Dorset Cancer Centre Poole Hospital (M Bayne)
Edinburgh Cancer Center (J Ironside)
Ipswich Hospital (J Morgan)
Kent Oncology Center (T Sevitt)
Mount Vernon Cancer Center (S Mawdsley)
Ninewells Hospital (H Lord)
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The Christie Hospital NHS Foundation Trust (C Faivre-Finn)
The James Cook Univ Hospital / S Tees NHS Found Trust (C Peedell)
The Royal Marsden NHS Foundation Trust (I Locke)

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Manchester Academic Health Science Centre Trials Coord. Unit and the UK National Cancer Research Network,
VU University medical center
ES-SCLC
No brain- /leptomeningeal mets
No pleural mets
No previous RTX brain/thorax
Any response after 4-6 cycles of platinum-based chemotherapy
WHO 0-2
Age 18+
Encompassable volume

PCI + TRT (10x 3 Gy)

Stratification:
- Residual intrathoracic disease
- Institution

PCI

Study treatment should start between 2 and 7 weeks after last chemotherapy

Slotman et al., Lancet 2015, 385, 36-42
Statistics

Study endpoints

- Primary: overall survival
- Secondary: PFS, local control, failure pattern, toxicity

Study objectives

- The study had 80% power to detect a hazard ratio for overall survival of 0.76 at 1 year (2-sided 5% sign.)
- Accounting for 5% dropout between randomization and start of treatment, 483 patients had to be randomized

Slotman et al., Lancet 2015, 385, 36-42
Trial diagram

Randomly allocated
n=498

Thoracic RT
n=249

No IC/wd n=2
TRT completed n=240

ITT n=247
PFS 231; OS 201 events

Allocation

Control
n=249

Therapy

No IC/wd n=1

Analysis

ITT n=248
PFS 239; OS 224 events

Slotman et al., Lancet 2015, 385, 36-42
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>(n=495)</th>
<th>Sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>63 yrs</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>271</td>
<td>54.7</td>
</tr>
<tr>
<td>Female</td>
<td>224</td>
<td>45.3</td>
</tr>
<tr>
<td>WHO 0</td>
<td>167</td>
<td>33.7</td>
</tr>
<tr>
<td>WHO 1</td>
<td>276</td>
<td>55.8</td>
</tr>
<tr>
<td>WHO 2</td>
<td>52</td>
<td>10.5</td>
</tr>
<tr>
<td>Complete response</td>
<td>25</td>
<td>5.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>350</td>
<td>70.7</td>
</tr>
<tr>
<td>Good response</td>
<td>120</td>
<td>24.2</td>
</tr>
<tr>
<td>Persistent intrathoracic disease</td>
<td>434</td>
<td>87.7</td>
</tr>
<tr>
<td>ES only based on intrathoracic extent</td>
<td>34</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Slotman et al., Lancet 2015, 385, 36-42
Toxicity (CTCAE v3) G3+

<table>
<thead>
<tr>
<th></th>
<th>TRT (n=247)</th>
<th>Control (n=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTC Grade</td>
<td>G3</td>
<td>G4</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea / vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Slotman et al., Lancet 2015, 385, 36-42
Overall survival

HR = 0.84 (95%CI 0.69-1.01)
p=0.066

Slotman et al., Lancet 2015, 385, 36-42
Overall survival

24 months (95% CI)
Thoracic RT 13% (9-19)
Control: 3% (2-8)
p=0.004

Slotman et al., Lancet 2015, 385, 36-42
Progression-free survival

HR = 0.73 (95% CI 0.61-0.87)
p = 0.001

Slotman et al., Lancet 2015, 385, 36-42
Benefit of TRT in SCLC

Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.

Overall survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Thoracic RT</th>
<th>No Thoracic RT</th>
<th>HR</th>
<th>Thoracic RT better</th>
<th>No Thoracic RT better</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/N</td>
<td>Events/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = male</td>
<td>115/135</td>
<td>122/136</td>
<td>1.01</td>
<td>0.72 – 1.41</td>
<td></td>
</tr>
<tr>
<td>2 = female</td>
<td>86/112</td>
<td>102/112</td>
<td>0.68</td>
<td>0.46 – 1.00</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[36, 70]</td>
<td>152/193</td>
<td>170/189</td>
<td>0.82</td>
<td>0.61 – 1.09</td>
<td></td>
</tr>
<tr>
<td>[70, 85]</td>
<td>49/54</td>
<td>54/59</td>
<td>0.96</td>
<td>0.58 – 1.60</td>
<td></td>
</tr>
<tr>
<td>Response CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = CR</td>
<td>10/13</td>
<td>12/13</td>
<td>1.38</td>
<td>0.45 – 4.22</td>
<td></td>
</tr>
<tr>
<td>2 = PR</td>
<td>148/179</td>
<td>153/170</td>
<td>0.81</td>
<td>0.60 – 1.10</td>
<td></td>
</tr>
<tr>
<td>3 = good response</td>
<td>43/55</td>
<td>59/65</td>
<td>0.76</td>
<td>0.45 – 1.28</td>
<td></td>
</tr>
<tr>
<td>WHO Perf status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ps 0</td>
<td>74/97</td>
<td>65/70</td>
<td>0.85</td>
<td>0.55 – 1.32</td>
<td></td>
</tr>
<tr>
<td>ps 1</td>
<td>101/121</td>
<td>136/155</td>
<td>0.84</td>
<td>0.60 – 1.18</td>
<td></td>
</tr>
<tr>
<td>ps 2</td>
<td>26/29</td>
<td>23/23</td>
<td>0.83</td>
<td>0.39 – 1.78</td>
<td></td>
</tr>
<tr>
<td>ED based on</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>intrathor.dis</td>
<td>11/19</td>
<td>9/15</td>
<td>0.68</td>
<td>0.20 – 2.31</td>
<td></td>
</tr>
<tr>
<td>distant mets</td>
<td>161/190</td>
<td>172/188</td>
<td>0.87</td>
<td>0.66 – 1.16</td>
<td></td>
</tr>
<tr>
<td>both</td>
<td>29/38</td>
<td>43/45</td>
<td>0.89</td>
<td>0.48 – 1.65</td>
<td></td>
</tr>
</tbody>
</table>

Subgroups at 99%, overall at 95% confidence

Slotman et al., Lancet 2015, 385, 36-42
### Overall survival

**With Residual intrathoracic disease (p<0.05)**
- Overall result: 176/215, 197/219, 0.81 (0.66 – 1.00)

**Without Residual intrathoracic disease (NS)**
- Overall result: 25/32, 27/29, 1.02 (0.59 – 1.77)

Slotman et al., Lancet 2015, 385, 1292-3
Progression-free survival

With residual intrathoracic disease (p=0.002)

Overall result 202/215 212/219 0.70 (0.57 – 0.85)

Without residual intrathoracic disease (NS)

Overall result 29/32 27/29 1.00 (0.59 – 1.70)

Slotman et al., Lancet 2015, 385, 1292-3
Overall survival (Pts with RITD)

HR = 0.81 (95% CI 0.66-1.00)  
*p<0.05*
Intrathoracic progression

<table>
<thead>
<tr>
<th></th>
<th>TRT</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>43.7%</td>
<td>79.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>As first site of relapse</td>
<td>41.7%</td>
<td>77.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>As only site of relapse</td>
<td>19.8%</td>
<td>46.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Progression occurring at different organ sites within 30 days was considered as simultaneous progression.
Thoracic radiotherapy (30Gy in 10fx)
• Improves overall survival
• Improves progression-free survival
• Improves intrathoracic control

TRT should be offered in addition to PCI to patients with a response but residual intrathoracic disease after chemotherapy
The next step in ES-SCLC
Phase II trial of PCI plus extracranial consolidative RTX

Objectives
• To determine the overall median survival and 1-year survival
• Evaluation of recurrence patterns and time-to-failure

Inclusion
• 1-4 extra-cranial metastatic lesions prior to chemo and radiographic evaluation

Phase II trial of PCI plus extracranial consolidative RTX CLOSED
Thank you for your attention