THERAPY OF SMALL-CELL LUNG CANCER

Peter Berzinec

Specialised Hospital of St Zoerardus Zobor
Teaching Base of the Slovak Medical University
Nitra, Slovakia
COMPARATIVE TRIAL OF SURGERY AND RADIOThERAPY FOR THE PRIMARY TREATMENT OF SMALL-CELLED OR OAT-CELLED CARCINOMA OF THE BRONCHUS

FIRST REPORT TO THE MEDICAL RESEARCH COUNCIL BY THE WORKING-PARTY ON THE EVALUATION OF DIFFERENT METHODS OF THERAPY IN CARCINOMA OF THE BRONCHUS

In 1958, the Medical Research Council’s steering committee for the evaluation of different methods of cancer therapy established a working-party to investigate methods of therapy in carcinoma of the bronchus, and in particular the use of radiotherapy. The working-party decided to compare, in a controlled trial, surgery and radical radiotherapy in patients with a small-celled or oat-celled carcinoma that was considered to be operable.

or oat-celled carcinoma; (b) there was no evidence of extrathoracic metastasis; (c) the condition was regarded as operable; (d) the patient was considered fit enough for a resection of the growth; and (e) the patient was considered fit enough for radical radiotherapy.

In some centres the eligibility of patients for the trial was considered jointly by the surgeon and radiotherapist, but most, because of the distances involved, the decision on eligibility was made by the surgeon, the radiotherapist having previously indicated willingness to accept the surgeon’s decision.

Before the trial began the pathologist at each of the centres was provided with standard slides with appearances regarded as typical by the reference pathologist.

ALLOCATION TO TREATMENT

When a patient was considered suitable for the trial, the Tuberculosis and Chest Diseases Research Unit was con...
First standard treatment: radiotherapy

Medical Research Council 1960 - 1964

- 144 pts with SCLC thought to be operable
  allocated at random to the RT or surgery

<table>
<thead>
<tr>
<th></th>
<th>Mean ST (days)</th>
<th>ST at 5 years (pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>284 days</td>
<td>4</td>
</tr>
<tr>
<td>Surgery</td>
<td>199 days</td>
<td>0</td>
</tr>
</tbody>
</table>

Veterans Administration Hospitals

- 2000 pts with lung cancer in studies with chemotherapy

- MST (months) in SCLC:
  - cyclophosphamide*: 4
  - placebo: 1.5

*8 mg/kg/day for 5 days at 30-day intervals

Second standard treatment: RT + chemo

Ontario Cancer Foundation (London, Ottawa, Toronto)
- 115 pts*
- RT or RT → CFA**
- MST in SCLC (days)
  - RT: 149
  - RT → CFA: 291

*SCLC limited to a region where the primary lesion and the central lymphatics could be adequately covered by an irradiation field equal to, or less than, 200 cm.

**1g/m2 i.v., every 3 weeks 4 or 8 cycles

Third standard treatment: chemo, ≥2 drugs

- 1970 - 1980
  Combinations > single drug therapy
  **complete remissions: 20%**
  CV, CMDV, CAV...

- 1980 - 1992
  LD: chemotherapy *or* chemo + RT?
Chemo + RT > chemo in LD SCLC

- 1992
  Meta-analysis of TRT for SCLC*
  Combined chemo + RT > chemo
  3-year survival:
    chemo + RT: 14.3%
    chemo: 8.9% (p = 0.001)
  RR of death:
    decreased by 16% (SD ± 5%)

*Randomised trials, enrollment 1976 - 1988

Further advances in LD SCLC

"SCLC at the millennium: radiotherapy innovations improve survival while new chemotherapy treatments remain unproven“

### Interval between chemo and RT - metaanalysis

<table>
<thead>
<tr>
<th>Interval (weeks)</th>
<th>Patients</th>
<th>Survival *&lt;sup&gt;3 years&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean range</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>0 0-2</td>
<td>426</td>
<td>18.9%</td>
</tr>
<tr>
<td>4 3-5</td>
<td>304</td>
<td>22.2%</td>
</tr>
<tr>
<td>9 6-10</td>
<td>376</td>
<td>14.1%</td>
</tr>
<tr>
<td>17 11-19</td>
<td>453</td>
<td>12.7%</td>
</tr>
<tr>
<td>20 20+</td>
<td>358</td>
<td>13%</td>
</tr>
<tr>
<td>- RT</td>
<td>493</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide

*Intergroup Trial 0096*

<table>
<thead>
<tr>
<th>RT</th>
<th>RR (%)</th>
<th>MST (months)</th>
<th>2 years S (%)</th>
<th>3 years S (%)</th>
<th>5 years S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  RT 1x/D</td>
<td>87.1</td>
<td>19</td>
<td>41</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>(45 Gy, 5 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II RT 2x/D</td>
<td>87.2</td>
<td>23</td>
<td>46</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>(45 Gy, 3 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Concurrent versus sequential TRT

Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>MST (months)</th>
<th>2 years S (%)</th>
<th>3 years S (%)</th>
<th>5 years S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent (day 2)</td>
<td>27.2</td>
<td>54.4</td>
<td>29.8</td>
<td>23.7</td>
</tr>
<tr>
<td>Sequential (day 120)</td>
<td>19.7</td>
<td>35.1</td>
<td>20.2</td>
<td>18.3</td>
</tr>
</tbody>
</table>

RT: 45 Gy over 3 weeks (1.5 Gy twice daily), Chemo: 4x EP

TRT: early versus late?

Systemic reviews and metaanalyses

• Fried DB et al.

• Pijls-Johannesma MC et al.

• Spiro SG et al.
  J Clin Oncol 2006;24(24):3823-3830

• De Ruysscher D et al.

• Pijls-Johannesma M et al.
  - better 2- and 5-year survival rates with early radiation
  - HR 0.65, 95% CI: 0.45–0.93, p=0.02

• Lu H et al.
### Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis

#### No. Events / No. Entered

<table>
<thead>
<tr>
<th>Survival</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>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 3588</td>
<td>190/211</td>
<td>194/206</td>
<td>-17.5</td>
<td>94.8</td>
<td>0.83</td>
<td>[0.68;1.02]</td>
</tr>
<tr>
<td>NCCTG 892052</td>
<td>115/132</td>
<td>123/136</td>
<td>-4.1</td>
<td>59.3</td>
<td>0.93</td>
<td>[0.72;1.20]</td>
</tr>
<tr>
<td>Total OS</td>
<td>305/343</td>
<td>317/342</td>
<td>-21.7</td>
<td>154.0</td>
<td>0.87</td>
<td>[0.74;1.02], p=0.08</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 3588</td>
<td>194/211</td>
<td>198/206</td>
<td>-17.1</td>
<td>96.8</td>
<td>0.84</td>
<td>[0.69;1.02]</td>
</tr>
<tr>
<td>NCCTG 89 20 52</td>
<td>118/132</td>
<td>124/136</td>
<td>-3.2</td>
<td>60.4</td>
<td>0.95</td>
<td>[0.74;1.22]</td>
</tr>
<tr>
<td>Total PFS</td>
<td>312/343</td>
<td>322/342</td>
<td>-20.3</td>
<td>157.2</td>
<td>0.88</td>
<td>[0.75;1.03], p=0.11</td>
</tr>
</tbody>
</table>

#### Test for heterogeneity:

- OS: $\chi^2 = 0.48$, $p = 0.49$, $I^2 = 0\%$
- PFS: $\chi^2 = 0.56$, $p = 0.45$, $I^2 = 0\%$

PCI - metanalysis

PCI for SCLC in CR

RR of death: 0.84 (95%CI: 0.73 - 0.97)

RR of brain metastasis: 0.46 (95%CI: 0.38 - 0.57)

PCI - standard or higher dose?

Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage SCLC in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial

720 randomly allocated

360 standard dose 25Gy  360 higher dose 36Gy

**Higher-dose:** No significant reduction in the incidence of brain metastases
There was a significant increase in mortality.
**PCI at 25 Gy should remain the standard of care in limited-stage SCLC**

PCI in LD-SCLC with CR and without CR

Rates of Brain Metastases As First Recurrence With and Without PCI in Deceased Patients

<table>
<thead>
<tr>
<th>Response After Chemoradiation</th>
<th>Treatment</th>
<th>Brain Recurrence</th>
<th>No Brain Recurrence</th>
<th>Fisher Exact Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (n = 177)</td>
<td>PCI (n = 128)</td>
<td>6</td>
<td>122</td>
<td>.18</td>
</tr>
<tr>
<td></td>
<td>No PCI (n = 49)</td>
<td>5</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>IR (n = 88)</td>
<td>PCI (n = 40)</td>
<td>2</td>
<td>38</td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td>No PCI (n = 48)</td>
<td>8</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Overall Rates of Brain Recurrence Before Death With and Without PCI in Deceased Patients

<table>
<thead>
<tr>
<th>Response After Chemoradiation</th>
<th>Treatment</th>
<th>Brain Recurrence</th>
<th>No Brain Recurrence</th>
<th>( \chi^2 ) Test P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (n = 177)</td>
<td>PCI (n = 128)</td>
<td>24</td>
<td>104</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>No PCI (n = 49)</td>
<td>20</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>IR (n = 88)</td>
<td>PCI (n = 40)</td>
<td>11</td>
<td>29</td>
<td>.70</td>
</tr>
<tr>
<td></td>
<td>No PCI (n = 48)</td>
<td>15</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR = complete response; IR = incomplete response; PCI = prophylactic cranial irradiation.

Patients with IR benefited from PCI: reduced rate of and a delayed time for the development of brain metastases, although without significant OS benefit.

PCI - still doubts

Commentary

Prophylactic cranial irradiation (PCI). Still a no-brainer?

- PCI - standard of practice for successfully treated LD SCLC for decades
- Changes in patient selection
- *Updated brain imaging guidelines*
- Increased understanding of the mechanisms underlying the *deleterious effects of whole brain irradiation*
- Ongoing investigations into improving radiation treatment delivery

*HAVE BEGUN TO QUESTION THE CURRENT ROLE OF PCI*

Davey P et al. Lung Cancer. 2015;89(1):4-7
ESMO Guidelines - LD SCLC

Small-cell lung cancer

Curative
- T1-4 N2,3 M0
- T1-4 N1-3 M1a,b solitary and not confirmed*
- T1,2 N0,1 M0

Palliative
- T1-4 N1-3 M1a,b multiple or confirmed
- Chemotherapy

Concomitant chemoradiotherapy

Surgery plus adjuvant chemotherapy**

Prophylactic cranial irradiation if response***

*if no confirmation of solitary metastasis is obtained, radiotherapy may be added after first response evaluation and is omitted in case of obvious metastatic involvement

** concomitant chemoradiotherapy as an alternative option

*** or stable disease in case of localised disease

ESMO Guidelines - ED SCLC

Small-cell lung cancer

Curative
- T1-4 N2,3 M0
- T1-4 N1-3 M1a,b solitary and not confirmed*
- T1,2 N0,1 M0
- Concomitant chemo-radiotherapy
- Concomitant chemo-radiotherapy*
- Surgery plus adjuvant chemotherapy**
  - Prophylactic cranial irradiation if response***

Palliative
- T1-4 N1-3 M1a,b multiple or confirmed
- Chemotherapy

*if no confirmation of solitary metastasis is obtained, radiotherapy may be added after first response evaluation and is omitted in case of obvious metastatic involvement
** concomitant chemoradiotherapy as an alternative option
*** or stable disease in case of localised disease

## Chemotherapy options - 1st line

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>Cisplatin and etoposide</td>
</tr>
<tr>
<td>CE</td>
<td>Carboplatin and etoposide</td>
</tr>
<tr>
<td>CAV</td>
<td>Cyclophosphamide, doxorubicin, and vincristine</td>
</tr>
<tr>
<td>CAE</td>
<td>Cyclophosphamide, doxorubicin, and etoposide</td>
</tr>
<tr>
<td>ICE</td>
<td>Ifosfamide, carboplatin, and etoposide</td>
</tr>
<tr>
<td>VIP</td>
<td>Ifosfamide, etoposide, and cisplatin</td>
</tr>
</tbody>
</table>
The role of etoposide/cisplatin (E/P)

Systematic review

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Trials (No)</th>
<th>Patients (No)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>+E -P : -E -P</td>
<td>17</td>
<td>3,454</td>
<td>0.72</td>
<td>0.67 – 0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+E +P: -E -P</td>
<td>9</td>
<td>1,945</td>
<td>0.57</td>
<td>0.51 – 0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+E +P: +E -P</td>
<td>9</td>
<td>1,663</td>
<td>0.74</td>
<td>0.66 – 0.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+E: -E</td>
<td>26</td>
<td>5,399</td>
<td>0.65</td>
<td>0.61 – 0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+P: -P</td>
<td>19</td>
<td>3,719</td>
<td>0.61</td>
<td>0.57 – 0.66</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The role of cisplatin

Meta-analysis

Randomized trials of a cisplatin-containing regimen versus a regimen without cisplatin

Eagan, 1981
Fukuoka, 1986
Wolf, 1987
Haveman, 1987
Evans, 1987
Chahinian, 1989
Sculier, 1990
Goodman, 1990
Smith, 1990
Fukuoka, 1991
Wampler, 1991
Kanitz, 1992
Roth, 1992
Sculier, 1993
Farriss, 1993
Veronesi, 1994
Joss, 1994
Souhami, 1997
Urban, 1999

Overall

CDDP-containing regimen better
Regimen without CDDP (control) better

Cisplatin or carboplatin?

Carboplatin- or Cisplatin-Based Chemotherapy in First-Line Treatment of Small-Cell Lung Cancer: The COCIS Meta-Analysis of Individual Patient Data

Elderly patients

- Single agent therapy (oral etoposide)
  - Specific regiments
  - Standard iv chemotherapy (± reduced doses)

Phase 3 trials comparing oral etoposide vs combined iv chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Therapy</th>
<th>RR (%)</th>
<th>OS, median (mos)</th>
<th>1-year survival (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girling</td>
<td>1996</td>
<td>339</td>
<td>E vs CAV or EV</td>
<td>45</td>
<td>4,6</td>
<td>11</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51</td>
<td>6,5</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Souhami</td>
<td>1997</td>
<td>155</td>
<td>E vs PE/CAV</td>
<td>33</td>
<td>4,8</td>
<td>9,8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46</td>
<td>5,9</td>
<td>11,3</td>
<td></td>
</tr>
</tbody>
</table>

E - etoposide, CAV - cyclophosphamide, adriamycin, vincristine, EV - etoposide, vincristine, PE - cisplatin, etoposide

„Single-agent etoposide: a lesson learned at the expense of older persons with small-cell lung cancer“.
# Alternating non-cross-resistant chemotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (No)</th>
<th>Chemo</th>
<th>MST (mos)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans (1987)</td>
<td>289</td>
<td>CAV</td>
<td>8.0</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAV/PE</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>Fukuoka (1991)</td>
<td>142</td>
<td>CAV</td>
<td>8.7</td>
<td>0.898</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAV/EP</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Roth (1992)</td>
<td>437</td>
<td>CAV</td>
<td>8.6</td>
<td>0.425</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAV/PE</td>
<td>8.1</td>
<td></td>
</tr>
</tbody>
</table>

# Chemotherapy intensification in SCLC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intensification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard chemotherapy</td>
<td><img src="#" alt="Standard chemotherapy" /></td>
</tr>
<tr>
<td>+30% in first cycles</td>
<td><img src="#" alt="plus 30%" /></td>
</tr>
<tr>
<td>Weekly therapy</td>
<td><img src="#" alt="Weekly therapy" /></td>
</tr>
<tr>
<td>Late intensification with ABMT</td>
<td><img src="#" alt="Late intensification with ABMT" /></td>
</tr>
<tr>
<td>+25% with growth factors</td>
<td><img src="#" alt="plus 25%" /></td>
</tr>
<tr>
<td>+200% with PBPC (dose dense)</td>
<td><img src="#" alt="plus 200%" /></td>
</tr>
<tr>
<td>+300% with PBPC (dose dense)</td>
<td><img src="#" alt="plus 300%" /></td>
</tr>
</tbody>
</table>
...strategy which „should be abandoned“

Overall survival among patients in the trial comparing H-ICE with Std-ICE
Peak dose, total dose, dose density – increase by 300% in H-ICE

Maintenance therapy – failed strategies

- Chemotherapy
- Targeted therapies
  - Interferons
  - Imatinib
  - Marimastat
  - Thalidomide
  - Temsirolimus
  - Vakcination
  - Vandetanib
  ...

Maintenance with sunitinib after CE

Chemotherapy With or Without Maintenance Sunitinib for Untreated Extensive-Stage Small-Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase II Study—CALGB 30504 (Alliance)

## New drugs/P versus E/P - Phase 3 trials

<table>
<thead>
<tr>
<th>New drug</th>
<th>Patients (No)</th>
<th>Studies (No)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11</td>
<td>1966</td>
<td>6</td>
<td>In favour of CPT-11 in Asia/non-caucasians only</td>
</tr>
<tr>
<td>Topotecan</td>
<td>1464</td>
<td>2</td>
<td>In favour of topotecan: 1 - improved RR and TTP</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>1476</td>
<td>4</td>
<td>In favour of paclitaxel: 1 - in LD patients only</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>419</td>
<td>1</td>
<td>Detrimental</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>241</td>
<td>1</td>
<td>Same PFS and OS</td>
</tr>
<tr>
<td>Amrubicin</td>
<td>299</td>
<td>1</td>
<td>Better PFS, RR, in China</td>
</tr>
</tbody>
</table>
PCI in ED-SCLC with response to chemotherapy

## PCI in ED SCLC - YES

### EORTC phase III trial

<table>
<thead>
<tr>
<th></th>
<th>PCI (n = 143)</th>
<th>Control (n = 143)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic BM at 1yr</td>
<td>14.6%</td>
<td>40.4%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Overall survival at 1yr</td>
<td>27.1%</td>
<td>13.3%</td>
<td>p=0.003</td>
</tr>
</tbody>
</table>

- Lack of imaging assessment to confirm the absence of BM at enrollment
- Lack of follow-up imaging assessment for BM

### PCI in ED SCLC - NO

**Japanese phase III trial**

<table>
<thead>
<tr>
<th>Pts with any response</th>
<th>PCI (n = 84)</th>
<th>Control (n = 79)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic BM at 1yr</td>
<td>32.4%</td>
<td>58.0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Median PFS (95%CI), mo</td>
<td>2.2 (2.0 - 2.6)</td>
<td>2.4 (2.1 - 2.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Median OS (95%CI), mo</td>
<td>10.1 (8.5 - 13.2)</td>
<td>15.1 (10.2 - 18.7)</td>
<td>p= 0.091</td>
</tr>
</tbody>
</table>

- MRI confirmed absence of BM at enrollment
- Follow-up by MRI every 3 months

Seto T et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 7503)
Chemo + RT in ED SCLC

“ACC HFX RT to the treatment of the most favorable subset of patients led to improved OS over that obtained with CHT alone”.

Median OS

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR thoracic</td>
<td>17</td>
</tr>
<tr>
<td>CR extrathoracic</td>
<td>11</td>
</tr>
<tr>
<td>PR extrathoracic</td>
<td>8</td>
</tr>
<tr>
<td>Supportive care</td>
<td>6</td>
</tr>
<tr>
<td>Oral VP-16</td>
<td>3</td>
</tr>
</tbody>
</table>

Chemo + RT in ED SCLC

EORTC Phase III trial

- Lack of a significant benefit in OS at 1 year
- Reduction of intrathoracic recurrence by 50%
- Significant improvement in OS at 2 years, 13% vs 3%
- Significant improvement in PFS, P ≤ 0.001

Which patients are most likely to benefit from RT after chemo?

1. No benefit in patients without residual intrathoracic disease

2. Benefit in OS for those with residual thoracic disease: 
   \[ P=0.03; \text{HR } 0.81; \text{95\% CI: } 0.66-0.98 \]

Answer: “TRT should be offered to patients with a good or partial response after chemotherapy, but not those without residual disease in the thorax”.

2. Slotman BJ. Transl Lung Cancer Res. 2015
Relapsed or resistant SCLC

Failure after the 1\textsuperscript{st} line therapy

Sensitive SCLC: relapse $> 3$ months
   (late relapse $> 6$ months)

Resistant (refractory\textsuperscript{*}) SCLC: $\leq 3$ months

\textsuperscript{*}Not responding or progressing on the 1\textsuperscript{st}-line therapy
What should be considered?

- Anatomic site of relapse
- Symptoms
- Regimens used in 1st line
  - Response
  - Treatment free interval
  - Cumulative toxicities
- Patient’s PS
Treatment options

Irradiation
Local relapse – chest (if not irradiated)
Distant metastases – symptom palliation

Chemotherapy
Reinduction (same chemo) if late relapse
2\textsuperscript{nd} line chemo (”non-cross-resistant“)
2nd line chemotherapy - topotecan vs CAV

SCLC ED Sensitive (>60 days) N = 211

Topotecan 1.5 mg/m2 IV D1-5 q21D until disease progression (if PR, CR) at least 4 cycles (if SD)

Cyclophosphamide 1000 mg/m2 IV D1
Doxorubicin 45 mg/m2 IV D1
Vincristine 2 mg IV D1 q21D (treatment duration as with topo)

<table>
<thead>
<tr>
<th>Pts (211)</th>
<th>Topotecan</th>
<th>CAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>24.3</td>
<td>18.3</td>
</tr>
<tr>
<td>OS (median), wks</td>
<td>25</td>
<td>24.7</td>
</tr>
</tbody>
</table>

## Symptom improvement

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Topotecan (%)</th>
<th>CAV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>27.9*</td>
<td>6.6</td>
</tr>
<tr>
<td>Cough</td>
<td>24.6</td>
<td>14.8</td>
</tr>
<tr>
<td>Chest pain</td>
<td>25.0</td>
<td>17.1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>26.7</td>
<td>33.3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>32.1*</td>
<td>15.8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>33.3</td>
<td>18.9</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>32.5*</td>
<td>13.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22.9*</td>
<td>9.2</td>
</tr>
<tr>
<td>Daily Activities</td>
<td>26.9*</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*p < 0.05
Supportive care (SC) vs oral topotecan + SC

Phase III trial

MST: Topo + SC: 25.9 wks 95% C.I. (18.3, 31.6)
SC Alone: 13.9 wks 95% C.I. (11.1, 18.6)
HR: 0.64 (95% CI): (0.45, 0.90) p = 0.0104

“Chemotherapy with oral topotecan is associated with prolongation of survival and quality of life benefit in patients with relapsed SCLC”.

Median Survival
oral=33, IV=35 (weeks)
Hazards ratio (95% CI): 0.95 (0.75, 1.21)

6-mos survival (95% CI)
oral=62% (54.4, 69.8)
IV=67% (59.4, 74.4)

1-yr survival (95% CI)
oral=32% (24.6, 39.4)
IV=29% (21.6, 36.3)

Post Study Chemotherapy
oral=33%, IV=35%

Oral topotecan is clinically equivalent to IV topotecan in relapsed SCLC

New drugs in clinical trials

Chemotherapy
- Amrubicin
- Belotecan
- Bendamustine
- Picoplatin

Targets/targeted therapies
- Angiogenesis inhibitors
- Bcl-2 antagonists
- Sonic hedgehog pathway
- DNA damage repair

Immunotherapy
- PD1 inhibitors
- PDL1 inhibitors
- CTLA4 inhibitors
## New drugs in clinical trials

<table>
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<th>Chemotherapy</th>
<th>Targets/targeted therapies</th>
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<tr>
<td>Amrubicin</td>
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### Immunotherapy
- PD1 inhibitors
- PDL1 inhibitors
- CTLA4 inhibitors
ESMO Guidelines in SCLC

Small-cell lung cancer

Curative

T1-4 N2,3 M0

Concomitant chemo-radiotherapy

T1-4 N1-3 M1a,b solitary and not confirmed*

Concomitant chemo-radiotherapy*

T1-2 N0,1 M0

Surgery plus adjuvant chemotherapy**

Palliative

T1-4 N1-3 M1a,b multiple or confirmed

Chemotherapy

Sequential chemo-radiotherapy

*if no confirmation of solitary metastasis is obtained, radiotherapy may be added after first response evaluation and is omitted in case of obvious metastatic involvement

** concomitant chemoradiotherapy as an alternative option

*** or stable disease in case of localised disease