Prophylactic Cranial Irradiation and Thoracic Radiotherapy in Extensive Stage Small-Cell Lung Cancer

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PCI
Prophylactic cranial irradiation
PCI meta-analysis in LS-SCLC
7 trials - 987 patients with SCLC in CR

3 year incidence brain mets: 33.3% vs 58.6%
RR 0.46; 95% CI 0.38–0.57; p < 0.001

3 year overall survival: 20.7% vs 15.3%
RR of death 0.84; 95% CI 0.73–0.97; p = 0.01
PCI in LD-SCLC
RTOG 0212
720 patients, age < 70: 25Gy/10F vs 36Gy/18F

25Gy in 10F standard of care for limited-stage SCLC PCI

No difference in acute toxicity

Lancet Oncol 2009; 10: 467-74
PCI in the elderly

PCI meta-analysis
• 25% ≥65 years
• Median age 59
• Oldest patient 80
• Reduction in risk of BM in patients ≥65 years
  RR 0.37, 95% CI 0.25–0.59
• No significant reduction in risk of death in patients ≥65 years
  RR 0.79, 95% CI 0.60-1.01

SEER data
• 1926 patients with LS-SCLC ≥70 yrs
• Median age 75 years (70-94 years)
• 7.2% received PCI
• Adjusted for age, stage, tumour size, TRT, surgery; PCI was an independent predictor of OS
  HR, 0.72; 95% CI, 0.54-0.97; p=0.032
• No OS benefit in patients >80 yrs

Auperin. NEJM 1999
Eaton et al. Cancer 2013
Toxicity of PCI in LS-SCLC

No reports of significant increase in long term neurological sequelae in RCTs comparing PCI to no PCI

  - Neuropsychological assessment at 6 and 12 months
  - Auditory mental tracking (PASAT), perceptual organisation and visual memory (CFT) and memory span and verbal learning (AVLT)
  - For each test baseline evaluation was abnormal in 24-42% of patients
  - No significant difference between PCI and no PCI arms

<table>
<thead>
<tr>
<th>Cognitive function test</th>
<th>PCI (%)</th>
<th>No PCI (%)</th>
<th>PCI (%)</th>
<th>No PCI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASAT</td>
<td>5/26 (19)</td>
<td>3/21 (14)</td>
<td>5/16 (31)</td>
<td>2/12 (17)</td>
</tr>
<tr>
<td>CFT</td>
<td>4/18 (22)</td>
<td>1/19 (5)</td>
<td>2/13 (15)</td>
<td>2/12 (17)</td>
</tr>
<tr>
<td>AVLT learning</td>
<td>7/23 (30)</td>
<td>5/17 (29)</td>
<td>9/13 (69)</td>
<td>4/10 (40)</td>
</tr>
<tr>
<td>AVLT retention</td>
<td>4/26 (15)</td>
<td>3/17 (18)</td>
<td>0/16 (0)</td>
<td>3/8 (38)</td>
</tr>
</tbody>
</table>

  - Neuropsychological assessment at 6, 12, 18, 30 and 48 months
  - Neurological tests and evaluation of higher brain function (eg minimental test)
  - Abnormal at baseline in 40% of patients
  - No significant difference between PCI and no PCI arms

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Toxicity of PCI in LD-SCLC

Significant increase in long term neurological sequelae in RCTs comparing PCI to no PCI (RTOG 0214 and 0212)

- PCI was associated with a higher risk of decline in Self-Reported Cognitive Function SRCF at 6 months (odds ratio 3.60, 95% confidence interval 2.34-6.37, P<.0001) and 12 months (odds ratio 3.44, 95% confidence interval 1.84-6.44, P<.0001).
- Decline on HVLT (Hopkins Verbal Learning Test)-Recall at 6 and 12 months was also associated with PCI (P=.002 and P=.002, respectively)

Gondi et al, IJROBP, 2013: 86(4), 656-664
PCI in ED-SCLC
(EORTC 08993-22993)

Chemotherapy (4-6 cycles)

No response

Any response

Random

< 5 weeks

4-6 weeks

No brain imaging

PCI 20-30 Gy in 5-12 fractions

No PCI

Primary endpoint: 1 year survival

n=286, all ≤ 75yrs, PS0-2 (>90% PS0-1)

PCI in ED-SCLC
(EORTC 08993-22993)

Risk of brain metastases
- HR for BM : 0.27 (95% CI, 0.16 to 0.44)
- 1 year risk of BM: 14.6% vs 40.4% (p<0.001)

Overall survival
- HR for death: 0.68 (95 % CI, 0.52-0.88)
- 1 year survival: 27.1% vs 13.3% (p=0.03)

PCI in ED-SCLC (EORTC 08993-22993)
Impact of PCI on QoL

Table 3. Global Quality-of-Life Results With Data Cut-Off at 9 Months

<table>
<thead>
<tr>
<th>Assessment Time</th>
<th>PCI Mean</th>
<th>PCI SD</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>P for Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall*</td>
<td>.1134</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>66.5</td>
<td>1.68</td>
<td>66.1</td>
<td>1.72</td>
<td>.9633</td>
</tr>
<tr>
<td>At 6 weeks</td>
<td>60.2</td>
<td>2.34</td>
<td>67.9</td>
<td>2.25</td>
<td>.0183</td>
</tr>
<tr>
<td>At 3 months</td>
<td>51.7</td>
<td>2.85</td>
<td>59.7</td>
<td>3.03</td>
<td>.0554</td>
</tr>
<tr>
<td>At 6 months</td>
<td>52.8</td>
<td>3.41</td>
<td>52.8</td>
<td>3.67</td>
<td>.9919</td>
</tr>
<tr>
<td>At 9 months</td>
<td>52.4</td>
<td>4.81</td>
<td>54.4</td>
<td>5.21</td>
<td>.7764</td>
</tr>
</tbody>
</table>

Abbreviations: PCI, prophylactic cranial irradiation; SD, standard deviation. *Multivariate test of no difference at any follow-up time point.

Significant reduction in QoL at 6 weeks
No difference in QoL at 3, 6, and 12 months

(A) global health status, (B) hair loss, (C) fatigue, (D) role functioning, (E) cognitive functioning, and (F) emotional functioning

Slotman et al, J Clin Oncol 2009
PCI in ED-SCLC
Japanese Phase III trial

1st line chemo
Platinum-based doublet

Any response
No BM by MRI assessment

No response

PCI: 25 Gy
10 fractions

Any response
No BM by MRI assessment

< 6 weeks

3-8 weeks

no PCI

Follow-up by MR imaging
every 3 months

Stratification
• Age (70≤ / <70)
• PS (0-1 / 2)
• Response (CR / PR+MR)
• Institutions

Primary endpoint
Overall Survival

Seto et al, ASCO 2014    Closed early for futility

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# Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>range</td>
<td>43-83</td>
<td>37-86</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>man</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>%</td>
<td>81%</td>
<td>89%</td>
</tr>
<tr>
<td>woman</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>%</td>
<td>19%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>%</td>
<td>95%</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Response to Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>%</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>PR+MR</td>
<td>74</td>
<td>67</td>
</tr>
<tr>
<td>%</td>
<td>88%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Seto et al, ASCO 2014
Time to Brain Metastasis

Gray’s test: $P < 0.001$ (2-sided)

Seto et al, ASCO 2014
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI</th>
<th>Arm B: no PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>No. of OS Events</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.38 (0.95-2.02); p=0.091</td>
<td></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>
</tr>
</tbody>
</table>

Stratified log-rank test: P=0.091 (2-sided)

Seto et al, ASCO 2014
# EORTC vs Japanese PCI Trials

<table>
<thead>
<tr>
<th></th>
<th>EORTC (Slotman) Published</th>
<th>Japanese (Seto) Unpublished</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Patients</td>
<td>286</td>
<td>163 (closed early for futility)</td>
</tr>
<tr>
<td>Age limit</td>
<td>75</td>
<td>No upper age limit</td>
</tr>
<tr>
<td>PCI Dose/Fr</td>
<td>20 Gy/5#; 30 Gy/10 or 12#; 25/10#</td>
<td>25 Gy/10 #</td>
</tr>
<tr>
<td>Brain imaging prior to enrolment</td>
<td>Not required</td>
<td>BM excluded by brain MRI</td>
</tr>
<tr>
<td>Follow-up brain imaging</td>
<td>Not required</td>
<td>MR Brain 3 monthly</td>
</tr>
<tr>
<td>Neurocognitive function data</td>
<td>Limited</td>
<td>Limited</td>
</tr>
</tbody>
</table>

**Alternative conclusion**

No survival benefit for ES-SCLC patients with absence of BM on imaging at baseline and regular imaging during FU
Guidelines

• First line treatment of metastatic disease: Patients in a reasonably good PS with any response to first-line treatment should be evaluated for PCI [II, B]

ESMO 2013

• In patients with LS or ES SCLC who achieve a complete or partial response to initial therapy, prophylactic cranial irradiation [PCI] is recommended (grade 1B).

Remark: The panel notes that a recent Japanese study failed to demonstrate survival advantage with PCI in patients with ES SCLC. On publication of the mature data from this study, the recommendation for PCI in ES SCLC might be subject to revision.

ACCP/ASCO 2015
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PCI Summary

- Reduces rate of brain metastases and improves survival
- Caution in elderly, history of epilepsy/CVA
- Acute toxicity: Increased fatigue, hair loss, appetite loss, nausea/vomiting,
- ? Risk of neuro-cognitive decline

- No survival advantage in recent Japanese study (full publication awaited)
Rationale for using hippocampus avoidance PCI

• The hippocampus is pivotal for memory function
• The hippocampus is particularly sensitive to RT

• HA-PCI techniques:
  • Helical tomotherapy, IMRT or VMAT
  • Reduction of mean dose to the hippocampus: ≤ 10 Gy/10 fractions for a PCI prescription dose of 25 Gy/10 fractions, while achieving a target (brain) coverage of ~97%
Inclusion criteria
- Patients with either limited disease (LD) or extensive disease (ED) small cell lung cancer (SCLC) candidate for PCI after a partial or complete response to chemotherapy or chemoradiation
- WHO-performance status ≤ 2 (see Appendix IV)
- Sufficient proficiency in Dutch language
- No evidence of progressive extracranial metastatic disease

Exclusion criteria
- Prior radiotherapy to the brain
- Patients receiving any systemic anticancer treatment during PCI
- Pregnancy or lactation

Primary objective
To reduce memory function loss 4 months after PCI

Randomization
- The patient had chemoradiation or chemotherapy less than 6 weeks prior the randomization
- The patient will receive PCI within 2 weeks after randomization
- No signs of progressive disease after chemotherapy
- Signed informed consent

Flow Chart
PCI with hippocampus avoidance

SCLC (LD or ED) with response on treatment
Baseline tests: N(P)O + QOL MRI research protocol
Randomize
PCI 10 x 2.5 Gy or 5 x 4 Gy 4-6 weeks after chemotherapy or chemoradiation

Hippocampal Avoidance

Standard PCI 10 x 2.5 Gy or 5 x 4 Gy 4-6 weeks after chemotherapy or chemoradiation

N(P)O QOL

MRI brain (contrast) + research protocol

4 months after PCI N(P)O QOL MRI brain (contrast) + research protocol

8 months after PCI N(P)O QOL

12 months after PCI N(P)O QOL MRI brain (contrast) + research protocol

18 and 24 months after PCI N(P)O QOL

N=100
EDSCLC
Consolidation Thoracic Radiotherapy
Consolidation Thoracic RT in ED-SCLC

Chemotherapy (4-6 cycles)

- No response
  - No brain imaging
  - Thoracic RT 30Gy/10F PCI
  - PCI

- Any response
  - Random
  - < 6 weeks
  - 2-7 weeks

Primary endpoint: 1 year survival

n=495, 8% > 75 yrs, PS0-2 (90% PS0-1)

Slotman et al. Lancet 2015
Progression less likely in thoracic RT group (HR=0.73, 95% CI 0.61-0.87, p=0.01)

Intrathoracic progression (+/- distant progression):
43.7% thoracic RT vs 79.8% control (p<0.0001)

OS at 1 year:
33% thoracic RT vs 28% control
HR 0.84, 95% CI 0.69-1.01; p=0.066
No difference in acute toxicity

<table>
<thead>
<tr>
<th></th>
<th>Thoracic radiotherapy group (n=247)</th>
<th>Control group (n=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough (grade 3)</td>
<td>0 (0.0%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Dysphagia (grade 3)</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dyspnoea (grade 3)</td>
<td>3 (1.2%)</td>
<td>4 (1.6%)</td>
</tr>
<tr>
<td>Oesophagitis (grade 3)</td>
<td>4 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Fatigue (grade 3)</td>
<td>11 (4.5%)</td>
<td>8 (3.2%)</td>
</tr>
<tr>
<td>Fatigue (grade 4)</td>
<td>0 (0.0%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Insomnia (grade 3)</td>
<td>3 (1.2%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Nausea or vomiting (grade 3)</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Headache (grade 3)</td>
<td>3 (1.2%)</td>
<td>2 (0.8%)</td>
</tr>
</tbody>
</table>

*Table 2: Grade 3 and higher toxic effects*
Summary
Consolidation Thoracic Radiotherapy in EDSCLC

- Reduces rate of intra-thoracic progression
- No benefit in 1-year survival but increases rate of 2-year survival
- Well tolerated