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

Dr Neil Bayman
Consultant Clinical Oncology
The Christie NHS Foundation Trust

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DISCLOSURE OF INTEREST

I have no actual or potential conflict of interest in relation to this program/presentation.
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

2 yr incidence brain metastases, - 29% vs 23% (p=0.18)
2 yr overall survival - 42% vs 37% (p=0.05)

No difference in acute toxicity

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

*Lancet Oncol* 2009; 10: 467-74

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PCI in CONVERT Trial

- 449/547 (89%) received PCI
- Baseline brain imaging
  - 79% CT
  - 18% MRI
- 75 (17%) patients receiving PCI developed brain mets
  - 35 [8%] in OD and 40 [9%] in BD arms

Thoracic Gross Tumour Volume associated with risk of brain metastases after PCI

- Univariate analysis HR: 1.37 [95% CI: 1.09–1.73]; p = 0.007
- Multivariate analysis HR: 1.43 [95% CI: 1.11–1.85]; p= 0.006

Levy et al, Journal Thoracic Oncol 2018
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

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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

- EORTC study Gregor. Eur J Cancer 1997
  - 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

  - 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
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 SRF 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)
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%
PCI with hippocampus avoidance

The Christie NHS Foundation Trust

SCLC (LD or ED) with response on treatment

Randomize

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

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

Baseline tests: N(P)O + QOL MRI 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

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

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

Primary objective
To reduce memory function loss 4 months after PCI

N=100
PCI in ED-SCLC
(EORTC 08993-22993)

Chemotherapy (4-6 cycles)

- No response
  - PCI: 20-30 Gy in 5-12 fractions
  - No PCI

- Any response
  - Random
    - < 5 weeks
      - No brain imaging
    - 4-6 weeks
      - No response

Primary endpoint: 1 year survival

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


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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>66.5</td>
<td>1.68</td>
<td>66.1</td>
<td>1.72</td>
<td>.1134</td>
</tr>
<tr>
<td>Baseline</td>
<td>66.5</td>
<td>1.68</td>
<td>66.1</td>
<td>1.72</td>
<td>.8633</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 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

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

Follow-up by MR imaging every 3 months

Primary endpoint
Overall Survival

PCI in ED-SCLC: 25 Gy, 10 fractions
Any response
No BM by MRI assessment

PCI: 25 Gy
10 fractions

PCI in ED-SCLC
Japanese Phase III trial

Follow-up by MR imaging every 3 months

Primary endpoint
Overall Survival

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Any response
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PCI: 25 Gy
10 fractions

Follow-up by MR imaging every 3 months

Primary endpoint
Overall Survival
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI n=113</th>
<th>Arm B: no PCI n=111</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>69</td>
<td>69</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>male</td>
<td>95</td>
<td>84%</td>
</tr>
<tr>
<td>female</td>
<td>18</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>12%</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>108</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Response to Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>17</td>
<td>15%</td>
</tr>
<tr>
<td>PR+MR</td>
<td>96</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>95</td>
<td>86%</td>
</tr>
</tbody>
</table>
Time to Brain Metastasis

Takahashi et al, Lancet Oncol 2017

Grey's test: P < 0.0001 (2-sided)
### Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Arm A: PCI n=113</th>
<th>Arm B: no PCI n=111</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of OS Events</td>
<td>106</td>
<td>99</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td><strong>1.27 (0.96-1.68)</strong>; <em>p</em>=0.094</td>
<td></td>
</tr>
<tr>
<td>Median OS (95%CI), mo</td>
<td><strong>11.6 (9.5-13.3)</strong></td>
<td><strong>13.7 (10.2-16.4)</strong></td>
</tr>
</tbody>
</table>

Stratified log-rank test: *P*=0.094 (2-sided)
### Subsequent treatments

<table>
<thead>
<tr>
<th></th>
<th>Prophylactic cranial irradiation (n=113)</th>
<th>Observation (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy for brain metastases</td>
<td>25 (46%)*</td>
<td>64 (83%)*</td>
</tr>
<tr>
<td>Second-line chemotherapy</td>
<td>99 (88%)</td>
<td>99 (89%)</td>
</tr>
<tr>
<td>Single agents</td>
<td>69 (61%)</td>
<td>67 (60%)</td>
</tr>
<tr>
<td>Platinum-based doublet</td>
<td>24 (21%)</td>
<td>28 (25%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (5%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Third-line chemotherapy</td>
<td>56 (50%)</td>
<td>68 (61%)</td>
</tr>
<tr>
<td>Single agents</td>
<td>38 (34%)</td>
<td>47 (42%)</td>
</tr>
<tr>
<td>Platinum-based doublet</td>
<td>15 (13%)</td>
<td>16 (14%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Fourth-line chemotherapy</td>
<td>29 (26%)</td>
<td>40 (36%)</td>
</tr>
<tr>
<td>Single agents</td>
<td>16 (14%)</td>
<td>27 (24%)</td>
</tr>
<tr>
<td>Platinum-based doublet</td>
<td>13 (12%)</td>
<td>12 (11%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

Data are n (%). *Denominator is number of patients with brain metastases during follow-up (prophylactic cranial irradiation, n=54; observation, n=77).

**Table 3: Post-study treatment**

Takahashi et al, Lancet Oncol 2017
Neuro-cognitive Toxicity

Mini-Mental State Examinations at baseline, 12 and 24 months

Wilcoxon test: P>0.05

Takahashi et al, Lancet Oncol 2017
# EORTC vs Japanese PCI Trials

<table>
<thead>
<tr>
<th></th>
<th>EORTC (Slotman)</th>
<th>Japanese (Takahashi)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number Patients</strong></td>
<td>286</td>
<td>224 (closed early for futility – 330 planned)</td>
</tr>
<tr>
<td><strong>Age limit</strong></td>
<td>75</td>
<td>No upper age limit</td>
</tr>
<tr>
<td><strong>PCI Dose/Fr</strong></td>
<td>20 Gy/5#; 30 Gy/10 or 12#; 25/10#</td>
<td>25 Gy/10 #</td>
</tr>
<tr>
<td><strong>Brain imaging prior to enrolment</strong></td>
<td>Not required</td>
<td>BM excluded by brain MRI</td>
</tr>
<tr>
<td><strong>Follow-up brain imaging</strong></td>
<td>Not required</td>
<td>MR Brain 3 monthly</td>
</tr>
<tr>
<td><strong>Neurocognitive function data</strong></td>
<td>Limited</td>
<td>Limited</td>
</tr>
</tbody>
</table>

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**Alternative conclusion**

No survival benefit for ES-SCLC patients with absence of BM on imaging at baseline and regular imaging during FU.
Prophylactic cranial irradiation in small-cell lung cancer

1.4.59 Offer prophylactic cranial irradiation at a dose of 25 Gy in 10 fractions to people with limited-stage disease SCLC and WHO performance status 2 or less, if their disease has not progressed on first-line treatment. [2011]

1.4.60 Consider prophylactic cranial irradiation for people with extensive-stage disease SCLC and WHO performance status 2 or less, if their disease has responded to first-line treatment. [2019]
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).

ACCP/ASCO 2015
PCI Summary

- Reduces rate of brain metastases
- LDSCLC – OS advantage
- EDSCLC - OS advantage demonstrated by EORTC trial not recognised in Japan trial where patients had MRI scan after chemotherapy to exclude BMs and surveillance MRI brain after
- Caution in elderly, history of epilepsy/CVA
- Acute toxicity: Increased fatigue, hair loss, appetite loss, nausea/vomiting,
- Neuro-cognitive decline – no evidence in ESCLC, conflicting data in LDSCLC, hippocampal sparing?
EDSCLC
Consolidation Thoracic Radiotherapy
Consolidation Thoracic RT in ED-SCLC

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

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

The Christie
<table>
<thead>
<tr>
<th>Condition</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*

No difference in acute toxicity

*Lancet 2015; 385: 36-42*
Stratification factor: Presence or absence of residual intrathoracic disease after chemotherapy

No Residual Intrathoracic Disease
- Thoracic RT: 32
- Control: 29
No difference in OS

Residual Intrathoracic Disease
- Thoracic RT: 215
- Control: 219
OS significantly longer in thoracic radiotherapy group (HR 0.81, 95% CI 0.66-1.00)

…”presence of residual intrathoracic disease after chemotherapy is a factor that should be considered in patient selection.”

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
• Benefit might be reserved for patients with residual thoracic disease after chemotherapy