Prophylactic Cranial Irradiation in Lung Cancer

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Prophylactic cranial irradiation

- PCI was introduced in the early seventies
- Retrospective studies showed it decreased the rate of brain metastases
- Then several randomized studies were carried on, in the 70-80s
  - Lung cancer in the earlier studies
  - Small cell lung cancer ++
Small Cell Lung cancer

Less frequent
Much more data on PCI

Before PCIO PCI to all patients?

- With PCI, significant reduction in the risk of brain metastasis (about 50%)
  - Incidence of BM 22% vs 6% in old trials
  - Incidence of BM 50% vs 25% in new trials (CR)

- PCI as part of standard ttt: a controversial issue
  - No prolongation of survival in individual trials
  - Possible neurotoxic effects of irradiation as reported in retrospective studies
Toxicity related to PCI

- Acute toxicity:
  - Headache
  - Nausea
  - Fatigue
  - Concentration difficulties
  - Alopecia

- Late toxicity:
  - Memory deficiency
  - Ideation deficiency
  - Neuro-cognitive deficit
  - Ataxia, Epilepsy, Dementia rare
  - Abnormalities on CT or MRI frequent: affecting white matter

PCI neurotoxicity

Possible confounding factors

- Treatment-related
  - Total dose
  - Dose per fraction (> 3 Gy)
  - Concomitant chemotherapy (MTX, Nitroso-urea)

- Patient and/or tumour related
  - Long-term tobacco use
  - Age > 60
  - Paraneoplastic syndromes, micrometastases
  - Depression
Controversy over PCI  Neurotoxicity

- Neurotoxicity reported in retrospective studies++
- Importance of baseline evaluations
  - Abnormal in 60% of pts (Gregor et al)
  - Abnormal in 40% of pts (Arriagada et al)
- No significant neurological deterioration in 2 large randomised trials among PCI patients in the available follow-up of 2 years (Arriagada et al, Gregor et al)

Controversy over PCI  Survival

- The Prophylactic Cranial Irradiation Overview Collaborative Group undertook a Meta-analysis to determine whether PCI might lead to a moderate improvement in survival:
  - 7 trials (987 patients with SCLC in CR)
    - No PCI (461 pts)
    - PCI (526 pts): Doses 8 Gy/1 fr to 40 Gy/20 fr
PCI prevents the emergence of BMets and not simply delays them!

3 yrs rate of BM 58.6% versus 33.3% in the PCI group (p<0.001)

Overall Survival
3 yrs OS: 15.3% versus 20.7% in the PCI group (p=0.01)
PCIO What about extensive disease?

- About 15% of patients included in the meta-analysis had extensive disease
- PCI improved survival even in this subgroup of patients
- A specific EORTC trial has addressed this issue

EORTC randomized study PCI in ED SCLC

Stratification: WHO and Institute

Slotman et al, NEJM 2007
Symptomatic brain metastases

Slotman et al, NEJM 2007

Overall survival

At 1 year: 27.1% vs. 13.3%
HR: 0.68 (0.52-0.88)  p=0.003
■ Unanswered questions for limited disease?
  ❖ Optimal timing
    ➢ Late?
    ➢ Early?
  ❖ Optimal dose

Objective of a new trial in LD?

■ Trend for a PCI dose effect

■ Hypothesis: To further reduce incidence of BM by increasing PCI dose with minimal and acceptable toxicity

■ Assessment of a possible neurotoxicity mandatory

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<table>
<thead>
<tr>
<th>Category</th>
<th>PCI</th>
<th>No PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Gy / 1F</td>
<td>88/6</td>
<td>78/9</td>
</tr>
<tr>
<td>30 Gy / 10F</td>
<td>100/52</td>
<td>172/53</td>
</tr>
<tr>
<td>18 Gy / 8F</td>
<td>121/10</td>
<td>128/10</td>
</tr>
<tr>
<td>18 Gy / 18-20 F</td>
<td>91/1</td>
<td>163/9</td>
</tr>
</tbody>
</table>

Interaction test, p=0.11
Trend test, p=0.02

Hazard ratio
0.76
0.52
0.27
0.34

8 Gy / 1 F: 9/26, 7/16
30 Gy / 10 F: 21/118, 32/80
18 Gy / 8 F: 105/329, 172/338
18 Gy / 18-20 F: 8/51, 31/59
Randomized trial of standard dose to a higher dose prophylactic cranial irradiation (PCI) in limited-stage small cell cancer (SCLC) complete responders (CR): Primary end-point analysis (PCI99-01, IFCT 99-01, EORTC 22003-08004, RTOG 0212)

Inclusion criteria

- Histologically proven limited-stage SCLC
- Complete response to induction therapy (established on at least a chest X-ray)
- Brain CT-scan or MRI at <1 month pre-randomisation
- Baseline QOL and neurological assessment
- Age < 70*, WHO performance status < 2
- PCI starting as soon as possible after CR
- Informed consent

* except in the US, no age limit
Trial profile

Standard dose: 25 Gy
10 fractions/12 days
N=360 patients

Higher dose: 36 Gy
N=360 patients

centers optional choice*

Conventional RT
18 fractions/24 days (78%)

Accelerated hyperfract. RT
24 twice-daily fractions/16 days (22%)

* except in the US, where it is randomized

Stratification factors:
- centre
- delay between start of induction treatment and rand. (≤90, 91-180, >180 days)
- age (≤ 60 yrs, > 60 yrs)

Brain metastasis incidence

143 brain metastases observed before March 1st 2007
HR of brain metastasis in 36 Gy versus 25 Gy: 0.77 (0.55-1.08), p=0.13

Le Pechoux et al, Lancet Oncol 09
Overall survival

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>25 Gy</th>
<th>36 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI toxicity</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thoracic irradiation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy toxicity</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Progression</td>
<td>184</td>
<td>216</td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>29</td>
</tr>
</tbody>
</table>

466 deaths observed before March, 1st 2007
HR of death in 36 Gy versus 25 Gy: 1.22 (1.02-1.47), p=0.03

Neuro-cognitive follow-up among pts with LD SCLC treated with 2 different PCI doses

- Few patients had severe deterioration of neuropsychological and cognitive functions over 3 years.
- No significant difference between 25 Gy and 36 Gy arms in terms of QoL and SOMA-LENT evaluation
- Over time, mild deterioration of certain items such as memory, intellectual deficit and cognitive functions
- PCI with a total dose of 25 Gy remains the standard of care in limited-stage SCLC.
Conclusion: PCI in SCLC

- PCI with a total dose of 25 Gy remains the standard of care in limited-stage SCLC.
- PCI is a standard in patients with extensive disease who respond to treatment.

Le Pechoux et al., Lancet Oncol 09

Non-Small Cell Lung cancer
PCI or no PCI?
in high risk NSCLC patients

- In SCLC: very controversial for years, small trials
- Results of Meta-analysis: 5% benefit on survival

- What about PCI in NSCLC??
- As systemic extra-cerebral control has improved, higher rate of BM
- Need for a large trial to evaluate PCI in NSCLC

After years, PCI has become a standard for SCLC complete responders

### PCI - LA-NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>PCI Dose</th>
<th>No PCI</th>
<th>PCI</th>
</tr>
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<tbody>
<tr>
<td>VALG 1981</td>
<td>20 Gy (2 Gy X 10)</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>RTOG 1991</td>
<td>30 Gy (3 Gy X 10)</td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td>SWOG 1995</td>
<td>36 Gy (2 Gy X 18)</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>CALGB 1992</td>
<td>30 Gy (2 Gy X 15)</td>
<td>12%</td>
<td>0</td>
</tr>
<tr>
<td>Stuschke 1999 *</td>
<td>30 Gy (2 Gy X 15)</td>
<td>54%</td>
<td>13%</td>
</tr>
</tbody>
</table>
New evidence in favor of PCI in NSCLC?

Prophylactic Cranial Irradiation in Operable Stage IIIA Non–Small-Cell Lung Cancer Treated With Neoadjuvant Chemoradiotherapy: Results From a German Multicenter Randomized Trial


• After mediastinoscopic staging,
• Stage IIIA operable NSCLC

30 Gy
2 Gy/Fraction
15 Daily Fractions
3 cycles CT (EP)
HFRT 45Gy and CTcc(EPX2)
Surgery AND

SCHEMA Essen Trial
Pottgen et al, JCO 07

112 patients randomized from Nov 1994 to July 2001
43 pts had PCI

112 patients randomized from Nov 1994 to July 2001
43 pts had PCI

5yr-Risk of BM (1st site)  
Arm A 34.7%  Arm B 7.8%  p 0.02
5yr-Risk of BM  
Arm A 27.2%  Arm B 9.1%  p 0.04

No difference in neurocognitive deficit
RTOG 0214: A Phase III Comparison of Prophylactic Cranial Irradiation versus Observation in Patients with Locally Advanced Non-Small Cell Lung Cancer

Elizabeth Gore, Kyounghwa Bae, Stuart Wong, James Bonner, Alexander Sun, Steven Schild, Laurie Gaspar, Jeffrey Bogart, Maria Werner-Wasik, Hak Choy

Schema of RTOG 0214

No progression after curative therapy for Stage IIIA/B NSCLC

STRATIFY

Stage
1. IIIA
2. IIIB

Histology
1. SCCa
2. Non-SCCa

Treatment
1. Surgery
2. No Surgery

RANDOMIZE

PCI 30Gy at 2Gy/Fx

OBSERVATION

340 pts analysed out of 1058 needed to show a survival improvual
Primary objective: survival
Secondary objectives: BM, DFS, QoL, Neuropsychological Function
Conclusion

- PCI in SCLC is now part of the standard treatment of patients who have had a CR to treatment
- PCI in NSCLC: insufficient evidence to support the use of PCI in the management of patients with NSCLC treated with curative intent (Conclusion of Cochrane Overview). New trials needed+++