ANY ROLE OF PROPHYLACTIC CRANIAL IRRADIATION IN NSCLC

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elcc2016.org
DISCLOSURE SLIDE

No disclosures to declare
Brain: Frequent site of failure in SCLC and NSCLC but BM are less frequent in NSCLC than SCLC,

- Risk of BM: 15 to 40% as 1st site of recurrence, but 10 to 54% overall
- Higher rate in
  - adenocarcinoma
  - Higher stage
  - Nodal involvement

Steeg, Nature Reviews Cancer, 2011
PCI or no PCI?
in high risk NSCLC patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Stage</th>
<th>Dose N fr</th>
<th>BM No PCI</th>
<th>BM PCI</th>
<th>p</th>
<th>OS No PCI</th>
<th>OS PCI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox 1981 VALG</td>
<td>281</td>
<td>inoperable</td>
<td>20/10</td>
<td>13%</td>
<td>6%</td>
<td>0.038</td>
<td>41.4 wks</td>
<td>35.4 wks</td>
<td>0.5</td>
</tr>
<tr>
<td>Umsawasdi 1984</td>
<td>97</td>
<td>I, II or III</td>
<td>30/10</td>
<td>27%</td>
<td>4%</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Russel 1991 RTOG</td>
<td>187</td>
<td>II/III</td>
<td>30/10</td>
<td>19%</td>
<td>9%</td>
<td>0.1</td>
<td>2-yr SR 21%</td>
<td>2-yr SR 13%</td>
<td>0.36</td>
</tr>
<tr>
<td>Resected Pts</td>
<td>26</td>
<td>25%</td>
<td>0%</td>
<td></td>
<td>0.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inop</td>
<td>161</td>
<td>18%</td>
<td>10%</td>
<td></td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Old trials!! No imaging ...
- As systemic extra-cerebral control has improved, higher rate of BM
- Need for trials to reconsider PCI in NSCLC
RISK FACTORS OF DEVELOPMENT OF BM

- Outside of histology (adenocarcinoma), and stage (Stage III)
- Other factors have been described
- Age: Younger age or older
- Gender
- Response to treatment:
  - Good responders after Neo adjuvant CT or Neoadjuvant CTRT
  - Persistent nodal involvement after neoadjuvant treatment
- Superior sulcus location
- Genotype (patients with ALK rearrangement, EGFR mutation at higher risk)
Role of PCI in stage III treated with 3modality

- Seventy-five patients: first 28 pts had no PCI, then following 47 pts were administered PCI (30 Gy/15 fr)
- PCI reduced the rate of BM as first site of relapse from 30% to 8% at 4 years (P=0.005) and that of overall brain relapse from 54% to 13% (P < .0001).
- Neuropsychologic testing: impairments in attention and visual memory in long-term survivors whether they received or not PCI

Stuchke et al, JCO 1999
Evidence in favour 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

Christoph Pöttgen, Wilfried Eberhardt, Andreas Grannass, Soenke Korfee, Georg Stüben, Helmut Teschler, Georgios Stamatis, Horst Wagner, Bernward Passlick, Volker Petersen, Volker Budach, Hans Wilhelm, Isabel Wanke, Herbert Hirche, Hans-Jochen Wilke, and Martin Stuschke
SCHEMA Essen Trial  Pottgen et al, JCO 07

- After mediastinoscopic staging,
- Stage IIIA operable NSCLC

Randomize

ARM A:
Control ARM
Surg + PORT 50-60 Gy

ARM B:
3 cycles CT (EP)
HFRT 45Gy and
CTcc(EPX2)
Surgery AND

PCI: 30 Gy
2 Gy/Fraction
15 Daily Fractions

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

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5yr-Risk of BM(1st site)</td>
<td>34.7%</td>
<td>7.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>5yr-Risk of BM</td>
<td>27.2%</td>
<td>9.1%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

No difference in neurocognitive deficit
Brain relapse as 1st site of failure in stage III resected patients

**Fig 1.** Actuarial probabilities of brain relapse at first site of failure by intent-to-treat analysis.

**Fig 2.** Actuarial probabilities of brain relapse at first site of failure according to the treatment actually administered. PCI, prophylactic cranial irradiation.

<table>
<thead>
<tr>
<th></th>
<th>Surg + TRT, No PCI</th>
<th>CTRT Surg + PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 yr Rate BM</td>
<td>23,7% ITA</td>
<td>22,8% 8,8%</td>
</tr>
<tr>
<td>5 yr Rate BM</td>
<td>30,7% ITA</td>
<td>34,7% 15,8%</td>
</tr>
</tbody>
</table>

Pottgen et al, JCO 2007
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** / **1058** needed to show a survival improvement

**Primary objective:** survival

**Secondary objectives:** BM, DFS, QoL, Neuropsychological Function

Gore et al, JCO 2010
RTOG 0214: PCI vs no PCI in NSCLC

5 yr update will soon be published: it shows
- decreased rate of BM
- improved DFS, but no effect on OS

Gore et al, JCO 2011
Phase III Trial evaluating PCI in Locally Advanced NSCLC: Neurocognitive and Quality-of-Life Analysis.

340 pts analysed

Sun et al, JCO 2011

**Table 3. Testing of Deterioration Status From Baseline in Mini-Mental Status Examination During Follow-Up Using Reliable Change Index**

<table>
<thead>
<tr>
<th></th>
<th>Prophylactic Cranial Irradiation</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No significant differences at 1 year in</strong></td>
<td><strong>Mini mental Status Examination MMSE (P &lt;0 .60)</strong> or <strong>Activities of Daily Leaving scale ADLS (P &lt;0 .88).</strong></td>
<td></td>
</tr>
</tbody>
</table>

*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.

**Table 4. Testing of Deterioration Status From Baseline in Hopkins Verbal Learning Test During Follow-up Using Reliable Change Index**

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater decline of memory (HVLT) in the PCI arm at 1 year</td>
<td>Immediate recall (P &lt;0 .03)</td>
<td>Delayed recall (P &lt; .008)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delayed recall</th>
<th>8</th>
<th>15</th>
<th>44</th>
<th>85</th>
<th>8</th>
<th>14</th>
<th>50</th>
<th>86</th>
<th>.81</th>
<th>.81</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>10</td>
<td>26</td>
<td>28</td>
<td>74</td>
<td>3</td>
<td>7</td>
<td>42</td>
<td>93</td>
<td>.01</td>
<td>.03</td>
</tr>
<tr>
<td>Recall</td>
<td>10</td>
<td>32</td>
<td>21</td>
<td>68</td>
<td>2</td>
<td>5</td>
<td>38</td>
<td>95</td>
<td>.003</td>
<td>.008</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>10</td>
<td>32</td>
<td>21</td>
<td>68</td>
<td>2</td>
<td>5</td>
<td>38</td>
<td>95</td>
<td>.003</td>
<td>.008</td>
</tr>
</tbody>
</table>
Trials evaluating PCI in resected St III NSCLC

- 156 patients (81 to PCI group and 75 to control group).
- DFS PCI group > control group
  - median DFS of 28.5 mo vs 21.2 mo [HR 0.67; P= 0.037]
- Decrease in risk of brain metastases
  - 5-year BM rate, 20.3% versus 49.9%; HR, 0.28;P < 0.001).
- No difference in Median OS
  - 31.2 months in the PCI group and 27.4 months in the control group (HR, 0.81; 95% CI 0.56-1.16; P = 0.310).

Li et al, Ann Onc 2015
Trials evaluating PCI in resected St III NSCLC

Li et al, Ann Onc 2015
Figure 2. Results of the meta-analysis on studies evaluating the effect of PCI on brain metastases: OR: 0.30 (95% CI: 0.21–0.43).

Xie et al, PLOS1 2014
### Meta-analysis Results

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[HR]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox 1981</td>
<td>0.0862</td>
<td>0.1273</td>
<td>21.7%</td>
<td>1.09 [0.85, 1.40]</td>
<td>1981</td>
</tr>
<tr>
<td>Unsawasdi 1984</td>
<td>0.01</td>
<td>0.2554</td>
<td>5.4%</td>
<td>1.01 [0.61, 1.67]</td>
<td>1984</td>
</tr>
<tr>
<td>Russell 1991</td>
<td>0.1484</td>
<td>0.1581</td>
<td>14.1%</td>
<td>1.16 [0.85, 1.58]</td>
<td>1991</td>
</tr>
<tr>
<td>Miller 1998</td>
<td>0.3185</td>
<td>0.1106</td>
<td>28.8%</td>
<td>1.38 [1.11, 1.71]</td>
<td>1998</td>
</tr>
<tr>
<td>Pöttgen 2007</td>
<td>0.3023</td>
<td>0.21</td>
<td>8.0%</td>
<td>1.35 [0.90, 2.04]</td>
<td>2007</td>
</tr>
<tr>
<td>Gore 2012</td>
<td>0.0677</td>
<td>0.1266</td>
<td>22.0%</td>
<td>1.07 [0.83, 1.37]</td>
<td>2012</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- **Weight**: 100.0%
- **HR**: 1.19 [1.06, 1.33]

**Heterogeneity**:
- $\tau^2 = 0.00$; $\chi^2 = 3.70$, df = 5 ($P = 0.59$); $I^2 = 0$

**Test for overall effect**: $Z = 2.88$ ($P = 0.004$)
SEER Data base study
17852 Stage III NSCLC pts diagnosed 1988-1997
326 pts (1.8%) had PCI
No difference in OS
No difference in subgroups of pts at higher risk

Park, Clin Lung Cancer 2015
Potential toxicity of PCI to be discussed with pts

Beneficial effects of PCI on survival and incidence of BM.

Deterioration generally mild, of cognitive functions
Rationale of hippocampus sparing to reduce possible neurotoxicity

- Hippocampus primarily involved in the consolidation of new memories and “good humour”.
- Contains neural stem cells involved in the repair of damage to the CNS
- Hippocampal involvement by metastatic disease is rare in NSCLC (5-12%)
- Hippocampus sparing may result in lower rates of memory loss to be evaluated in PCI prospective trials with close follow-up++ in terms of BM
- Phase II trial showed less NC decline/historical series
- Ongoing trials

Monje Nat Med 2002; Marsh et al, 2010; Gondi, Rad&Oncol 2010; Ghia IJROBP 2007; Gutierrez IJROBP 2007; Gondi et al 2014
## Trials in PDQ ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01282437</td>
<td>Prophylactic Cranial Irradiation (PCI) vs Observation in Stage III NSCLC (NVALT11) completed trial</td>
</tr>
<tr>
<td>NCT00745797</td>
<td>Prophylactic Cranial Irradiation (PCI) Versus no PCI in Non Small Cell Lung Cancer After a Response to Chemotherapy (PCI) Closed because of slow accrual</td>
</tr>
<tr>
<td>NCT02448992</td>
<td>Hippocampal-Sparing Prophylactic Cranial Irradiation in Pathologically Nodal Positive Non-Small-Cell Lung Cancer ?</td>
</tr>
<tr>
<td>NCT01158170</td>
<td>Prophylactic Cranial Irradiation in Erlotinib/Gefitinib-responders With Non-small Cell Lung Cancer (NSCLC) (RT1001) ?</td>
</tr>
<tr>
<td>NCT01603849</td>
<td>Prophylactic Cranial Irradiation in Patients With Lung Adenocarcinoma With High Risk of Brain Metastasis (PCI) ?</td>
</tr>
<tr>
<td>NCT00955695</td>
<td>A Randomized, Phase III Trial of Prophylactic Cranial Irradiation (PCI) in Patients With Advanced Non-small Cell Lung Cancer (NSCLC) Who Are Nonprogressive on Gefitinib or Erlotinib ?</td>
</tr>
<tr>
<td>NCT02341170</td>
<td>A Phase III Trial of Hippocampal-sparing Prophylactic Cranial Irradiation (HS-PCI) in Locally Advanced (Stage IIIA/IIIB) Adenocarcinoma of the Lung (not yet started, 438 pts planned)</td>
</tr>
</tbody>
</table>
Conclusion

- PCI reduces the incidence of BM (18% at 1 yr vs 8%)
- No effect on survival:
- Updated results are awaited from RTOG 0214
- PCI in NSCLC is not recommended
- New MA?? With new generation of randomized trials…
- Hippocampus sparing PCI may contribute to reduce neurotoxicity