Particle Therapy for Tumors of the Skull Base

Eugen B. Hug
Center for Proton Therapy
Paul Scherrer Institute
• Primary-Tumors:
  • Chordomas, Chondrosarcomas

• Primary / secondary infiltration via intracranial tumors:
  • Meningiomas

• Secondary infiltration from H&N tumors:
  • Nasopharynx Ca,
  • Paranasal Sinus Ca,
  • Adenoid-cystic Ca (ACC) Karzinom
  • Rhabdomyosarcomas - a.o.
Long Term Results of Proton Radiation Therapy for *Chordomas and Chondrosarcomas* of the Skull Base
Chordomas: Midline, soft, gelatinous, 

Chondrosarcomas: Midline or lateral, can be calcified, hard
In Proton Therapy we typically recommend more surgery: 1) in case of compression of critical OAR’s prior to PTx to improve dose coverage.
Low grade Chondrosarcoma

However:...in case of calcified tumors ("rock hard"), additional surgery might be too risky... treat with PTx as is...
Current treatment concepts at PSI

Skull Base Chordoma – Proton RT Volume Definitions

GTV = Gross Tumor Volume = residual macroscopic tumor

CTV = Clinical Target Volume = preop. Volume plus anatomic areas at risk for microscopic disease
Fractionated Proton Therapy
at  Paul Scherrer Institute

Fraction Dose: 2.0 Gy (RBE), 5 frcts. per week

CTV = 54 Gy (RBE)  
GTV = 74-76 Gy (RBE) (Chordoma)

OAR constraints: OPTIC Chiasm and Nerves: 60 Gy(RBE); Brainstem surface 64 Gy(RBE), BS-Center: 53 Gy(RBE), BS max. volume: 60 Gy(RBE) < 1.0 cc.
Tumor Control Data of fractionated Proton Therapy for Skull Base Chordomas and Chondrosarcomas
Chondrosarcoma and Chordoma

Long term tumor control: MGH data

Local recurrence-free survival (skull base)

Histology

- Chondrosarcoma
- Chordoma

<table>
<thead>
<tr>
<th></th>
<th>Chondrosarcoma</th>
<th>Chordoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>98%</td>
<td>73%</td>
</tr>
<tr>
<td>10 years</td>
<td>95%</td>
<td>54%</td>
</tr>
</tbody>
</table>

$\text{p < .0001}$

Courtesy: John Munzenrider, MGH/HCL, 1999
Chondrosarcoma:

Long term tumor control: MGH data

- 1987 to 1993, either "70.2 (LD) vs. 76 CGE (HD)"
- F/U: median 16.7 y (4.5-20 y).

Results:
- LC for CSA (LD – HD) 94 vs. 85 %  89 vs. 67 %  89 vs. 58 %
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Radiation</th>
<th>Mean dose</th>
<th>LC 3-yr</th>
<th>LC 5-yr</th>
<th>LC 10-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munzenrider, 1999</td>
<td>229</td>
<td>PT, RT</td>
<td>72</td>
<td></td>
<td></td>
<td>98</td>
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<tr>
<td>Hug, 1999</td>
<td>25</td>
<td>PT, RT</td>
<td>71</td>
<td></td>
<td></td>
<td>79</td>
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<td>Johnson, 2002</td>
<td>58</td>
<td>PT, RT</td>
<td>71</td>
<td></td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>Noel, 2004</td>
<td>26</td>
<td>PT, RT</td>
<td>67</td>
<td></td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Ares, 2009</td>
<td>22</td>
<td>PT</td>
<td>68.4</td>
<td></td>
<td></td>
<td>94</td>
</tr>
</tbody>
</table>
## Skull Base Chordomas:
Proton series

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Radiation</th>
<th>Mean dose</th>
<th>LC 3-yr</th>
<th>LC 5-yr</th>
<th>LC 10-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munzenrider, 1999</td>
<td>290</td>
<td>PT, RT</td>
<td>76</td>
<td>73</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>Terahara, 1999</td>
<td>115</td>
<td>PT, RT</td>
<td>69</td>
<td>59</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>Hug, 1999</td>
<td>33</td>
<td>PT, RT</td>
<td>71</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noel, 2005</td>
<td>100</td>
<td>PT, RT</td>
<td>67</td>
<td>53</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Igaki, 2004</td>
<td>13</td>
<td>PT, RT</td>
<td>72</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ares, 2008</td>
<td>42</td>
<td>PT</td>
<td>74</td>
<td></td>
<td></td>
<td>81</td>
</tr>
</tbody>
</table>

*Excellent Review: Amichetti et al., Neurosurg Rev., 32:403, 2009*
Prognostic Factors of Local Control after fractionated Proton Therapy for Skull Base Chordomas and Chondrosarcomas
Chordomas:

Long Term outcome – the MGH Data

Courtesy: John Munzenrider, MGH/HCL, 1999
Prognostic Factors of Local Control of fractionated Proton Therapy for Skull Base Chordomas and Chondrosarcomas

- Tumor Size
- Compression of critical OAR‘s
- Primary versus Recurrent Disease
- Age
- Gender
- Dose
Proton-RT for Skull Base Chordomas

Prognostic Factor: Tumor Size and Local Control

Improved LC for “smaller” size

• LLUMC: < 25 ml vs. > 25 ml (100% vs. 56%) \( p = \text{signif.} \)
• CPO: < 29ml vs. > 29ml \( p = \text{signif.} \)
• PSI: > 25 ml vs. > 25 ml (90% vs. 74%) \( p = \text{signif.} \)
• MGH: < 70 ml vs. > 70 ml (disease-freesurvival) \( p = \text{signif.} \)
• LBL: < 20cc vs. <35 vs. > 35 cc (80% vs. 33%) \( p = \text{signif.} \)

Loma Linda UMC Analysis

Hug, Laredo, et al.
*J Neurosurg.* 91:432-439, 1999
Proton-RT for Skull Base Chordomas

Prognostic Factor: Tumor Size and Local Control

Improved LC for “smaller” size

- LLUMC: < 25 ml vs. > 25 ml (100% vs. 56%) p=signif.
- CPO: <29ml vs. >29ml p=signif.
- PSI: > 25 ml vs. > 25 ml (1/4 vs. 4/5 failures) p=signif.
- MGH: < 70 ml vs. > 70 ml (disease-free survival) p=signif.
- LBL: < 20cc vs. >35 cc (80% vs. 33%) p=signif.

Loma Linda UMC Analysis

Hug, Laredo, et al.
J Neurosurg. 91:432-439, 1999
Prognostic Factor: Tumor Compression of Critical Structures and Local Control


- 95% GTV encompassed by 95% Isodose (p=0.01)
- Minimal dose < 56 Gy to GTV (p=0.04)
Proton-RT for Skull Base Chordomas

Prognostic Factor: Tumor Compression of Critical Structures and Local Control

PSI: 5/6 failures with brainstem compression  \( p=\text{signif.} \)

MGH: 15/26 failures with BS or OC compression  \( p=\text{signif.} \)
Prognostic Factor: Tumor Compression of Critical Structures and Local Control

PSI: 5/6 failures with brainstem compression p=signif.

MGH: 15/26 failures with BS or OC compression p=signif.
## Prognostic factor: primary versus recurrence

<table>
<thead>
<tr>
<th>Institution</th>
<th>Result</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH</td>
<td>no info</td>
<td></td>
</tr>
<tr>
<td>LLUMC</td>
<td>no difference</td>
<td></td>
</tr>
<tr>
<td>CPO</td>
<td>not significant</td>
<td></td>
</tr>
<tr>
<td>PSI</td>
<td>not significant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GSI – Carbon Ions</strong></td>
<td>primary vs. recurrence</td>
<td>P = signif.</td>
</tr>
<tr>
<td></td>
<td>92% vs. 62%</td>
<td></td>
</tr>
<tr>
<td>LBL</td>
<td>primary vs. recurrentce</td>
<td>p = signif.</td>
</tr>
<tr>
<td></td>
<td>78% vs. 33%</td>
<td></td>
</tr>
</tbody>
</table>

MGH = Massachusetts General Hospital  
LLUMC = Loma Linda University Medical Center  
CPO = Centre de Protontherapie d’Orsay  
PSI = Paul Scherrer Institute  
LBL = Lawrence Berkely Laboratory  
GSI = Gesellschaft für Schwerionenforschung
<table>
<thead>
<tr>
<th>Prognostic factor: AGE and Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proton-RT for Skull Base Chordomas</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Institution</th>
<th>Age Comparison</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH</td>
<td>&lt; 40 years vs. &gt;40 years</td>
<td>trend only</td>
</tr>
<tr>
<td></td>
<td>DFS worse &gt; 40 years</td>
<td></td>
</tr>
<tr>
<td>LLUMC</td>
<td>No info</td>
<td></td>
</tr>
<tr>
<td>CPO</td>
<td>&lt; 52 years vs. &gt; 52 years</td>
<td>P = signif.</td>
</tr>
<tr>
<td></td>
<td>94% vs. 65% (at 3 years)</td>
<td></td>
</tr>
<tr>
<td>PSI</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatric vs. adult **</th>
<th>Prognostic factor</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>some reports worse</td>
<td>conflicting data</td>
</tr>
<tr>
<td></td>
<td>some reports better</td>
<td></td>
</tr>
</tbody>
</table>
# Prognostic factor: GENDER and Local Control

<table>
<thead>
<tr>
<th>Center</th>
<th>Gender Comparison</th>
<th>Local Control Rate</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH</td>
<td>male vs. female</td>
<td>85% vs. 65% (5 yrs.)</td>
<td>p = signif.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62% vs. 42% (10 yrs.)</td>
<td></td>
</tr>
<tr>
<td>LLUMC</td>
<td></td>
<td>70% vs. 54% (5 yrs.)</td>
<td>trend</td>
</tr>
<tr>
<td>CPO</td>
<td></td>
<td>not significant</td>
<td></td>
</tr>
<tr>
<td>PSI</td>
<td></td>
<td>female worse (4/5 failures)</td>
<td>trend</td>
</tr>
<tr>
<td>E: Hug (pediatric patients)</td>
<td></td>
<td>female worse (4/5 failures)</td>
<td>trend</td>
</tr>
</tbody>
</table>

*MGH = Massachusetts General Hospital, LLUMC = Loma Linda University Medical Center, CPO = Centre de Protontherapie d‘Orsay, PSI = Paul Scherrer Institute*
Proton-Radiotherapy for Skull Base *Chordomas and (Chondrosarcomas)*

**Prognostic factors**

(****) Skull base: Chondrosarcomas versus Chordomas

(****) Tumor Size

(****) Tumor Compression of Critical Structures, i.e. OAR-Tumor-Dose-Gradient

(****) Radiation Dose

(****) Gender

(+-/-) Primary versus recurrent disease

(+-/-) Age

(+-/-) Pediatric versus Adult

*Note: In favorable subgroups: LC > 90% with protons*
Proton-Radiotherapy for Skull Base

Chordomas and (Chondrosarcomas)

**High-Grade Toxicities:**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH</td>
<td>5- (13)%</td>
</tr>
<tr>
<td>LLUMC</td>
<td>5%</td>
</tr>
<tr>
<td>CPO</td>
<td>6%</td>
</tr>
<tr>
<td>PSI</td>
<td>6%</td>
</tr>
</tbody>
</table>

Risk Variables:

*Tumor size, tumor compression of normal brain, critical structure involvement, dose to normal tissues, number of prior surgeries, general medical risk factors (diabetes, HTN, smoking,), KPS*

*Low-risk group: < 5%*

*High-risk group: > 10 % - ?? *
Toxicities:

Are there potentially “proton-specific” toxicities?

CAVEATS (of undetermined clinical significance):

a) **Passive Scattering**: Patch combinations

b) **Active Scanning**: Highly weighted Spots

c) Both: The issue of “ranging out towards a critical structure”:
   - range uncertainty
   - high LET component at end of range
   - *avoid ranging out*
Toxicities:
Are there potentially “proton-specific” toxicities?

CAVEATS:

a) Passive Scattering:

Patch combinations

Patchline in tumor

Patch-line in normal tissue:

Rule: use several combinations

For „clinical evidence“ see: Kim et al, MGH, IJROBP 39(suppl 2):272, 1997
Toxicities:

Are there potentially “proton-specific” toxicities?

CAVEATS (of undetermined clinical significance):

b) Active Scanning:

Position of highly weighted spots
Treatment with 2 vertical fields:

overlapping position of high weighted spots in the Brainstem
Treatment with 3 fields:

Reduction of high weighted dose spots in Brainstem

F0

F1

F2

Dose spots F0

Dose spots F1

Dose spots F2
Question:
Which is the „better“ plan?

- Given the unknown clinical significance of persistent irradiation of the same area with highly weighted spots
- Given the trade-off:
  > fields = > integral dose
Toxicities:

Are there “proton-specific” toxicities?

**CAVEATS:**

The issue of using a single field approach

72 Gy(RBE) for malignant falcine meningioma with postop. residual

Preoperatively. Postop.

Single vertex field
Brain Necrosis:

- Patient required on-and-off steroids for 2 years,
- complete resolution of symptoms and regression of changes on MRI at 3 years,
- local tumor control throughout

12 months after PT
**PSI:** 64 Skull Base Patients treated at (40 Chordoma, 22 Chondrosarcoma)

7 pts. Identified: 2 pts. Grade 3, 5 pts. Grade 1

(4 pts. bilateral, 3 pts. Unilateral)

Patient characteristics with G1 or G3 temporal adverse events

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Toxicity Grade</th>
<th>PT dose (Gy(RBE))</th>
<th>Overall F/U time (months)</th>
<th>LC</th>
<th>Dx of adverse event (months after PT)</th>
<th>Location temporal lobe change</th>
<th>Symptoms</th>
<th>Status MRI at last F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>74</td>
<td>22</td>
<td>yes</td>
<td>12</td>
<td>Bilateral</td>
<td>Impaired short term memory, desorientation</td>
<td>Stable with edema reduction</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>74</td>
<td>23</td>
<td>yes</td>
<td>19</td>
<td>Bilateral</td>
<td>Impaired short term memory, desorientation</td>
<td>Stable with edema reduction</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>68</td>
<td>50</td>
<td>yes</td>
<td>35</td>
<td>Bilateral</td>
<td>N/A</td>
<td>stable on MRI resolution</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>74</td>
<td>21</td>
<td>yes</td>
<td>10</td>
<td>Bilateral</td>
<td>N/A</td>
<td>no change</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>74</td>
<td>61</td>
<td>yes</td>
<td>38</td>
<td>Left</td>
<td>N/A</td>
<td>no change</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>74</td>
<td>35</td>
<td>yes</td>
<td>31</td>
<td>Left</td>
<td>N/A</td>
<td>no change</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>74</td>
<td>21</td>
<td>yes</td>
<td>18</td>
<td>Right</td>
<td>N/A</td>
<td>increase</td>
</tr>
</tbody>
</table>

#: number; PT: proton-radiotherapy; F/U: follow-up; LC: local control; Dx: diagnosis; N/A: not applicable

* B. Pehlivan, C. Ares, T. Lomax, E. Hug (submitted IJROBP)
cont. PT **Temporal Lobe Toxicity**

* B. Pehlivan, C. Ares, T. Lomax, E. Hug (submitted IJROBP)
### Table 3. Dose-volume values to 3 different neurological structures in relation with grade of CNS toxicity

**Brain parenchyma**

<table>
<thead>
<tr>
<th>Grade Toxicity</th>
<th>D3 mean ± SD (Gy(RBE))</th>
<th>D2 mean ± SD (Gy(RBE))</th>
<th>D1 mean ± SD (Gy(RBE))</th>
<th>D0.5 mean ± SD (Gy(RBE))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70 ± 5</td>
<td>71 ± 5</td>
<td>72 ± 5</td>
<td>73 ± 5</td>
</tr>
<tr>
<td>1</td>
<td>73 ± 5</td>
<td>74 ± 5</td>
<td>75 ± 4</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>3</td>
<td>75 ± 1</td>
<td>76 ± 2</td>
<td>76 ± 2</td>
<td>77 ± 2</td>
</tr>
</tbody>
</table>

**Right temporal lobe**

<table>
<thead>
<tr>
<th>Grade Toxicity</th>
<th>D3 mean ± SD (Gy(RBE))</th>
<th>D2 mean ± SD (Gy(RBE))</th>
<th>D1 mean ± SD (Gy(RBE))</th>
<th>D0.5 mean ± SD (Gy(RBE))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50 ± 23</td>
<td>52 ± 23</td>
<td>56 ± 22</td>
<td>58 ± 22</td>
</tr>
<tr>
<td>1</td>
<td>67 ± 15</td>
<td>69 ± 12</td>
<td>73 ± 9</td>
<td>75 ± 7</td>
</tr>
<tr>
<td>3</td>
<td>71 ± 4</td>
<td>73 ± 3</td>
<td>75 ± 2</td>
<td>76 ± 2</td>
</tr>
</tbody>
</table>

**Left temporal lobe**

<table>
<thead>
<tr>
<th>Grade Toxicity</th>
<th>D3 mean ± SD (Gy(RBE))</th>
<th>D2 mean ± SD (Gy(RBE))</th>
<th>D1 mean ± SD (Gy(RBE))</th>
<th>D0.5 mean ± SD (Gy(RBE))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>53 ± 21</td>
<td>56 ± 21</td>
<td>59 ± 20</td>
<td>62 ± 19</td>
</tr>
<tr>
<td>1</td>
<td>57 ± 18</td>
<td>62 ± 15</td>
<td>67 ± 12</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>3</td>
<td>68 ± 1</td>
<td>71 ± 0</td>
<td>74 ± 1</td>
<td>75 ± 1</td>
</tr>
</tbody>
</table>

* B. Pehlivan, C. Ares, T. Lomax, E. Hug (in preparation)
Q: What is a „reasonable“ temp. lobe max. Dose Constraint, i.e. balancing toxicity risk with risk of failure?

- \( D_{2cc} \leq 70 \text{ or } 72 \text{ Gy (RBE)}? \)
- „absolute“ or „relative“ Maximum Dose?

* B. Pehlivan, C. Ares, T. Lomax, E. Hug (submitted IJROBP)
9/96 patients have white matter changes within the irradiation field on follow-up MRI with clinical symptoms

RTOG grading  G2 1pt., G3 8 patients

• The cumulative TL damaged rates
  – 2y  →  7.6%  5y  →  13.2%

• Only gender - male patients have higher risk (p= 0.0155)

**MGH**: Temporal lobe necrosis for skull base tumors


• 100 chordoma patients, median follow-up 31 months (range 0-87)

• One patient with asymptomatic bilateral necrosis, diagnosed on imaging
## Constraints Temporal Lobe

<table>
<thead>
<tr>
<th>Volume Temporal lobe</th>
<th>Facility</th>
<th>MGH</th>
<th>Loma Linda</th>
<th>Orsay</th>
<th>PSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative max. dose Gy RBE (1.8-2.0)</td>
<td></td>
<td></td>
<td>2 cc ≤ 70 (&quot;soft&quot; OAR)</td>
<td>Avoid Planning Hot spots 2cc ≤72 (?)</td>
<td></td>
</tr>
<tr>
<td>Absolute max. dose Gy RBE (1.8-2.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>?</td>
</tr>
</tbody>
</table>
Tumor Control Data on Carbon Ion Therapy for Skull Base Chordomas and Chondrosarcomas
<table>
<thead>
<tr>
<th>Reference</th>
<th>Yrs of study</th>
<th>No of pts</th>
<th>Median F/U in months (range)</th>
<th>Treatment regimen</th>
<th>Techn. notes</th>
<th>% LC (Years)</th>
<th>% survival (years)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berson et al. 1988</td>
<td>1977 – 1986</td>
<td>32 (10 cervical)</td>
<td>min. 12</td>
<td>P only: TD 59.4-80 CGE; P+Ph (16 pts): TD 30-50.4 Gy with Ph (dpfx 2-2.5 Gy, 4 x a week), + boost with P 10.8-56 (median 9) CGE</td>
<td>Helium-neon</td>
<td>-</td>
<td>55</td>
<td>three visual loss, two blindness, four brain stem injury (doses &gt;55 CGE)</td>
</tr>
<tr>
<td>Castro et al. 1994</td>
<td>1977 – 1992</td>
<td>53</td>
<td>51 (4-191)</td>
<td>TD 60-80 CGE (mean 65) dpfx 2 (four fr per week); RBE helium 1.3, neon 1.6</td>
<td>Helium</td>
<td>-</td>
<td>63</td>
<td>27% gr.3-5 tox. in 85 controlled pts with BOS tumors, no specific data on Ch</td>
</tr>
<tr>
<td>Schulz-Ertner et al. 2007</td>
<td>1998 – 2005</td>
<td>96</td>
<td>31 (3-91)</td>
<td>TD 60-70 CGE (median 60) in 20 fx in 3 weeks</td>
<td>Carbon</td>
<td>80.6</td>
<td>70</td>
<td>Gr. 3 optic nerve neuropathy 4.1%, Gr.1-2 temporal lobe injury 7.2%, Gr.3 acute mucositis 2%</td>
</tr>
<tr>
<td>Tsujii et al. 2007</td>
<td>1994 – 2006</td>
<td>n/a</td>
<td>TD 48-60.80 CGE, dpfx 3.6-3.8, four times a week</td>
<td>Carbon</td>
<td>88</td>
<td>-</td>
<td>100</td>
<td>No serious toxic effects</td>
</tr>
<tr>
<td>Total</td>
<td>206</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td>82</td>
<td>64</td>
<td>93.5 79.9</td>
</tr>
</tbody>
</table>
Carbon Ion Radiotherapy for Skull Base Chordoma
J. Mizoe, H. Tsujii et al. NIRS, Chiba
Skull Base, May 2009 (vol. 19(3)).

• start: June 1995
• June 1995 - August 1996: pilot study;
• July 1997 - July 2003: Phase I/II dose escalation study;
• April 2004 - June 2007: Phase II study.
• All of the patients: 16 fractions for 4 weeks.
• Total doses:
  • 48.0 GyE pilot study;
  • 48.0, 52.8, 57.6, and 60.8 GyE phase I/II study;
  • 60.8 GyE phase II study.

LC: 34 cases
OS: 33 patients
F/U: 8-129 months, mean 53 mos.

No ≥ Grade III Toxicity

60.8 GyE/16 fractions for 4 weeks.
14 patients analyzed. F/U: „short“
EFFECTIVENESS OF CARBON ION RADIOTHERAPY IN THE TREATMENT OF SKULL-BASE CHORDOMAS
D SCHULZ-ERTNER, Univ. Heidelberg, IJROBP vol 68(2), 2007

• 1998 and July 2005
• 96 pts.
• 100% gross residual tumors.
• Median total dose 60 CGE (range, 60–70 CGE), 20 frct. within 3 weeks.
• Mean follow-up 31 months (range, 3–91 months).
• 15 pts. with local recurrences
  • LC: 80.6% (3 yrs.), 70.0% (5 yrs)
  • OS: 91.8% (3 yrs.), 88.5% (5 yrs)
• Late toxicity:
  • optic neuropathy RTOG/EORTC Grade 3 in 4.1%
  • Minor temporal lobe injury (RTOG/EORTC Grade 1–2) in 7.2%

Local control probability after carbon ion radiotherapy according to dose. Solid line target dose of 60 CGE (n 84), dotted line target dose exceeding 60 CGE (n 12) (p 0.01, log rank).
Proton Radiation Therapy for *Meningiomas* of the Skull Base
Meningioma
Patients treated at PSI:

“complex” benign meningiomas
atypical meningiomas
anaplastic / malignant meningiomas

Benign Meningeoma
Recurrent (3 surg.)
Reduced vision
atypical meningioma
13 y.o. male
atypical meningioma

Only 1 seeing eye ipsilaterally. Create a „technical OAR volume“ of the anterior seeing eye
Ten academic medical centers
119 cases of patients with atypical or malignant meningiomas treated with external beam radiotherapy (EBRT) after surgery or for recurrence.
mean age was 57.6 years.
Surgery: macroscopically complete (Simpson Grades 1-3) in 71%
atypical and malignant histology in 69% and 31%
Mean dose of EBRT was 54.6 Gy (range, 40-66 Gy).
Median follow-up was 4.1 years.

RESULTS:
Actuarial overall survival rates: 5-year 65%, 10-year 51%
Factors (univariate analysis): age >60 years (p = 0.005), Karnofsky performance status (KPS) (p = 0.01), and high mitotic rate (p = 0.047).
Factors (multivariate analysis) age >60 years and high mitotic rate.
Disease-free survival rates: 5-year 58% and 10-year 48%.
Factors: KPS (p = 0.04) and high mitotic rate (p = 0.003) (univariate analysis).
Factors: (multivariate a.): only high mitotic rate (p = 0.003).
Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy


• 31 patients treated at Massachusetts General Hospital:
  • 15 Atypical, 16 Malignant Meningioma
  • Primary Dx: 16 pts., Recurrent: 15 pts.
  • 8 total, 21 pts. subtotal resection, 2 biopsy
  • RT: 15 photons, 16 protons/photons
  • mean F/U time 59 months (range: 7-155 months)

• Actuarial local control rates at 5- and 8-years were similar for both histologies:
  • 38% and 19% for Atypical Meningioma
  • 52% and 17% for Malignant Meningioma
Improved **Local Control** at 5 years:
- Proton versus Photon RT: 80% versus 17% (p = 0.003)
- Target doses > or = 60 Gy for both, atypical (p = 0.025) and malignant meningioma (p = 0.0006).

**Actuarial 5- and 8-year survival rates** for Malignant Meningioma were significantly improved by use of proton over photon RT and radiation doses > 60 CGE.
Combined Proton and Photon Conformal Radiotherapy for Intracranial Atypical and Malignant Meningioma
Boskos et al., Centre Protontherapie d'Orsay, France

Patients and Methods
• 1999 and October 2006,
• 24 patients (12 male, 12 female): atypical 19, malignant 5
• postoperative combined photon / proton RT
• 6 patients underwent gross total resection and 18 a subtotal resection.
• Median GTV 44.7 cm3
• Mean total irradiation dose was 65.01 CGE with a mean proton dose of 34.05 CGE and a mean photon total dose 30.96 Gy (mean total dose 64 CGE atypical, 68 CGE malignant)

Results
• Median (range) follow-up 32.2 (1–72) months.
• 10 tumors recurred locally.
• 3- and 5- year LC rates for the entire group were 61.3% and 46.7%
• > LC rate with doses > 60 Gy

• 3- and 5- year overall survival rates were 80.4% and 65.3%
• Survival was significantly associated with total dose.
• One patient developed radiation necrosis 16 months after treatment.
Carbon ion radiation therapy for high-risk meningiomas.
S. Combs et al., Univ. Heidelberg

- 10 patients, part of a Phase I/II trial. 8 primary, 2 re-irradiation
- Carbon ion RT as boost, median dose 18 Gy E, photon dose median 50.4 Gy.
- Median follow-up time 77 months.
- 5 patients died, 4 of tumor progression.

- 8 pts. with primary RT:
  - LC: 86% (5 yrs.) 72% (7 yrs.)
  - Survival 75% at 5, 63% at 7 years.
- 2 pts. with re-irradiation died at 10 and 67 months,

Progression-free survival, 10 patients treated with actuarial PFS 72% at 5 years and 58% at 7 years. The 2 patients treated as re-irradiation developed tumor recurrences at 10 and 67 months after C12 RT.
Proton Radiation Therapy for

**Adenoid-cystic Carcinoma**

of the Skull Base
ACC
Adenoid-cystic Carcinoma with infiltration of the skull base

Protons:
Pommier et al.
MGH, 2006

C-ions:
Neutrons
Photons
Proton-Radiotherapy for Skull Base Tumors:

- Referral Centers for rare disease
- Accumulation of large series of patients treated homogeneously
- Add to understanding of natural history of disease
- Foster multidisciplinary approach
- Accomplishes previously unknown CURE in some patients/tumors
- Understand Prognostic Factors for others
- Develop new treatment algorithms.
Thank you