Particle Therapy
for Tumors of the Skull Base

Eugen B. Hug, MD
Medical Director,
ProCure Proton Therapy Centers, NY
Primary skull base tumors:

- Chordoma, Chondrosarcoma

Primary SB or Secondary infiltration from intracranial tumors:

- Meningioma
  - Acoustic Neuromas

Secondary infiltration from primary H&N tumors:

- Nasopharynx CA,
- Paranasal Sinus CA,
- Adenoid-cystic CA
- Rhabdomyosarcomas
Chordomas:
Midline, soft, gelatinous
Developed from remnants of embryonal Notochord.
Only located Skull base and axial skeleton including sacrococcygeal
Incidence: 300 new patient per year in the US
Proton Therapy: approx. 150-200 per year = > 60%

Chondrosarcomas:
Midline or lateral, can calcify
Can arise from any cartilage. Majority in extremities
Incidence (ACS-2013):
Approx. 1,200 new cases / year
Approx. 600 / year along paraspinal/trunc/skull base
Approx. 40-50% will receive protons

Example of a rare disease with high acceptance of protons by referring surgeons
Why do we need Particle Therapy for Skull base Chordomas and Chondrosarcomas?
Management of intracranial and extracranial chordomas with CyberKnife stereotactic radiosurgery.

Department of Neurosurgery, Stanford

- skull base and spinal chordomas
- 20 patients treated between 1994 and 2010
- Average tumor volume 16.1 cm$^3$ (2.4-45.9 cm$^3$)
- Mean marginal dose of 32.5 Gy (18-50 Gy).

- Median follow-up was 34 months (2-131 months).
- Local Control: in 11 patients (LC = 55% - crude rate)
- Overall Kaplan-Meyer survival at five years OS = 52.5%.

Note: Local failure precedes death by average 2-3 years. Thus 5-yr actuarial LC rate likely < 40%
Note: mean volume 16 cc small
Photon-based Fractionated Stereotactic Radiotherapy for Postoperative Treatment of Skull Base Chordomas

Darlene M. Bugoci, MD,* Michael R. Girvigian, MD,* Joseph C.T. Chen, MD, PhD;† Michael M. Miller, MD,* and Javad Rahimian, PhD*

(Am J Clin Oncol 2012;00:000–000)

- Kaiser Permanente, Los Angeles, CA
- FSRT between 2002 - 2009,
- 12 patients with skull base chordomas.
- **Median dose of 66.6 Gy** (range, 48.6 to 68.4 Gy), at 1.8 Gy.
- Median follow-up 42 months.
- **5-year Overall survival 76.4%**
- Progression-free survival **46.9% at 2-years and 37.5% at 5-years.**
- Author’s CONCLUSIONS: “FSRT resulted in promising overall survival results. Our technique for treating skull base chordomas can be considered a safe and less costly alternative to proton RT.”

*Note:* Conclusion misleading. There is no salvage after local failure.
Particle Therapy for Skull Base Chordomas and Chondrosarcomas:

Treatment concepts
Target Contouring
Fraction Dose: 1.8-2.0 Gy (RBE), 5 frcts. per week

CTV = 54 – 60 Gy (RBE)

Chordomas GTV = CH: 74-78 Gy (RBE) Chondrosarcomas: 68-72

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.
67 y.o. F with skull base chordoma
s/p 2 major subtotal resection
Involvement of entire clivus, brainstem compression
extracranial extension
Posterior pharynx

GTV: 74 Gy(RBE) / 1.8 Gy (RBE)
CTV: 54 Gy(RBE)

OAR constraints: Brainstem Surface 64 Gy(RBE), Brainstem Center 53 Gy(RBE), Optic Nerves and Chiasm 60 Gy(RBE)
Skull Base Target Contouring

... compartmental CTV and GTV definition, .... postoperative bed coverage
Skull Base Tumor Contouring: The Cavernous sinus

Normal CS anatomy: CONCAVE on axial and coronal cuts

Loss of concavity or difference in signal between CS’s indicates involvement!
**Skull Base Tumor Contouring: The Cavernous sinus**

Cavernous Sinus = “Space” between Dura and Bone

1) **6th CN palsy** most frequent Sx

2) No internal septations. Once involved, contour ENTIRE CS

**Cavernous sinuses connected via venous complex at posterior wall of clivus**

![Diagram of Cavernous Sinus and related structures with labels for anatomical features.](image-url)
Skull Base Tumor Contouring: The Cavernous Sinus

Example:
“Preop. Tumor Contour”

Edited Version:

1) Once CS is involved ENTIRE Sinus needs to be contoured
2) Loss of Concavity or “fullness” suggests involvement
3) Include contralateral sinus at least in CTV
Chordoma Extension into nasal cavity / infratemp. fossa

Large chordoma – High dose volume includes gross disease plus high risk / radiographically undetermined. CTV: NOT with automatic expansion, but risk-determined
Target Contouring – Skull Base Chordoma inferior and extracranial extension

Large Chordoma in 68 y.o. female.

Note: Inferior Extension
- Frequently non-contiguous extensions
- CAVEAT: extracranial extension in posterior pharyngeal tissues
  - (longus capitis musculature)

Inferior extension:

Longus capitis involvement on CT small asymmetry only
Extracranial Extension: Under-contouring can be significant source of marginal failure

Involvement of posterior pharynx / longus capitis muscle requires generous target coverage – most importantly inferior: Rule: CTV extends 1 vertebral body inferior to GTV as per MRI.
Skull Base Tumor Contouring

Rules of contouring in skull base tumors:

• If in doubt, include in GTV. Patient can’t afford that you are wrong. There is no cure after failure.
• Surgical report: “I accomplished complete tumor resection” means I accomplished complete resection of all tumor visible at time of surgery”.
• Know surgical techniques and their limitations.
• An area suspicious for tumor preop. that remains with unchanged MR signal postop. is tumor until proven otherwise and needs to be included as GTV
• Think “sarcoma” when contouring: think “compartment”
• Use CTV to generously include preop. tumor extension, compartments, and uncertain areas.
• Contour CTV individually as per risk and anatomic compartment
Particle Therapy for Skull Base Chordomas and Chondrosarcomas:

Results
Chordomas of the Skull Base and Occipito-Cervical Junction
Range of tumor sizes treated with proton therapy

- Rarely: small lesions (< 15-20 cc)
- Frequently: Large lesions (>100 cc) with significant postop. residual
  - Pre-pontine extension, bilat. middle cranial fossa (A)
  - Extracranial (B)
  - Occipito-cervical junction with large bony destruction, BS and SC compression (C)

Preop. Extensions, large residual GTV’s postoperatively
Proton Therapy at PSI for Chordomas and Chondrosarcomas of the Skull base

Ares, Lomax, Hug, Goitein et al. IJROBP 2009 Nov 15;75(4)

• N = 64 patients (Oct-98 Nov-05)
  Chordoma 42 (65%)
  Chondrosarcoma 22 (34%)

• Mean age 44.5 years
• Mean follow-up 38 months (14 - 92 months)

• Prescription dose (mean) (at 2 CGE per frct., 4 fractions per week).
  Chordoma (Ch) 73.5 CGE (range 67 - 74)
  Chondrosarcoma (ChSa) 68.4 CGE (range 63 - 74)

• GTV volume: mean 25.8 cc (1.5 -100.5 cc)
Ares et al. cont. ……

**Actuarial Local Control**

<table>
<thead>
<tr>
<th></th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chordomas</td>
<td>87 %</td>
<td>81 %</td>
</tr>
<tr>
<td>Chondrosarcomas</td>
<td>94 %</td>
<td>94 %</td>
</tr>
</tbody>
</table>

**Local control**

![Local control graph](attachment:image.png)
**Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Chordoma, N=42</th>
<th>Chondrosarcoma, N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong></td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

**Time to local failure**

<table>
<thead>
<tr>
<th></th>
<th>Chordoma</th>
<th>Chondrosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong></td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

**Time to change of white matter**

<table>
<thead>
<tr>
<th></th>
<th>Chordoma</th>
<th>Chondrosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong></td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

**Time to event**

<table>
<thead>
<tr>
<th></th>
<th>Chordoma</th>
<th>Chondrosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong></td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

**Disease Specific Survival**

<table>
<thead>
<tr>
<th></th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chordomas</td>
<td>90%</td>
<td>81%</td>
</tr>
<tr>
<td>Chondrosarcomas</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Disease Specific Survival**

[Ares et al. cont. ……](#)
Radiation induced toxicity (CTCAE v3.0)

- High grade late toxicity (all Ch) $\rightarrow$ 4 pts (6%)
  - optic pathway  
    - G 4 $\rightarrow$ 1 patient (unilat. blindness)
    - G 3 $\rightarrow$ 1 patient (unilat. visual deficit)
  - neurologic  
    - G 3 $\rightarrow$ 2 patients (sympt. brain necrosis)

> Grade 3 Actuarial Toxicity-Free Survival: 94%
### Skull Base Chondrosarcomas:

#### Particle 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>Munz. MGH 1999</td>
<td>229</td>
<td>PT, RT</td>
<td>72</td>
<td>98</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Hug, LLUMC 1999</td>
<td>25</td>
<td>PT, RT</td>
<td>71</td>
<td>79</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Johnson, LLU ‘02</td>
<td>58</td>
<td>PT, RT</td>
<td>71</td>
<td>91</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Noel, CPO 2004</td>
<td>26</td>
<td>PT, RT</td>
<td>67</td>
<td>91</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Schulz-E., GSI 2007</td>
<td>54</td>
<td>Carbon, RT</td>
<td>60*</td>
<td>96</td>
<td>88 @4y</td>
<td></td>
</tr>
<tr>
<td>Ares, PSI 2009</td>
<td>22</td>
<td>PT</td>
<td>68.4</td>
<td>94</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Uhl, Heidelberg, ‘14</td>
<td>79</td>
<td>Carbon</td>
<td>60</td>
<td>95.9</td>
<td>88</td>
<td>88</td>
</tr>
</tbody>
</table>

* Ongoing RCT at Heidelberg: protons (70Gy) versus Carbons (60 GyE)
<table>
<thead>
<tr>
<th>Author</th>
<th>Institution</th>
<th>Year</th>
<th>Pts</th>
<th>Tx</th>
<th>Mean dose</th>
<th>Local control 3 y</th>
<th>Local control 5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUNZENRIDER</td>
<td>MGH</td>
<td>1999</td>
<td>290</td>
<td>PT, RT</td>
<td>76</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td>TERAHARA</td>
<td>MGH</td>
<td>1999</td>
<td>115</td>
<td>PT, RT</td>
<td>69</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>HUG</td>
<td>LLUMC</td>
<td>1999</td>
<td>33</td>
<td>PT, RT</td>
<td>71</td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>Yasuda</td>
<td>CPO</td>
<td>2012</td>
<td>40</td>
<td>PT</td>
<td>68.9</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>ARES</td>
<td>PSI</td>
<td>2009</td>
<td>42</td>
<td>PT</td>
<td>74</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>Rombi</td>
<td>PSI Peds</td>
<td>2011</td>
<td>26</td>
<td>PT</td>
<td>75</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>Deraniyagala</td>
<td>UFPTI</td>
<td>2014</td>
<td>33</td>
<td>PT</td>
<td>78</td>
<td></td>
<td>86% 2yr</td>
</tr>
</tbody>
</table>

Protons for Re-irradiation: McDonald MW IU 2013 16 PT 75.6 85% 2 yrs (IJROBP 2013).
## Skull Base Chordomas: Carbon Ions

<table>
<thead>
<tr>
<th>Institution/Publication</th>
<th>Particle</th>
<th># Pts.</th>
<th>Follow-up</th>
<th>Local control</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSI / Heidelberg Schulz-Ernter IJROBP 2007; 68(2)</td>
<td>Carbon 60 GyE median</td>
<td>96</td>
<td>31 m. median</td>
<td>15/96 LF 5- yrs. 70% LC</td>
<td>Higher LC if doses &gt;75CGE</td>
</tr>
<tr>
<td>NIRS Mizoe Skull Base 2009</td>
<td>Carbon 48-60.8 GyE</td>
<td>36</td>
<td>4.6 yrs</td>
<td>5-yr 81%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60.8 GyE</td>
<td>27</td>
<td>3.8 yr</td>
<td>5-yr 94%</td>
<td></td>
</tr>
</tbody>
</table>
Long-term Side Effects of high-dose Proton Therapy for Skull Base Tumors:

The risks of severe (> Grade 3) side effects following high dose, precision RT depend on several 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

Rule of Thumb for Proton RT for Skull Base requiring > 70 Gy:

Low-risk group: < 5%
Mod.-risk group: 5-8%
High-risk group: > 8% - ?? *

* PT as last modality after multiple failures
## Skull base Chordomas and Chondrosarcomas: SRS and Cyberknife LC data

<table>
<thead>
<tr>
<th>Study</th>
<th>Chordomas</th>
<th></th>
<th>Chordrosarcomas</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>5-y LC</td>
<td>n</td>
<td>5-y LC</td>
</tr>
<tr>
<td>Krishan, 2005</td>
<td>25</td>
<td>32%</td>
<td>4</td>
<td>100%</td>
</tr>
<tr>
<td>Martin, 2007#</td>
<td>18</td>
<td>63%</td>
<td>10</td>
<td>80%</td>
</tr>
<tr>
<td>Hasegawa, 2007</td>
<td>30</td>
<td>72%</td>
<td>7</td>
<td>2/7 failed</td>
</tr>
<tr>
<td>Henderson, 2009</td>
<td>18</td>
<td>59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu, 2008</td>
<td>28</td>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kano, Pittsburg, 2012</td>
<td>71</td>
<td>66%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koga, U. Tokyo, 2010</td>
<td>14</td>
<td>combined Ch + ChS 43% 5-yr LC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iyer, Pittsburg, 2012</td>
<td>22</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jiang, Adler, Stanford, 2014</td>
<td>20</td>
<td>41%*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: median target volumes significantly smaller compared to particle series*
Particle Therapy for Skull Base Chordomas:

Prognostic Factors
….or…… Why do we need surgery?

From:
Preop. Optic chiasm and brainstem compression

To:
Postop. decompression with small islands of residual disease
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-free survival)  \( p=\text{signif.} \)
- LBL: < 20cc vs. <35 vs. > 35 cc (80% vs. 33%)  \( p=\text{signif.} \)
**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: < 29 ml vs. > 29 ml ($p=\text{signif}$).
- PSI: > 25 ml vs. > 25 ml (90% vs. 74%, $p=\text{signif}$).
- MGH: < 70 ml vs. > 70 ml ($p=\text{signif}$).
- LBL: < 20 cc vs. < 35 cc vs. > 35 cc (80% vs. 33%, $p=\text{signif}$).

Note:
1) 5-year LC for ‘small’ lesions: approx. 85 – 95%.
2) There is no evidence in the neurosurg. literature that local control is better following gross total resection compared to “small’ residual.

_Hug, Laredo, et al._
*J Neurosurg. 91:432-439, 1999*
Skull Base Chordomas: Importance of high-dose

Tumor Compression of Critical Structures = under-dosage of GTV

Influence of tumor compression on local control

**LLUMC: Hug, Laredo, et al.**
*J Neurosurg.* 91:432-439, 1999

**Orsay/France:**
Noel, et al.
*Acta Oncol* 2005;44(7):700-8

- 95% GTV encompassed by 95% Isodose (p=0.01)
- Minimal dose < 56 Gy to GTV (p=0.04)
Skull Base Chordomas: Importance of high-dose

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

Mass. General Hospital
15/26 failures with BS or OC compression \( p=\text{signif.} \)

\( OAR \text{ compression} = \text{underdosage of GTV portion causing compression} \)
Skull Base Chordomas: Importance of high-dose

- The majority of skull base tumors require 70-76 Gy(RBE) GTV-dose
- This exceeds OAR constraints of brainstem, optic nerves, optic chiasm and most other structures
- Underdosage of tumor causes failures (approx. 2/3 of failures)
- Goal: minimize “GTV shoulder” on DVH
- Hence: surgical decompression of OAR’s recommended
- Hence: only high OAR constraint will permit adequate tumor dose in many / most patients
What are the results comparing:

Particle Therapy vs. Stereotactic or conv. photons

5-year Local Control rates (%)

Dose Gy (RBE)

Protons
- Munzenrider 1999
- Ares 2009
- Hug 1999

C-ions
- Schulz-Ertner
- Mizoe - NIRS

Photons
- Bugoci 2012
- Romero 1993
- Zorlu 2000
- Debus 2002
What are the results comparing:
Particle Therapy vs. Stereotactic or conv. photons

Protons
- Munzenrider 1999
- Ares 2009
- Hug 1999

C-Ions
- Schulz-Ertner
- Mizoe - NIRS

Photons
- Bugoci 2012
- Romero 1993
- Zorlu 2000
- Debus 2002

Protons for small Chordomas or distant from OAR
Chondrosarcomas
Carbons for chordomas

5-year Local Control rates (%) vs. Dose Gy (RBE)
Conclusion

• Proton and Carbon Ion Therapy for skull base chordomas and chondrosarcomas consistently demonstrate lasting local tumor control with acceptable late toxicity profile

• Chondrosarcomas are highly curable with particle therapy – even in cases of unresectability / large residual disease

• Chordomas consist of subgroups with varying risk profiles:
  • Small chordomas and chordomas without OAR compression have 80-90% LC at 5 years after protons.
  • Younger Age (<45y.), female gender might indicate poorer prognosis

• The results from NIRS are impressive indicating high LC-rates even for large /very large chordomas.
Conclusion

• Development of pathologic/biologic prognostic markers emerging: EGFR, c-MET, PDGF, PDGFRα

• SRS and FSRT photon-based data appear consistently inferior – however, no comparative study has been performed.

• Comparison of protons and carbon ions for chordomas in a randomized clinical trial of great interest.

• Given the relative homogeneity of treatment approaches in skull base proton therapy, multi-institutional clinical trials should be feasible.