Proton-Radiotherapy for Tumors of the Skull Base: Indications, Advantages, Limitations

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Proton Radiation Therapy for Skull Base Chordomas and Chondrosarcomas

The Clivus
Proton Radiation Therapy for Skull Base Chordomas and Chondrosarcomas:

Available Results:

- Massachusetts General Hospital / Harvard Cyclotron Laboratory: The World’s largest, long-term experience. The largest data base
- Loma Linda Univ. Med Center
- Paul Scherrer Institute
- Centre de Protontherapie d’Orsay
Chordomas:
Midline, soft, gelatinous,

Chondrosarcomas:
Midline or lateral, can be calcified, hard
Chordomas & chondrosarcoma: Population through 9/98

- 622 patients treated through 9/98
  - Chordomas (60%)
  - Mean age 39 (1.8 - 80 years)
  - Males 323 (52%)
  - Females 299 (48%)
  - Dose 66 - 83 CGE (CGE = p+ Gy x 1.1)
  - Median follow-up 41 months

Courtesy: John Munzenrider, MGH/HCL
Proton Radiotherapy for Chondrosarcomas
SURGERY for Chondrosarcomas

• Chondrosarcoma:
  • "Adequately", completely resected lesions:
    - Local control: 94%
    - Survival: 78% (Gitellis, 1991)
  • "Inadequate" resection
    - Local recurrence: 75-92%
    - Survival: 55 – 60% (Dahlin, Evans)
• Most "adequately" resected lesions are in the extremities
• The challenge: to obtain complete resection in the skull base
Mass. General Hospital: Long term results

Local recurrence-free survival (skull base)

- **Histology**

<table>
<thead>
<tr>
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<th>Chordoma</th>
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<tbody>
<tr>
<td>5 years</td>
<td>98 %</td>
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*Courtesy: John Munzenrider, MGH/HCL*
Local Recurrence–Free Survival
Chondrosarcoma By Sex

Log-Rank p = 0.9923

Female
Male

Skull Base

0 2 4 6 8 10
Years

95.26 ± 4.69%
94.40 ± 5.60%

Percent
0 20 40 60 80 100

Courtesy: John Munzenrider, MGH/HCL
Proton and Carbon-Ion-Radiotherapy for Chondrosarcomas: Summary of Data

  - LC: 91.6% at 3 years

  - LC: 100% at 3 years

- Loma Linda / USA: *(Hug, J Neurosurg, 1999, 91(3)).* 25 pts., mean dose 70.7 CGE, mean F/U 33 mos.
  - LC: 92% (23/25)

- Heidelberg/GSI: *(Schulz-Ertner, IJROBP, 2007, 67(1)).* 54 pts., median dose 60 GCGE (7X3.0), median F/U 33 mos.
  - LC: 96.2% and 89.8% (at 3 and 4 years)
Outcome after modern microsurgical resection of Skull Base Chondrosarcomas

Patient outcome at long term follow up after aggressive microsurgical resection of cranial base chondrosarcomas
Tzortzidis, Wright, Sekhar et al. Neurosurgery, 2006, 58(6), 1090-8

M&M:

47 patients with cranial base chondrosarcoma
• over a 20 year period 72 operative procedures

• Gross total Res. (GTR) 62%
• Subtotal Res. (STR) 38%.

• Postop. RT after Subtotal Resections: Protons (16%), SRS (68%), fract. RT (16%)

• Average F/U 86 months
Outcome after modern microsurgical resection of Skull Base Chondrosarcomas

Patient outcome at long term follow up after aggressive microsurgical resection of cranial base chondrosarcomas

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RESULTS:

„At conclusion of study“:
36 pts. (76.6%) alive,
21 pts. (45%) without disease

Recurrence-Free Survival:
32% at 10 years.
42% primary versus 14% recurrent disease

COMPLICATIONS:
No operative deaths.
18% postoperative complications.
Patient outcome at long term follow up after aggressive microsurgical resection of cranial base chondrosarcomas

Tzortzidis, Wright, Sekhar et al. Neurosurgery, 2006, 58(6), 1090-8

•CONCLUSION by the authors:

•“…Approximately half of the patients survived without recurrence at long-term follow-up (>132 mo).

•Cranial base chondrosarcomas can be managed well by complete surgical resection or by a combination of surgery and radiotherapy.

•The study cannot comment about the efficacy of radiotherapy….”
Neoplasms of the Skull Base: The present state of Tx for Chondrosarcomas

- Long-term outcome data suggest possible CURE following subtotal surgical resection and high-dose radiation therapy (protons) to approx. 70 – 75 Gy.
- This represents a dramatic improvement of prognosis in a skull base tumor considered universally fatal 20 years ago.
Proton Radiotherapy for Chordomas
# Mass. General Hospital: Long term results

## Chordomas: Local Control - Skull Base (Histology)

Local recurrence-free survival (skull base)

- **Histology**

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*Courtesy: John Munzenrider, MGH/HCL*
Proton Radiotherapy of the Skull Base at the Paul Scherrer Institute:
The Center for Proton-Radiotherapy
Proton treatment delivery

**Spot Scanning Technique:** Developed at PSI and in Clinical Practice since 1996

- **Magnetic scanner**
- **Proton pencil beam**
- **‘Range shifter’ plate**

**Spot scanning speed on Gantry 1:**

12 000 Spots/min
Chordoma case using IMPT for 2nd series (2004)

1st series (0-40CGE)
3 field 'hand' plan to PTV

2nd series (40-74CGE)
4 field IMPT plan with constraints on brainstem and optic structures

Patient P04109

Full treatment

+ =

=
## Normal Tissue constraints at PSI (2007)

### Structures at risk and dose limitations

<table>
<thead>
<tr>
<th>OAR</th>
<th>Dmax</th>
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<tbody>
<tr>
<td>Brainstem surface</td>
<td>64 CGE</td>
</tr>
<tr>
<td>Brainstem center</td>
<td>53 CGE</td>
</tr>
<tr>
<td>Brainstem opposite side</td>
<td>48 CGE</td>
</tr>
<tr>
<td>Optic Chiasma</td>
<td>60 CGE</td>
</tr>
<tr>
<td>Optic Nerve(s)</td>
<td>60 CGE</td>
</tr>
<tr>
<td>Cochlea left</td>
<td>62 CGE</td>
</tr>
<tr>
<td>Cochlea right</td>
<td>62 CGE</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>no constraint</td>
</tr>
<tr>
<td>R_TMJ</td>
<td>60 CGE</td>
</tr>
<tr>
<td>L_TMJ</td>
<td>60 CGE</td>
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Clinical results for skull-base lesions at PSI.

Weber DC et al. IJROBP 2005, 63(2):401-9

- Median age 39 (14.9-76.5)
- Chordomas:
  - n = 18
  - Prescription dose 74CGE
  - Median GTV volume 16.4ml (1.8 – 48.1ml)
- Chondrosarcomas:
  - n = 11
  - Prescription dose 68CGE
  - Median GTV volume 15.2ml (2.3 - 57.3ml)
- Median follow-up 28.7 months (6.2 – 67.9 months)
Clinical results for skull-base lesions at PSI.

*Weber DC et al. IJROBP 2005, 63(2):401-9*

- 3 year local control rate
  - Chordomas: 87.5%
  - Chondrosarcoma: 100%

- 3 year progression free survival
  - 90% (whole patient cohort)

- Overall 3 year survival:
  - 93.8% (whole patient cohort)

- 3 year complication free survival:
  - 82.2% (whole patient cohort)

- Radiation induced pituitary dysfunction (grade 2)
  - 4/29 (14%)

- Brainstem/optical pathway dysfunction
  - 0%

**Summary:** Early data indicate safety and efficacy of Proton-Radiotherapy based on Spot-Scanning Technique
PRELIMINARY UPDATE of skull base results at PSI.

Ares, personal communication / not ready for publication

- 65 patients (1998-2005)
- Chordomas:
  - n = 43
  - Prescription dose 74CGE, 2 CGE / frct., 4x per week
- Chondrosarcomas:
  - n = 22
  - Prescription dose 68CGE, 2 CGE 7 frct., 4x per week
- Mean follow-up 33.2 months (5 – 90.77 months)
Local Failures: 7 patients
Chordomas: 5
Chondrosarcoma: 2 (with brainstem compression)

Local Control (not actuarial):
88% Chordomas, 91% Chondrosarcomas

Deaths: 5 patients
3 DOD, 2 unrelated

Overall survival (not actuarial):
92% (patient cohort)

Radiation induced high Grade Toxicity:
3 in 3 patients

PRELIMINARY UPDATE for skull-base results at PSI.

Ares, personal communication
Proton Radiotherapy for Chordomas:

Prognostic Factors

Local recurrence-free survival (skull base)

- **Histology**

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The MGH-Data suggest a strong correlation of local control with gender.
Female Gender as negative Prognostic Factor:

MGH data need to be confirmed by other centers
Proton-RT for Skull Base Chordomas

Prognostic Factors:
Influence of (residual) tumor size on the ability to achieve local control:

Improved LC for “smaller” size

- $< 70 \text{ ml vs. } > 70 \text{ ml (MGH)}$
- $< 20 \text{ cc vs. } 20 - 35 \text{ cc vs. } > 35 \text{ cc (LBL) (80% vs. 33%)}$
- $< 25 \text{ ml vs. } > 25 \text{ ml (LLUMC) (100% vs. 56%)}$

Loma Linda UMC Analysis

*J Neurosurg. 91:432-439, 1999*
RT for Skull Base Chordomas

Prognostic Factors:
Influence of ability to deliver dose vs. limitations of dose delivery 2nd to normal structure constraints:

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

Factors predicting Local Control:
- High minimum dose (p=0.02)
- High GTV encompassed by 90% Isodose (p=0.01)
- Small GTV excluded from 90% isodose (p=0.04)

Noel, Habrand, et al.
Neurosurg. 55:1252, 2004

Brainstem compression

Local control

p = 0.04
Importance of interdisciplinary collaboration between the Surgeons and Radiation Oncologists:

1) Accomplish tumor reduction

2) Remove tumor component compressing or close to critical structures

3) However: no need to attempt gross total resection if high-risk of permanent neurologic deficits for patient
CAVEAT for Proton Therapy

in the Skull Base or Spine (..for spot scanning?):

Multiple Surgical Implants and subsequent distortion of CT images
Chordomas and chondrosarcomas of the spinal axis

Rutz et al, To be submitted to IJROBP
Chordomas and chondrosarcomas of the spinal axis

- More advanced initial tumour at diagnosis?
- Difficulties defining CTV?
- Difficulties in dose calculation?
- Difficulties in range calculations?

Overall significance of finding presently not clear
Proton-Radiotherapy for CHORDOMAS and (CHONDROSARCOMAS) of the Skull Base and Axial Skeleton

Prognostic factors:

• (+++) Chondrosarcomas versus Chordomas
• (+++) Tumor Size
• (++) Skull Base versus Spine
• (+) Primary versus recurrent disease
• (+) Chondroid versus Non-Chondroid Pathology
• (++) Gender
• (+) Age
• (+) Pediatric versus Adult
• (+++) Ability versus Inability to deliver dose: Optimal/suboptimal Dose Distribution by involvement or abutment of critical structures
• (+++) Radiation Dose
• (+++) Protons versus Photons
The risks of severe 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**

  - Low-risk group:   < 5%
  - High-risk group:  > 10% - ?? *

* RT as last modality after multiple failures
RT for Skull Base Chordomas

**GOAL:**

Develop a risk-classification

low - intermediate - high

to correlate with recommendations for adjuvant Tx

observation - aggressive Tx - palliative Tx

Rather than stating “all skull base chordoma patients should / should not undergo adjuvant Tx” - the question should be “WHICH patient will likely benefit from adjuvant Tx”
Draft-Proposal for a Chordoma Protocol

Diagnosis of Chordoma. Case-specific Allocation of Prognostic Factors.

Arm I: Favorable Prognosis
- "standard dose" Proton-RT

Arm II: Unfavorable Prognosis
- Treatment Plan to "high dose" DVH-Analysis
  - Arm II A: Acceptable DVH = Good Candidate
    - "high dose" Proton-RT*
  - Arm II B: Unacceptable DVH = Poor Candidate
    - CONSIDER SURGERY
      - NO
      - YES
        - repeat Treatment plan

* "standard dose“ Proton-RT with / without Biologic Agent
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
Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy

• Improved Local Control at 5 years:
  • Proton versus Photon RT: 80% versus 17% (p = 0.003)
  • Target doses ≥ 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.
Proton Radiotherapy for Pediatric Neoplasms involving the Base of Skull
HIGH DOSE Proton RT for Pediatric Neoplasms

PEDIATRIC Skull Base and Paraspinal Sarcomas

• Base of Skull Chordomas (Benk, IJROBP, 1995)

• Base of Skull and Head & Neck mesenchymal tumors (Willers, Hug et al, IJROBP, 1997)

• Paraspinal Sarcomas (Hug, IJROBP, )

• Pediatric BOS Chordomas (Liebsch, NASBS-meeting, 2001)

• Pediatric BOS Tumors (Hug et al, IJROBP, 2002)

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>29</strong></td>
</tr>
<tr>
<td><strong>Malignant Histology</strong></td>
<td><strong>20</strong></td>
</tr>
<tr>
<td>Chordoma</td>
<td>10</td>
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<tr>
<td>Chondrosarcoma</td>
<td>3</td>
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<tr>
<td>Epithelioid Sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Malignant Fibrous Histiocytoma</td>
<td>1</td>
</tr>
<tr>
<td>Myxoid Sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>4</td>
</tr>
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Median dose: 70 CGE (45 – 78.6)

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</tr>
<tr>
<td><strong>Benign Histology</strong></td>
<td><strong>9</strong></td>
</tr>
<tr>
<td>Giant Cell Tumor</td>
<td>6</td>
</tr>
<tr>
<td>Angiofibroma</td>
<td>2</td>
</tr>
<tr>
<td>Chondroblastoma</td>
<td>1</td>
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Median dose: 60.4 CGE (45 – 71.8)
Example: 13 y.o. M with Malignant Fibrous Histiocytoma

20 pts. with Malignant Histology
5-yr LC: 72%
5-Yr OS: 56%

9 pts. Benign Histology
LC: 8/9, OS 100%
Applications of Proton-Therapy in the Skull Base:

- **Skull Base:**
  - Chordomas, Chondrosarcomas
  - Giant Cell Tumors
  - Soft Tissue- and Osteogenic Sarcomas
  - other mesenchymal tumors
  - Nasopharynx CA
  - Paransal Sinus Carcinomas
  - Olfactory Neuroblastoma
  - Adenoid Cystic Carcinoma
  - Pediatric Tumors

There is sufficient evidence to recommend Protons for Skull Base Tumors irrespective of Histology
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.
EXTERNAL Beam Radiation Therapy for Skull Base Tumors

Single Fraction RT
(photons)

Multiple Fraction RT
(photons)

PARTICLES

Electrons
Neutrons
Protons
Carbon Ions

RADIOSURGERY (RS)

2D-standard RT
3D-standard RT
Stereotactic RT
Intensity Modulated RT (IMRT) (IGRT etc.)
Gamma-Knife for Skull Base Tumors – the Mayo Clinic Experience

Radiosurgery for cranial base chordomas and chondrosarcomas
Krishnan, Foote et al. Neurosurgery, 2005, 56(4), 777-784

• 29 patients with cranial base chordoma (n = 25) or chondrosarcoma (n = 4)
  • SRS between September 1990 and December 2002.

  • Median tumor volume: 14.4 cm³.
  • Median tumor margin dose: 15 Gy (range, 10-20 Gy);
  • Median maximum radiation dose was 30 Gy (range, 20-40 Gy).

• 19 patients had SRS combined with fractionated RT either before or in conjunction (median dose 50 Gy)

• Median clinical and imaging follow-up periods: 4.8 and 4.5 years
Gamma-Knife for Skull Base Tumors
– the Mayo Clinic Experience

Radiosurgery for cranial base chordomas and chondrosarcomas
Krishnan, Foote et al. Neurosurgery, 2005, 56(4), 777-784

• RESULTS:

• CHORDOMAS: Tumor progression: 7 patients (28%) (in-field, n = 3; out-of-field, n = 4), Actuarial tumor control rates: 89% at 2 yrs., 32% at 5 years

• CHONDROSARCOMAS: Tumor control: All 4 patients

COMPLICATIONS: Ten patients (34%) had radiation-related complications. Cranial nerve deficits (n = 6), radiation necrosis (n = 5), and pituitary dysfunction (n = 3). NO complications if SRS alone (10 patients).
Gamma-Knife for Skull Base Tumors – the Mayo Clinic Experience

Radiosurgery for cranial base chordomas and chondrosarcomas

Krishnan, Foote et al. Neurosurgery, 2005, 56(4), 777-784

•CONCLUSION by the authors:

•“...Cranial base chordomas and chondrosarcomas remain a formidable management challenge. Radiosurgery as an adjunct to surgical resection provides in-field tumor control for some patients, but radiation-related complications are relatively high, especially when radiosurgery is combined with fractionated radiation therapy....”
Limitations of Radiosurgery:

Target Size/ Volume *(max. diameter 3-4 cm, risk of side effects increases with size)*

Location  
- **a)** proximity to critical structures, i.e. brainstem, chiasm – relative indication if abutting or compressing brainstem, no RS for tumors compressing optic chiasm or inside the brainstem
- **b)** inferior limitation of skull base coverage by frame

Need to deliver RT to microscopic target BEYOND visible target *(malignant tumors)*

Age *(pediatric patient = relative contraindication)*

These limitations largely do not apply for Protons
Proton Radiotherapy of the Skull Base at the Paul Scherrer Institute: The Center for Proton-Radiotherapy
Layout of the new Center of Proton Radiation Therapy

- Installation of a dedicated cyclotron (completed)
- Beam for Gantry 1 for year-round operation (starting fall 2007) patients treatments restarted in February
- Second generation compact gantry for scanning: Gantry 2 (start 2008)
- Horizontal beam line for OPTIS 2 (start 2008)
Treatment planning for advanced scanning

‘PSI-mulate’
Dose and optimisation module

- Optimisation options
- Generalised pencil beam structures (Initial)
- Re-calculation options
- Optimisation modes
- Dose calculation engines
- Re-calculation modes
- Generalised pencil beam structures (Optimised)
- Optimised dose distributions
- Re-calculated dose distributions
- Generalised pencil beam structures (Re-calculated)

Work of Alexander Tourovsky
Spot weight degeneracy in IMPT

- 2 field IMPT plan (1)
- 2 field IMPT plan (2)
- 1690 spots/field
- 770 spots/field

Work of Mathias Bosshardt.
Spot weight degeneracy in IMPT

‘Spot reduction optimisation’ over 7 cases

Possible advantages:

- Reduced dynamic range
- Reduced dead time
- Reduced utilisation of low energy Bragg peaks
Thank you!