Proton Radiation Therapy for Osteosarcomas, Chondrogenic Tumors and Soft Tissue Sarcomas

Eugen B. Hug
Center for Proton Radiation Therapy
Paul Scherrer Institute
Histologies

- **Osteogenic Tumors**
  - Osteogenic Sarcoma
  - (Ewing Sarcoma)

- **Chondrogenic Tumors**
  - Chordomas
  - Chondrosarcomas

- **Soft Tissue Sarcomas**
  - STS
  - (Rhabdomyosarcoma)
Is there a place for Proton/Particle Radiotherapy in the treatment of Sarcomas?

Is there still a need to improve outcome for a subgroup of Sarcoma patients?

Is it desirable to reduce side effects and improve functional outcome?
RT for **UNRESECTED Soft Tissue Sarcoma**

*(Kepka, Delaney et al., MGH, IJROBP, 2005)*

- 112 patients with STS
- RTx between 1970 - 2001
- Gross disease (unresected or unresectable)
- RT Dose: median 64 Gy (21% > 70 Gy, max. 87.5 Gy) (included 4/112 pts. with Proton-RT)
- F/U: median 139 months (max. 365 months)
- Location: 43% extremities, 26% retroperitoneal, 24% H&N, 7% trunk
- Tumor size: median 8 cm (max. 30 cm)
Prognosticators for LC – multivariate analysis:
Size
RT-Dose
AJCC Stage
### Grade 3-4 Complications: 18/112

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Radiation dose (details on techniques)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHD requiring amputation</td>
<td>76 Gy (1.2 Gy per fraction, b.i.d)</td>
</tr>
<tr>
<td>WHD coupled with massive tissues necrosis requiring amputation</td>
<td>75 Gy (1.8 Gy per fraction, b.i.d)</td>
</tr>
<tr>
<td>WHD requiring amputation</td>
<td>64 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>WHD requiring major surgery</td>
<td>66 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>WHD requiring major surgery</td>
<td>75 Gy (60 Gy with 2 Gy per fraction)</td>
</tr>
<tr>
<td>WHD requiring major surgery</td>
<td>76 Gy (2 Gy per fraction, b.i.d)</td>
</tr>
<tr>
<td>WHD requiring major surgery</td>
<td>68 Gy (1.8 Gy per fraction)</td>
</tr>
<tr>
<td>Skin necrosis and cellullites after minor injury requiring skin</td>
<td>70 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>graft</td>
<td></td>
</tr>
<tr>
<td>Skin necrosis requiring skin graft</td>
<td>68 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>Severe neuropathy</td>
<td>66 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>Severe neuropathy</td>
<td>75 Gy (1.8 Gy per fraction, b.i.d)</td>
</tr>
<tr>
<td>Severe fibrosis, limb strength leaving useless leg</td>
<td>68 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>Severe fibrosis, limb strength leaving useless leg</td>
<td>70 Gy (50 Gy at 2 Gy and 20 Gy IORT)</td>
</tr>
<tr>
<td>Bone necrosis and bone fracture</td>
<td>65 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>Ureteral stenosis requiring surgery</td>
<td>68.5 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>Ureteral stenosis requiring surgery</td>
<td>56 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>Sigmoid stenosis requiring surgery</td>
<td>68.5 Gy (2 Gy per fraction)</td>
</tr>
<tr>
<td>Radiation induced malignancy</td>
<td>66.5 Gy (1.8 Gy per fraction)</td>
</tr>
</tbody>
</table>

9/18: wound healing delay or skin necrosis

9/18 fibrosis, bone necrosis, ureteral and sigmoid stenosis, SM

8% < 68 Gy dose > 26%
Mundt, Weichselbaum et al., U Chicago, IJROBP 1995

RT for extremity sarcomas

<table>
<thead>
<tr>
<th>Dose Range (Gy)</th>
<th>Mild-Moderate</th>
<th>Severe</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 63</td>
<td>4/20 (20.0%)</td>
<td>0/20 (0%)</td>
<td>4/20 (20.0%)</td>
</tr>
<tr>
<td>≥ 63</td>
<td>10/39 (25.6%)</td>
<td>9/39 (23.1%)</td>
<td>19/39 (48.7%)</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>2/2</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>60–62.9</td>
<td>2/16 (12.5%)</td>
<td>0/16 (0%)</td>
<td>2/16 (12.5%)</td>
</tr>
<tr>
<td>63–65.9</td>
<td>4/22 (18.2%)</td>
<td>5/22 (22.7%)</td>
<td>9/22 (40.9%)</td>
</tr>
<tr>
<td>≥ 66</td>
<td>5/17 (29.4%)</td>
<td>5/17 (29.4%)</td>
<td>10/17 (58.8%)</td>
</tr>
</tbody>
</table>


S + postop RT for extremity sarcomas

23 / 213 pts. With Severe Late Complications

<table>
<thead>
<tr>
<th></th>
<th>&gt; 66 Gy</th>
<th>&lt; 66 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone fracture</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Per. Neuropathy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Wound complic.</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>
Opportunity for Protons:

- Tumor subgroups with unsatisfactory local control:
  - Tumor size
  - Anatomic site
  - Status of tumor resection
- Reduction of Adverse Events
- Improvement of functional outcome
- Local control translates into survival
CPT

Histologies

• Osteogenic Tumors
• Chondrogenic Tumors
• Soft Tissue Sarcomas

• Indications and Sites presently treated with Protons
• Published Data
Indications and Sites presently treated with Protons

- Skull Base
- Paraspinal / Neck / Trunk / Pelvis
- (Extremities)

Published Data

- Retrospective review
- Prospective data gathering
- Phase I-II studies
- (obviously) no Level I evidence (Phase III randomized trial)
There is a paucity of proton-literature specifically on Osteosarcoma and Soft Tissue Sarcomas

Essentially one has to anticipate Osteo- and STS outcomes data from extrapolating data from Chordomas and Chondrosarcomas
Histologies

• **Osteogenic Tumors**
  - Osteogenic Sarcoma
  - (Ewing Sarcoma)

• **Chondrogenic Tumors**
  - Chordomas
  - Chondrosarcomas

• **Soft Tissue Sarcomas**
  - STS
  - Rhabdomyosarcoma
MGH update: „Radiotherapy for Local Control of Osteosarcoma“

Delaney, Park et al., IJROBP 61(2), 2005

• Retrospective review of 41 patients
• RT 1980 – 2002
• Location: H&Skull Base 17 pts., extremity 8, spine 8, pelvis 7, trunk 1
• Chemo-Tx: 85%
• 23 patients (56%) combined photons/protons (H&Skull Base, Spine)
• 66% primary, 24% recurrent, 10% metastatic disease
• Dose: 10 – 80 Gy (median 66 Gy),
Local control:
68 % at 5-years

Local control:
Axial versus Extremity versus H&N location

\[ P = \text{n. s.} \]
Local control:

Total and subtotal resection: 78% versus Biopsy only: 40%

Dose-response?

LC: 54 % <55 Gy > 71% (P= n.s.)

*NO subgroup analysis protons/photons versus photons*
Initial MGH / HCL report,
1995, IJROBP 31(3)

LOCALLY CHALLENGING OSTEO- AND CHONDROGENIC TUMORS OF THE AXIAL SKELETON: RESULTS OF COMBINED PROTON AND PHOTON RADIATION THERAPY USING THREE-DIMENSIONAL TREATMENT PLANNING

EUGEN B. HUG, M.D., MARKUS M. FITZEK, M.D., NORBERT J. LIEBSCHE, M.D.
AND JOHN E. MUNZENRIDER, M.D.

• 47 patients
• 1980-1992 tx with combined photons/protons
• 3 groups: Chordomas/Chondrosarc. (20 pts.), Osteogenic Sarc. (15 pts.), GCT, Osteo-and chondroblastomas (12 pts.)
• Dose: mean 73.9 Gy (Gr.I), 69.8 Gy (Gr.II), 61.8 Gy (Gr. III) (55.3 – 82 Gy (RBE))
• F/U: mean: 3.2 years, min. 1/2 year, max. 11.3 yrs.)
### Anatomic site

<table>
<thead>
<tr>
<th>Histology</th>
<th>No.</th>
<th>Base of skull</th>
<th>C-spine</th>
<th>T-spine</th>
<th>L-spine</th>
<th>Sacrum</th>
<th>Range (CGE)</th>
<th>Mean (CGE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chordoma</td>
<td>14</td>
<td>t</td>
<td>t</td>
<td>1</td>
<td>5</td>
<td>8</td>
<td>67.1–82.0</td>
<td>74.6</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>6</td>
<td>t</td>
<td>t</td>
<td>4</td>
<td>—</td>
<td>2</td>
<td>66.1–77.9</td>
<td>72.2</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td>(15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteogenic Sarcoma</td>
<td>15</td>
<td>7</td>
<td>3</td>
<td>—</td>
<td>2</td>
<td>3</td>
<td>61.1–80.0</td>
<td>69.8</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td>(12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>54.0–70.0</td>
<td>61.8</td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>63.9, 70.2</td>
<td></td>
</tr>
<tr>
<td>Chondroblastoma</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>66.6, 70.2</td>
<td></td>
</tr>
</tbody>
</table>

### Local Failure

<table>
<thead>
<tr>
<th>Histology</th>
<th>No.</th>
<th>Total</th>
<th>Pre-/Postop</th>
<th>Postop</th>
<th>Bx only</th>
<th>RT-mode*</th>
<th>Extent of resection</th>
<th>Distant metastasis</th>
<th>Died of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chordoma</td>
<td>14</td>
<td>5</td>
<td>4/10</td>
<td>1/2</td>
<td>0/2</td>
<td></td>
<td>1/4, 4/8, 0/2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>6</td>
<td>0</td>
<td>—</td>
<td>0/4</td>
<td>0/2</td>
<td></td>
<td>0/4, 0/2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteogenic Sarcoma</td>
<td>15</td>
<td>4</td>
<td>0/4</td>
<td>2/8</td>
<td>2/3</td>
<td></td>
<td>0/3, 2/9, 2/3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>8</td>
<td>1</td>
<td>1/1</td>
<td>0/5</td>
<td>0/2</td>
<td></td>
<td>0/3, 1/2, 0/3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td>2</td>
<td>1</td>
<td>1/2</td>
<td>—</td>
<td>—</td>
<td></td>
<td>0/1, 1/1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chondroblastoma</td>
<td>2</td>
<td>0</td>
<td>—</td>
<td>0/2</td>
<td>—</td>
<td></td>
<td>—, 0/2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
15 patients with osteogenic sarcoma of the axial skeleton
LC and OS after combined photon/proton RT

60 % LC
Bone and Soft Tissue Sarcoma (Phase II: 9901)

Fixed dose: 70.4 or 73.6 GyE/16fr/6wks

Survival

Local Control

Time (months)

Probability

Carbon Ions

n=46

Courtesy of H. Tsujii
CPT

Osteosarcoma of the Pelvic Bone

before *carbon ion* RT

after *carbon ion* RT

Phase I/II Studie, Chiba, Japan
CPT

Histologies

- **Osteogenic Tumors**
  - Osteogenic Sarcoma
  - (Ewing Sarcoma)

- **Chondrogenic Tumors**
  - Chordomas
  - Chondrosarcomas

- **Soft Tissue Sarcomas**
  - STS
  - Rhabdomyosarcoma
Proton-Radiotherapy for Chordomas and Chondrosarcomas:

• Practiced since 1973
• Published data: MGH, LBL; Loma Linda, PSI, Orsay
• Skull base and paraspinal location
• approx. **2500** patients treated with protons thus far
Proton Radiation Therapy for

**Skull Base Chordomas and Chondrosarcomas:**

Published Results:

- Massachusetts General Hospital
- Loma Linda Univ. Med Center
- Paul Scherrer Institute
- Centre de Protontherapie d’Orsay
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
World wide largest experience: Mass. General Hospital (since 1974)

Chordomas: Local Control- Skull Base (Histology)

Local recurrence-free survival (skull base)

<table>
<thead>
<tr>
<th></th>
<th>Chondrosarcoma</th>
<th>Chordoma</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>98 %</td>
<td>73 %</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>10 years</td>
<td>95 %</td>
<td>54 %</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Courtesy: John Munzenrider, MGH/HCL
Long term tumor control: MGH data

Local Recurrence – Free Survival
Chondrosarcoma By Sex

Log-Rank p = 0.9923

Skull Base

Years

Percent
0 20 40 60 80 100

Female

Male

95.29 ± 4.69%
94.40 ± 5.60%

Courtesy: John Munzenrider, MGH/HCL
Chordomas: Prognostic Factors

Local Recurrence – Free Survival
Non-Chondroid Chordoma By Sex

Percent

Years

Log-Rank p = 0.0001

Female
Male

Skull Base

90.07 ± 6.80%
82.71 ± 9.52%
71.08 ± 13.78%
40.56 ± 14.12%

0 2 4 6 8 10

0 20 40 60 80 100

female

Courtesy: John Munzenrider, MGH/HCL
Proton Radiation Therapy (PRT)
for Chondrosarcomas and Chordomas of the Skull Base.
*Hug, Laredo, Slater, Devries et al. J Neurosurg. 91:432-439, 1999*

**Tumor size at PRT and Local Control**

\[ p = 0.03 \]

- \(< 25\text{ml GTV}\)
- \(\geq 25\text{ml GTV}\)
Proton Radiation Therapy (PRT) for Chondrosarcomas and Chordomas of the Skull Base.

Proton-Radiotherapy for CHORDOMAS of the Skull Base and Axial Skeleton

Prognostic factors:

+++ 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
Skull Base Chordomas and Chondrosarcomas at PSI: 5-year outcome* of spot scanning based PT

To be presented by Dr. Ares

- Mean follow-up time: > 3 years
- Local Control for Chordomas: > 75%
- Local control for Chondrosarcomas: > 90%
- High Grade Toxicity: < 7%

* Ares, Lomax, Hug, Goitein – in preparation
Chordomas of the Base of Skull

- **Photons**
  - Romero 1993
  - Zorlu 2000
  - Debus 2000

- **Protons**
  - Munzenrider 1999
  - Ares 2007
  - Hug 1999

- **C-Ions**
  - Schulz-Ertner

5-year local control rates (%) vs. Dose [Gy (RBE)]

CPT
Chordomas and Chondrosarcomas of the Base of Skull

- Small Chordomas
- Chondrosarcomas

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

- Photon sources:
  - Romero 1993
  - Zorlu 2000
  - Debus 2000

- Proton sources:
  - Munzenrider 1999
  - Ares 2007
  - Hug 1999

- C-Ions source:
  - Schulz-Ertner
Neoplasms of the Skull Base: The present state of Tx for Chordomas and Chondrosarcomas

- The majority of Chondrosarcomas of the skull base are of low grade histology.

- Long-term outcome data suggest possible CURE for the majority of patients following subtotal surgical resection and high-dose radiation therapy (protons) to approx. 70 – 75 Gy.

- Gross total resection should not be pursued if increased surgical risks (the “last 5 % = 90% risk”)

- This represents a dramatic improvement of prognosis in a disease considered universally fatal 20 years ago.
GOAL:
Develop a risk-classification

low - intermediate - high

to correlate with recommendations for adjuvant Tx,
i.e. treatment algorithm:

observation - aggressive Tx - palliative Tx
Long-term Side Effects of Skull Base Irradiation

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
Optic neuropathy and temporal lobe toxicity

1.5 yrs.

2.0 yrs.
## Dose limitations for OAR at PSI

<table>
<thead>
<tr>
<th>OAR</th>
<th>Dmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem surface</td>
<td>64 CGE</td>
</tr>
<tr>
<td>Brainstem center</td>
<td>53 CGE</td>
</tr>
<tr>
<td>Optic Chiasm</td>
<td>60 CGE</td>
</tr>
<tr>
<td>Optic Nerves</td>
<td>60 CGE</td>
</tr>
</tbody>
</table>
Extracranial *Chordomas of the Axial Skeleton* treated with spot scanning Proton Therapy at PSI:

Hans Peter Rutz et al.
Extracranial *chordomas of the Axial Skeleton* treated with spot scanning Proton Therapy at PSI:

(Rutz et al.)

- Update of the initial publication (*Rutz HP et al. IJROBP* 67(2):512; 2007). Updated manuscript in progress.

- $N = 40$

- $Tx: 1999 - 2005$

- Location:
Chordomas of the Axial Skeleton at PSI:

- Surgical Stabilization - Reconstruction (plates, screws, cage, rods etc.) in \(21/40\) patients.

- \(19/40\) patients without inserted instrumentation

- IMPT part of treatment plan since 2004

- Median total dose: 72 Gy (RBE) (range: 59.4 – 75.2 Gy (RBE))

- Follow-up period:
  - Minimum: 2 years (24 months)
  - Median: 43 months
  - Maximum: 91 months
Chordomas of the Axial Skeleton at PSI: 5-year outcomes data

Local control

13 / 40 patients with local failure

60%
Impact of Surgical Stabilization – Reconstruction (SS-R) on Local control

No SS-R:
- only 1 LF in 19 pts.

With SS-R:
- 12 LF in 21 pts.
  or
- 12 / 13 Local Failures

P = 0.003
Extracranial chordoma

CT artifacts for surgical implants for stabilization / fusion on spinal axis tumors

- **Clinical factors:**
  - Negative selection of patients with more advanced tumor – i.e. larger and more complex tumor presentation requiring more extensive surgery?

- **Treatment planning issues:**
  - (Difficulties defining Targets?)
  - Difficulties in dose calculation?
  - Difficulties in range calculations?

Similar experience for passive scattering technique?
Proton RT for Sacral Chordomas: MGH results

Park et al., MGH, IJROBP 65(5), 2006

- 27 patients, treated 1982 – 2002
- photons and/or protons
- 16 primary chordomas, 11 recurrent
- Combined S + RT = 21 patients
  - Mean dose 71 Gy(E) for primary
  - Mean dose 77 Gy (E) for recurrent chordoma
- RT alone: 6 patients
  - 60, 62, Gy photons and 73-77 Gy photons/protons
Local Control following S + RT (21 pts.): Primary >>> Recurrent

<table>
<thead>
<tr>
<th>Description</th>
<th>Time</th>
<th>Local control %</th>
<th>Disease free survival %</th>
<th>Overall survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 primary chordomas treated by surgery &amp; radiation</td>
<td>5 years</td>
<td>90.9 ± 8.7</td>
<td>90.9 ± 8.7</td>
<td>92.9 ± 6.9</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>90.9 ± 8.7</td>
<td>90.9 ± 8.7</td>
<td>92.9 ± 6.9</td>
</tr>
<tr>
<td>7 recurrent chordomas treated by surgery &amp; radiation</td>
<td>5 years</td>
<td>57.1 ± 18.7</td>
<td>42.9 ± 18.7</td>
<td>66.7 ± 19.3</td>
</tr>
<tr>
<td></td>
<td>10 years</td>
<td>19.1 ± 16.8</td>
<td>14.3 ± 13.2</td>
<td>44.4 ± 22.2</td>
</tr>
</tbody>
</table>
Local Control following RT alone (6 pts.):

Photons only:
- 60 Gy LFailure
- 62 Gy LFailure

Mixed photons / protons:
- 77, 74, 77 Gy (E) Local control
- 73 Gy (E) LFailure
Histologies

- **Osteogenic Tumors**
  - Osteogenic Sarcoma
  - Ewing Sarcoma

- **Chondrogenic Tumors**
  - Chordomas
  - Chondrosarcomas

- **Soft Tissue Sarcomas**
  - STS
  - Rhabdomyosarcoma
Proton – Photon planning comparison for Soft Tissue Sarcomas
Planning Comparison for STS::

**Photon IMRT** versus **Proton IMPT**

Weber, Delaney et al., PSI + MGH, IJROBP 2004

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Histology</th>
<th>Localization</th>
<th>Stage (UICC/AJCC)</th>
<th>Grade</th>
<th>CTV volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Angiosarcoma</td>
<td>L1</td>
<td>IIB</td>
<td>3</td>
<td>41.4</td>
</tr>
<tr>
<td>2</td>
<td>Angiosarcoma</td>
<td>L1</td>
<td>IA</td>
<td>2</td>
<td>214.6</td>
</tr>
<tr>
<td>3</td>
<td>Leiomyosarcoma</td>
<td>T11–12</td>
<td>IA</td>
<td>1</td>
<td>520.1</td>
</tr>
<tr>
<td>4</td>
<td>Epitheloid sarcoma</td>
<td>T5–7</td>
<td>III</td>
<td>3</td>
<td>181.3</td>
</tr>
<tr>
<td>5</td>
<td>Chondrosarcoma</td>
<td>T5–7</td>
<td>Recurrent</td>
<td>1</td>
<td>360.5</td>
</tr>
</tbody>
</table>

**Step 1:** Planning assumptions: 77.4 Gy (RBE) to CTV with identical OAR constraints. Calculate target coverage and DVH’s for normal tissues.

**Step 2:** Attempt dose escalation with protons leaving OAR constraints unchanged.
Weber, Delaney et al., PSI + MGH, IJROBP 2004 cont.
The optimization IMPT algorithm was used to increase the total dose to the target by 10% and 20%, within the maximal OAR dose constraints. Dose escalation could be achieved in all patients, at the 20% (92.9 CGE) dose escalation level, regardless of tumor size, location, and geometry.

Inhomogeneity coefficients and Conformity Indices were not significantly different.

Integral Normal Tissue dose consistently reduced by IMPT (factor 1.3 – 25)

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{OAR} & D_{\text{Max}} & D_{\text{Mean}} & D_{50\%} & D_{10\%} \\
\hline
\text{Spinal cord} & 1.0 & 1.4 & 1.7 & 1.1 \\
\text{Heart} & 6.0 & 24.7 & 30.8 & 35.3 \\
\text{Lung} & 1.1 & 6.5 & 32.7 & 11.3 \\
\text{Kidney} & 1.0 & 2.1 & 6.4 & 1.3 \\
\text{Stomach} & 2.6 & 6.9 & 40.0 & 7.4 \\
\text{Liver} & 1.0 & 1.3 & 1.1 & 1.0 \\
\text{Small bowel} & * & * & * & * \\
\hline
\end{array}
\]

Weber, Delaney et al., PSI + MGH, IJROBP 2004 cont.
The Integral Dose Differential

Comparative dose distributions for 9-field photon intensity-modulated photon (IMXT) and 3-field intensity-modulated proton radiation (IMPT) treatment plans for a patient with pelvic Ewing’s sarcoma.

(Courtesy of A.R. Smith and A.J. Lomax, in Delaney, Cancer Control, 2005)
Proton Therapy for Adult Patients with STS: the PSI experience

(Weber et al., IJROBP 2007)

- 13 patients with STS
- 1998-2005 tx with protons (6) or mixed protons/photons (7)
- Location: H&N, Skull Base, Paraspinal. Pelvis, Trunk, Reroperitoneal (2 pts), Shoulder (2 pts.)
- Primary: 9 (69%), recurrent: 4 pts.
- Dose: median 69.4 Gy (RBE) (50.4 – 76 Gy (RBE))
- F/U: minimum 1 year, 12 pts. > 2 years, median for surviving patients: 48 months.
Tumor histology: liposarcoma \((n = 3)\), peripheral nerve sheet tumor (PNST, \(n = 3\)), leiomyosarcoma \((n = 2)\), desmoid tumors \((n = 2)\), angiosarcoma \((n = 1)\), spindle cell sarcoma \((n = 1)\), and malignant hemoangiopericytoma \((n = 1)\)

Treatment plan for (A) retroperitoneal, (B) head and neck, and (C) paravertebral sarcoma.
Sparing of the kidney (A), spinal cord (A, C), and brainstem (B).
Weber et al., IJROBP 2007 cont.

Local control: 10 / 13 pts.
3-year actuarial LC: 74%

Late adverse events: 2 pts.
1 cataract
1 Grade 3 temporal lobe necrosis
Proton – Radiotherapy

for STS

in Children
Proton Radiotherapy for pediatric STS treated at PSI

(Timmermann et al., PSI, IJROBP, 2007)

16 children with STS (including 12 with RMS or RMS-like histology)

14/16 children with chemotherapy

Age: median 3.7 years (1.4-14.1 years). 9 children requiring anesthesia

Tumor volume: 52 cc – 1225 cc

Location: H&N, Skull Base, Paraspinal, Pelvis

Proton RT Dose: median 50 Gy (RBE) (46 – 61.2 Gy (RBE)) – doses according to CWS2002, MMT-95, COG-D9803 in 14 pts.

F/U: median 18.6 months (4.3 -71 months)
Outcome (very preliminary)

Local control:
12/16 = 75% at 2 years

2/12 Failures in RMS- Group

2/4 in Non-RMS Group (after 50.4, 50 GY(RBE))

Late toxicity: F/U too short
2 principal Concepts for applying Proton RT in relation to Photon-RT Pediatric Clinical Trials

Concept 1

Enrollement in photon trials or Tx according to photon trial study board recommendations

dose and volume regimen identical to photon concepts

Advantage: Proton-RT embedded in multi-institutional concepts. Matched-case comparability of outcomes data with photons

Disadvantage: no increase in tumor control probability from protons by applying Tx-prescriptions similar to photons
2 principal Concepts for applying Proton RT in relation to Photon-RT Pediatric Clinical Trials

Concept 2

**High risk** STS (mainly Non-RMS STS with gross residual)
- Apply high doses based on peds. skull base chordoma data
- High dose proton-RT: 68 - 76 Gy(RBE)
- Enrollement in photon trials *only* if high doses permissible

**Low risk** STS (mainly RMS STS)
- Enrollement in photon trial
- Example: COG / IRS RMS dose and volume regimen
- Normal tissue sparing advantage, but no expectation for increased tumor control
Example Concept 2:

Proton Radiation Therapy in the management of pediatric base of skull tumors
(Hug et al., MGH+LLUMC, IJROBP, 2002)

• 29 children with mesenchymal tumors
• 1992-1999 tx with protons or mixed protons/photons
• Age: median 12 years (1-19 years).
• Gross tumor: 28/29 patients (97%)
• Tumor histology grouped in „malignant“ versus „benign“
• Dose for malignant histologies according to adult experience
• F/U: mean 40 months (13 -92 months)
<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>29</td>
</tr>
<tr>
<td><strong>Malignant Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Chordoma</td>
<td>10</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>3</td>
</tr>
<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>
<tr>
<td><strong>Benign Histology</strong></td>
<td></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>
</tr>
</tbody>
</table>

Median dose: 70 CGE (45 – 78.6)

Median dose: 60.4 CGE (45 – 71.8)
Example: 13 y.o. M with Malignant Fibrous Histiocytoma

CTV: 50.4 Gy (RBE)
GTV: 66.6 Gy (RBE)

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

9 pts. Benign Histology
LC: 8/9, OS 100%

Severe late effects: 2 pts. (motor weakness, sensory deficit)
Proton/Particle - Radiotherapy for Sarcomas:

There is a need for improving local controle by RT for high-risk, unresected/resectable sarcomas
**Increasing Local Control by dose escalation:**

- Residual disease or unresectable disease
- Disease at high risk for failure

**Decreasing Late Adverse Events by reduction of Integral dose:**

- Improving functional outcome by reducing normal tissue dose
- Reducing risks of Secondary malignancy
Proton Radiotherapy for STS: possible trial designs

**Scenario 1**: „Proton- versus Photon - Radiotherapy for STS“. A Phase III Trial using moderately high dose levels

**Scenario 2**: „High dose RT for high-risk STS using stereotactic precision-modality radiotherapy“. A Phase II trial open for QA-approved equipment

**Scenario 3**: „Dose-escalation study using proton radiotherapy for unresectable STS“
Proton Radiotherapy for STS: possible trial designs

**Scenario 1**: „Proton- versus EB-Photon Radiotherapy for ….Sarcoma“. A Phase III Trial using moderately high dose levels

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THANK YOU