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

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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?
Osteosarcoma of the pelvis: COSS-Group results
Ozaki et al., JCO, 21(2), 2003

- COSS = German/Austrian Coop. Osteosarc. Study Group
- 1,982 patients on sequential protocols 1979-1998

- 67 patients with pelvic, high grade osteosarcoma
- Chemotherapy plus maximum possible surgery
- 11 patients with XRT

Is there a need for (improved) RT?
Surgical Margin and Local Failure

<table>
<thead>
<tr>
<th>Margin</th>
<th>No. of Patients</th>
<th>No. of Local Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radical</td>
<td>2 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Wide</td>
<td>23 (0)</td>
<td>11 (0)</td>
</tr>
<tr>
<td>Marginal</td>
<td>10 (0)</td>
<td>7 (0)</td>
</tr>
<tr>
<td>Intralesional</td>
<td>13 (4)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No operation</td>
<td>17 (7)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>67 (11)</td>
<td>47 (9)</td>
</tr>
</tbody>
</table>

NOTE: Values in parentheses indicate radiotherapy.
Osteosarcoma of the pelvis: COSS-Group results
Ozaki et al., JCO, 21(2), 2003

Impact of RT on Survival:
30 pts. Intralesional or no surgery:
RT $p = 0.033$

Multivariate analysis:
RT independently prognostic
Photon - IMRT for paraspinal Chordomas and Rare Sarcomas

Terezakis et al., MSKCC, IJROBP 69(5), 2007

- 27 patients partially resected or unresected tumors
- treated 2001 – 2005
- IMRT photons
- 5/27 re-irradiation
- Histology:
  - 18 Sarcomas (6/18 chondrosarcomas)
  - 7 Chordomas
  - 2 Ependymomas
### Tx- Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed dose (cGy)</td>
<td>6,600</td>
<td>6,000–7,000</td>
</tr>
<tr>
<td>Fractions (n)</td>
<td>33</td>
<td>32–35</td>
</tr>
<tr>
<td>PTV (cm)</td>
<td>164</td>
<td>110–436</td>
</tr>
<tr>
<td>Maximal dose (cGy)</td>
<td>7,746</td>
<td>7,051–8,170</td>
</tr>
<tr>
<td>$V_{95}$ (%)</td>
<td>94</td>
<td>92–97</td>
</tr>
<tr>
<td>Mean dose to spinal cord (cGy)</td>
<td>2,949</td>
<td>1,350–3,409</td>
</tr>
<tr>
<td>Maximal dose to spinal cord (cGy)</td>
<td>5,261</td>
<td>3,303–5,383</td>
</tr>
<tr>
<td>Previous radiation dose (cGy)</td>
<td>4,400</td>
<td>4,000–5,000</td>
</tr>
</tbody>
</table>
Photon - IMRT for paraspinal Chordomas and Rare Sarcomas

Terezakis et al., MSKCC, IJROBP 69(5), 2007

F/U period: range 2.1 – 47.3 months, median 17.4 months

Local control: 65% at 2 years only
**Toxicity of photon RT for Soft Tissue Sarcomas**

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>0/2</td>
<td>2/2</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>Toxicity</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>
Is there a place for Proton/Particle Radiotherapy in the treatment of Soft Tissue Sarcomas?

= 

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

Is it desirable to reduce side effects and improve functional outcome?

YES
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
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 = 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
• 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.)
<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>Group 1</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>†</td>
<td>†</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>†</td>
<td>†</td>
<td>4</td>
<td>—</td>
<td>2</td>
<td>66.1–77.9</td>
<td>72.2</td>
</tr>
<tr>
<td>Group 2</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>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>Group 3</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>2</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>3</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>

<table>
<thead>
<tr>
<th>Histology</th>
<th>No.</th>
<th>Total</th>
<th>Pre-/Postop</th>
<th>Postop</th>
<th>Bx only</th>
<th>Extent of resection</th>
<th>Distant metastasis</th>
<th>Died of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>(20)</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>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>0/4, 0/2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group 2</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>4</td>
<td>0/4</td>
<td>2/8</td>
<td>2/3</td>
<td>0/3, 2/9, 2/3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Group 3</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>1</td>
<td>1/1</td>
<td>0/5</td>
<td>0/2</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>0/1, 1/1</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Chondroblastoma</td>
<td>2</td>
<td>0</td>
<td>—</td>
<td>0/2</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
Carbon Ion Therapy for Osteosarcoma

Local Control at 5 years: 65%
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
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

![Graph showing local recurrence-free survival for chondrosarcoma by sex.]

Log-Rank $p = 0.9923$
Female
Male

Skull Base

Years

Percentage

0 2 4 6 8 10

95.28 ± 4.66%
94.40 ± 5.60%

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

Local Recurrence – Free Survival
Non-Chondroid Chordoma By Sex

<table>
<thead>
<tr>
<th>Percent</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>90.07 ± 6.80%</td>
<td>82.71 ± 9.52%</td>
</tr>
<tr>
<td>90</td>
<td>71.08 ± 13.78%</td>
<td>40.56 ± 14.12%</td>
</tr>
</tbody>
</table>

Log-Rank p = 0.0001

Skull Base

female

Courtesy: John Munzenrider, MGH/HCL
Proton Radiation Therapy (PRT) for Chondrosarcomas and Chordomas of the Skull Base. 

Tumor size at PRT and Local Control

\[ p = 0.03 \]

**Local Control**

- No Brainstem involvement
- Brainstem involvement

\[ p = 0.04 \]

**Overall Survival**

\[ p = 0.09 \]
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
Chordomas of the Base of Skull

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

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

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

- C-Ion data:
  - Schulz-Ertner
Chordomas and Chondrosarcomas of the Base of Skull

5-year Local Control rates (%)

Dose [ Gy (RBE)]

- Small Chordomas
- Chondrosarcomas

- Photons
  - Romero 1993
  - Zorlu 2000
  - Debus 2000

- Protons
  - Munzenrider 1999
  - Ares 2007
  - Hug 1999

- C-ions
  - 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

\textit{low - intermediate - high}

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

\textit{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
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

Local control [all] at 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.
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 (2pts.)
- 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).
Late adverse events: 2 pts.
1 cataract
1 Grade 3 temporal lobe necrosis

Local control: 10 / 13 pts.
3-year actuarial LC: 74%
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
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>
<th>Median Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>20</td>
<td>70 CGE (45 – 78.6)</td>
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<tr>
<td>Chordoma</td>
<td>10</td>
<td></td>
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<tr>
<td>Chondrosarcoma</td>
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<tr>
<td>Epithelioid Sarcoma</td>
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</tr>
<tr>
<td>Malignant Fibrous Histiocytoma</td>
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<td></td>
</tr>
<tr>
<td>Myxoid Sarcoma</td>
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<td></td>
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<tr>
<td>Rhabdomyosarcoma</td>
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<tr>
<td><strong>Benign Histology</strong></td>
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<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>9</td>
<td>60.4 CGE (45 – 71.8)</td>
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<tr>
<td>Giant Cell Tumor</td>
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<tr>
<td>Chondroblastoma</td>
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</tr>
</tbody>
</table>
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 Radiotherapy for Sarcomas: Potential and Future

**Pre-operative** Proton-Radiotherapy:

- Presently infrequently performed for logistical reasons (referrals initiated after surgery)
- Dose-sparing of skin and SC-tissues identified as surgical access route for deep seated tumors.
- Further decrease of irradiated volume (compared to postop.RT)
- Mainly for deep seated tumors, including extremity sarcomas.
- Potential of decreasing wound healing delay or wound complications
Initial Volume (CTV) = preop. tumor extension plus margin plus scar

50 Gy (RBE) / 2 Gy

Boost volume (GTV) = postop. residual tumor plus 5 mm

18 Gy (RBE) / 2 Gy

Total dose: 68 Gy (RBE)
Proton-Radiotherapy for **EXTREMITY** Sarcomas:

- Presently only rarely performed
- Decrease of Irradiated Volume, i.e. decrease of muscle mass at risk of fibrosis
- Potential to spare circumferential dose to bones, i.e. decreasing the risk of late fracture.
Proton Radiotherapy for Sarcomas: Potential and Future

Proton-Radiotherapy for CENTRAL Sarcomas:

• Well established indications for chondrogenic sarcomas - H&N, skull base, paraspinal, pelvis.

• Protons an excellent tool for areas, where doses > 70 Gy remain difficult to deliver

• There is a significant need to improve local control for unresectable/subtotally resected sarcomas in these locations.

• Excellent tool for pediatric population
Proton Radiotherapy for Sarcomas: Potential and Future

Proton-Radiotherapy in case of co-morbidity unrelated to sarcoma and reducing normal tissue tolerance:

• Example: Irritable bowel syndrom, Inflammatory bowel disease, Crohn’s disease, Ulcerative Colitis and paraspinal, retroperitoneal, or pelvic sarcoma

• Reduction of Integral Volume, i.e. reduction of low-moderate dose important for adult patients

• „Safe“ OAR dose levels not established for affected organs
Proton-Radiotherapy:

Advantage of reduced normal tissue dose in adult patients with unrelated co-morbidity

*Example: Sacral Sarcoma coincident with diagnosis of Crohn’s disease*
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/particle radiotherapy for unresectable STS“
Scenario 1: „Proton- versus EB-Photon Radiotherapy for ….Sarcoma“. A Phase III Trial using moderately high dose levels

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

Scenario 3: „Dose-escalation study using proton/particle radiotherapy for unresectable ..S“
THANK YOU