Spot Scanning Proton Radiation Therapy: Paul Scherrer Institut Experience

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Proton treatment delivery
Proton treatment delivery

Extending the dose in depth – the ‘Spread-out-Bragg-peak’

![Diagram showing target dose distribution for proton therapy](image-url)
Proton treatment delivery

Passive scattering in practice

Scatterer
Proton treatment delivery

Passive scattering in practice

Collimator

Scatterer

Patient
Proton treatment delivery

Passive scattering in practice

Range-shifter wheel
Scatterer
Collimator
Compensator
Target
Proton treatment delivery

Dynamic proton therapy at PSI: Spot scanning

Basic principle used for beam scanning with protons

Through the delivery of individual proton pencil beams one can shape the distribution of the dose in three-dimensions at wish directly under computer control.

Single beam...

+ scanning in depth

( lateral scanning

= 3d conformed dose)
Proton therapy at PSI

The proton gantry at PSI

3.5m diameter, eccentric gantry
+/−180 degree rotation
Discrete scanning system
Start of patient treatments 1996
Gantry 1: dose delivery by pencil beam scanning

- Gaussian pencil beam: 3 mm $\sigma$
- Cartesian scanning (infinite SSD)
  “step-and-shoot” on a 5 mm grid
- Energy changes slow

Elements of scanning:

<table>
<thead>
<tr>
<th>Element</th>
<th>Time</th>
<th>Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>X: Sweeper magnet (*)</td>
<td>5 ms / step</td>
<td>fast</td>
</tr>
<tr>
<td>Y: Range shifter</td>
<td>30 ms</td>
<td>medium</td>
</tr>
<tr>
<td>Z: Patient table (*)</td>
<td>1 cm/s</td>
<td>slow</td>
</tr>
</tbody>
</table>
A spot scanned plan consists of the addition of one or more individually optimised fields. Note, each individual field is homogenous across the target volume.
Proton Radiation Therapy at PSI

Clinical experience

• Ocular tumors
• Deep seated tumors
  ➢ Skull base tumors
    ▪ Chordomas & chondrosarcomas
    ▪ Meningiomas
    ▪ Adenocystic carcinomas and other H&N tumors
  ➢ Paraspinal and pelvic tumors
  ➢ Pediatric tumors
Proton Radiation Therapy at PSI: Ocular Tumors
Proton Radiation Therapy: Ocular Tumors

- Start 1976 in USA (MGH / MEEI / Harvard Cyclotron)
- Since 1984 in Europa (PSI)
- >15 000 patients treated world wide
- > 98% Diagnosis: Melanoma of the Retina
Proton Radiation Therapy: Ocular Tumors

Fundus Exam
PRIOR to therapy

Fundus Exam
AFTER Therapy

Diagnosis:
Primary Symptom: reduced / disturbed vision
Proton Radiation Therapy: Ocular Tumors

Surgery:
to document tumor extension and placement of fiducial markers
Proton Radiation Therapy: Ocular Tumors

Tumor base is delineated with tantalum clips
Proton Radiation Therapy: Ocular Tumors

Simulation

Bite block and face mask

Lid retractor

In treatment room: X-ray acquisition
Proton Radiation Therapy: Ocular Tumors

X-ray images digitized

correlation with clinical data (eye dimension and US-images)

Eye model with clips
Proton Radiation Therapy: Ocular Tumors

Individual treatment plan (Eyeplan)

- Tumor drawn based on clinical data
- Determine optimal eye position („gazing angle“)
- Margins: 2mm lateral margin for collimator; macula and optic disc maximally spared, 2.5 mm distal margin

Eyeplan: First computer based treatment planning program. Eye model first assuming round ball, later ellipsoid configuration. First application 1976 at Harvard Cyclotron (M. Goitein). At present >15'000 patients treated world wide.
Pre-treatment Verification of Plan:
Real-life applicability of gazing angle and eyelid position (separate session prior to Tx)

LED on polar coordinate system
Proton Radiation Therapy: Ocular Tumors

• Fabrication of individual collimators
Proton Radiation Therapy: Ocular Tumors

Treatment Start: Patient positioning
Proton Radiation Therapy: Ocular Tumors

Identifying the Clips on orthogonal X-ray Images
Proton Radiation Therapy: Ocular Tumors

Eye Position Adjusted until Clips are Matched (<0.2 mm)
Results:

» Local Tumor Control
» Cure
» Eye Retention
» Retention of Useful Vision
Uveal Melanomas: the Paul Scherrer Institute experience

- Since 1984 more than 4700 patients treated
- Approx. 200-250 patients treated per year during 10-12 blocks of "OPTIS Weeks". Capacity: +/- 22 patients/OPTIS week
- Tx Regimen: 4 fractions in one week; 15 CGE dose/fraction
- 60 CGE Total prescribed Dose

- Local Control: 98%@10 years (> 2000 patients analyzed)
Proton Radiation Therapy: for Ocular Melanomas

“The learning curve”: Experience influences results

1994 – 2000
9 rec. / 1518 pat.

1988 – 1993
39 rec. / 1122 pat

1984 – 1987
32 rec. / 323 pat.

Local tumor control

Cum Recurrence Free Survival

Time [years]

100%
95%
90%
87%
The importance of local control for survival
Survival Functions

Total number of patients: 2837

No recurrence:
2756 patients
309 tumor related deaths / 2756 Patients = 11.2%

Recurrence later than 2 y:
42 patients
12 tumor related deaths / 42 patients = 28.5%

Recurrence before 2 y:
39 patients
22 tumor related deaths / 39 patients = 56.4%
Proton Radiation Therapy: for Ocular Melanomas

Eye Retention
i.e.
Risk of Enucleation
Eye retention after proton beam radiotherapy for uveal melanoma


- 2645 patients (2648 eyes) with uveal melanoma
- Age 9 - 90 years
- Tumor diameter: 4 to 27.5 mm
- Tumor height: 0.9 to 15.6 mm.
- Tx: 1984 - 1999
- Analysis as of 2/2001
- Median follow-up time was 44 months. (almost 4 years)
Eye retention after proton beam radiotherapy for uveal melanoma

Results:

- Overall eye retention rate
  - 89% at 5 years
  - 86% at 10 years
  - 84% at 15 years
- 218 eyes enucleated

Risk analysis: Enucleation was related to larger tumor size, mainly tumor height, proximity of posterior tumor margin to optic disc, male gender, high intraocular pressure, and large degree of retinal detachment at treatment time

- Influence of time and experience:

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<tr>
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</thead>
<tbody>
<tr>
<td>Small tumors</td>
<td>97.1%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Midsized tumors</td>
<td>86.7%</td>
<td>92.0%</td>
<td>99.7%</td>
</tr>
<tr>
<td>Large tumors</td>
<td>71.1%</td>
<td>83.5%</td>
<td>89.5%</td>
</tr>
</tbody>
</table>
Proton Radiation Therapy: for Ocular Melanomas

Visual Outcome

–

Risks of Papillopathy and Maculopathy
Proton Therapy at Paul Scherrer Institute for Small Posterior Uveal Melanoma: Subgroup Analysis. *Rutz, Zografos, Verwey et al. (to be published)*

- 236 of 2837 patients treated between 1984 and 2000 had small posterior uveal melanomas

- Analysis according to infiltration and/or irradiation of Macula
Distribution (%) of tumor types:

87% choroidal melanoma

2.6% relapses of choroidal melanomas
4.1% choroidal hemangiomas
2.3% conjunctival tumors
1.3% intraocular metastases
1.2% ARMD (Age Related Macular Degeneration)
0.5% iris melanomas
0.4% vascular retinal tumors
0.2% miscellaneous
New Developments at PSI

Physically and logistically transferring the Eye-program (from OPTIS to OPTIS2)

Improving a > 20 year old technology
Center for Proton Radiation Therapy at PSI:

A New Era
OPTIS2 Nozzle with robot-chair

Robotchair positioning < 0.1 mm

Robotchair shown without mask-holder
The OPTIS2 Project

Project Mission:
• Continue ocular proton therapy at PSI
• Using the COMET cyclotron
• Maintaining, as far as possible, the existing OPTIS treatment parameters
• Projected start of routine patient treatments: Dec, 2008

OPTIS2 is a completely new design, bringing together the latest techniques already tested and/or in operation at other institutes in Europe (HMI, CPO). Primary aim, however, is to match the clinical outcome of OPTIS, and as such the treatment philosophy remains unchanged.
Deep seated tumors treated at Gantry-1

Spot scanning technology
Remote patient positioning at PSI

1. Patient preparation: 5 minutes
2. Patient positioning checks: 5 minutes minimum
3. Transfer to treatment room: 2+2+2 minutes
4. Treatment delivery: 5-30 minutes
5. Transfer out of treatment room: 2+2 minutes

Post treatment checks: 2+2+5 minutes

In-situ X-ray positioning checks: 5 minutes

Coupling/decoupling time: 2 min
Total preparation time: 20 [35] min
Working in parallel: 10 [15] min
Treatment time: 5-30 min
Requirements for a ‘remote’ positioning system.

- A patient transporter system
- Identical, accurate and reproducible coupling of patient couch on imaging and gantry systems
- Exact correspondence between imaging device coordinate system and treatment device system
- Reliable patient fixation – robust enough that patient is not disturbed during transport process
EIPATRANS Patient Transporter

- Twin system for parallel operation
- Operatable by one person
- Guided by optical tracks
- Connecting various predefined locations:
  - Preparation room
  - Anesthesia room
  - CT room
  - Gantry room
- Table coupling at CT and Gantry
- Reliable operation
  - Increased comfort for patient
  - Decreased physical work for staff
Patient in moulage waiting to be positioned…
Table, moulage and patient coupled to CT…
Final fixation of bite block performed by MTRA…
‘Images-of-the-day’ compared to reference (planning) scout images…
On the way to the gantry (treatment room)…
Patient ready for treatment...
Treatment delivered under video surveillance…
Patient, moulage and table removed from treatment room…
Daily pre-treatment positioning at CT

- Horizontal and vertical scouts
- Compared against reference scouts (from treatment planning CT series).
- No axial CT scan acquired
- Online matching of anatomical landmarks
  - Semi-automatically and/or manually
  - Offsets for table coordinates at Gantry (translations only)
  - Linked to Gantry Control System (via PatBase “R&V” interface)
- Software developed in-house (“ppp”)
Patient positioning: Remote Positioning at CT

Error distribution before correction (whole course of treatment)

- Cranial cases (Bite block): 1.1-1.3mm
- Head and neck (Thermoplastic): 1.4-1.8mm
- Spinal axis: 1.8-2.2mm

Error distribution after correction
Reliability of patient positioning during the transport process

Differences between pre- and post-treatment scout images.
Post-treatment topograms taken every 10\(^{th}\) fraction (72 patients)

<table>
<thead>
<tr>
<th></th>
<th>R/L Lat</th>
<th></th>
<th>Ant/Post</th>
<th></th>
<th>Sup/Inf</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Bite-block (head)</td>
<td>-0.1</td>
<td>1.0</td>
<td>0.2</td>
<td>1.3</td>
<td>-0.5</td>
<td>1.8</td>
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<tr>
<td>Thermoplast. Mask (Head)</td>
<td>-0.4</td>
<td>2.4</td>
<td>1.4</td>
<td>2.4</td>
<td>-0.1</td>
<td>2.1</td>
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<tr>
<td>Abdomen/Pelvis</td>
<td>0.3</td>
<td>2.4</td>
<td>1.6</td>
<td>2.4</td>
<td>-0.7</td>
<td>2.7</td>
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</tbody>
</table>
Patient Positioning: Summary

• Like any highly conformal therapy, proton therapy requires precise patient positioning and fixation

• Patient fixation is usually relatively standard, but watch out for objects in way of beam (fixations of masks, support arms, ear rings....)

• All proton facilities use some form of daily imaging protocol for even more precise daily positioning (this is remotely done at PSI)
Effectiveness and Safety of Spot Scanning Proton Radiation Therapy for Skull Base Tumors
Introduction

Skull Base Chordomas and Chondrosarcomas:
PSI Experience 1998 - 2005
Skull base tumors: PSI experience

Material and Methods

• 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)
Material and Methods

- Prescription dose (mean) (at 2 Gy (RBE) per fraction, 4 fractions per week)
  - Chordoma (Ch) 74 Gy (RBE) (range 68 - 74)
  - Chondrosarcoma (ChSa) 68 Gy (RBE) (range 64 - 74)

- 5 patients mixed photons/protons (4 Ch, 1 ChSa)

- mean GTV volume
  - Ch 27 cc
  - ChSa 23 cc
Skull base tumors: PSI experience

Dose constraints for organs at risk

<table>
<thead>
<tr>
<th>OAR</th>
<th>D_max</th>
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<tbody>
<tr>
<td>Brainstem surface</td>
<td>64 Gy (RBE)</td>
</tr>
<tr>
<td>Brainstem center</td>
<td>53 Gy (RBE)</td>
</tr>
<tr>
<td>Optic Chiasm</td>
<td>60 Gy (RBE)</td>
</tr>
<tr>
<td>Optic Nerves</td>
<td>60 Gy (RBE)</td>
</tr>
</tbody>
</table>
Since 2003 introduction of Intensity Modulated Proton Therapy (IMPT)

20 patients received IMPT as part of their treatment
Intensity Modulated Proton Therapy: The simultaneous optimisation of all Bragg peaks from all incident beams. E.g.: Proton treatment delivery: Active scanning at PSI
Proton treatment delivery: Active scanning at PSI

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

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

Full treatment

Carmen Ares, Center for Proton Radiation Therapy
Skull base tumors: PSI experience

Local control definition

• **Local control** defined as
  - radiological control by MRI ± CT

• **Local failure** defined as
  - radiological tumor progression or
  - clinical symptomatic progression confirmed radiologically
<table>
<thead>
<tr>
<th></th>
<th>Chordoma (n = 42)</th>
<th>Chondrosarcoma (n = 22)</th>
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<tbody>
<tr>
<td>Local failure</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Deaths</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Local progression</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>NED</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Brainstem compression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Abutment</td>
<td>0</td>
<td>0</td>
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</table>

* patient with surgical pathway failure

Skull base tumors

- * patient with surgical pathway failure

Chondrosarcoma (n = 22)

- Chondrosarcoma (n = 22)

Deaths

- Deaths

Brainstem compression

- Brainstem compression

Abutment

- Abutment

Local failure

- Local failure

Yes

- Yes
Skull base tumors: PSI experience

Example of chondrosarcoma with subsequent local relapse

Pre-Proton-RT

GTV

V95 → 48%

Brainstem compression
Skull base tumors: PSI experience

Skull base chondrosarcoma compressing the brainstem

Calcifications on CT → difficulties for resection
Skull base tumors: PSI experience

Local control

Actuarial Local Control

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>3 years</th>
<th>5 years</th>
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<tbody>
<tr>
<td>Chordomas</td>
<td>87 %</td>
<td>81 %</td>
</tr>
<tr>
<td>Chondrosarcomas</td>
<td>94 %</td>
<td>94 %</td>
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</table>
Skull base tumors: PSI experience

Disease Specific Survival

<table>
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<tr>
<th>Disease Specific Survival</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>

P = 0.09
## Prognostic factors for LC in chordoma:

- **Brainstem compression**
  - yes / no  
  - $p = 0.0077$

- **Residual tumor volume**
  - $\leq / > 25 \text{ cc}$  
  - $p = 0.03$

- **Gender**  
  - n.s.

- **Age**  
  - n.s.

- **PT for**
  - primary / recurrence  
  - n.s.

- **GTV V95**  
  - n.s.

- **GTV max, mean or min dose**  
  - n.s.
## Skull Base Chordomas: Comparison of Literature

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Radiation</th>
<th>Mean dose</th>
<th>LC 3-yr</th>
<th>LC 5-yr</th>
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<tr>
<td>Munzenrider, 1999</td>
<td>169</td>
<td>PT, RT</td>
<td>76</td>
<td>73</td>
<td>54</td>
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<td>Terahara, 1999</td>
<td>115</td>
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<td>69</td>
<td>59</td>
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<td>33</td>
<td>PT, RT</td>
<td>71</td>
<td>67</td>
<td>59</td>
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<td>Noel, 2005</td>
<td>100</td>
<td>PT, RT</td>
<td>67</td>
<td>86 @2y</td>
<td>53 @4y</td>
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<td>Igaki, 2004</td>
<td>13</td>
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<td>72</td>
<td>67</td>
<td>46</td>
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<td>Schulz-Ertner, 2007</td>
<td>96</td>
<td>Carbon, RT</td>
<td>60 *</td>
<td>81</td>
<td>70</td>
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<td>Tsujii, 2007</td>
<td>25</td>
<td>Carbon</td>
<td>57 *</td>
<td>88</td>
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<td>Weber, (PSI) 2005</td>
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<td>74</td>
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<td>42</td>
<td>PT</td>
<td>74</td>
<td>87</td>
<td>81</td>
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</tbody>
</table>

*at 3.0 Gy (RBE) per fraction
** to be published
**Skull Base Chondrosarcomas: Comparison of Literature**

<table>
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<tr>
<th>Study</th>
<th>n</th>
<th>Radiation</th>
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<td>11</td>
<td>PT</td>
<td>68</td>
<td>100</td>
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<td></td>
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<tr>
<td>Ares, (PSI) 2007 **</td>
<td>22</td>
<td>PT</td>
<td>68</td>
<td>94</td>
<td>94</td>
<td></td>
</tr>
</tbody>
</table>

* * at 3.0 CGE per fraction
** ** to be published
Skull base tumors: PSI experience

Radiation induced late toxicity (CTCAE v3.0)

• **Asymptomatic MRI white matter changes:** 5 patients
  (= G1 neurologic toxicity)

• **High grade late toxicity (all Ch):** 4 patients
  – optic pathway  G 4 → 1 patient (unilateral blindness)
    G 3 → 1 patient (unilateral visual deficit, steroid dependent)
  – neurologic G 3 → 2 patients (symptomatic brain necrosis)

• **Any patient presented brainstem toxicity**
Skull base tumors: PSI experience

Radiation induced toxicity (CTCAE v3.0)

Actuarial 5-year freedom for high grade late toxicity

94%

Due to the small number of events no risk factors predictive of high grade toxicity were identified.
Skull base tumors: PSI experience

Radiation induced toxicity (CTCAE v3.0)

• High grade late toxicity ($\geq$ grade 3)
  
  • Grade 3 unilateral optic nerve neuropathy
    – developed 20 months after treatment
  
  • Grade 4 unilateral optic nerve neuropathy
    – 12 months after treatment
    (preexistent unilateral visual field deficits due to tumor involvement around the optic nerve)
  
  • 2 cases of Grade 3 temporal lobe brain necrosis
    – at 12 and 19 months after treatment
Skull base tumors: PSI experience

Conclusions - 1

• Toxicity rates similar to passive scattering based proton-radiotherapy series, with comparable target definition, dose prescription and normal organ tolerance levels

• As the majority of late toxicities are commonly detected during the 2 first years after RT, our data demonstrate the safety and efficacy of Spot-Scanning based Proton-Radiotherapy technology delivery for skull base tumors
Skull base tumors: PSI experience

Conclusions - 2

• Established **outcome data for a cohort of patients** treated homogeneously, that will be the **basis for introducing new technologies and develop new treatment algorithms**
Spot Scanning Proton Radiation Therapy
for Para-vertebral Tumors
## Para-vertebral Tumors: Introduction

- Primary malignant tumors of the vertebral column are relatively rare with prevalence of **2.5 to 8.5 cases per 100,000 persons per year**

- **In adults**
  - Plasmocytoma: 30%
  - Chondrosarcoma: 10%
  - Chordoma: < 5%
  - Osteosarcoma: < 5%

- **In children**
  - Ewing’s sarcoma: 4 – 10%
Para-vertebral Tumors: Treatment generalities

- Difficult treatment paradigm because of the complexities of tumor resection (en-bloc resection) and significant resistance to chemotherapy and radiotherapy

- Novel uses and improvements in advanced radiation techniques improve local control
Para-vertebral Tumors: Treatment generalities

- High-dose RT can provide local control to these “radioresistant” tumors
- Doses > 70 Gy have demonstrated the benefit
- These doses are greater than OAR tolerance (i.e. spinal cord)
  - Due to the dose restrictions for the spinal cord and other surrounding structures (esophagus, bowel, kidney) the results of conventional RT have been disappointing
Lumbar spine chordoma
Thoracic spine chordoma
Pelvic Ewing’s Sarcoma
Extracranial *Chordomas of the Axial Skeleton* treated with Spot Scanning Proton Therapy at PSI
Extracranial Chordomas of the Axial Skeleton treated with Spot Scanning Proton Therapy at PSI

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

- N = 40

- Tx: 1999 – 2005

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

• 19 / 40 patients without inserted instrumentation

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

• Follow-up period:
  - Median 43 months (range 24 – 91 months)
Chordomas of the Axial Skeleton at PSI: 5-year outcome data

Local control
13 / 40 patients with local failure
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
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?
Example: Sacral chordoma

Important point: Planification of the surgery
Example: Sacral chordoma

- Staged anterior/posterior resection performing an en block resection at the level S2/S3
- Gap reconstructed with a vascularized rectus abdominus flap from the right which was translocated posteriorly
- Negative resection margins
Cervical spine chordoma

Status after transoral approach
Pediatric tumors
Proton Beam Radiation Therapy of Childhood Malignancies at the Paul Scherrer Institute:

A prospective Analysis
Childhood Malignancies: Introduction

- **Survival rates** in childhood malignancies have increased considerably
- **Late toxicity and QL** more important
- **Radiotherapy is still crucial part of therapy** within the multidisciplinary concept
- **PT** has the potential to **spare normal structures more effectively**
- Thus reducing the risk for late adverse events and SMN
- At PSI specific **focus on paediatric treatments** mainly sarcomas and brain tumors (at non-movable sites)
- **Cooperation with the respective study boards** (CWS, Ewing, HIT …)
- **Younger ages** prioritised for PT
- **Since 2004** even PT under **anaesthesia** provided at PSI
Since 2004 - Anaesthesia for paediatric cases at PSI

Anaesthesia equipment is mounted on the patient table and monitored during the treatment

A close collaboration between PSI and KiSpi, Zurich
# Patients and Methods

## Children

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number:</td>
<td>n = 51 (total)</td>
</tr>
<tr>
<td>Age:</td>
<td>4 mo – 20 yrs. (med 2.6) at Dx</td>
</tr>
<tr>
<td>Gender:</td>
<td>22 f / 29 m</td>
</tr>
<tr>
<td>Country:</td>
<td>CH, D, NL, DK, F, UK, ES, A (n=8)</td>
</tr>
<tr>
<td></td>
<td>(33 Centers)</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td>Bone-/STS-Tumours 24</td>
</tr>
<tr>
<td></td>
<td>Brain Tumours 19</td>
</tr>
<tr>
<td></td>
<td>Chordomas/Chondrosarc. 5</td>
</tr>
<tr>
<td></td>
<td>miscellaneous 3</td>
</tr>
<tr>
<td>Site:</td>
<td>Head/Neck 41</td>
</tr>
<tr>
<td></td>
<td>(para-) spinal 8</td>
</tr>
<tr>
<td></td>
<td>Pelvis 2</td>
</tr>
</tbody>
</table>
## Patients and Methods

### Treatment - Characteristics

<table>
<thead>
<tr>
<th>Proton Beam Therapy</th>
<th>Dose</th>
<th>XRT/PT med. 54.0 Gy (45-79.4 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval</td>
<td>Dx-RT</td>
<td>med. 7.1 Mo (2.43-25.03)</td>
</tr>
<tr>
<td>RT</td>
<td>PT only</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>PT + XRT</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>(Sedation</td>
<td>34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>before PT</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>parallel</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Biopsy</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STR</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>GTR</td>
<td>12</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>med. 29.43 Mo (5.0 - 62.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local recurrence</strong></td>
<td>7/51 (in-field 7/7)</td>
</tr>
<tr>
<td><strong>Dissemination</strong></td>
<td>0/51</td>
</tr>
</tbody>
</table>

**embryonal RMS (2x)**  
**undifferentiated RMS**  
**unclassified RMS**

**high grade Chondrosarcoma**  
**ependymoma**  
**Ewing-Sarcoma**

<table>
<thead>
<tr>
<th>Survival</th>
<th>46/51 (3 under Salvage-Tx)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>time to recurrence</strong></td>
<td>med. 18.0 Mo (11.2 - 37.4)</td>
</tr>
<tr>
<td><strong>time to death</strong></td>
<td>med. 20.0 Mo (10.0 – 70.7)</td>
</tr>
</tbody>
</table>
### Results

**Early toxicity**

<table>
<thead>
<tr>
<th>OAR</th>
<th>Patients, evaluable (n=)</th>
<th>Grade 0</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky</td>
<td>51</td>
<td>38</td>
<td>10</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM</td>
<td>44</td>
<td>5</td>
<td>8</td>
<td>12</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Skin</td>
<td>50</td>
<td>4</td>
<td>31</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mucosa</td>
<td>46</td>
<td>27</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI-Tract</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GU-Tract</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>42</td>
<td>37</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>43</td>
<td>31</td>
<td>9</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>43</td>
<td>38</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Results

**Late toxicity**
*(evaluable in 35 Patients with FU > 6 Mo)*

**Skin:**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td>54.0 - 60.0 Gy + OP/CX</td>
</tr>
<tr>
<td>NET</td>
<td>54.0 Gy + OP/CX</td>
</tr>
<tr>
<td>Parotid Ca</td>
<td>58.0/66.0 Gy + OP</td>
</tr>
<tr>
<td>3x embryonal RMS</td>
<td>50.0 – 52.0 Gy + PE/CX</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>62.0 Gy + OP</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>50.0 Gy + OP/CX</td>
</tr>
</tbody>
</table>

**Fibrosis**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoblastoma</td>
<td>50.0 Gy + OP/CX</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>70.0 Gy + PE/CX</td>
</tr>
</tbody>
</table>

*³*
<table>
<thead>
<tr>
<th></th>
<th>Radiation Dose</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alveol. RMS (Orbit)</td>
<td>54 Gy + OP/CHX</td>
<td>myopia, Cataract</td>
</tr>
<tr>
<td>neuroepithelial TU</td>
<td>54 Gy + OP/CHX</td>
<td>vision ↓, Cataract bilat.</td>
</tr>
<tr>
<td>embr. RMS (Orbit)</td>
<td>50 Gy + OP/CHX</td>
<td>cataract</td>
</tr>
<tr>
<td>osteosarcoma</td>
<td>62 Gy + OP</td>
<td>“dry eye”, Vision ↓</td>
</tr>
<tr>
<td>retinoblastoma</td>
<td>50 Gy + OP/CHX</td>
<td>inflammation (°3)</td>
</tr>
<tr>
<td>embr. RMS (Orbit)</td>
<td>50 Gy + OP/CHX</td>
<td>cataract, “dry eye”, vision ↓</td>
</tr>
<tr>
<td><strong>(C)NS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ependymoma</td>
<td>60 Gy + OP/CHX</td>
<td>seizures</td>
</tr>
<tr>
<td>medulloblastoma</td>
<td>56 Gy + OP/CX</td>
<td>social &amp; psycho. problems</td>
</tr>
<tr>
<td>osteosarcoma</td>
<td>70 Gy + OP/CHX</td>
<td>weakness lower leg</td>
</tr>
<tr>
<td>chordoma</td>
<td>74 Gy + OP</td>
<td>paresis N. Hypoglossus</td>
</tr>
<tr>
<td>ependymoma</td>
<td>54 Gy + OP/CHX</td>
<td>minimal Hemisyndrom</td>
</tr>
<tr>
<td><strong>Radionecrosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ependymoma</td>
<td>60 Gy + OP/CHX</td>
<td>after rep. OP, meningitis (°5)</td>
</tr>
</tbody>
</table>
## Results

### Endocrine Function

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Radiation Dose</th>
<th>Treatment</th>
<th>Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>56 Gy + OP/CX</td>
<td>GH, TH hormones</td>
<td></td>
</tr>
<tr>
<td>Neuroepithelial TU</td>
<td>54 Gy + OP/CHX</td>
<td>GH, TH hormones</td>
<td></td>
</tr>
<tr>
<td>Embryonal RMS (Orbit)</td>
<td>50 Gy + OP/CHX</td>
<td>GH</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>60 Gy + OP/CHX</td>
<td>GH</td>
<td></td>
</tr>
</tbody>
</table>

### Ear

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Radiation Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma</td>
<td>60 Gy + OP/CHX</td>
<td>Hearing deficit unilat.</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>60 Gy + OP/CHX</td>
<td>Deafness unilat. (°4)</td>
</tr>
</tbody>
</table>

### TM Joint

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Radiation Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonal RMS</td>
<td>50 Gy + OP/CHX</td>
<td>Mild trismus</td>
</tr>
</tbody>
</table>

→ in total 4 late adverse events (in 3 pat.) > grade 2
Results

Case 1:
2 yrs, boy, RMA orbit, res. TU after CTX. PT (50 Gy)
Results

Case 2:
3 yrs, girl, RME skull base, res. TU after CTX. PT (54 Gy)
Results

Case 3:
1.5 yrs., boy, RME prostate, res. TU after CTX, PT (52 Gy)
Proton Beam Radiation Therapy of Childhood Malignancies at the Paul Scherrer Institute: Conclusion I

- **Feasibility** and early toxicity of PT proven
- **Dose distribution advantageous** to spare normal structures → Promising! Still, too early to analyse Late effects and risk for SMN
- **Clinical benefit needs to be quantified** → prospective standardised long-term evaluation
- In each child, RT carries the risk for adverse events!
- **For children** we should provide the **safest method**!
- PT is competing with other modern, conformal technologies
- Appropriate indications for PT to be defined individually
For optimal treatment and FU, PT needs to be embedded in multidisciplinary protocols!
Summary - proton radiation therapy

• Proton therapy is a mature technique, with more than 50,000 patients treated worldwide.

• Spot scanning/IMPT provides improved flexibility and conformality in comparison to passive scattering.

• Many comparative planning studies have shown substantial advantages of protons over IMRT.

• However, protons bring their own challenges – e.g. detecting and dealing with range uncertainties, moving targets...
Summary - PSI experience

1. By the end of 2008, more than 400 patients will have been treated with dynamic proton therapy at PSI
2. IMPT has been used since 1999, and last year >40% of all delivered plans were IMPT
3. Outcome results and rates of toxicity are very encouraging
4. About 30% of our patients are pediatric, and nearly a half of these have required anesthesia
5. Expansion of our facility will allow us to increase capacity to about 150 - 200 patients a year
6. With Gantry-2 new indications as moving targets will be established
Thank you for your attention