25 Years of Proton Radiation Therapy at PSI – an Overview

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for the Team of the Center for Proton Therapy

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The eye is the „perfect model“ for proton therapy:
NO bones, NO strong inhomogeneities, a mobile and controlable organ,
a well circumscribed functional compartment –
but nevertheless not an easy case!
Proton therapy for ocular melanoma

• Previous analysis of 2837 patients treated between 1984-2000 has shown that

  Local recurrence has influence on survival (Tumor Related Death).

  TRD from ocular melanoma is death from distant metastases

Therefore, local tumor control is the primary goal of proton radiotherapy for ocular melanoma
2993 Patients analyzed (2006), who received proton radiation therapy between III/1984 and VIII/2005

• Follow up 15 months – 21 years; median 5ys 3ms

• Confirmed diagnosis of melanoma (HOJG Lausanne)

• Unilateral disease

• No reduced (<2mm) safety margin

• Negative familial history

• Visible fundus

• No adjuvant chemotherapy

• Proton dose of 4x15= 60 Gy RBE (former CGE, Cobalt Gray Equivalent)
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Survival Functions

Local relapse – 78/61/61% @ 5_10_15ys
NO local relapse – 91/84/80%
Conclusion - OPTIS

Proton radiotherapy for ocular melanoma results in very satisfying local control (overall 97%@5ys, 96%@10ys, 94%@15ys) and tumor specific survival (overall 91%@5ys, 83%@10ys, 79%@15ys)

Differentiated outcome analysis shows that age tumor size (diameter and thickness) localization and relation to other structures (optic disc, ciliary body, iris) have the strongest influence on local failure, enucleation rate and survival
The Spot Scanning Gantry at PSI

Spot scanning and a compact gantry for proton therapy of deep seated tumors – PSIs (and Eros Pedronis) pioneering contribution to cancer treatment

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Proton Radiation Therapy

Dose conformation = higher dose to the tumor/target volume and reduced dose to normal tissues.

Higher target doses are expected (and have proven in selected tumor entities) to result in better local tumor control and survival.

Less radiation dose = less stress to normal tissues ➔ lower probability of treatment induced toxicity better quality of life less risk for secondary tumors
Dose distribution for a relapsing desmoid tumor in a 12 y/o boy, irradiated with 50 Gy E protons + 10 Gy photons (logistic reasons)
Site, size and shape of a lesion may require proton beams

Meningiomas: large, bizarre shapes, in radiation-sensitive environment
Development of patient treatments at Gantry-1

Start of continuous operation 8/07

Slide courtesy of E. Hug

Commissioning of dedicated cyclotron
Histologies 1996 –2008
n = 427

- Chord/ChSa
- Sarcoma (ST incl. Desmoid, & B)
- Meningioma
- Rhabdomyosarcoma
- Miscell. incl M1
- Ependymoma
- Nasopharynx Ca.
- Glioma
- Prostate
- Esthesioneuroblast.
- Basalioma
## Primary Skull Base Tumors – PSI Experience

<table>
<thead>
<tr>
<th>Disease Specific Survival</th>
<th>3 yrs</th>
<th>5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chordomas</td>
<td>90%</td>
<td>81%</td>
</tr>
<tr>
<td>Chondrosarcomas</td>
<td>100%</td>
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### Actuarial Local Control

<table>
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Slide courtesy of C. Ares
Asymptomatic MRI white matter changes: 5 patients
(= G1 neuro-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)

No patient presented with brainstem toxicity

Actuarial 5-year freedom from high grade late toxicity 94%
## Shull base chordomas – literature comparison

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Radiation</th>
<th>Mean dose</th>
<th>LC 3-yr</th>
<th>LC 5-yr</th>
<th>LC 10-yr</th>
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</thead>
<tbody>
<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>
<td>PT, RT</td>
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<td>67</td>
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<tr>
<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>
<td>PT, RT</td>
<td>72</td>
<td>67</td>
<td>46</td>
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<tr>
<td>Schulz-Erterner, 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>
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<td>Carbon</td>
<td>57 *</td>
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<tr>
<td>Ares, (PSI) 2008 **</td>
<td>42</td>
<td>PT</td>
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*at 3.0 Gy (RBE) per fraction

** in press IJROBP

Slide courtesy of C. Ares
# Shull base chondrosarcomas – literature comparison

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<td>Johson, 2002</td>
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* at 3.0 CGE per fraction
** in press IJROBP
Primary EXTRA-Cranial Chordomas and Chondrosarcomas
Chordomas of the spinal axis

Fem. pat., 65 ys.
C-spine chordoma, 69 Gy E, LC at 53 m.

Fem. pat., 57 ys.
Sacral chordoma, 74 Gy RBE, 1st DF at 8m., died at 28 m. from distant metastases

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Extra-cranial chordomas and chondrosarcomas of the spinal axis including the sacrum/coccygis are as well locally invasive tumors with low metastatic potential.

However, the site of the disease requires in many cases, after tumor resection, extensive metal implants for stabilization of the spinal axis.

The entire anatomical compartment of the spinal axis is characterized by strong density inhomogeneities (bone – spinal cord - soft tissues – lung - interfaces), which are worsened by metal implants.

Pre-surgical discussion between surgeon and radiation oncologist is absolutely mandatory to reduce these unavoidable difficulties as far as or where ever possible.

The PSI experience shows clear differences in outcome for patients with and without metal implants. Whether the less favourable local control rates for patients with metal implants are uni- or multifactorial (e.g. tumor size, resectability, number of surgical interventions, …) will be subject to further careful analysis.
Pediatric Tumors
Choroid-Plexus Carcinoma

2 year old girl

Slide courtesy of B. Timmermann
Results

Follow-Up med. 29.43 Mo (5.0 - 62.3)

Local recurrence 7/51 (in-field 7/7)
embryonal RMS (2x); high grade Chondrosarcoma
undifferentiated RMS; ependymoma; Ewing-Sarcoma
unclassified RMS

Dissemination 0/51

Survival 46/51 (3 under salvage-Tx)

Time to recurrence med. 18.0 Mo (11.2 - 37.4)
Time to death med. 20.0 Mo (10.0 – 70.7)

Slide courtesy of B. Timmermann
Pediatric Proton Therapy

Conclusion

Patients are treated within or in adaptation to existing protocols

Outcomes are very satisfying with good local control rates

Acute toxicities are unavoidable if e.g. tumor extension and protocol-defined safety margins require irradiation of normal tissues up to dose levels that are associated with acute (and late) toxicities. Acute toxicities correlate also with systemic treatments (CTX-specific toxicities). Protons on the other hand also reduce CTX-related toxicities through sparing of normal tissues (e.g. oral mucosa).

Local recurrences occurred in-field; no geographic misses, but local relapses due to aggressiveness of the disease (? higher local doses beneficial?)

Late toxicities Grade 3 & 4 were related to the tumor geometry – site, size, shape and necessary dose levels; 1 grade 5 fatality occurred in a high risk patient who was treated for recurrent disease.
25 Years of Proton Radiation Therapy at PSI - Conclusion

The philosophy and the performance in all medical and related projects at SIN/PSI were positive.

The indications for proton therapy at a physics research institute were wisely chosen according to medical needs and technical/logistic possibilities.

A new technology was introduced into the spectrum of Radiation Oncology with caution and great care, ongoing improvement and learning.

All developments were focussed on patient safety & comfort and were optimized according to medical needs.

The new technology did not allow for concurrent changes in medical regimens, in order to maintain the ability to judge and validate the spot scanning technique.

Clinical outcomes for various tumors and sites were good to excellent.

Outcome analyses and comparison with other centers showed appropriate and in part outstanding treatment results – adverse effects or events were understood and reaction was taken.

Technology and medical results have made PSI a reference place for PT.
Outlook

*From bony tumors, tumors attached to bones or in immobile anatomic positions to*

Intermediate Step: Gating
Breast-CA (complex) Pilot study

*Soft tissue tumors in a soft tissue environment to*

*Soft tissue tumors moving with respiration*

Collaboration: “Netzwerk Radioonkologie Aarau”

Slide courtesy of E. Hug
From bony tumors, tumors attached to bones or in immobile anatomic positions to

Soft tissue tumors in a soft tissue environment

Pilot study Pelvic tumors (with Lymphnode RT) to

Soft tissue tumors moving with respiration
Outlook

*From bony tumors, tumors attached to bones or in immobile anatomic positions to Soft Tissue tumors in a soft tissue environment to Mobile soft tissue tumors moving with respiration*

Step I. upper GI (Liver / Bile / Pancreas)

Step II. Lung Ca, Mesothelioma, Mediastinal tumors
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