2) Proton - Radiotherapy and PSI: More than 20 years of experience - R. Schneider

Center for Proton Radiation Therapy, Paul Scherrer Institut, Villigen, Switzerland
E-mail: Ralf.Schneider@psi.ch

Abstract

For more than 20 years now the Paul Scherrer Institute has experience in particle therapy. The proton research project started with the fixed beam OPTIS eye program in 1984, mainly for malignant uveal melanomas and according to the eye program at Harvard cyclotron. To date more than 5000 patients have been treated with a local tumor control rate of more than 95% (Egger et al. IJROBP 2003;55:867-880). This is still the largest group of patients worldwide. In 1996 the first human patient was treated with the innovative spot scanning technique at gantry I. Deep seated non-moving tumors mainly of the skull, spinal chord and lower pelvic region like chordomas and chondrosarcomas and other sarcomas were treated. In the meantime more than 440 patients have been irradiated with beam scanning at PSI. First results of chordoma and chondrosarcoma treatments are published by Rutz et al. (IJROBP 2008;71:220-225). In 2004 the successful pediatric program was initiated (Timmermann et al. IJROBP 2007;67:497-504). The start of year-round operation in August of 2007 resulted in a shift from a technical research oriented institute, with a very low number of patients, treated per year, to a more clinical oriented treatment research center with expected 120 gantry patients in 2009, most of them suffering from rare and complex diseases. One third will be pediatric patients mainly with daily treatments under anesthesia. With about 40 irradiated children per year PSI will become one of the largest pediatric oncology facilities in Switzerland.

Next steps will be the new fixed beam facility OPTIS2 with expected start of patient treatment in April 2009. Gantry II with a further developed beam scanning system and the possibility to treat moving targets will become operational in 2010. The maximum capacity of the expanded facility (2 gantries, one fixed beam) will be about 500 patients per year.

Apart from an increased capacity for patient treatment PSI will be still a research center for clinical studies (new indications and applications) as well as for technological developments (product improvements). Basic science (radiobiology, translational research) and teaching will be in focus of interests.
Proton-Radiotherapy at PSI: More than 20 years of experience
Status and Vision

Ralf A. Schneider
Paul Scherrer Institute, Villigen
Switzerland

The Era of modern, contemporary Proton Radiation Therapy (PRT):

1973 First patient treated at HARVARD CYCLOTRON LABORATORY / MGH using standard, fractionated, "large field" technique (2 CGE / fraction)

The Era of modern, contemporary Proton Radiation Therapy (PRT):

1991 First hospital-based Proton facility at Loma Linda University Medical Center, Loma Linda, CA.
Proton RT – current applications in the U.S.

- CNS: primary brain tumors, skull base tumors
- Head & Neck: including eye and orbit
- Thoracic RT: lung, mediastinal tumors
- GI: currently limited to liver and selected local boost
- GU: prostate
- Sarcomas: STS, Osteo-, chondrogenic, (trunk, H&N)
- Pediatric malignancies: primarily solid tumors
- Breast: complex breast and lymphatic drainage RT, partial breast RT

Proton RT

- after >30 years no single disease entity ever treated with protons was later found unsuitable
- no publication has raised the issue of unexpected acute or late toxicity
- any incidence of late toxicity is related to high dose escalation rather than use of protons.
- The initial concept of physical dose distribution and effectiveness has not been called into question by clinical results
- HOWEVER: NO Phase III trials available comparing protons and photons. All data based on Phase I/II trials or retrospective reviews.
  Limited multi-institutional collaboration.

Pion therapy: 1980-1993

- 503 patients (high-LET radiation)
- PROTRON
  - 60 concentric pion beams
  - Pion raster scanning (20 fract.)
    - CT-based 3D-conformal planning
    - Some good results
  - Large tumors in the low pelvis (sarcomas)
- No clear evidence of benefits from high-LET radiation
  - Conformation as the most important factor
    - Since 1982 ... wish to treat the same cases with protons
      - 5 x smaller spot with protons
  - Lesson with the pions (neutrons)
  - Precautions in using high-LET due to late complications

Eye melanomas

- 5100 patients treated since 1984
- using the 70 MeV beam of injector 1
- 4 fractions (all in one week)

Eye retention

- Local control 99%
  - from 100% to 90% depending on tumour size
- Survival 90%
Characteristics:
- Magnetic scanning started before the last bending magnet
- Eccentric mounting of patient table on the gantry front wheel
- 360° axial rotation
- Patient couch rotation in the horizontal plane by ±120°
- Gantry radius 2m (scattering gantries R=5-6 m)

Clinical use of GANTRY 1:
- >440 patients treated since 1996
- Low availability of the proton beam
- Mainly tumors in the skull, spinal chord and low pelvis
- Only non-moving targets
- First human patient treated in 1996
- 30-40 fractions (treatment > 7 weeks)
- Capability
  - Max 19 patients/ day
  - 2.8 fields/ fractions in average
  - Multiple fields delivered without personnel entering treatment room

In 2000:
the decision to upgrade the PSI facility with a dedicated cyclotron
The project PROSCAN

In 2007:
Decision to upgrade the status of the division of Radiation Medicine at PSI to a Center of Proton Radiation Therapy
Layout of the new Center of Proton Radiation Therapy

- Installation of a dedicated cyclotron (completed)
- Beam for Gantry 1 for year-round operation (09/2007)
- Second generation compact gantry for scanning: Gantry 2 (start 2010)
- Horizontal beam line for OPTIS 2 (start 04/2009)

Status: October 2008

Strengths of PSI:
world wide leaders in technological development
(accelerator, spot scanning, IMPT etc.)

Weakness:
it is not a hospital

Proton treatment delivery
Extending the dose in depth – the 'Spread-out-Bragg-peak'
Passive scattering in practice

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

Spot scanning speed on Gantry 1: 12,000 Spots/min
Intensity Modulated Proton Therapy: The simultaneous optimisation of all Bragg peaks from all incident beams. E.g.,


Proton-Radiotherapy at PSI: The Immediate Future

• CLINICAL RESEARCH – Indications and Applications
• TECHNOLOGICAL DEVELOPMENTS: Product improvements
• INTERDISCIPLINARY COOPERATIONS
• BASIC SCIENCE – Radiobiology, translational research
• TEACHING

Established Indications treated historically at PSI (and accepted by insurance carrier)

• Ocular Melanomas
• Chordomas and Chondrosarcomas of skull base and axial skeleton
• Meningiomas
• (Low Grade Gliomas)
• Unresectable Sarcomas
• Other histologies related to skull base and paraspinal location
• Pediatric Neoplasms

No indication is based on Phase III trial evidence nor will that evidence be available any time soon!
Tumors of the Skull Base

• Primary Tumors:
  - Chordomas, Chondrosarcomas

• Secondary Infiltration by intracranial Tumors:
  - Meningiomas

• Secondary Infiltration by ENT Tumors:
  - Nasopharyngeal Carcinoma,
  - Paranasal Carcinoma,
  - Adenoid cystic Carcinoma
  - others

Chordoma and Chondrosarcomas n=64

Paul Scherrer Institute:
- LC 5 years
  - Chordomas 81%
  - Chondrosarcomas 94%

Mass. General Hospital:
- LC 5 years
  - Chordomas 73%
  - Chondrosarcomas 98%

Local control

Grade III-IV late toxicities: 5 – 7%

Skull base Chordomas:
Comparison of Literature

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Radiation</th>
<th>Mean dose</th>
<th>LC 5%</th>
<th>LC 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marzei, 1999</td>
<td>20</td>
<td>PT, RT</td>
<td>76</td>
<td>73</td>
<td>54</td>
</tr>
<tr>
<td>Lembach, 1990</td>
<td>15</td>
<td>PT, RT</td>
<td>69</td>
<td>59</td>
<td>44</td>
</tr>
<tr>
<td>Hug, 1990</td>
<td>36</td>
<td>PT, RT</td>
<td>71</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>Noel, 2003</td>
<td>27</td>
<td>PT, RT</td>
<td>67</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>Schade-Eilers, 2007</td>
<td>96</td>
<td>Carbon, PT</td>
<td>66*</td>
<td>51</td>
<td>70</td>
</tr>
<tr>
<td>Igaki, 2004</td>
<td>13</td>
<td>PT, RC</td>
<td>72</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Weber, (PSI, 2005)</td>
<td>48</td>
<td>PT</td>
<td>74</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Aus, (PSI) 2006*</td>
<td>64</td>
<td>PT</td>
<td>74</td>
<td>47</td>
<td>81</td>
</tr>
</tbody>
</table>

* at 3.0 GSE per fraction
** IJROBP in press
Some proton / IMXT comparisons - Sarcoma (12 Yrs boy)

Factor 6 lower integral dose for protons

3 intensity-modulated beams, evenly spaced over 360°
3 Target Volumes
  Brain stem: 76 Gy
  Maxillary sinus: 66 Gy
  Optic nerves: 47 Gy

Nominal constraints
  Optic nerves < 56 Gy
  Brain stem < 53 Gy
  Eyes < 50 Gy

Dose Volume IMPT vs. IMXT comparisons – Maxillary Sinus

Proton Therapy at PSI in very young Children

Pediatric Anesthesia: max. 4 Children per day
Protontherapy in Pediatrics

Protontherapy world wide accepted as the preferred radiation therapy (but not yet available...):

- Highly conformal (dose escalation!) with few field arrangements
- Low integral dose
- Thus, potentially reduction of late effects and secondary cancer
- Requiring high precision, time consuming

Proton-Radiotherapy at PSI:

Tumor- and Patient-Selection

Established Indications

Skull Base Tumors, Paraspinal Tumors, Pediatric Tumors, Uveal Melanomas

- Continue improvements of techniques
- Offer it as patient care service
- Reduce toxicities for diseases with excellent tumor control (uveal melanomas)
- Aggressively look for innovative approaches based on Trials for tumors with unsatisfactory control
- Large patient numbers on rare diseases (centralized referral) offer unique research possibilities

Proton-Radiotherapy at PSI:

The Immediate Future

- CLINICAL RESEARCH – NEW Indications and Applications

Applications for proton-radiotherapy will undergo rapid changes with increasing availability of protons in larger academic centers and evolving data

A static list of indications is a desired goal of health care politicians and insurance companies but has no medical meaning or practicality.
Patient / Disease Selection Policy at PSI:
The DON'Ts: Example: Prostate CA

- The FACTS:
  - Several thousand patients have been and continue to be treated with Proton-RT UNSELECTIVELY (compared to photons) for early stage, localized Prostate CA to doses similar to photon IMRT.
  - NO publication has ever resulted in a local control or survival benefit
  - The ONLY advantage is a presumed REDUCTION in incidence of severe side-effects from < 5% (photon IMRT?) to 1-2% (protons) (Not based on Phase III evidence) and a subjectively reported improved tolerance during the course of RT.

Patient / Disease Selection Policy at PSI:
The DON'Ts: Example: Prostate CA

- The logical Question:
  - Is it a prudent use of a limited resource that will not benefit 97% of the patients and only benefit 3% - but will not cure a single, additional patient?

PSI Goals: Identify specific disease subgroups potentially benefitting from PRT

IMRT Boost Planning on Dominant Intraprostatic Lesions: Gold marker-based Three-dimensional Fusion of CT with Dynamic Contrast-Enhanced and 1H-Spectroscopic MRI

E. Van Lin (Nijmegen), IJROBP 65:291; 2006

a) IMRT plan to 70 Gy entire prostate and 90Gy simultaneous boost to dominant intraprostatic lesion (DIL)
b) Conventional IMRT plan 78 Gy to entire prostate
Patient / Disease Selection Policy at PSI:
The (possible) DOs: Example: Prostate CA

- Think innovatively about the treatment of prostate cancer to identify a subgroup of patients
- REMEMBER: even a small percentage of prostate patients amounts to a significant absolute number

Proton-Radiotherapy at PSI:
HOW to explore new indications

- Example: A SYSTEMATIC approach
  - Identify specific site/disease in general terms
  - Identify outside Collaborator/Institution with high-end photon capabilities and medical physics capacity
  - Choose a variety of clinical scenarios and perform proton /photon comparison plans
  - Identify most promising result/scenario
  - Focus on most promising scenario and perform in-depth analysis.
  - IF difference to photons considered clinically relevant:

- DESIGN PILOT Phase III Study

Photon-Proton Planning Comparison of COMPLEX breast and nodal irradiation for breast cancer:
Collaboration PSI (C. Ares, T. Lomax) and KS-Aarau (S. Bodis)

The „emerging“ role of Proton Radiotherapy in the framework of conventional RT

Scenario 1: minimally agreed upon applications

Small or no role in frequent malignancies
Exclusive role in rare diseases
The “emerging” role of Proton Radiotherapy in the framework of conventional RT

Scenario 2: possible applications in a subgroup of patients in more frequent diseases, i.e. breast, lung, GI, ORL, GU etc.

Proton-Radiotherapy at PSI:

**The Immediate Future**

- CLINICAL RESEARCH – Indications and Applications
- TECHNOLOGICAL DEVELOPMENTS: Product improvements
  - INTERDISCIPLINARY COOPERATIONS
  - BASIC SCIENCE – Radiobiology, translational research
  - TEACHING

**Proton-Radiotherapy at PSI:**

**QUO VADIS? – TECHNOLOGICAL developments**

- Treat faster: new generation spot scanning, continuous dynamic scanning
- Treat more exact: scanning for mobile tumors, 4D-planning and treatment
- Improved target/volume definition: integrate diagnostic images. IGRT
- Inter- and intrafrac. changes: IGRT
- Incorporate other modalities (tradition of surgery needs to expand to chemotherapy)
- Fully embrace any progress in PHOTON-RT

New technological developments: Example

- Fast advanced beam scanning techniques for delivering IMPT on moving tumors with repainting

multiple opportunities to collaborate with photon-departments
Scan modes of Gantry 2: discrete scanning

- **MODE A**
  - Discrete spot scanning
  - Scanning sequence
    - 1. Magnetic in T
    - 2. Magnetic in U
    - 3. Energy variation
  - More robust against organ motion than with Gantry 1
  - Dose painted on the target only once or a few times

**STEP AND SHOOT METHOD**

- "The magnets wait for the beam"

- Beam size 7 mm FWHM
- 5 mm steps
- 10,000 spots/liter (21 x 21 x 21)
- ~1 Gy/liter/minute

**Proton-Radiotherapy at PSI:**

**The Immediate Future**

- **CLINICAL RESEARCH** – Indications and Applications
- **TECHNOLOGICAL DEVELOPMENTS:** Product improvements
- **INTERDISCIPLINARY COOPERATIONS**
  - **BASIC SCIENCE** – Radiobiology, translational research
  - **TEACHING**

**Mode 2: continuous scanning + modulated beam intensity**

- **Max. speed of sweeping in T**
- Beam intensity modulated scan (BISM)
  - Lines: 1 modulation @ max. speed
    - 10 ms for a 10 cm line
  - Planar lines at 5 mm distance
    - 10 cm: 20 lines > 200 ms
    - change of energy > 150 ms.
  - Volumes: 20 energy (5 mm) steps
    - 14 for a 1 liter-volume.
  - Frame merging capability
    - 17 scans / liter / in 2 minutes
    - (in development)
  - A long-range development
    - … software release

**Proton-Radiotherapy at PSI:**

**The Immediate Future**

**INTERDISCIPLINARY COOPERATIONS**

- Opportunities too numerous to list
Proton-Radiotherapy at PSI:
Interdisciplinary clinical Collaborations - Examples

• Diagnostic Radiology and Nuclear Medicine:
  - Project 1 - Characterize rare diseases by use of biologic and pathophysiologic imaging (MT-spectroscopy, various PET ligands etc.)
  - Project 2 - Evaluate pathophysiologic changes during and after proton-radiotherapy to correlate with outcome parameters

Note: PSI has accumulated large number of rare mesenchymal diseases treated homogenously.
Opportunity to acquire more knowledge of natural history and ability to study treatment outcome and improve treatment

Proton-Radiotherapy at PSI:
Interdisciplinary clinical Collaborations - Examples

• Pediatric Oncology:
  - Expect 5-7 children continuously under treatment at PSI
  - Approx. 60-80 infants, children and adolescents treated at PSI per year referred from CH and European neighbors

  • PSI will become one of the largest pediatric radiation oncology facilities in Switzerland

Proton-Radiotherapy at PSI:
The Immediate Future

• CLINICAL RESEARCH – Indications and Applications
• TECHNOLOGICAL DEVELOPMENTS: Product improvements
• INTERDISCIPLINARY COOPERATIONS
• BASIC SCIENCE – Radiobiology, translational research
• TEACHING

Proton-Radiotherapy at PSI:
Research Collaborations:

• Radiobiology at USZ: Prof. Dr. Martin Pruschy
  • Re-establish Particle-Radiobiology
  • Explore possible unique features and effects of proton-energy deposition (Bragg Peak) on molecular signal pathways
Proton-Radiotherapy at PSI: The Immediate Future

- CLINICAL RESEARCH – Indications and Applications
- TECHNOLOGICAL DEVELOPMENTS: Product improvements
- INTERDISCIPLINARY COOPERATIONS
- BASIC SCIENCE – Radiobiology, translational research
- TEACHING

Proton-Radiotherapy at PSI: Teaching Opportunities

1) Medical School Curriculum at University of Zurich
   - Proton-Radiotherapy as part of the discipline “Radioonkology”
   - Proton-Radiotherapy as part of Oncology
   - Disease-specific and -oriented role of Proton-Radiotherapy (disease-oriented teaching)
   - Proton-Radiotherapy

Maximize potential inter-institutional collaboration with ETH

2) Training opportunities prior to board certification on Radiation Oncology:
   - PSI Rotation for physicians
   - Official Recognition as training facility: opportunity open to all Swiss Institutions

3) Participation in various continuous medical education events