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

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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.

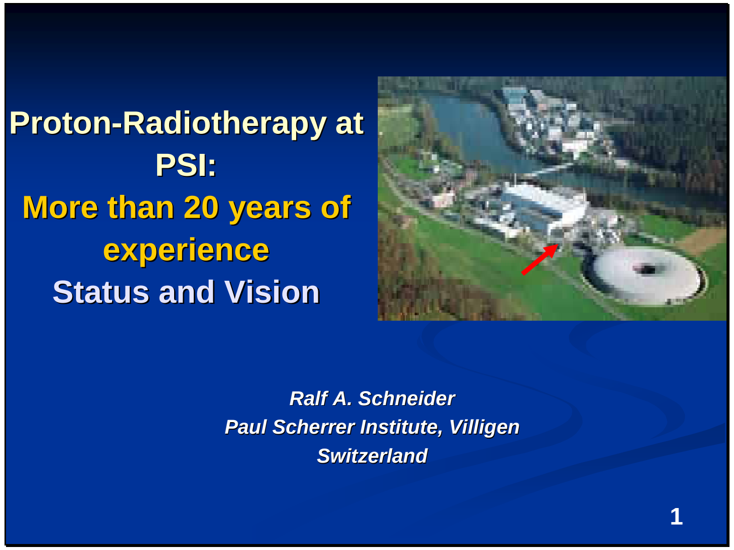
In 1996 the first human patient was treated with the innovative spot scanning technique at gantry I. Deep seated non-moving tumors mainly of the skull, spinal chord and lower pelvic region like chordomas and chondrosarcomas and other sarcomas were treated. In the meantime more than 440 patients have 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
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Switzerland
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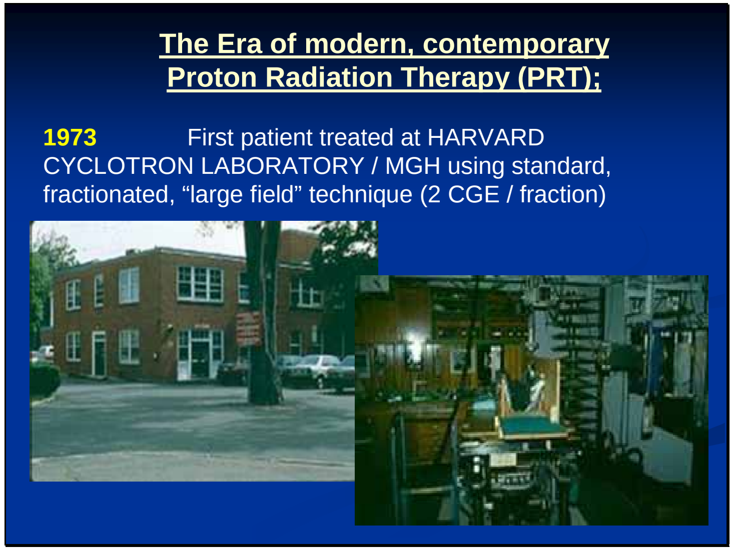
The Era of modern, contemporary Proton Radiation Therapy (PRT);
1973 First patient treated at HARVARD CYCLOTRON LABORATORY / MGH using standard, fractionated, "large field" technique (2 CGE / fraction)


The Era of modern, contemporary Proton Radiation Therapy (PRT);
1991 First hospital-based Proton facility at Loma Linda University Medical Center, Loma Linda, CA.
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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

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Proton 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.

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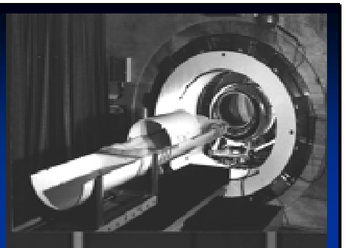
PSI
Pion therapy: 1980-1993



- 503 patients (high-LET radiation)
- PIOTRON
  - 60 concentric pion beams
  - Pion raster scanning (20 fract.)
    - CT-based 3d-inverse 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

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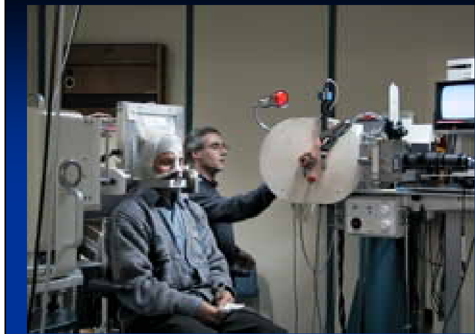
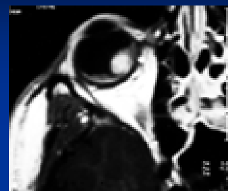


OPTIS: 1984-…



- Eye retention
- Local control 99%
  - from 100% to 90% depending on tumour size
- Survival 90%

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

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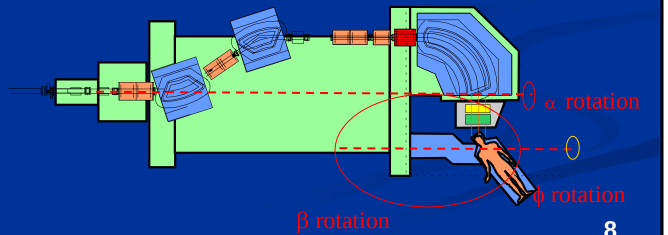
PSI gantry 1: 1991…

- 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)



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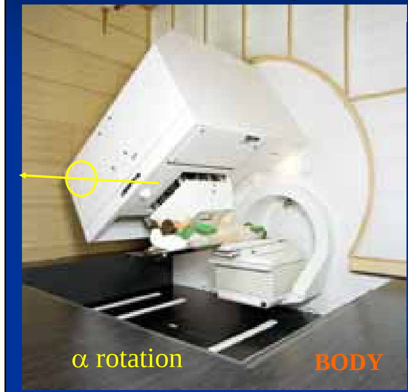
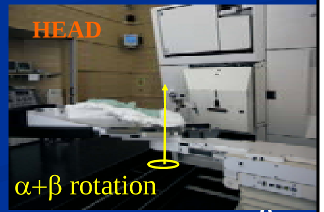
Gantry 1

- A compact gantry system dedicated to beam scanning



- Flexibility to apply the beam from almost any direction
  - Critical: <u>when the beam comes from below ..</u>



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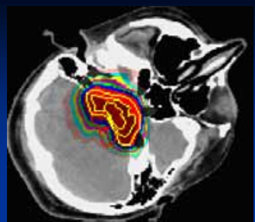
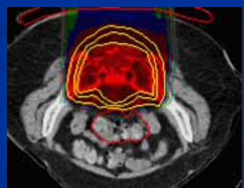
Clinical use of GANTRY 1

- > 440 patients treated since 1996
  - <u>Low availability of the proton beam</u>
- Mainly tumors in the skull, spinal chord and low pelvis
  - <u>only non moving targets!</u>
  - 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



SKULL



PELVIS

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

In 2007:
Decision to upgrade the status of the division of Radiation Medicine at PSI to a
<u>Center of Proton Radiation Therapy</u>

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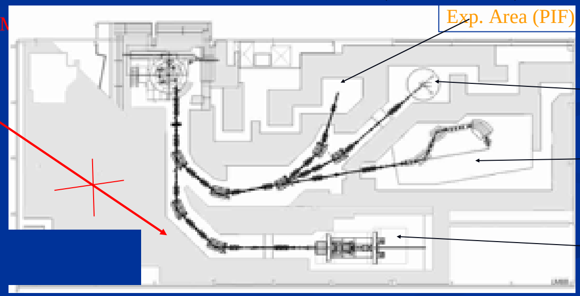
Layout of the new Center of Proton Radiation Therapy

- Installation of a dedicated cyclotron (completed)
- Beam for Gantry 1 for year-round operation (08/2007)
  Second generation compact gantry for scanning: Gantry 2 (start 2010)
- Horizontal beam line for OPTIS 2 (start 04/2009)



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Gantry 2 layout

Status: October 2008

- Large patient-friendly open treatment area
- On a fixed floor (as with a horizontal beam line - but with a gantry)
- Fast patient positioning with two fixed 45° X-rays tube-imager pairs

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

Weakness:
it is not a hospital

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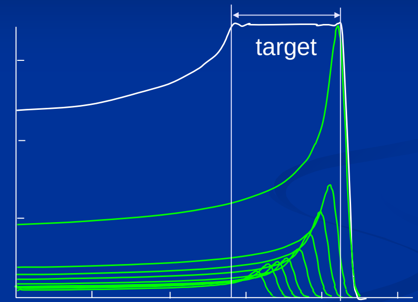
Proton treatment delivery

Extending the dose in depth – the 'Spread-out-Bragg-peak'



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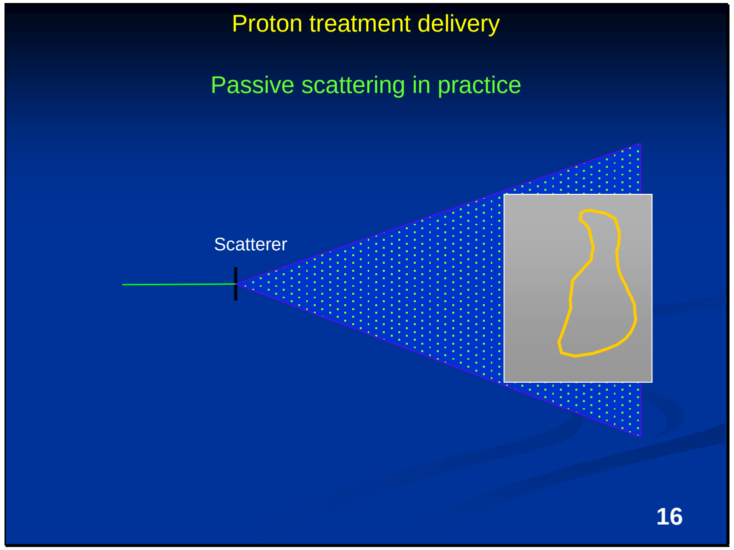
Proton treatment delivery
Passive scattering in practice
Scatterer
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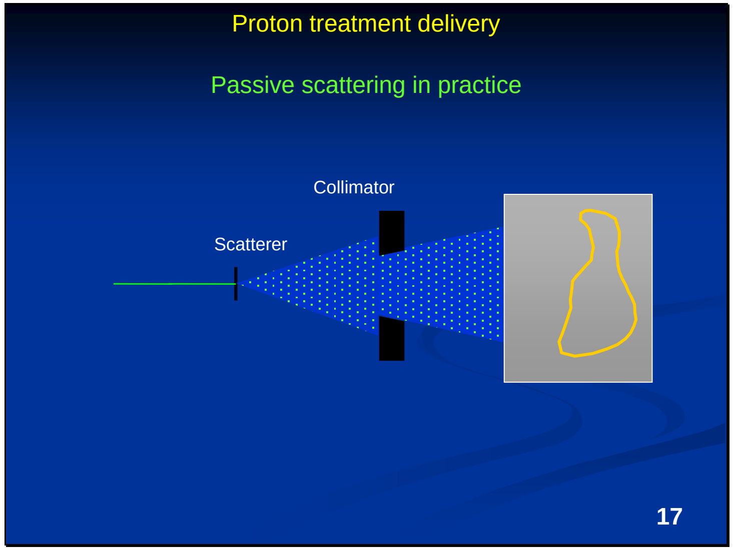
Proton treatment delivery
Passive scattering in practice
Collimator
Scatterer
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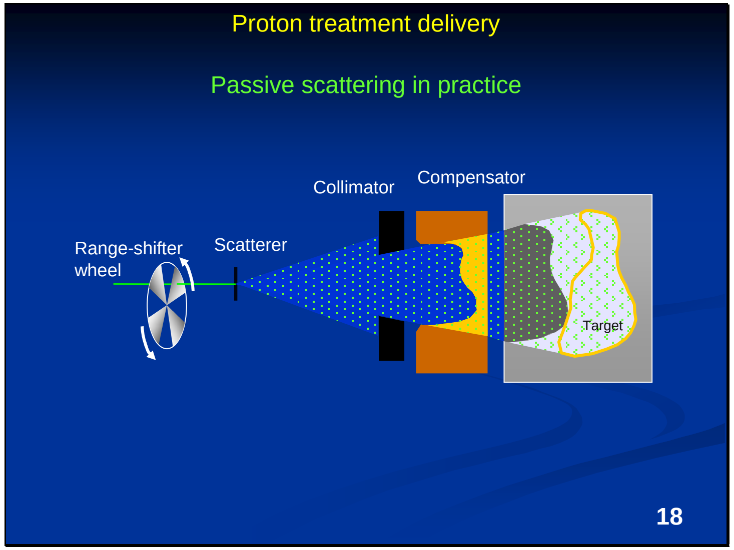
Proton treatment delivery
Passive scattering in practice
Collimator
Compensator
Range-shifter wheel
Scatterer
Target
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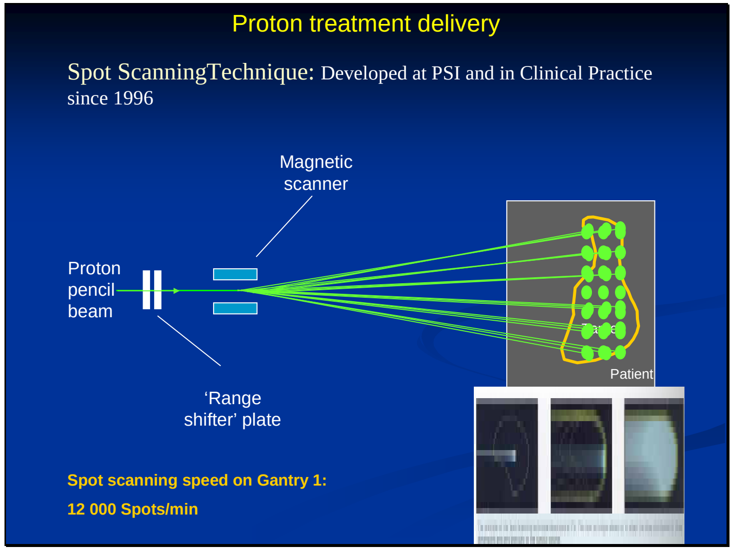
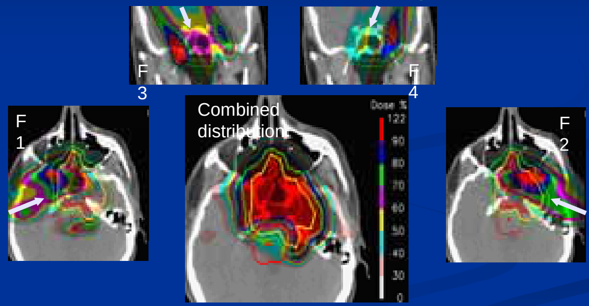

Proton treatment delivery
Spot ScanningTechnique: Developed at PSI and in Clinical Practice since 1996
Magnetic scanner
Proton pencil beam
'Range shifter' plate
Patient
Spot scanning speed on Gantry 1:
12 000 Spots/min

PSI: the only center world wide to offer IMPT

Intensity Modulated Proton Therapy: The simultaneous optimisation of all Bragg peaks from all incident beams. E.g..



Lomax, *Phys. Med. Biol.* 44:185-205, 1999

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Proton-Radiotherapy at PSI:

The Immediate Future

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

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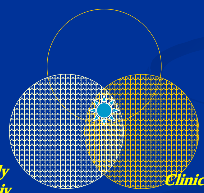
Proton-Radiotherapy at PSI:

The Immediate Future

- CLINICAL RESEARCH – Indications and Applications



Patient treatment at PSI: the mission

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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 !

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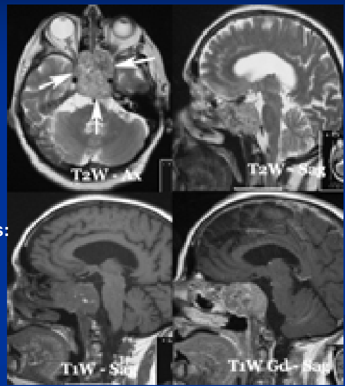
Tumors of the Skull Base

• **Primary Tumors:**
  - **•Chordomas, Chondrosarcomas**

•Secondary Infiltration by intracranial Tumors:
  - **•Meningiomas**

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

Chordoma



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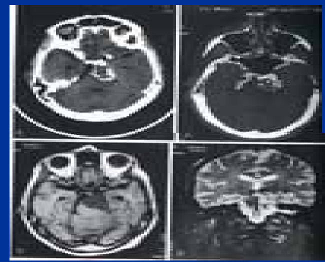
Chordomas:

Midline, soft, gelatinous,

Chondrosarcomas:

Midline or lateral, can be calcified, hard



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Tumors of the Skull base:

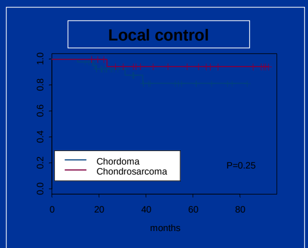
Chordomas and Chondrosarcomas n=64

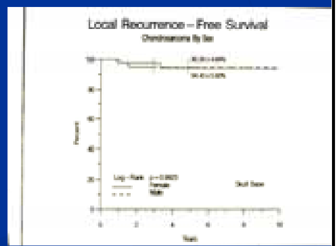
Paul Scherrer Institute:

LC	5 years
Chordomas	81 %
Chondrosarcomas	94 %

Mass. General Hospital:

LC	5 years
Chordomas	73 %
Chondrosarcomas	98 %





Grade III-IV late toxicities: 5 – 7 %

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Skull base Chordomas:

Comparison of Literature

	n	Radiation	Mean dose	LC 3-yr	LC 5-yr	LC 10-yr
Munzenrider, 1999	290	PT,RT	76		73	54
Terahara, 1999	115	PT, RT	69		59	44
Hug, 1999	58	PT, RT	71	67	59	
Noel, 2003	67	PT, RT	67	69		
Schulz-Ertner, 2007	96	Carbon, RT	60*	81	70	
Igaki, 2004	13	PT, RT	72	67	46	
Weber, (PSI) 2005	18	PT	74	87		
Ares, (PSI) 2008**	64	PT	74	87	81	

*at 3.0 CGE per fraction

** IJROBP in press

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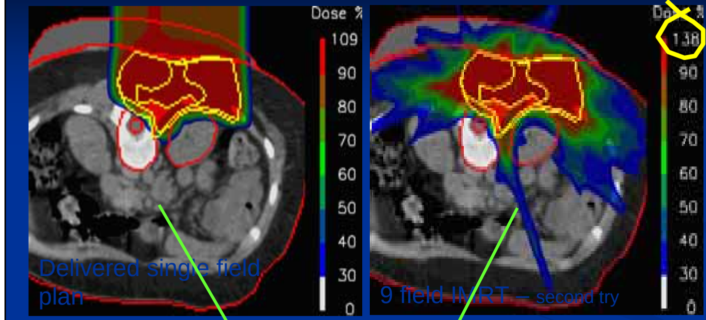
Some proton / IMXT comparisons - Sarcoma (12 Yrs boy)



Factor 6 lower integral dose for protons

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IMPT vs. IMXT comparisons – Maxillary Sinus

MGH

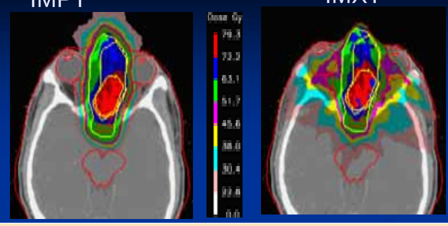
9 intensity-modulated beams, evenly spaced over 360°

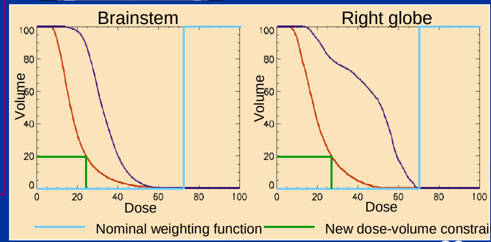
3 Target Volumes

Gross volume: 76Gy
Subclinical: 66Gy
Microscopic: 54Gy

Nominal constraints

Optic nerves < 56Gy
Brainstem < 53Gy
Eyes < 50Gy





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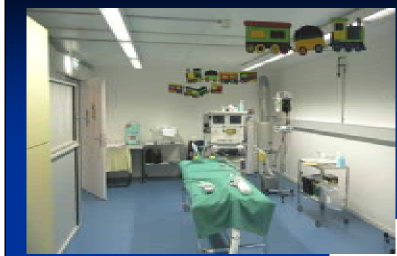
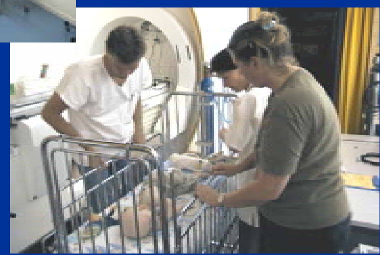
Proton Therapy at PSI in very young Children



Pediatric Anesthesia: max. 4 Children per day



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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

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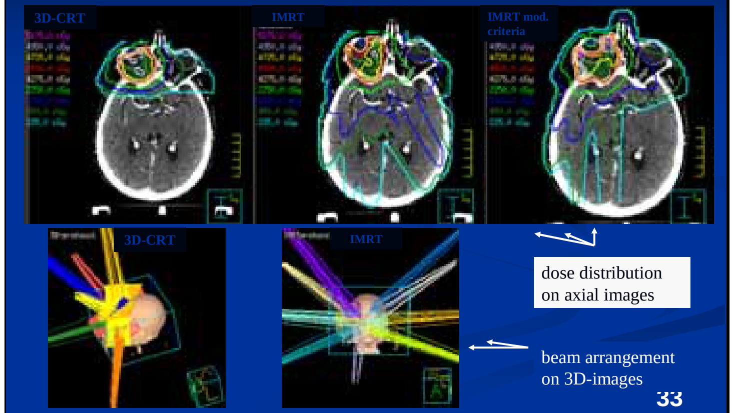
Dose distribution to the brain following planning with 3D-CRT / IMRT



dose distribution on axial images

beam arrangement on 3D-images

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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**

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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.

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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.

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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?

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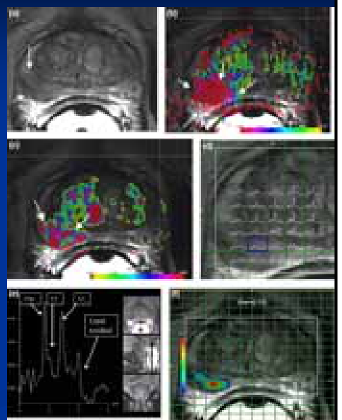
PSI Goals: identify specific disease subgroups potentially benefitting from PRT

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



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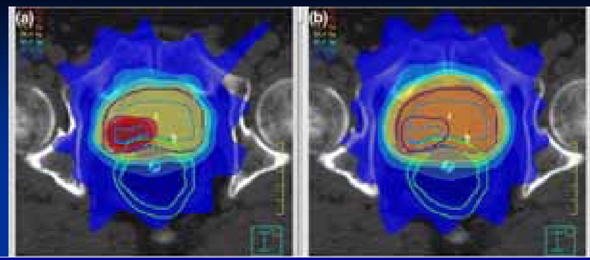
E. Van Lin (Nijmegen), IJROBP 65:291; 2006



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

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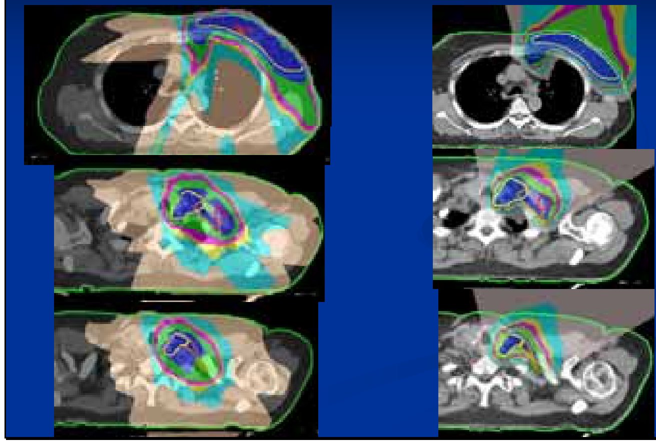
Photon-Proton Planning Comparison of COMPLEX breast and nodal irradiation for breast cancer:

Collaboration PSI (C. Ares, T. Lomax) and KS-Aarau (S. Bodis)



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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 I/II Study

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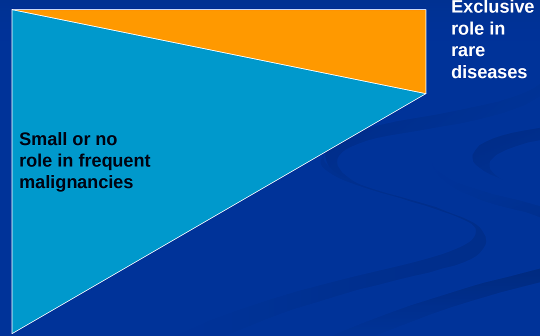
The „emerging" role of Proton Radiotherapy in the framework of conventional RT

Scenario 1: minimally agreed upon applications



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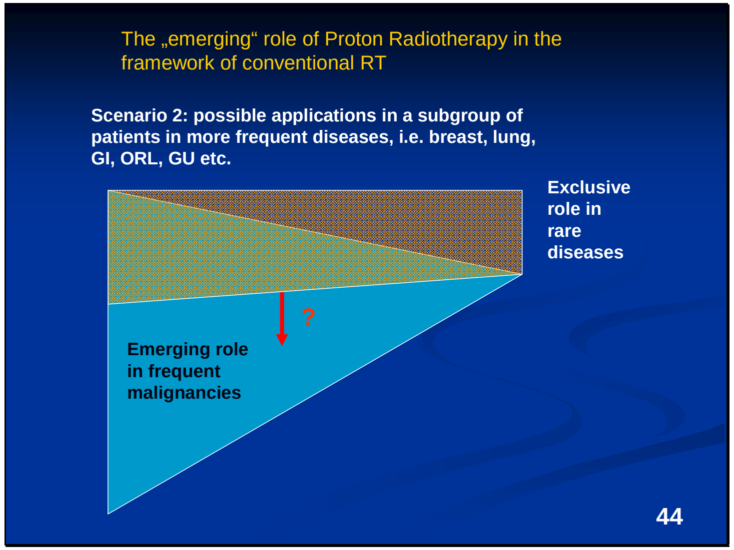
The „emerging“ role of Proton Radiotherapy in the framework of conventional RT
Scenario 2: possible applications in a subgroup of patients in more frequent diseases, i.e. breast, lung, GI, ORL, GU etc.
Exclusive role in rare diseases
?
Emerging role in frequent malignancies
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Proton-Radiotherapy at PSI:
The Immediate Future
• CLINICAL RESEARCH – Indications and Applications
•TECHNOLOGICAL DEVELOPMENTS: Product improvements
•INTERDISCIPLINARY COOPERATIONS
•BASIC SCIENCE – Radiobiology, translational research
•TEACHING
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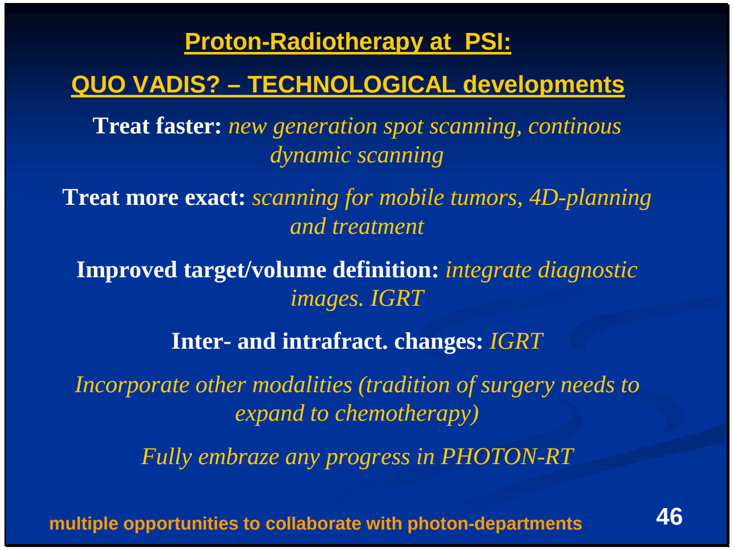
Proton-Radiotherapy at PSI:
QUO VADIS? – TECHNOLOGICAL developments
Treat faster: new generation spot scanning, continous dynamic scanning
Treat more exact: scanning for mobile tumors, 4D-planning and treatment
Improved target/volume definition: integrate diagnostic images. IGRT
Inter- and intrafract. changes: IGRT
Incorporate other modalities (tradition of surgery needs to expand to chemotherapy)
Fully embraze any progress in PHOTON-RT
multiple opportunities to collaborate with photon-departments
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New technological developments: Example
Fast advanced beam scanning techniques for delivering IMPT on moving tumors with repainting
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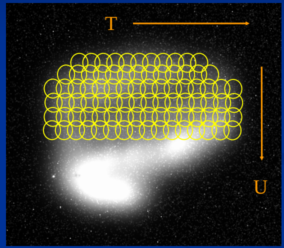
Scan modes of Gantry 2: discrete scanning

- 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

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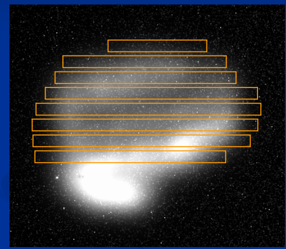
Mode 2: continuous scanning + modulated beam intensity

- Max. speed of sweeping in T
  Beam-intensity modulated scan (BIM)
  - Lines: I-modulation @ max. speed
    - 10 ms for a 10 cm line
  - Planes: lines at 5 mm distance
    - 10cm -> 20 lines -> 200 ms
    - change of energy-> 150 ms.
  - Volume: 20 energy (5mm) steps
    - 7 s for a 1 liter volume.
  - Target repainting capability
    - 17 scans / liter / in 2 minutes
      - *(to be shown)*
    - A long-range development
      - …software release

Continuous modulated scanning along overlapping T-lines
„The beam follows the magnet“



Triggering and tumor tracking:
Apply offsets to U and T sweepers / per plane

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Proton-Radiotherapy at PSI:
The Immediate Future

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

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Proton-Radiotherapy at PSI:
The Immediate Future

- INTERDISCIPLINARY COOPERATIONS

Opportunities too numerous to list

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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

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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

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Proton-Radiotherapy at PSI:

The Immediate Future

- • CLINICAL RESEARCH – Indications and Applications
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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

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Proton-Radiotherapy at PSI:

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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

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Proton-Radiotherapy at PSI: Teaching Opportunities

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

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