PAUL SCHERRER INSTITUT

# Advances in Spot Scanning

## Proton Therapy at PSI

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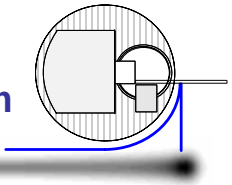
PARTICLE THERAPY CO-OPERATIVE GROUP



## ADVANCES

- are based on something that has the potential to advance
- in our case = particle therapy this can be technical or medical or a combination of both, or understanding and learning
- or another achievement (e.g. the OPTIS program at PSI)
- "*advances in physics" are in fact better understanding of physics*

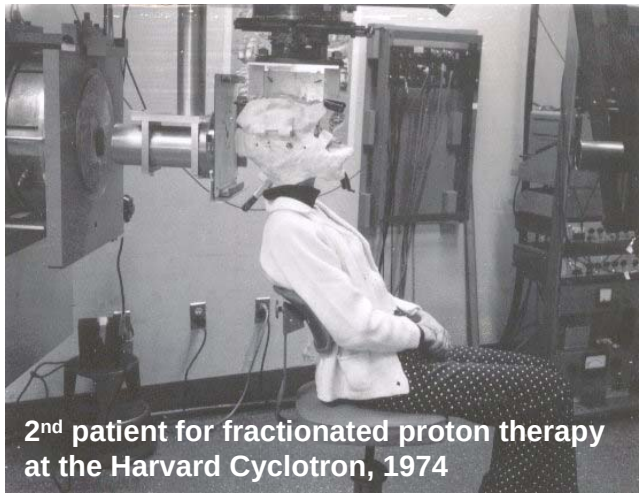
**Basis for possible advances in spot scanning proton therapy**

- technical achievement of 3-d, dynamic pion therapy at PSI and
- medical outcomes
- technical possibilities to realize pencil beam scanning for medical use
- medical results of broad beam proton therapy
- clinical needs in (radiation) oncology

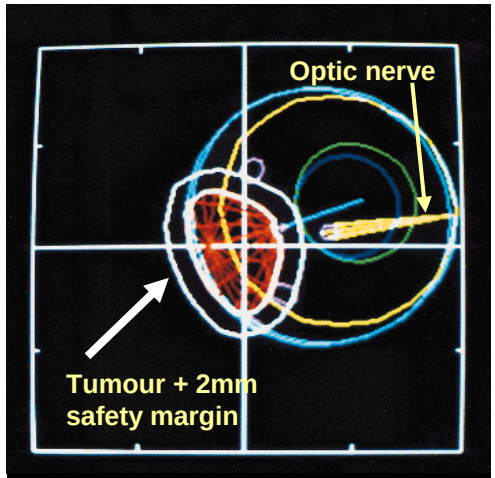
**"Real" advances would be**

- better LC and/or survival combined with less toxicity
- spot scanning protons as "natural" element of modern oncological treatment concepts

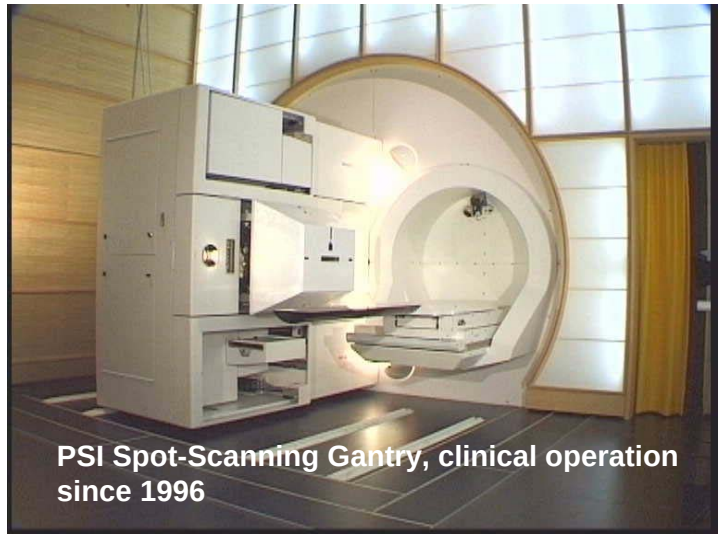
# Proton Therapy Program



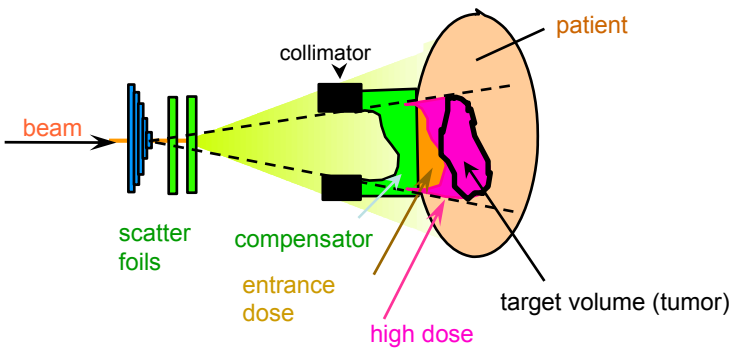
2nd patient for fractionated proton therapy at the Harvard Cyclotron, 1974

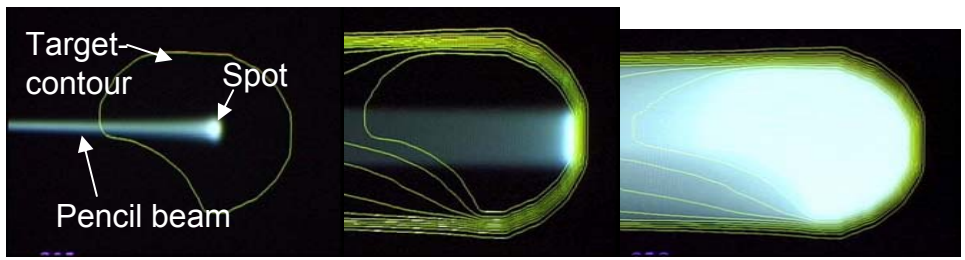



Treatment plan for proton therapy of ocular melanoma, 1976 to date

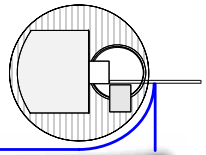


PSI Spot-Scanning Gantry, clinical operation since 1996




## Protons – applied physics in medicine since 1954



# Basis for possible advances in spot scanning proton therapy

PSI (SIN) realized for the first time a facility for 3-d conformal, dynamic particle beam therapy
The idea had been fascinating for many physicists (and doctors)
The technology was very sophisticated (incl. superconductivity)
The treatment planning program had been written in house (SIN)
The medical concept had been made by an international group of experts
The expectation was to control relatively radio-resistant tumors by using a particle with an RBE greater than that of x-rays and in addition to take advantage of 3-d conformation of the high dose region to the target volume

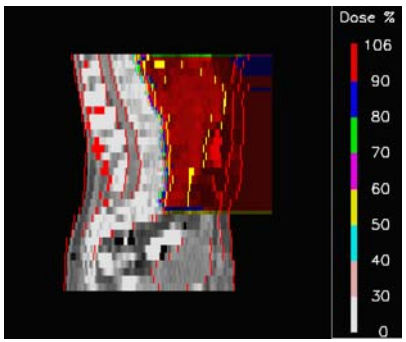
The outcome taught us that dynamic 3-d dose conformation was the prominent benefit of the project

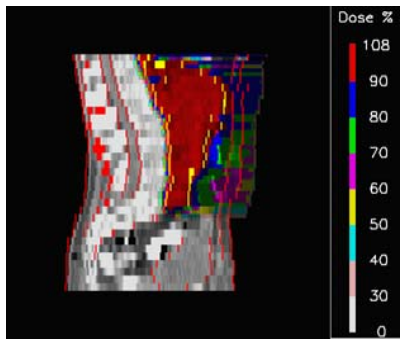
Glioblastomas e.g. were not better controlled with pions, as the concept of a strictly localized disease turned out to be incorrect
Large sarcomas responded well to conformal high dose irradiation, they were “treatable”, the high LET component of the pions contributed (probably) to the local control

The advance – after the shutdown of the pion project – in particle radiotherapy at PSI came with the concept for 3-d conformal proton therapy = a less exotic particle, less RBE uncertainty, better medical programs based on the experience with pions and ! with protons (HCL/MGH, PSI OPTIS), modern scanning technology for pencil beams

# Geometry of high dose deposition in depth. SITE, SIZE and SHAPE

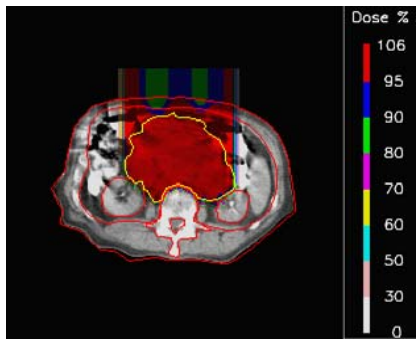
do matter for the choice of the best tool to control a lesion.
Example of a huge retroperitoneal tumor;
treatment planning for spot scanning protons and broad proton beams.

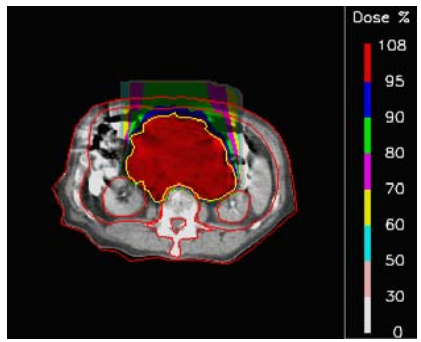



Broad beam

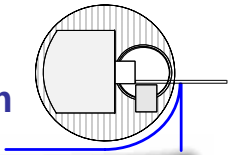
Spot scanning




Broad beam

Spot scanning



# Advances on the non-technical side

Creation of the Swiss Proton Users Group SPUG, a community of radiation oncologists and medical physicists who agreed upon 5 main categories of tumors as focus for the project's activities:

- **Lesions of the base of skull (chordomas, chondrosarcomas, H&N)**
- **Low grade gliomas**
- **Meningiomas, benign & atypical/malignant**
- **Sarcomas outside the skullbase, BS, STS**
- **Prostate cancer**

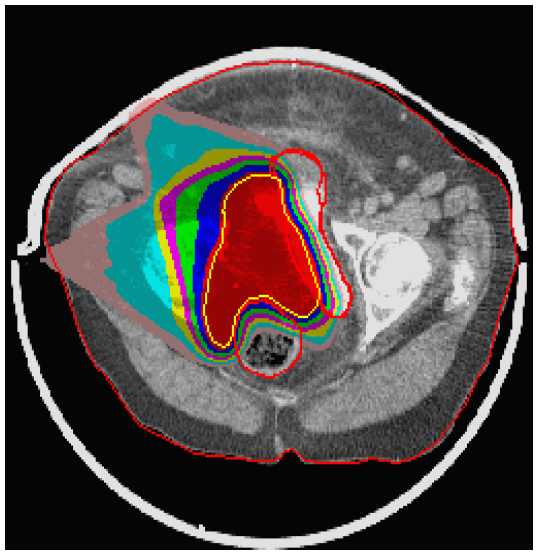
The choice had been made on the grounds of extensive engagement, which included on PSI's side

**information, presentation of the possibilities the new technology was offering, comparative treatment planning studies, finding out what the users' wishes were**

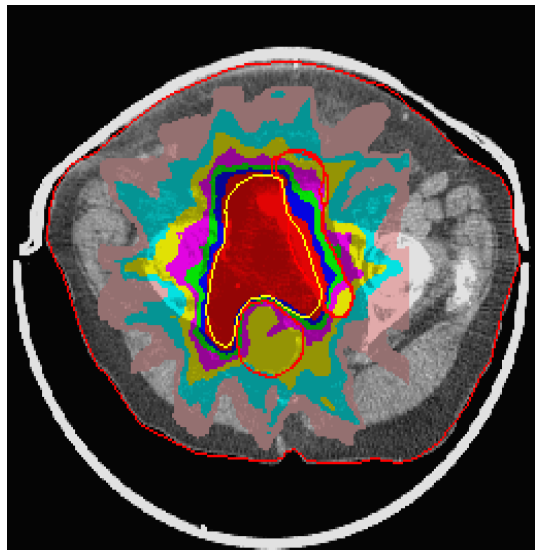
and on the users' side

**looking at own data and experience, discussion amongst centers, analyzing needs and wishes, decision-making**

# Die PSI Spotscanning – Technik – verglichen mit moderner Photonen – T



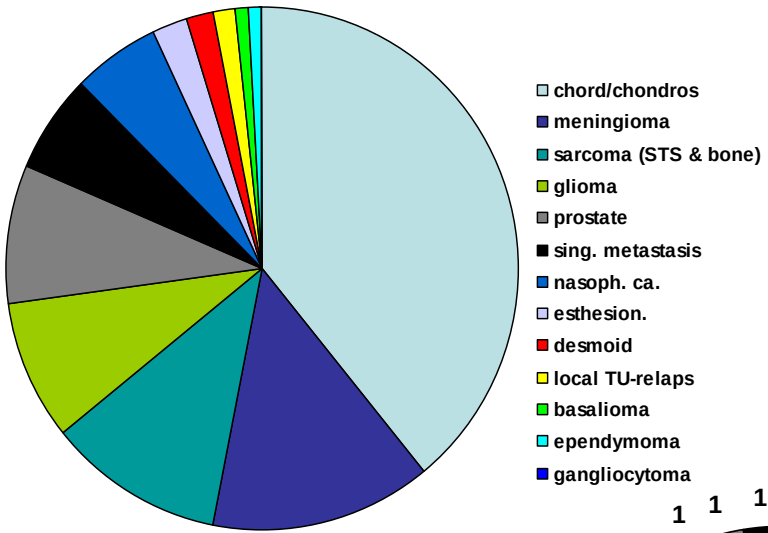
Der Fall:
60j., Patientin mit Rezidiv eines Zervixkarzinoms, nach Chirurgie und Chemotherapie .
Beispiel für einen grossen (ca. 1 Liter) , irregulär geformten Tumor, mit Befall der angrenzenden Wände von Blase und Rektum, Umgebungsstrukturen radiosensitiv.



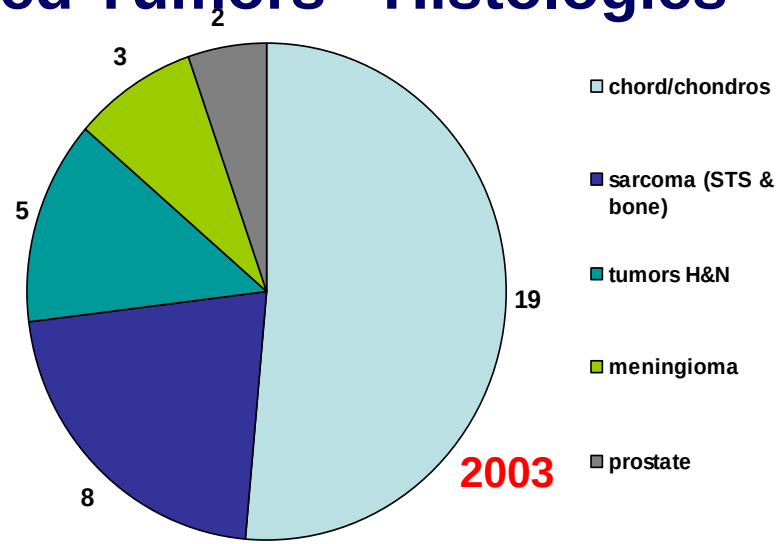
Protonendosisverteilung
Sehr gute Konformierung der Hochdosis an das Zielvolumen durch 2 Strahlrichtungen. Die nicht-befallenen Anteile der Blasen- und Darmwand werden durch den Dosisabfall geschont.

Intensitätsmodulierte, high-tech (9 Strahlen) Photonendosisverteilung (DKFZ)
Gleichgute Hochdosiskonformierung, aber höhere Belastung der gesamten Blase und der Rektumzirkumferenz. Höhere integrale Dosis im Becken.

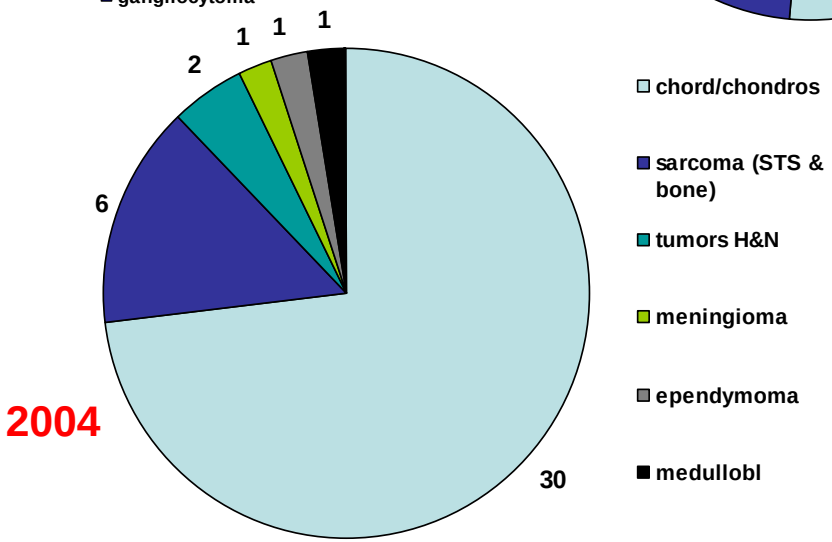
# Proton Therapy of Deep Seated Tumors - Histologies




1996 - 2002

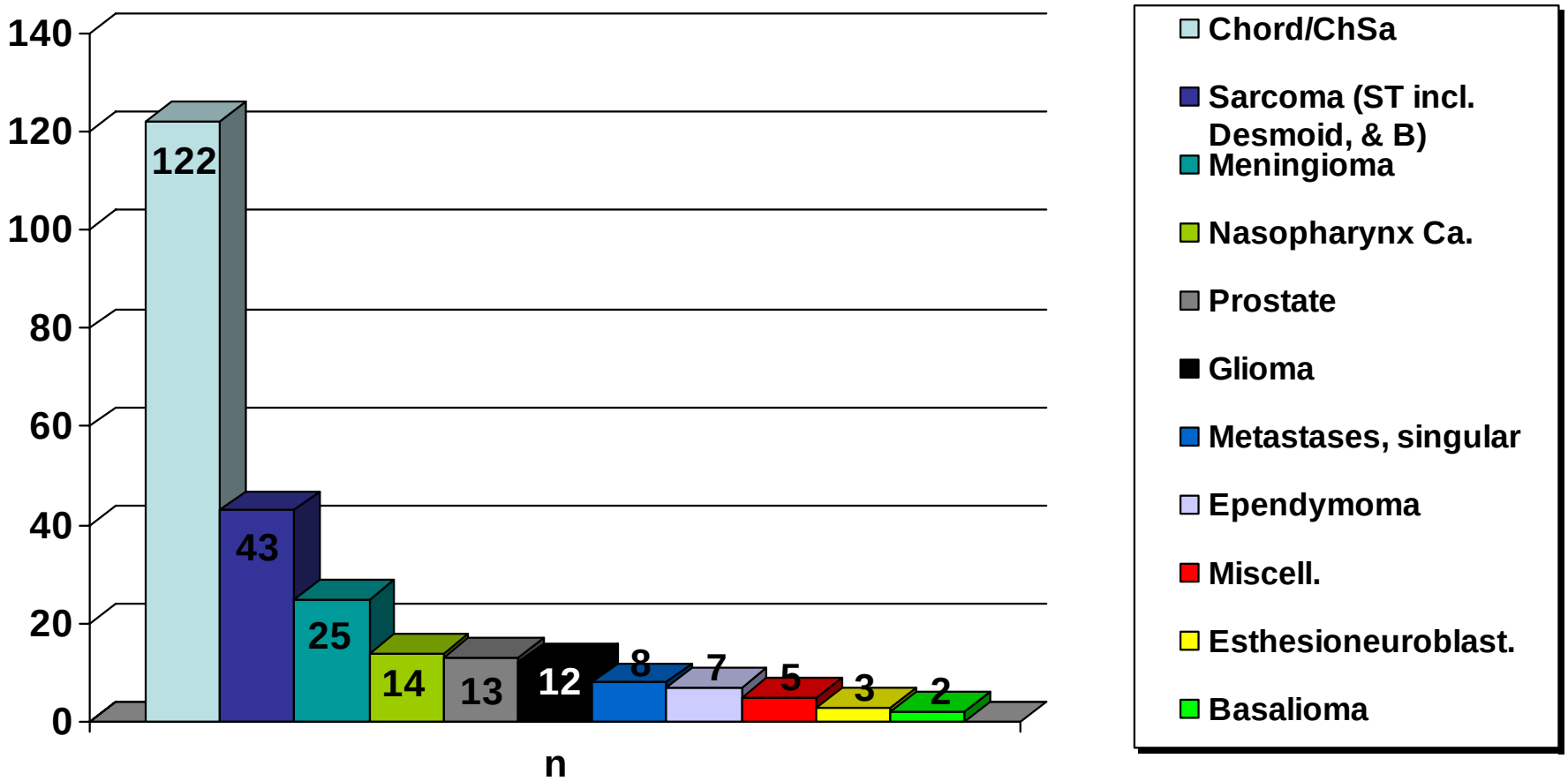



2003

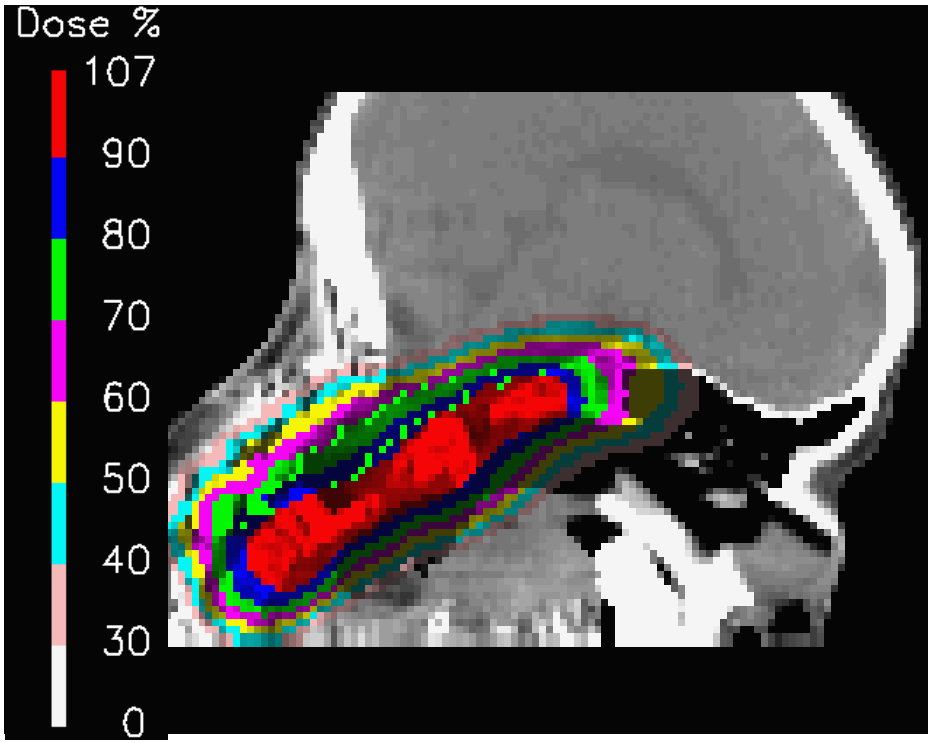



2004

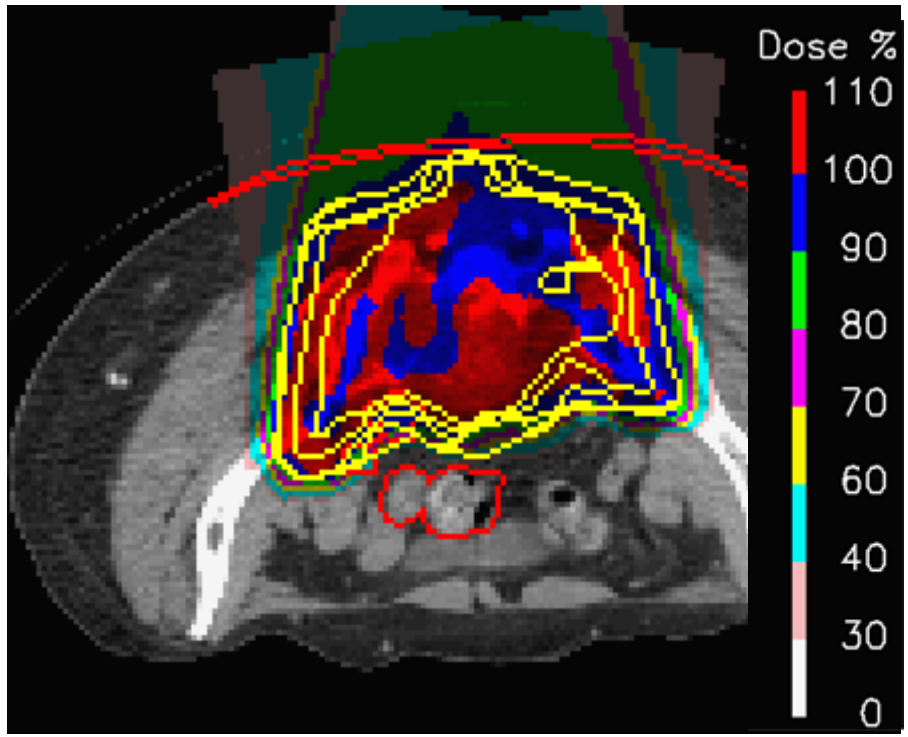
# Histologies 1996 – 2005
# n = 262



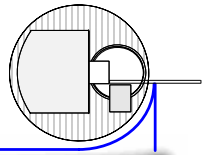
# Chordomas of the spinal axis




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




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



# Advances in patient referral, daily performance, treatment

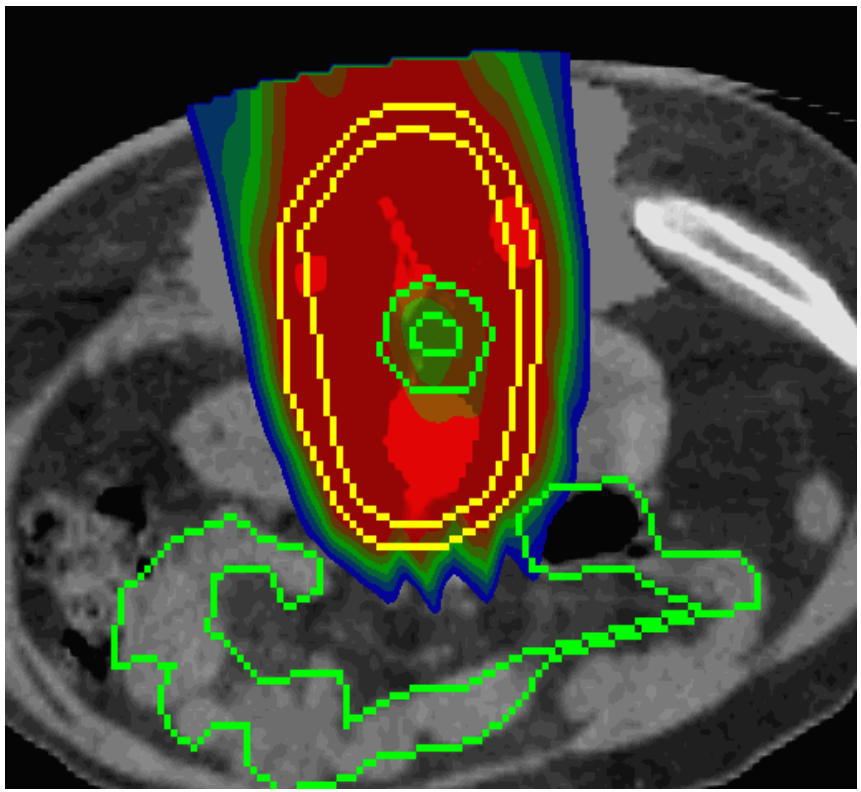
**Referrals were less focused during the first 5years**, the variety of tumor histologies and sites was large, not all treatment concepts were curative …..
However, chordomas and chondrosarcomas of the skullbase and spine presented the largest group
**With time** and with IMXT being introduced in Swiss centers (and abroad), the **referrals became more selected** according to the agreed upon indications.

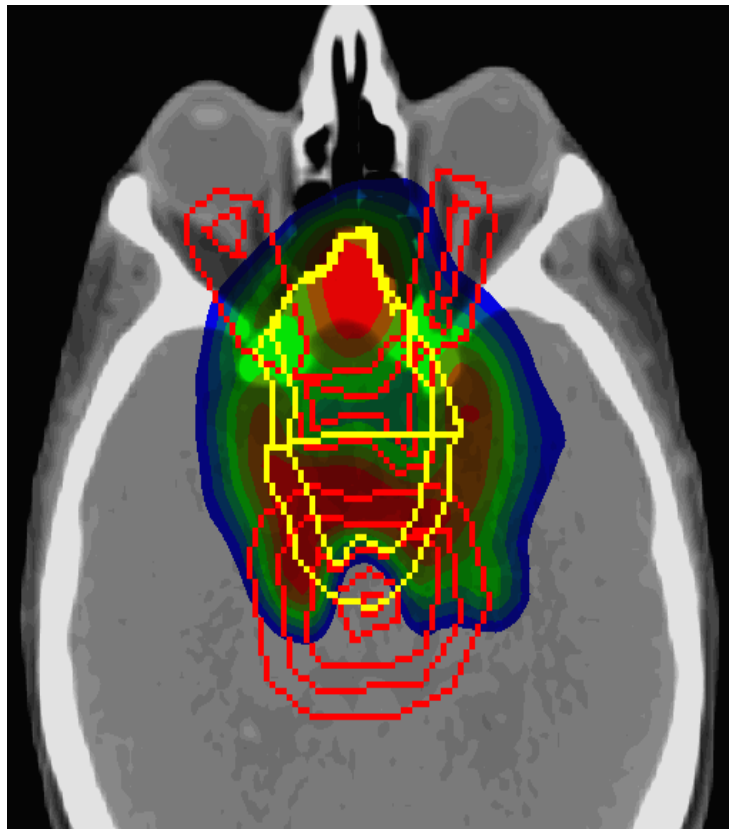
**Ongoing improvements** of procedures, hardware and software resulted in
better = more efficient and more comfortable daily procedures of patient setup and treatment and in
**development of IMPT and introduction into patient treatments**

**Outcome analysis**, though based on short follow up, **was promising**

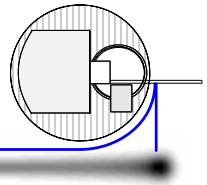
**Plans for** continuation of the medical program at PSI with a **2nd generation gantry and a dedicated proton accelerator** were made.
Realization depended on Health Insurance Coverage for the five tumor groups

# Intensity Modulated Proton Therapy (IMPT)
## Developed at PSI, introduced with great care, still under closest observation





Chordoma of the skullbase,
LC at 3 ys, no neurological toxicity



# Application for obligatory Health Insurance Coverage for "new services" in Switzerland

A formal process was started in 2000/2001with submission of an application to the **Federal Office for Social Insurance,** today to the ***Federal Office for Public Health***

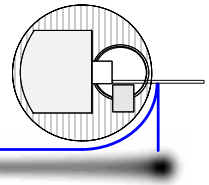
The written application had to cover the following topics

- Description of the service
- Rationale for the activity
- Existing and expected relevance in comparison to competitor services, national and international
- Analysis of existing data (own data, national and international data)
- Description of the so far measured and also the expected medical gain
- Analysis of immediate costs for the public health system
- Estimation of long term costs for the public health system (pilot project started with PSI's application, today routine)

In addition, an oral defense of the application had to be done in two sections.

The Federal Commission for Medical Services (ELK) accepted our application with one modification..

All new services in CH are granted for an evaluation period of 5 years, yearly short reports are obligatory; a final report must be submitted at the end of five years

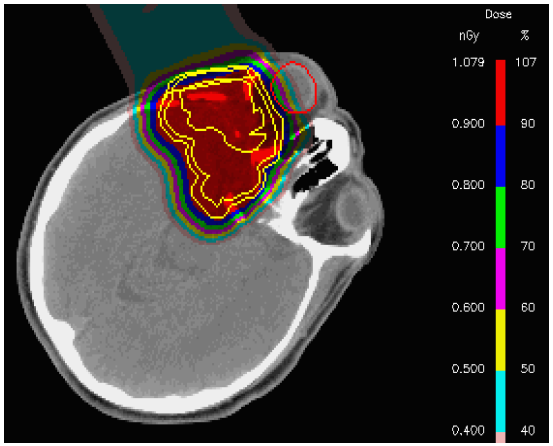


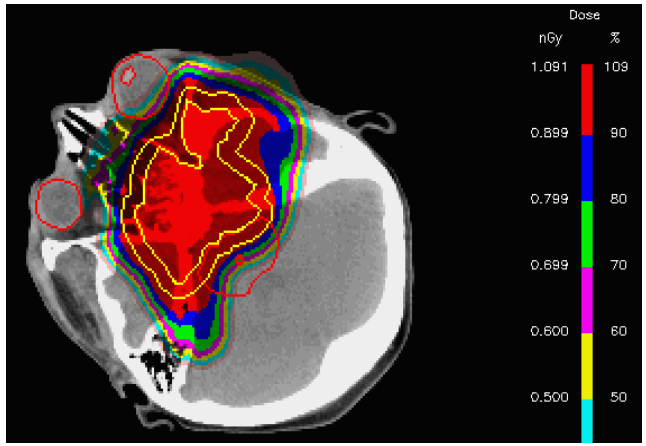
# Proton therapy of deep seated tumors using the PSI Spot Scanning Gantry

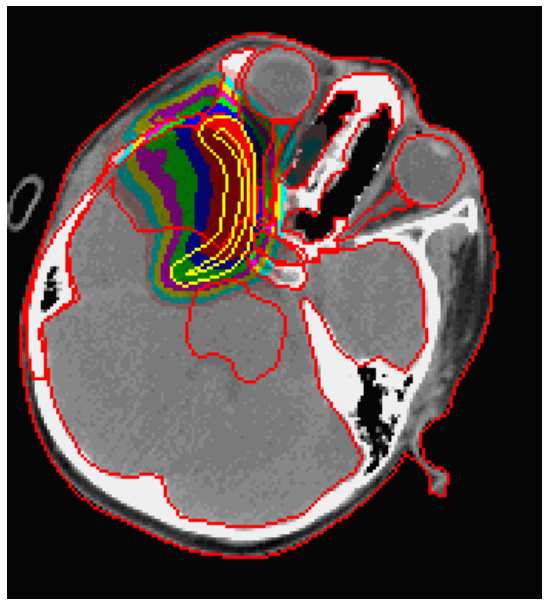
## Indications for PRT, which are accepted by the Swiss Health Insurance System as obligatory service (evaluation period of 5 ys. mandatory)

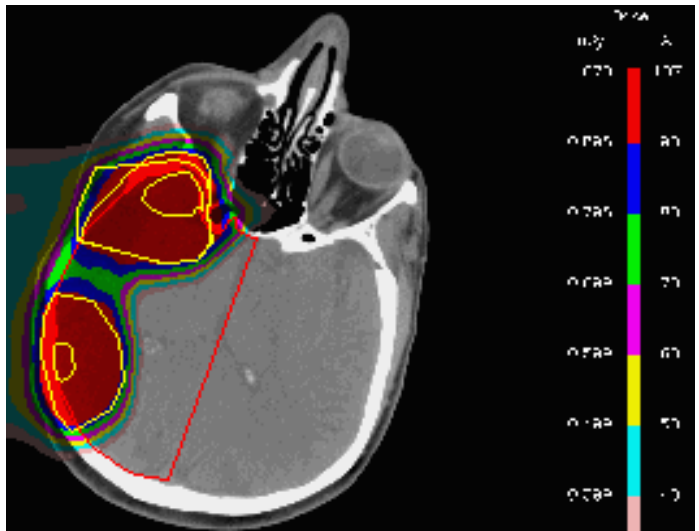
- tumors in the area of the base of skull (chordomas, chondrosarcomas, H&N lesions)
- meningiomas, benign and atypical/malignant
- low grade gliomas
- sarcomas/chordomas outside the base of skull
- pediatric tumors when conformal irradiation is required
- prostate cancer was denied due to very limited availability of the facility at PSI and consecutively too high expected costs for proton therapy abroad in a large number of patients

# Meningiomas:
# Dose distributions for lesions of various size and shape

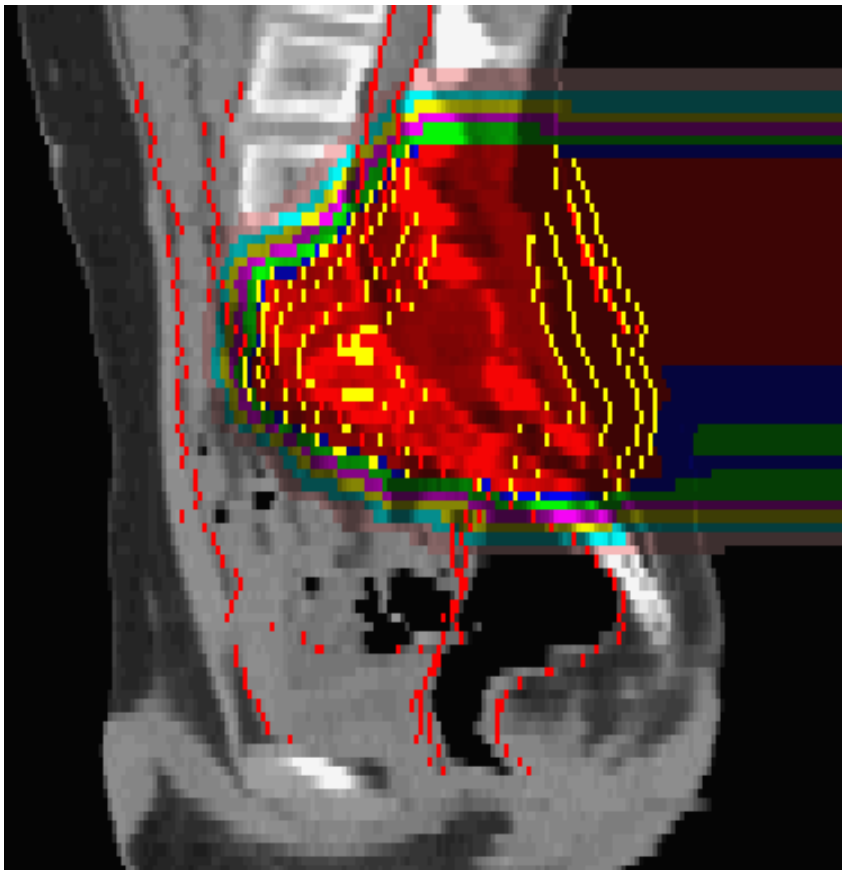


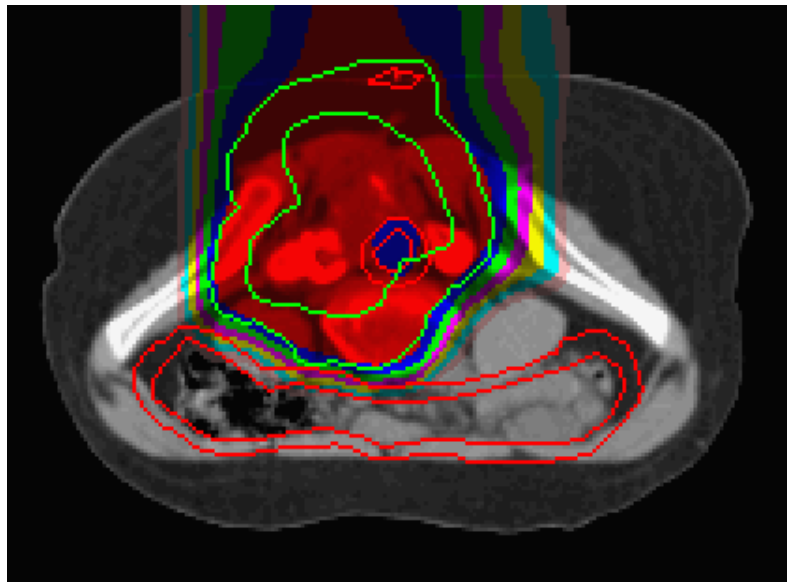





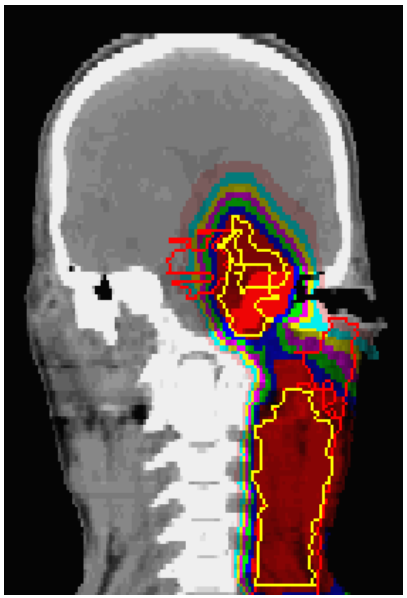
# Osteosarcoma in a 7 y/o boy

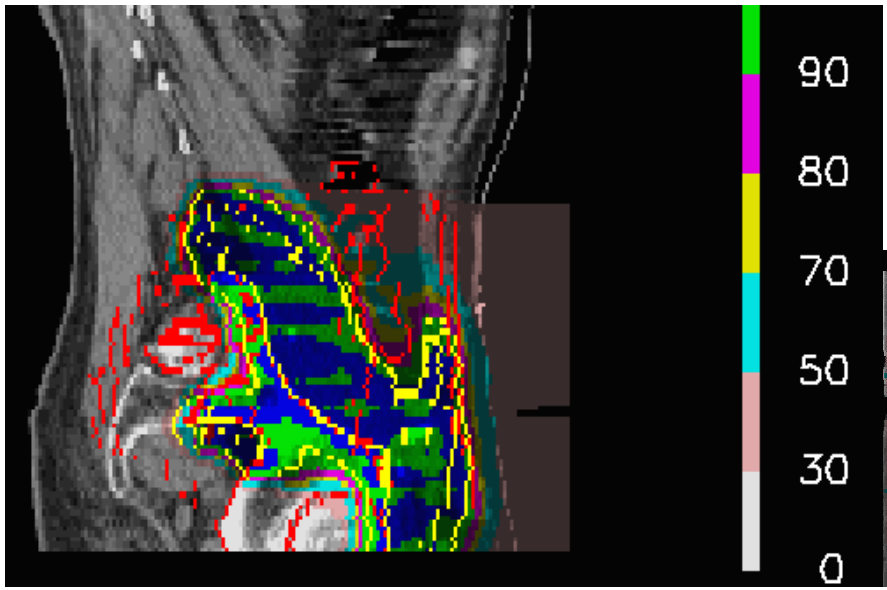


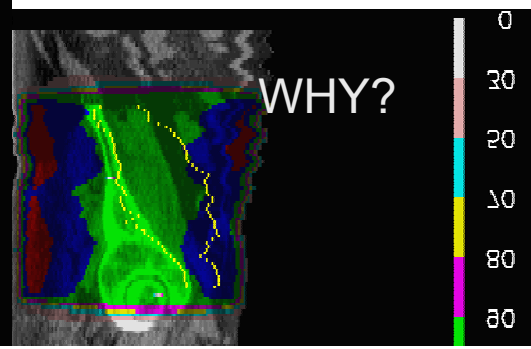



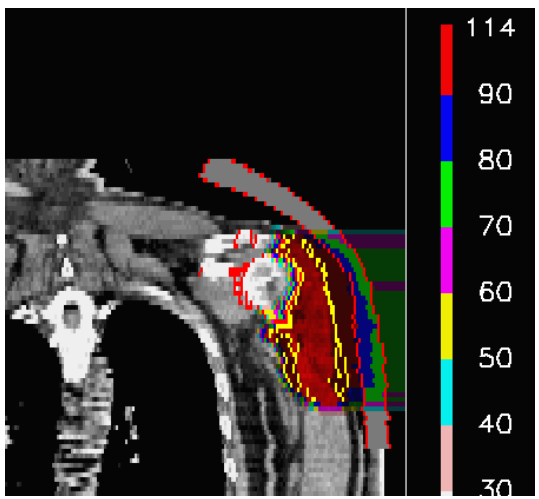
70 GyE, 3 series, 1-2 fields per series,
2 series with IMPT
(COSS protocol)

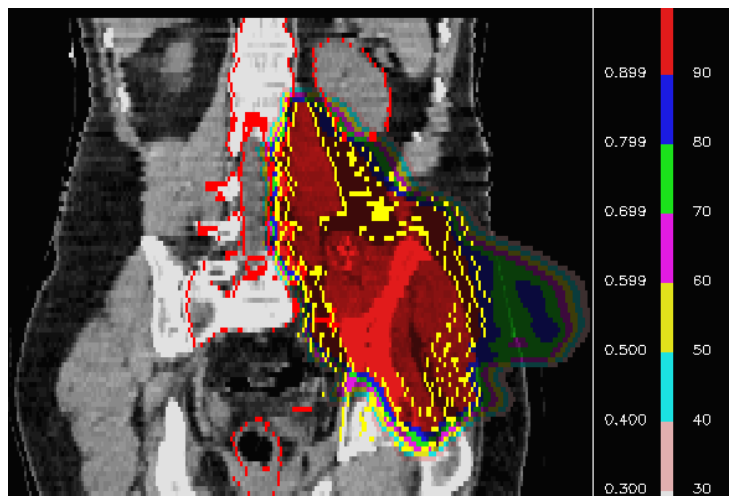
# Reduction of intergral dose, sparing normal tissues

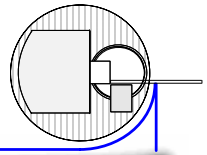






# Health Insurance Coverage was one big advance with consequences

Installation of a dedicated medical proton accelerator

Design and fabrication of a second generation spot scanning gantry

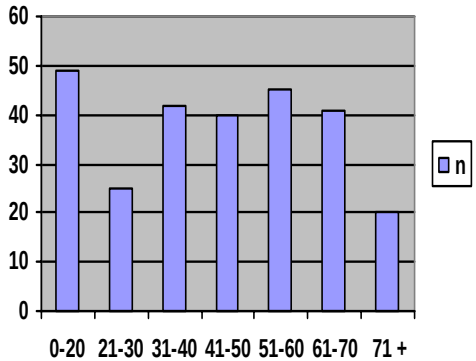
Transfer of the continuously successful eye treatment program OPTIS to the new accelerator

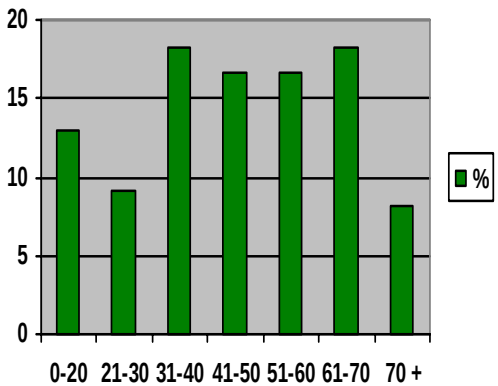
Extension to the existing building for patient care and treatment preparation, including facilities for pediatric anaesthesia

Initiation of the pediatric program

Concept for future activities including integration of proton radiotherapy into academic teaching at the university level

# Age distribution 1996 –2005
# n = 262,
## with 20 very young children treated in anesthesia (since 2004 )




| | |
|---|---|
| 12.9% | < 20 ys; |
| 9.1% | 21 – 30 ys |
| 18.2% | 31 – 40 ys |
| 16.7% | 41 – 50 ys |
| 16.7% | 51 – 60 ys |
| 18.2% | 61 – 70 ys |
| 8.1 % | >70 ys |

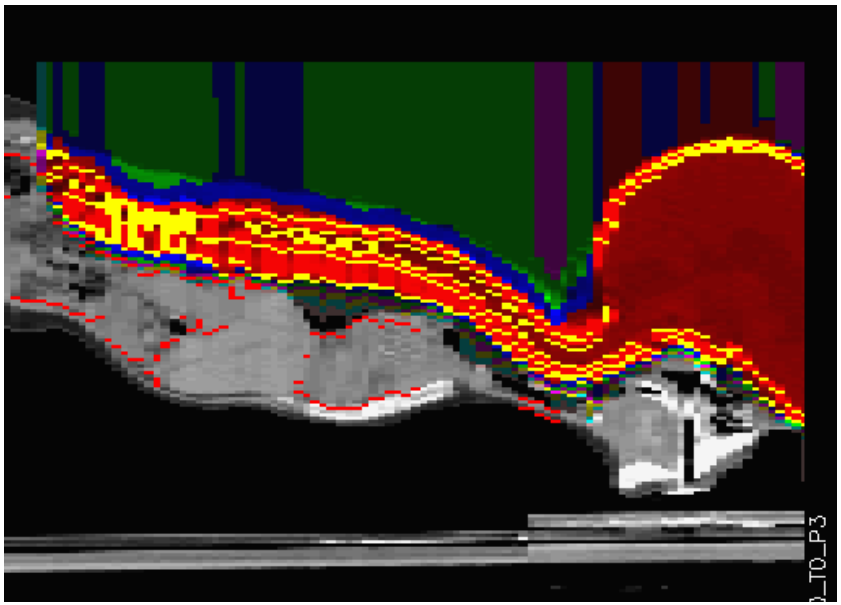
# Pediatric treatments under anaesthesia have become a fosuc at PSI.

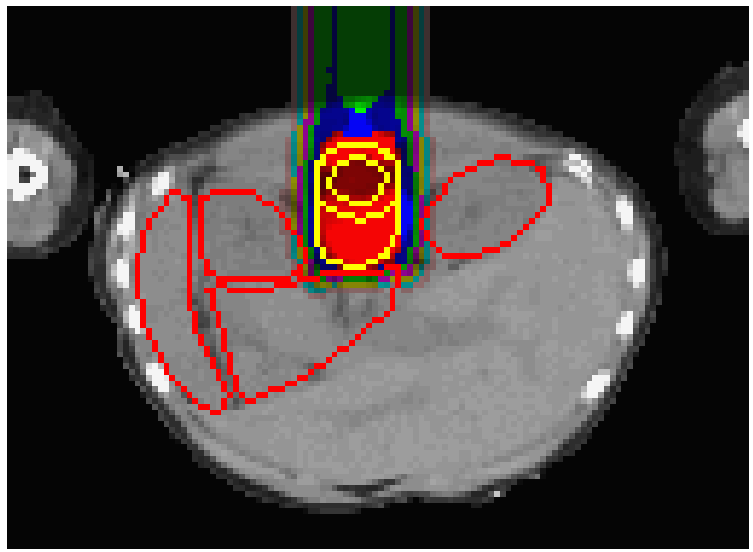
# Pediatric treatments under anaesthesia have become a fosuc at PSI.

Patient for head treatment, immobilization with bite block, body in a whole-body vacuum mold. Devices for monitoring during anaesthesia behind the child,on the table.

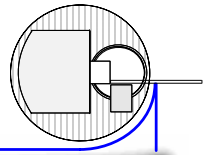
During treatment, the anaesthetized baby is monitored, as usual in anaesthesia, and surveilled via video cameras. The anaesthesiology team sees the monitoring on screens at the control desk outside the treatment room.

# Dose distribution for the first patient who received proton irradiation of the cranio-spinal axis (medulloblastoma, 5 y/o boy)





**Excellent dose sparing of all organs and tissues anteriorly to the brain and the spinal axis.**



# Application for definitive Health Insurance Coverage – a step for one more important achievement

Out of 262 patients, 216 were analyzed for this application.
(Tumors fitting the list of accepted indications and curative treatments)

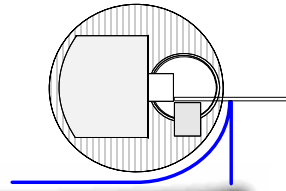
Good news: Overall survival and LC rates are very good, complication rates are low for all 216 patients

Bad news: This statement is of almost no value, except maybe for the low complication rate

Characteristics of the various groups which have been analyzed:
Small patient numbers per group, statistical analysis has different weight as compared to large cohorts
Results after relatively short follow up period are positive trends

Validation of specific outcomes:
e.g. LGG proposed for prolongation of evaluation time, as pediatric patients will contribute the cleaner cohort

PARTICLE THERAPY CO-OPERATIVE GROUP

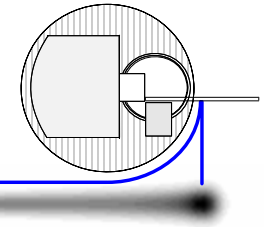


# Spot Scanning Proton Radiation Therapy : Clinical Experience @ PSI, Summary

Outcome analysis of 216 curative treatments

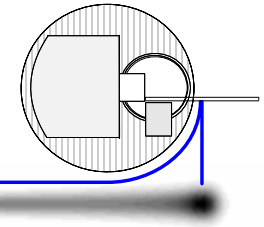
Med. follow up = 24.4 m. (2 – 104 m.)
Local failure in 33 pts.
Complications ≥ RTOG grade 3 in 9 patients
Deaths = 25

| | | |
|---|---|---|
| Overall survival | = 87% @ 3 ys, | 77% @ 5ys |
| Local control | = 84% , | 71% |
| Absence of complications | = 95% , | 93% |



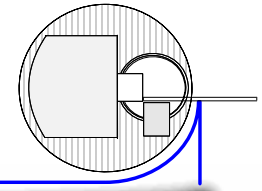
| Histology | number of | | 3-year survival | | | 5-year survival | | |
|---|---|---|---|---|---|---|---|---|
| | patients | events | KME | 70% CI | 90% CI | KME | 70% CI | 90% CI |
| All patients | 216 | 25 | 0.87 | 0.84 | 0.81 | 0.77 | 0.72 | 0.68 |
| Carcinomas | 12 | 3 | 0.69 | 0.40 | 0.21 | 0.69 | 0.33 | 0.12 |
| Chondrosarcomas (all) | 34 | 0 | 1 | | | 1 | | |
| Chondrosarcomas (skullbase) | 21 | 0 | 1 | | | 1 | | |
| Chondrosarcomas (spine) | 13 | 0 | 1 | | | 1 | | |
| Chordomas (all) | 86 | 9 | 0.86 | 0.79 | 0.73 | 0.72 | 0.59 | 0.50 |
| Chordomas (females) | 43 | 7 | 0.81 | 0.69 | 0.60 | 0.63 | 0.46 | 0.36 |
| Chordomas (males) | 43 | 2 | 0.94 | 0.82 | 0.67 | 0.83 | 0.60 | 0.40 |
| Chordomas (skullbase) | 43 | 3 | 0.92 | 0.78 | 0.62 | 0.62 | 0.37 | 0.22 |
| Chordomas (skullbase females) | 25 | 1 | 1 | | | 0.67 | 0.32 | 0.12 |
| Chordomas (skullbase males) | 18 | 2 | 0.75 | 0.44 | 0.22 | 0.50 | 0.18 | 0.05 |
| Chordomas (spine) | 43 | 6 | 0.83 | 0.72 | 0.64 | 0.76 | 0.60 | 0.49 |
| Chordomas (spine females) | 18 | 6 | 0.66 | 0.49 | 0.38 | 0.55 | 0.36 | 0.25 |
| Chordomas (spine males) | 25 | 0 | 1 | | | 1 | | |
| Gliomas | 8 | 5 | 0.62 | 0.42 | 0.29 | 0.38 | 0.20 | 0.12 |
| Meningiomas | 25 | 3 | 0.91 | 0.81 | 0.71 | 0.86 | 0.74 | 0.65 |
| Sarcomas bone | 9 | 0 | 1 | | | 1 | | |
| Sarcomas soft tissue | 16 | 2 | 1 | | | 0.86 | 0.59 | 0.34 |
| Rhabdomyosarcomas | 13 | 3 | 0.47 | 0.09 | 0.01 | 0.47 | 0.09 | 0.01 |

Table 2: *Kaplan-Meier estimates (KME) of overall survival rates after 3 and 5 years, together with lower bounds of 70% and 90% confidence interval (CI), for different histologies.*



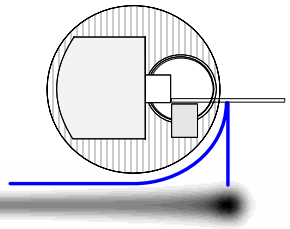
| Histology | number of | | 3-year local control | | | 5-year local control | | |
|---|---|---|---|---|---|---|---|---|
| | patients | events | KME | 70% CI | 90% CI | KME | 70% CI | 90% CI |
| All patients | 216 | 33 | 0.84 | 0.80 | 0.77 | 0.71 | 0.65 | 0.62 |
| Carcinomas | 12 | 3 | 0.64 | 0.36 | 0.19 | 0.64 | 0.29 | 0.11 |
| Chondrosarcomas (all) | 34 | 3 | 0.95 | 0.83 | 0.67 | 0.69 | 0.49 | 0.35 |
| Chondrosarcomas (skullbase) | 21 | 2 | 0.93 | 0.79 | 0.62 | 0.80 | 0.59 | 0.42 |
| Chondrosarcomas (spine) | 13 | 1 | 1 | | | 0 | 0 | 0 |
| Chordomas (all) | 86 | 15 | 0.81 | 0.74 | 0.68 | 0.65 | 0.53 | 0.45 |
| Chordomas (females) | 43 | 10 | 0.75 | 0.64 | 0.57 | 0.67 | 0.52 | 0.42 |
| Chordomas (males) | 43 | 5 | 0.89 | 0.75 | 0.62 | 0.65 | 0.42 | 0.26 |
| Chordomas (skullbase) | 43 | 7 | 0.73 | 0.60 | 0.51 | 0.61 | 0.41 | 0.28 |
| Chordomas (skullbase females) | 25 | 6 | 0.70 | 0.54 | 0.43 | 0.47 | 0.25 | 0.13 |
| Chordomas (skullbase males) | 18 | 1 | 0.80 | 0.49 | 0.24 | 0.80 | 0.32 | 0.05 |
| Chordomas (spine) | 43 | 8 | 0.86 | 0.76 | 0.67 | 0.69 | 0.52 | 0.41 |
| Chordomas (spine females) | 18 | 4 | 0.79 | 0.62 | 0.47 | 0.79 | 0.57 | 0.39 |
| Chordomas (spine males) | 25 | 4 | 0.92 | 0.76 | 0.56 | 0.62 | 0.33 | 0.17 |
| Gliomas | 8 | 5 | 0.50 | 0.31 | 0.20 | 0.38 | 0.20 | 0.12 |
| Meningiomas | 25 | 0 | 1 | | | 1 | | |
| Sarcomas bone | 9 | 1 | 0.67 | 0.08 | 0 | 0.67 | 0.08 | 0 |
| Sarcomas soft tissue | 16 | 3 | 0.92 | 0.75 | 0.56 | 0.63 | 0.39 | 0.24 |
| Rhabdomyosarcomas | 13 | 3 | 0.53 | 0.11 | 0.01 | 0.53 | 0.11 | 0.01 |

Table 3: *Kaplan-Meier estimates (KME) of local control rates after 3 and 5 years, together with lower bounds of 70% and 90% confidence interval (CI), for different histologies.*



| Histology | number of | | 3-year complication-free | | | 5-year complication-free | | |
|---|---|---|---|---|---|---|---|---|
| | patients | events | KME | 70% CI | 90% CI | KME | 70% CI | 90% CI |
| All patients | 216 | 9 | 0.95 | 0.92 | 0.89 | 0.93 | 0.88 | 0.85 |
| Carcinomas | 12 | 0 | 1 | | | 1 | | |
| Chondrosarcomas (all) | 34 | 0 | 1 | | | 1 | | |
| Chondrosarcomas (skullbase) | 21 | 0 | 1 | | | 1 | | |
| Chondrosarcomas (spine) | 13 | 0 | 1 | | | 1 | | |
| Chordomas (all) | 86 | 1 | 0.98 | 0.92 | 0.81 | 0.98 | 0.82 | 0.42 |
| Chordomas (females) | 43 | 0 | 1 | | | 1 | | |
| Chordomas (males) | 43 | 1 | 0.97 | 0.85 | 0.66 | 0.97 | 0.65 | 0.14 |
| Chordomas (skullbase) | 43 | 1 | 0.97 | 0.83 | 0.60 | 0.97 | 0.56 | 0.05 |
| Chordomas (skullbase females) | 25 | 0 | 1 | | | 1 | | |
| Chordomas (skullbase males) | 18 | 1 | 0.9 | 0.58 | 0.24 | 0.90 | 0.34 | 0.02 |
| Chordomas (spine) | 43 | 0 | 1 | | | 1 | | |
| Chordomas (spine females) | 18 | 0 | 1 | | | 1 | | |
| Chordomas (spine males) | 25 | 0 | 1 | | | 1 | | |
| Gliomas | 8 | 2 | 0.88 | 0.61 | 0.34 | 0.88 | 0.48 | 0.14 |
| Meningiomas | 25 | 2 | 0.94 | 0.84 | 0.72 | 0.87 | 0.74 | 0.62 |
| Sarcomas bone | 9 | 0 | 1 | | | 1 | | |
| Sarcomas soft tissue | 16 | 1 | 0.91 | 0.75 | 0.59 | 0.91 | 0.64 | 0.33 |
| Rhabdomyosarcomas | 13 | 0 | 1 | | | 1 | | |

Table 4: *Kaplan-Meier estimates (KME) of absence of complication rates after 3 and 5 years, together with lower bounds of 70% and 90% confidence interval (CI), for different histologies.*



# Chordomas & chondorsarcomas of the base of skull

## Dose constraints

brainstem surface $\leq$ 64 CGE  brainstem center $\leq$ 53 CGE

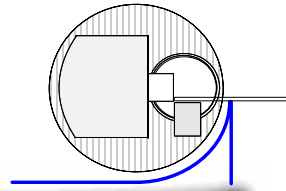
Late toxicity assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, v3.0) grading system

**No patient presented with brainstem necrosis or dysfunction after spot scanning proton radiation therapy. The first trend with regards to late complication is very positive.**

**The MGH experience with 367 analyzed cases results in an actuarial toxicity free survival rate at 5 y: 94%, 10 y: 88%.**



C. Ares, PTCOG 43, December 2005, Munich



# Spot Scanning Proton Radiation Therapy : Clinical Experience @ PSI, Summary

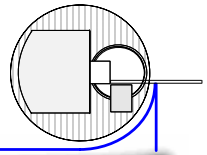
## Chordomas, outcome analysis

Skull base lesions, n = 43

| | | |
|---|---|---|
| Overall survival | @ 3 ys = 92%, | @5 ys = 62% |
| Local control | = 81%, | = 61% |
| | *70%/80% f/m* | *47%/80% f/m* |
| Absence of compl. | = 98% | = 97% |

Extracranial lesions, n = 43

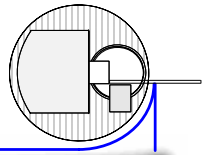
| | | |
|---|---|---|
| Overall survival | @ 3 ys = 83%, | @5 ys = 76% |
| Local control | = 86%, | = 69% |
| | *79%/92% f/m* | *79%/62% f/m* |
| Absence of compl. | = 100% | = 100% |



**The application for definitive Health Insurance Coverage for the so far accepted tumor entities has been filed in summer 2006. The decision is still pending.**

The topics of the application are predefined, as was the case for the first application:

**Application for funding for**
**Proton Radiation Therapy of deep seated tumors,**
**using the Proton Therapy Facility at PSI**
**Description of service and compliance with regulatory requirements**
**Indications for the service and therapeutic claim**
**Clinical need, public health significance and patient selection**
**Description of the service**
**Choice of comparator**
**Estimated utilization**
**Summary of the literature search**
**Summary of the evidence**
**Economic information**



# Summary

## The advances in spot scanning proton therapy at PSI were

- Learning from past experience and current activities
- Creative design and realization of novel technologies
- Continuous reflection about our work
- Courage to go for new approaches combined with great care in application
- Health Care Coverage
- Decision for establishing the project inside and outside PSI
- Increasingly better referrals
- Plans for the future
- Center for Proton Therapy in Switzerland with academic link

# PROSCAN @ PSI
## Head of program: Martin Jermann

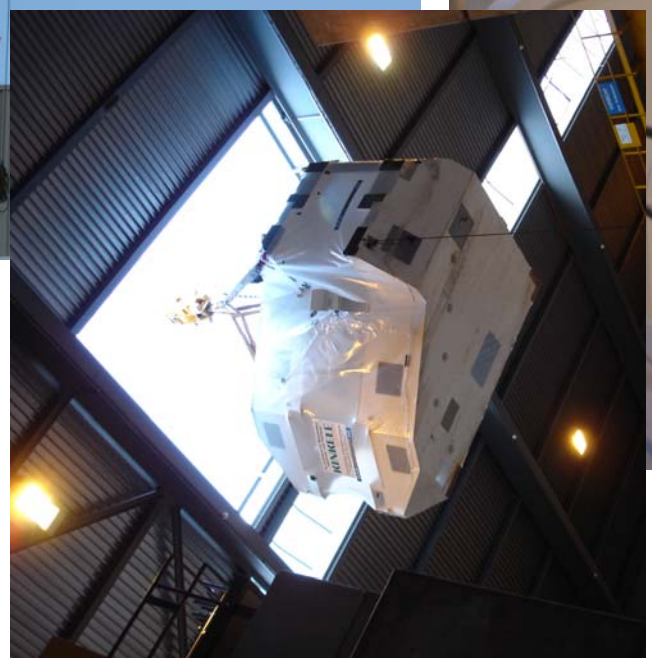
COMET

PIF

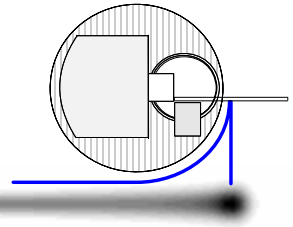
OPTIS

New Gantry 2

Existing Gantry 1



# Technical Advances at PSI
# Thanks to all who contributed!



# Thanks to my Dream Team

Eros Pedroni, Antony Lomax, Adolf Coray, Martin Jermann, Francesca Albertini, Carmen Ares, Claire Baumeler, Terence Boehringer, Christian Bula, Alessandra Bolsi, Ruth Eggspühler, Frank Emert, Martin Grossman, Sandra Hersperger, Christian Hilbes, Lydia Lederer, Daniel Lempen, Shixiong Lin, David Meer, Anita Obrist, Frieda Obrist, Petra Rhiner, Benno Rohrer, Hans Peter Rutz, Beate Schulz, April Siegwolf, Otto Stadelman, Hansueli Stäuble, Beate Timmermann, Alexander Tourovsky, Jorn Verwey, Heidi Wagner

# Thanks to all colleagues and centers who are working with us


PTCOG 44
See you next time in Houston
Now we are here, enjoying PTCOG 45