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PSI

Proton- Radiotherapy at Paul Scherrer Institute:

Clinical Results

Eugen B. Hug for the *PSI-TEAM*

Center for Proton Radiation Therapy,
Paul Scherrer Institute

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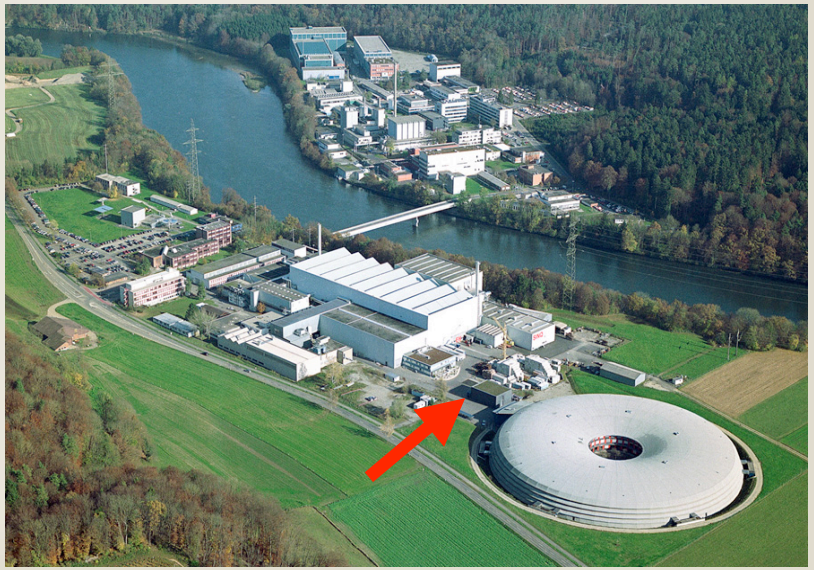
Martin Jermann

Gudrun Goitein



Tony Lomax

Eros Pedroni

Dolf Coray

…just to name a few

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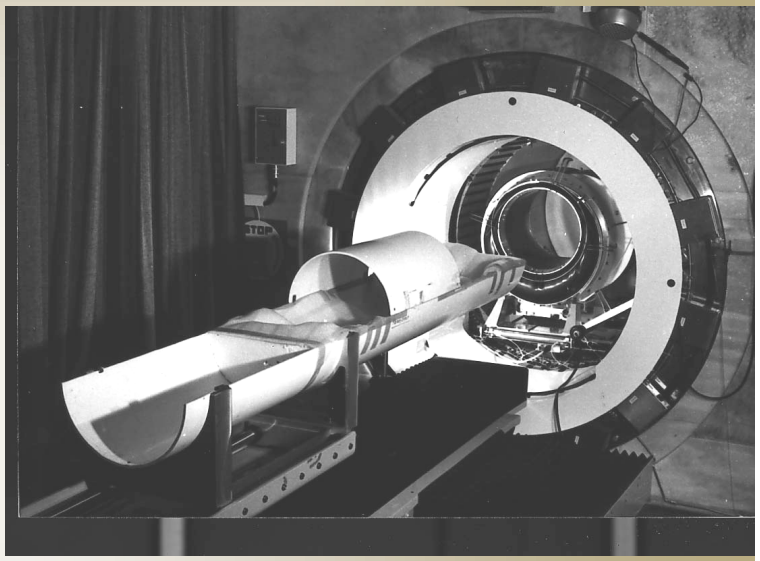
Particle Therapy at PSI (I)

Pion therapy: 1980-1993



- **PIOTRON**
  - 60 concentric pion beams
  - **Raster scanning (20 fract.)**
  - **CT-based 3d-inverse planning**
  - 503 patients
  - RBE= 2, general dose prescription: 33 pion Gy
  - Some good results:
    - Large tumors in the low pelvis (sarcomas)
    - Since 1982 ... wish to treat the same cases with protons
      - 5 x smaller spot with protons

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Particle Therapy at PSI (II)

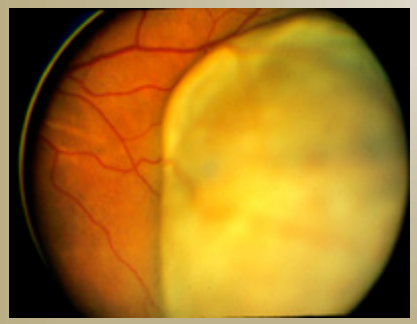
Proton Radiation Therapy: 1984

The Eye Program

- Technique adopted from Mass. General Hospital / Harvard Cyclotron (start 1976)
- Passive Scattering Technique
- World's largest uveal melanoma series
- 5000 patients treated by 2008

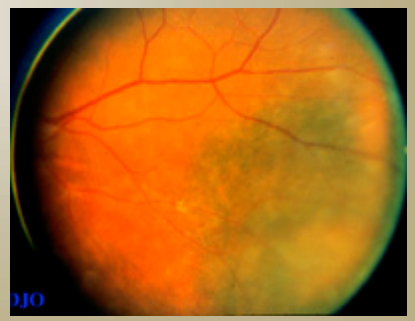
Fundus Exam

PRIOR to therapy



Fundus Exam

AFTER Therapy



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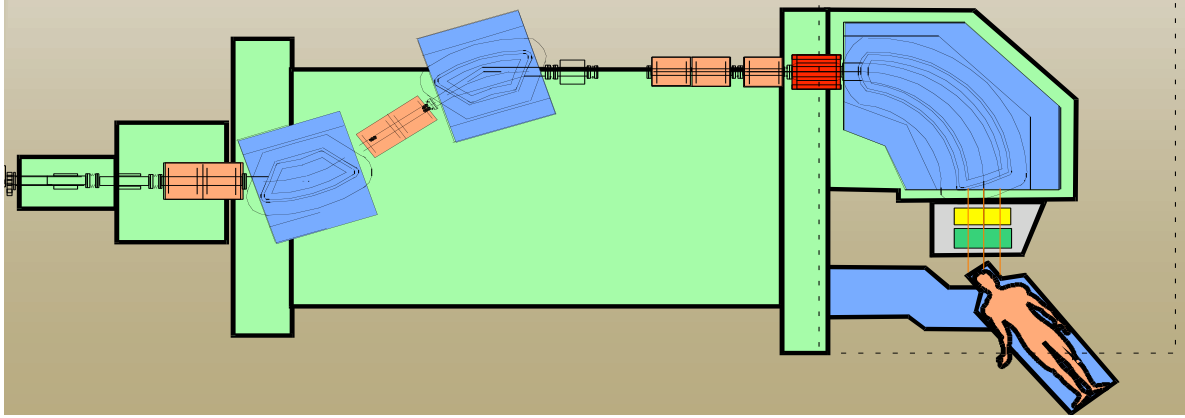
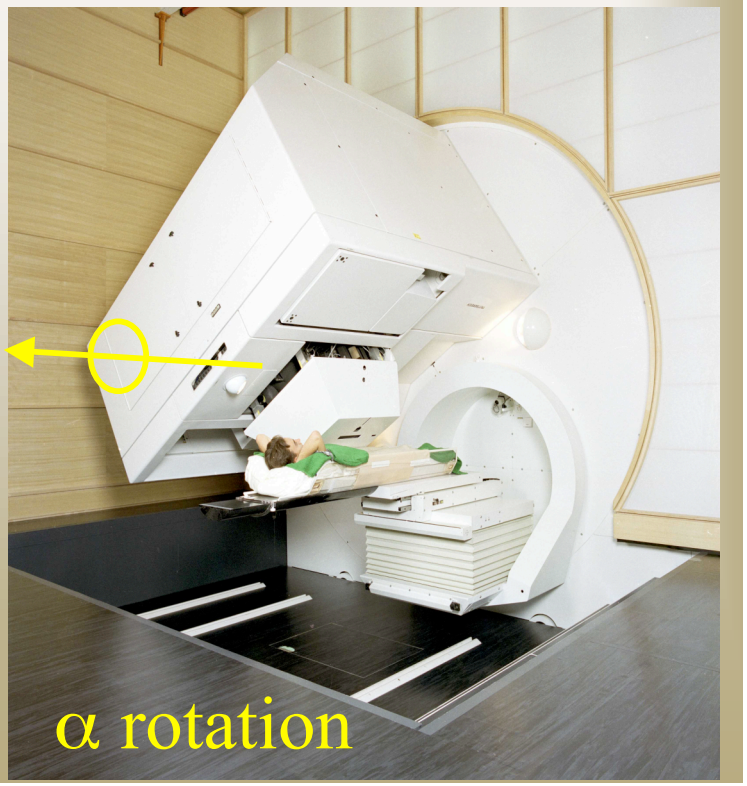
Particle Therapy at PSI (III)

Spot Scanning based Proton RT: 1996

- Introduction of *"Active Spot Scanning" Technology*
- Gantry-based treatment delivery
- Design 1991
- Deep seated tumors





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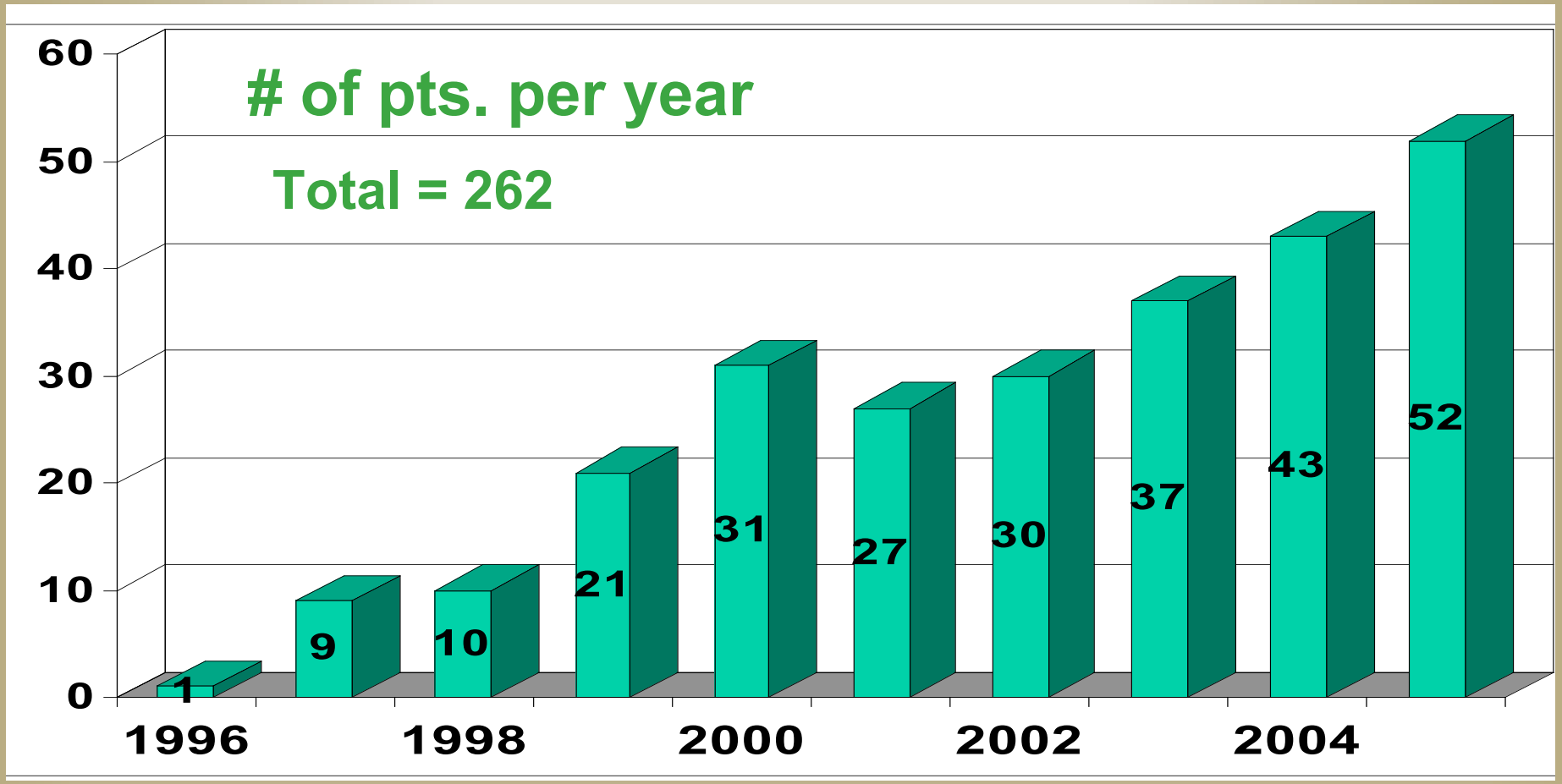
Particle Therapy at PSI (IV)

Patients tx with spot scanning PRT *1996 – 2005*
Tx-periods of 6 months / year only



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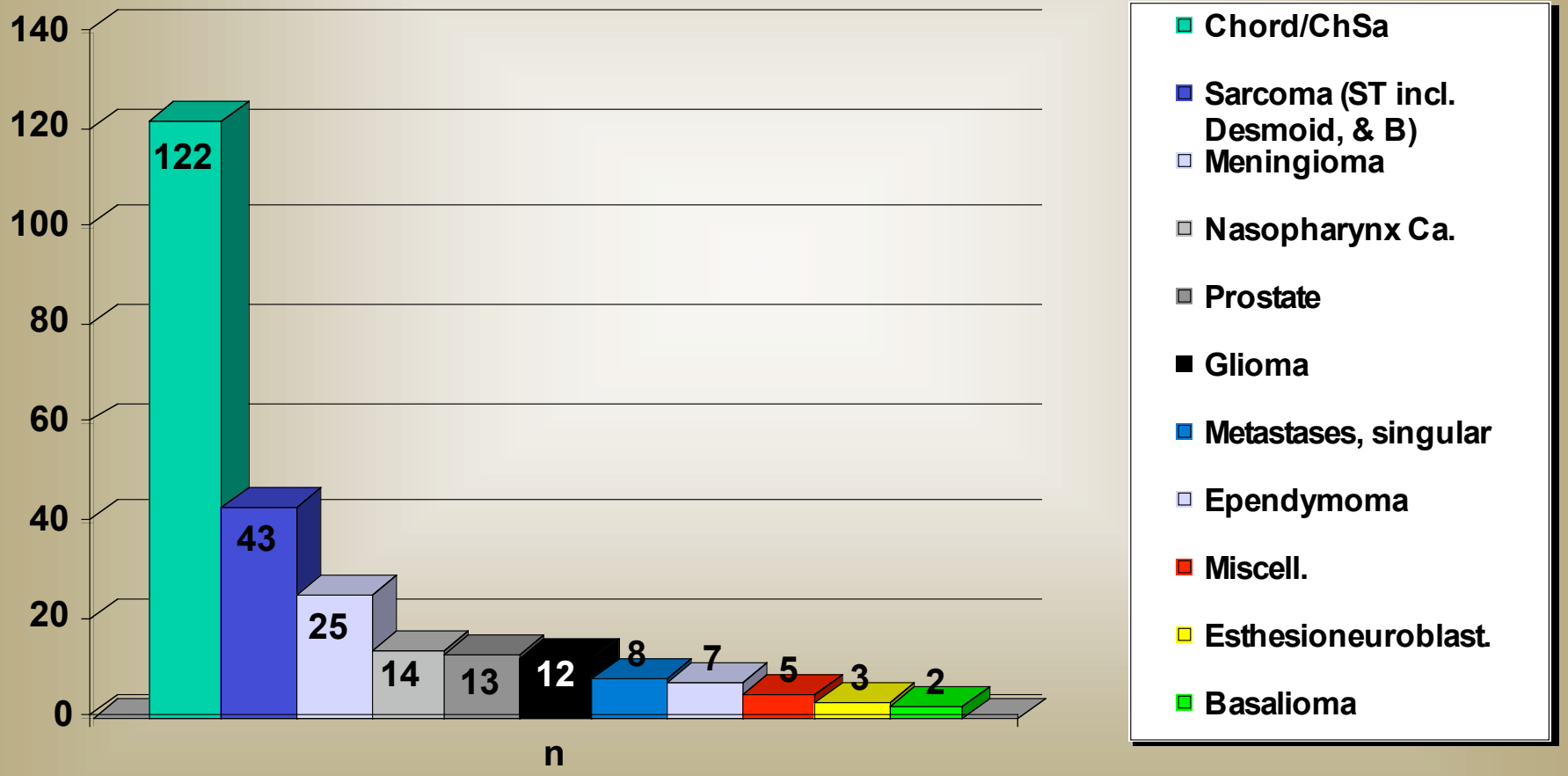
Particle Therapy at PSI (V)

Patients tx with spot scanning PRT *1996 – 2005*

Tumor histologies, n = 262



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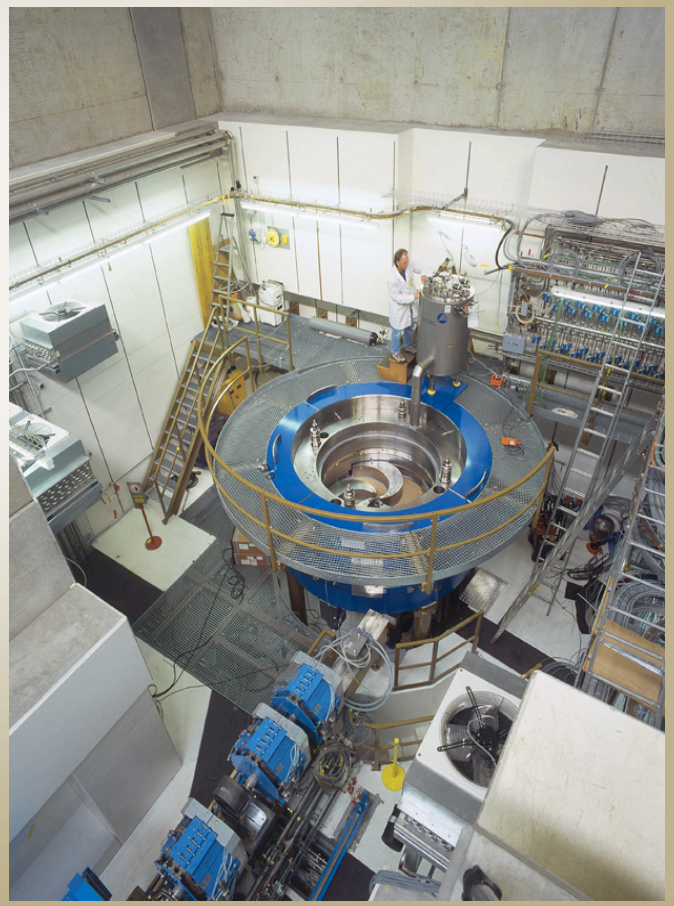
Particle Therapy at PSI (VII)

Dedicated Cyclotron: 2007

Supraconducting Cyclotron (Varian / ACCEL) (250 MeV, 500 nA, 90 t, d=3,5 m)

Dedicated for scanning technology

R & D collaboration with industry



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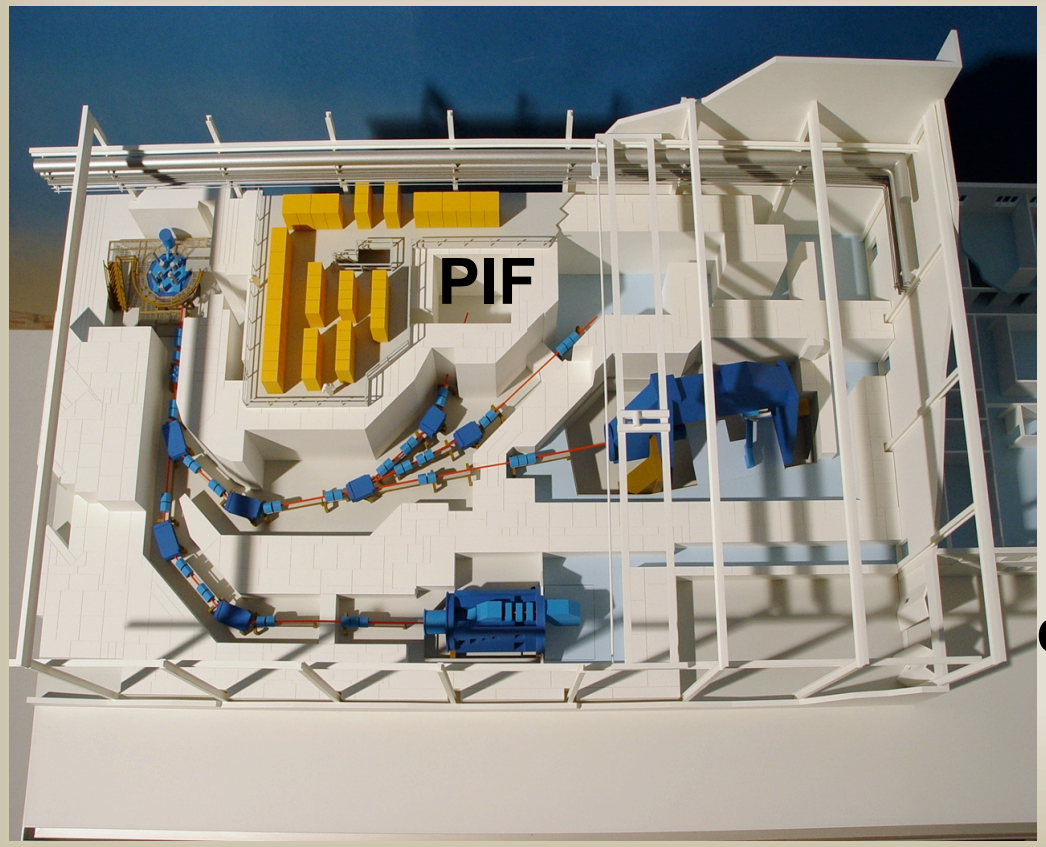
Particle Therapy at PSI (VIII)

Year-round clinical operation: August 2007



OPTIS2 (2008)

new Gantry 2 (2009)

existing Gantry 1

Lay out: 2 Gantry rooms, one fixed beam room, 1 reseach room

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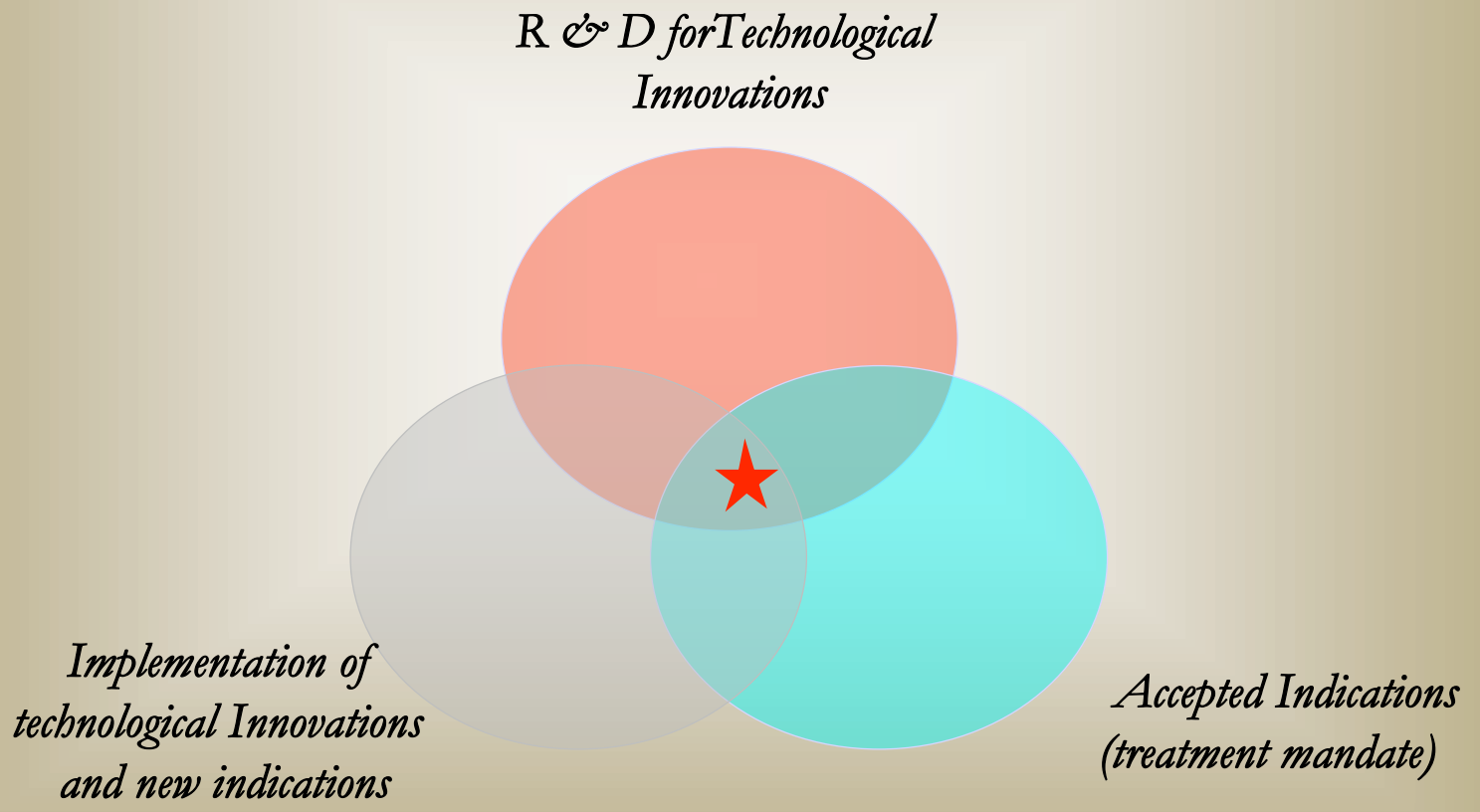
Center for Proton Radiation Therapy at PSI:

Central mssions compete for beam time



PSI: R&D, Producer, Test site, Enduser in one facility

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Indications treated at PSI

(past, presence, not future)

- ***Ocular Tumors*** (Uveal Melanomas)
- ***Skull Base Tumors***
  - Chordomas and Chondrosarcomas
  - Meningiomas
  - H&N histologies with SB-infiltration
- ***Paraspinal*** location / axial skeleton
  - Chordomas and Chondrosarcomas
  - Other soft tissue or osteogenic sarcomas
- ***CNS***-tumors
  - Meningiomas, Low Grade Gliomas
- ***Unresectable*** Sarcomas
- ***Pediatric Neoplasms***

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Clinical results on *safety and efficacy of spot scanning based proton RT* at PSI

- *5 –year actuarial data:*
  - Skull Base Tumors
  - Chordomas and Chondrosarcomas
  - Paraspinal tumors / Chordomas
- *3 – year actuarial data*
  - soft tissue sarcomas
  - meningiomas
- *4 – years experience with Pediatric Neoplasms*

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Skull Base Chordomas and Chondrosarcomas at PSI: *5-year outcome** *of spot scanning based PT*

To be presented by Dr. Ares

- **Local Control for Chordomas and Chondrosarcomas: similar to reslts of other proton-centers**
- **High Grade Toxicity: < 7%**

* Ares, Lomax, Hug, Goitein – in preparation

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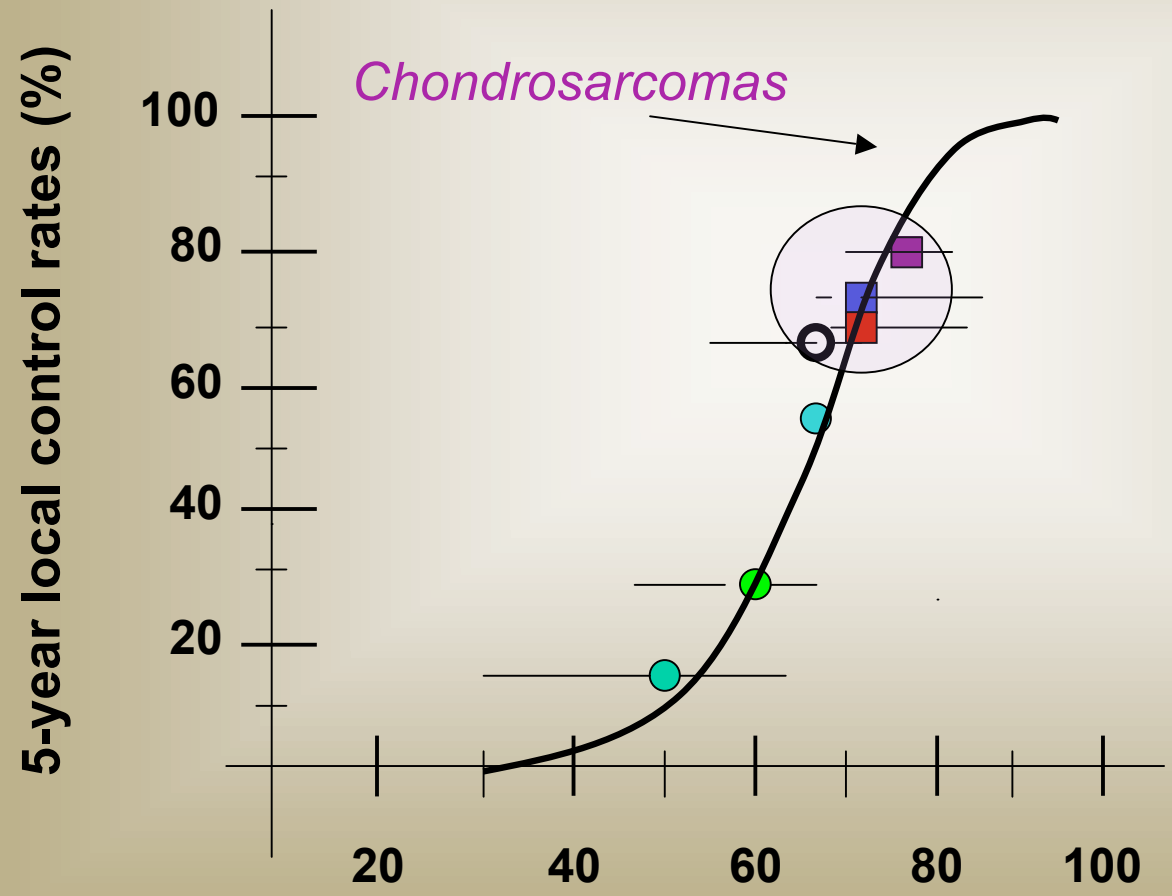
Chordomas of the Base of Skull



Photons

- Romero 1993
- Zorlu 2000
- Debus 2000

Protons

- Munzenrider 1999
- Ares 2007
- Hug 1999

C-Ions

- Schulz-Ertner

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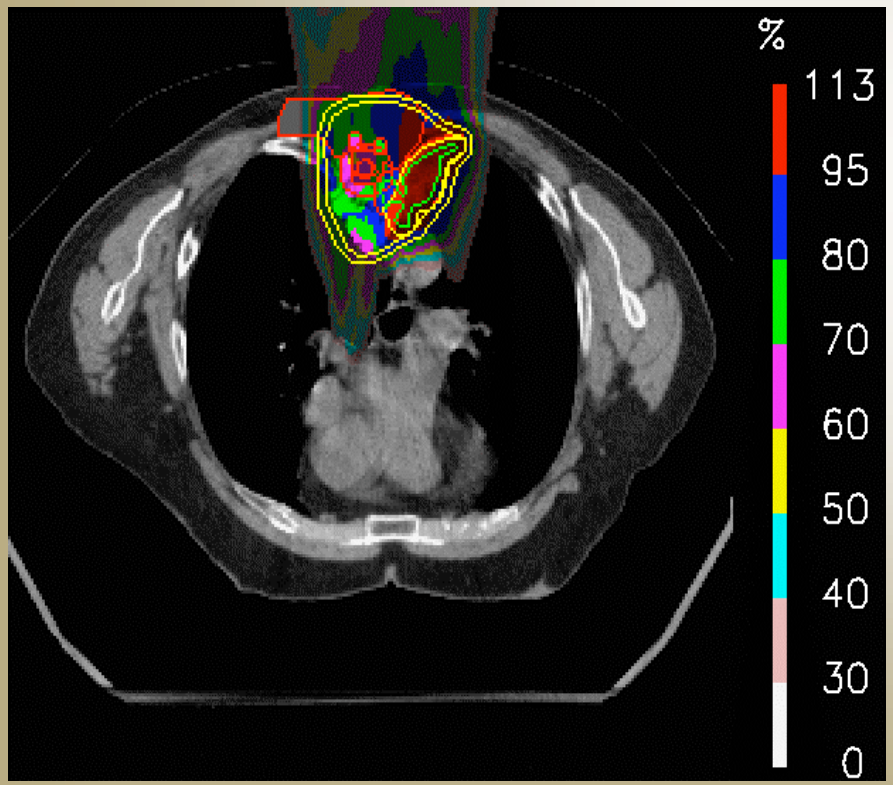
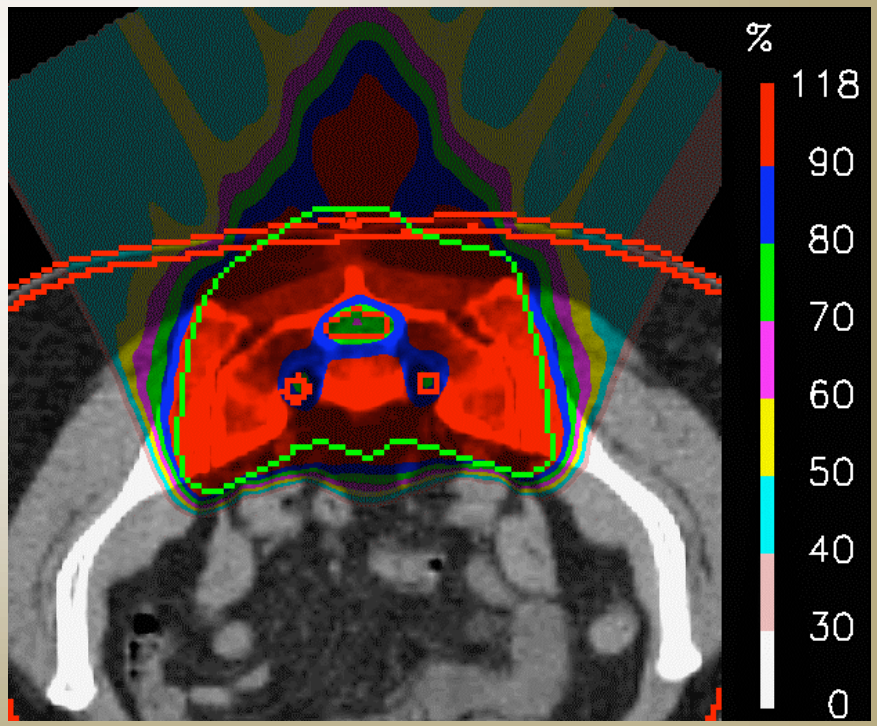
Extracranial *Chordomas of the Axial Skeleton* treated with spot scanning Proton Therapy at PSI:

5-year clinical data





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Extracranial *chordomas of the Axial Skeleton* treated with spot scanning Proton Therapy at PSI:

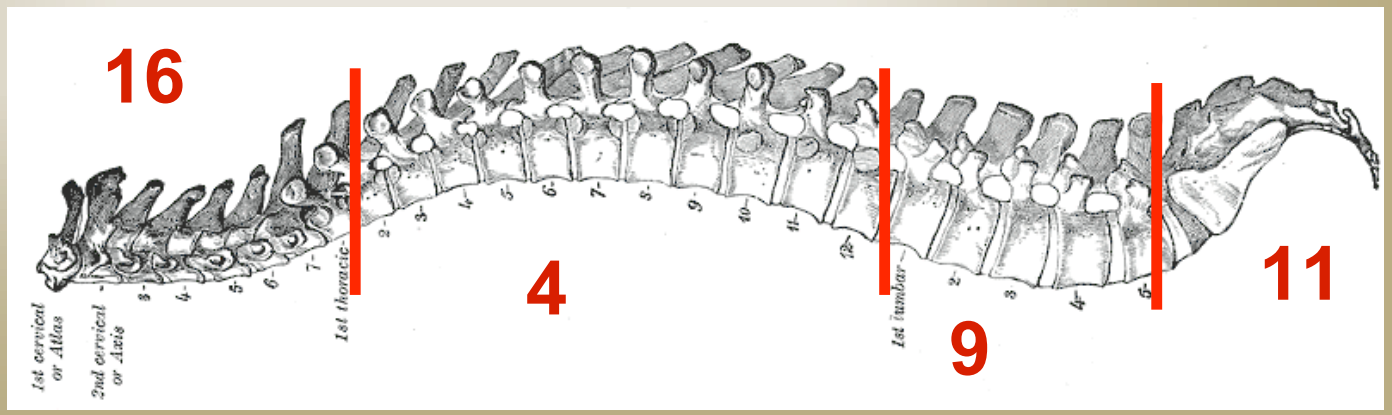
5-year clinical data (Rutz et al.)

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

- N = 40

- Tx: 1999 – 2005

- Location:



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Chordomas of the Axial Skeleton at PSI: *5-year* outcomes data

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

- *19 / 40* patients without inserted instrumentation

- IMPT part of treatment plan since 2004

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

- Follow-up period:
  - Minimum: 2 years (24 months)
  - Median: 43 months
  - Maximum: 91 months

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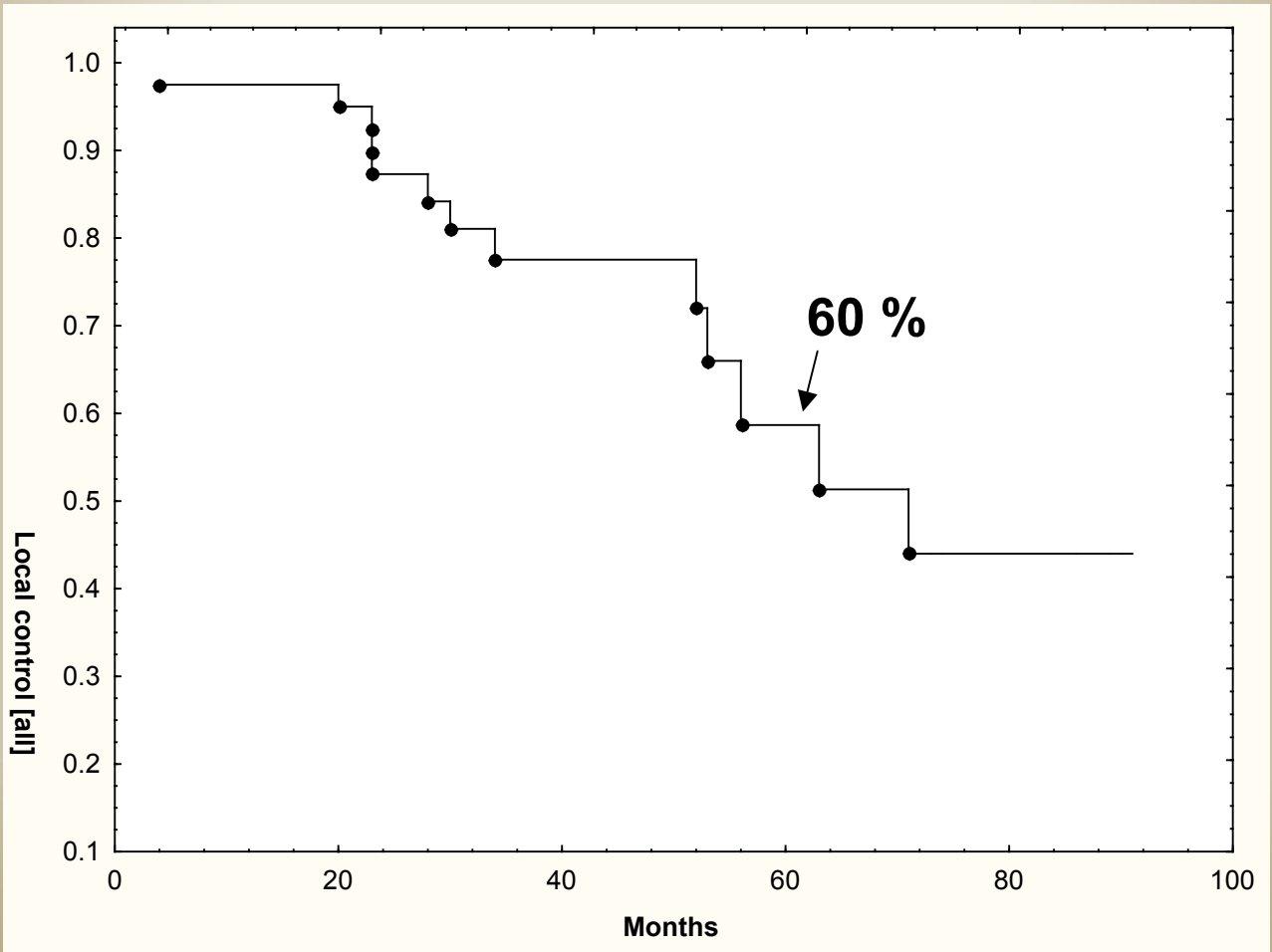
Chordomas of the Axial Skeleton at PSI: *5-year* outcomes data

Local control

13 / 40 patients with local failure



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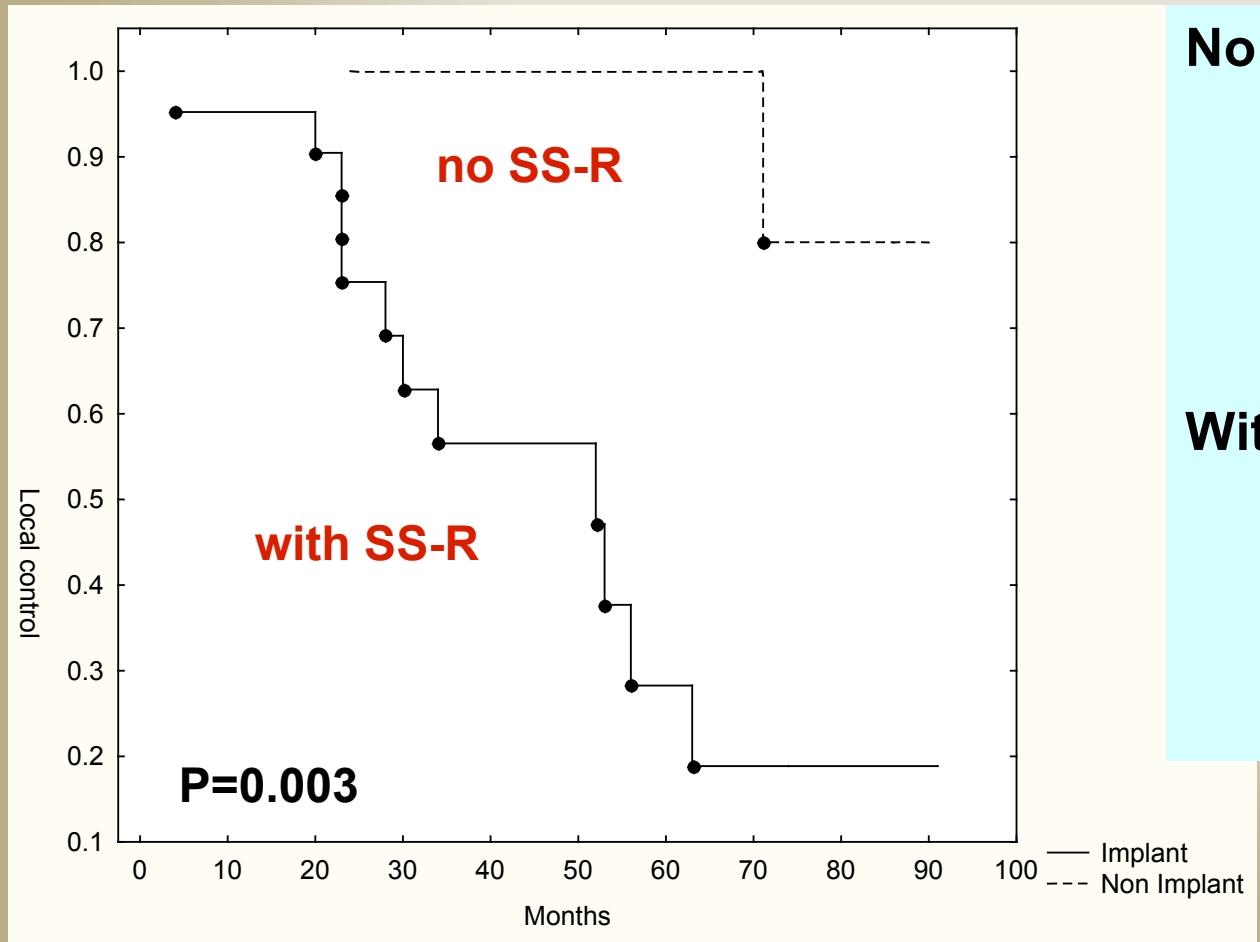
Chordomas of the Axial Skeleton at PSI: *5-year* outcomes data

Impact of Surgical Stabilization – Reconstruction (SS-R) on Local control



No SS-R:

- **only 1 LF in 19 pts.**

With SS-R:

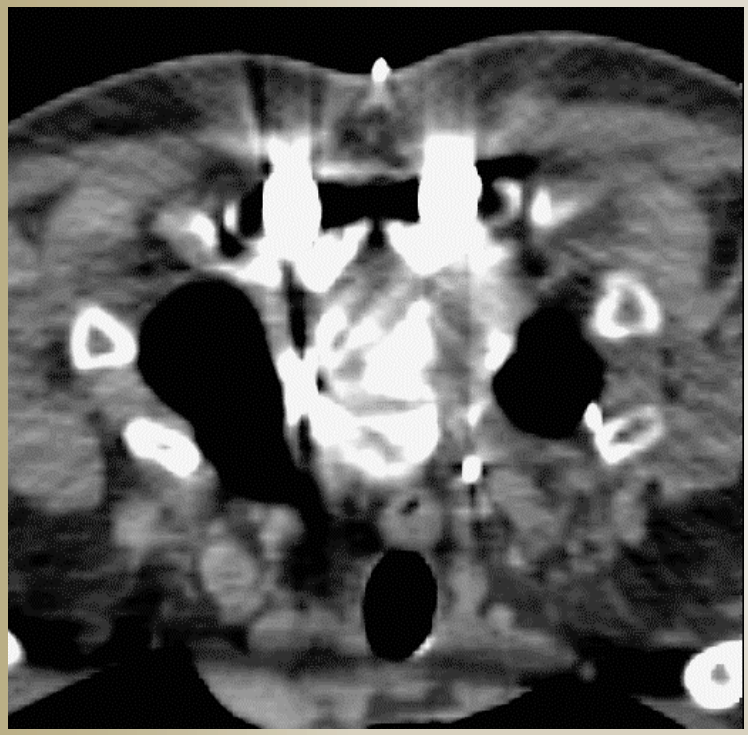
- **12 LF in 21 pts.**

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?

Extracranial chordoma

Late adverse events (CTCAE v3.0)

Neurologic side effects

- ***No*** high-grade spinal cord or cauda equina late event.
- 2 low-grade neurologic events:
  - 1 Gr. 2 Lhermitte‘s syndrome,
  - 1 Gr.1 cervical nerve dysesthesia

Other side effects

- 2 high grade radiation-induced late adverse events in 2 patients (2/26)
  - G3 osteonecrosis
  - G3 subcutaneous necrosis

- 1 Second Malignancy after combined photon / proton RT with 2nd malignancy in photon-field

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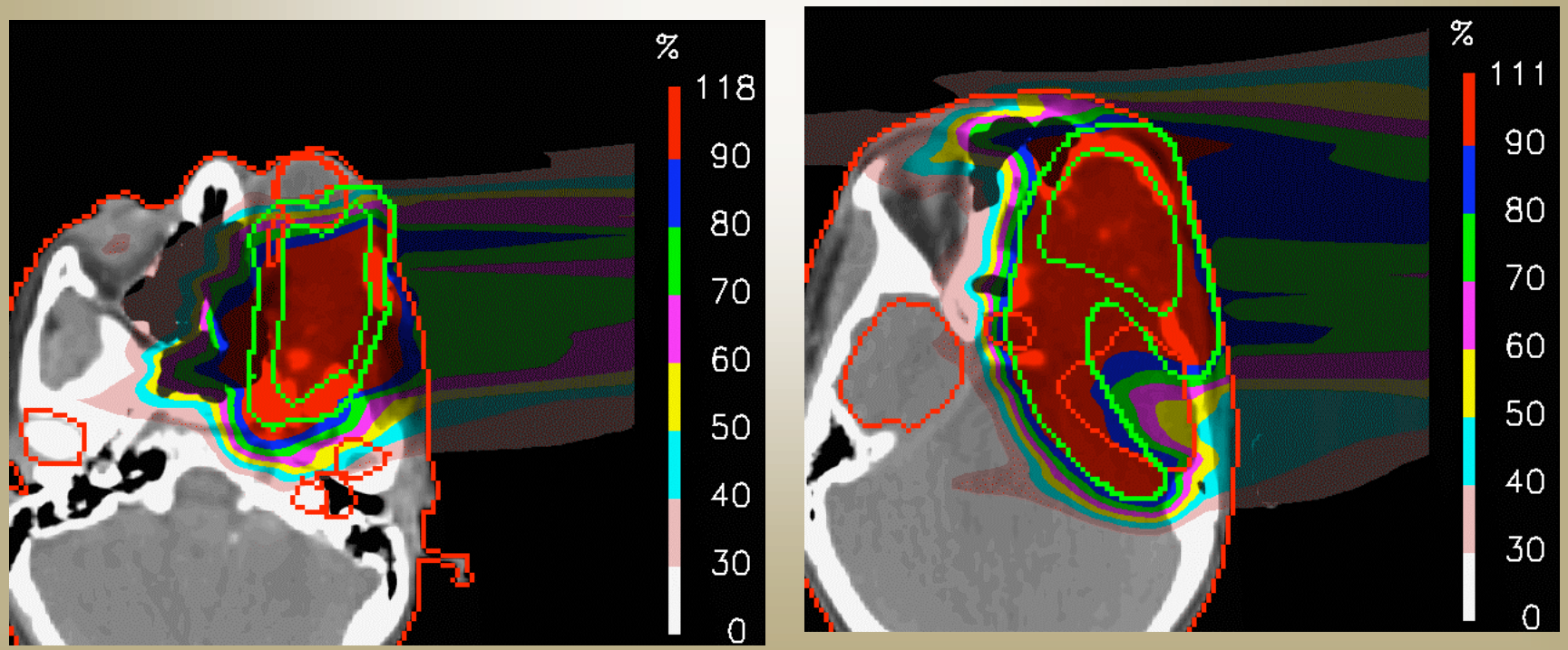
Proton-Radiotherapy for *complex meningiomas:*

3-year clinical results

12 year old boy, neurofibromatosis, blind contralateral, ipsilaterlal subtotally resected orbital and intracranial meningioma



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Proton Therapy for *benign meningioma*: *3-year* clinical results

(Weber et al., Radiother Oncol, 2004)

- 16 patients with intracranial meningioma
- Treated 1997-2002
- Recurrent, residual or untreated
- GTV: 0.8 – 87.6 cc
- Dose: median 56 Gy (RBE) (52.2 – 64 Gy (RBE))
- F/U: median 34 months (6.5 – 67.8 months)

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Proton Therapy for *benign meningioma*: *3-year* clinical results

(Weber et al., Radiother Oncol, 2004)

- Local Control: 92% at 3-years. 1 patient with LF
- 3-year toxicity-free survival: 76 %
  - Toxicity: 1 temporal lobe necrosis
  - 2 patients: 1 with optic neuropathy (Grad3 3) and 1 retinopathy (Gr. 3): doses higher than OAR constraints

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Proton Therapy for *Adult Patients* with *Soft Tissue Sarcomas*: *3-year data*

(Weber et al., IJROBP 2007)

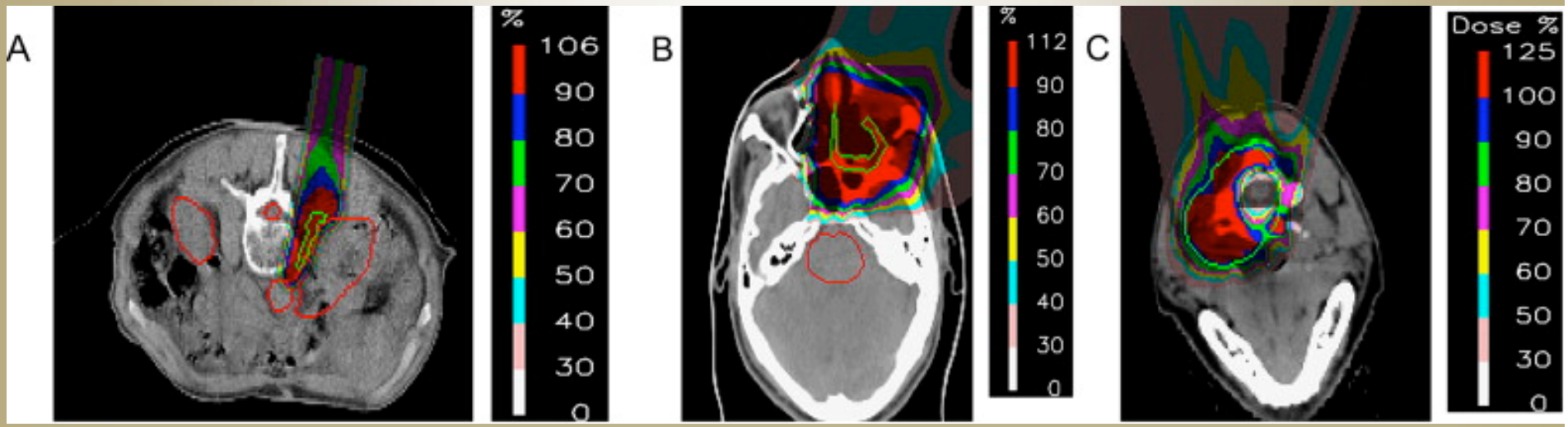
- 13 patients with STS
- 1998-2005 tx with protons (6) or mixed protons/photons (7)
- Age: median 41 years (22-62 years).
- Gross tumor: 9 / 13. R1 resection: 4 / 13
- Location: H&N, Skull Base, Paraspinal. Pelvis, Trunk, Reroperitoneal (2 pts), Shoulder (2pts.)

- Dose: median 69.4 Gy (RBE) (50.4 – 76 Gy (RBE))
- F/U: minimum 1 year, 12 pts. > 2 years, median for surviving patients: 48 months.

Weber et al., IJROBP 2007 cont.

Tumor histology: liposarcoma (*n* = 3), peripheral nerve sheet tumor (PNST, *n* = 3), leiomyosarcoma (*n* = 2), desmoid tumors (*n* = 2), angiosarcoma (*n* = 1), spindle cell sarcoma (*n* = 1), and malignant hemoangioperiocytoma (*n* = 1)

Treatment plan for (A) retroperitoneal, (B) head and neck, and (C) paravertebral sarcoma.
Sparing of the kidney (A), spinal cord (A, C), and brainstem (B).



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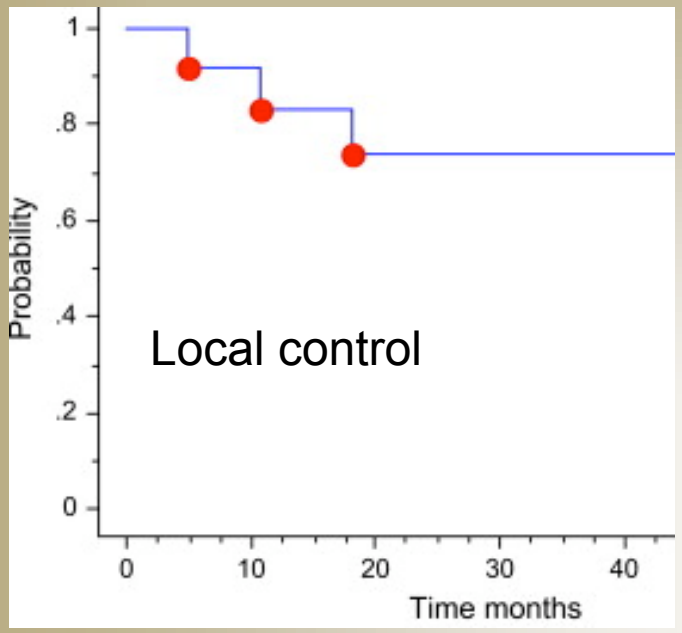
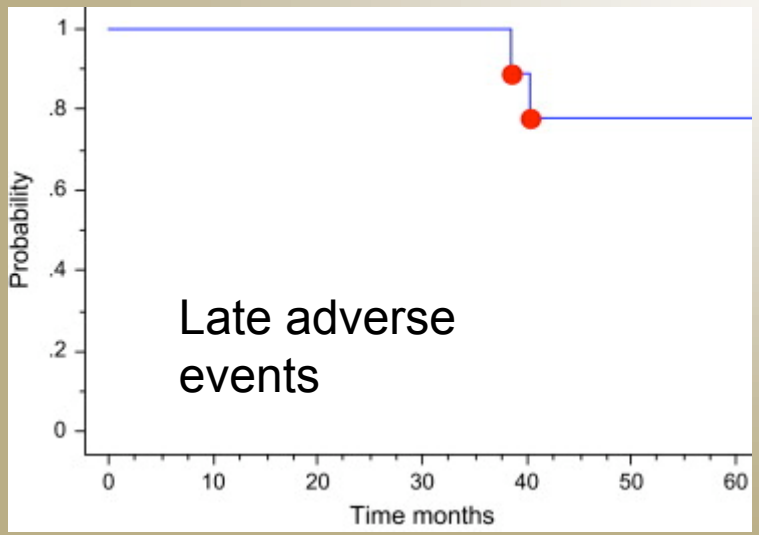
Weber et al., IJROBP 2007 cont.



<u>Local control:</u> 10 / 13 pts.

3-year actuarial LC: 74%



<u>Late adverse events</u>: 2 pts.

1 cataract

1 Grade 3 temporal lobe necrosis

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Proton Radiotherapy for *pediatric* STS treated at PSI

(Timmermann et al., PSI, IJROBP, 2007)

- 16 children with STS (including 12 with RMS or RMS-like histology)
- 14/16 children with chemotherapy
- Age: median 3.7 years (1.4-14.1 years). 9 children requiring anesthesia
- Tumor volume: 52 cc – 1225 cc
- Location: H&N, Skull Base, Paraspinal, Pelvis
- Proton RT Dose: median 50 Gy (RBE) (46 – 61.2 Gy (RBE) – doses according to CWS2002, MMT-95, COG-D9803 in 14 pts.
- F/U: median 18.6 months (4.3 -71 months)

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Timmermann et al., PSI, IJROBP 2007 cont.

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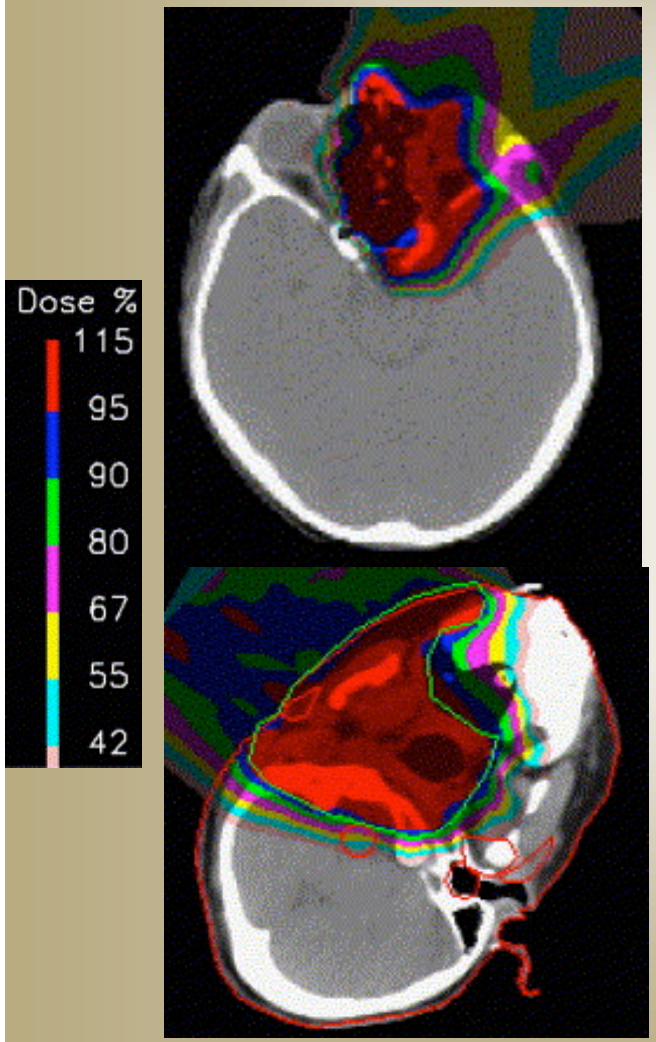
Outcome (very preliminary)



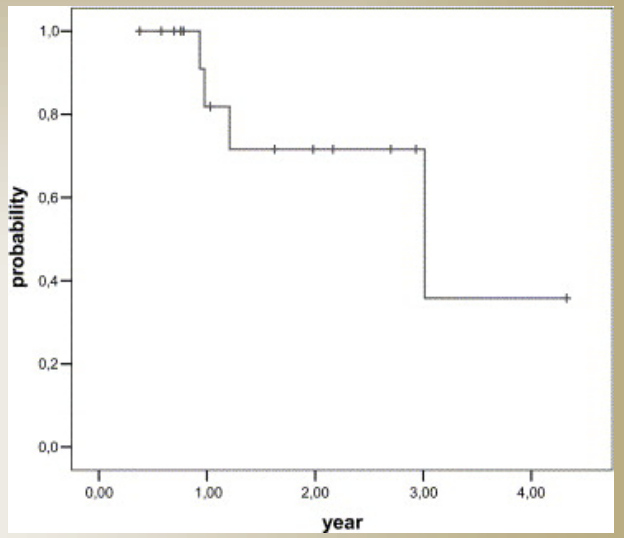
Local control:

12/16 = 75% at 2 years

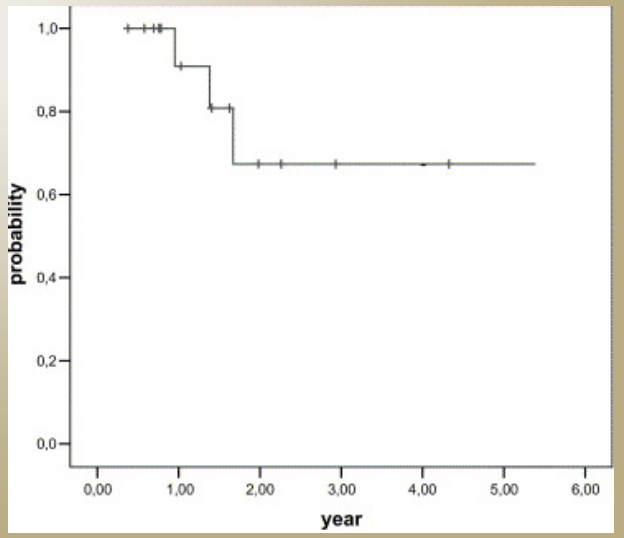
2/12 Failures in RMS- Group

2/4 in Non-RMS Group (after 50.4, 50 GY(RBE))

Local control



Overall Survival



Late toxicity: F/U too short

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Indications treated at PSI

- Ocular Tumors (Uveal Melanomas)
- ***Skull Base Tumors***
  - Chordomas and Chondrosarcomas
  - Meningiomas
  - H&N histologies with SB-infiltration
- ***Paraspinal*** location / axial skeleton
  - Chordomas and Chondrosarcomas
  - Other soft tissue or osteogenic sarcomas
- ***CNS***-tumors
  - Meningiomas, Low Grade Gliomas
- ***Unresectable*** Sarcomas

→ ***Pediatric Neoplasms***

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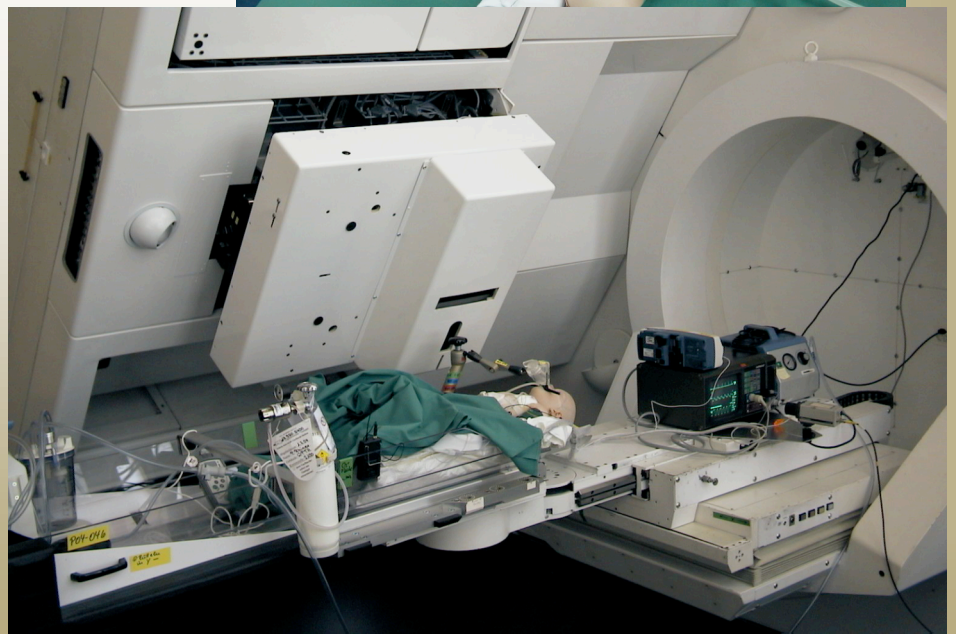
Proton Therapy at PSI for children and infants:

Collaboration: PSI, University Hospital Zürich and Childrens' Hospital Zürich



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Proton Therapy at PSI for Pediatric malignancies: A prospective evaluation.

The pediatric proton team:

Beate Timmermann, Sandra Maier, Carmen Ares, Cezarina Negreanu-Macian, Alessandra Bolsi, Eugen Hug

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Pediatric Proton Radiotherapy at PSI:

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Children: (prospective evaluation since 2004)

Patients:	n = 51 (overall 75 pts. treated at PSI since 1996)		
Time period:	2004-2007		
Age:	4 months – 20 years (median 2,6 years) at Dx		
Gender:	22 f / 29 m		
Diagnosis:	Sarcomas		24
	CNS tumors		19
	Chord./Chondrosarc.		5
	others		3
Location:	H & N	41	
	para-spinal		8
	pelvis		2
PT	Dose: med. 54 Gy (45-79,4 Gy)		
	PT only		46
	PT + XRT		5
	(anesthesia		34)
CTX	prior to PT: 41, concurrent: 26		
Surgery	biopsy; 20,	STR: 19, GTR: 12	

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Spot scanning based Proton RT at PSI: Safety and Efficacy

- 350 patients treated to date, approx. 130 will be tx in 2008
- > 250 patients with > 2 year follow-up
- > 100 patients analyzed with actuarial 5-year outcomes data
- First 5-year data at PSI demonstrate:
  - *Safety (acute and late toxicity)*
  - *and efficacy (local control)*

  are at minimum similar to passive scattering, using comparable treatment parameters of target definition, dose prescription and OAR tolerance doses

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Spot scanning based Proton RT at PSI: Safety and Efficacy

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- Upcoming 5-year analysis: Meningiomas, Soft tissue sarcomas,
- Pediatrics: tumor specific analysis upcoming and prospective trial-based late effects analysis

- The "*next generation*" scanning system will offer significantly expanded capabilities
- *Caveats* of active scanning technology:
  - At present only single institution results with actively scanned protons with very experienced team
  - Mobile tumors will be treated with new scanning system – but this has not been accomplished, yet.

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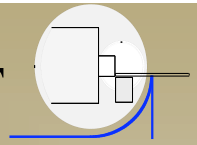

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PSI

THANK YOU !

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Skull Base Chordomas and Chondrosarcomas at PSI: *5-year outcome**

- N = 64 patients (Oct-98 Nov-05)
  - Chordomas 42 (65%)
  - Chondrosarcomas 22 (34%)
- Mean age 44.5 years
- Mean follow-up time: 38 months (14 – 92)
- Mean tumor dose
  - Chordomas 73.5 CGE (67 - 74)
  - Chondrosarcomas 68.4 CGE (63 - 74)
- mean GTV volume: 25.8 cc (1.5 -100.5 cc)

* Ares, Lomax, Hug, Goitein – in preparation

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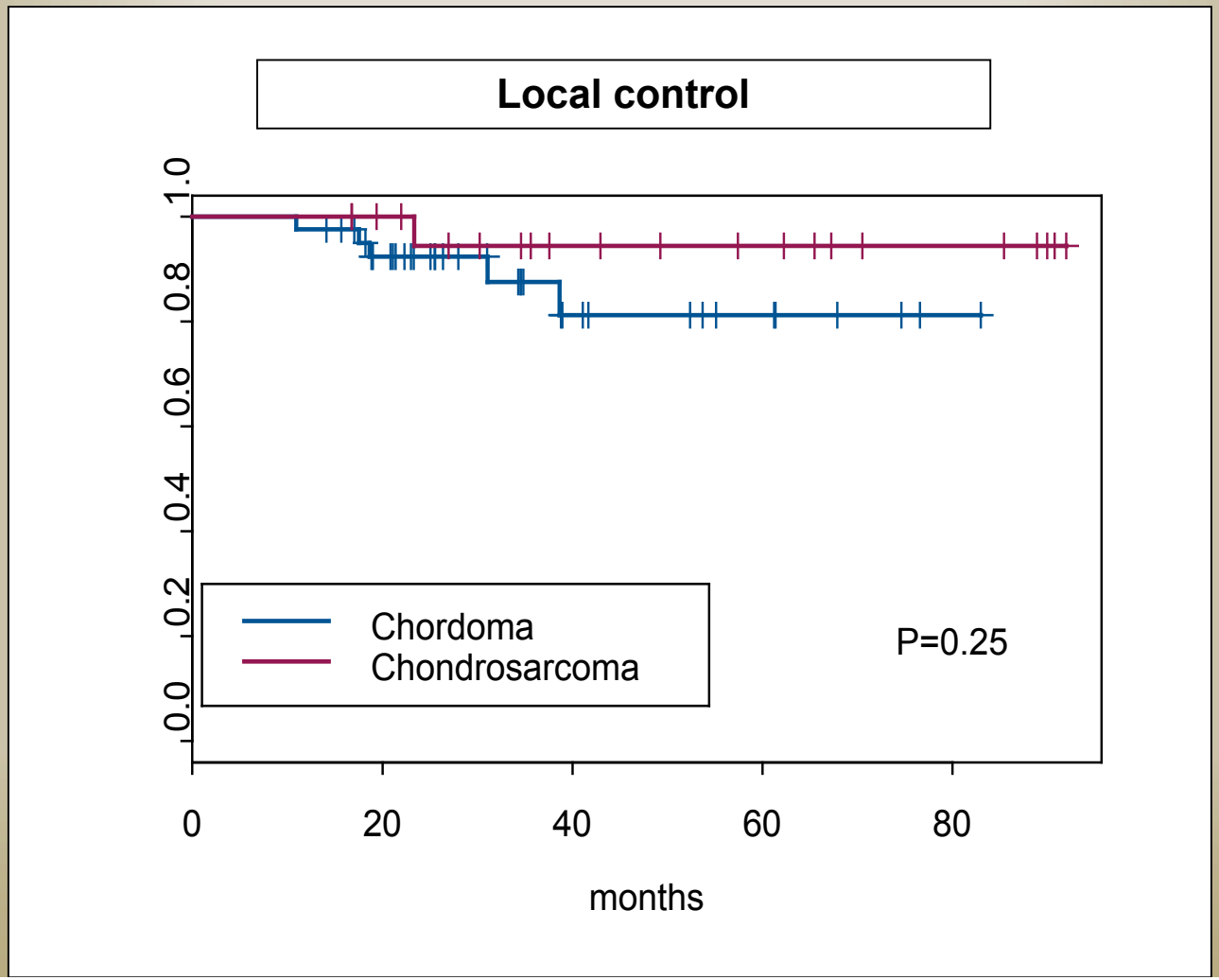
actuarial *Local Control*	3 years	*5 years*
Chordomas	87 %	*81 %*
Chondrosarcomas	94 %	*94 %*



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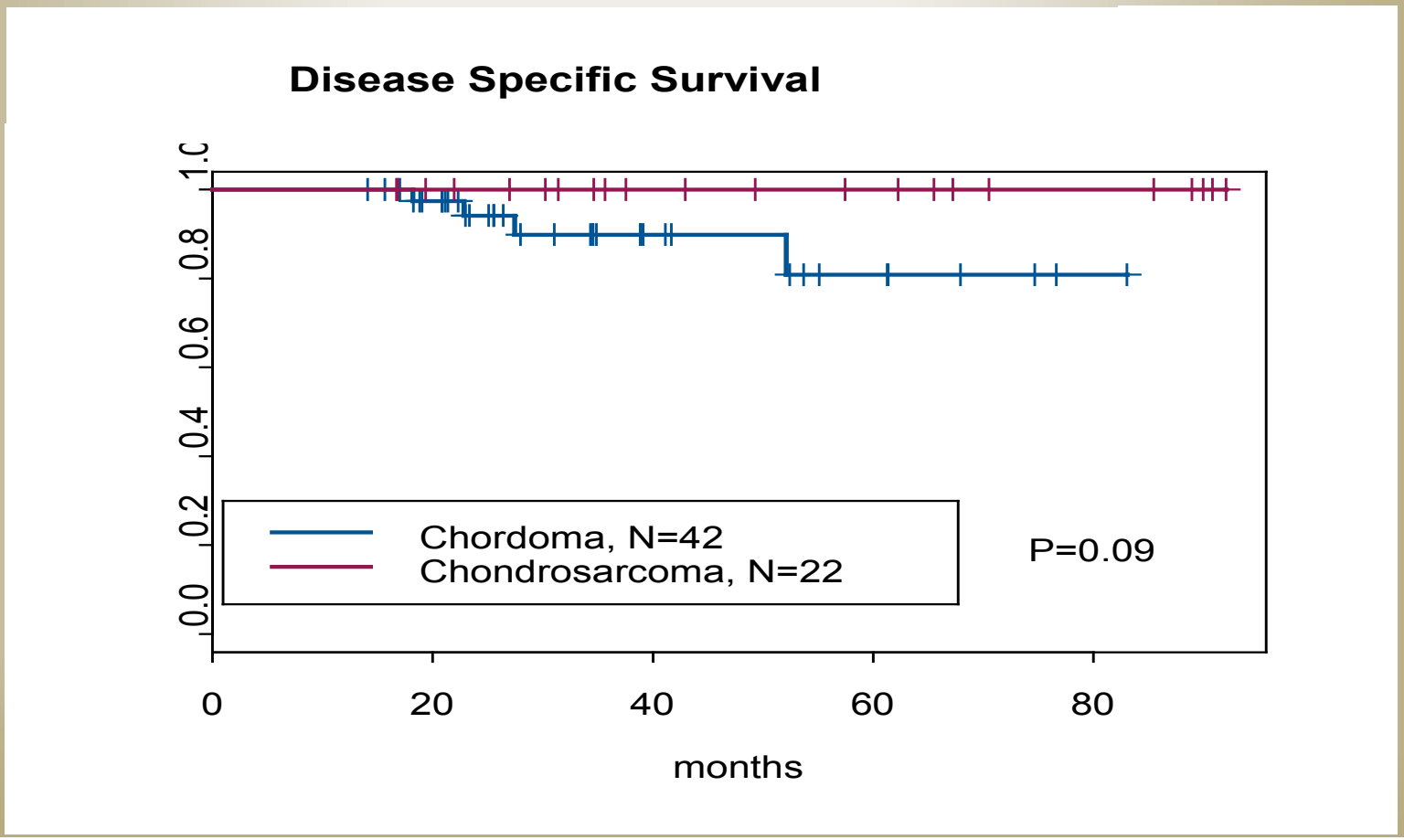
Disease-specific Survival	3 years	*5 years*
Chordomas	90%	*81%*
Chondrosarcomas	100 %	*100 %*



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Late Toxicity (CTCAE v3.0)

- ***High grade late toxicity (all Ch) → 4 pts (6.25%)***

  - **2 pts. optic pathway toxicity**
    - **G 4 → 1 patient (unilat. blindness)**
    - **G 3 → 1 patient (unilat. visual deficit)**

  - **2 pts. brain parenchyma toxicity**
    - **G 3 → 2 patients (sympt. temporal lobe necrosis)**

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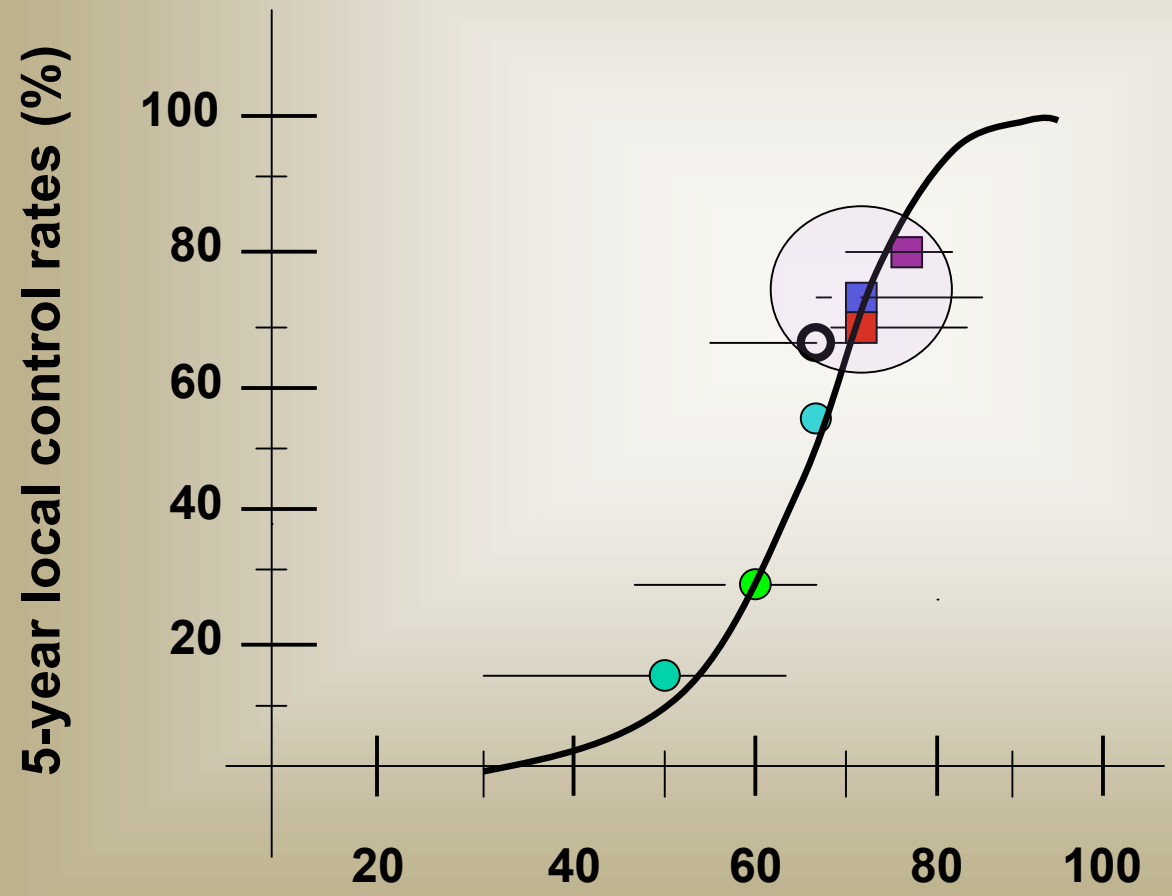
Chordomas of the Base of Skull



Photons

- Romero 1993
- Zorlu 2000
- Debus 2000

Protons

- Munzenrider 1999
- Ares 2007
- Hug 1999

C-Ions

- Schulz-Ertner

CPT

Pediatric Proton Radiation Therapy

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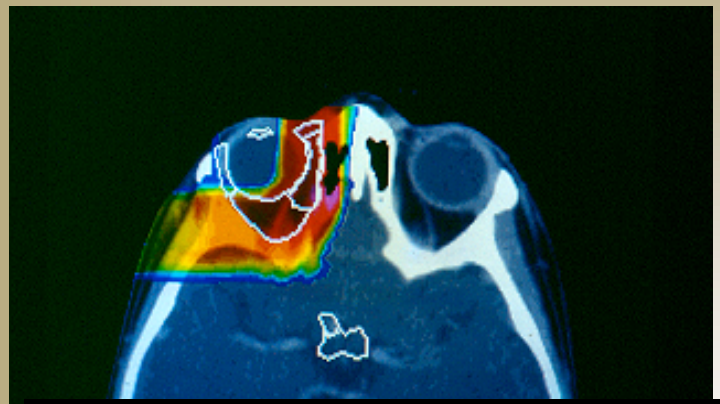

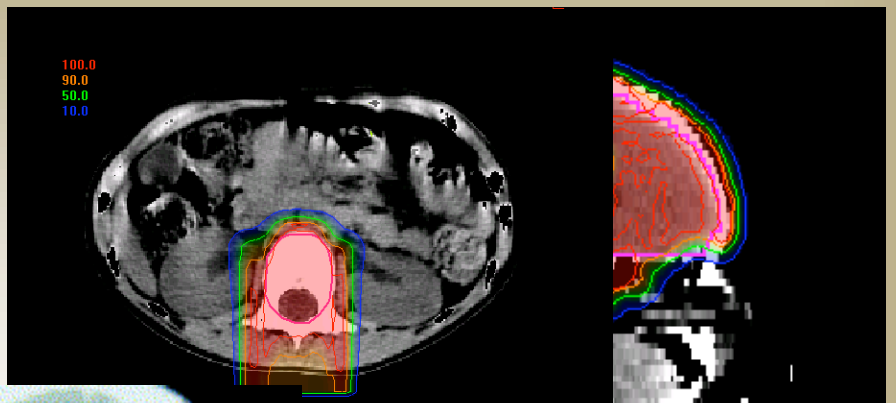

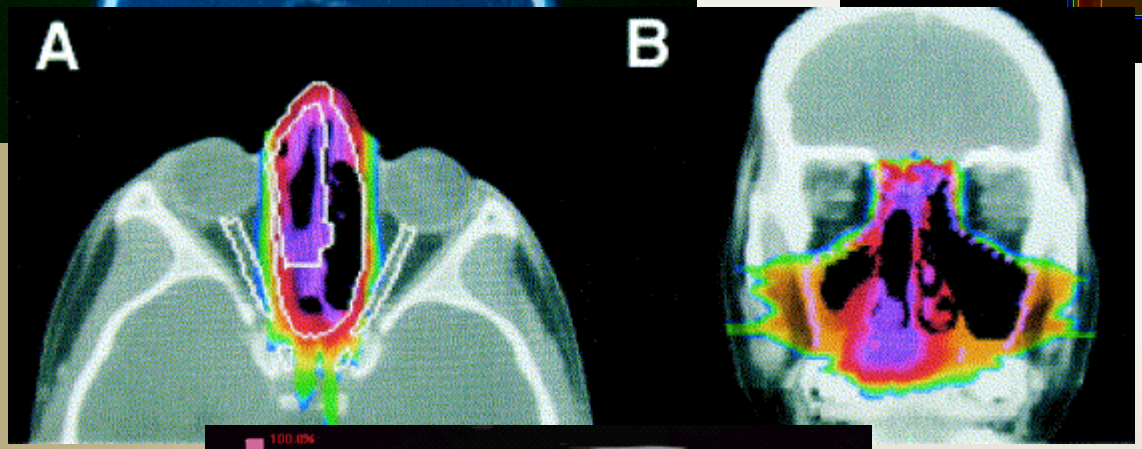

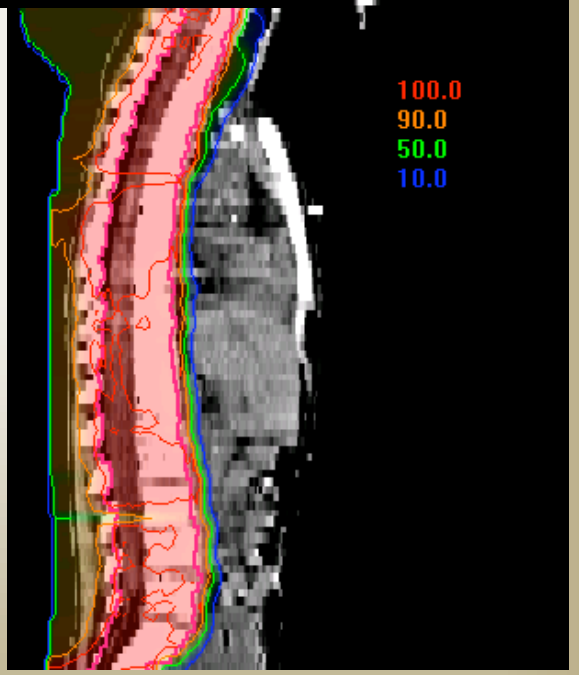

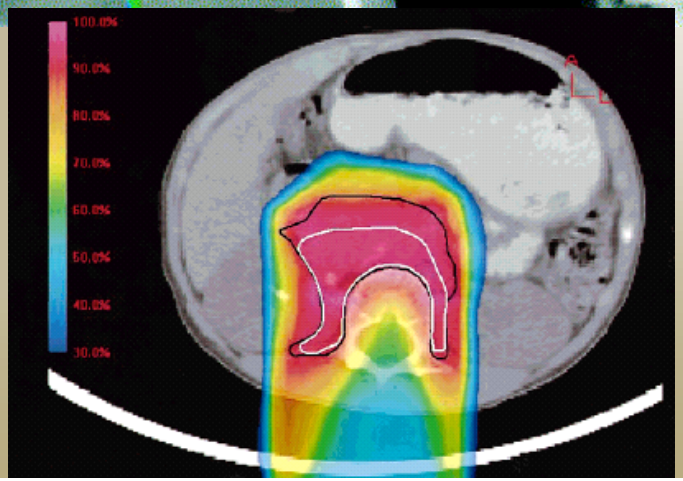

CPT

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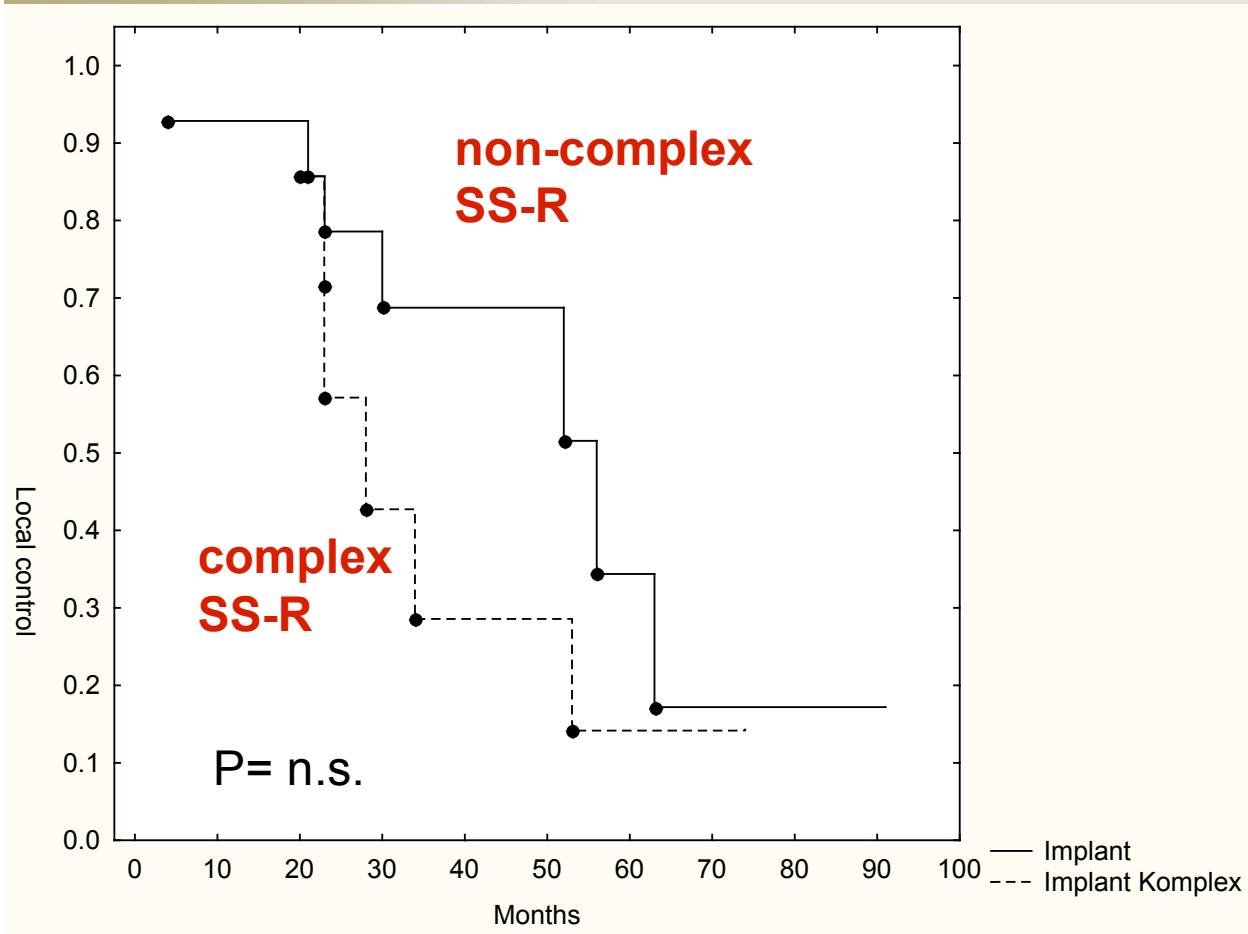
Chordomas of the Axial Skeleton at PSI: *5-year* outcomes data

Impact of complexity (= artifacts) of Surgical Stabilization – Reconstruction (SS-R) on Local control

P= n.s.



Complex SS-R = ventral and dorsal instrumentation

Non-complex SS-R = dorsal or ventral instrumentation only

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Indications treated at PSI

- ***Ocular Tumors***

  - Passive scattering delivery
  - > 95 % Uveal Melanomas
  - Approx. 200 – 230 patients per year treated.
  - The ***5000th*** patients will be treated at PSI this year.
  - Analysis of > 2000 patients: LC 98%

CPT

Particle Therapy at PSI (VI)

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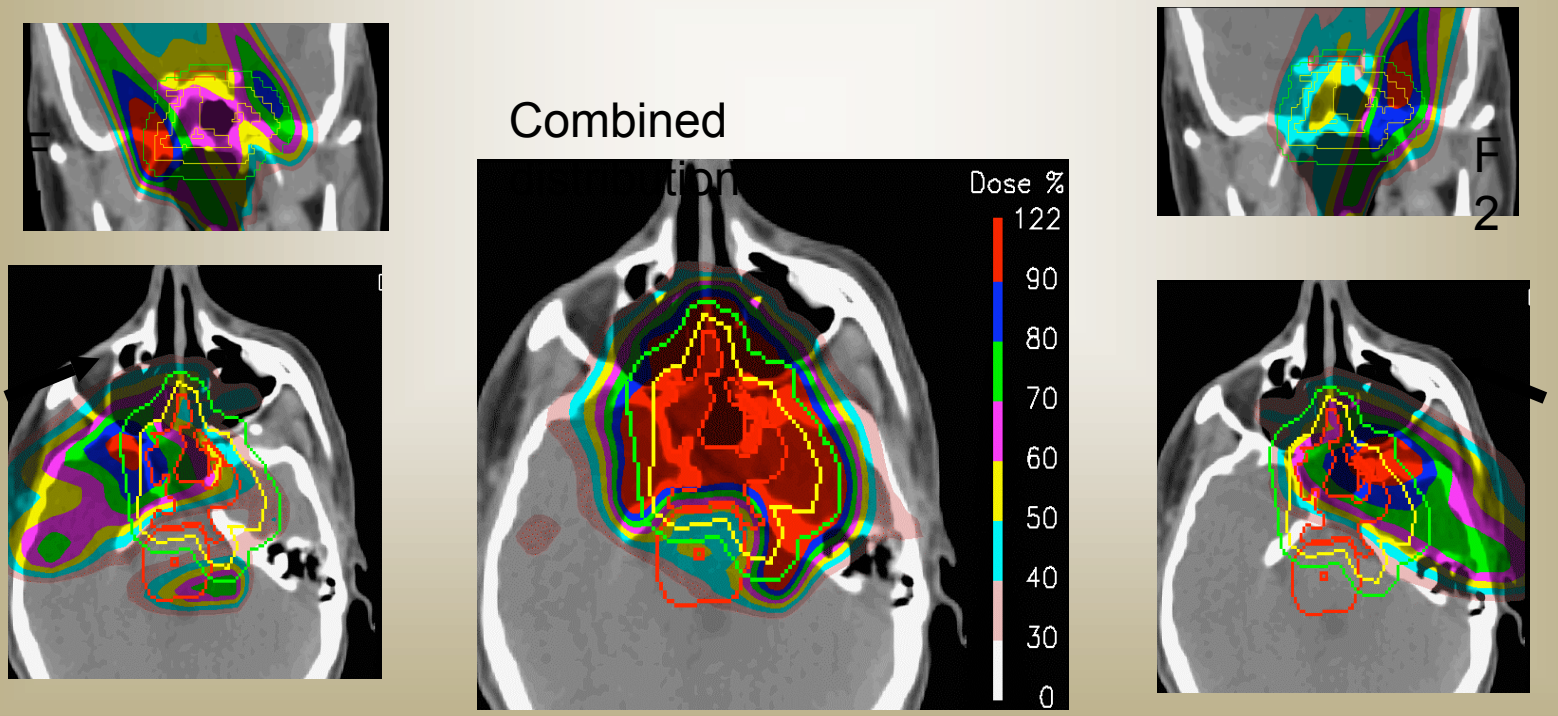
Intensity Modulated Proton Therapy:

- **Simultaneous optimisation of all Bragg peaks from all incident beams.**
- **Routine clinical use**



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