Pediatrics
-Proton Beam Therapy in Children -

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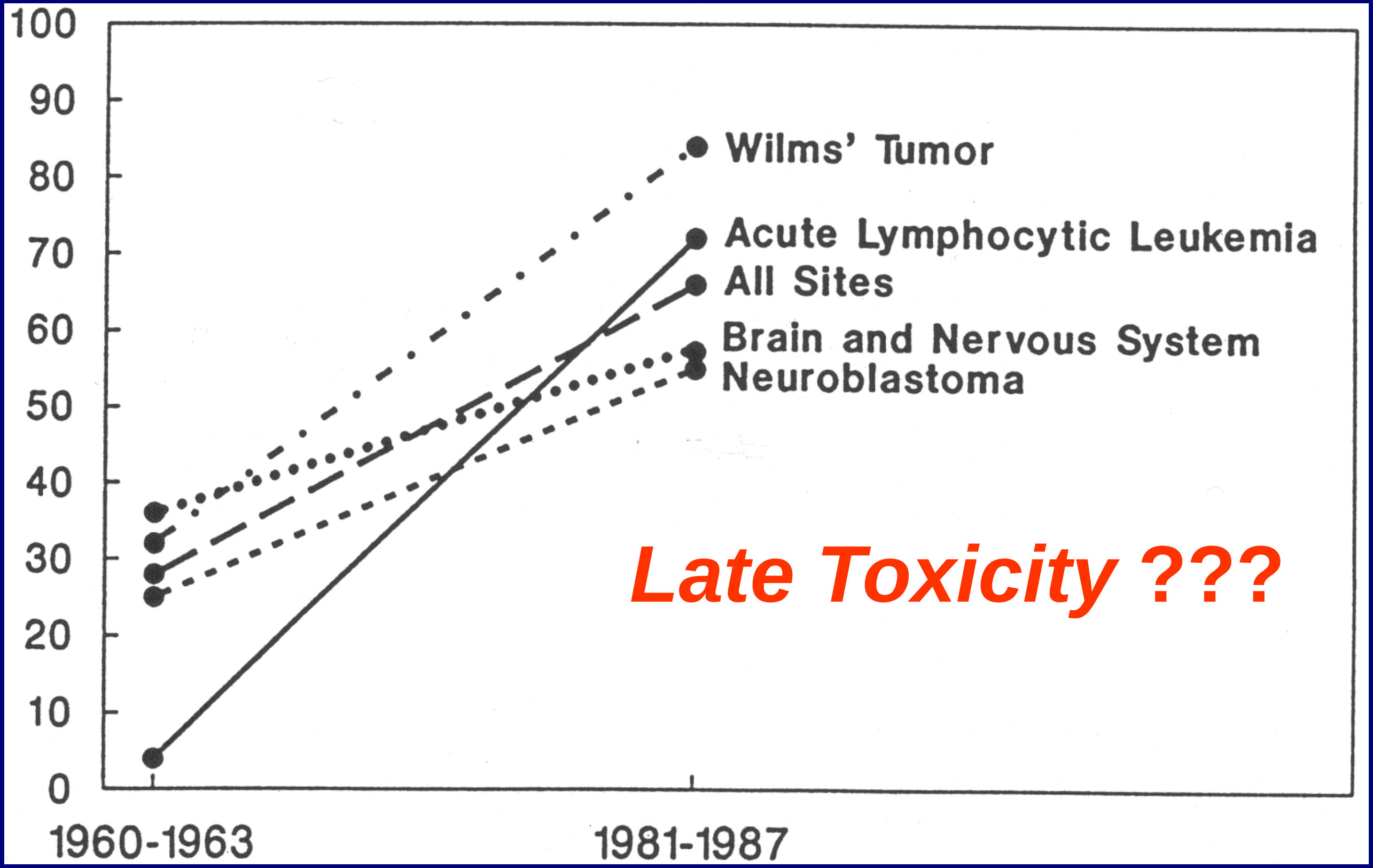
West German Proton Therapy Centre Essen
Germany

Preview

- Survival – Toxicity
- Why protons ? (theoretically)
- Experiences so far (clinically)
- A Case Study – PT means more than physics
- Conclusions and Outlook

Survival



Late Toxicity ???

Price of Survival

Including:

- Neurological Deficits
- Growth Retardation
- Endocrinology Dysbalance
- Psycho-social Impairment
- Mental Retardation
- Secondary Cancer etc.

Depending on:

- Age at Diagnosis
- Tumor
- Dose and Volume of RT
- Surgeries
- Chemotherapy etc.

Price of survival

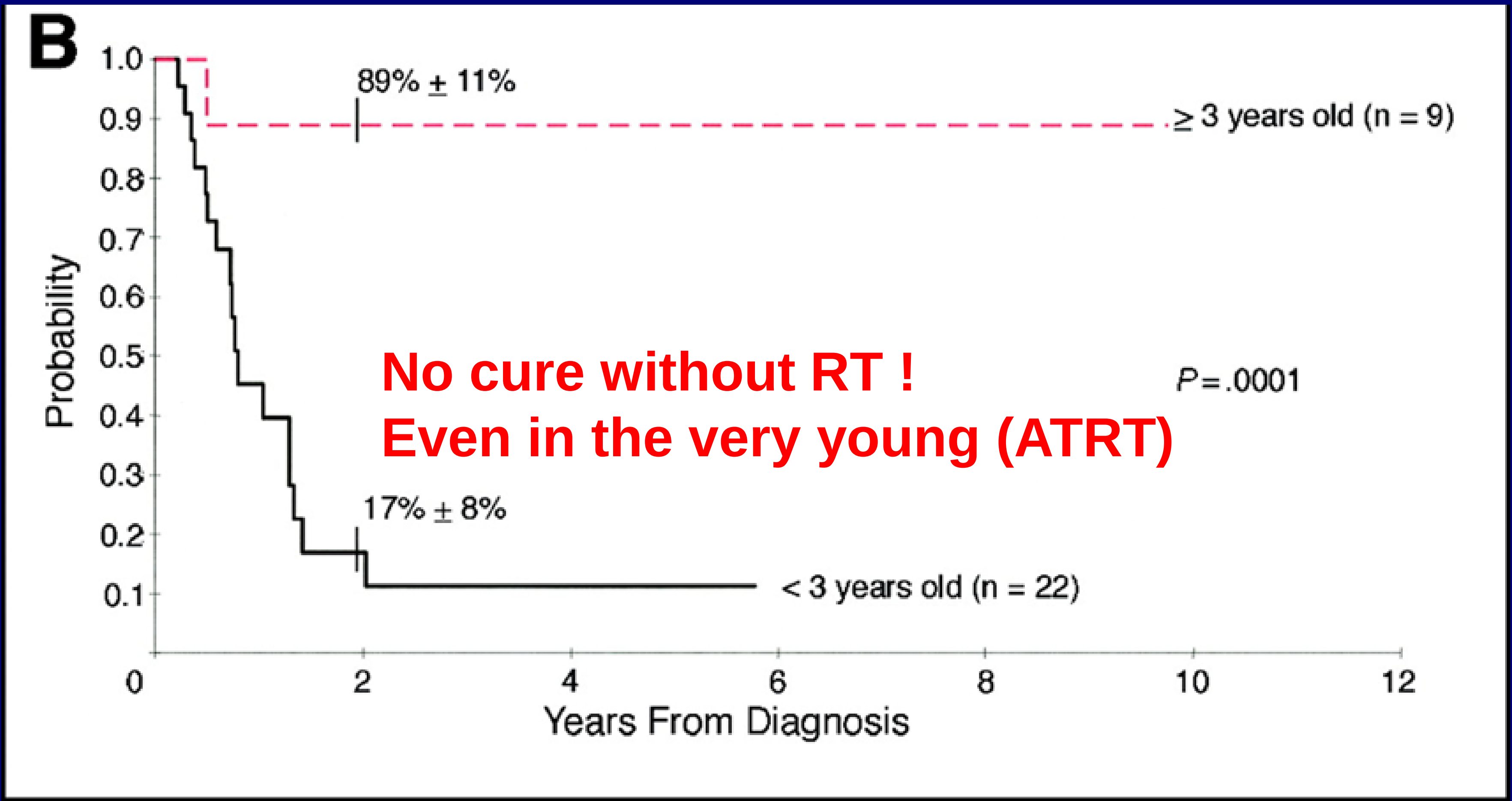
Risk of
selected severe (62% total; 25% > 3 issues) or life threatening (25%)
health conditions among childhood cancer survivors *compared to their sibling*

- **RT should be as intensive as necessary and as safe as possible**

Condition
Renal failure or dialysis
Hearing loss not corrected by aid
Legally blind or loss of an eye
Ovarian failure‡

Oeffinger et al. (MSKCC).
NEJM 355(15):1572-82; 2006:

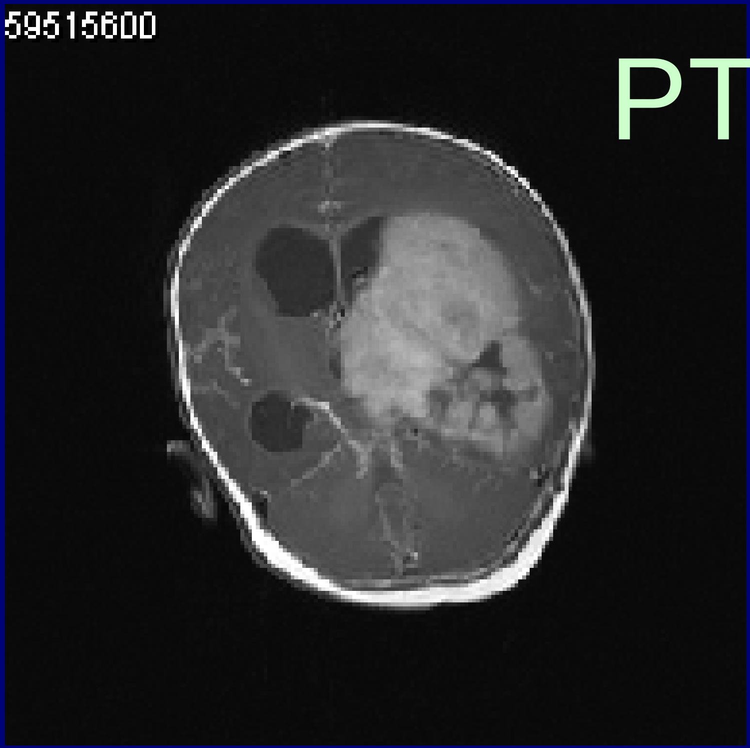
Local control/survival

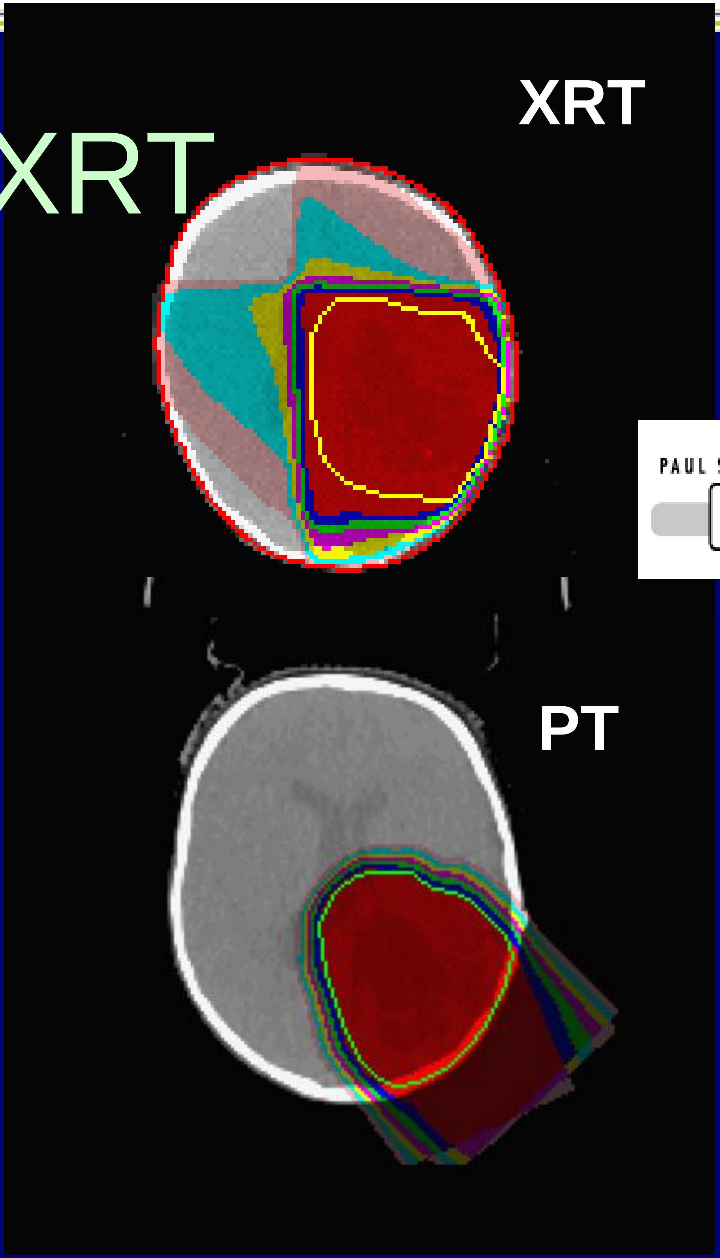


Journal of Clinical Oncology, Vol 23, No 7 (March 1), 2005: pp. 1491-1499

Why Protons?

PT - XRT





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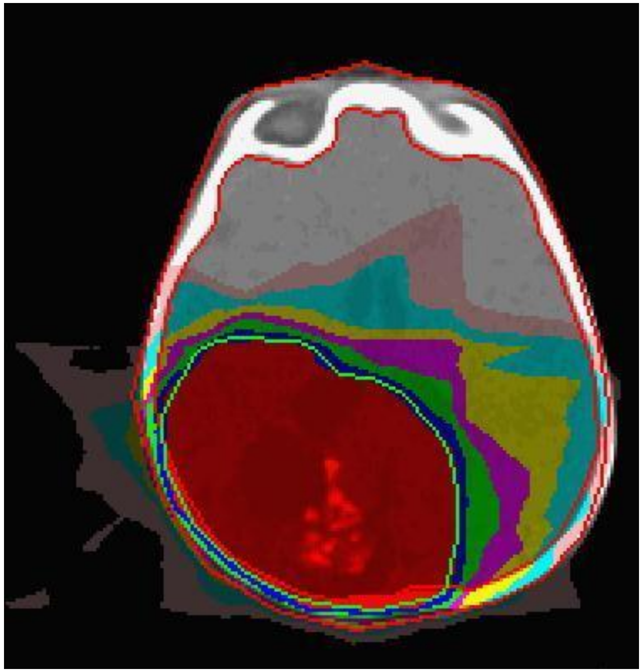
Choroid-Plexus Carcinoma

2 year old girl

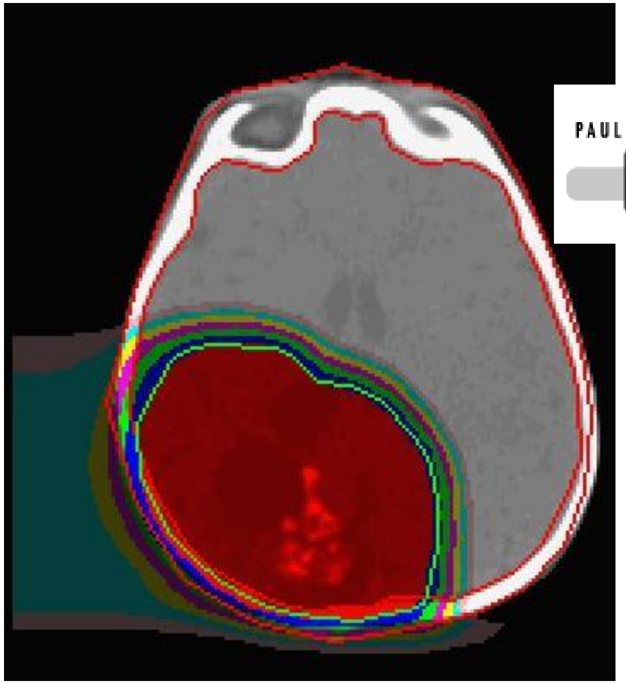
Modern Photon vs. Proton Therapy

Photons, IMRT



7 Fields

Protons



2 Fields

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Timmermann et al., presented at PTCOG in June 2006

Clinical Experiences

Evidence PT

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Protonentherapiezentrum
Essen gGmbH

B. Timmermann, DEC 2012

Tumour	Reports, n	Patients, n	FUs (months)
CH/CS	5		
CNS	9		
RMS	5		
Others	3		
1995-2012	**22 total**	**560 total**	
	4 prospective	22.3 mean	**35.9 mean**

Kulthau, 2012	QoL	N=142	~36 mo	prospective
Hattagandi,				
Yasuda, 201				
Chields, 201				
McDonald, 2				
Rombi, 2011				
Möller, 2011				
Cotter, 2010				
Chan, 2010				
Winkfield, 20				
Habrand, 20				
McDonald, 2				
Rutz, 2007				
Timmermann				
Timmermann				
Luu, 2006				
Noel, 2003				
Hug, 2002				
Hug, 2002				
Habrand, 19				
McAllister, 1997	CNS	N=28	25 mo	retro
Benk, 1995	CH	N=18	72 mo	retro

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Patients treated with particles

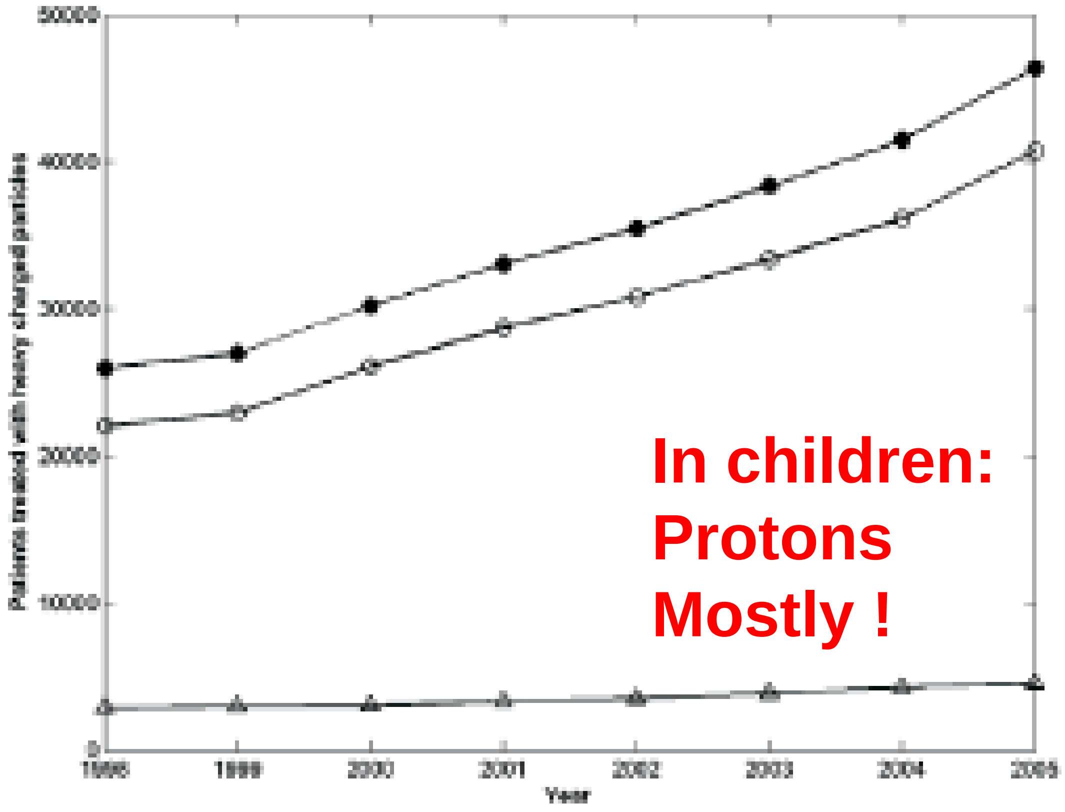

Figure 2. The total number of patients treated with heavy charged particles. (Total number treated ●, protons ○, other heavy charged particles △).

Evidence IMRT

Tumour	Reports, n	Patient, n	FUs (months)
CH/CS	0		
CNS	7		
RMS	4		
Others	3		
	13 total	**354 total**	
	1 prospective	25.3 mean	**34.8 mean**

Panandiker, 2012	neuroblastoma	N=20	FU 24.5 mo	retro
Paulino,				
Weber, 2				
Paulino,				
Sterzing				
Penagar				
Curtis, 2				
McDona				
Laskar,				
Jain, 200				
Schröde				
Combs,				
Wolden,				
Huang, 2002	Medullo	N=15	FU 18 Mo	Retro

Proton – SMN?

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17 **Comparative Analysis of Second Malignancy Risk in Patients Treated with Proton Therapy versus Conventional Photon Therapy**

C. S. Chung[1], N. Keating[2], T. Yock[3], N. Tarbell[3]

[1]Harvard Radiation Oncology Program, Boston, MA, [2]Harvard Medical School, Boston, MA, [3]Massachusetts General Hospital, Boston, MA

Background: Compared to photon radiation, proton radiation improves dose distribution to the target and decreases dose to adjacent normal tissues. The most common method of delivering proton radiation involves passive scattering. However, passive scattering produces secondary low-dose neutrons, which may induce late radiation-induced malignancies. The magnitude of second cancer risk in patients treated with proton radiation compared to photon radiation therapy has not been reported to date.

Purpose/Objective(s): To quantify the risk of a second malignancy associated with the use of proton radiation therapy compared to photon radiation therapy.

Materials/Methods: Matched retrospective cohort study of 1,450 patients treated with proton radiation therapy from 1974-2001 at the Harvard Cyclotron in Cambridge, MA, and patients treated with photon therapy in the Surveillance, Epidemiology, and End Results (SEER) cancer registry. We matched patients by age at radiation treatment, year of treatment, cancer histology, and site of treatment. We restricted the study to patients with ≥1 year of follow-up. The primary endpoint was the risk of a second malignancy in any site after radiation therapy.

Results: We matched 503 Harvard Cyclotron proton patients with 1591 photon patients from the SEER registry. 6.4% of proton patients (32 patients) developed a second malignancy, while 12.8% of photon patients (203 patients) developed a second malignancy. The median duration of follow-up was 7.7 years in the proton cohort and 6.1 years in the photon cohort. The median age at treatment was 56 years in the proton cohort and 59 years in the photon cohort. After adjusting for gender and the age at treatment, treatment with photon therapy was significantly associated with an increased risk of a second malignancy (Adjusted Hazard Ratio 2.73, 95% CI 1.87 to 3.98, $p < 0.0001$).

Conclusion: The results of our preliminary analysis indicate that the use of proton radiation therapy is associated with a significantly lower risk of a second malignancy compared to photon radiation therapy. Additional analyses are required, and ongoing close surveillance of these patients is necessary, given the prolonged latency period for the development of second cancers.

Author Disclosure: C.S. Chung, None; N. Keating, None; T. Yock, None; N. Tarbell, None.

I. J. Radiation Oncology ● Biology ● Physics Volume 72, Number 1, Supplement, 2008

O081

NEUROBEHAVIORAL FUNCTIONING IN PEDIATRIC BRAIN TUMOR PATIENTS AFTER PROTON BEAM RADIATION TREATMENT

Margaret Pulsifer[1], Irene Delgado[1], Nancy Tarbell[2], Karen Kuhlthau[3], Shannon MacDonald[2], Torunn Yock[2]

[1]*Massachusetts General Hospital, Psychiatry, Boston, MA, United States*
[2]*Massachusetts General Hospital, Radiation Oncology, Boston, MA, United States*
[3]*Massachusetts General Hospital, Pediatrics, Boston, MA, United States*

rapy is integral in treating pediatric brain tumors. However, is associated with neurobehavioral sequelae, including ifficulties with attention/executive skills. Proton beam s better targeting of tumors than XRT, sparing surrounding :, radiation-related neurobehavioral deficits should be reduced RT effects. This study examines changes in neurobehavioral functioning in pediatric brain tumor patients treated with PBT at MGH.

Method: Since 2004, baseline (BL) neurobehavioral testing has been routinely conducted with brain tumor patients receiving PBT. To date, 56 have received follow-up testing (M = 2.1 years, SD = 1.3). Neurobehavioral functioning was assessed in: 1) IQ; 2)emotional/behavioral functioning; 3)adaptive abilities, and 4) executive functioning. Three standardized parent rating scales were administered: Behavior Assessment System for Children-2, Scales of Independent Behavior-Revised, and Behavior Rating Inventory of Executive Functioning.

Results: 30 males (46%) and 26 females (54%) received PBT for treatment of medulloblastoma (50%), craniopharyngioma (16%), ependymoma (13%), and other (21%) tumors. Mean age was 8.2 years (SD = 4.5) at BL. Average radiation dose was 52.7 GyE (SD = 4.1). 71% received chemotherapy. IQ at BL (M = 107.9, SD = 13.9) and follow-up (M = 105.4, SD = 13.2) were average and stable as were adaptive skills (BL M = 106.4, SD = 15.8; follow-up M = 103.6, SD = 13.6). Parent rating scales from both evaluations revealed no difficulty with emotional/behavioral or executive functioning, including depression, anxiety, and inattention. Comparisons between pre- and post- treatment ratings revealed no significant change regardless of histology, age, gender or average radiation dose.

Conclusion: At two-year follow-up, IQ and neurobehavioral functioning remained intact and stable in this proton treated cohort. While findings are preliminary, they compare favorably to reports from photon radiation treatment. Data collection is ongoing and will refine these preliminary findings.

Siop 2010, Boston

Data German RiSK study

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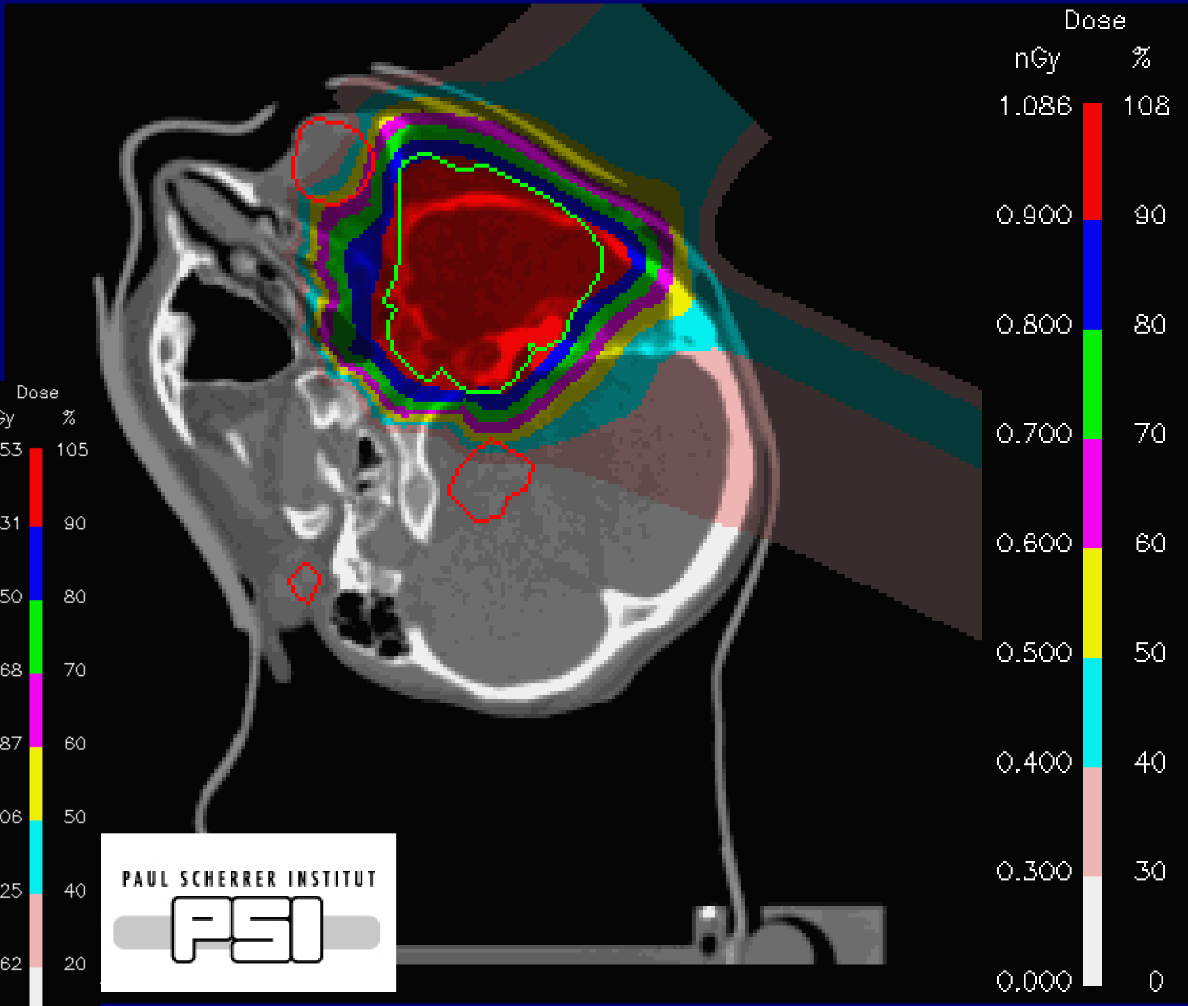
- **“Acute and late side effects to salivary glands and oral mucosa following head/neck radiotherapy in children and adolescents. Results of the “Registry for the evaluation of side effects after radiotherapy in childhood and adolescence” (RiSK).”**

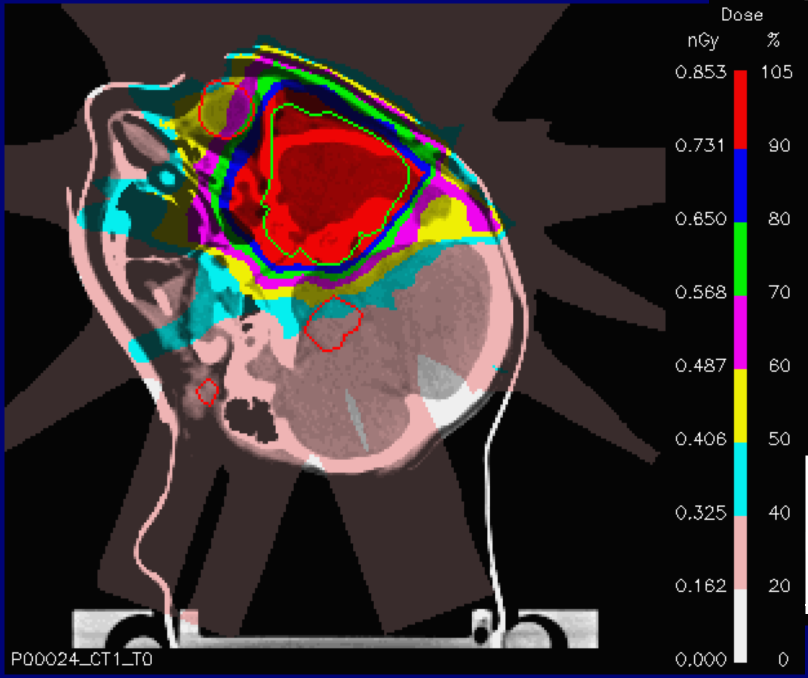
….The radiation techniques (photons (n=105) vs. protons (n=27)) also showed significant differences. Patients treated with protons had an Odds ratio of 0.12 (0.03-0.45, CI; p=0.002) in view of acute side effects to the salivary glands (lower toxicity)….

T. Bölling et. al., (submitted for pub.)

PT - XRT

Embryonal RMS,
Boy, 7.5 J.





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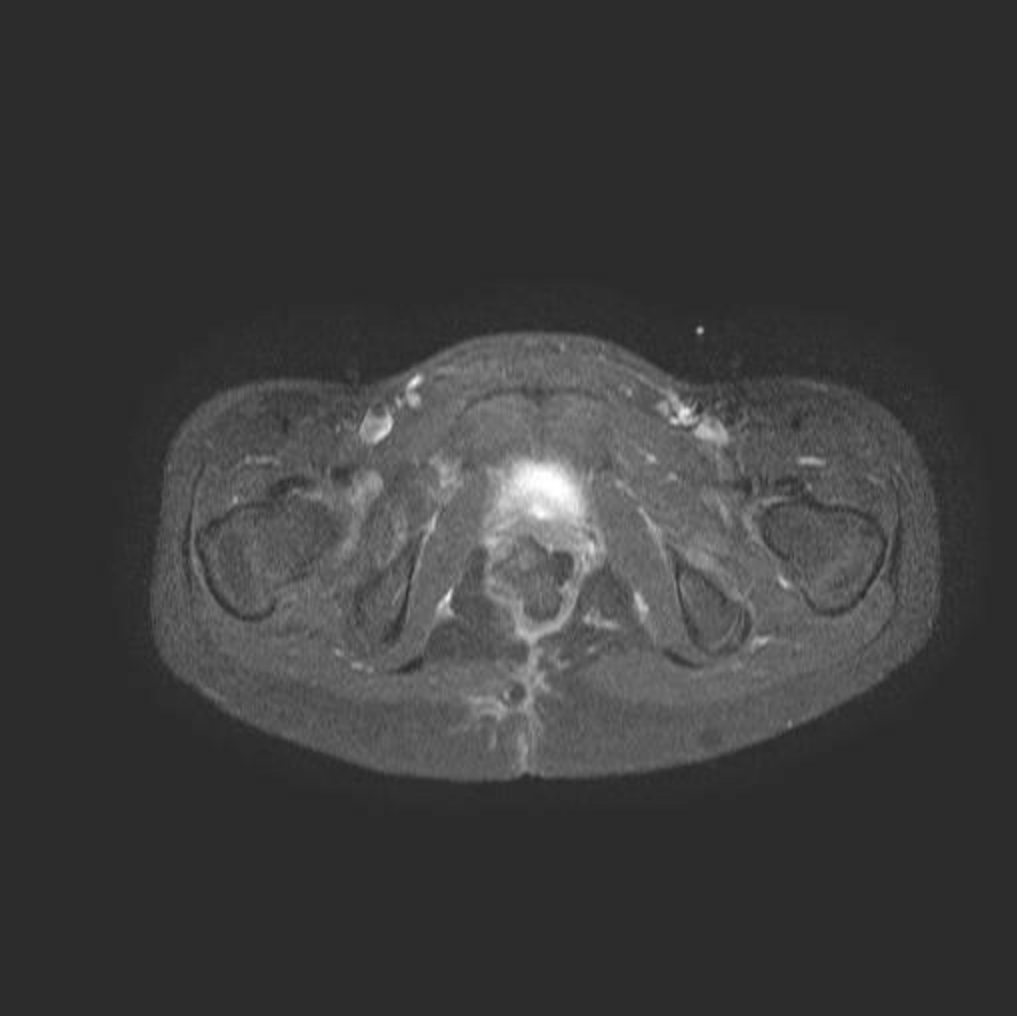
Dose delivery techniques

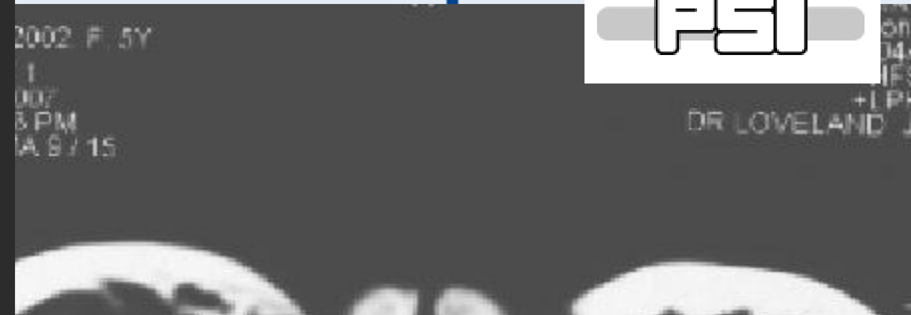
A Case Study -
more than physical features…

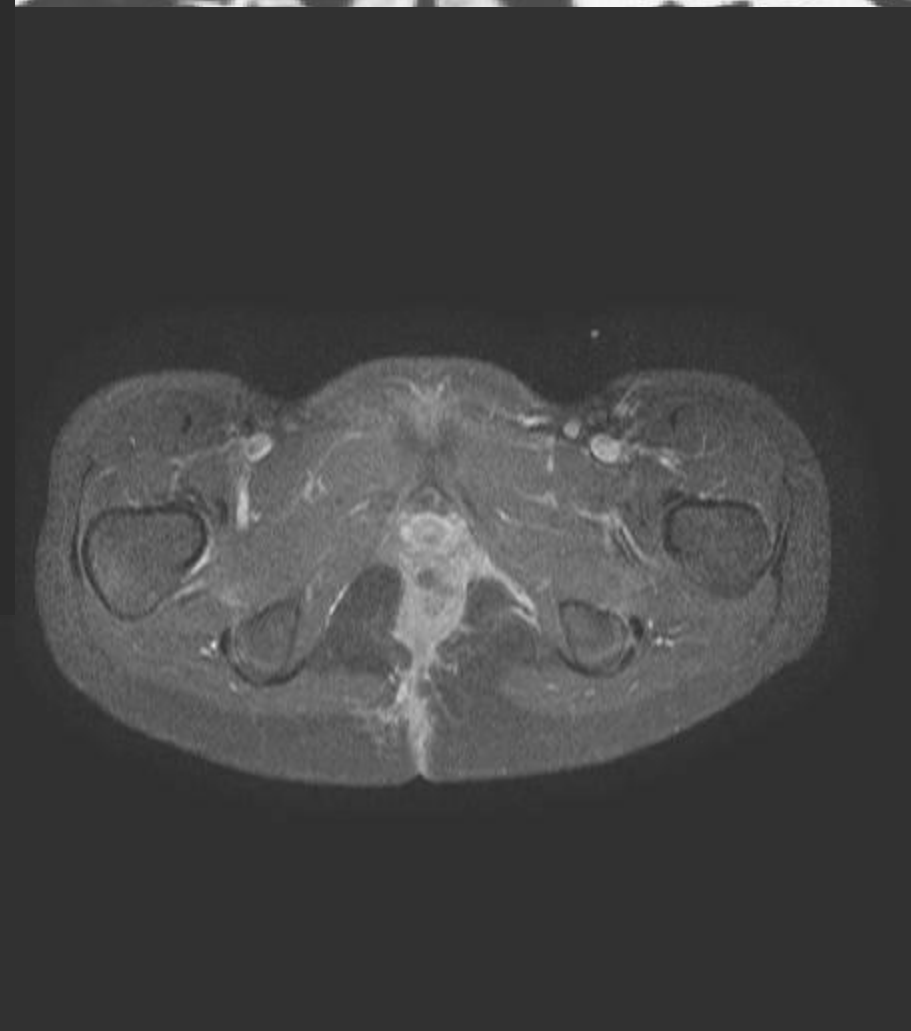
(see review Paper from T. Merchant)

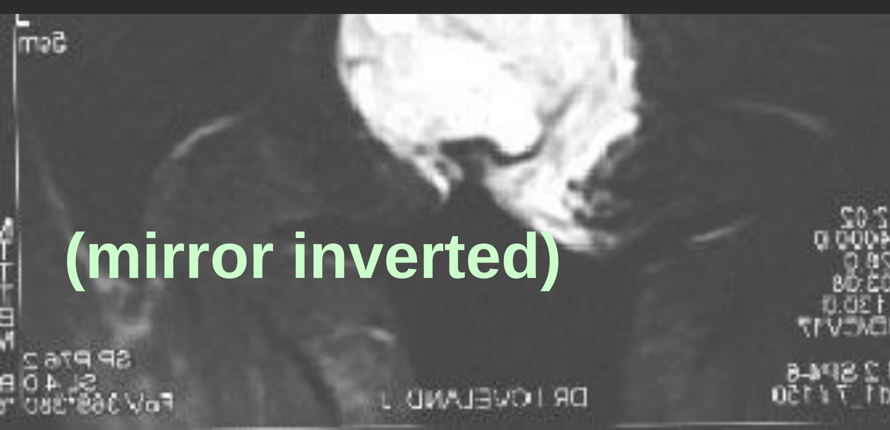
Pelvic Alveolar RMS

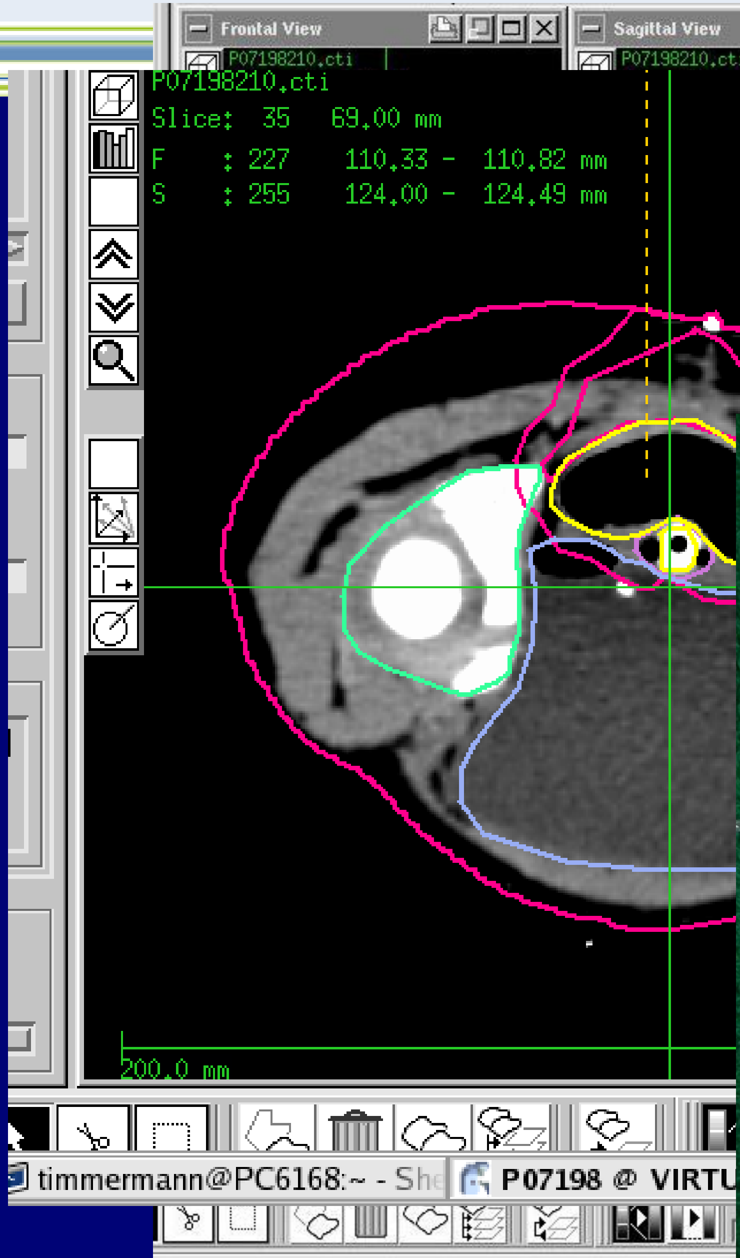
• Patient:	DOB 15th Jan. 2002, f
• Diagnose:	RMA
• Site:	small pelvis
• Therapy:	partial resection,
•	Chemo according to CWS, secondary resection (R1)
• RT-Concept:	PT 45 Gy (2007)




2002 F 5Y
DR LOVELAND




(mirror inverted)



- Ovaropexy
- Reproducible Positioning

- Bladder catheterization
- Dilatation/spacer
- Daily care

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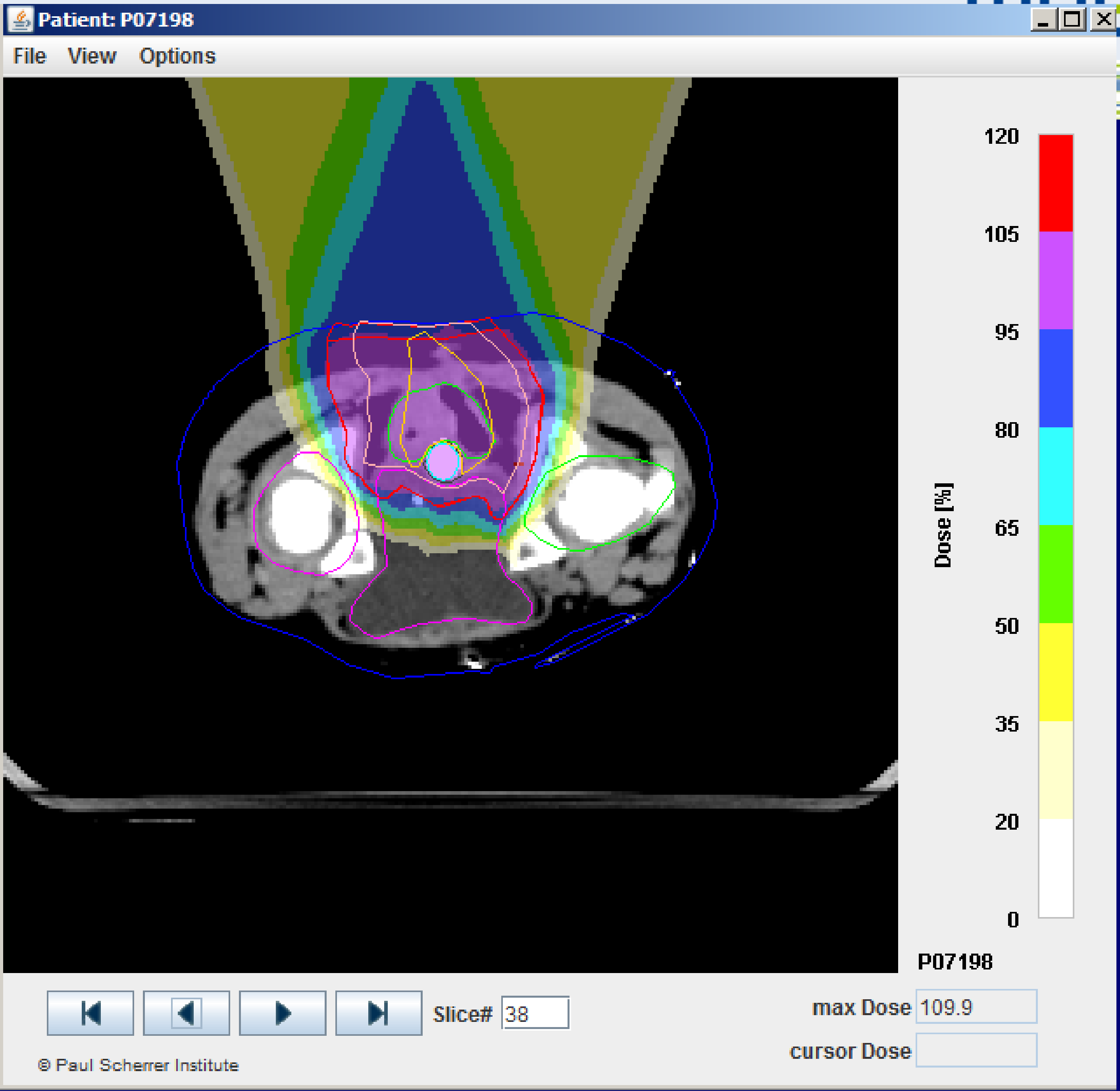

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Current clinical implementation

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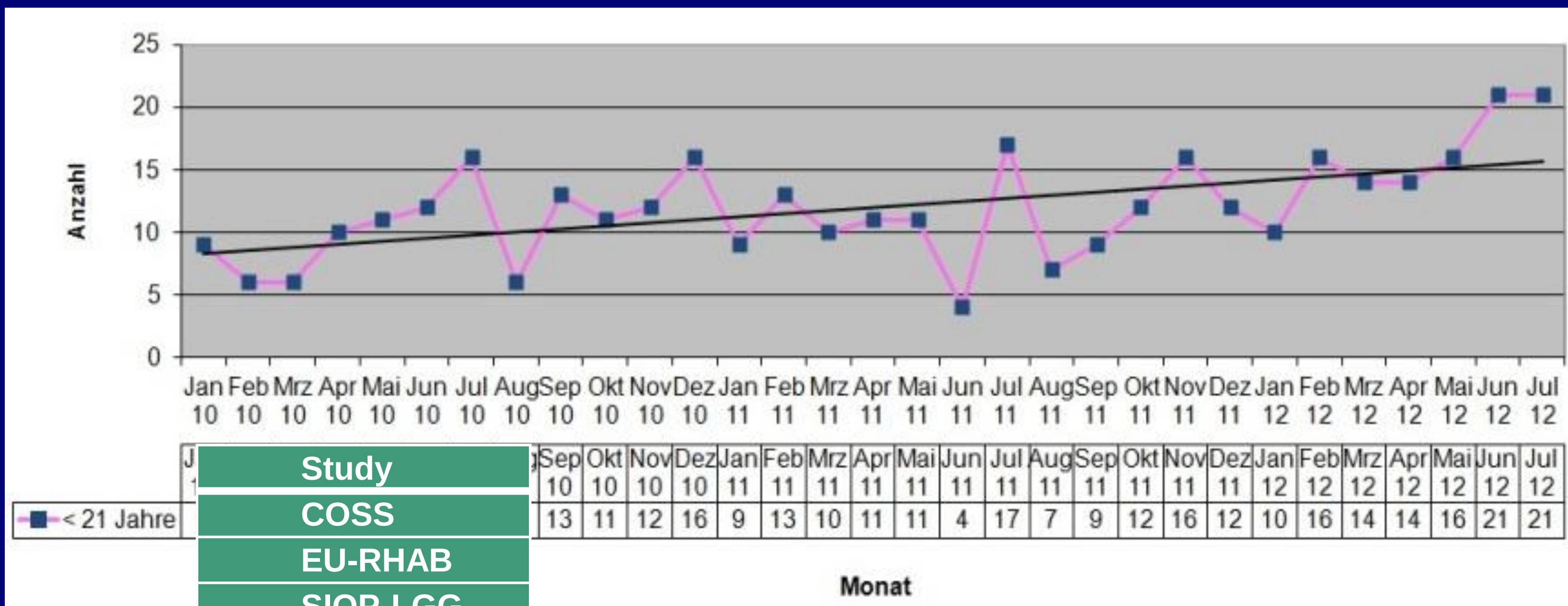
- To be improved („Physics science“ field)
- In US/GE according to COG and GPOH studies
- Increasingly centers situated in hospitals (Essen, Heidelberg etc.)
- Increasingly including multidisciplinary care incl. Anaesthesia etc.

The Demand

- Advisory Center for PT of the GPOH; supported by
  - > 300 inquieries/a



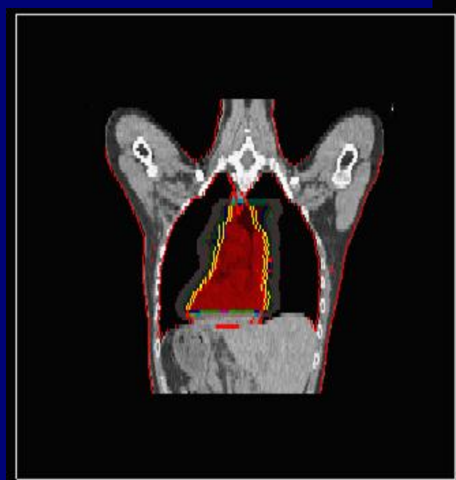
Study
COSS
EU-RHAB
SIOP-LGG
HIT 2000
EWING
CWS
Kranio 2007
MAKEI 96,GCT
HIT-Rez 2007

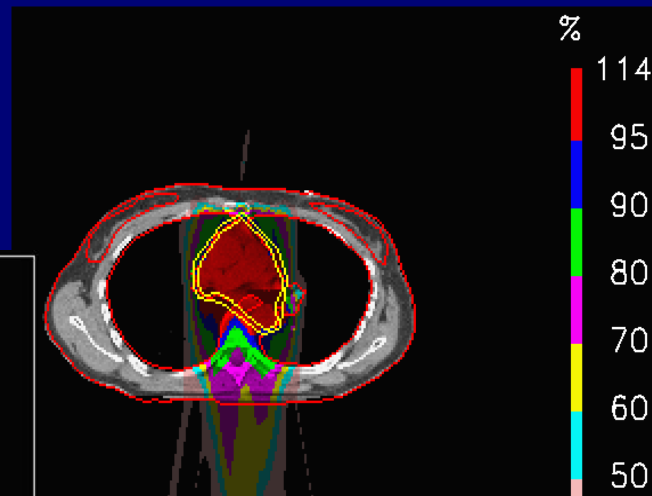
-> see our poster

Advice requested by	No
Study board	43
Hospital	37
Patient/Family	27
Proton Center	5

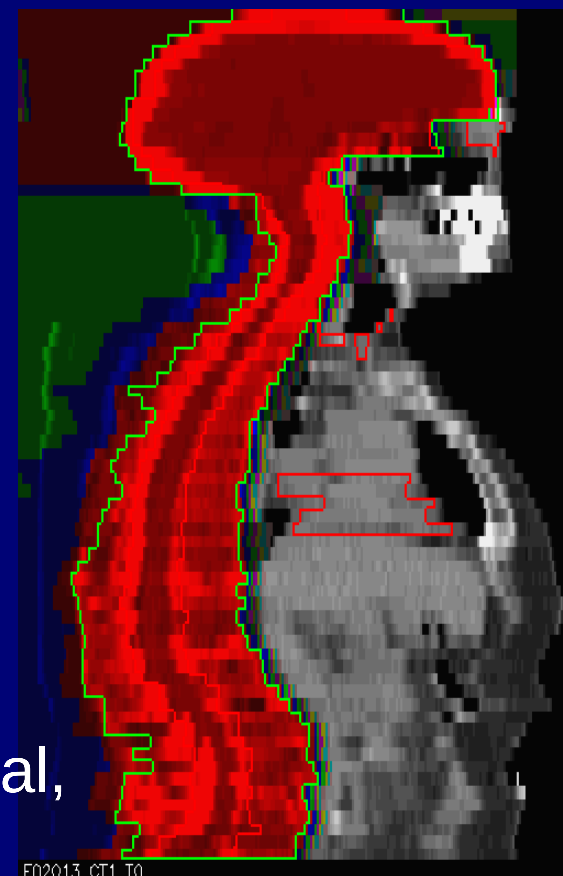
Vision – Overcoming technical hurdles

- Moving targets





- PBS for complex cases



Timmermann et al, STRONK 2007

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Treatment System Configuration

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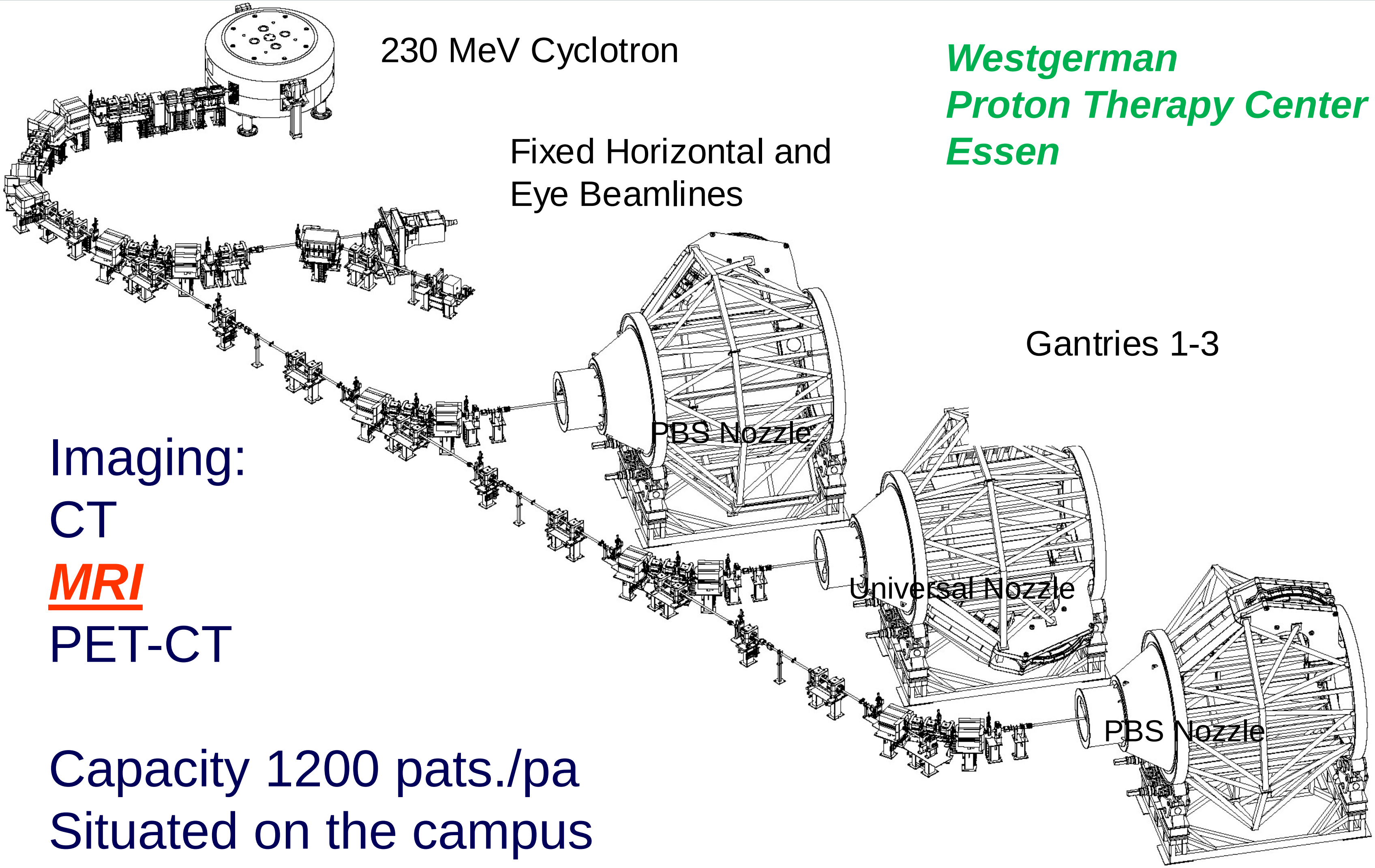

Westgerman Proton Therapy Center Essen

Imaging:
CT
MRI
PET-CT

Capacity 1200 pats./pa
Situated on the campus

The best option is…?

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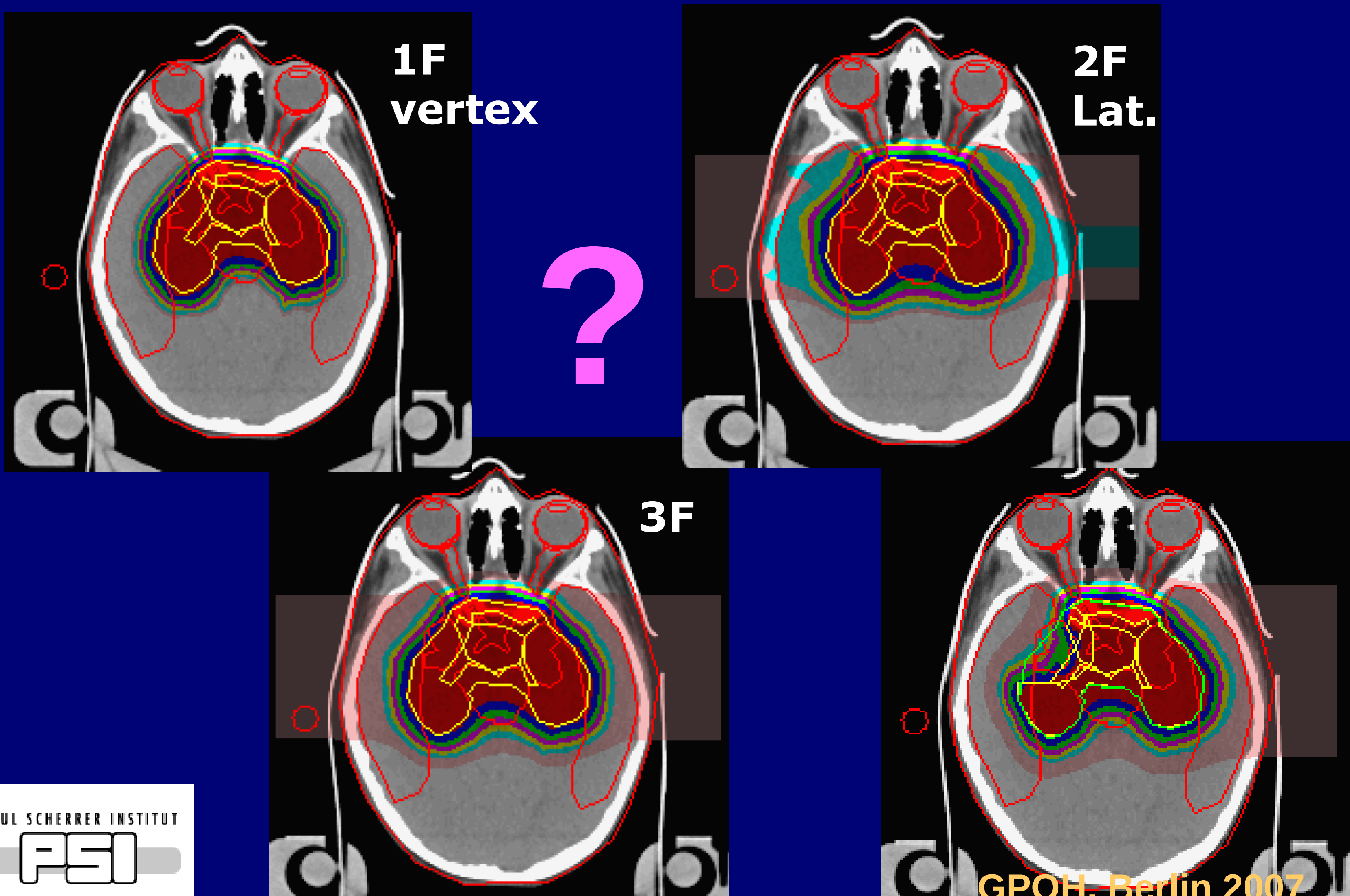

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Conclusions

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- PT is providing excellent conformal dose coverage and sparing of OARs (-> IMRT)
- PT is reducing the irradiated volume (low- and medium dose level) and the risk for secondary cancer
- Inside the target volume all techniques carry the same risk of treatment sequelae!
- Results of PT are promising
- no higher level evidence in paeds. (no randomization foreseen; rare diseases, ethical concerns…)
- Still technical restrictions to overcome

Outlook

- PT *will* play a major role in pediatric oncology if available on a broader base!
- The younger the patient the more benefit from protons to be expected!

(…and the larger the volume is)

- In US and also increasingly in Germany, PT is implemented in the treatment protocols->
- Integration in multidisciplinary framework and prospective evaluation is essential!
- Technical improvements ongoing

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+TEAM

Thank You

Referring Centers

Deutsche Kinderkrebsstiftung

oncosuisse

GPOH

Parents & Patients