Proton Radiation Therapy in Pediatric Oncology

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Medical Director
Professor of Radiation Oncology
President, PTCOG of North America
A Dosimetric Comparison of Intensity-Modulated Proton Therapy, Volumetric-Modulated Arc Therapy, and $4\pi$ Non-Coplanar Intensity-Modulated Radiation Therapy for a Patient with Parameningeal Rhabdomyosarcoma


Example: Parameningeal Rhabdomyosarcoma

DVH’s comparing IMPT (triangles) and $4\pi$ plans (squares) From right to left: the planning/scanning target volume (red), left cochlea (green), left temporal lobe (dashed dark red), left optic nerve (light blue), right temporal lobe (dashed grey), left retina (orange), left lacrimal gland (dark blue), and left lens (cyan).
Photons vs protons
Dose differential
Unnecessary Dose to normal Tissues

Photons minus Protons
Dose differential
Unnecessary Dose to normal Tissues

Unnecessary Dose with Photons:
Not just “low dose”, but moderate dose ranges affecting brain development even in older children.

Protons invariably and independent of anatomic site reduces the integral volume of normal tissue receiving radiation dose

Randomized trials of photons versus protons in children considered largely unethical

Photons minus Protons
Dose differential
Unnecessary Dose to normal Tissues

Photons minus Protons
Let’s assume you do not believe that in patients the low dose bath of 5 Gy will have deleterious effects………

I offer you 5000 SEK for giving you 5 Gy half-brain radiation
If you don’t take this deal or hesitate – then you can not possibly run a randomized clinical trial comparing photons with protons since you have violated the essential principle of EQUIPOISE

*This was the essence of the statement of 3 ASTRO Gold Medal Recipients*

* M. Goitein
* J. Cox
* H. Suit

Hein, Hug et al. IJROBP 62, 2005
Clinical equipoise, also known as the principle of equipoise, provides the ethical basis for medical research that involves assigning patients to different treatment arms of a clinical trial.

The term was first used by Benjamin Freedman in 1987.

“…….a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Should the investigator discover or be of the opinion that one treatment is of superior therapeutic merit, he or she is ethically obliged to offer that treatment. “
Proton Therapy in Pediatric Malignancies

2 main justifications

Normal tissue damage reduction

Increase tumor dose without increase of normal tissue damage

Primary Focus:
- Medulloblastoma
- Rhabdomyosarcoma
- Craniopharyngioma
- Ependymoma…
- Enrolled in protocols

Exchange photons with protons – same dose

Osteogenic Sarcoma
- Non-Rhabdo Soft Tissue Sarcomas
- Chordomas
- Chondrosarcomas etc.

Conventional doses insufficient.
- Require high doses 70-76 Gy as in adults for gross disease.
Chronic Health Conditions in Adult Survivors of Childhood Cancer: The Childhood Cancer Survivor Study
Oeffinger et al. (MSKCC). NEJM 355(15):1572-82, 2006

- 10,397 Survivors, > 3000 matched siblings
- Minimal survival time 5 years (up to 31 years):

**Results:**

62% at least one chronic condition

1/4 severe or life-threatening condition

1/4 had 3 or more chronic health problems
Cumulative Incidence of Chronic Health Conditions among 10,397 Adult Survivors of Pediatric Cancer, Severity of subsequent health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3) as:
- mild (grade 1),
- moderate (grade 2),
- severe (grade 3),
- life-threatening or disabling (grade 4),
- or fatal (grade 5).
Estimate of the proportion of pediatric cancer diagnosis treated at proton centers over five years in the US. 2012–2013 data from the Pediatric Proton Foundation (PPF) and 2014–2016 from the Pediatric Proton Consortium Registry (PPCR)

D. Weber et al. Proton therapy for pediatric malignancies..A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN. Radiother. Oncol 2018
# An Update From the Pediatric Proton Consortium Registry

Clayton B. Hess¹, Daniel J. Indelicato², Arnold C. Paulino³, William F. Hartsell⁴, Christine E. Hill-Kayser⁵, Stephanie M. Perkins⁶, Anita Mahajan⁷, Nadia N. Laack⁸, Ralph P. Ermoian⁹, Andrew L. Chang⁹, Suzanne L. Wolden¹⁰, Victor S. Mangona¹¹, Young Kwok¹², John C. Breneman¹³, John P. Perentesi¹³, Sara L. Gallotto¹, Elizabeth A. Weyman¹, Benjamin V. M. Bajaj¹, Miranda P. Lawell¹, Beow Y. Yeap¹ and Torunn I. Yock¹*

## Table: Tumor Sites and Associated Numbers

<table>
<thead>
<tr>
<th>Institution</th>
<th>Open to enrollment</th>
<th>Patient accrual</th>
<th>Intracranial and CNS tumors</th>
<th>N*</th>
<th>%</th>
<th>Tumors outside the CNS</th>
<th>N*</th>
<th>%</th>
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<tr>
<td>Massachusetts General Hospital (Boston, MA, USA)</td>
<td>Jul 2012</td>
<td>478</td>
<td>Medulloblastoma/PNET</td>
<td>276</td>
<td>25.4</td>
<td>Rhabdomyosarcoma (RMS)</td>
<td>191</td>
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<td>Northwestern Medicine Chicago Proton Center (Chicago, IL, USA)</td>
<td>Sep 2013</td>
<td>242</td>
<td>Ependymoma</td>
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<td>Ewing sarcoma</td>
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<td>University of Florida Health Proton Therapy Institute (Jacksonville, FL, USA)</td>
<td>Nov 2013</td>
<td>490</td>
<td>Glial/astrocytoma</td>
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<td>18</td>
<td>Hodgkin lymphoma</td>
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<td>Washington University (St. Louis, MO, USA)</td>
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<td>81</td>
<td>Tumors/gangliomas</td>
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<td>14.1</td>
<td>Neuroblastoma</td>
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<td>M.D. Anderson Cancer Center (Houston, TX, USA)</td>
<td>Jun 2014</td>
<td>278</td>
<td>Craniopharyngioma</td>
<td>108</td>
<td>9.9</td>
<td>Chordoma</td>
<td>47</td>
<td>7.5</td>
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<td>University of Pennsylvania (Philadelphia, PA, USA)</td>
<td>Jun 2014</td>
<td>89</td>
<td>Germ cell tumor</td>
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<td>2.5</td>
<td>Non-rms soft tissue sarcomas (NRSTS)</td>
<td>47</td>
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<td>University of Washington (Seattle, WA, USA)</td>
<td>Feb 2016</td>
<td>41</td>
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<td>Carcinoma (NOS)</td>
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<td>ProCure Proton Therapy Center (Somerset, NJ, USA)</td>
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<td>Mayo Clinic (Rochester, MN, USA)</td>
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<td>58</td>
<td>Vascular lesions</td>
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<td>Osteosarcoma/bone sarcoma</td>
<td>11</td>
<td>1.6</td>
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<td>ProCure Proton Therapy Center (Oklahoma City, OK, USA)</td>
<td>Oct 2016</td>
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<td>Nerve sheath tumor</td>
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<td>47</td>
<td>Chondrosarcoma</td>
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<td>1.3</td>
<td>Choroid plexus</td>
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<td>Maryland Proton Therapy Center (Baltimore, MD, USA)</td>
<td>Apr 2017</td>
<td>9</td>
<td>Esthesioneuroblastoma</td>
<td>6</td>
<td>1.0</td>
<td>sPineal parenchymal tumor</td>
<td>7</td>
<td>&lt;1</td>
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<td>Cincinnati Children's Hospital Medical Center (Cincinnati, OH, USA)</td>
<td>Oct 2017</td>
<td>0</td>
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<td>7</td>
<td>&lt;1</td>
<td>Wilms tumor</td>
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<td>1.0</td>
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<td>TOTAL</td>
<td></td>
<td>1,854</td>
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</table>
Neurocognitive Outcome: Emerging data in pediatric population

Early Cognitive Outcomes Following Proton Radiation in Pediatric Patients With Brain and Central Nervous System Tumors.


60 pts.v with medulloblastoma (38.3%), gliomas (18.3%), craniopharyngioma (15.0%), ependymoma (11.7%), and other CNS tumors (16.7%)
Mean age was 12.3 yrs., mean F/U 2.5 years. Treatment included prior surgical resection (76.7%) and chemotherapy (61.7%).
No significant change in mean Wechsler Full Scale IQ, Verbal Comprehension, Perceptual Reasoning/Organization, or Working Memory. However, Processing Speed scores declined significantly (mean 5.2 points), with a significantly greater decline for subjects aged <12 years and those with the highest baseline scores.

Left hippocampal dosimetry correlates with visual and verbal memory outcomes in survivors of pediatric brain tumors.

Zureick AH, Yock T et al. MGH Cancer. 2018 May 15;124(10):2238-2245
70 pts, F/U: Median 3.1 years
Immediate and delayed visual memory scores were not found to change significantly. Only delayed verbal memory scores declined statistically significantly. Left hippocampal-sparing PRT plans may assist patients with pediatric brain tumors in preserving memory-retrieval abilities.
Methods and Materials: Sixty patients receiving PRT for medulloblastoma (38.3%), gliomas (18.3%), craniopharyngioma (15.0%), ependymoma (11.7%), and other CNS tumors (16.7%) were administered age-appropriate measures of cognitive abilities at or near PRT initiation (baseline) and afterward (follow-up). Patients were aged ≥6 years at baseline to ensure consistency in neurocognitive measures.

Fig. 1. Wechsler Full Scale Intelligence Quotient and Index mean standard scores and standard error of the mean at baseline and follow-up.

F/U: mean 3.2 years
- No decline in Wechsler IQ
- Verbal Comprehension, Reasoning, Working Memory no decline
- Processing speed declined significantly
Rhabdomyosarcomas
Parameningeal Rhabdomyosarcoma

Dose sparing of normal tissues
with standard prescription doses

4 year old boy – Parameningeal embryonal Rhabdomyosarcoma
D. K. DoB 5/29/2008, 9 y.o. boy
Parameningeal Rhabdomyosarcoma
Proton Therapy 7/18/2017 – 8/31/2017
CTV1 to 41.4. Gy; CTV2 to 50.4, GTV to 54 at 1.8 dose per fraction
## Proton Therapy for Rhabdomyosarcomas

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Overall survival (%)</th>
<th>Local control (%)</th>
<th>Late side effects ≥ G2 (%)</th>
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<tbody>
<tr>
<td>Yock 2005</td>
<td>Rhabdomyosarcoma (orbit)</td>
<td>7</td>
<td>Proton</td>
<td>100 (median 6.3Y)</td>
<td>86 (median 6.3Y)</td>
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<td>Timmerman 2007</td>
<td>STS</td>
<td>16</td>
<td>Proton</td>
<td>63.3 (2Y)</td>
<td>75.0 (2Y)</td>
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<tr>
<td>Cotter 2011</td>
<td>Rhabdomyosarcoma (GU)</td>
<td>7</td>
<td>Proton</td>
<td>86</td>
<td>86.0</td>
<td>none</td>
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<tr>
<td>Childs 2012</td>
<td>Rhabdomyosarcoma (paramening.)</td>
<td>17</td>
<td>Proton</td>
<td>64</td>
<td>82</td>
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<tr>
<td>Indelicato 2014</td>
<td>Rhabdomyosarcoma</td>
<td>66</td>
<td>Proton</td>
<td>89.0 (2Y)</td>
<td>88.0 (2Y)</td>
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</tr>
<tr>
<td>Ladra 2014</td>
<td>Rhabdomyosarcoma</td>
<td>57</td>
<td>Proton</td>
<td>78.0 (5Y)</td>
<td>81.0 (5Y)</td>
<td>7</td>
</tr>
</tbody>
</table>

Yock et al. IJROBP 2005; 63(4):1161-68.
Childs et al. IJROBP 2012; 82(2):635-42.
Indelicato et al. SIOP 2014
Tumour Control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy.


- 83 RMS (embryonal, n=74; 89%), median age 4.5 years (08-15.5)
- Treated 2000-2014
- Low-, intermediate-, and high-risk disease in 24%, 63%, and 13%
- Median total dose delivered was 54Gy(RBE) (range, 41.4-64.8).

- Median follow-up time of 55.5 months
- 5-year local-control survival rate 78.5%
- Significant predictors for local failure were group/stage, tumour location, and size.
- 5-year overall survival was 80.6%
- 5-year incidence of grade 3 non-ocular late toxicity was 3.6%. No grade 4-5.
- Quality of Life (QoL) scores increased significantly after PT compared to baseline values.
Example Rhabdomyosarcoma:

Dose Coverage of Bones in Children:

Protons may lead to and afford a change in paradigm:

Partial bone irradiation compared to the decades-old paradigm of total bony coverage to reduce risks of uneven bony growth
Example:

Proton plans in comparison to photon plans.

Patient: Y. R. 2 y.o. child with rhabdomyosarcoma.
Target Definition by referring MD and decision to intentionally expand 35 Gy isodose to include entire vertebral body (right plan)
Proton Plan comparison adopting rationale and contours (left)-
Volumes shaded in proton plan, outlined only in photon plan.
Sagittal View at mid-plane.

Note almost entirety of oral cavity including jaws and teeth covered by 10 Gy isodose line in case of photons and significantly less by protons.
Separate Proton Plan with coverage of PTV target volumes only WITHOUT intentional inclusion of vertebral bodies. Note that 20Gy isodose line intersects vertebral bodies only about 25-30% of lateral volume.
Proton Therapy in Pediatric Malignancies

2 main justifications

Normal tissue damage reduction

Increase tumor dose without increase of normal tissue damage

Primary Focus:
- Medullblastoma
- Rhabdomyosarcoma
- Craniopharyngioma
- Ependymoma...
- Enrolled in protocols

Exchange photons with protons – same dose

Osteogenic Sarcoma
- Non-Rhabdo Soft Tissue
- Sarcomas
- Chordomas
- Chondrosarcomas etc.

Conventional doses insufficient.
Require high doses 70-76 Gy as in adults for gross disease.
Numerous Manuscripts have documented Treatment Plan superiority of Protons over Photons — but what are the truly distinctive features and clinical scenarios that will make a compelling case for protons in your clinical practice?
The physical Advantages of Particles – a simplistic view:

“The Bath”

“The Donut”

“The Canal”

“The Bridge”
The physical Advantages of Protons – a simplistic view:

“The Bath”:

“The Donut”:
Reduced dose to critical organ if INSIDE a target volume

“The Canal”
Reduced dose to nerve roots, cranial nerves etc. INSIDE a target volume

“The Bridge”
Three or more targets with normal organs/tissue in between require simultaneous RT. Particles can avoid the “bridge” of dose connecting targets with photons. Example: Pelvic tumor with inguinal LN”s, Oral Cavity GTV and enlarged nodes
Donut dose distribution  Note: distinct feature of PBS

Create 15-20% dose reduction to permit boost to GTV yet not exceeding cord tolerance
The „Canal“
Paravertebrale soft tissue sarcoma after resection

- Pre-operative images

- Prescription 54/66/74 Gy_RBE

The „Canal“
Summed doses for all phases
SUMMED DOSES FOR ALL PHASES
Proton Therapy for thoracic/pelvic tumors – advantages of pencil beam scanning technology

Active scanning: “sculpting” the dose:
Creating differential dose distributions within targets with relative ease – hot (SIB) or cold regions (OAR)
Example: sparing of selective nerve roots / nerves

The „Canal“
High demand on Treatment Accuracy, Intra-and Interfraction Imaging, Adapting Therapy to changes in anatomy and tumor
Patient: M. N., Dx: perianal Rhabdomyosarcoma. Prescription: 59.4 Gy to Primary Tumor, 41.4 Gy to Lymphnodes. Photon Plan by Dr. L, Israel, Proton Plan by ProCure Center, New Jersey, based on Dr. L’s planning CT with target definitions.

Axial Slice with Isodose distributions

The „Bridge“ Avoidance
Axial Slice with Isodose distributions

Note:
Sparing of Labia and Vagina by Protons
Dose-Volume histogram (DVH): Femural Heads and Prescription dose of 59.4 Gy

<table>
<thead>
<tr>
<th>ROI</th>
<th>ROI vol. [cm³]</th>
<th>Dose [cGy]</th>
<th>D99</th>
<th>D98</th>
<th>D95</th>
<th>Average</th>
<th>D50</th>
<th>D2</th>
<th>D1</th>
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<tr>
<td>Femur head</td>
<td>193.53</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>170</td>
<td>413</td>
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<tr>
<td>Femur head</td>
<td>193.61</td>
<td>1593</td>
<td>1702</td>
<td>1892</td>
<td>2746</td>
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<td>PTV 59.4</td>
<td>350.78</td>
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<td>5761</td>
<td>5878</td>
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<td>6090</td>
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<tr>
<td>PTV 59.4</td>
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<td>5684</td>
<td>5807</td>
<td>5983</td>
<td>5998</td>
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</table>

- Protons Femural Heads
- Photons Femural Heads
Proton Therapy in Pediatric Malignancies

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Ependymoma…
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Chondrosarcomas etc.

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Require high doses 70-76 Gy as in adults for gross disease.
Chordomas of the Skull Base and Occipito-Cervical Junction

Range of tumor sizes / Patient Selection

- Rarely: small lesions (< 15-20 cc)
- Frequently: Large lesions (>100 cc) with significant postop. residual
  - Pre-pontine extension, bilat. middle cranial fossa (A)
  - Extracranial (B)
  - Occipito-cervical junction with large bony destruction, BS and SC compression (C)
Patient: S Y, 16 year old. Dx: Chordoma
S/P partial resection. Proton Therapy: 11-12/2016
GTV: 75.6 Gy(RBE), CTV 54 Gy(RBE), at 1.8
Gy/fraction

Clinical Target Volume (CTV): green volume reflects CTV plus planning margin (=PTV)
Gross Tumor Volume = GTV: red volume
Fraction Dose: 1.8-2.0 Gy (RBE), 5 frcts. per week

\[ CTV = 54 - 60 \text{ Gy (RBE)} \]

Chordomas GTV = CH: 74-79 Gy (RBE) Chondrosarcomas: 68-72

OAR constraints: OPTIC Chiasm and Nerves: 60 Gy(RBE) (Max. Dose);

Brainstem surface 64 Gy(RBE),

BS-Center: 53 Gy(RBE), BS max. volume: 60 Gy(RBE) < 1.0 cc.

Note: Discussion about RBE and BS necrosis after 54-59 Gy for peds. CNS tumors
Spot-Scanning Proton Radiation Therapy for Pediatric Chordoma and Chondrosarcoma: Clinical Outcome of 26 Patients Treated at Paul Scherrer Institute

Barbara Rombi, MD, *† Carmen Ares, MD, * Eugen B. Hug, MD, *§ Ralf Schneider, MD, *
Gudrun Goitein, MD, * Adrian Staab, MD, * Francesca Albertini, PhD, *
Alessandra Bolsi, MSc, * Antony J. Lomax, PhD, * and Beate Timmermann, MD*†

Methods and Materials: Between June 2000 and June 2010, 19 CH and 7 CS patients with tumors originating from the skull base (17) and the axial skeleton (9) were treated with PT. Mean age at the time of PT was 13.2 years. The mean prescribed dose was 74 Gy (relative biological effectiveness [RBE]) for CH and 66 Gy (RBE) for CS, at a dose of 1.8-2.0 Gy (RBE) per fraction.
- Mean follow-up 46 months.
- 5-year LC rates 81% for CH and 80% for CS.
- 5-year OS 89% for CH and 75% for CS.
- No high-grade late toxicities.
Proton Therapy for CNS / Skull Base Tumors:
Atypical meningioma

13 y.o. M; contralateral blindness due to congential vitrous body malformation. Atypical meningioma sphenoid wing with large orbital involvement and intracranial extension
Atypical meningioma

58 Gy(RBE) at 1.8 Gy/fract.
Atypical meningioma
“Spot-scanning based Proton Therapy for Intracranial Meningioma: Long-term Results from the Paul Scherrer Institute. “

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics (n = 39)</th>
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<td>Characteristic</td>
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<td>Gender</td>
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<td>Female/male</td>
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<td>Age (y)</td>
</tr>
<tr>
<td>median</td>
</tr>
<tr>
<td>range</td>
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<tr>
<td>Histology (n = 34)</td>
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<td>Benign meningioma (WHO Grade I)</td>
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<td>Atypical (WHO Grade II)</td>
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<td>Anaplastic (WHO Grade III)</td>
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<td>Simpson (n = 34)</td>
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<td>Skull base meningioma*</td>
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<tr>
<td>Non-skull base meningioma</td>
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</table>

* Abbreviations: GTV = gross tumor volume; SSPT = spot scanning proton beam therapy; WHO = World Health Organization.
* Skull base lesions are defined as lesions located in the sphenoid wing, clivus, cavernous sinus, or foramen magnum.
Local control

Late adverse events Grade > 3:
5/39 patients (13%)
Orbital Tumors
Orbital Rhabdomyosarcoma: Protons versus Photons

Hein, Hug et al. IJROBP 62, 2005

Hug, et al. IJROBP, 47, 2000
Dx: Osteogenic Sarcoma
Proton Therapy 7/13/-8/25/2017
54 Gy(RBE) to CTV-1, 64 to CTV-2 at 2 Gy(RBE) per fraction

Target Volumes:
CTV-1 = low-mod. Risk microscopic volume (blue)
CTV-2 = high-risk microscopic volume (red)

Representative coronal slice of planning CT

<table>
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<th>Isovalues (cGy)</th>
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<td>6080.0</td>
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<td>5400.0</td>
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<tr>
<td>4500.0</td>
</tr>
<tr>
<td>4000.0</td>
</tr>
<tr>
<td>3500.0</td>
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</table>
Dx: Osteogenic Sarcoma
Proton Therapy 7/13/-8/25/2017
54 Gy(RBE) to CTV-1, 64 to CTV-2 at 2 Gy(RBE) per fraction

Isodose Distribution

CTV-1 = low-mod. Risk microscopic volume (blue)
CTV-2 = high-risk microscopic volume (red)

Representative axial slices of planning
By now I likely went overtime...

..it’s time for final thoughts.......
The ALARA principle
(…as low as reasonably achievable…)

☑ Every human has a right to be protected from unnecessary radiation dose
☑ There is no „good“ radiation
☑ Even small amounts of radiation are potentially harmful

☑ Data mostly derived from WWII atomic bombing of Nagasaki and Hiroshima – (plus Chernobyl)
☑ Data for low dose exposure derived from theoretical calculations and have been a matter of debate for decades (exponential versus linear extrapolations to low doses)

❖ No clinical trial ever undertaken to proof validity
❖ ALARA for public radiation exposure is undisputed and not subject to discussion
The ALARA principle
(,.as low as reasonably achievable…

- …applies to general public
- …applies to the individual human being
- …applies to patients with chronic diseases with limited life expectancy (examples: efforts to reduce diagnostic CT scans)
- …applies to the individual human being regardless of life expectancy, i.e. applies equally to young and old humans (you don‘t build retirement homes next to nuclear reactors for cheap land)

- BUT IT DOES APPARENTLY NOT APPLY TO CANCER PATIENTS TREATED FOR CURE; i.e. HUMANS EXPECTED TO SURVIVE CANCER AND RETURN TO THE POOL OF OTHER HUMANS AFTER TREATMENT AT WHICH TIME ALARA WILL APPLY AGAIN
The ALARA principle
(..as low as reasonably achievable…)

- .....there is complete disconnect in the radiation oncology community in the discussions about protons versus photons from the ALARA principle.

- .....protons have to provide the clinical proof that less radiation will result in less radiation complications.

- ...ALARA is beyond requiring proof.

- Do we seriously have to prove that doses of 5-10 Gy unnecessarily given to the majority of a brain in a child treated for cure are harmful when an incidental exposure of a child in general public to a couple of milli-Sievert will result in public outcry?