Proton therapy in pediatric malignancies
Still in infancy?

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Chief Medical Division,
Orsay Proton Therapy Center (CPO),
U. Paris-Orsay
Proton therapy in pediatrics: summary

- **Background**: Pediatric tumors, the challenge
- **Dosimetrical evidences**: brain, orbital, other tumors
- **Clinical evidences**: MGH / LLUMC, CPO, PSI
- **Technical advances**: towards the ideal radiotherapy in children?
Proton therapy in pediatrics: BACKGROUND

Pediatric tumors, the challenge...
INTRODUCTION

Very rare:
- 2 % all cancers
- 130 / million children
- Total / year:
  - US: 8,000
  - France: 2,000

But:
- 2nd cause of death between 5 - 14 years (18 %)
- 1 / 500 young adults cured from cancer in childhood
DIFFERENCES WITH ADULTS

- **TYPES**: Central + peripheral nervous system; Bone + soft tissues; Kidney (Lung, Breast, ENT, Digestive, Gyne)
- **SITES**: Deep (Superficial)
- **PATHO**: Embryonal sarcomas (Carcinomas)
- **SCREENING**: Rare (frequent)
- **STAGE**: Advanced (localized)
TUMOR TYPE / INFLUENCE OF AGE

- AL
- LYMPH
- BRAIN
- GERM C
- SARC
- CARCIN

<5 Y
>5<10 Y
>10<15 Y
>15<20 Y
TUMOR TYPE / INFLUENCE
GEOGRAPHICAL PLACE

- France
- USA
- ZIMBAB

A.L.
BR
AIN
LYMPH
NEURO
SOFT
NEPHRO
BONE
RETINO

0 10 20 30 40 (%)

Franco
USA
ZIMBAB
Genetic risks well known for sub groups of patients: multiple cancers in family, very young children with bilateral tumors / malformations.

Paradigm of Retinoblastoma: inactivation both suppressor genes alleles (1 transmitted, 1 somatic) (Knudson, 1972).

Paradygm of associated morbid condition: NF1 and optic gliomas.
Almost exclusively multidisciplinary
Multicentric trials
Chemosensitivity +++
Fast + massive « response » therapy
Considerable improvement survival, past 3 decades
CHEMOTHERAPY: BENEFIT

- DEMONSTRATED: 68%
- PROBABLE: 12%
- UNCERTAIN: 20%

- Brain
- Osteo, Neuro
- AL, Lymph, Nephro, RMS, Ewing, Germ
OUTCOME « EXCELLENT »
(# 1/3 cases)

Light management
Light sequelae!

HODGKIN
NHL
LOC NEURO
NEPHRO
OUTCOME « ENCOURAGING » (# 1/3 cases)

Heavy management frequent sequelae!

OSTEO

EWING

SOFT T

1970

1990
OUTCOME
« DISAPPOINTING »
(# 1/3)

Heavy treatment, substantial sequelae

Brain

Met Neuro

1960

1990
Radiotherapy has lost prominence in the management of most pediatric tumors.

But remains essential, as far as the local-regional control of most of them,

With recent emphasis on technical refinements and innovations.
PEDIATRIC RADIOTHERAPY: PLACE

- Necessary approx. half cases
- Dreadful reputation RX-induced sequelae!
PEDIATRIC RADIOTHERAPY: PLACE

- RT -
  - NHL, Osteo
- RT +
  - LA, Neuro, Nephro
- RT ++
  - CNS, Soft tissue
- RT +++
  - Ewing, Retino
PEDIATRIC RADIOTHERAPY: CURATIVE DOSES

- Nephro
- LA
- Dysgerm
- Neuro
- RMS
- Benign gliom
- Medullo
- Ewind
- Malign Gliom
- Nasopharynx

(Gy)

0 20 40 60 80

10 20 25 35 40 40 50 50 50 60 60 70

micr
MAC
DOSES TO CRITICAL STRUCTURES IN CHILDREN

(Gy)

Male sterility
Cataract
Mammary bud
Cartilage
Kidney
Female sterility
Lungs
STH
Muscles
Brain
Other pituitary

2
5
10
11
12
15
15
20
23
25
40
PEDIATRIC RADIOTHERAPY: LONG-TERM TOXICITY

- **BONE**: Growth disturbances
- **BRAIN**: Neuro-psychological impairments
- **2nd MALIGNANCIES**: 10-15% at 15 years
- **(GONADS)**: Sterility, early menopause
RADIATION-INDUCED SEQUELAE IN CHILDHOOD
White matter is more sensitive to radiation damage than grey matter.

In summary, pediatric tumors are...

- **A major challenge for radiation oncologist =**
  - cure with the least morbidity
  - Radiation therapy deleterious when administered alone to high doses esp. young children

- **Brain and soft-bone part tumors are paradigms**

- **Need for considerable technical improvements...**
Proton therapy in pediatrics: 

**PROS:**

**DOSIMETRICAL EVIDENCES**
Medulloblastomas

Posterior fossa: clear benefit
CNS coverage: more controversial
POSTERIOR FOSSA: anatomical situation

- Posteriorly: occipital bone
- Laterally: temporal (petrous + mastoid)
- Anteriorly: sphenoid
- Superiorly: tentorium cerebelli
- Inferiorly: foramen magnum
POSTERIOR FOSSA: indications for radiotherapy

The most commonly irradiated site in brain tumors!

- *Either alone in*: localized medulloblastomas in very youngs, ependymomas, gliomas ...

- *Or as a boost, following cranio-spinal irradiation in*: medulloblastomas in older children, PF tumors metastatic to CSF
POSTERIOR FOSSA: critical structures (SIOP, Porto, 2003)

- **Within**: brain stem, cranial nerves, internal ears, cerebellum, vessels

- **Outside**: pituitary, cerebral hemispheres, temporo-mandibular joint, parotid glands, spinal cord ...
POSTERIOR FOSSA: internal ear

VII

cochlea
vestibule
RX-related ototoxicity in literature

- Concerns mainly higher frequencies: difficulties speech discrimination
- Potentiated by CDDP - based chemotherapy
- Exact risk unknown.
  - Estimates: Threshold 30 Gy
    24% after 59.5 - 76.5 Gy
    (Kwong, 1996)
RESULTS: cochlea

<table>
<thead>
<tr>
<th></th>
<th>Lat</th>
<th>Obl</th>
<th>Non cop</th>
<th>Opti obl</th>
<th>Obl prot</th>
<th>Post prot</th>
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: Tolerance at 55 Gy tumor
RESULTS: pituitary

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<td>Post prot</td>
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RESULTS: supra tentorial brain

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<td>29,3</td>
<td>33,5</td>
<td>26,5</td>
<td>13,7</td>
<td>13</td>
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<tr>
<td>MAX</td>
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<td>107,6</td>
<td>108,5</td>
<td>100,3</td>
<td>100,6</td>
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: Tolerance at 55 Gy
RESULTS: parotids

Tolerance at 55 Gy tumor

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<th>Obl</th>
<th>Non cop</th>
<th>Opti obl</th>
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<td>38,9</td>
<td>4,2</td>
<td>33,6</td>
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COMPARISON CONVENTIONAL, IMRT, PROTONS IN MEDULLOBLASTOMA

St Clair et al, IJROBP, 2004
**Predicted IQ**

(Miralbell R - IJROBP - 1997: 38: 477-484)

- **PLAN 1**: Photons: 2 opposed laterals
- **PLAN 2**: Photons: 6 beams
- **PLAN 3**: 9 beams X IMRT
- **PLAN 4**: Protons: 3 beams... in Whole Brain ± ventricles

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**Table 1. Favorable medulloblastoma.**

NLCP for IQ: predicted results averaged over all ages

<table>
<thead>
<tr>
<th>Volume*</th>
<th>RT dose</th>
<th>RT source</th>
<th>% Risk of IQ &lt;90</th>
</tr>
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<tbody>
<tr>
<td>Plan 1</td>
<td>30 Gy</td>
<td>x-rays</td>
<td>25.1</td>
</tr>
<tr>
<td>Plan 2</td>
<td>30 Gy</td>
<td>x-rays (hand plan)</td>
<td>18.2</td>
</tr>
<tr>
<td>Plan 3</td>
<td>30 Gy</td>
<td>x-rays (inverse plan)</td>
<td>16.0</td>
</tr>
<tr>
<td>Plan 4</td>
<td>30 Gy</td>
<td>Protons</td>
<td>15.7</td>
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</tbody>
</table>

* Plan 1: standard WBI (TV1), 30 Gy. Plan 2, 3, and 4: TV2, 30 Gy (see text).

**Table 2. Unfavorable medulloblastoma.**

NLCP for IQ: predicted results averaged over all ages

<table>
<thead>
<tr>
<th>Volume*</th>
<th>RT dose</th>
<th>RT source</th>
<th>% Risk of IQ &lt;90</th>
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<tbody>
<tr>
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<td>30 Gy</td>
<td>x-rays</td>
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</tr>
<tr>
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<td>30 Gy</td>
<td>x-rays (inverse plan)</td>
<td>17.0</td>
</tr>
<tr>
<td>Plan 4</td>
<td>30 Gy</td>
<td>Protons</td>
<td>16.3</td>
</tr>
</tbody>
</table>

* Plan 1: standard WBI (TV1), 30 Gy. Plan 2, 3, and 4: TV1, 10 Gy; TV2, 30 Gy (see text).
Spinal canal (Miralbell R - IJROBP - 2002; 54:824-829)

Images:
- Photons
- IM Photons
- IM Protons
RAPID COMMUNICATION

PHYSIOLOGIC AND RADIOGRAPHIC EVIDENCE OF THE DISTAL EDGE OF THE PROTON BEAM IN CRANIOSPINAL IRRADIATION

Stephanie C. Krejcarek, B.Sc.,* P. Ellen Grant, M.D.,† John W. Henson, M.D.,‡ Nancy J. Tarbell, M.D.,* and Torunn I. Yock, M.D., M.C.H.*

Departments of *Radiation Oncology and †Radiology and the ‡Pappas Center for Neuro-oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA
Ado: canal only

Young: full spinal width
PEDIATRIC BRAIN TUMORS: IS PROTON THERAPY SUPERIOR TO PHOTONS IMRT?

(SIOP, Vancouver, 2005)

JL HABRAND, S BOLLE, A BEAUDRE, G NOEL, C GAUTHIER, C PICHENOT et al.

Dept. Radiation Oncology, IGR: Villejuif and CPO: Orsay, France
Case #2: pre RT imaging

T1  T2
Ependymoma, left Frontal lobe: XR-IMRT plan

Axial

Sagittal

30Gy

10Gy
Pt Ozb.: proton planning

10+30 Gy

10+30 Gy
Ependymoma: brain DVH (PTV excluded)
CLINICAL INVESTIGATION

PROTON RADIATION THERAPY (PRT) FOR PEDIATRIC OPTIC PATHWAY GLIOMAS: COMPARISON WITH 3D PLANNED CONVENTIONAL PHOTONS AND A STANDARD PHOTON TECHNIQUE

MARTIN FUS, M.D.,*† EUGEN B. HUG, M.D.‡§, ROSEMARY A. SCHAEFER, B.S.,*†
MENHARD NEVINNY-STICKEL, M.D.,* DANIEL W. MILLER, PH.D.,* JAMES M. SLATER, M.D.,*† AND JERRY D. SLATER, M.D.,*†

Departments of *Radiation Medicine and †Pediatrics, Loma Linda University Medical Center, Loma Linda, CA, and ‡Department of Radiation Oncology, University of Heidelberg, Heidelberg, Germany
Fig. 7. Dose distribution of proton, 3D photon, and standard photon plans superimposed onto representative slices of the planning CT in axial, sagittal, and coronal planes. Display of GTV in red, and 25% (blue), 50% (red), 80% (orange), 90% (yellow), and 95% (green) isodose lines in color wash technique. Prescribed total dose was 54 CGE/Cv. CT scan of a 5-year-old male patient (patient 5, Table 1) with extensive bilateral optic pathway glioma and associated diagnosis of neurofibromatosis type 1 (NF1).
M Fuss (cont): normal brain

Fig. 3. Relative increase of amount of normal tissue included in the respective isodose volumes for small tumor volumes (< 20 cm³). X-axis: 95%, 90%, 80%, 50%, and 25% isodose of proton, 3D photon, and lateral photon plans. Y-axis: normal tissue volume encompassed by respective isodose levels minus GTV according to treatment modality. Average values in relation to the normal tissue volume enclosed in the 95% proton isodose (= base value: 1).

Fig. 4. Relative increase of amount of normal tissue included in the respective isodose volumes for large tumor volumes (> 80 cm³). X-axis: 95%, 90%, 80%, 50%, and 25% isodose of proton, 3D photon, and lateral photon plans. Y-axis: normal tissue volume encompassed by respective isodose levels minus GTV according to treatment modality. Average values in relation to the normal tissue volume enclosed in the 95% proton isodose (= base value: 1).
M Fuss (cont): optic/pituitary

Fig. 5. Prescribed average treatment doses to 50% and 10% tissue volume (x-axis) of contralateral optic nerve, optic chiasm, and pituitary gland. Y-axis: doses in CGE or Gy according to the displayed proton, 3D photon, or lateral beam photon technique.
Fig. 6. Prescribed average treatment doses to 50% and 10% tissue volume (x-axis) of temporal lobes, frontal lobes, and brain stem. Y-axis: doses in CGE or Gy according to the displayed proton, 3D photon, or lateral beam photon technique.
CLINICAL INVESTIGATION

FRACTIONATED, THREE-DIMENSIONAL, PLANNING-ASSISTED PROTON-RADIATION THERAPY FOR ORBITAL RHABDOMYOSARCOMA: A NOVEL TECHNIQUE

EUGEN B. HUG, M.D.,*†§ JUDY ADAMS, C.M.D.,*† MARCUS FITZK, M.D.,*† ALEXANDER DE VRIES, M.D.,*† AND JOHN E. MUNZENRIDER, M.D.*†

*Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA; and †Harvard Cyclotron Laboratory, Cambridge, MA; and Departments of ‡Radiation Medicine and §Pediatrics, Loma Linda University Medical Center, Loma Linda, CA
Orbital RMS: Medial site (Hug)
Orbital RMS: Medial+Lateral sites (Hug)

Fig. 2. Patient A. Planning CT scan in coronal (1) and transverse (2) sections with clinical target volume (CTV, medial and retrobulbar), gross tumor volume (GTV, medial structures) and non-target lacrimal gland (lateral) contoured. Color display of dose distribution starting at 10 CGE (blue) with prescribed dose levels of 40 and 50 CGE to the CTV and GTV, respectively. Patient B. Planning CT scan in transverse (1) and sagittal (2) sections with clinical target volume (CTV) and non-target lens and optic nerve contoured. Gross tumor volume (GTV) is located superorly and is prominent on these representative sections. Color display of dose distribution starting at 10 CGE (blue) with prescribed dose levels of 40 and 50 CGE to the CTV and GTV, respectively.

Fig. 4. Patient B. Dose-volume histograms (DVH) for clinical target volume (CTV), gross tumor volume (GTV), 1.2 cm³, lens (0.3 cm³), and optic nerves (0.5 cm³). Volume of target and non-target structures (percent) plotted against radiation dose (CGE).
PHYSICS CONTRIBUTION

OPTIMIZING RADIOTHERAPY OF ORBITAL AND PARAORBITAL TUMORS: INTENSITY-MODULATED X-RAY BEAMS VS. INTENSITY-MODULATED PROTON BEAMS

RAYMOND MIRALBELL, M.D.,* LAURA CELLA, M.Sc.,* DAMIEN WEBER, M.D.,* AND ANTONY LOMAX, PH.D.†

*Division de Radio-Oncoologie, Hôpitaux Universitaires, Genève; †Strahlenmedizin Abteilung, Paul Scherrer Institut, Villigen, Switzerland
Table 1. Tolerance doses (TD) in Gy or the organs at risk in both optimization procedures (see Ref. 19)

<table>
<thead>
<tr>
<th>Organ at risk</th>
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<tbody>
<tr>
<td>Lens</td>
<td>10</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>30</td>
</tr>
<tr>
<td>Retina</td>
<td>45</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>55</td>
</tr>
<tr>
<td>Optic chiasm</td>
<td>55</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>35</td>
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</tbody>
</table>
Para meningeal (RMS)
Normal structures: PM RMS
PM RMS: Mean dose X
IMRT-P

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>X-rays</th>
<th>Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL lens</td>
<td>8.8</td>
<td>7.6</td>
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<tr>
<td>HL lacrimal gland</td>
<td>18.4</td>
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</tr>
<tr>
<td>HL retina</td>
<td>30.5</td>
<td>27.4</td>
</tr>
<tr>
<td>HL parotid</td>
<td>17.0</td>
<td>5.2</td>
</tr>
<tr>
<td>CL lens</td>
<td>7.5</td>
<td>6.6</td>
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<tr>
<td>CL lacrimal gland</td>
<td>12.6</td>
<td>8.0</td>
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<tr>
<td>CL retina</td>
<td>19.0</td>
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<td>CL optic nerve</td>
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<td>CL parotid</td>
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<tr>
<td>Optic chiasm</td>
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<tr>
<td>Pituitary gland</td>
<td>21.9</td>
<td>14.6</td>
</tr>
<tr>
<td>Brain stem</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Whole orbit (Lymphoma)
Left optic nerve (meningioma)
Sphenoid ridge (meningioma)
NTCP: all

Table 3. Predicted normal tissue complication probabilities (NTCPs) according to Lyman (see Ref. 21) for both intensity-modulated (IM) X-rays and IM protons

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Orbital lymphoma</th>
<th>Optic nerve meningioma</th>
<th>Paraorbital meningioma</th>
<th>Rhabdomyosarcoma</th>
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<td>X-rays</td>
<td>Protons</td>
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<tr>
<td>HL parotid</td>
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<td>0.0</td>
<td>0.0</td>
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</table>

Abbreviations: HL = homolateral (in relation to tumor location); CL = contralateral (in relation to tumor location).

for the homolateral lens and all structures in the contralateral orbit. The mean integral nontarget dose was 1.9 times higher with IM X-rays (8.37 Gy) compared to IM protons (4.43 Gy). Table 3 presents the NTCPs predicted for cataracts and for severe retinal toxicity for both concurrent treatment techniques. Both treatment techniques succeeded
Conformation photons vs protons

(Baumert BG, IJROBP, 2001)
T concave: PTV P>X
Elipsoid shape: PTV P=X

Baumert BG, IJROBP, 2001)
Irregular shape: PTV P>X

Baumert
Proton therapy in children: neuroblastomas (Hug, MPO, 2001)
Retinoblastoma
(Lee CT et al, IJROBP, 2005)
Pelvic sarcomas
(Lee CT et al)
Proton therapy in pediatrics:

CLINICAL EVIDENCES
CLINICAL INVESTIGATION

PROTON RADIOTHERAPY IN MANAGEMENT OF PEDIATRIC BASE OF SKULL TUMORS


*Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA; ‡Harvard Cyclotron Laboratory, Cambridge, MA; Departments of ‡Radiation Medicine and §Pediatrics, Loma Linda University Medical Center, Loma Linda, CA
Table 2. Treatment results in 29 pediatric and adolescent patients with mesenchymal tumors of the skull base

<table>
<thead>
<tr>
<th>Histologic findings</th>
<th>Patterns of failure* (n)</th>
<th>Outcome (%)</th>
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<tr>
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<td>Surgical access</td>
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<td>Chondrosarcomas (3)</td>
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<td>Rhabdomyosarcomas (4)</td>
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<td>0</td>
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<tr>
<td>Others* (3)</td>
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<td>Benign (9)</td>
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<td>0</td>
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<td>Giant cell (5)</td>
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<td>Chondroblastoma (1)</td>
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<td>0</td>
</tr>
</tbody>
</table>

* No regional failures noted.
† Myxoid sarcoma, epithelioid sarcoma, malignant fibrous histiocytoma.
Fig. 4. Actuarial rates of local control and overall survival of 20 pediatric patients with malignant skull base tumors after high-dose, conformal proton or combined proton/photon RT.
Fig. 1. Planning CT scan of an 8-year-old boy with parameningeal rhabdomyosarcoma. Transverse section with CTV, GTV, and non-target optic nerves, lens, and pituitary gland contoured. Color display of dose distribution starting at 20 CGE (blue) with prescribed dose levels of 41.4 and 50.4 CGE to the CTV and GTV, respectively.
Fig. 2. Planning CT scan of a 13-year-old boy with malignant fibrous histiocytoma. (A) Transverse and (B) coronal section with CTV and nontarget optic nerves contoured. Color display of dose distribution starting at 20 CGE (blue) with prescribed dose levels of 50.4 and 66.6 CGE to CTV and GTV, respectively.
SPOT-SCANNING PROTON THERAPY FOR MALIGNANT SOFT TISSUE TUMORS IN CHILDHOOD: FIRST EXPERIENCES AT THE PAUL SCHERRER INSTITUTE

Beate Timmermann, M.D.,* Andreas Schuck, M.D.,† Felix Niggli, M.D.,‡ Markus Weiss, M.D.,§ Antony Jonathan Lomax, Ph.D.,* Eros Pedroni, Ph.D.,* Adolf Coray, Ph.D.,* Martin Jermann, Ph.D.,* Hans Peter Rutz, M.D.,* and Gudrun Goitein, M.D.*

Fig. 1. Example of the dose distribution for “conventional” proton therapy of a paranasal rhabdomyosarcoma in a 13-year-old girl. Thin green line: planning target volume.

Fig. 2. Example of an intensity-modulated proton therapy plan with sparing of the lacrimal gland for a 12-year-old boy with an orbital rhabdomyosarcoma initially infiltrating the surrounding soft tissue.
Table 2. Acute toxicity related to proton therapy

<table>
<thead>
<tr>
<th>Critical organ</th>
<th>Patients evaluable (n)</th>
<th>Grade 0</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karnofsky</td>
<td>16</td>
<td>13</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>13</td>
<td>—</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Skin</td>
<td>16</td>
<td>1</td>
<td>11</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Musosa</td>
<td>13</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>GI tract</td>
<td>3</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>GU tract</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CNS</td>
<td>13</td>
<td>13</td>
<td>5</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Eye</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ear</td>
<td>12</td>
<td>11</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Abbreviations:* GI = gastrointestinal; GU = genitourinary; CNS = central nervous system.
Proton Beam Therapy in the Management of Central Nervous System Tumors in Childhood: The Preliminary Experience of the Centre de Protonthérapie d’Orsay

Georges Noel, MD,1* Jean-Louis Habrand, MD,2 Sylvie Helfre, MD,3 Hamid Mammar, MD,1 Chantal Kalifa, MD,2 Régis Ferrand, PhD,1 Anne Beaudre, PhD,2 Geneviève Gaboriaud, PhD,3 and Jean-Jacques Mazeron, MD, PhD1,4

**Background.** The purpose of the study was to evaluate clinical results and complications of a combination of proton and photon irradiation administered to 17 children with selected central nervous system (CNS) tumors. **Procedure.** Between July 1994 and September 2000, 17 children, aged from 5 to 17 years (median: 12 years) with intracranial benign (6 cases) or malignant (11 cases) tumors, were treated with photons (median dose: 40 Gy; 24–54) and protons (median dose: 20 CGE; 9–31) at the Centre de Protonthérapie d’Orsay (CPO). **Results.** Mean follow-up was 27 months (3–81). Two patients recurred locally (one marginal and one in situ). Fifteen patients are alive and doing well. Overall, 12, 24, and 36-month local control rate was 92 ± 8% and, 12, 24, and 36-month overall survival rates were 93 ± 6%, 83 ± 11%, and 83 ± 11%, respectively. Clinical initial symptoms remained stable or subsided in all patients. Early toxicities were in the expected range. **Conclusions.** With a mean 27 months follow-up, protontherapy was well tolerated for doses up to 69 CGE and with an excellent local control rate. Med Pediatr Oncol 2003;40:309–315. © 2003 Wiley-Liss, Inc.

**Key words:** protontherapy; central nervous system tumor; childhood tumor
fiche_statistiques_enfants

Date début 1991  Date fin 2007  Age limite enfant 16

Nombre d'enfants en % par rapport au nombre total de patients

Nombre d'enfants par année
Child’s set up in Orsay
Adolescent imaging with acrylic cast
Patients set up

- Contention + ROBOT
- RX
- Correction
- Mvt Robot
- RX

Precision 0.3 mm to 1mm
Set up time: 20 to 25 min/field
12 intracranial pts
6 ophthamo pts
General anesthesia: Children < 4Y
NEW FACILITY : 2009

- 230 MeV 1 isocentric gantry
- 2 existing fixed lines
- 650 patients/year
PEDIATRIC CNS TUMORS: ORSAY SERIES (08/05): Tumor types

1994-2005: 60 pts

22 CH, 4 CS, 3 soft, 1 Osteo

46% Sarcomas
18% Cranioopharyngiomas
18% Brain
18% Others

4 Glios, 6 mening, 1 PNET, 1 pblastom
PEDIATRIC CNS TUMORS: ORSAY SERIES (08/05): outcome

- Controlled: 90%
- Failed: 10%

Legend:
- Local
- Nodal
- Distant
- Combined
- Controlled
PEDIATRIC CNS TUMORS: ORSAY SERIES (08/05): Toxicity

15 cases (25%)

- 9% Sarcomas
- 30% craniopharyngiomas
- 18% Brain
- 35% Others

27
MENINGIOMAS: PEDIATRIC CASE

Previously irradiated with $\gamma$ knife

Chiasm shielding
CPO perspectives

ē 2006: Develop indications very youngs (GA)
ē → 2010:
  ▪ Replace equipment, ie new accelerator (240 MeV) + 1 isocentric gantry + 2 fixed beams (45 M Euros)
  ▪ Increase # patients & % pediatrics: 350 → 650 pts
  ▪ New ped indic: medullo, RMS, optic Gl, Ependymoma, nasopharynx
Proton-facility and K2: the controversy

Pros...
K2 estim risk in PM RMS

Table 2. Estimated absolute yearly rate (%) of secondary cancer incidence after treating a parameningeal rhabdomyosarcoma with either X-rays, IM X-rays, protons, or IM protons

<table>
<thead>
<tr>
<th></th>
<th>X-rays</th>
<th>IM X-rays</th>
<th>Protons</th>
<th>IM protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yearly rate (%)</td>
<td>0.06</td>
<td>0.05</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Relative risk compared to standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ray plan</td>
<td>1</td>
<td>0.8</td>
<td>0.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Abbreviation: IM = intensity-modulated.*
## K2 estim risk in médulloblastoma

Estimated absolute yearly rate (%) of secondary cancer incidence after treating a médulloblastoma case with either conventional X-ray, IM X-ray, or proton beams

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>X-rays (%)</th>
<th>IM X-rays (%)</th>
<th>Protons (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach and esophagus</td>
<td>0.15</td>
<td>0.11</td>
<td>0.00</td>
</tr>
<tr>
<td>Colon</td>
<td>0.15</td>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>Breast</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Lung</td>
<td>0.07</td>
<td>0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.18</td>
<td>0.06</td>
<td>0.00</td>
</tr>
<tr>
<td>Bone and connective tissue</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.07</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>All secondary cancers</td>
<td>0.75</td>
<td>0.43</td>
<td>0.05</td>
</tr>
<tr>
<td>Relative risk compared to standard X-ray plan</td>
<td>1</td>
<td>0.6</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Abbreviation:* IM = intensity-modulated.
Proton-facility and K2

Cons...

(Hall E et al, IJROBP, 2006)
NEUTRON DOSE IN SCATTERED AND SCANNED PROTON BEAMS: IN REGARD TO ERIC J. HALL (INT J RADIAT ONCOL BIOL PHYS 2006;65:1-7)

To the Editor: Dr. Hall’s Fig. 10 (1) is incorrect by a factor ≥9 to the detriment of scattered vs. scanned protons. We wish to clarify the source of neutrons in scattering systems, to correct his Fig. 10, and to put neutron doses into perspective.

NEUTRON DOSE IN PROTON RADIATION THERAPY: IN REGARD TO ERIC J. HALL (INT J RADIAT ONCOL BIOL PHYS 2006;65:1-7)

To the Editor: Dr. Hall (1) comes to the conclusion that proton therapy offers an advantage with respect to scattered doses relative to photons only if pencil beam scanning (PBS) is applied but not for broad-beam modulated (BBM) beams. We disagree with this conclusion.
Major technical innovation in pediatrics: Spot scanning

Single Spot

Few Spots

Total Picture

Courtesy PSI
IN REPLY TO DR. MACKLIS GOTTSCHALK, PAGANETTI, ET AL.

To the Editor: We are indebted to Drs. Gottschalk, Paganetti, and colleagues for their elegant clarifications of the sources of whole-body neutron exposures in modern proton therapy facilities: their collective knowledge and experience in this field are unmatched. We should, at the outset, say that we agree with Drs. Gottschalk and Paganetti that the facility at the Institute Curie in Paris is the world's best. However, neutron dose due to neutrons produced by passive beam modulators to be about 100 mSv for a typical (72 Gy) current proton therapy treatment (4). For a cured patient who underwent treatment at age 60, this corresponds to an estimated lifetime cancer risk of about 0.5% (5). However, for a cured 10 year old, this corresponds to a lifetime cancer risk of about 3% (5)—all entirely avoidable with the use of a scanned proton beam.
Spot-scanning benefit over passive scattering protons

- Better conformation
- Reduced # beams and integral dose
- Reduced neutron-dose (=K2)

Courtesy B Timmermann, PSI
Cost of protons

- Fixed beam existing equipment (CPO):
  - Adaptation 2 rooms: 600,000 €
  - Running cost: 2 M€/Y
  - Treatment cost: 1,300 €/fr
Cost of protons
(Goitein M et al, Clin Oncol, 2003)

- Accelerator + Isocentric gantries: 62.5 M€
- Running cost: 15 M€
- Treatment cost: 1,025 € / fraction
## Comparative costs P vs X (Goitein)

<table>
<thead>
<tr>
<th></th>
<th>Cost/f</th>
<th>Cost/RT Tt</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton IMRT</td>
<td>1,025</td>
<td>25.6</td>
<td>2.4</td>
</tr>
<tr>
<td>XR IMRT</td>
<td>0.425</td>
<td>10.6</td>
<td>1</td>
</tr>
</tbody>
</table>
Cost-Effectiveness of Proton Radiation in the Treatment of Childhood Medulloblastoma

Lundkvist J, Ekman M, Rehn Erickson S, Jönsson B, Glimelius B
(Cancer, 2005, 13: 793-801)
Conclusion

- Dramatic expansion of proton facilities worldwide
- Considerable potentialities in children, include brain, head & neck, trunk sarcomas
- Reduced long term toxicity (growth, cognition…) remains to be validated clinically
CPO:
G Noël, MD
L Feuvret, MD
R Ferrand, PhD
C Gauthier, RT
A Leroy, RT...

Paris hosp:
JJ Mazeron, MD, PhD
G Boisserie, PhD...

IGR:
F Dhermain, MD
J Datchary, MD
A Beaudré, PhD...

I CURIE:
P Bey, MD
H Mammar, MD
C Alapetite, MD
S Helfre, MD
G Gaboriaud, PhD
A Mazal, PhD...
Thank you!