Proton therapy : the revival of pediatric radiotherapy ?

Jean-Louis HABRAND, MD

Pr. Radiation Oncology, U. Paris

Chief Medical Division,

Institut Curie-Orsay Proton Therapy Center (ICPO),

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Centre de Protonthérapie d'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?*

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Proton therapy in pediatrics: BACKGROUND

Pediatric tumors, the challenge…

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INTRODUCTION

- *Very rare :*
  - 2 % all cancers
  - 130 / million children
  - Total / year :
    - US : 10,000
    - France : 2,000
- *But :*
  - 2 nd cause of death between 5 - 14 years (18 %)
  - 1 / 500 young adults cured from cancer in childhood

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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)

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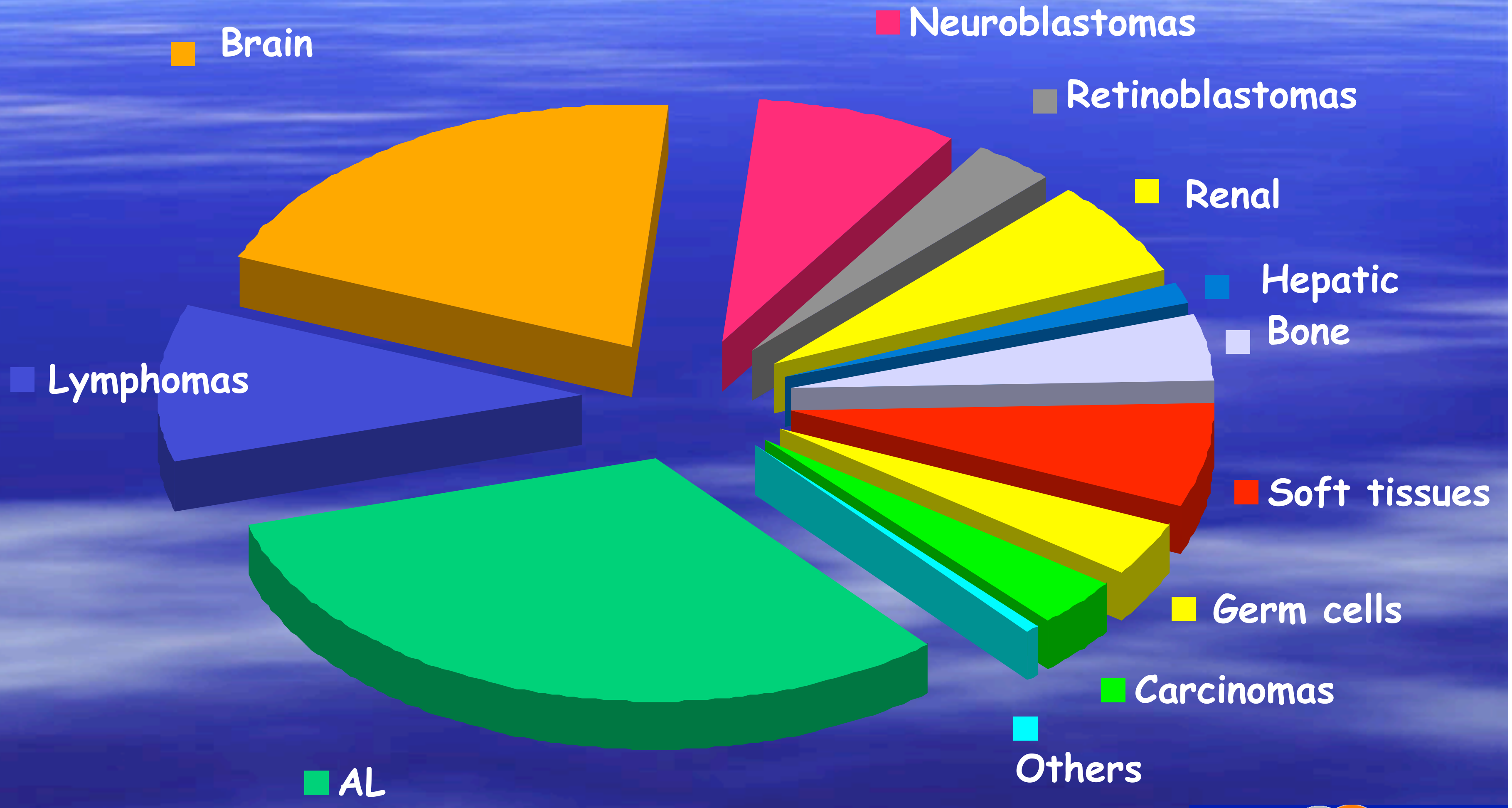
Frequency by Tumor type



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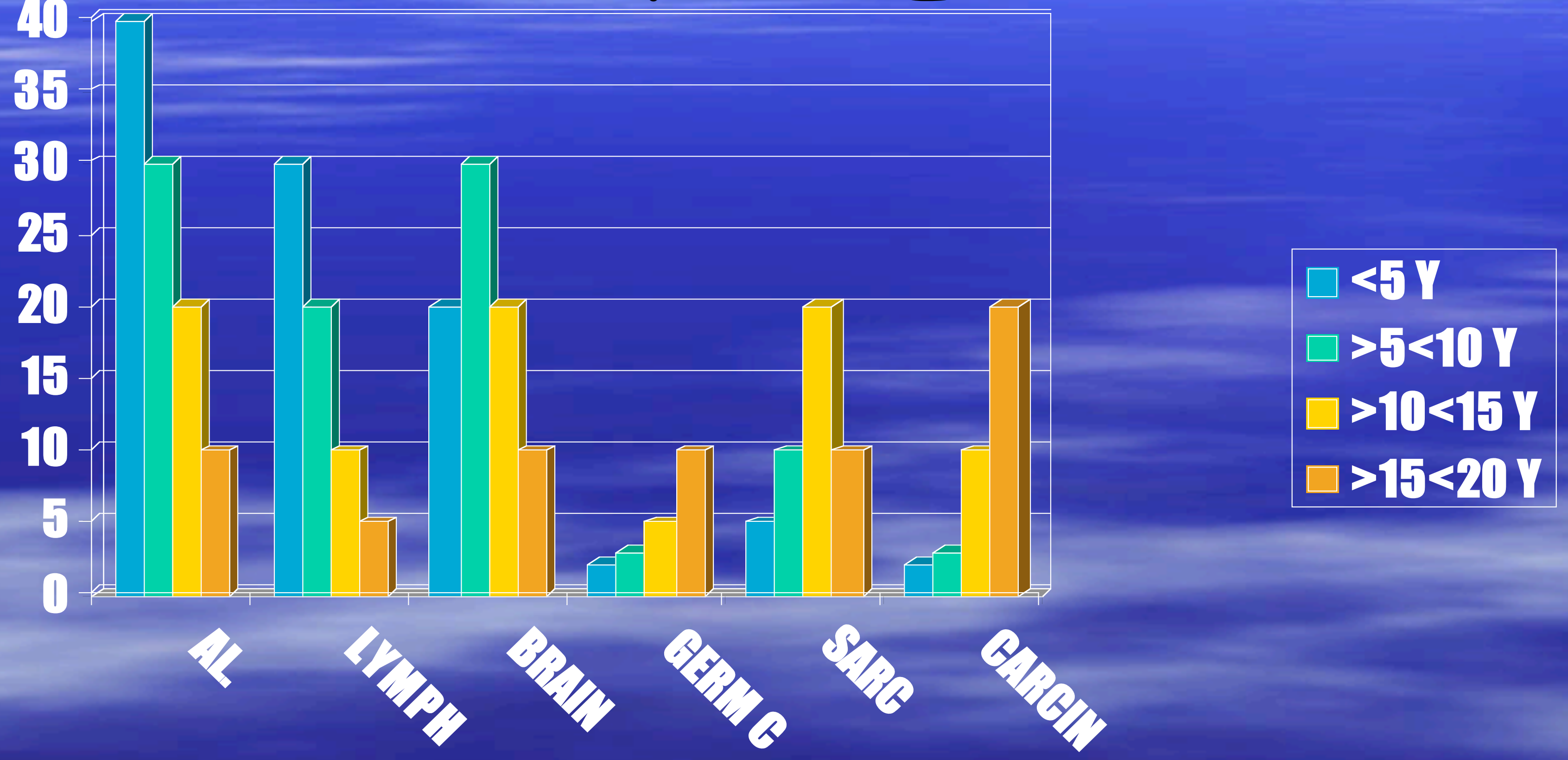
TUMOR TYPE / INFLUENCE OF AGE



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GENETICS

- *Genetic risks well known for sub groups of patients :* multiple cancers in family, very young children with bilateral tumors / malformations
- *But < 5% cases*
- *Paradigm of Retinoblastoma :* inactivation both suppressor genes alleles (1 transmitted, 1 somatic) (Knudson, 1972)
- *Paradygm of associated morbid condition: NF1 and optic gliomas*

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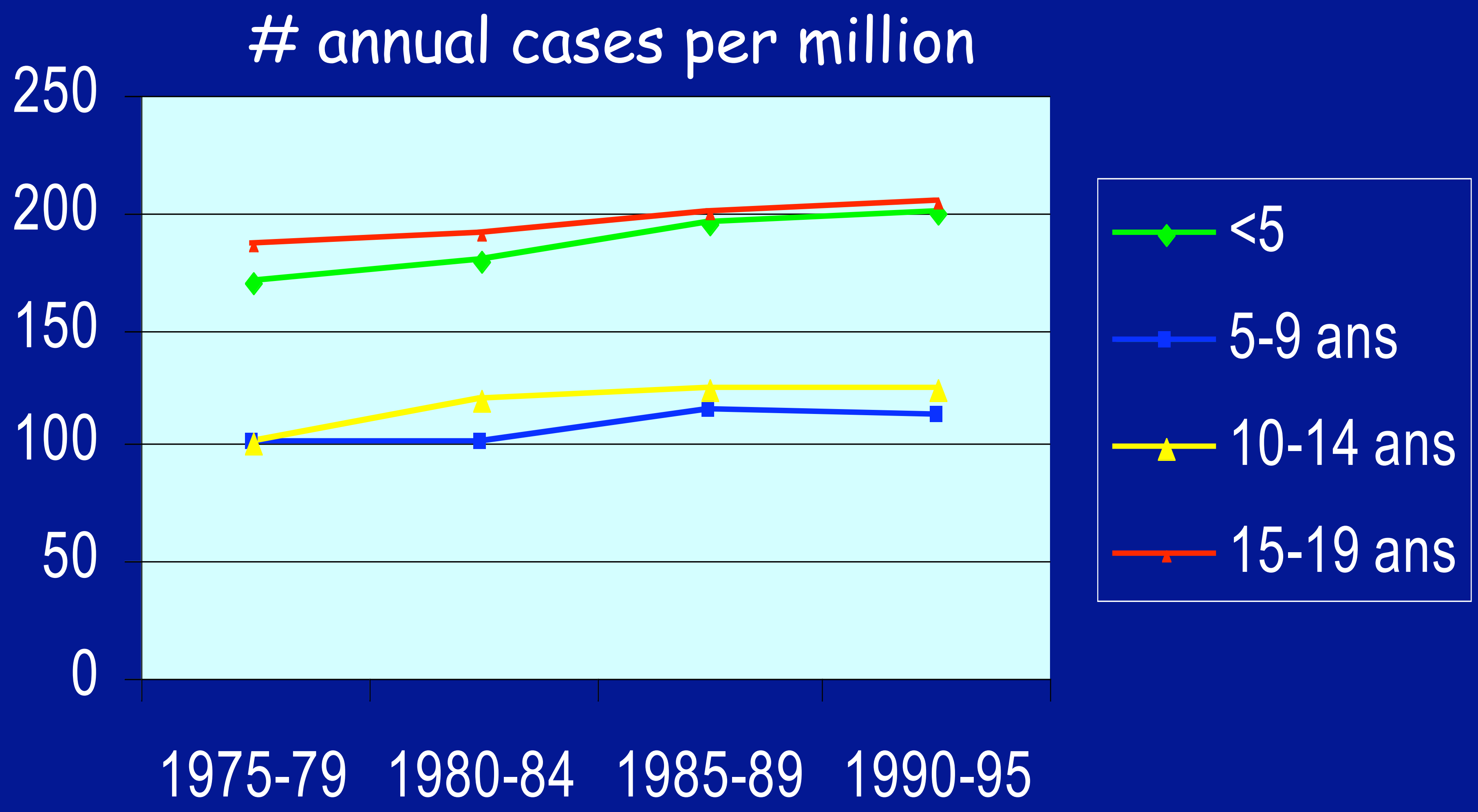
Cancer incidence vs age



SEER 1975-95

Other predisposing factors

- *Ionizing radiations:* thyroid carcinomas (Tchernobyll : X 100)
- *UV:* melanomas
- *Magnetic fields* (AL: x 1.5, Brain: x 1.9)
- *Chemical agents:* Distilben administered during pregnancy (Clear cell adeno vagina)
- *Infectious:* EBV (Nasopharynx, HD),
 HVB (hepatoca)

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MANAGEMENT

- Almost exclusively multidisciplinary
- Multicentric trials
- Chemosensitivity +++
- Fast + massive « response » therapy
- Considerable improvement survival, past 3 decades

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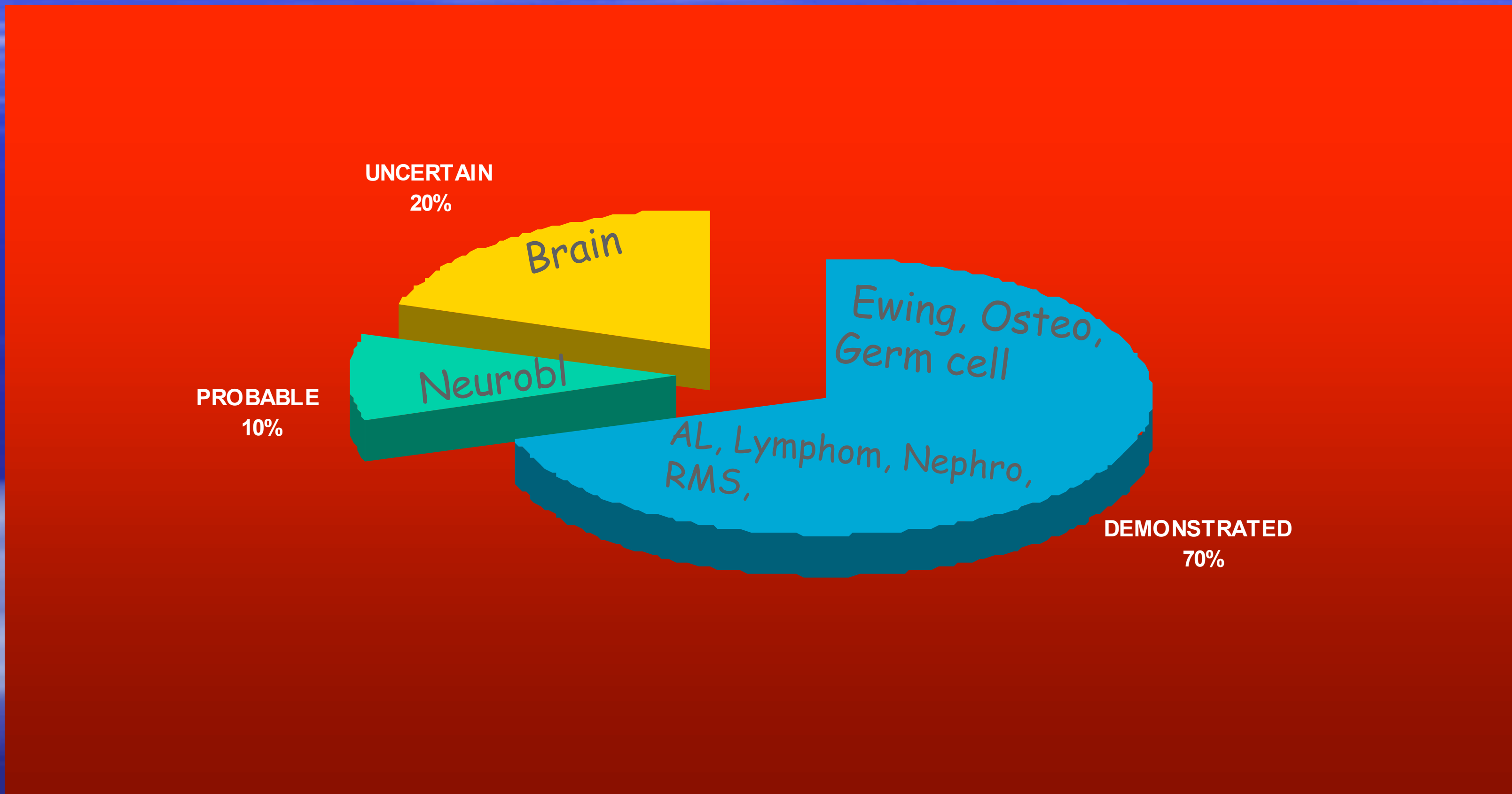
CHEMOTHERAPY : BENEFIT



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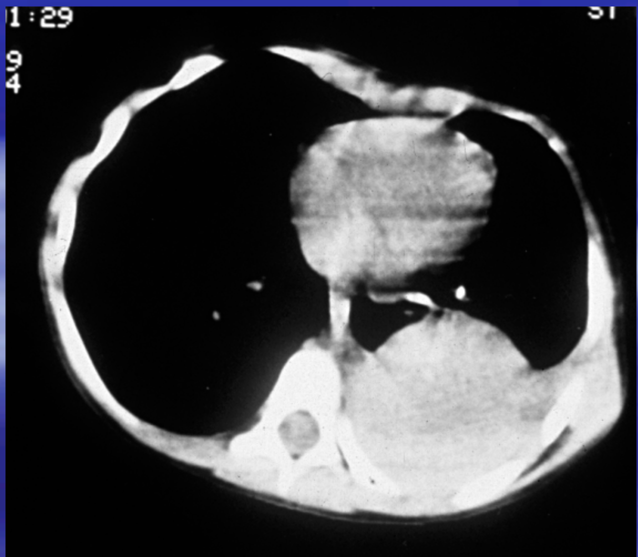
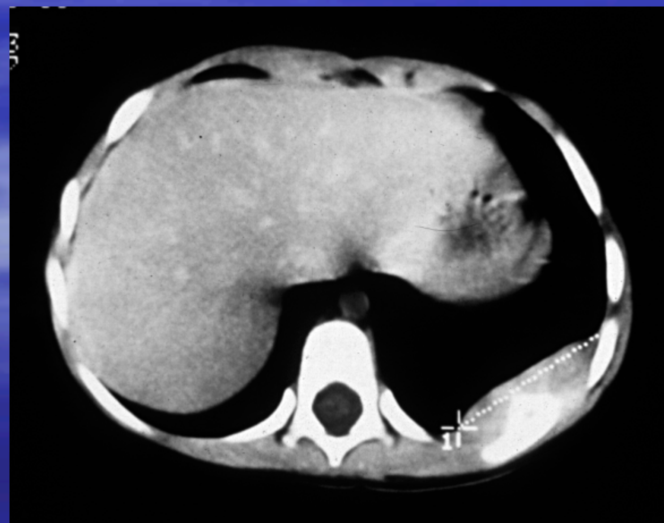
CHEMOSENSITIVITY
EWING TUMOR

Pre chemo

Post chemo





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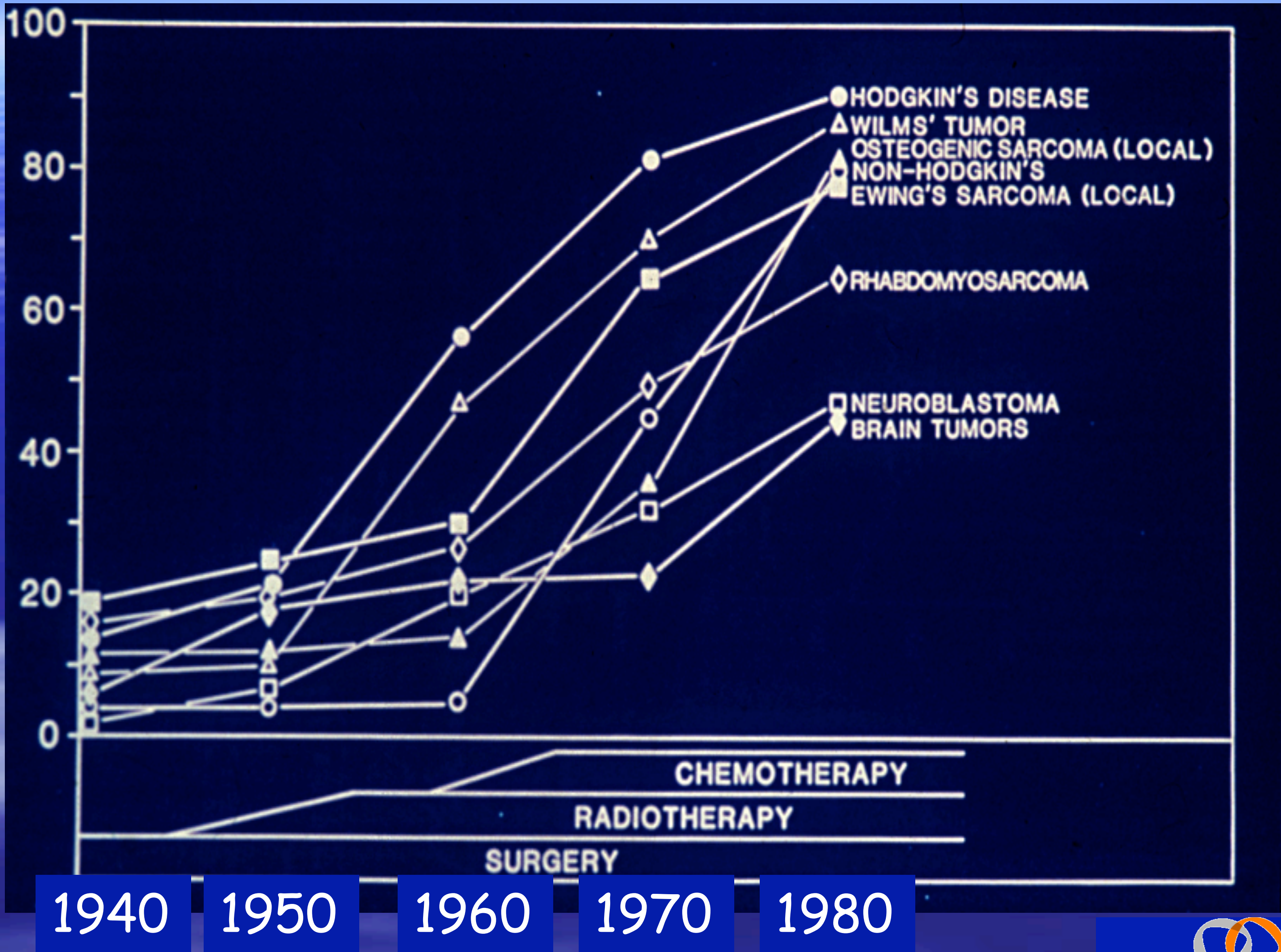

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OUTCOME « EXCELLENT »
(# 1/3 cases)

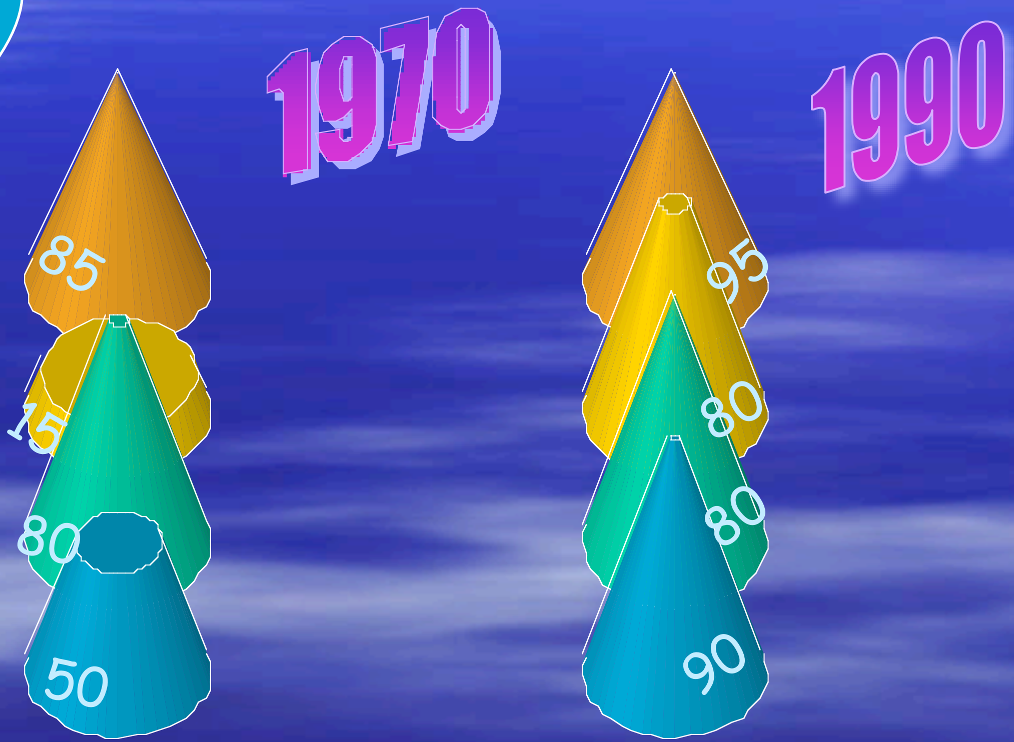
Light management
Light sequelae !

HODGKIN

NHL

LOC NEURO

NEPHRO



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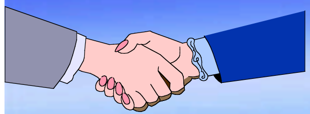

OUTCOME « ENCOURAGING » (# 1/3 cases)

Heavy management
frequent sequelae !

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OUTCOME
« DISAPPOINTING »
(# 1/3)

Heavy treatment,
sustantial sequelae

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PEDIATRIC RADIOTHERAPY : PLACE

- Necessary approx. half cases
- Dreadful reputation RX-induced sequelae !

RADIOTHERAPY IN MODERN TREATMENT STRATEGIES

- *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*

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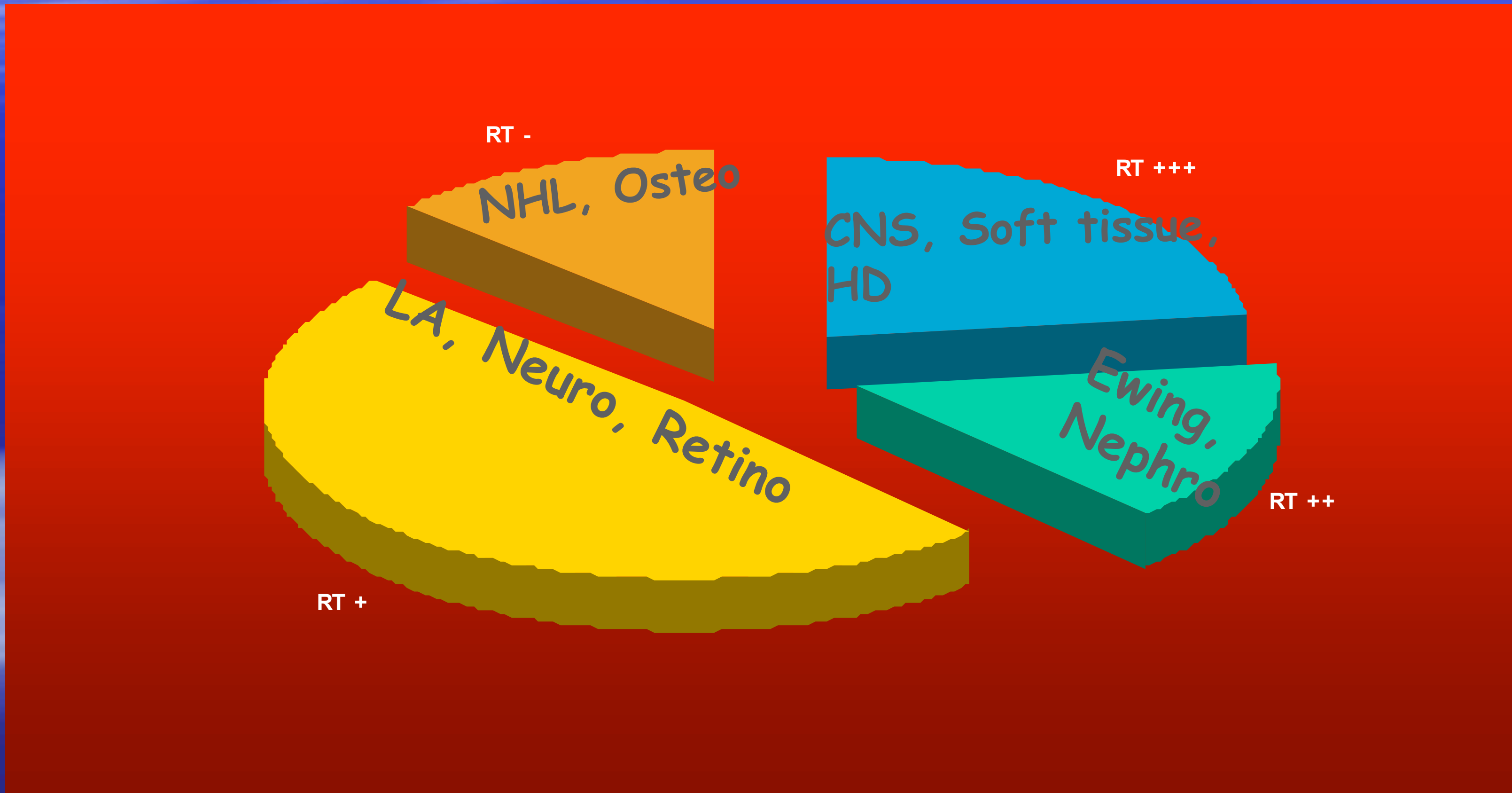
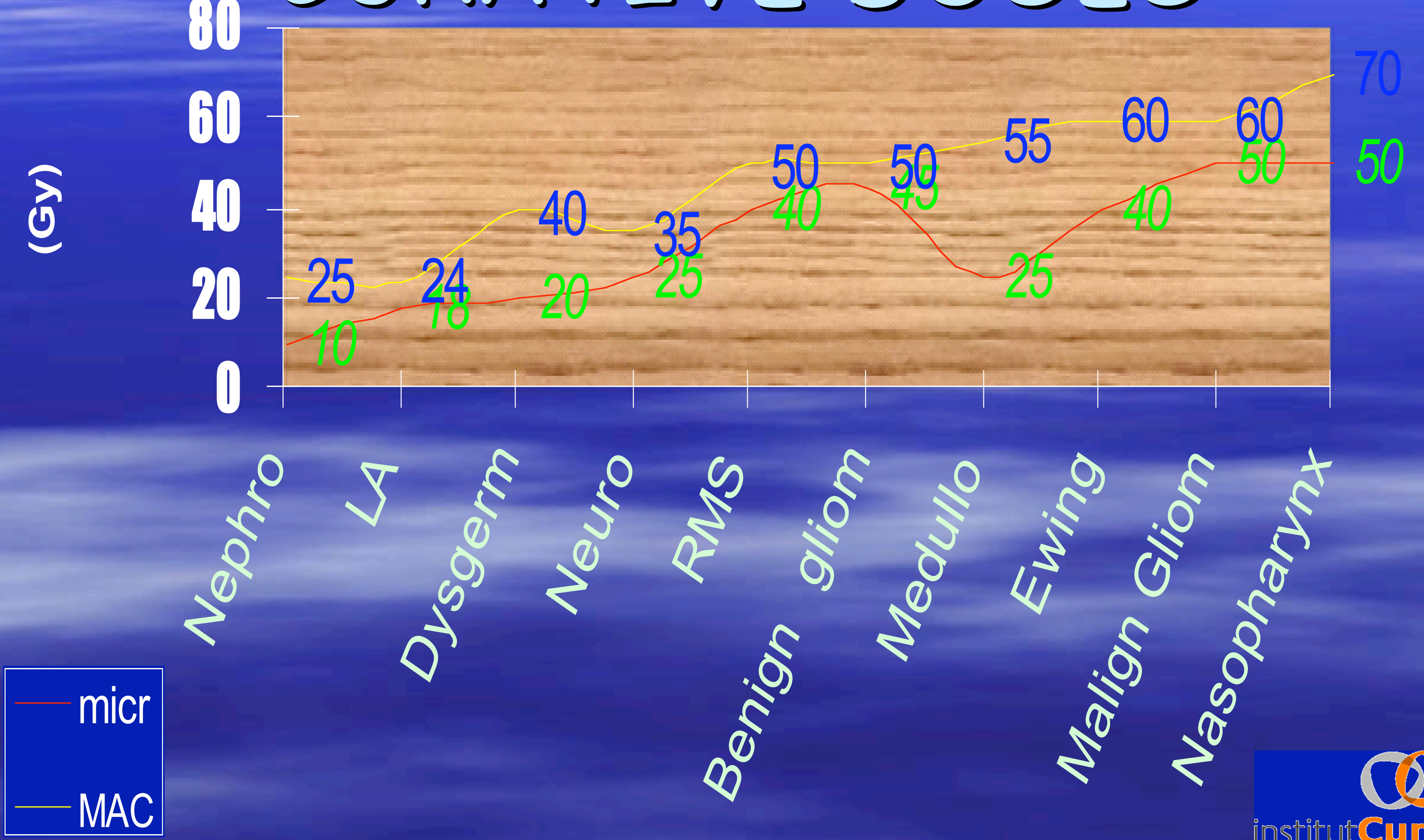
PEDIATRIC RADIOTHERAPY : PLACE



PEDIATRIC RADIOTHERAPY : CURATIVE DOSES



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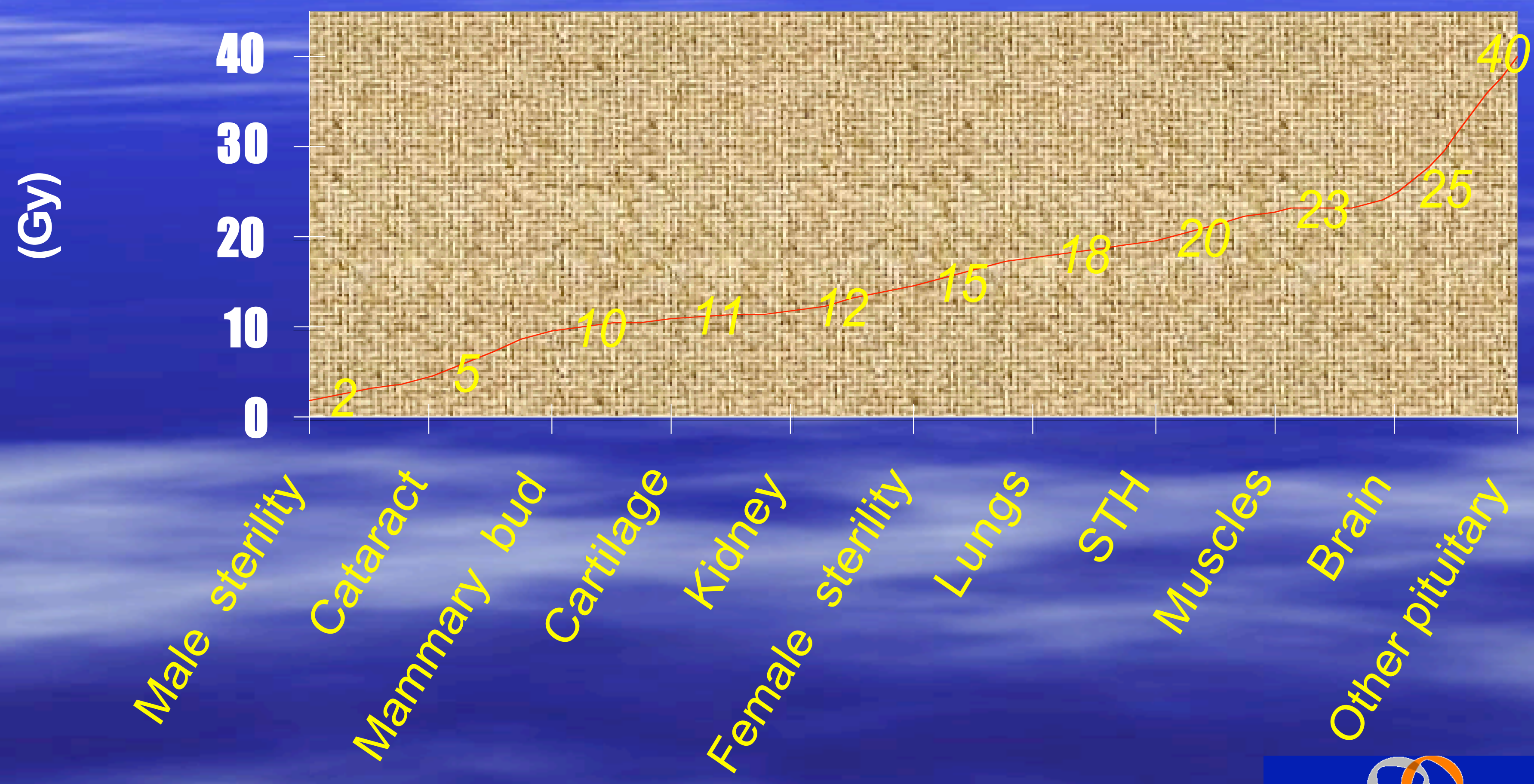
DOSES TO CRITICAL STRUCTURES IN CHILDREN



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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

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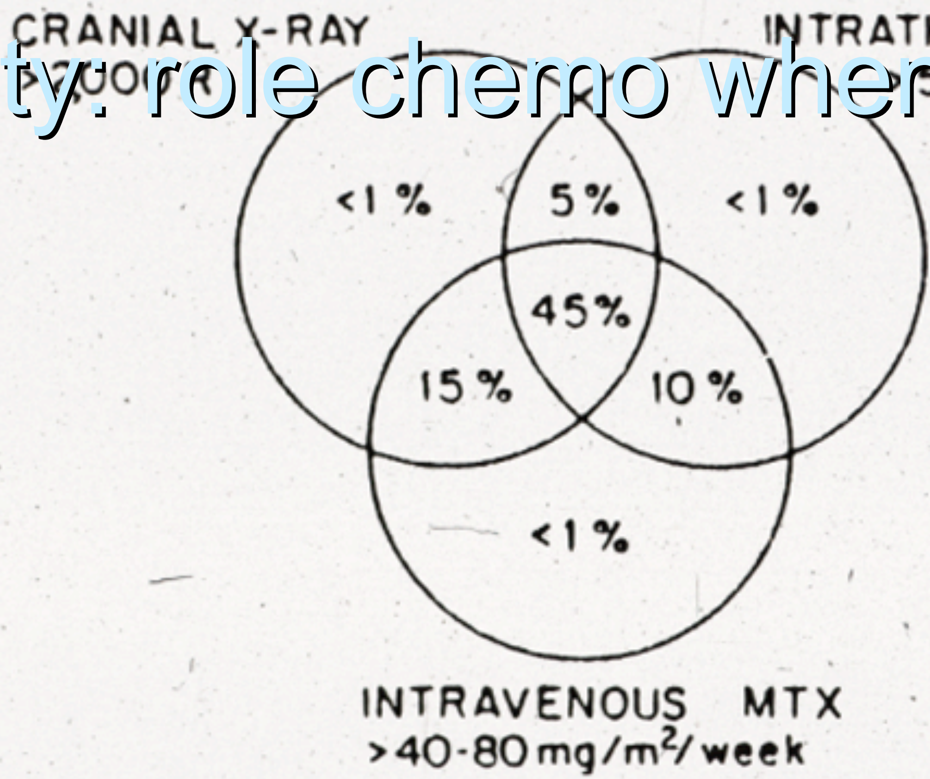
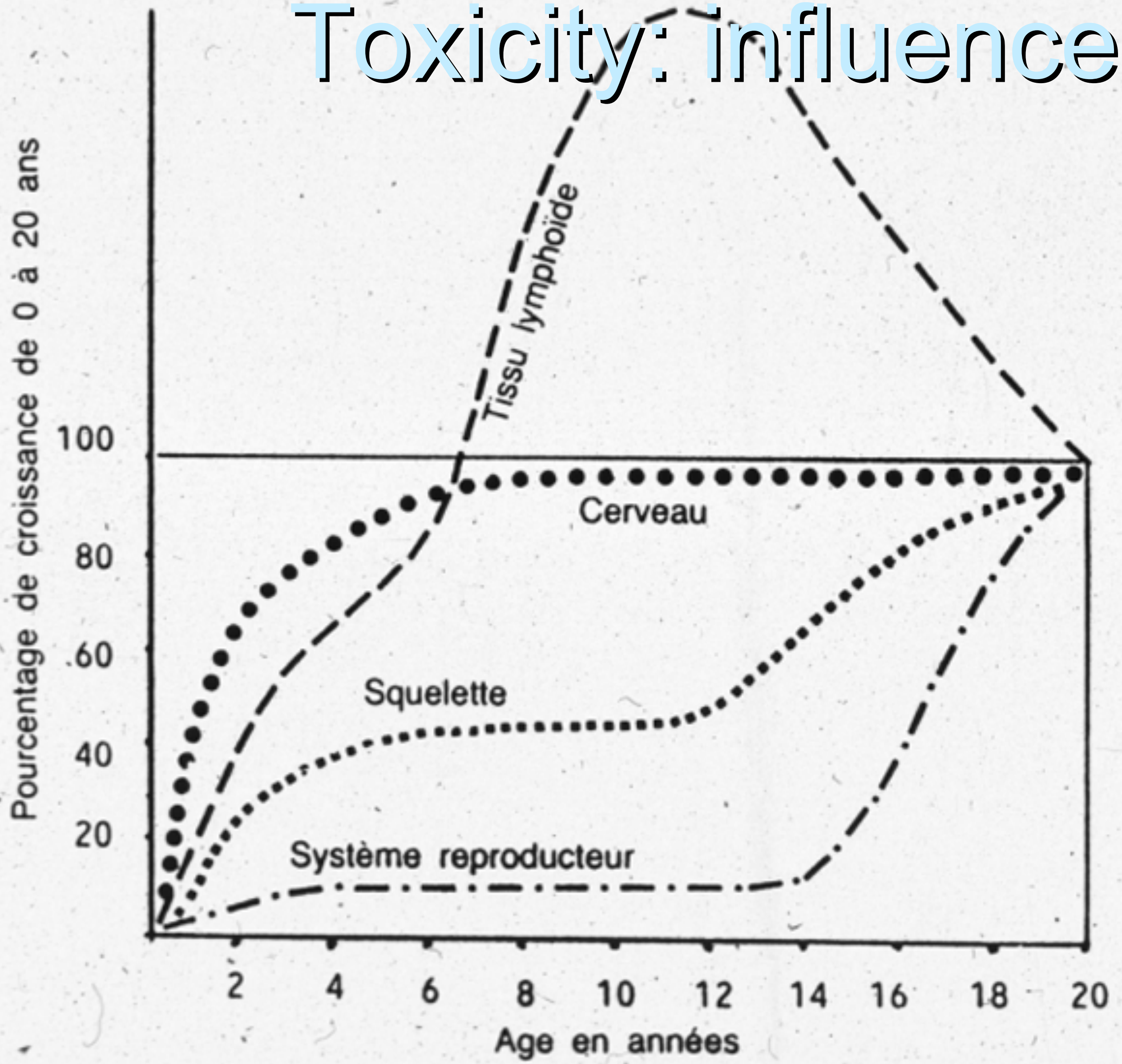
Toxicity: role chemo when combined



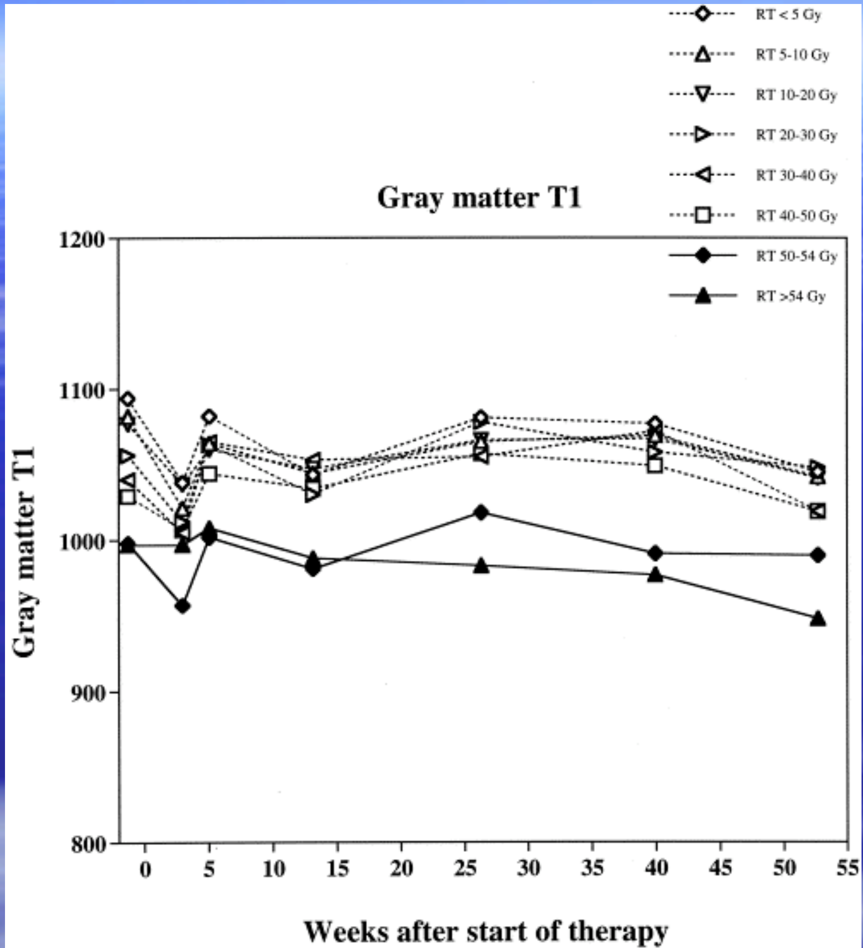
—Risk of leukoencephalopathy according to therapy. The figures on risk, which were estimated by the author from a review of the literature, should be interpreted as rough approximations.

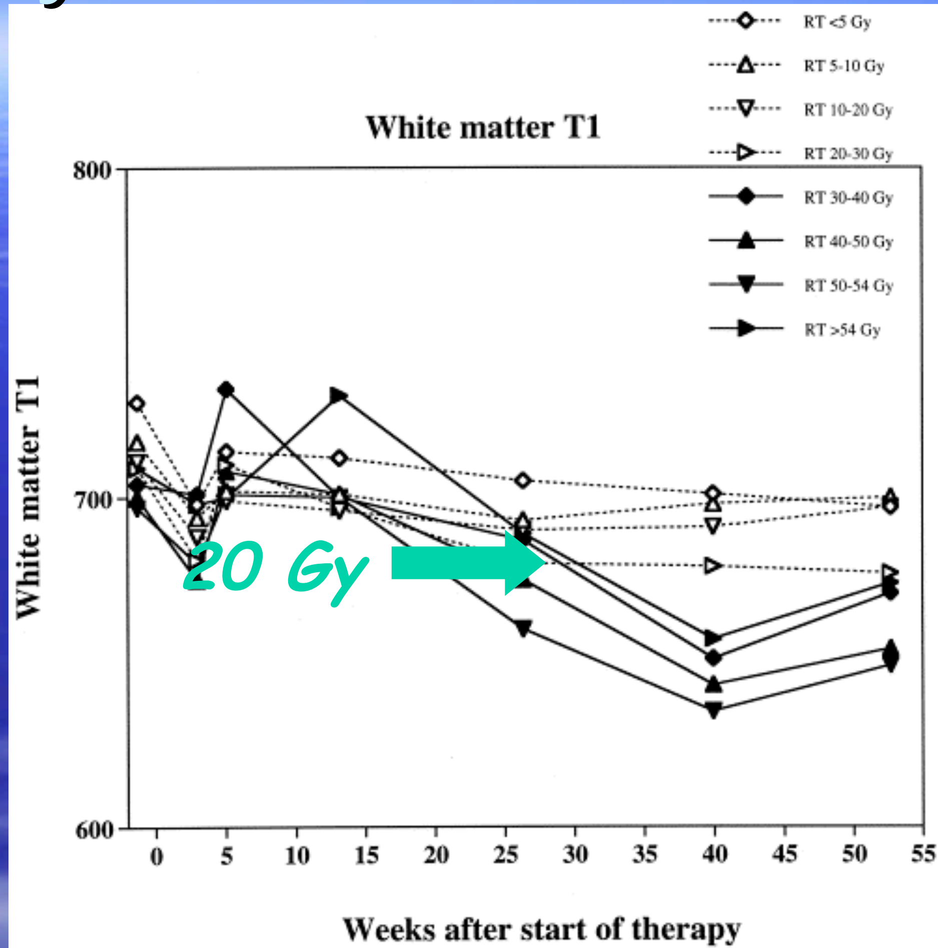
Toxicity: influence age



Courbes de croissance de différents tissus en fonction de l'âge (d'après Rubin).

brain: sensitivity white matter





Effect of ionizing radiation on the human brain: white matter and grey matter T1 MRI in pediatric brain tumor patients treated with conformal radiotherapy.

Steen et al, IJROBP 2001.

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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 paradygms***
- ***Need for considerable technical improvements…***

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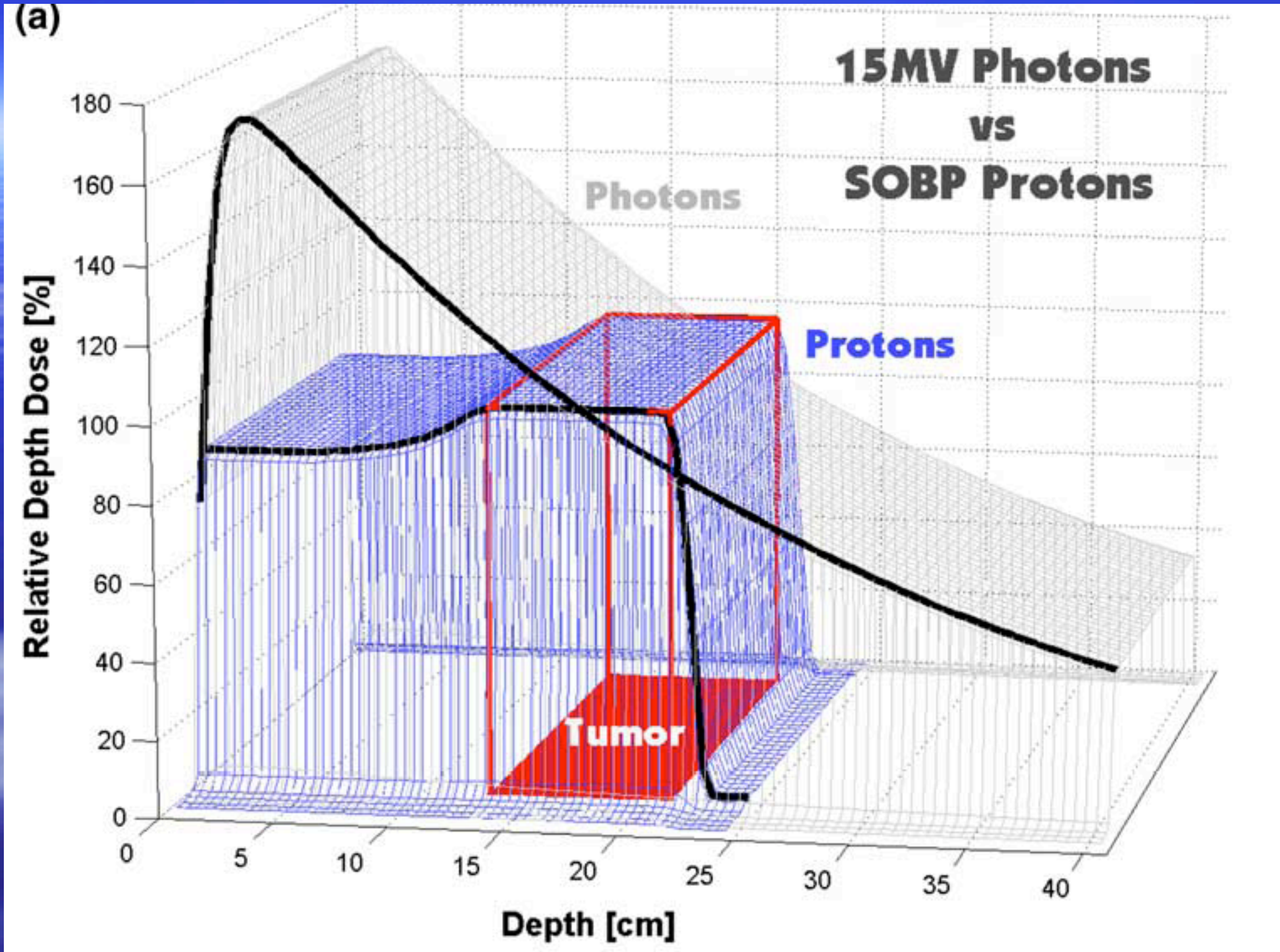

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Proton therapy in pediatrics:

DOSIMETRICAL EVIDENCES

Plenty !

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Medulloblastomas

Posterior fossa: clear benefit of protons

CNS coverage: more controversial

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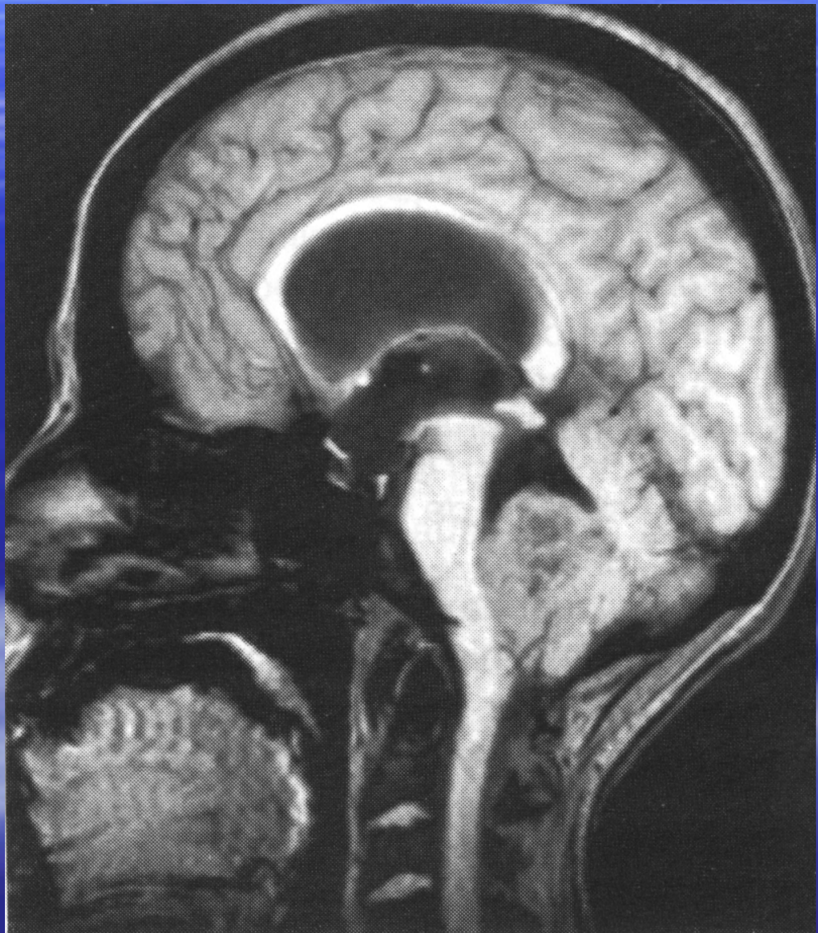
POSTERIOR FOSSA : anatomical situation



- *Posteriorly* : occipital bone
- *Laterally* : temporal (petrous + mastoid)
- *Anteriorly* : sphenoid
- *Superiorly* : tentorium cerebelli
- *Inferiorly* : foramen magnum

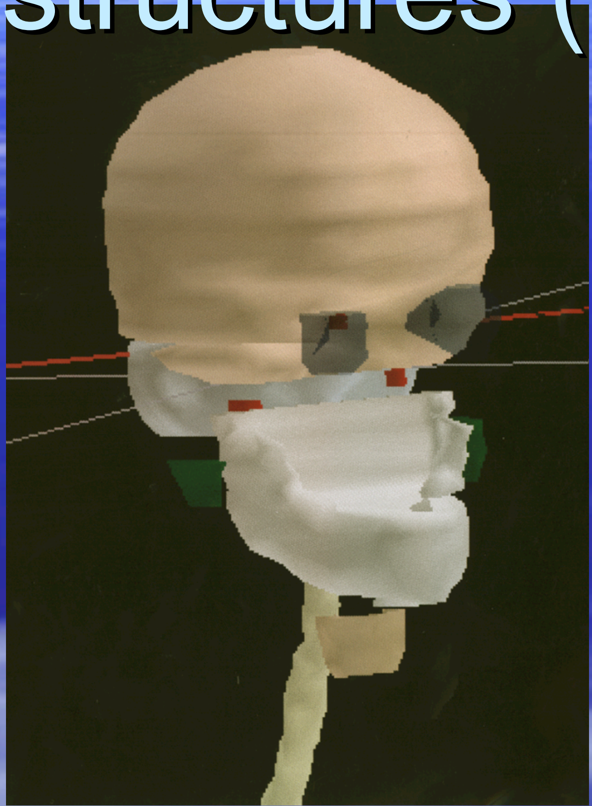
POSTERIOR FOSSA : indications for radiotherapy

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 ...

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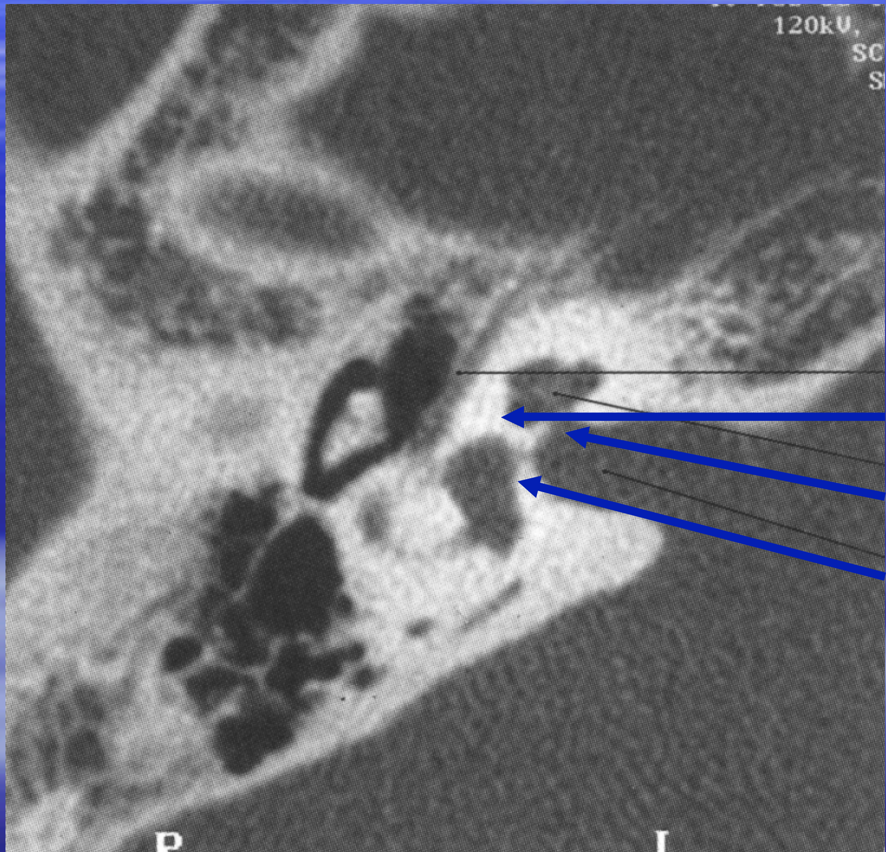
POSTERIOR FOSSA : internal ear



VII

cochlea
vestibule

RX-related ototoxicity in literature

- Concerns mainly higher frequencies : difficulties speech discremination
- Potentiated by CDDP - based chemotherapy
- Exact risk unknown.
  - Estimates : Threshold 30 Gy

    24 % after 59.5 - 76.5 Gy

    (Kwong, 1996)

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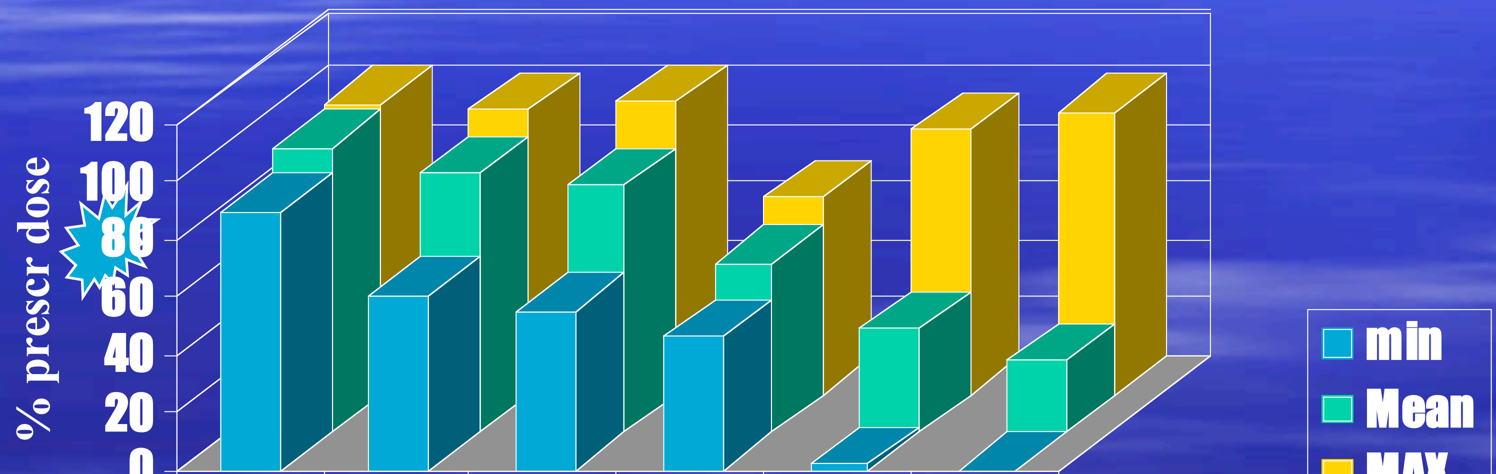
RESULTS : cochlea



	Lat	Obl	Non cop	Opti obl	Obl prot	Post prot
min	90,1	61,4	55,9	46,3	2,1	0
Mean	98,8	90,2	85,8	58,9	35,9	24,9
MAX	101,2	99	101,6	68,5	92,1	98,3

: *Tolerance at 55 Gy tum*

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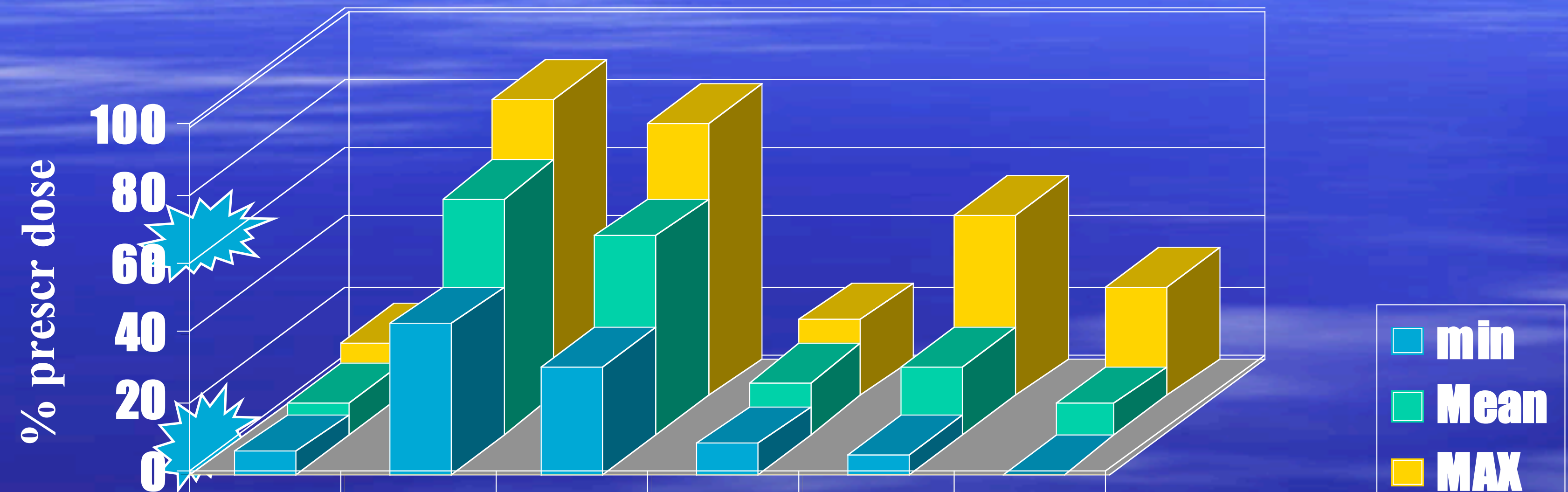
RESULTS : pituitary



	Lat	Obl	Non cop	Opti obl	Obl prot	Post prot
min	6,3	42,9	30,6	8,5	5,5	0,2
Mean	9,4	68,5	57,2	15,1	20	8,9
MAX	15,3	85,9	78,5	22	52	31,9

: Tolerance at 55 Gy tumor

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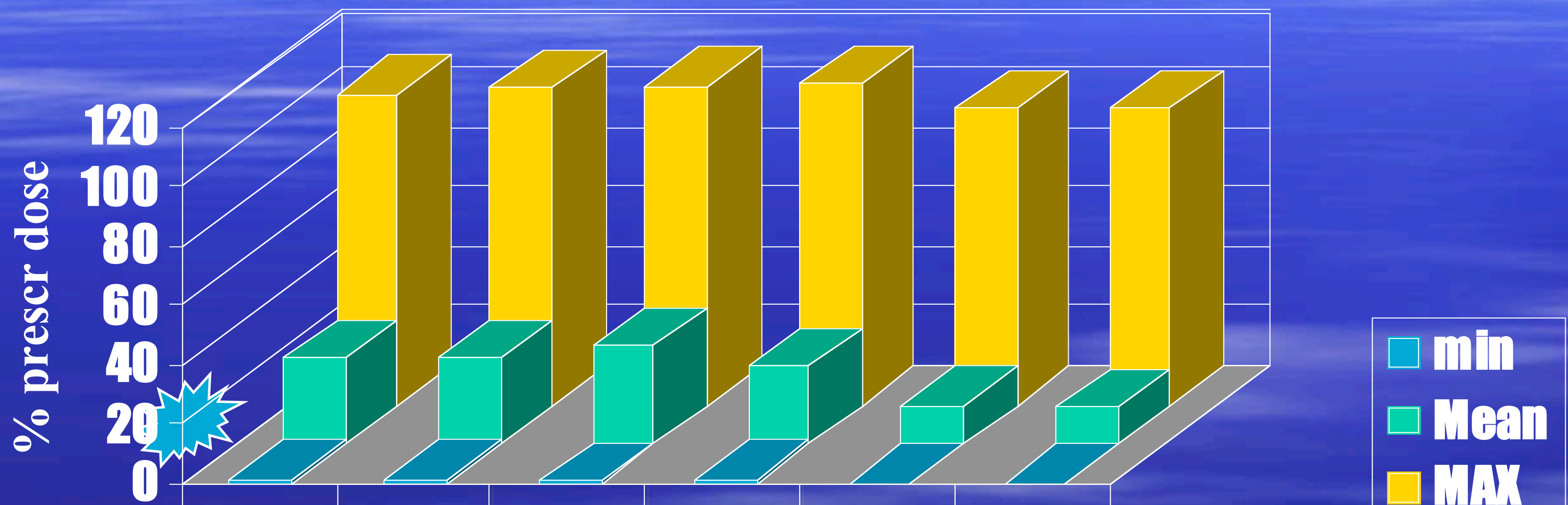
RESULTS : supra tentorial brain



	Lat	Obl	Non cop	Opti obl	Obl prot	Post prot
min	2	1,6	0,8	1,7	0	0
Mean	29,5	29,3	33,5	26,5	13,7	13
MAX	105,5	107,5	107,6	108,5	100,3	100,6

: *Tolerance at 55 Gy tumor*

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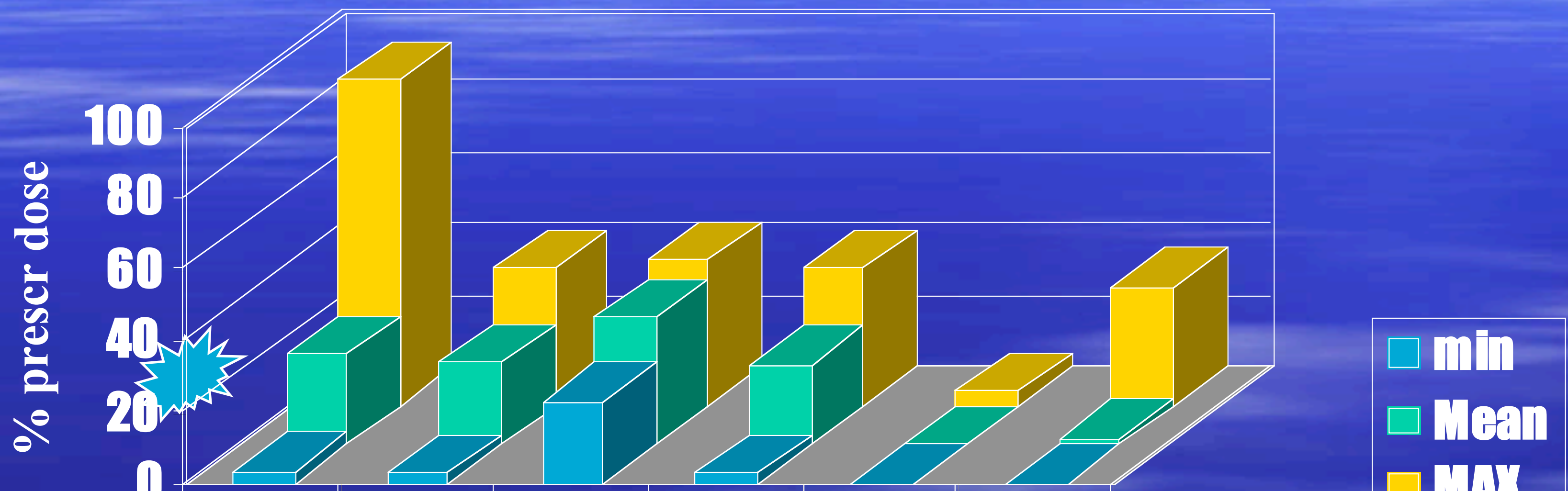
RESULTS : parotids



	Lat	Obl	Non cop	Opti obl	Obl prot	Post prot
min	3,8	3,3	23,3	3,4	0	0
Mean	25,6	23,4	36	22,4	0	1,8
MAX	91,9	38,7	40,8	38,9	4,2	33,6

Tolerance at 55 Gy tumor

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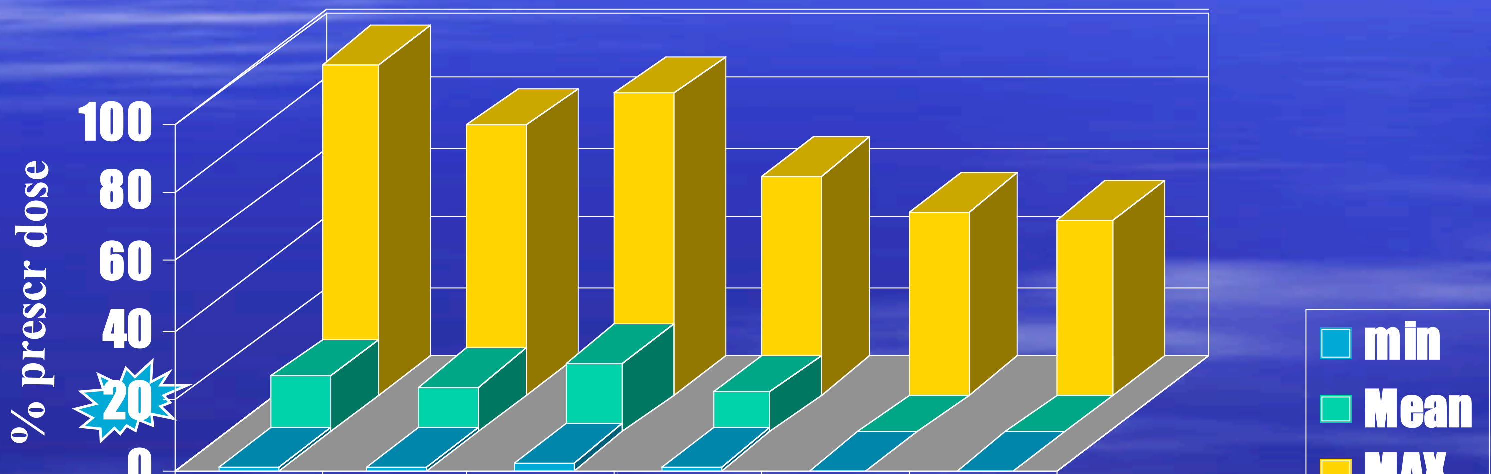
RESULTS : mandible



	Lat	Obl	Non cop	Opti obl	Obl prot	Post prot
min	1,2	1,4	2,6	1,4	0	0
Mean	16,6	13,4	20,5	11,9	0,4	0,3
MAX	96	77,9	87,2	63,4	52,9	50,6

: *Tolerance at 55 Gy tumor*

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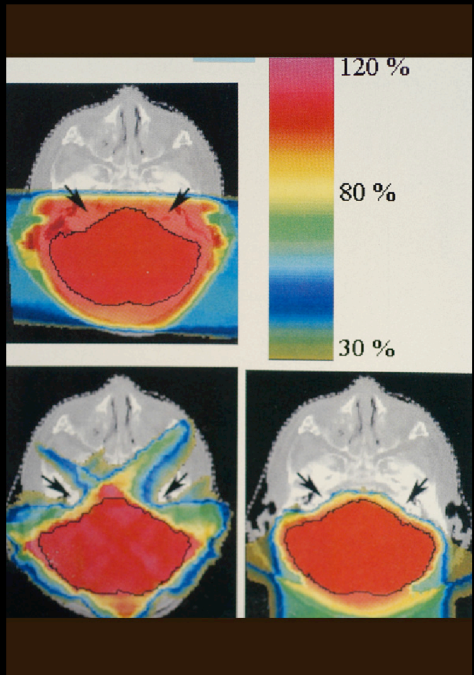
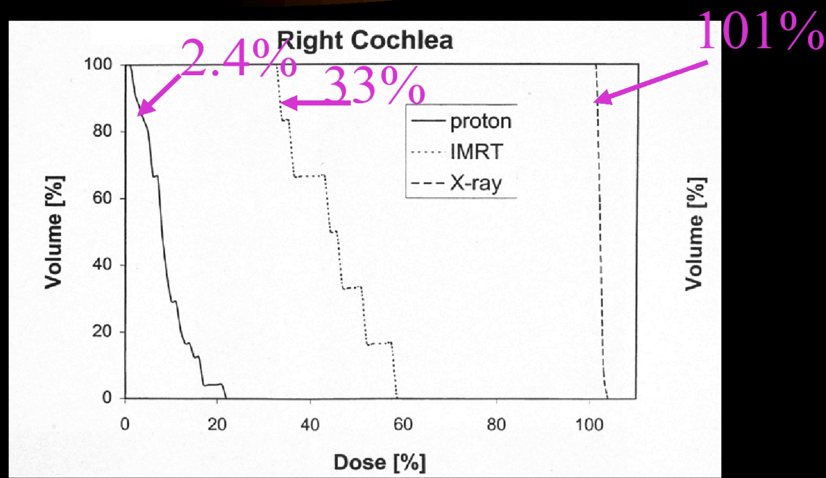
COMPARISON CONVENTIONAL, IMRT, PROTONS IN MEDULLOBLASTOMA

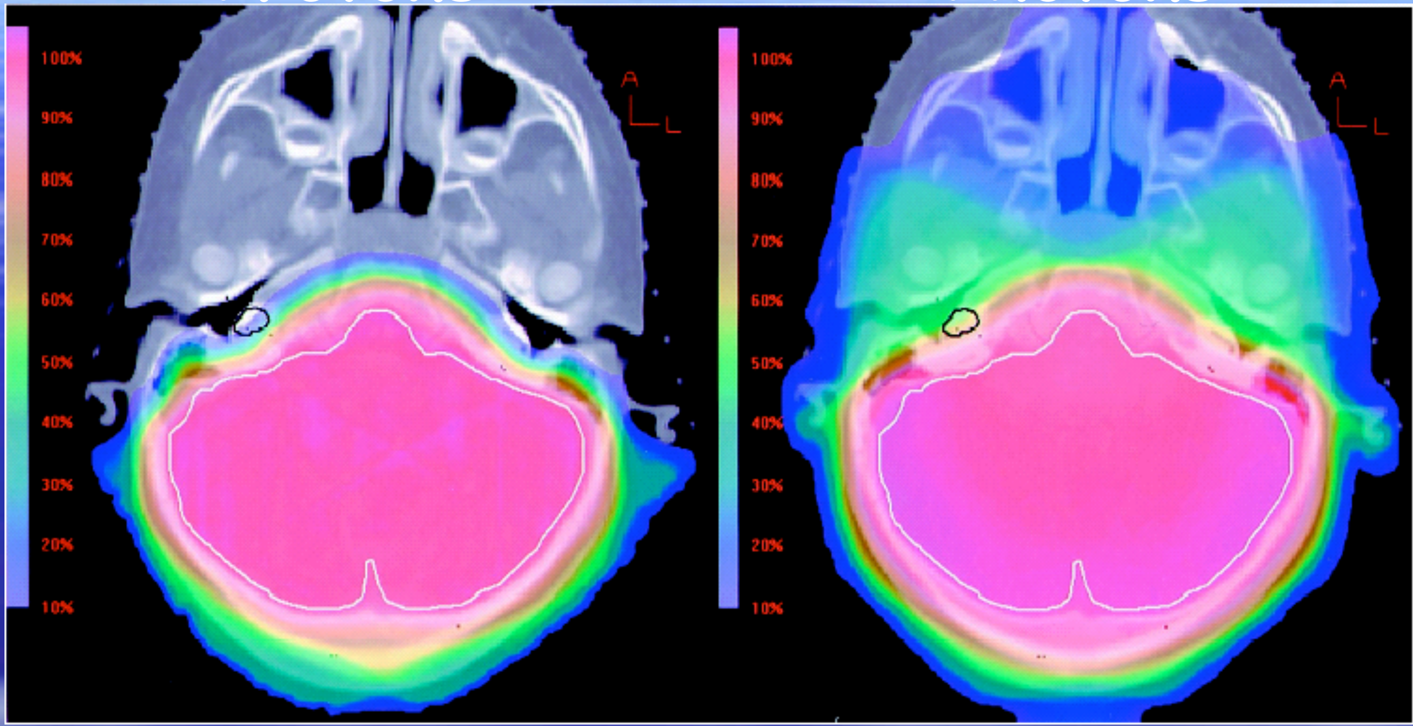


St Clair et al, IJROBP, 2004



Lin R - IJROBP - 2000; 48: 1219-1228

Protons Photons



% mean D/prescribed D

	Cochlea	Inner ear	Middle ear	Temporal lobe
Proton	25 ± 4%	46 ± 6%	10 ± 6%	22 ± 5%
Photon	75 ± 6%	90 ± 3%	54 ± 4%	64 ± 5%

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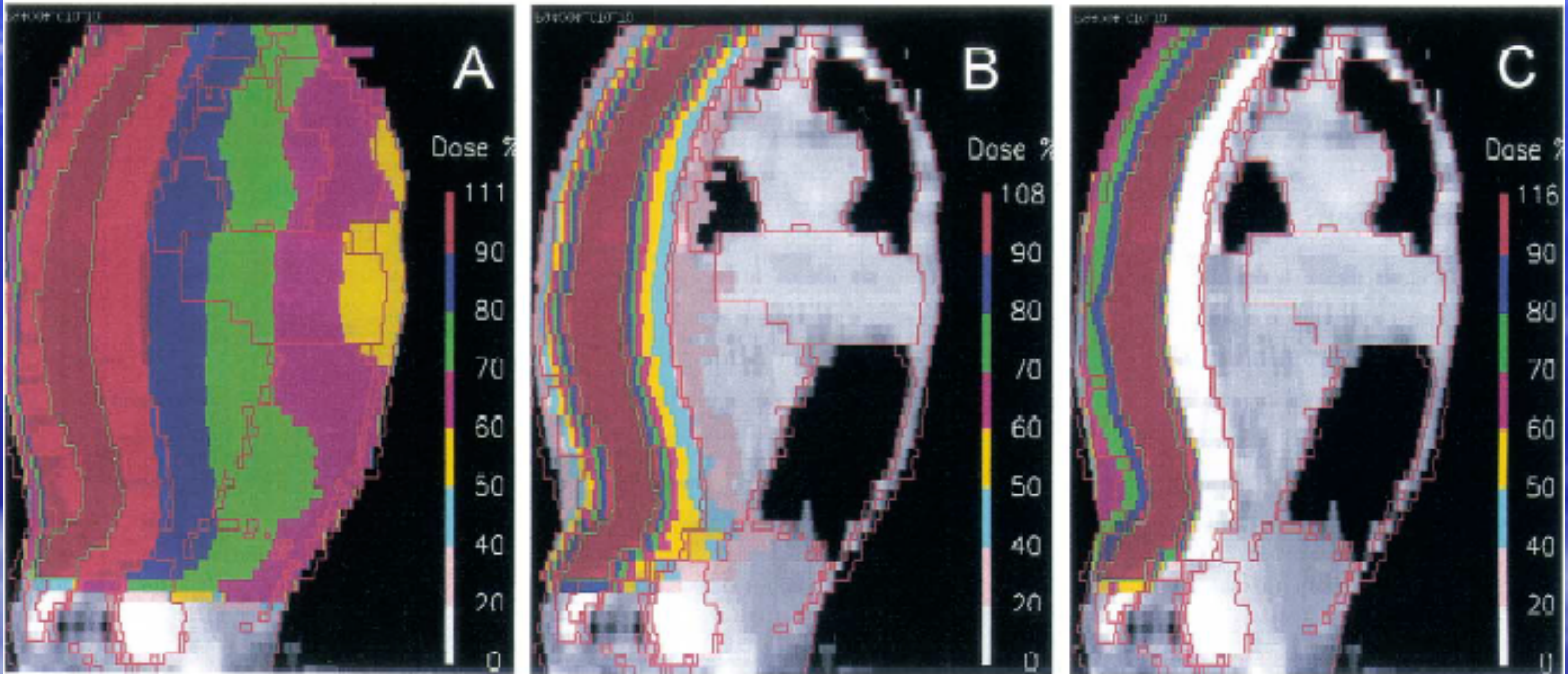
Spinal canal (Miralbell R - IJROBP - 2002; 54:824-829



Photons

IM Photons

IM Protons

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Int. J. Radiation Oncology Biol. Phys., Vol. xx, No. x, pp. xxx, 2007

0360-3016/07/$–see front matter

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doi:10.1016/j.ijrobp.2007.02.021

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

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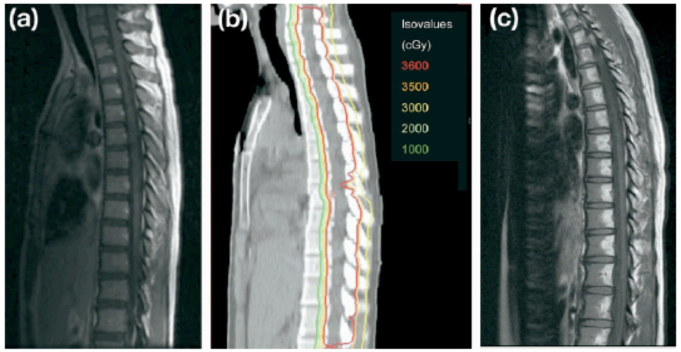

Fig. 1. A 14-year-old girl with supratentorial primitive neuroectodermal tumor: craniospinal irradiation prescribed to the thecal sac and exiting nerve roots only. (a) T1-weighted magnetic resonance image 1 week before radiation treatment. (b) Computed tomography–proton radiotherapy treatment plan. (c) T1-weighted magnetic resonance image showing hyperintense fatty changes in posterior aspect of vertebral bodies 1 month after completion of proton radiotherapy.

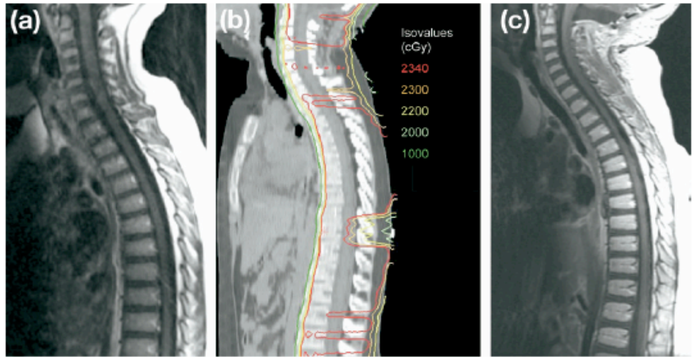

Fig. 2. A 7-year-old boy with medulloblastoma: craniospinal irradiation prescribed to the thecal sac and entire vertebral body. (a) T1-weighted magnetic resonance image 1 week before radiation treatment. (b) Computed tomography–proton radiotherapy treatment plan. (c) T1-weighted magnetic resonance image showing hyperintense fatty changes throughout entire vertebral bodies 1 month after completion of proton radiotherapy.

Ado: canal only

Young: full spinal width

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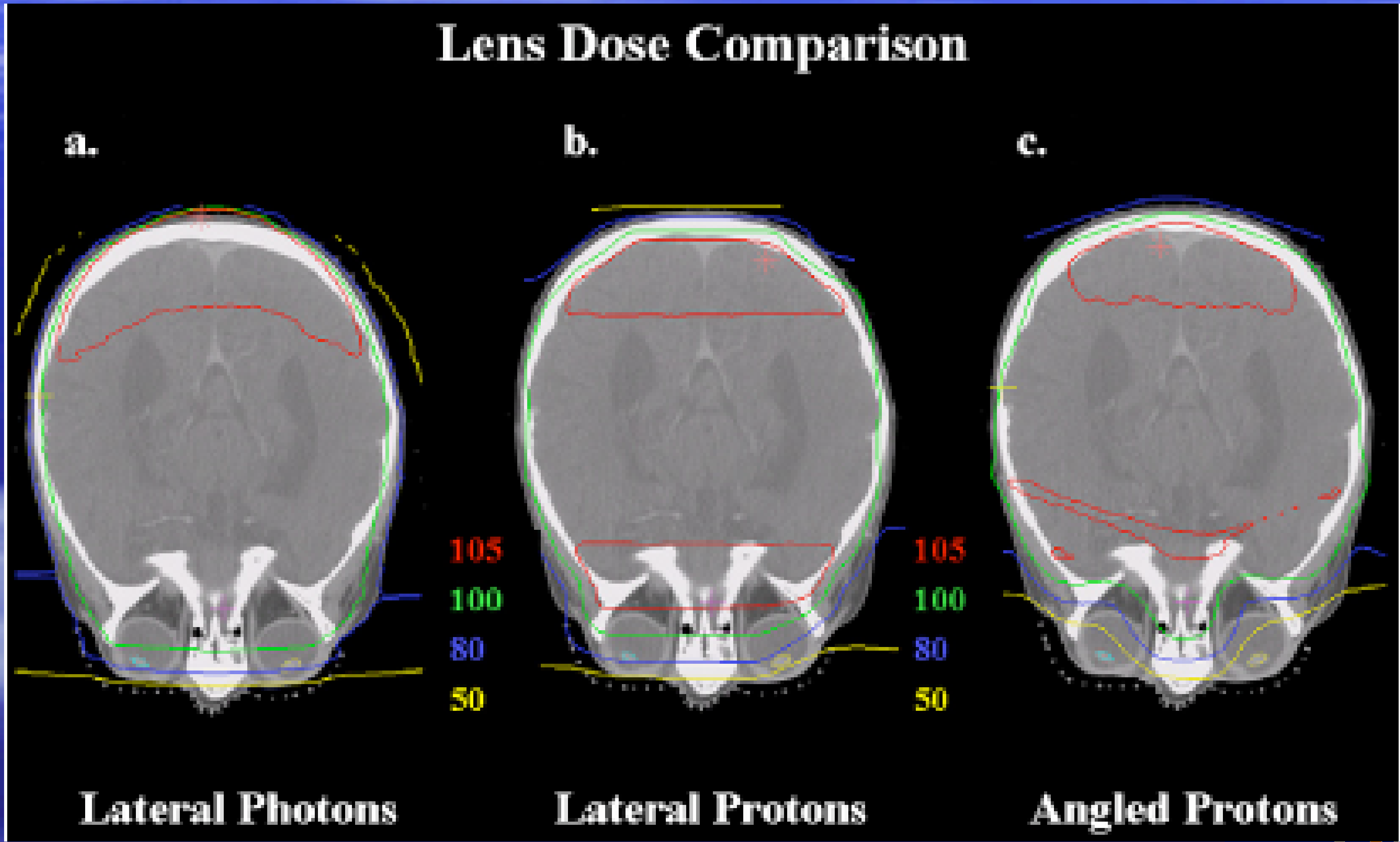
Radiation dose to the lens (Cochrane et al, IJROBP, 2008)



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

Table 1. Favorable medulloblastoma.
NTCP for IQ: predicted results averaged over all ages

Volume*	RT dose	RT source	% Risk of IQ <90
Plan 1	30 Gy	x-rays	25.1
Plan 2	30 Gy	x-rays (hand plan)	18.2
Plan 3	30 Gy	x-rays (inverse plan)	16.0
Plan 4	30 Gy	Protons	15.7

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

Table 2. Unfavorable medulloblastoma.
NTCP for IQ: predicted results averaged over all ages

Volume*	RT dose	RT source	% Risk of IQ <90
Plan 1	30 Gy	x-rays	25.1
Plan 2	30 Gy	x-rays (hand plan)	18.7
Plan 3	30 Gy	x-rays (inverse plan)	17.0
Plan 4	30 Gy	Protons	16.3

* Plan 1: standard WBI (TV1), 30 Gy. Plan 2, 3, and 4: TV1, 10 Gy; TV2, 30 Gy (see text).

K2 estim risk in PM RMS

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

	X-rays	IM X-rays	Protons	IM protons
Yearly rate (%)	0.06	0.05	0.04	0.02
Relative risk compared to standard X-ray plan	1	0.8	0.7	0.4

Abbreviation: IM = intensity-modulated.

Miralbell R - IJROBP - 2002; 54:824-829

K2 estim risk in médulloblastoma

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

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

Abbreviation: IM = intensity-modulated.

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

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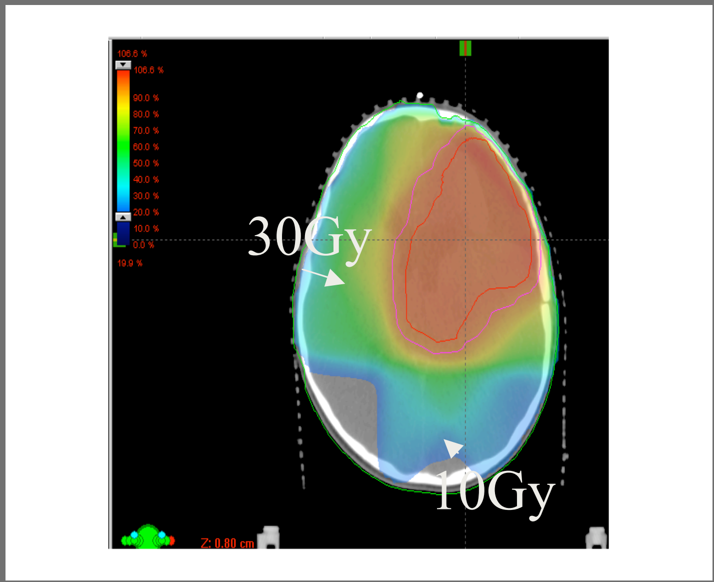
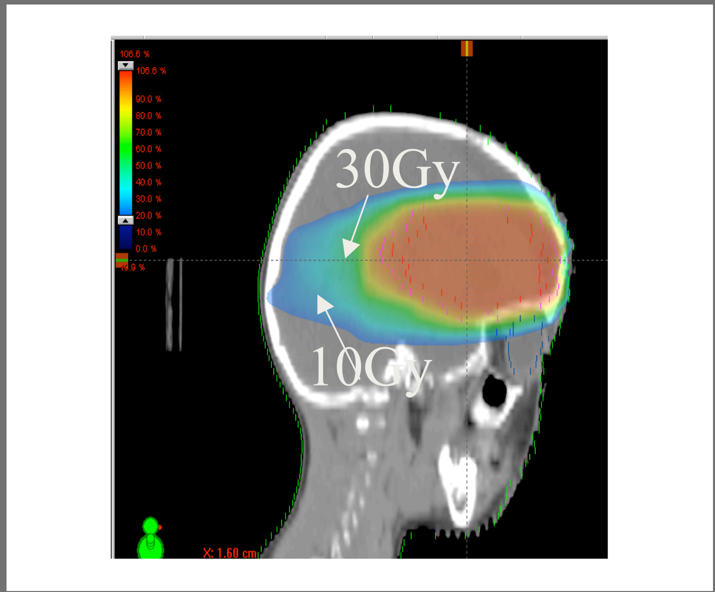
Ependymoma, left Frontal lobe: XR-IMRT plan

Axial



Sagittal



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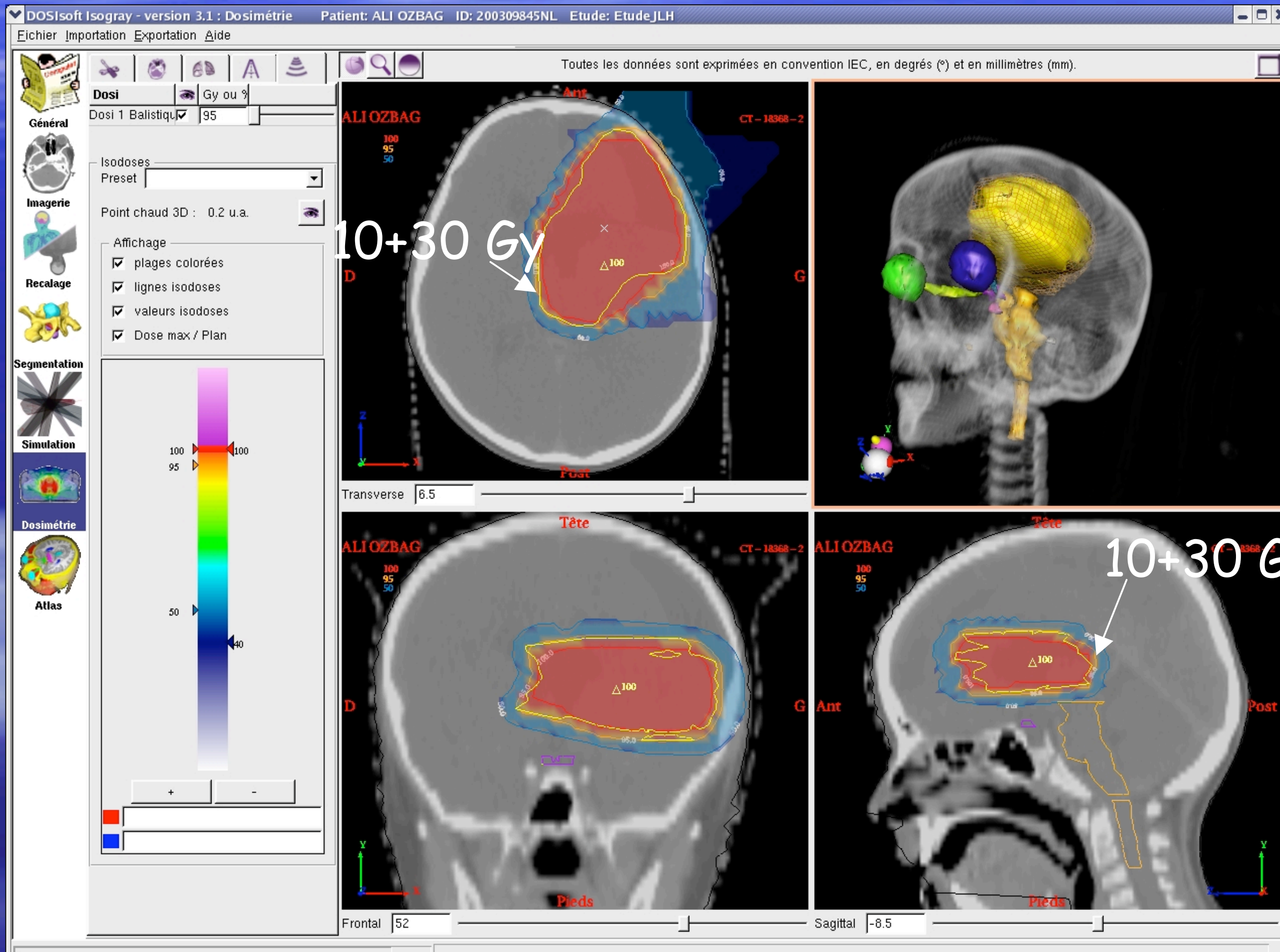
Pt Ozb. : proton planning



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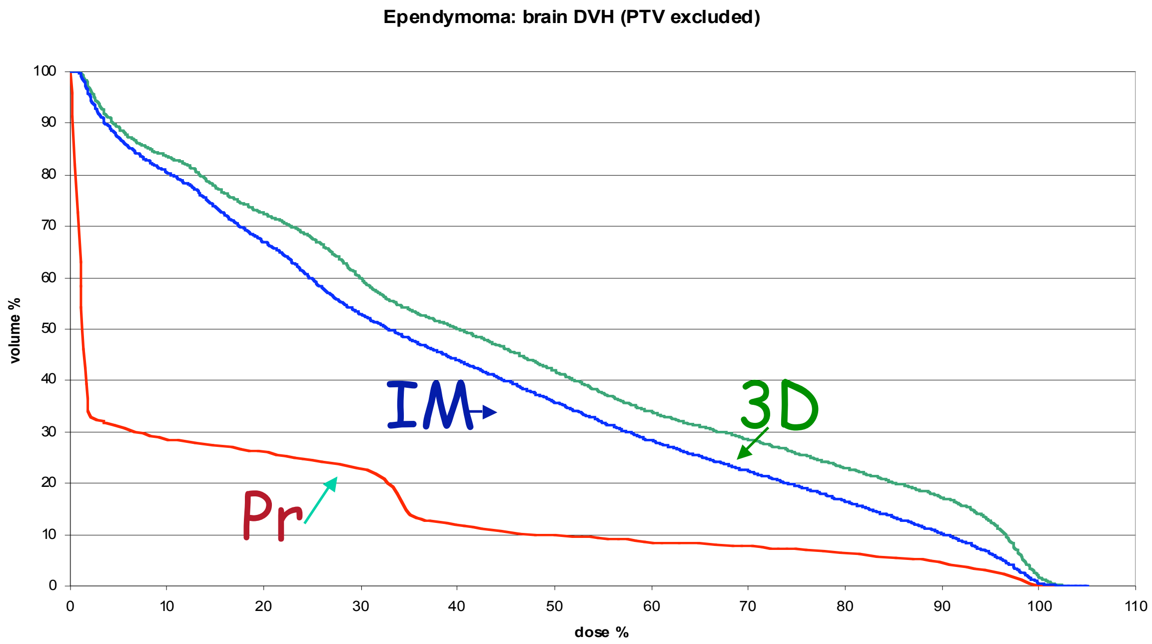
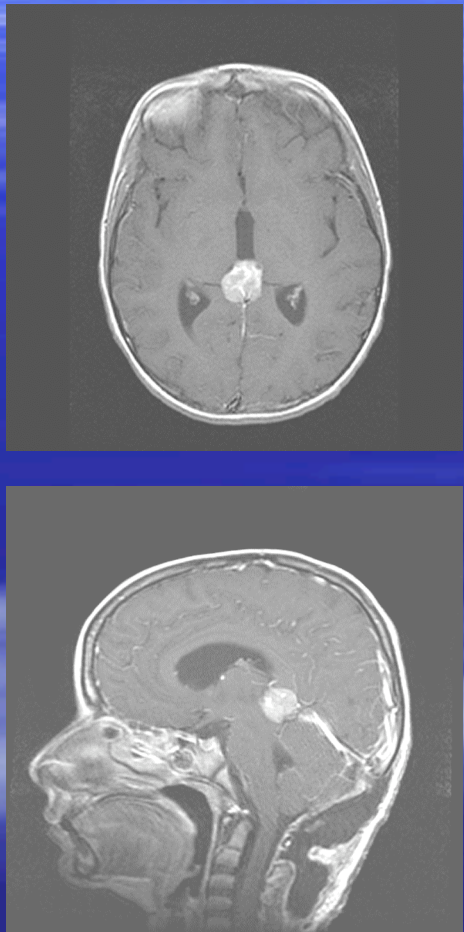
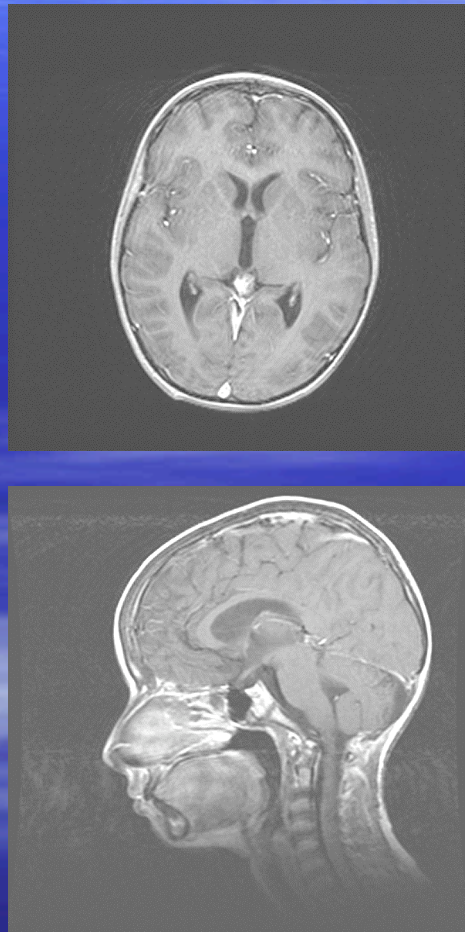


Ependymoma: brain DVH (PTV excluded)
volume %
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
110
dose %
IM
3D
Pr

Case #3: pineal dysgerminoma

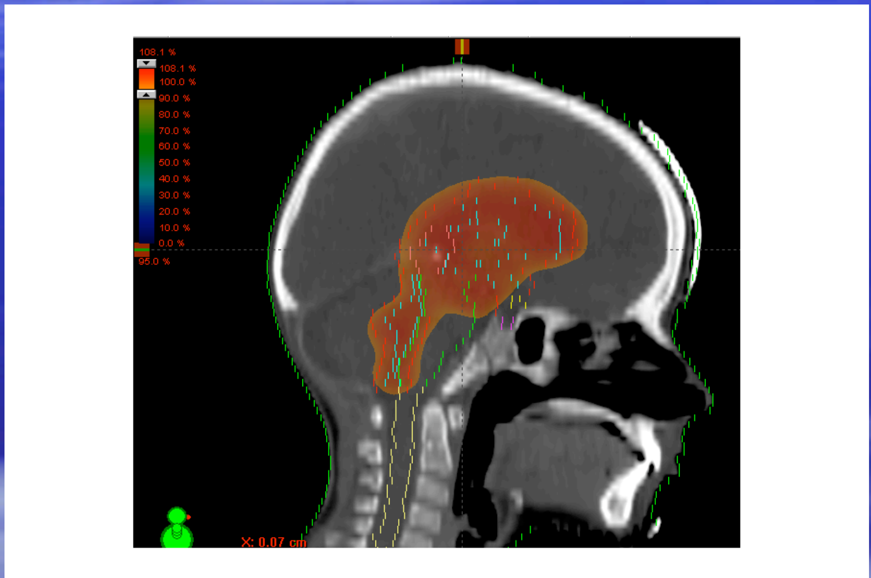


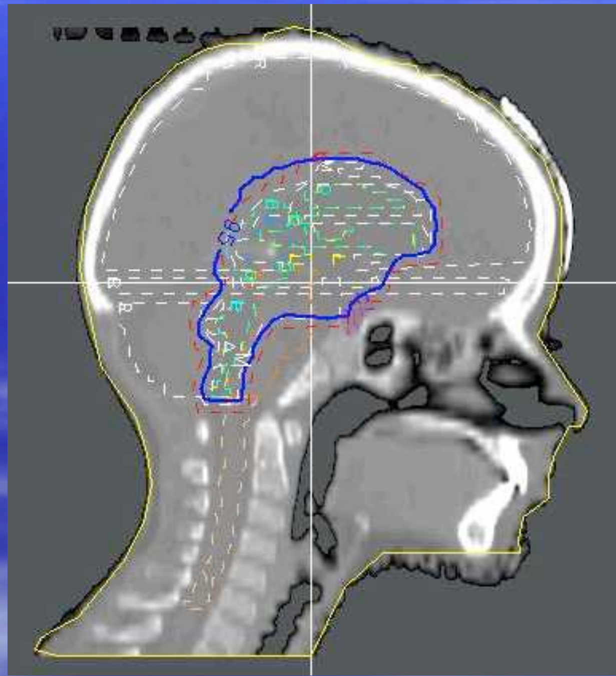
Before chemotherapy



After chemotherapy

High dose (95%)





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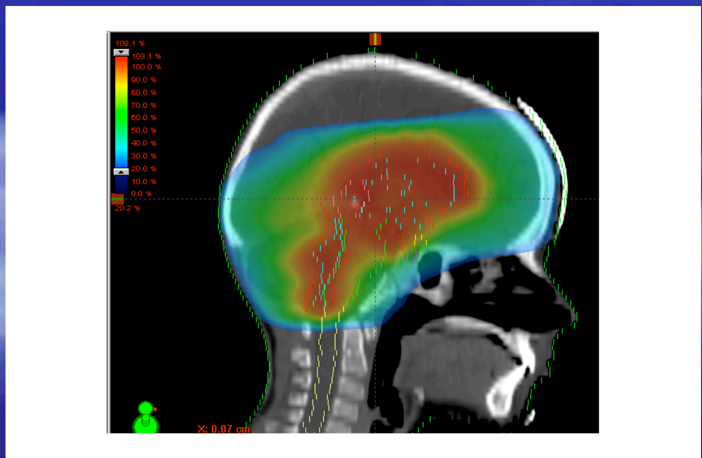
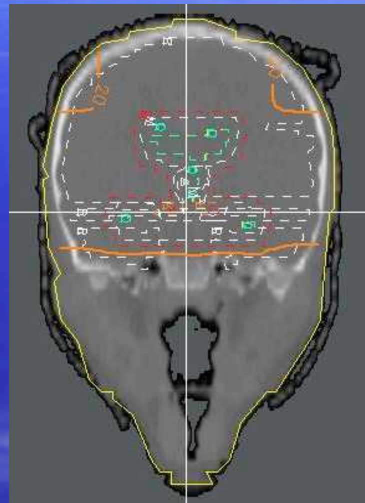
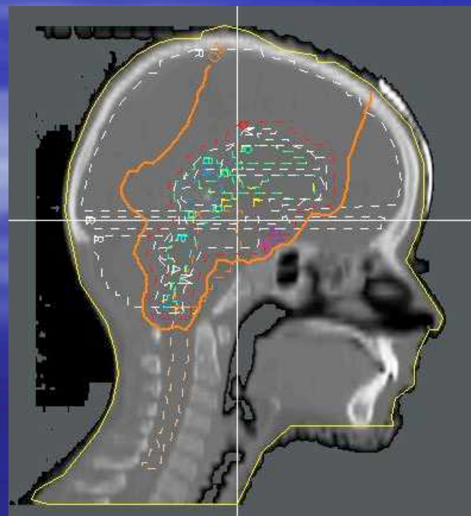
Low dose (20%)







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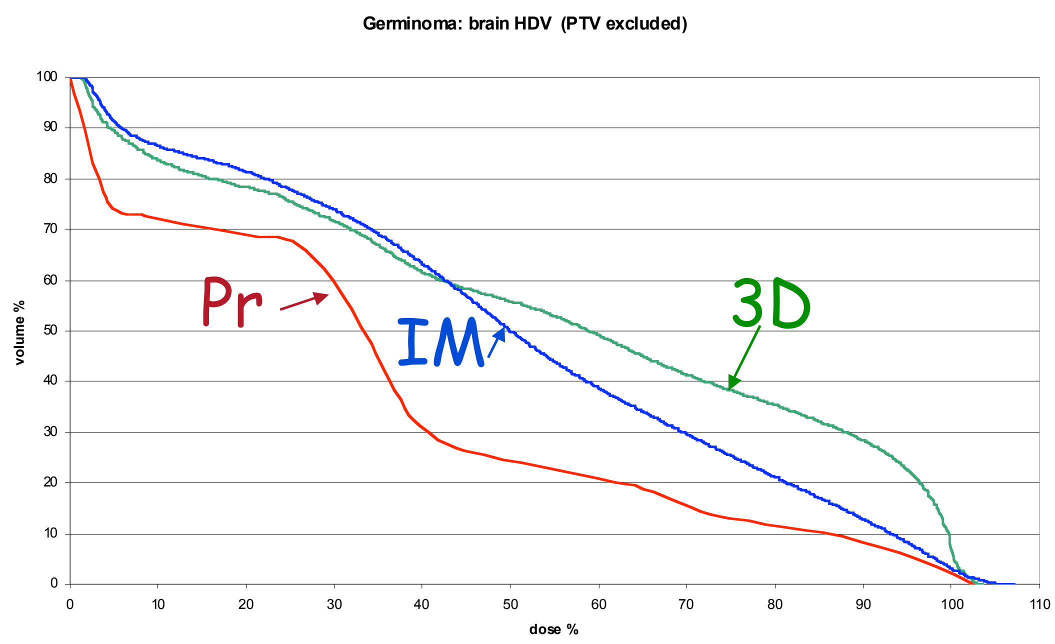

Germinoma: brain HDV (PTV excluded)
volume %
dose %
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
110
Pr
IM
3D

Int. J. Radiation Oncology Biol. Phys., Vol. 45, No. 5, pp. 1117–1126, 1999

0360-3016/99/$–see front matter

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PII S0360-3016(99)00337-5

CLINICAL INVESTIGATION **Brain**

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

Martin Fuss, M.D.,[‡] Eugen B. Hug, M.D.[*†], Rosemary A. Schaefer, B.S.,[*]
Meinhard 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

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M Fuss (cont)

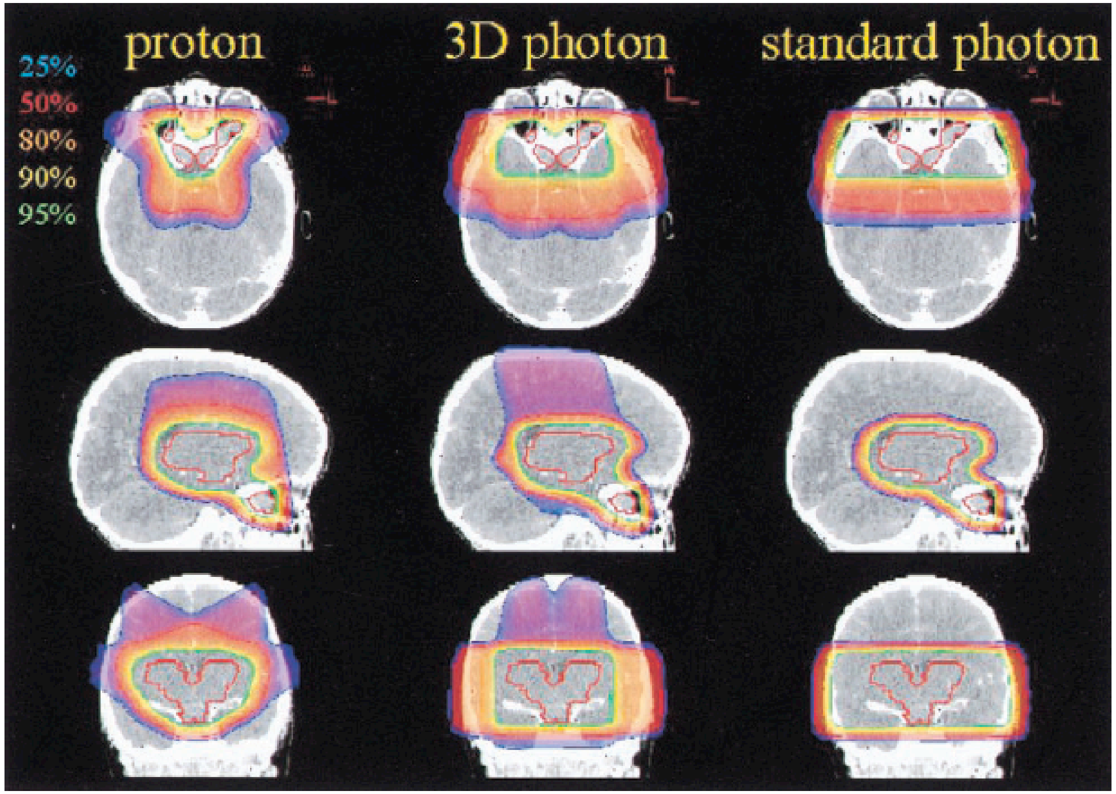

Fig. 7. Dose distribution of proton, 3D photon, and standard photon plans superimposed onto representative slices of the planning CT in axial, sagittal, and coronal planes. Display of GTV in red, and 25% (blue), 50% (red), 80% (orange), 90% (yellow), and 95% (green) isodose lines in color-wash technique. Prescribed total dose was 54 CGE/Gy. 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

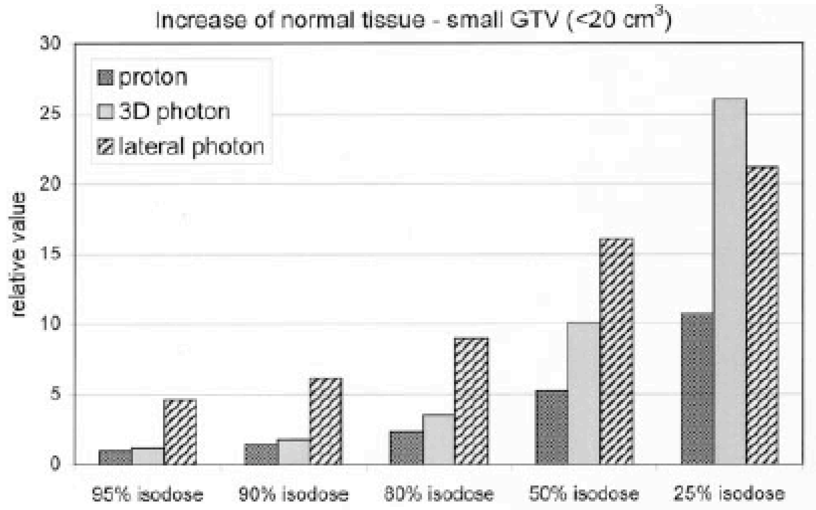

Fig. 3. Relative increase of amount of normal tissue included in the respective isodose volumes for small tumor volumes (< 20 cm^3). X-axis: 95%, 90%, 80%, 50%, and 25% isodose of proton, 3D photon, and lateral photon plans. Y-axis: normal tissue volume encompassed by respective isodose levels minus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

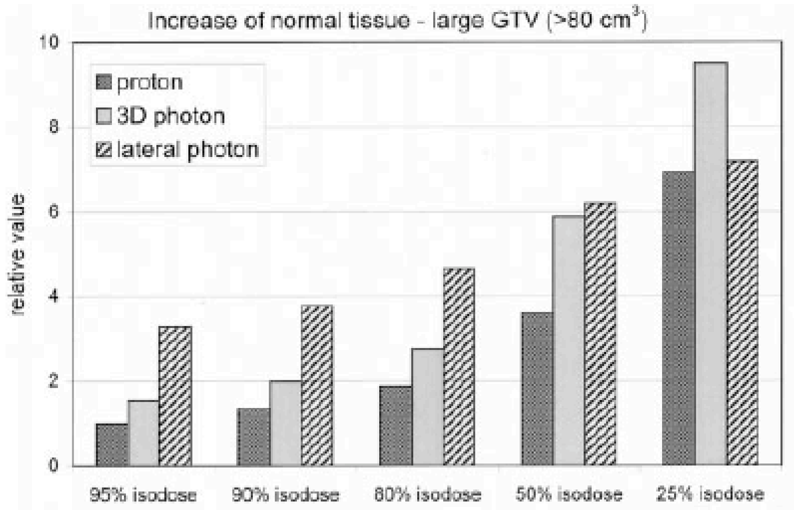

Fig. 4. Relative increase of amount of normal tissue included in the respective isodose volumes for large tumor volumes (> 80 cm^3). X-axis: 95%, 90%, 80%, 50%, and 25% isodose of proton, 3D photon, and lateral photon plans. Y-axis: normal tissue volume encompassed by respective isodose levels minus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

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M Fuss (cont): optic/pituitary

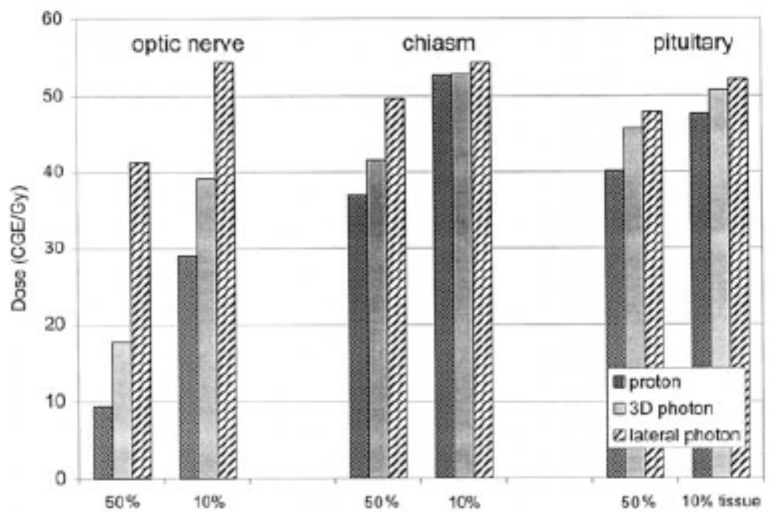

Fig. 5. Prescribed average treatment doses to 50% and 10% tissue volume (x-axis) of contralateral optic nerve, optic chiasm, and pituitary gland. Y-axis: doses in CGE or Gy according to the displayed proton, 3D photon, or lateral beam photon technique.

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M Fuss (cont): lobes/BS

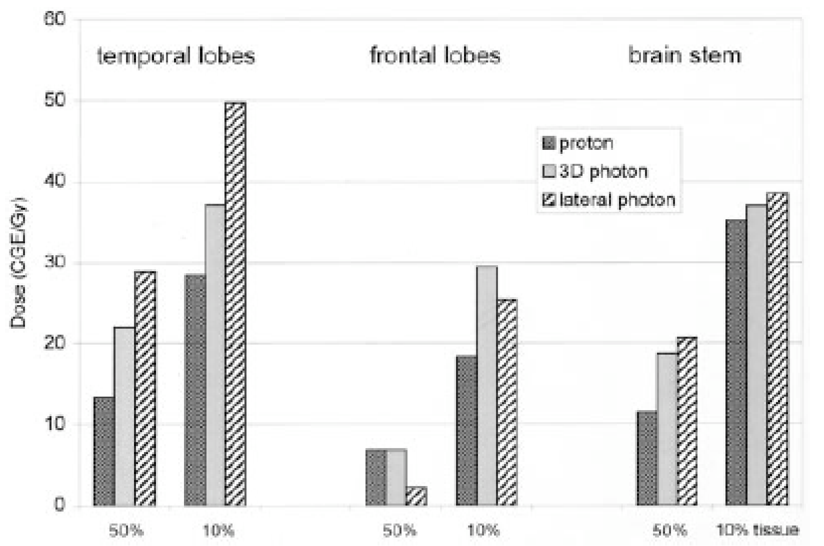
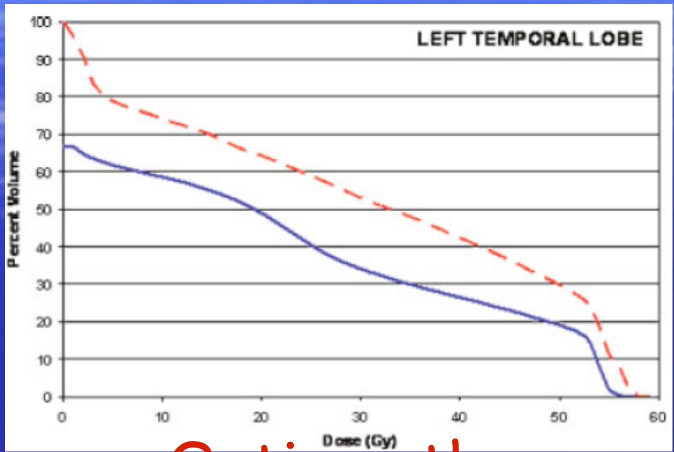
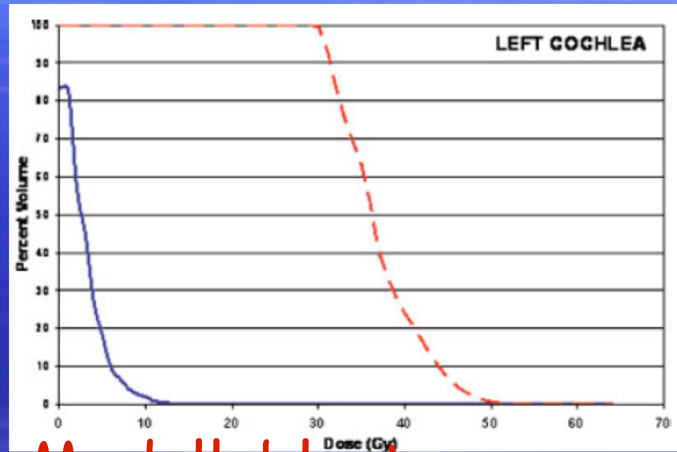


Fig. 6. Prescribed average treatment doses to 50% and 10% tissue volume (x-axis) of temporal lobes, frontal lobes, and brain stem. Y-axis: doses in CGE or Gy according to the displayed proton, 3D photon, or lateral beam photon technique.

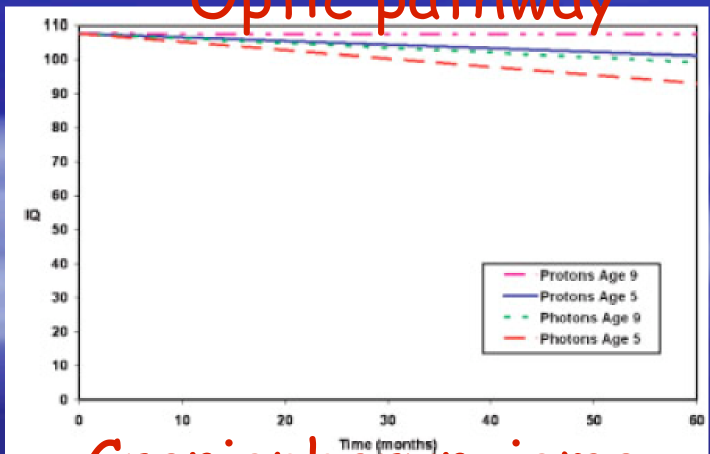
Protons vs photons (Merchant, PBC, 2008)



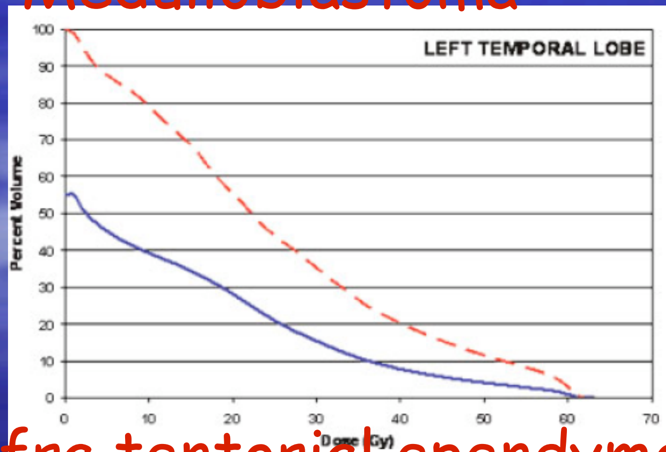
Optic pathway



Medulloblastoma



Craniopharyngioma



Infra tentorial ependymoma

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Conformation photons vs protons

(Baumert BG, IJROBP, 2001)

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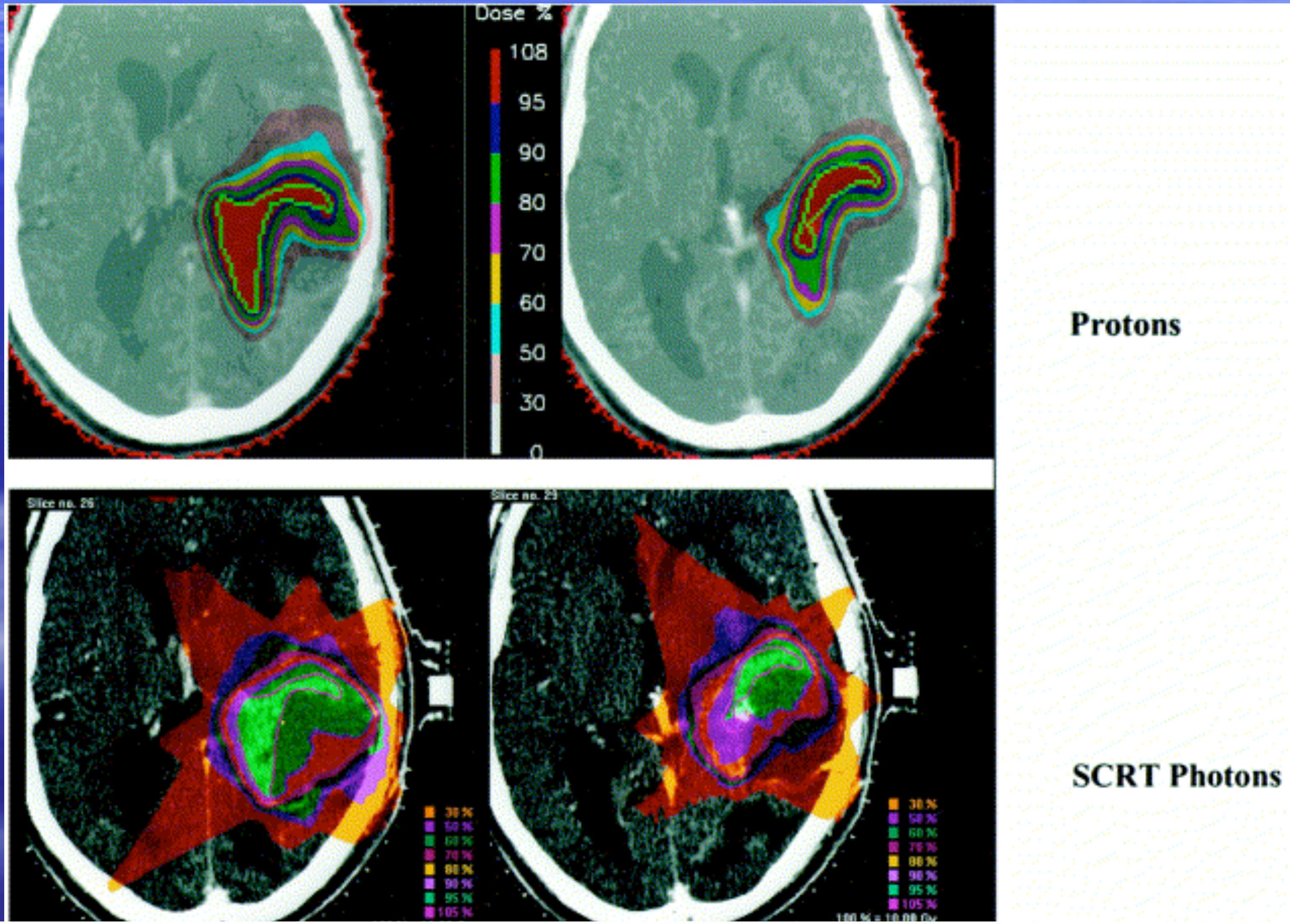
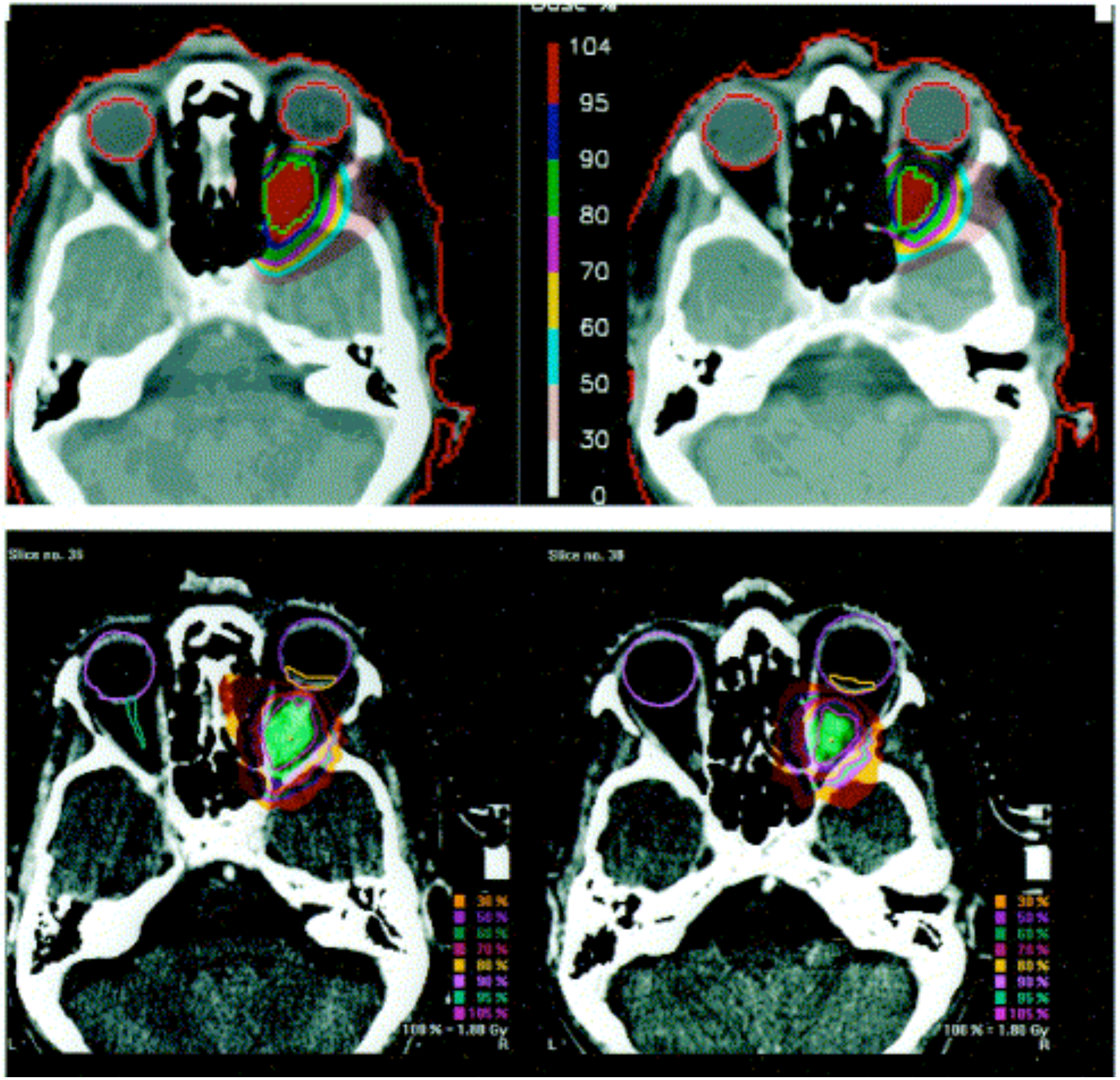
T concave: PTV P>X

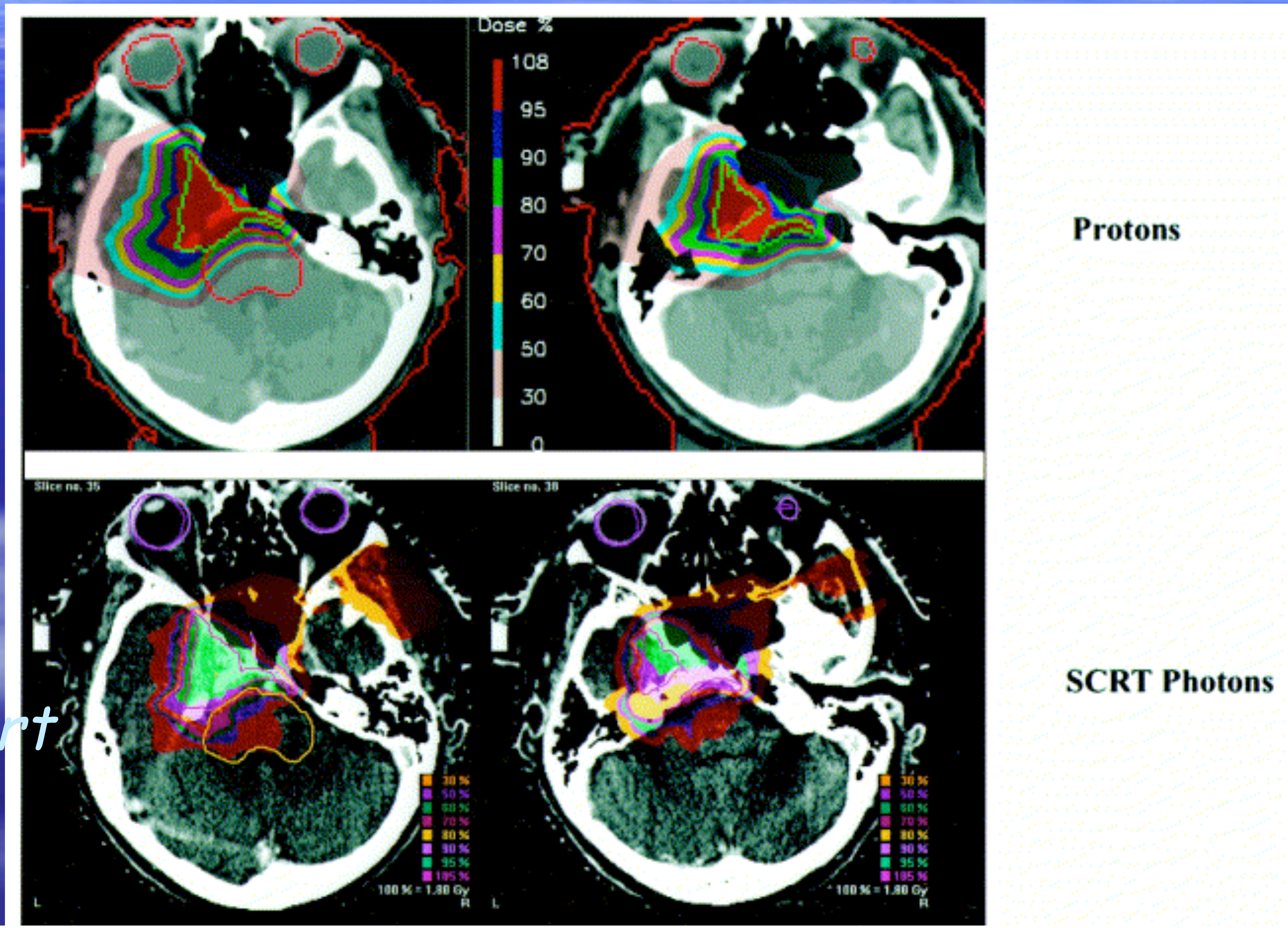


Elipsoid shape: PTV P=X

Baumert BG, IJROBP, 2001)



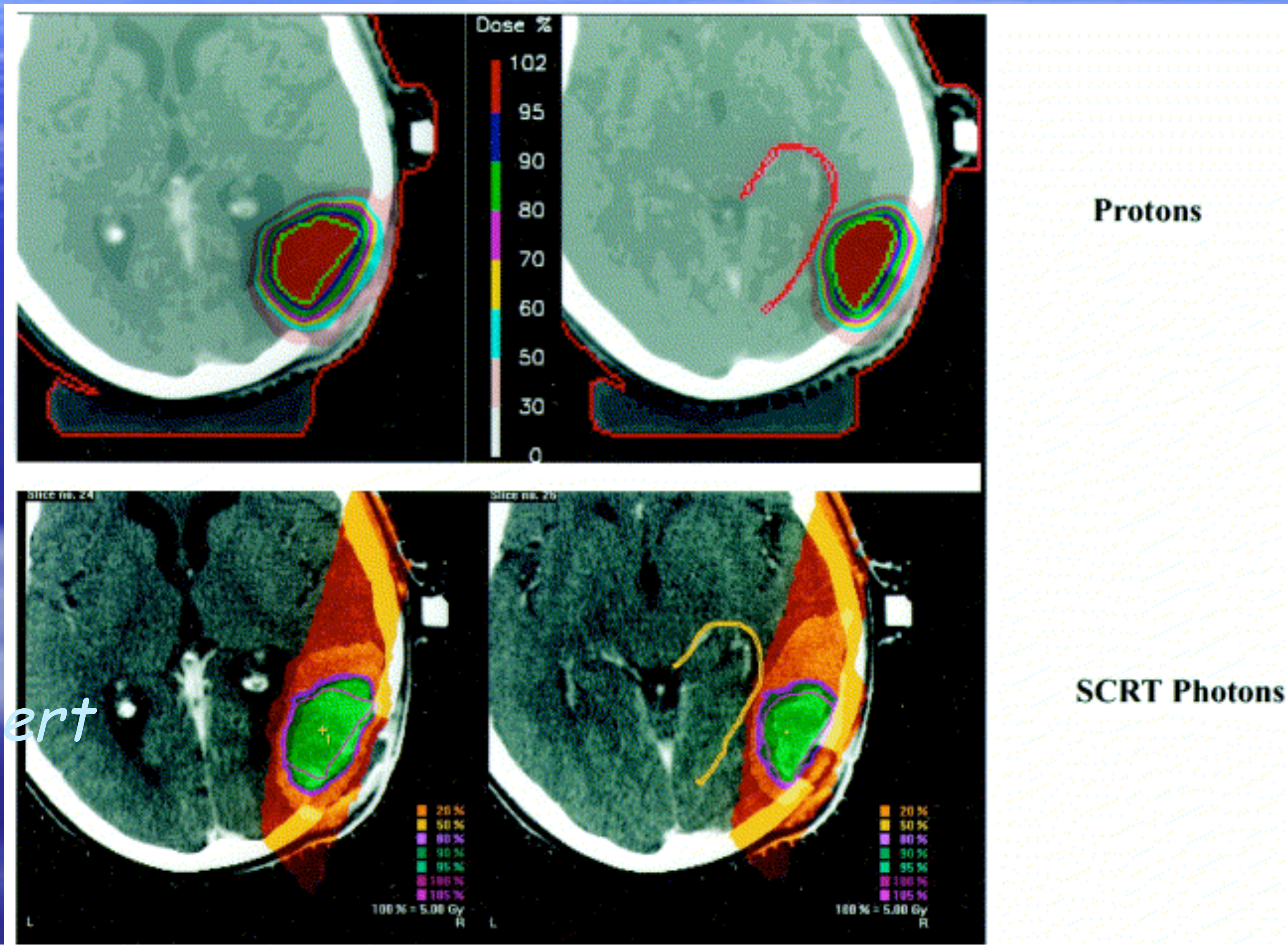
Irregular shape: PTV P>X



Baumert

e d'Orsay

Close OAR : PTV P>X



Baumert

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Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 4, pp. 979–984, 2000

0360-3016/00/$–see front matter

PII S0360-3016(00)00545-9

CLINICAL INVESTIGATION **Childhood Cancer**

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

EUGEN B. HUG, M.D.,*†‡§ JUDY ADAMS, C.M.D.,*† MARKUS FITZEK, 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

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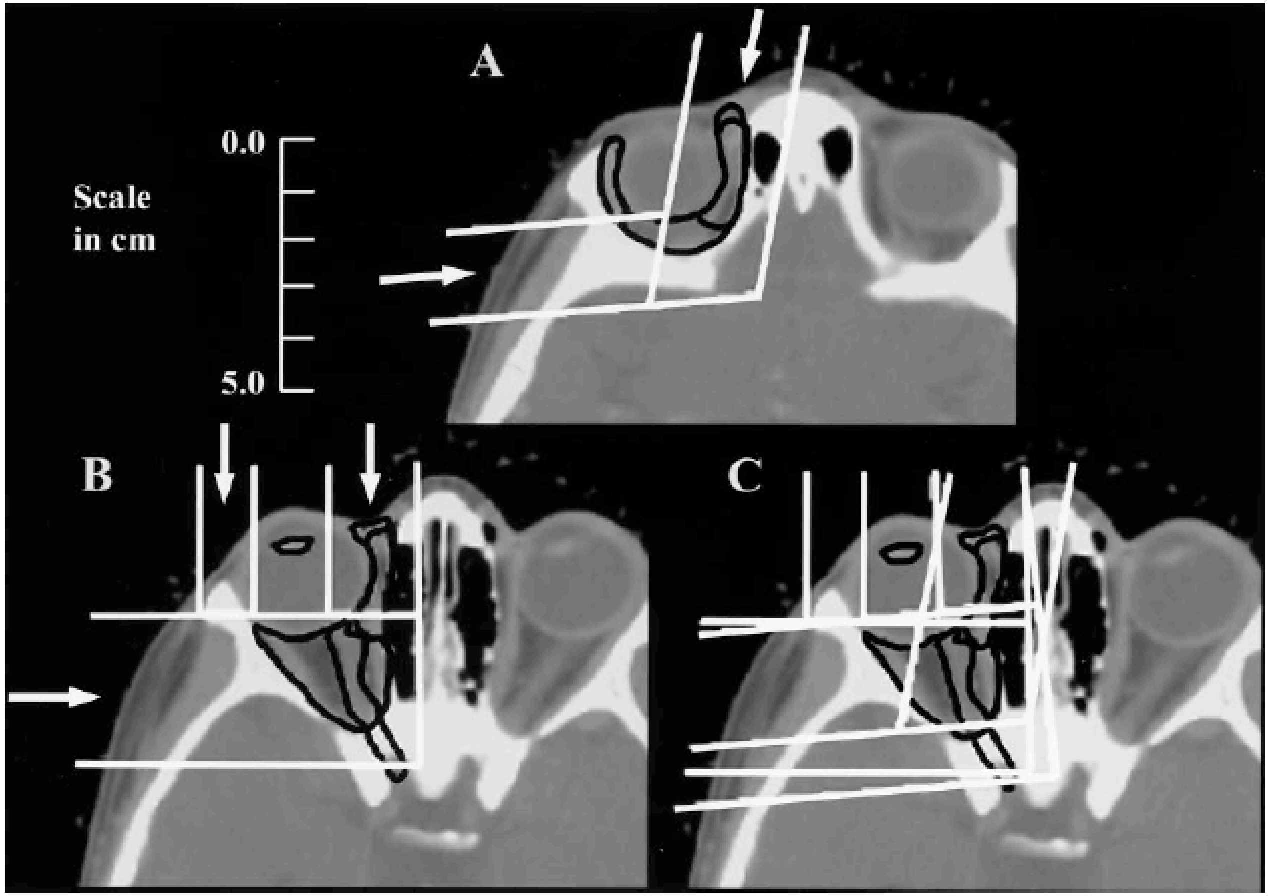

Fig. 1. Planning CT of patient A. Schematic outline of field arrangements. Patch field with sparing of lacrimal gland (A), lens-sparing patch field (B), and combined field arrangements (C).

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 4, pp. 1111–1119, 2000

0360-3016/00/$–see front matter

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PII S0360-3016(00)00494-6

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-Oncologie, Hôpitaux Universitaires, Genève; †Strahlenmedizin Abteilung, Paul Scherrer Institut, Villigen, Switzerland

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Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 4, pp. 1111–1119, 2000

0360-3016/00/$–see front matter

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PII S0360-3016(00)00494-6

PHYSICS CONTRIBUTION

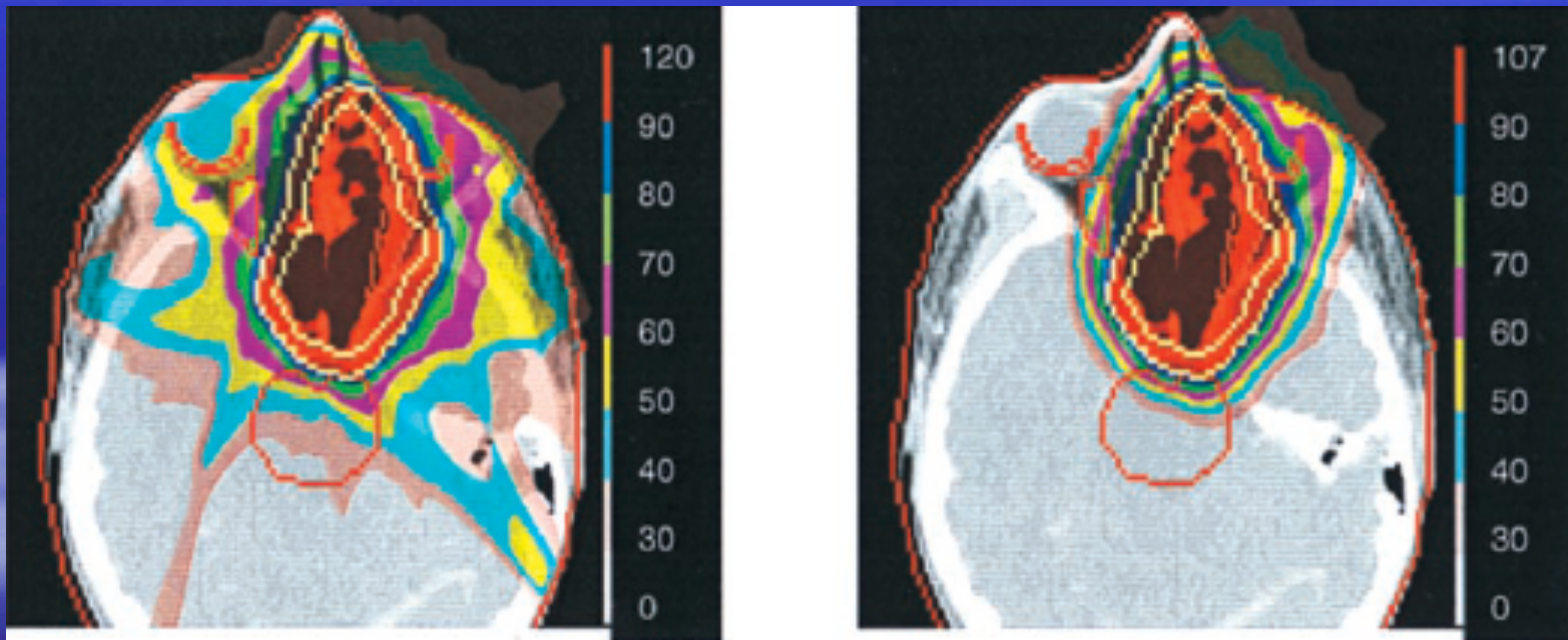
OPTIMIZING RADIOTHERAPY OF ORBITAL AND PARAORBITAL TUMORS: INTENSITY-MODULATED X-RAY BEAMS VS. INTENSITY-MODULATED PROTON BEAMS

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

*Division de Radio-Oncologie, Hôpitaux Universitaires, Genève; †Strahlenmedizin Abteilung, Paul Scherrer Institut, Villigen, Switzerland

IM X-rays

IM protons



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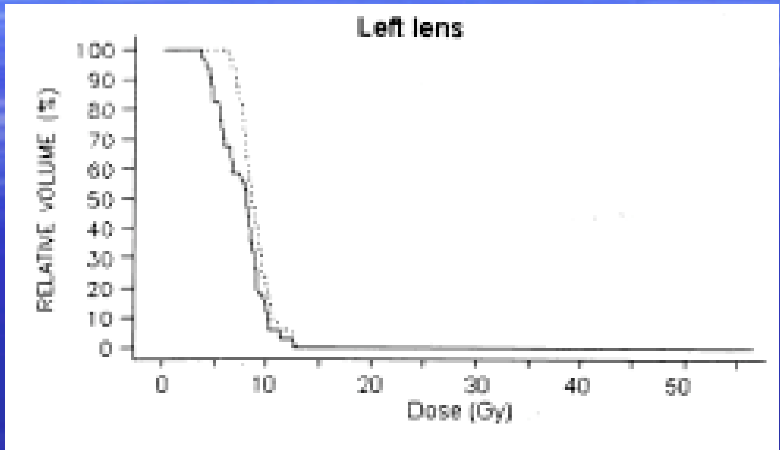
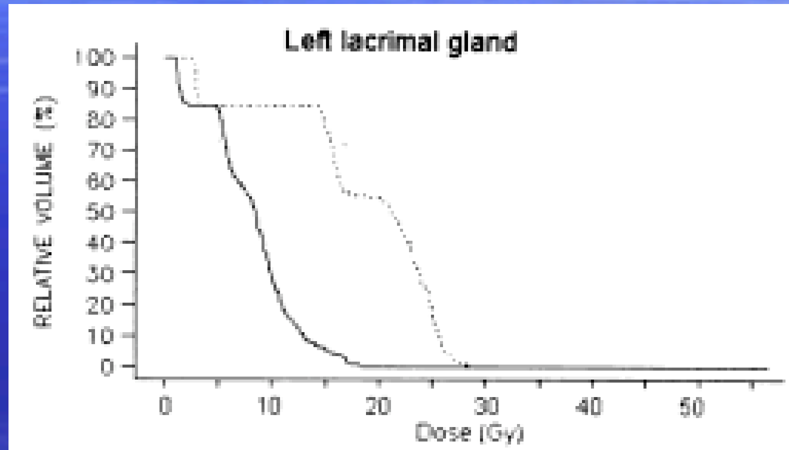
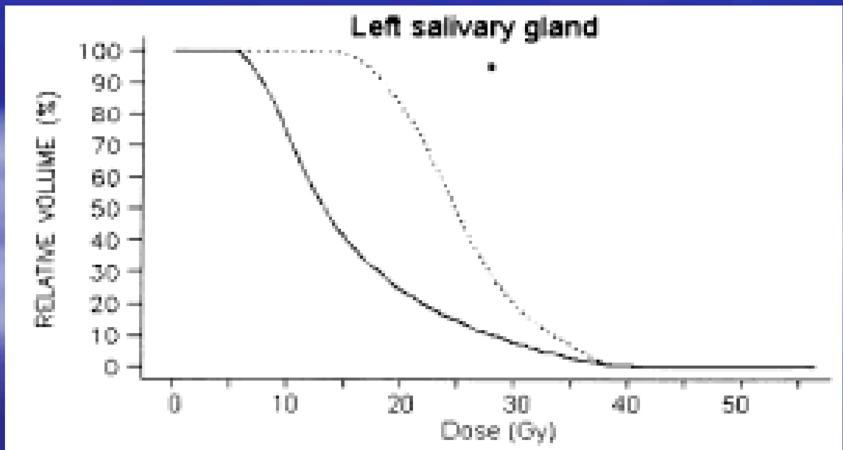
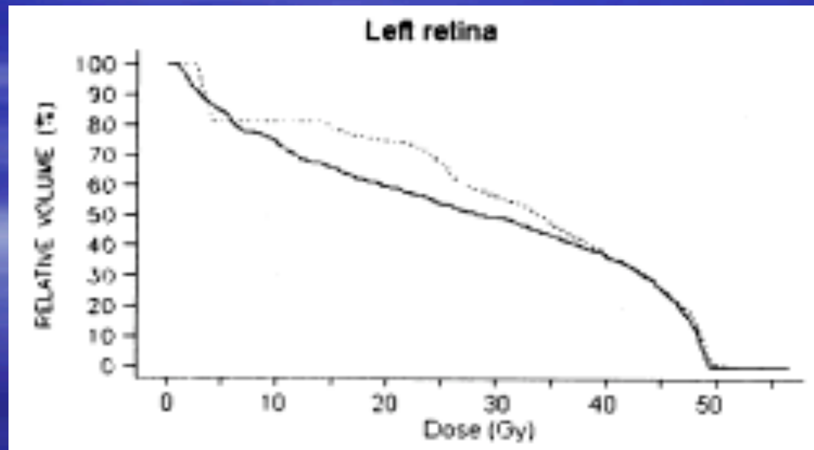
Normal structures: PM RMS









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PM RMS: Mean dose X IMRT-P

Organ at risk	X-rays	Protons
HL lens	8.8	7.6
HL lacrimal gland	18.4	8.0
HL retina	30.5	27.4
HL parotid	17.0	5.2
CL lens	7.5	6.6
CL lacrimal gland	12.6	8.0
CL retina	19.0	8.8
CL optic nerve	34.2	27.7
CL parotid	16.9	5.1
Optic chiasm	20.9	15.7
Pituitary gland		
Brain stem	21.9	14.6

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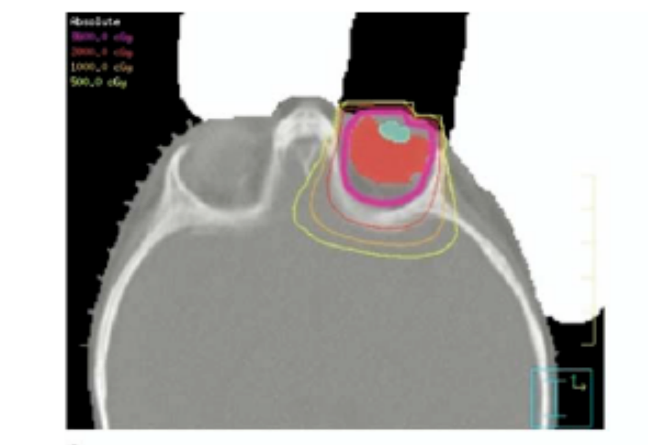
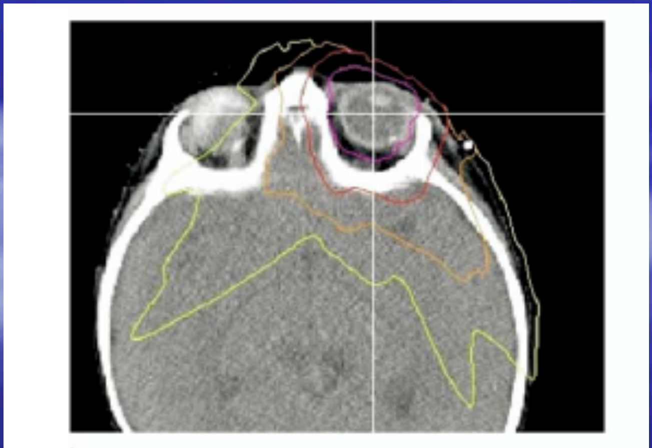
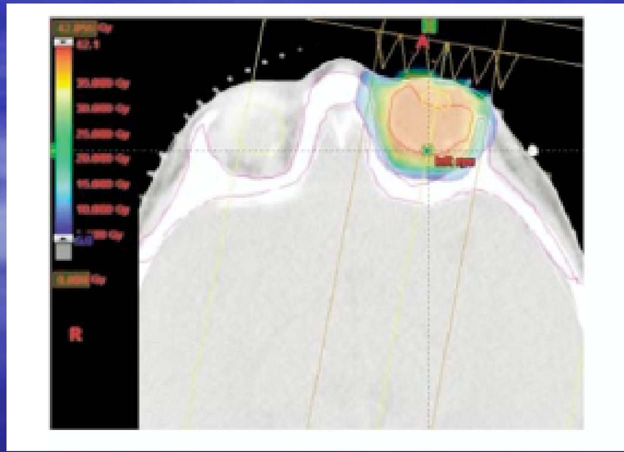
Retinoblastoma

(Lee CT et al, IJROBP, 2005)







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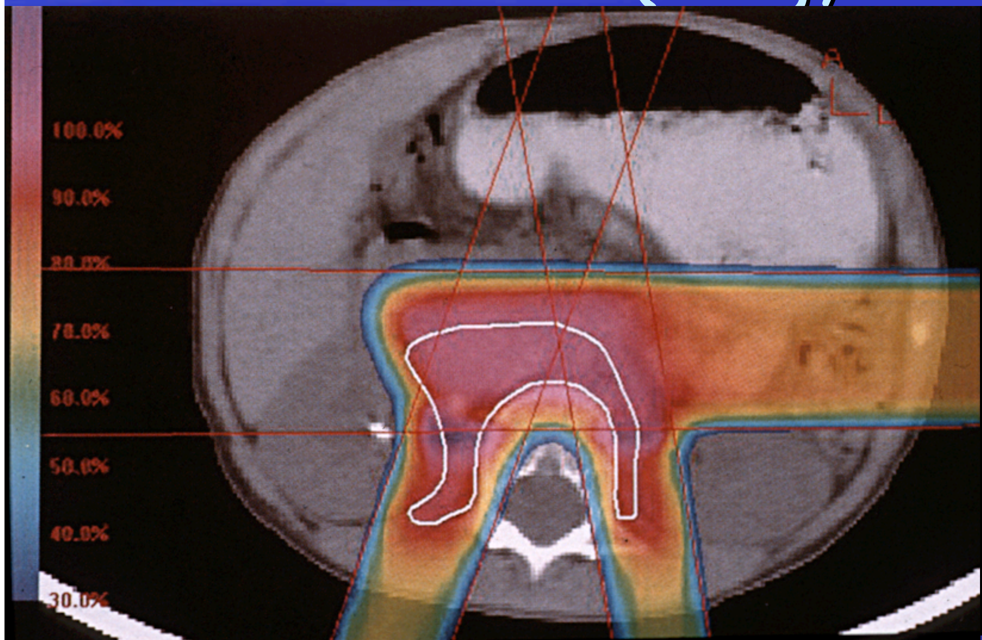
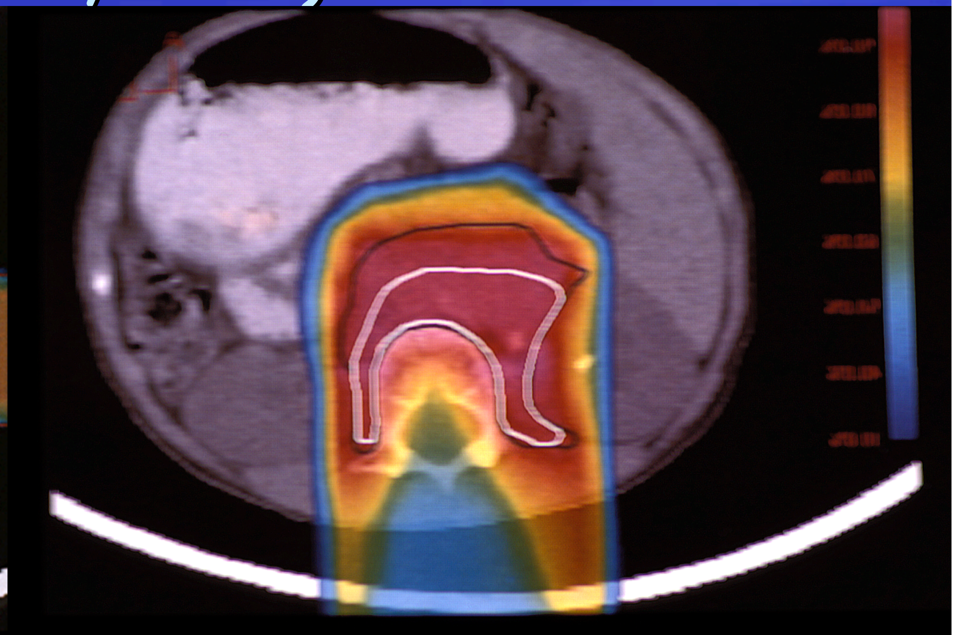
Proton therapy in children: neuroblastomas
(Hug, MPO,2001)





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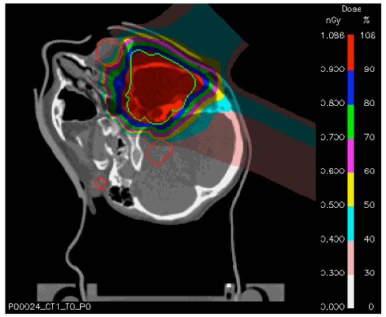
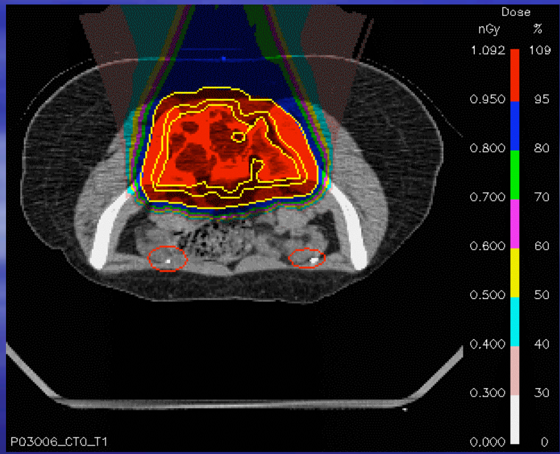
Spot-scanning benefit over passive scattering protons

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



Courtesy of B. Timmermann, PSI



Courtesy B Timmermann, PSI

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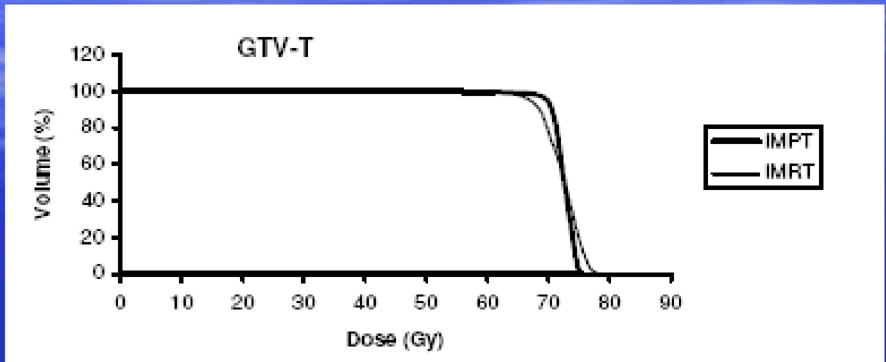
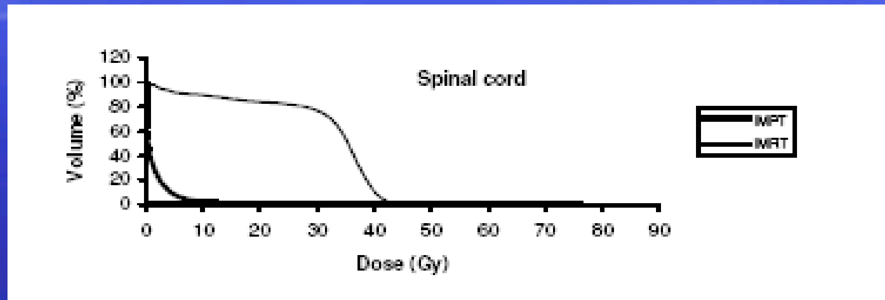
Nasopharynx: IMRT vs IMPT

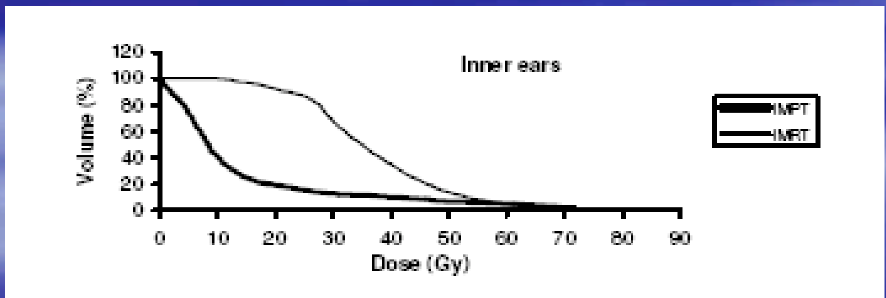
(Rad Oncol, Z Teheri-Kadkhoda, 2008)

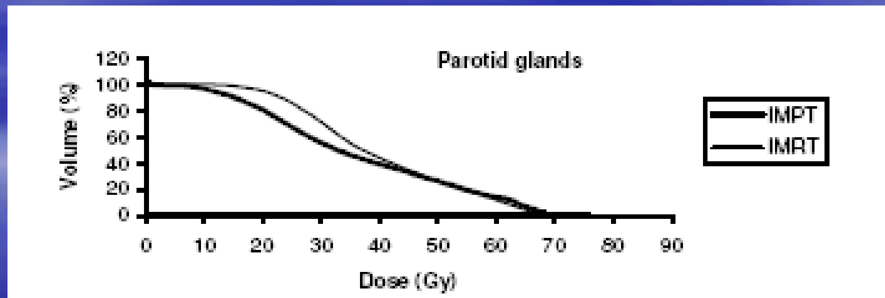
- 6 adults , 2 children
- T1 to T4
- Prescribed (Gy/CGE): GTV: 72.6, PTV: 66, N:52.8
- Respect: homogeneity: +7/-5%; GTV:95/95% dose; Max:< 105%

Nasopharynx: OARs









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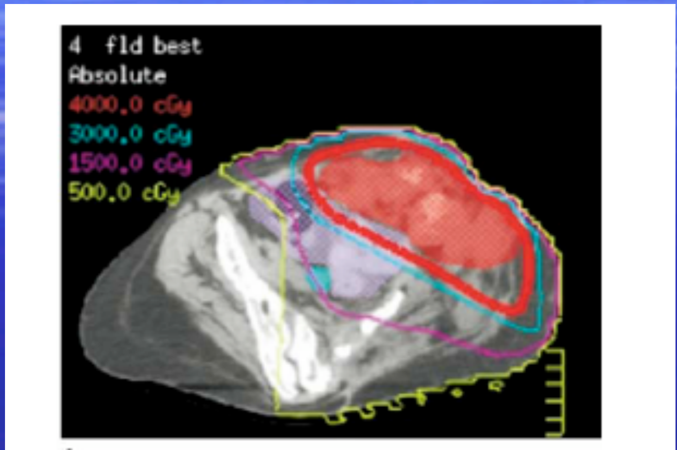
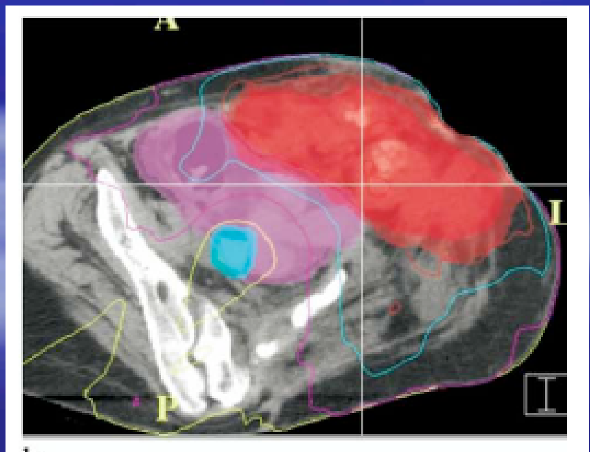
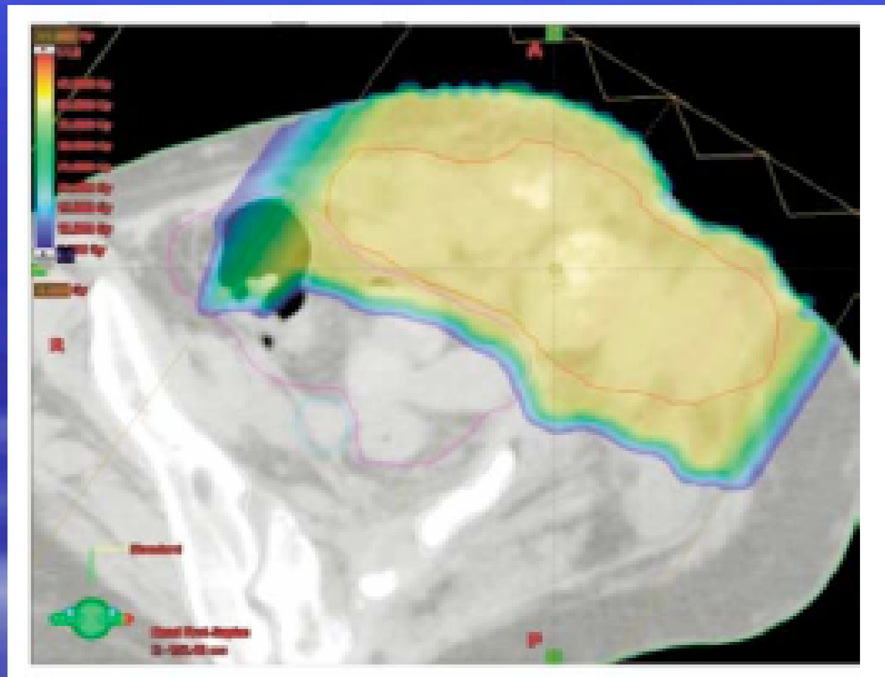
Pelvic sarcomas
(Lee CT et al)







Proton therapy in pediatrics:

CLINICAL EVIDENCES

Not so many…

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Int. J. Radiation Oncology Biol. Phys., Vol. 52, No. 4, pp. 1017–1024, 2002

0360-3016/02/$–see front matter

PII S0360-3016(01)02725-0

CLINICAL INVESTIGATION **Pediatric Tumors**

PROTON RADIOTHERAPY IN MANAGEMENT OF PEDIATRIC BASE OF SKULL TUMORS

Eugen B. Hug, M.D.,[*†‡§] Reinhart A. Sweeney, M.D.,[‡] Pamela M. Nurre, B.S., R.T.(T.),[‡] Kitty C. Holloway, R.T.,(R.)(T.),[‡] Jerry D. Slater, M.D.,[‡] and John E. Munzenrider, M.D.[*]

[*]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

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Hug (cont)

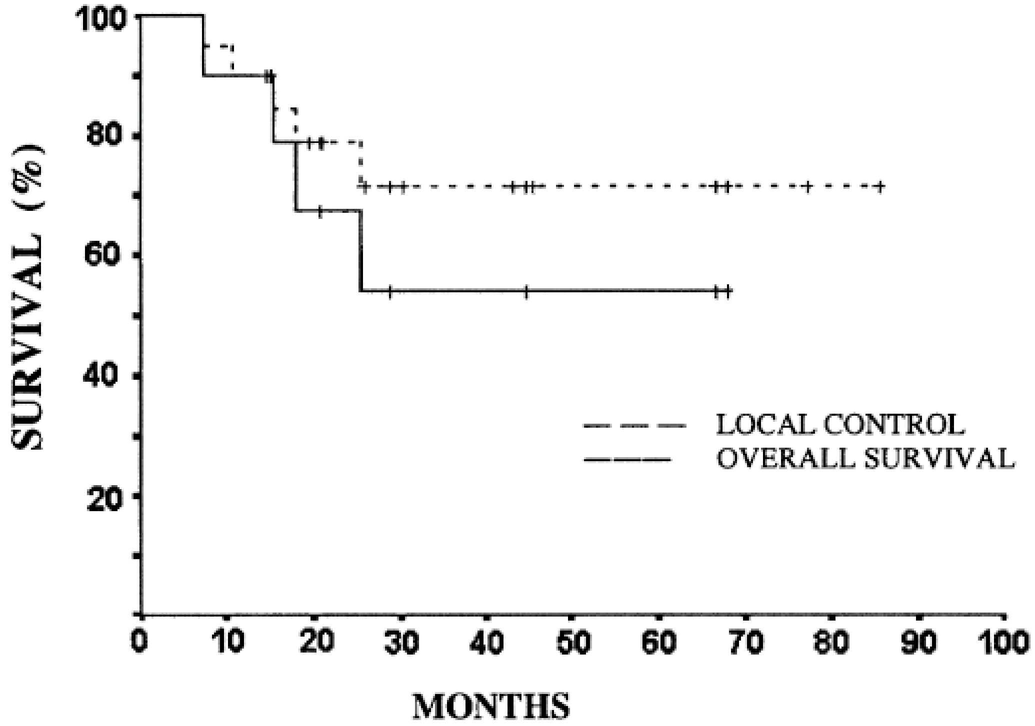

Fig. 3. Actuarial rates of local control and overall survival of 20 pediatric patients with malignant skull base tumors after high-dose, conformal proton or combined proton/photon RT.

Hug (cont)

Table 2. Treatment results in 29 pediatric and adolescent patients with mesenchymal tumors of the skull base

Histologic findings (No. of patients)	Patterns of failure* (*n*)			Outcome (%)		
	Local	Surgical access	Distant	Local control	Overall control	Overall survival
Malignant (20)	5	1	3	15/20 (75)	11 (55)	13 (65)
Chordomas (10)	4	1	1	6/10 (60)	4 (40)	6 (60)
Chondrosarcomas (3)	0	0	0	3/3 (100)	3 (100)	3 (100)
Rhabdomyosarcomas (4)	0	0	2	4/4 (100)	2 (50)	2 (50)
Others† (3)	1	0	0	2/3 (66)	2/3 (66)	2/3 (66)
Benign (9)	1	0	0	8 (89)	8 (89)	9 (100)
Giant cell (6)	1	0	0	5 (83)	5 (83)	6 (100)
Angiofibromas (2)	0	0	0	2 (100)	2 (100)	2 (100)
Chondroblastoma (1)	0	0	0	1	1	1

* No regional failures noted.
† Myxoid sarcoma, epithelioid sarcoma, malignant fibrous histiocytoma.

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Med Pediatr Oncol 2003;40:309–315

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, PhD[1,4]

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 upto 69 CGE and with an excellent local control rate. Med Pediatr Oncol 2003;40:309–315.

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

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Child's set up in Orsay

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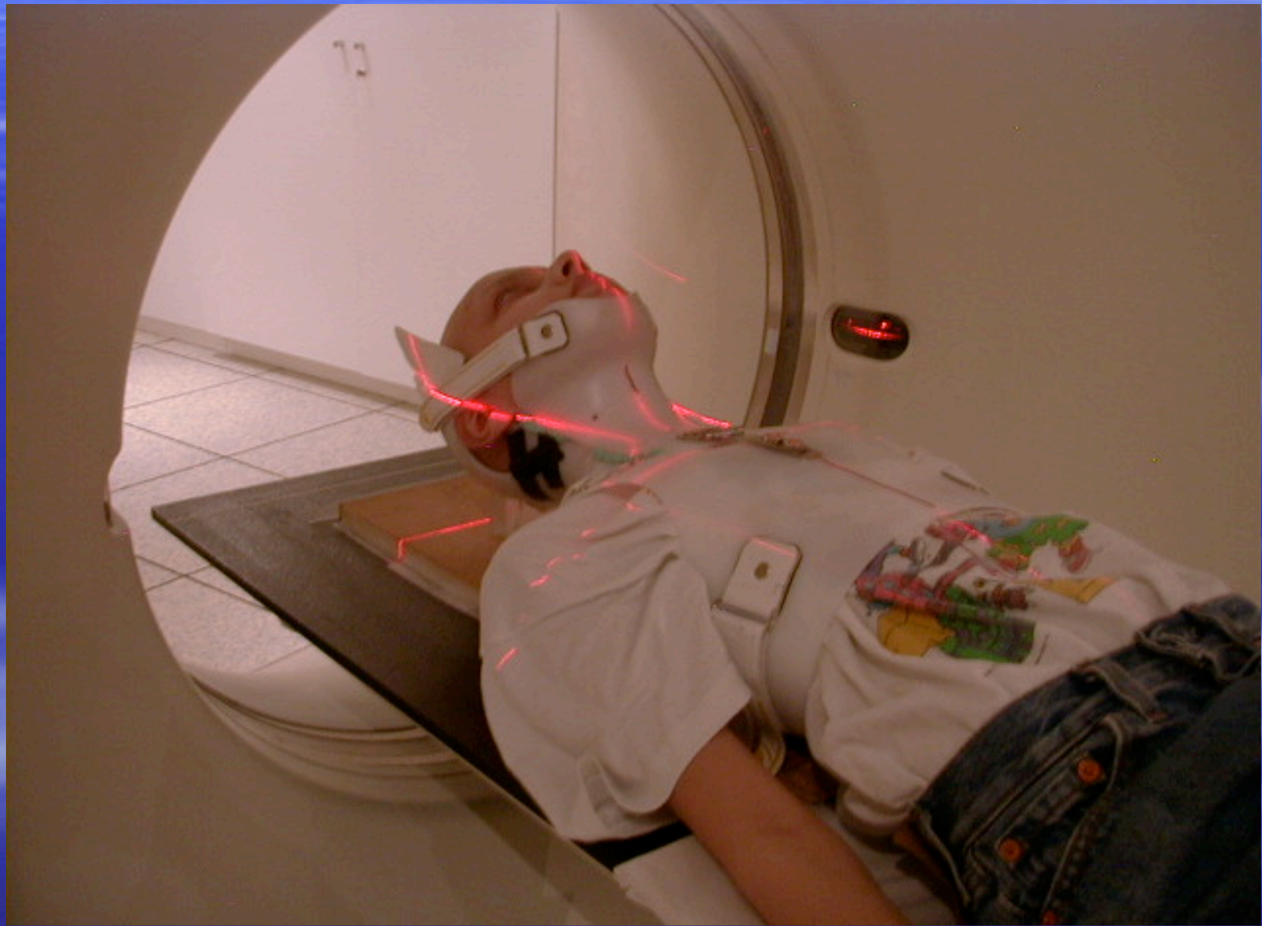
Adolescent imaging with acrylic cast



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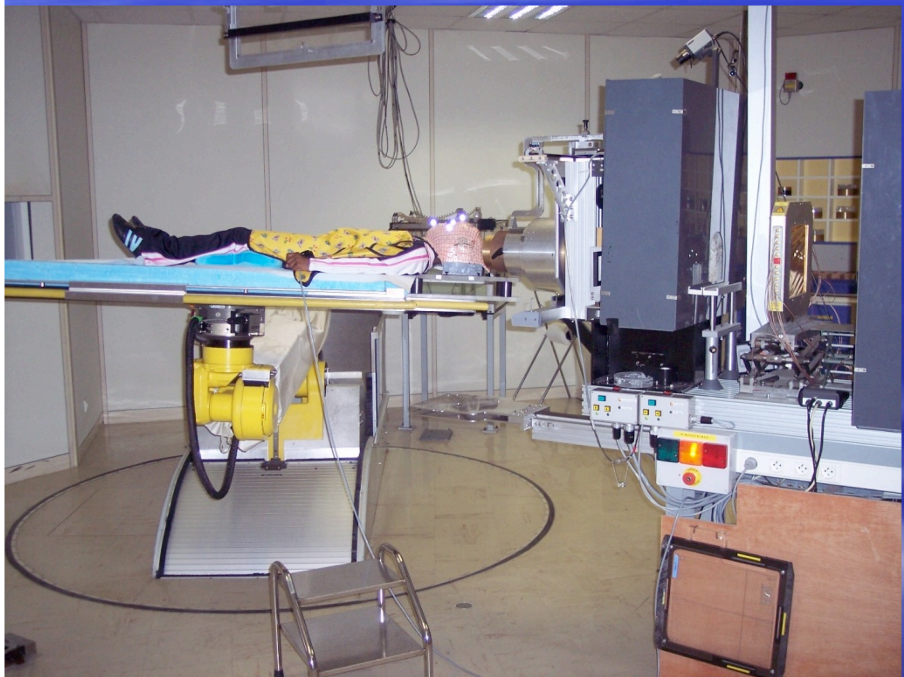
General anesthesia: Children < 4Y



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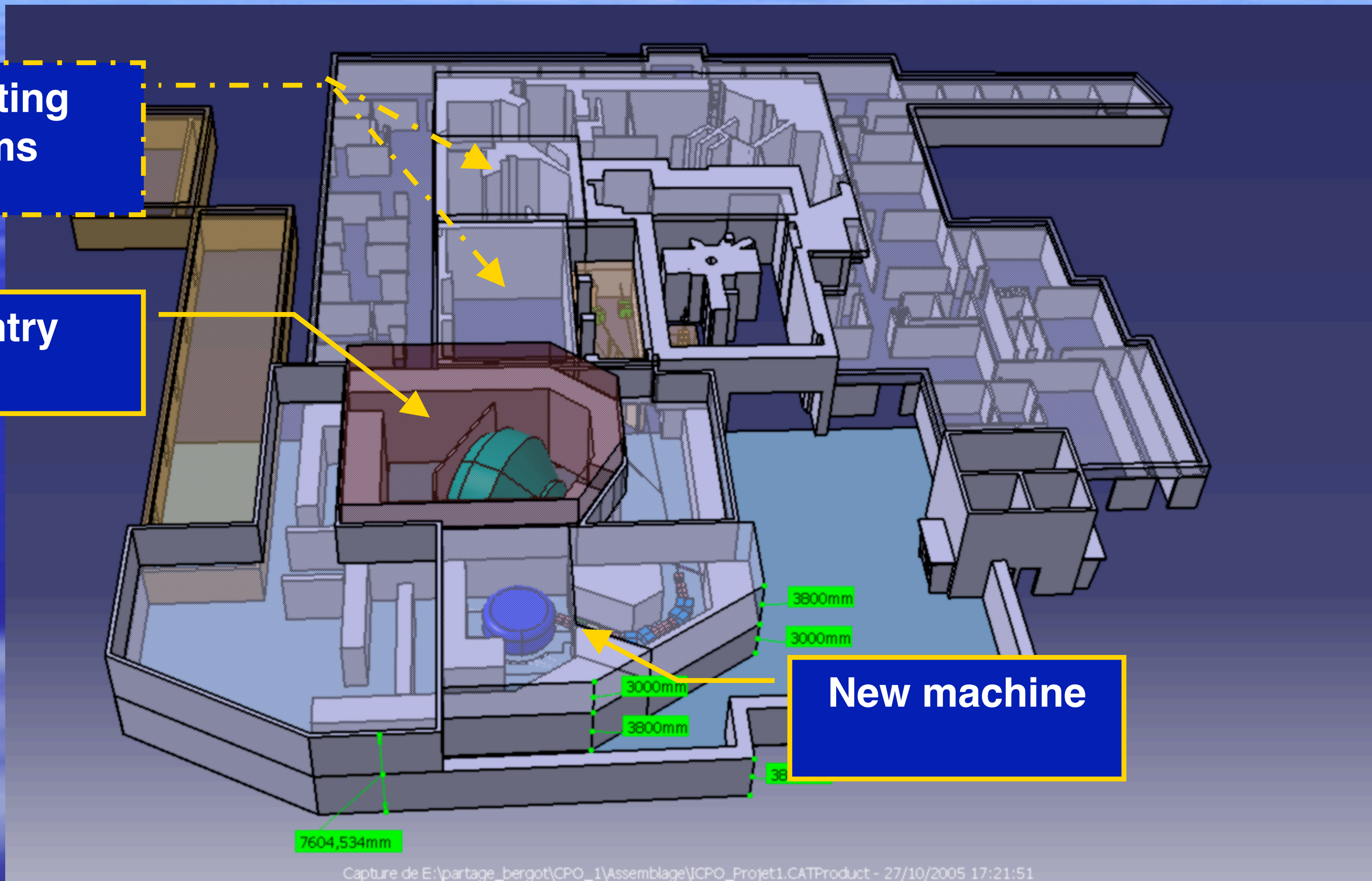
New CPO Center



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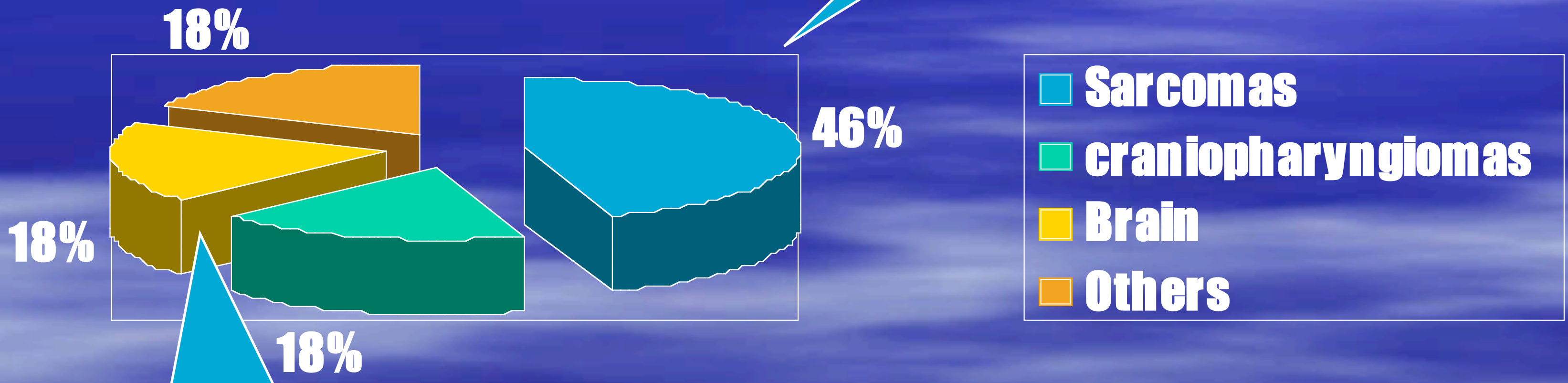
PEDIATRIC CNS TUMORS: ORSAY SERIES (08/05):Tumor types

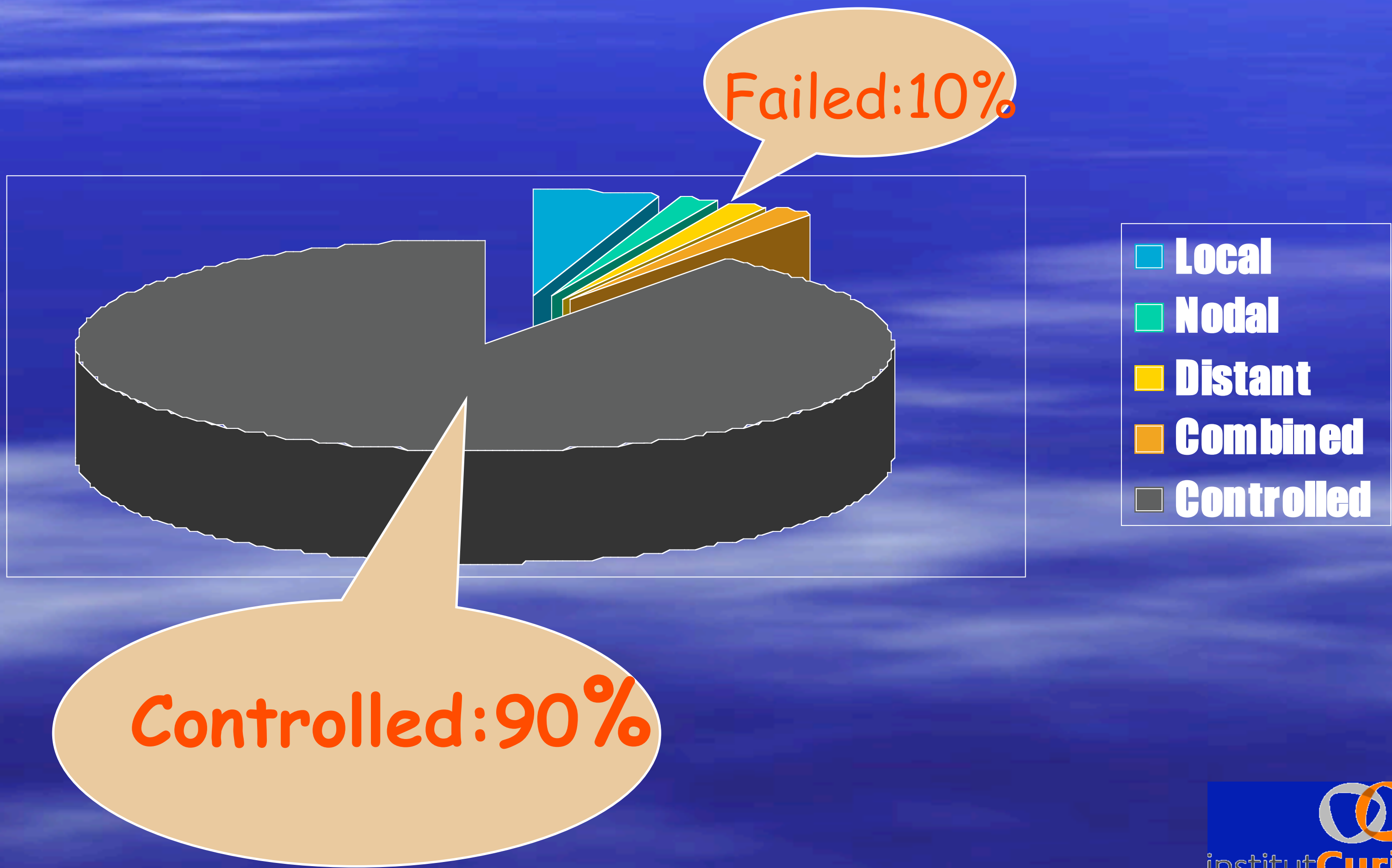
1994-2005: 60 pts

22CH, 4CS,3soft,1Osteo



4glio,6mening,1PNET,
1pblastom

PEDIATRIC CNS TUMORS: ORSAY SERIES (08/05):outcome



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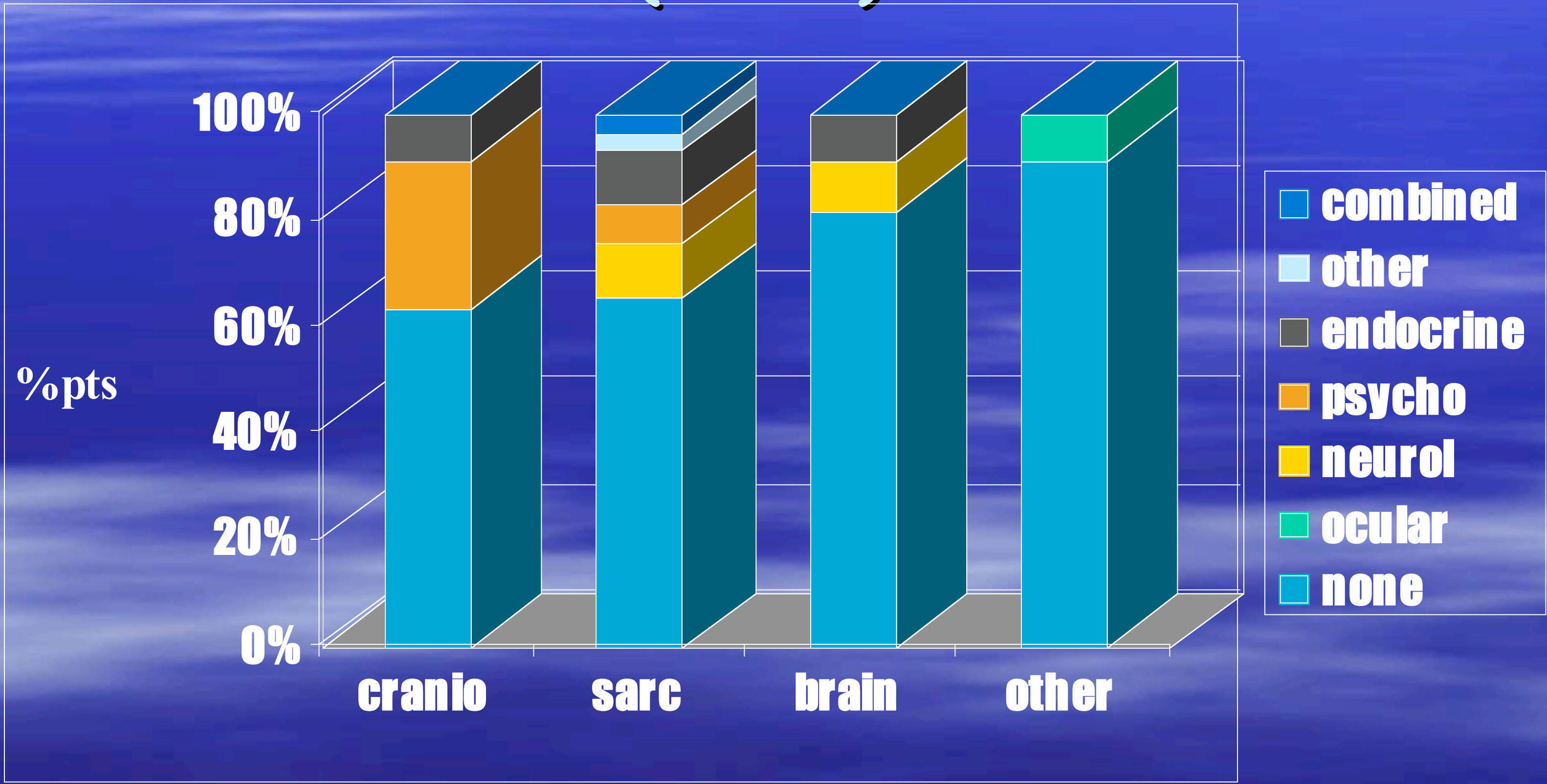
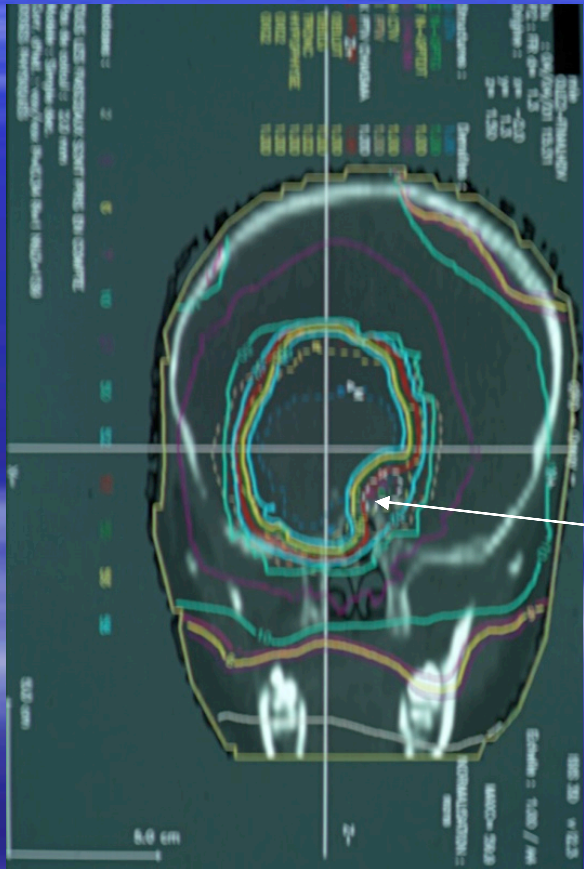
PEDIATRIC CNS TUMORS: ORSAY SERIES (08/05):Toxicity (cont)



MENINGIOMAS : PEDIATRIC CASE



Chiasm shielding

Previously irradiated with γ knife

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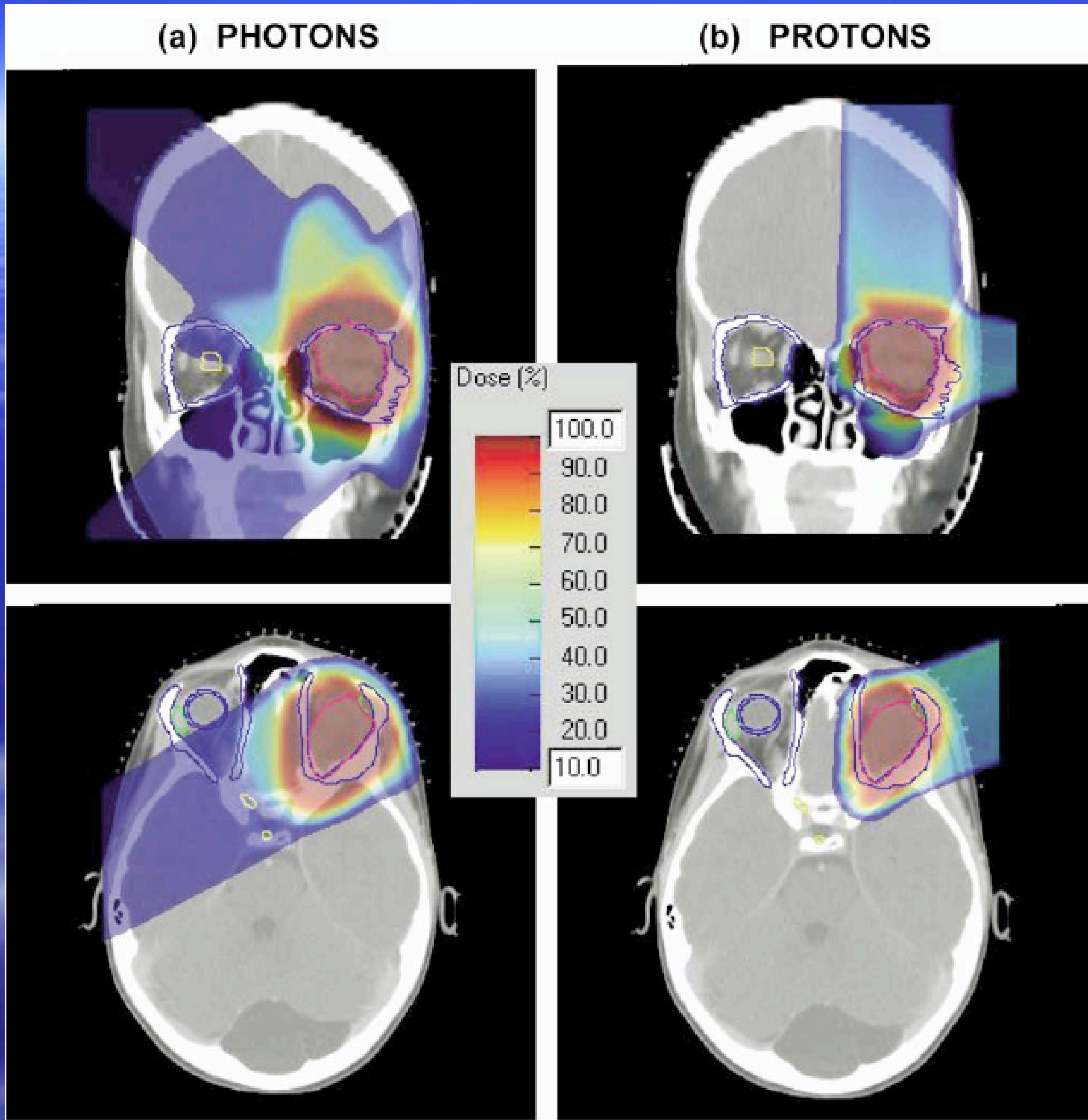
PROTON RADIOTHERAPY FOR ORBITAL RHABDOMYOSARCOMA: CLINICAL OUTCOME AND A DOSIMETRIC COMPARISON WITH PHOTONS

TORUNN YOCK, M.D., M.C.H., ROBERT SCHNEIDER, C.M.D., ALISON FRIEDMANN, M.D., JUDITH ADAMS, C.M.D., BARBARA FULLERTON, PH.D., AND NANCY TARBELL, M.D.

Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

- 7 children
- Med dose: 46.6 CGE
- Med FUp: 6.3 Y
- Local control: 6/7
- Sequelae: excellent vision preserv, mild orbital asymetry, no pituitary dysfunction



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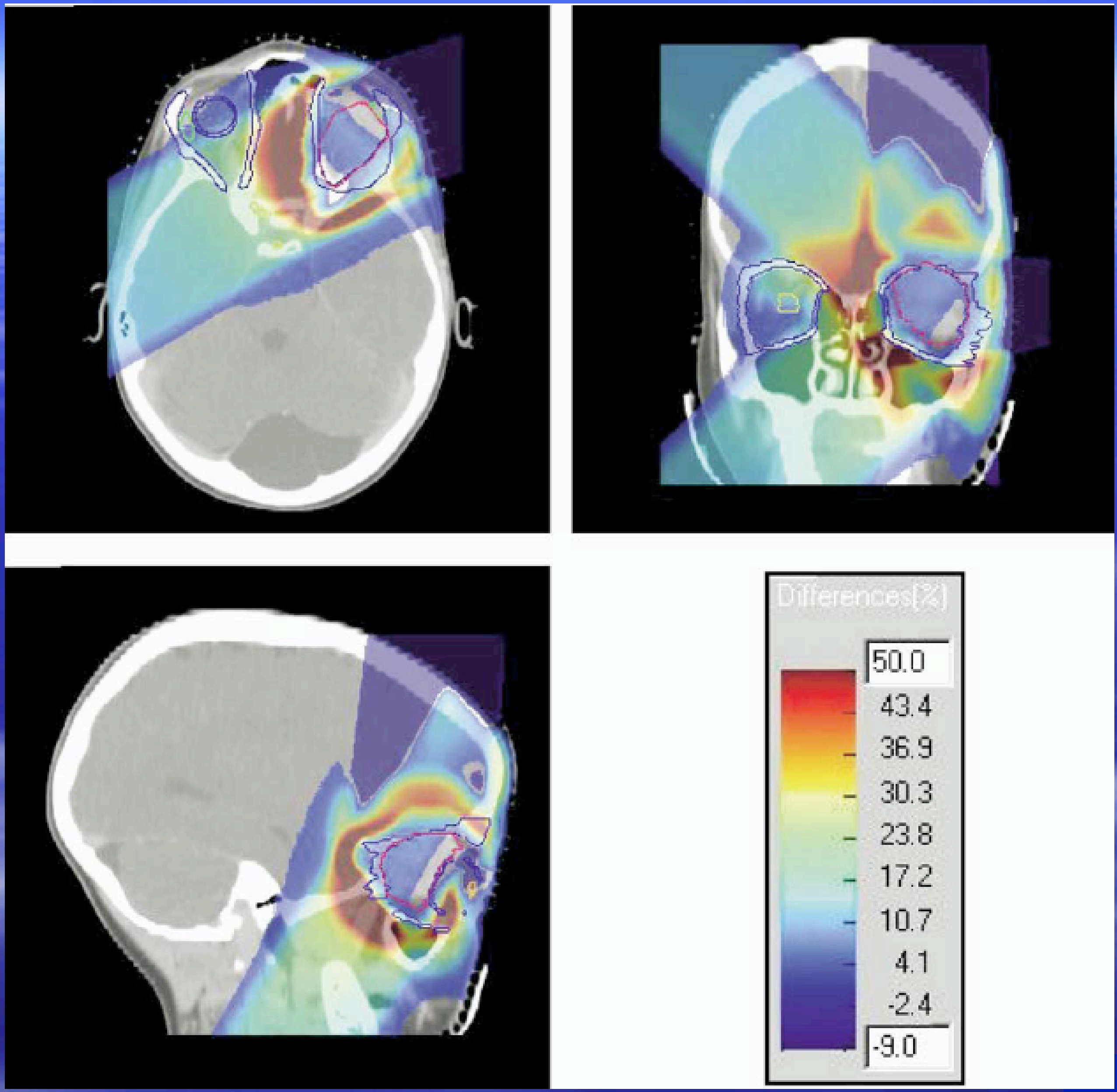

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Ipsilateral orbital structures	X-ray dose average (%)*	Proton dose average (%)*	Difference (%)	Percent savings†
Retina	73.8	53.4	20.4	27.6
Optic nerve	86.1	62.9	23.1	26.9
Orbital bone	83.0	53.9	29.1	35.0
Lens	61.5	21.4	40.1	65.1
Lacrimal gland	94.3	69.8	24.5	26.0

* Mean average of the 90%, 50%, and 10% DVH values for all 7 patients.
† Percent savings: Difference of the means per structure/photon average × 100.

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Contralateral orbital structures	X-ray dose average (%)*	Proton dose average (%)*	Difference (%)	Percent savings†
Orbital bone	11.3	0.8	10.5	93.2
Lens	3.3	0.8	2.5	76.8
Lacrimal gland	2.8	0.7	2.1	74.6
Retina	6.2	0.6	5.6	90.8
Optic nerve	15.2	0.7	14.5	95.3

* Mean average of the 90%, 50%, 10% DVH values for all 7 patients.
† Percent savings: Difference of the means per structure/photon average × 100.

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Structure	X-ray dose average (%)*	Proton dose average (%)*	Difference (%)	Percent savings[†]
Hypothalamus	6.3	0.7	5.6	88.7
Pituitary	21.7	1.3	20.4	94.1
Brain	10.4	1.2	9.1	88.1
Temporal lobe (contralateral)	6.3	0.7	5.6	88.6
Temporal lobe (ipsilateral)	18.1	3.3	14.8	81.8
Chiasm	19.8	1.9	17.9	90.4

* Mean average of the 90%, 50%, and 10% DVH values for all 7 patients.
[†] Percent savings: Difference of the means per structure/photon average × 100.

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Proton radiotherapy for childhood ependymoma (MacDonald et al, IJROBP,2008)

- 17 cases (4 supra tent, 11 infra tent)
- Age: 13 m-13 Y
- Med dose: 55.8 CGE
- Med F Up: only 26 m
- Loc failure: 1/17
- PFS: 86%; OS: 89%
- Toxicity ?

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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.*

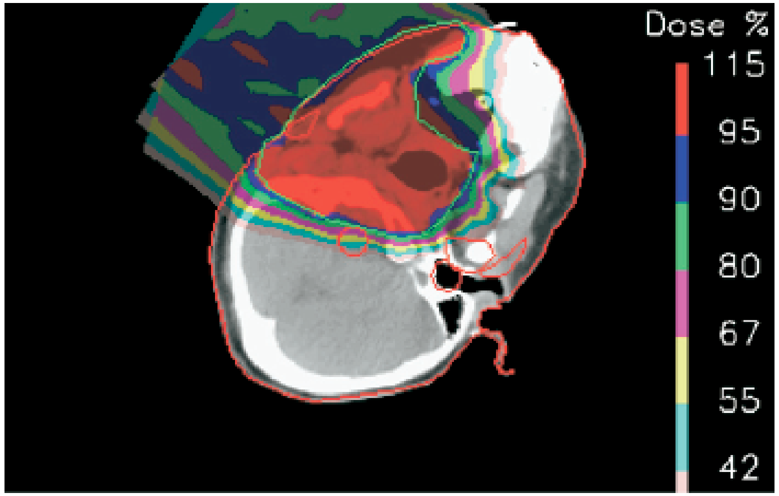

Fig. 1. Example of the dose distribution for "conventional" proton therapy of a parameningeal rhabdomyosarcoma in a 13-year-old girl. Thin green line: planning target volume.

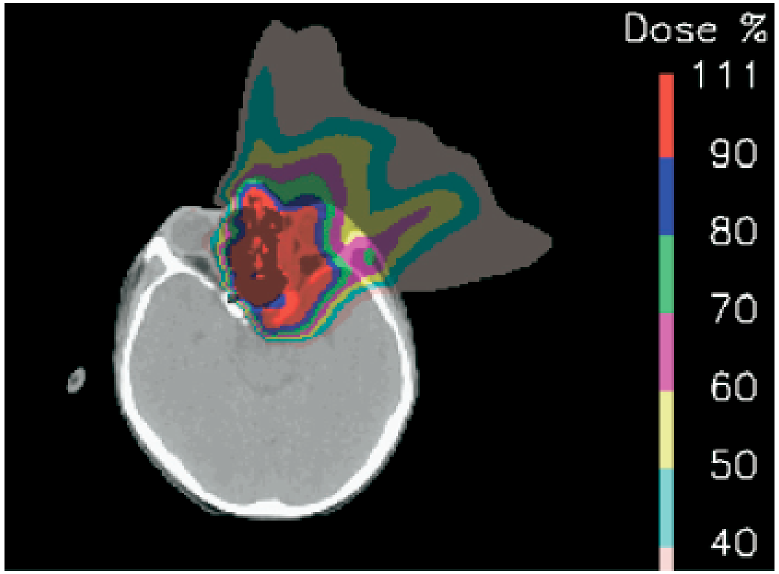

Fig. 2. Example of an intensity-modulated proton therapy plan with sparing of the lacrimal gland for a 12-year-old boy with an orbital rhabdomyosarcoma initially infiltrating the surrounding soft tissue.

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Timmermann B (cont)

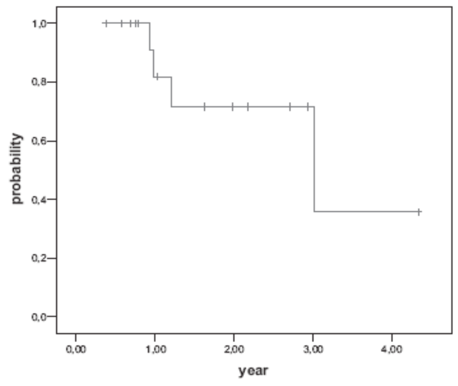

Fig. 3. Kaplan-Meier plot of the estimated progression-free survival rates.

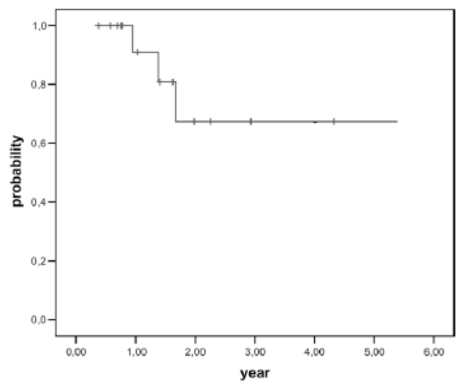

Fig. 4. Kaplan-Meier plot of the estimated overall survival rates.

Table 2. Acute toxicity related to proton therapy

Critical organ	Patients evaluable (*n*)	Grade 0	Grade I	Grade II	Grade III	Grade IV
Karnofsky	16	13	3	—	—	—
Bone marrow	13	—	1	5	4	3
Skin	16	1	11	4	—	—
Mucosa	13	2	5	6	—	—
GI tract	3	3	—	—	—	—
GU tract	2	2	—	—	—	—
CNS	13	13	—	—	—	—
Eye	12	5	5	2	—	—
Ear	12	11	1	—	—	—

Abbreviations: GI = gastrointestinal; GU = genitourinary; CNS = central nervous system.

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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)

Radiation-Induced Events per 100 Patients

Variable	Hearing loss	Hypothyroidism	Osteoporosis	GHD	Nonfatal secondary malignancies	Fatal events
Conventional radiation	11.9	16.3	0.4	17.1	[illegible]	1.91
Proton radiation	1.4	2.7	0.1	2.0	[illegible]	0.38
Difference	10.5	13.6	0.3	15.1	[illegible]	1.53

GHD: growth hormone deficiency.

Distribution of Cost and Utility Differences: Proton Radiation versus Conventional Radiation

Cost source	Cost difference (€)	Utility difference
Total difference	−23646.5	[illegible]
Radiation	[illegible]	—
IQ loss	−12206.9	—
Hearing loss	−2735.5	0.057
GHD	−14263.2	0.367
Hypothyroidism	−202.0	0.009
Osteoporosis	−18.3	0.001
Fatal and nonfatal secondary malignancies	95.6	0.021
Other fatal adverse events	—	0.230

IQ: intelligence quotient; GHD: growth hormone deficiency.

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Conclusion

- ***Considerable potentialities*** *of protontherapy in children, esp brain, head & neck, trunk sarcomas*
- ***Pediatrics*** *is becoming a major component of proton projects*
- ***Reduced long term toxicity*** *(cochlea, pituitary, cognition, K2…), and improved cost*

effectiveness: future challenges

CPO :
G Noel, MD
L Feuvret, MD
R Ferrand, PhD
C Gauthier, RT
A Leroy, RT…

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

IGR :
- O Oberlin, MD

F Dhermain, MD

J Datchary, MD

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P Bey,MD
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Thank you !

iba Particle Therapy

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