L'hadronthérapie, Indications cliniques *En neuro-oncologie*

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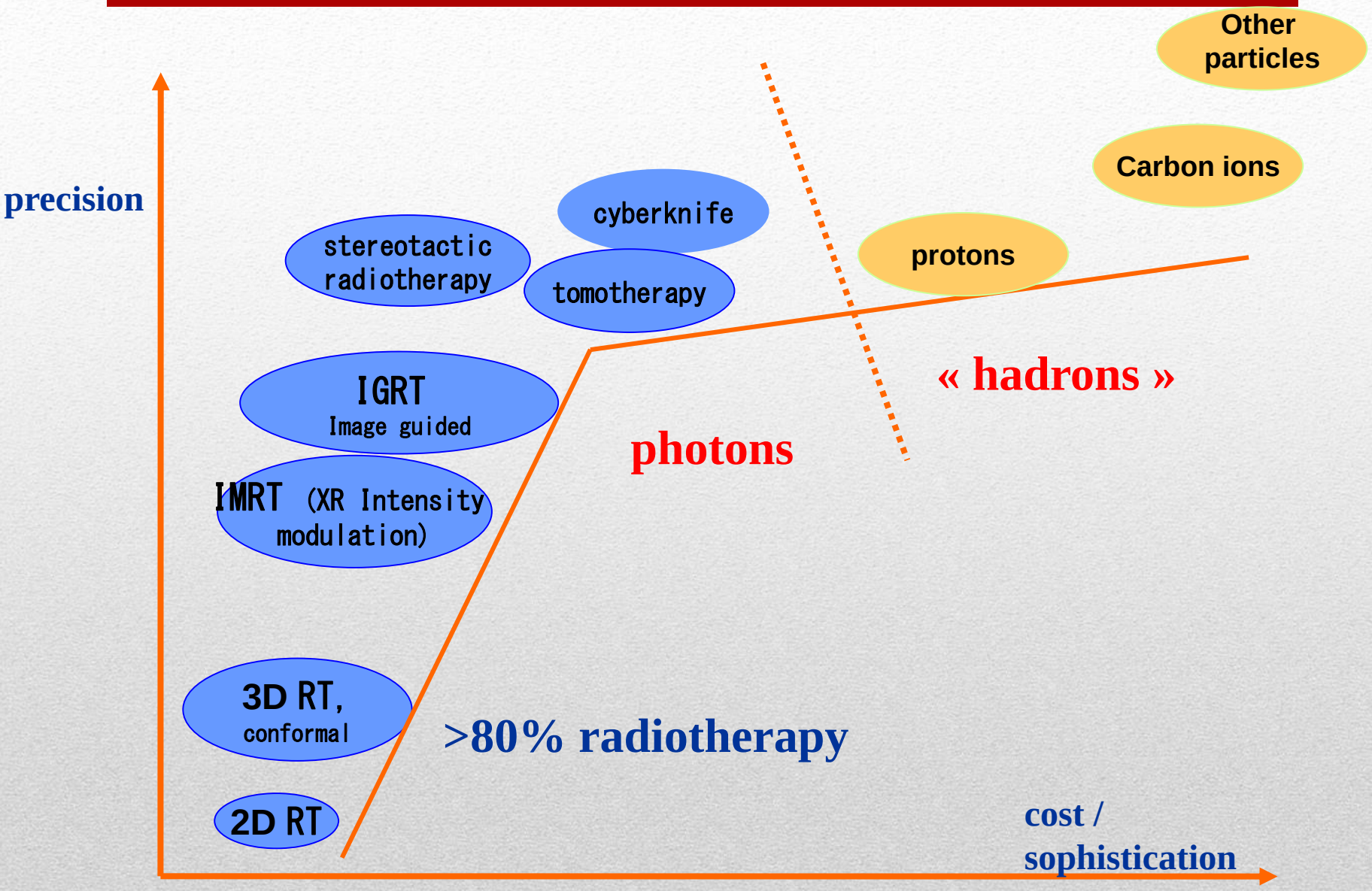
Sommaire

- **L'hadronthérapie qu'est ce que c'est et pouquoi ?**
- **Applications à la neuro-oncologie adulte**
- **Applications chez l'enfant**
- **Le projet ARCHADE,**
  une « Normandy Hadrontherapy »

L’hadronthérapie qu’est ce que c’est ? Pourquoi faire


Other particles
Carbon ions
precision
cyberknife
stereotactic radiotherapy
tomotherapy
protons
« hadrons »
IGRT
Image guided
photons
IMRT (XR Intensity modulation)
3D RT, conformal
>80% radiotherapy
2D RT
cost / sophistication

RA ID'ARC

RAPID'ARC

SATURNE

CT SIMULATORS 1+2

TOMO. 2

Caen experience:

large access most advanced photon technologies

DAR AC

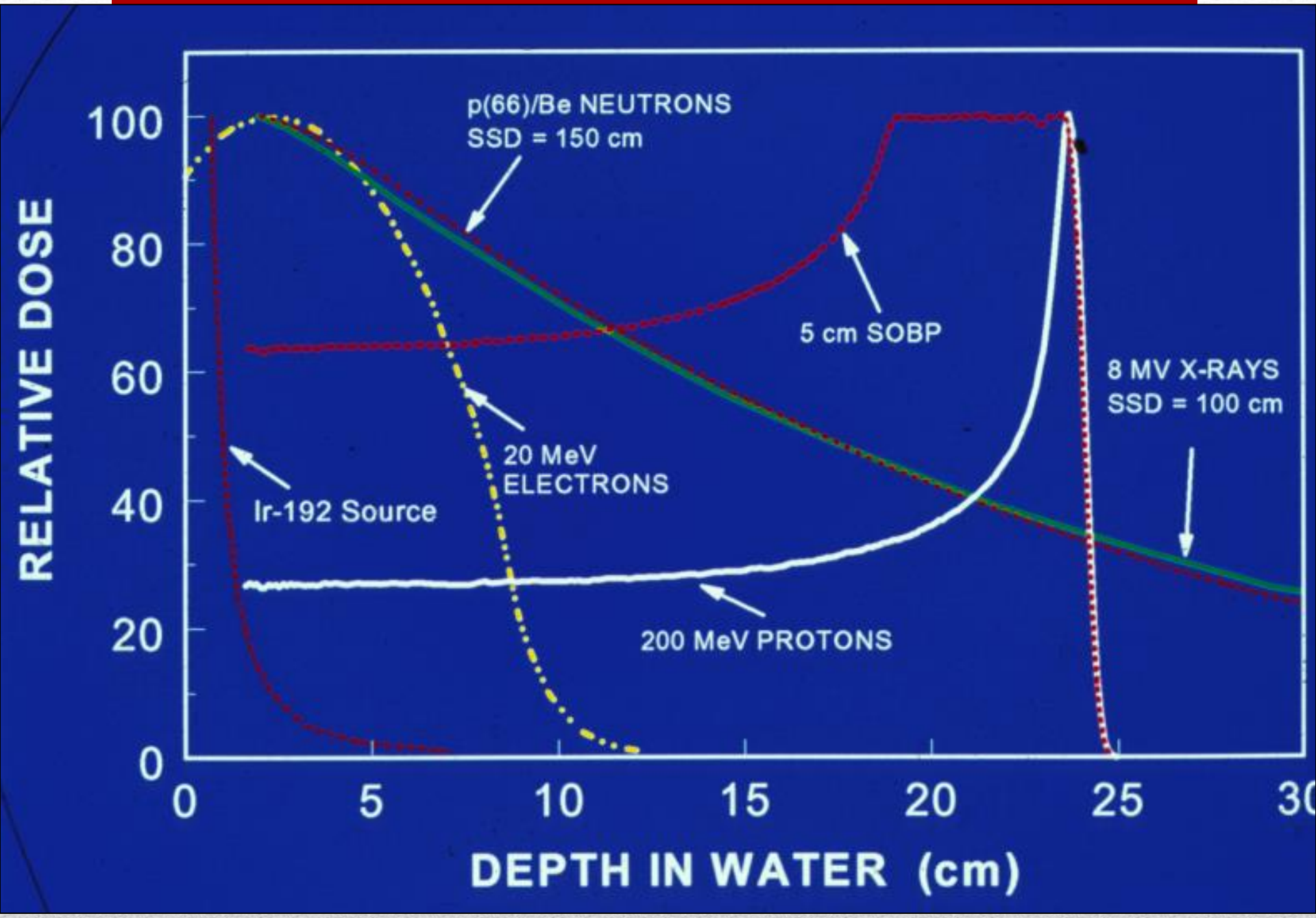
CYBERKNIFE

TOMOTHERAPIE

ARTISTE

CLINAC

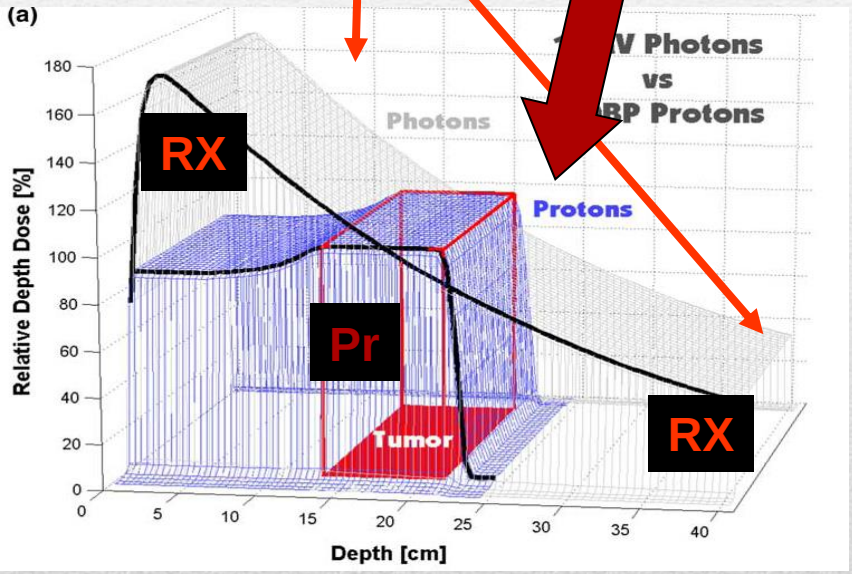
UNICANCER Centre de Lutte contre le Cancer François Baclesse

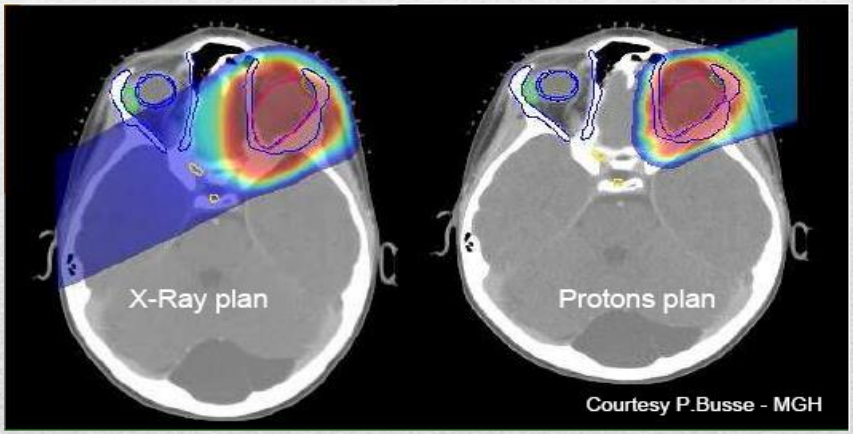

p(66)/Be NEUTRONS
SSD = 150 cm
5 cm SOBP
8 MV X-RAYS
SSD = 100 cm
20 MeV
ELECTRONS
Ir-192 Source
200 MeV PROTONS
RELATIVE DOSE
100
80
60
40
20
0
0
5
10
15
20
25
30
DEPTH IN WATER (cm)

Protons
Ballistical advantages

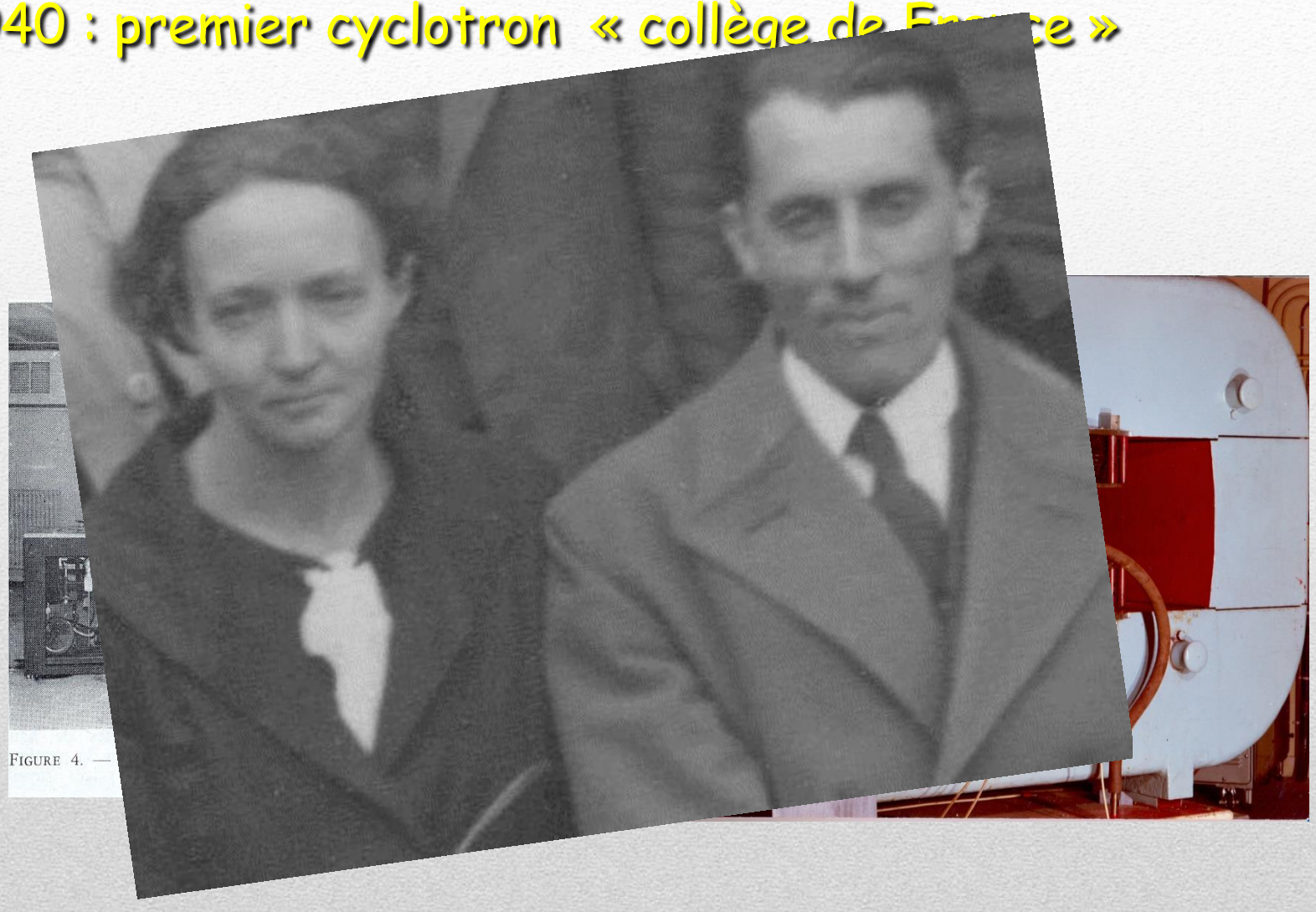
Photons vs protons:
Native Bragg peak & SOBP

Chidren, AYAs:
Preserve healthy tissues





1940 : premier cyclotron « collège de France »



N° 3292

Août 1959

LA NATURE

Le synchrocyclotron d'Orsay

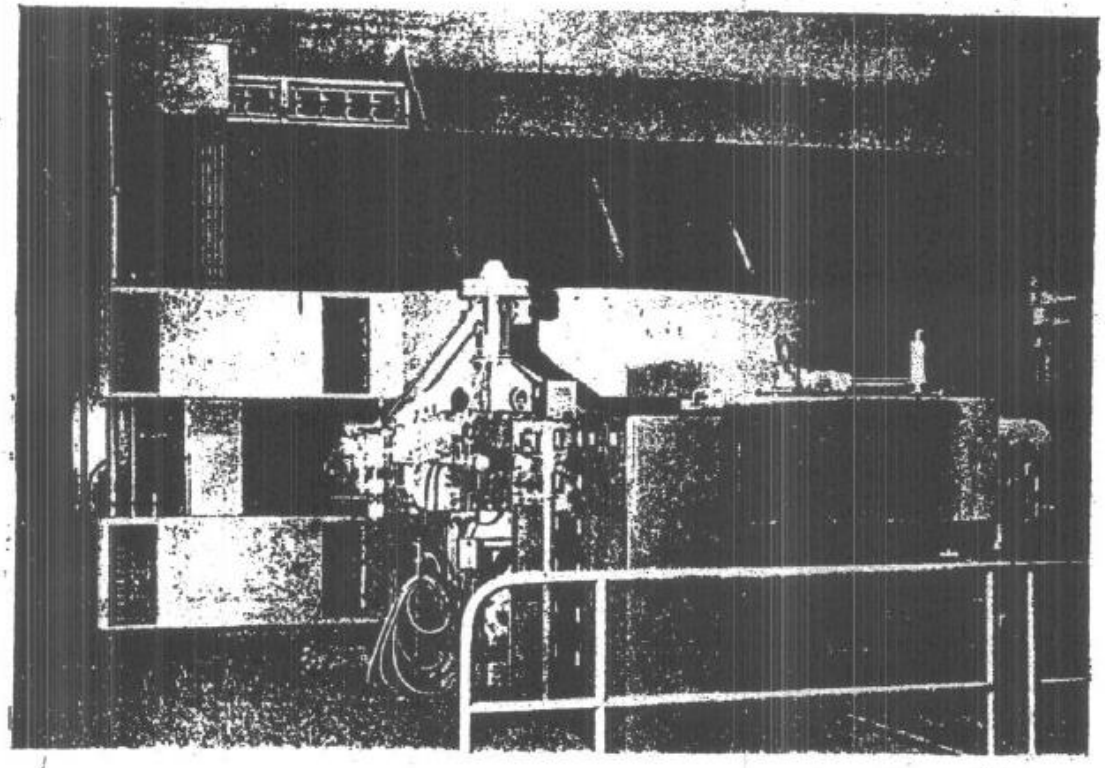
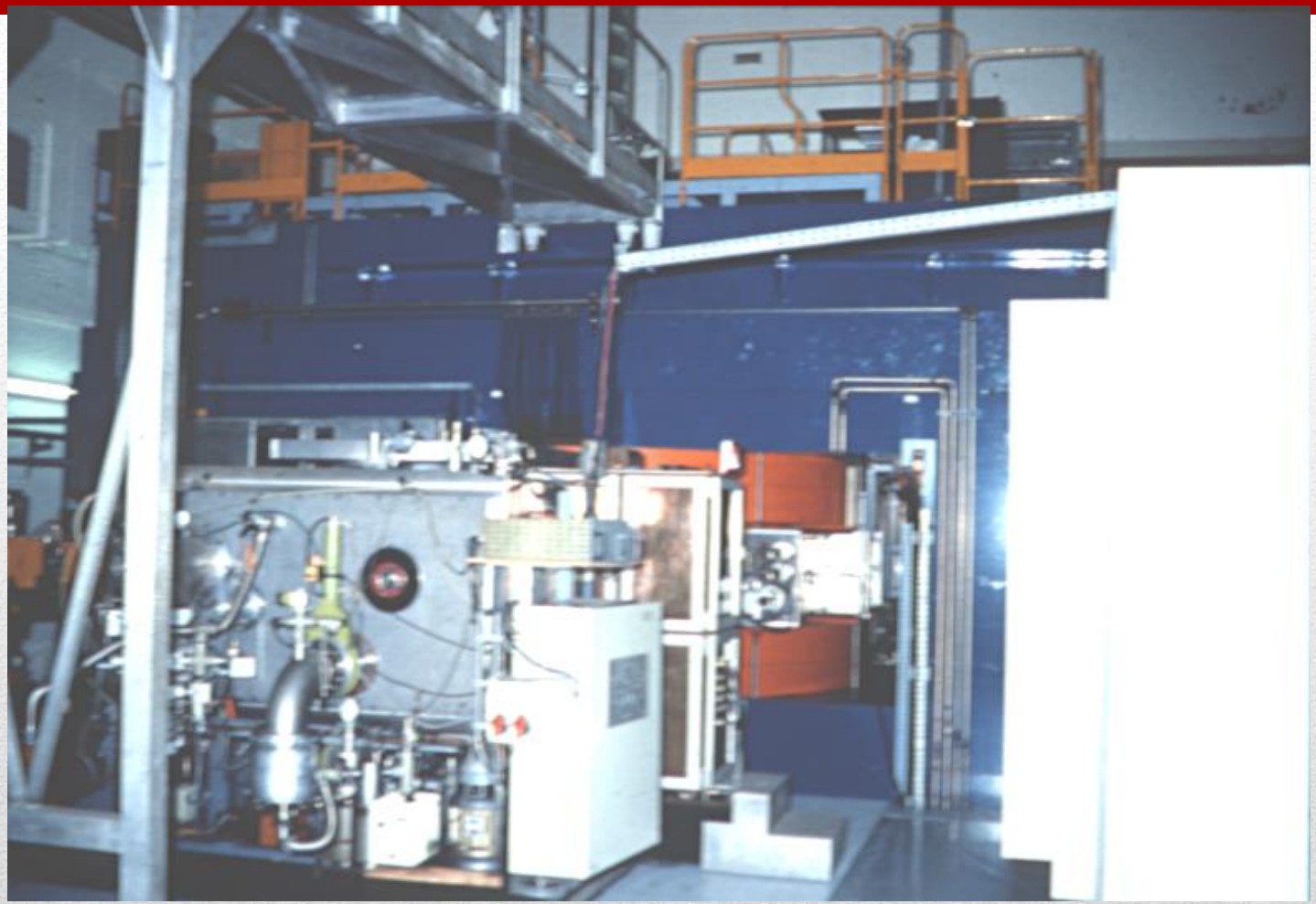


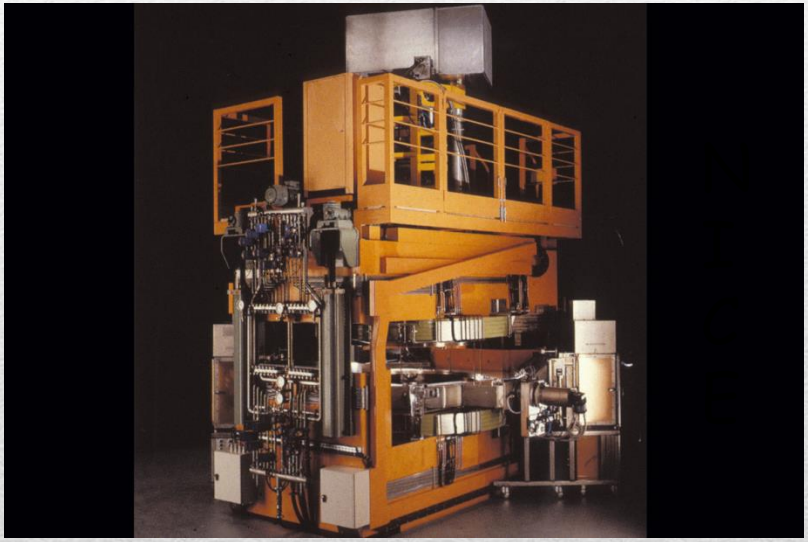
Fig. 1. — *Le synchrocyclotron d'Orsay, côté haute fréquence.*

Devant l'électroaimant de 650 t, le groupe de pompage de la chambre d'accélération. Au premier plan, le tableau de contrôle du vide. A droite, le modulateur et son groupe de pompage.

ORSAY ANNEES 60



Synchrocyclotron de 200 MeV



2ème centre français de protonthérapie : Nice

Proton equipments: Towards compacity…

Orsay synchro cyclo (1958)

Cyclo 230 (2001)

Cryo synchro cyclo 230 (2012)

World market for hadrontherapy

US

- 16 centres opérationnels en proton thérapie
- 8 projets en planification

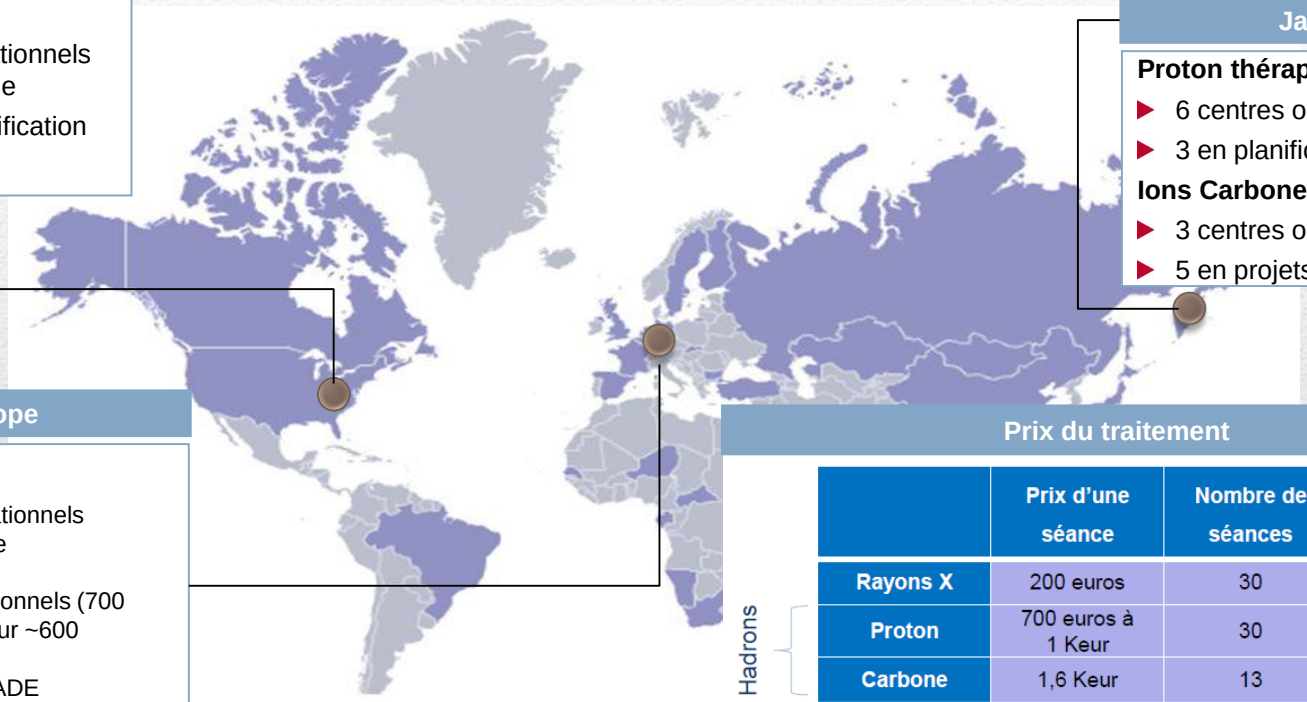
Japon

Proton thérapie:

- 6 centres opérationnels
- 3 en planification

Ions Carbone:

- 3 centres opérationnels
- 5 en projets



Europe

Proton thérapie:
15 centres opérationnels
Dont 2 en France
Ions Carbone:
2 centres opérationnels (700 patients / ans pour ~600 séances) et
1 Project ARCHADE

Prix du traitement

		Prix d'une séance	Nombre de séances	Coût total
	Rayons X	200 euros	30	6 Keur
Hadrons	Proton	700 euros à 1 Keur	30	20 – 30 Keur
Hadrons	Carbone	1,6 Keur	13	21 Keur

Commentaires

- 50 centres opérationnels en proton thérapie, 6 centres en ions de Carbone et 27 projets en planification : Japon est le leader mondial,
- Fin 2013, on a identifié 6 centres d' ions Carbone en planification,
- 120 000 patients traité par Hadron thérapie (Proton + ions Carbone),
- 15 pathologies possibles à date pour la thérapie par ions carbone.

Courtesy IBA

Applications
à la neuro-oncologie adulte

Quelles sont les principales indications ?

- SNC
  - Méta cérébrales
  - Gliomes
  - MAV
  - Adénomes hypophyse
  - Méningiomes
  - Neurinomes acoustique
- Base du crâne
  - Chordomes
  - Chondrosarcomes

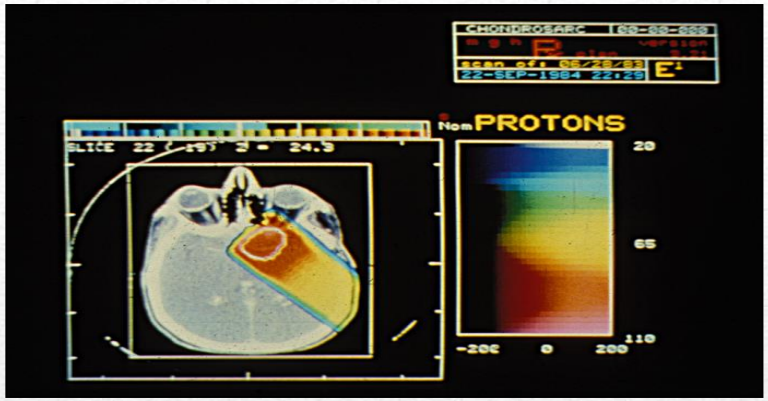
Indications cliniques

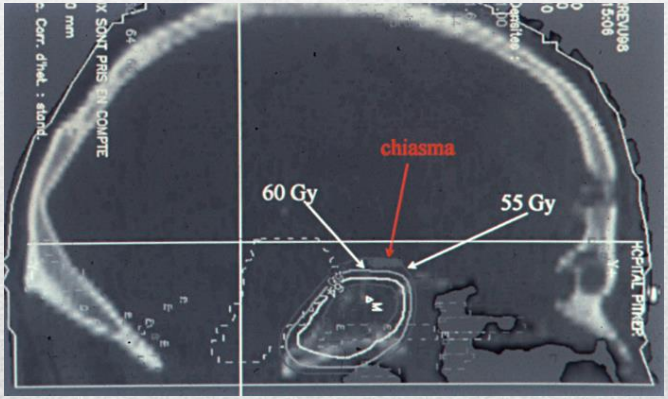
(Loma Linda, R Schulte, 2000)

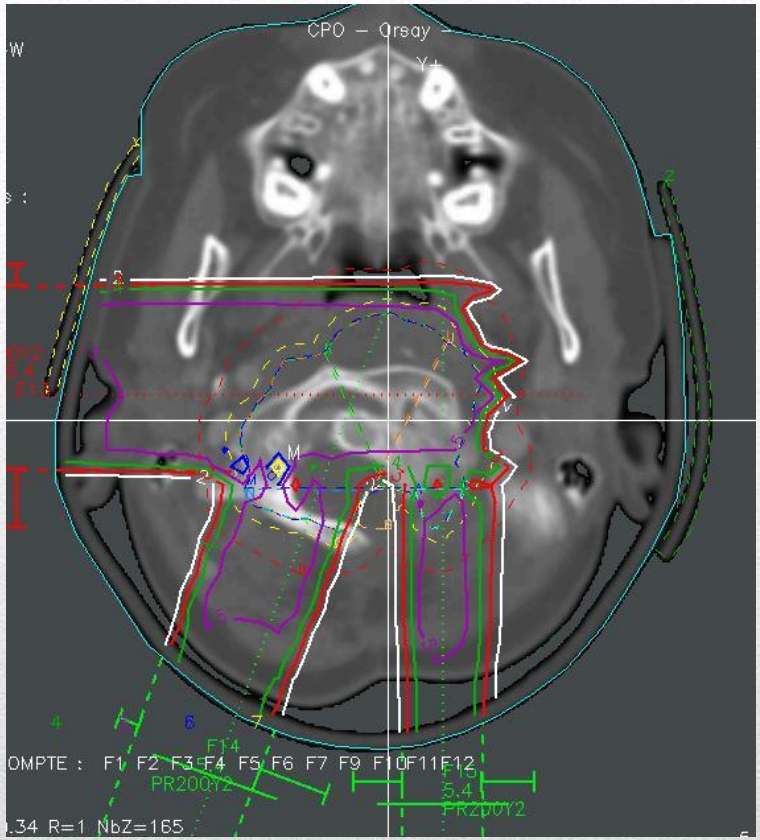
- Œil
  - Mélanomes
  - DMLA
- Tête et cou
  - Nasopharynx (initial ou rechute)
  - Oropharynx (avancé)
  - Sinus de la face

Indications cliniques, suite

(Loma Linda, R Schulte)







Faisceaux P+ = Jeu de construction

(« Patching »)

Les tumeurs de la base du crâne et du canal rachidien

WHO classif, 2000

- Cartilage:
  - Chondromas, osteochondromas
  - chondroblastomas
  - Chondromyxoid fibroma
  - ***Chondrosarcomas (CS)***
  - Dediff CS
  - Mesenchymal CS
  - Clear cell CS…
- Notochord:
  - ***Chordomas (CH)***

Chordomes et chondrosarcomes

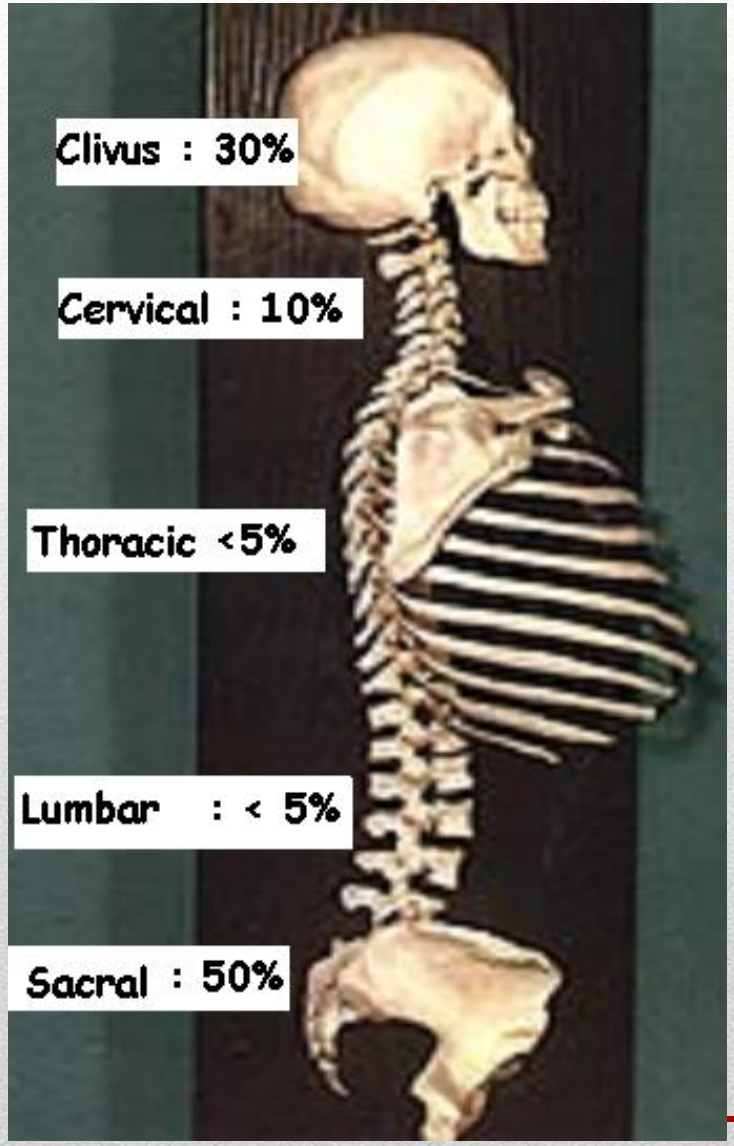
- Tumeurs rares, localisations en patch ou en spirale dans le clivus
- Evolution lente
- Extension :
  - Vers l'arrière comprimant le tronc cérébral
  - Vers l'avant envahissant les fosses nasales
  - Vers le haut repoussant le chiasma
  - Latéralement englobant les nerfs optiques
- Métastase : extrêmement rare
  - 5% : chordome
  - < 5% : chondrosarcome

Pathology

- Chordoma
  - Typical
  - Chondroid : better prognosis: DD chondrosarcoma
  - Undifferenciated
- Chondrosarcoma
  - Grade I or II
  - Grade III, highly malignant

	Immunohistochemistry	
	chordoma	chondrosarcoma
Cytokeratin	(+)	(-)
Epithelial Membrane Antigen (EMA)	(+)	(-)
Vimentin	(+)	(+)
S100 Protein	(+)	(+)

Chordomas sites

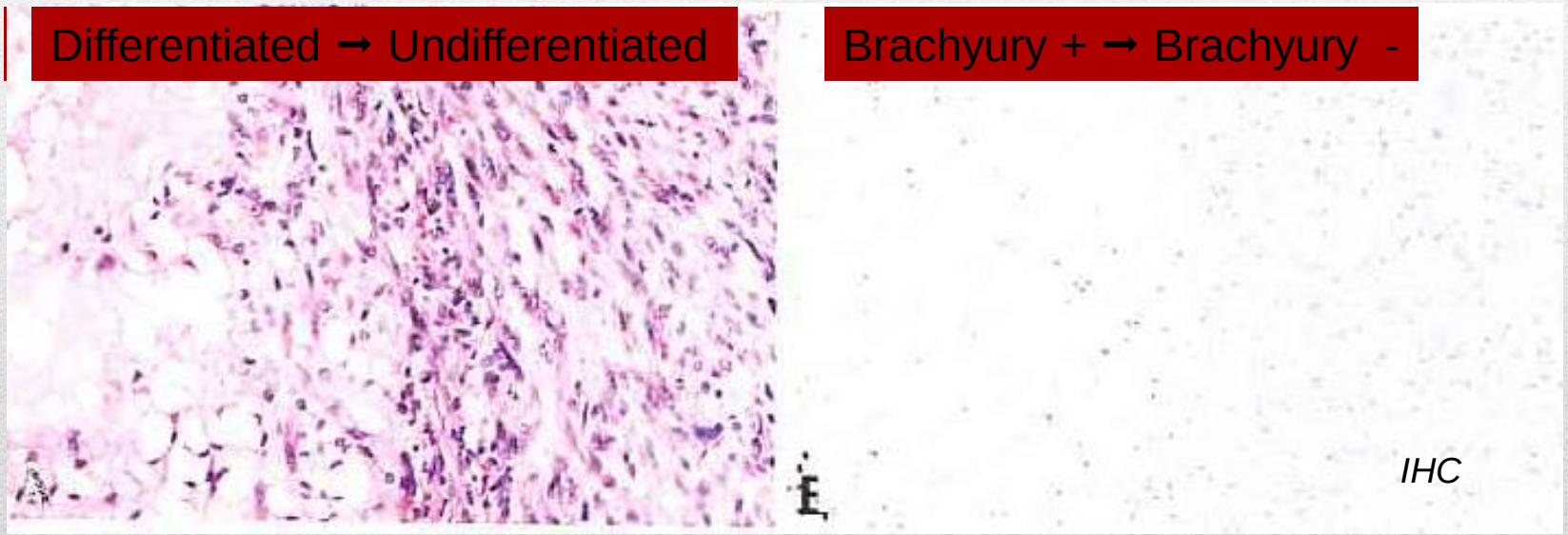


Epidemiology of chordomas

- 1973-1995 : 400 cases published
- Incidence : 0.08 / 100 000
  - Males: 0.1 / 100 000
  - Females: 0.06 / 100 000
- Med Age : 58.5 A
- Rare before 40 Y : 0.02 / 100 000

McMaster Cancer Cause Control 2001

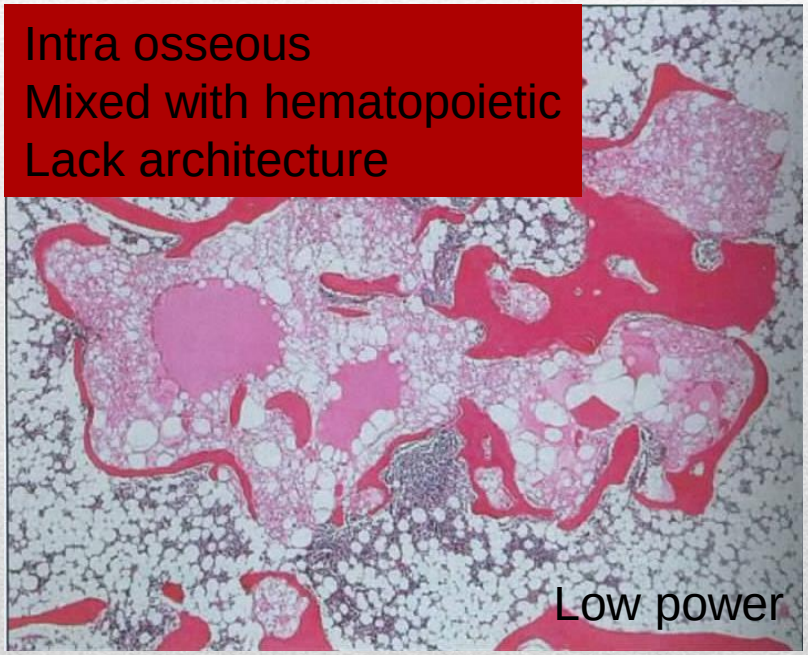
Malignant subtypes
Differentiated & undifferentiated
(WHO, 2013)



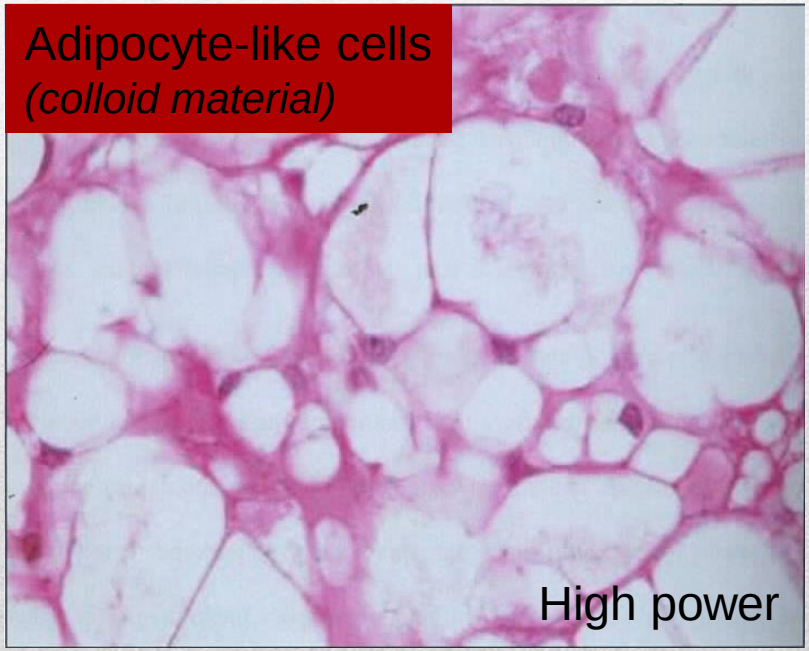
Flanagan, Yamaguchi, 2013

Benign subtypes: precursors ?
BNCT*, EP** *(WHO, 2013)*

Intra osseous
Mixed with hematopoietic
Lack architecture

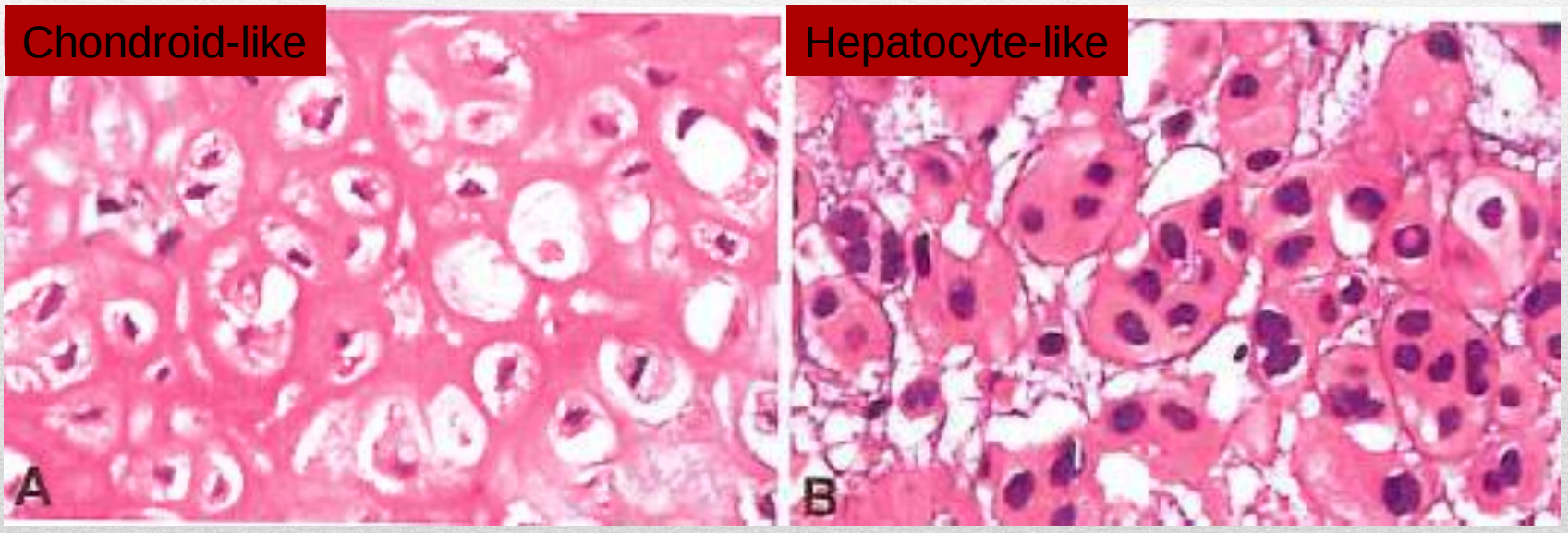


Adipocyte-like cells
(colloid material)



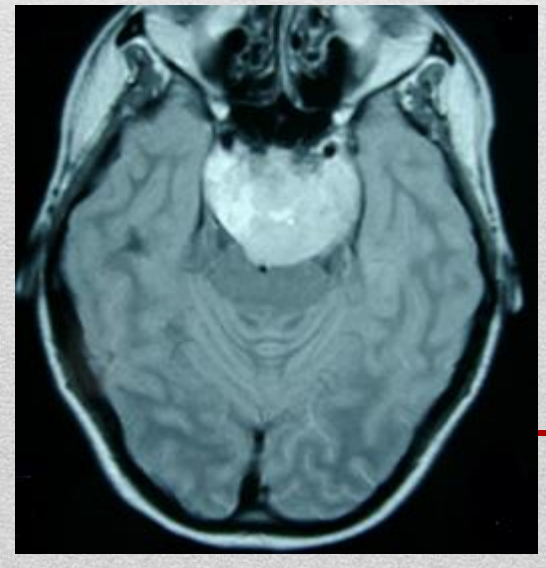
Flanagan, Yamaguchi, 2013

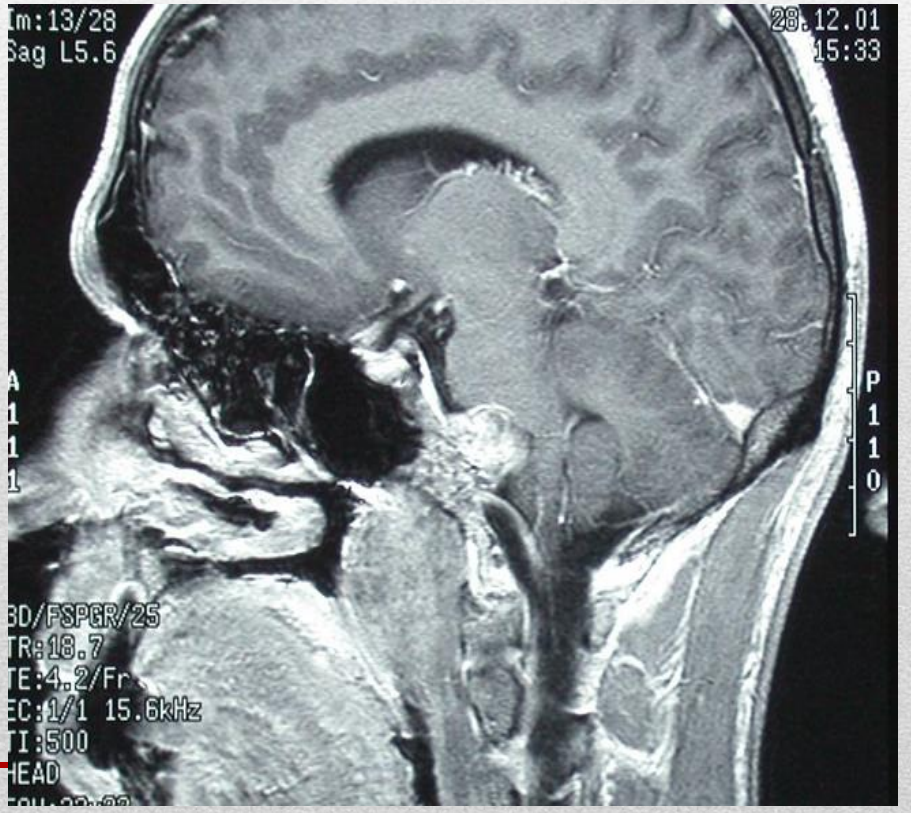
**Benign Notochordal Cell Tumours*
***Ecchordosis Physaliphora Spheno-occipitalis*



Altered differentiations

Chondrosarcomas



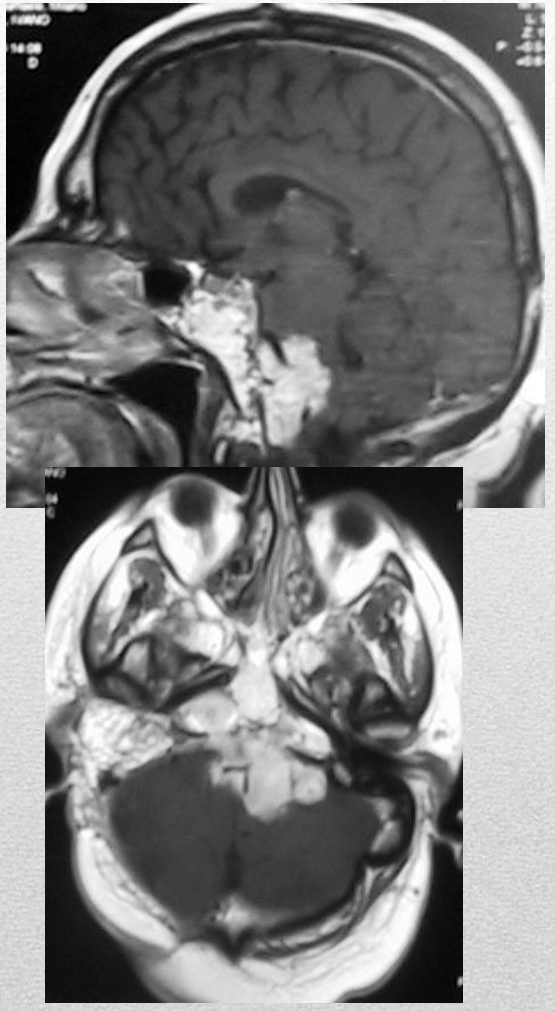


Epidemiology: chondrosarcomas

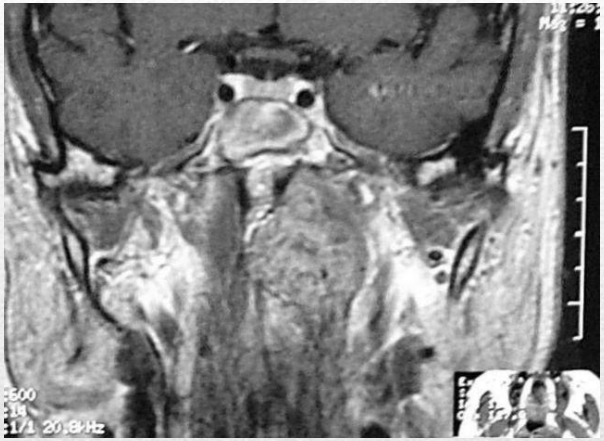
- Pic incidence: 4^{th} – 5^{th} decades
- Pelvis , metaphysis /diaphysis , proximal extremities humerus + distal femur
- Skull base very rare

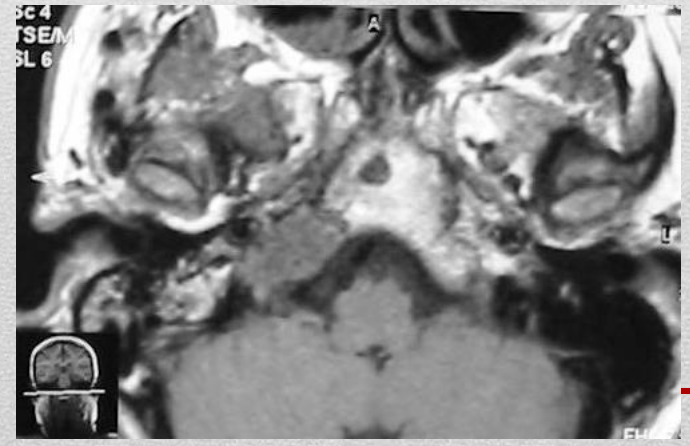
Symptoms / natural history

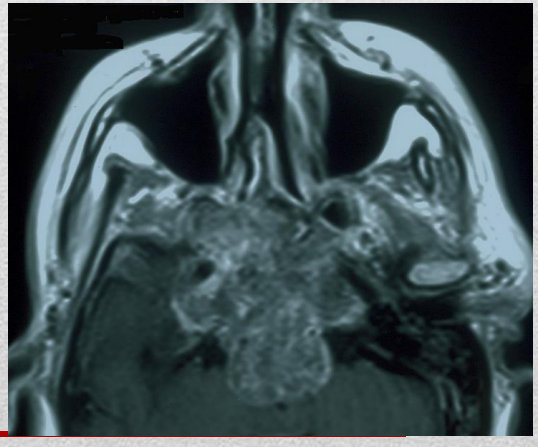
- Insidious
- Non specifique
- Nerve palsies (III,VI) , headaches

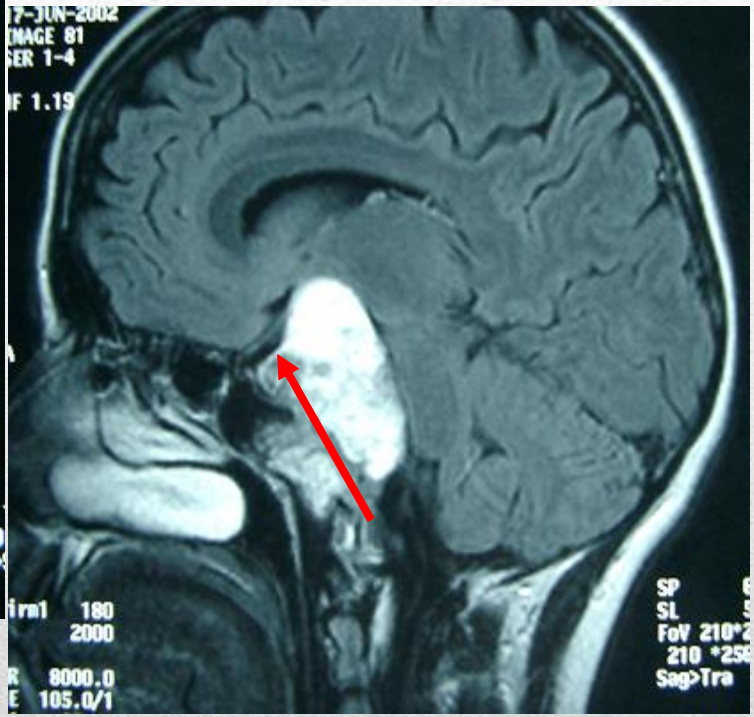


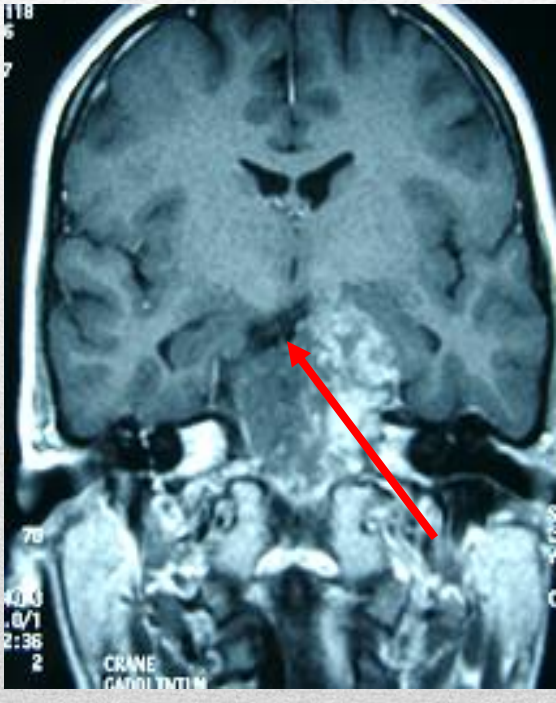
Local Extension : 1/ brain stem











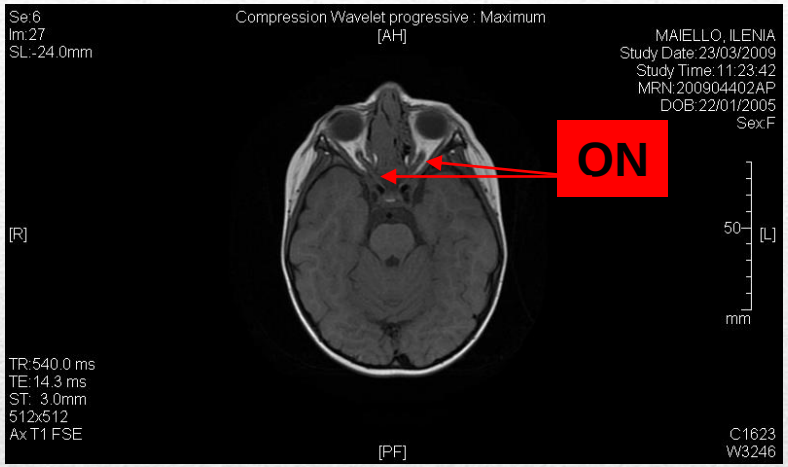
2/ optic pathway

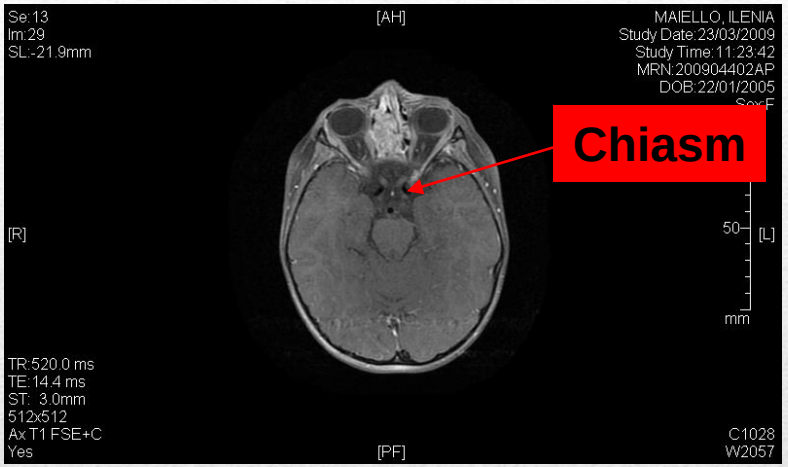
Which technology do we need ?

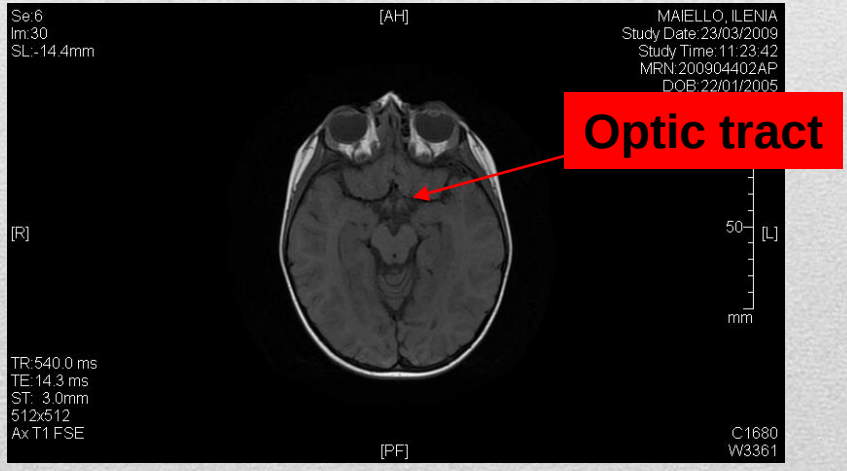
1. *Passive double scattering with fixed beam: covers most our current indications*

2. *No compromise on precision and reproducibility !*

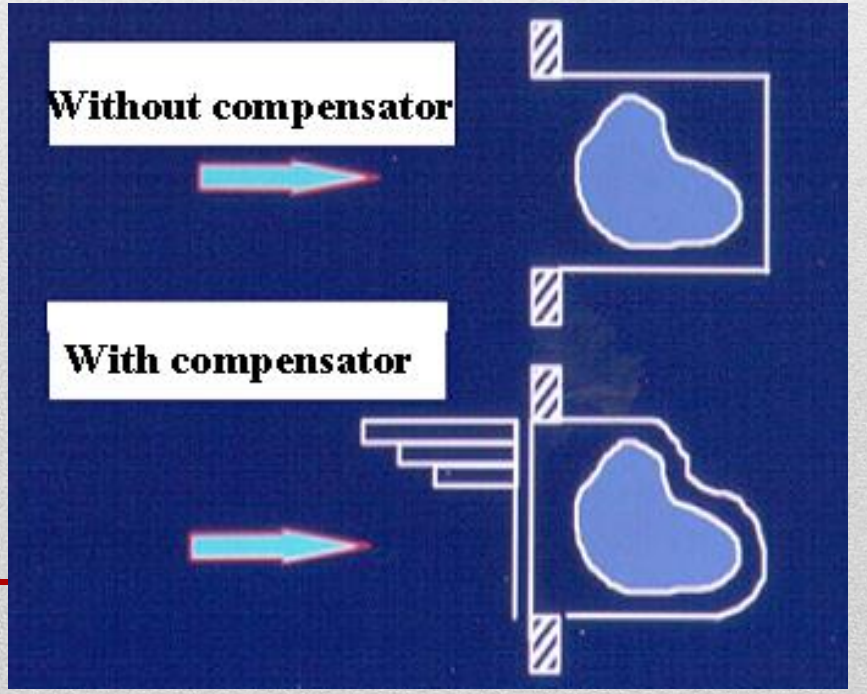
High definition CT/MRI





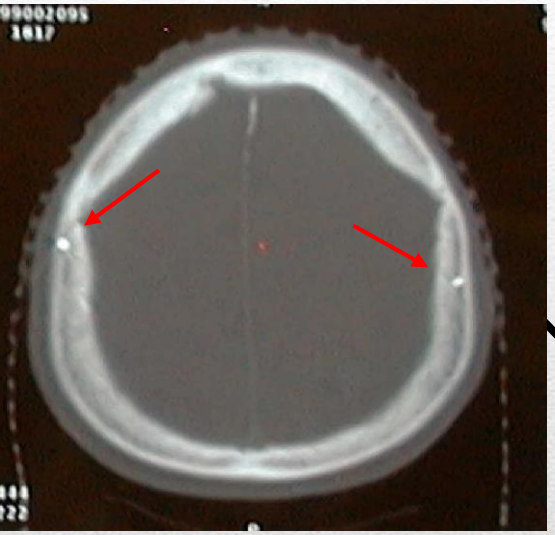


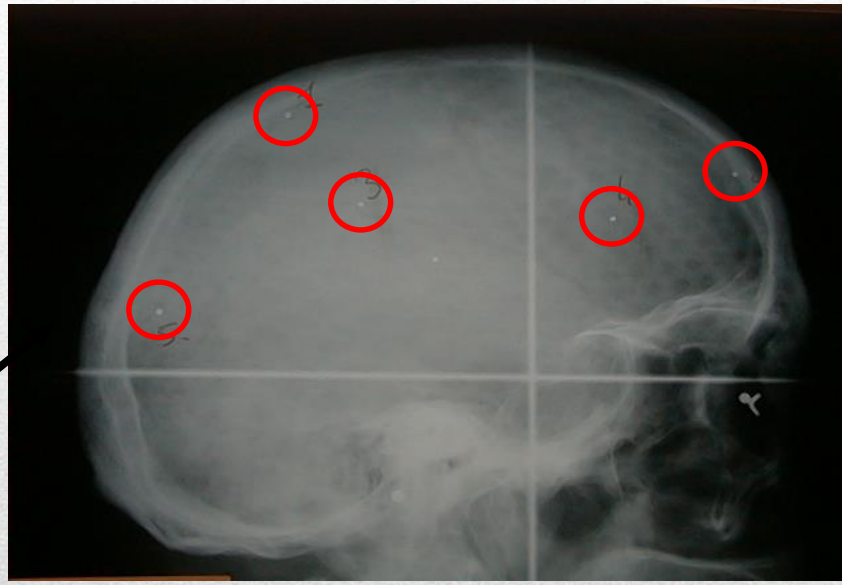
Beam's « shaping »: *passive double scattering*

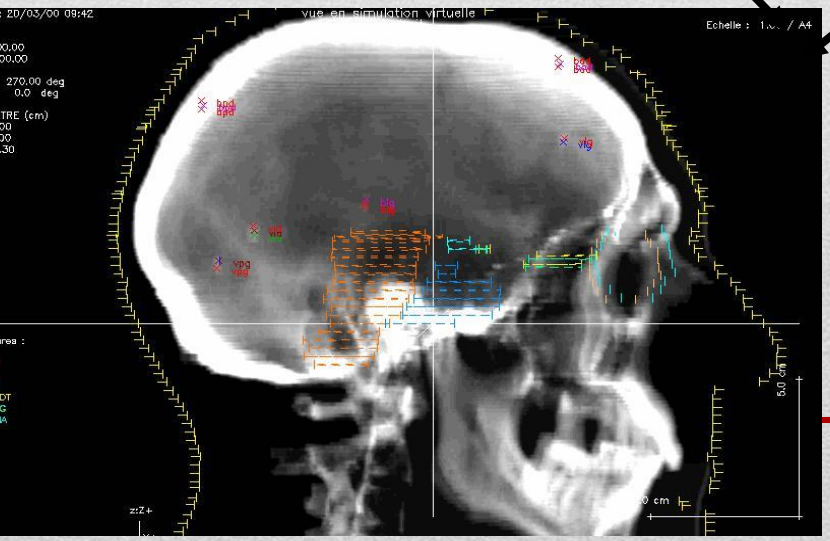


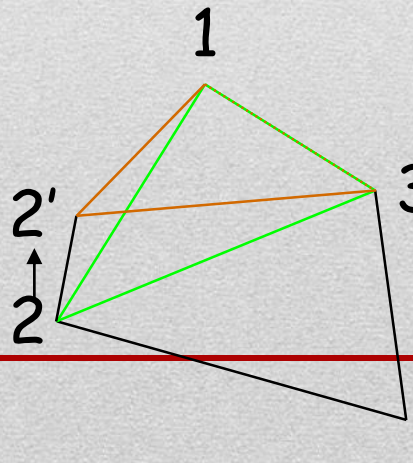
Stereotactic alignment :implanted fiducial markers

Stereotactic alignment :Rotaplus program





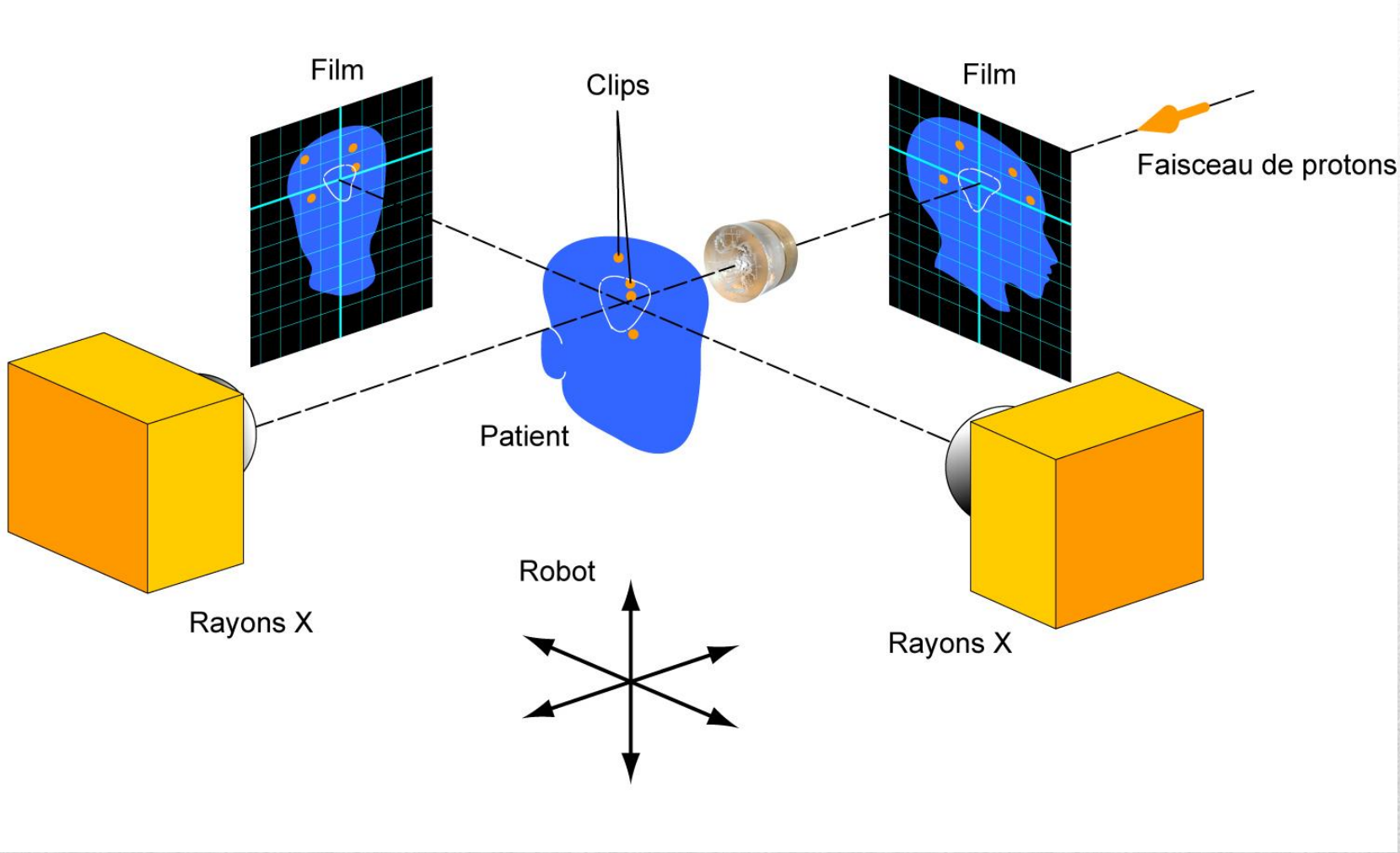




-Virtual triangles between gold seeds (DRRs)...

-Compared with actual position on orthogonal X-Rays

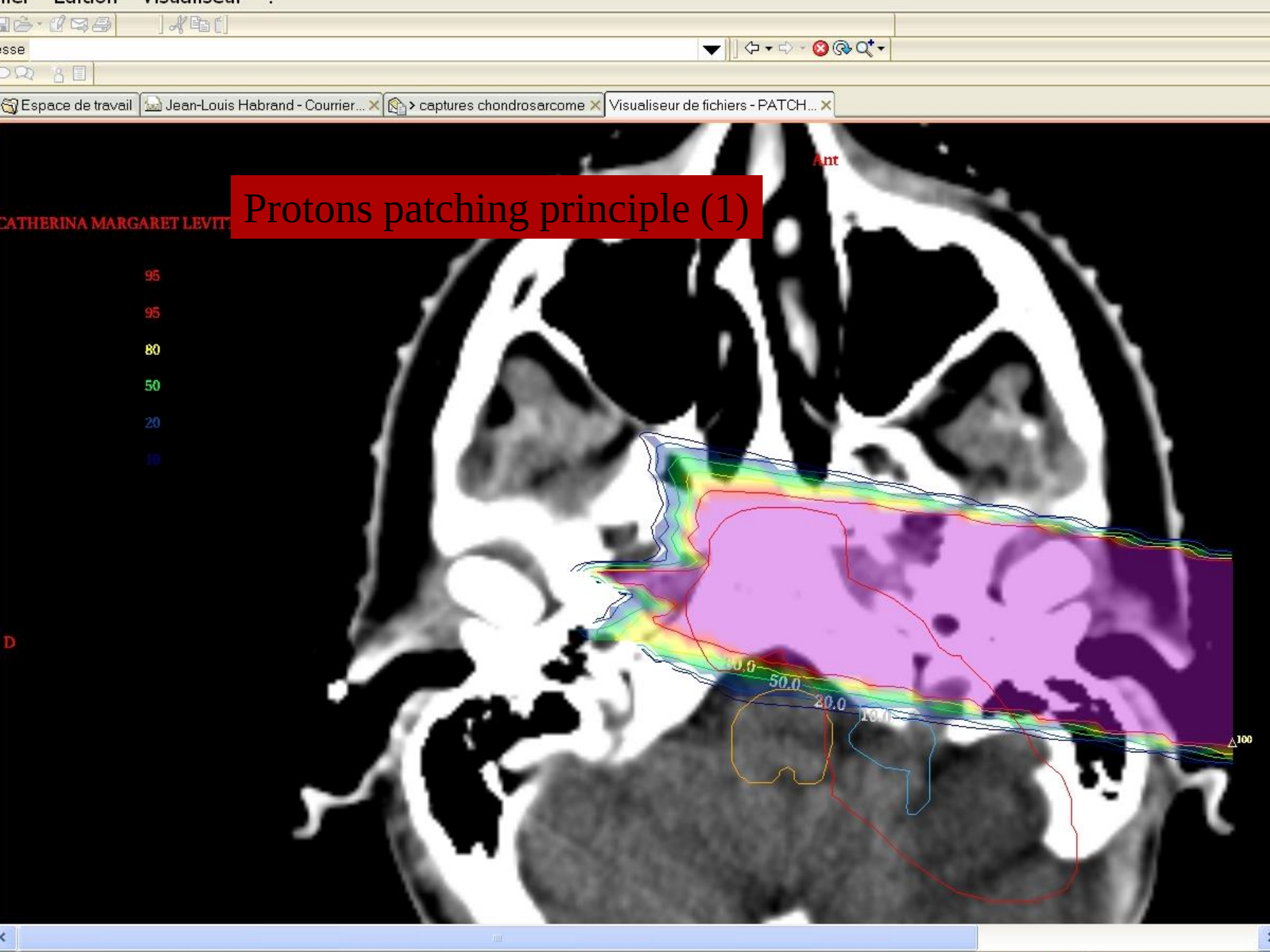
Patient positioning



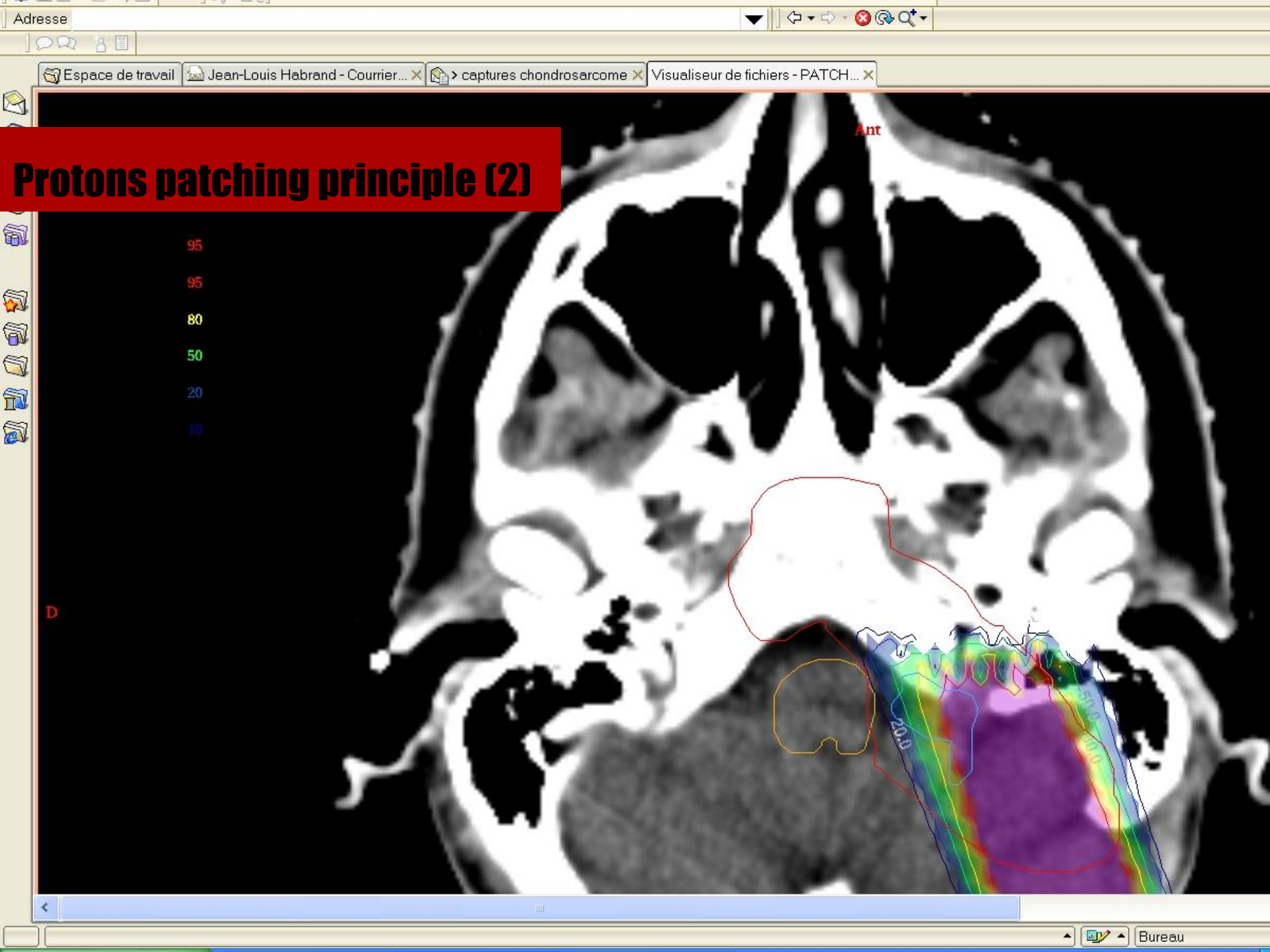
Use of robots

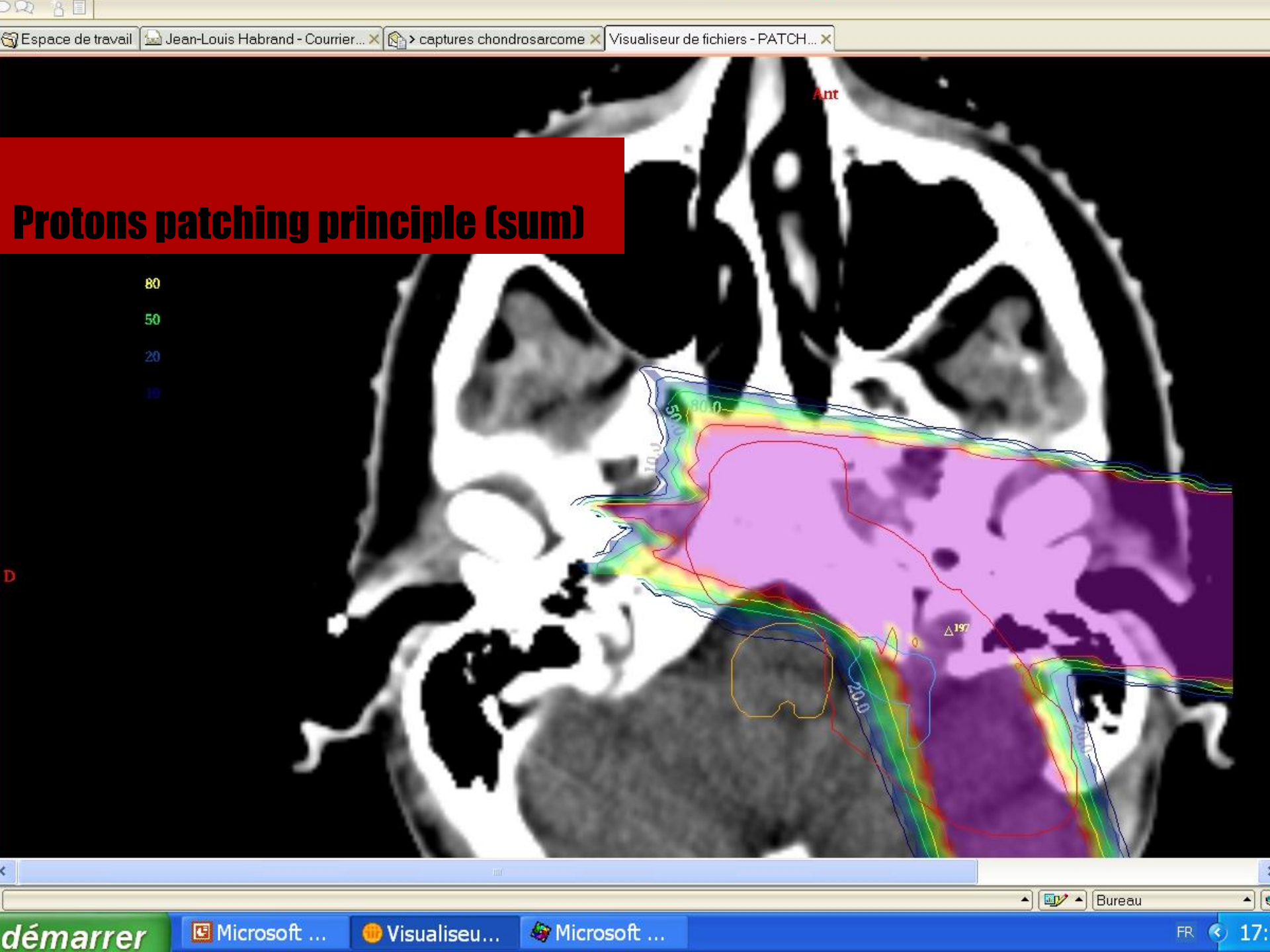
Isocentricity

Six degrees freedom


Espace de travail
Jean-Louis Habrand - Courrier...
> captures chondrosarcome
Visualiseur de fichiers - PATCH...
Protons patching principle (1)
Ant
CATHERINA MARGARET LEVIT
95
95
80
50
20
D
50.0
20.0

Protons patching principle (2)




Espace de travail
Jean-Louis Habrand - Courrier...
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Visualiseur de fichiers - PATCH...
Protons patching principle (sum)
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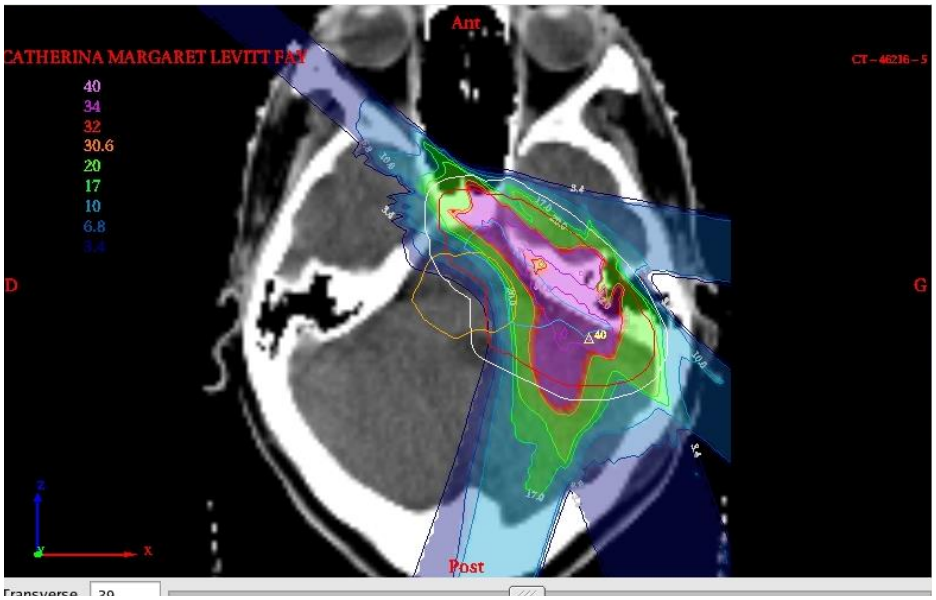
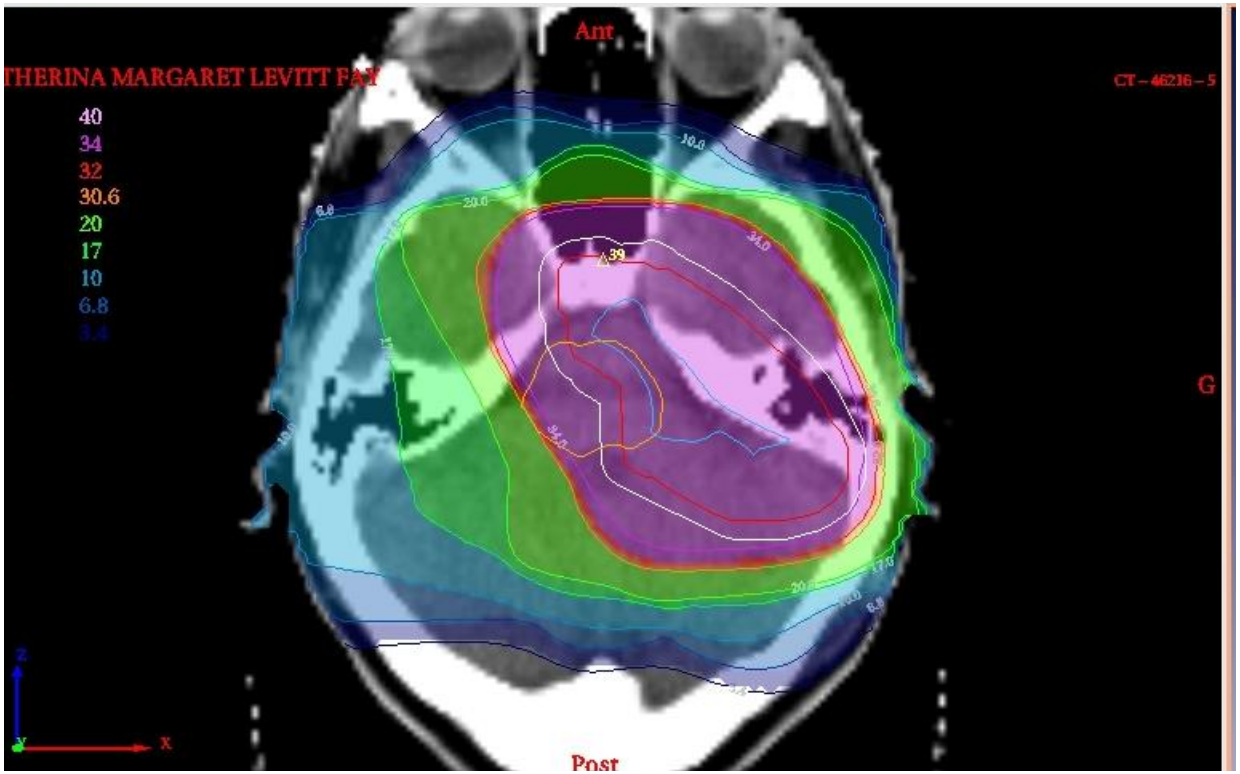
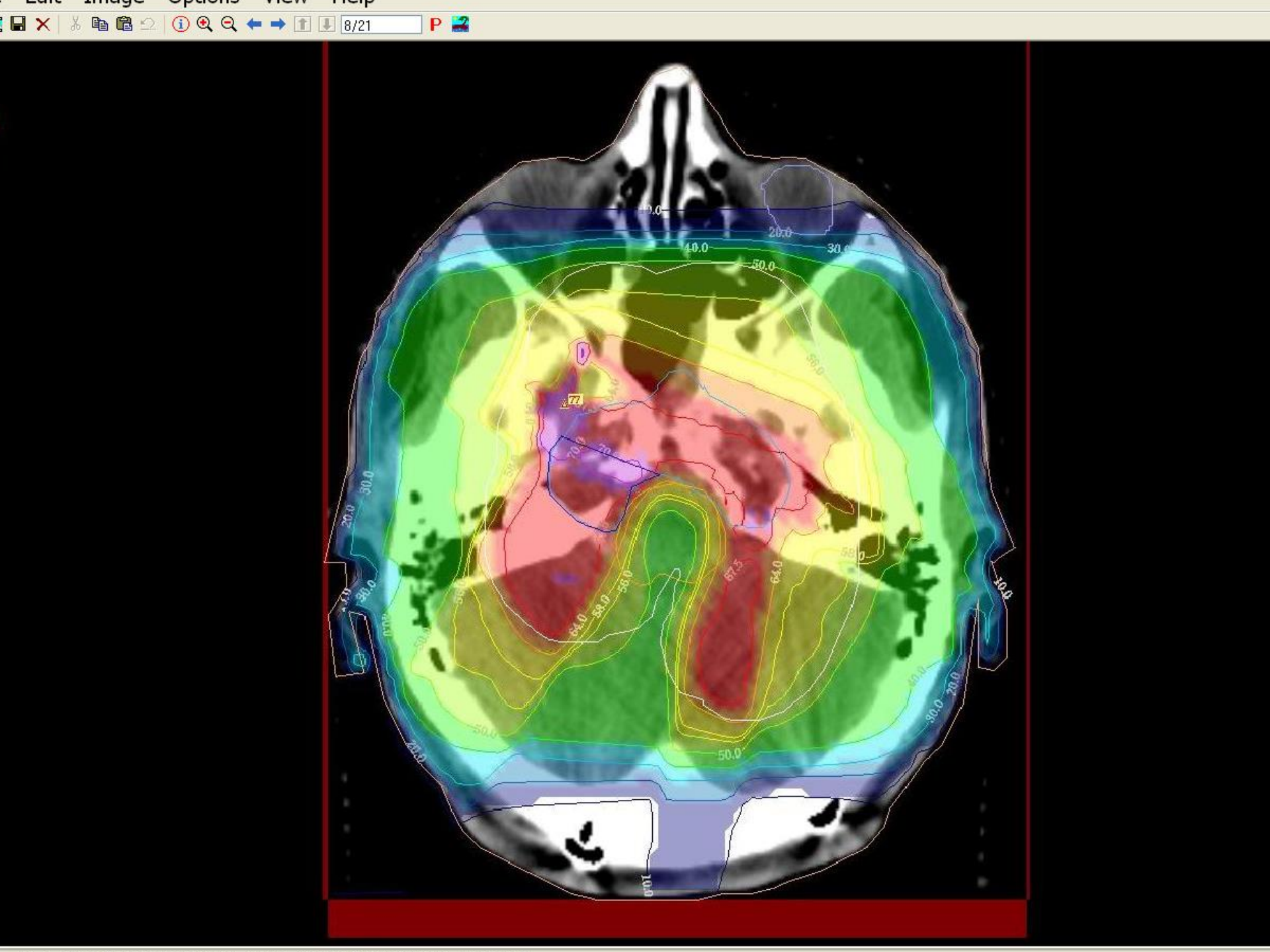
Microsoft ...
Visualiseu...
Microsoft ...
FR
17:

Protons to CTV (Axial)



Photons to CTV (Axial)

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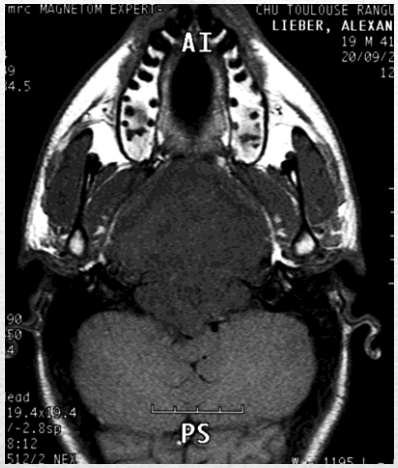
Is upfront surgery important ?

YES ! Allows:

1. *Pathological assessment*
2. *Tumor debulking*
3. *Spacing critical organs (+++)*

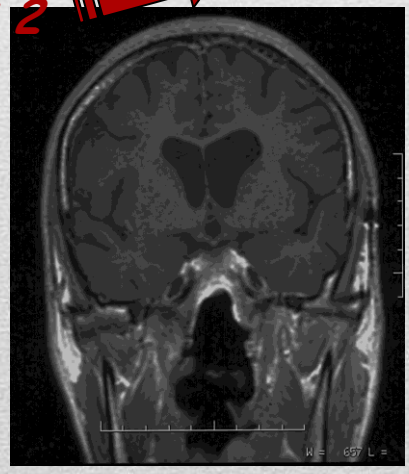
Young adult: 2 Y stuffy nose..

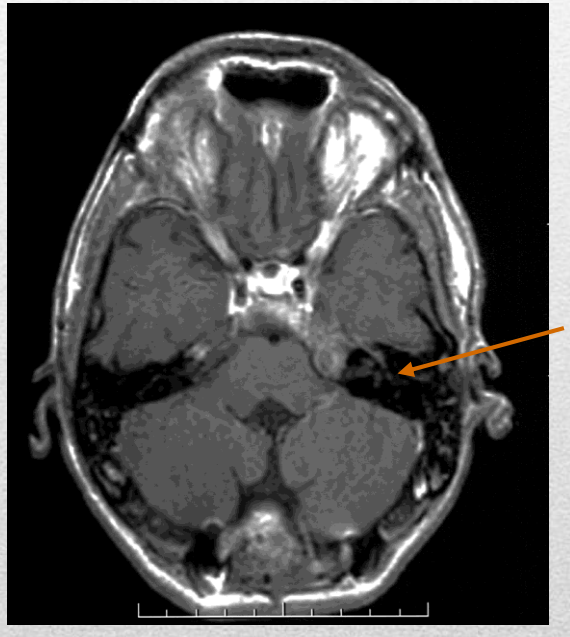


Post op imaging

Op # 1

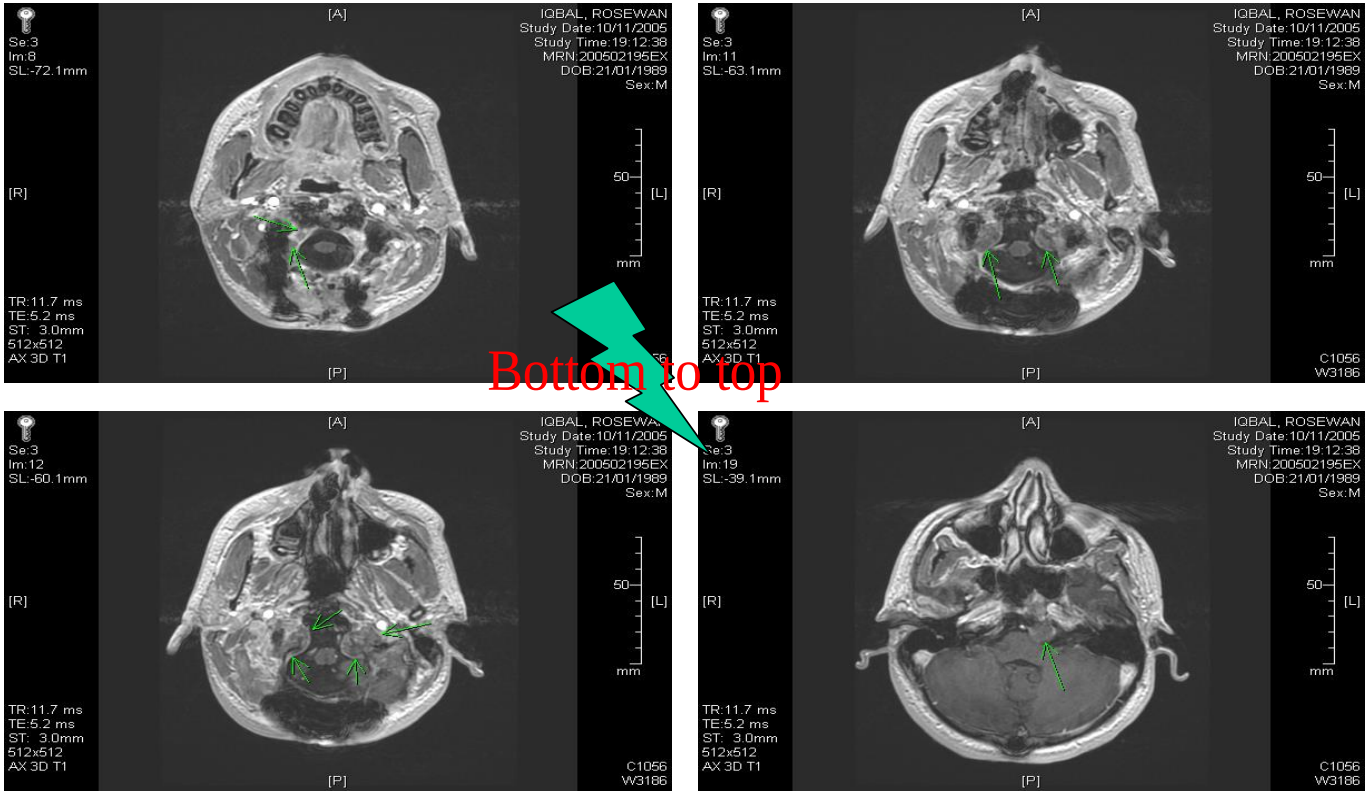
Op # 2





Minime residu ?

I.R: 16 Y CH, post op imaging



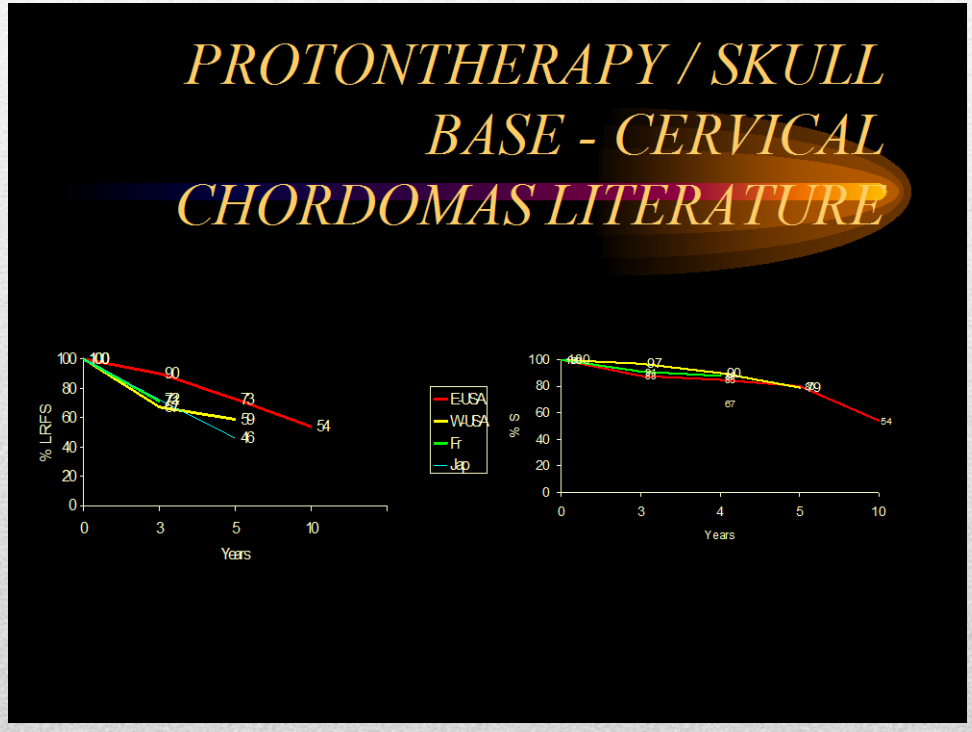
Are protons the best in skull base sarcomas ?

- **Chordomas:** YES, but still perfectible…

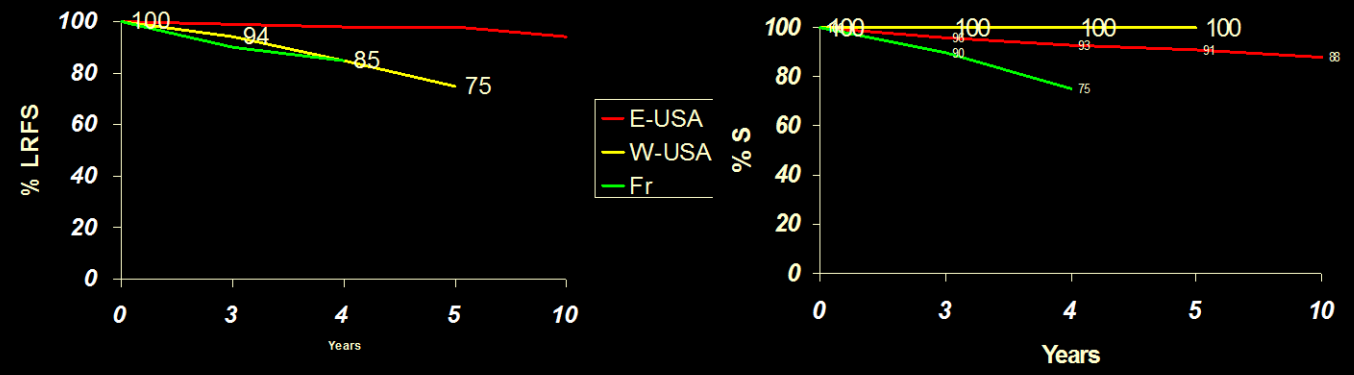
- **Chondrosarcomas:** YES,

but high tech photons can become competitive

Sarcomes de la base : résultats



PROTONTHERAPY SKULL BASE - CERVICAL CHONDROSARCOMAS : LITERATURE



Photons in skull base sarcomas Literature

(Habrand et al, in Thieme Ed, 2009)

Authors	Tumors	No. of Cases	Management	Dose (Range)/ dpf	Results
Foweraker et al[47]	CH and CS	12	EBFRT	64.3 Gy (60–65)/1.66 Gy	Med f-up: 38 m 5-y DFS/OS: CH: 80%/62% CS: 100%/100%
Catton et al[48]	CH	48	EBFRT	50 Gy (25–60)/2 Gy (1 Gy bid in 8)	5-y OS: 54% 5-y PFS: 23%
Romero et al[49]	CH	18	EBFRT	50.1 Gy (29.9–64.8) /1.5–2.0 Gy (1.0–1.5 Gy bid in 8)	5-y PFS: 17% 5-y OS: 38%
Magrini et al[50]	CH	15	EBFRT		5-y OS: 58% 10-y PFS: 25%
Zorlu et al[51]	CH	18	EBFRT	60 Gy (50–64)/ 2 Gy	Med f-up: 43.2 m 5-y PFS: 23% 5-y OS: 35%

Abbreviations: bid, twice a day; CH, chordoma; CS, chondrosarcoma; DFS, disease-free survival; dpf, dose per fraction; EBFRT, external beam fractionated radiotherapy; f-up, follow-up period; m, months; med, median; OS, overall survival; ped, pediatric; PFS, progression-free survival; y, year.

Protons in skull base sarcomas Literature (Habrand, id)

Authors	Tumors	No. of Cases	Dose (Range)/dpf	Results
Hug et al[13]	CH and CS	58	71 CGE (65–79)	Med f-up: 33 m 5-y LC/OS: CH: 59%/79% CS: 75%/100%
Munzenrider and Liebsch[14]	CH and CS	621	67 CGE (66–83)/1.8 CGE	Med f-up: 41 m 10-y LC/OS: CH: 54%/54% CS: 94%/88%
Noel et al[15]	CH and CS	67	67 CGE (60–70)/2 CGE	Med f-up: 29 m 3-y LC/4-y OS: CH: 71%/88% CS: 85%/75%
Igaki et al[16]	CH	13	72 CGE (63–95)	Med f-up: 69.3 m 5-y LC/OS:[Q21] 46%/66.7%
Weber et al[17]	CH and CS	29	68–74 CGE[Q22]	3-y LC/OS: CH: 87.5%/93.8% CS: 100%/93.8%
Habrand et al[18]	CH and CS (ped)	30	68.3 (54.6–71.0)/1.8 CGE	Med f-up: 26.5 m 5-y PFS/OS: CH: 77%/81% CS:100%/100%

Abbreviations: bid, twice a day; CGE, cobalt gray equivalent; CH, chordoma; CS, chondrosarcoma; dpf, dose per fraction; f-up, [Q23]follow-up period; LC, [Q24]local control; med, median; m, months; OS, [Q25]overall survival; ped, pediatric; PFS, [Q26]progression-free survival; y, years[Q27].

Radiosurgery in skull base sarcomas (Habrand, Id)

Author	Tumors	No. of Cases	Technique	Dose/Dractionation	Results
Feigl et al[61]	CH and CS	13	GKS	17 Gy (14–18), SD	Med f-up: 17 m LC: 14%/15%
Krishnan et al[62]	CH and CS	29	GKS ± EBFRT	15 Gy (10–20), SD ± 50.4 Gy (45–54)/C	Med f-up: 4.8 y 5-y LC: CH/CS 32%/100%
Debus et al[63]	CH and CS	45	FSRT – linac	64.9–66.6 Gy/ C	Mean f-up: 19–27 m 5-y LC/OS: CH: 50%/82% CS: 100%/100%
Gwak et al[64]	CH and CS	9	CBK (primary + reirradiation)	21.0–43.6 Gy/ 3–5 f	Med f-up: 24 m LC: 8%/9%
Chang et al[65]	CH	10	linac or CBK	19.4 Gy (18–24)	Mean f-up: 4 y LC: 8%/10%
Hasegawa et al[66]	CH and CS	37	GKS	14 Gy	Mean f-up: 59 m 10-y LC/ OS: 67%/53%
Martin et al[67]	CH and CS	28	GKS	16 Gy	5-y LC/OS: CH: 62.9%/62.9% CS: 80%/[Q28]?
Cho et al[68]	CH and CS	30	EBFRT ± GKS	EBFRT: 60.22 Gy (50.4–39.6)/C GKS 17 Gy (15–20)/ SD	Mean f-up: 56 m 5-y PFS/ OS: CH: 40%/80% CS: 80%/100%

Abbreviations: bid, twice a day; [Q29]C, TK; CBK, [Q30]TK; CH, chordoma; CS, chondrosarcomas; dpf, dose per fraction; EBFRT, external beam fractionated radiotherapy; f, [Q31]TK; FSRT, [Q32]TK; f-up, follow-up period; GKS, [Q33]TK; LC, local control; linac, linear accelerator; med, median; m, months; OS, overall survival; ped, pediatric; PFS, progression-free survival; SD, [Q34]TK; y, year.

Do we need protons alone or protons with photons (for economical / organisational reasons) ?

Combined approach acceptable, provided the patient is not a child …

Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 3, pp. 944–954, 2007

0360-3016/07/$–see front matter

ELSEVIER

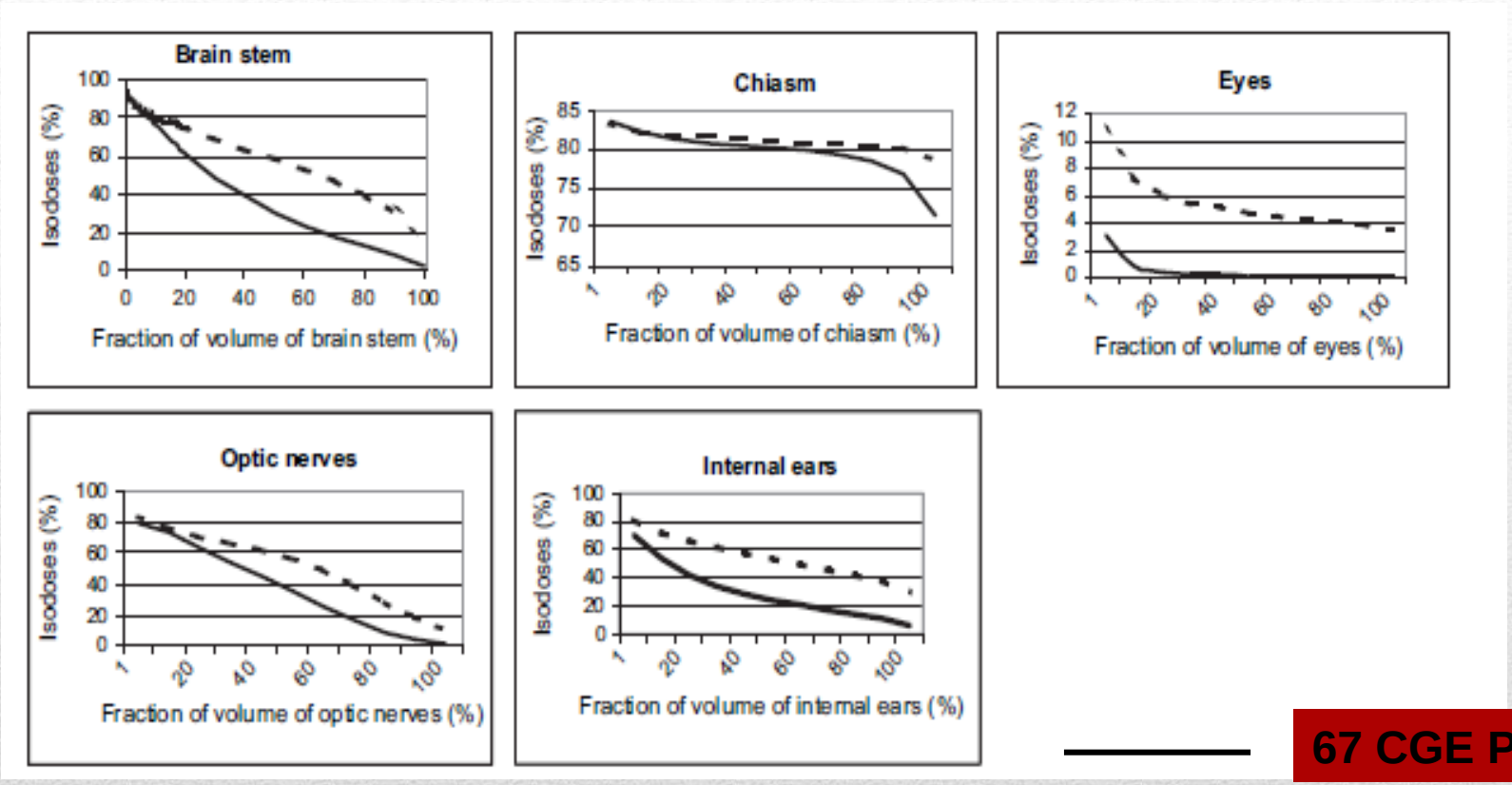
doi:10.1016/j.ijrobp.2007.07.2326

PHYSICS CONTRIBUTION

A TREATMENT PLANNING COMPARISON OF COMBINED PHOTON–PROTON BEAMS VERSUS PROTON BEAMS–ONLY FOR THE TREATMENT OF SKULL BASE TUMORS

Loïc Feuvret, M.D.,*# Georges Noel, M.D.,† Damien C. Weber, M.D.,‡ Pascal Pommier, M.D., Ph.D.,§ Regis Ferrand, Ph.D.,* Ludovic De Marzi, Ph.D.,* Frederic Dhermain, M.D.,‖ Claire Alapetite, M.D.,*¶ Hamid Mammar, M.D.,*¶ Gilbert Boisserie, Ph.D.,# Jean-Louis Habrand, M.D.,*‖ and Jean-Jacques Mazeron, M.D., Ph.D.*#

Finding #1: GTV/CTV coverage acceptable both approaches (mean/min doses)



Finding #2: OARs better spared with protons alone

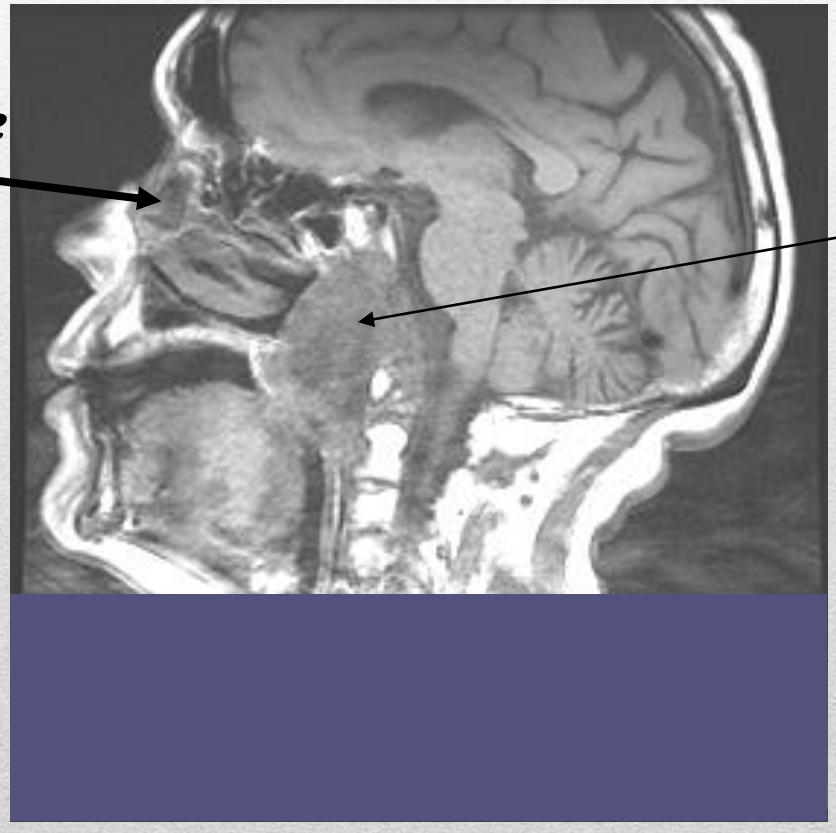
Do we need an extensive work up ?

No need distant tumor evaluation

But need:

1. High quality local/regional imaging
2. And OARs evaluation

Warning ! « A train can hide a second…and even a third one ! »



What is the optimal dose ?

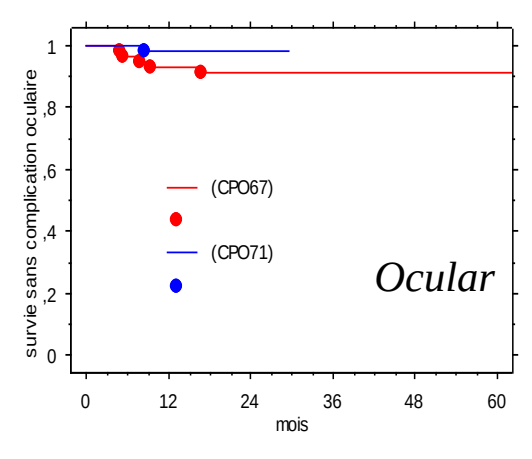
Skull base protocols in adults at ICPO since 1995

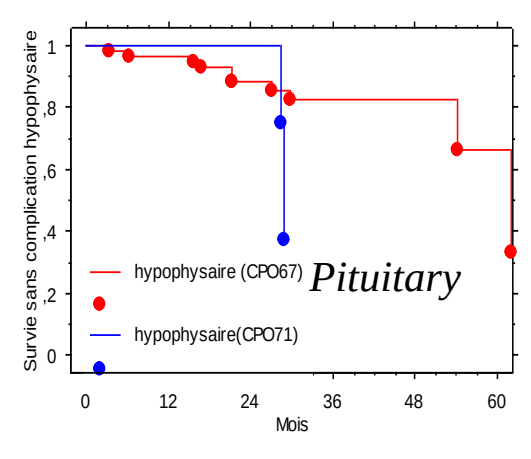
- **Chondrosarcomas**:
  - *2 succesive studies with dose-escalation :*
    - 1995-2000: 67 CGE, fractionated,combined X+P
    - 2001-on going: 71 CGE, fractionated,combined X+P*
- **Chordomas**:
  - *3 successive studies with dose-escalation :*
    - 1994-2000: 67 CGE, fractionated,combined X+P
    - 2001-2006: 71 CGE, fractionated,combined X+P
    - 2006-on going: 74 CGE, fractionated,combined X+P*

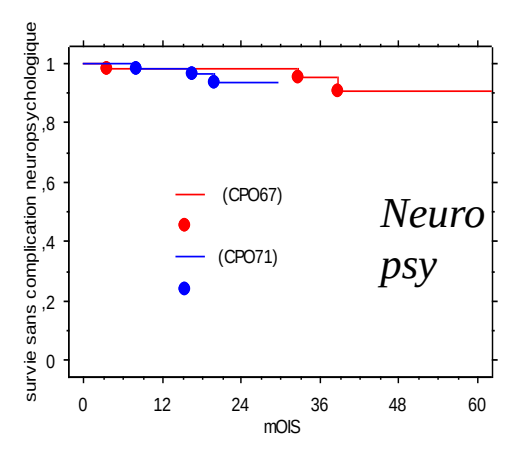
** Changes in X/P proportion (2006): from 2/3 X to 1/2 X*
Changes dpf: all 1.8 CGE

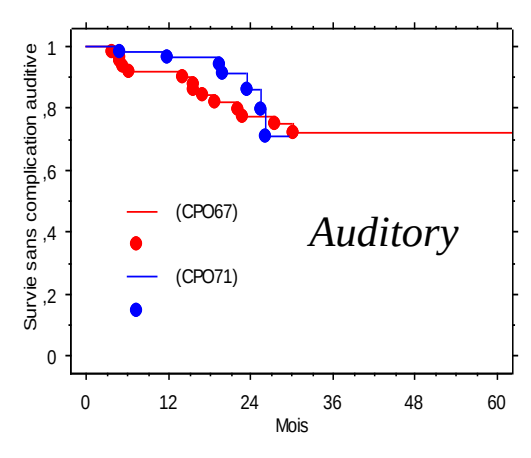
Structure	Level A	Level B	Level C
Chiasm	*58*		
Contr ON	*58*		*60*
Ipsi ON **No invaded**	*58*	*60*	*62*
Invaded: ***Functional**	*60*		*68*
***Non functional**	*No limit*		
B Stem	*Max: 64(contact:67):*		
	to ≤.5	*to ≤1*	*to ≤1.5*
Controlat Cochl	*Max: 58*		
Ipsi Cochl	*58*	*64*	*No limit*

Long term sequelae: CPO results in first 2 successive studies





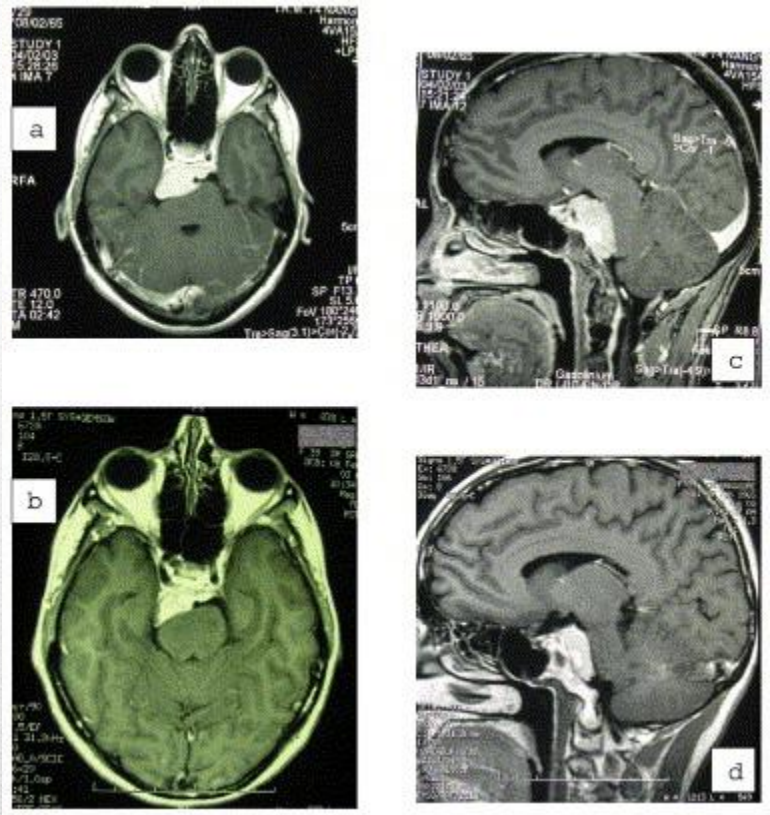




AUTRES TUMEURS DU SNC

Les méningiomes

- T fréquente: 20% TC, 25% T médullaires
- Evolution var. selon histo: bénins (90%); atypiques (5%); malins (5%)
- Tt: essentiellement chir (possible 40-60%)
- RT: semble ↘ risque (90 ↘ 20% a 15A)



Méningiome bénin avant et après protonthérapie

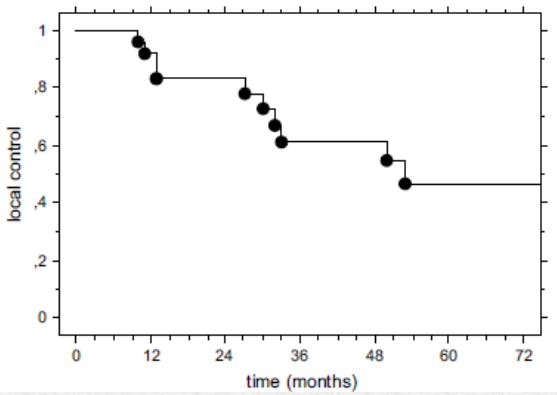
(Noel G, IJROBP, 2005)

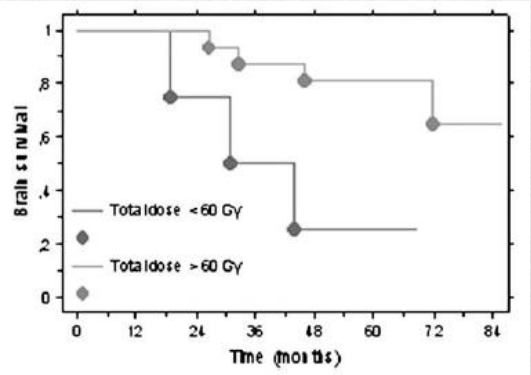
- CPO, 1994-2002
- 51 pts, dose moy 60,6 CGE(54-64)
- F Up my: 25 m
- Evolution: Regr: 72%, Stabil: 20%
- Complic: 2 gr3 (audition, Ins pituit)

Méningiome bénin , série CPO

(Noel G, IJROBP, 2005)

- ICPO exp., 1999-2006
- 24 meningioma pts
  - Atyp: 19
  - Malignant: 5
- Dose: mean 65 Gy(RBE), frac
- FUp: med 32 m (1-72)
- Failures: 10 cases
- Severe tox: 1 Rnecrosis



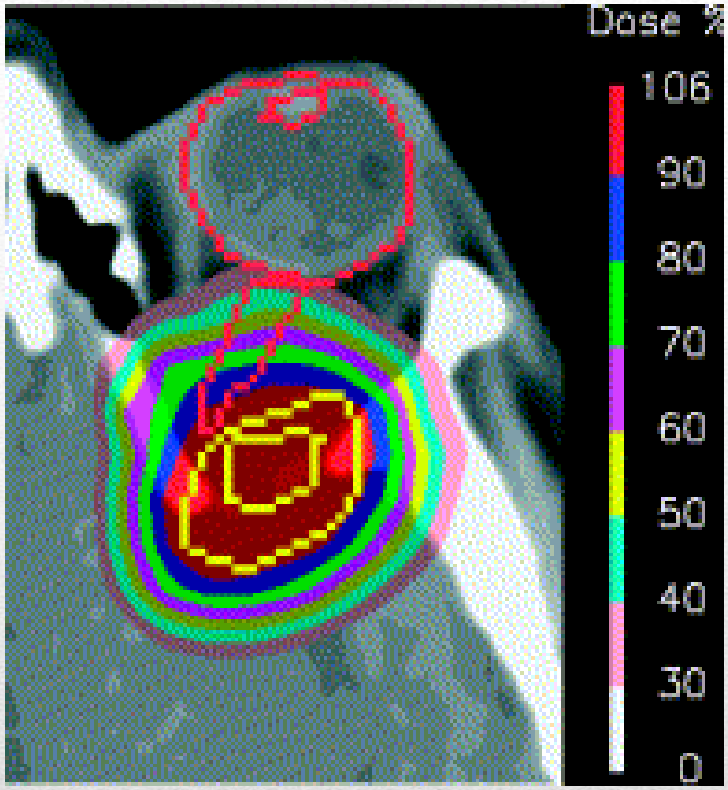


COMBINED PROTON AND PHOTON CONFORMAL RADIOTHERAPY FOR INTRACRANIAL ATYPICAL AND MALIGNANT MENINGIOMA

CHRISTOS BOSKOS, M.D.,*† LOIC FEUVRET, M.D.,*‡ GEORGES NOEL, M.D., PH.D.,§ JEAN-LOUIS HABRAND, M.D.,* PASCAL POMMIER, M.D., PH.D.,‖ CLAIRE ALAPETITE, M.D.,* HAMID MAMMAR, M.D.,¶ REGIS FERRAND, PH.D.,* GILBERT BOISSERIE, PH.D.,‡ AND JEAN-JACQUES MAZERON, M.D., PH.D.‡

Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 2, pp. 399–406, 2009

Ex: M orbite:
52 CGE, 3 fx



Pr (spot S) dans méningiomes

(Weber DC, Rad Onc, 2004)

- Med F Up: 34 m
- 3Y PFS: 91,7 %
- 3Y S: 92,9 %
- IRM: stable:12; regr.: 3, prog.: 1

Pr (spot S) dans méningiomes: résultats (16)

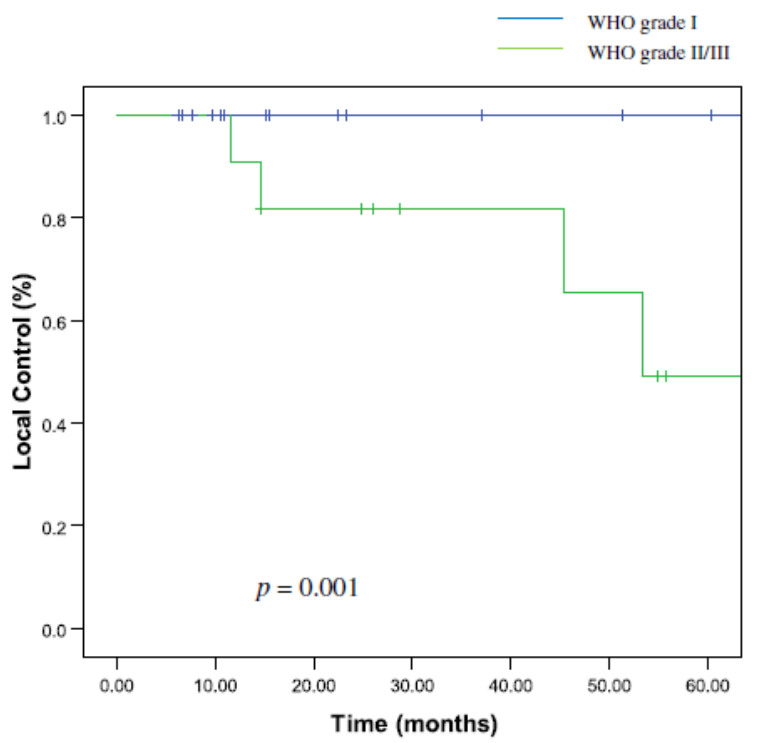
(Weber DC, Rad Onc, 2004)

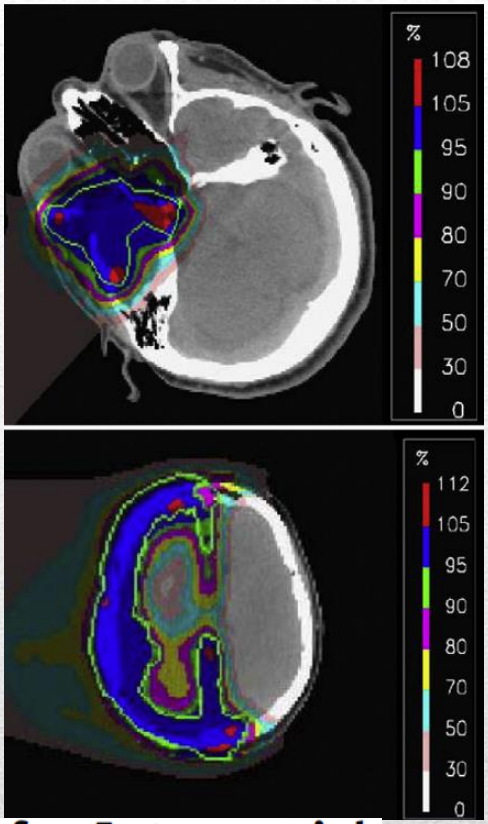
- 3Y SS complic: 76%
- 2 détérioration visuelles:

rétine (max: 55.9 CGE) & NO (max: 66,8 CGE)

- 1 radionécrose (64 CGE)

Pr (spot S) dans méningiomes: complications (3/16) *(Weber DC, Rad Onc, 2004)*



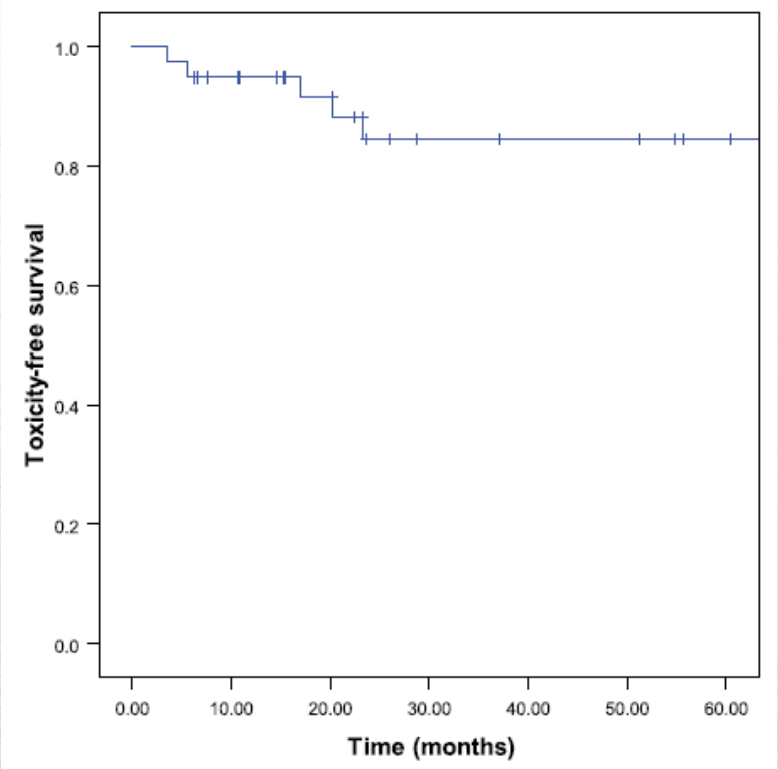


Example:
Dose distribution
2 levels

Spot Scanning-Based Proton Therapy for Intracranial Meningioma: Long-Term Results From the Paul Scherrer Institute

Damien C. Weber, M.D.,* Ralf Schneider, M.D.,† Gudrun Goitein, M.D.,† Tamara Koch, M.Sc.,† Carmen Ares, M.D.,† Jan H. Geismar, M.D.,† Andreas Schertler, M.D.,† Alessandra Bolsi, D.Sc.,† and Eugen B. Hug, M.D.†

Int J Radiation Oncol Biol Phys, Vol. 83, No. 3, pp. 865–871, 2012



- 5 cases (31%) with > G3 tox:
  - Rnecrosis: 3
  - Neuropathy: 2

Weber DC, Spot Scan. P+ in meningioma (Cont), 2012 : toxicity

- MGH experience
- 10 meningiomas treated with P+
- Replanned for IMXRT

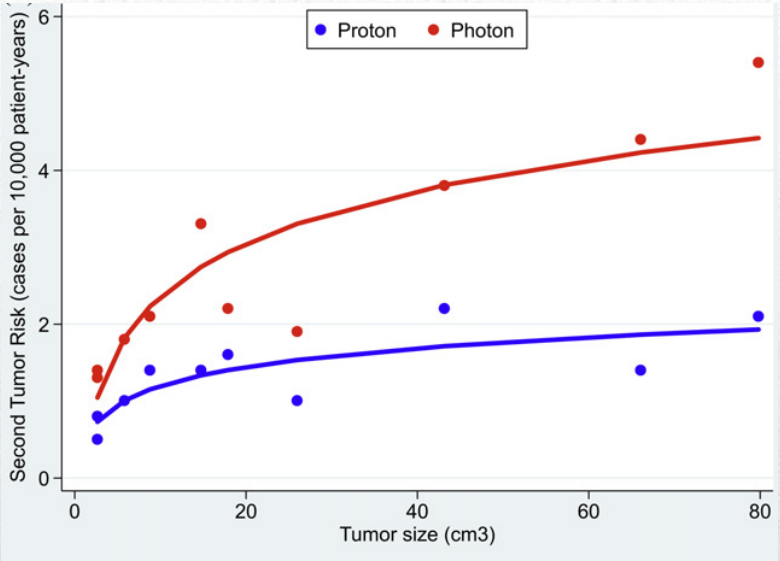
Table 3 Dose characteristics for proton and photon treatment plans ($n = 10$)

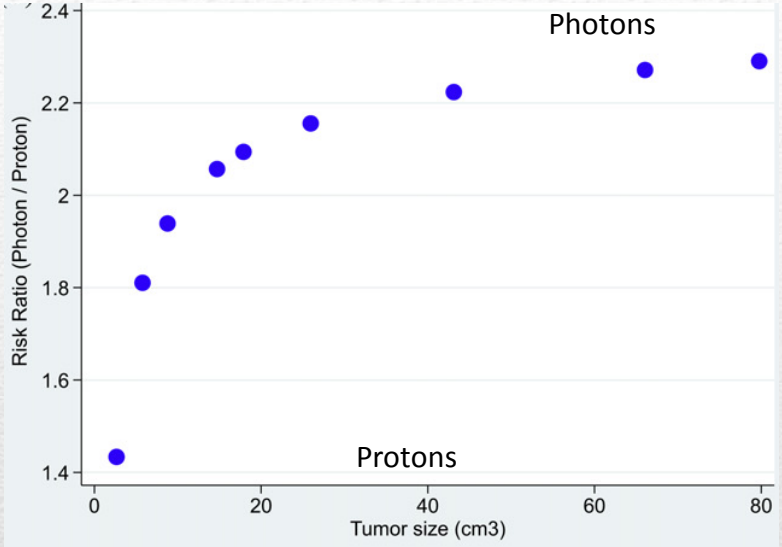
Organ at risk	Mean EUD (Gy)		P *
	Proton RT	Photon RT	
Whole brain	19.0	22.8	<.0001
Temporal lobe			
Left	25.8	34.6	.007
Right	25.8	32.9	.008
Hippocampus			
Left	13.5	25.6	<.0001
Right	7.6	21.8	.001
Brainstem	23.8	35.2	.004
Optic chiasm	29.6	36.8	.11
Optic nerve			
Left	28.5	33.8	.04
Right	25.1	31.1	.07
Cochlea			
Left	12.2	15.8	.39
Right	1.5	8.8	.01
Pituitary gland	29.2	37.0	.047
Hypothalamus	23.5	59.0	.24

Projected Second Tumor Risk and Dose to Neurocognitive Structures After Proton Versus Photon Radiotherapy for Benign Meningioma

Nils D. Arvold, M.D.,* Andrzej Niemierko, Ph.D.,† George P. Broussard, B.S.,† Judith Adams, C.M.D.,† Barbara Fullerton, Ph.D.,† Jay S. Loeffler, M.D.,† and Helen A. Shih, M.D., M.S., M.P.H.†

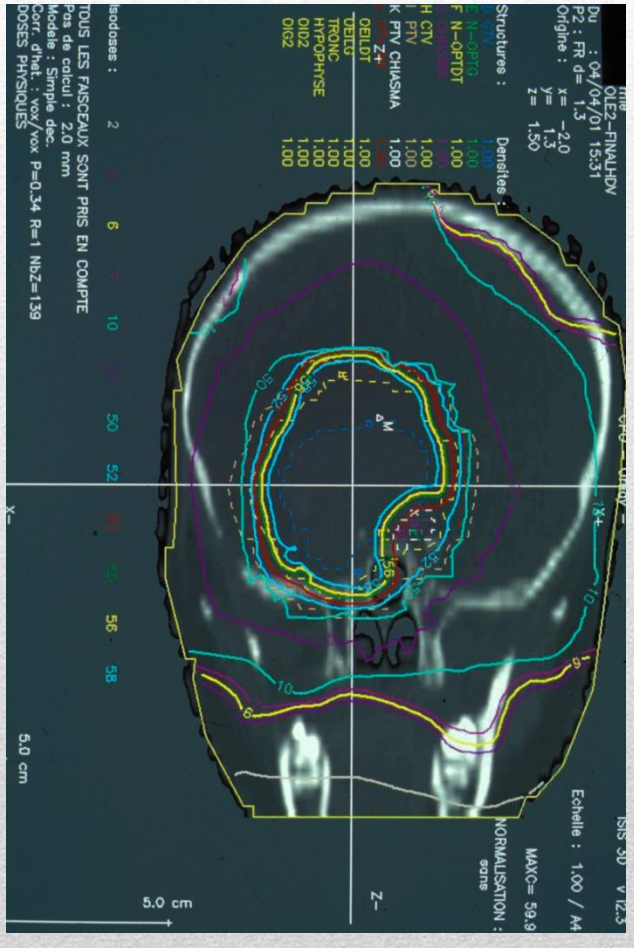
Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. e495–e500, 2012





Arvold ND et al (cont): K2 associated XR vs P

Pediatric Case report



Post Gknife meningioma

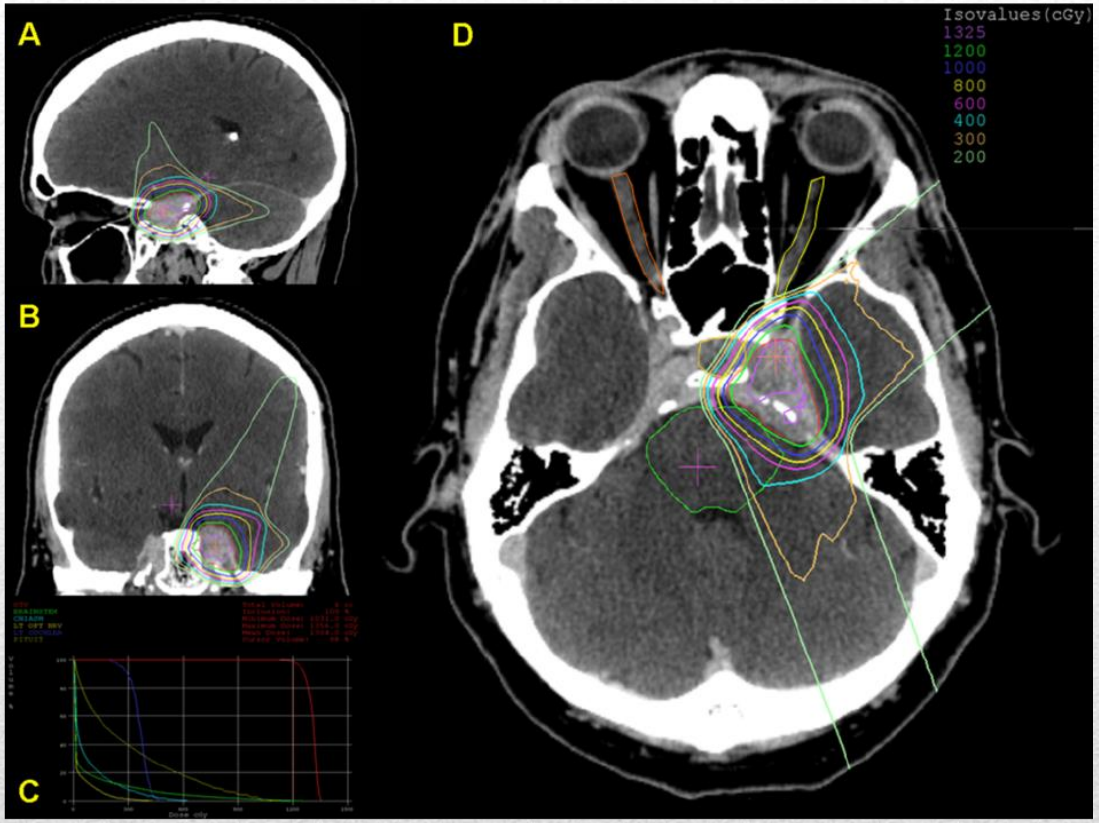
La « radiochirurgie »

- Stereotactic radiosurgery review:
  - 1980-2011, English literature
  - 298 reports (9 protons): #10,000 pts
  - Types: meningiomas (104), schwannomas/acoustic N (26), pituit adenoma (19), CH/CS (11), chemodectomas (7), others (10)

Radiosurgery with photons or protons for benign and malignant tumours of the skull base: a review

Maurizio Amichetti[1*], Dante Amelio[1] and Giuseppe Minniti[2,3]

Radiation Oncology 2012, **7**:210



Proton radiosurgery (MGH)

Amichetti M, Rad Oncol, 2012

- 85 patients, traités au Cap
- 64 evaluables
- 2 « tailles »: <14cc (26); >14cc (38)
- Fraction: 1,2, ou 3
- Dose « equivalente »: 10,4-22 Gy (moy:17,4)

Radiochir Pr dans MAV *(Vernimmen FJ, IJROBP, 2005*)

Résultats cliniques: oblitération

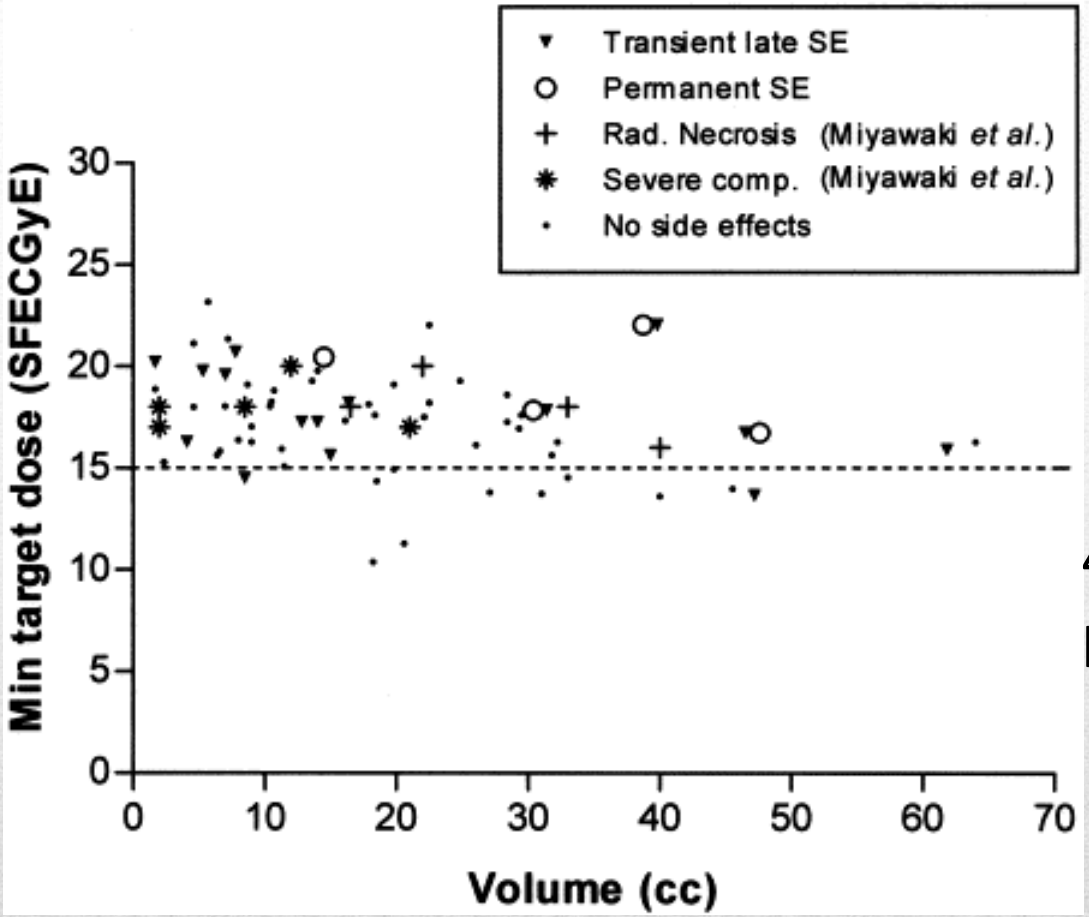
- Excellent: 48,5 %
- Bon: 2 %
- Moyen: 34 %
- Inchangé: 8,5 %
- DC: 2/64

Volume (cc)			No. of patients		Complete response		CT	MRI	Angiogram
<14	<10	Male	6	13	6	8 (61.5%)	5	4	3
		Female	7		2				
	10–13.9	Male	2	5	2	4 (80%)	3	—	2
		Female	3		2				
≥14		Male	18	28	8	12 (43%)	8	5	3
		Female	10		4				
Total		Male	26	44	16	24 (54.5%)	16	9	8
		Female	18		8				

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging.

Resultats selon taille

(Vernimmen FJ, IJROBP, 2005)



4/64 deficits perm ± épilepsie

Complications tardives (15/64)

(Vernimmen FJ, IJROBP, 2005)

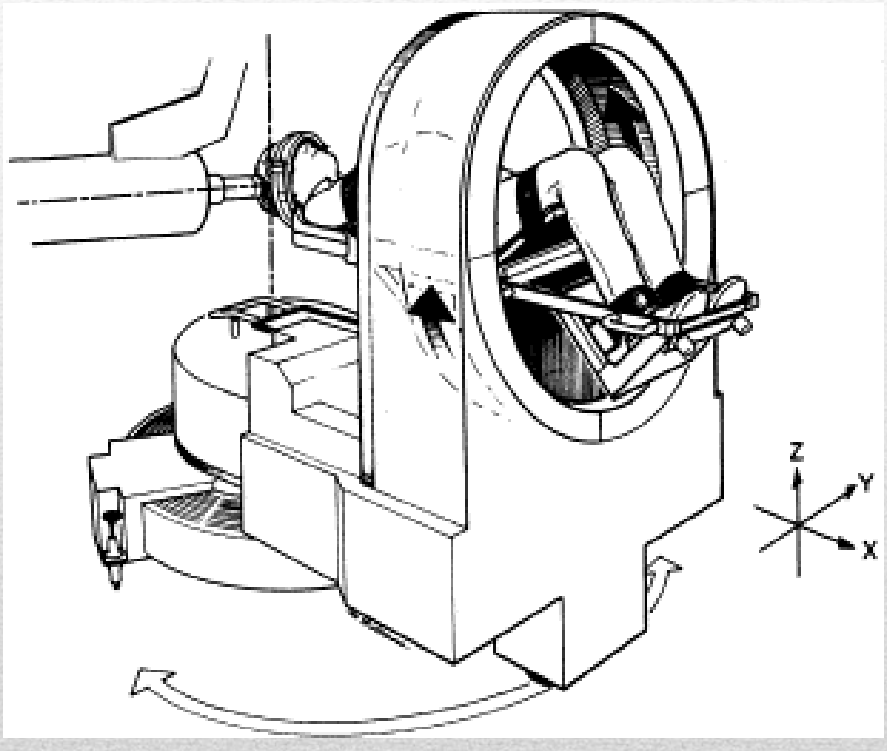
Table 5. Incidence of acute and late side effects (RTOG/EORTC morbidity scoring)

Volume cc		Acute side effects					Permanent late side effects	
		G I	G II	G III	G IV	Transient late side effects, (requiring steroids)*	G III	G IV
<14	<10	—	1	—	—	6 (4)*	—	—
	10–13.9	1	—	—	—	1	—	—
≥14		—	6	—	2	8 (8)*	2	2
Total		1	7	—	2	15	2	2

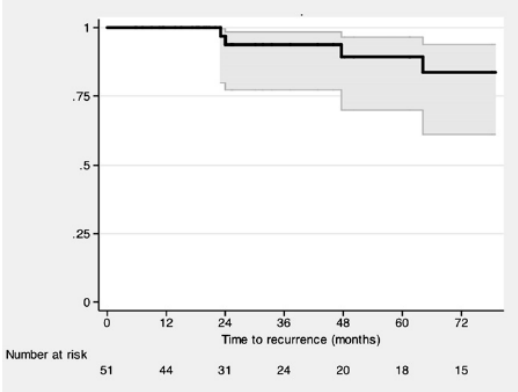
Abbreviations: RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer.

Complications : influence taille *(Vernimmen FJ, IJROBP, 2005)*

Positionneur MGH, Boston



Treatment characteristic	Median	Range	IQR
Tumor volume	2.1 cm^3	0.3–9.7	1.1–3.4
Prescription volume*	4.3 cm^3	1.1–17.7	2.7–7.0
Conformity index*	2.2	1.1–4.7	1.8–2.7
Prescribed dose	13.0 Gy(RBE)	10.0–15.5	12.0–15.0
Maximum dose to tumor*	14.4 Gy(RBE)	11.3–17.1	13.6–16.7
Minimum dose to tumor*	12.2 Gy(RBE)	4.5–15.7	11.8–13.5
Homogeneity index*	1.1	1.0–1.3	1.1–1.1
Gradient score†	81.7	67.1–113.5	76.3–89.8



- **MGH: 50 cases, 1996-2007**
  - Med FUp: 32 m(6-133)
  - 46/51 (91%) LC (No ↗ size)
    - Patho: Atyp : 80%, B : 96%
    - Timing: SRT#1: 100% LC
      SRT#2: 75% LC
  - Tox: 3/51(6%): epil, necrosis, panhypo

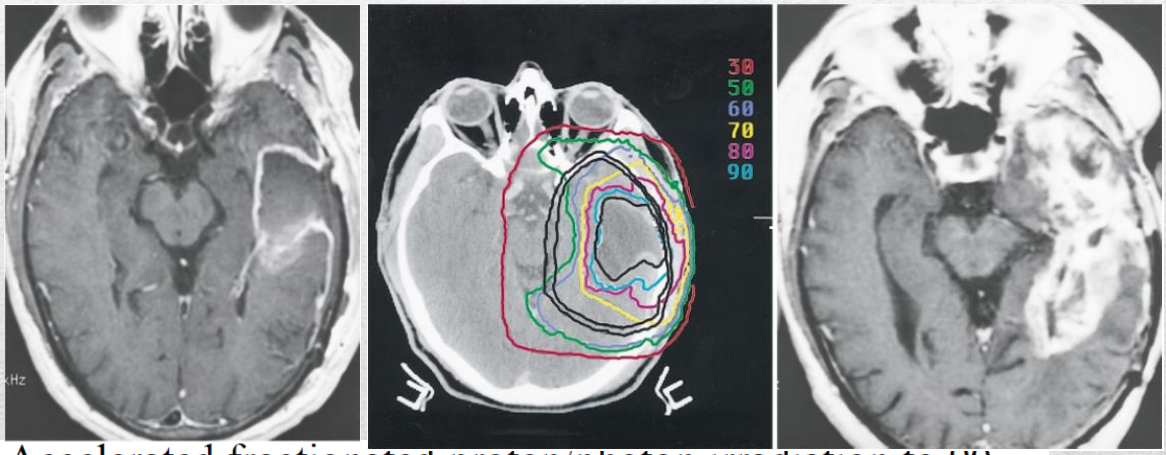
PROTON STEREOTACTIC RADIOSURGERY FOR THE TREATMENT OF BENIGN MENINGIOMAS

LIA M. HALASZ, M.D.,*§ MARC R. BUSSIÈRE, M.SC.,† ELIZABETH R. DENNIS, M.SC.,† ANDRZEJ NIEMIERKO, PH.D.,† PAUL H. CHAPMAN, M.D.,†‡§ JAY S. LOEFFLER, M.D.,†§ AND HELEN A. SHIH, M.D., M.P.H.†§

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 5, pp. 1428–1435, 2011

LES GLIOMES MALINS

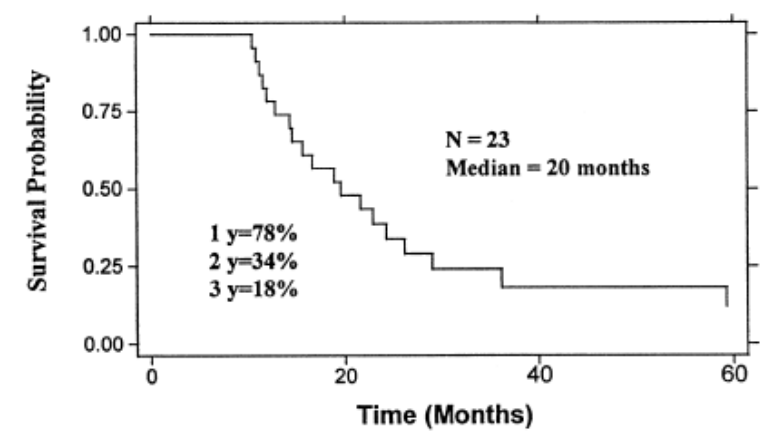
- MGH series, 23 cases, 1992-96
- High dose protonT: 90 Gy, frac
- Favorable case: Control at 29 m post resection, but Rnecrosis +++

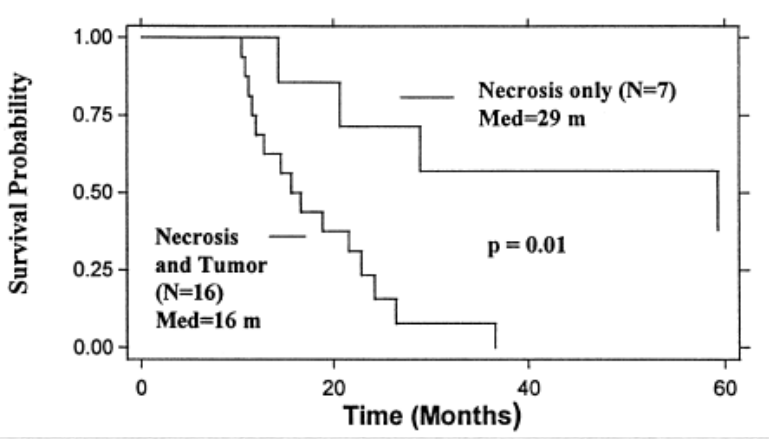


Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial

MARKUS M. FITZEK, M.D., ALLAN F. THORNTON, M.D., JAMES D. RABINOV, M.D., MICHAEL H. LEV, M.D., FRANCISCO S. PARDO, M.D., JOHN E. MUNZENRIDER, M.D., PAUL OKUNIEFF, M.D., MARC BUSSIÈRE, M.SC., ILANA BRAUN, B.SC., FRED H. HOCHBERG, M.D., E. TESSA HEDLEY-WHYTE, M.D., NORBERT J. LIEBSCH, M.D., PH.D., AND GRIFFITH R. HARSH IV, M.D., M.B.A.

J Neurosurg 91:251–260, 1999





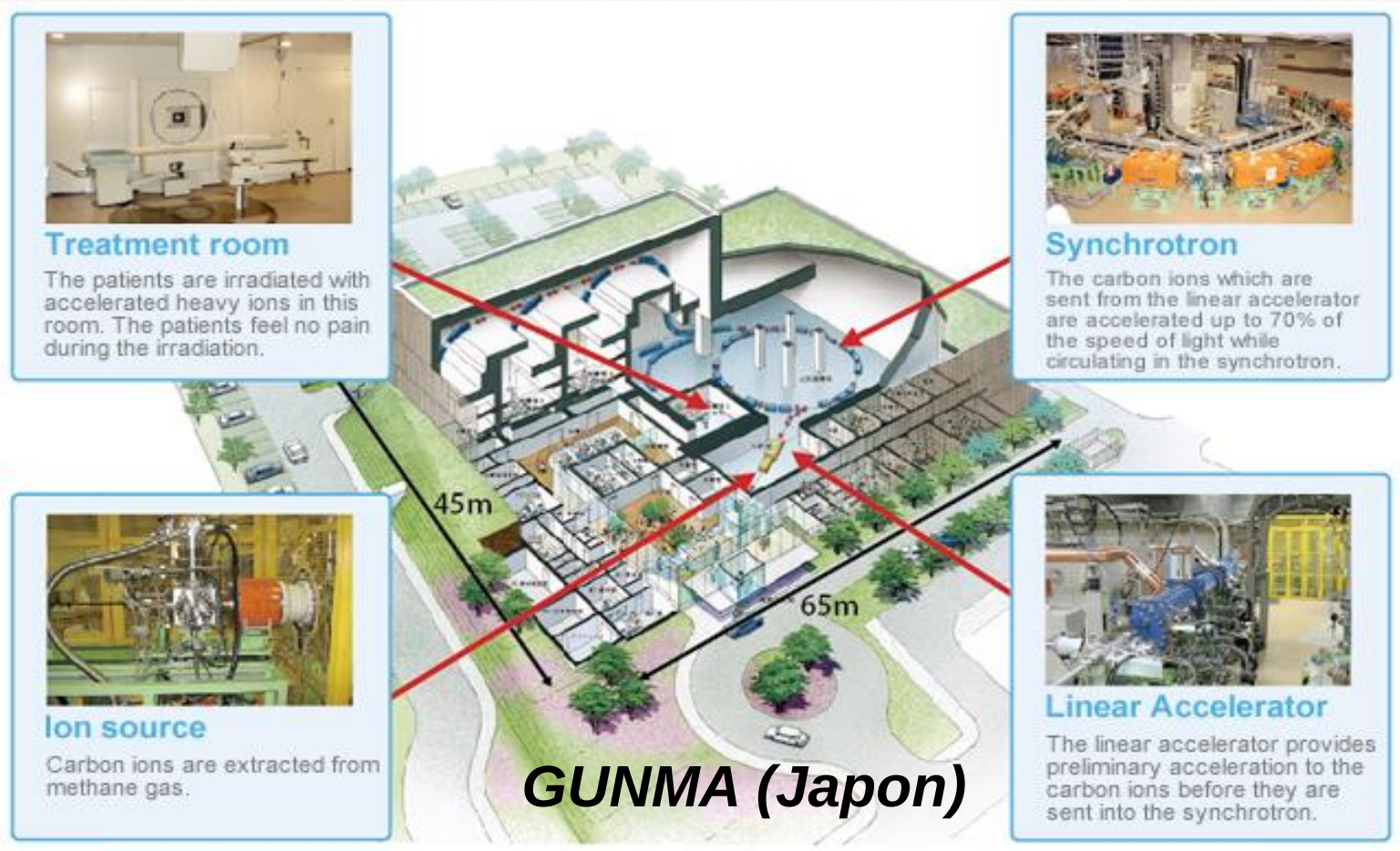
Necrosis = prolonged survival…
Failure = < 70 Gy (RBE)

Fitzek, P+ in GBL (cont)

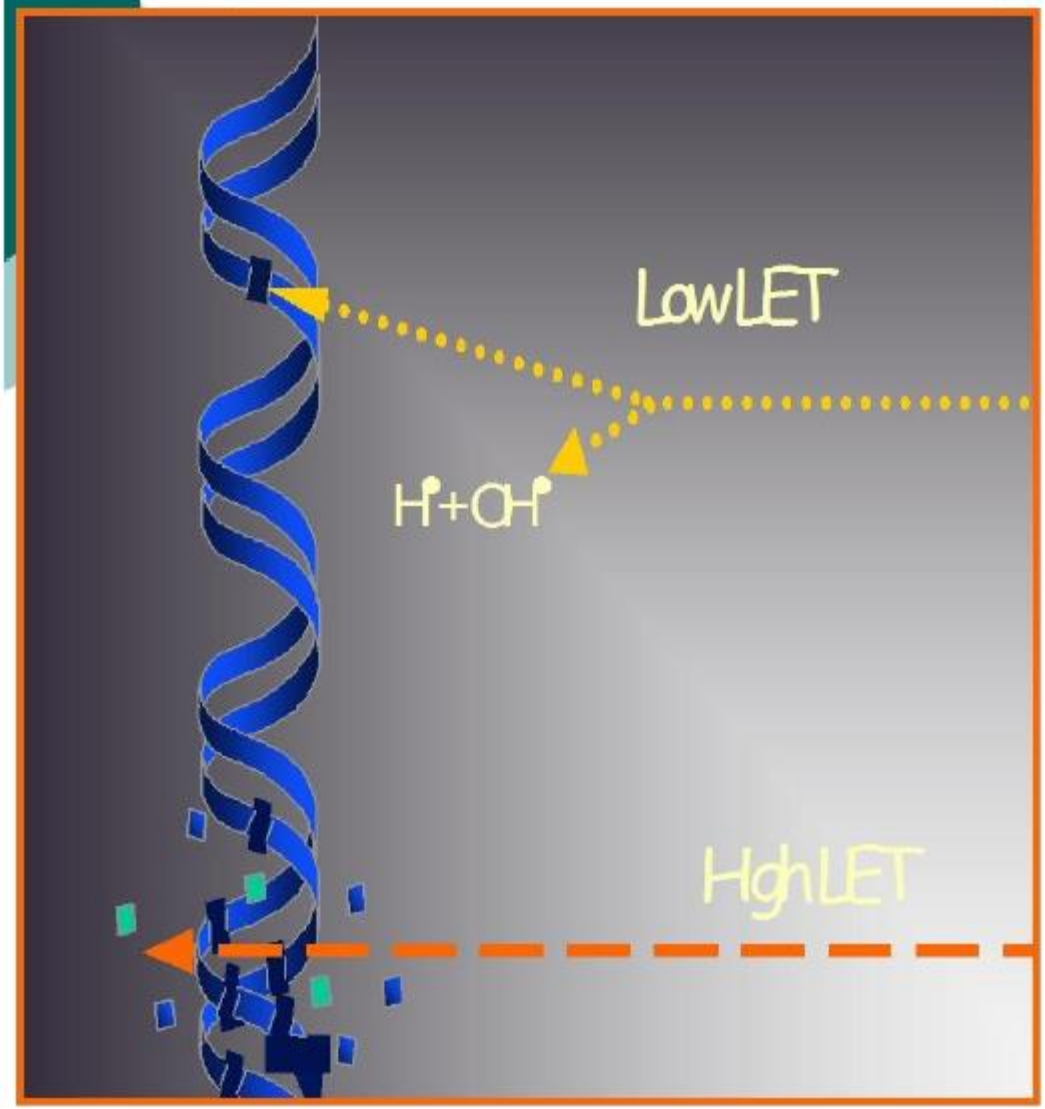
LES IONS LÉGERS: BESOIN DE PLUS D'EFFICACITÉ

Synchrotron -based carbon facilities

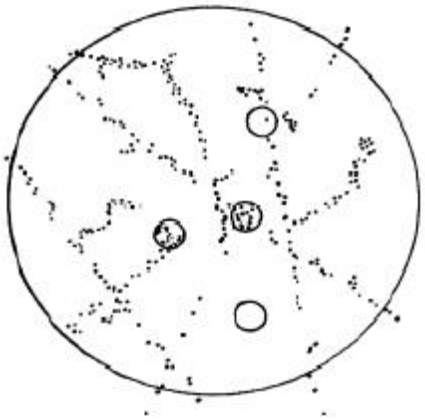
HIMAC CHIBA (Japon), HEIDELBERG (Allemagne),HIOGO (Japon), PAVIE (Italie) et GUNMA (Japon). Coming : Medaustron (Autriche)



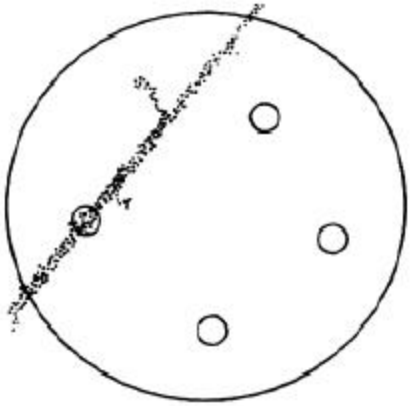
HIGH LET PARTICLES
INTERACTIONS Of IONIZING RADIATIONS WITH DNA



Low LET (X-Rays)

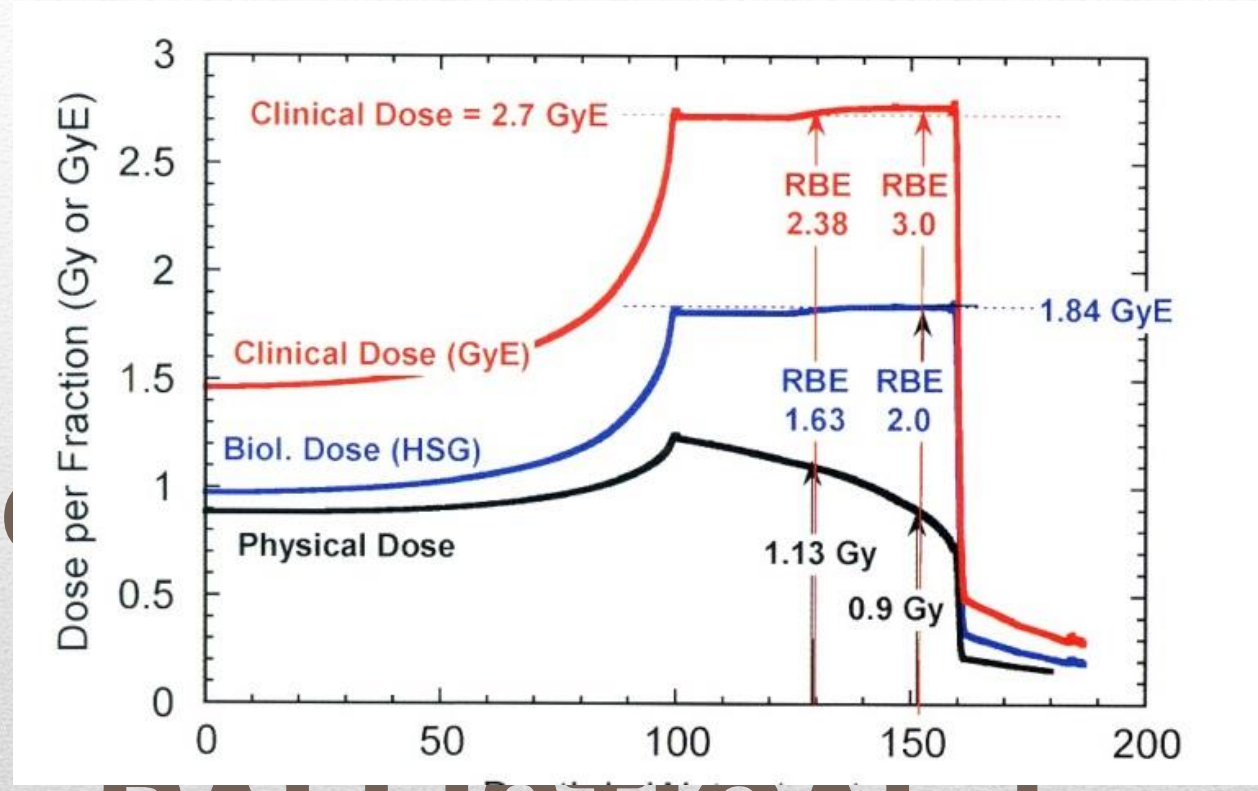


High LET (C…)



⦸ *Cell nucleus*

Radiobiologie - M Tubiana, J Dutreix, A Wambersie, Hermann Ed. 1986

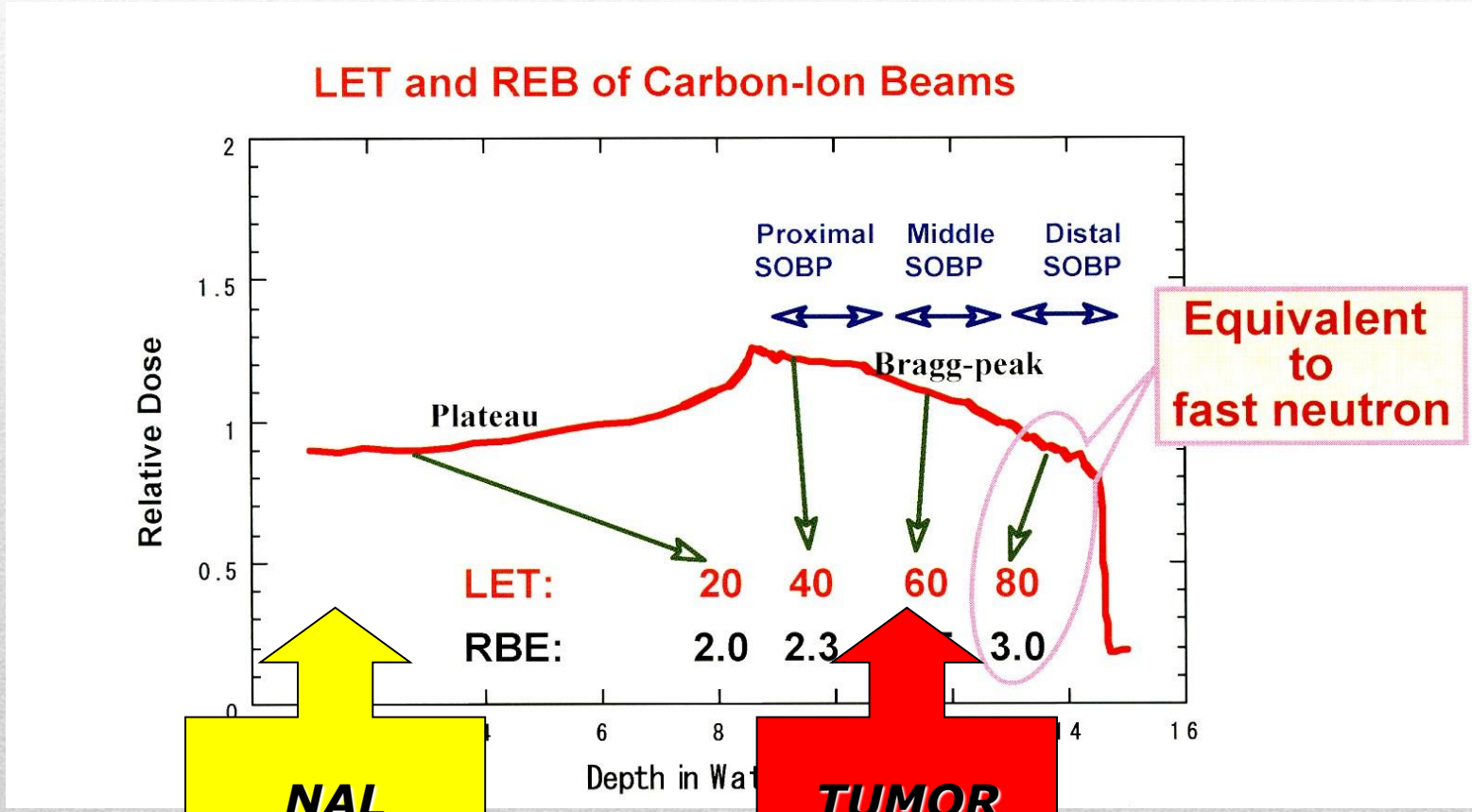


BALLISTICAL + BIOLOGICAL

ca n : diffe effect on ti

LOW/MED LET

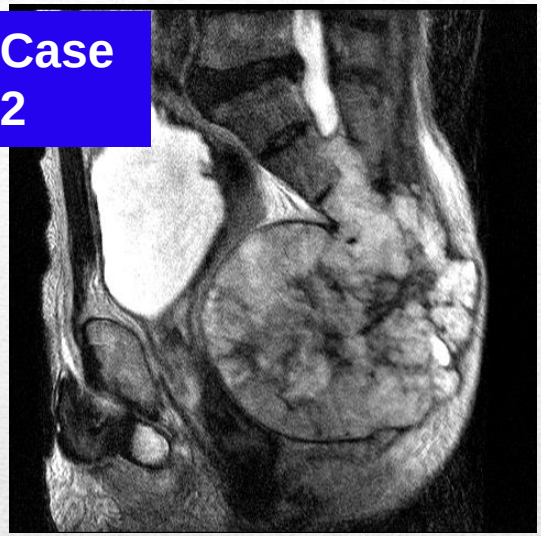
HIGH LET



NAL TISSUES

TUMOR

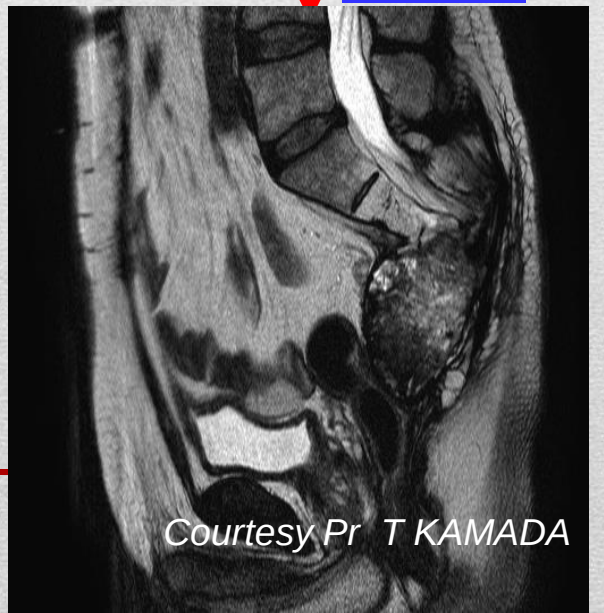
Chordoma of the sacrum



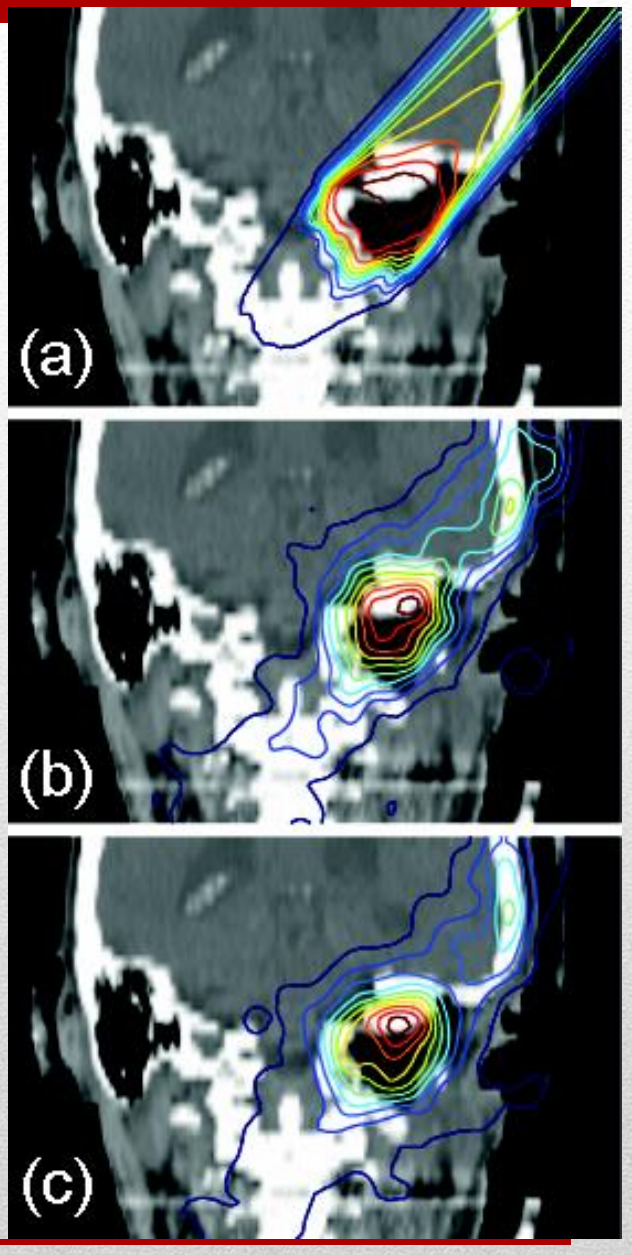
6 years

5 years

6 years

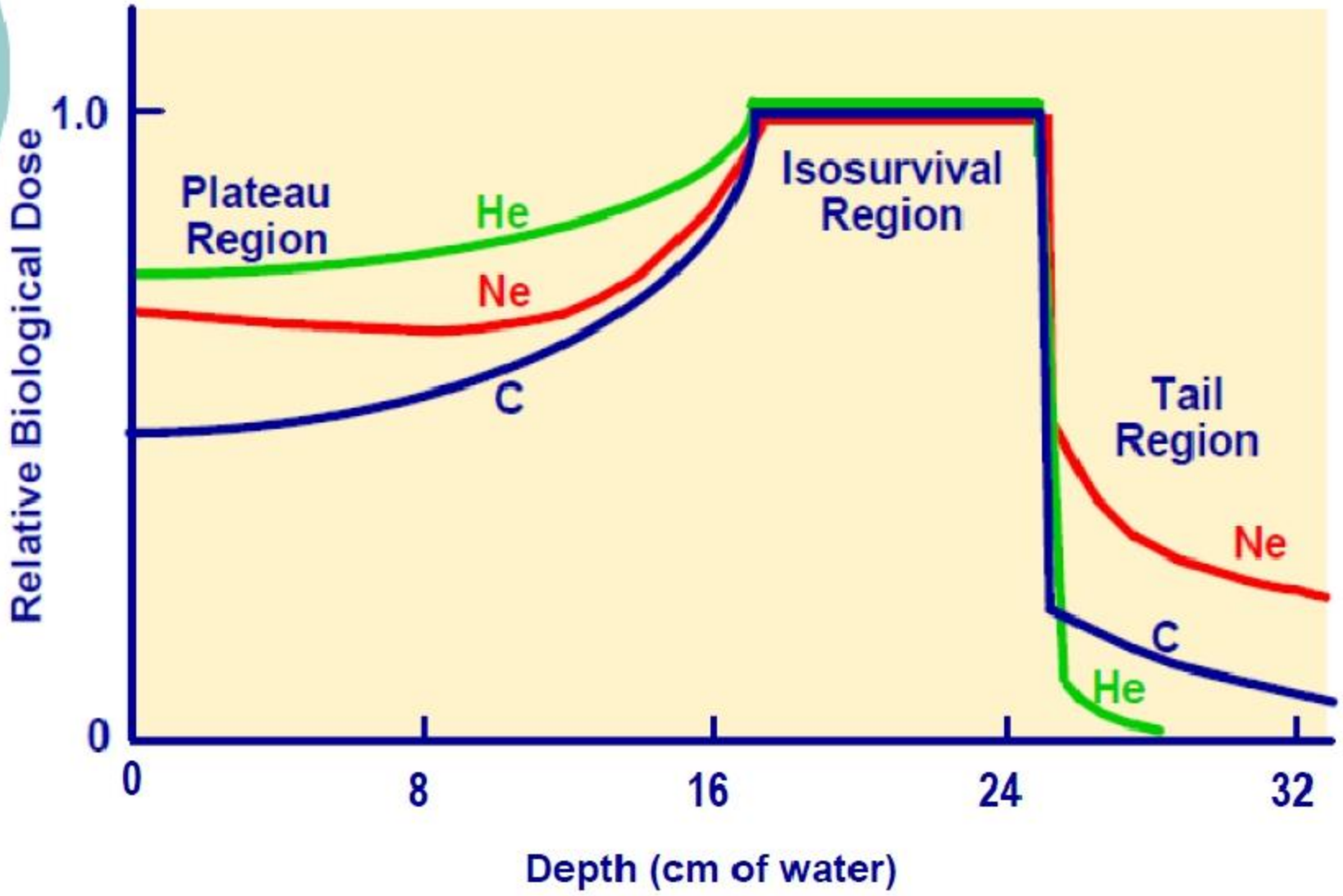


Online control :PET imaging (GSI-Darmstadt)



G. Kraft & W. Enghardt

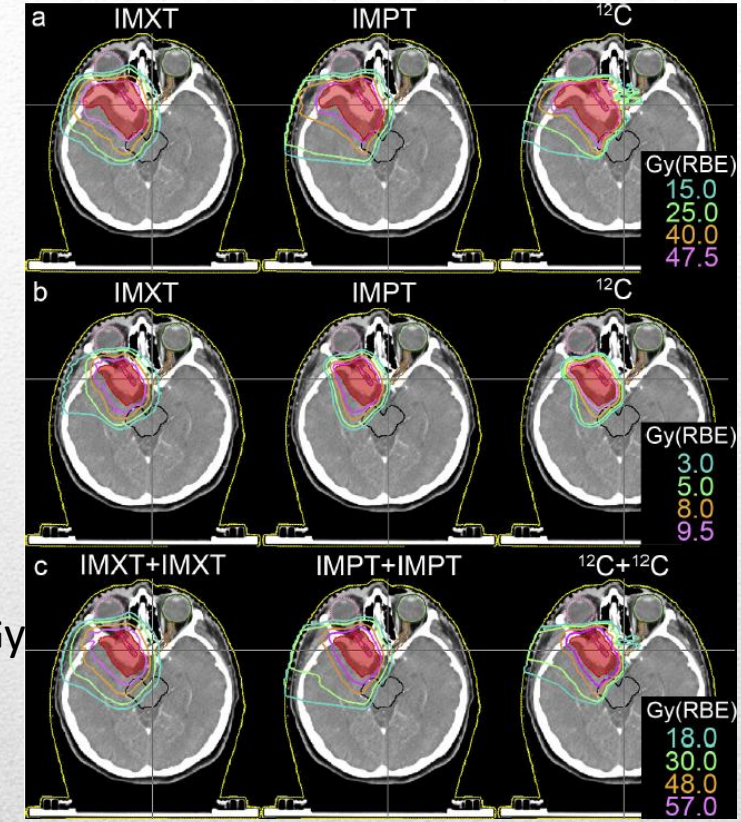
RELATIVE BIOLOGICAL DOSES FOR IONS SPECIES

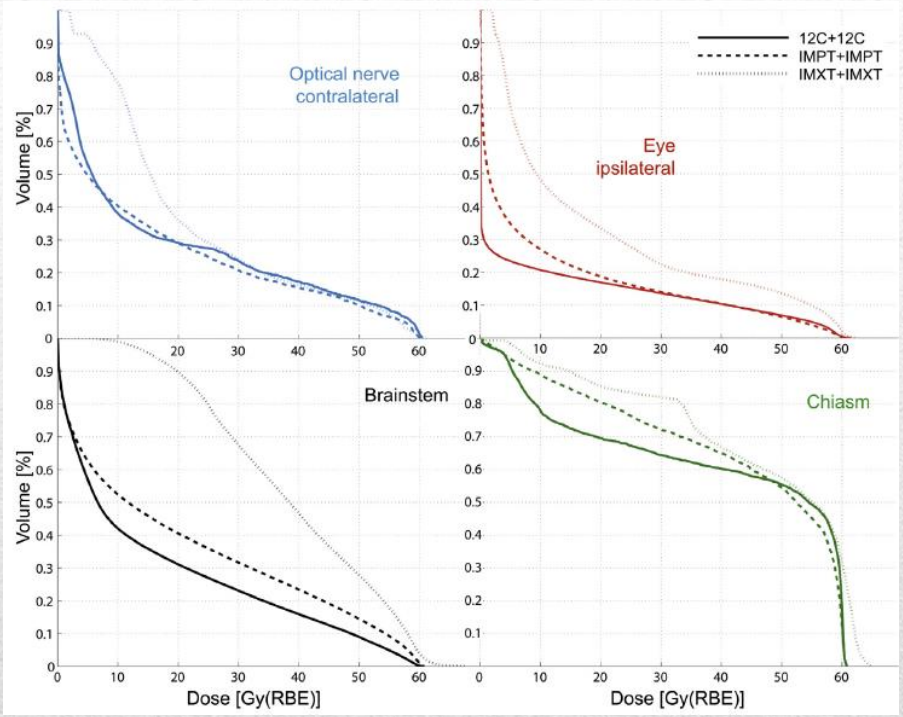


50 Gy

+ 10 Gy

50+10Gy





Meningioma. Dosimetrical intercomparison

(Mock U, Radiother Oncol, 2014)

- **Heidelberg experience in brain tumors (P+,C+,RXC+):**
- 260 pts, Med FUp: 12 m (2-29), ±conventional frac (1.8-3 Gy)
  - **B Meningioma** (58 Gy): 71/71 alive
  - **M meningioma** : 19/36 alive
  - **M Gliomas** (RX50Gy, C+18Gy): 22/34 alive (med PFS:6m)
  - **M Gliomas** (reirr): 8/21 alive

Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base

STEPHANIE E. COMBS[1], KERSTIN KESSEL[1], DANIEL HABERMEHL[1], THOMAS HABERER[2], OLIVER JÄKEL[1,2] & JÜRGEN DEBUS[1]

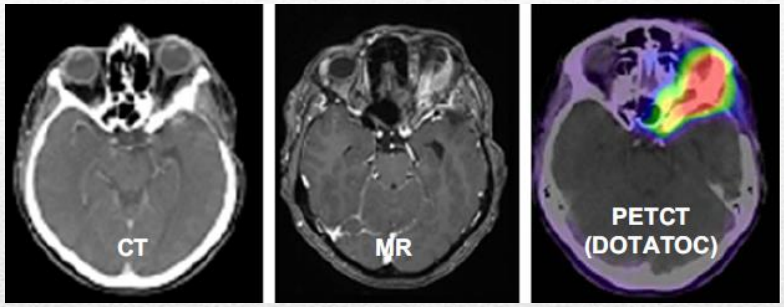
Acta Oncologica, 2013; 52: 1504–1509

- **Heidelberg experience in meningiomas (41 P+,13 C+,16 RX/C+). Recurrence (6m):**
  - **Benign** (P+, 52-7 Gy): 0/26
  - **Atypical+ Malignant** (RX50Gy,C+18Gy : 5/27(19%)
  - **Reiiradiation** (P+: 5, C+: 14), 45-58 Gy (RBE): 4/19 (33%)
  - **Toxicity:** 0 severe (including reiiradiation)

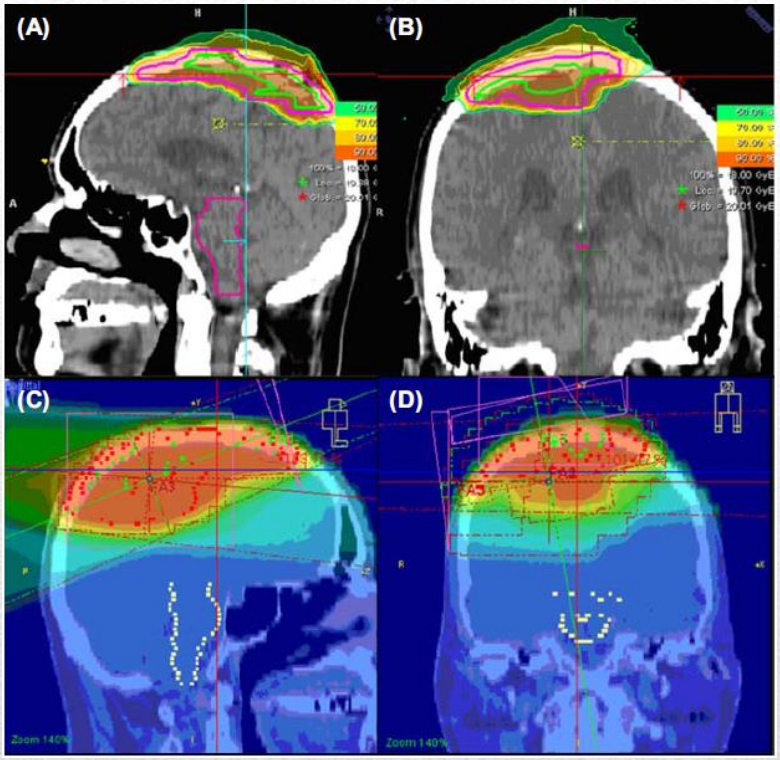
Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and ^{68}Ga-DOTATOC-PET

Stephanie E. Combs, Thomas Welzel, Daniel Habermehl, Stefan Rieken, Jan-Oliver Dittmar, Kerstin Kessel, Oliver Jäkel, Uwe Haberkorn & Jürgen Debus

Acta Oncol, 2013

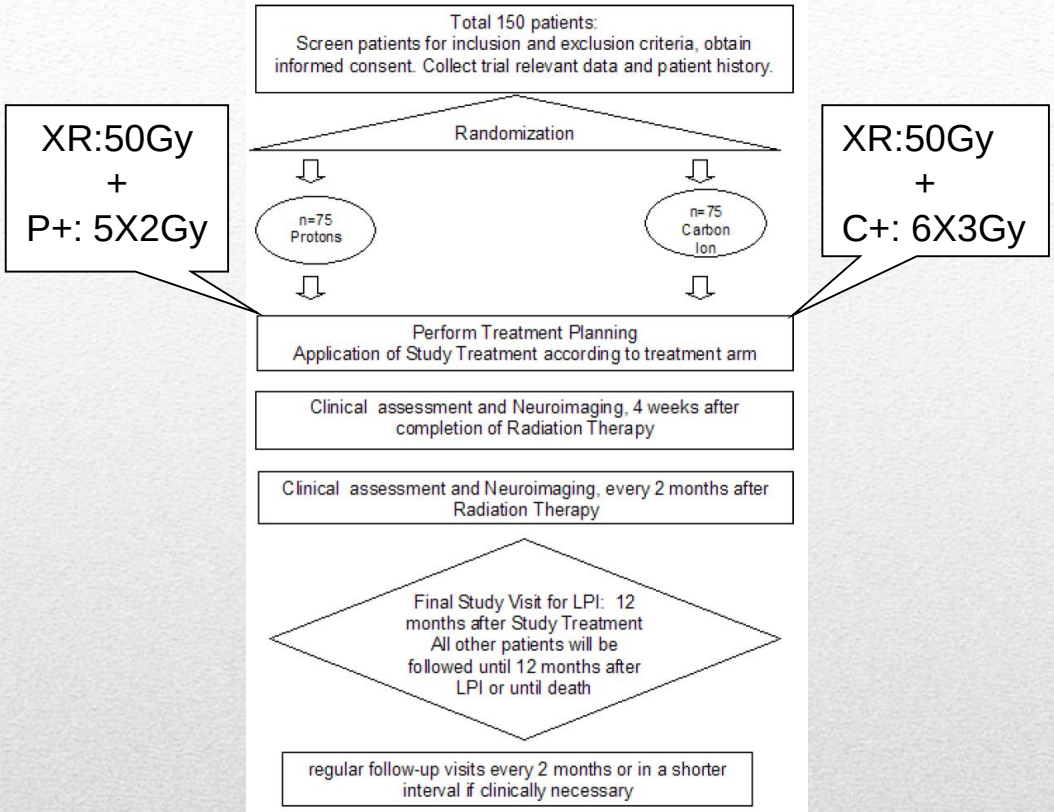


Molecular Dg imaging



Combined RX (bottom) / C+ (top) plan

Meningioma, HIT exp.*(cont)*



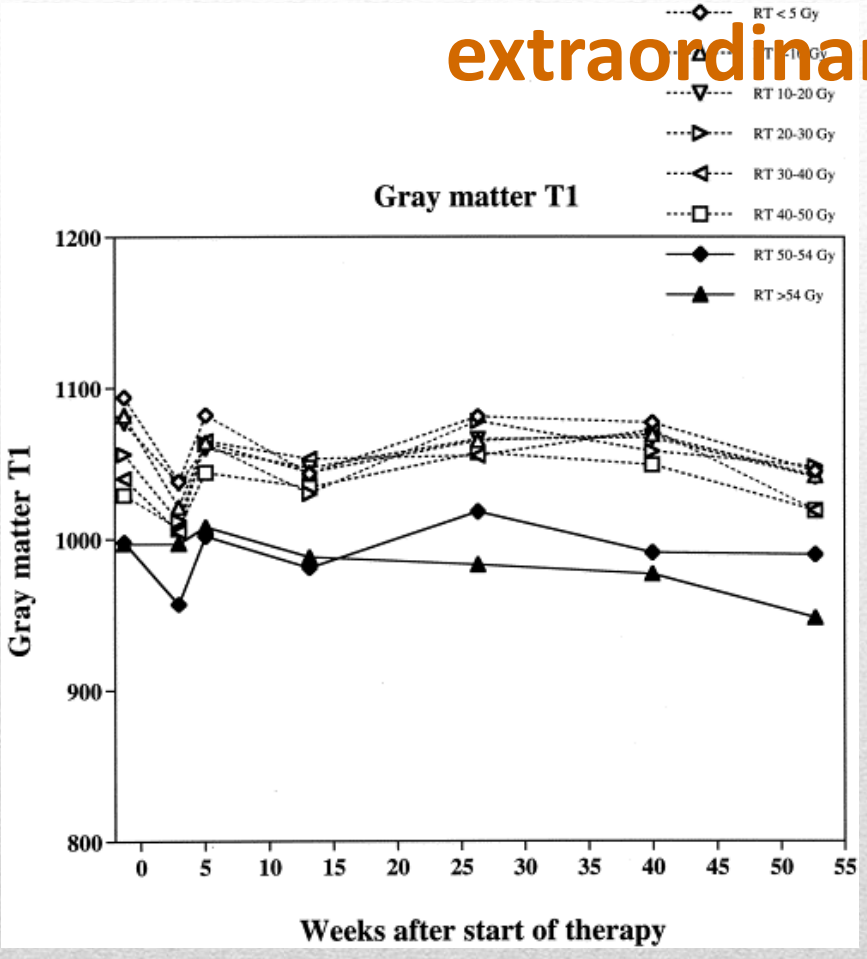
Randomized phase II study evaluating a carbon ion boost applied after combined radiochemotherapy with temozolomide versus a proton boost after radiochemotherapy with temozolomide in patients with primary glioblastoma: The CLEOPATRA Trial

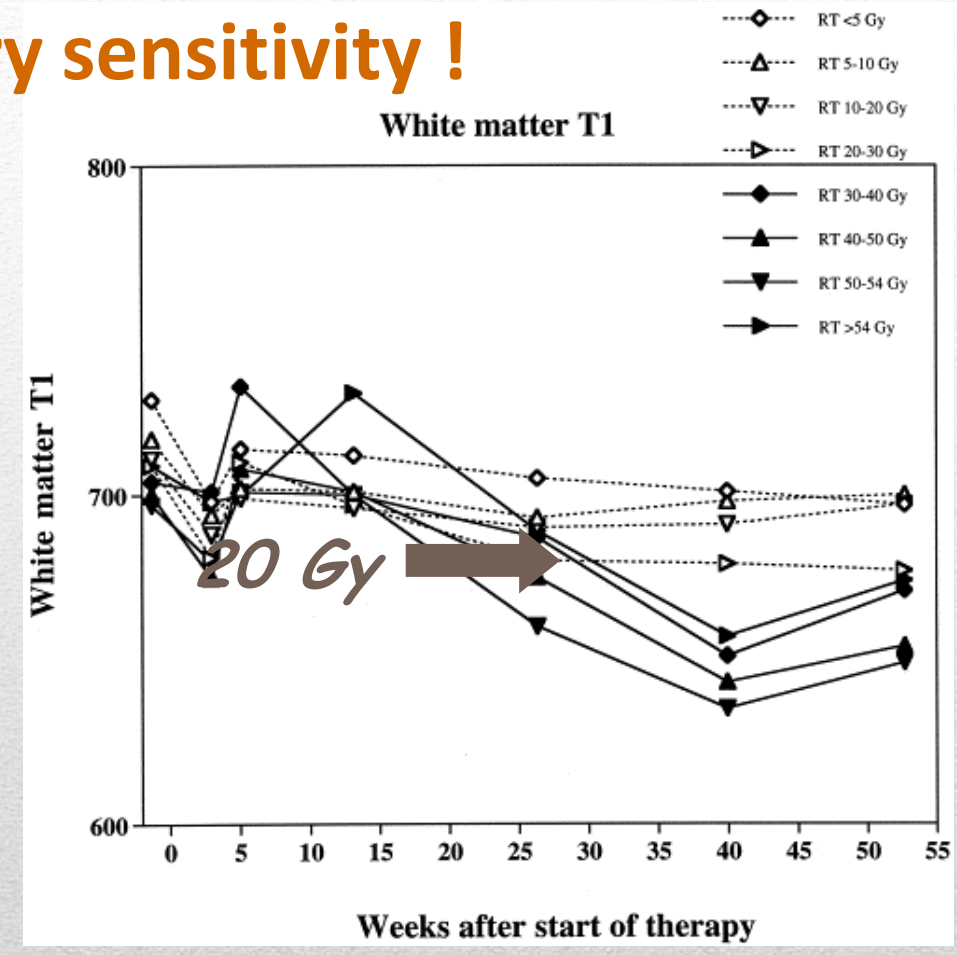
Stephanie E Combs[1*], Meinhard Kieser[2], Stefan Rieken[1], Daniel Habermehl[1], Oliver Jäkel[3], Thomas Haberer[3], Anna Nikoghosyan[1], Renate Haselmann[1], Andreas Unterberg[4], Wolfgang Wick[5], Jürgen Debus[1]

BMC Cancer 2010, **10**:478

Applications chez l’enfant

Effect on brain white matter in youngs: extraordinary sensitivity !





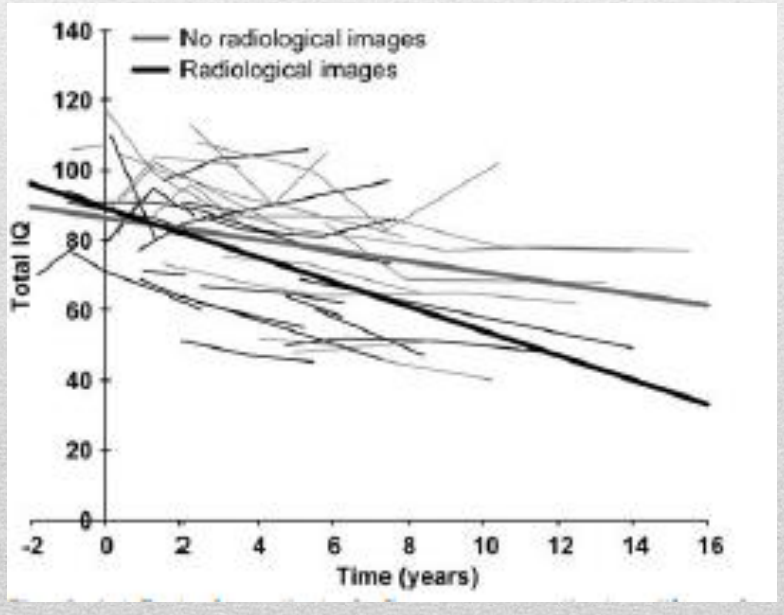
T1 MRI in pediatric brain tumor patients treated with conformal radiotherapy. Steen et al, IJROBP, 2001.

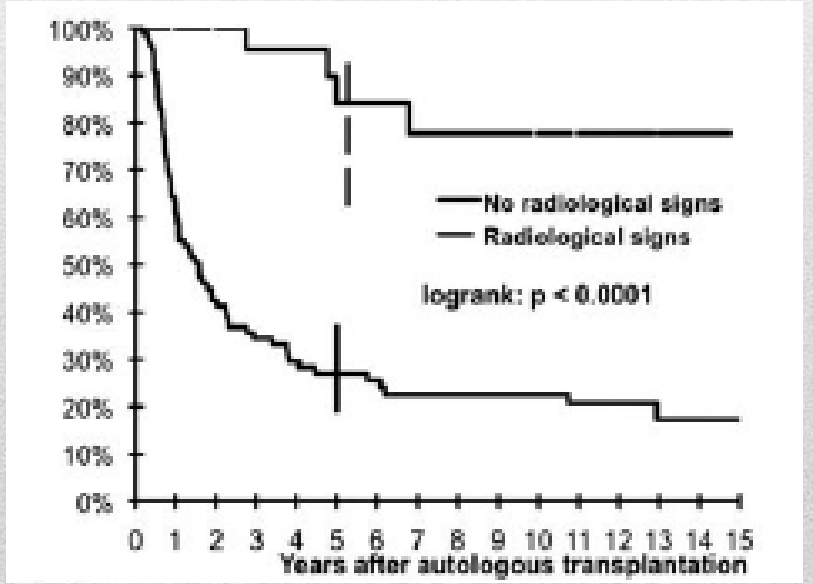
Post combined RT-HD Busulfan demyelination *(1 Year)*

Busulfan-based megatherapy + RT:

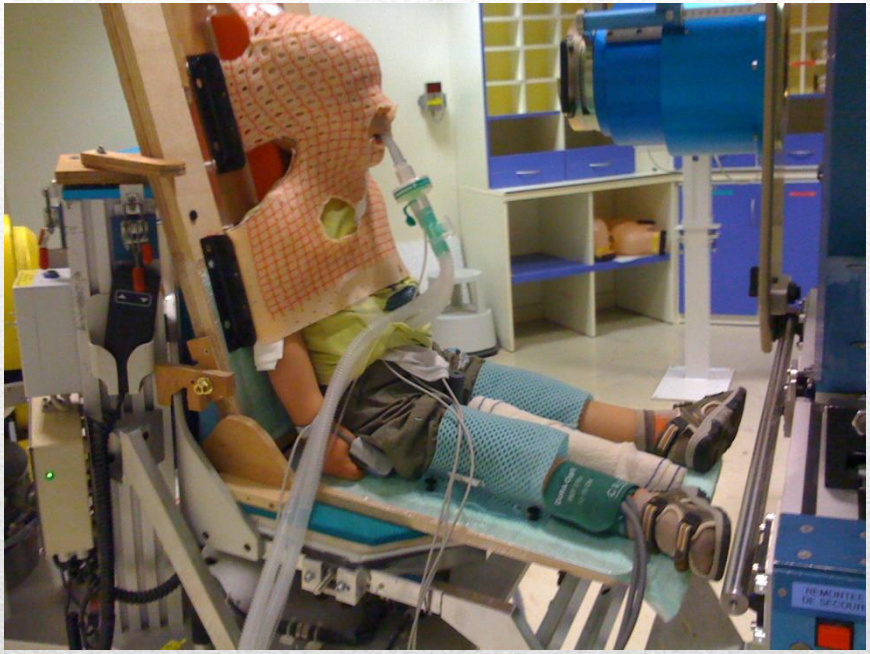
« a double-edged sword »…

Radiological anomalies





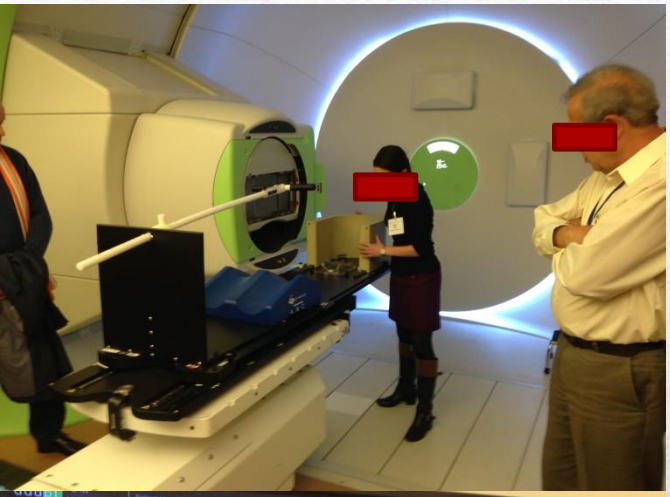
Negretti IL, NeuroOncol, 2012

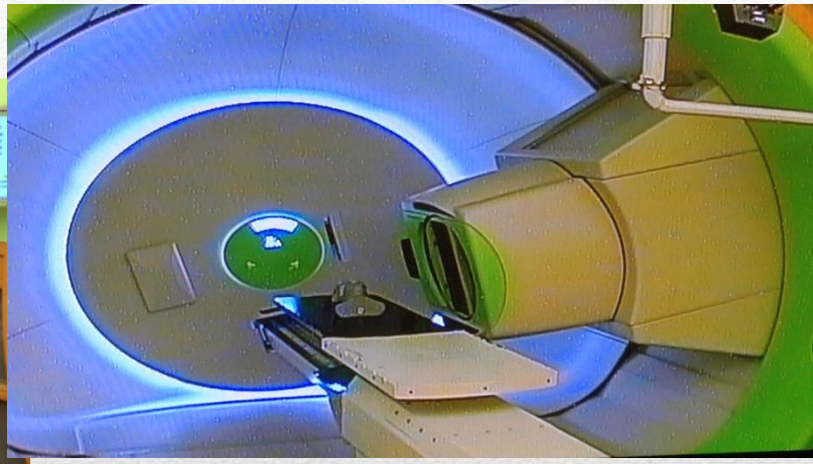


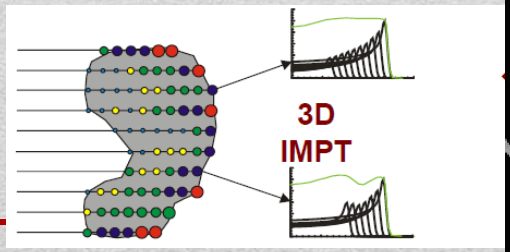
GA in supine & seated position

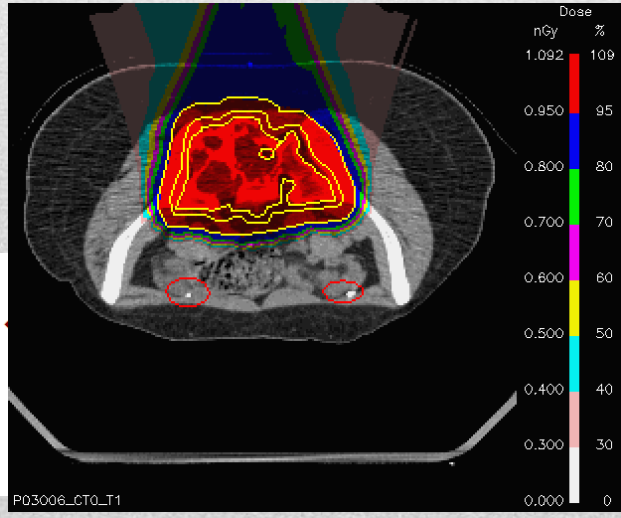
ICPO coll

Proton technology catching-up quickly most advanced photon technology

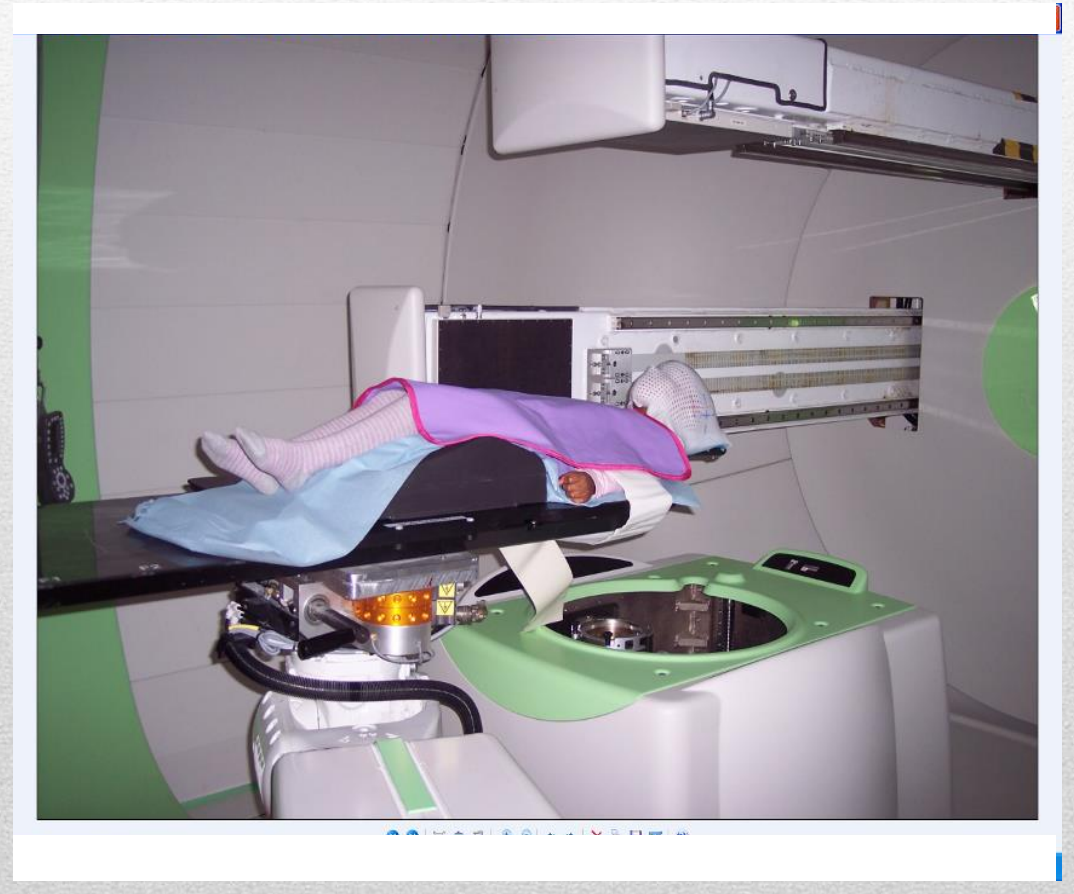








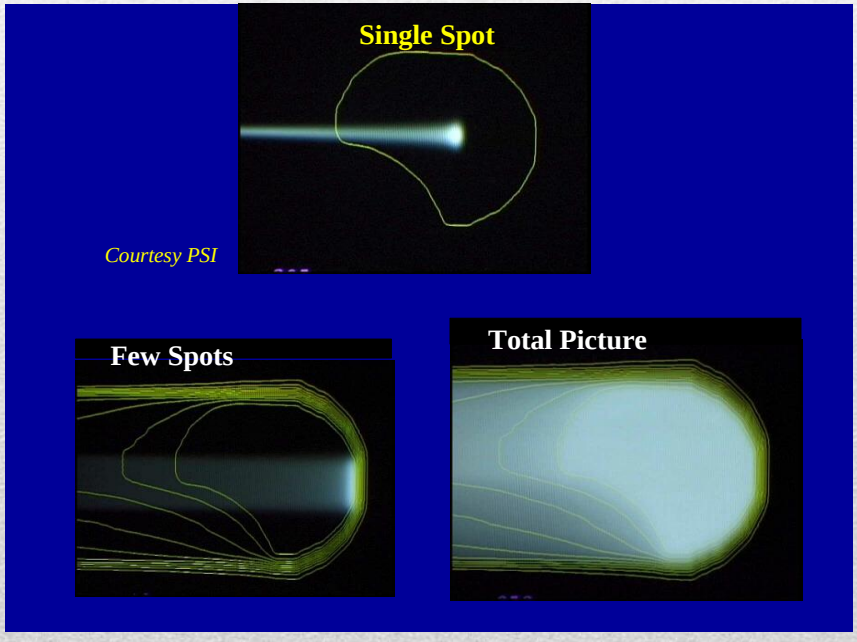
Positionnement enfant par source isocentrique

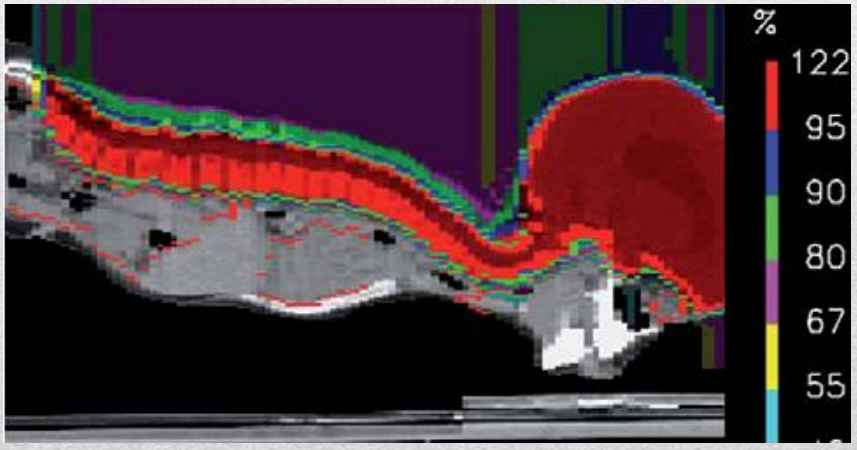


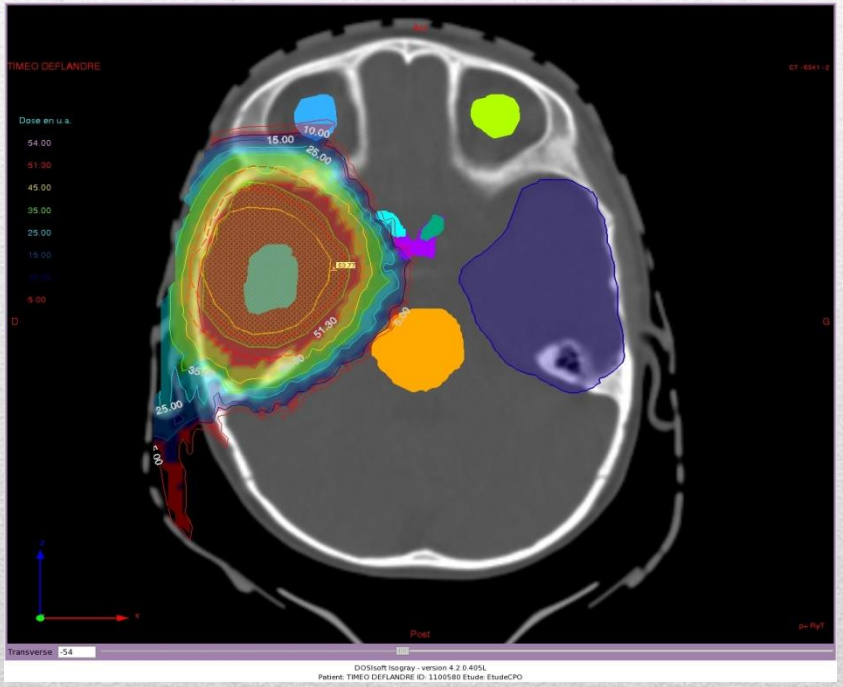
Major technical innovation:

Spot scanning

3D painting: Delivering of the dose by several spots (each of them having one beam E, location and fluency): conform the dose to the tumor geometry



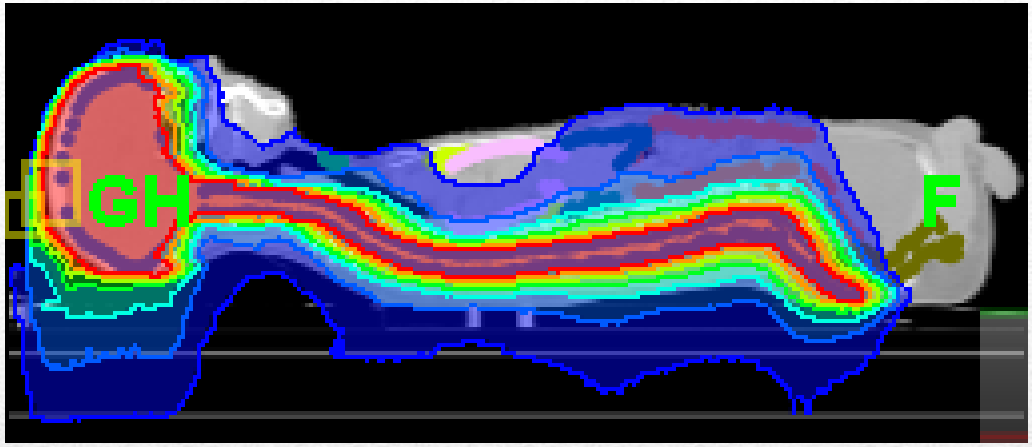




Ependymoma

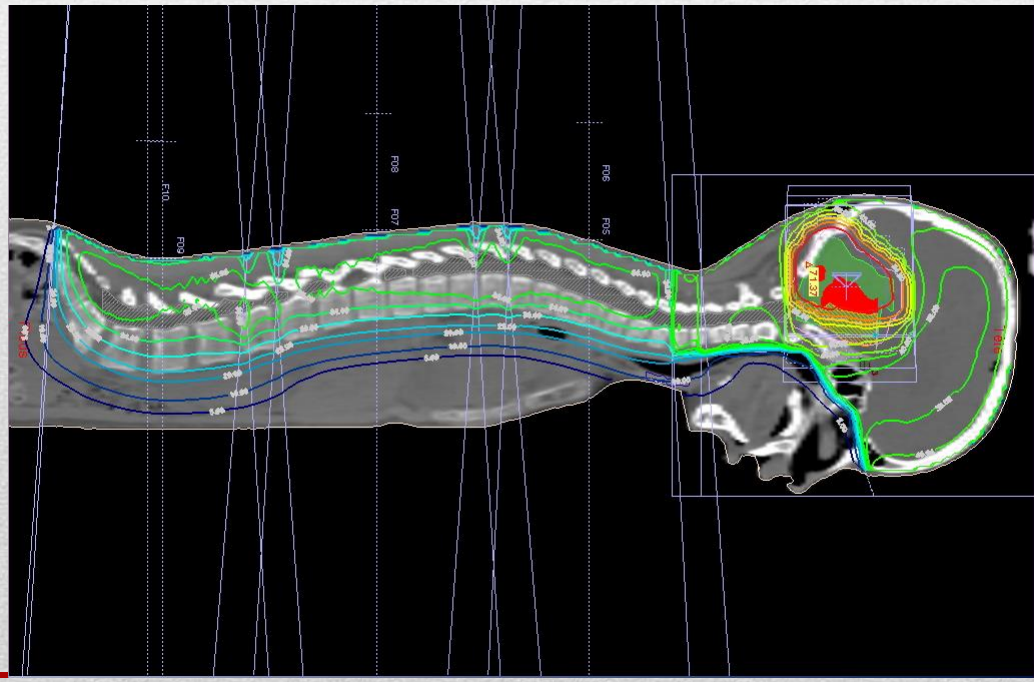
Craniopharyngioma

Personal coll.



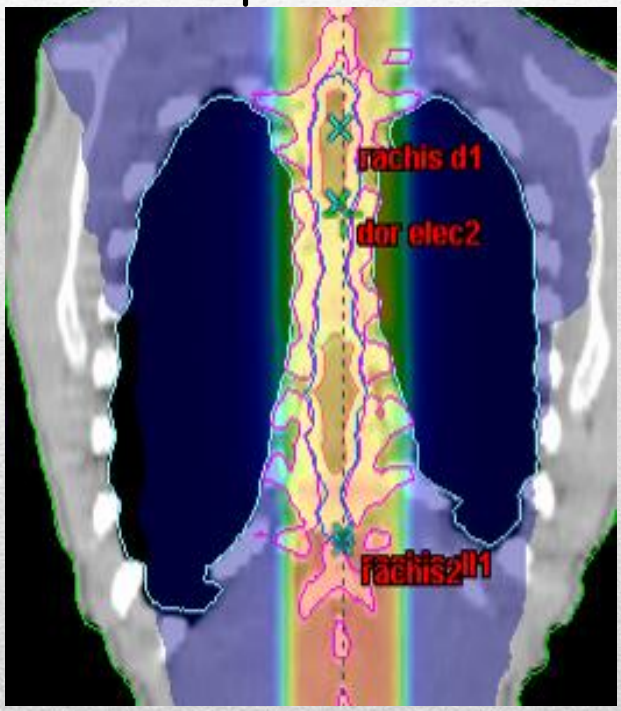
Tomotherapy vs 3D CRT

- Supine position vs prone
- No junction
- High homegeniety/conformity
- On board imaging

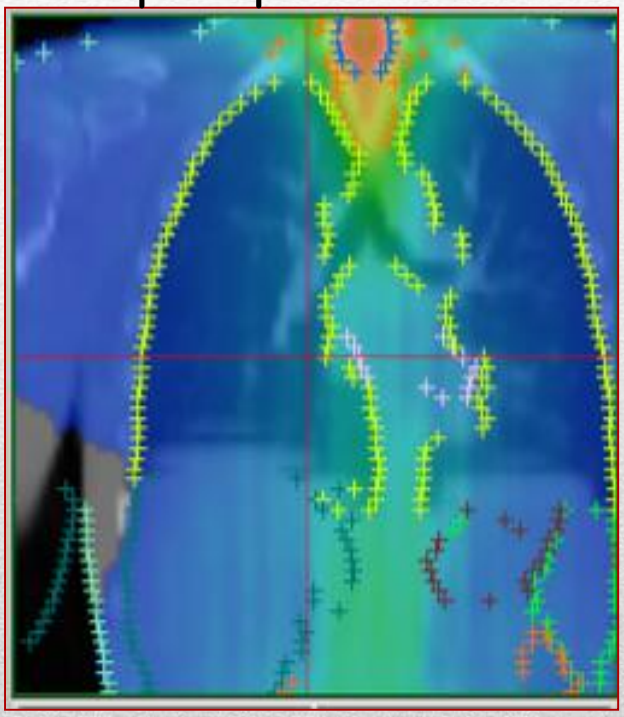


Lungs	V20	V10	V5	Dmax
Tomo	**1%**	**11%**	**55%**	**26Gy**
3D	**7%**	**16%**	**20%**	**36Gy**

Prone position: 3D



Supine position: Tomo



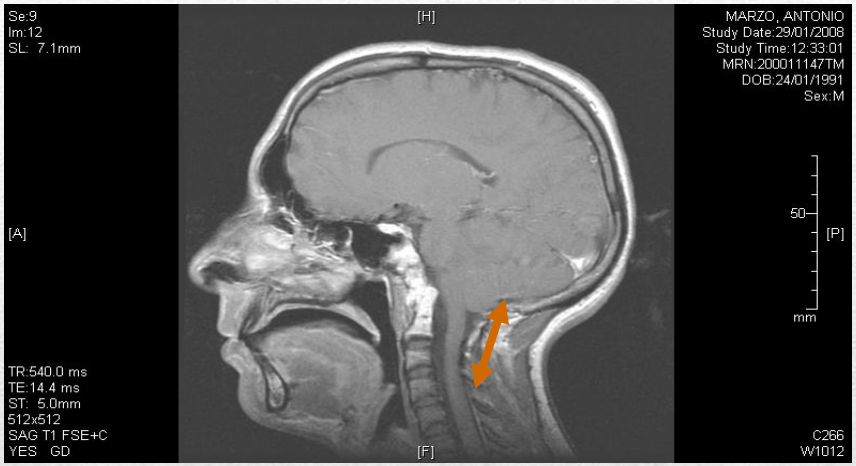
The reverse side…

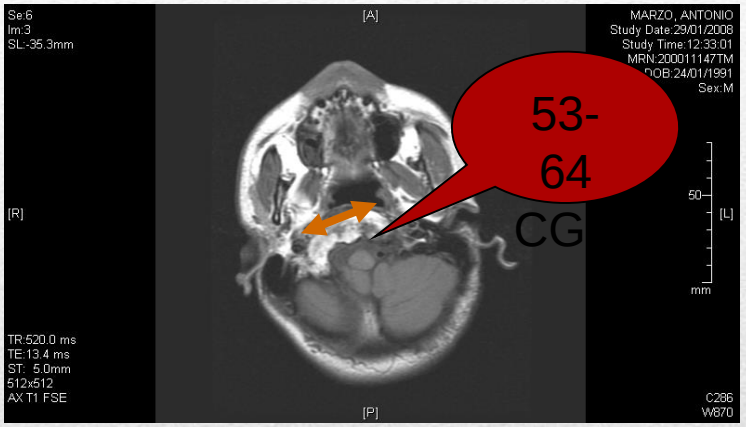
Courtesy C.Dejean, Nantes

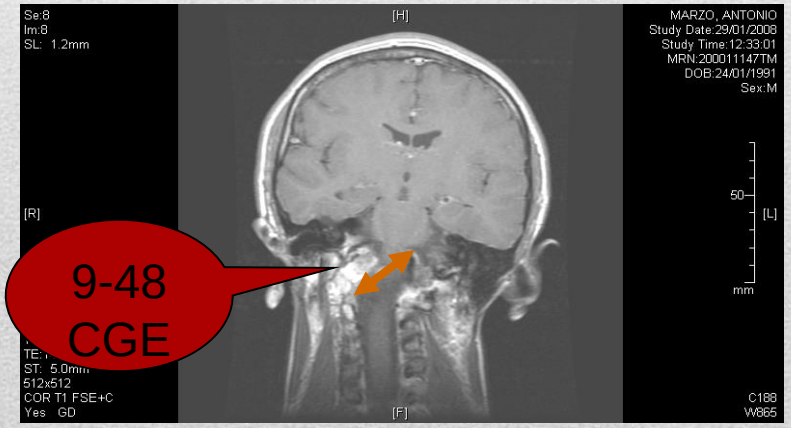
Pt M A: 10 Y-old;

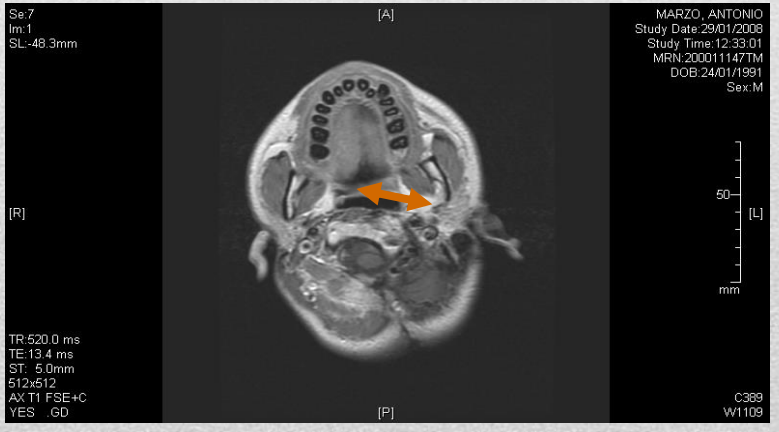
(2001: 34 X+34 P)

4Y-MRI : gr II joint-distorsion









Le projet ARCHADE,
Une « Normandy Hadrontherapy »

Photons vs PARTICLES: EQUIPMENTS

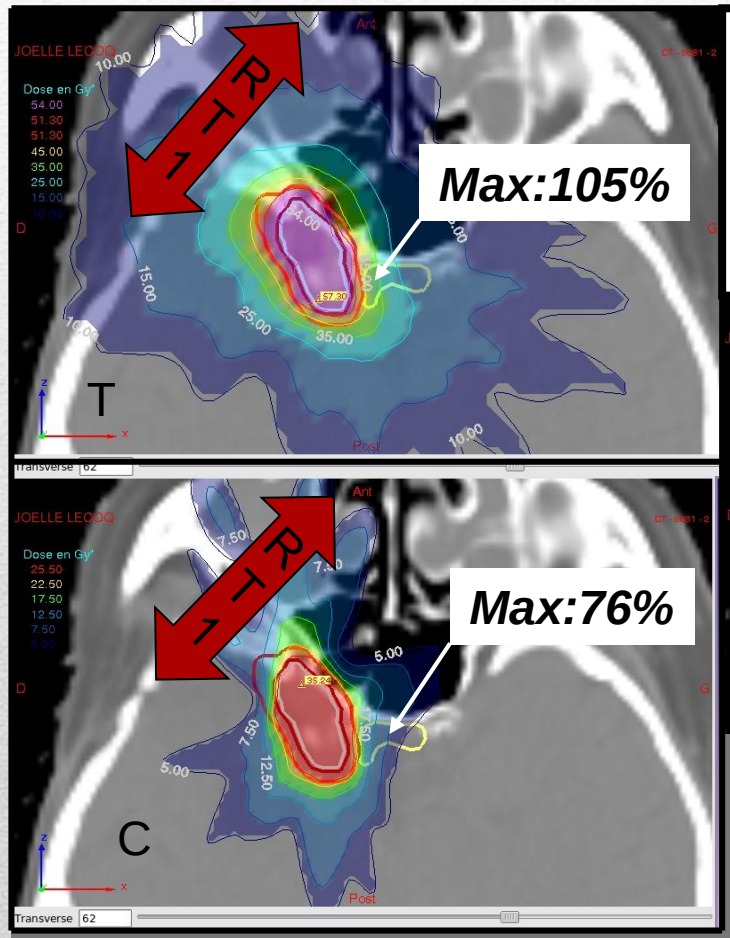
TOMOTHERAPY

CYBERKNIFE

PROTONS

Case #1: Which best ?

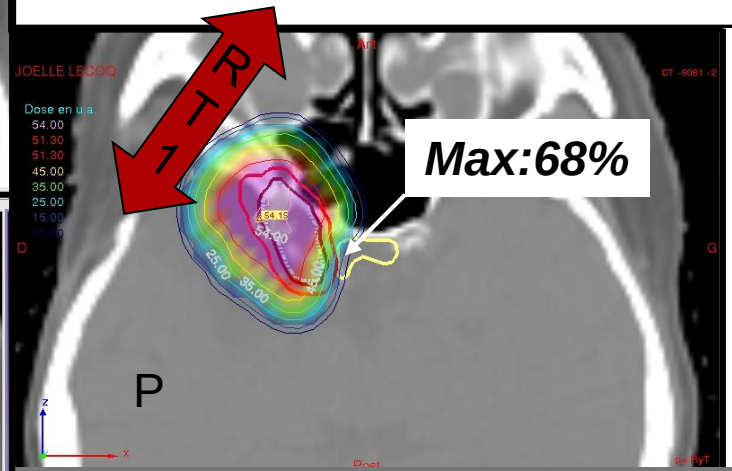
(LEC. Joelle)



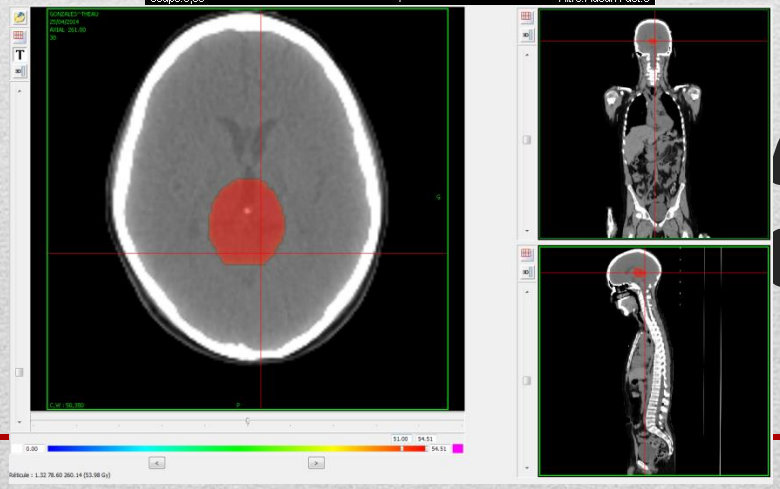
- *56Y old, RIII palsy*

Past history: RON glioma as young adult(±45 Gy)

- *Work up: B meningioma Rt ant clinoid*
- *Management: partial resection+RT(52Gy)*

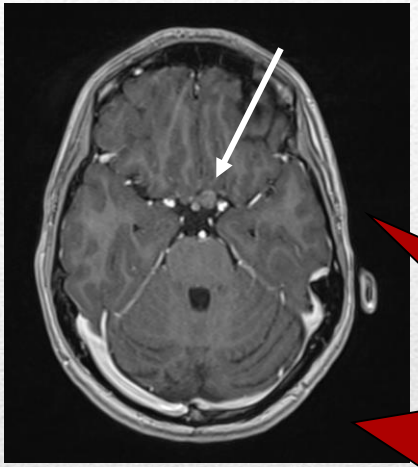


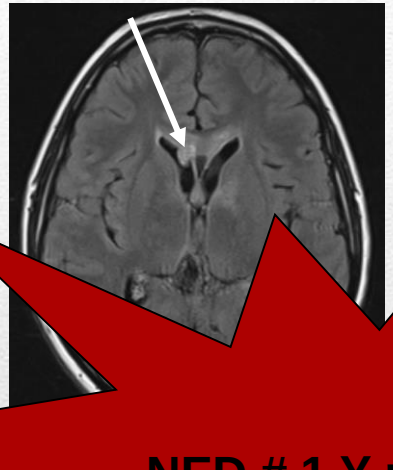
- 12 YO,M
- *Acute ICP*
- MRI (Nov 2012): *homogeneous 2.5X3.5 cm mass, pineal region, with IIIrd ventricle compression, gado +*
- Serum markers: *↗AFP (185 ng/ml)*
- Management:
  - *Ventricular shunt*
  - Chemo : *4 PEI (CDDP,CBDCA,VP)*
  - *Proton based-RT: focal 54 Gy/frac*



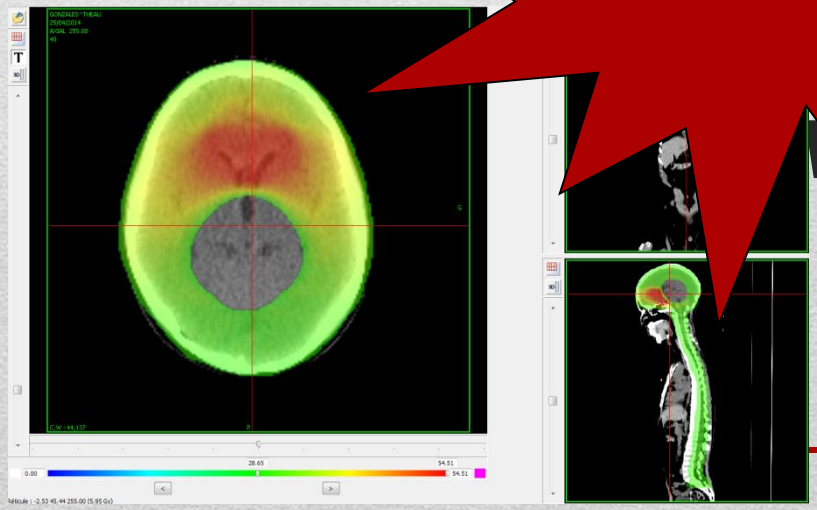
circumferential

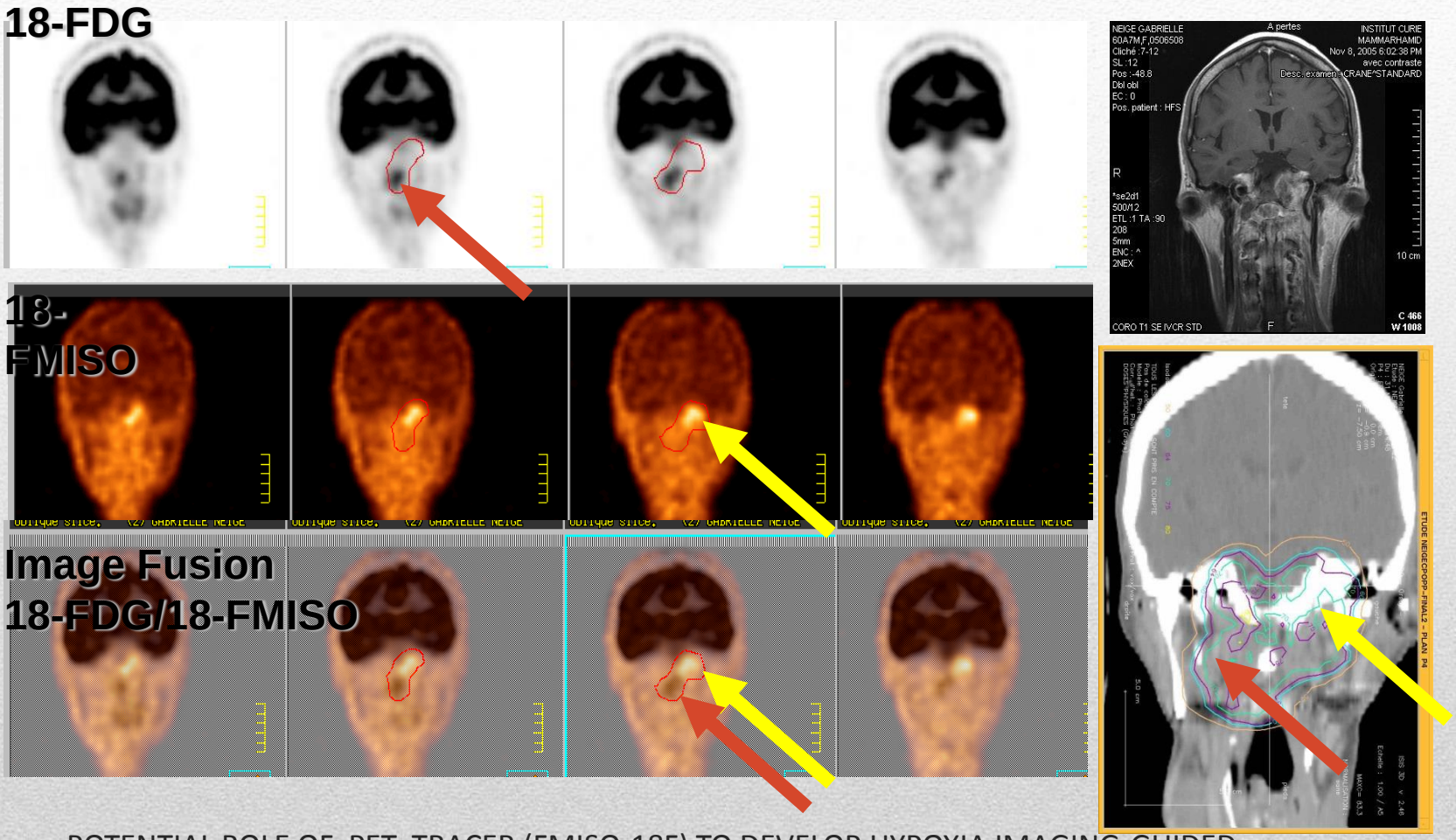
- 9 m FUp MRI:
  multiple nodules in lateral V.
- Serum markers:
  ↗βHCG (19 ng/ml)
- Biopsy:
  NSGCT (yolk sac)
- alvage:
  herapy
  30 Gy CS
  V. boost
  ing RT1 volume





NED # 1 Y post salv.

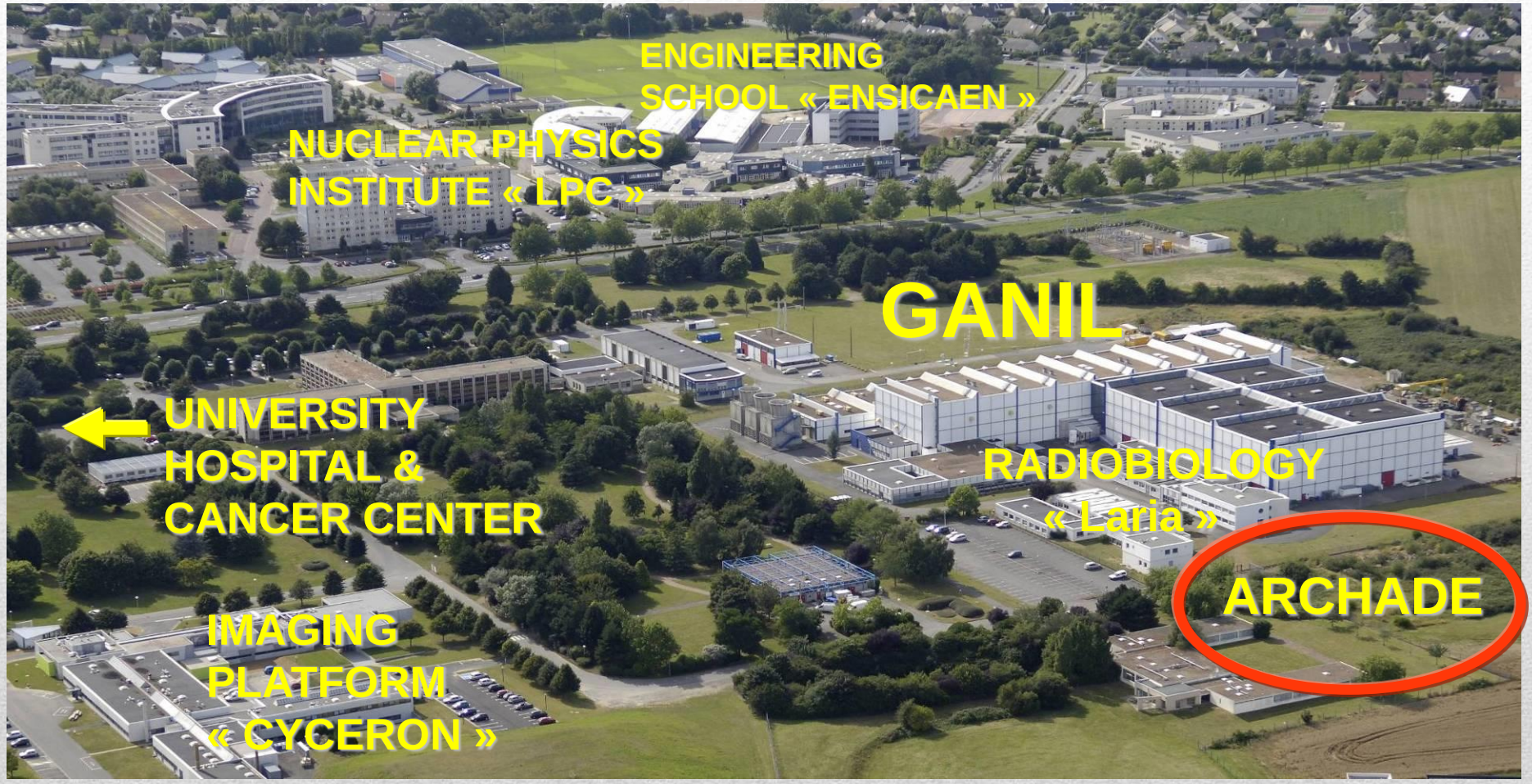


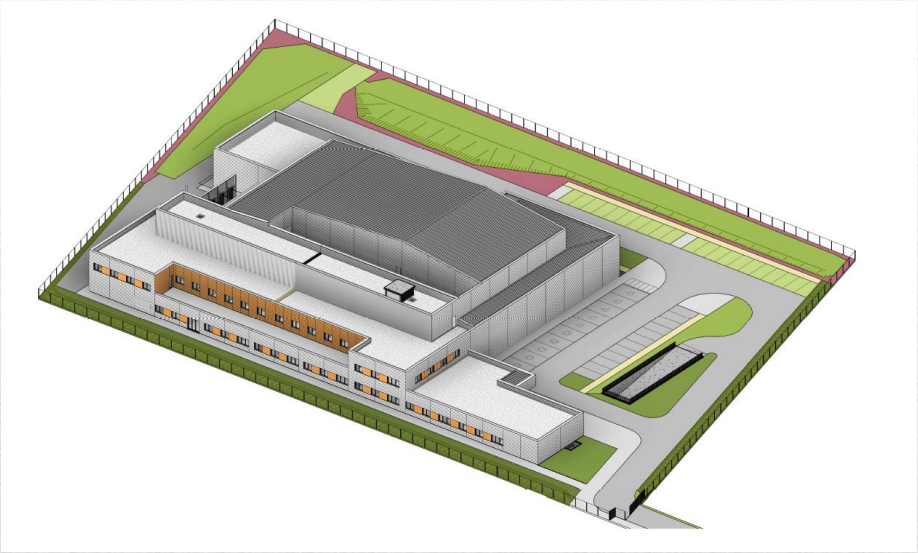


POTENTIAL ROLE OF PET TRACER (FMISO-18F) TO DEVELOP HYPOXIA IMAGING-GUIDED PROTONTHERAPY FOR SKULL BASE CHORDOMA (COOPERATION WITH CPO)

« France HADRON »

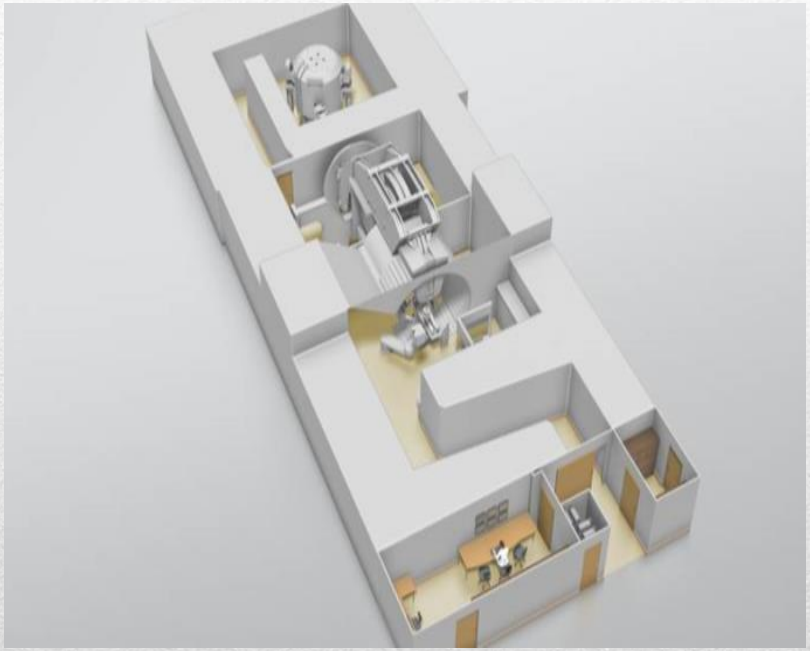
Location : Northern Campus of Caen (GANIL)



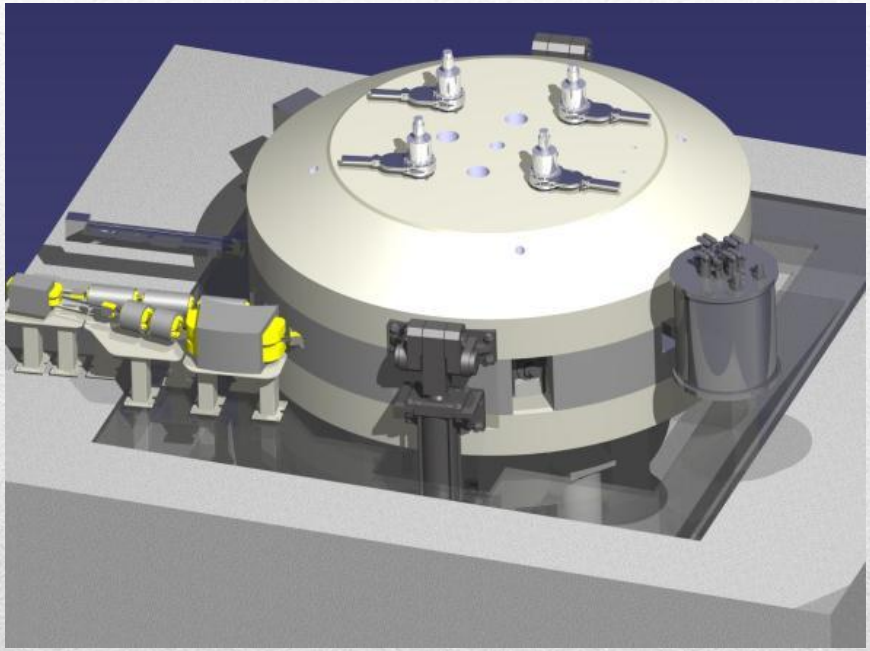


« ARCHADE »: ARTIST view

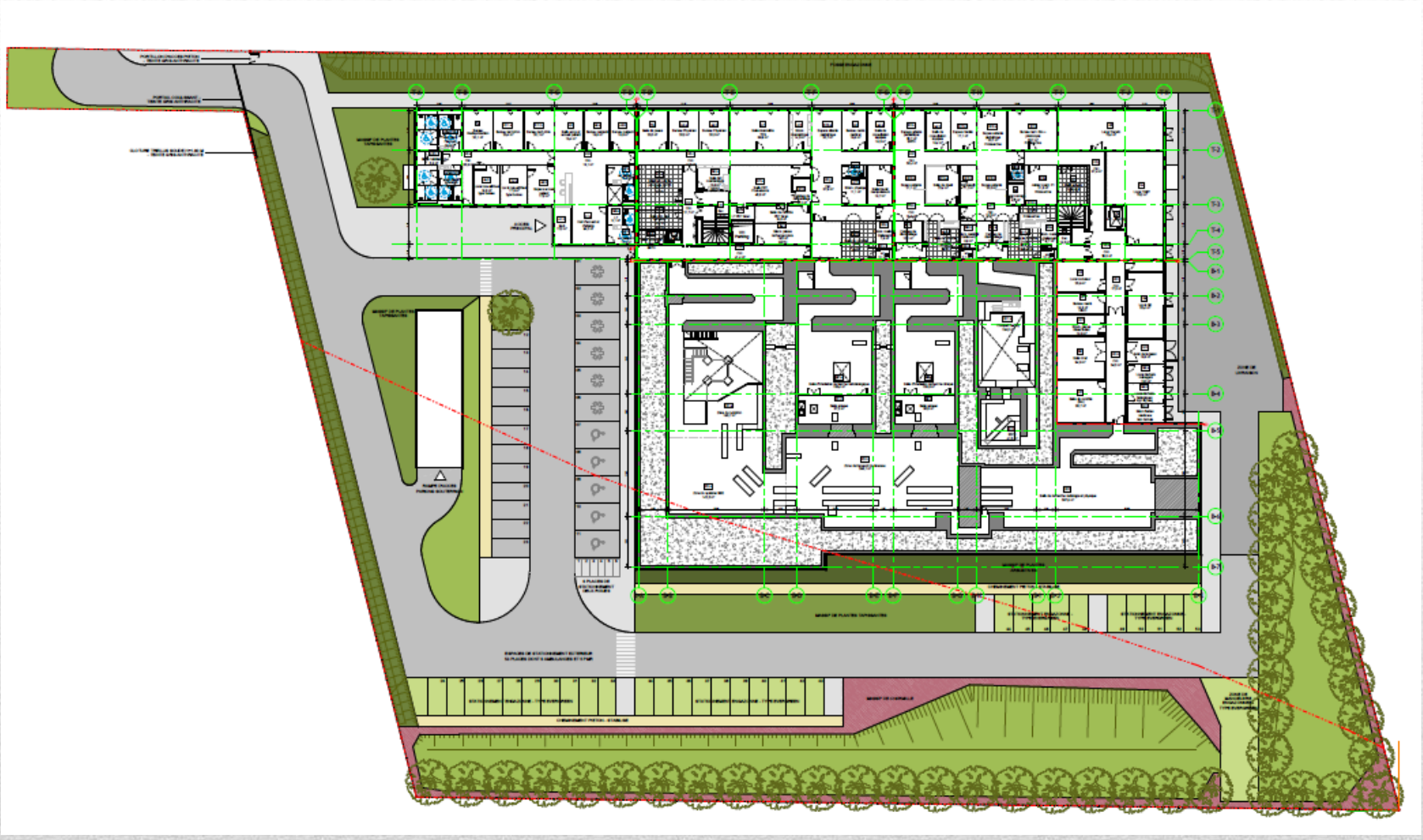
2 Core-equipments



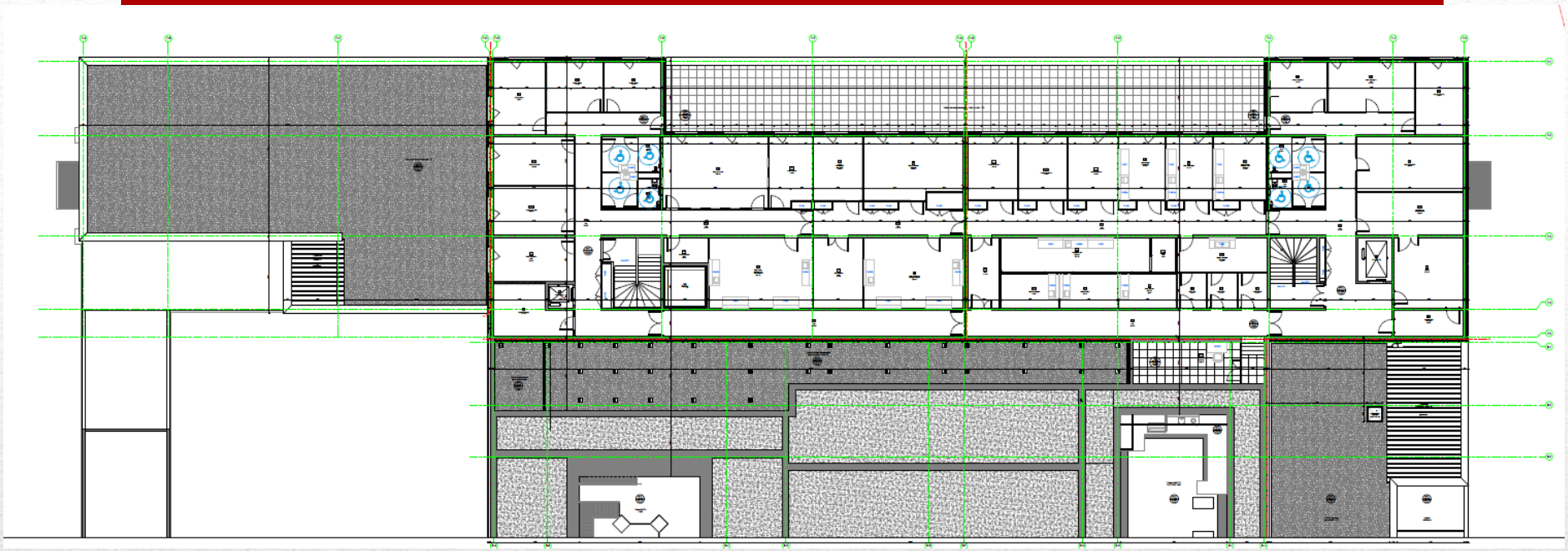
1/ IBA S2C2
superconducting
synchrocyclotron



2/ C400
IBA design
Realisation:
« Normandy-Hadrontherapy » consortium



GROUND FLOOR



FIRST FLOOR: RESEARCH DIVISION (biology, physics)

Time table ARCHADE project

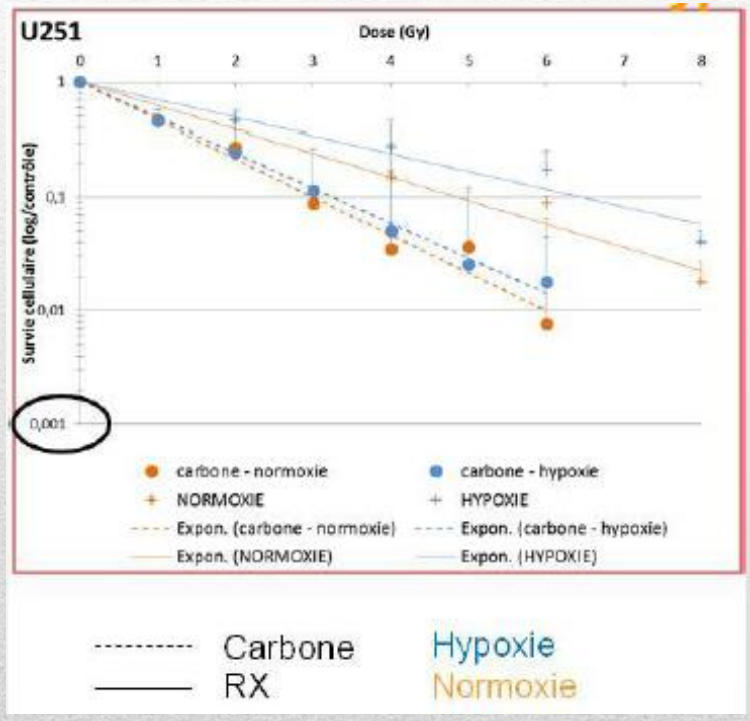
2012	C400 design validated by international panel
2014	Financing agreements betwwen RCBN and banks (EBI…). Contract signatures
2015	Begining of building construction
2016	Normandy-hadrontherapy consortium
2017	End of building, Proton machine installation
2018	First Proton patients with Proteus one (345 Pr pts)
2019-21	Begining research programs with C400 (175 Pr, 100 Carbon Pts)

CLINICAL PROGRAM.Ramp-up

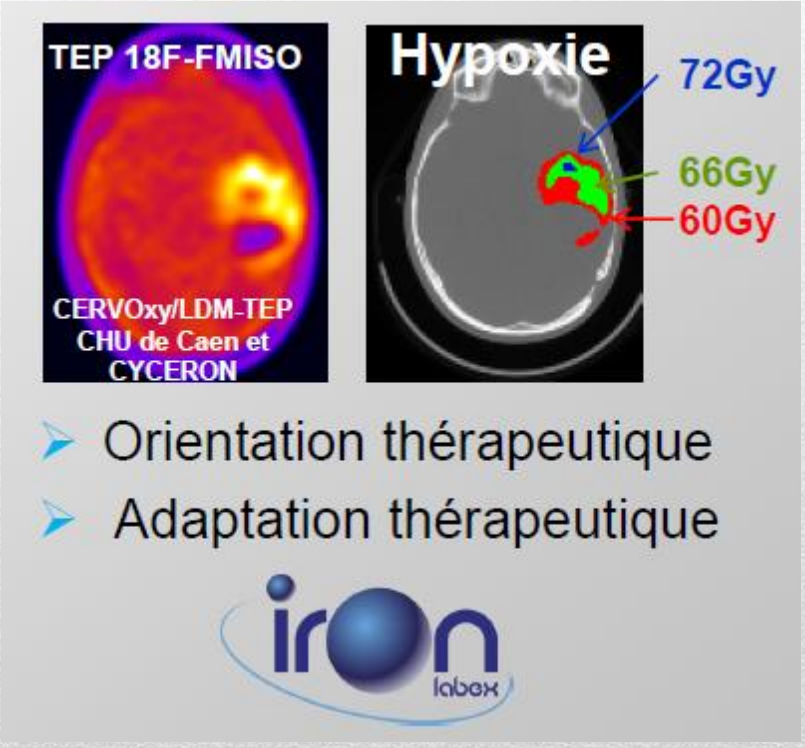
	1	2	3	4	5	6	7
Proteus One							
# patients	150	250	345	345	345	345	345
# fractions	5 000	8 065	10 755	10 755	10 755	10 755	10 755
C400 protons							
# patients	-	-	-	55	110	175	175
# fractions	-	-	-	1 716	3 432	5 460	5 460
Total protons							
# patients	150	250	345	400	455	520	520
# fractions	5 000	8 065	10 755	12 471	14 187	16 215	16 215
C400 carbon ions							
# patients	-	-	-	-	-	50	100
# fractions	-	-	-	-	-	1 000	2 000
TOTAL # FRACTIONS	5 000	8 065	10 755	12 471	14 187	17 215	18 215

RADIOBIOLOGY PROJECT: GLIOBLASTOMA

Meilleure efficacité sur la cellule tumorale même en conditions d'hypoxie



Imagerie pour guider la radiothérapie (IRM/TEP)



Effets sur le tissu sain cérébral : Cellules (astrocytes, neurones, macrophages…) / Cerveau entier

« pre clinical » affiliated teams

Local regional

CIMAP (Radio-Chimie)

LPC Caen (Fragmentation, Moniteurs faisceaux)

CERVOxy/ISTCT-CYCERON (cerveau)

LARIA-CEA/DSV/iRCM (cartilages)

BioConnect-Université de Caen (cartilages)

ARCHADE/SAPHYN-ABTE/ToxEMAC Universités de Caen et Rouen (peau)

GANIL (faisceaux)

National partnerships

GDR MI2B (contrôles, imageries)

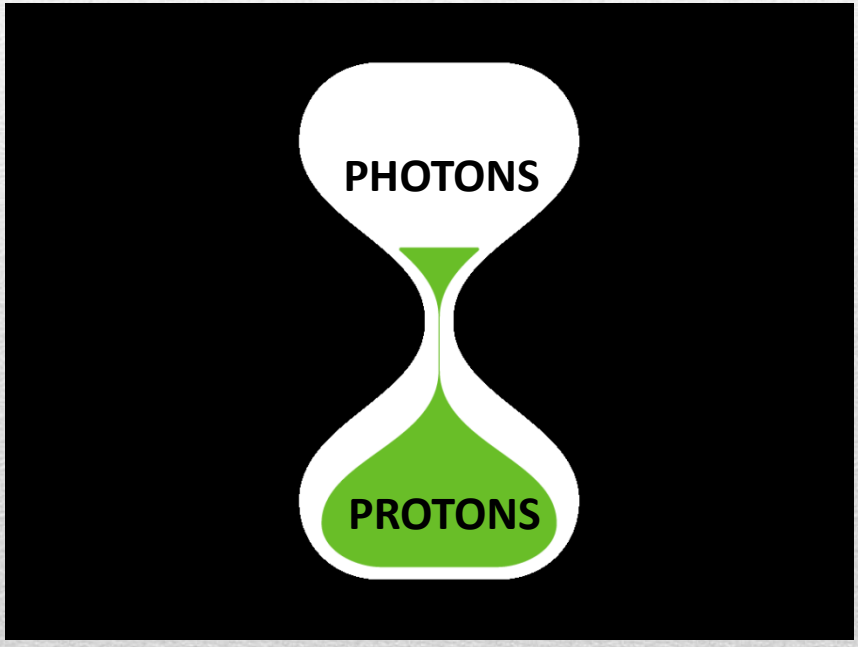
France-Hadron

« Clinical » affiliated teams

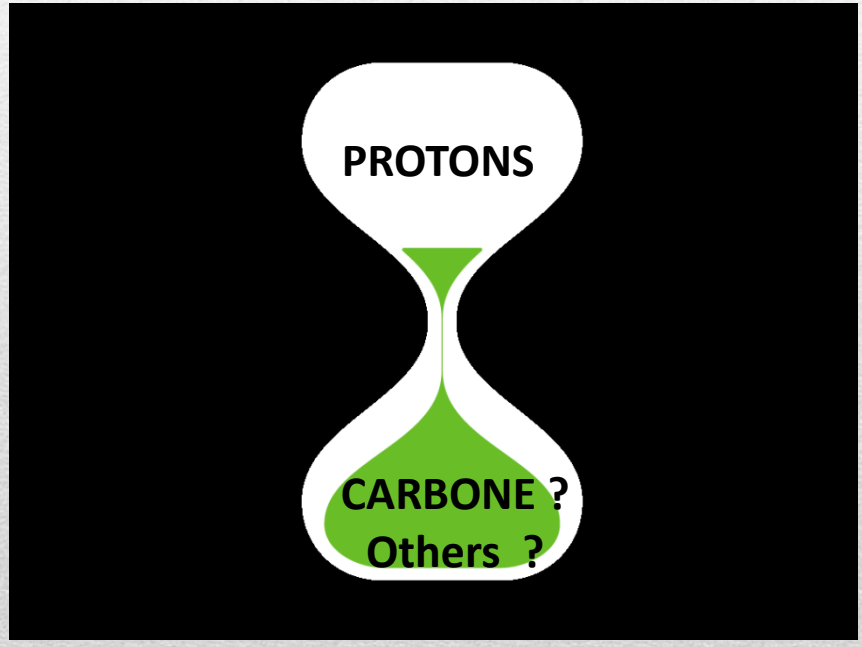
- *Local*
- Centre François Baclesse
- CHU
- *Partnerships*
- Institut Curie
- Gustave Roussy Cancer Campus
- Centre Antoine Lacassagne, Nice
- Centre Henri Becquerel, Rouen

The future ?

Today…



Tomorrow…



Courtesy IBA company


MERCI !

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Gustave Roussy Cancer Campus
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Compagnie IBA