Hadrontherapy in France

Past, present and future

Jean-Louis Habrand, MD
Pr Radiation Oncology, U Caen
Chief Dpt Radiation Oncology, F Baclesse Cancer Center, Caen, Fr
Coordinator ARCHADE program for Hadrontherapy, Caen, Fr

Centre de Lutte contre le Cancer François Baclesse

UNICANCER

1940 ! first cyclo

FIGURE 4. — *Cyclo*

1956 ! Orsay University *(South Paris)*

IPN: Institut de Physique Nucléaire

31 DÉCEMBRE 1955 :
LE DÉBUT DU CHANTIER DE
CONSTRUCTION DE L'I.P.N.

ORSAY IN THE 60s

1959 ! By Philips

N° 3292

Août 1959

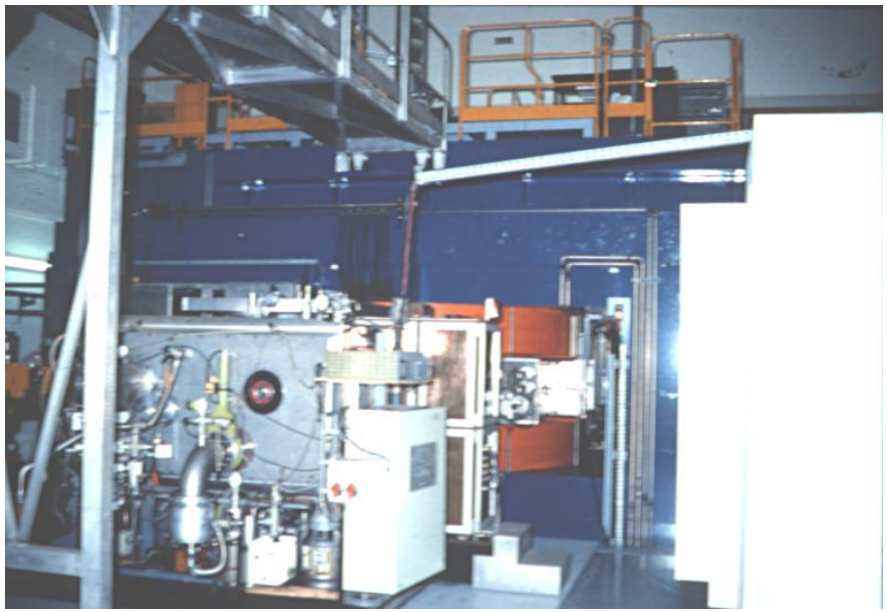
LA NATURE

...e ...rsay

Fig. 1. — *Le synchro-cyclotron 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.

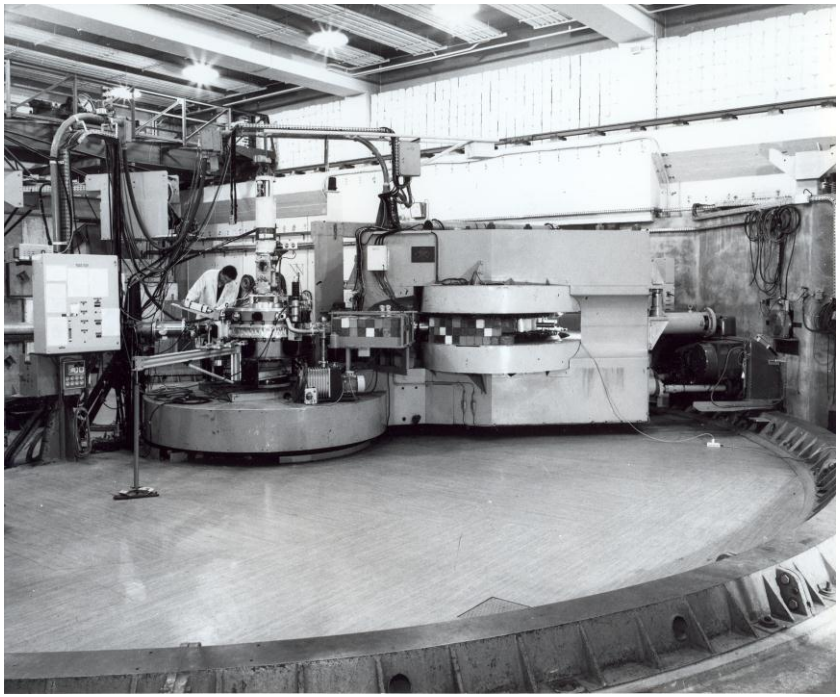
Orsay Synchro
50 years operation !



Same with upgrading in 1977…

1974 ! Orsay Synchro a « double bladded sword»

PHYSICAL: MASS SPECTROMETER



BIOLOGICAL: ANIMAL EXPERIMENTS

Extrait des Archives d'Ophtalmologie 1974, T, 34, n° 8-9 (pp. 557-568).

TRAVAUX ORIGINAUX

Mots clés (1) :
Protons,
Cristallin,
Radiations ionisantes,
Cataracte.

Étude de l'action des protons du pic de Bragg sur le cristallin.

Par

C. HAYE et G. LEMAIRE
(Paris)

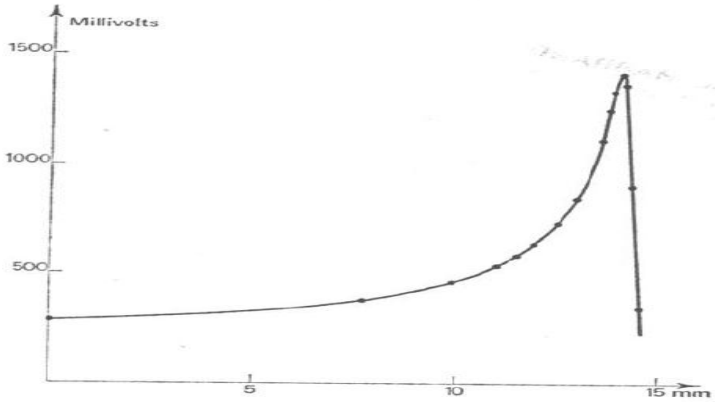


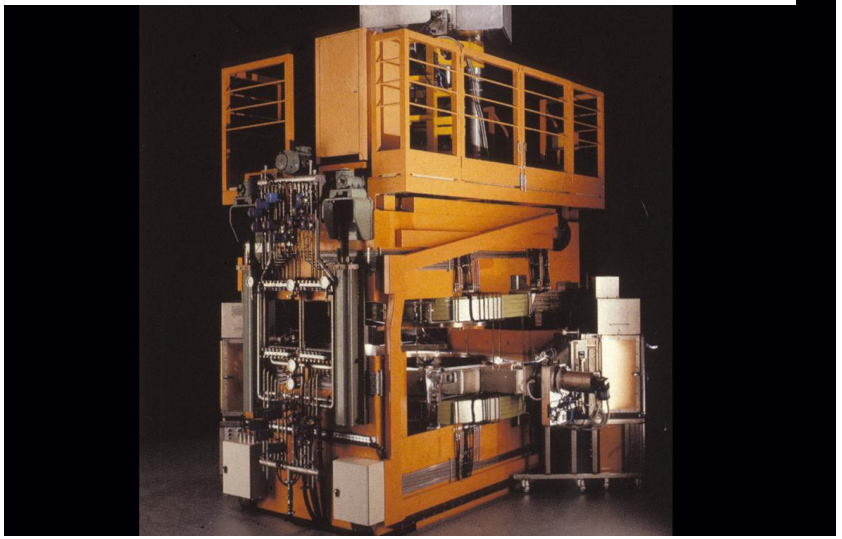
Fig. 1. — Courbe de Bragg.

Two « competitors » in heavy particles

ORLEANS

NICE

[NEUTRONS]/PROTONS
(1991→)



Cancer

- **Cancer in Europe :** **3.2 millions new cases/Y**
  1.7 million deaths/Y
- **Cancer en France :** **350, 000 new cases/Y**
  150, 000 deaths/Y
- **Cancer: first cause of mortality in France**
- **Trends: + 50% new cases 2000-2020**

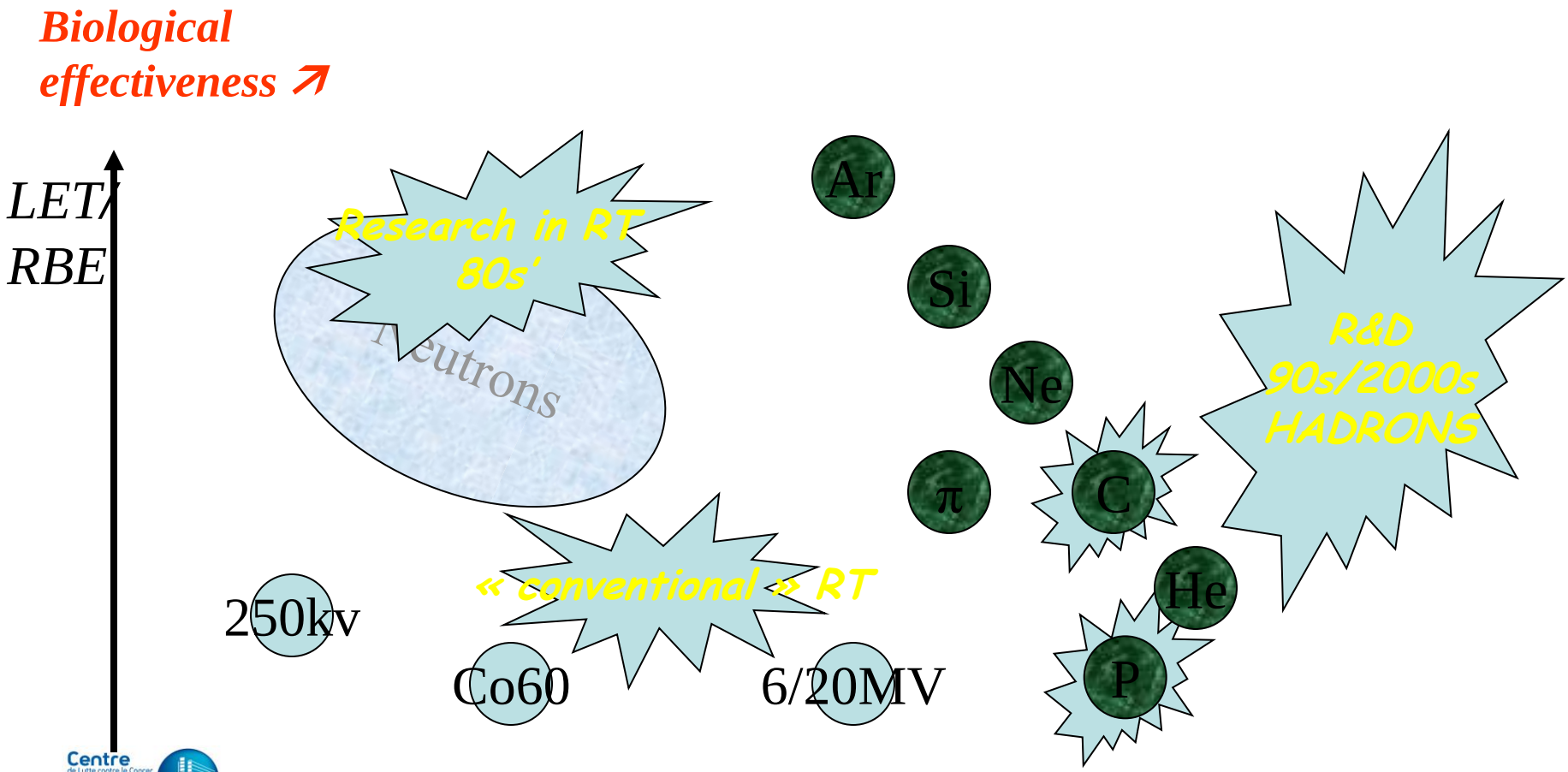
Cancer

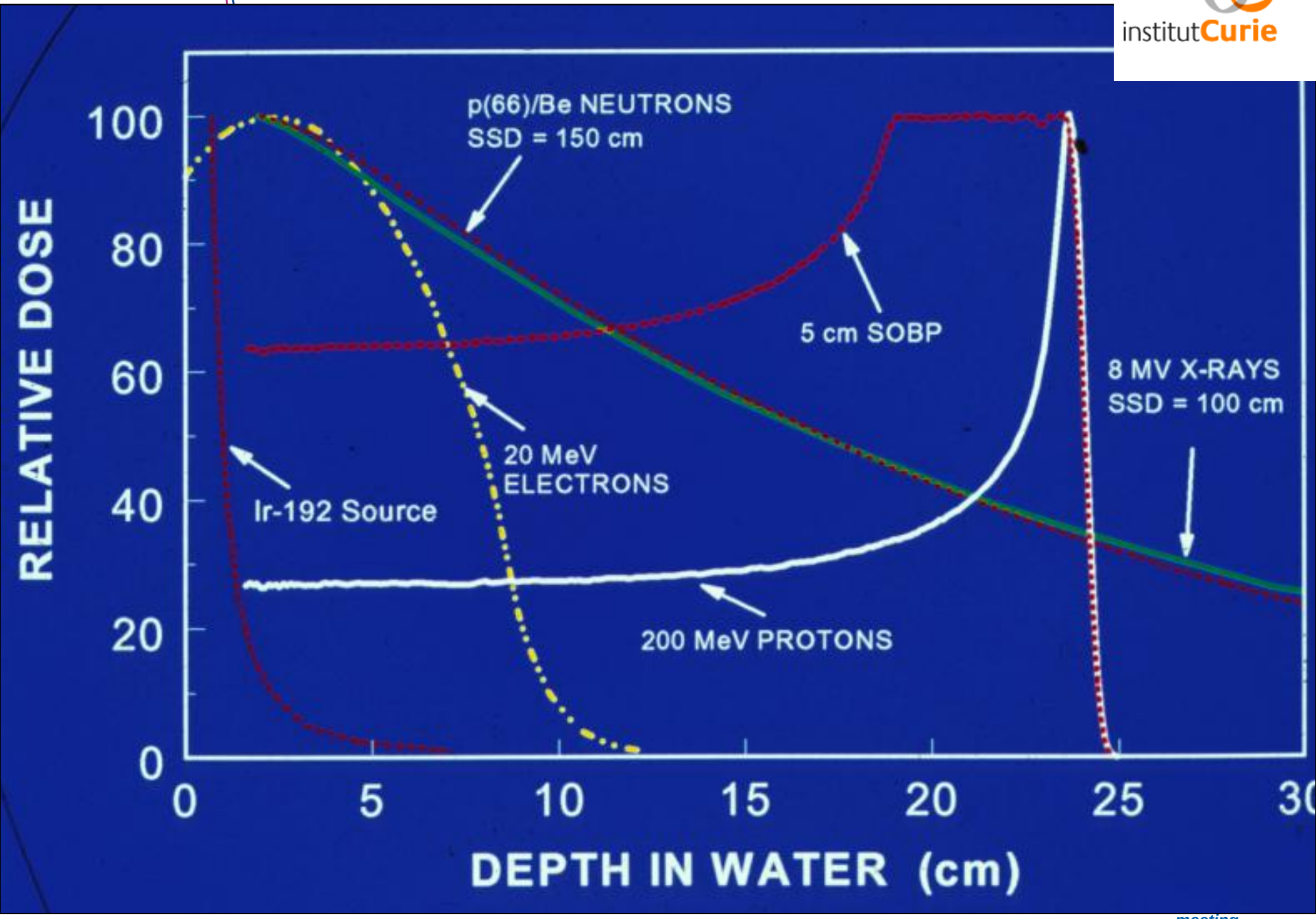
- Cancer management
  - Surgery
  - Radiotherapy (200,000 pts/Y)
  - Chemotherapy
- Alone or combined➔50%cure

Most advanced photon therapy equipments

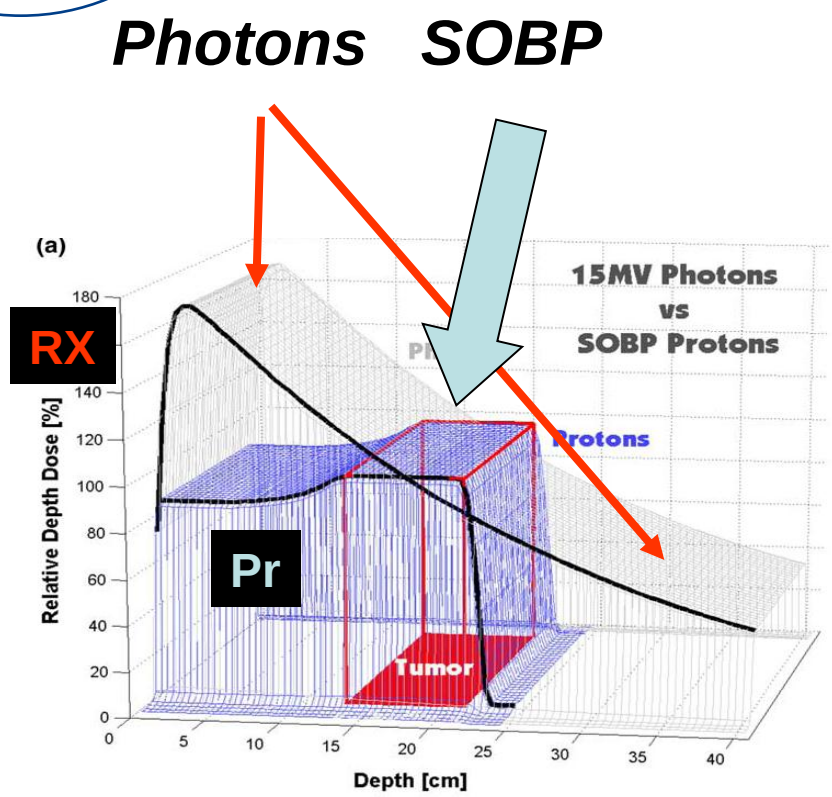
CYBERKNIFE

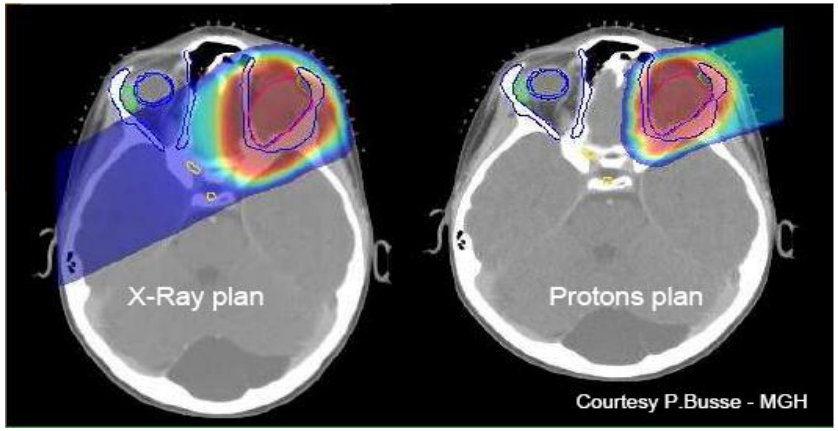
Particle radiotherapy



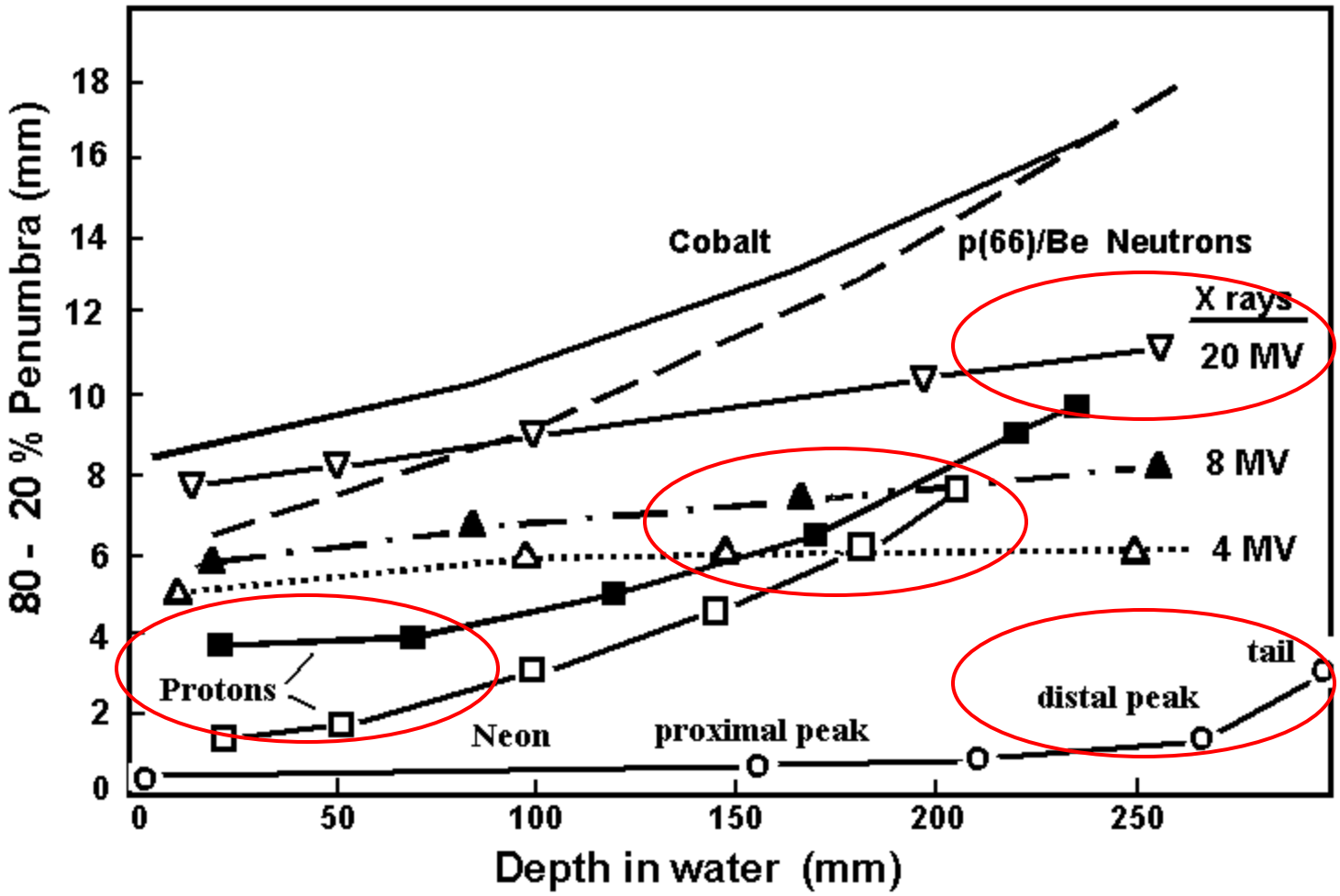

p(66)/Be NEUTRONS
SSD = 150 cm
5 cm SOBP
8 MV X-RAYS
SSD = 100 cm
20 MeV
ELECTRONS
Ir-192 Source
200 MeV PROTONS
RELATIVE DOSE
100
80
60
40
20
0
0
5
10
15
20
25
30
DEPTH IN WATER (cm)

Avantages balistiques

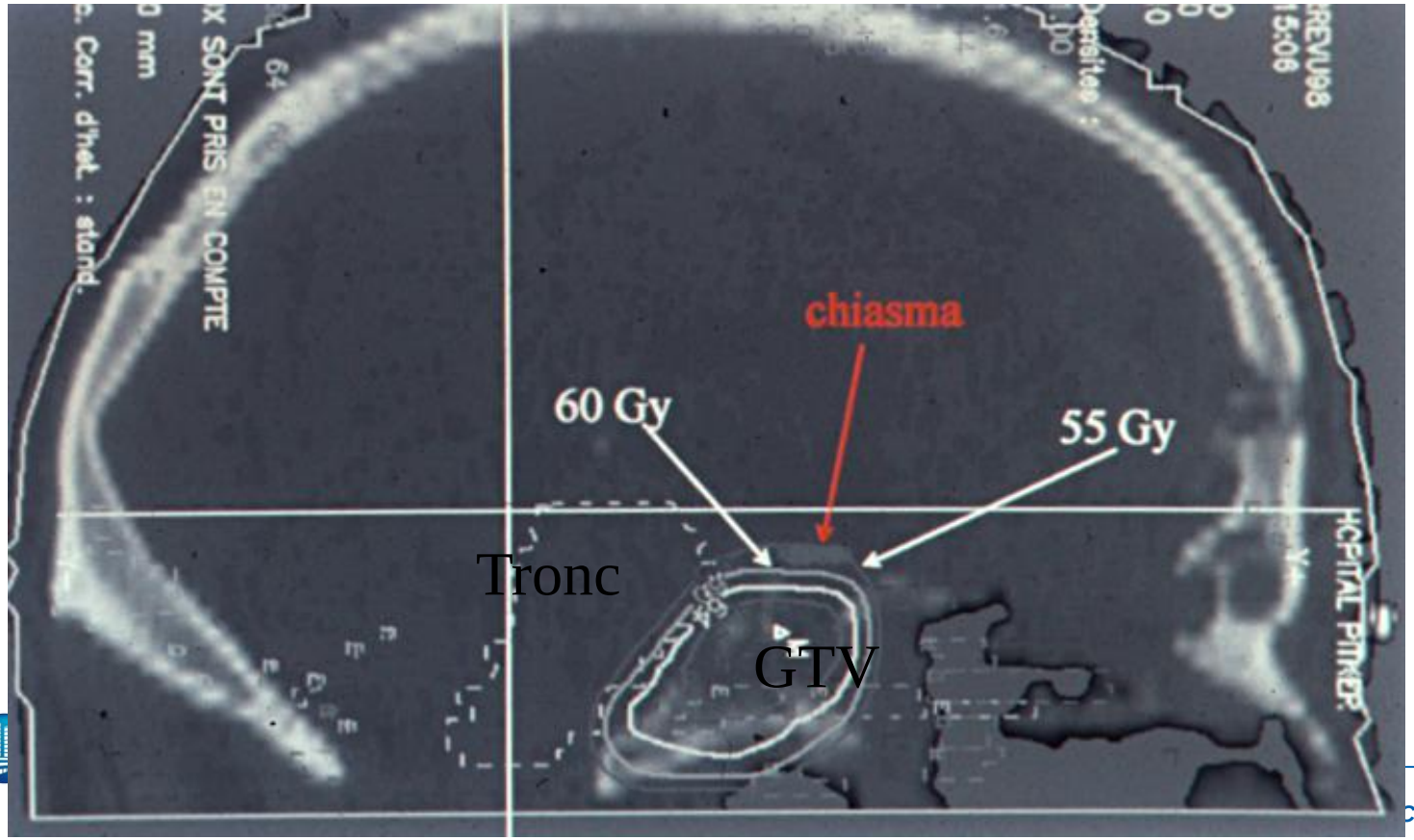




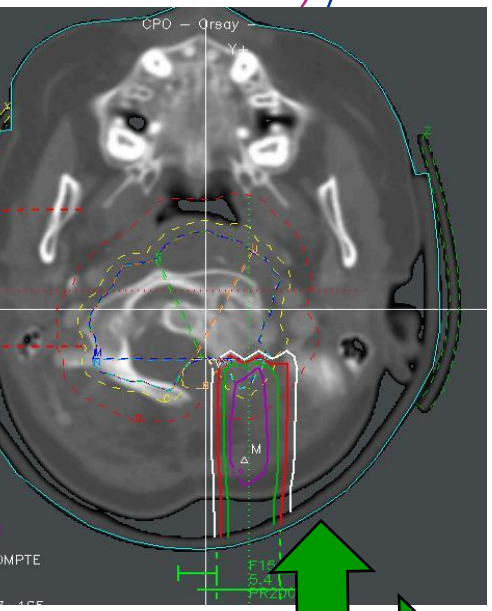
Lateral penumbra in depth

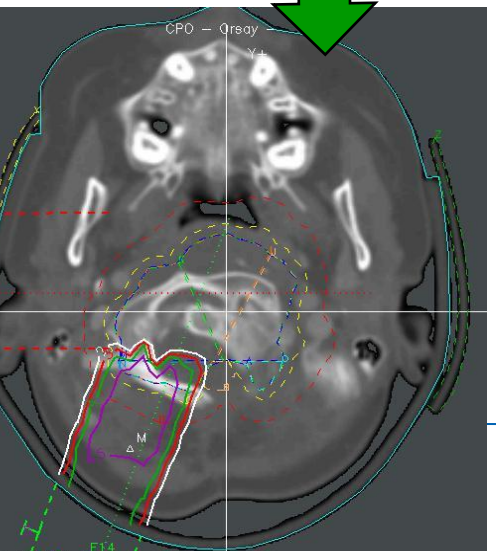


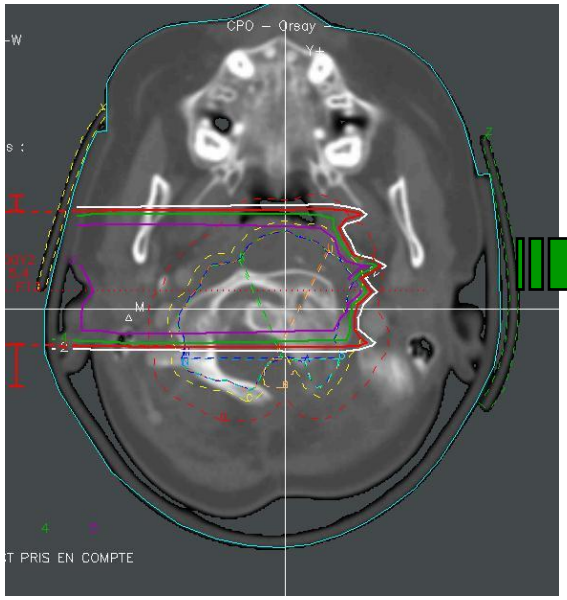
PROTONS : ADVANTAGES LATERAL PENUMBRA

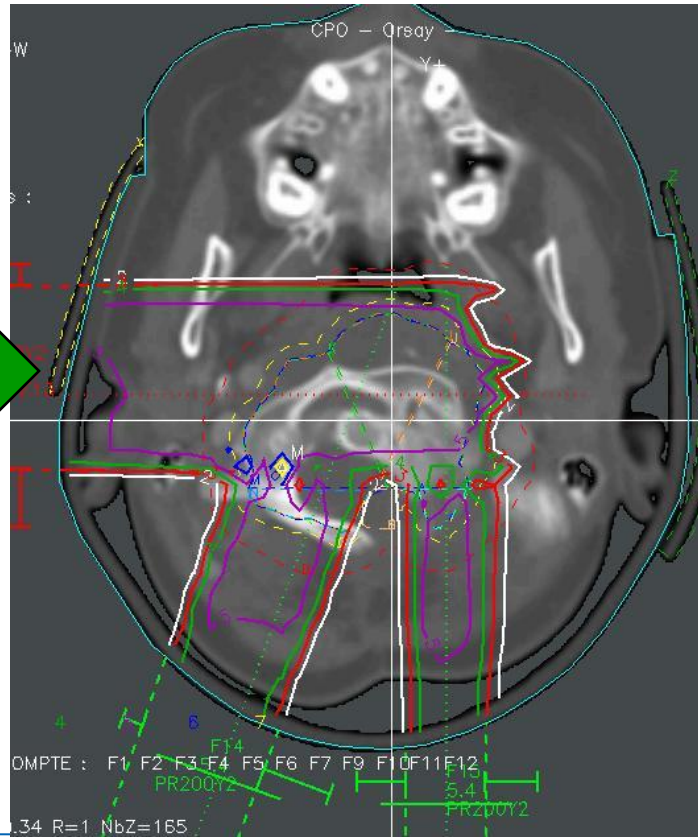


Ballistical advantages HCP: beams'« PATCHING »










CENTRE DE PROTONTHERAPIE D'ORSAY
Consortium (1991-2004):
- I Curie-Paris
- IGRoussy-Villejuif
-Paris public hosp. (AP-HP)

CPO: physical achievements

ELSEVIER

Radiotherapy and Oncology 41 (1996) 169–177

RADIOTHERAPY & ONCOLOGY

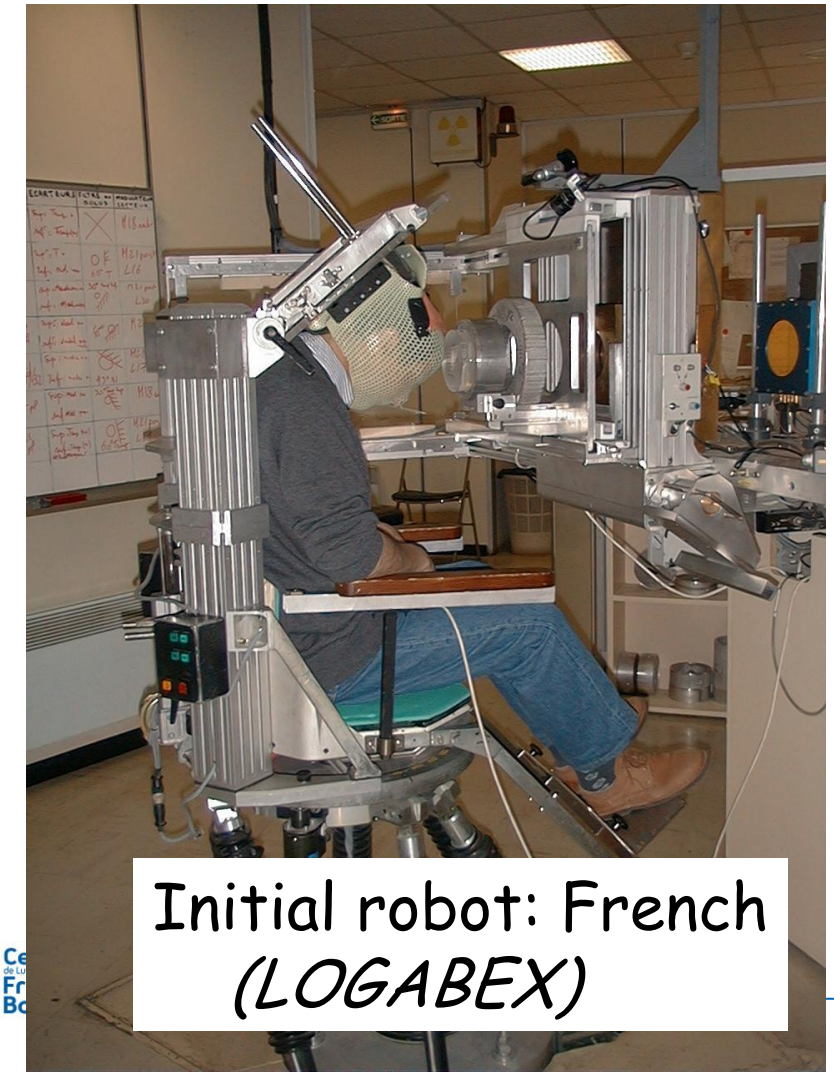
Proton dosimetry intercomparison

S. Vatnitsky[a,*], J. Siebers[a], D. Miller[a], M. Moyers[a], M. Schaefer[a], D. Jones[b], S. Vynckier[c], Y. Hayakawa[d], S. Delacroix[e], U. Isacsson[f], J. Medin[f], A. Kacperek[g], A. Lomax[h], A. Coray[h], H. Kluge[k], J. Heese[k], L. Verhey[l], I. Daftari[l], K. Gall[m], G. Lam[n], T. Beck[p], G. Hartmann[p]

[a]*Loma Linda University Medical Center Loma Linda, CA, USA*
[b]*National Accelerator Centre, Faure, South Africa*
[c]*Catholic University of Louvain, Louvain, Belgium*
[d]*Proton Medical Research Center, Tsukuba, Japan*
[e]*Proton Therapy Center of Orsay, Orsay, France*
[f]*University Hospital/The Svedberg Laboratory, Uppsala, Sweden*
[g]*Clatterbridge Centre for Oncology, Clatterbridge, UK*
[h]*Paul Scherrer Institute, Villigen, Switzerland*
[k]*Hahn-Meitner Institute, Berlin, Germany*
[l]*University California-San Francisco, San Francisco, CA, USA*
[m]*Massachusetts General Hospital, Boston, MA, USA*
[n]*University of British Columbia TRIUMF, Vancouver, Canada*
[p]*German Cancer Research Center, Heidelberg, Germany*

Received 7 October 1995; revised 10 February 1996; accepted 3 June 1996

CPO : technological achievements



Initial robot: French
(LOGABEX)

Final robots: partly French
(PROCURE)
(FANUC/GIAT)

Clinical achievements
(P in Ocular T)

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 3, pp. 780–787,

doi:10.1016/j.ijrobp.2006.01.020

CLINICAL INVESTIGATION

PROTON BEAM RADIOTHERAPY FOR UVEAL MELANOMA: RESULTS OF CURIE INSTITUT–ORSAY PROTON THERAPY CENTER (ICPO)

Rémi Dendale, M.D.,*‡ Livia Lumbroso-Le Rouic, M.D.,† Georges Noel, M.D.,‡ Loïc Feuvret, M.D.,‡ Christine Levy, M.D.,† Sabine Delacroix, Ph.D.,‡ Anne Meyer, M.D.,§ Catherine Nauraye, Ph.D.,‡ Alejandro Mazal, Ph.D.,*‡ Hamid Mammar, M.D.,* Paul Garcia, Ph.D.,‡ François D'Hermies, M.D.,§ Eric Frau, M.D.,‖ Corine Plancher, D.M.,¶ Bernard Asselain, M.D.,¶ Pierre Schlienger, M.D.,*‡ Jean Jacques Mazeron, M.D.,‡ and Laurence Desjardins, M.D.†‡

Departments of *Radiation Oncology, †Ophthalmology, and ¶Biostatistics, Curie Institut, Paris, France; ‡Curie Institut–Orsay Protonthérapie Center, Orsay, France; §Department of Ophthalmology, Hotel Dieu Hospital, Paris, France; ‖Department of Ophthalmology, Le Kremlin Bicêtre Hospital, Le Kremlin Bicêtre, France

Purpose: This study reports the results of proton beam radiotherapy based on a retrospective series of patients treated for uveal melanoma at the Orsay Center.

Methods and Materials: Between September 1991 and September 2001, 1,406 patients with uveal melanoma were treated by proton beam radiotherapy. A total dose of 60 cobalt Gray equivalent (CGE) was delivered in 4 fractions on 4 days. Survival rates were determined using Kaplan–Meier estimates. Prognostic factors were determined by multivariate analysis using the Cox model.

Results: The median follow-up was 73 months (range, 24–142 months). The 5-year overall survival and metastasis-free survival rates were 79% and 80.6%, respectively. The 5-year local control rate was 96%. The 5-year enucleation for complications rate was 7.7%. Independent prognostic factors for overall survival were age ($p < 0.0001$), gender ($p < 0.0003$), tumor site ($p < 0.0001$), tumor thickness ($p = 0.02$), tumor diameter ($p < 0.0001$), and retinal area receiving at least 30 CGE ($p = 0.003$). Independent prognostic factors for metastasis-free survival were age ($p = 0.0042$), retinal detachment ($p = 0.01$), tumor site ($p < 0.0001$), tumor volume ($p < 0.0001$), local recurrence ($p < 0.0001$), and retinal area receiving at least 30 CGE ($p = 0.002$). Independent prognostic factors for local control were tumor diameter ($p = 0.003$) and macular area receiving at least 30 CGE ($p = 0.01$). Independent prognostic factors for enucleation for complications were tumor thickness ($p < 0.0001$) and lens volume receiving at least 30 CGE ($p = 0.0002$).

Conclusion: This retrospective study confirms that proton beam radiotherapy ensures an excellent local control rate. Further clinical studies are required to decrease the incidence of postirradiation ocular complications.

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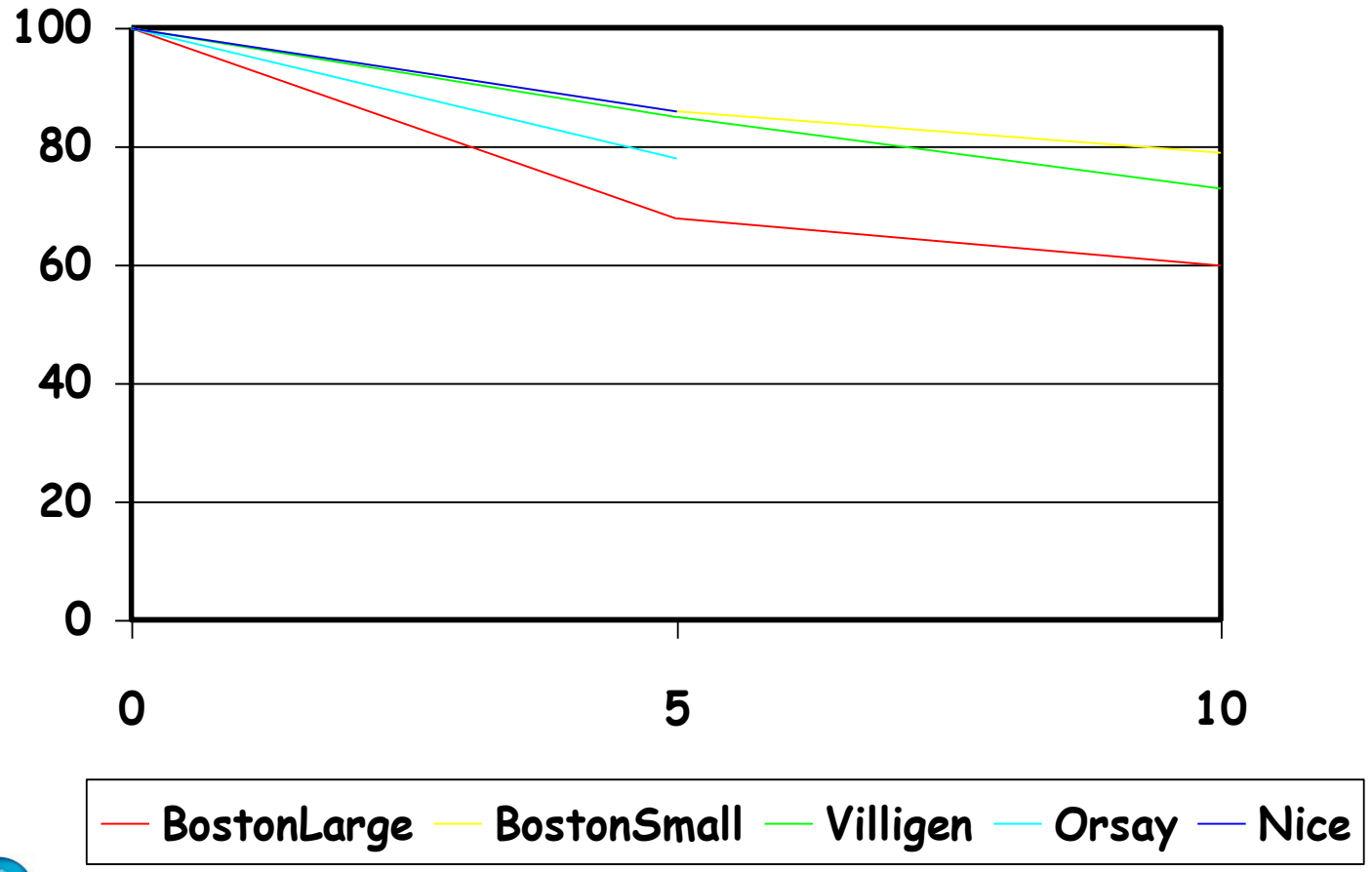
Ocular melanoma (2214 evaluable)

- Outcome (min 2YFup,Med:68m):
  - Death: 25% (2/3:melanoma)
  - Mets:20% (86%:liver)
  - Local failure: 4%

(3/4 enucleation, 1/4conservative)

  - 2ary enucleation: 6.7%

Ocular melanomas: DFS in particle therapy



Clinical achievements
(P in Skull base)

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 3, pp. 672–675, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2008.02.043

CLINICAL INVESTIGATION **Pediatrics**

PROTON THERAPY IN PEDIATRIC SKULL BASE AND CERVICAL CANAL LOW-GRADE BONE MALIGNANCIES

JEAN-LOUIS HABRAND, M.D.,* RALF SCHNEIDER, M.D.,* CLAIRE ALAPETITE, M.D.,* LOIC FEUVRET, M.D.,* SLAVO PETRAS, M.D.,† JEAN DATCHARY, M.D., PH.D.,* JACQUES GRILL, M.D., PH.D.,‡ GEORGES NOEL, M.D., PH.D.,* SYLVIE HELFRE, M.D.,* REGIS FERRAND, PH.D.,* STEPHANIE BOLLE, M.D.,* AND CHRISTIAN SAINTE-ROSE, M.D.§

*Centre de Protonthérapie de l'Institut Curie à Orsay, Campus Universitaire, Orsay, France; †University Hospital, Caen Cyceron Laboratory, Caen, France; ‡Department of Pediatric Oncology, Institut Gustave-Roussy, Villejuif, France; and §Department of Pediatric Neurosurgery, University Hospital Necker-Enfants Malades, Paris, France

Purpose: To evaluate outcomes and tolerance of high-dose photon and proton therapy in the management of skull base and cervical canal primary bony malignancies in children.

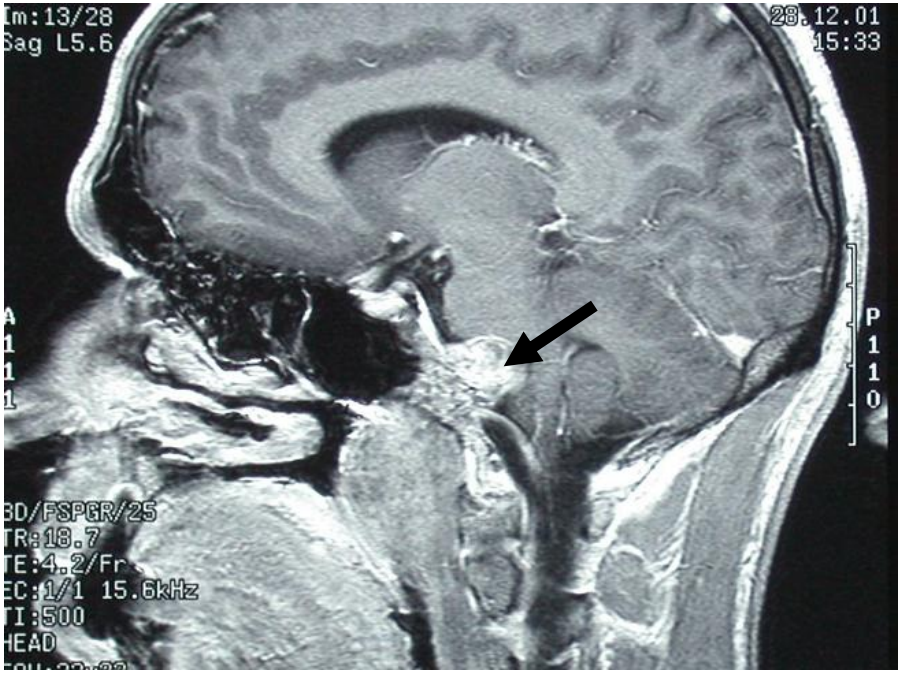
Patients and Methods: Thirty children were treated postoperatively with high-dose photon–proton (29 patients) or protons-only (1 patient) radiotherapy. Twenty-six patients had chordomas (CH), 3 had low-grade chondrosarcomas (CS), and 1 had an aggressive chondroma (AC). The mean age was 12.8 years. At the time of radiation, all but 1 patient had a gross residue. The anatomic sites affected were skull base ($n = 16$), cervical canal ($n = 1$), or both ($n = 13$). Mean total dose was 68.4 cobalt Gray equivalents, conventionally fractionated.

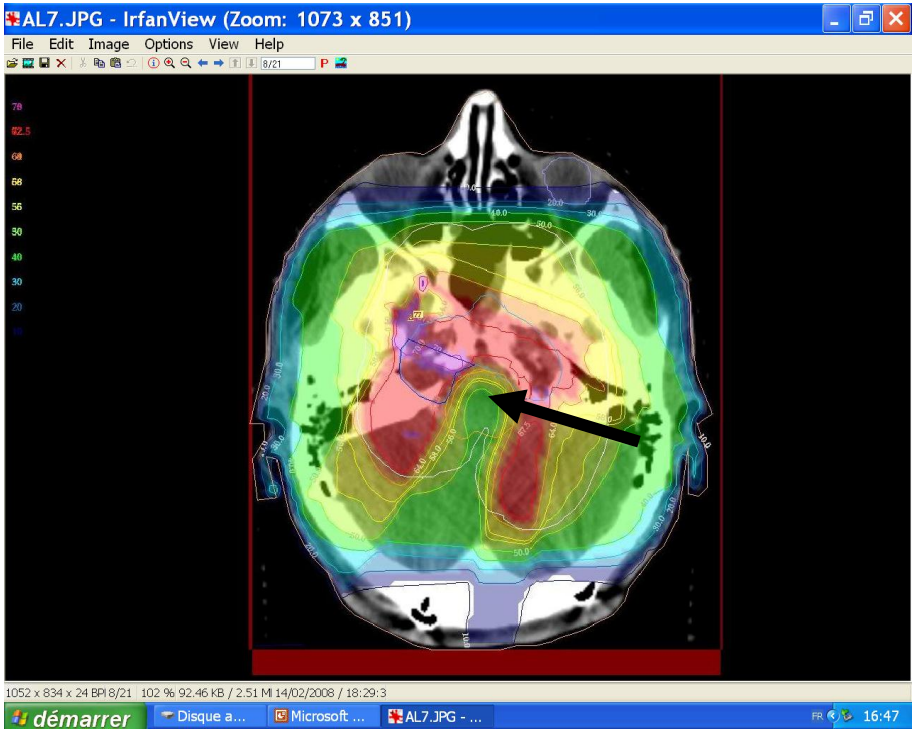
Results: With a mean follow-up of 26.5 months, 5 of 30 children failed locally: 5 of 5 lesions were CH, 5 of 5 patients had experienced pain at presentation ($p = 0.03$), and 4 of 5 had cervical extension ($p = 0.07$). The 5-year overall survival/progression-free survival rates for CS and CH were 100%/100% and 81%/77%, respectively. Side effects were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Acute toxicity ranged between 0 and 2. Late toxicity of radiotherapy was severe in 1 patient (Grade 3 auditory) and minor or mild in the rest of the population (7 patients with Grade 2 pituitary dysfunction).

Conclusions: High-dose combined fractionated photon–proton therapy is well tolerated in children and allows excellent local control with minimal long-term toxicity. © 2008 Elsevier Inc.

Centre de Lutte contre le Cancer François Baclesse

High dose protontherapy
Skull base sarcoma

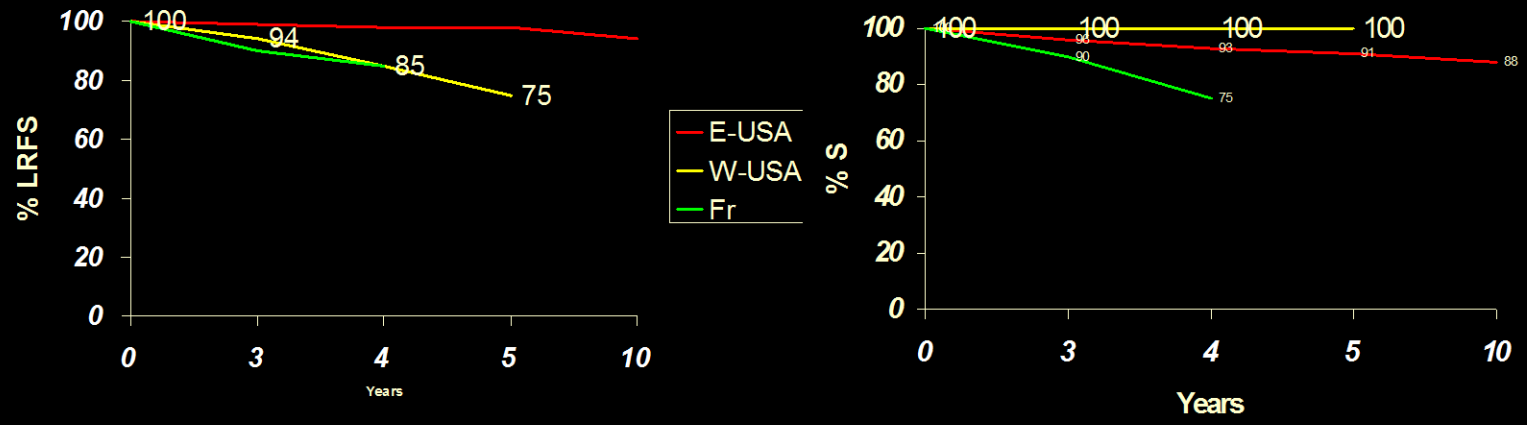




Centre de Lutte contre le Cancer François Baclesse

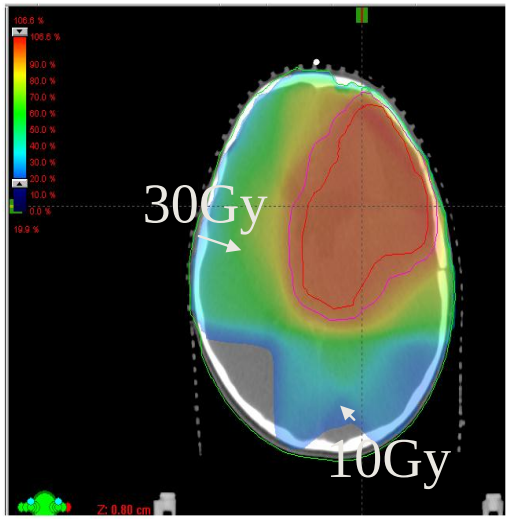
Sparing brain stem !

PROTONTHERAPY SKULL BASE - CERVICAL CHONDROSARCOMAS : LITERATURE

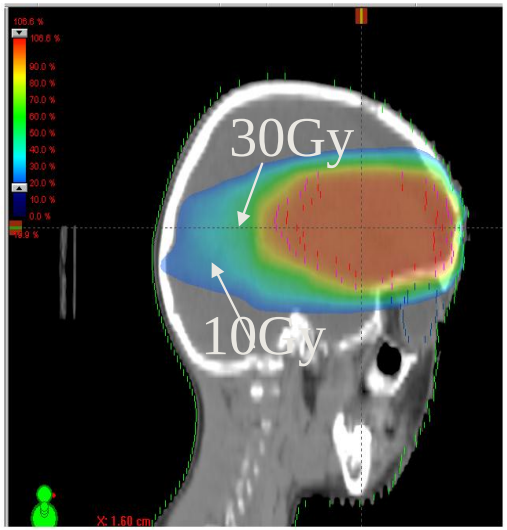


Brain T in child: *RX*: Intensity modulation

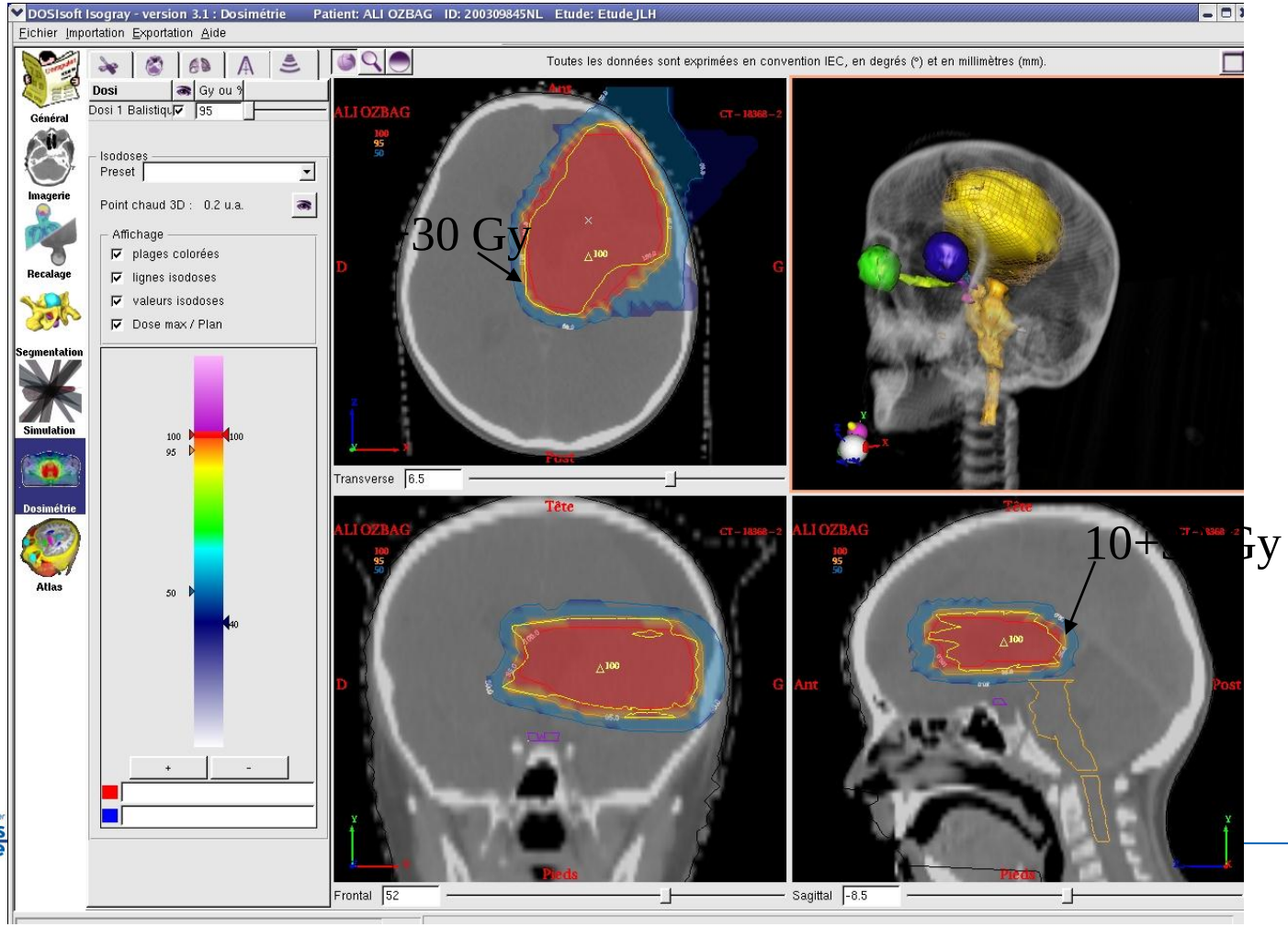
Axial



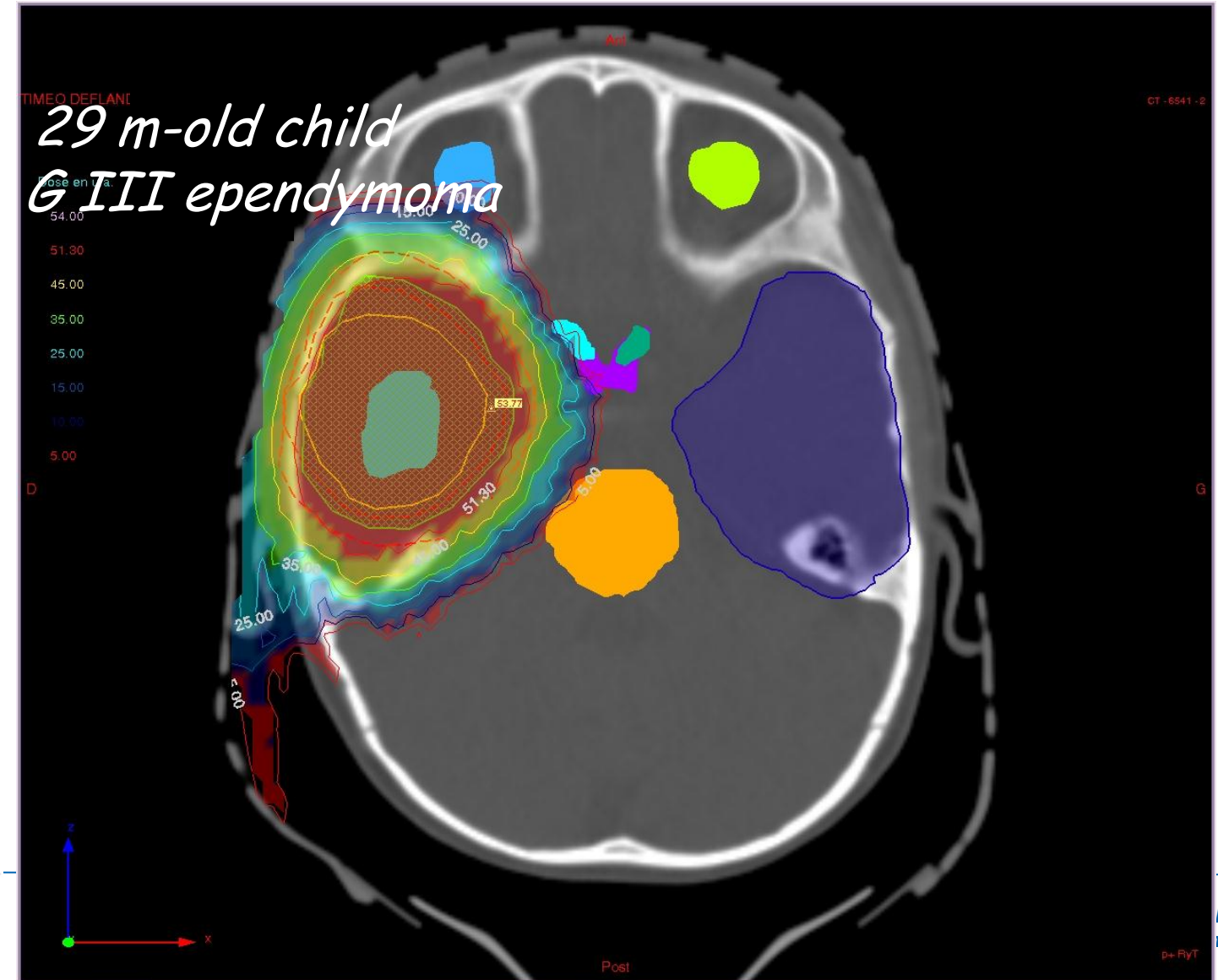
Sagittal



Brain T in child:
Protons : no intensity modulation

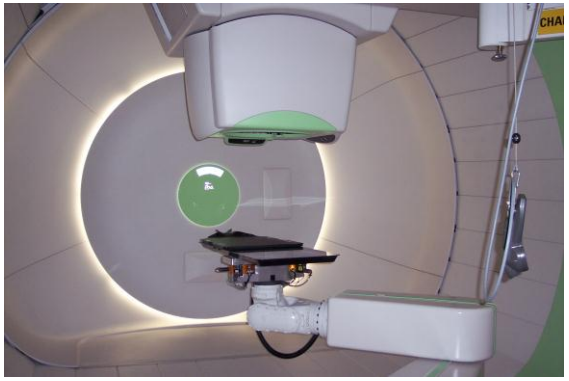


PEDIATRIC TUMORS: *breakthrough !*



High energy proton project, including pediatric program

Renovating ICPO (Orsay) *(2010)*



Expanding Nice Center to advanced photon technology

Protontherapy in Europe: France well-positioned

1994 ! End (modest) ion therapy program in France !!

- Shut down SATURN synchrotron in Saclay: phys and biol experiments on ions *(A Bridier, J Dutreix, IGR)*

- *End EULIMA project on ions based superconducting …cyclotron !*

1994 ! End ion therapy program in US

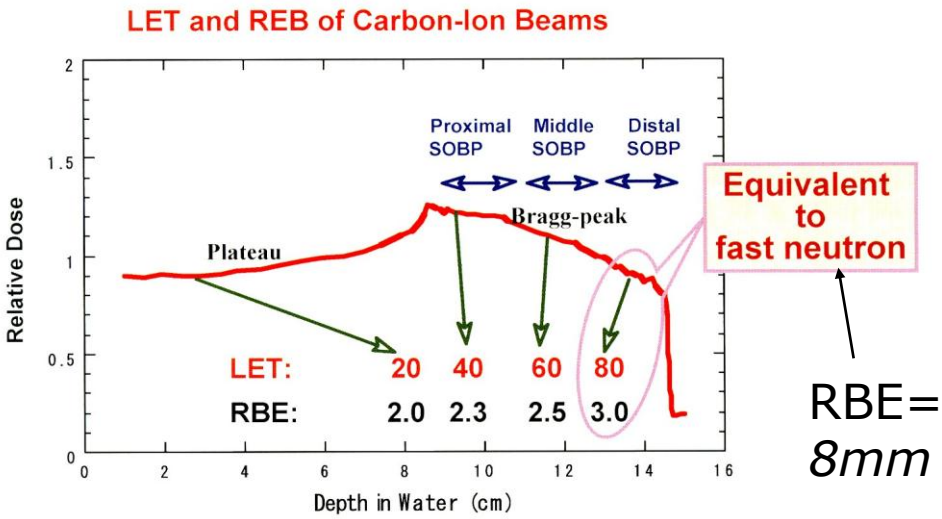
February 11, 1994

Dear Jean-Louis,

*I believe [ion] programs will benefit immensely from our limited experience in 400 patients at LBL… We mainly used **neon** and in retrospect this may have been unwise due to the amount of normal tissue damage encountered…I believe …to try something like **carbon ions**… may be of value…*

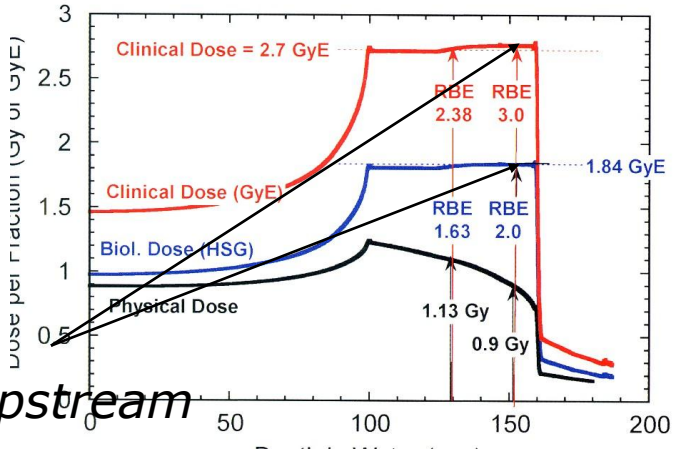
Joseph R. Castro, MD

90s': The Japanese era



RBE=N

8mm upstream



Carbon ions :
BALLISTICAL + BIOLOGICAL

Inoperable sinuso-nasal melanoma 57.6GyE/16fx

Centre de Lutte contre le Cancer François Baclesse

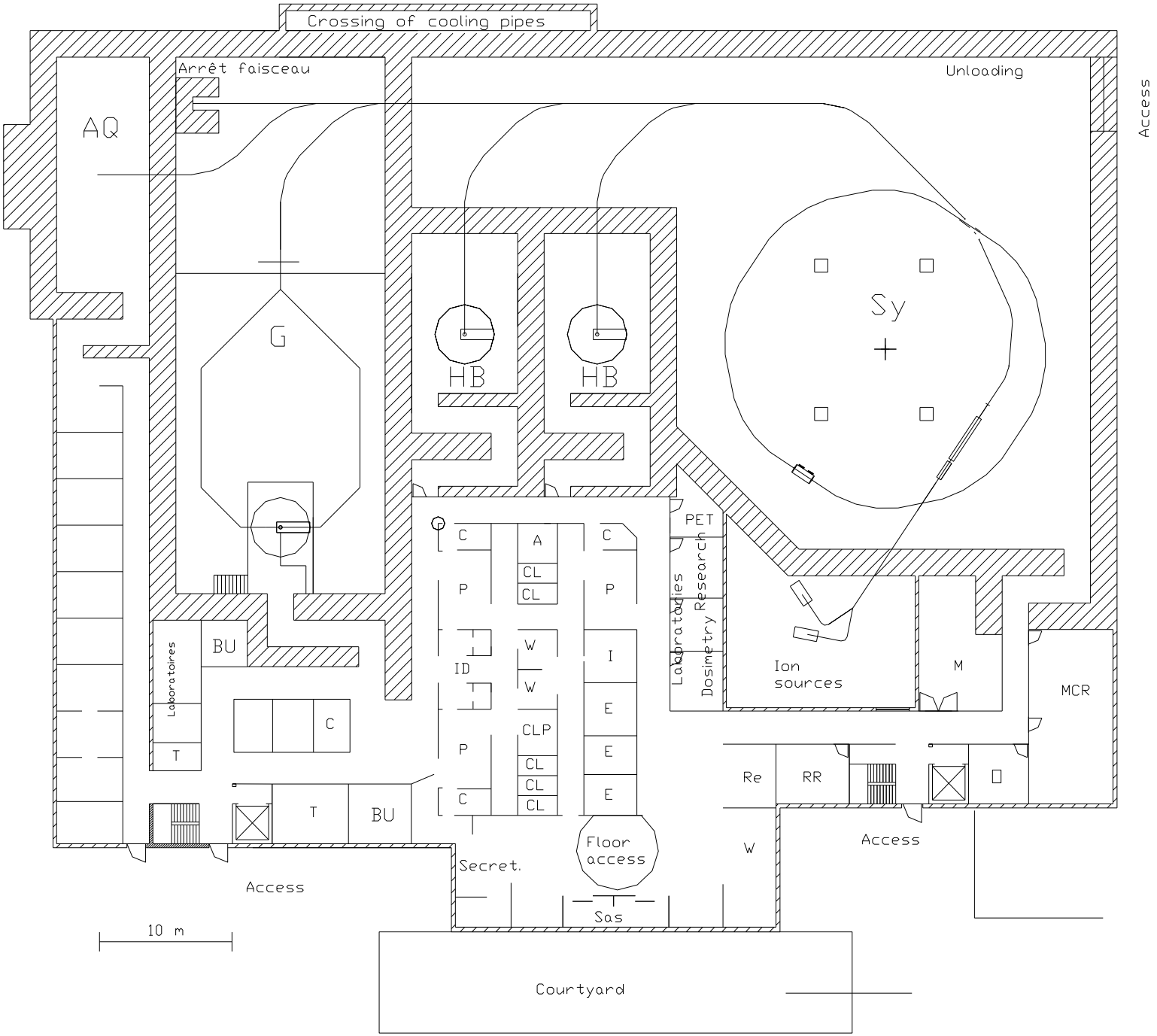
Pior RT **48 m post RT**

Courtesy Pr Tsujii, NIRS

ETOILE project (Lyon)

« Espace de Traitement Oncologique par Ions légers dans le cadre Européen »

- **Equipment: 1 accelerator + 3 or 4 C treatment rooms**
- **Financial investment: *Public***
- **Estimated cost: 200 M€**
- **Amortization: treatment sessions (Social Security: Health service)**
- **Starting: 2013 (?), operational in 5 years: objective: 1500 à 2000 patients per year with C**


Crossing of cooling pipes
Arrêt faisceau
Unloading
Access
AQ
G
HB
HB
Sy
PET
Laboratories
Dosimetry Research
Ion
sources
M
MCR
C
A
CL
CL
C
P
P
W
W
ID
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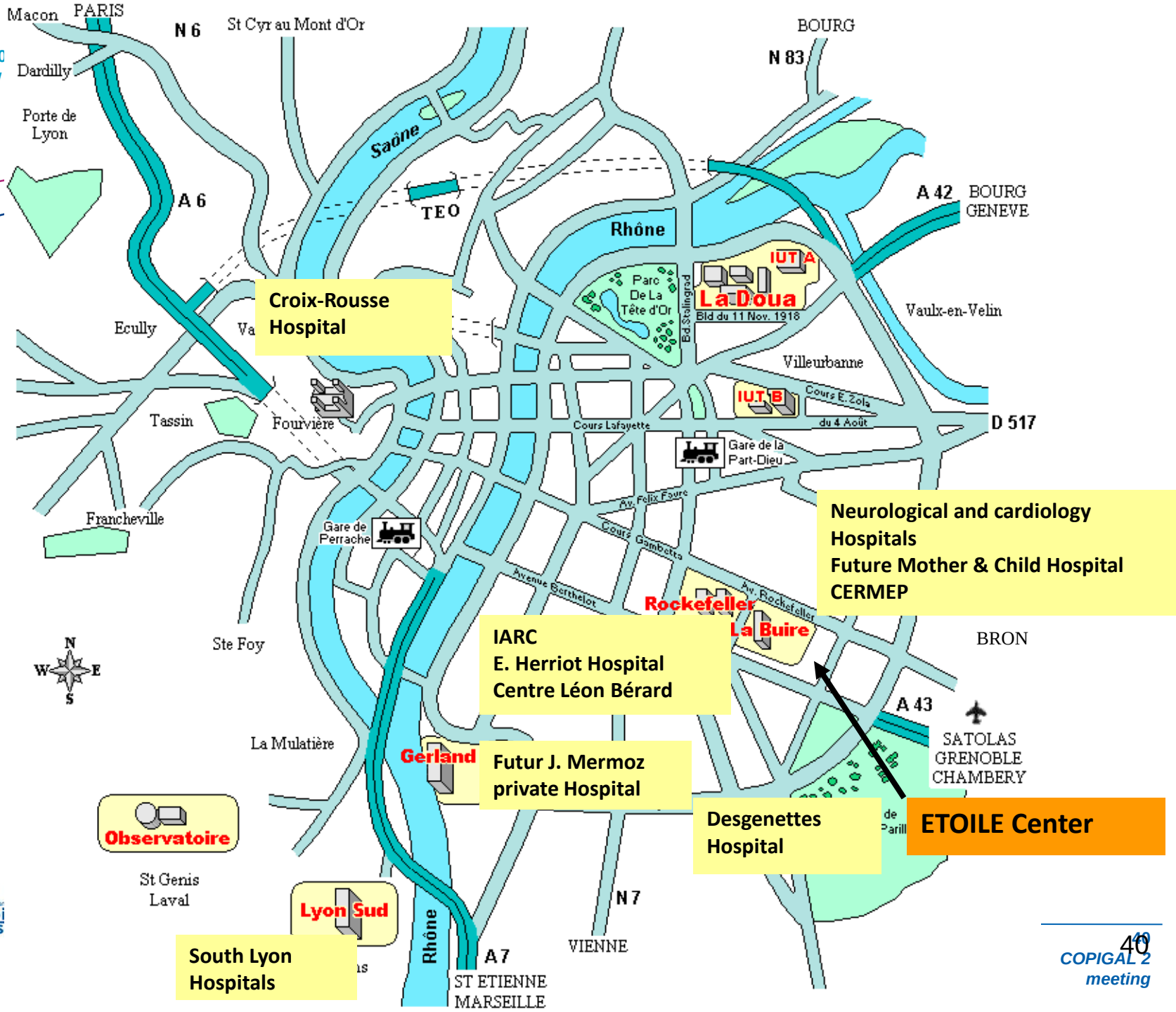
E
CLP
E
P
CL
CL
E
C
CL
Re
RR
W
BU
Laboratoires
C
T
T
BU
Access
Secret.
Floor
access
Sas
Access
10 m
Courtyard


Croix-Rousse Hospital
Neurological and cardiology Hospitals
Future Mother & Child Hospital
CERMEP
IARC
E. Herriot Hospital
Centre Léon Bérard
Futur J. Mermoz private Hospital
Desgenettes Hospital
ETOILE Center
South Lyon Hospitals
Macon
PARIS
N 6
St Cyr au Mont d'Or
BOURG
N 83
Dardilly
Porte de Lyon
Saône
A 6
TEO
Rhône
A 42
BOURG GENEVE
IUT A
La Doua
Bld du 11 Nov. 1918
Parc De La Tête d'Or
Bd Stalingrad
Vaulx-en-Velin
Ecully
Villeurbanne
IUT B
Cours E. Zola
du 4 Août
D 517
Tassin
Fourvière
Cours Lafayette
Gare de la Part-Dieu
Francheville
Gare de Perrache
Av. Félix Faure
Cours Gambetta
Avenue Berthelot
Av. Rockefeller
Rockefeller
La Buire
BRON
N
W
E
S
Ste Foy
A 43
SATOLAS
GRENOBLE
CHAMBERY
La Mulatière
Gerland
Observatoire
St Genis Laval
Lyon Sud
Rhône
N 7
VIENNE
A 7
ST ETIENNE
MARSEILLE

OMERRIC project: exploring new indications

Beginning 2002

Biological and physical **basic criteria** to apply Hadrontherapy

2002 - 2003

Local Working Groups

Screening of all topographies and histologies to identify *a priori* any potential indication for Hadrontherapy

2003 - 2004

"Evidence based medicine" approach

screening of all relevant literature to extract the present state of the art out-come of selected pathologies

"Epidemiological landscape"

search of national French collection of cancer registry (FRANCIM) and "One day survey" in French radiation oncology departments

International experts evaluation and validation

For 2005

Indications double hierarchy = priority table

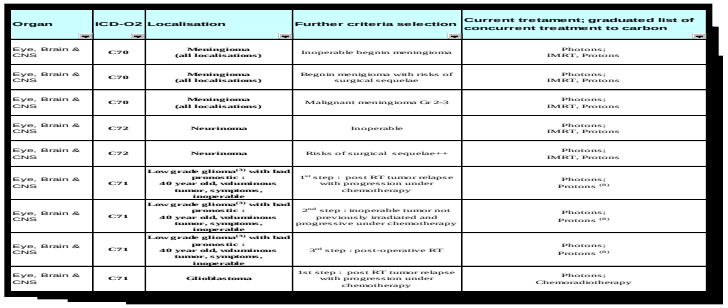
1) according to the frequency
2) according to the expected medical benefit

During 2005 to 2007

Rational choice of indications to organise the recruitment through international multicentric prospective clinical trials

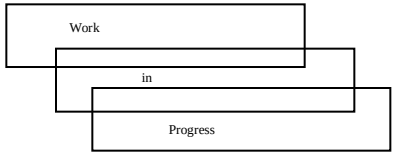
"General criteria have been defined for indication of hadrontherapy by carbon ions, for the patient, the tumor and the treatment possibilities :

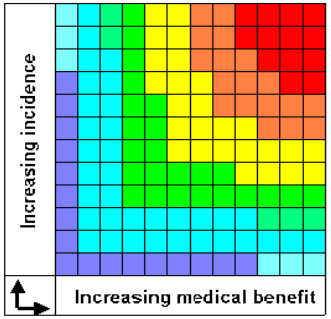
- For the patient
  - General physical and mental status compatible with the treatment
  - Lack of serious condition reducing the vital prognostic at short term
- For the tumor
  - Tumor for which the best existing treatment has a high rate of failure either because of the radioresistance of the tumor or because of the sensitivity of surrounding healthy tissues insufficiently protected by classical radiotherapy technique.
  - Disease limited to the local-regional stage or having a weak metastatic potential or having a very slow progression of the metastatic part or which metastatic part can be efficiently treated by chemotherapy
- For the treatment by carbon ions
  - Medical imaging and history allowing a precise definition of the clinical target volume (tumor and invisible extensions)
  - Possible use of an efficient repositioning mean for precise tumor repositioning and movement monitoring during treatment
  - Limitation to the anatomical sites that can be targeted by the irradiation setting in case of fixed beam (for the treatment centers without gantry)."



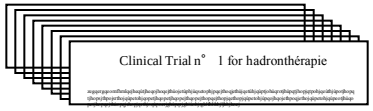
Organ	ICD-O2	Localisation	Further criteria selection	Current treatment; graduated list of concurrent treatment to carbon
Eye, Brain & CNS	C70	Meningioma (all localisations)	Inoperable begnin meningioma	Photons; IMRT, Protons
Eye, Brain & CNS	C70	Meningioma (all localisations)	Begnin meningioma with risks of surgical sequelae	Photons; IMRT, Protons
Eye, Brain & CNS	C70	Meningioma (all localisations)	Malignant meningioma Gr 2-3	Photons; IMRT, Protons
Eye, Brain & CNS	C72	Neurinoma	Inoperable	Photons; IMRT, Protons
Eye, Brain & CNS	C72	Neurinoma	Risks of surgical sequelae++	Photons; IMRT, Protons
Eye, Brain & CNS	C71	Low grade glioma[3] with bad pronostic : 40 year old, voluminous tumor, symptome, inoperable	1st step : post RT tumor relapse with progression under chemotherapy	Photons; Protons [6]
Eye, Brain & CNS	C71	Low grade glioma[3] with bad pronostic : 40 year old, voluminous tumor, symptome, inoperable	2nd step : inoperable tumor not previously irradiated and progressive under chemotherapy	Photons; Protons [6]
Eye, Brain & CNS	C71	Low grade glioma[3] with bad pronostic : 40 year old, voluminous tumor, symptome, inoperable	3rd step : post-operative RT	Photons; Protons [6]
Eye, Brain & CNS	C71	Glioblastoma	1st step : post RT tumor relapse with progression under chemotherapy	Photons; Chemoradiotherapy

The potential indications tables





The priority table



A portfolio of multicenter clinical trials

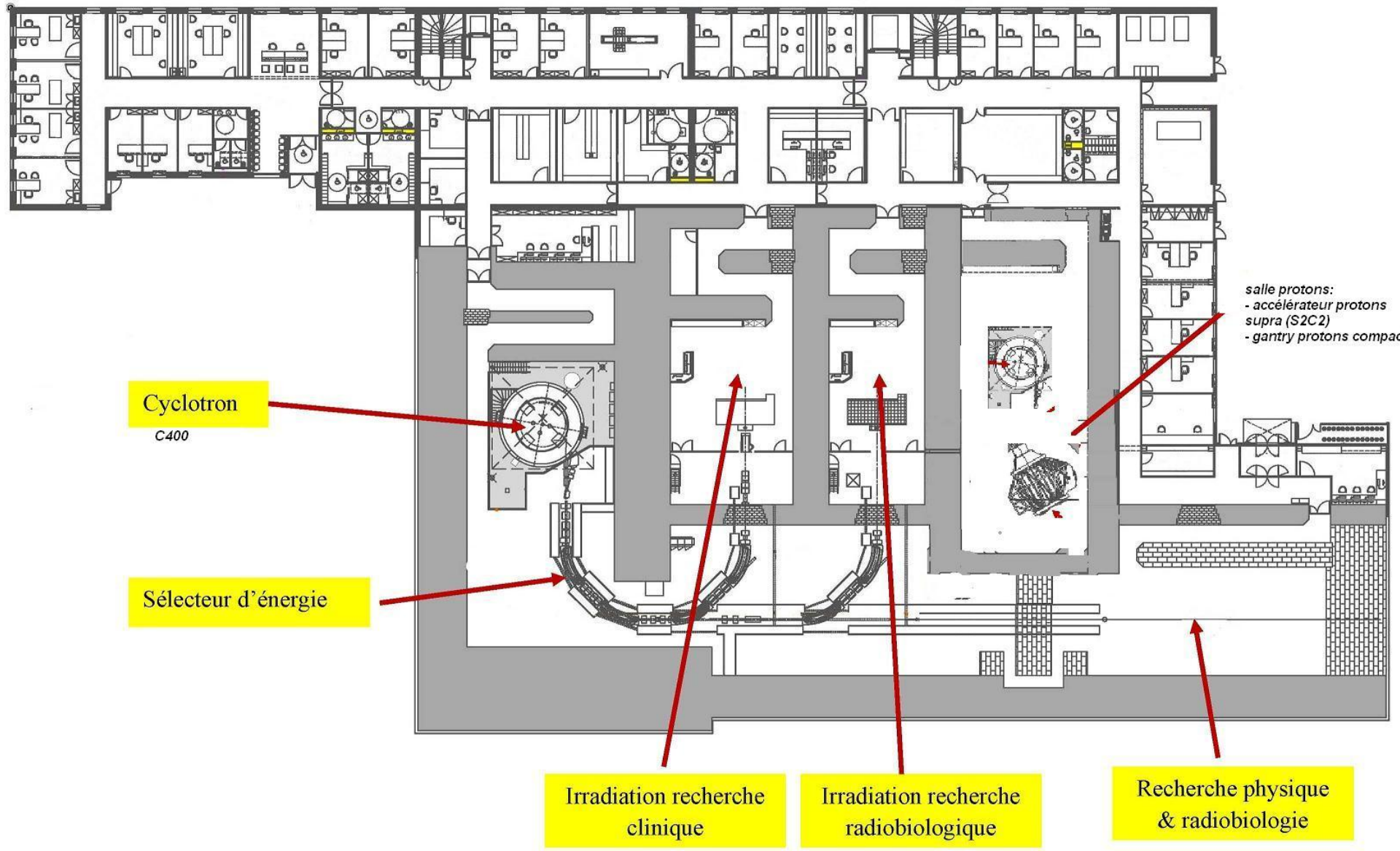
ARCHADE project (Caen)

Advanced Resource Centre for HADrontherapy in Europe

- Equipment: 1 accelerator + 2C + 1P treatment rooms
- Financial investment: Private *with public support*
- Estimated cost: 100 M€
- Amortization: treatment sessions (Social Security)
- Starting: 2013 (?),
  partly operational (P) in 3 Y: objective: 850 P patients per Y;
  fully operational in 5Y (P+C): Phys, Biol, selected patients for C

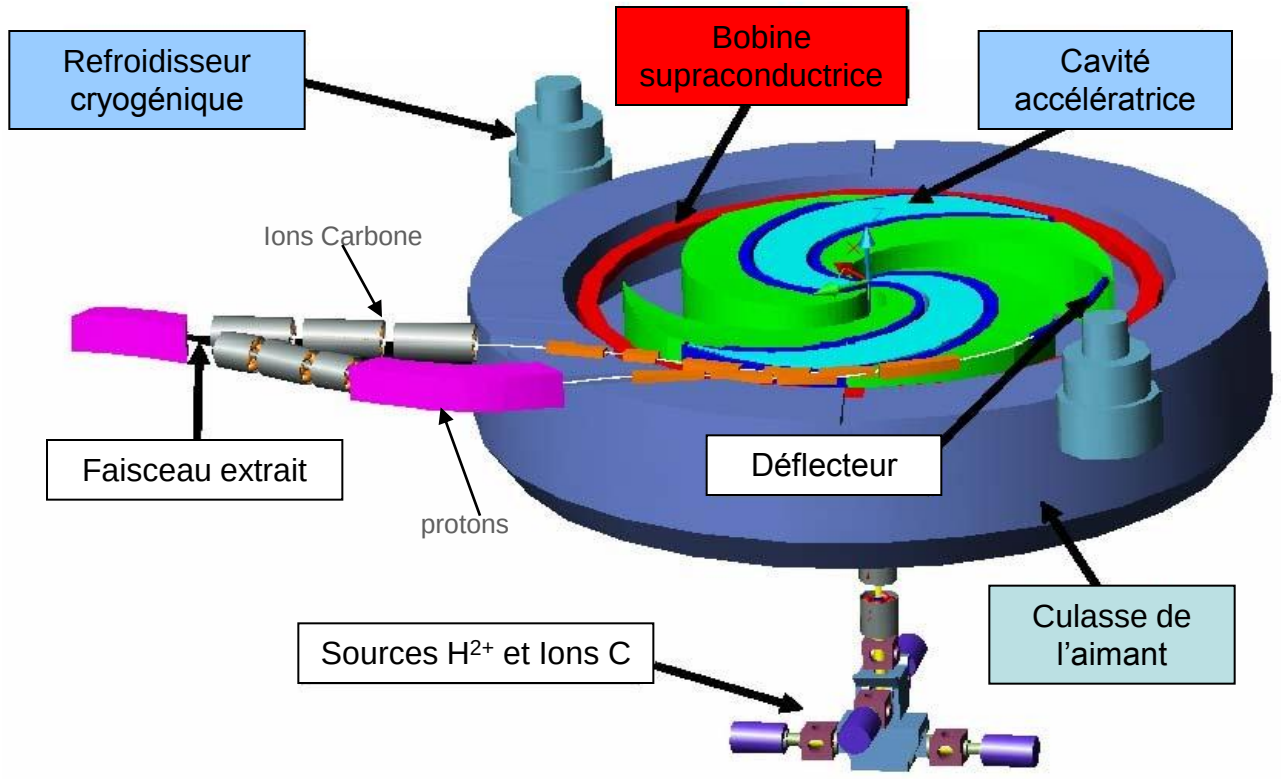
Tarif T2A : 03 / 2009

Libellé	*Tarif (€)*
Protons/s	1161
Curie/s	1030
Tech spéciale :ICT/s	892
Autres tech spéciale: névraxe/s	596
RTcomplexe/séance(IMRT…)	200
Autre technique/s	168
Préparation 3D	924
Préparation non 3D	360



Niveau des salles d'irradiation du centre ARCHADE

C400 (MeV) : cyclotron supra P + C
Comment faire du neuf avec du vieux !!



Archade : vient renforcer un campus déjà exceptionnel :

de la physique nucléaire fondamentale … imagerie… biologie… au traitement du cancer…

Centre François Baclesse

Centre de Lutte contre le Cancer François Baclesse

Which future for hadronT. in France ?

- We have existing equipments in protons
- We have clinical projects in proton therapy
- We have projects « from bench to bed side » in ion therapy
- We need coordination and support from governmental authorities…

France HADRON is a proposal for a unique national institution made of 5 centers

- A national infrastructure distributed on 5 nodes :
  - ETOILE Center in Lyon,
  - ARCHADE Center in Caen,
  - Centre Antoine Lacassagne / IMPACT in Nice,
  - Curie Institute / ICPO in Orsay,
  - Claudius Regaud Institute / PERICLES in Toulouse.

- with the partnership of CNRS/IN2P3 (IPNL & LPC) and of IRSN,

- and the support of INSERM, INCa, CEA, ENLIGHT, ULICE and 16 industrials et public institutions including CNES, Thales, Mérieux...

France HADRON - objectives

- To optimize technical means and procedure for hadrontherapy,
- To federate research teams and organize research at a national level,
- To build new research beam lines for protons and carbon ions,
- To fund beam time and beam line access for research.

France HADRON – scientific project (1)

- **Multidisciplinary**: medicine, physics, biology, computer, etc.
- **25 teams are involved :**
  - Lyon - Clermont-Fd : teams of C. Rodriguez-Lafrasse, M. Beuve, D. Dauvergne, G Montarou, N. Foray, D. Sarrut, B. Shariat, B. Ribba, P. Pommier.
  - Nice : teams of JM. Hannoun-Levi, P. Mandrillon.
  - Orsay : teams of A. Fourquet / R. Dendale, A. Mazal, J. Hall / F. Pouzoulet.
  - Caen : teams of D Cussol / J. Colin, M. Bernaudin, K. Boumediène, JL. Lefaix, MH. Moscatello, JL. Habrand.
  - Toulouse : teams of E. Moyal, P. Celsis / A. Laprie / M. Delannes, R. Ferrand

France HADRON – scientific project (2)

- Organized into four working packages:
  - WP1 - How to identify and assess the medical value of hadron therapy (clinical research)
  - WP2 - How to improve treatment plans (measurements, modeling and computer simulation)
  - WP3 - How to better understand the effect of treatment (radiation biology, radiotoxicology)
  - WP4 - How to improve the quality control of treatment (instrumentation).

MEDICAL COORDINATORS

Merci !
Thank you !