Workshop on Medical Physics & Biomedical Engineering,
25-28 July, 2018, Ohrid

Innovative RT, Multiple Particle RT, Nano-Part., Synchro-Radiation

J. Balosso, MD-PhD, Caen, Fr; 60 min

Centre de Lutte contre le Cancer François Baclesse
unicancer NORMANDIE - CAEN

UNIVERSITÉ Grenoble Alpes

Outline

1. The classical way to deliver radiotherapy
2. Everything could change: particles, beam shape, time and fractionation
    - 2.a. New beams
    - 2.b. New shape
    - 2.c. New timing
3. Conclusion and perspectives

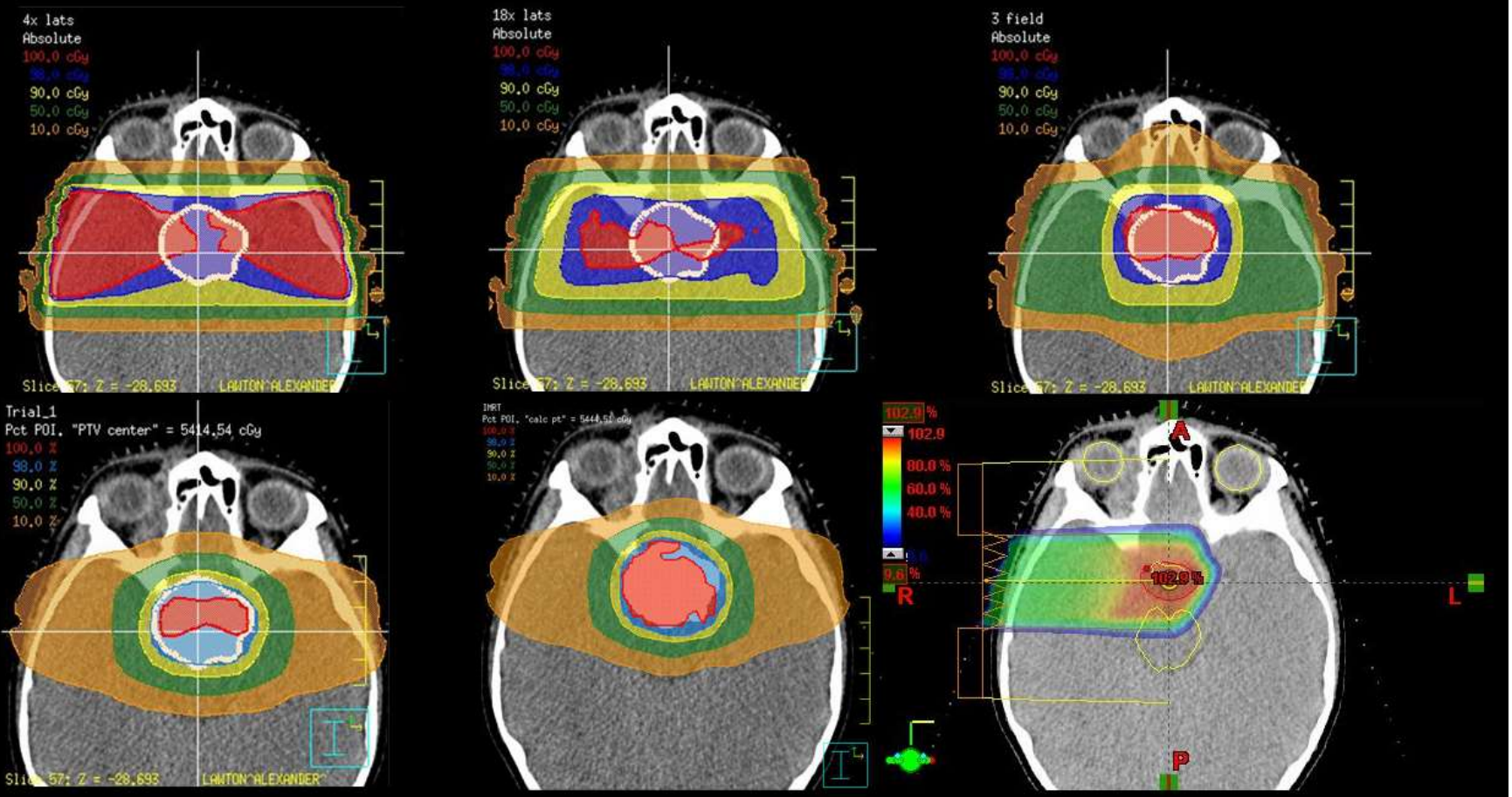
The classical way to deliver radiotherapy…

… **has not change much since almost one century!**

The 7 basic principles are still universally respected:

- Loco-regional treatment
- Whole irradiation of the defined tumor
- Continuous and homogeneous spatial dose
- Multi-beam focused on the target
- Maximum tolerated dose to the tumor site
- Fractionation of the total dose in about 2Gy fractions
- Use of X-rays

Improvements in Radiation dose distribution from 1980 to 2005.

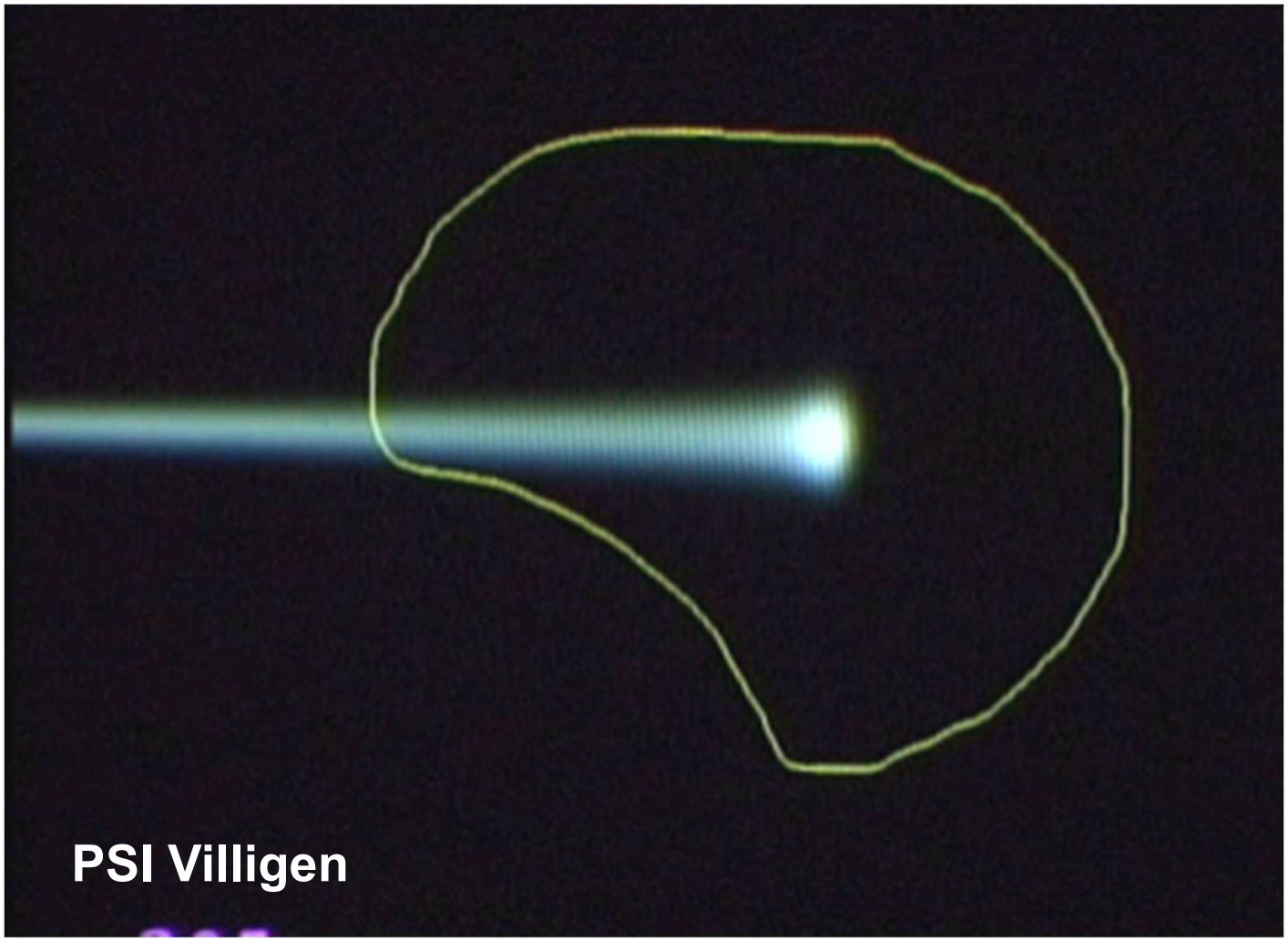


However, everything could change….

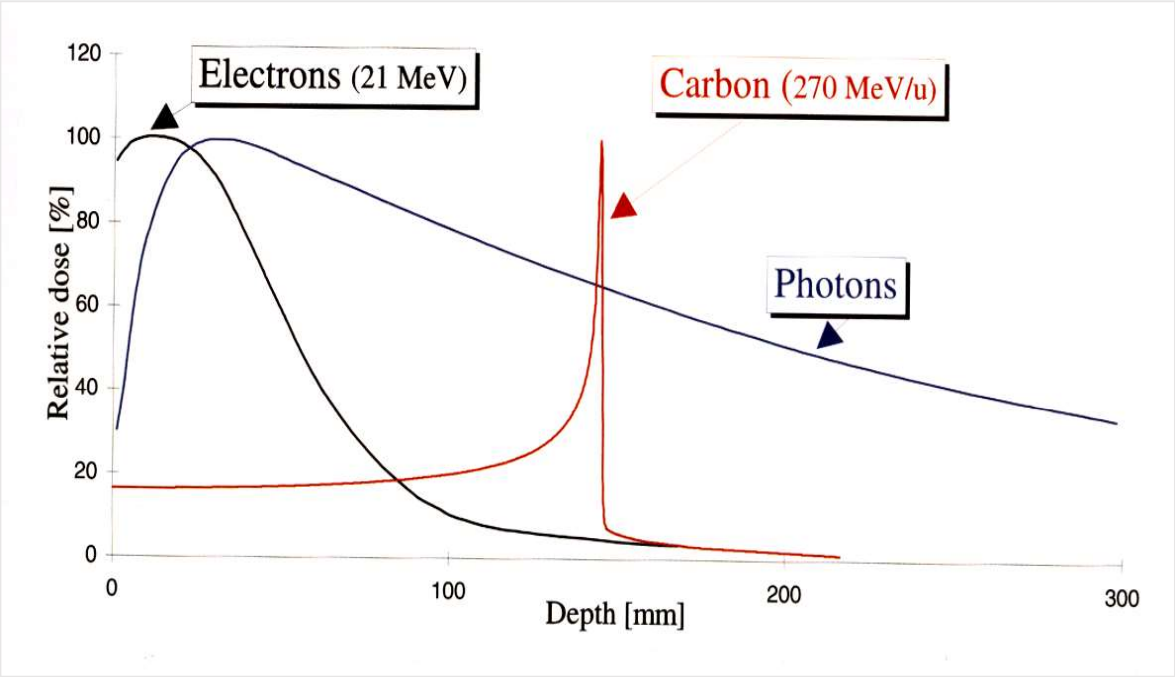
- Since more than 60 years (except electrons) **other particles** have been tested as different types of hadrontherapy:
  - Neutrons (BNCT is a kind of rebirth …)
  - Protons
  - Mesons
  - Ions: He, Ne, C, O, Si
- More recently the particular properties of the **synchrotron light** have been investigated with two very different concepts:
  - SSRT with photo-electric effect
  - and MRT introducing the fascinating concept of spatial fractionation
- And even more recently the properties of **very short irradiations** have been investigated: the FLASH concept

Hadrontherapy
or ion beam therapy
or particle therapy

The path of a charged particle beam: protons

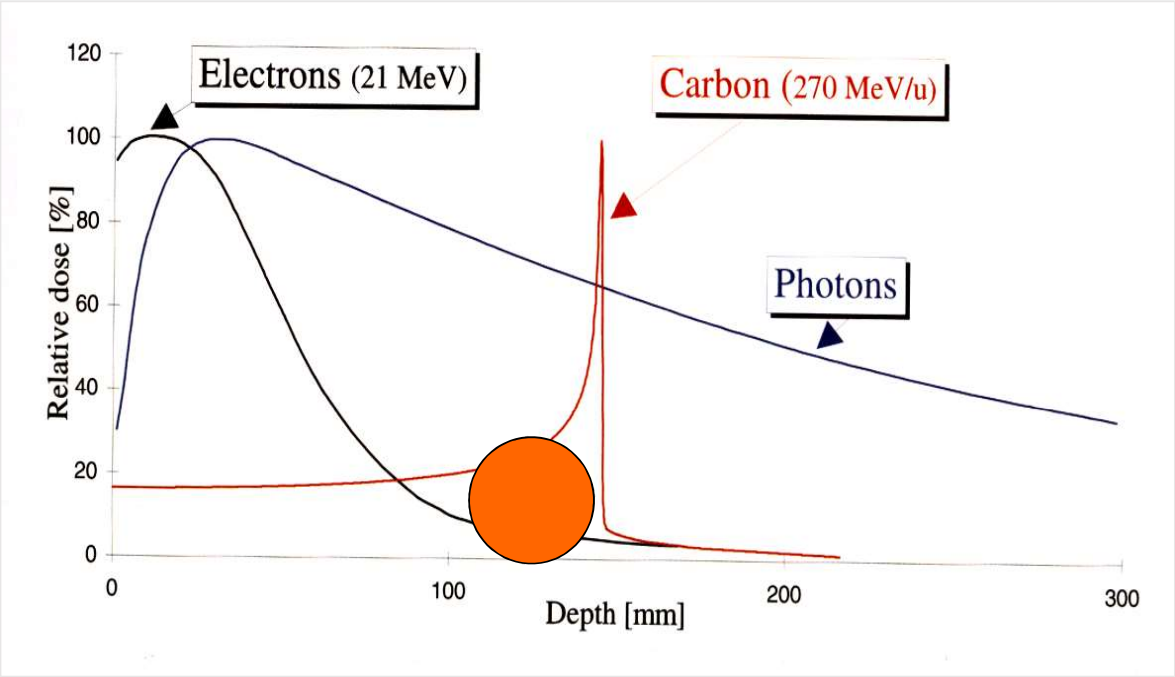


Beams and tumors



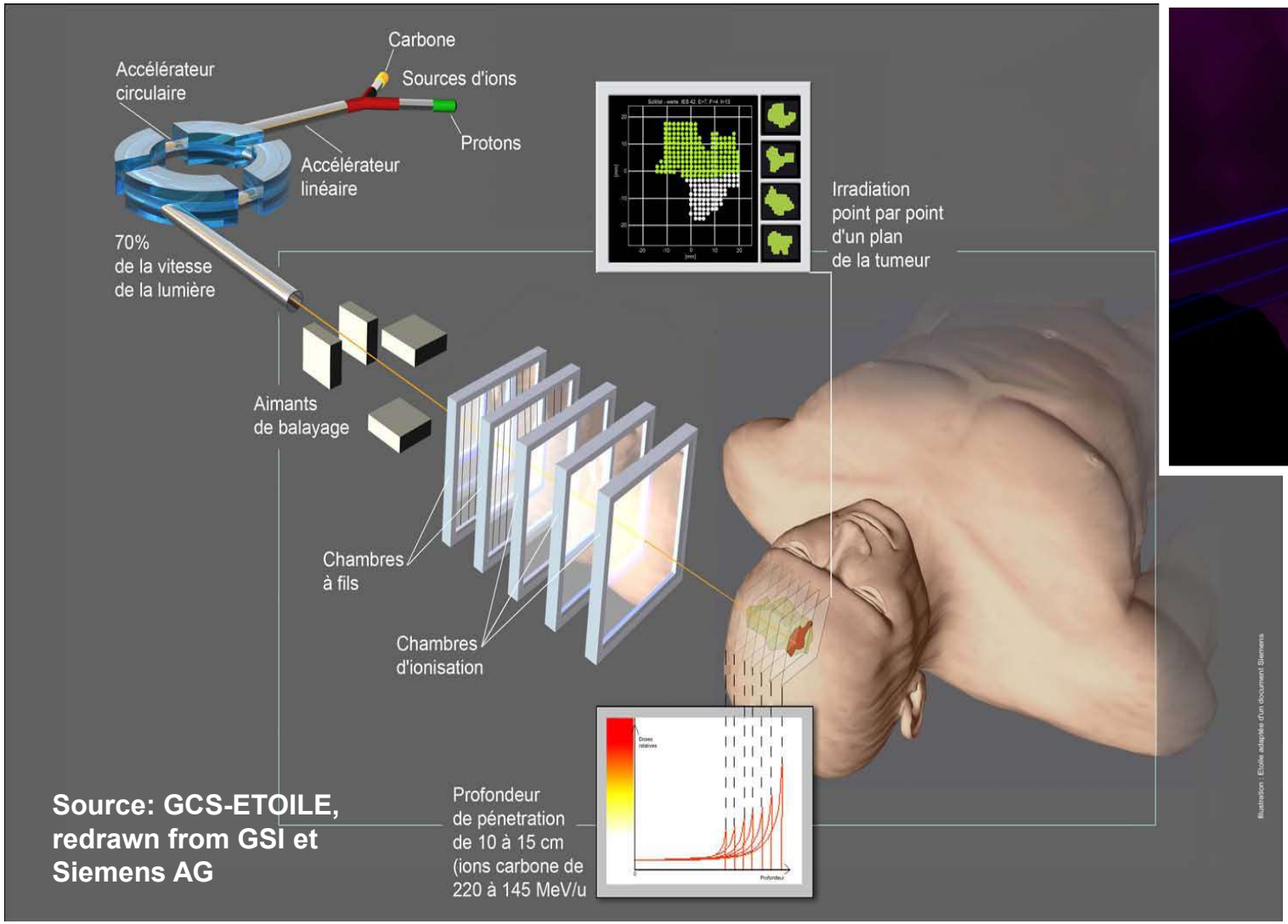
Comparison of the depth dose for high energy photons, 21 MeV electrons and carbon ions of 270 MeV/u . (GSI, Darmstadt, Allemagne)

Beams and tumors

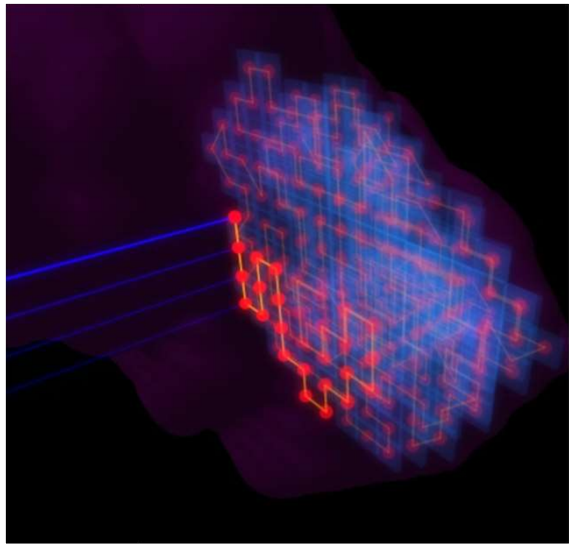


Comparison of the depth dose for high energy photons, 21 MeV electrons and carbon ions of 270 MeV/u . (GSI, Darmstadt, Allemagne)

Principle of the active beam scanning by synchrotron

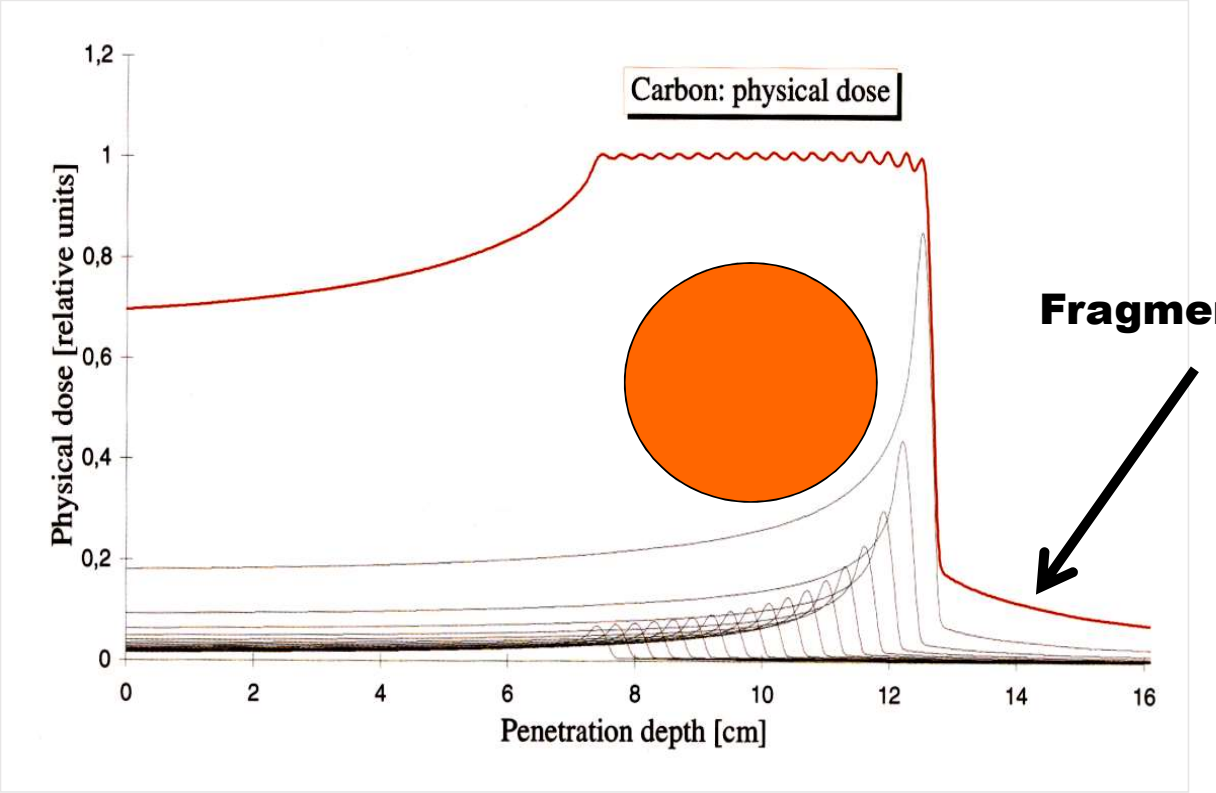


Source: GCS-ETOILE, redrawn from GSI et Siemens AG



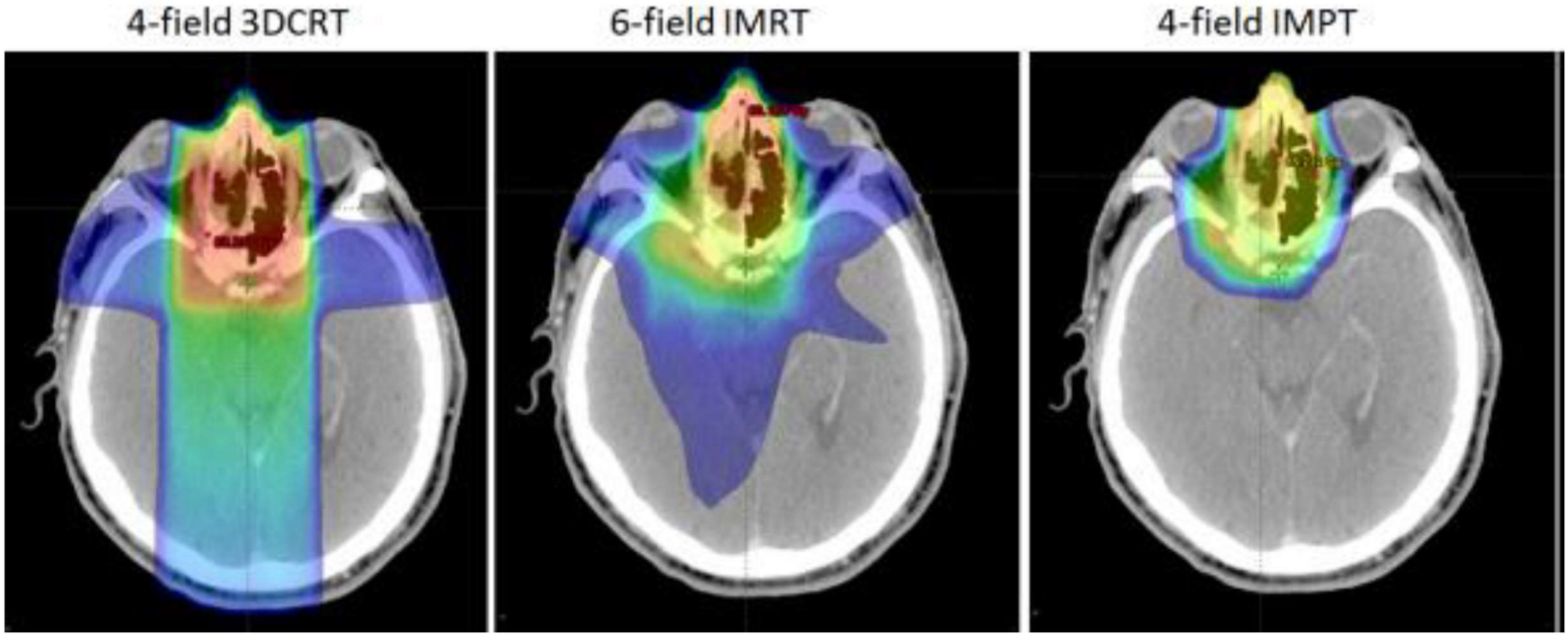
Doc. CNAO

The spread out Bragg peak (SOBP) of ions

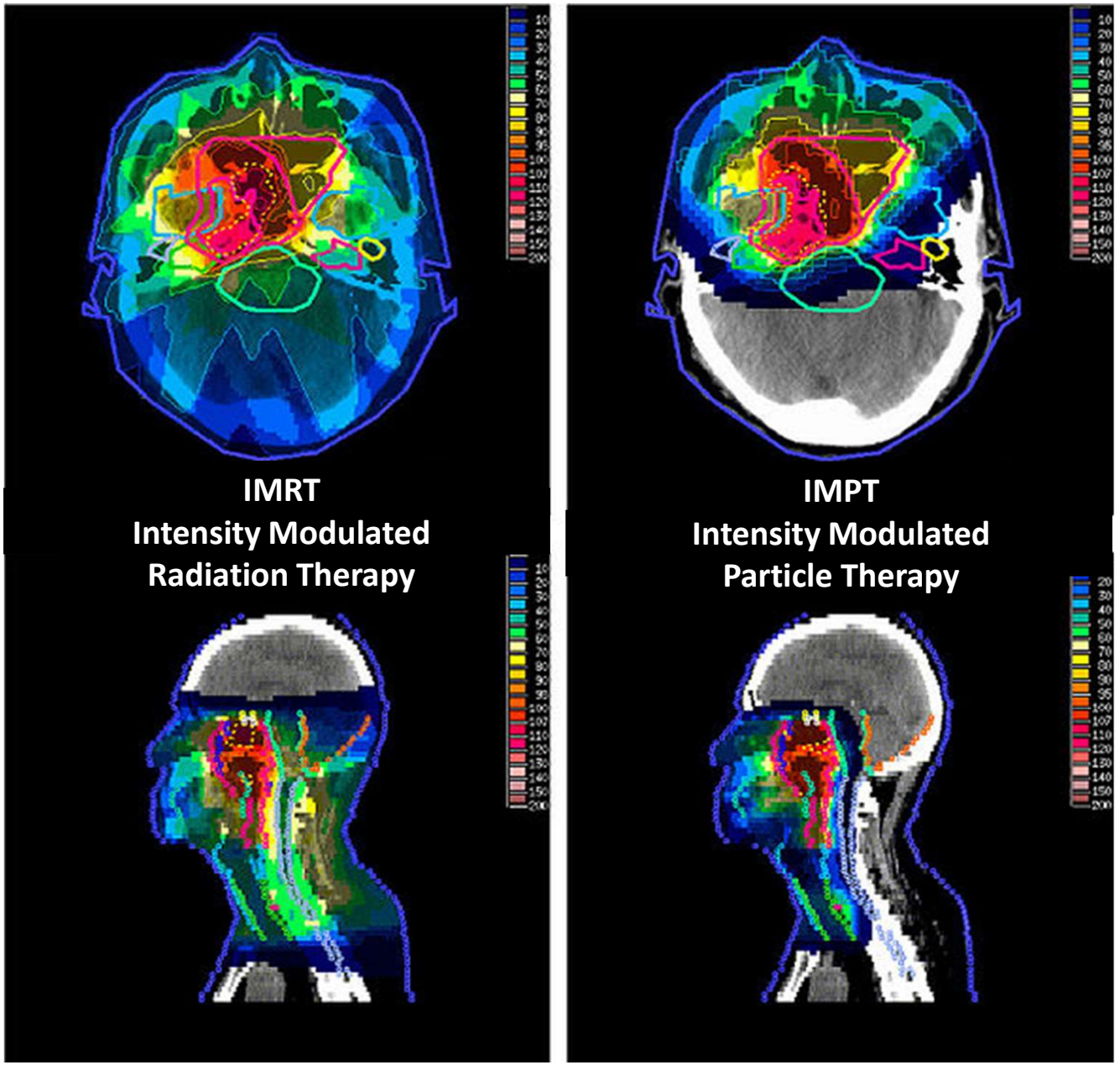


(GSI, Darmstadt, Allemagne)

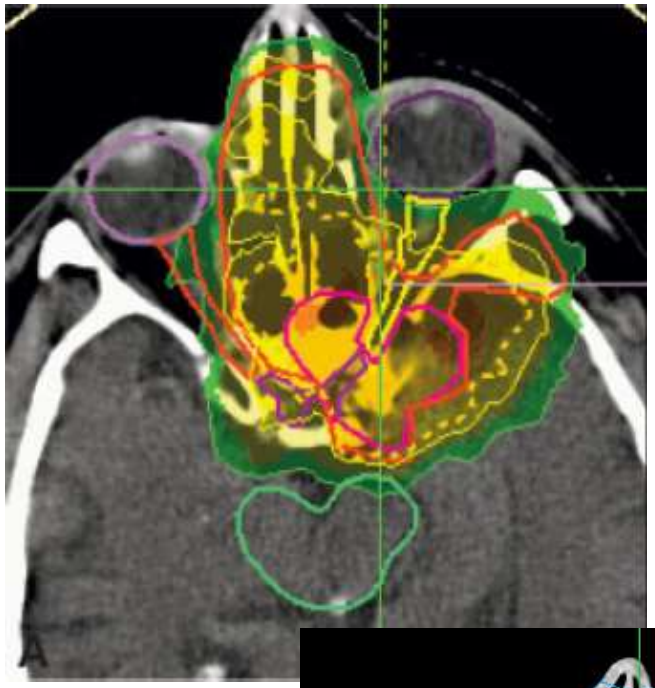
Comparative dose distributions: CRT vs IMRT vs proton IMPT



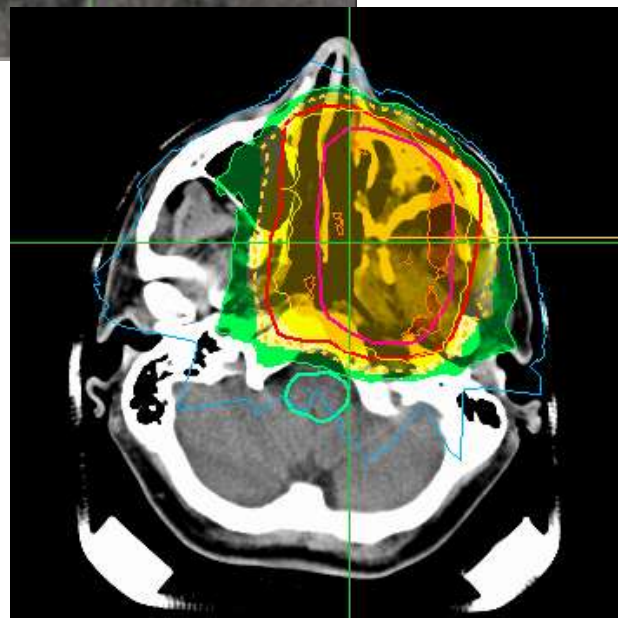
Comparison
IMRT vs IMPT



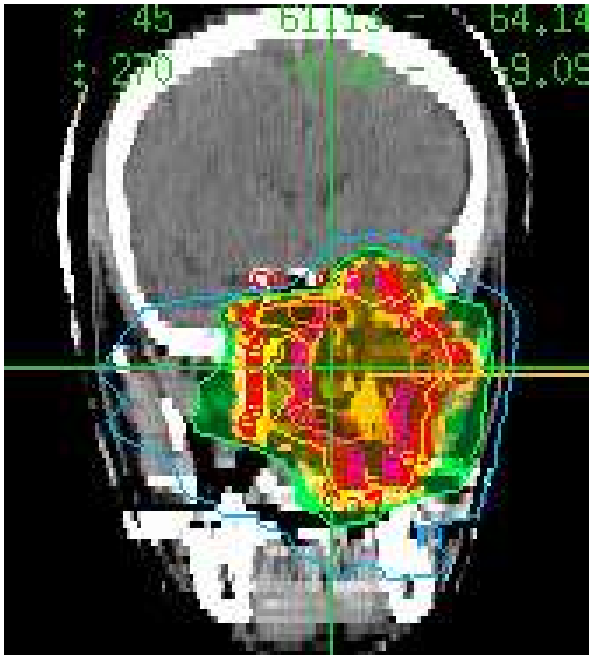
Carbon ions, GSI



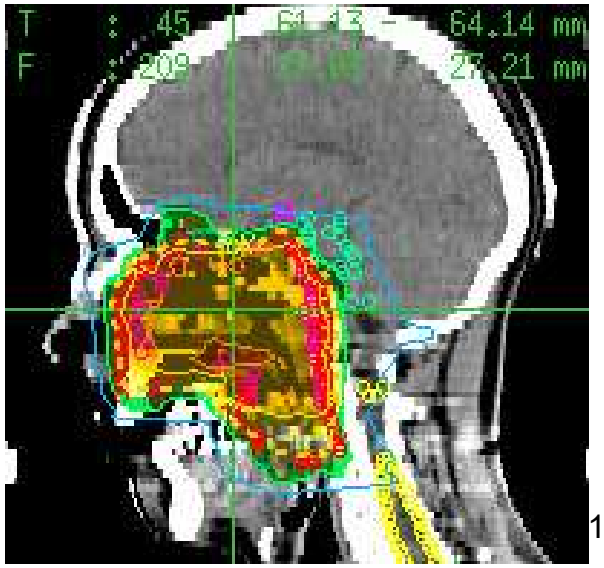
D Schulz-Ertner, GSI



a) axial plans



b) coronar plan

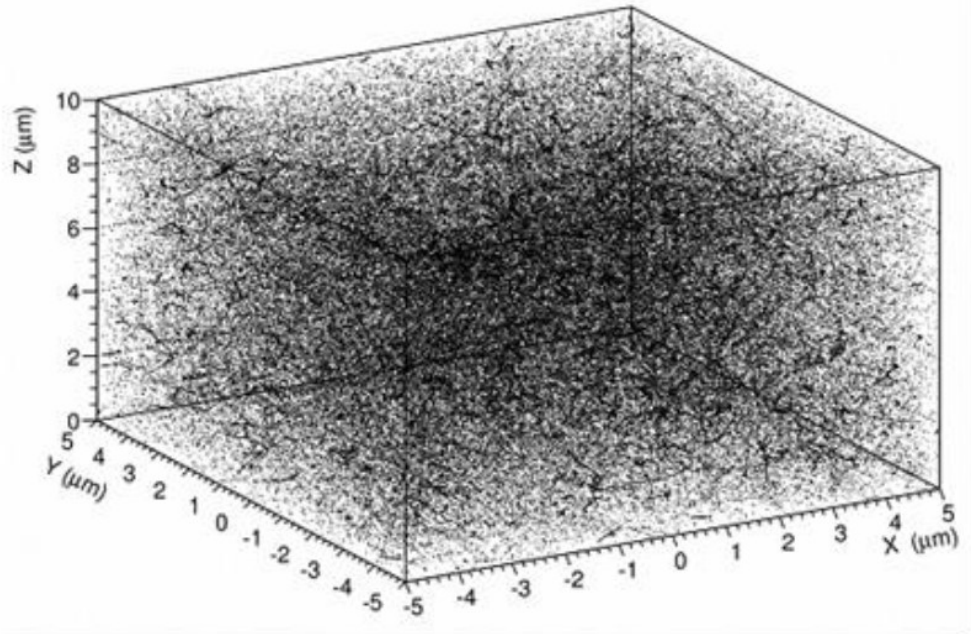


c) sagittal plan

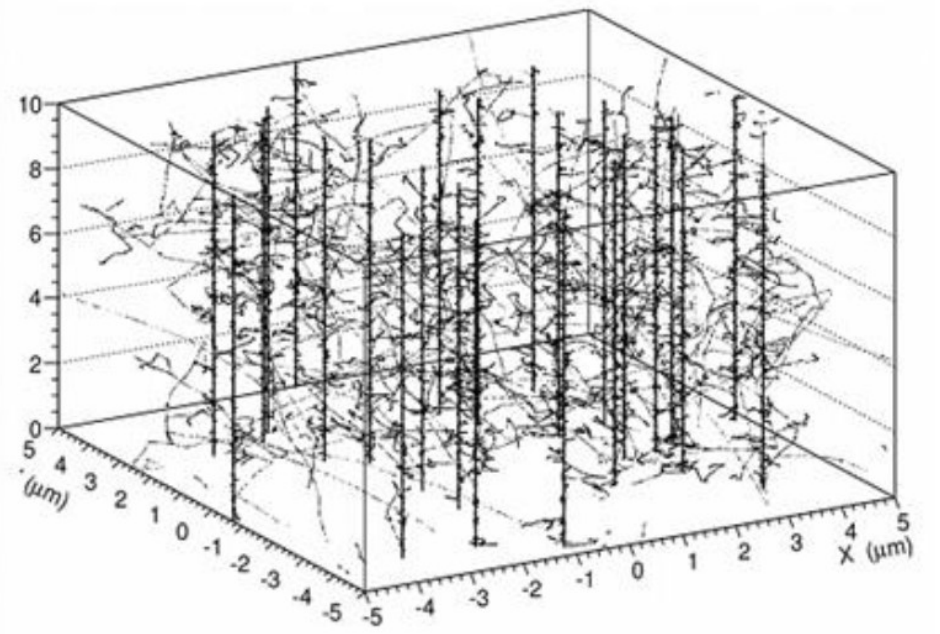
Ionisation density (LET) at the scale of the cell

The very different spatial distribution of oxydative radicals between low LET irradiation (X-ray, left) and high LET irradiation (C ions, right) is the main explanation of the different biological effect

OH• after 1 Gy X-ray

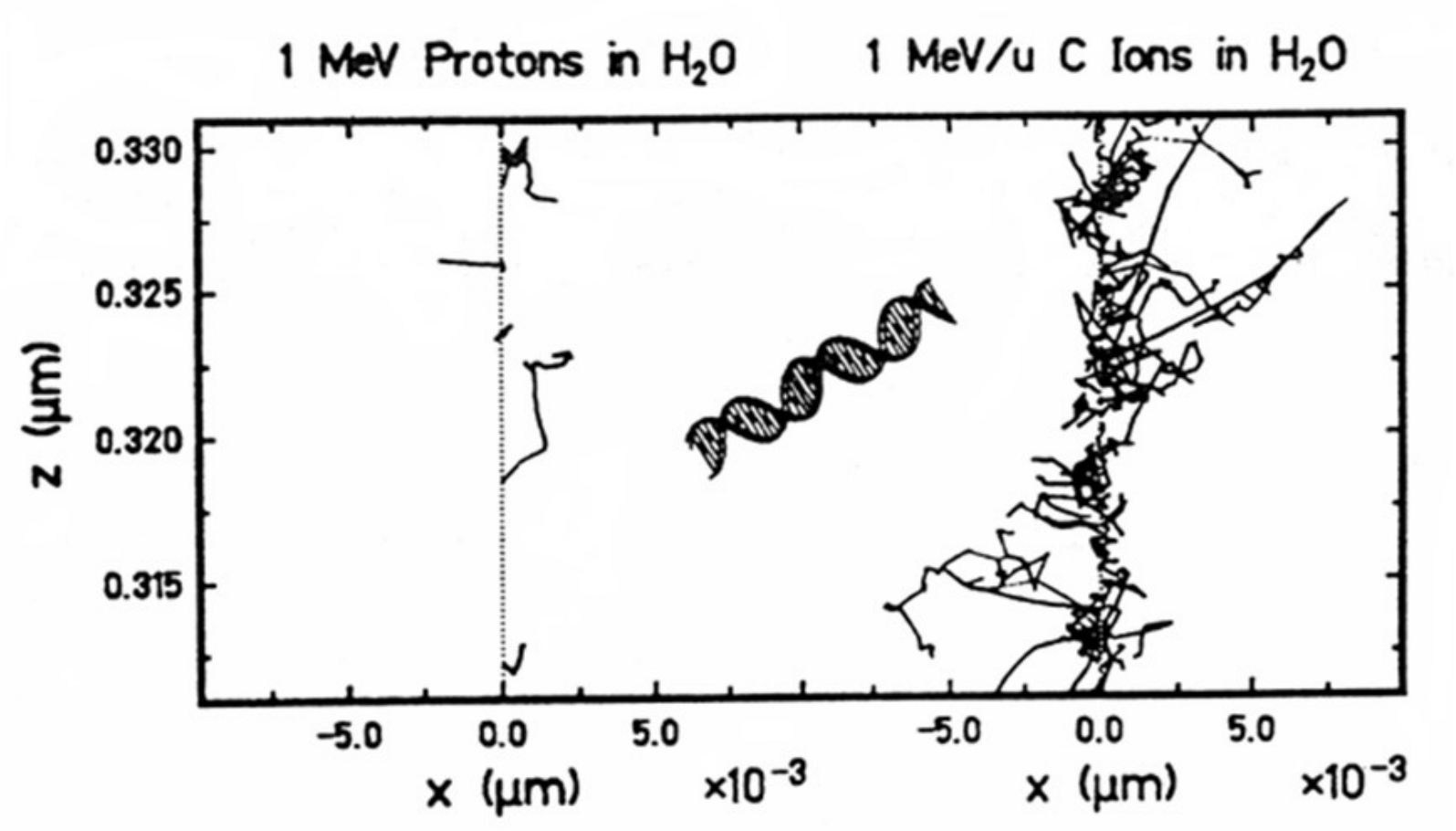


OH• after 1 Gy C ions

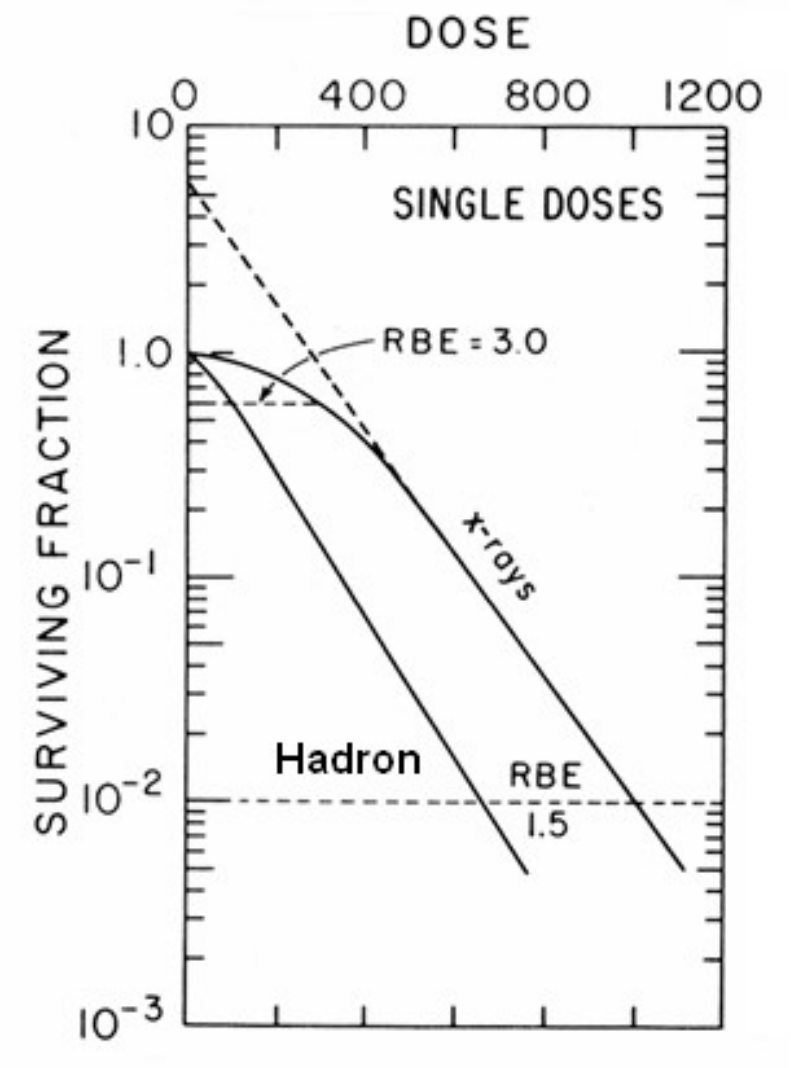


OH radicals distribution produced by a 1 Gy irradiation with either X-ray (250 kV) or carbon ions (75 MeV/u) as obtained by Monte Carlo simulation, A S Wozny et al. 2018

Ionisation density (LET) at the scale of the DNA

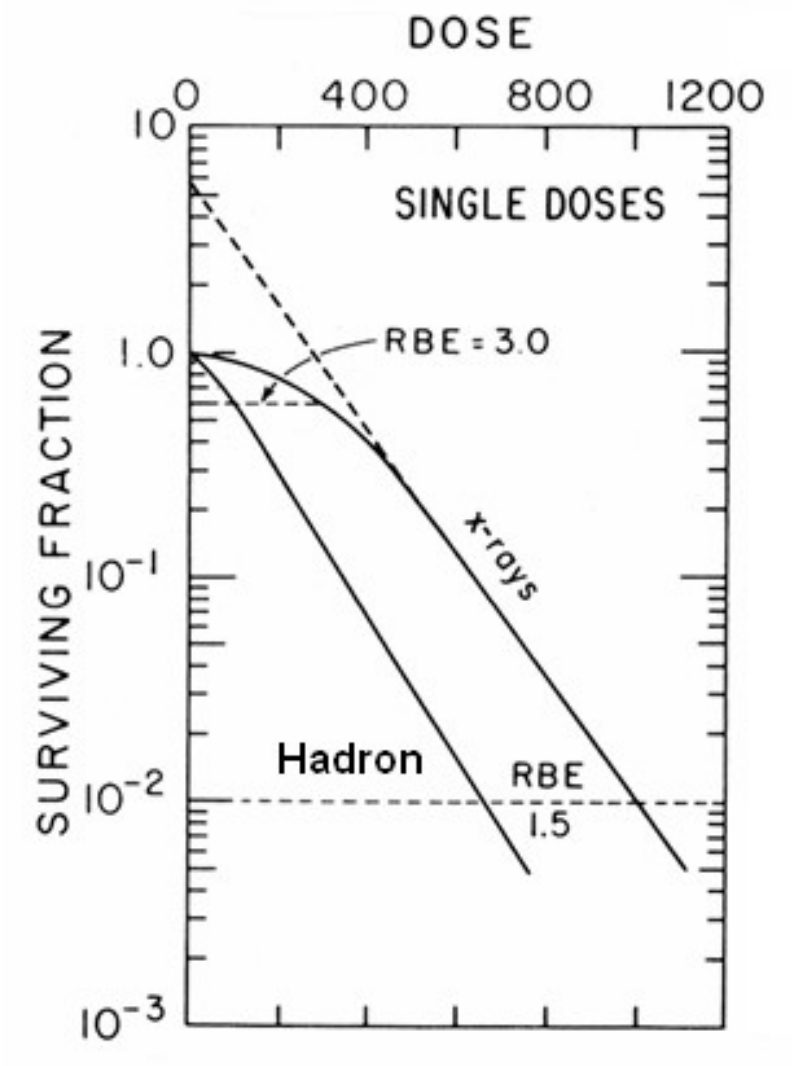


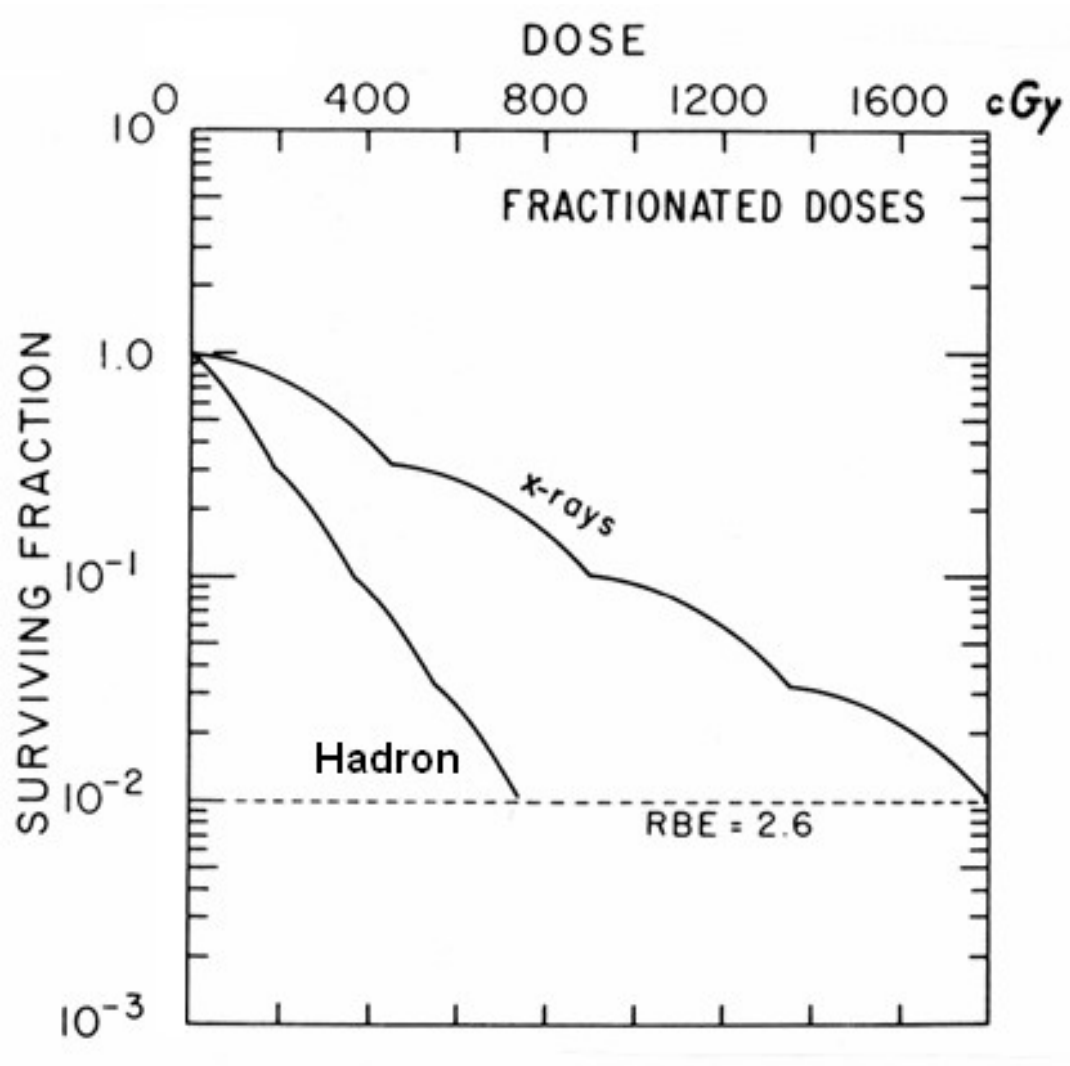
Reduced DNA damage repair:…



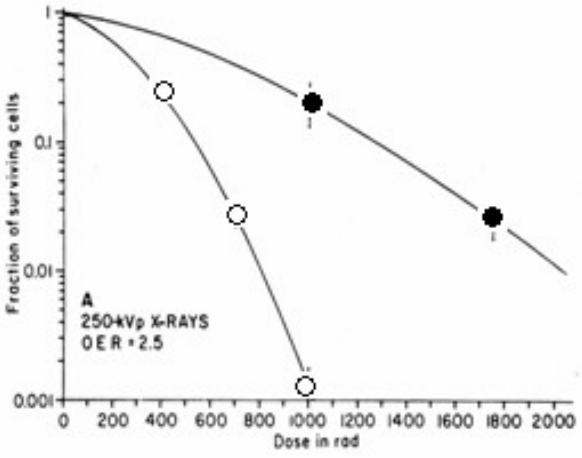
Mammalian cells irradiated with neutrons:E.Hall; Lippincott Co, 1994.

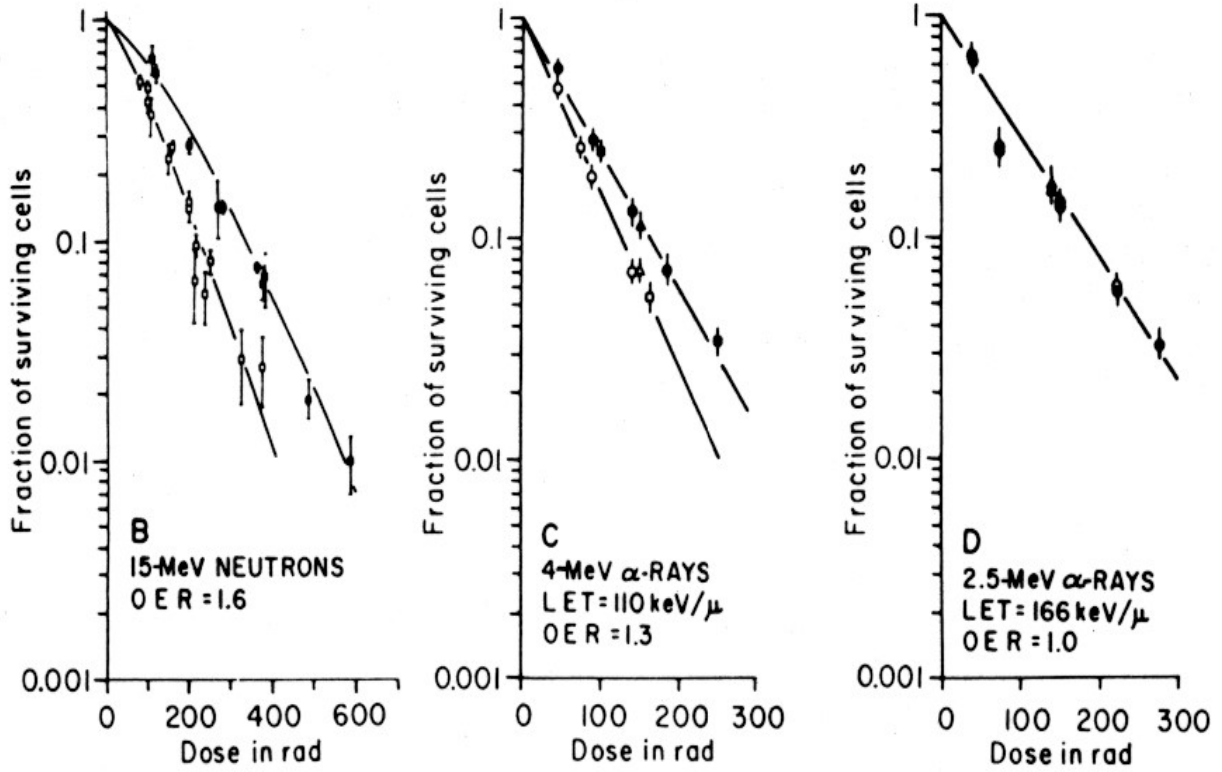
Reduced DNA damage repair: reduced fractionation effect





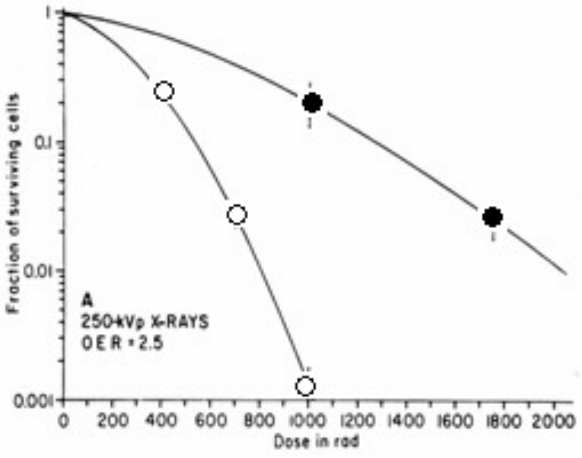
… and reduced hypoxic resistance to ions



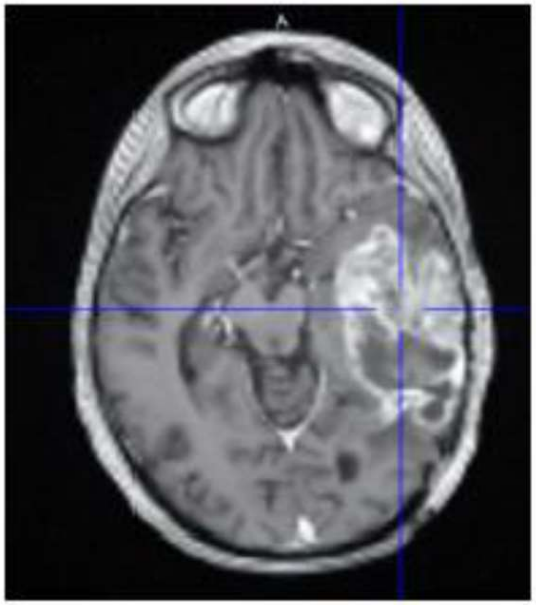


Human T1 renal cells, ● hypoxia, ○ normoxia; according to Broerse and Barendsen, IJRB, 13:559, 1967

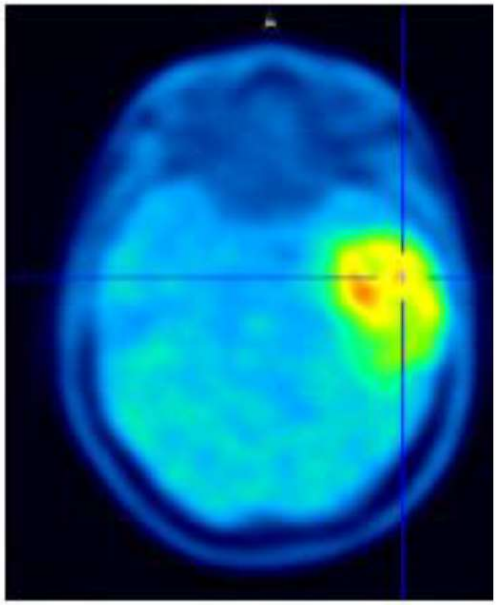
… and reduced hypoxic resistance to ions



60% of human tumors have hypoxia foci of variable level

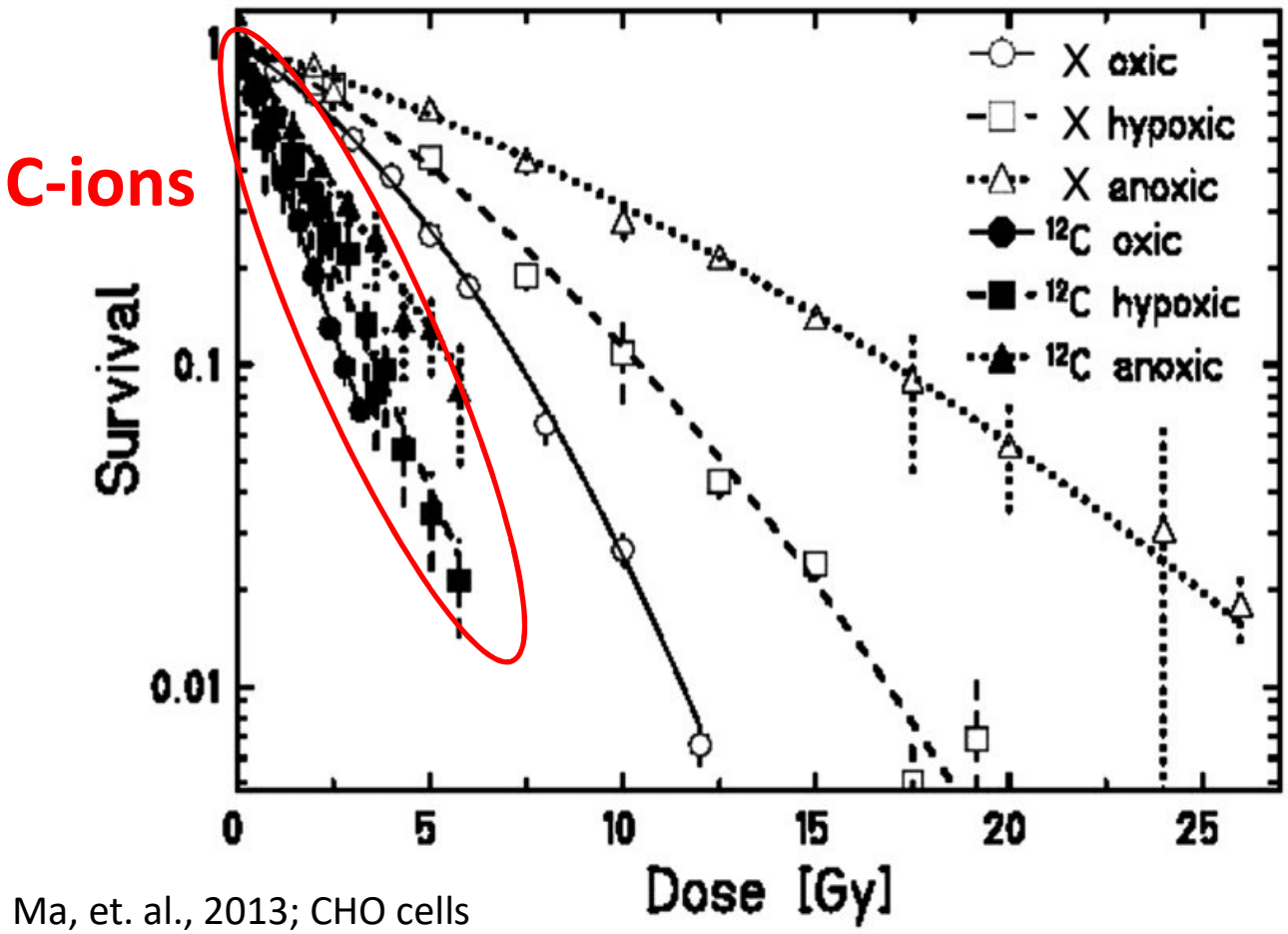


IRM: T1 post-Gd



TEP [^{18}F]-FMISO

High LET particle tend to reduce any radiobiological differences, *this is an non-universal advantage....*



Ning-Ya Ma, et. al., 2013; CHO cells

Thus, carbon ion therapy should be limited to particular tumors

- **Unresectable** tumors
- Tumors having **a high rate of local failure** by classical radiotherapy techniques due to "**radioresistance**".
- Tumors **limited to the local-regional stage** or having a weak metastatic potential
- Medical imaging allowing **a precise definition** of the clinical target volume
- Possibility of a **precise tumor repositioning and movement monitoring** during treatment

In Europe indications are divided in 2 sets

1. Indications of the highest priority :

- Tumors historically successfully treated by neutrons
- Tumors successfully treated by charged particles since years (Berkeley, USA; Chiba, Japan; Darmstadt, Europe)
- Very rare tumors with no possibility of prospective comparative trials but successfully treated with CIT

2. Indications of secondary priority (after clinical trial):

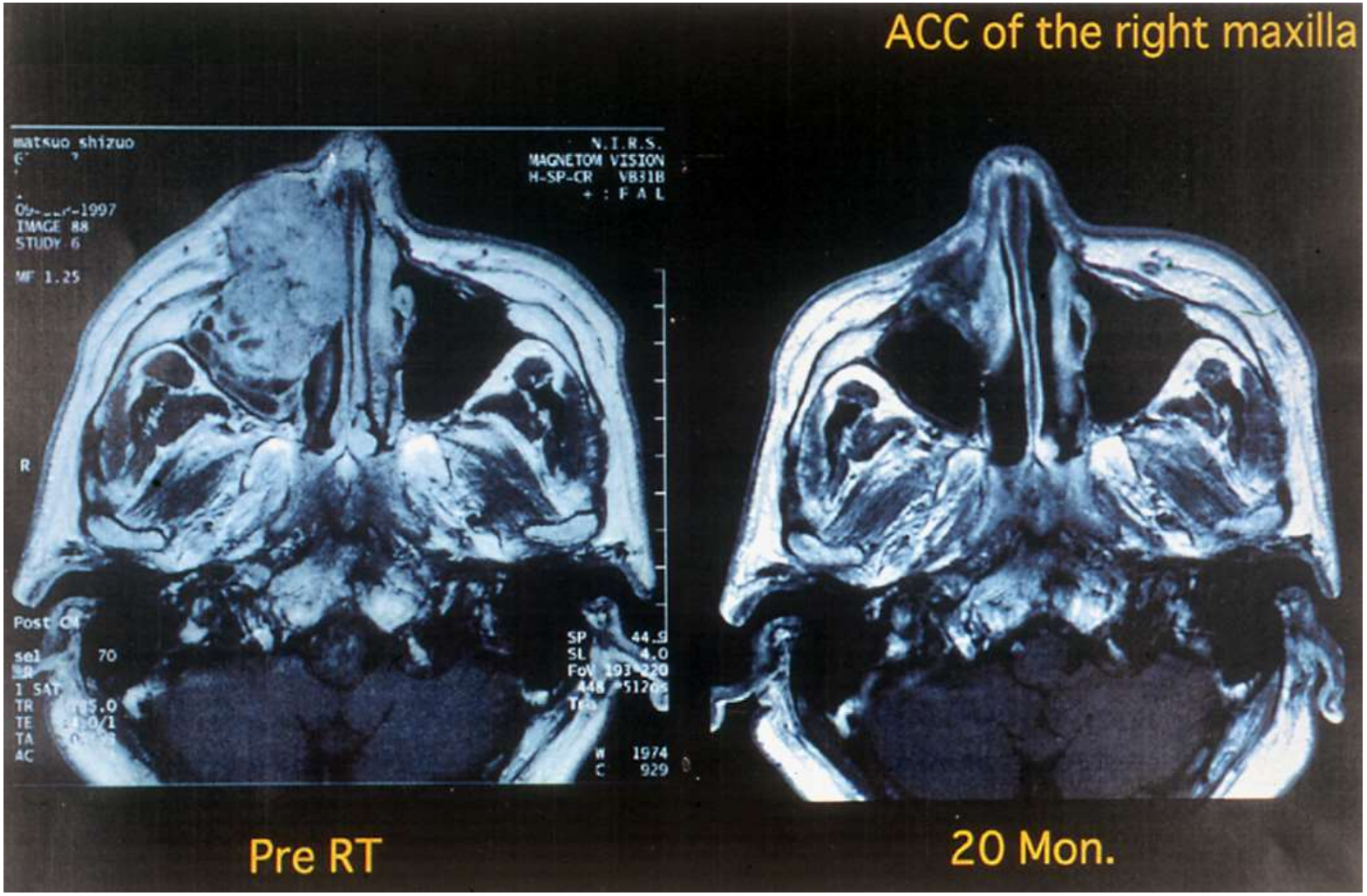
- Tumors newly treated
- Incidence is large enough to make possible prospective comparative trials

The Indications of the highest priority are the following

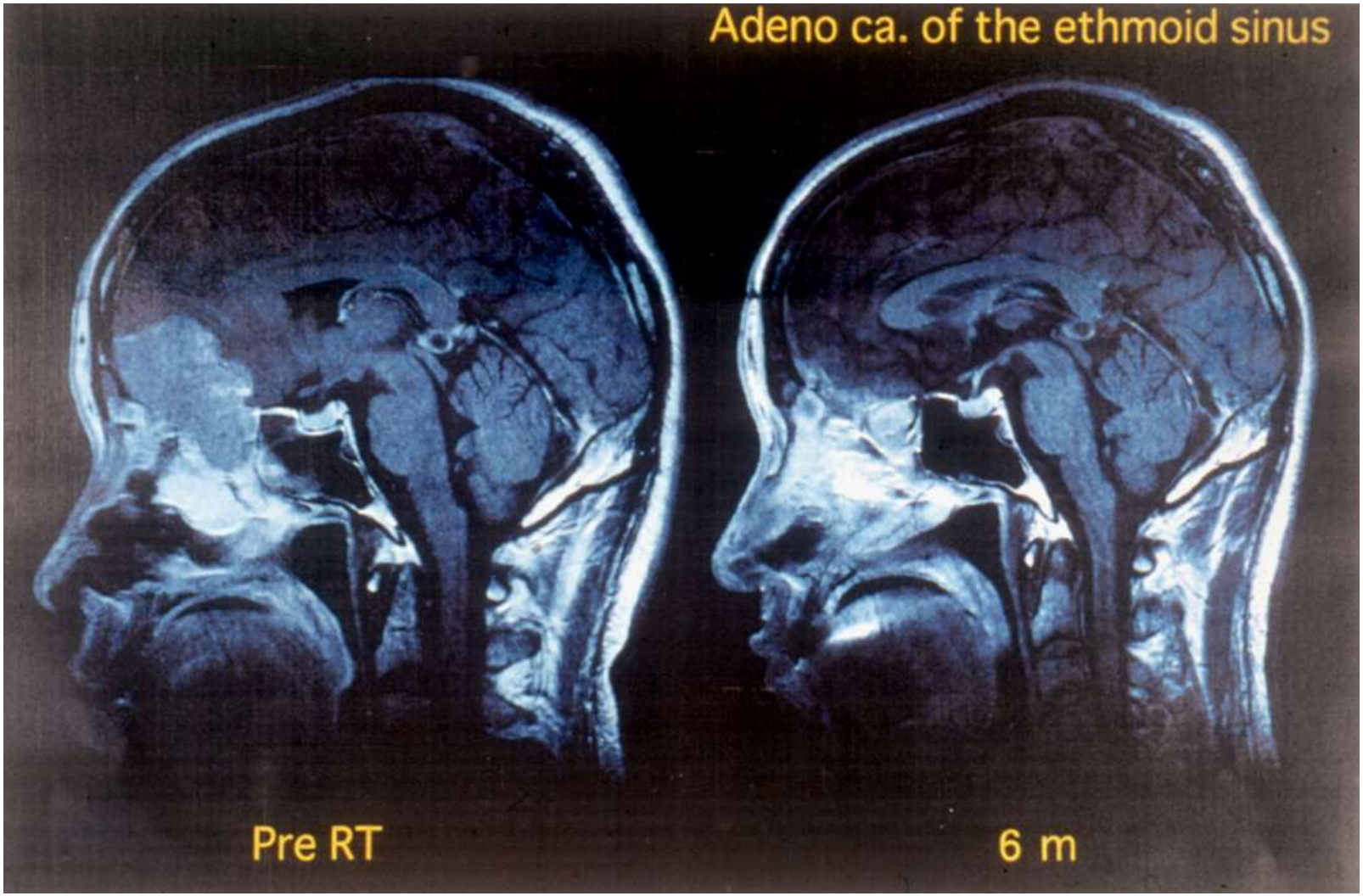
200/y cases for 10 millions inhabitants *[1270/y in F]*
Turning from ≈ 50% CR to > 75%

- **Adenoid cystic carcinomas** of salivary glands, including head & neck and thorax, sinus adenocarcinomas *[360/y in F]*
- **Mucinous melanomas** of head and neck *[40/y in F]*
- **Chordomas and chondrosarcomas** of skull base and spine *[70/y in F]*
- **Soft tissues sarcomas** of low and medium grade, unresectable or partially unresectable without threatening metastasis *[400/y in F]*
- **Non small cell lung** carcinomas, of small and medium size (N0,M0) unsuitable for surgery *[100/y in F]*
- **Pelvic adenocarcinomas,** local relapses M0 of previously irradiated by photons *[250/y in F]*
- **Hepatocarcinomas** unique and of large size *[50/y in F]*

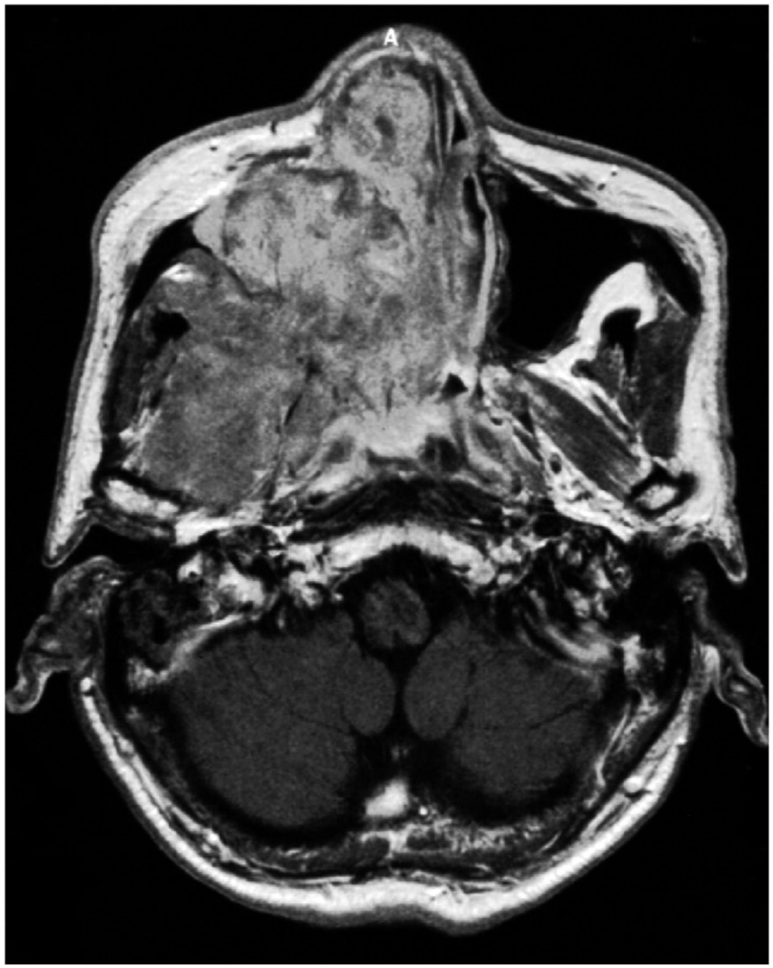
Adenoid Cystic carcinoma of maxillary sinus (Pr Tsujii, NIRS, Japan)



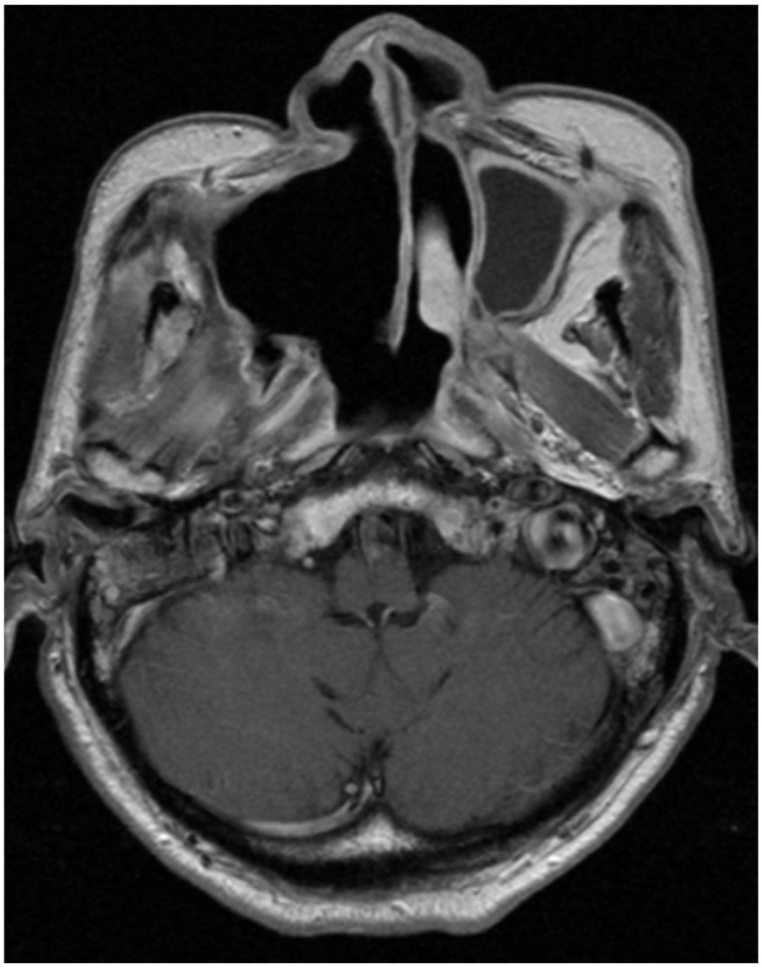
Ethmoid adenocarcinoma (NIRS Japon)



Malignant melanoma 57.6GyE/16fx (NIRS Japon)

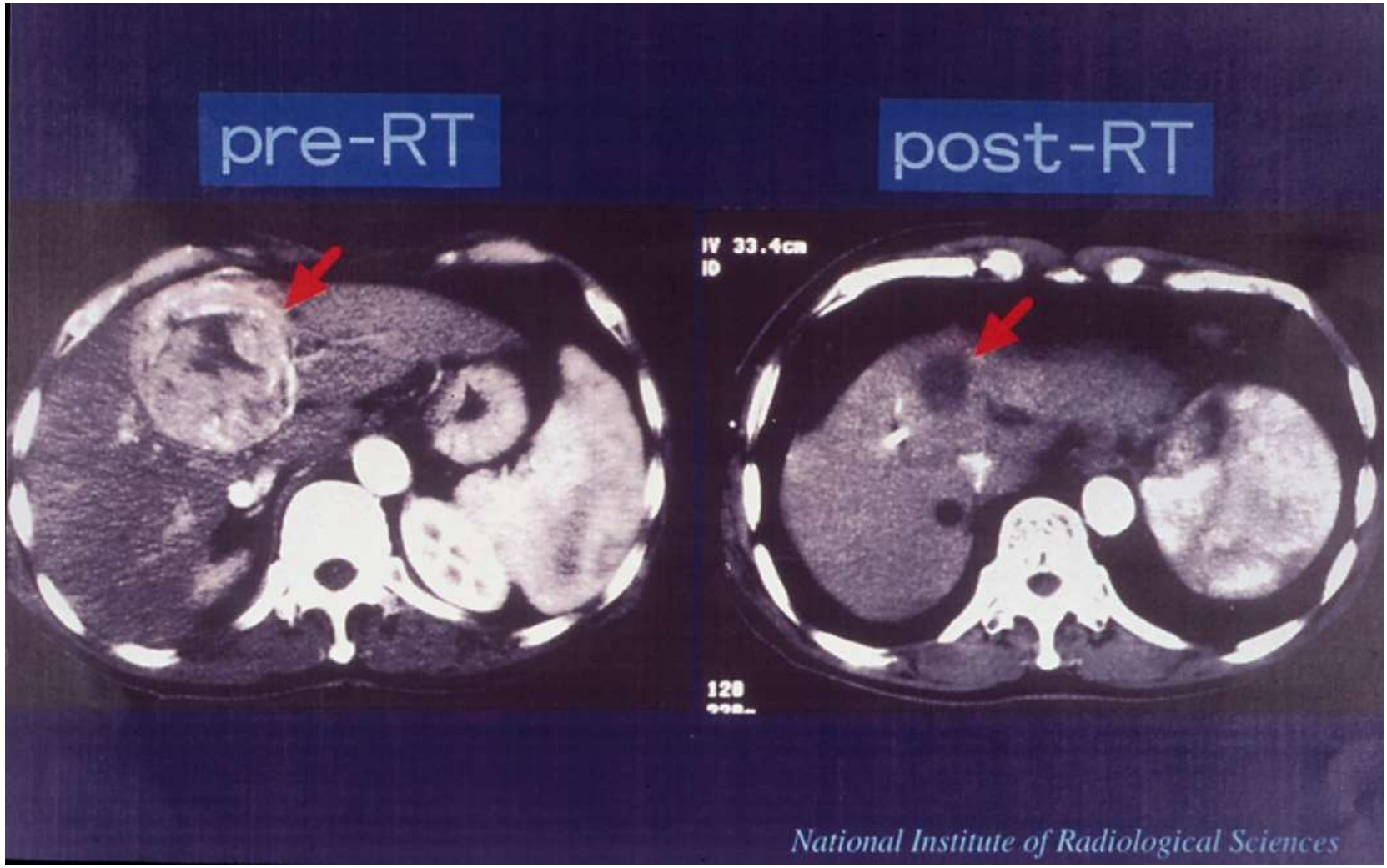


Before RT



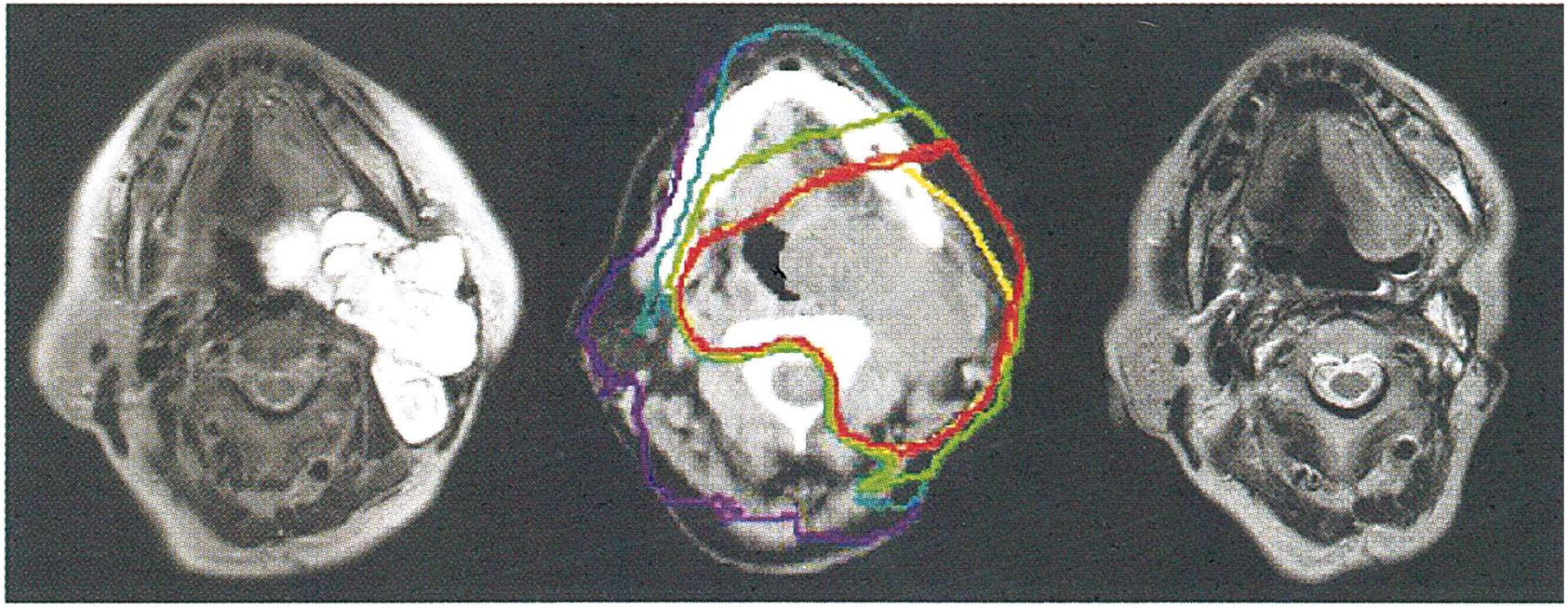
48 months after RT

Hepatocarcinoma (Pr Tsujii, NIRS)



Skull base chordoma (Pr Tsujii, NIRS)

Chordoma of the skull base relapsing after surgery, treated by carbon ions at the NIRS (Chiba, Japon), Isodoses : red = 96% ; orange = 90% ; green = 50% ; blue = 30% ; purple = 10% ; the target is segmented in yellow.



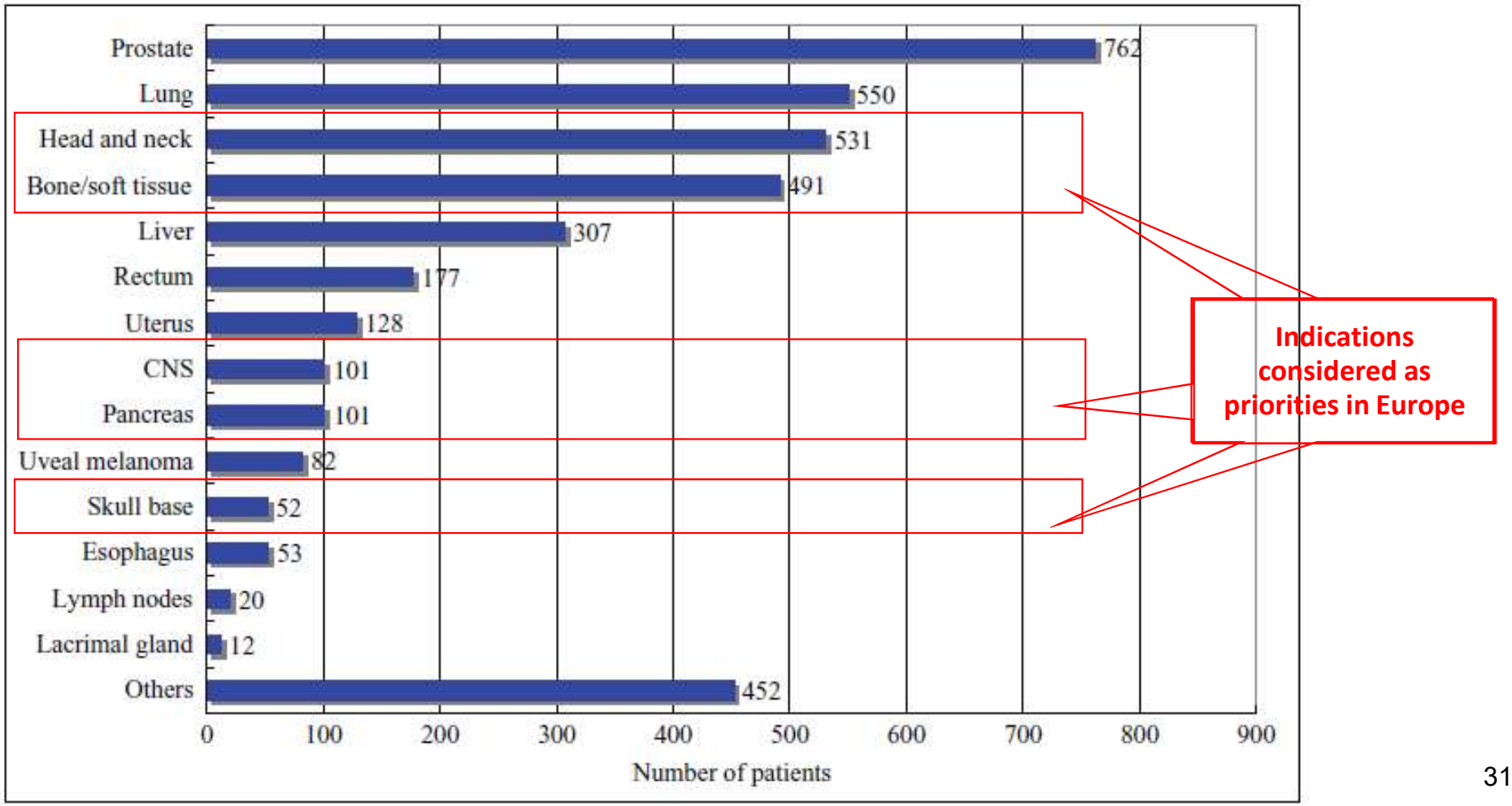
Pre c-ion RT | Dose distribution | Post 66 months

The Indications of secondary priority are the following

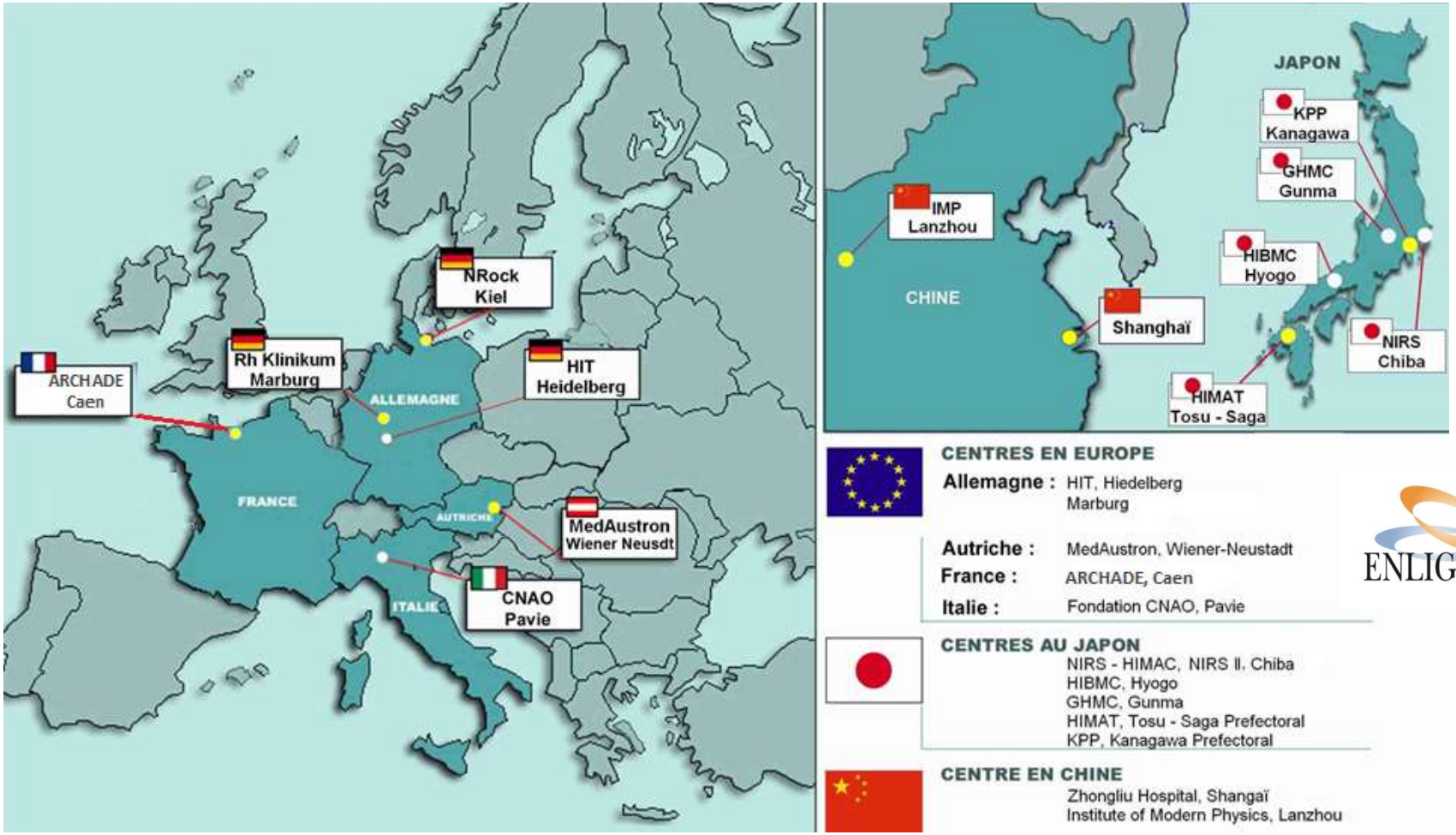
> 500/y cases for 10 millions inhabitants

- **Sarcomas** after definitive R1 resection (+ children)
- **Lung carcinomas** of medium size unsuitable for surgery
- **Prostate adenocarcinomas** locally aggressive
- **Head and Neck** locally advanced squamous cell carcinoma
- High grade **gliomas** (+ children)
- **Gastro-intestinal tumors** highly radioresistant or anatomically difficult
  (some pancreatic tumors, pelvic tumors….)
- **Skull base meningiomas**, unresectable
- **….**

NIRS is treating by carbon ions a larger set of indications, however pateints are paying fotr their treatment thus a different point of view regarding indications is obvious (Chiba, Japan) [2008 New J. Phys. 10 075009]



Hadrontherapy centers in the World

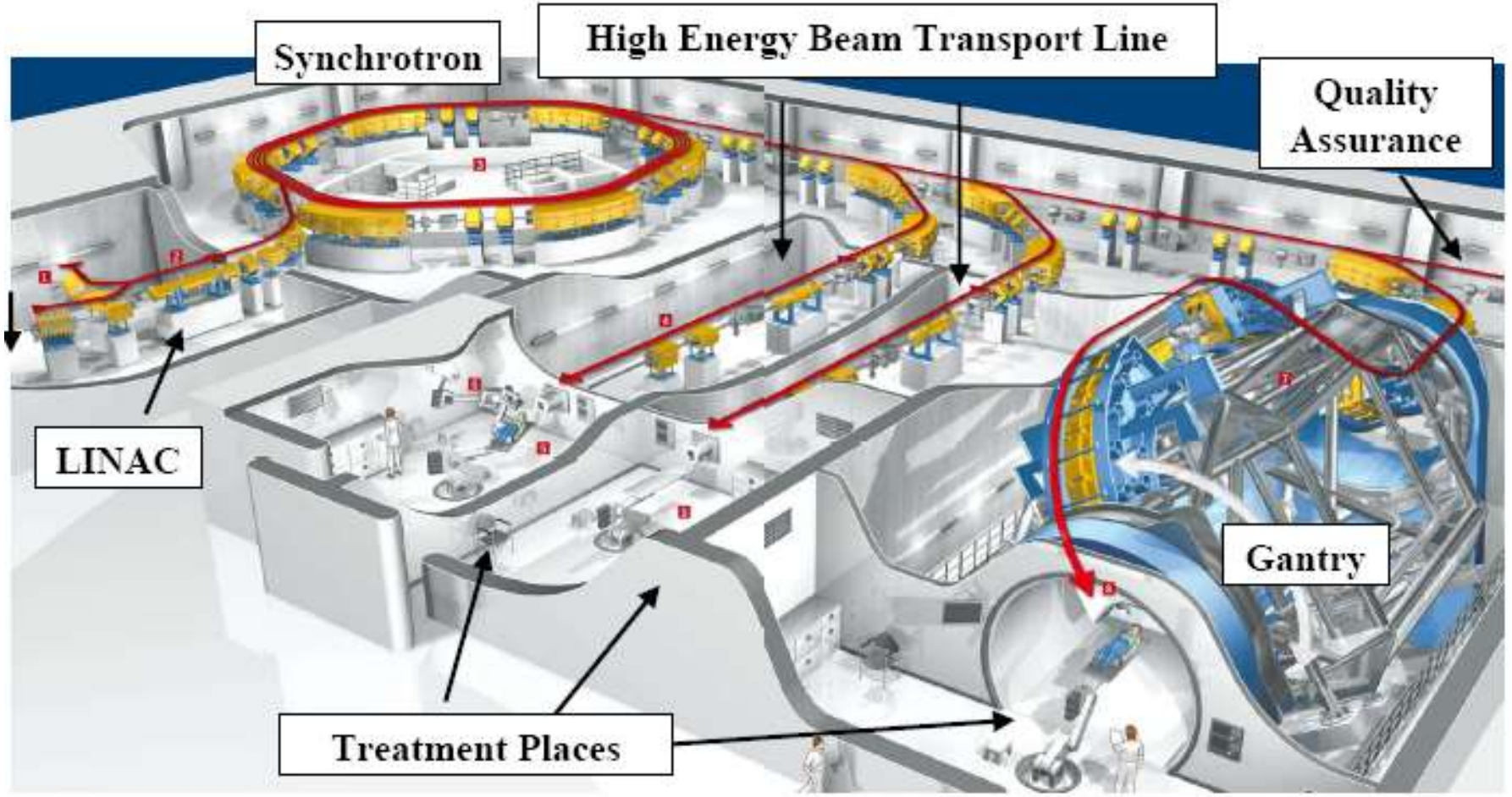


ENLIGHT

Two projects + an alliance for the development of particle therapy: NAPTA

NAPTA

The European reference: HIT in Heidelberg



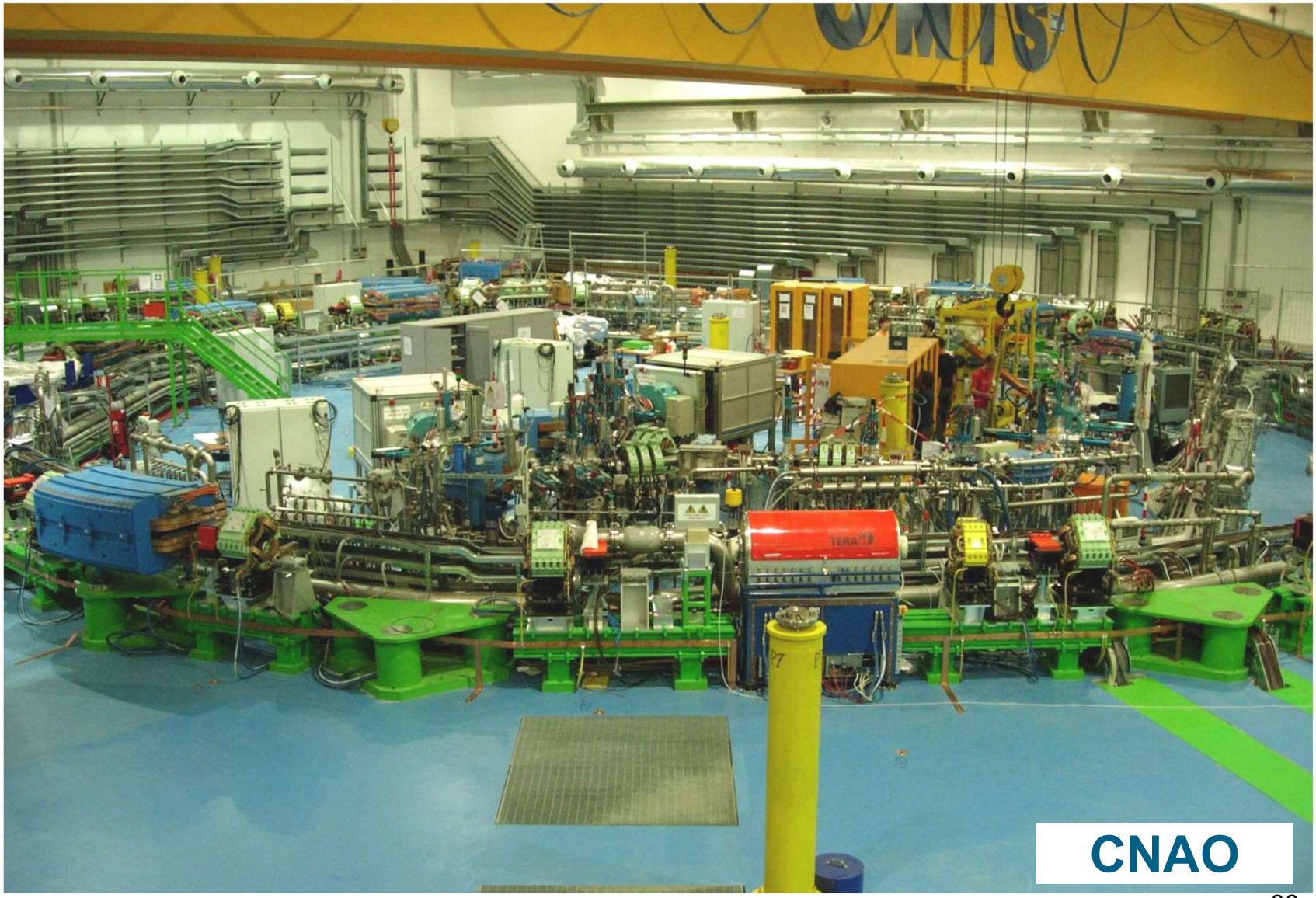
Source: Siemens AG and Heidelberg university

The gantry treatment room at HIT in Heidelberg

Heidelberg


Tosu Saga in
south Japan

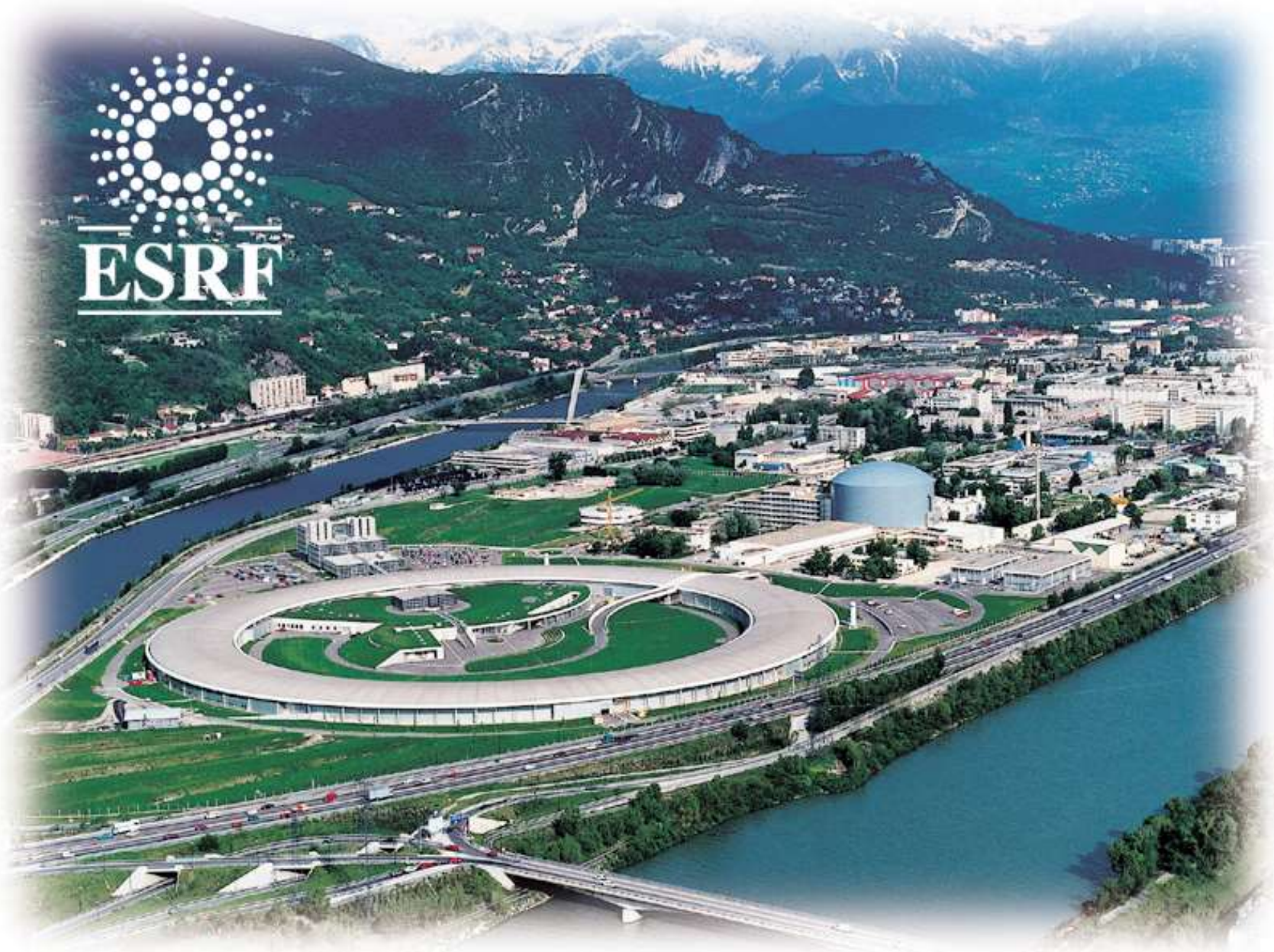
The European « model » with the PIMMS accelerator: CNAO at Pavia, Italy


CNAO

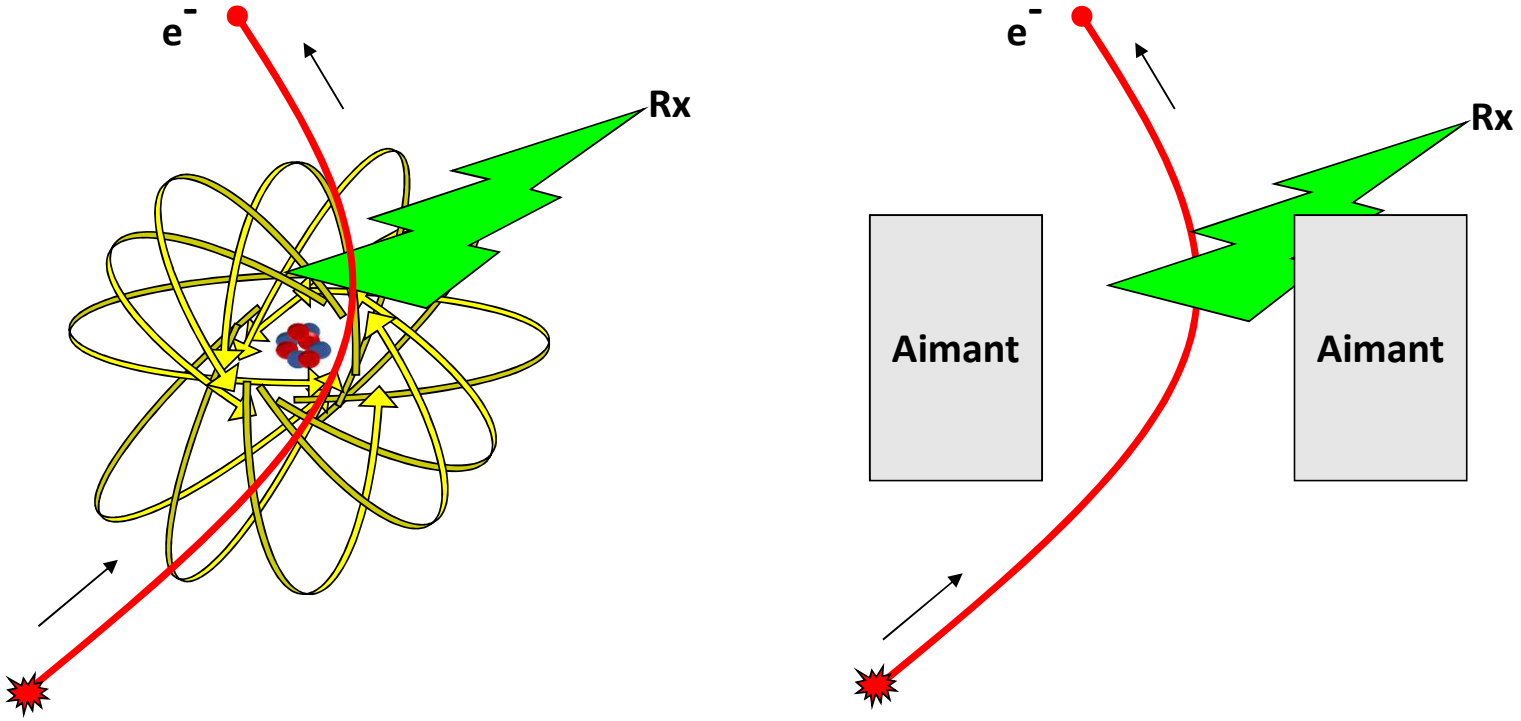

CNAO

Therapeutic use of synchrotron light

Lions club doyen de Grenoble


ESRF

The Synchrotron light / radiation is a kind of X-ray



Basically it is an artificial **Bremsstrahlung**

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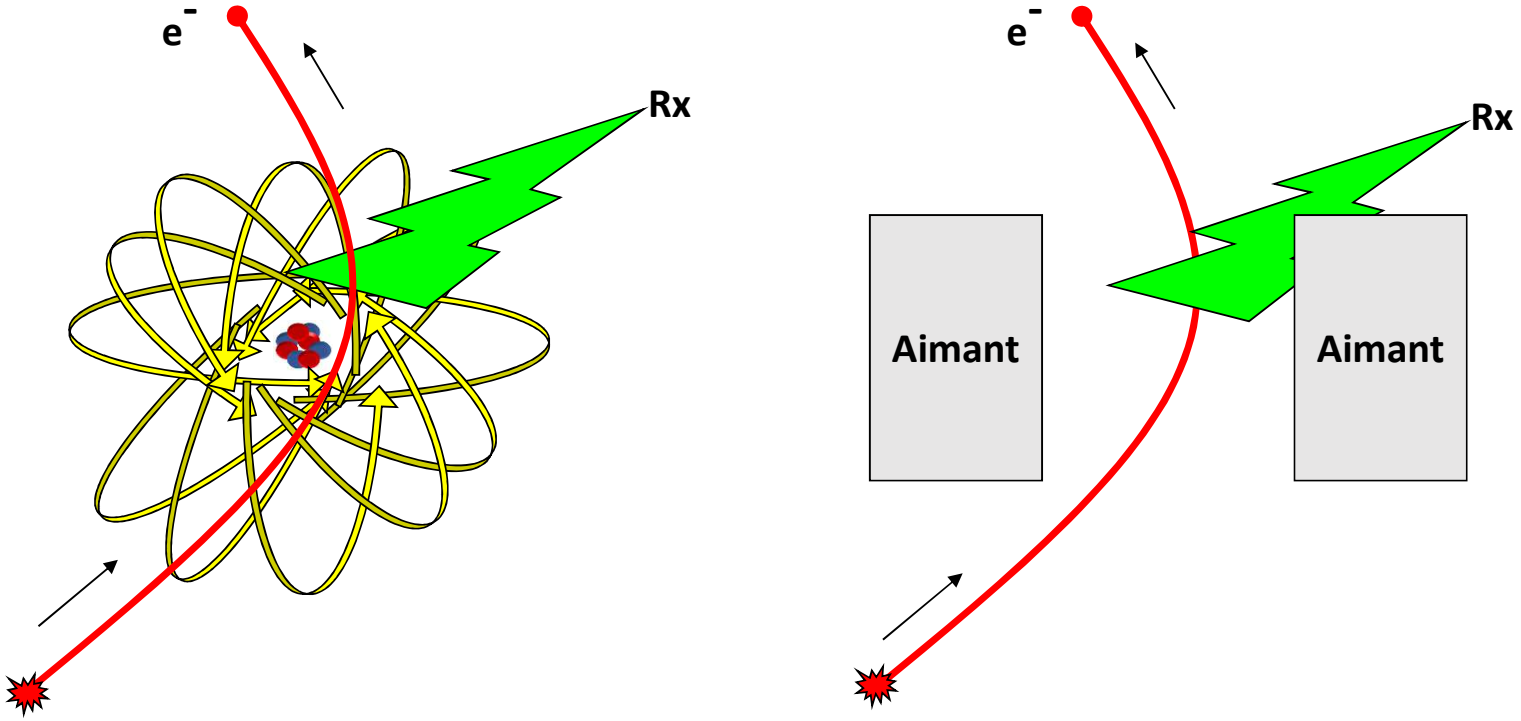

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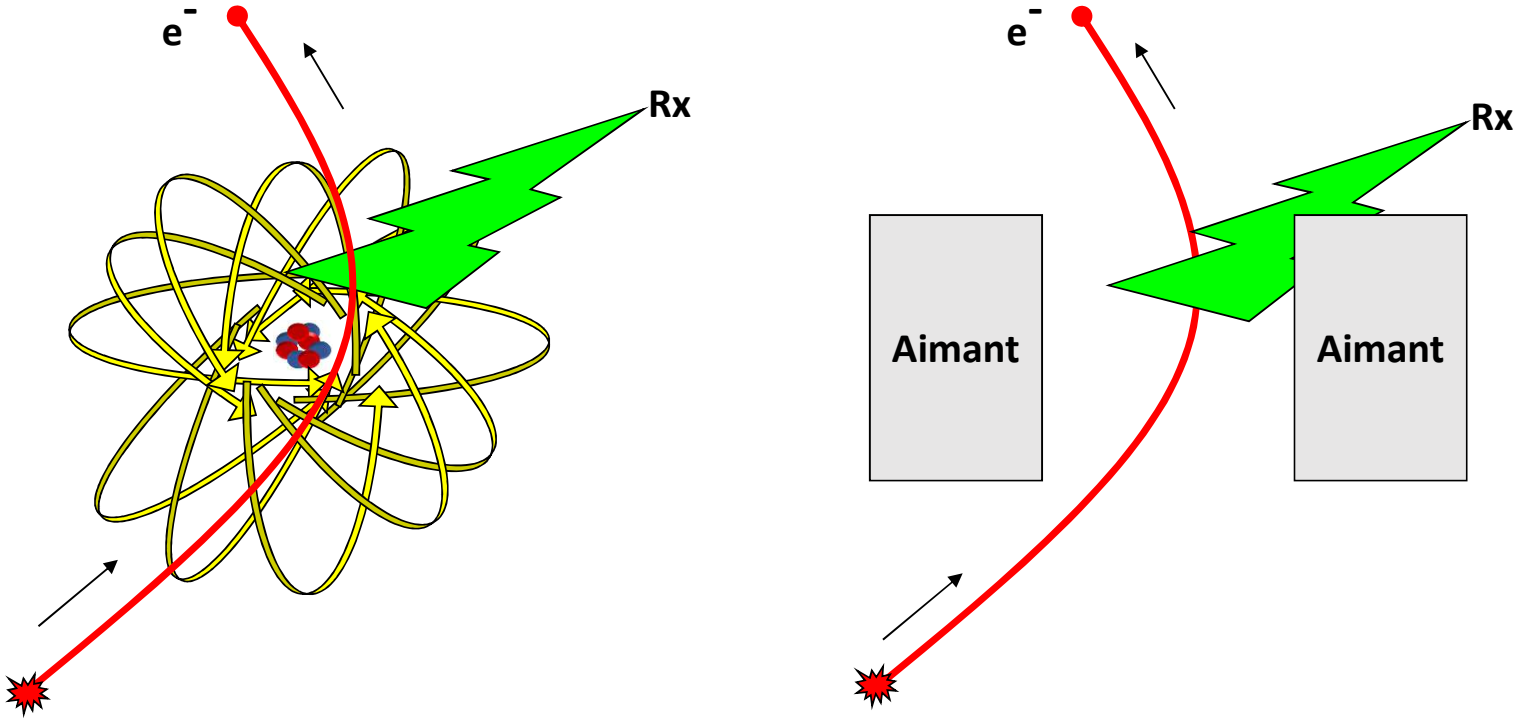
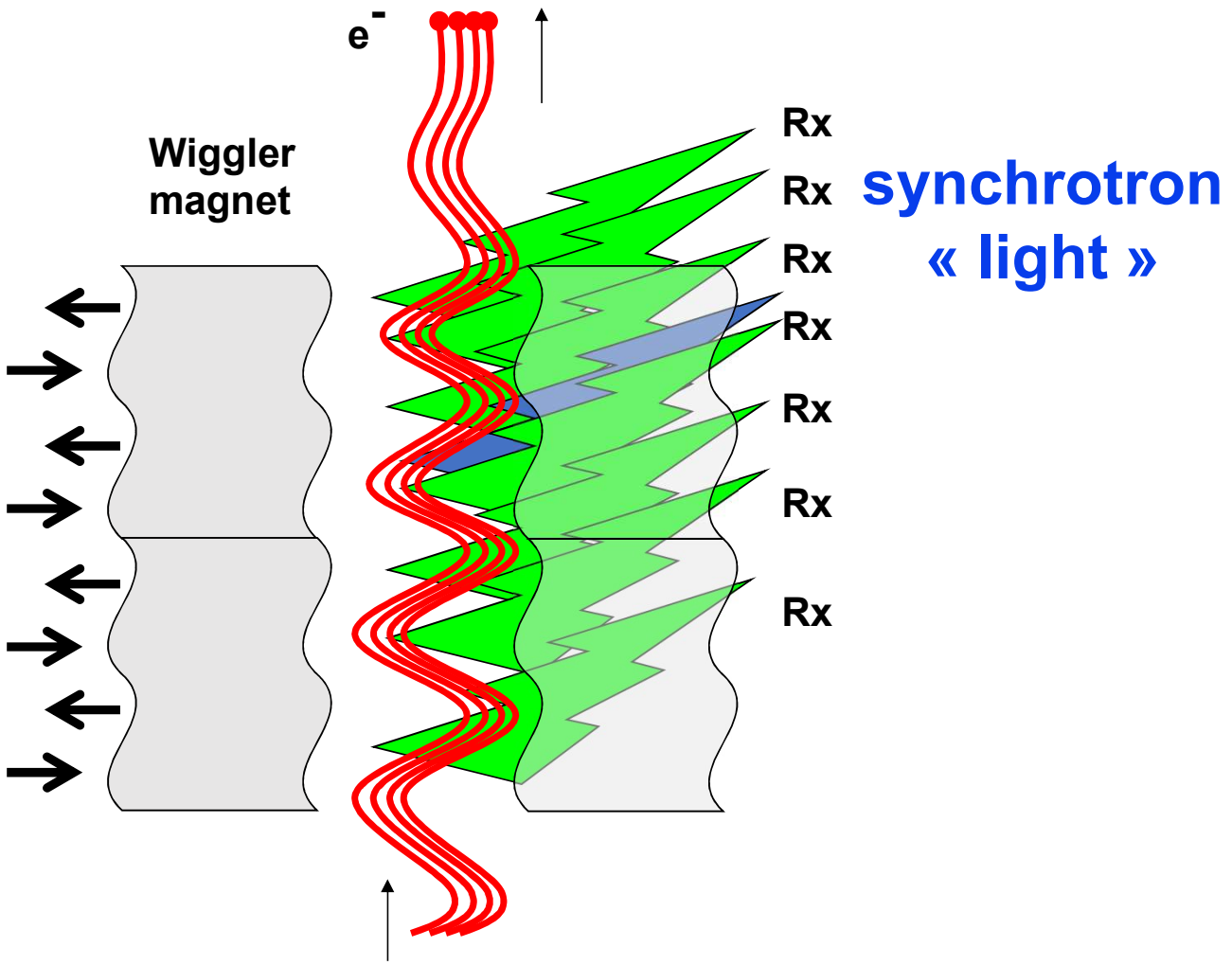
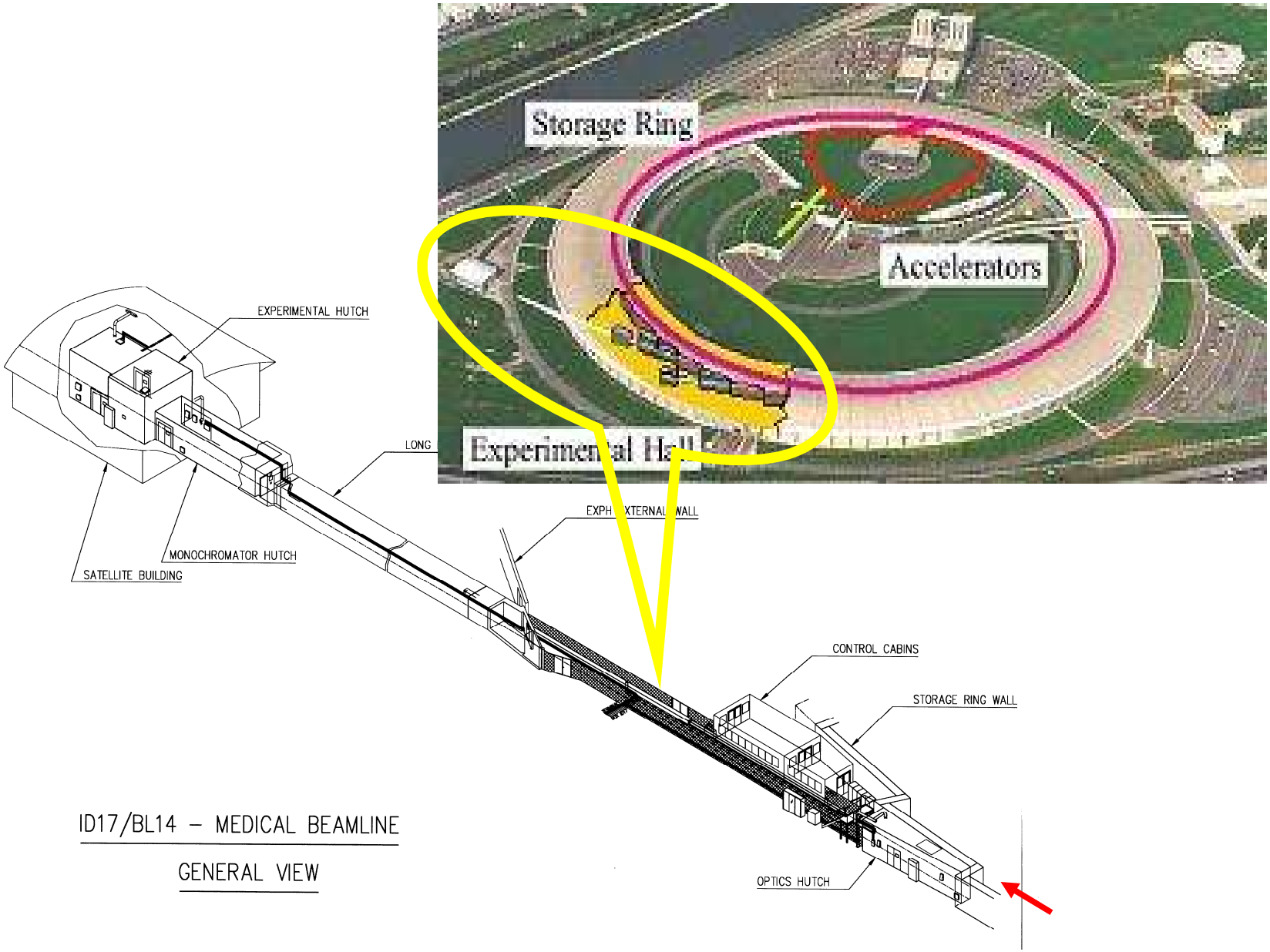


Basically it is an artificial **Bremsstrahlung**

The photon production is optimized by specific divices as bending magnets and wigglers magnets producing a huge flux

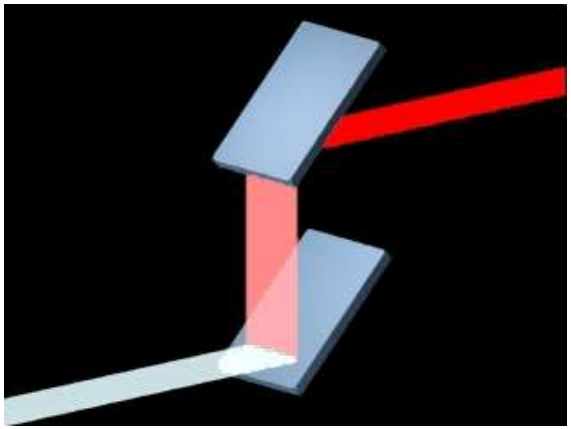




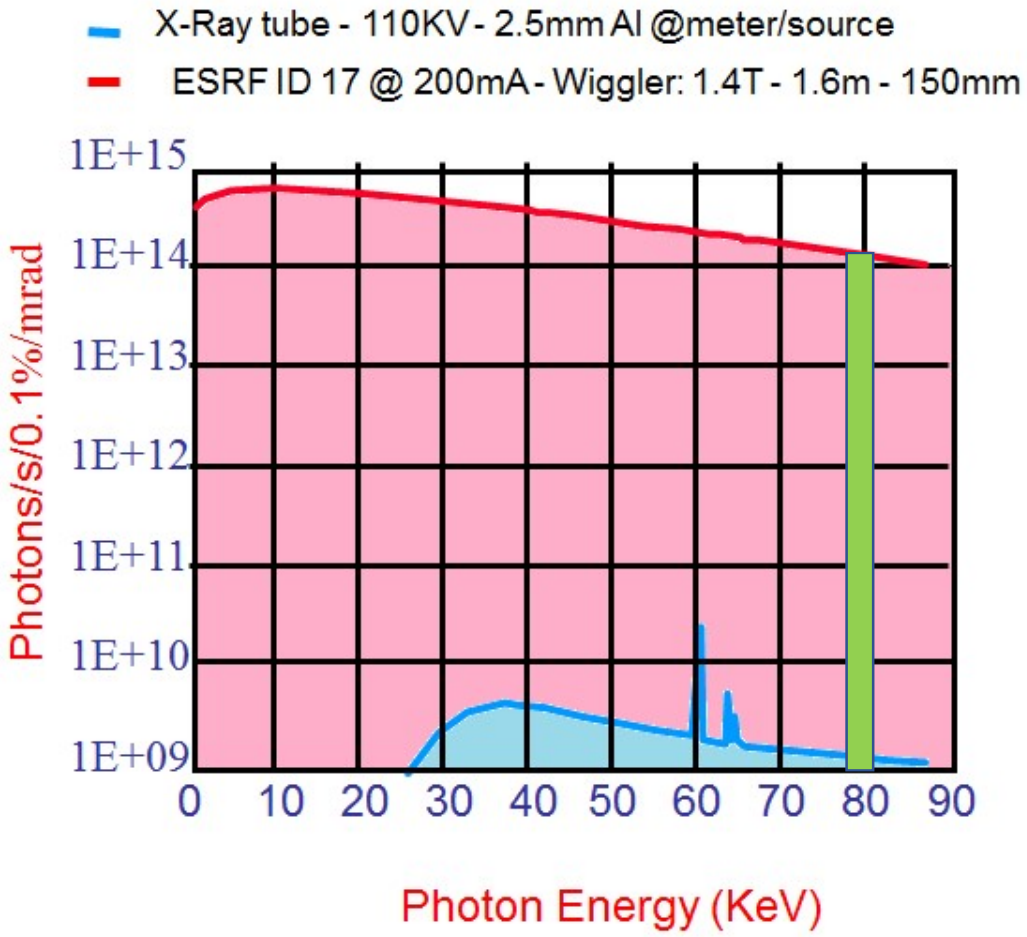
ID17/BL14 – MEDICAL BEAMLINE

GENERAL VIEW

Synchrotron X-ray source for radiation therapy



- A huge photon flux
- Continuous monochomatizatior (40 eV large)
- Very coherent and parallel beam
- Specific photo-electric interactions become significant by introducing heavy atoms

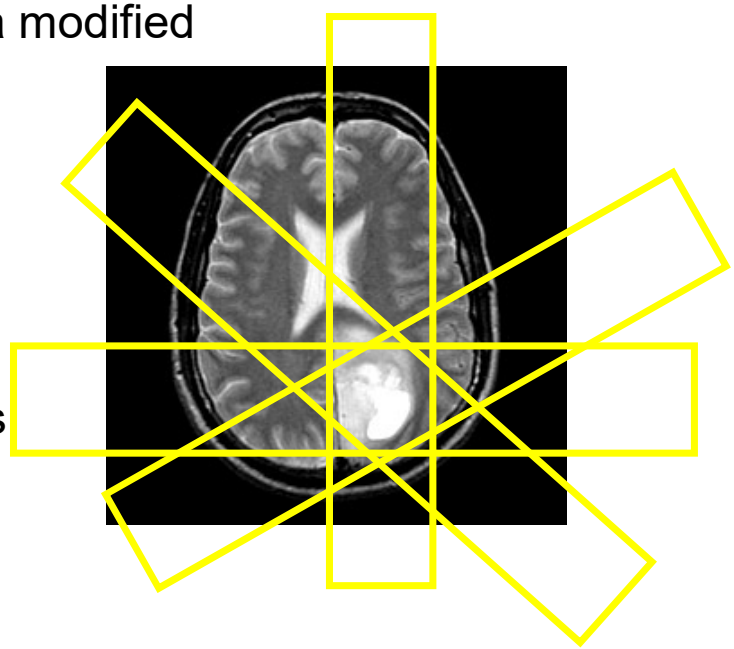


Norman's seminal work with CTscanX

- History:
  - 1980: Norman, Mello, Solberg, Iwamoto

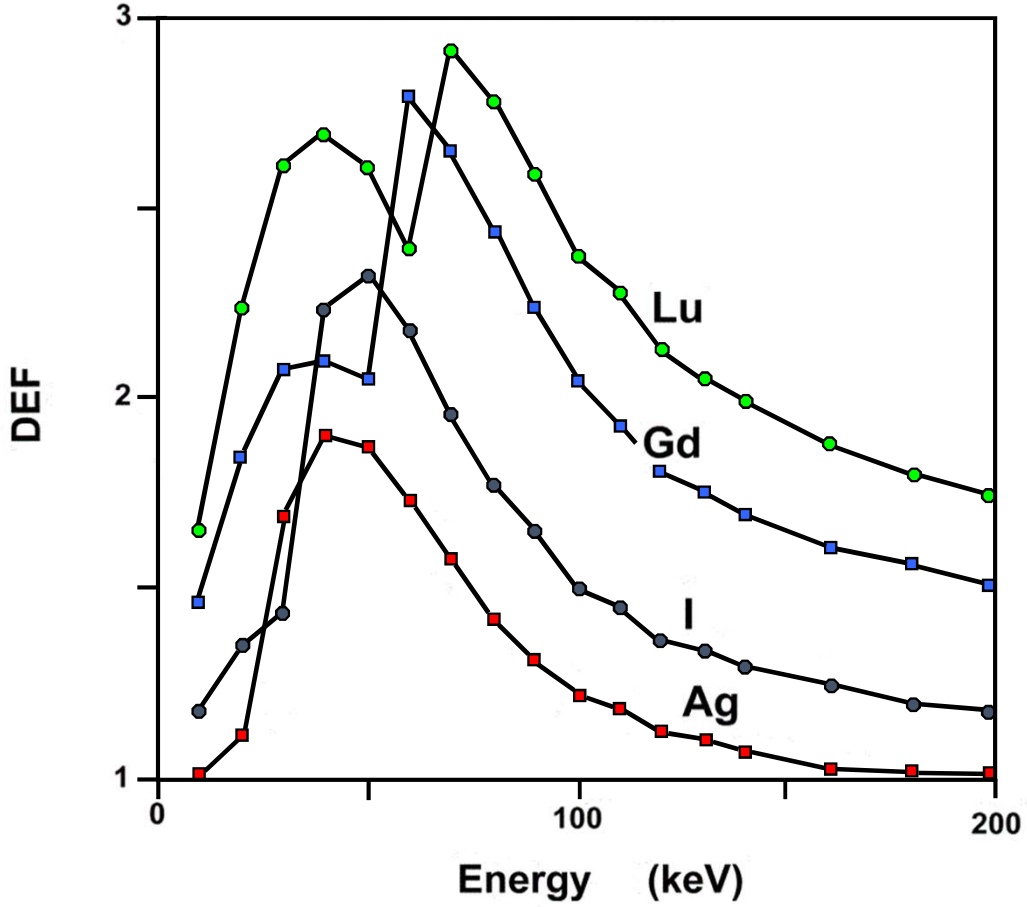
    "Radiation dose enhancement with iodine"
  - 1999: First CT-Therapy with patients using a modified CT scanner
- Principle:
  - Tumor loaded with a high Z element

    (iodine, gadolinium, platinum, gold)
  - Beam size adjusted to the tumor dimensions
  - Tumor positioned at the center of rotation.
  - Irradiation with kilo-Voltage X-ray beam.



Synchrotron X-ray used as monochromatic beam for photo-electric dose enhancement

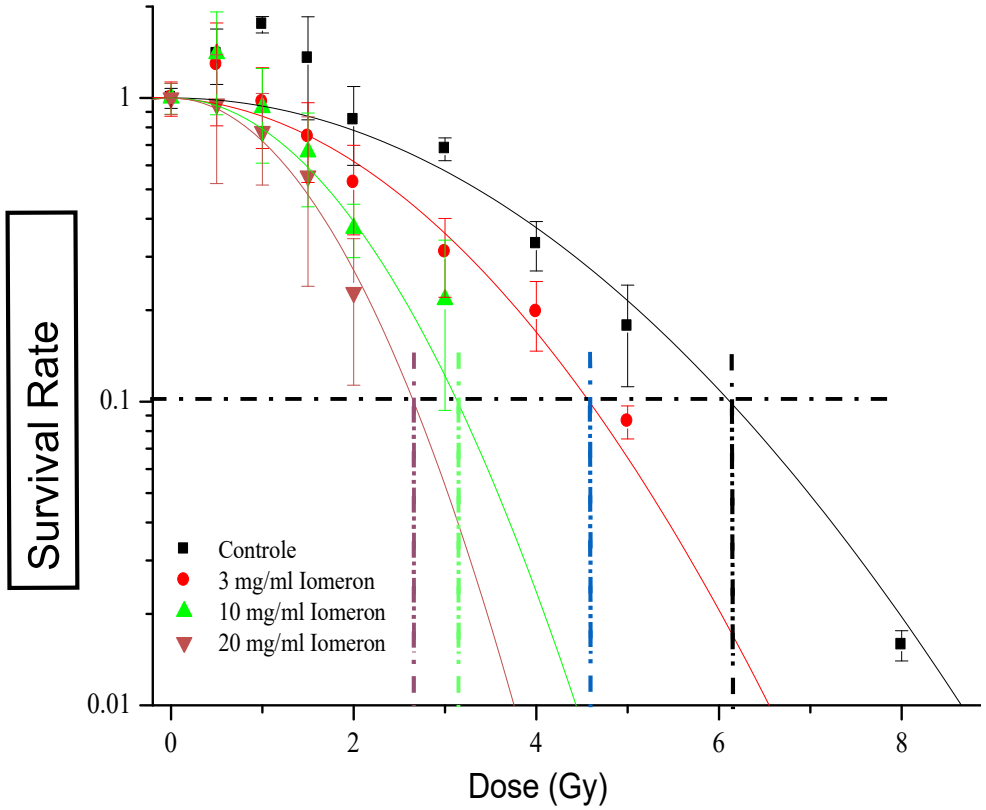
Higher dose with monochromatic X-ray and selected contrast agents



DEF vs. photon energy for equimolar concentrations of Ag, I, Gd, and Lu equal to that of 5 mg/ml Ag.

Amos NORMAN -MASR 2001-

50 keV Synchrotron X-ray for Iodine photo-electric enhancement *in-vitro*



SQ20B cells & iodine

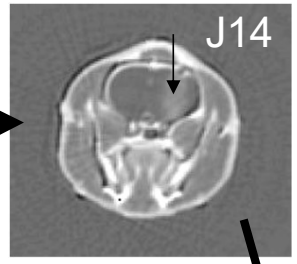
Iodine c_I [mg/ml]	DEF @ 10% survival
3	1.38
10	2.03
20	2.33

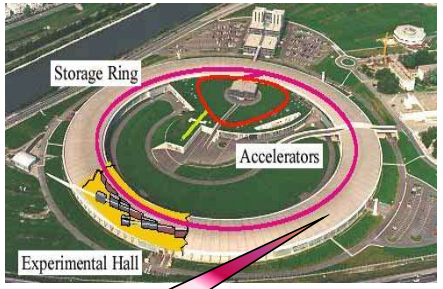
Energy: 50 keV

S. Corde, *et al*. Synchrotron radiation based experimental determination of the optimal energy for cell radiotoxicity enhancement…. *BJC,* 2004 91: 544-551

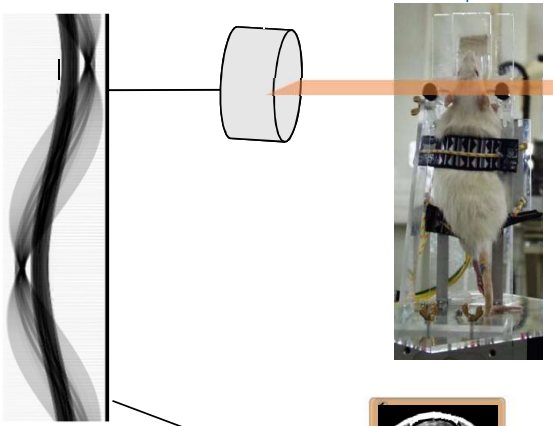
Animals preclinical trials with F98 glioma in Fisher rats

J0, F98 implantation





Detector



Polychromatic beam

Monochromator

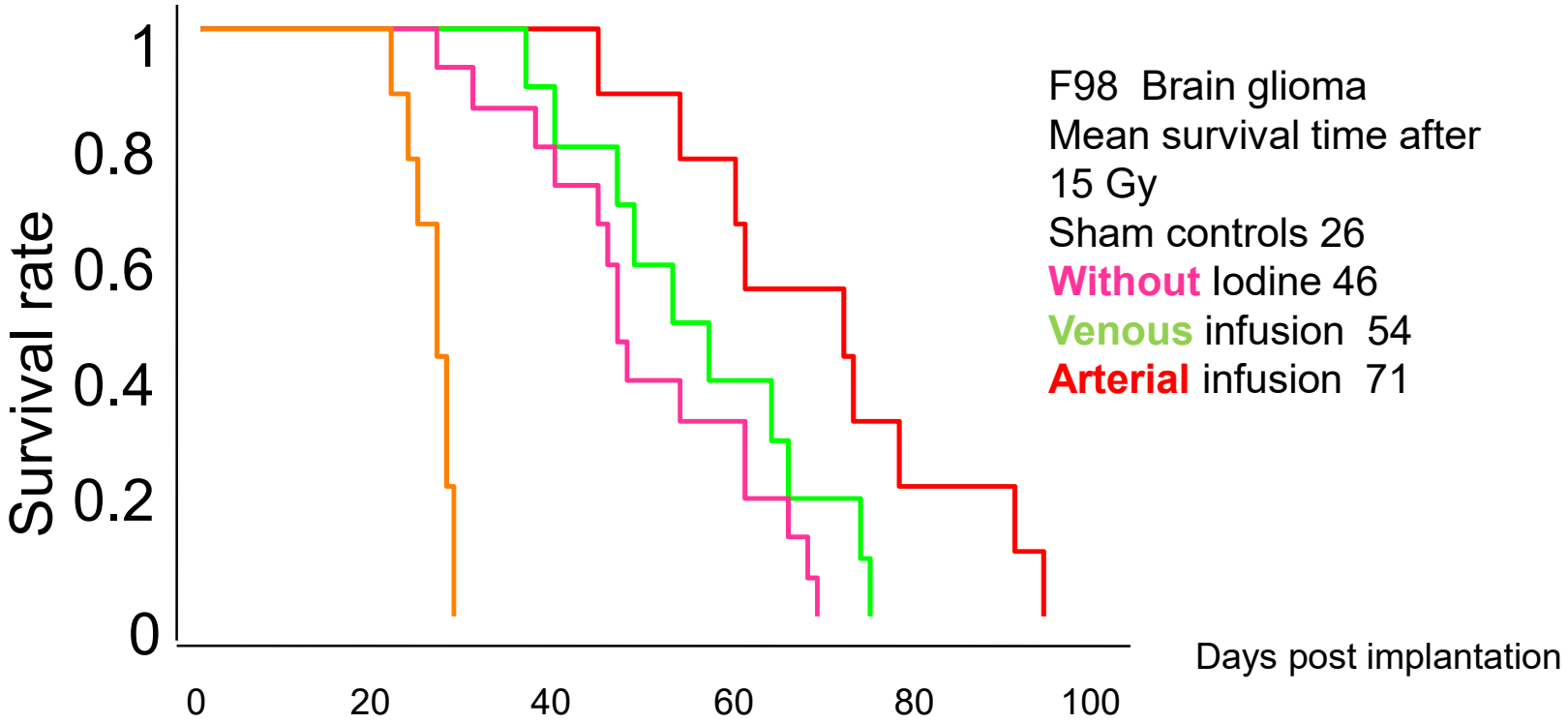
Irradiation at J14, one day after 3µM of CDDP directly injected in the tumor, one session of 15 Gy.

Sinogram

Image processing

(MC. BISTON et al)

Preclinical trials with iodine injected in blood with F98 glioma implanted Fisher rats



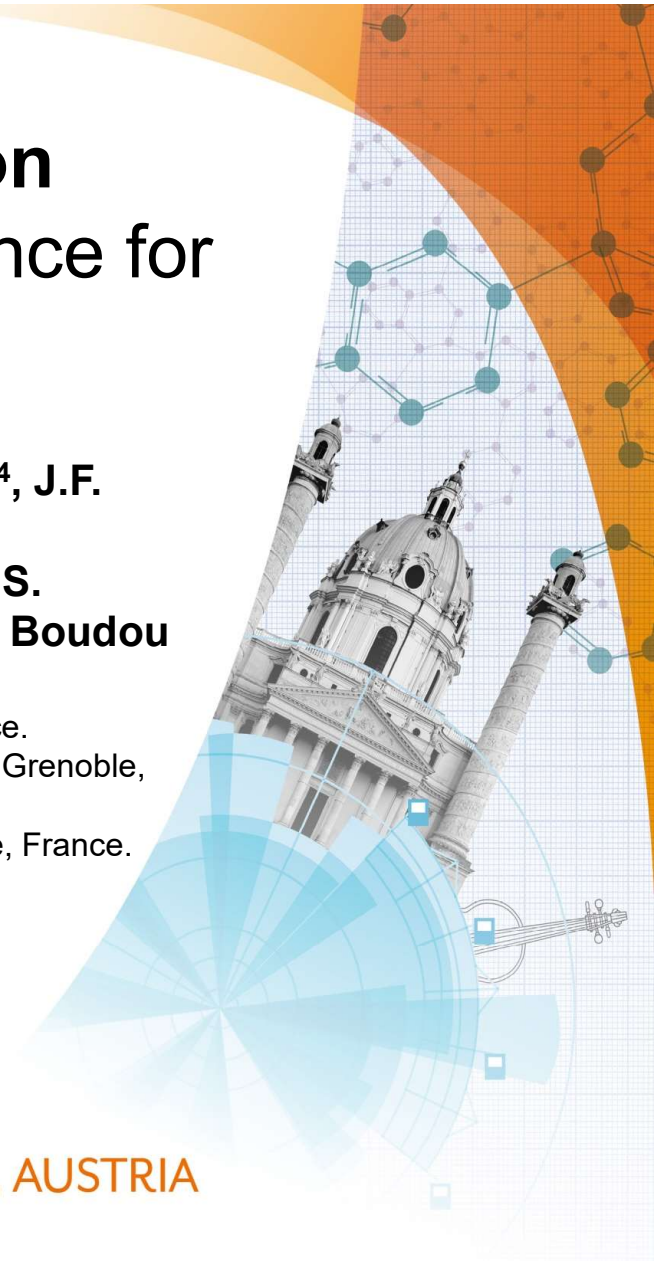
A Joubert, *et al.* Irradiation in presence of iodinated contrast agent results in radiosensitization. *IJROBP*, (2005) 62(5): 1486-1496

JF Adam, *et al.* Prolonged survival of Fischer rats bearing F98 glioma after iodine-enhanced synchrotron stereotactic radiotherapy. *IJROBP (*2006) 64(2):603-11.

Monoenergetic synchrotron beams: first human experience for therapeutic purpose

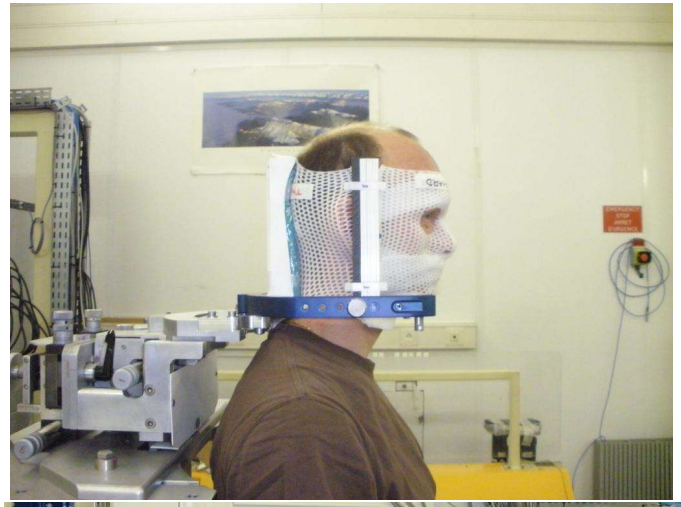
J. Balosso[1], F. Estève[2], H. Elleaume[3], A. Bravin[4], J.F. Adam[5], M. Renier[4], C. Nemoz[4], T. Brochard[4], P. Berkvens[6], J.F. Le Bas[7] and our PhD students: S. Corde, MC. Biston, A. Joubert, J. Rousseau, C. Boudou

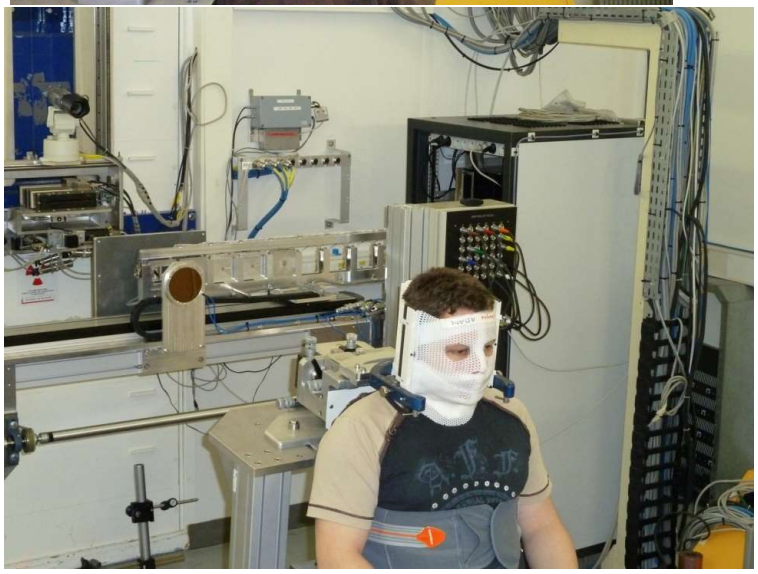
[1]University Joseph Fourier, Radiation Oncology, Grenoble, France.
[2]University Joseph Fourier, Grenoble Institute of Neurosciences, Grenoble, France.
[3]Inserm U836 E6, Grenoble Institute of Neurosciences, Grenoble, France.
[4]ESRF, Biomedical line ID17, Grenoble, France.
[5]University Joseph Fourier, Physics, Grenoble, France.
[6]ESRF, Radioprotection, Grenoble, France.
[7]University Joseph Fourier, Neuroradiology, Grenoble, France.



ESTRO 33 4 - 8 APRIL 2014 | VIENNA, AUSTRIA

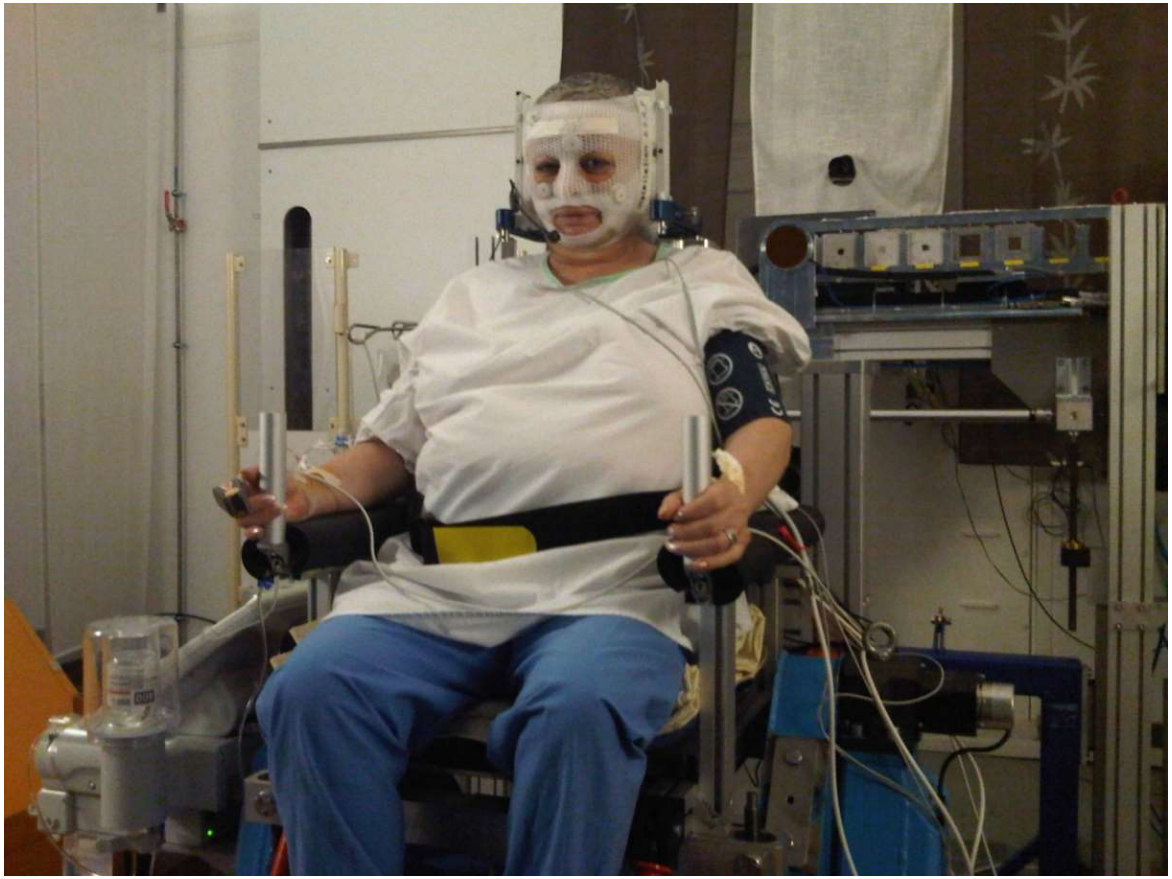
The special positioning system has been tested by the investigators…





Engineering **M. RENIER** courtesy, ESRF-SSRT coordinator

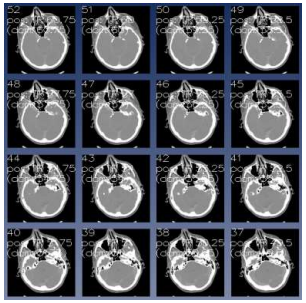
Before the patients! Here the patient n°7 treated in 2013



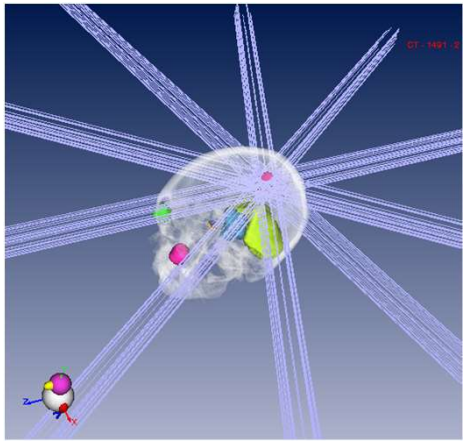
Patient n°7 the 7/11/2013

A specific MC calculation module has been introduced in the TPS for the SSRT clinical trials

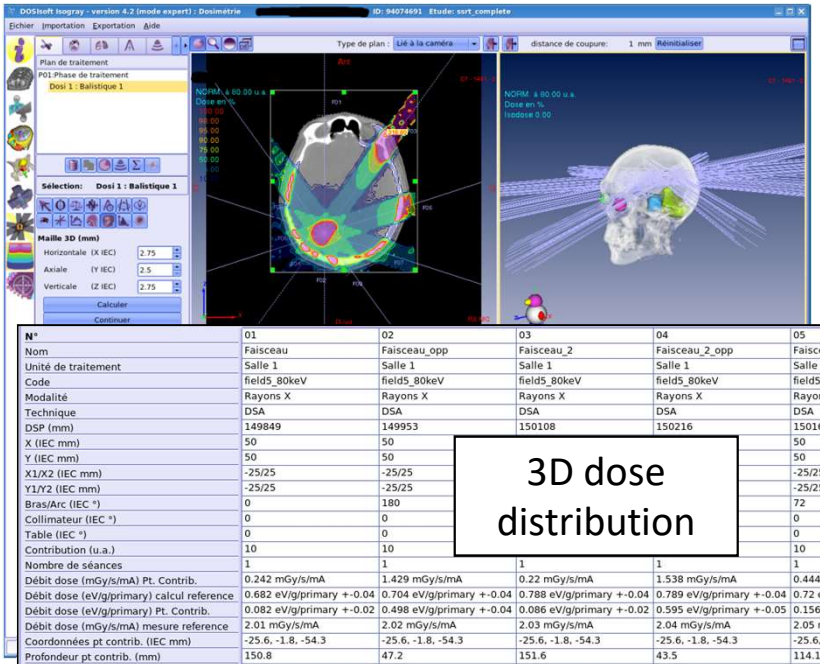
Patient model and contouing made at the hospital on an SRT TPS



CT scan made at the hospital

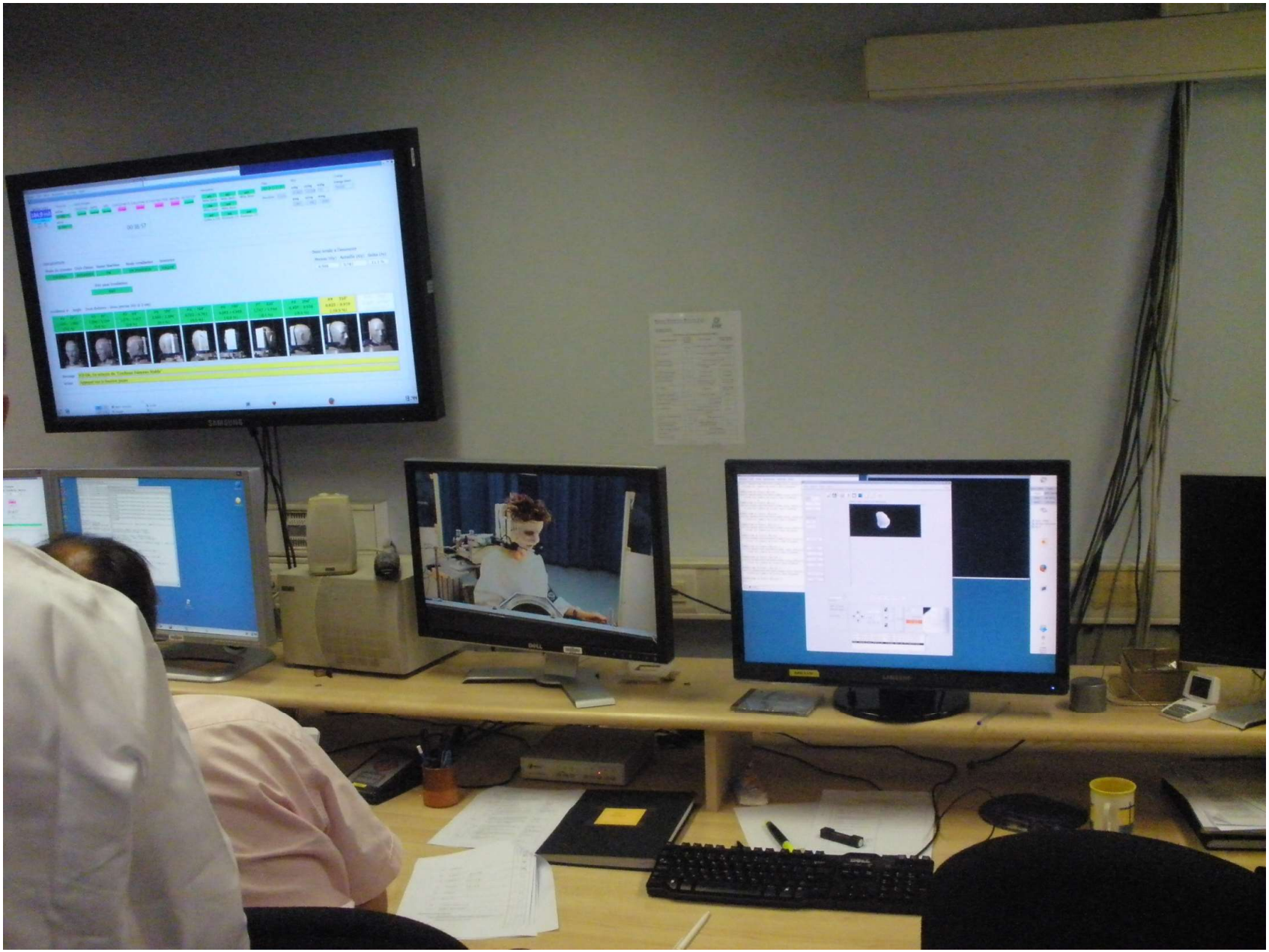


Irradiation plan calculated at ESRF

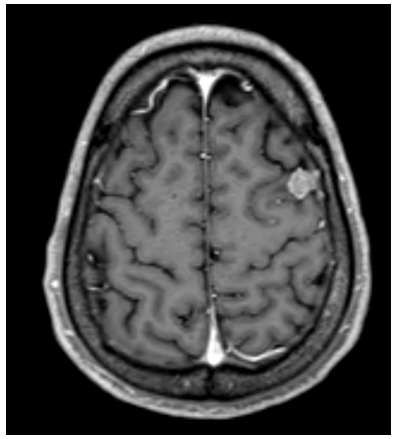


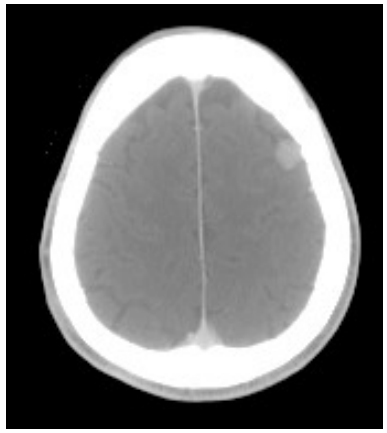
N°	01	02	03	04	05
Nom	Faisceau	Faisceau_opp	Faisceau_2	Faisceau_2_opp	Faisceau_3
Unité de traitement	Salle 1	Salle 1	Salle 1	Salle 1	Salle 1
Code	field5_80keV	field5_80keV	field5_80keV	field5_80keV	field5_80ke
Modalité	Rayons X	Rayons X	Rayons X	Rayons X	Rayons X
Technique	DSA	DSA	DSA	DSA	DSA
DSP (mm)	149849	149953	150108	150216	150161
X (IEC mm)	50	50			50
Y (IEC mm)	50	50			50
X1/X2 (IEC mm)	-25/25	-25/25			-25/25
Y1/Y2 (IEC mm)	-25/25	-25/25			-25/25
Bras/Arc (IEC °)	0	180			72
Collimateur (IEC °)	0	0			0
Table (IEC °)	0	0			0
Contribution (u.a.)	10	10			10
Nombre de séances	1	1	1	1	1
Débit dose (mGy/s/mA) Pt. Contrib.	0.242 mGy/s/mA	1.429 mGy/s/mA	0.22 mGy/s/mA	1.538 mGy/s/mA	0.444 mGy/
Débit dose (eV/g/primary) calcul reference	0.682 eV/g/primary +-0.04	0.704 eV/g/primary +-0.04	0.788 eV/g/primary +-0.04	0.789 eV/g/primary +-0.04	0.72 eV/g/p
Débit dose (eV/g/primary) Pt. Contrib.	0.082 eV/g/primary +-0.02	0.498 eV/g/primary +-0.04	0.086 eV/g/primary +-0.02	0.595 eV/g/primary +-0.05	0.156 eV/g/
Débit dose (mGy/s/mA) mesure reference	2.01 mGy/s/mA	2.02 mGy/s/mA	2.03 mGy/s/mA	2.04 mGy/s/mA	2.05 mGy/s
Coordonnées pt contrib. (IEC mm)	-25.6, -1.8, -54.3	-25.6, -1.8, -54.3	-25.6, -1.8, -54.3	-25.6, -1.8, -54.3	-25.6, -1.8,
Profondeur pt contrib. (mm)	150.8	47.2	151.6	43.5	114.1
Dose/séance pt contrib. (Gy)	1.375	1.375	1.375	1.375	1.375
Dose thérapeutique indicative (Gy)	56.1306	6.6419	57.5722	8.9843	25.024
Nb s*mA par seance	5689.02 s*mA +- 1261.37	962.31 s*mA +- 97.09	6240.75 s*mA +- 1400.49	893.88 s*mA +- 87.27	3099.12 s*m

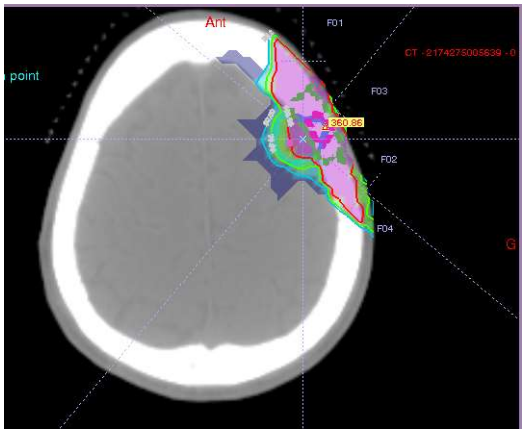
3D dose distribution

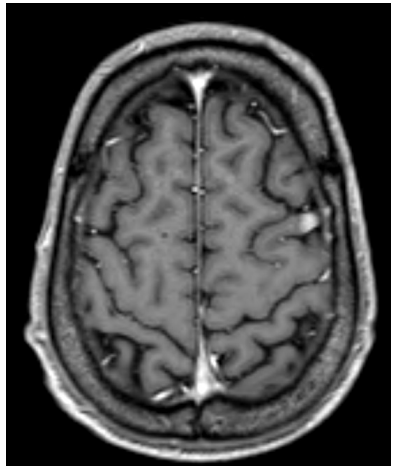


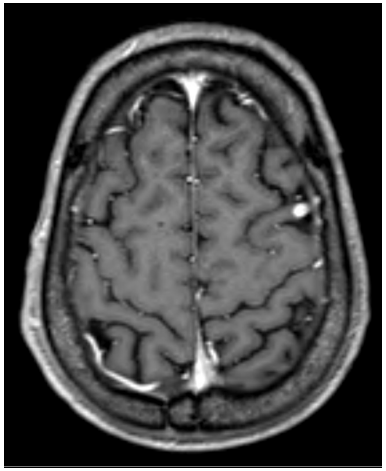
Example of patient n°6











Man 51 years old, with brain metastasis of invasive lung cancer (T4)
SSRT and conventional RxT
June 2013
to complete the **reference scheme of 33 Gy in three fractions of SRT**

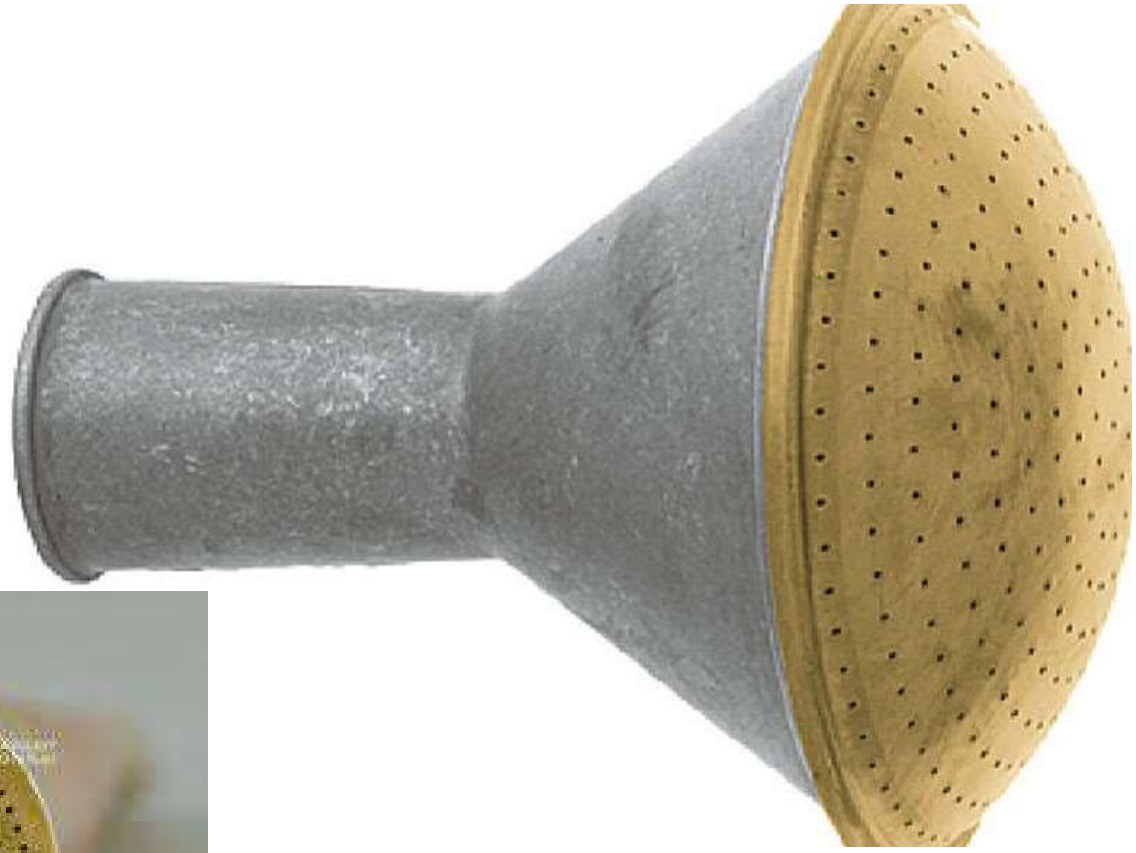
MR follow-up 2 & 3 months later after SSRT and radiation therapy, at 9 months the lesion was not any more visible

Conclusion on this study of feasibility

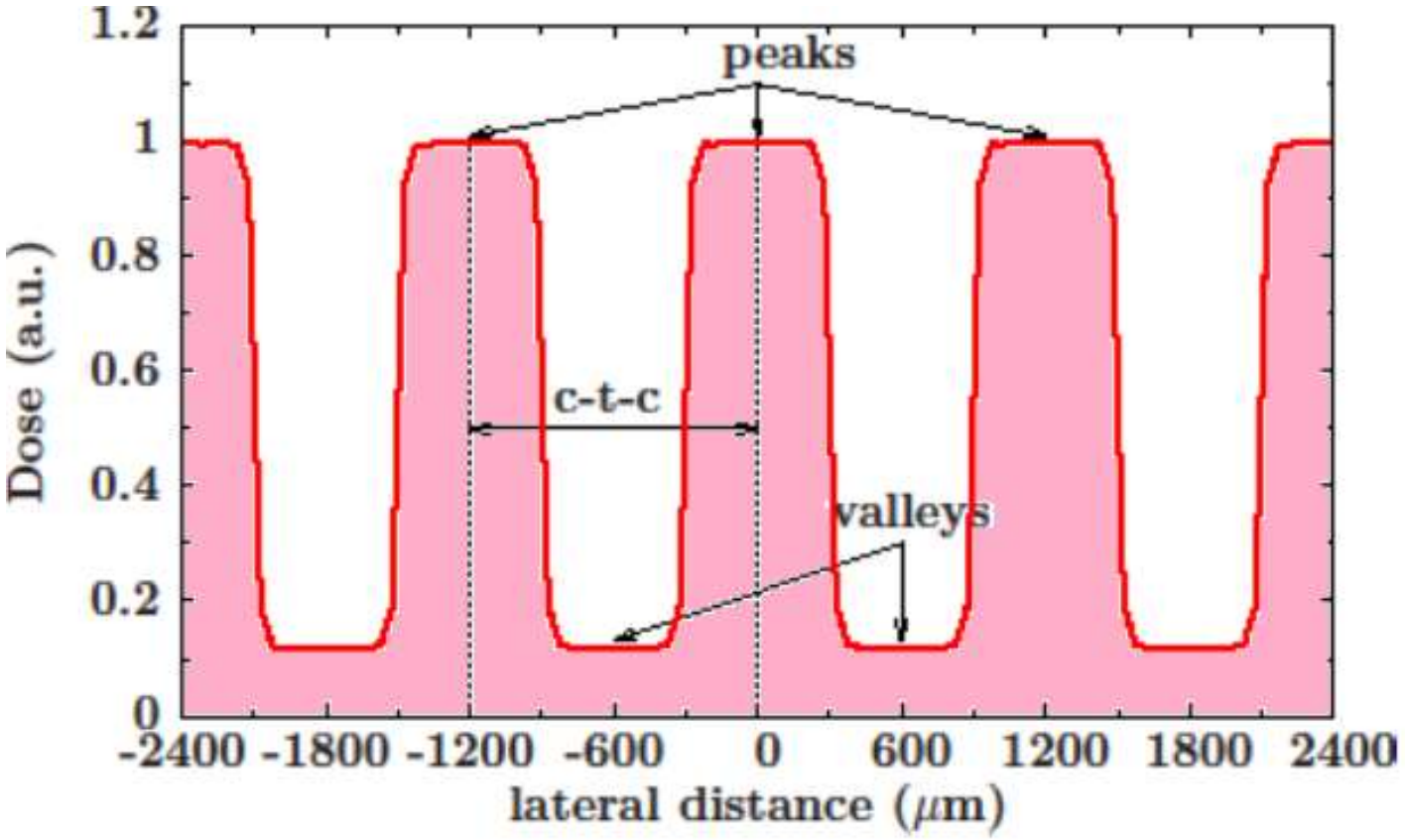
- The study has been completed in June 2017 with 14 patients treated, the last patient has just reach 1 year of follow-up beginning July 2018
- The technical feasibility is demonstrated up to two 7 Gy fractions and 250 ml contrast agent
- The immediate and late tolerances are good
- The possibility to have and enhanced efficiency is not demonstrated yet but was not the purpose of this study
- **This modality is now available for further clinical studies**
- At that stage, we are already preparing other trials, still based on iodine, before moving to more active compounds based on nanoparticles.

The micro spatial fractionation

- Presentation prepared with the halp of ESRF and Y. Prezado et al. du LMNC/CNRS/Orsay
- Hans Blattmann*, Ph.D., Paul Scherrer Institute, Villigen, Switzerland
- Jean A. Laissue*, M.D., Institute of Pathology, University of Bern, Bern, Switzerland,
- Raphael SERDUC, François ESTÈVE, Hélène ELLEAUME, J.F. ADAM OF THE “RSRM” team in Grenoble

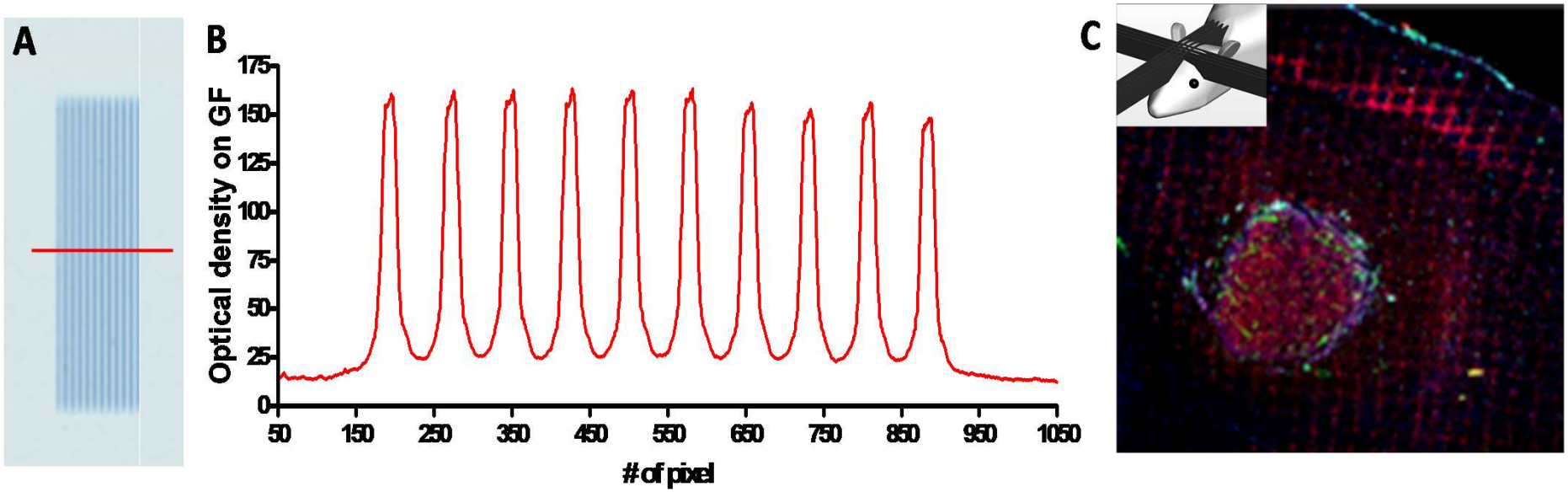


The concept of spatial fractionation



Example of dose profile in spatially fractionated techniques.

Initial animal experimentation



A-Gafchromic film showing MRT irradiation pattern. Microbeams are 50µm wide 200µm spaced apart. Dose profile is reported on B. C- pH2AX immunolabeling of DNA damages (red) induced by an orthogonal irradiation of the 9L gliosarcoma implanted in rat brain (Bouchet 2012) (of **Synchrotron radiation** at ESRF).

The remnent traces in the piglet cerebellum with no functional disability

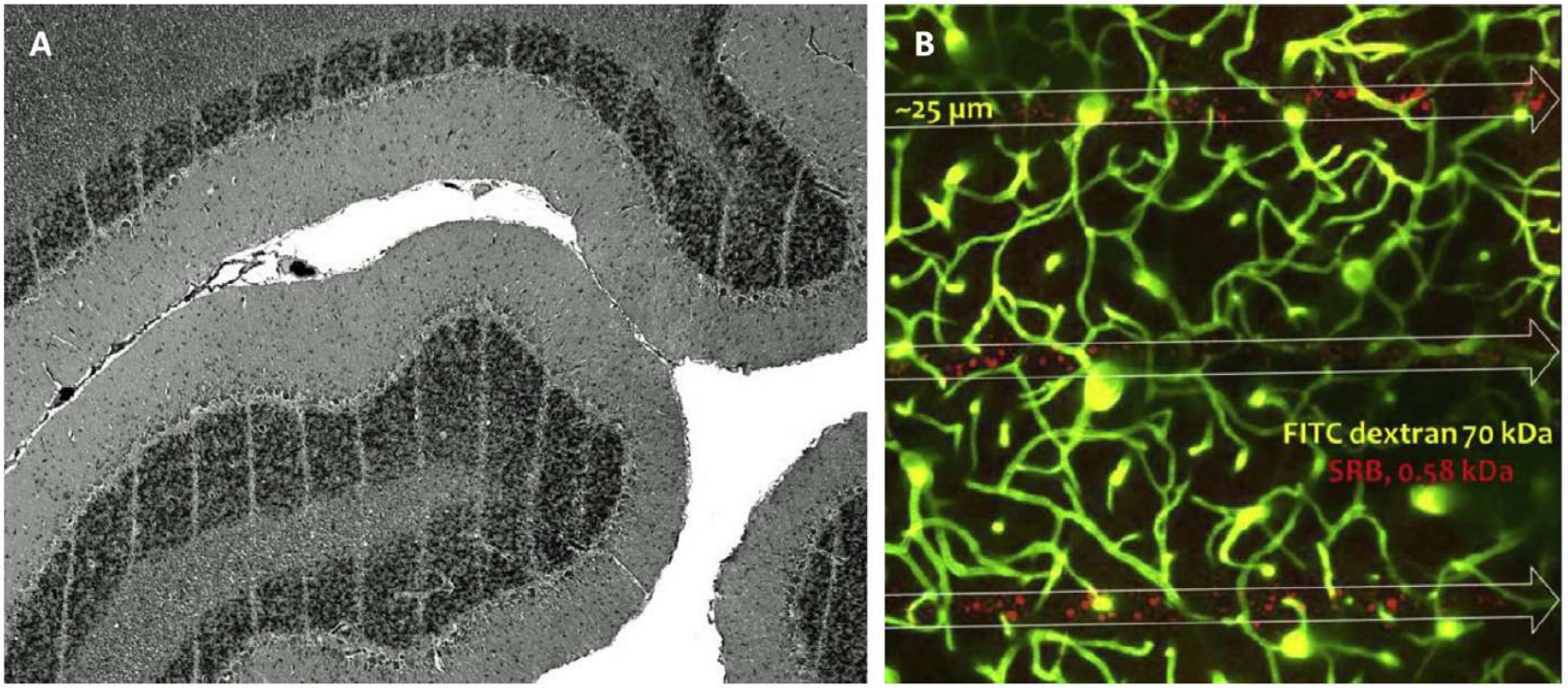
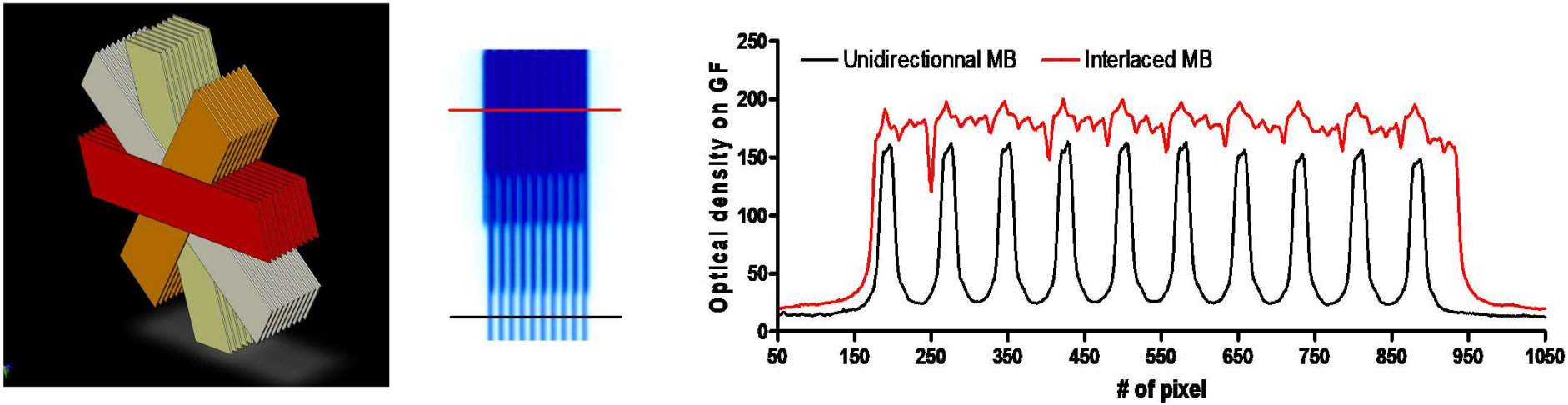


Figure 1. A- Histological section of a piglet cerebellum 15 months after irradiation with an array of 25 µm wide microbeams and an entrance dose of 300 Gy. Cellular damage is confined to the microbeam's paths. No macroscopic necrosis was detected in irradiated normal brains of rodents and piglets. Adapted from Laissue et al. 2001 [20]. B- Intravital two photon microscopy of a mouse vascular network 7 days after MRT, with an entrance dose of 1000 Gy, and microbeam width of 25 µm. The perfused blood vessels, visualized by intravascular injection of fluorescein isothiocyanate-dextran (FITC, green, 70kD) revealed transiently increased vessel permeability as demonstrated by a perivascular deposition of dextran of low molecular size (0.58 kD) labeled with sulforhodamine B (SRB, red) within the microbeams path (large arrow). There was no extravasation of fluorescein-labeled dextran (70 kD). Adapted from Serduc et al. 2006 [17]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

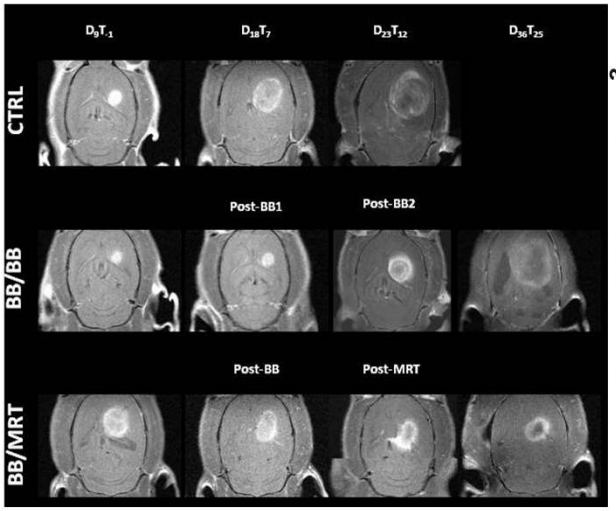
A. Bouchet et al. / Physica Medica 31 (2015) 634–641

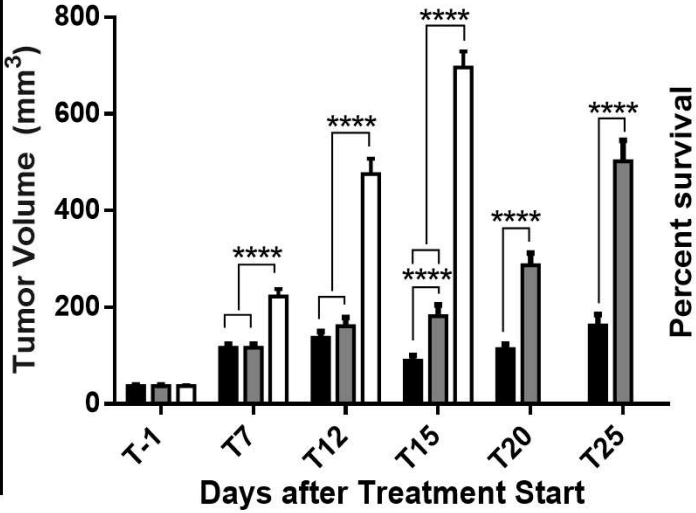
Exploring possibilities of crossfiring

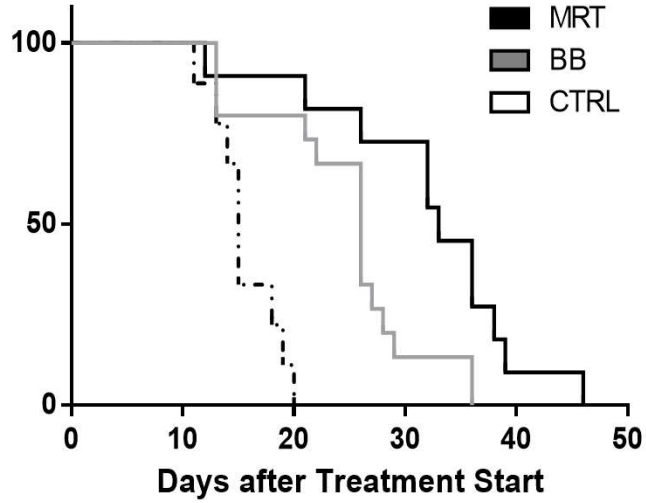


Schematic representation of the irradiation geometry in normal rats. Four arrays of 10 MBs (50 µm wide, 200 µm on-center distance) were interlaced and created a 2x2x2.2mm^3 target region where the radiation dose is homogenous. Gafchromic® film image of interlaced MBs; the upper part corresponds to a centre-to-centre distance of 200µm. The radiation target corresponds to the region where all the 4 arrays of MBs interlaced. E- Dose profiles measured on the Gafchromic® film shown in (D). The red line shows the dose in the interlaced region. The dose profile produced in the spatially fractionated irradiation and which is delivered by a single array of MBs (of **Synchrotron radiation** at ESRF) is shown with the black line.

Animal experimentation

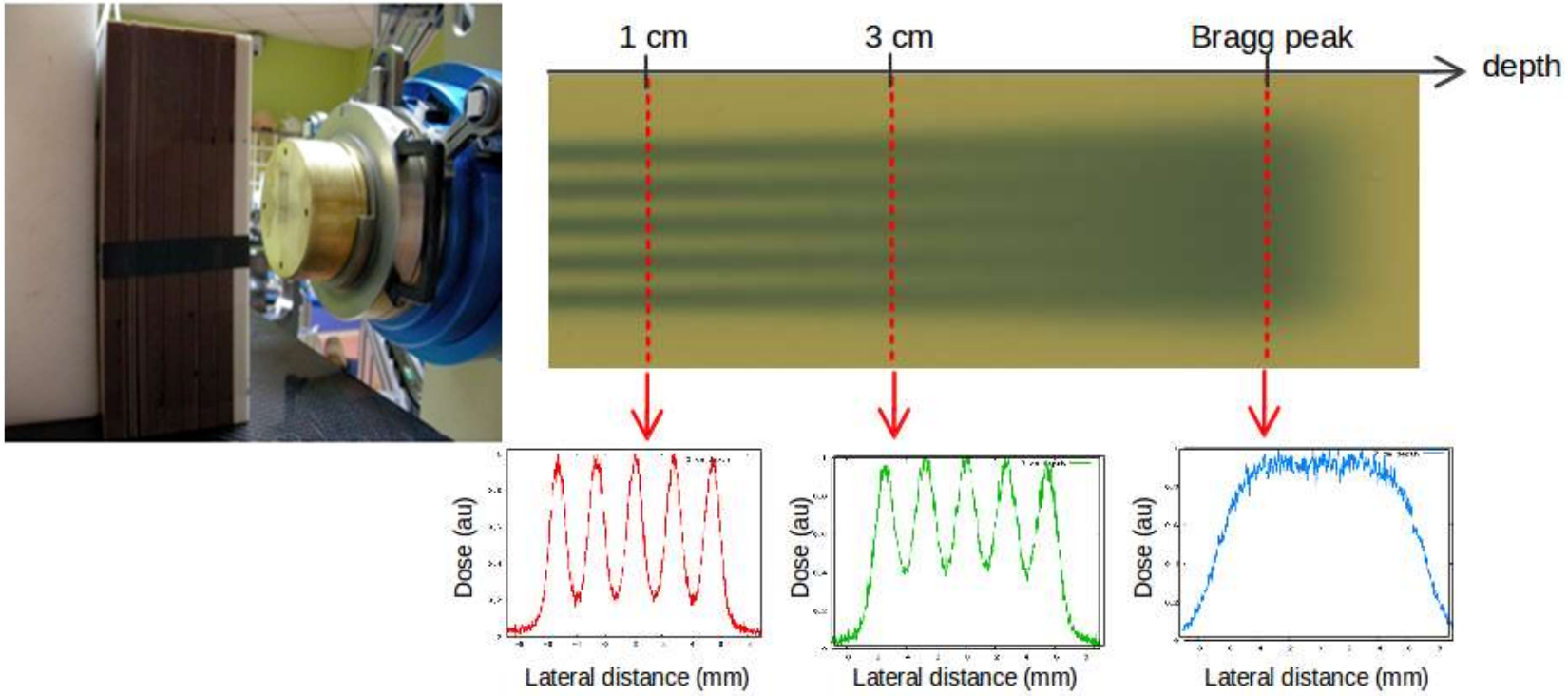






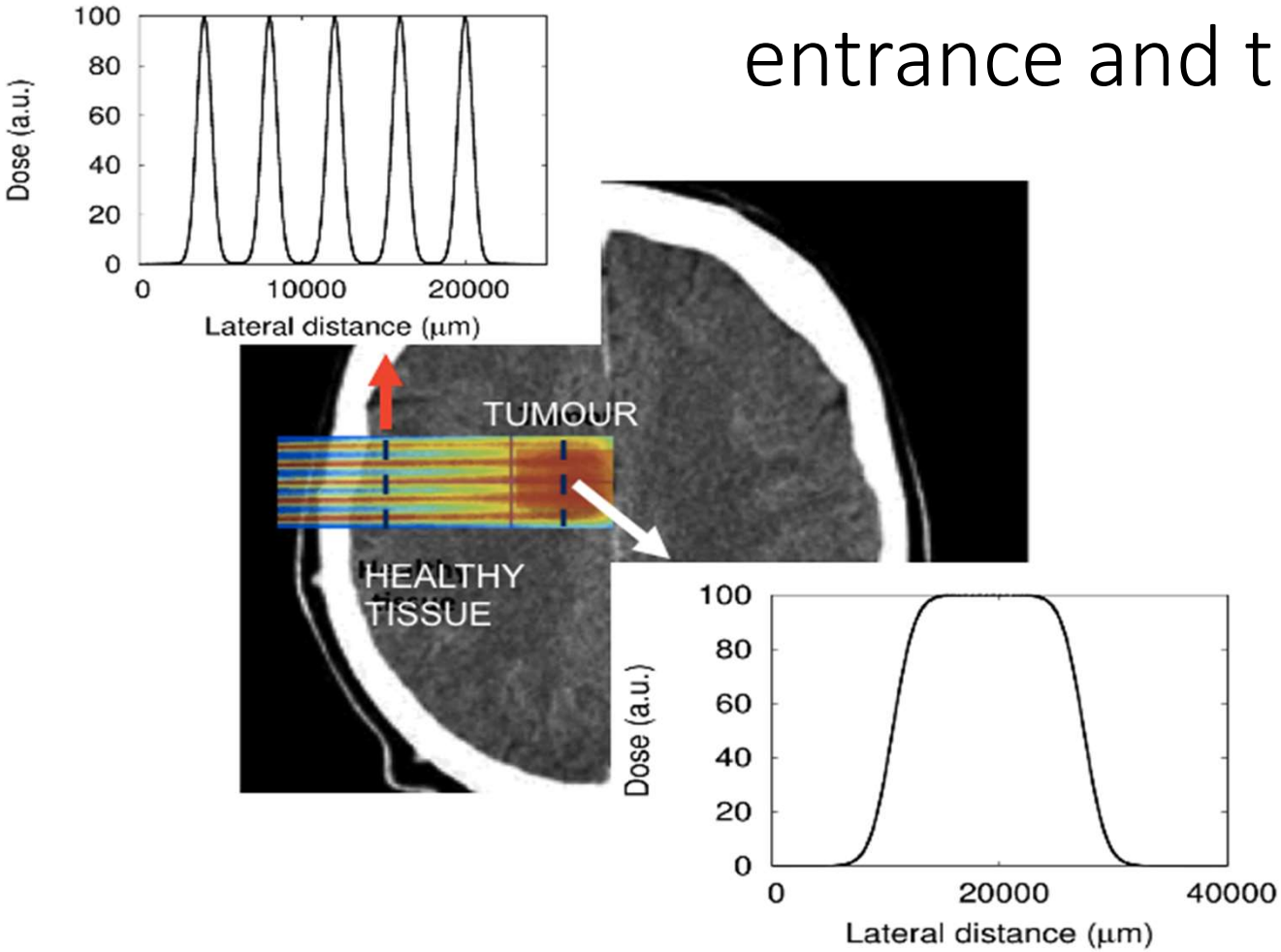
Typical evolutions of brain tumors after the 3 different dose regimens *i.e.*, control (no irradiation), BB and MRT 8 Gy fractions delivered after 3 initial fractions of 6Gy BB. (MRT, black, BB grey, controls white). Survival curves obtained according to the different irradiation configurations (MRT black, BB grey, controls dashed line). Unpublished data (of **Synchrotron radiation** at ESRF).

Extension to protons (ICPO, IMNC, Y Prezado)



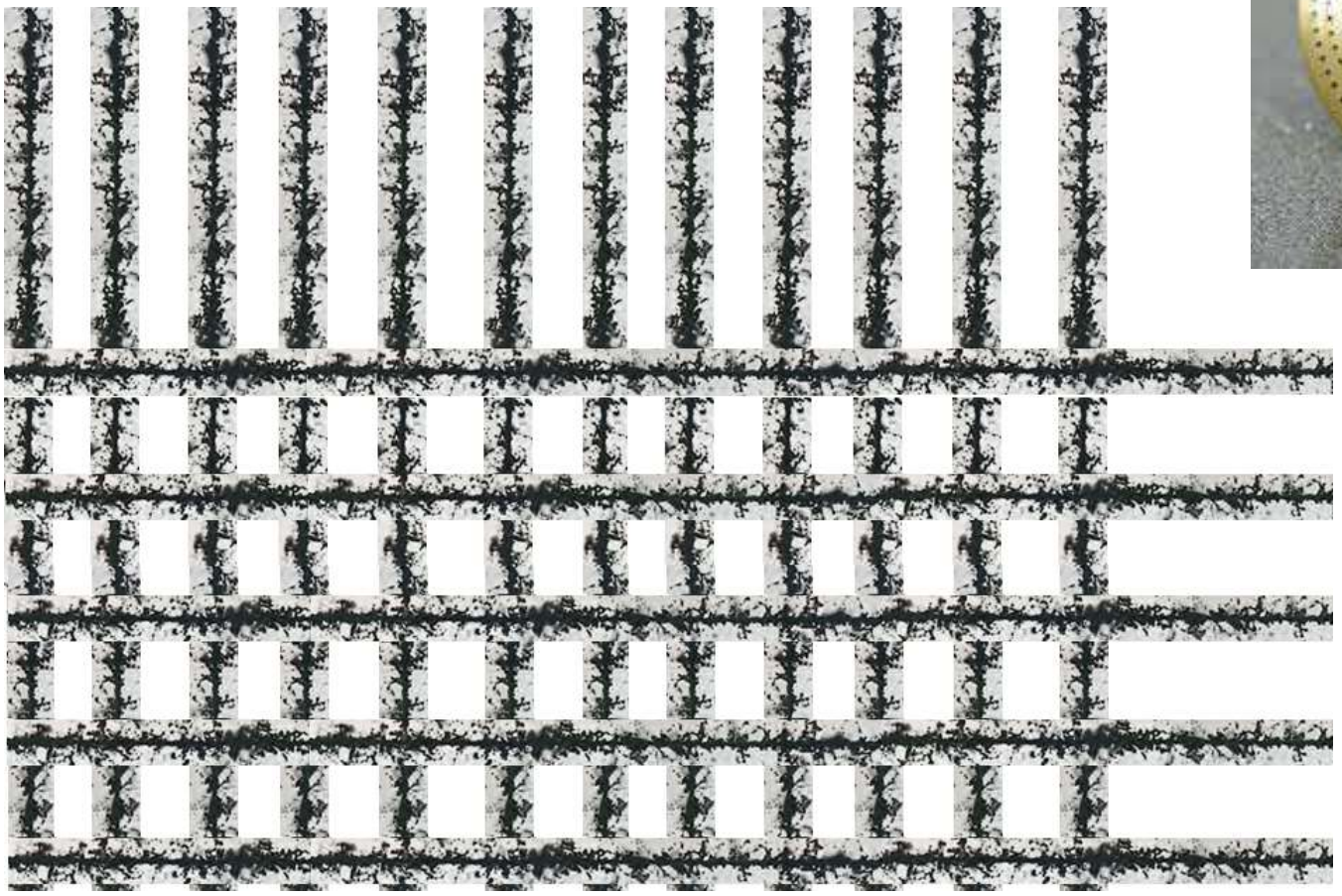
*Left: **proton** beams (beam energy of 105 MeV) Photograph of the minibeam collimator. Right: Gafchromic films irradiated at different depths in a water phantom and the corresponding experimental dose profiles.*

The difference between the entrance and the depth dose



*Dose distributions of pMBRT (**proton** beam energy 105 MeV). The healthy tissues would profit from the spatial fractionation of the dose: a lateral dose profile (peak and valleys pattern) at 3 cm depth is show on the left, while a homogenous dose distribution is obtained in the tumour (Bragg peak position).*

May be, in the future…..?



Conclusion and perspectives

- Spatial fractionation is a renewed concept properly explored by SR
- Its biological effects are very original, thus making this modality a really new type of radiotherapy
- Its applications are not yet explored but tumors, infant tumors and brain diseases, as resistant epilepsies, are in the scope of clinical studies projects
- The possibilities of application out of the narrow domain of SR are on the way with X-rays and particles (protons)
- The possibility to generalize this concept with random beam of low flux of very heavy particles is a subject for theoretical studies

The FLASH irradiations

Works of Vicent Favaudon team in Orsay, Institut-Curie Recherche and Marie-Catherine Wozenin at the CHU Vaudois in Lausanne (Swiss)

Ponette, …, Balosso et al. CR Acad Sciences 2000

In the study of the early effects of a chemotherapie after an irradiation, to excplore the first seconds we had the idea to use a second irradiation as a kind of probe : thus we discovered the « W effect ».

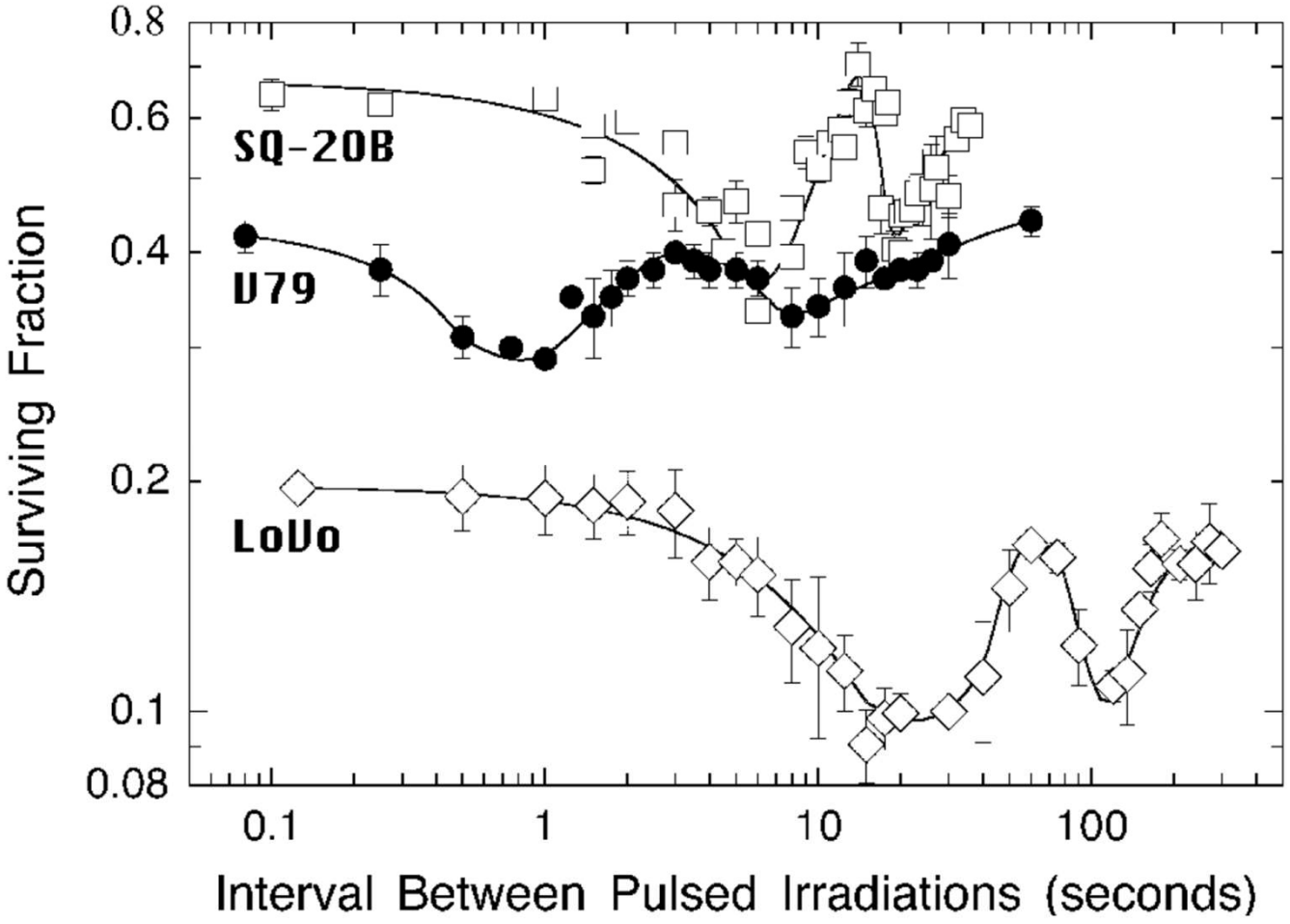
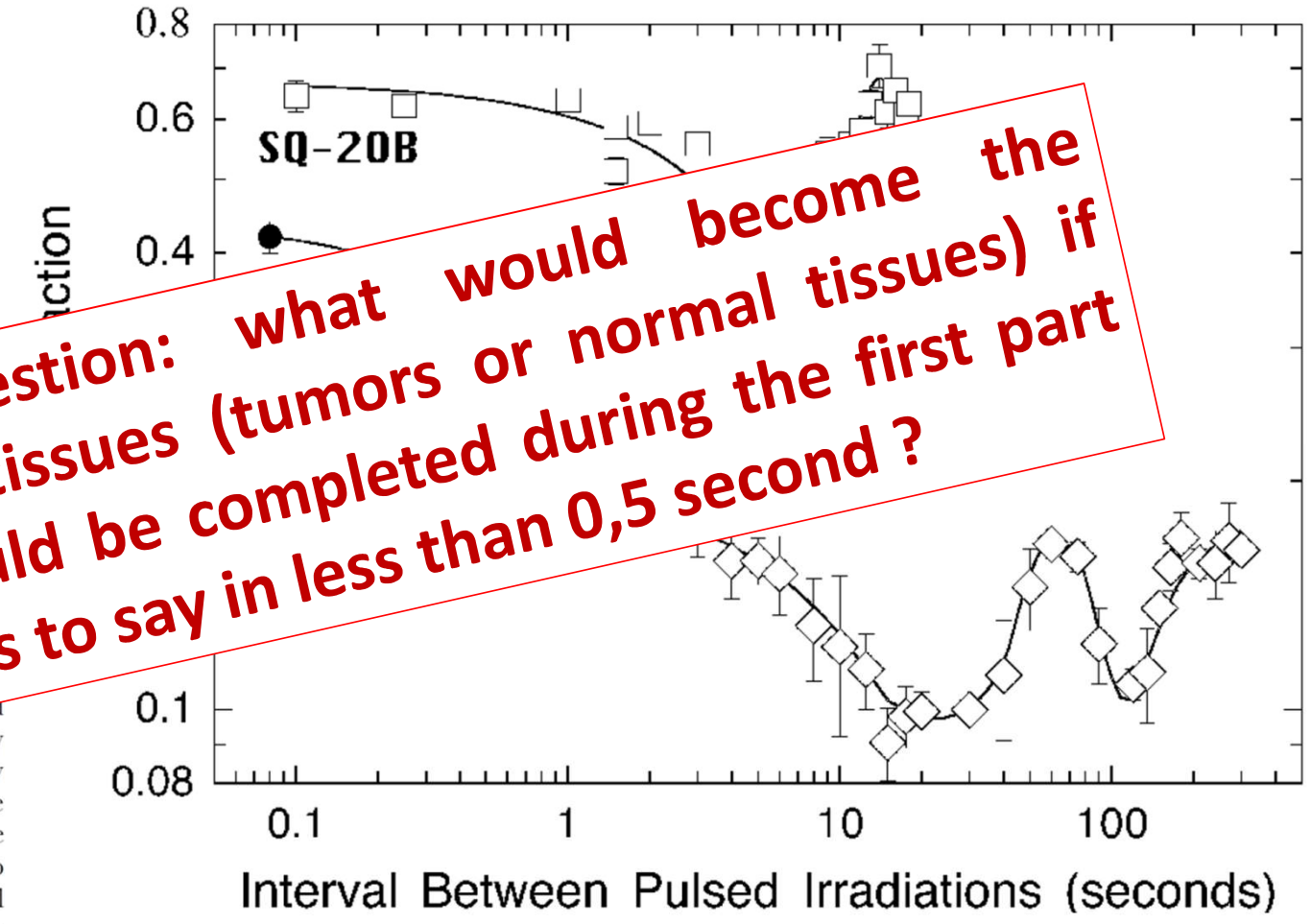


Figure 1. Time-dependent profile of the clonogenic survival of V79, SQ-20B and LoVo cells following pulsed, split-dose exposure to 3.5 MeV electrons. The first (priming) and second (probing) doses of pulse irradiation were 1 Gy then 4 Gy (V79), 2 Gy then 4 Gy (SQ-20B), and 1.5 Gy then 1.5 Gy (LoVo). The dose-rate was 12 Gy s^{-1}. The curves were fitted using a smoothing function. The figure represents the summation of results obtained from two experiments performed sequentially at two days interval with equally seeded and aged subcultures. Each data point came from a multiple of two culture flasks. Bars represent the SD.

Ponette, …, Balosso et al. CR Acad Sciences 2000

In the study of the early effects of a chemotherapie after an irradiation, to excplore the first seconds we had the idea to use a second irradiation as a kind of probe : thus we discovered the « W effect ».

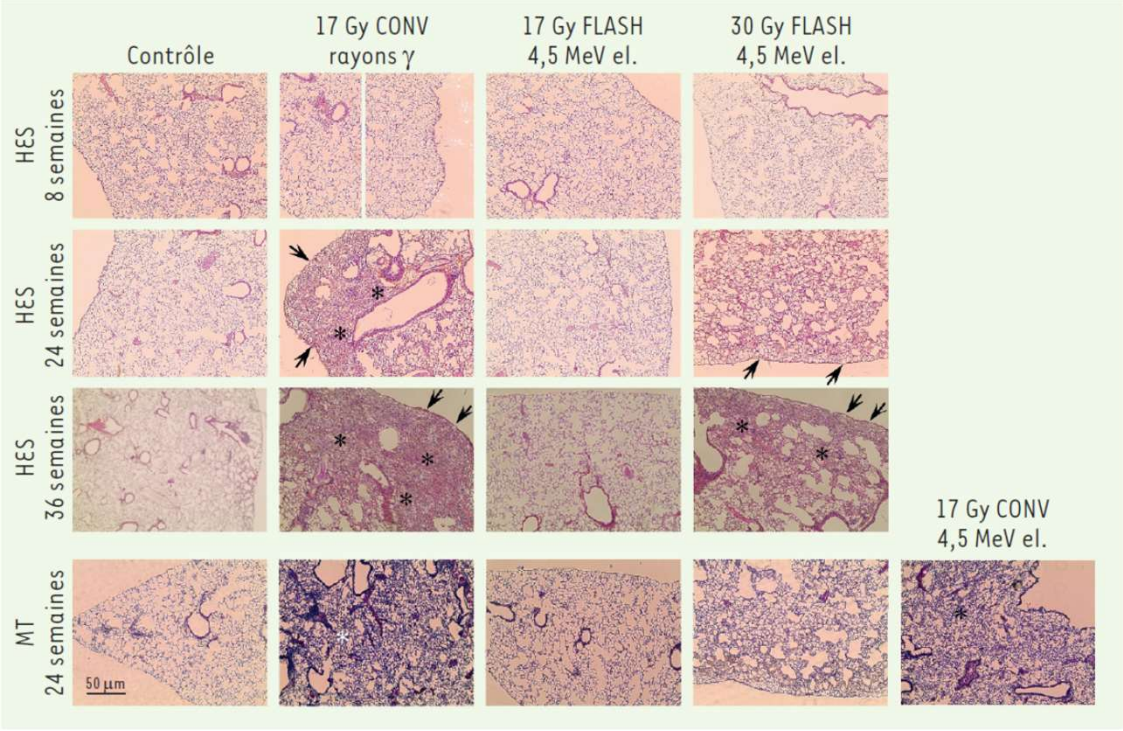


So came the question: what would become the radiosensitivity of tissues (tumors or normal tissues) if the irradiation would be completed during the first part of the W effect, it is to say in less than 0,5 second ?

Figure 1. Ti… V79, S… exposur… second … then 4 G… then 1.5 … curves were fitted using a smoothing function. The figure represents the summation of results obtained from two experiments performed sequentially at two days interval with equally seeded and aged subcultures. Each data point came from a multiple of two culture flasks. Bars represent the SD.

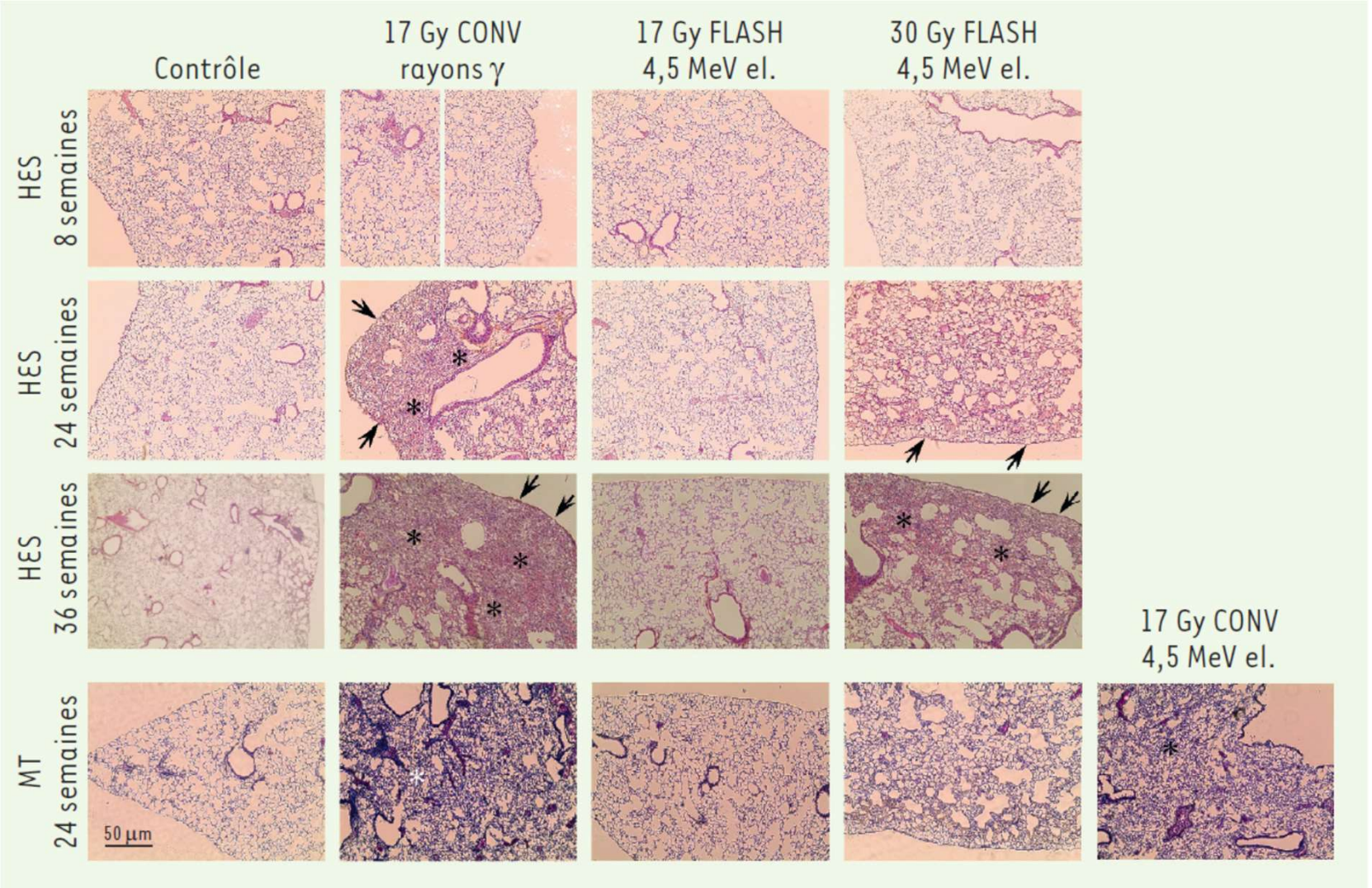
This question has been explored using the same device than for the W effect: a small electron linac specifically design to deliver very short irradiations (The Kinetron of the CGRmeV in Orsay)

The first model has been the lung fibrosis induction in mice, comparing « conventional » low dose rate (0;03 Gy/s) versus high dose rate (40 Gy/s, the whole irradiation in **less than 0,5 sec**).



Vincent Favaudon, Charles Fouillade, Marie-Catherine Vozenin m/s 2015 ; 31 : 121-38

L'irradiation flash modifie la radiosensibilité des tissus sains

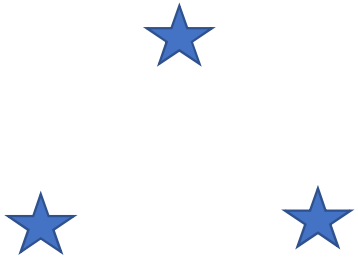


Beyond this founding work, what is the state of the question? (few papers 8 as a whole)

- Proton set up for about 40 Gy/sec on 12 x 12 mm^2 field (ICPO)
- Comparative test on pig skin tolerance with single dose (electrons): 20% sparing effect.
- Effectivness on cat nasal tumors with few or no toxicity in single fraction (electrons): no sparing effect on tumors
- Memory sparing in mice of 100 Gy/s versus 0.1 Gy/s
- By tuning a Varian Linac a FLASH electron irradiation of 200 Gy/s at 1 cm depth and for 40 x 40 mm^2 field has been obtained in CA, USA
- In the princeps study 30 Gy FLASH are equivalent to 17 Gy conventional: 76% increased tolerance for lung fibrosis with no decrease of the anti-tumor effect.

Futur studies for which questions?

- FLASH has to be reproduced for other types of beams: particles, photons.
- FLASH effect recovery time course has to be studied, actually it is necessary to consider to apply it as fractionated irradiation (several beam per session (??), several sessions per treatment course (!!))
- Technical developments for large field irradiations
- A priori pencil beam scanning should be precluded with FLASH (problem with particle therapy)



General conclusion and perspectives

- All these new modalities are offering great hopes for **improved tolerance**, **shorter treatment courses**, and may be **new applications** of irradiations in medicine
- Studies of **combinations** between spatial fractionation and flash irradiations are readily possible since both need very short irradiations
- The rising use of **nanoparticles** will take great advantage of the use of narrow spectrum photon irradiations of medium energy as prefigured by the SSRT irradiation
- For the development of all the presented applications, important technical developments and clinical studies are needed.
- Routine applications are not yet available, but surely, these modalities will influence the future of radiation oncology.

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Thank-you, questions?