MASTER DI II LIVELLO IN RADIOPROTEZIONE

Introduzione all'adroterapia oncologica

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Introduction to cancer hadrontherapy

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Introduction to cancer hadrontherapy

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Part 1

- Introduction to medical applications of radiation physics
- Conventional radiation therapy
- Hadrontherapy: basic physical and radiobiological concepts

Part 2

- Tools and techniques in hadrontherapy
- Some new ideas for the future of hadrontherapy
- Discussion

The starting point of a long adventure

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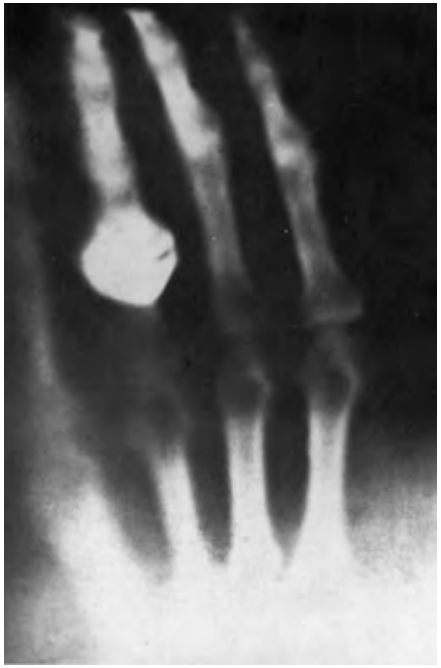
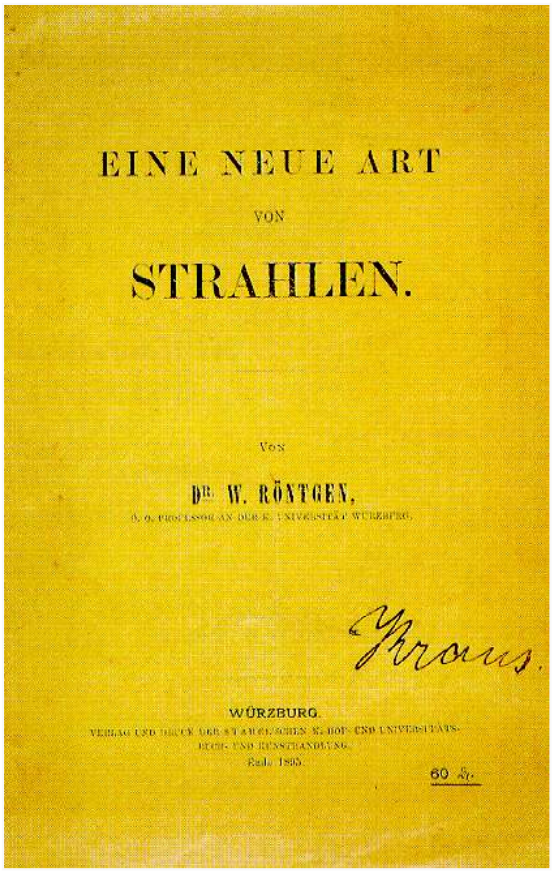
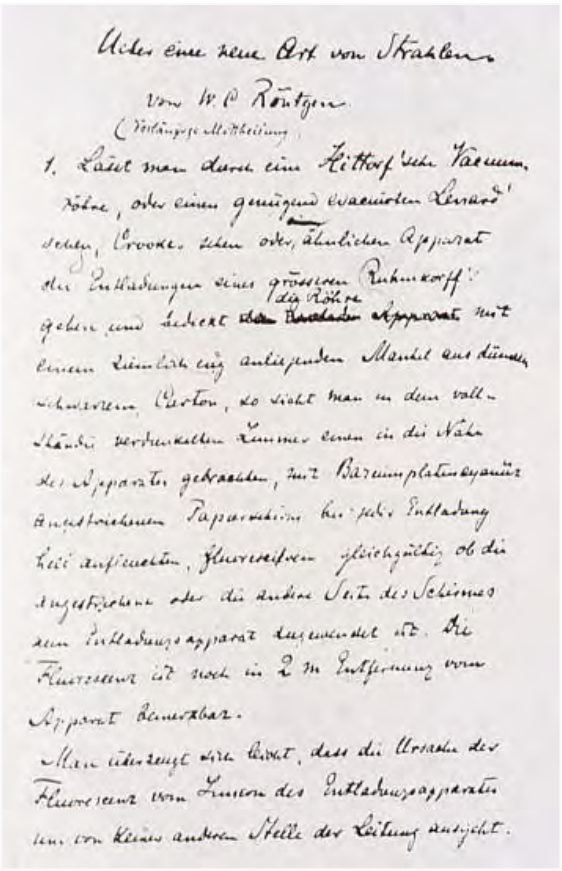


- Nov. 1895: W. Röntgen discovers X-rays
- Dec. 1895: first radiography


EINE NEUE ART
VON
STRAHLEN.
VON
DR. W. RÖNTGEN,
WÜRZBURG.
Aus 1895.
60 Kr.


Über eine neue Art von Strahlen.
Von W. C. Röntgen.
(Vorläufige Mittheilung.)
1. Lässt man durch ein Hittorf'sches Vacuum-
Röhre, oder einen genügend evacuirten Lenard'
schen, Crookes'schen oder ähnlichen Apparat
die Entladungen eines grossen Ruhmkorff'
gehen und befindet sich der Apparat mit
einem ziemlich eng anliegenden Mantel aus dünnem
schwarzem Carton, so sieht man in dem voll-
ständig verdunkelten Zimmer einen in die Nähe
des Apparates gebrachten, mit Baryumplatincyanür
angestrichenen Papierschirm bei jeder Entladung
hell aufleuchten, fluoresciren gleichgültig ob die
angestrichene oder die andere Seite des Schirmes
dem Entladungsapparat zugewendet ist. Die
Fluorescenz ist noch in 2 m Entfernung vom
Apparat bemerkbar.
Man überzeugt sich leicht, dass die Ursache der
Fluorescenz vom Inneren des Entladungsapparates
und von keiner anderen Stelle der Leitung ausgeht.

The first radiography: December 1895

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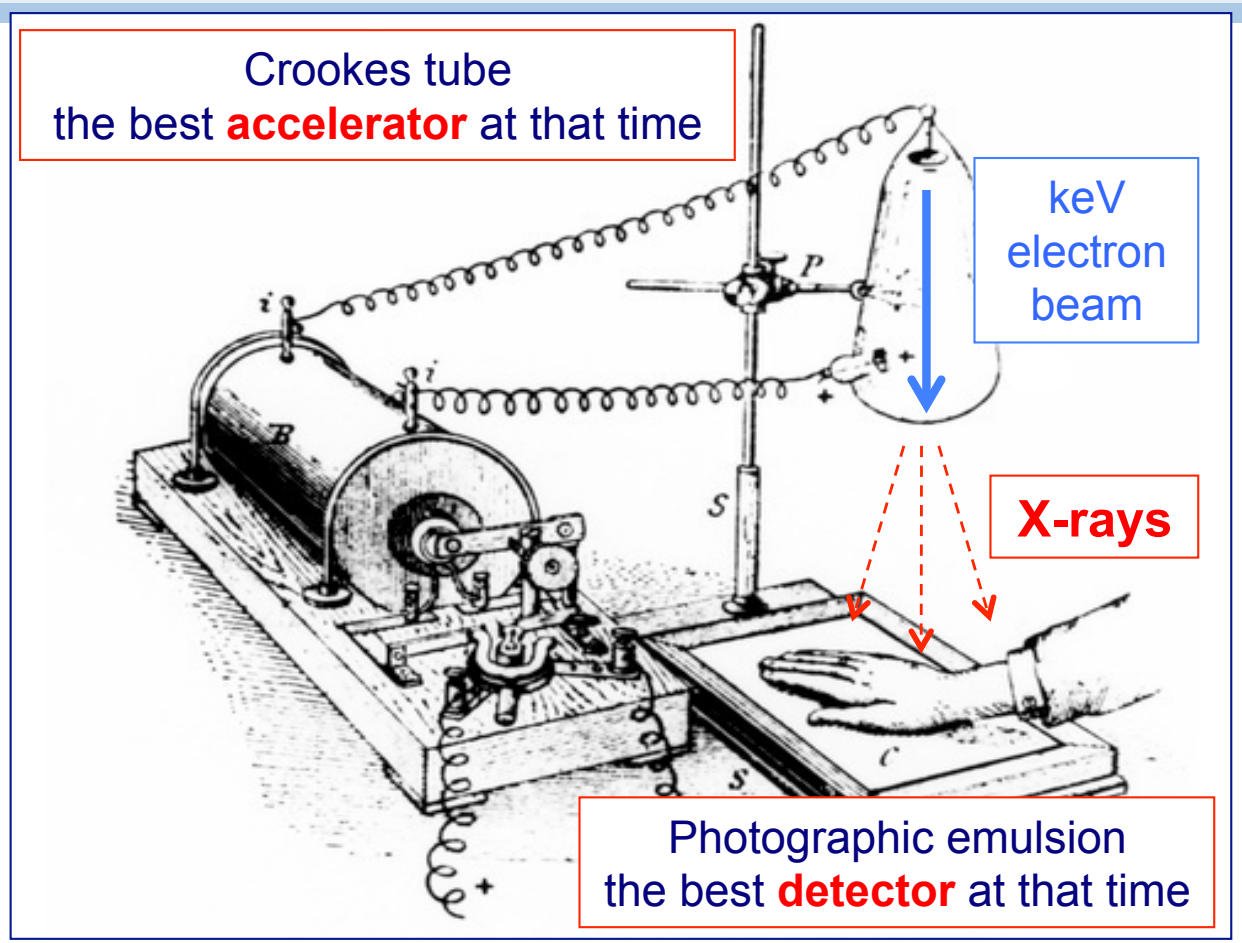

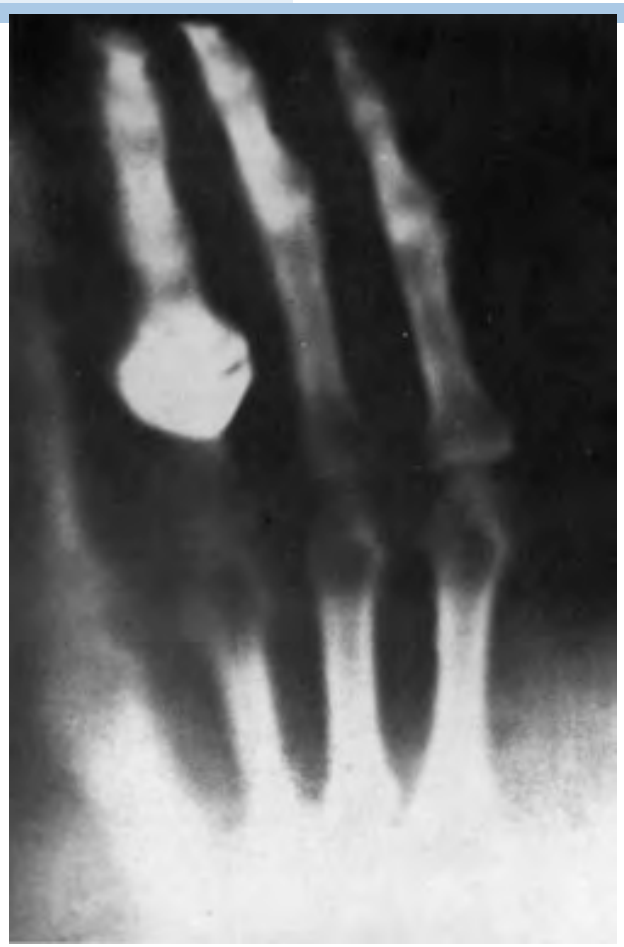

Question about radiation protection: was it harmful?

Only one year later

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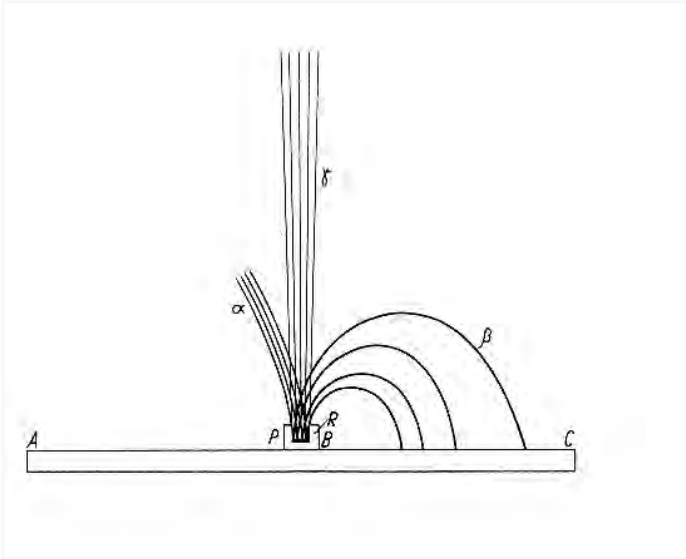
> 1896 : discovery of natural radioactivity

Henri Bequerel

Maria Skłodowska-Curie and Pierre Curie

From the thesis of Mme Curie – 1904
α, β, γ rays in a magnetic field



The birth of cancer radiation therapy

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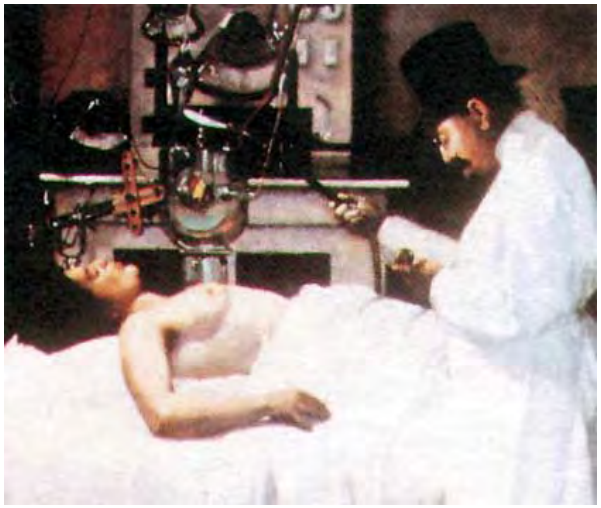
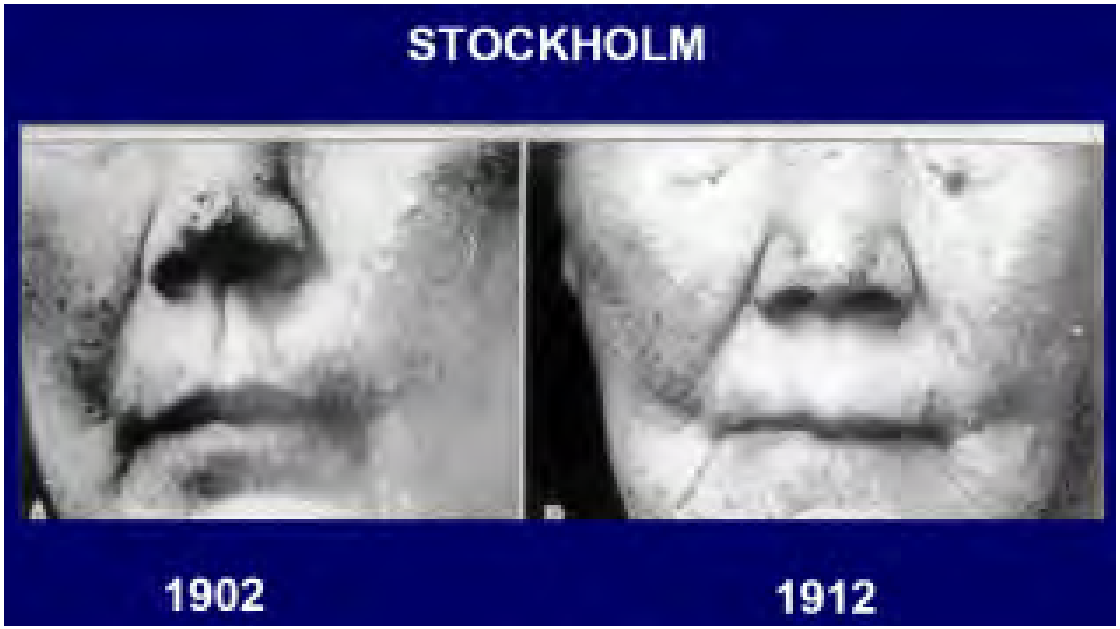


- 1908 : first attempts of radiation therapy in France
- The name "*curiethérapie*" is still used!

Picture: Dr. Chicolot, Musée de l'Assistance Publique, Paris

- Basic concept:

Local control of the tumour



Slow neutrons, Rome, 1934

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Oscar d'Agostino, Emilio Segrè, Edoardo Amaldi,
Franco Rasetti, Enrico Fermi

ANNO V - VOL. II - N. 7-8 QUINDICINALE 15-31 OTTOBRE 1934 - XIII

LA RICERCA SCIENTIFICA

ED IL PROGRESSO TECNICO NELL'ECONOMIA NAZIONALE

Azione di sostanze idrogenate sulla radioattività provocata da neutroni

Nel corso di esperienze sulla radioattività provocata nell'argento da bombardamento di neutroni si sono notate anomalie nella intensità della attivazione: uno spessore di alcuni centimetri di paraffina interposto fra la sorgente e l'argento invece di diminuire l'attivazione la aumenta. In seguito abbiamo potuto constatare che la presenza di grossi blocchi di paraffina circondanti la sorgente e l'oggetto irradiato esalta l'intensità della attivazione per un fattore che, a seconda delle condizioni geometriche, varia da alcune decine ad alcune centinaia.

In seguito a questa constatazione abbiamo cercato di riconoscere, in modo per ora sommario, le circostanze in cui si presenta questo fenomeno. I fatti che sono emersi fino ad ora sono i seguenti:

a) un preparato di radio senza berillio non produce effetto, ciò che induce ad attribuire i fenomeni ai neutroni e non ai raggi γ;

b) un effetto approssimativamente della stessa intensità di quello ottenuto colla paraffina si ha coll'acqua. Riteniamo molto probabile che esso dipenda dalla presenza dell'idrogeno perchè sostanze ossigenate prive di idrogeno ($NaNO_3$) non producono un aumento di attività, almeno nello stesso ordine di grandezza;

c) il fenomeno osservato nel caso dell'argento non si presenta in tutti gli elementi che si attivano con i neutroni. Abbiamo finora constatato che per il silicio, zinco e fosforo non si ha un aumento apprezzabile di intensità, mentre il rame, l'argento e lo iodio danno luogo ad effetti enormemente maggiori di quelli che si avrebbero senza la presenza dell'acqua.

Da questi pochi casi sembra valga la regola che siano sensibili solo quegli elementi che per bombardamento danno luogo a sostanze radioattive isotope con l'elemento di partenza.

Notevole è il caso dell'alluminio, il quale si attiva nell'acqua con un periodo di poco inferiore a tre minuti che corrisponde a quello del Al^{28} estratto dal silicio irradiato. Questa attività, prodotta in condizioni normali, è così debole che quasi sparisce di fronte alle altre dello stesso elemento.

Parimenti lo zinco ed il rame, che dànno origine agli stessi prodotti attivi (1) isotopi del rame, in condizioni normali hanno attività dello stesso ordine di grandezza, mentre nell'acqua il rame lascia a grande distanza lo zinco.

Una possibile spiegazione di questi fatti sembra essere la seguente: i neutroni per urti multipli contro nuclei di idrogeno perdono rapidamente la propria energia. E' plausibile che la sezione di urto neutrone-protone cresca al calare della energia e può quindi pensarsi che dopo alcuni urti i neutroni vengano a muoversi in modo analogo alle molecole diffondentesi in un gas, eventualmente riducendosi fino ad avere solo l'energia cinetica competente alla agitazione termica. Si formerebbe così intorno alla sorgente qualcosa di simile ad una soluzione di neutroni nell'acqua o nella paraffina. La concentrazione di questa soluzione in ogni punto dipenderebbe dalla intensità della sorgente, dalle condizioni geometriche della diffusione e da eventuali processi di cattura del neutrone da parte dell'idrogeno o di altri nuclei presenti.

Non è escluso che un simile punto di vista possa avere importanza nella spiegazione degli effetti osservati da Lea (2).

Sono in corso indagini su tutto questo complesso di fenomeni.

Istituto Fisico della R. Università.
Roma, 22 ottobre 1934-XII.

E. FERMI
E. AMALDI
B. PONTECORVO
F. RASETTI
E. SEGRÈ

(1) T. BAKER e C. H. WESTCOTT - «Nature» 134 396, 1934.
(2) D. E. LEA - «Nature» 133, 24, 1934.

From fundamental physics to medical applications

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Lecture by Enrico Fermi at Istituto di Sanità Pubblica 29 .5.1938

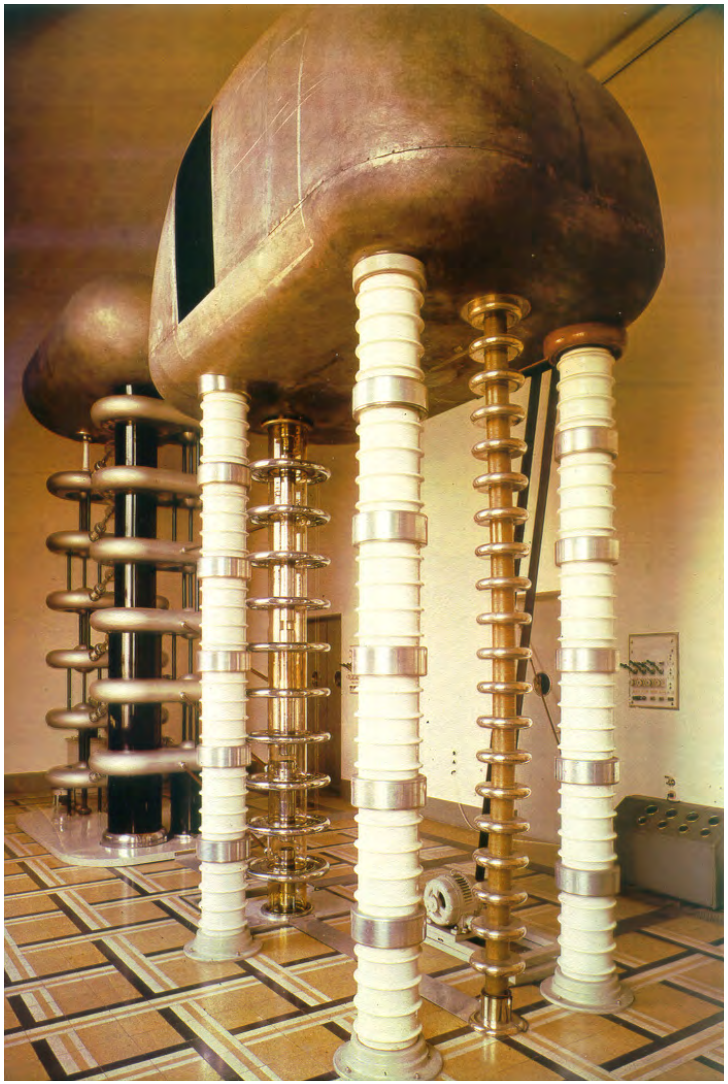
PROSPETTIVE DI APPLICAZIONE DELLA RADIOATTIVITÀ ARTIFICIALE

"It can be forseen WITHOUT DOUBTS that the (new) radioactive substances will find THERAPEUTICAL APPLICATIONS similar to the one of natural occurring radioactive substances.

Moreover and independently, the use of large quantities of radioactive substances will open, I HOPE, the way to many interesting studies in biology and chemistry through the use of radioelements as 'INDICATORS' "

È da prevedere senz'altro che le sostanze radioattive artificiali troveranno un impego terapeutico analogo a quello delle sostanze radioattive naturale.

Ma anche indipendentemente da queste possibilità , l'uso delle sostanze radioattive artificiali in quantità rilevanti renderà possibili, io spero, anche molte interessanti ricerche nel campo della biologia e della chimica, usando i radioelementi come " indicatori".



The 1 MV Cckroft-Walton accelerator built in Rome at the National Institute for Public Health (ISS) in 1938

Conventional radiation therapy

Conventional radiation therapy

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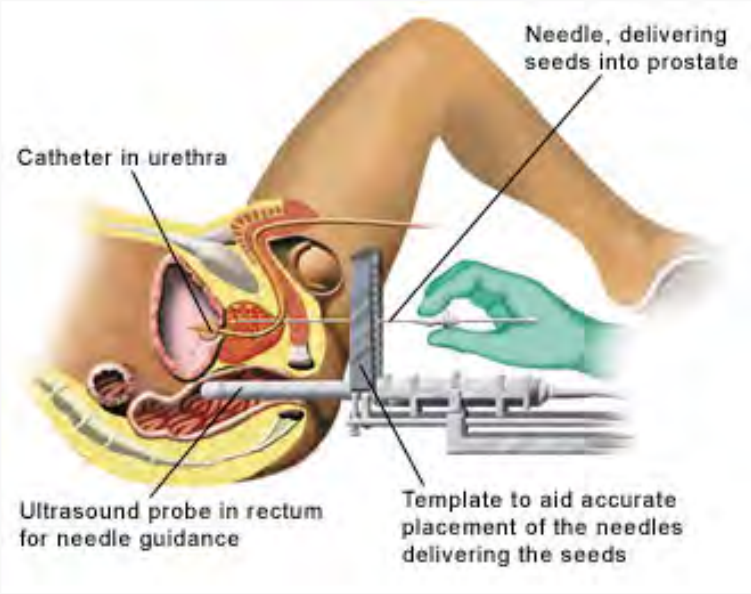

- Brachytherapy
  - Insertion of radiation sources in the body
  - ≈5% of all the patients
- Tele-therapy
  - Bombardment of the tumor tissues with radiation coming from outside the body of the patient
  - Based MeV gamma rays
  - It is the most common clinical modality (>95% of all the patients)

Interactions of photons with matter

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- Photoelectric effect
- Compton scattering
- Pair production

$$\propto \begin{cases} Z^4 \\ Z \\ Z^2 \end{cases}$$

Strong dependence on
- Z (atomic number of the target material)
- Photon energy

Which effects dominates? When?

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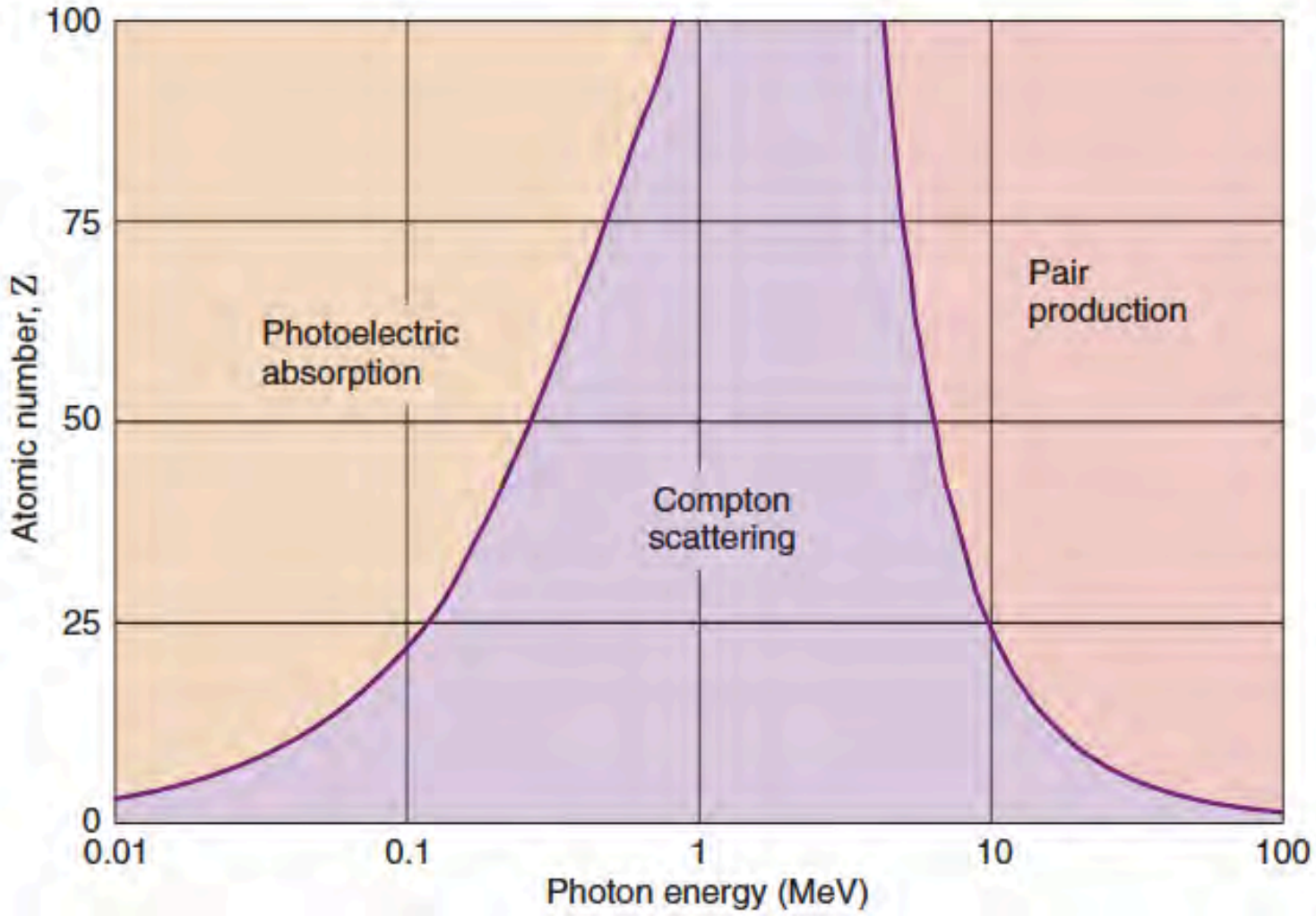


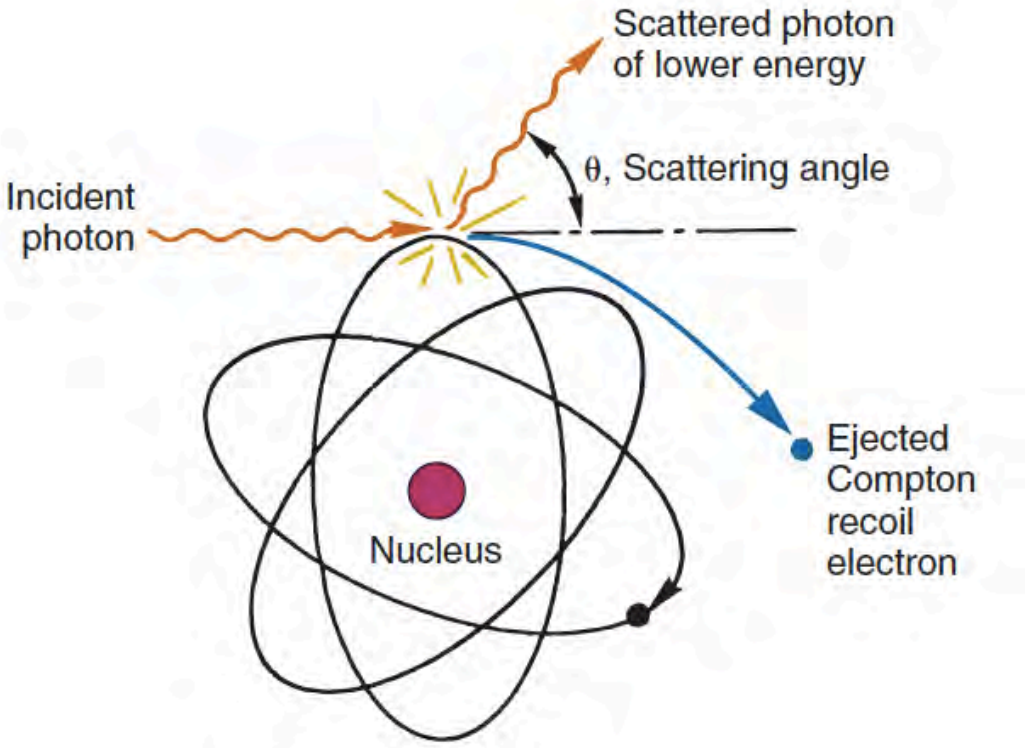
Compton scattering

$$\gamma + e^- \rightarrow \gamma' + e^-$$

- Collision photon-loosely bound outer electron (➔free)
  - Binding energy neglected
  - e^- is ejected (recoil electron)
  - γ' is scattered at angle θ with energy E'

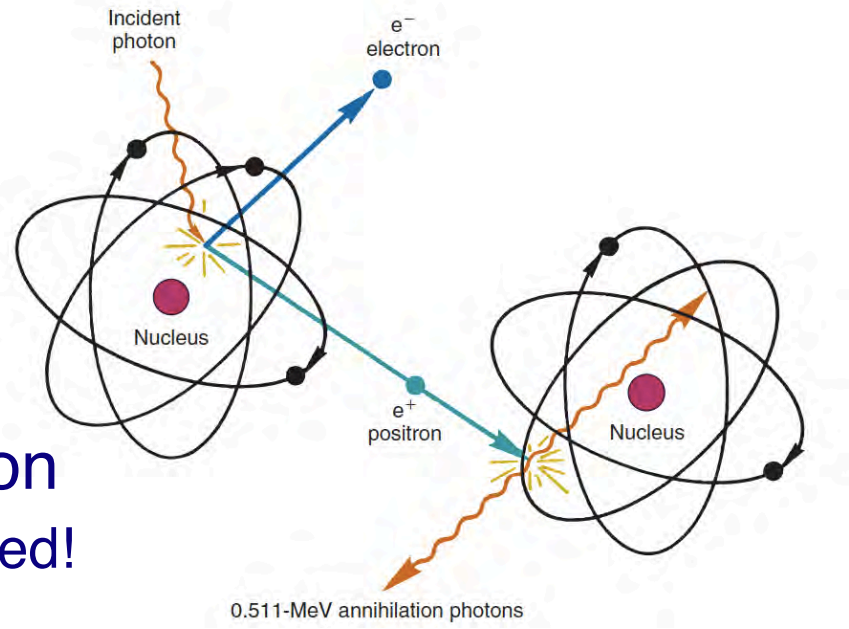
$$E' = \frac{E_0}{1 + \frac{E_0}{m_e c^2}(1 - \cos\theta)}$$

  - γ' has a lower energy !



Pair production

$$\gamma \rightarrow e^+ + e^-$$



- Momentum and energy conservation
  - The interaction with a nucleus is needed!
- The photon disappears
- Threshold: $2m_ec^2$
- The positron travels (ionization), stops in matter, annihilates with an electron and gives two back-to-back 511 keV photons
- These photons interact again …
- Process: varies as Z^2 and dominates at high energies

Absorbed dose

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$$D = \frac{d\bar{\varepsilon}}{dm}$$

- Consider a volume dV of mass dm and a radiation field
- $d\varepsilon$ is the average sum of all the energies imparted to the volume dV minus all the energy leaving the volume
- Mass–energy conversion is taken into account
  - Pair production, for example, decreases the energy by 1.022 MeV
  - Electron–positron annihilation increases the energy by 1.022 MeV
- Applicable to both indirectly and directly ionizing radiation
- Units: J / kg or Gy (Gray)

Photons in matter and the build-up effect: a simple model

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- Photon beam in water: 100 keV, 1 MeV, 10 MeV
- Assumption:
  - all the photons are parallel (one-dimensional model)
- Absorption coefficients from NIST (www.nist.gov)
  - 1 mm steps
  - 0.983, 0.992, 0.997 for 100 keV, 1 MeV, 10 MeV photons
- Assumption ("crude"):
  - all secondary electrons are monoenergetic ($E_e = E_\gamma/2$)
- Approximation:
  - Range of the secondary electrons R = (E_e[MeV]/2*10) [mm]
- Energy of the radiation field (Arbitrary units)

Photons in matter and the build-up effect: a simple model

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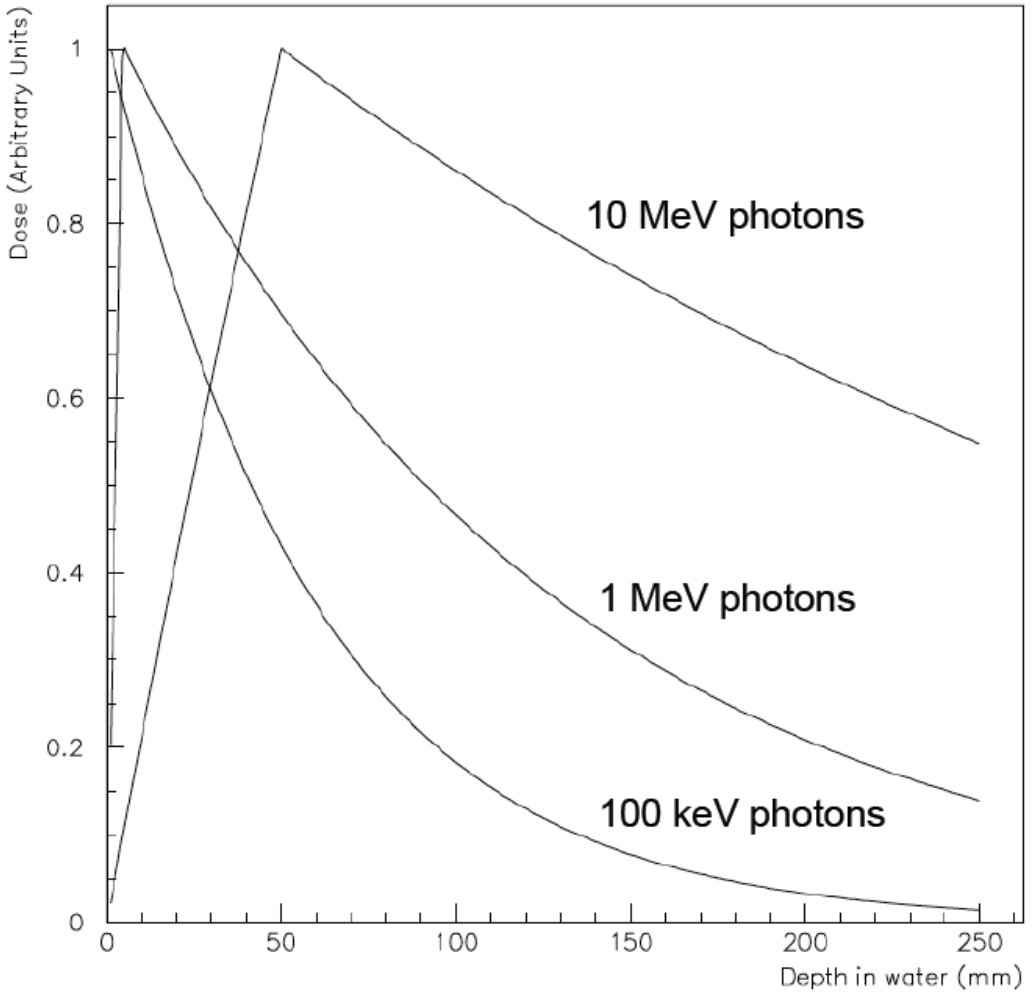
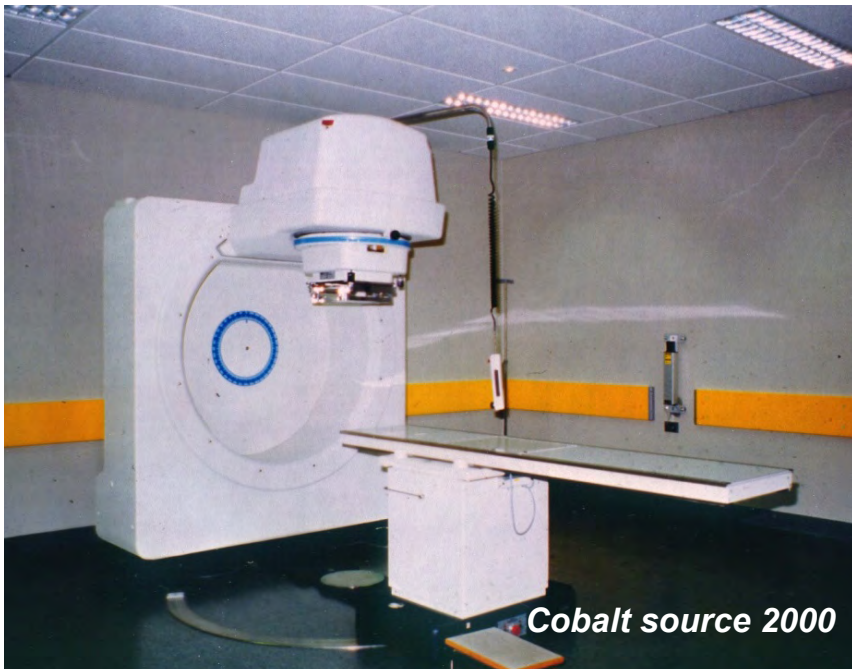


Cobalt sources

- Advantages:
  - Higher energy than X-rays, easy to install, no maintenance
- Disadvantages:
  - Half-life 5.27 years (the source has to be periodically replaced; radioactive waste issues)
  - The treatment time depends on the age of the source
  - Relatively low energy (high dose to the skin)


Cobalt source 2000

Cobalt-60 apparatus
(≈ 1 MeV gammas)
Produced in reactors
by slow neutrons
First treatments in 1951
Now obsolete

Electron linac mounted on a gantry

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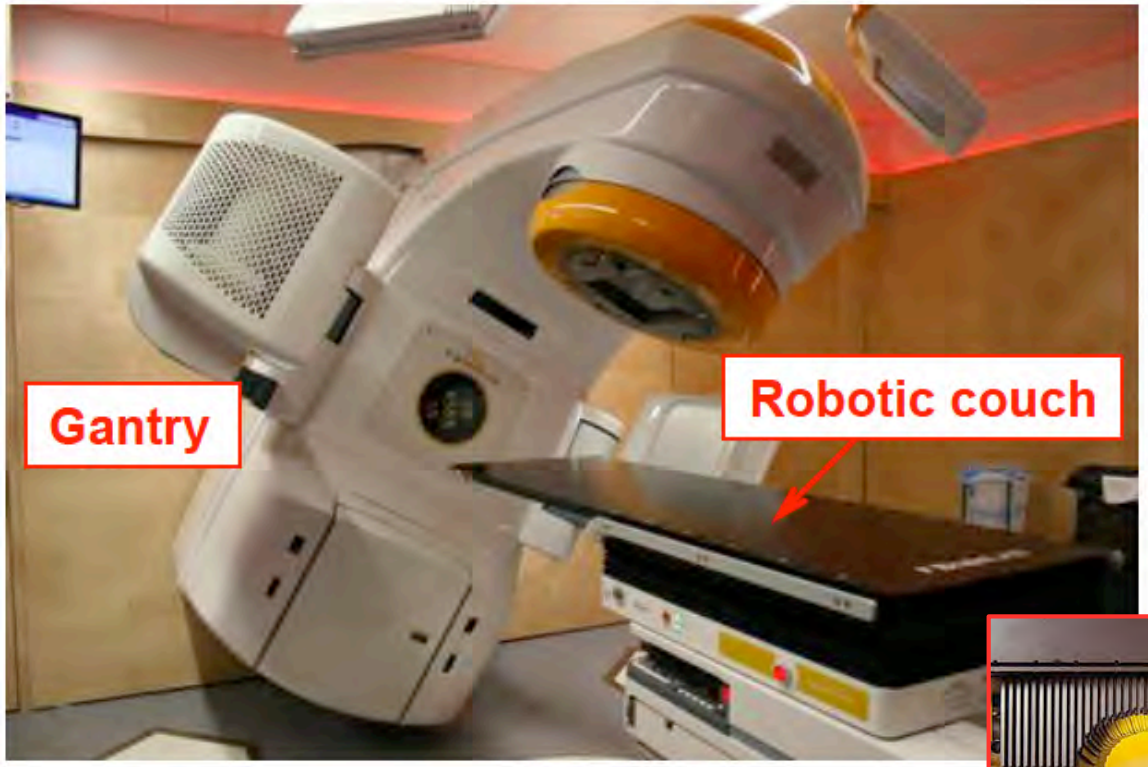

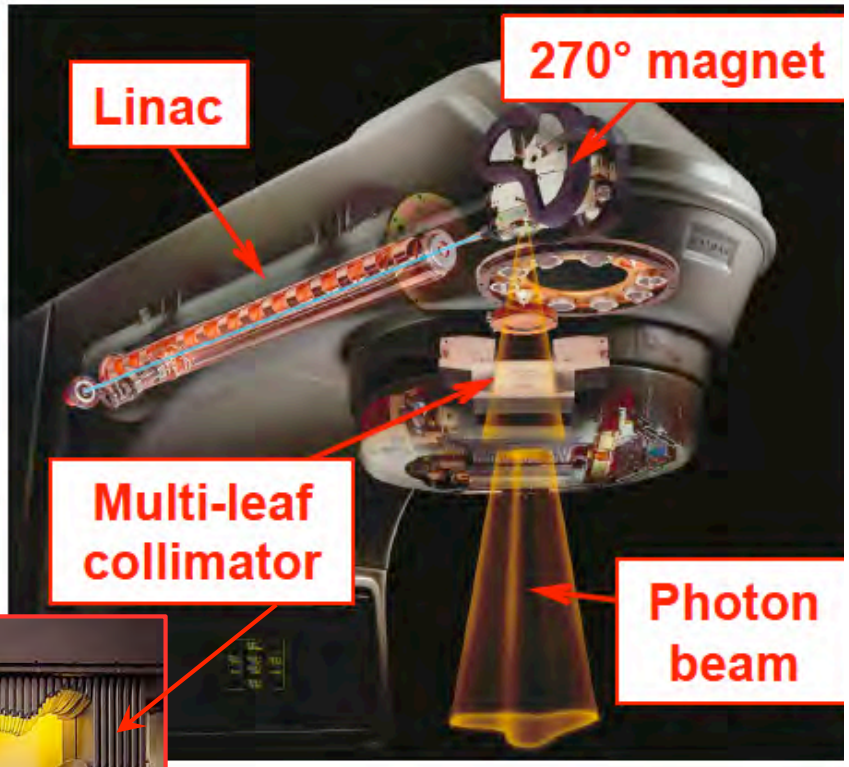

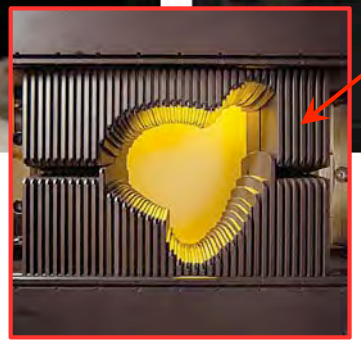

- About 10’000 installed in the world
- 6-20 MeV electron linacs produce gamma rays by Bremsstrahlung
- Today: 20'000 patients/year treated every 10 million inhabitants

Doses in conventional tele-therapy

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Standard Dose Parameters

- *Standard fractionation:*
  1.8-2 Gy/fraction; 1x day; 5 days/week.

- *Total dose:*

low	(20-30 Gy):	seminoma, lymphoma,...
medium	(45-55 Gy):	subclinical disease,...
high	(65-80 Gy):	prostate, sarcoma,...

Treatment planning

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- CT images with patient in treatment position:
  - Define the volume to be irradiated
  - Individuate the Organs At Risk (OAR) to be effectively spared
- On the basis of CT data
  - The radiation fields are chosen (direction, shapes, etc.)
  - The doses are calculated
  - The treatment plan is optimized
- The treatment plan is transformed into instructions for the accelerator
- Patient positioning plays a crucial role during irradiation

Definition of the volumes

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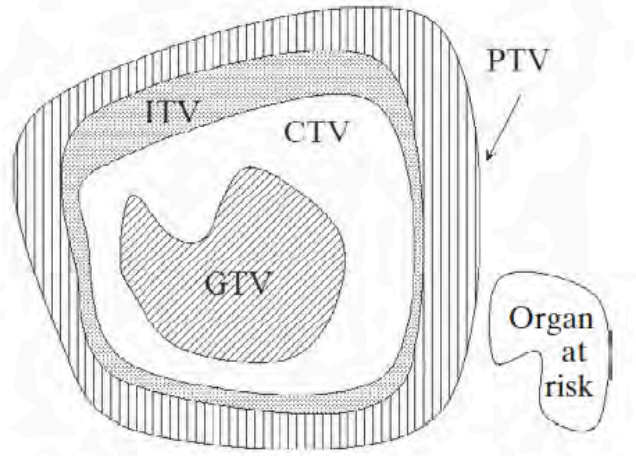

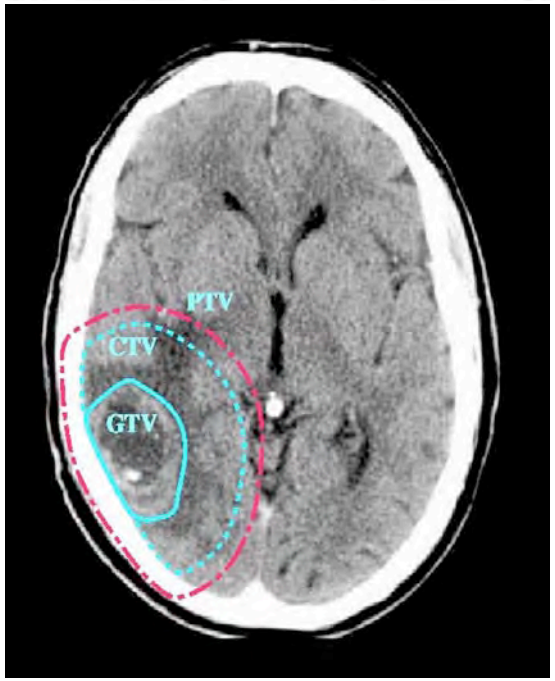

- Gross Tumor Volume (GTV)

  "The Gross Tumour Volume (GTV) is the gross palpable or visible/ demonstrable extent and location of malignant growth"

- Clinical Target Volume (CTV)

  contains a demonstrable GTV

- Internal Target Volume (ITV)

  takes into account the variations in the size and position of the CTV

- Planning Target Volume (PTV):

  it is a geometrical concept used in treatment planning

Dose-Volume Histograms (DVH)

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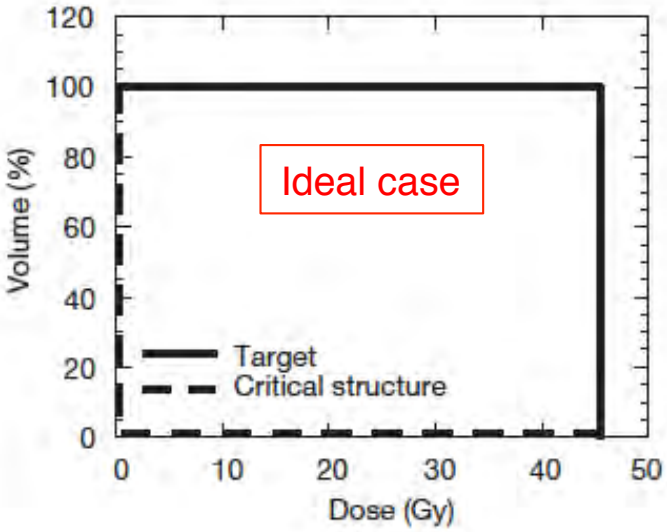
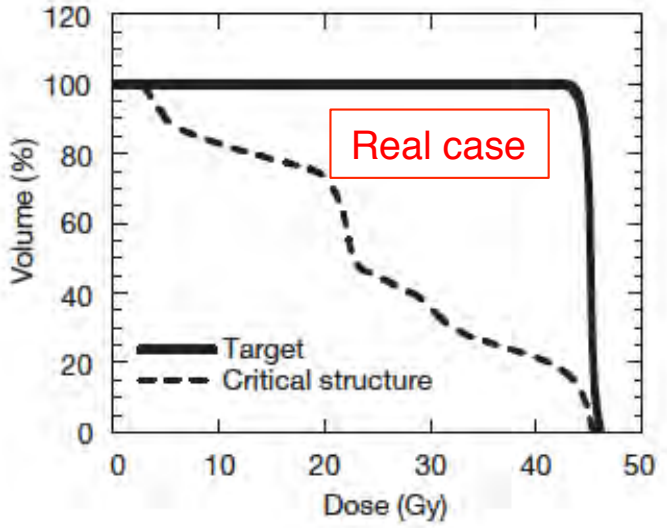
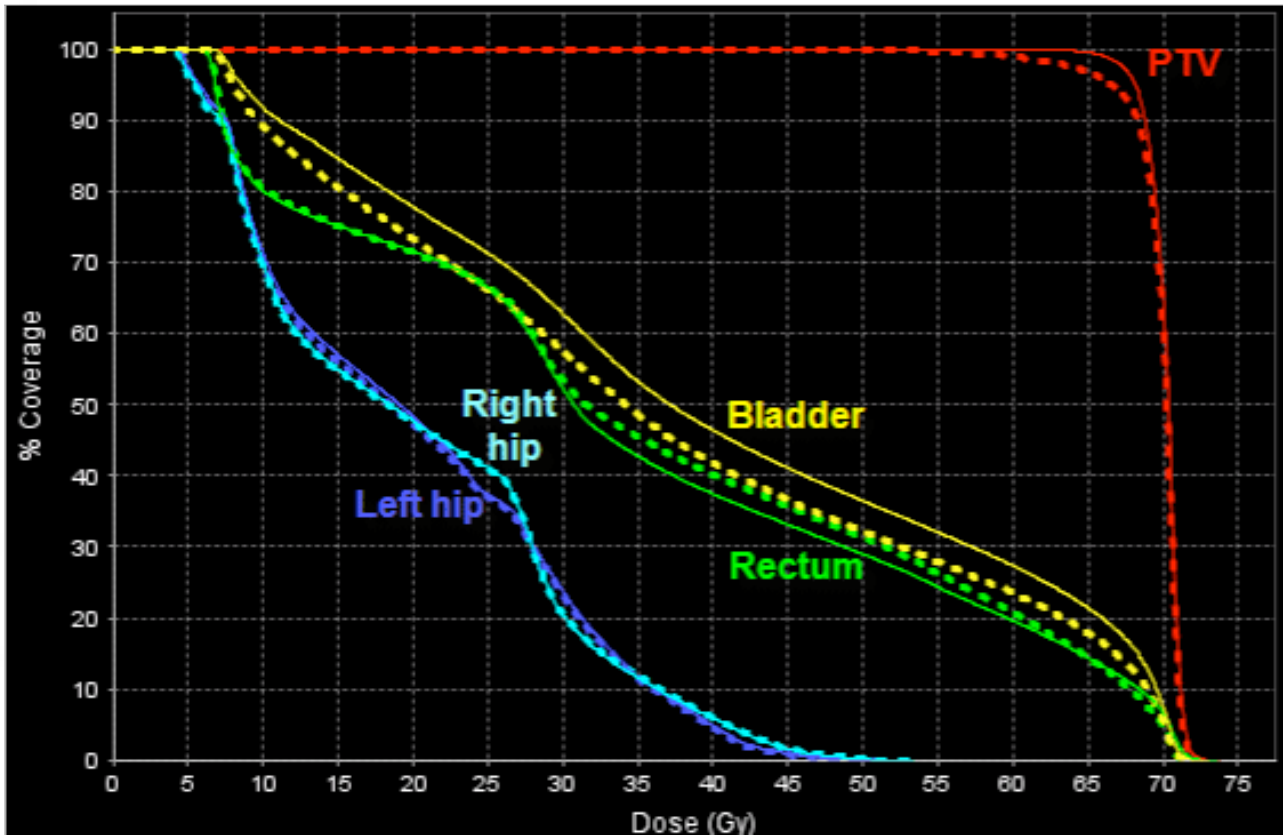
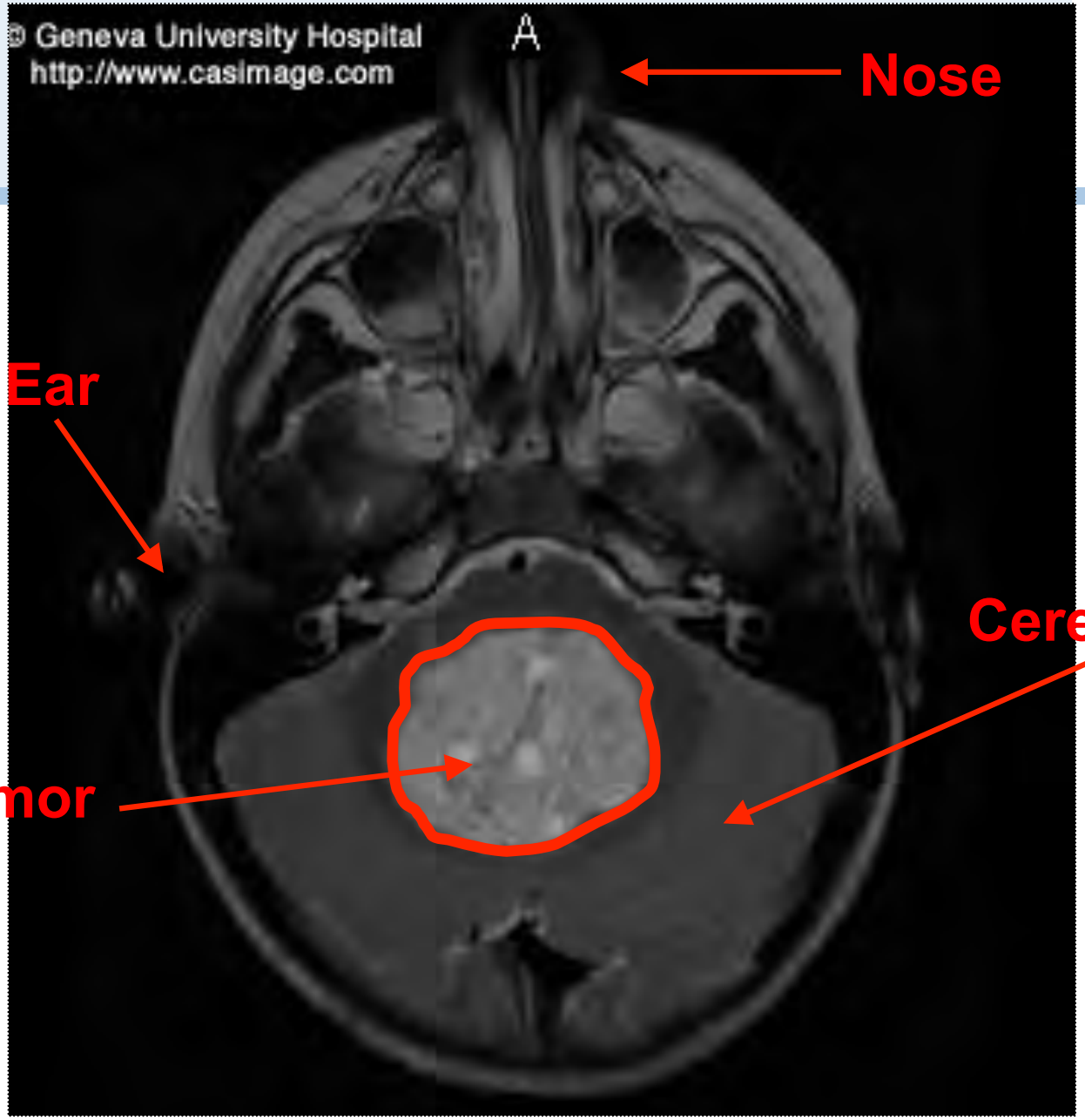




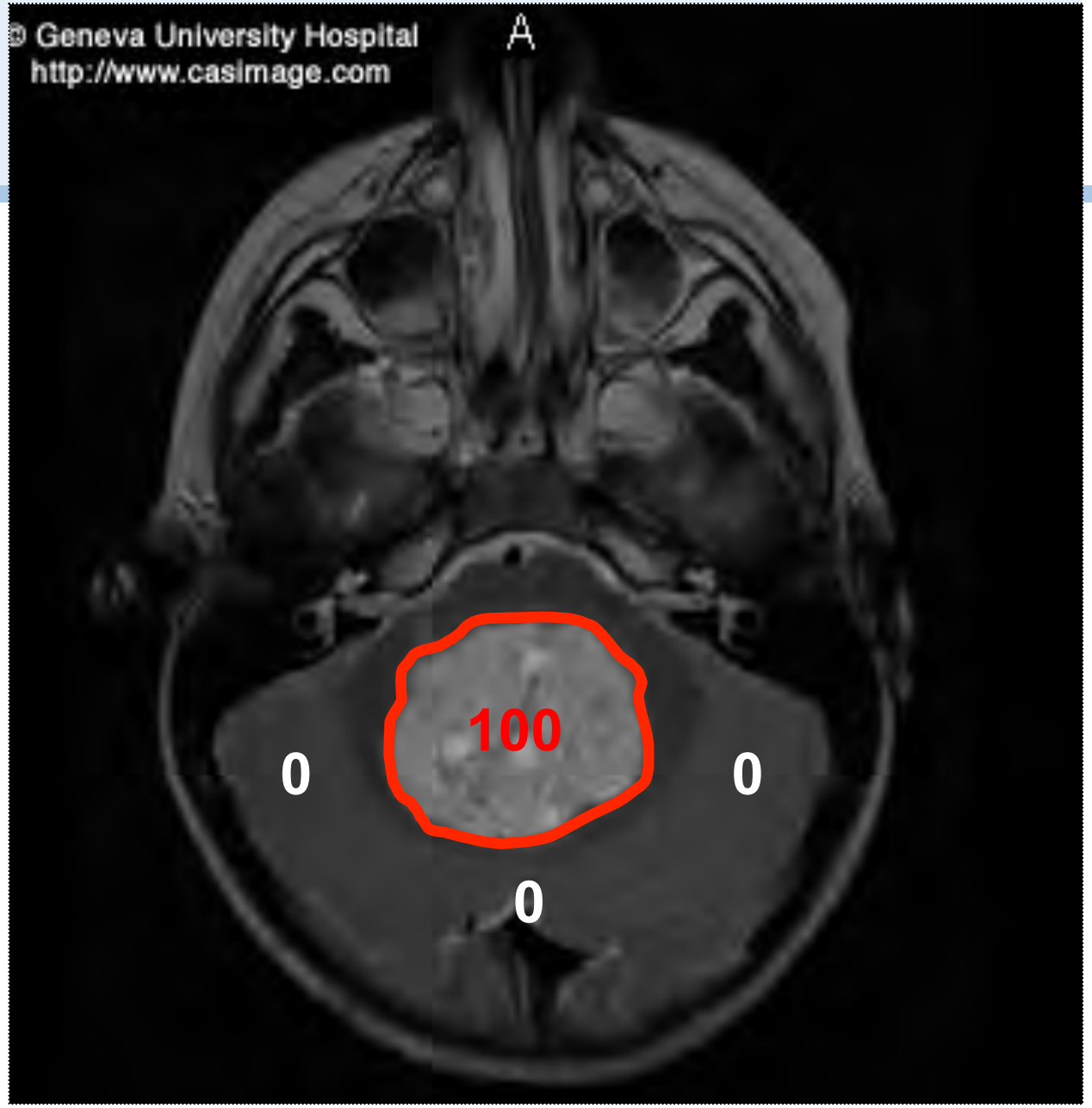


DVH for PTV and OARs derived from direct dose accumulation (solid lines) and deformable dose accumulation (dotted lines) in a prostate case (http://www.omicsonline.org)

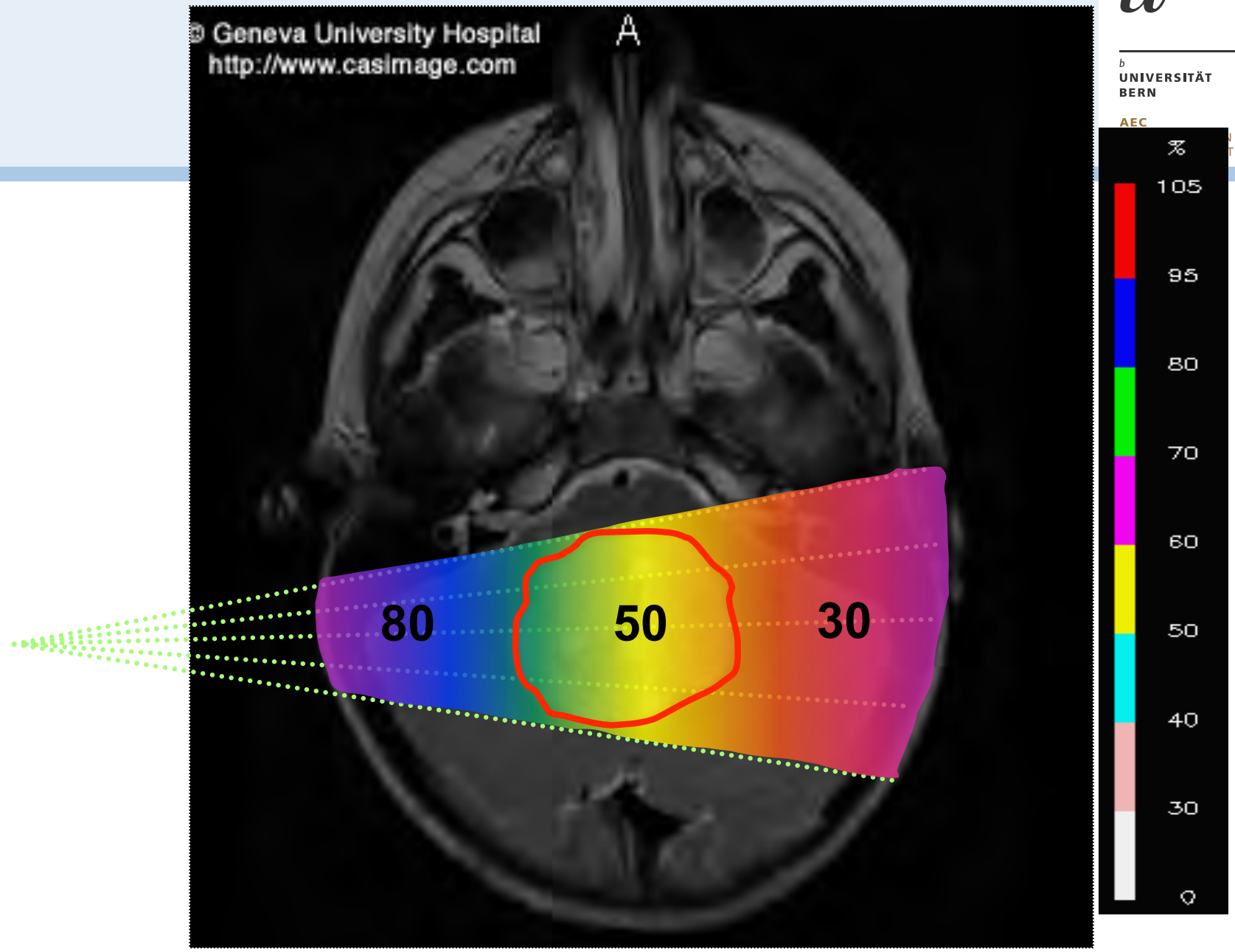


Courtesy
Prof. R. Miralbell,
HUG, Geneva

MRI: tumor of the Central Nervous System

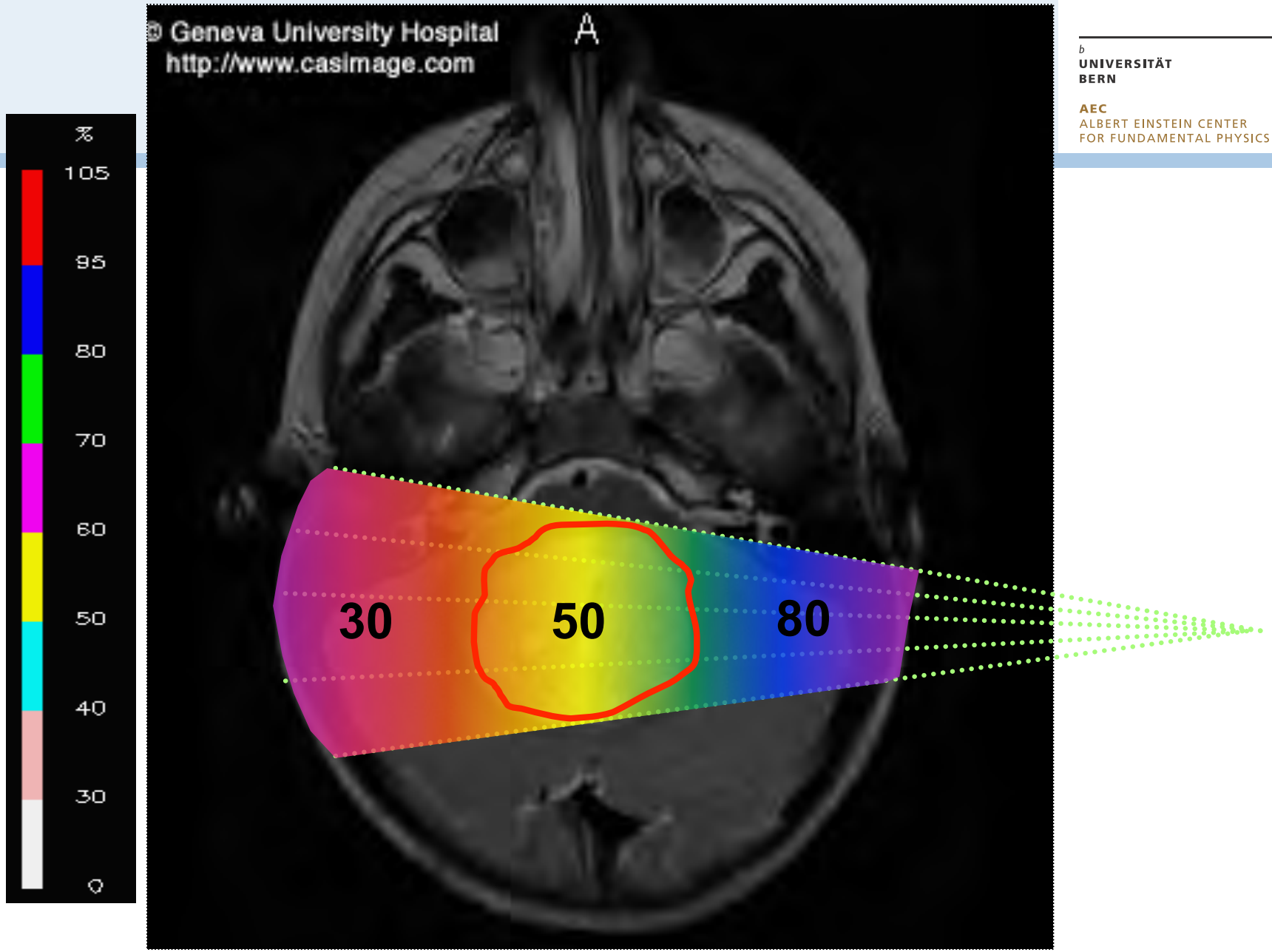


The ideal case… with ideal radiation !!!

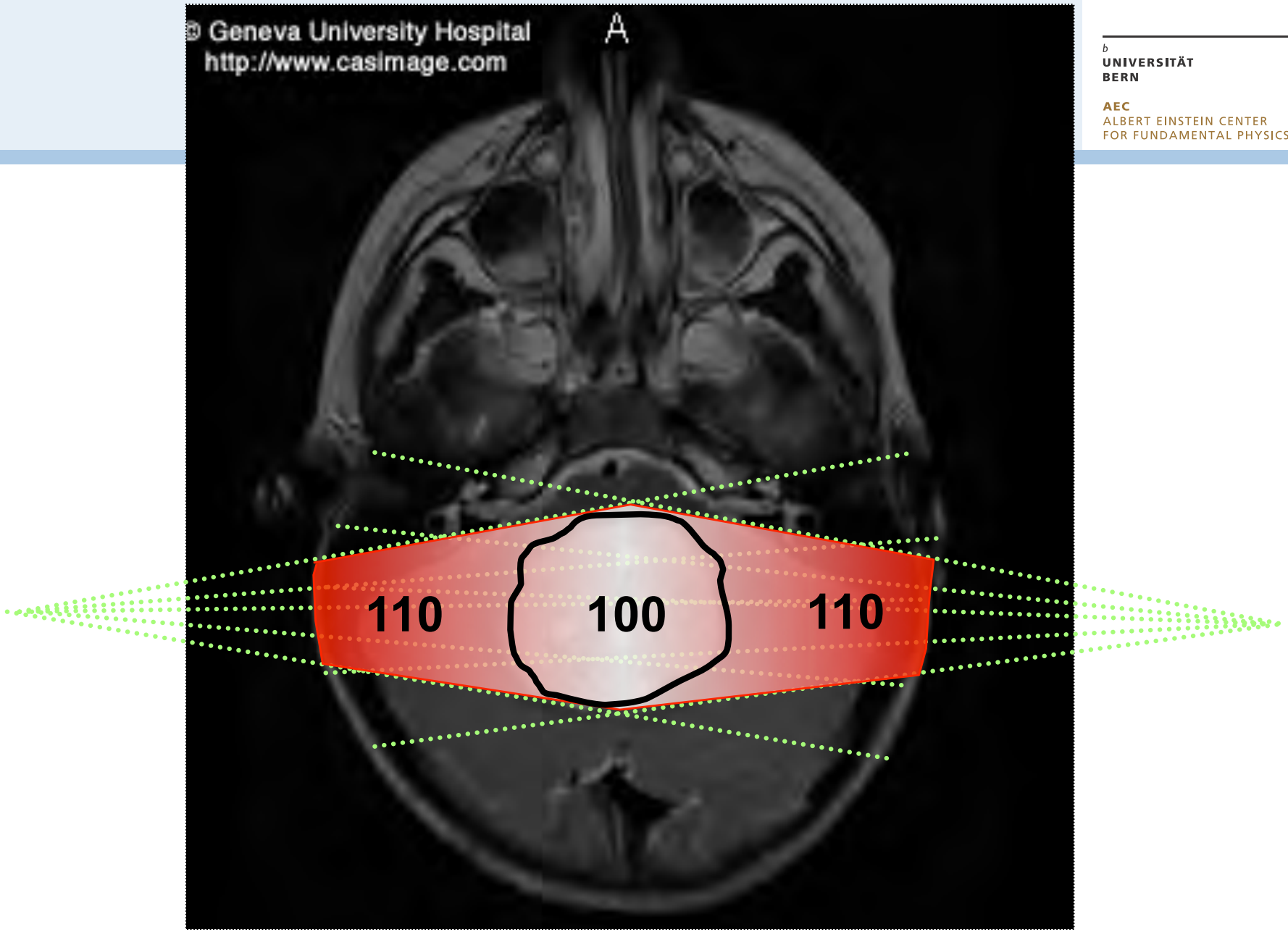


Conventional 3D conformal RT with photons

The real case !



Conventional 3D conformal RT with photons



Conventional 3D conformal RT with photons

Intensity Modulated Radiation Therapy (IMRT)

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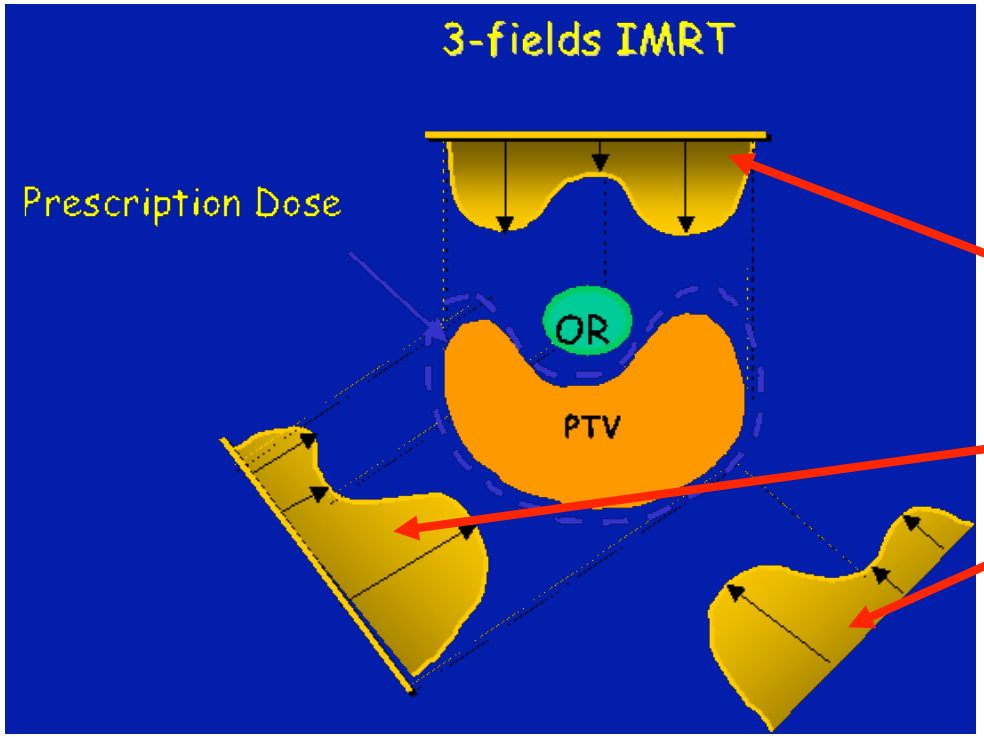
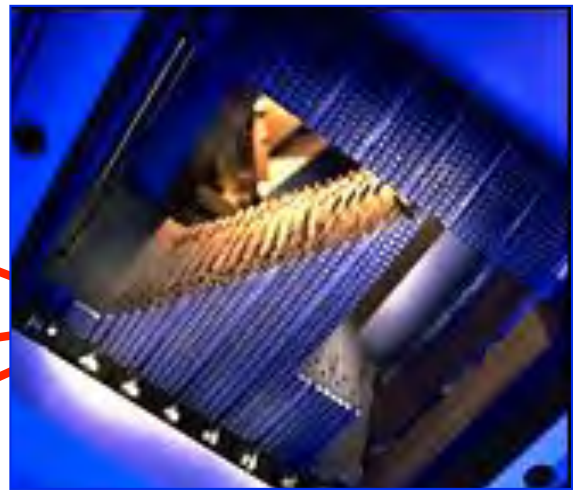
- Photons: non-optimal depth-dose distribution
- Limit always due to the dose to the healthy tissues (OAR in particular)
  ➔ Several beams from many directions and modulated intensity





The multi leaf collimator moves during irradiation

- It is possible to obtain concave dose volumes
- IMRT is time consuming and is used for selected cases

Tomotherapy

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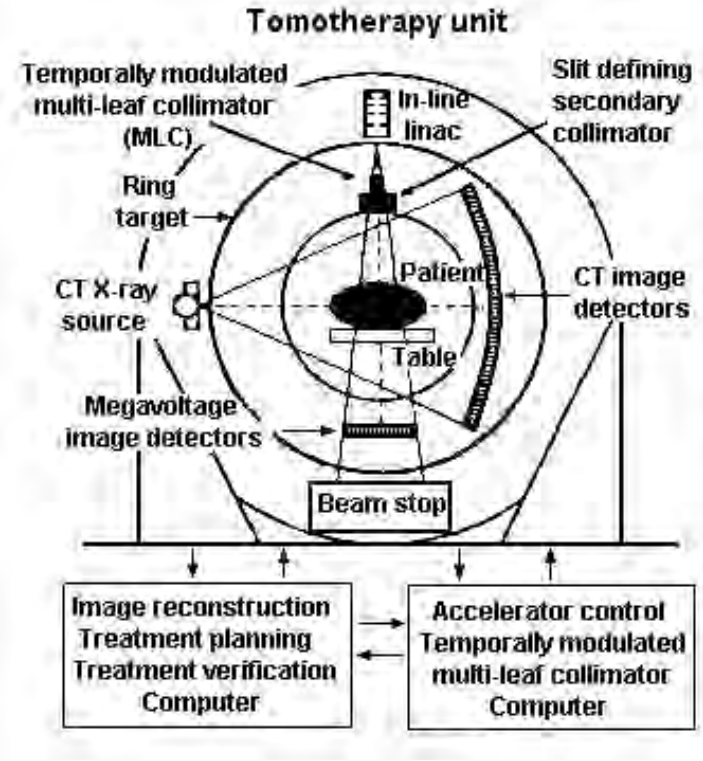

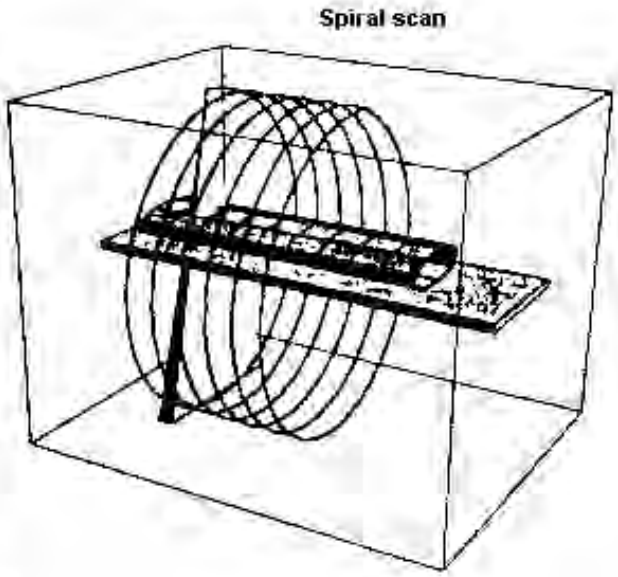

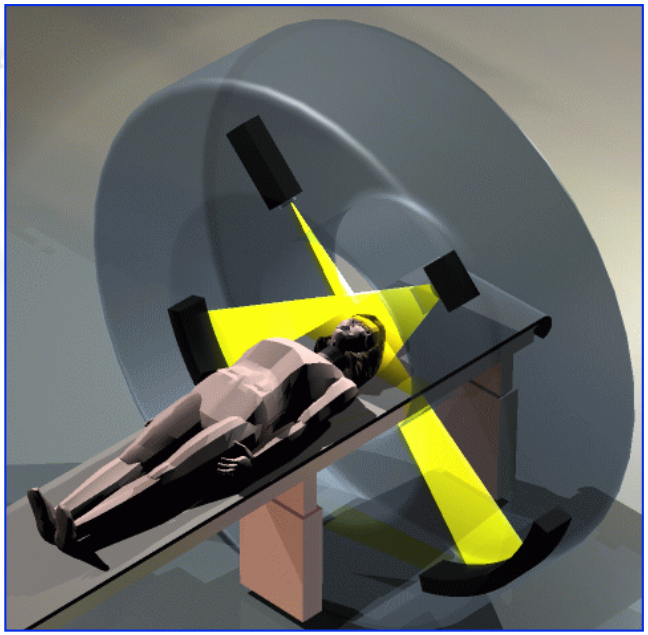

- The accelerator rotates and the patient is moved (spiral pattern) during irradiation
- The intensity is modulated through the use of a multi-leaf collimator
- CT imaging is integrated in the apparatus

Can we do better ?

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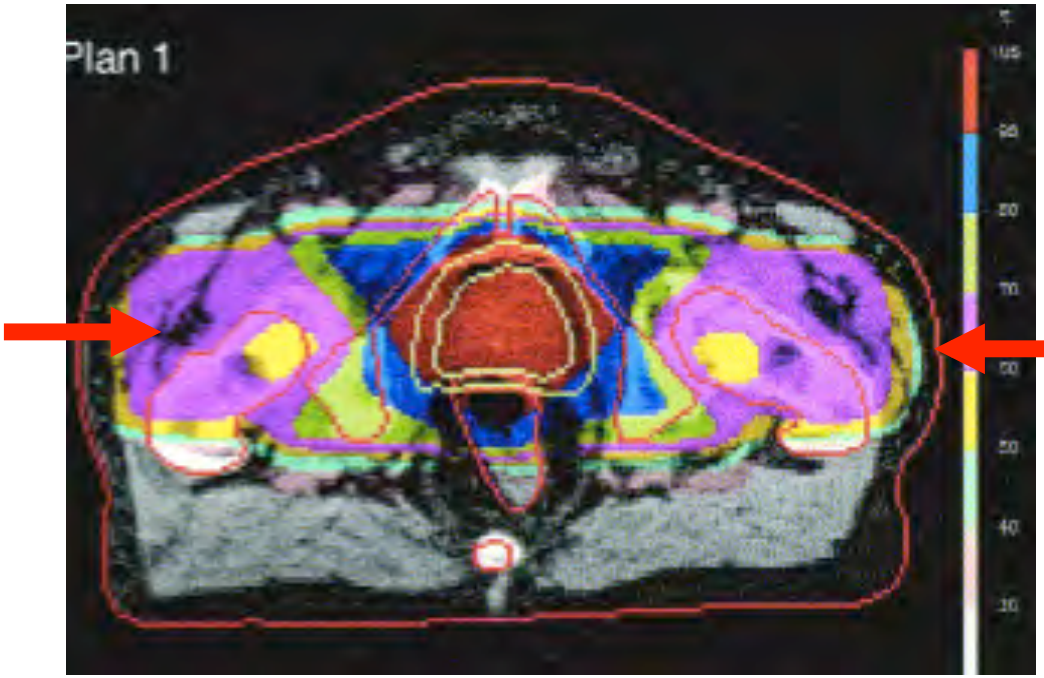
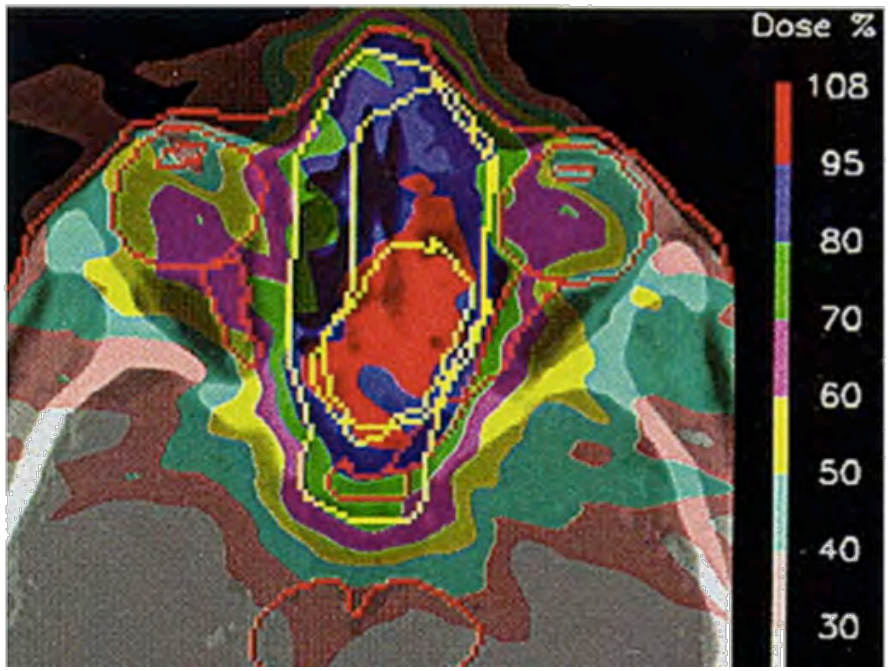
2 X-ray beams



9 X-ray beams (IMRT)



Question for physicists:

Are there better radiations to attack the tumor and spare at best the healthy tissues?

Answer : BEAMS OF CHARGED HADRONS

Hadrontherapy: basic physical and radiobiological concepts

The basic concept of hadrontherapy

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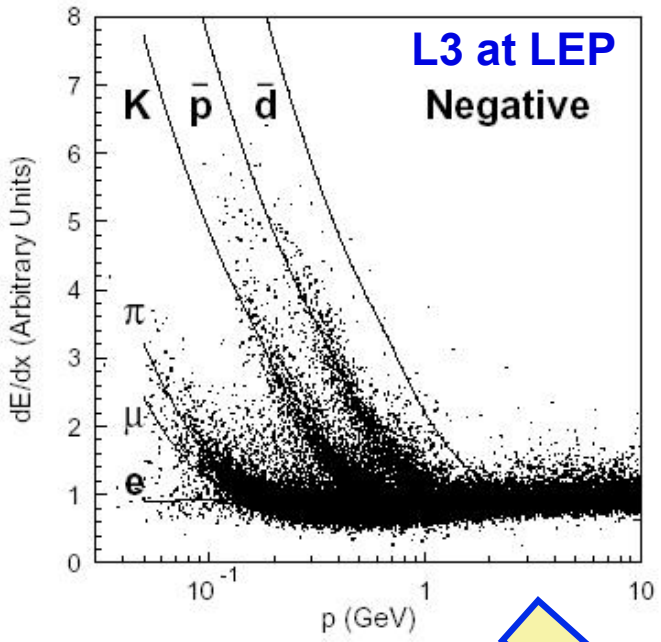
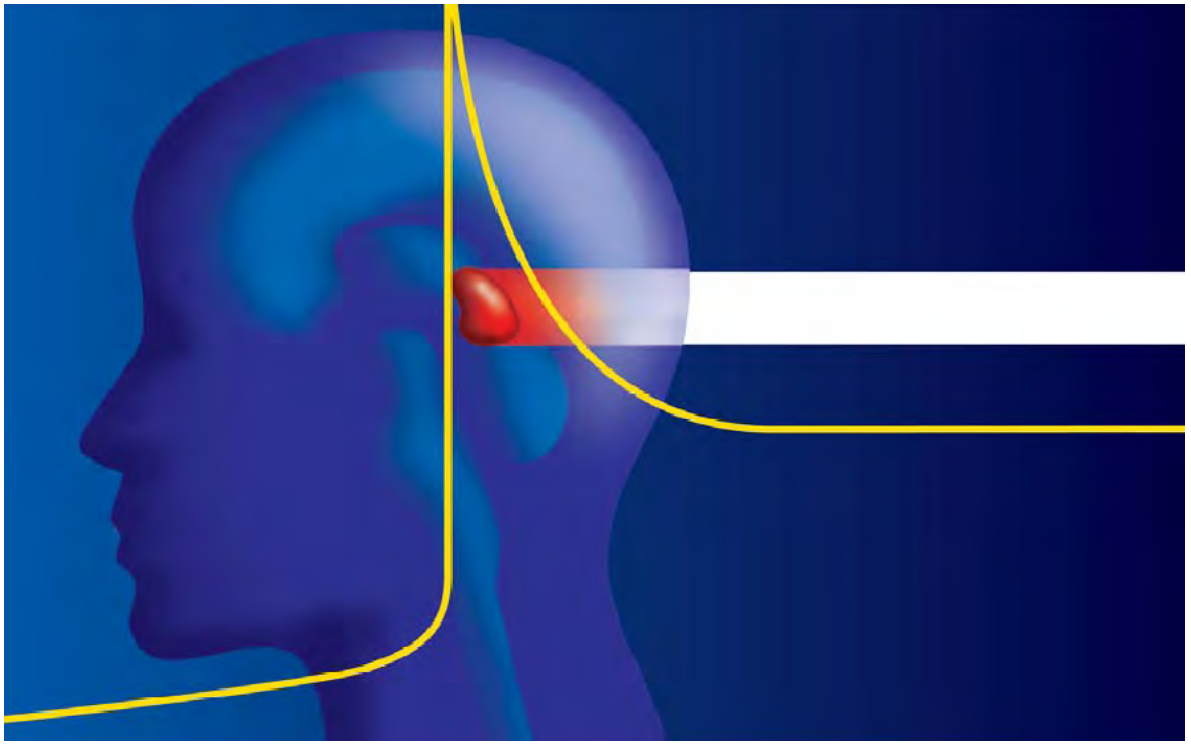
Fundamental physics

Particle identification





Medical applications

Cancer hadrontherapy

Interactions of heavy charged particles with matter : the Bethe-Block formula

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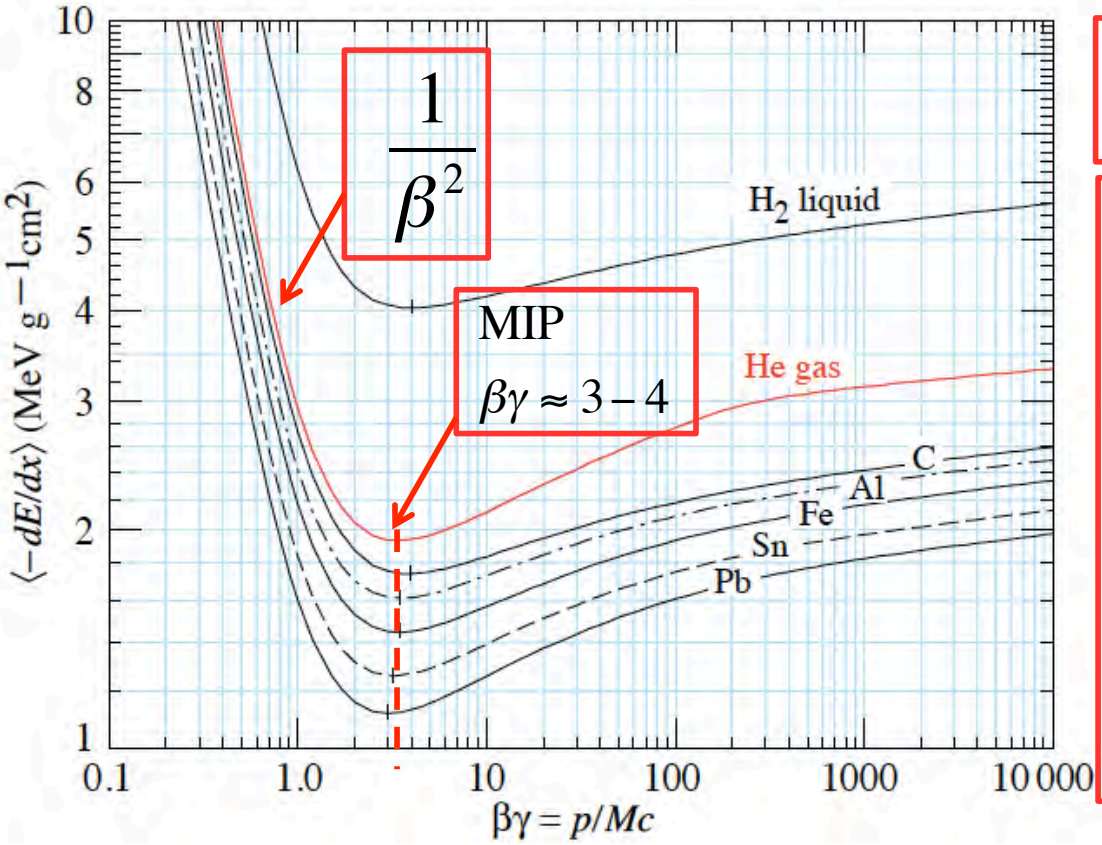
$$\frac{1}{\rho}\frac{dE}{dx} \approx \left(0.307\ \text{MeV g}^{-1}\text{cm}^2\right) \cdot \frac{Z_{medium}}{A_{medium}} \cdot \frac{Z^2}{\beta^2}\left\{\log\left[\frac{2m_0c^2 \cdot \beta^2\gamma^2}{I}\right] - \beta^2\right\}$$



$$\vec{\beta} = \frac{\vec{p}}{E} \quad \gamma = \frac{E}{M} \quad \vec{\beta\gamma} = \frac{\vec{p}}{M}$$

Example: proton MIP in carbon

$\frac{Z_m}{A_m} = 0.5$

$Z = 1$

$\beta\gamma = \frac{p}{M} = 4 \rightarrow \beta \approx 1$

$I \approx 12 \cdot Z$ eV

$$\frac{1}{\rho}\frac{dE}{dx} = 0.3 \cdot 0.5 \cdot \left(\ln\frac{2 \cdot 511000\ \text{eV} \cdot 4^2}{12 \cdot 6\ \text{eV}} - 1^2\right)\frac{\text{MeVcm}^2}{g} =$$

$$= 0.3 \cdot 0.5 \cdot 11.3\frac{\text{MeVcm}^2}{g} = 1.7\frac{\text{MeVcm}^2}{g}$$

The Bragg peak

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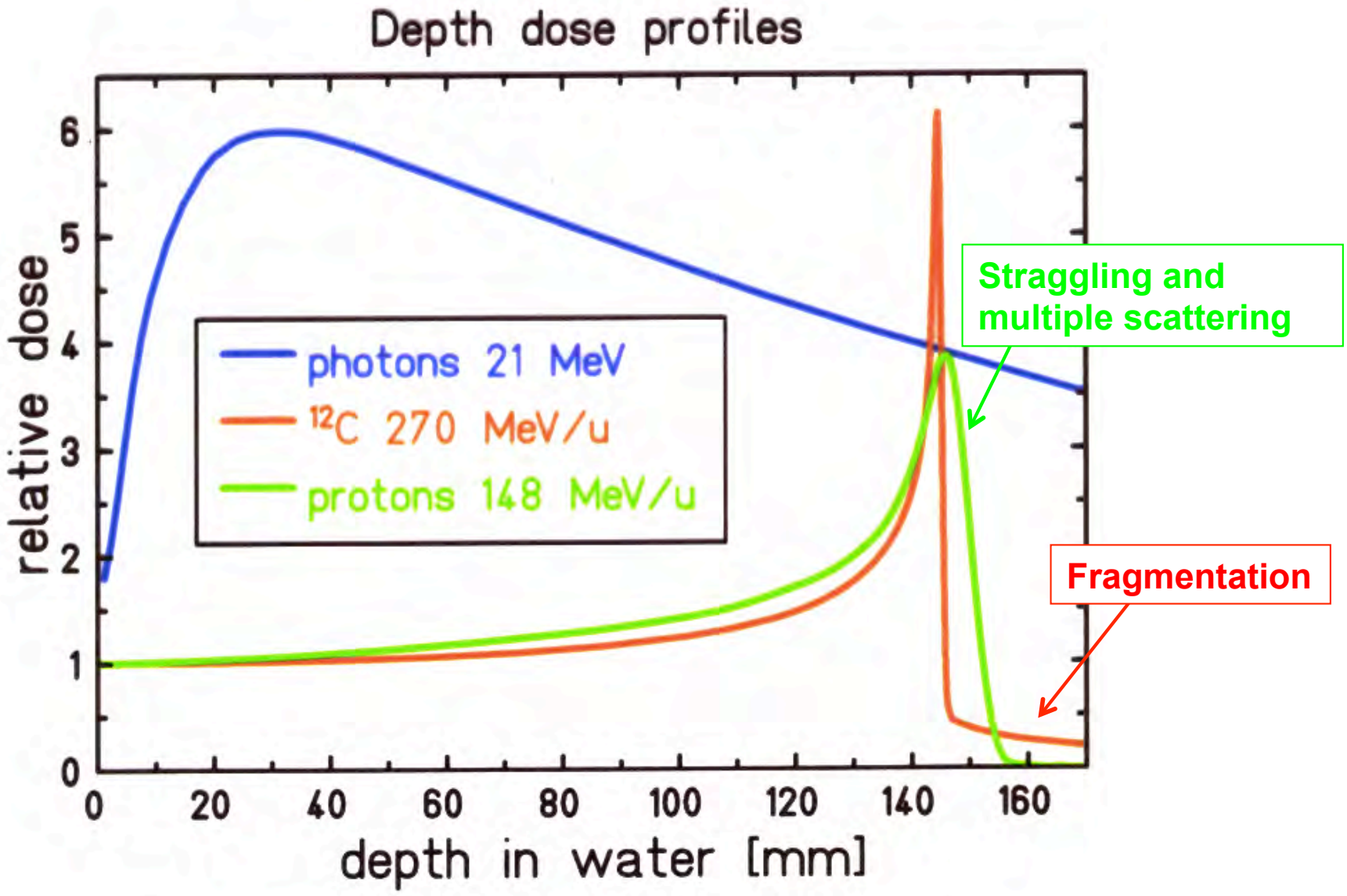

Single beam comparison

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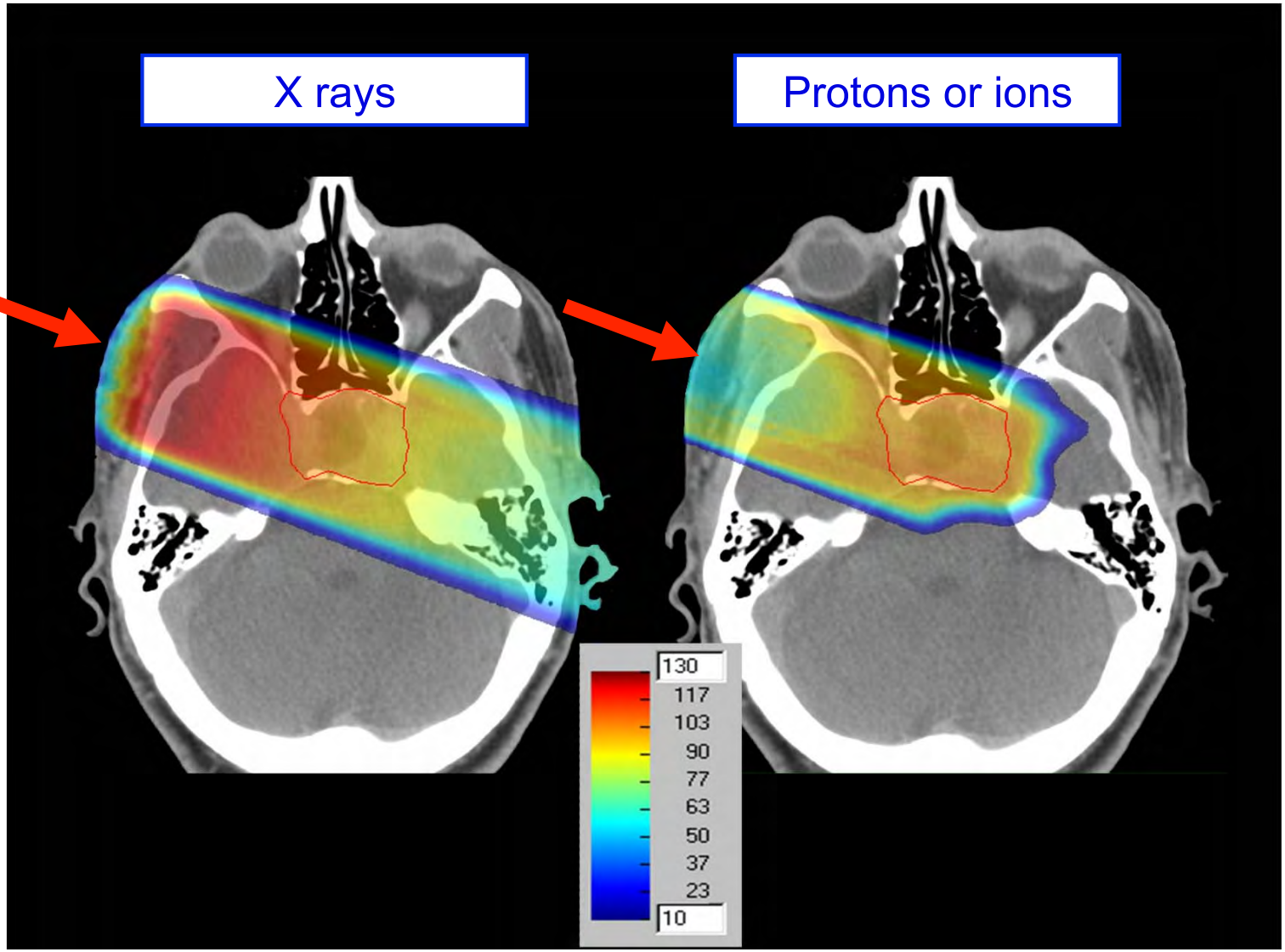

IMRT and protons

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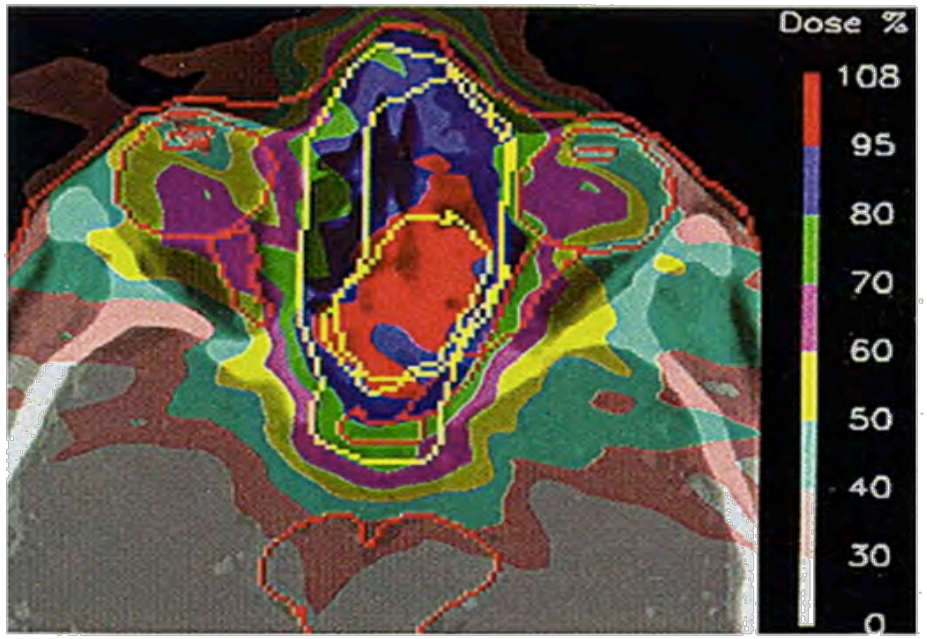
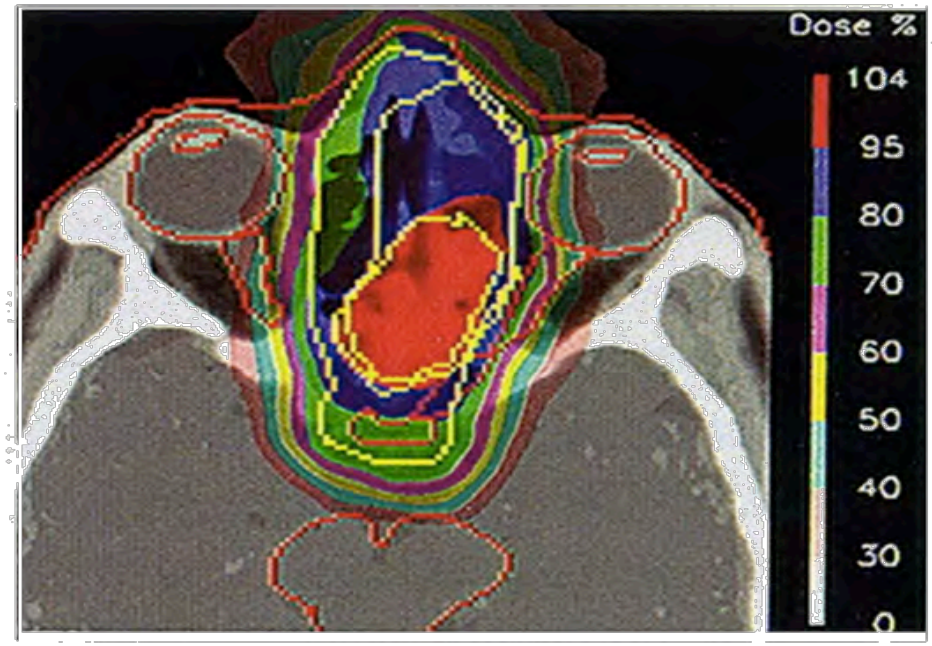
Tumour between the eyes

9 X ray beams



1 proton beam



Bob Wilson
and the birth of hadrontherapy

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Robert Rathbun Wilson
(1914 – 2000)

in Los Alamos during the
Manhattan Project (left)
and at CERN in 1996 (right)

«At Los Alamos, we had been working on one thing, and that was to kill people. When that became crystallized in my mind by the use of the atomic bomb at Hiroshima, it was a temptation, to salvage what was left of my conscience, I suppose, and think about saving people instead of killing them. Because one could hurt people with protons, one could probably help them too.»

Bob Wilson

A very interesting and still actual paper

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Radiological Use of Fast Protons

ROBERT R. WILSON
Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short penetration in tissue of protons, deuterons, and alpha particles from present accelerators. Higher-energy machines are now under construction, however, and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest. The object of this paper is to acquaint medical and biological workers with some of the physical properties and possibilities of such rays.

To be as simple as possible, let us consider only high-energy protons: later we can generalize to other particles. The accelerators now being constructed or planned will yield protons of energies above 125 Mev (million electron volts) and perhaps as high as 400 Mev. The range of a 125 Mev proton in tissue is 12 cm., while that of a 200 Mev proton is 27 cm. It is clear that such protons can penetrate to any part of the body.

The proton proceeds through the tissue in very nearly a straight line, and the tissue is ionized at the expense of the energy of the proton until the proton is stopped. The dosage is proportional to the ionization per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate intensely a strictly localized region within the body, with but little skin dose. It will be easy to produce well collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well defined small volumes within the body will soon be feasible.

Let us examine the properties of fast protons somewhat more quantitatively. Perhaps the most important biological quantity is the specific ionization, or number of ions per centimeter of track. This quantity is not difficult to calculate. The results of such calculations are shown in Figure 1, where the range of protons in tissue is plotted for protons of various energies. In the same figure, the specific ionization is plotted as a function of the range in tissue. For purposes of calculation, tissue has been assumed to have the molecular formula (1): $C_{6.6}H_8O_{2.4}N_{0.16}$, and to be of unit density, *i.e.*, 15 per cent protein and 85 per cent water. The calculations can be easily extended to other materials and densities.[2] The accuracy is perhaps 5 per cent. However, exact values for various tissues can be quickly measured as soon as the fast protons are available.

Figure 1 shows, for example, that if we want to expose a region located 10 cm. be-

[1] Accepted for publication in July 1946.
[2] The range of a proton in air in meters is given by the convenient formula $R = (E/9.29)^{1.8}$ where the energy is expressed in Mev. The range in tissue is 1.11×10^{-3} times the range in air. The stopping power of other substances may be found in Livingston and Bethe: Rev. Mod. Physics 9: 246, 1937. The physical calculations of this paper will be submitted to the *Physical Review* for publication.

- Bob Wilson was student of Lawrence in Berkley
- Studied the shielding for the new cyclotron ➔"re-discovered" the Bragg peak
- Interdisciplinary environment = new ideas!
- 1946: he suggested the use of protons and charged hadrons to better distribute the dose of radiation in cancer therapy
- At that time: no imaging and no powerful enough accelerators … hadrontharpy was just a dream …

R.R. Wilson, Radiology, 47 (1946) **487**

The beginning of hadronthearpy: Berkeley, 1954

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> 1954: first patient treated with the Berkley 340 MeV proton cyclotron

> First clinical trial: irradiation of the pituitary gland in 26 patients with metastatic breast cancer

C.A. Tobias, J.H. Lawrence et al., Cancer Research 18 (1958) 121

The basic figures of hadrontherapy

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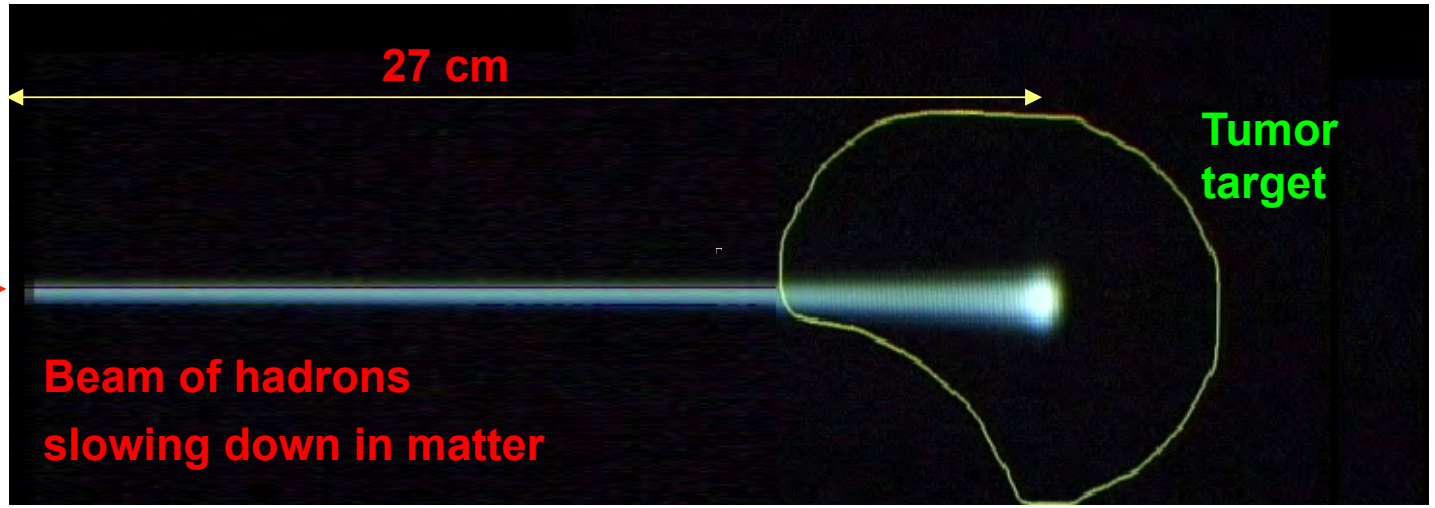
Protons
200 MeV
1 nA

Carbon ions
4800 MeV
0.1 nA



- Bragg peak
  - Better conformity of the dose to the target → Healthy tissue sparing
- Hadrons are charged
  - Can be magnetically driven → Beam scanning for dose distribution
- Heavy ions
  - Higher biological effectiveness → Cure of radio-resistant tumors

Cells and their dimensions

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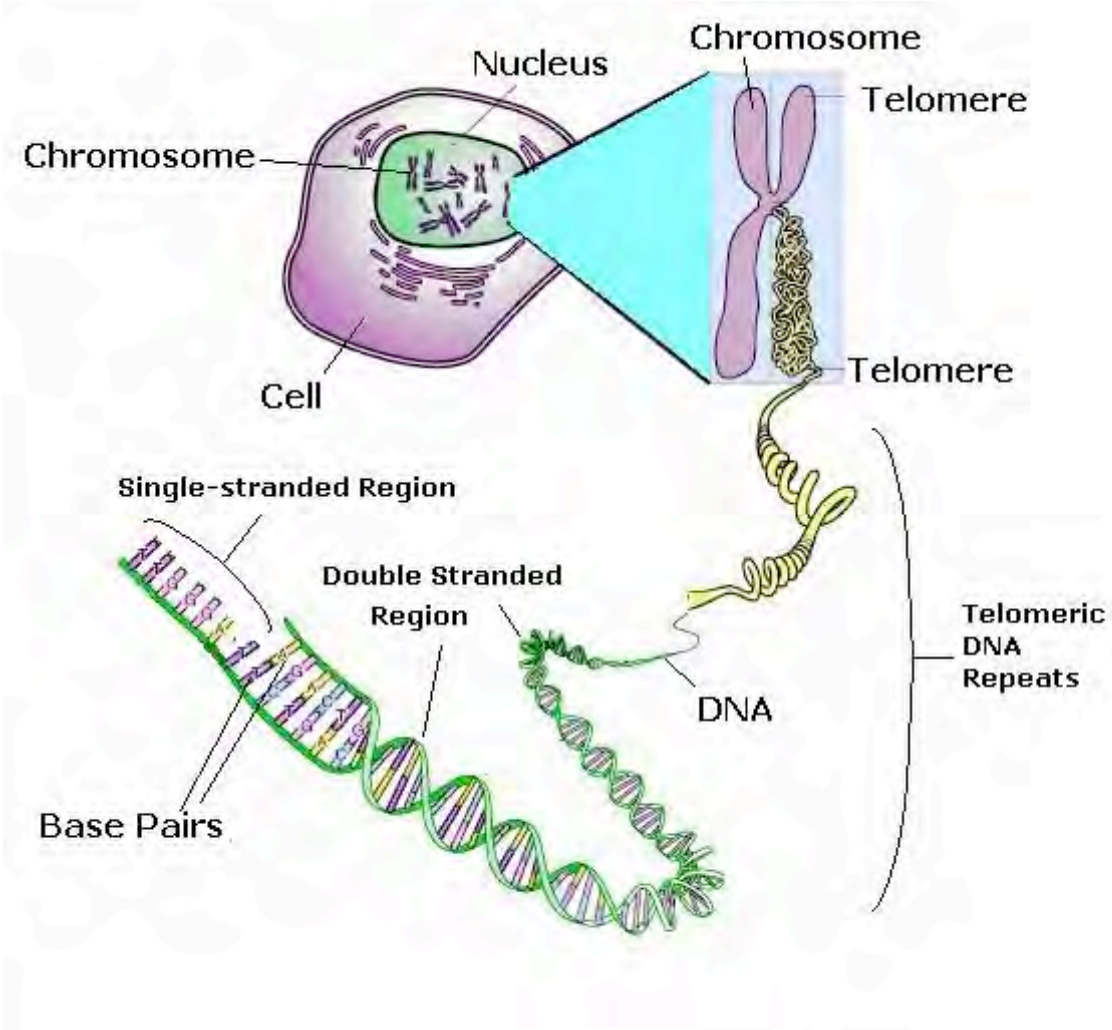

- Cell: 10-100 μm
- Cell nucleus: 3-10 μm
- DNA
  - Pitch and "diameter"": 3.4 nm
  - Total length: 3 m

What is the relation between these quantities and ionization?

Direct and indirect action of radiation

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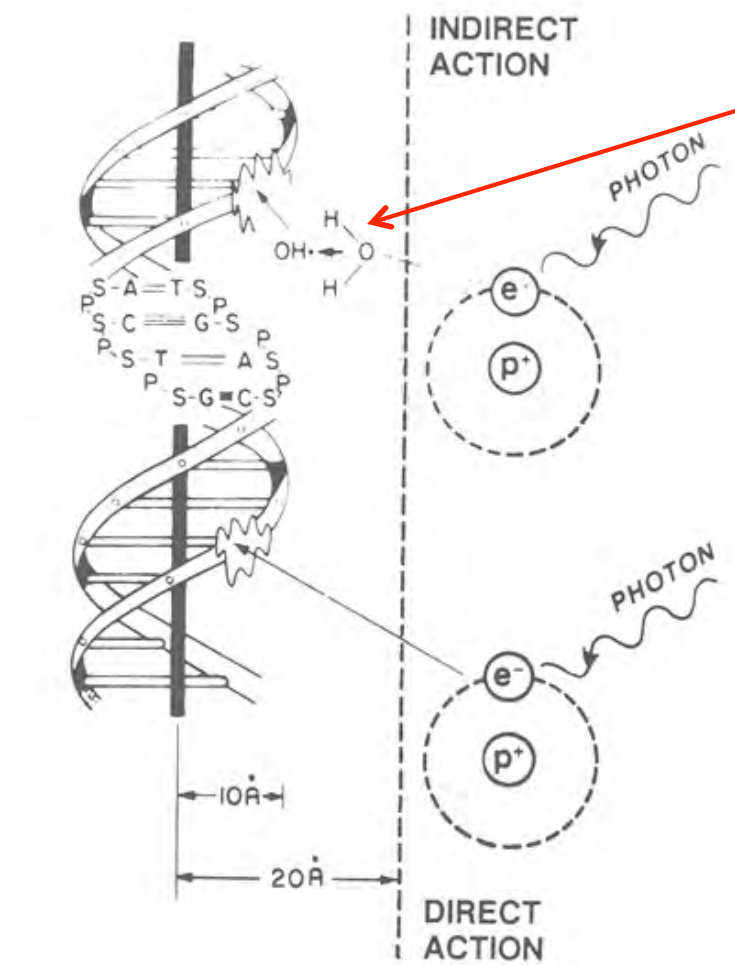
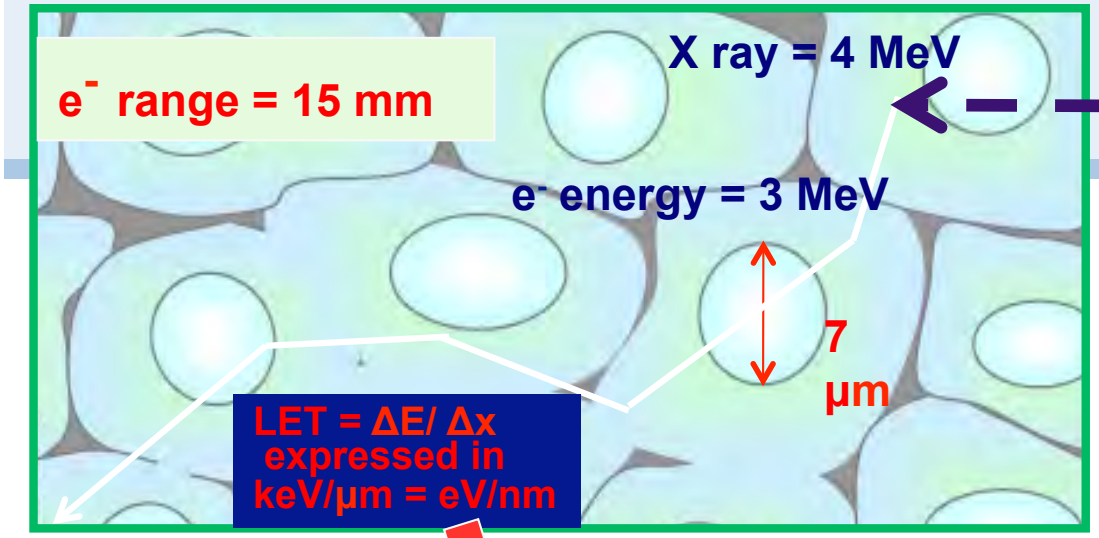
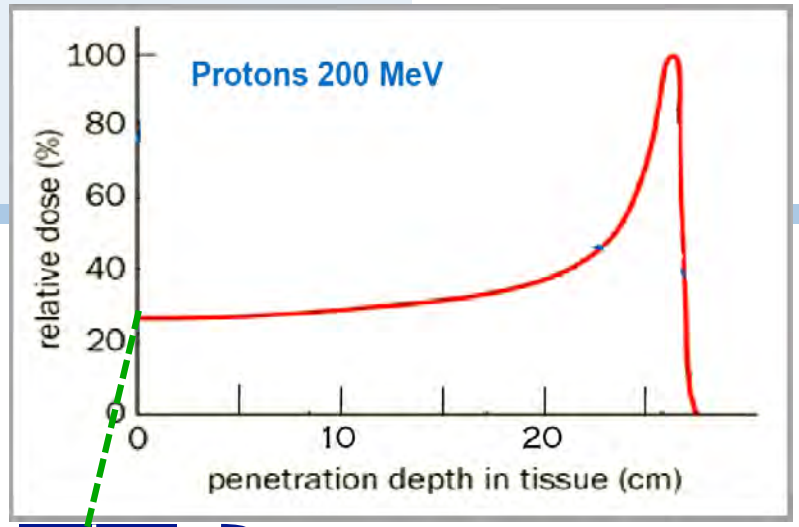


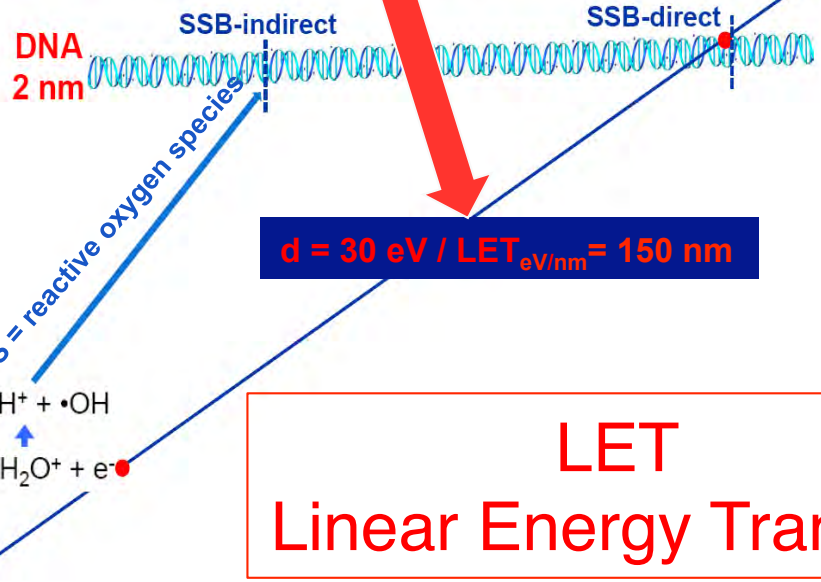
Free radicals

Microscopic distribution of ionizations

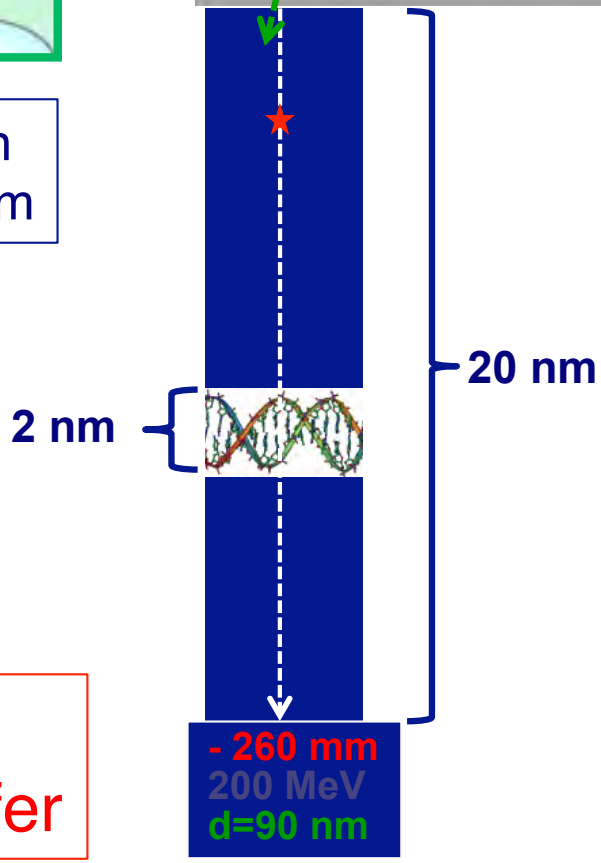




Electron
0.2 eV/nm

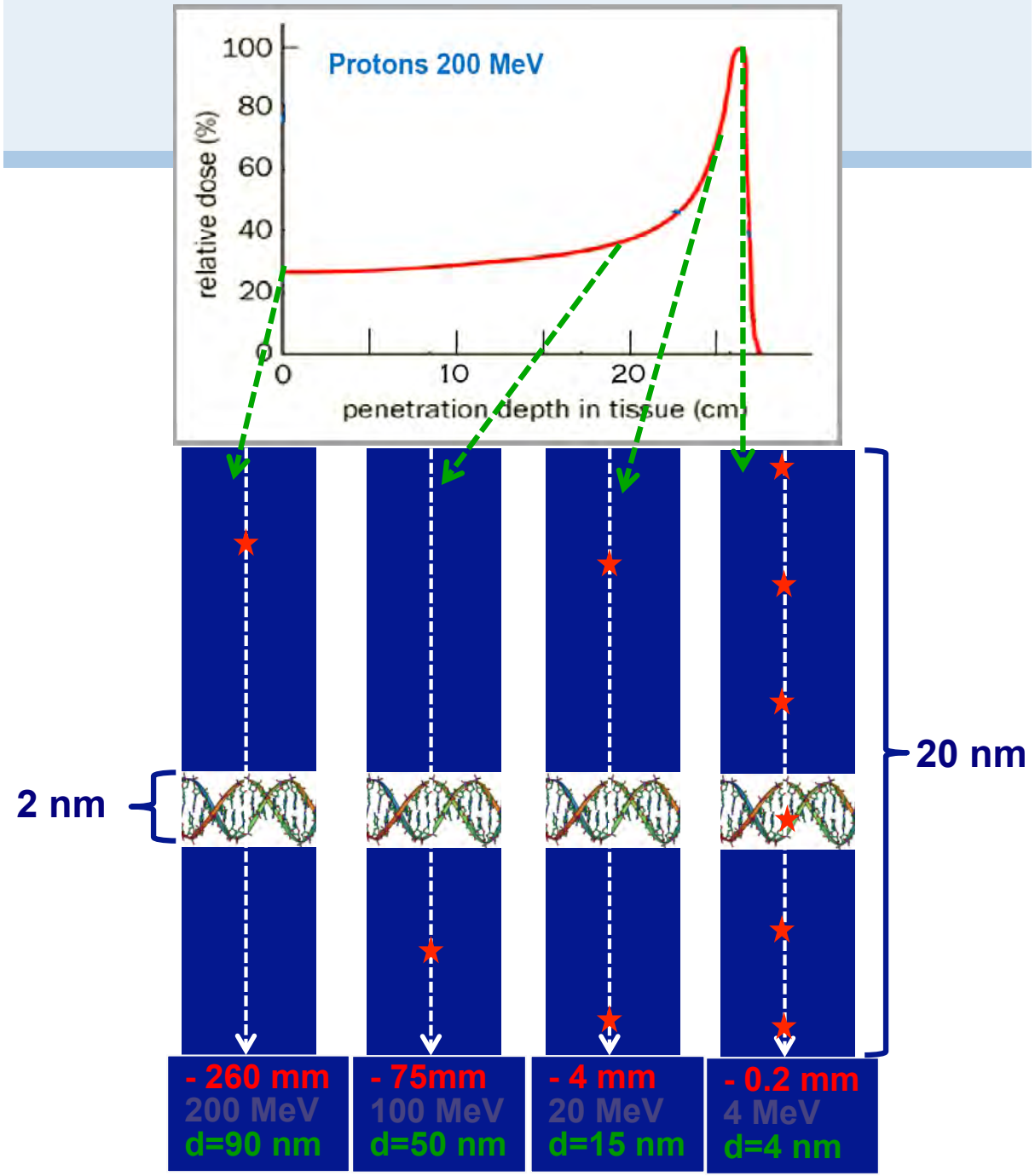


d = 30 eV / $LET_{eV/nm}$ = 150 nm



LET
Linear Energy Transfer

Microscopic distribution of ionizations



Microscopic distribution of ionizations

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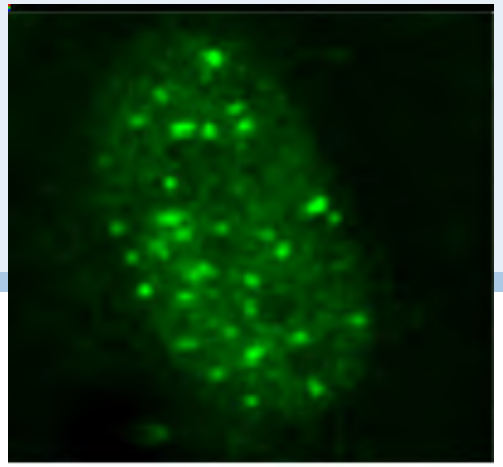
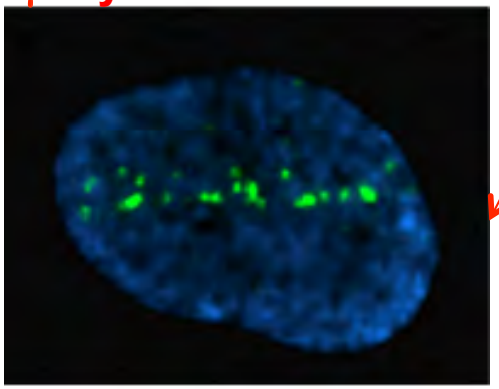
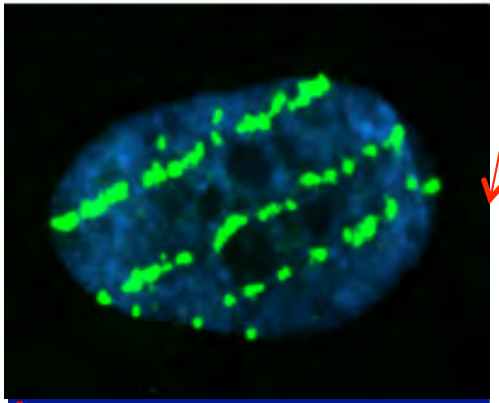


γ-rays

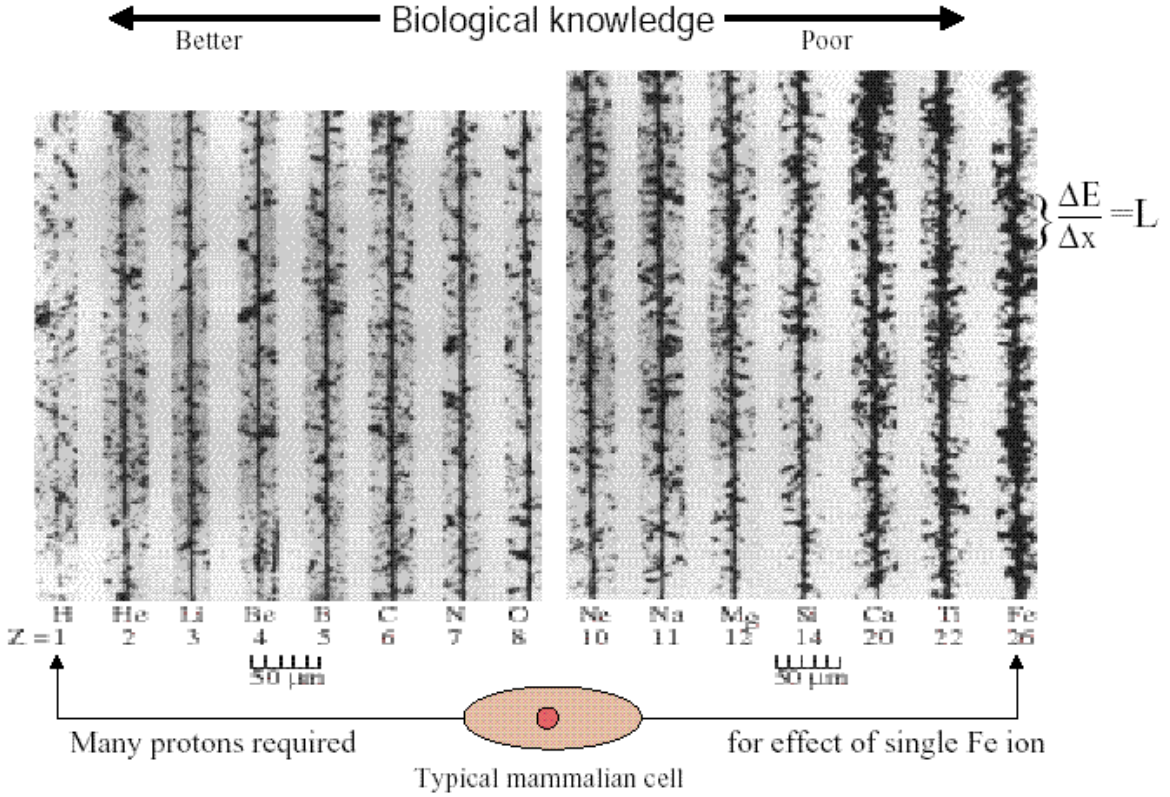


silicon



iron

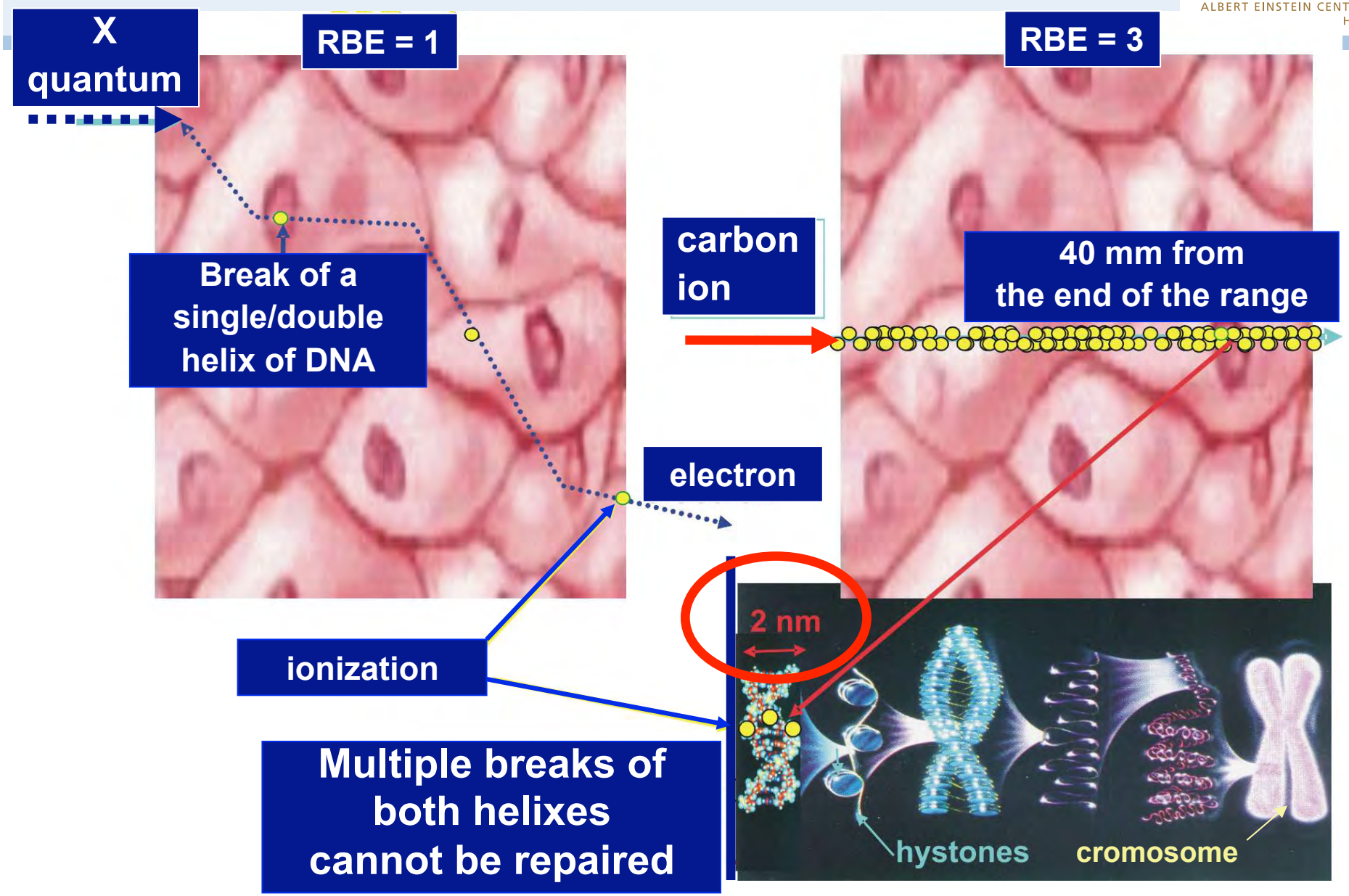
DNA visualized by immuno - fluorescence of γ-H2AX histone in human skin fibroblasts exposed to 2 Gy of ionizing radiation



Cucinotta and Durante, Lancet Oncol. 2006

Nuclear emulsions

Why ions have a large biological effectiveness? What is RBE?



Survival curves

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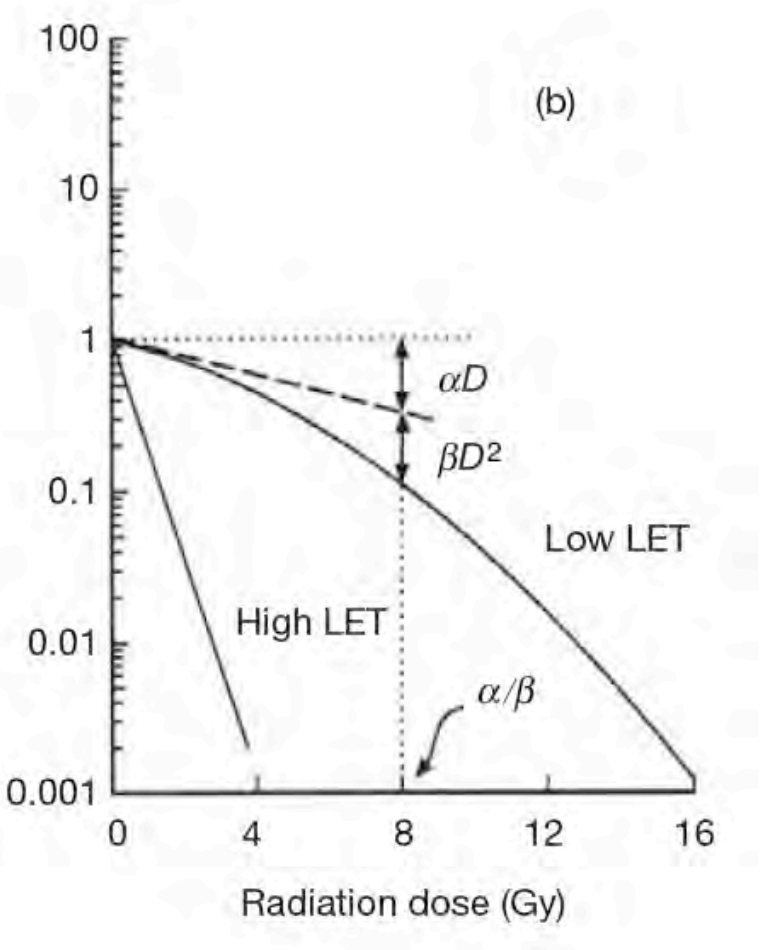

$$S(D) = e^{-\alpha D - \beta D^2}$$

$S(D)$ is the fraction of cells surviving a dose D;
α is a constant describing the initial slope of the cell survival curve;
β is a smaller constant describing the quadratic component of cell killing.

- **Example: α=0.25; β≈0 for a certain radiation. Which is the dose that gives a survival probability of 10^{-9} ? Answer: 80 Gy**

LET and RBE

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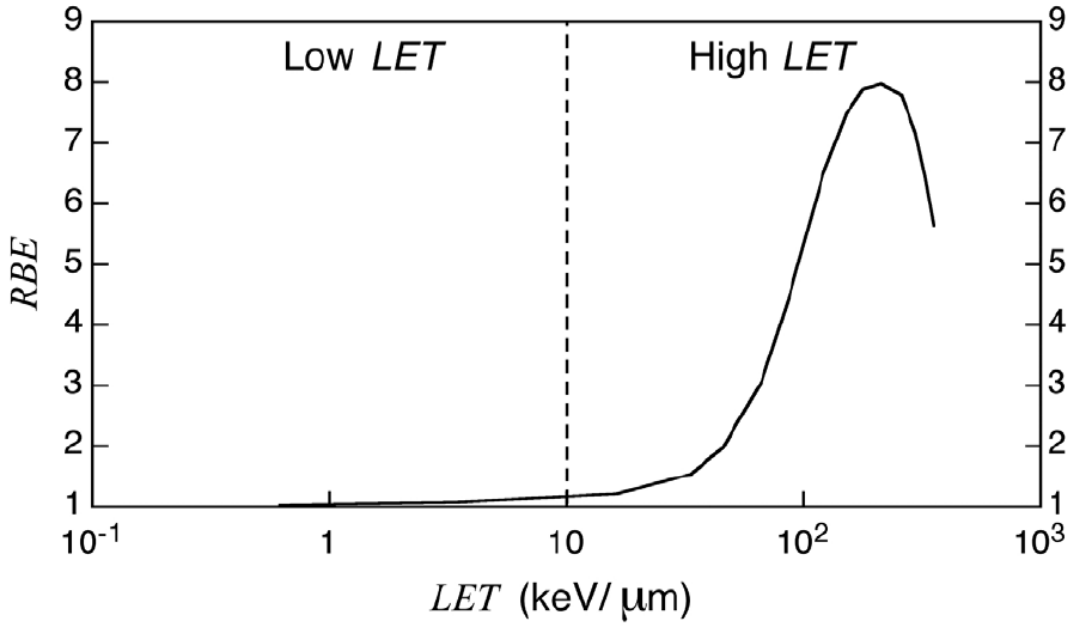

FIG. 14.7. Relative biological effectiveness (RBE) against LET. The vertical dashed line separates the low LET region where RBE ≈ 1 from the high LET region where RBE first rises with LET, reaches a peak of about 8 for LET ≈ 200 keV/μm and then drops with a further

$$\text{RBE} = \frac{\text{Dose from standard radiation to produce a given biological effect}}{\text{Dose from test radiation to produce the same biological effect}}$$

- **RBE – Relative Biological Effectivness with respect to X-rays (RBE =1 by definition)**

The oxigen effect and OER

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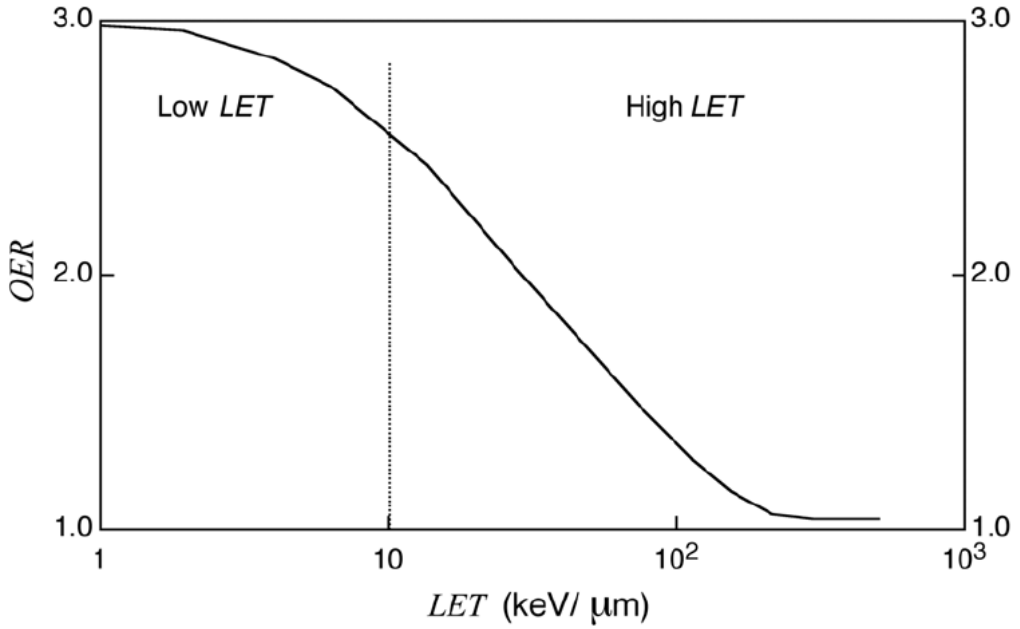

FIG. 14.6. Oxygen enhancement ratio (OER) against LET. The vertical dashed line separates the low LET region where LET <10 μm from the high LET region where LET > 10 μm.

$$\text{OER} = \frac{\text{Dose to produce a given effect without oxygen}}{\text{Dose to produce the same effect with oxygen}}$$

- **OER – Oxygen Enhancement Ratio – Low LET radiations are sensitive to oxygen (formation of free radicals)**

Effect of radiation on tissues

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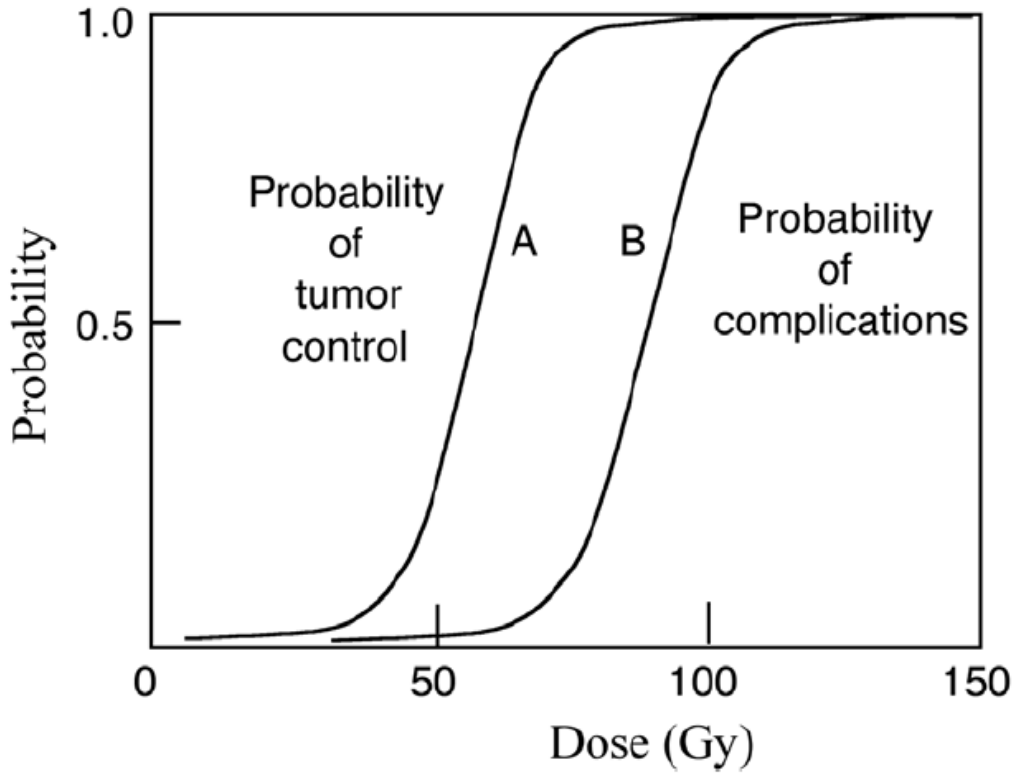

FIG. 14.4. The principle of therapeutic ratio. Curve (A) represents the tumour control probability, curve (B) the probability of complications. The total dose is delivered in 2 Gy fractions.

Sigmoids → small increase of dose may correspond to large increase of control!

Tools and techniques in hadrontherapy

The Loma Linda University Medical Center (LLUMC)

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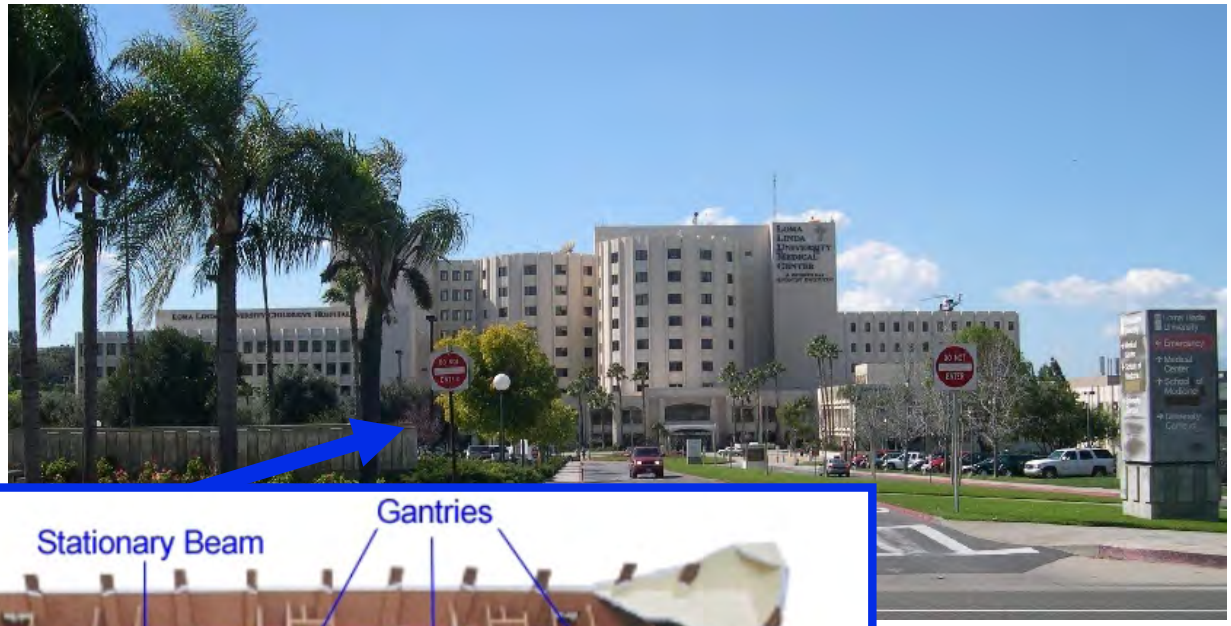
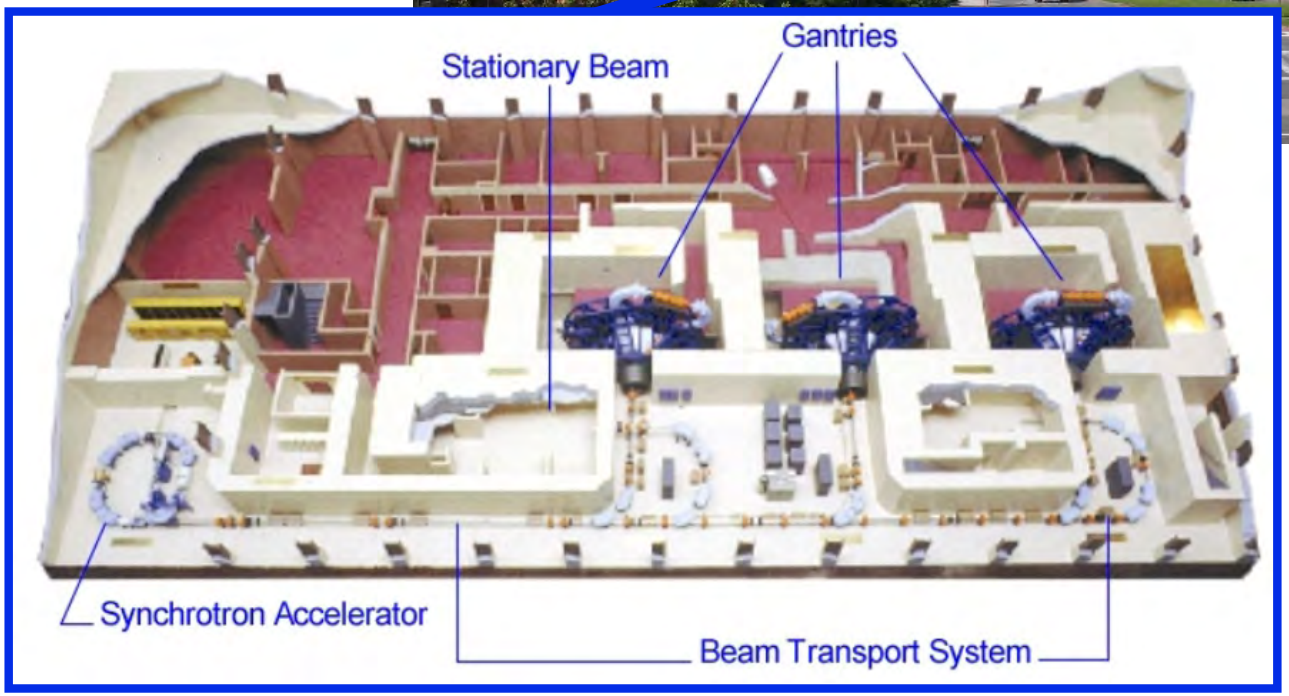
- Near Los Angeles
- First hospital-based proton-therapy centre, built in 1993
- ~160/sessions a day
- ~1000 patients/year





Proton-therapy: two main kind of treatments

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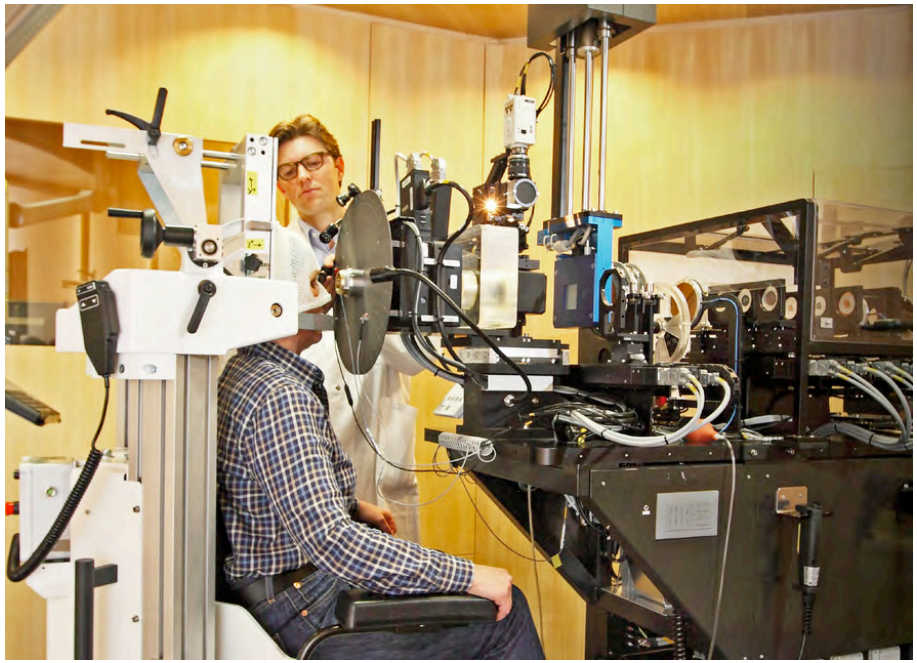
- Treatment of eye-melanoma
  - Shallow tumor
  - About 65 MeV of energy are needed
  - Relatively small cyclotrons
  - Very high local control
  - Many centers in operation
    - ex. Catania, Nice, PSI



OPTIS 2 at PSI

- Treatment of deep seated tumors
  - Energies up to about 250 MeV are used
  - Much larger infrastructure

What do we need to treat deep seated tumors with protons?

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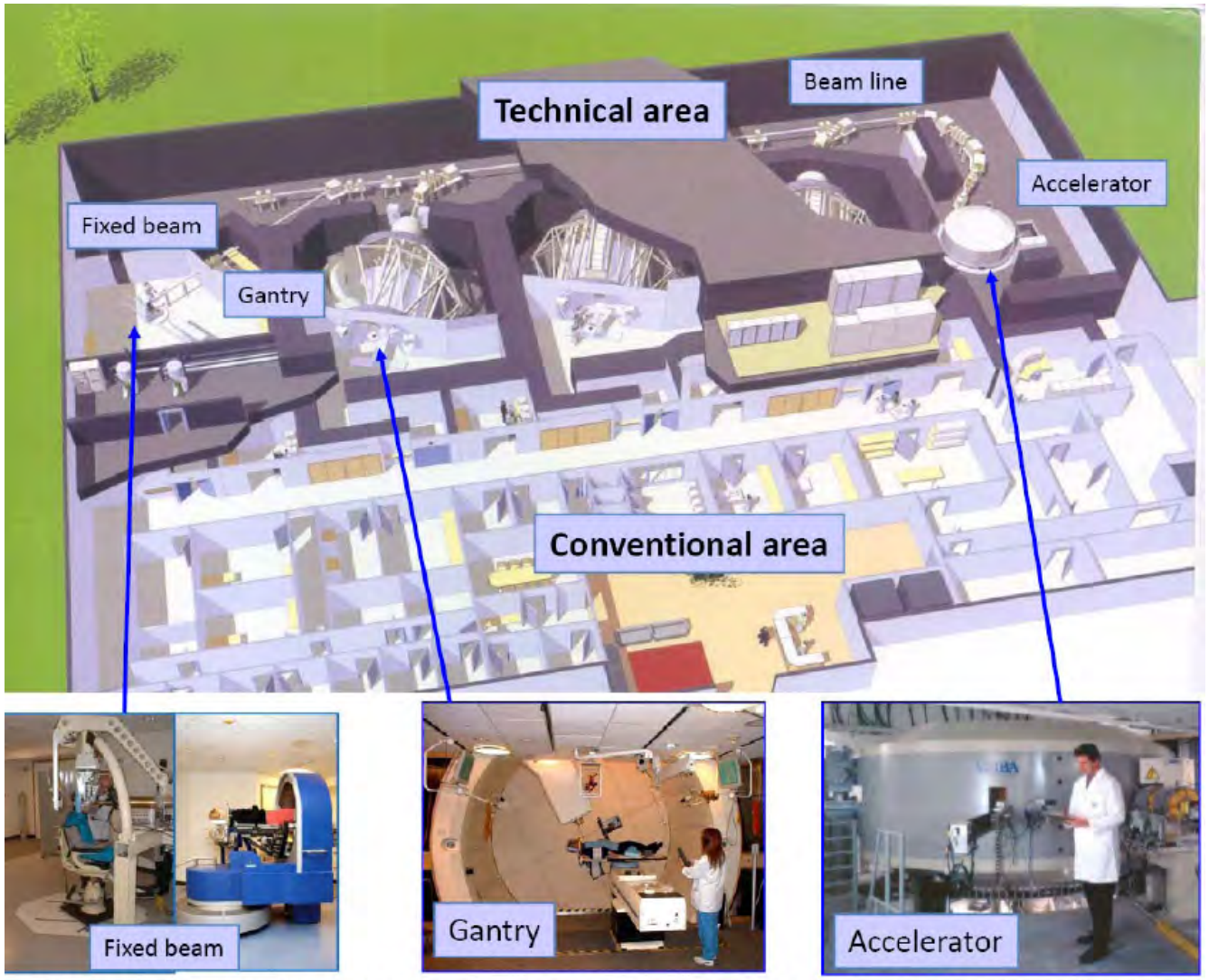
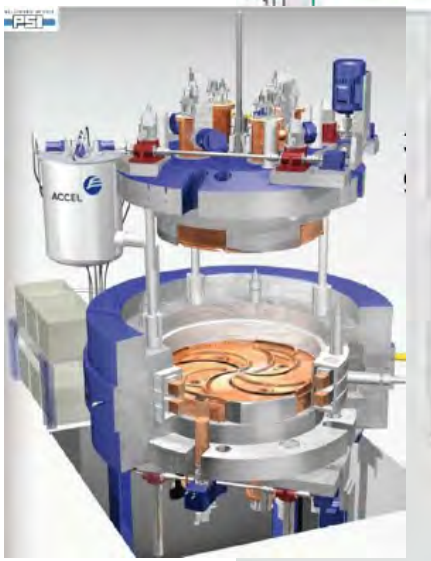
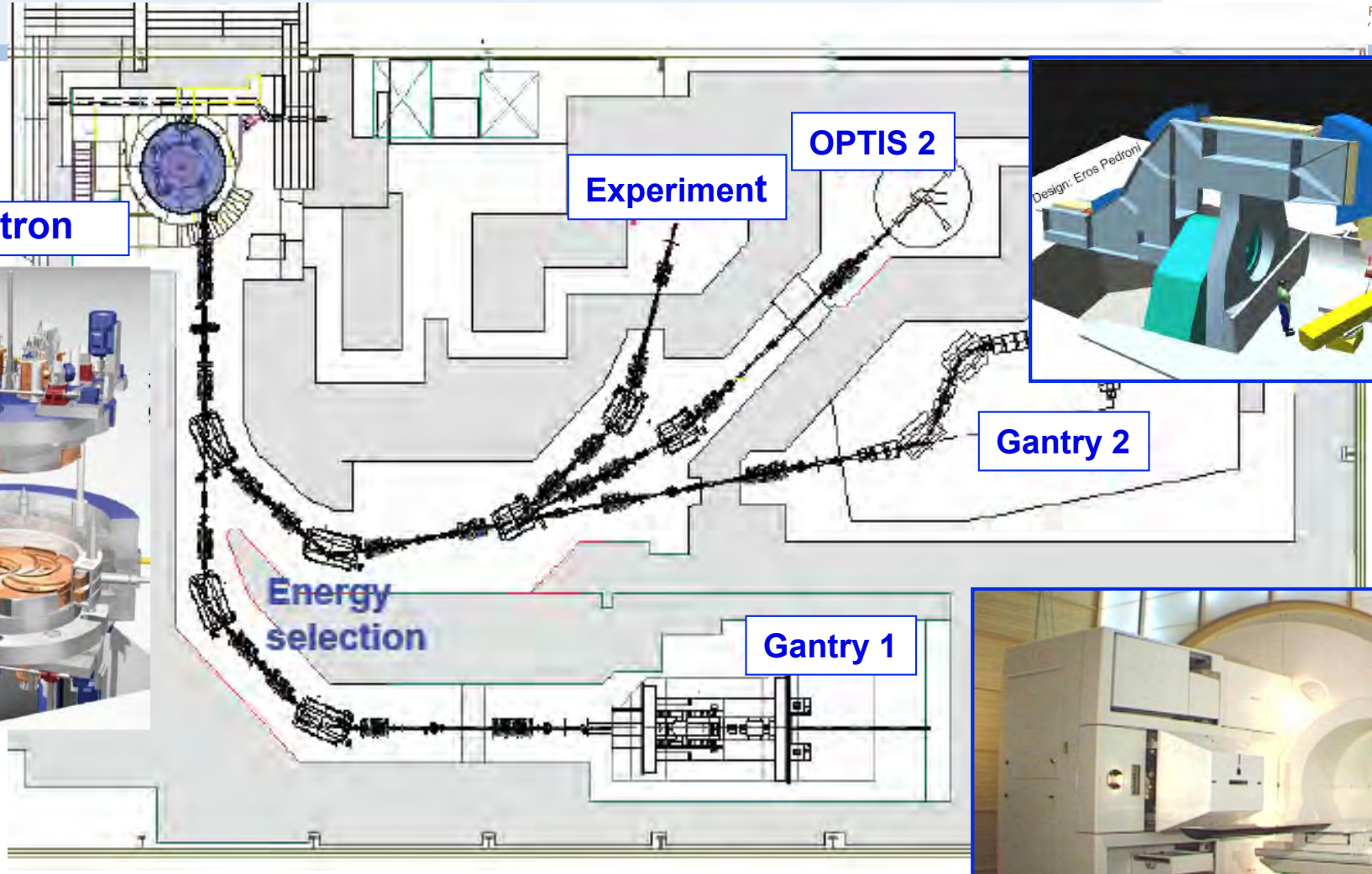


General scheme of a proton-therapy centre. The example reported here is based on the system commercialized by the company IBA (Belgium).

Proton therapy in Switzerland: PROSCAN at PSI





- Superconducting 250 MeV proton cyclotron
- New proton gantry for advanced scanning

Carbon ions: HIT in Heidelberg

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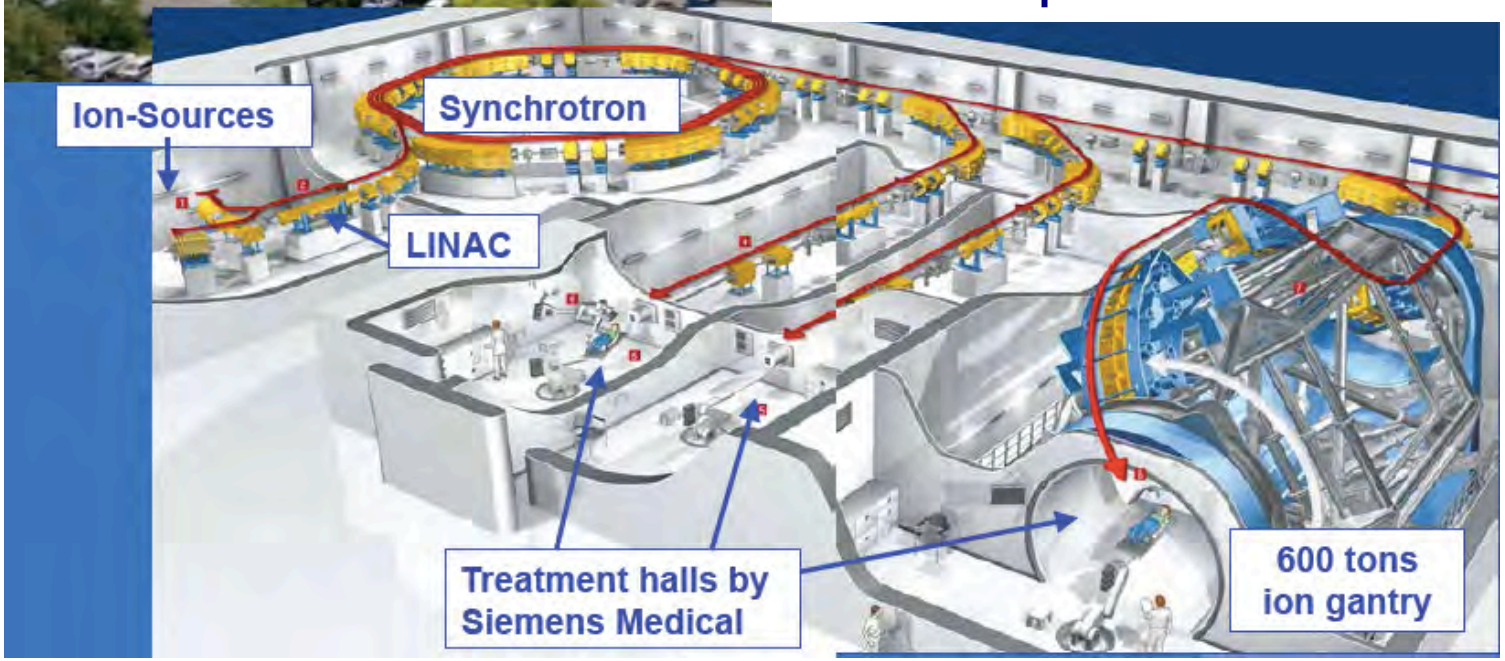
- 25 m diameter synchrotron
- Injectors: Source + RFQ + Linac
- 2 fixed beams + 1 gantry
- First patient in 2009
- 2500 patients treated (end 2014)



The Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia

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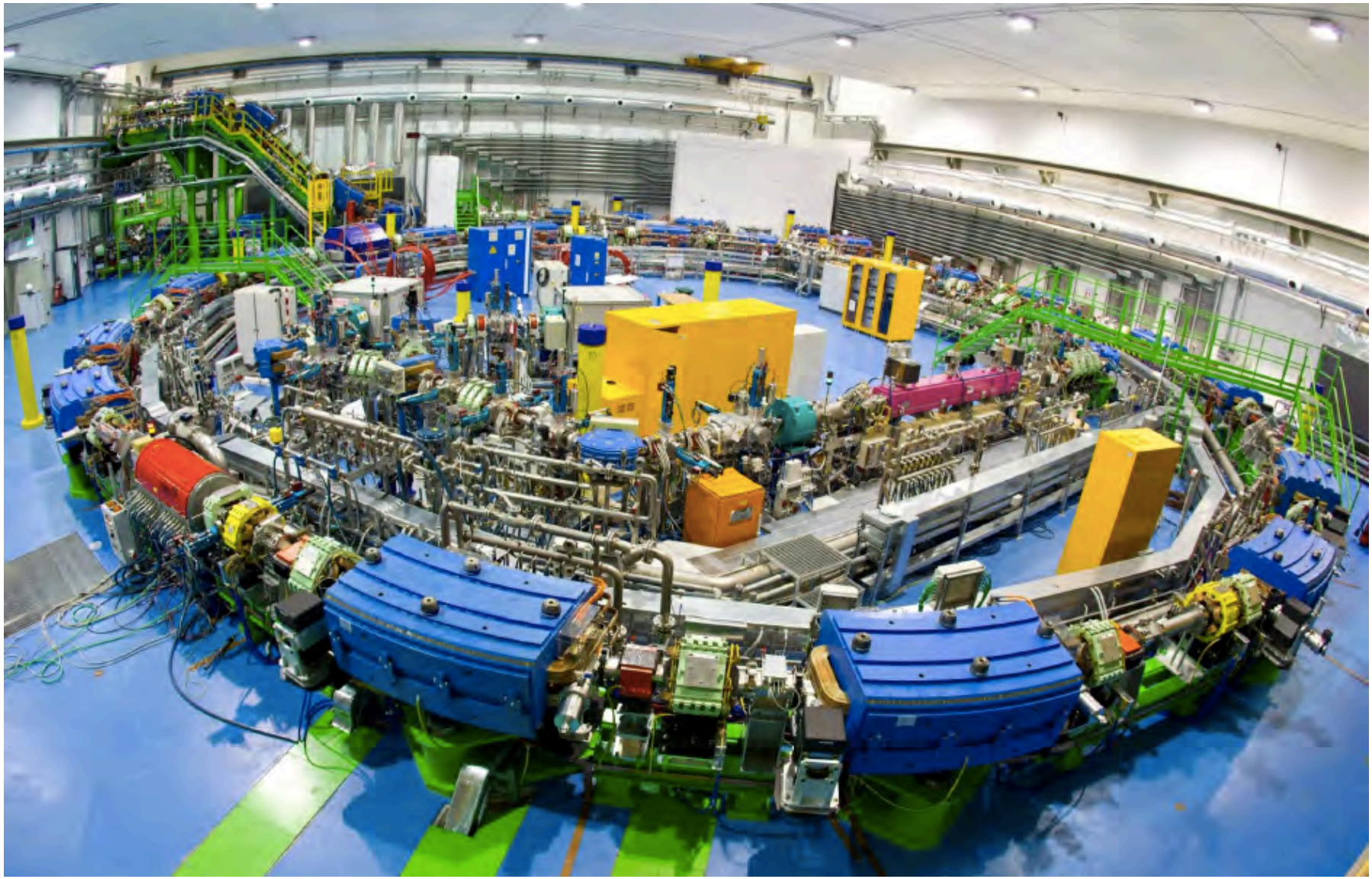

The Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia

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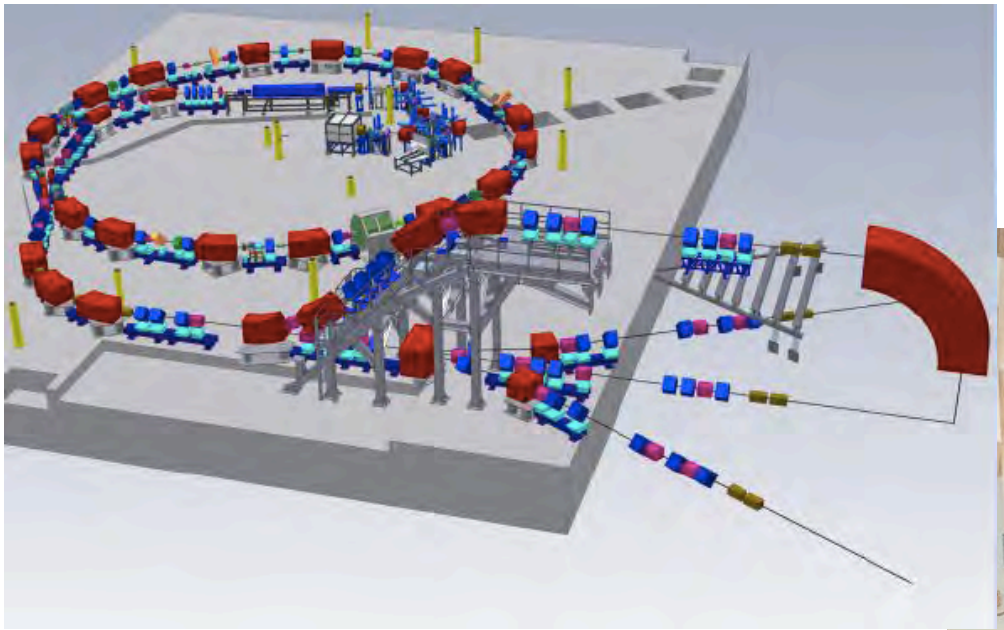

- 25 m diameter synchrotron
- Injectors: Source + RFQ + Linac
- 3 H + 1 V fixed beams
- First patient in 2011 (p) 2012 (C)
- 700 patients treated (end 2015)

Accelerators for hadrontherapy

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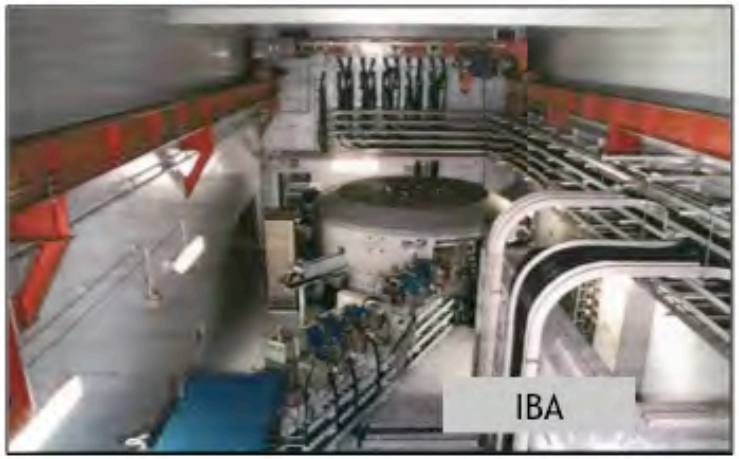
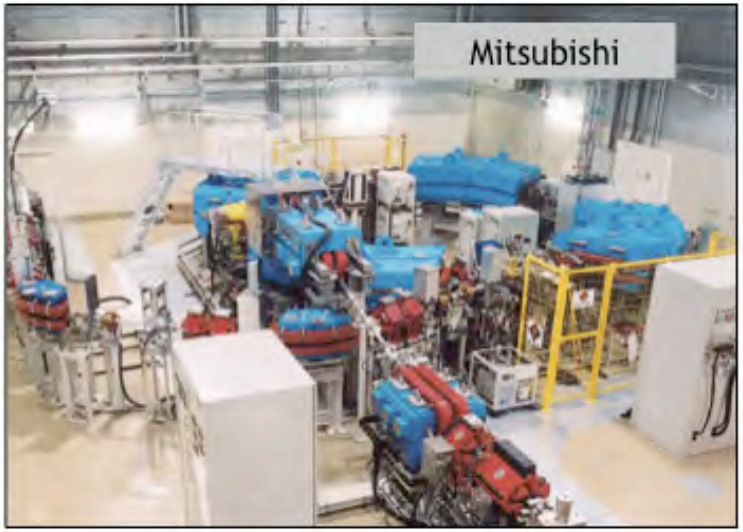
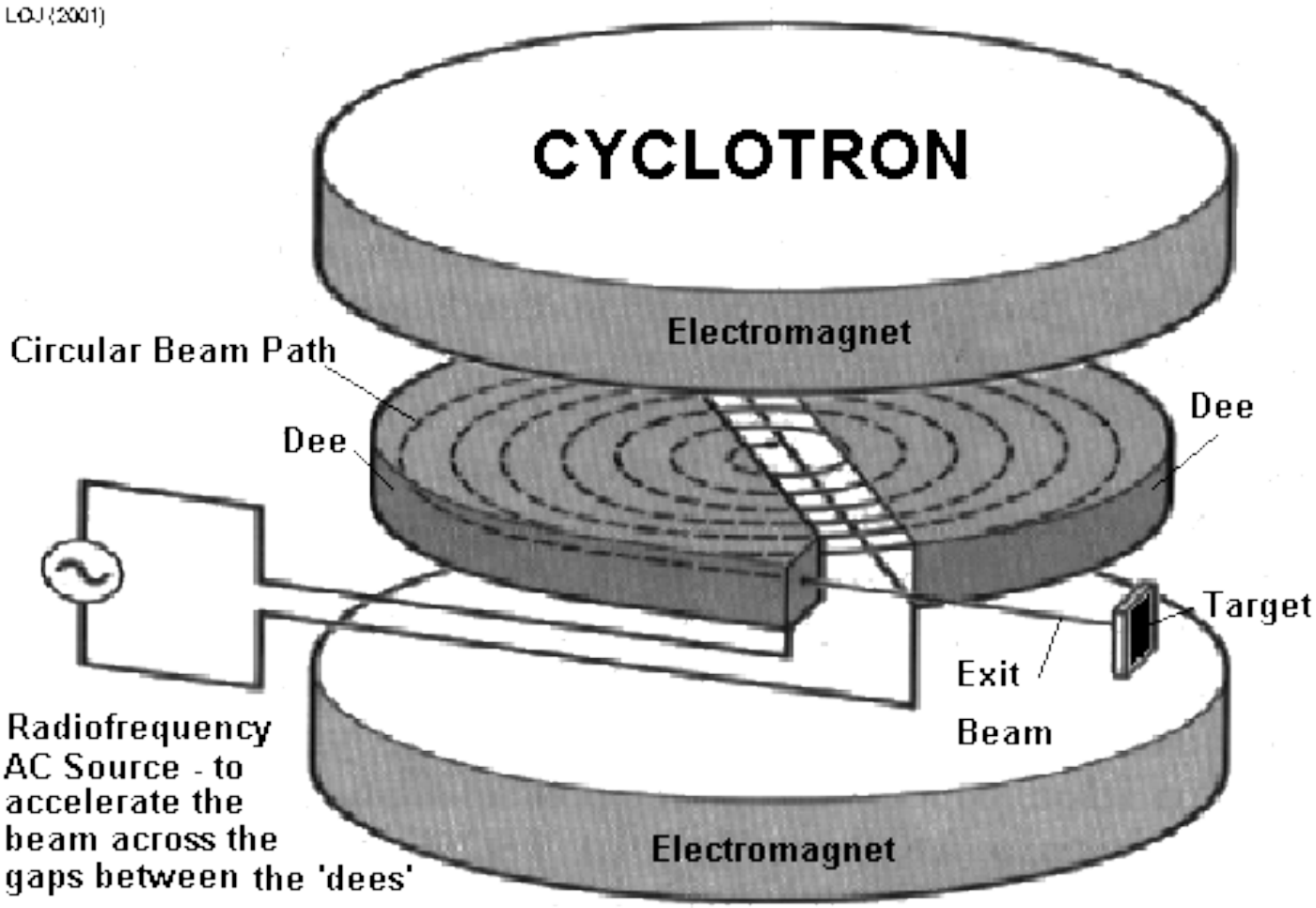




- Proton therapy: 4-5 m diameter cyclotrons and 6-8 m diameter synchrotrons
- Carbon ions: 20-25 meter diameter synchrotrons

Cyclotron


LOJ (2001)
CYCLOTRON
Electromagnet
Circular Beam Path
Dee
Dee
Target
Exit
Beam
Radiofrequency AC Source - to accelerate the beam across the gaps between the 'dees'
Electromagnet

Synchrotron

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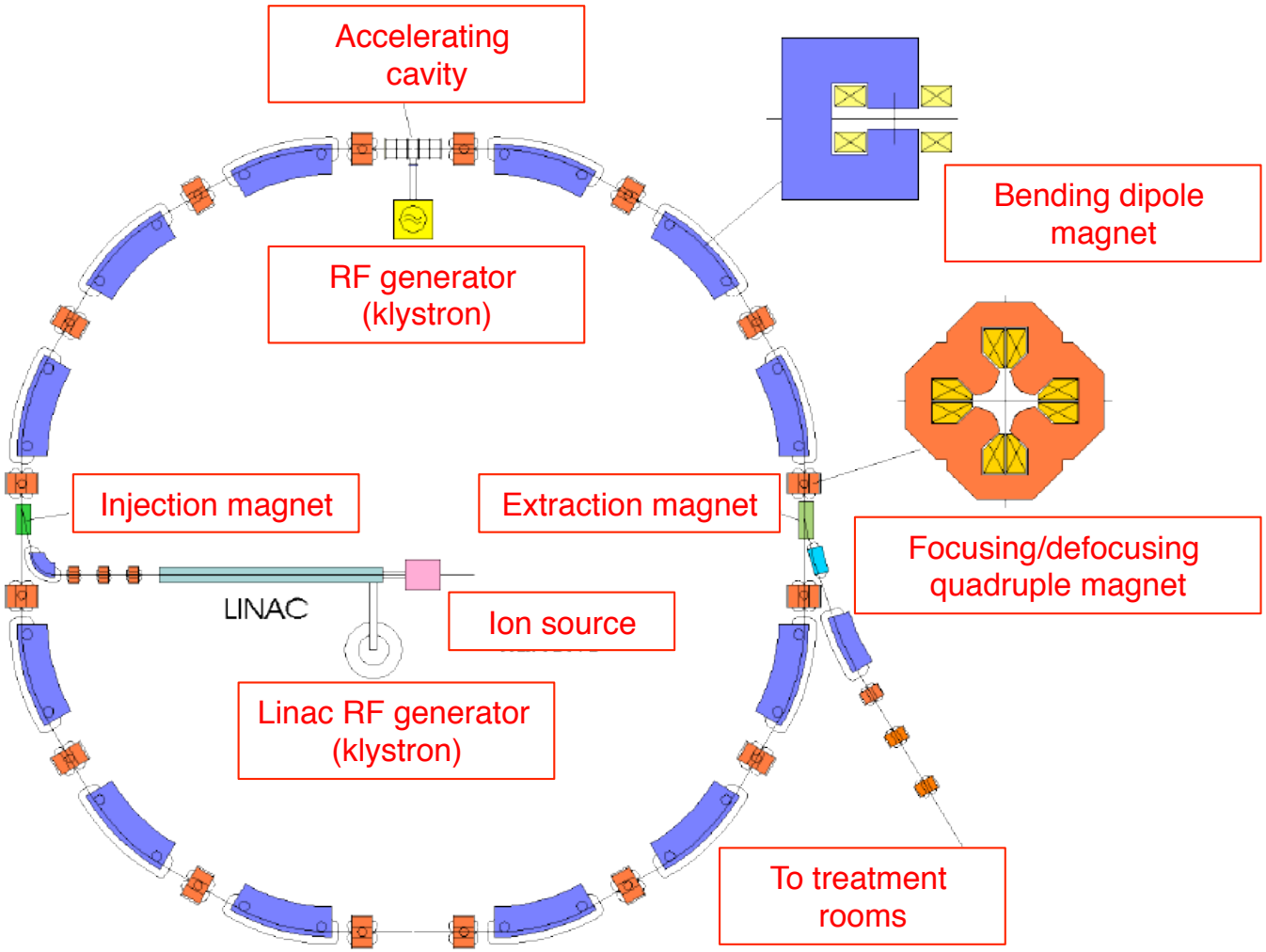

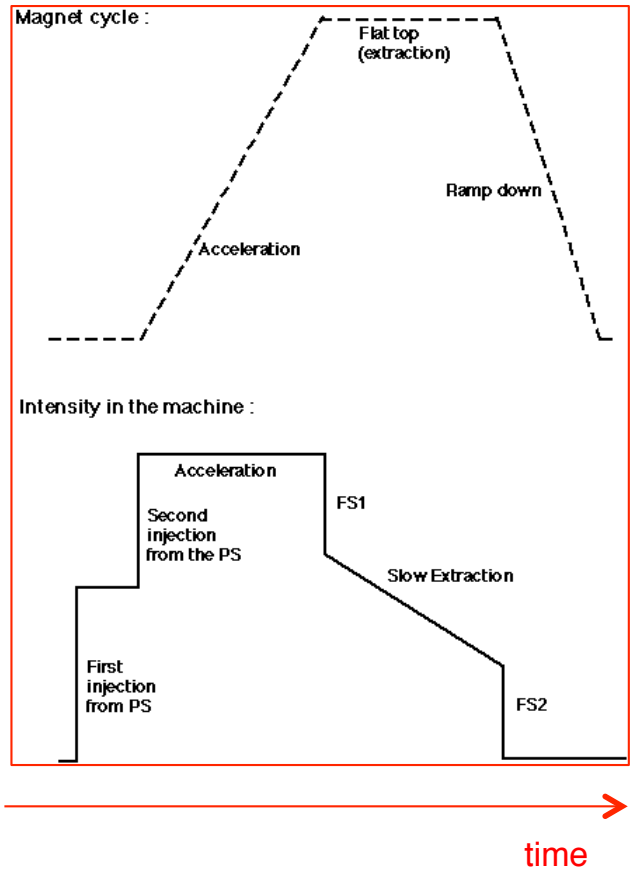

Radio Frequency (RF) linac

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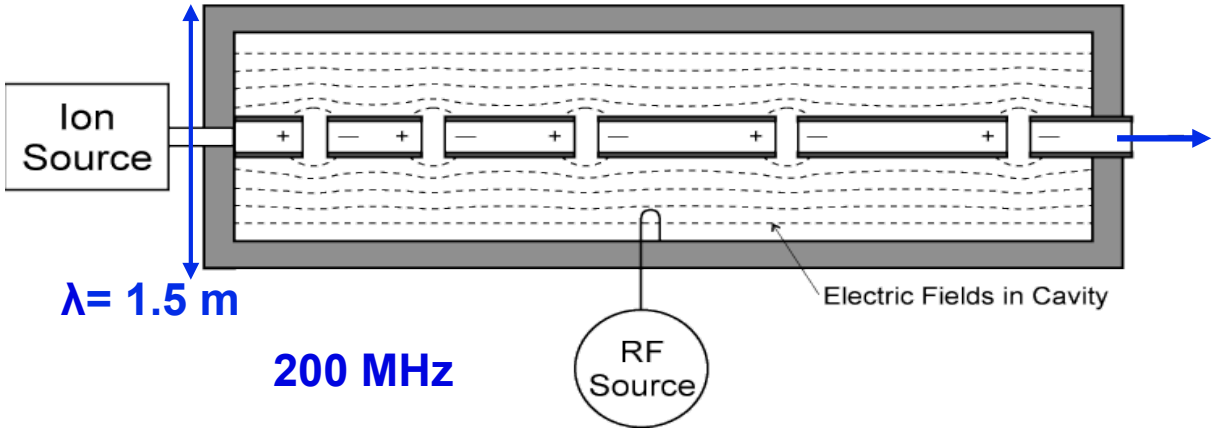
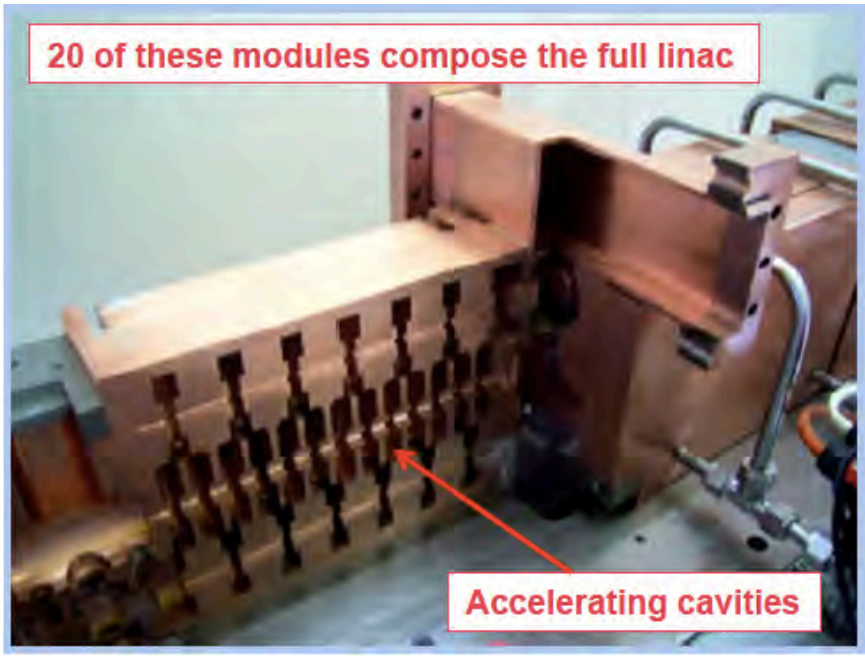
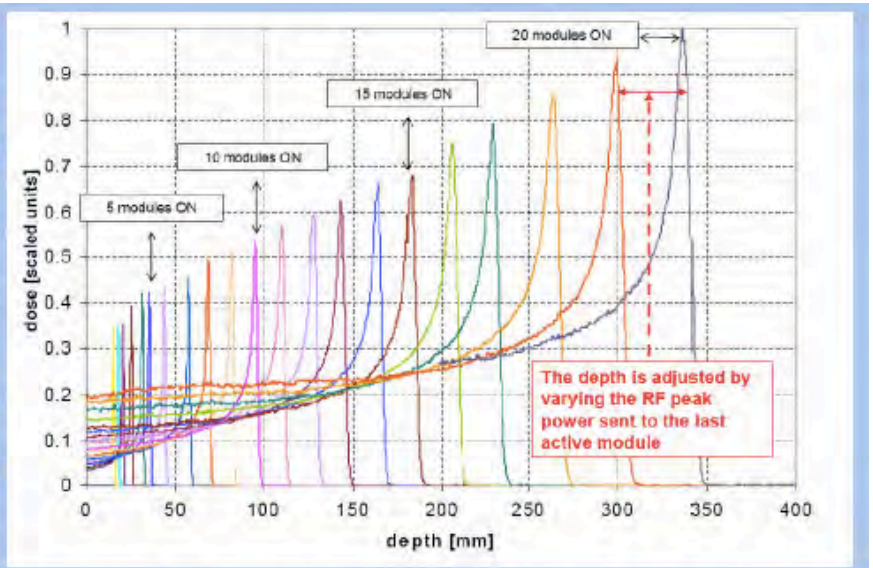


A modular variable energy linac for proton therapy:





U. Amaldi, S. Braccini and P. Puggioni, RAST2 (2009) 111.

Cyclotrons, synchrotrons or linacs?

Accelerator	Is the beam always available?	Is the output energy variable?	Which is the time to vary E_{clin} (ms)?
Cyclotron	Yes	No	100
Synchrotron	No	Yes	1000
Linac	Yes	Yes	2-5

Table 2.1: Proprieties of the beam of various accelerators relevant for hadrontherapy. E_{clin} is the energy of the clinical beam reaching the patient.

- Cyclotrons and synchrotrons are commercially available
- Linacs present some advantages and are today a research issue

Dose distribution: a gantry for proton therapy

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The Spread Out Bragg Peak (SOBP)

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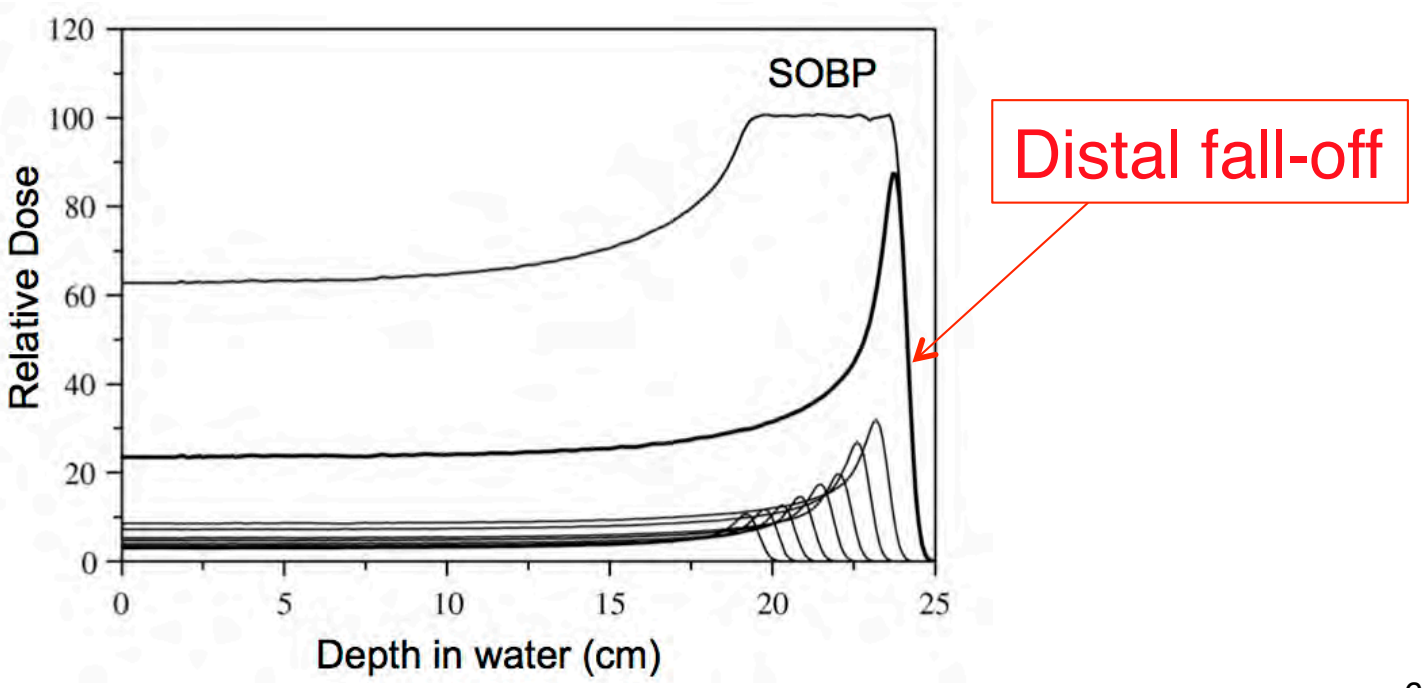
- A tumor is much larger (few cm) than the Bragg peak (few mm)
- Particles of different energies have to be used
- Many Bragg peaks have to be superimposed with the right weights to obtain a flat dose distribution (Spread Out Bragg Peak – SOBP)



SOBP and RBE for protons and carbon ions

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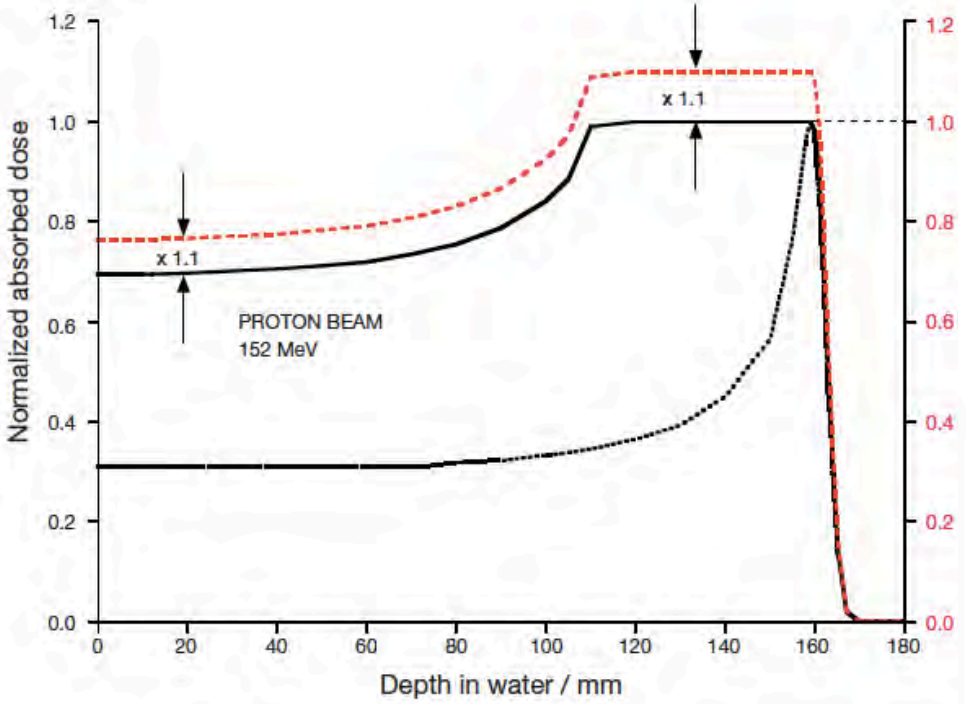
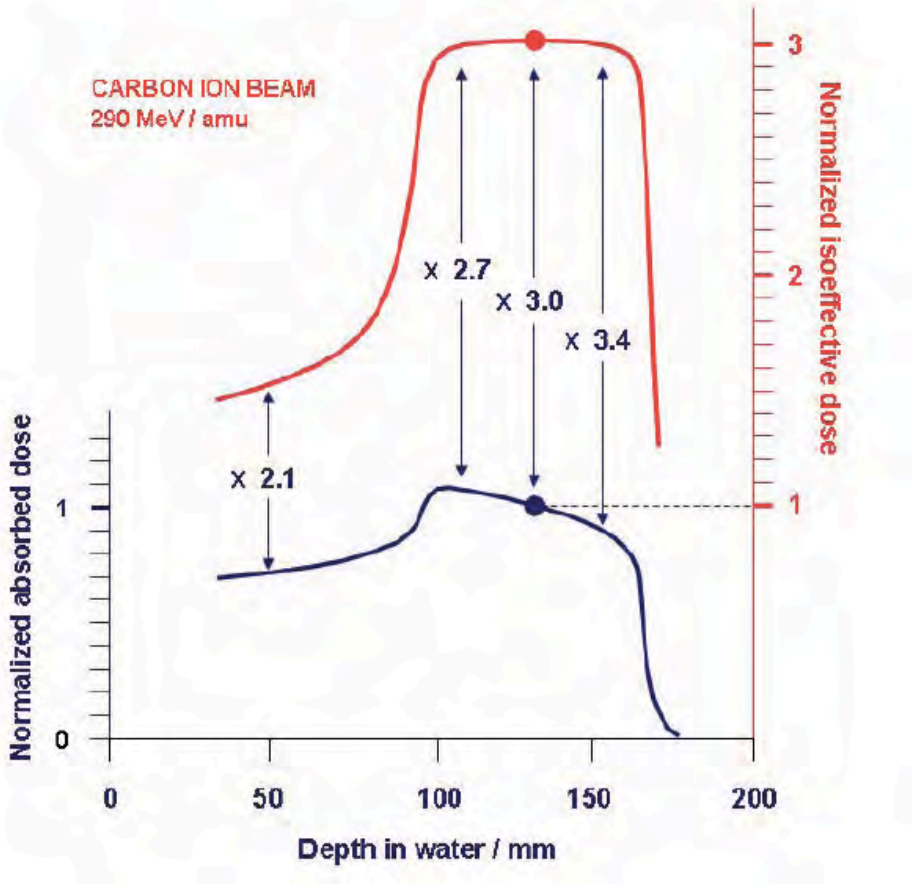
Protons



Carbon ions



IAEA – Technical report 461

Lateral penumbra

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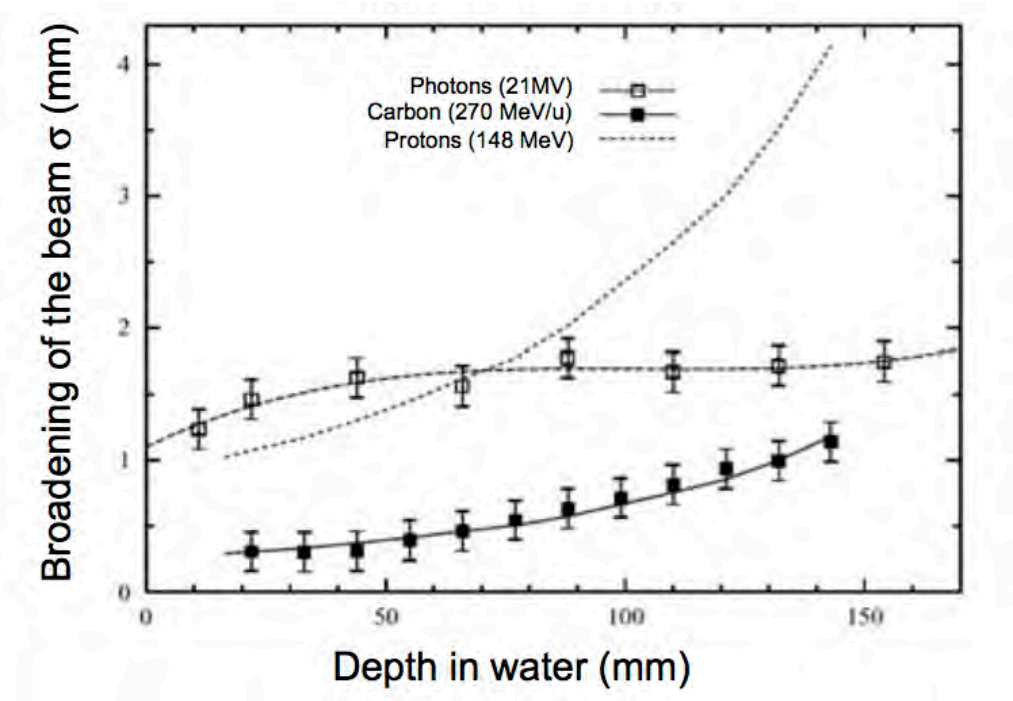
- Lateral scattering is a very important feature (lateral penumbra)
- Often the lateral penumbra – and not the distal - is used to protect the OARs (organs at risk)



Dose distribution: passive spreading

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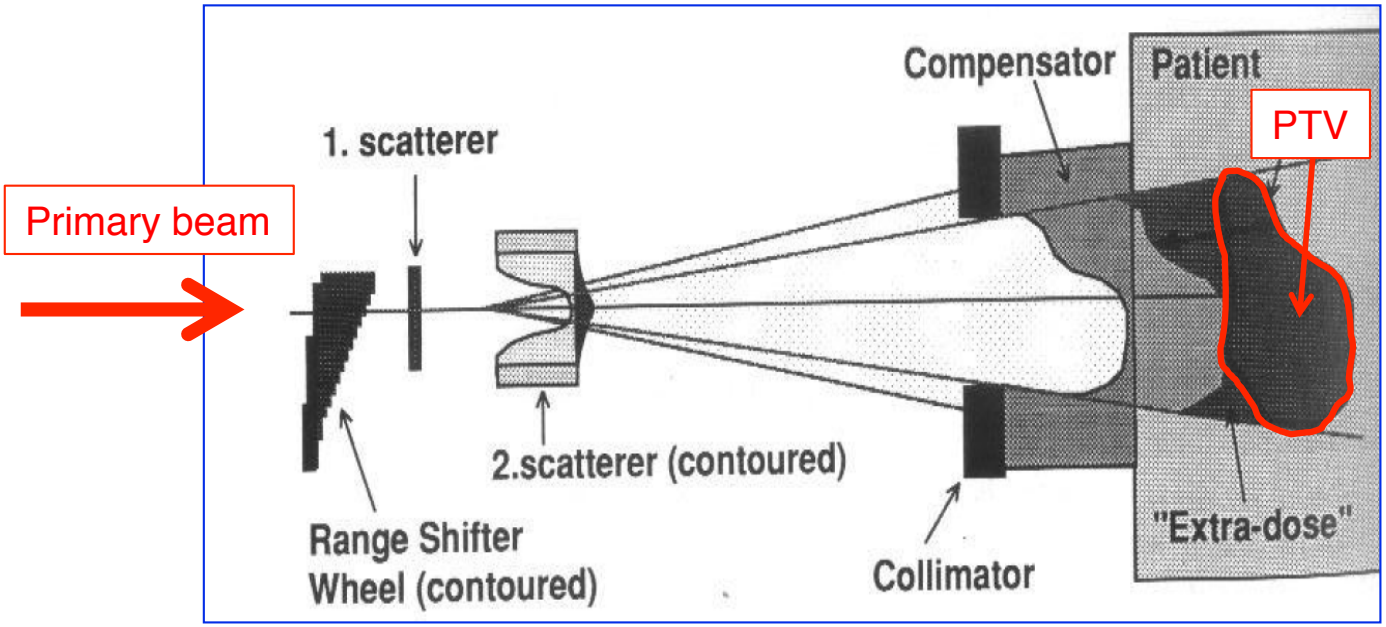

Double scattering technique

- Primary energy: determines the depth of the SOBP
- Range shifter: determines the width of the SOBP
- Scatterers: produce a transversally flat beam over the surface
- Collimator: shapes the beams in the transverse plane according to PTV
- Compensator (or bolus): shapes the beam in depth according to PTV

Dose distribution: raster scanning

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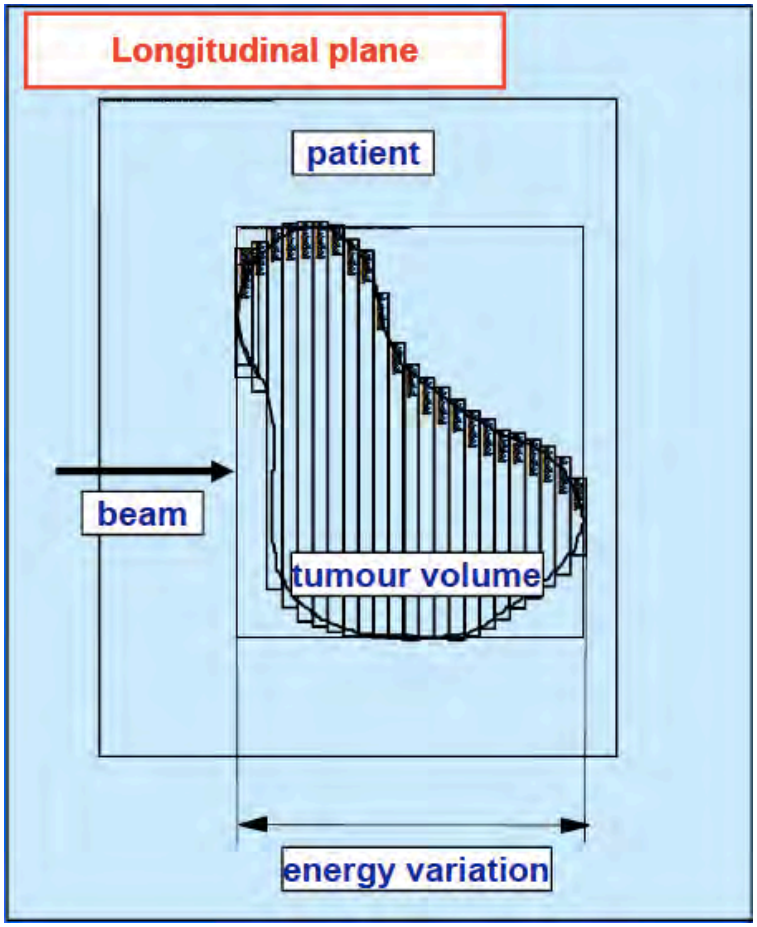

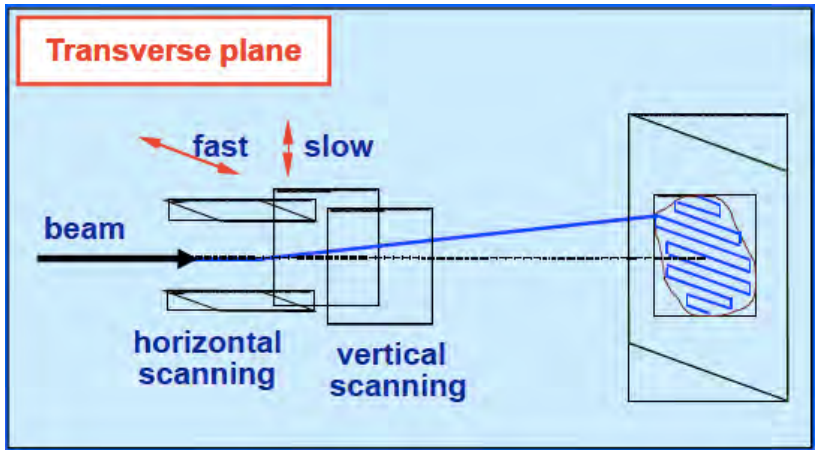

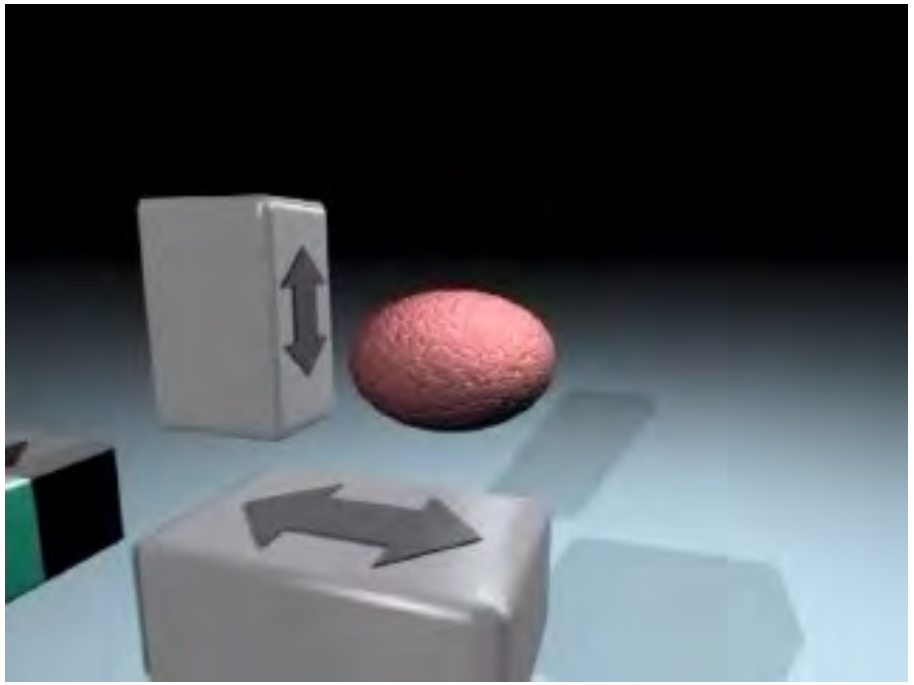

New technique developed at GSI

Spot scanning at PSI

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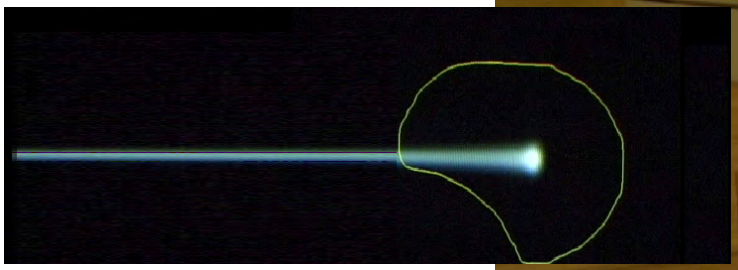
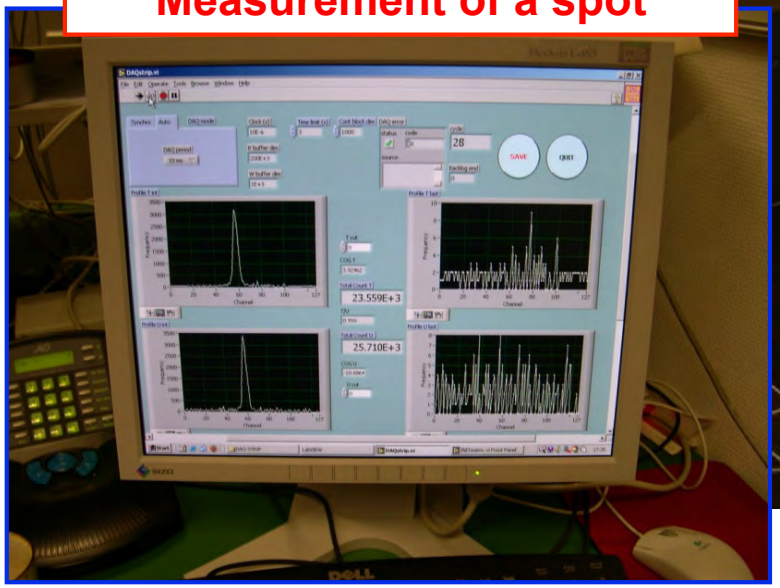
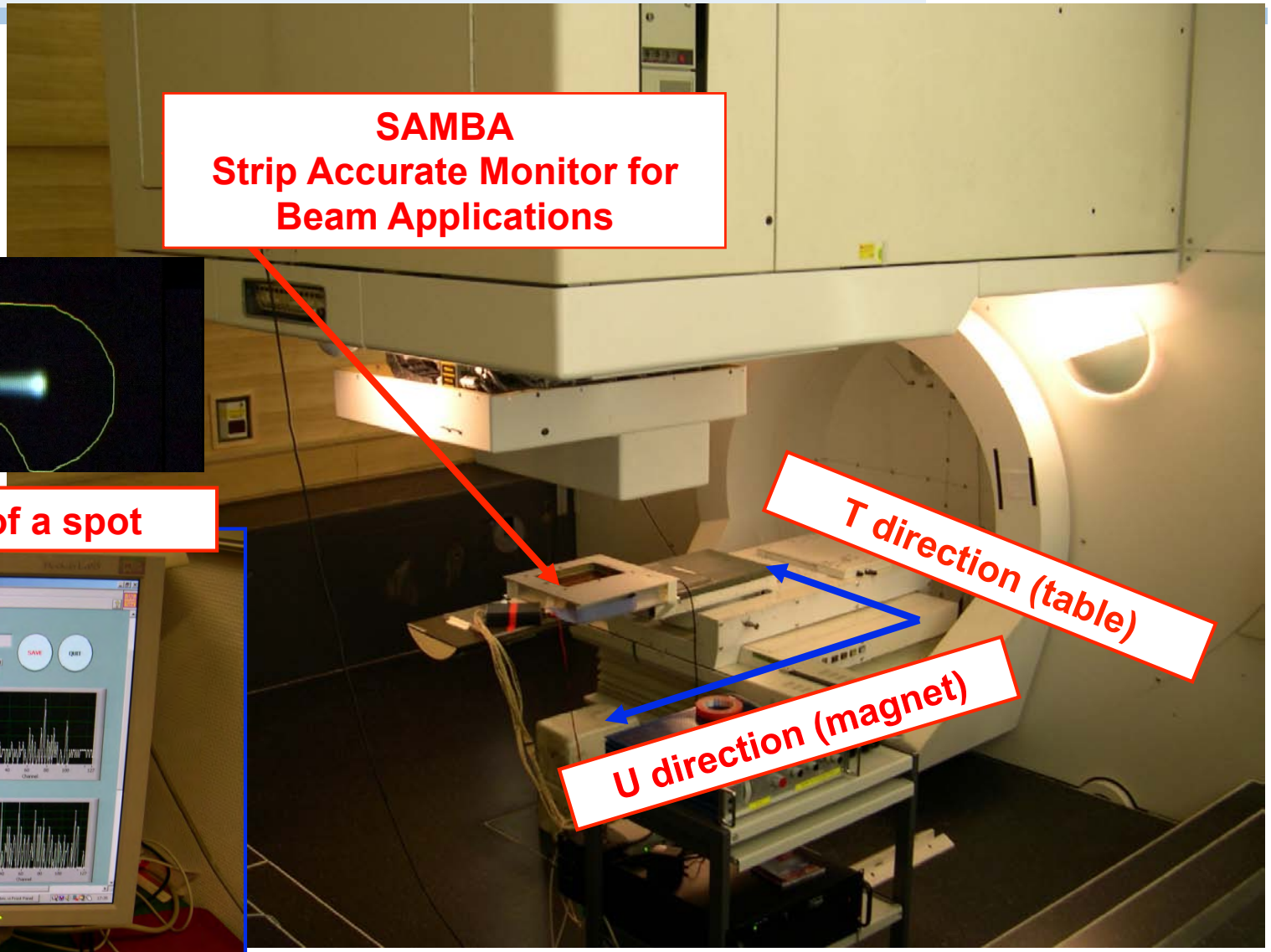
Superposition of discrete spots



Measurement of a spot





Time profile of the clinical beam

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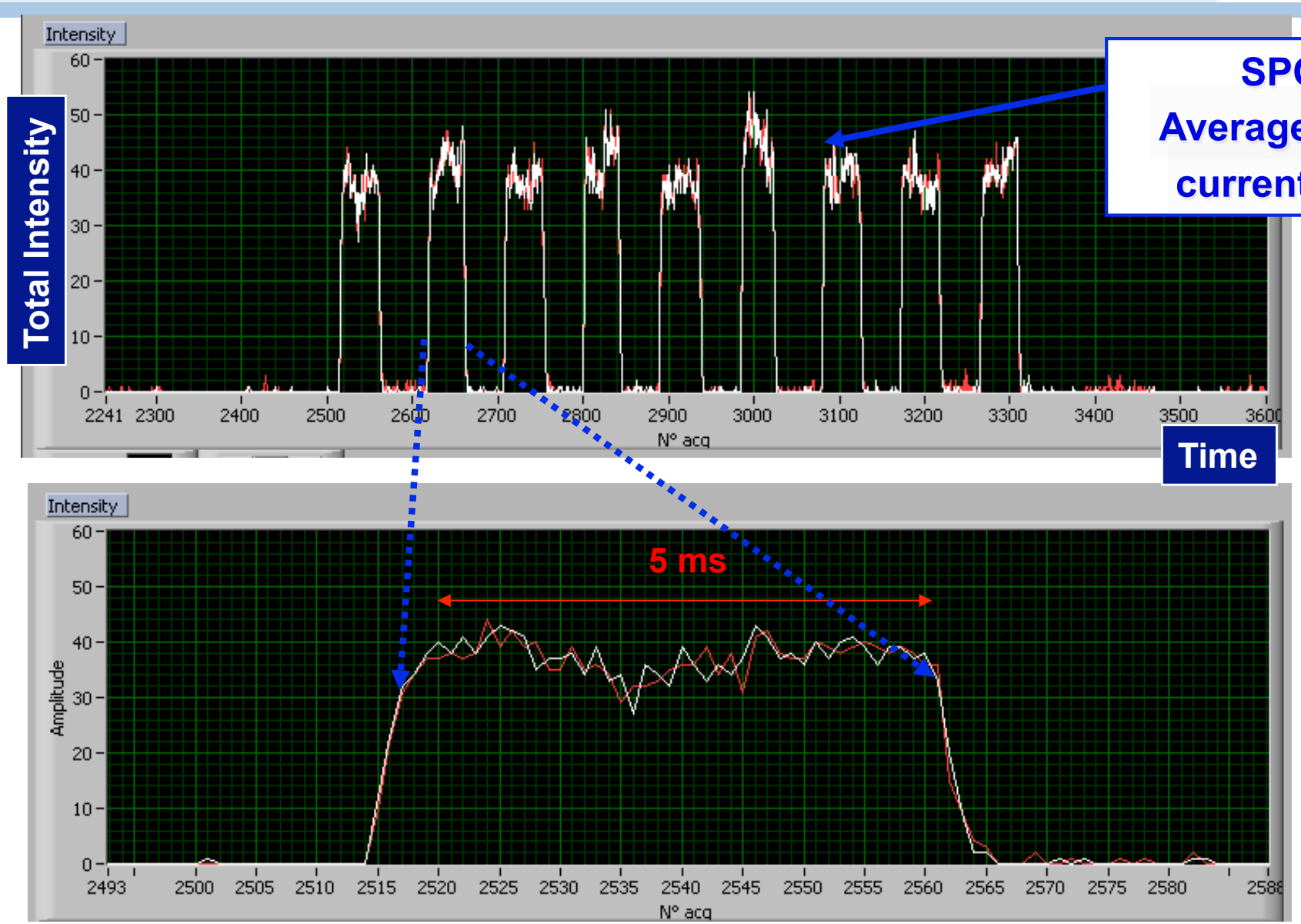
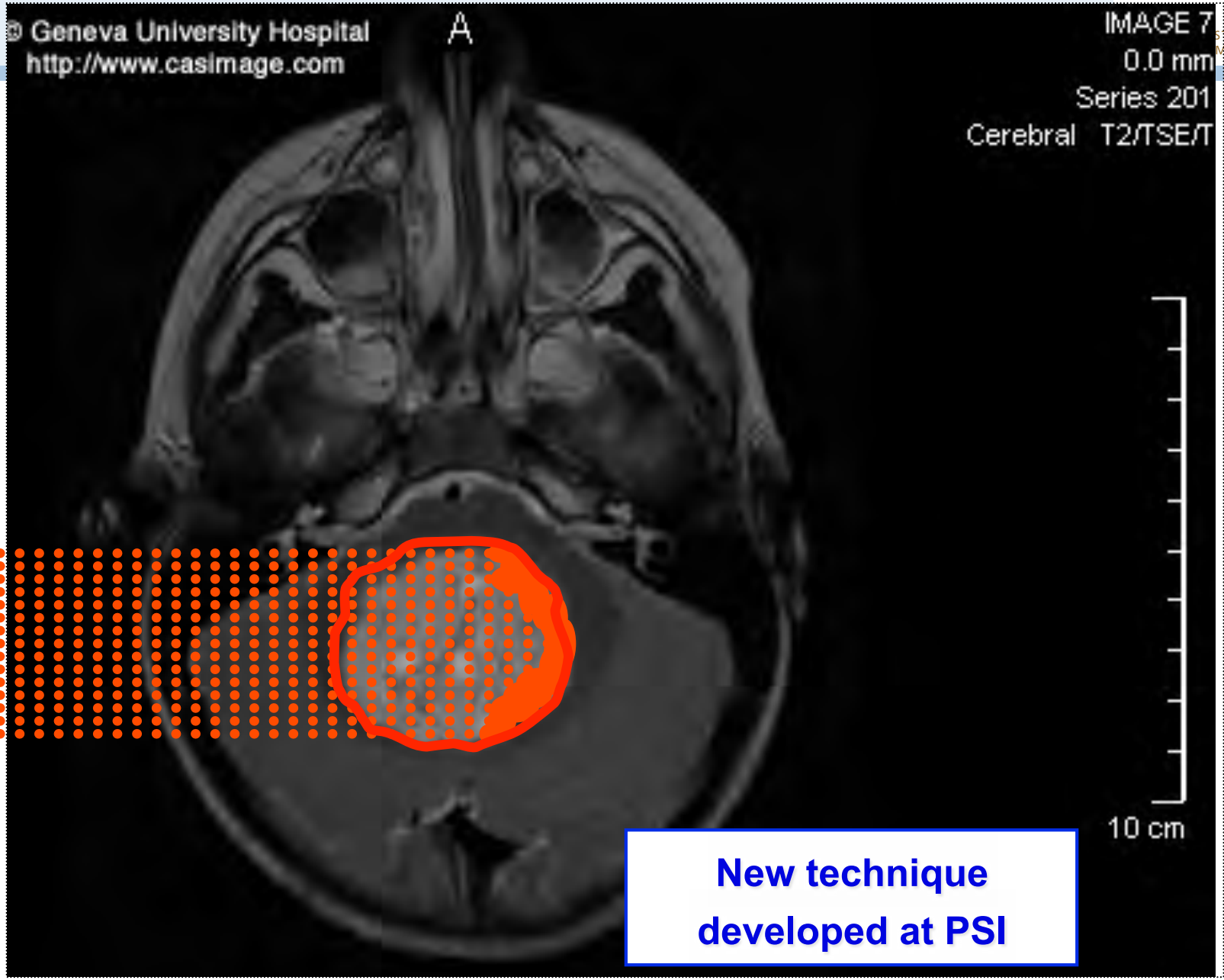
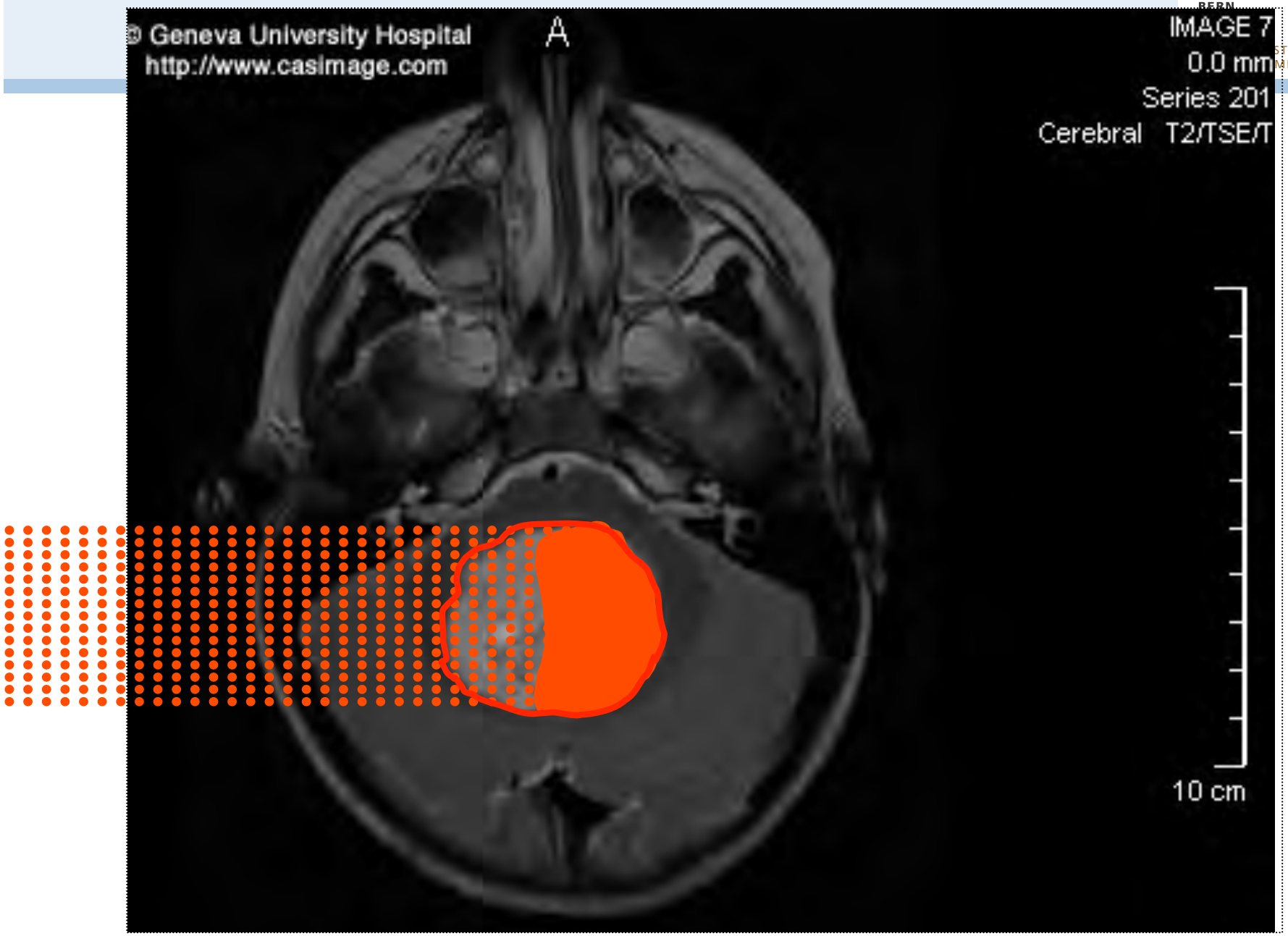


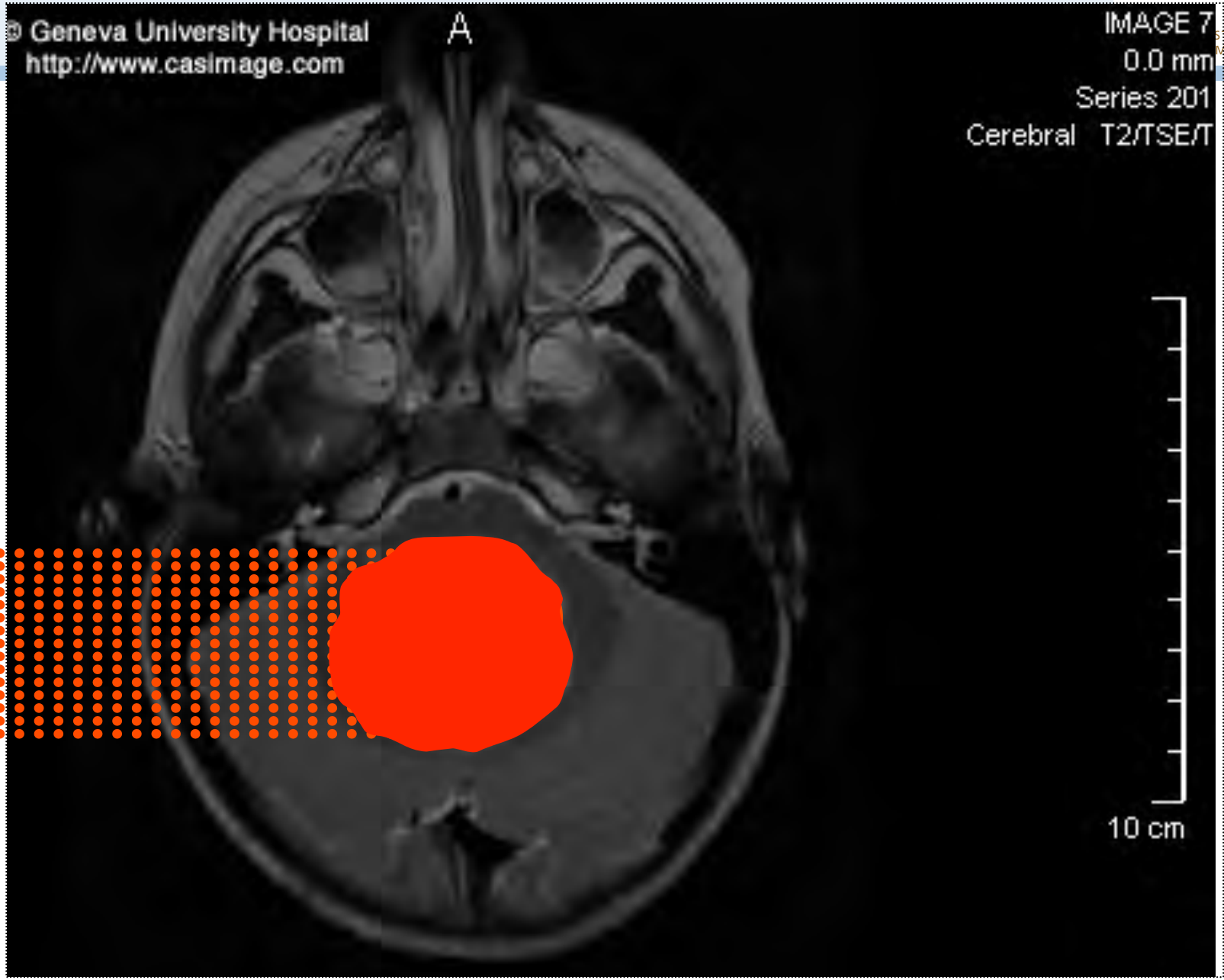
Dose distribution: spot scanning



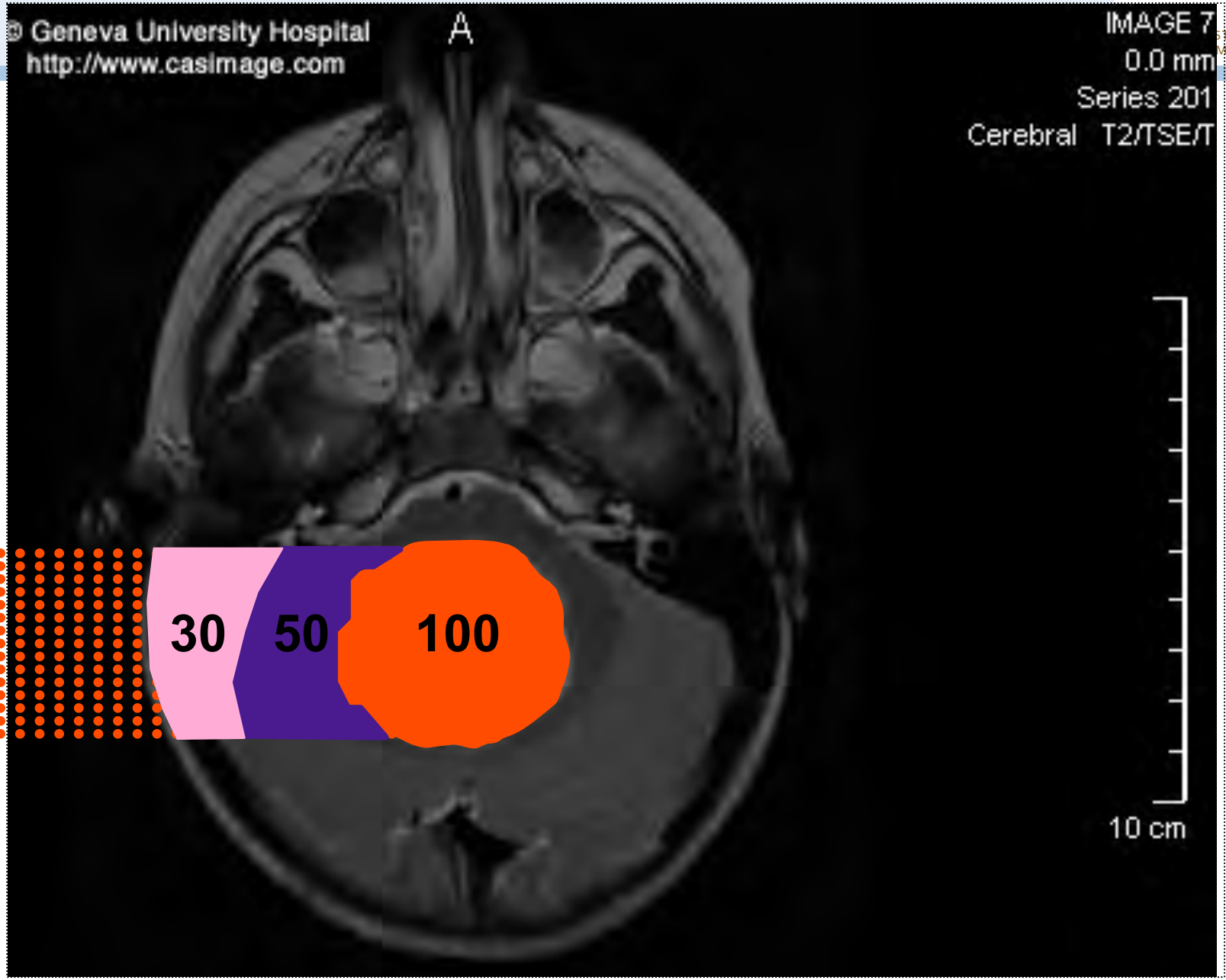
Dose distribution: spot scanning



Dose distribution: spot scanning



Dose distribution: spot scanning



Some clinical data

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Indication	End point	Results photons	Results carbon HIMAC-NIRS	Results carbon GSI
Chordoma	local control rate	30 – 50 %	65 %	70 %
Chondrosarcoma	local control rate	33 %	88 %	89 %
Nasopharynx carcinoma	5 year survival	40 -50 %	63 %	
Glioblastoma	av. survival time	12 months	16 months	
Choroid melanoma	local control rate	95 %	96 % (*)	
Paranasal sinuses tumours	local control rate	21 %	63 %	
Pancreatic carcinoma	av. survival time	6.5 months	7.8 months	
Liver tumours	5 year survival	23 %	100 %	
Salivary gland tumours	local control rate	24-28 %	61 %	77 %
Soft-tissue carcinoma	5 year survival	31 – 75 %	52 -83 %	

Similar to protons

Table by G. Kraft 2007

Results of carbon ions

Number of potential patients

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X-ray therapy every 10 million inhabitants: 20'000 pts/year

Protontherapy

14.5% of X-ray patients = 2'900 pts/year

Therapy with Carbon ions for radio-resistant tumours

3% of X-ray patients = 600 pts/year

TOTAL about 3'500 pts/year every 10 M

Results of clinical studies conducted in Italy, France, Germany, Austria and Sweden

Present of hadrontherapy

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- Proton-therapy
  - > 100 000 patients treated (but only 3% using scanning)
  - > 20 hospital based centers
  - Many centers under constructions and in project phase

- Carbon ion therapy
  - > 13 000 patients treated (mainly in Japan)
  - 8 centers in operation (4 in Japan, 2 in China and 2 in Europe)
  - Several projects
  - Clinical trials

More information on: http://ptcog.web.psi.ch/

Hadrontherapy, a developing discipline

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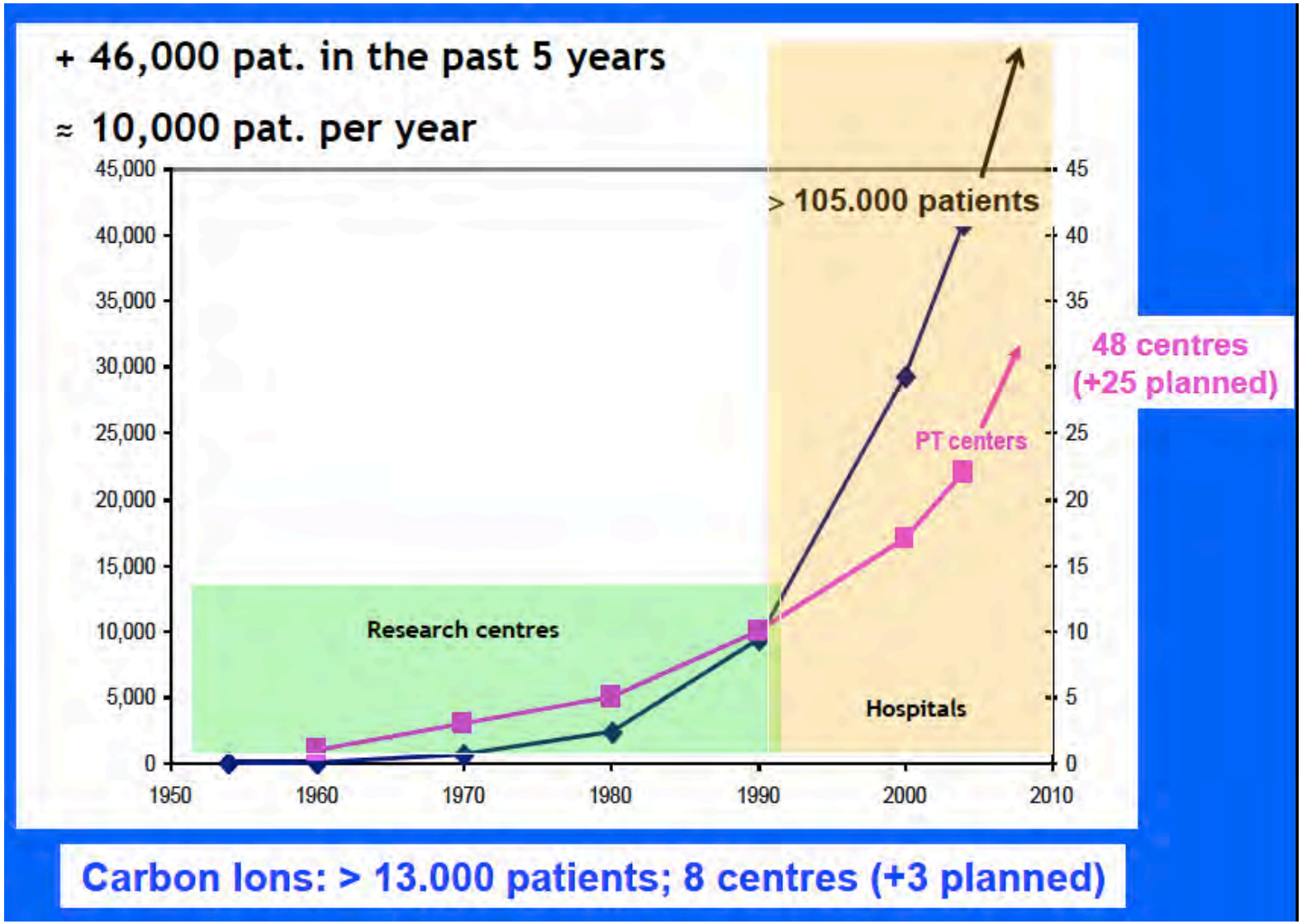

Courtesy: S. Rossi, CNAO

Some new ideas for the future of hadrontherapy

The future of hadrontherapy

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- Two main driving forces
  - Improve the local control and minimize secondary effects
  - Reduce costs, size and complexity

- There is a lot to do on
  - Accelerators
  - Gantries
  - Dose distribution systems (moving organs)
  - Imaging
  - …

As a summary on hadrontherapy you can read:
U. Amaldi and S. Braccini, Present challenges in hadrontherapy techniques, Eur. Phys. J. Plus (2011) 126: 70.

Patients and treatment rooms

Table 7. Estimate of the number of X ray and hadron treatment rooms.

Radiation treatment	Patients per year in 10^7 inhabitants	Av. number of sessions per patient	Sessions/d in 1 room (d = 12 h)	Patients/y in 1 room (y=230 d)	Rooms per 10 million people	Relative ratio
Photons	20 000	30	48	370	54	8^2
Protons (12%)	2 400	24	36	345	7.0	8
C ions (3%)	600	12	36	690	0.87	1

U. Amaldi, S. Braccini et al., Nucl. Instr. Meth. A 620 (2010) 563

Single room facilities: future of proton-therapy?

Compact superconducting synchrocyclotron

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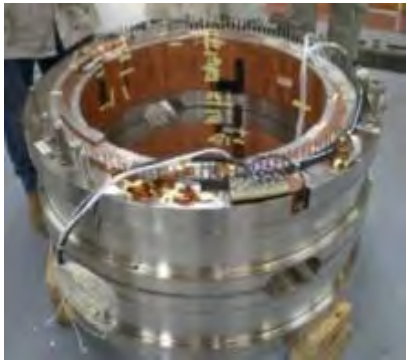
- 250 MeV, 15 tons synchrocyclotron mounted on its gantry
- 10 T superconducting magnet !
- 8 systems (in operation/construction)
- First patient treated December 2013



Courtesy Mevion Medical Systems

The IBA Proteus One single room facility

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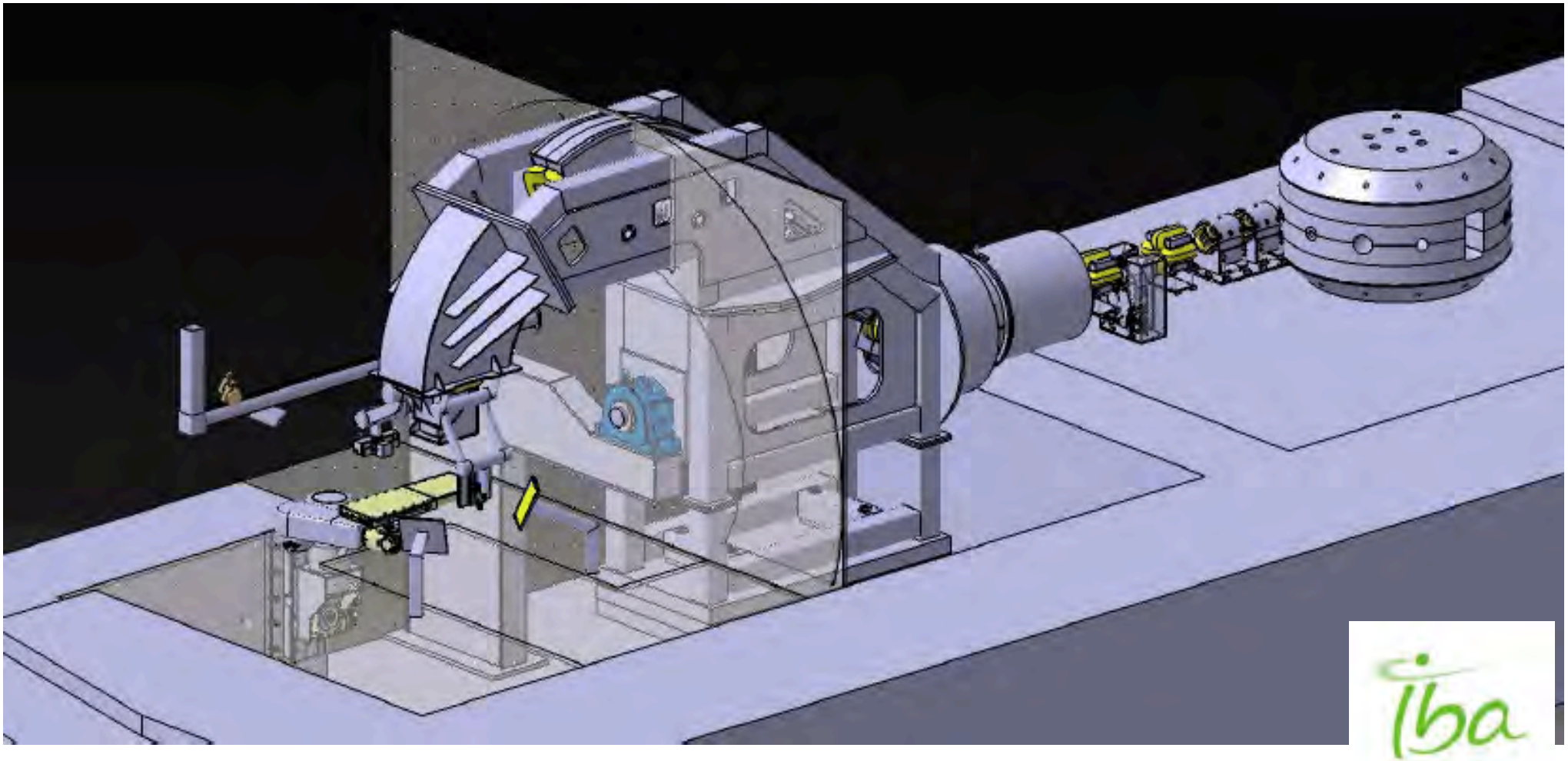

Courtesy IBA

A turning linac? … a dream?

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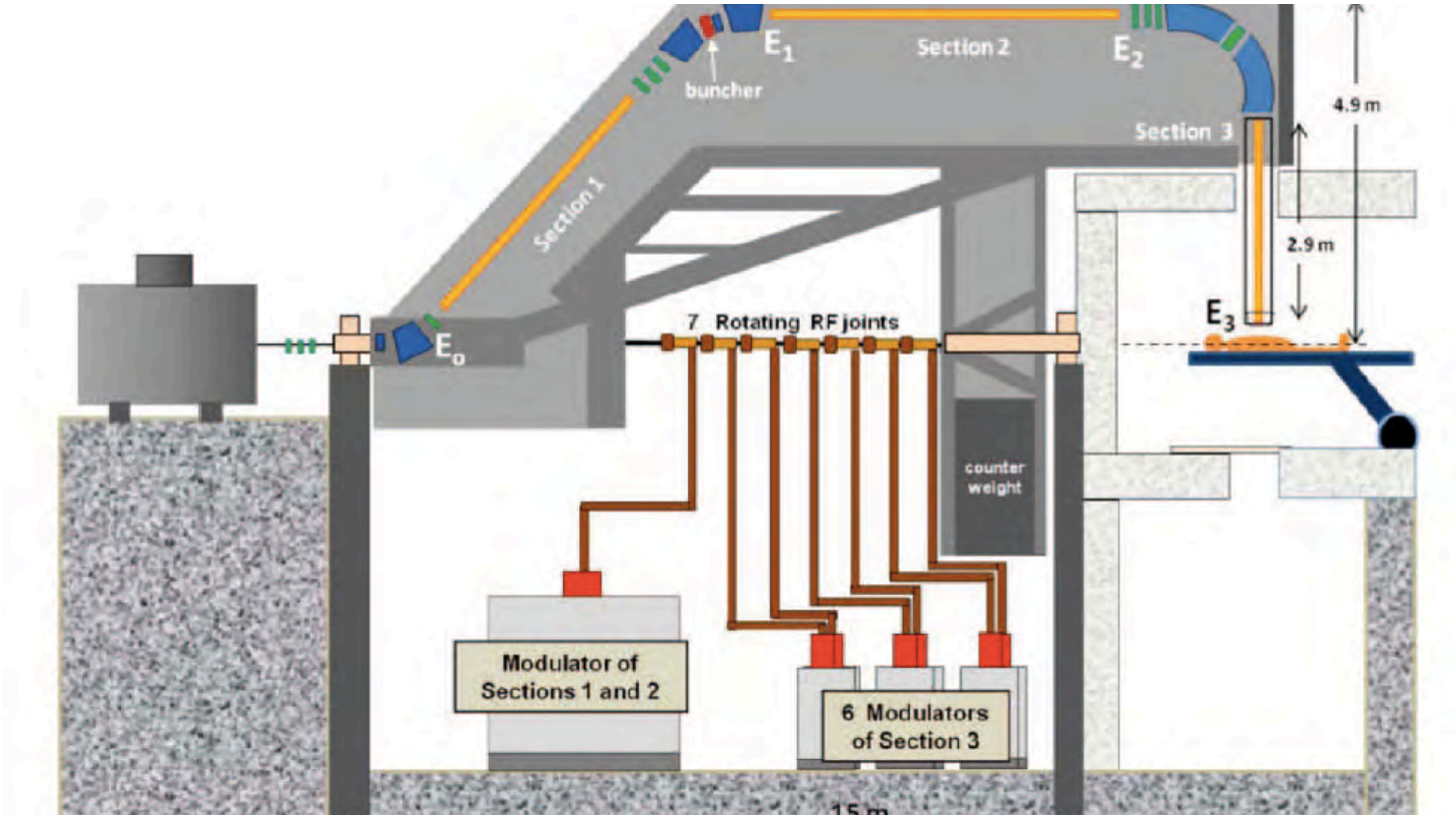
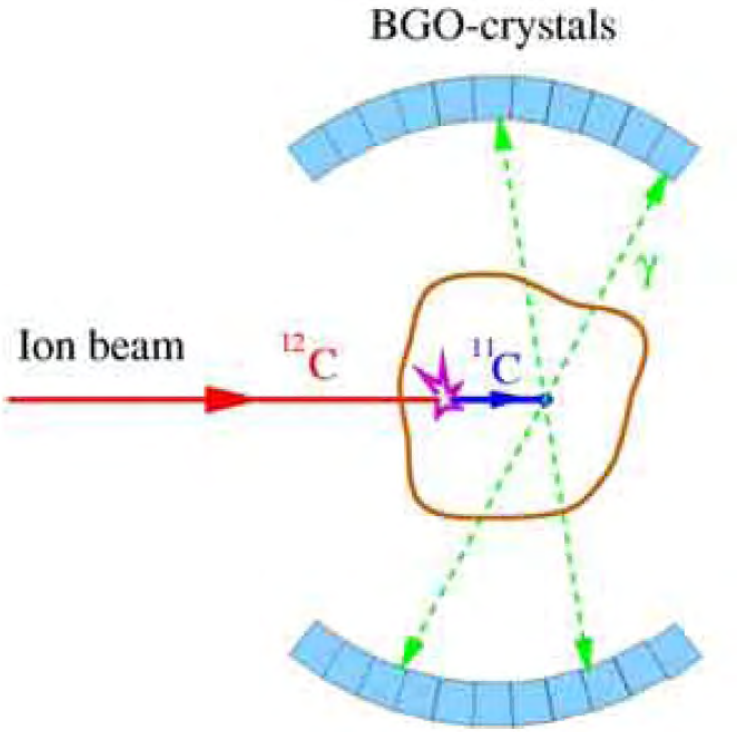


Patent US8405056 B2 and EP2106678 B1

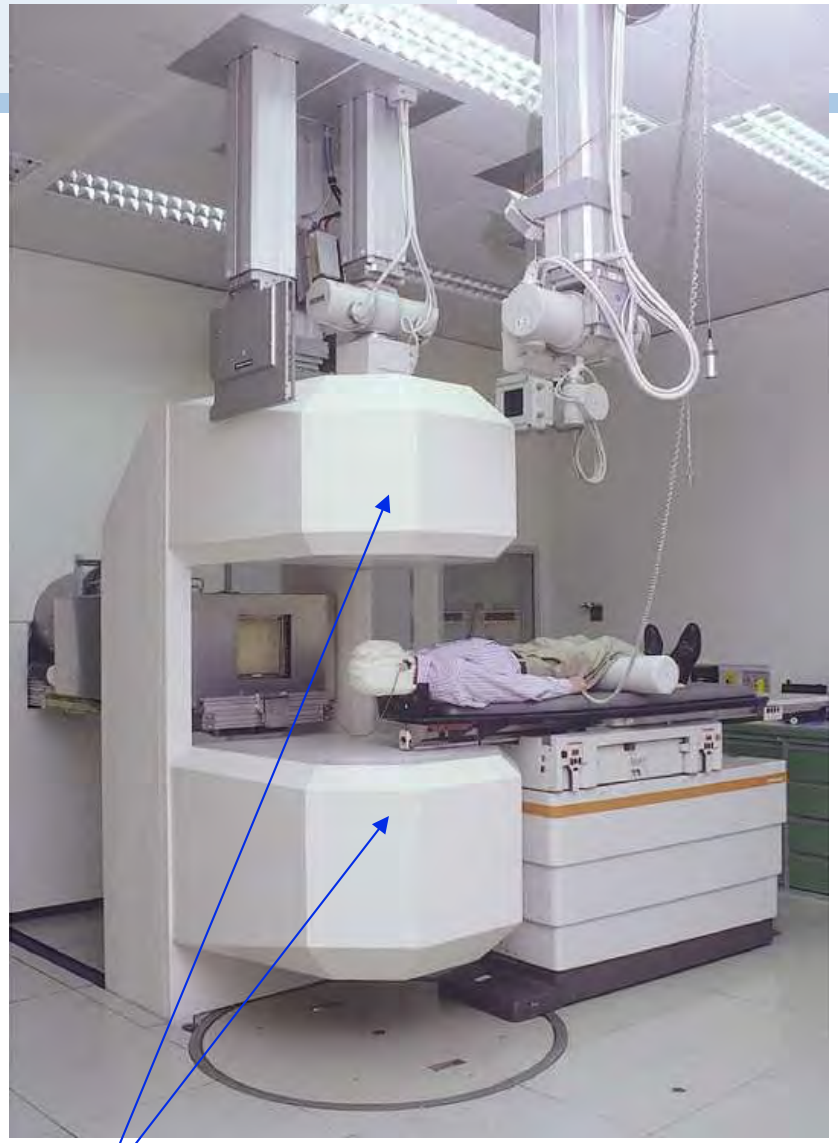
TUrning LInac for Proton-therapy (TULIP)

- 24 MeV cyclotron: injector (+ radioisotope production)
- Advanced spot scanning (moving organ tacking)
- On-line proton radiography

In-beam PET



Measurement of the ”real” 3D dose distribution given to the patient



PET detectors (GSI, Darmstadt)

In-beam PET

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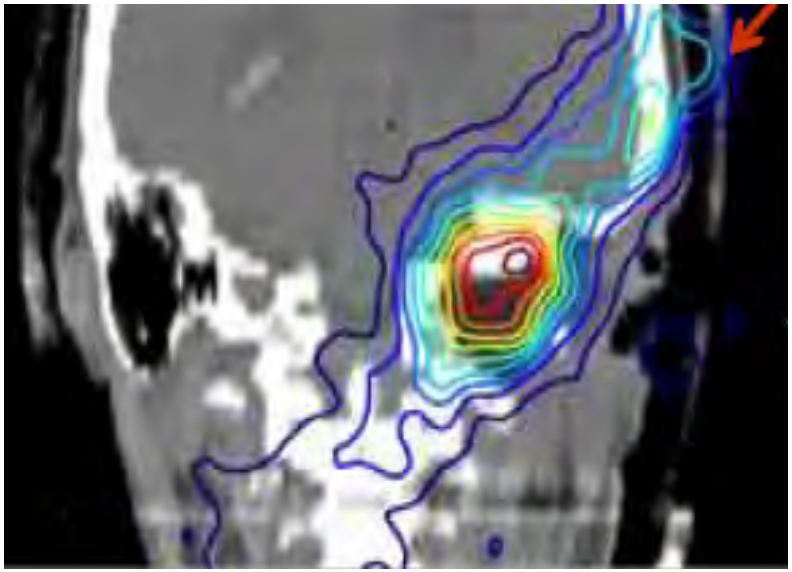
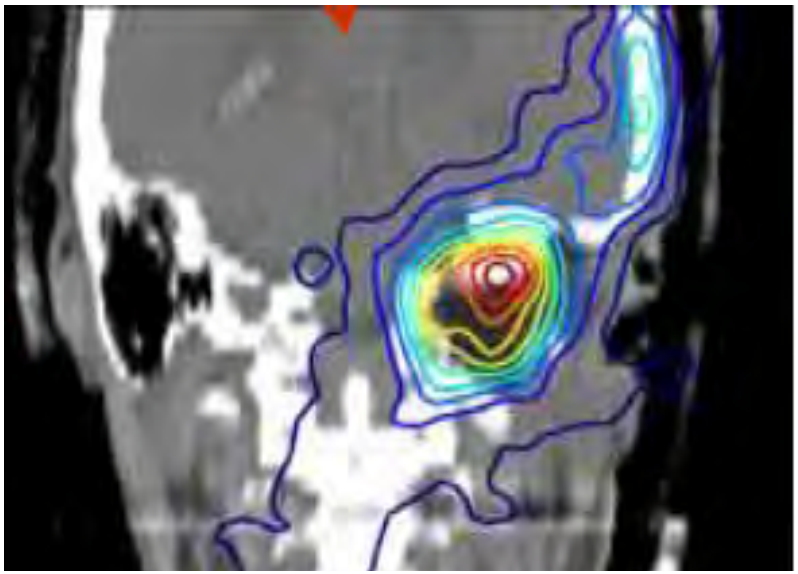


Simulated from TPS



Measured

Proton radiography

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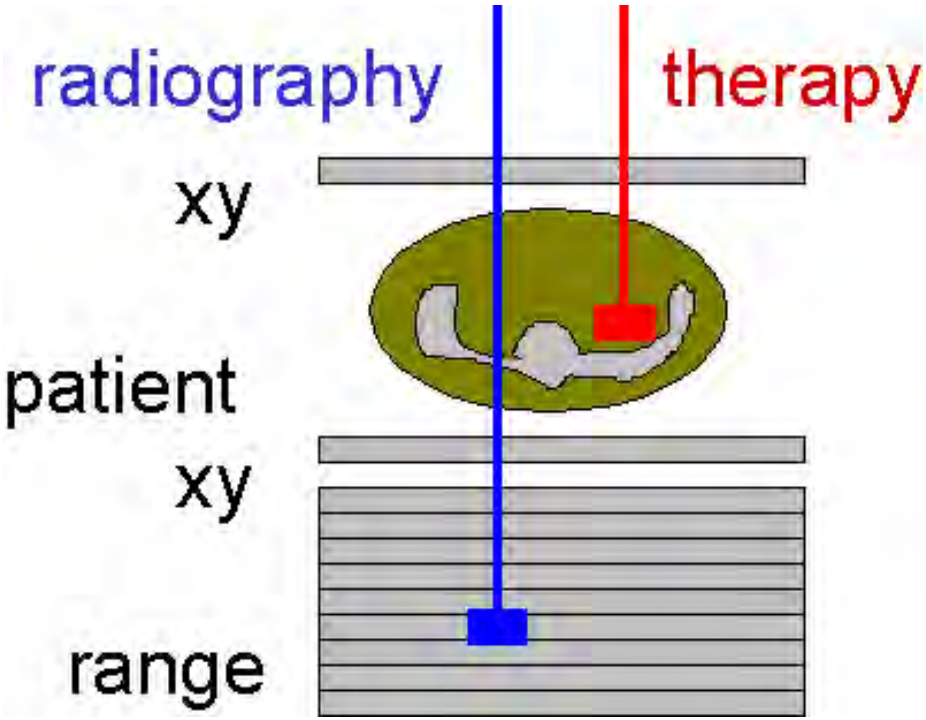

Radiography with X-rays

- **"Counts" the number of photons**
- **Almost all the photons stop in the patient's body giving unwanted dose**

Radiography with protons

- **Protons with enough energy penetrate the body**
- **Residual range measurement**
- **Every proton brings information!**

- High Z material dominate in X ray radiography (and CT scan)
  - Treatment planning in proton therapy is based on CT
  - Small density changes are hard to observe with X rays!
- Small density changes :
  - Produce uncertainties in the proton range
  - Distortions in proton-therapy planning (important for proton therapy!)

Proton radiography

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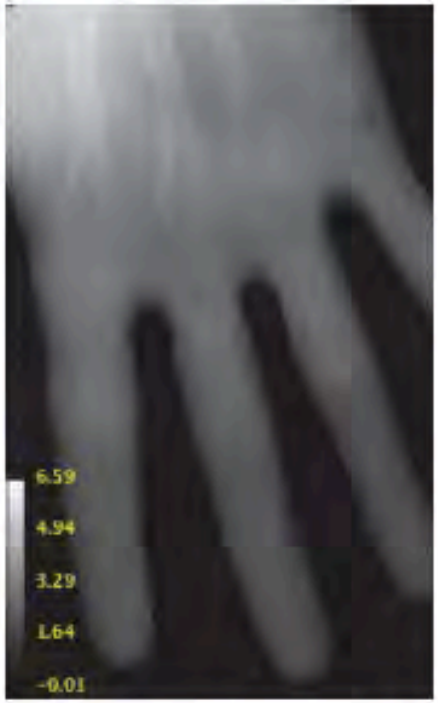
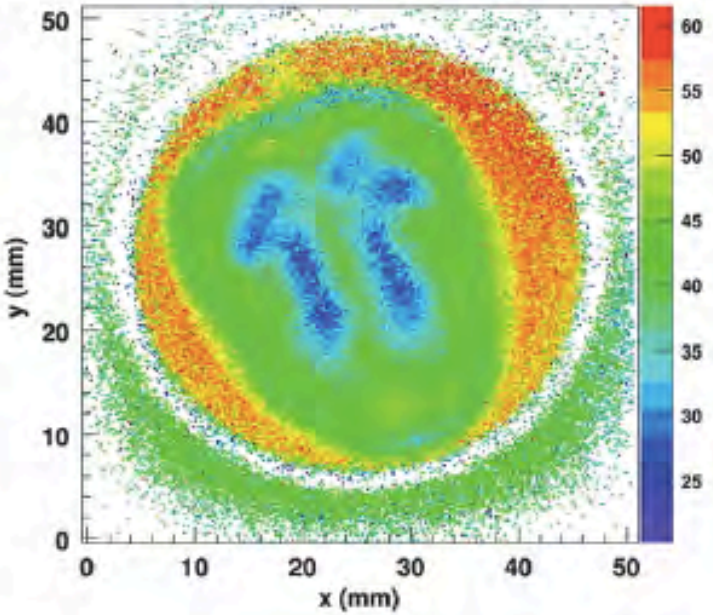


(a)



(b)

Fig. 10. (a) pCT of a hand phantom. © 2014 IEEE. Reprinted, with permission, from Ref. 32. (b) Proton radiography of a walnut at 62 MeV. © 2011 Elsevier. Reprinted, with permission, from Ref. 37. All rights reserved.

Ionoacustics: “hearing” the ions …

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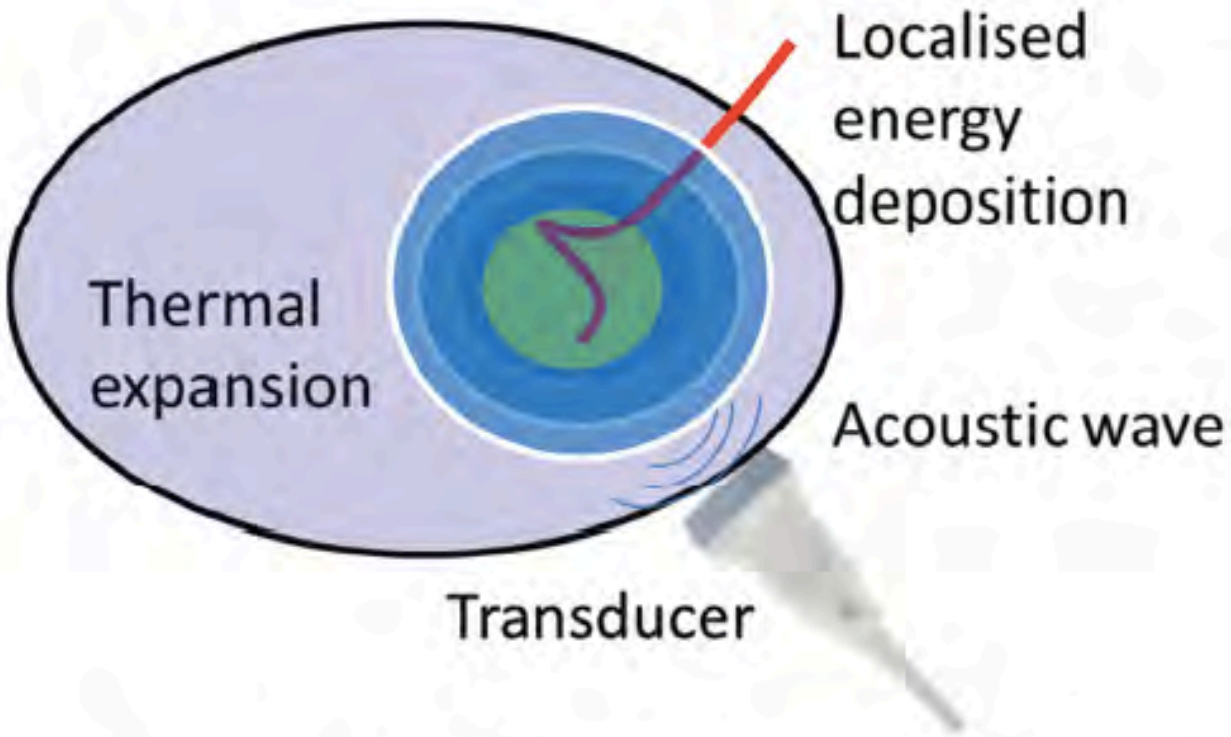

Fig. 1. A schematic illustration of the ionoacoustic signal formation and detection during the delivery of a mono-energetic pencil-like ion beam, with the characteristic Bragg peak.

Conclusions and Outlook

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To know more on hadrontherapy …

http://www.worldscientific.com/toc/mpla/30/17