ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

TERA Fondazione per Adroterapia Oncologica

Seminar on HADRONTHERAPY

Alberto Degiovanni

JUAS 2012 - 15.02.2012

alberto.degiovanni@cern.ch

OUTLINE

PART 1: Physics and radiobiology

- ***Physical basis of hadrontherapy***
  - Conformity of irradiation
  - Microscopic dose distribution in radiation therapy
- ***Biological effects***
  - Cell survival and fractionation
  - RadioBiological Effectiveness (RBE)

PART 2: Accelerators and technology

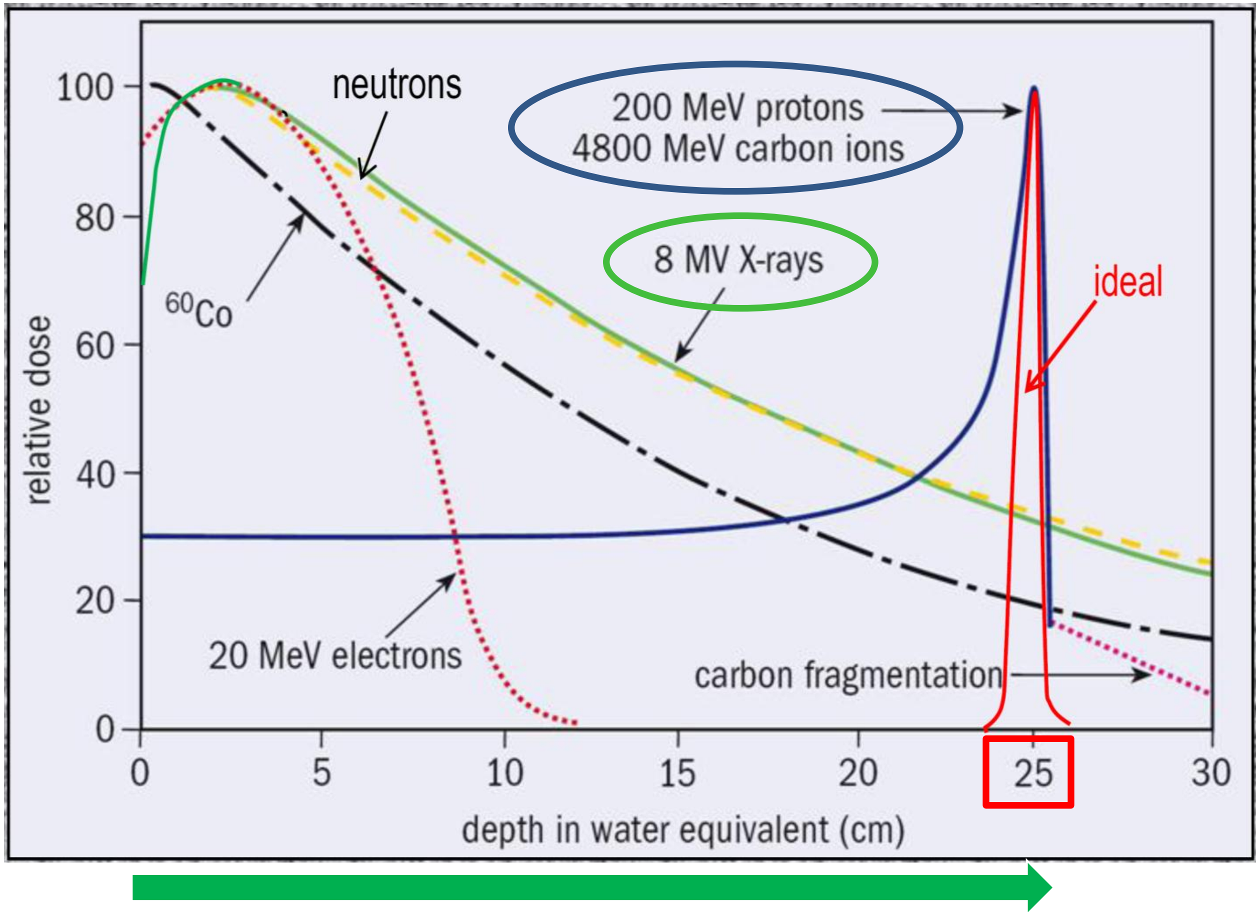
- ***Instrumentation and treatment modalities***
  - Accelerators for hadrontherapy
  - Active and passive scanning
- ***Future challanges in hadrontherapy (treatments and technologies)***
  - Moving organs
  - Single room facilities

CONCLUSION

Part 1: Physics and radiobiology

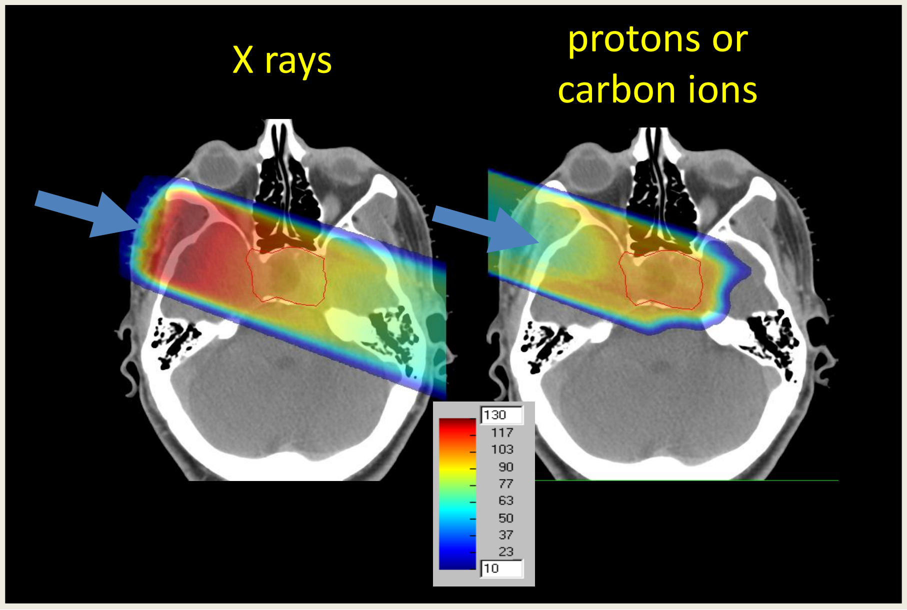
Physical basis of hadrontherapy

The icon of radiation therapy with charged hadrons



Radiation beam in matter

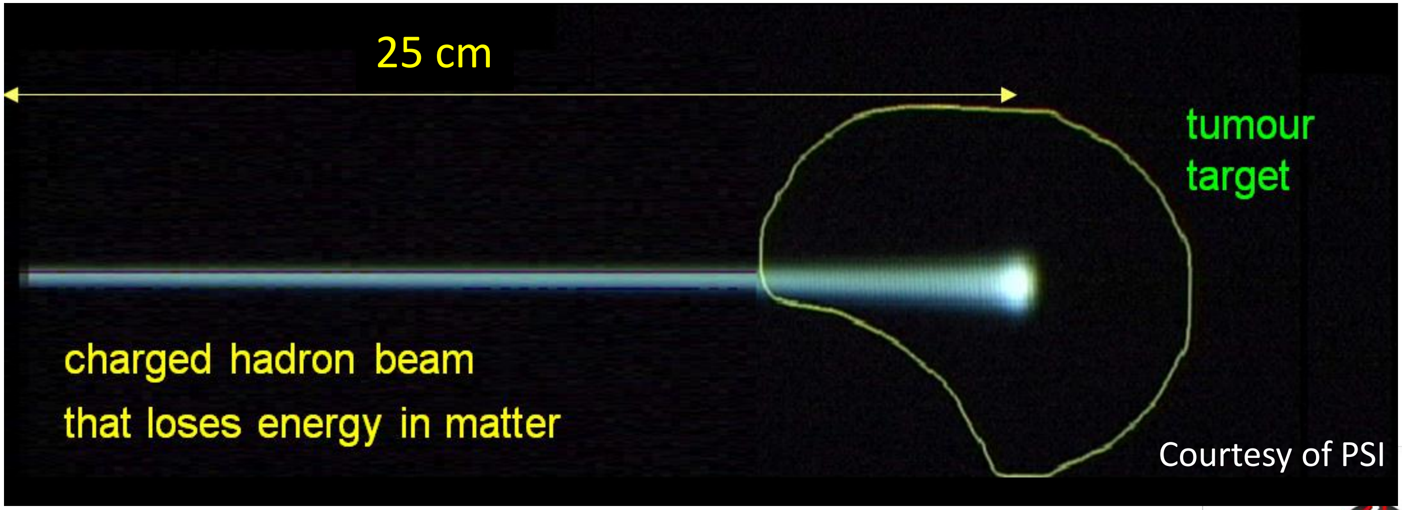
Protons and ions spare healthy tissues



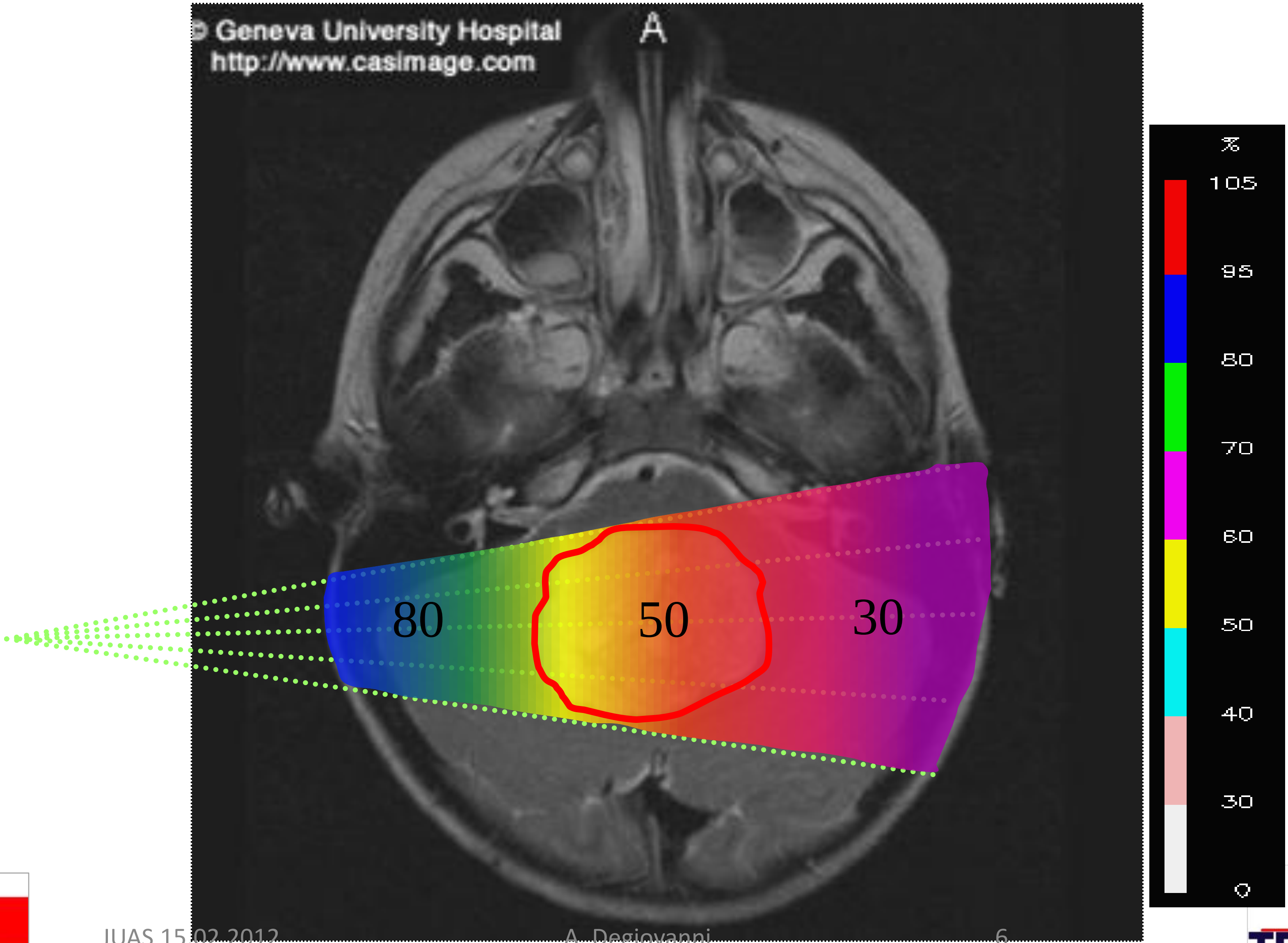
200 MeV - 1 nA protons

4800 MeV – 0.1 nA carbon ions

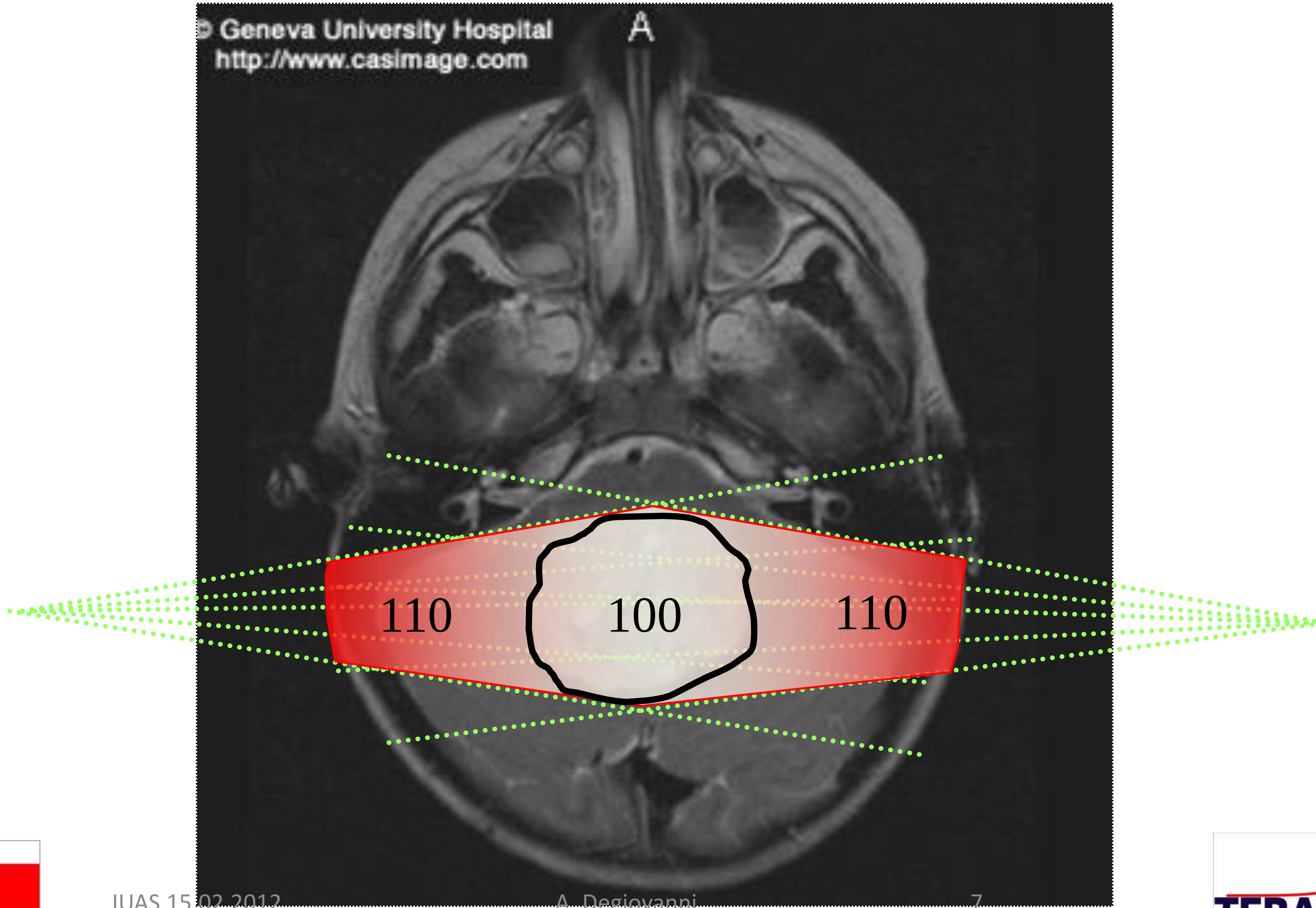
(radioresistant tumours)



One lateral photon beam deliver a non conformal dose



Two opposite photon beams are not enough to deliver a conformal dose



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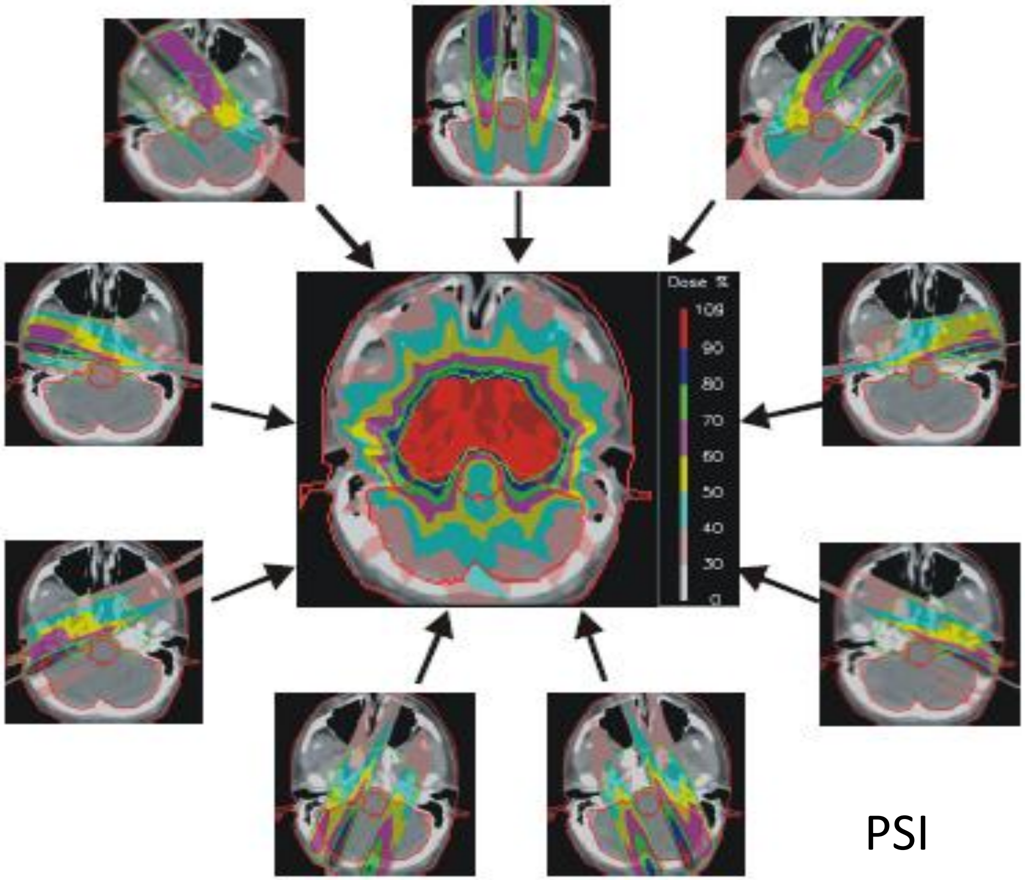
IMRT = Intensity Modulated Radiation Therapy with photons

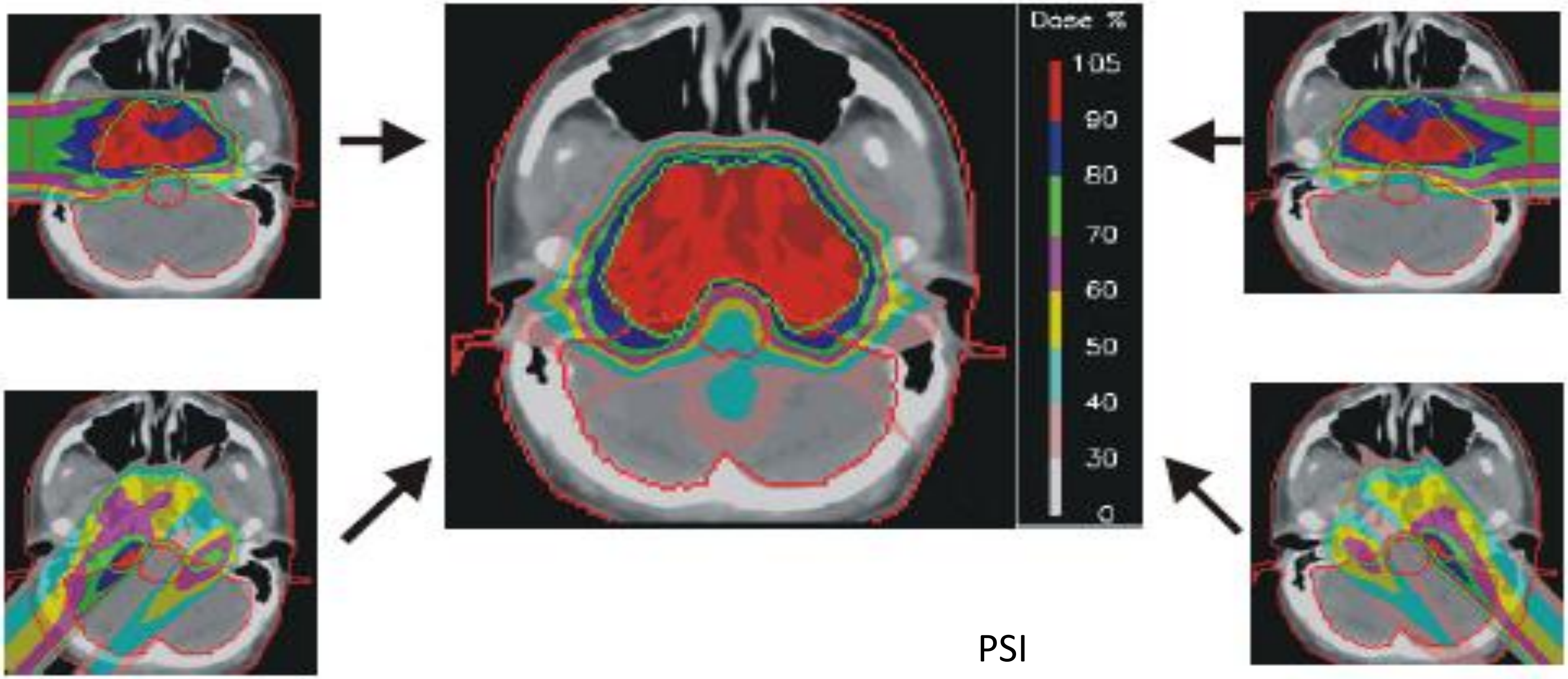
9 NON-UNIFORM FIELDS



PSI

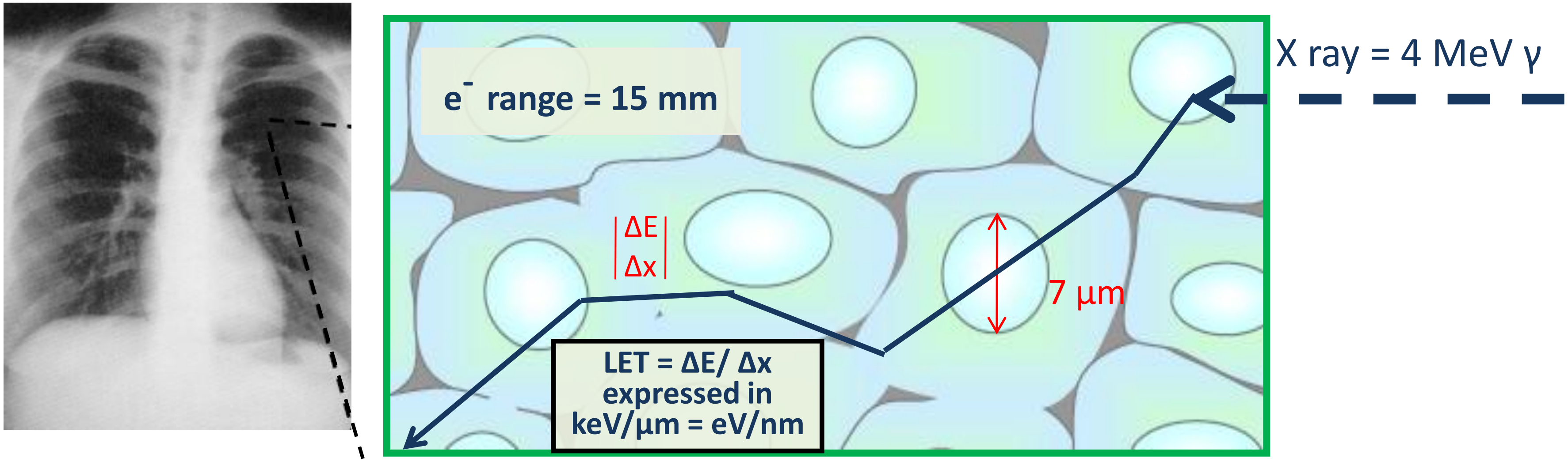
IMPT = Intensity Modulated Particle Therapy with protons

4 NON-UNIFORM FIELDS

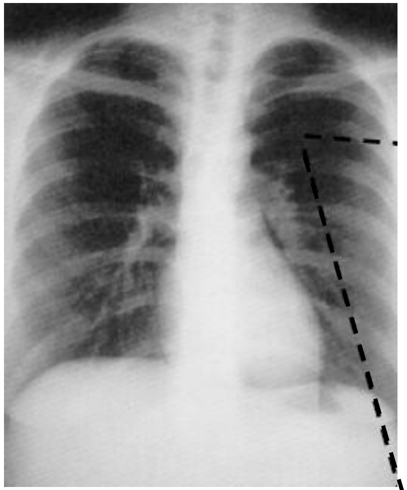


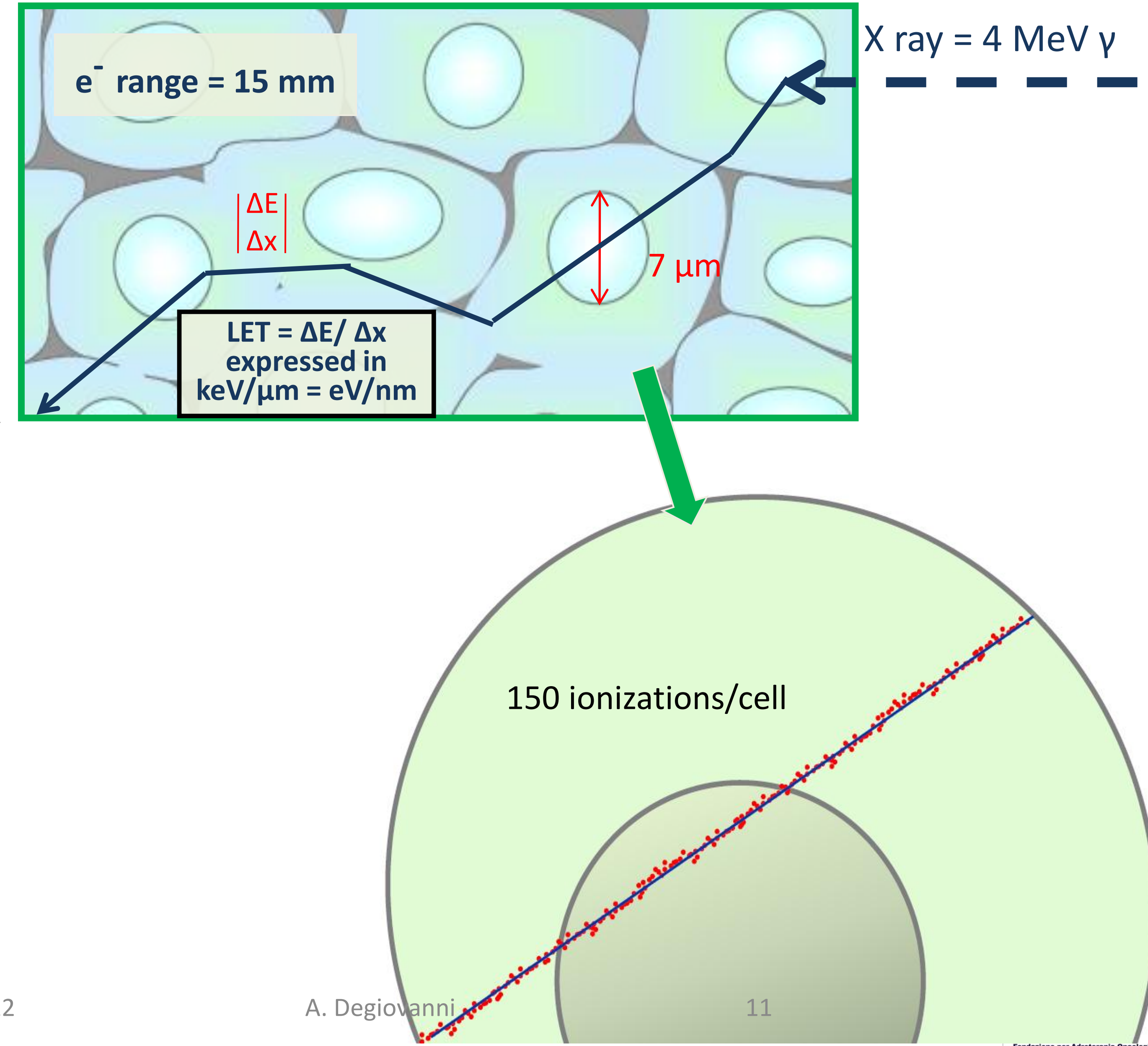
PSI

Microscopic distribution of the X-rays dose



Microscopic distribution of the X-rays dose





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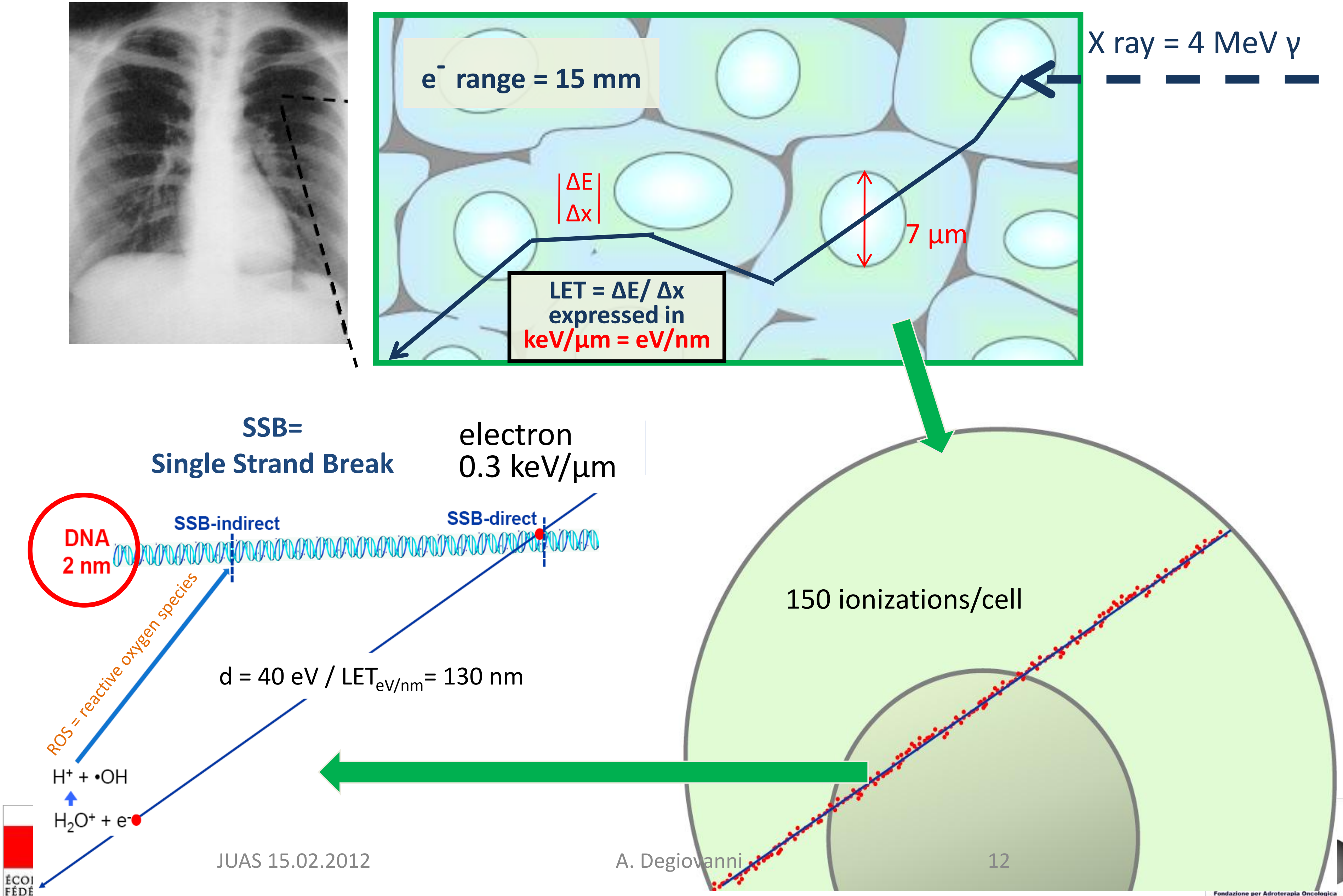
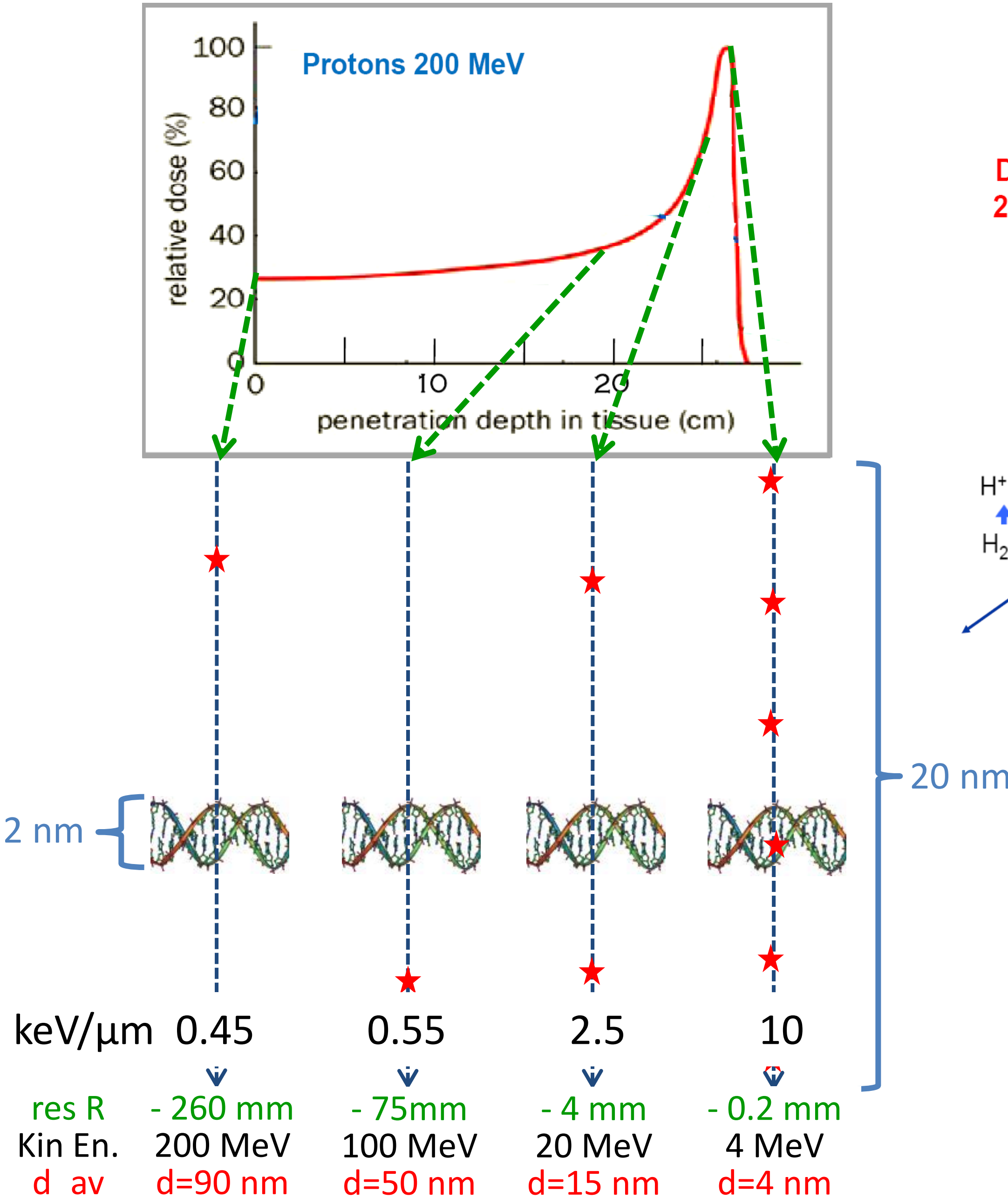
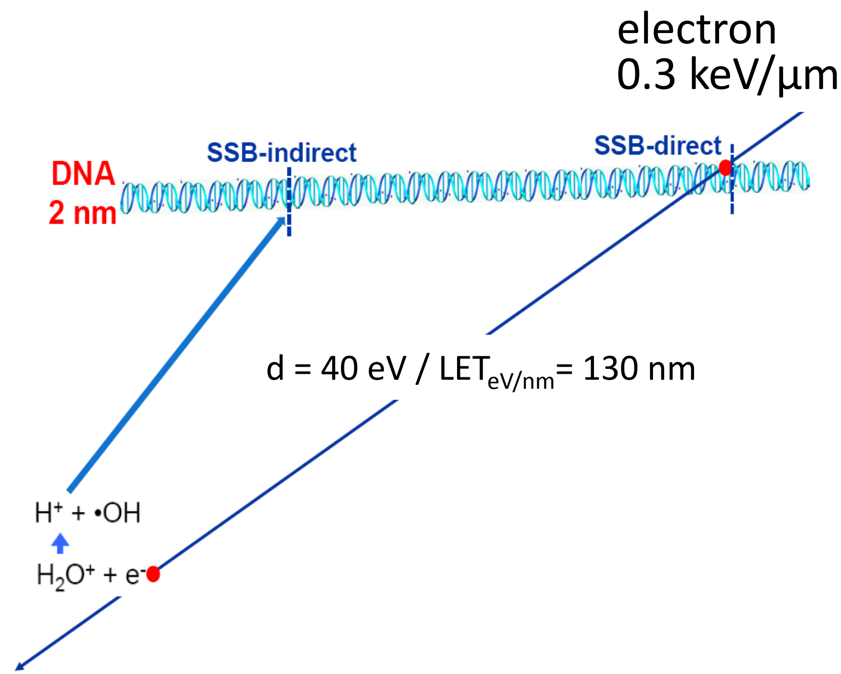
Fondazione per Adroterapia Oncologica

Microscopic distribution of the X-rays dose



Microscopic distribution of the hadronic ionizations

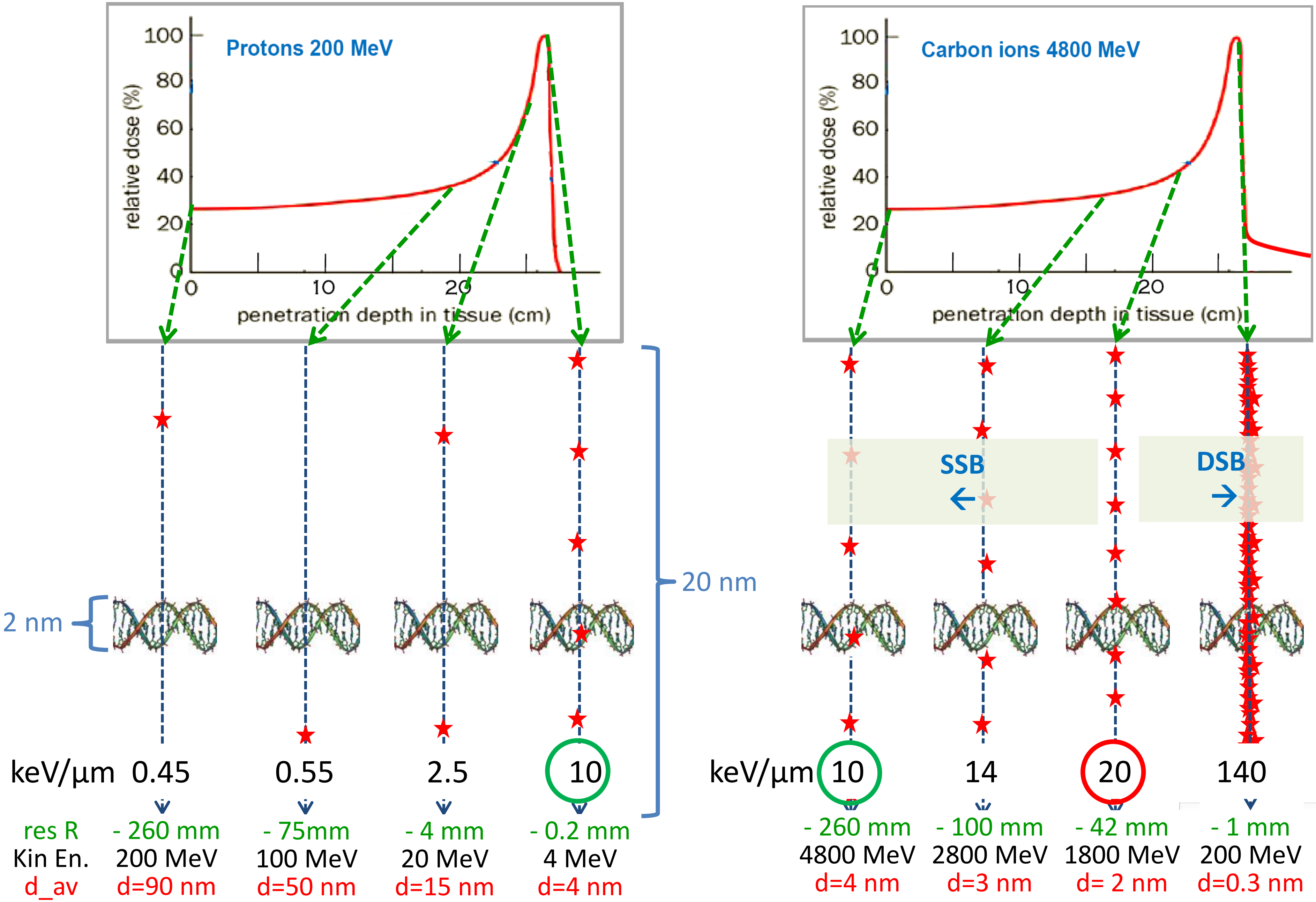




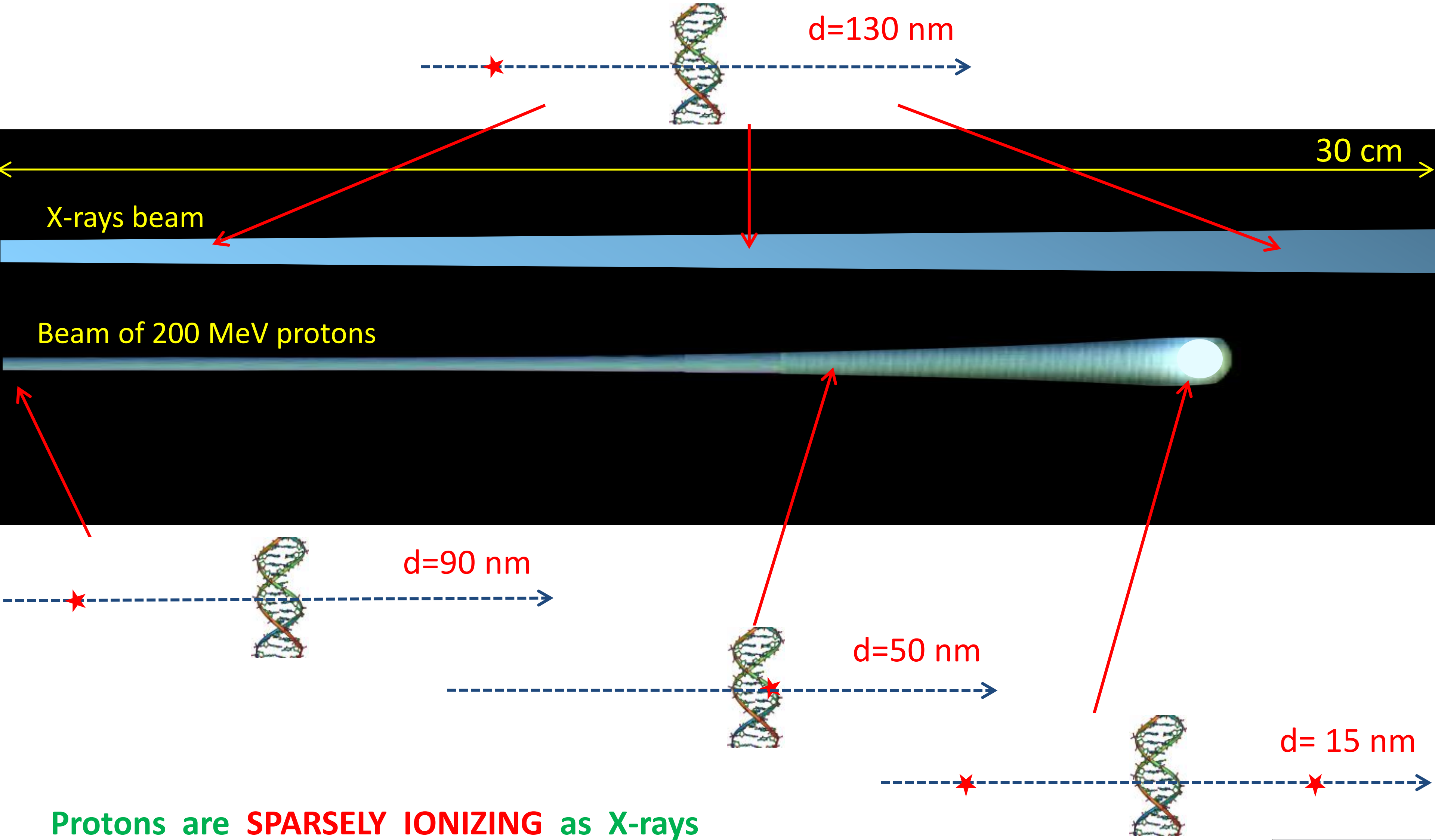
Protons are SPARSELY IONIZING

Protons are quantitatively different from X-rays

Microscopic distribution of the hadronic ionizations

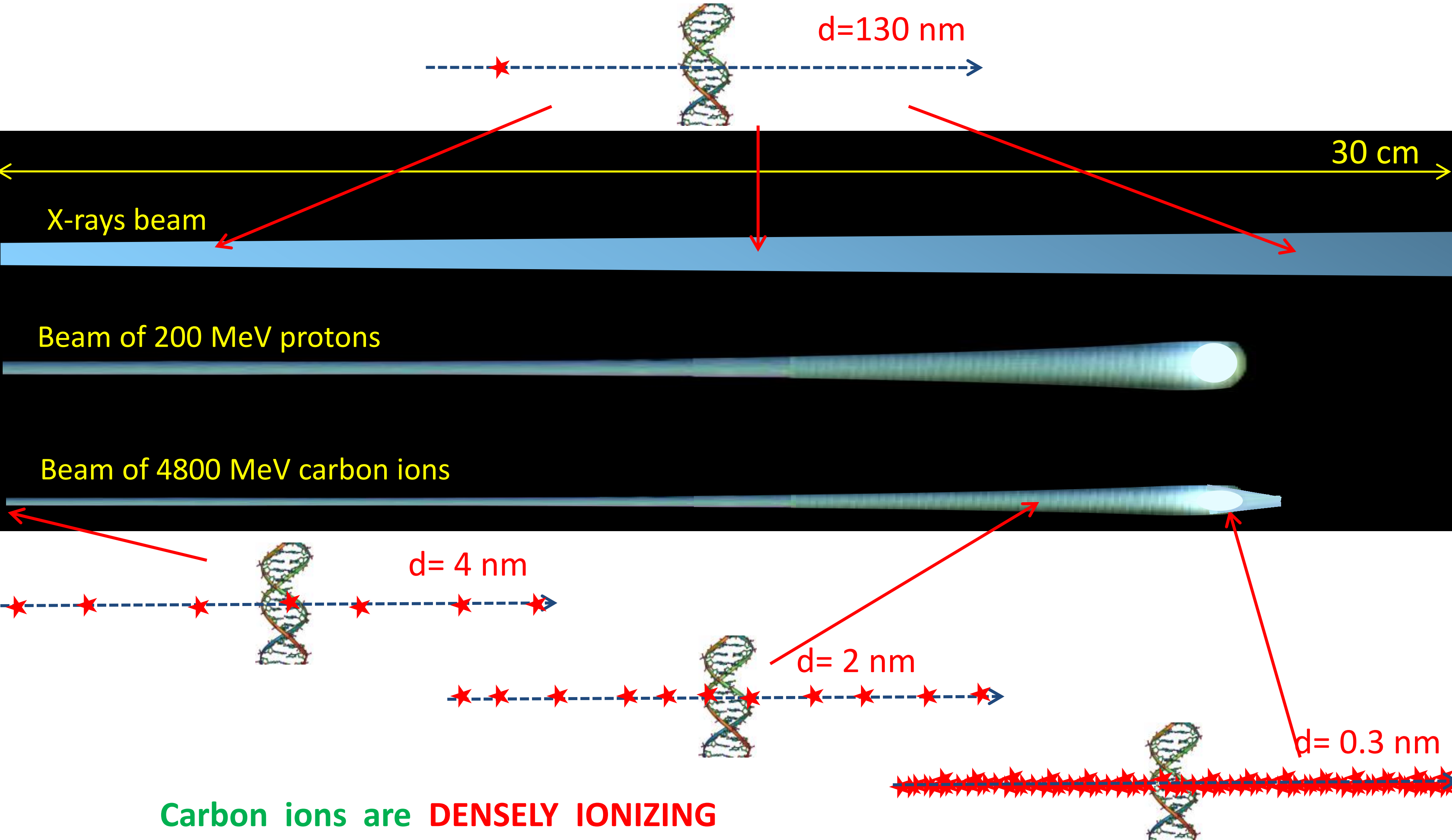


Protons: 1. more favorable dose 2. same '**indirect effects**'



Protons are SPARSELY IONIZING as X-rays

Carbon ions: 1. more favorable dose 2. '**direct effects**'



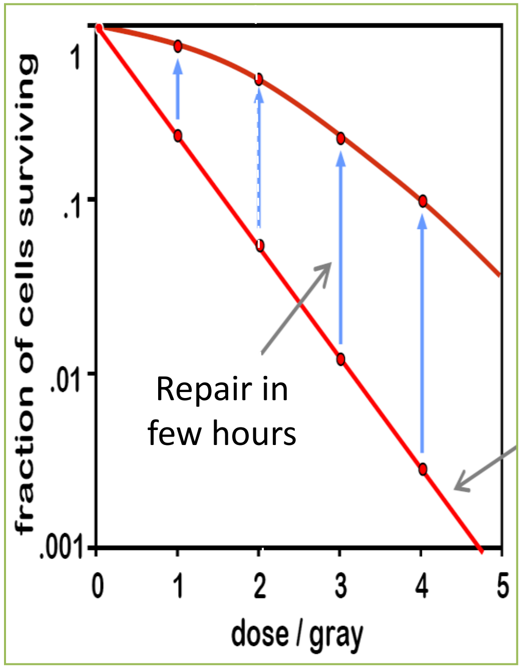
Carbon ions are DENSELY IONIZING
(higher biological effectiveness)

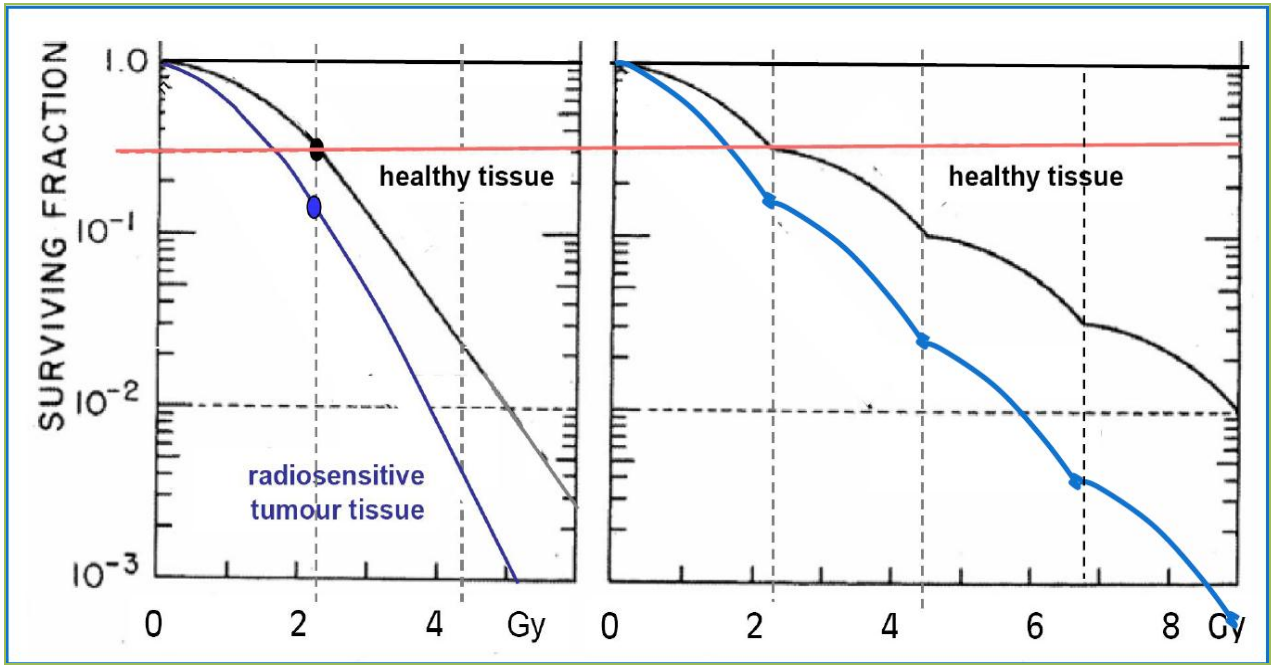
Part 1: Physics and radiobiology

Biological effects

Cell survival and fractionation

For 80-90 % of the solid tumours, the tumour tissues are more 'radiosensitive' than healthy tissues





1 gray = 1 Gy = 1 J/kg

30 000 ionizations per nucleus

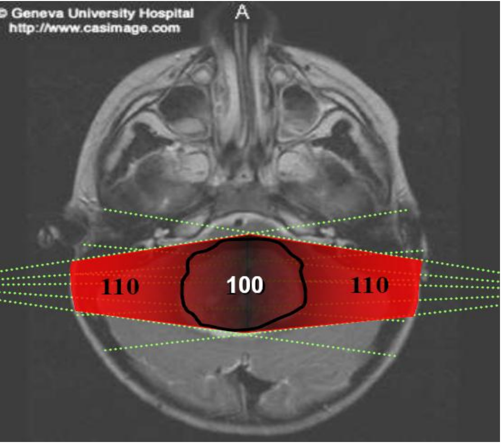
due to 200 electrons

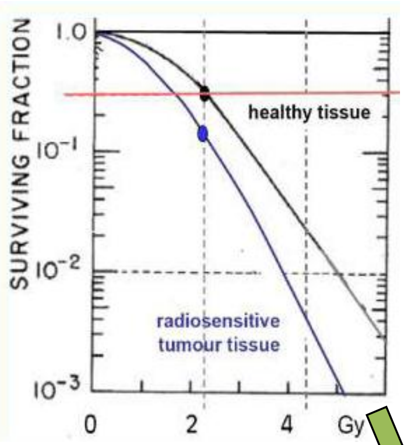
60-75 Gy are typically given in 30 fractions over 6 weeks so that healthy tissues have the time to repair. Argument:

$(1/2)^{30} = 10^{-9}$ and there are 10^{8} cells in 1 litre tumour

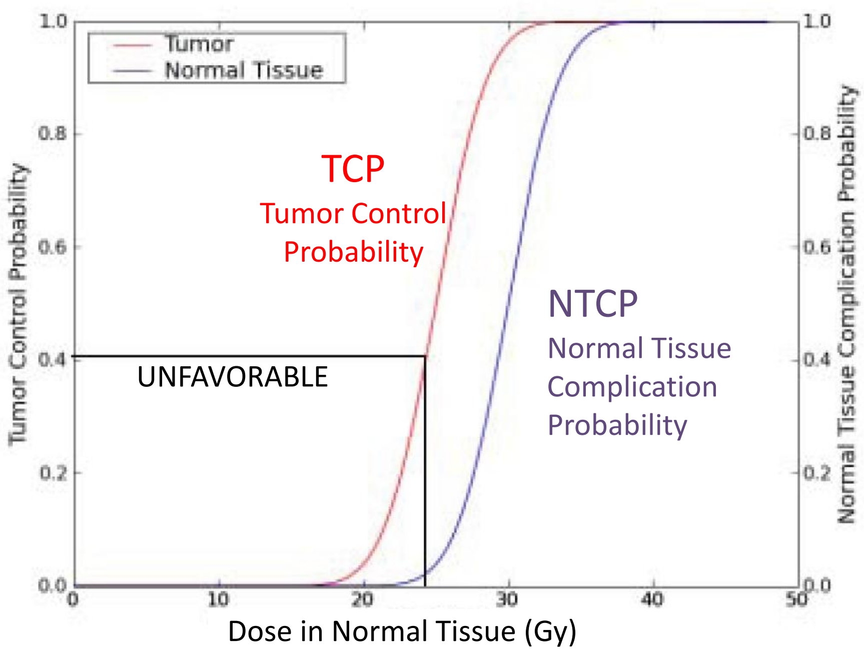
The tumour dose is limited by the nearby healthy tissues which cannot receive more than 30-40 Gy .

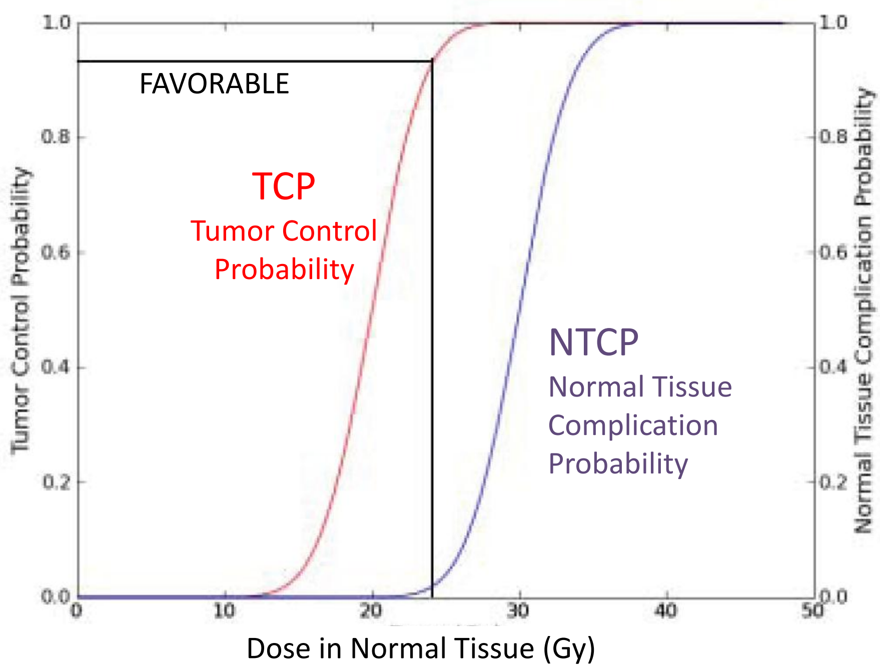
The therapeutic window





many biological and clinical phenomena in 30 sessions



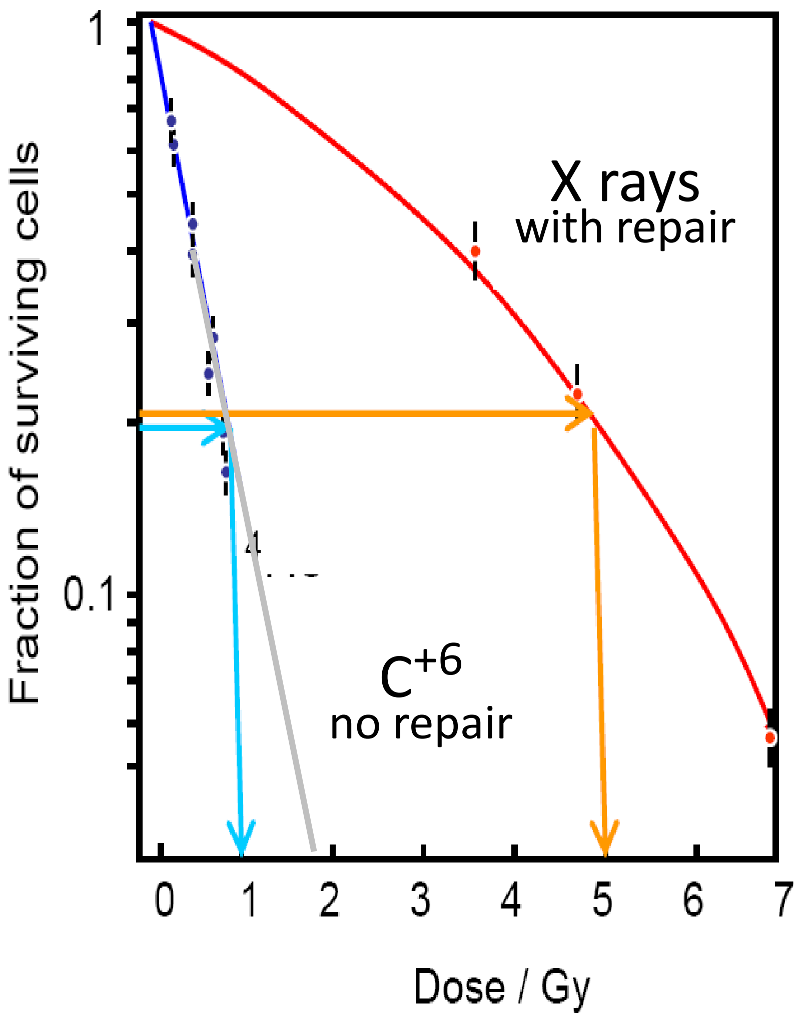


Definition of Radio-Biological Effectiveness (RBE)

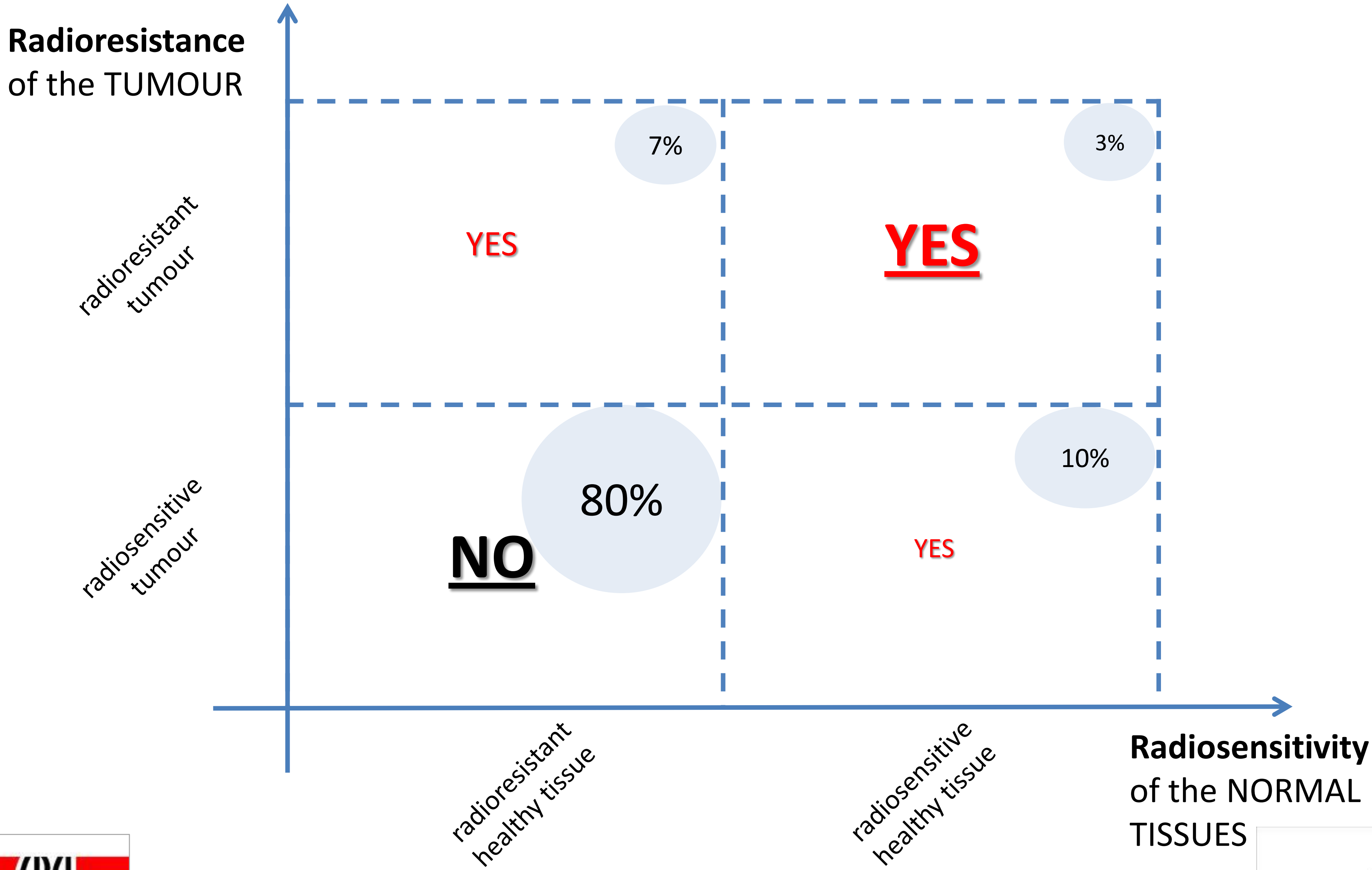
RBE is defined withe respect to standard X-rays:

$$RBE = \frac{D_\gamma}{D} = \frac{5}{1}$$

For a given effect on a given cell **the RBE value is a function of LET**



Elective indications of carbon ions



Numbers of potential patients (*)

- X-ray therapy

  every 10 million inhabitants: 20'000 pts/year

- Protontherapy

  12% of X-ray patients 2'400 pts/year

- Therapy with Carbon ions for radio-resistant tumour

  3% of X-ray patients 600 pts/year

TOTAL every 10 M about 3'000 pts/year

(*) Combining studies made in Austria, Germany, France and Italy in the framework of ENLIGHT - Coordinator: Manjit Dosanjh –

Projects in FP7: ULICE, PARTNER, ENVISION , ENTERVISION for a total of 22 MEuro

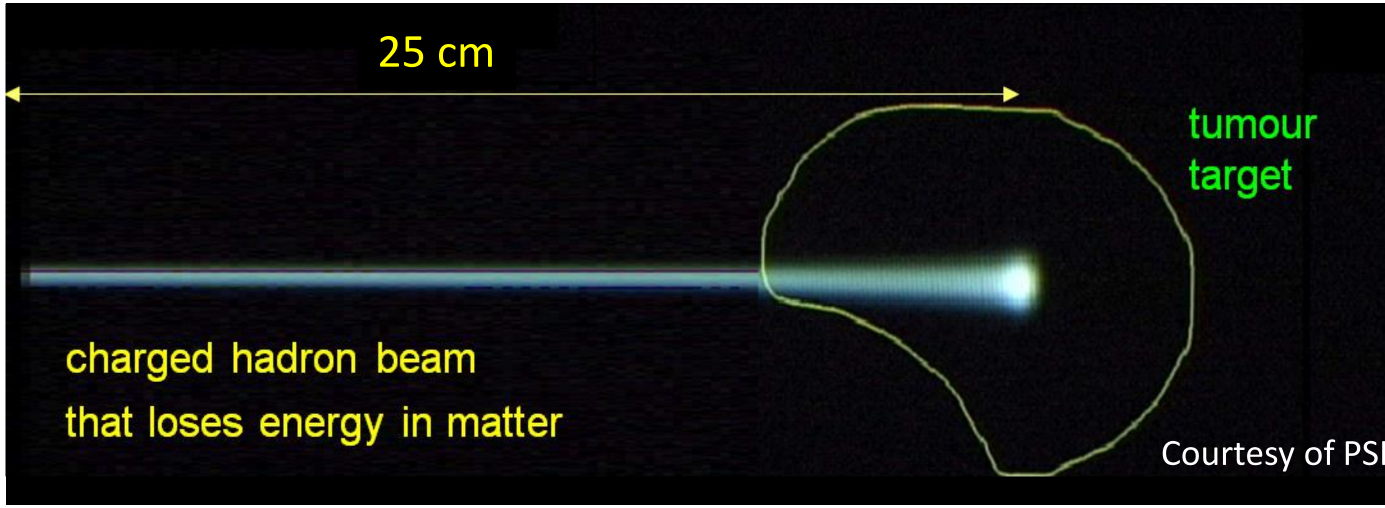
Summary 1st part

The basic principles of hadrontherapy

200 MeV - 1 nA protons

4800 MeV – 0.1 nA carbon ions

<u>(radioresistant tumours)</u>

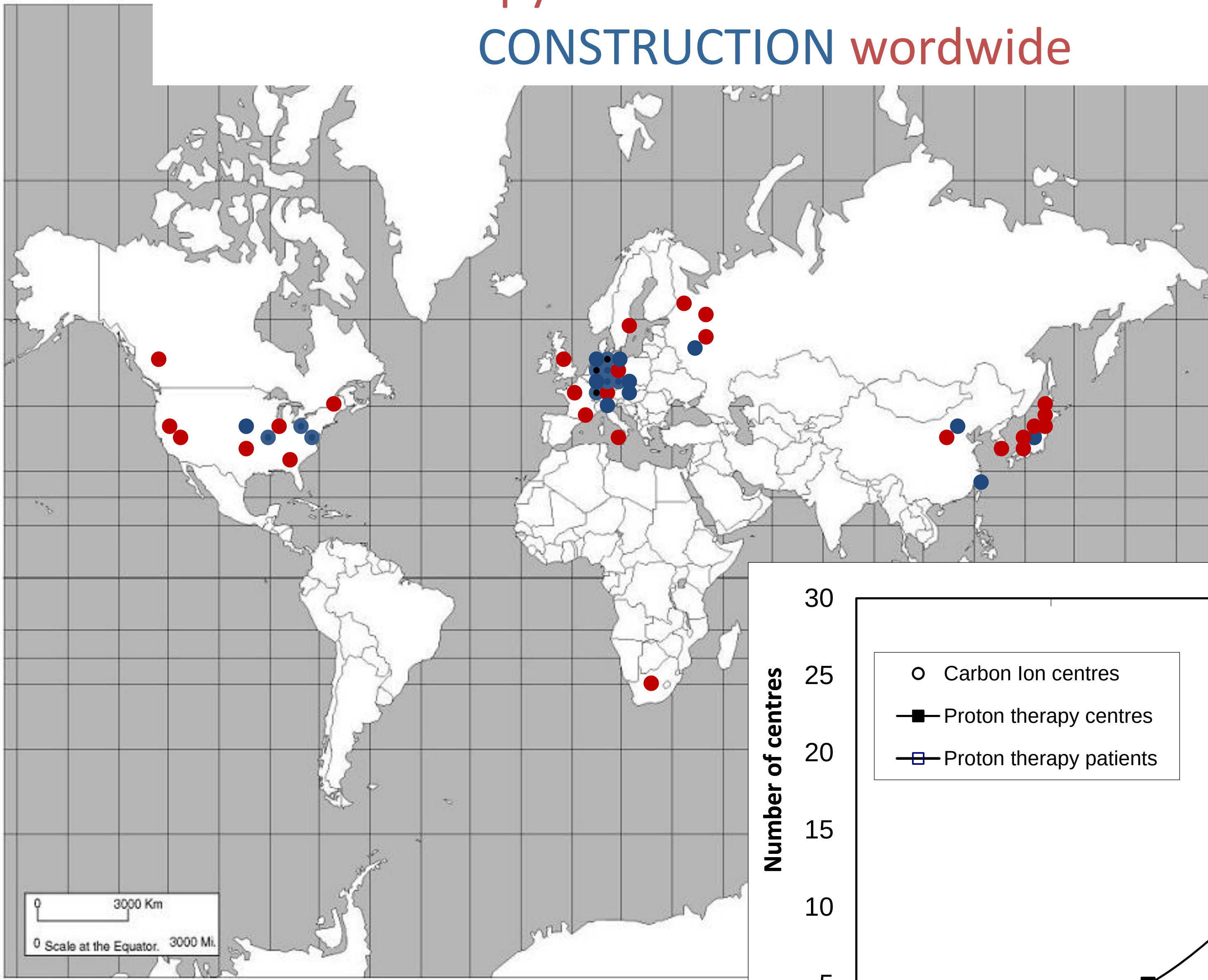


- ***First idea***
  - Bob Wilson, 1946 [R. R. Wilson, Radiology 47 (1946) 487]
- ***Bragg peak***
  - Better conformity of the dose to the target → <u>healthy tissue sparing</u>
- ***Hadrons are charged***
  - Beam scanning for dose distribution
- ***Heavy ions***
  - Higher biological effectiveness (RBE)

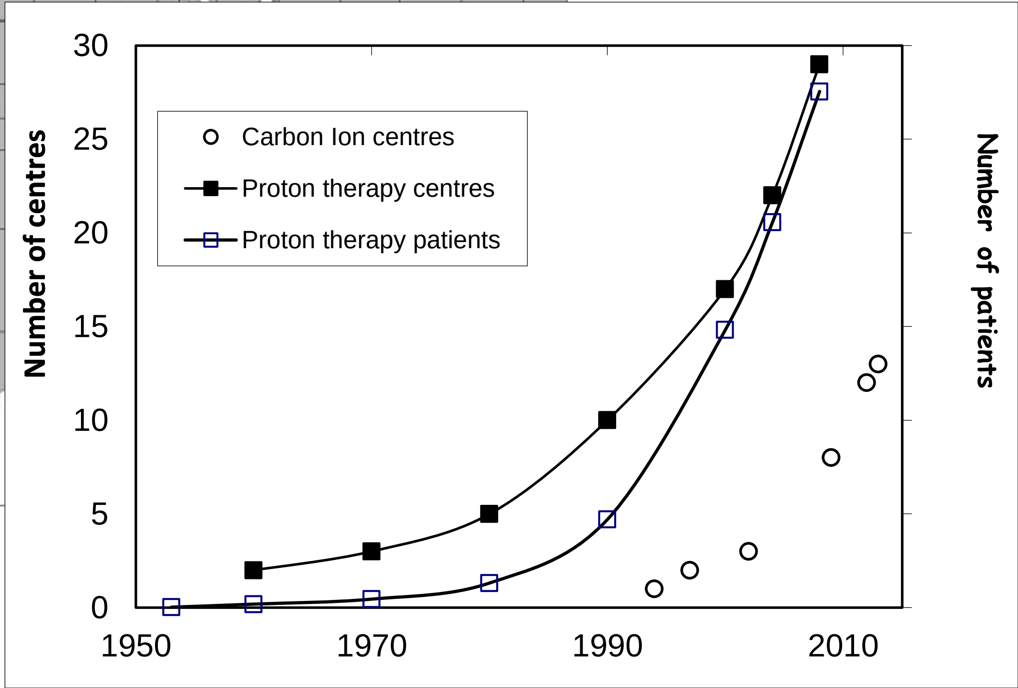
Part 2: Accelerators and technology

Accelerators for hadrontherapy

Hadrontherapy centres IN OPERATION and UNDER CONSTRUCTION wordwide



- Under construction
- In operation



M. Dosanjh (PTCOG Data)

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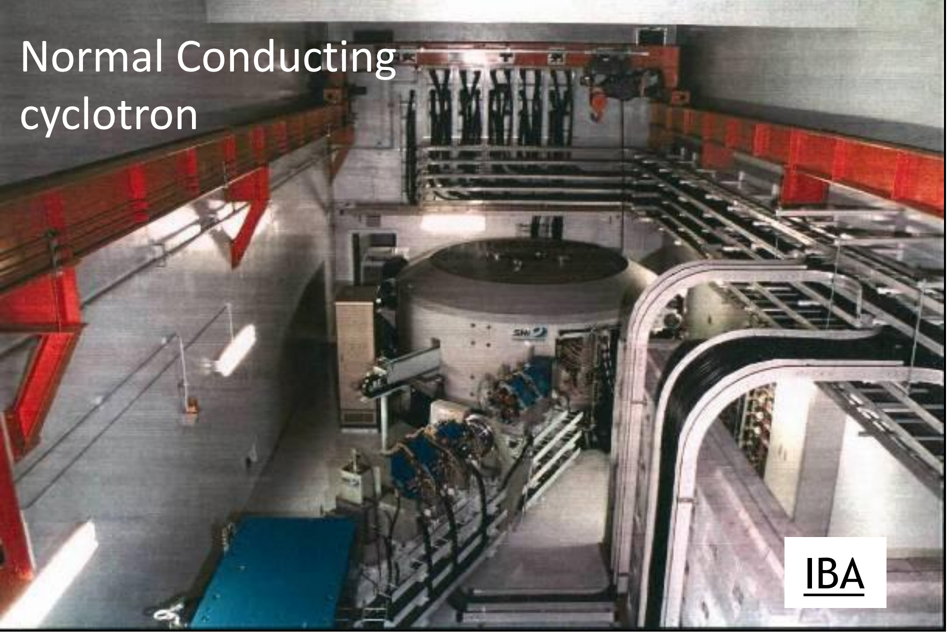
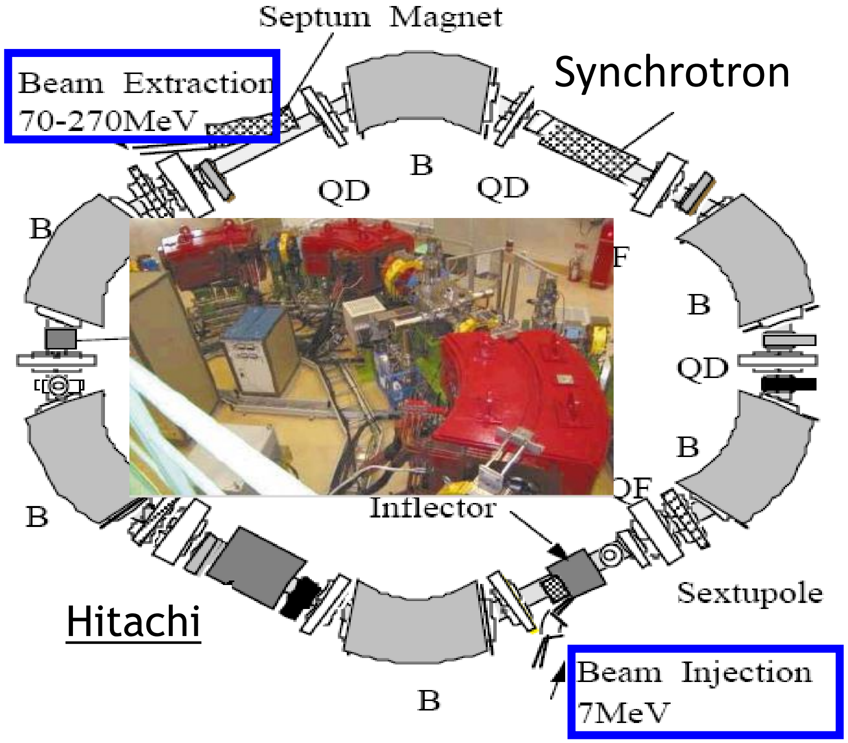
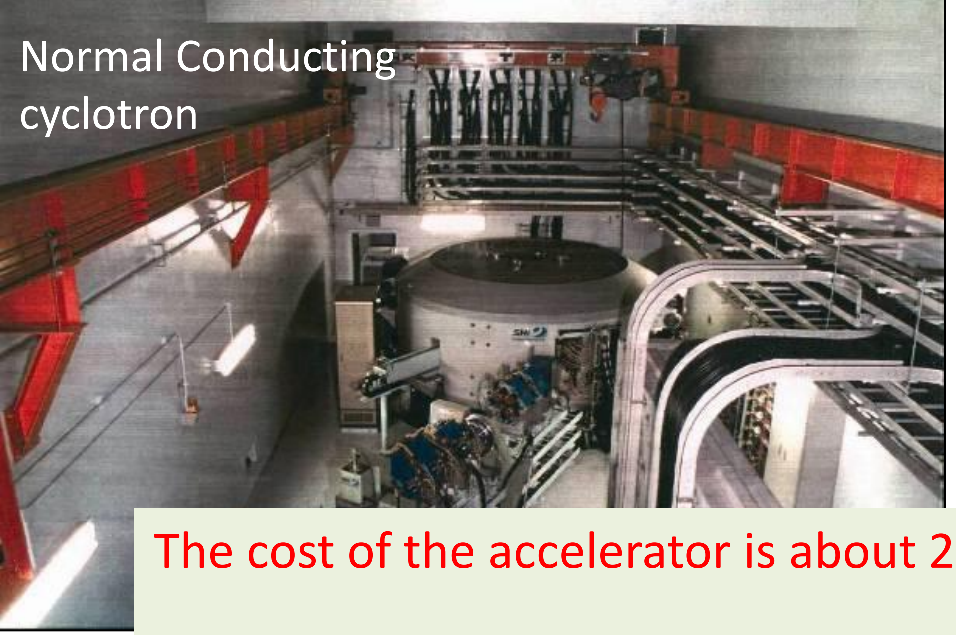
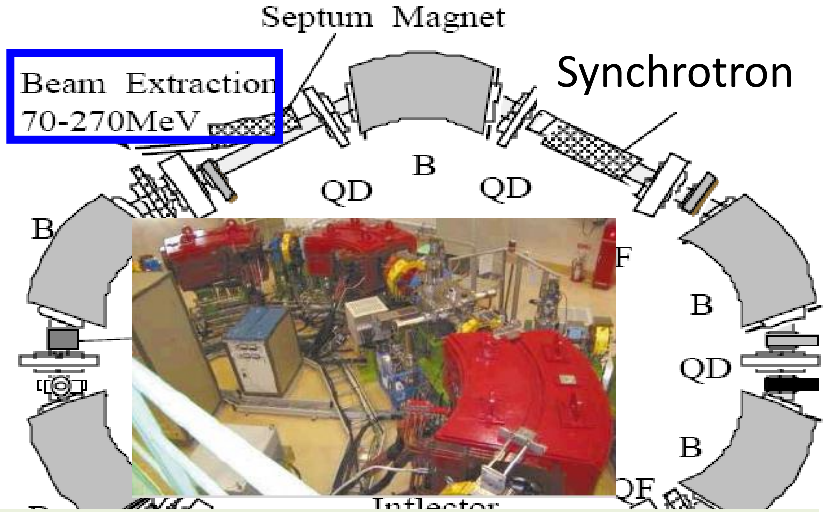
Proton accelerators





4 commercial 230-250 MeV p^+ accelerators



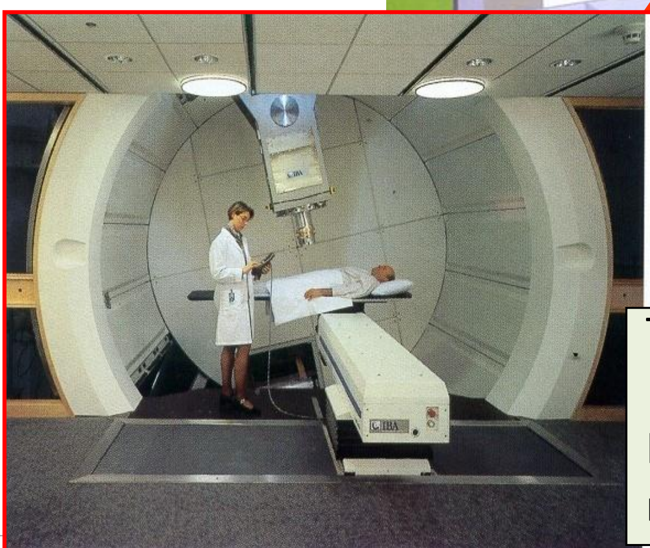


The cost of the accelerator is about 20% of the cost of the centre:

accelerator	20%	
building	20%	
3 gantries	20%	**(~30 MEuro)**

4 cor

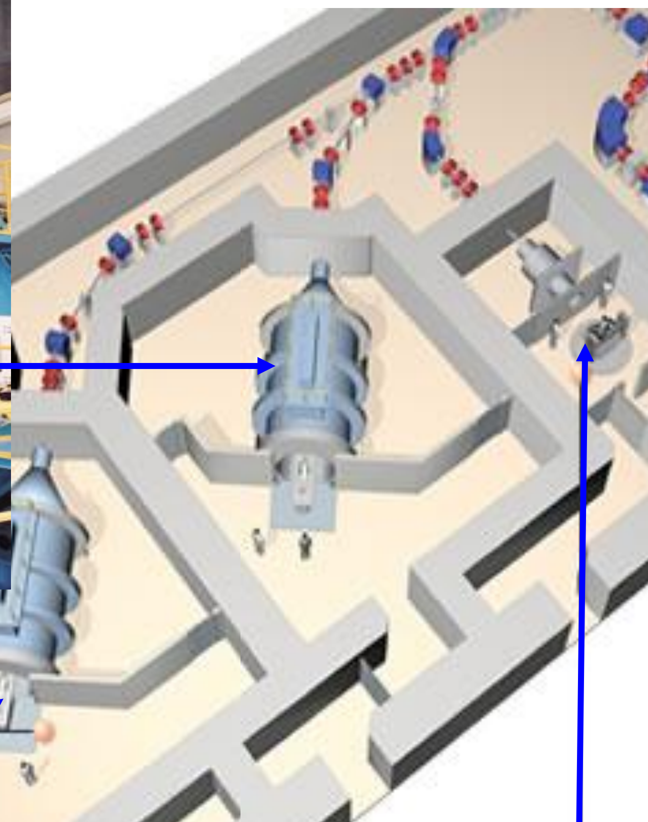
Cyclotron for protons by Ion Beam Applications - Belgium

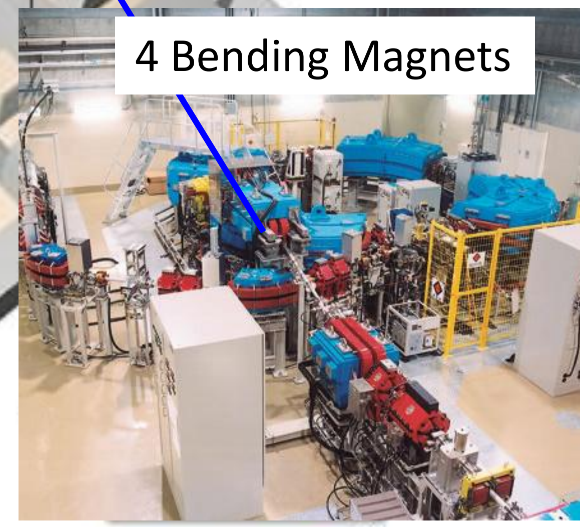


Turn-key centres are offered for ≈150-180 M€.

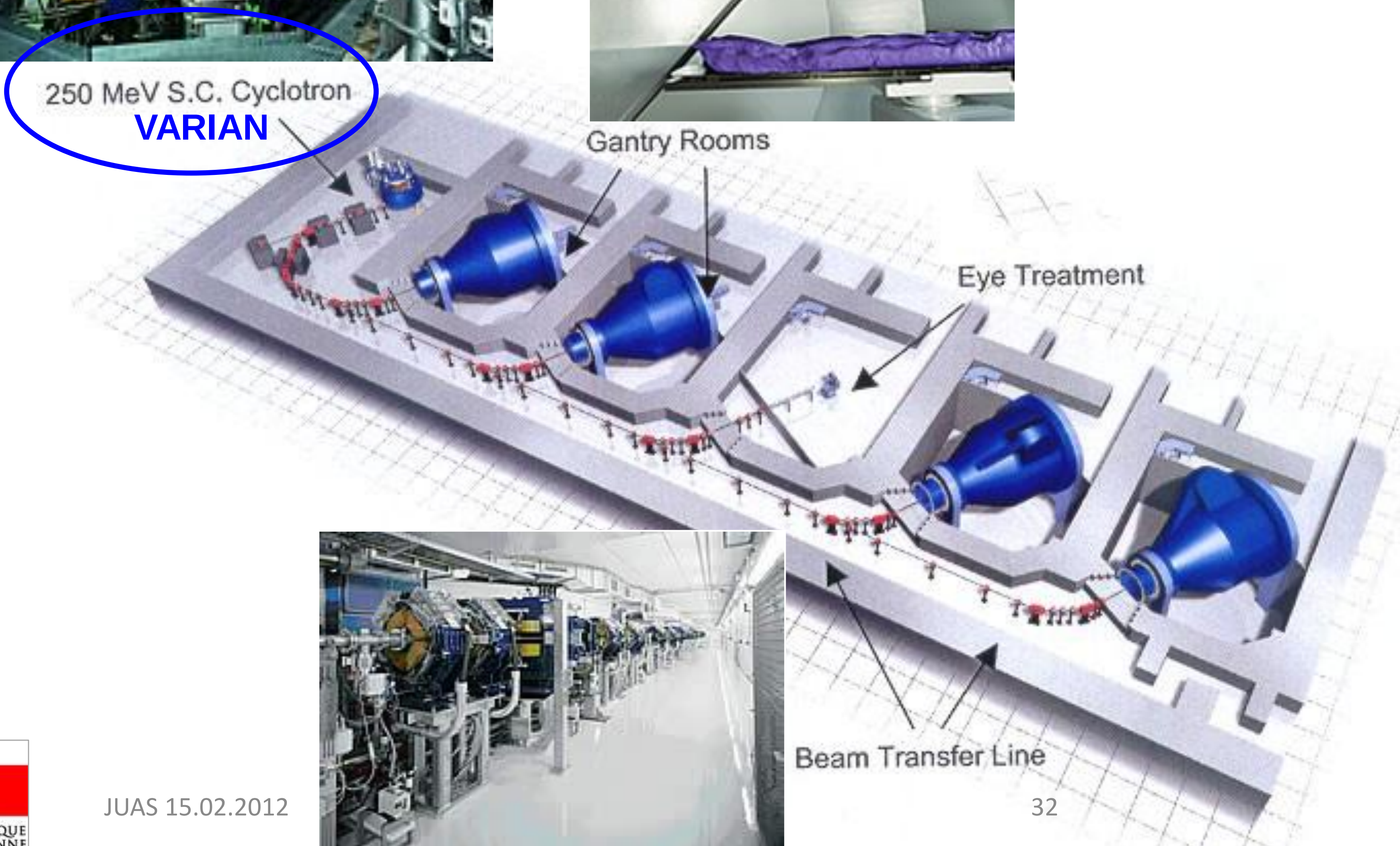
If proton accelerators were ‘small’ and ‘cheap’,
no radiation oncologist would use X rays.

Mitsubishi solution for Shizuoka - Japan





Rinecker Proton Therapy Centre Munich



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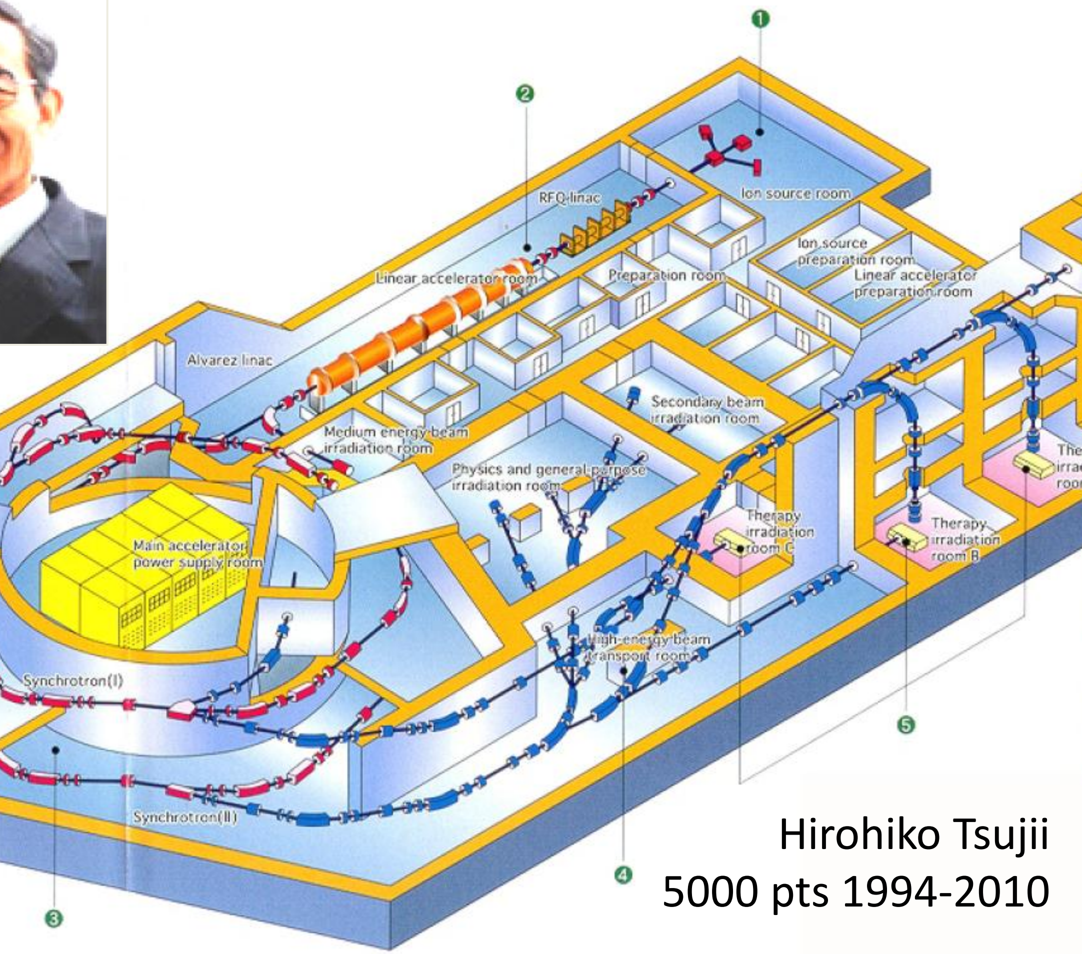
Dual centers
(p^+ / C^{6+} accelerators)

HIMAC in Chiba is the pioneer of carbon therapy

Yasuo Hirao

[15] Hirao, Y. et al, "Heavy Ion Synchrotron for Medical Use: HIMAC Project at NIRS Japan" Nucl. Phys. A538, 541c (1992)

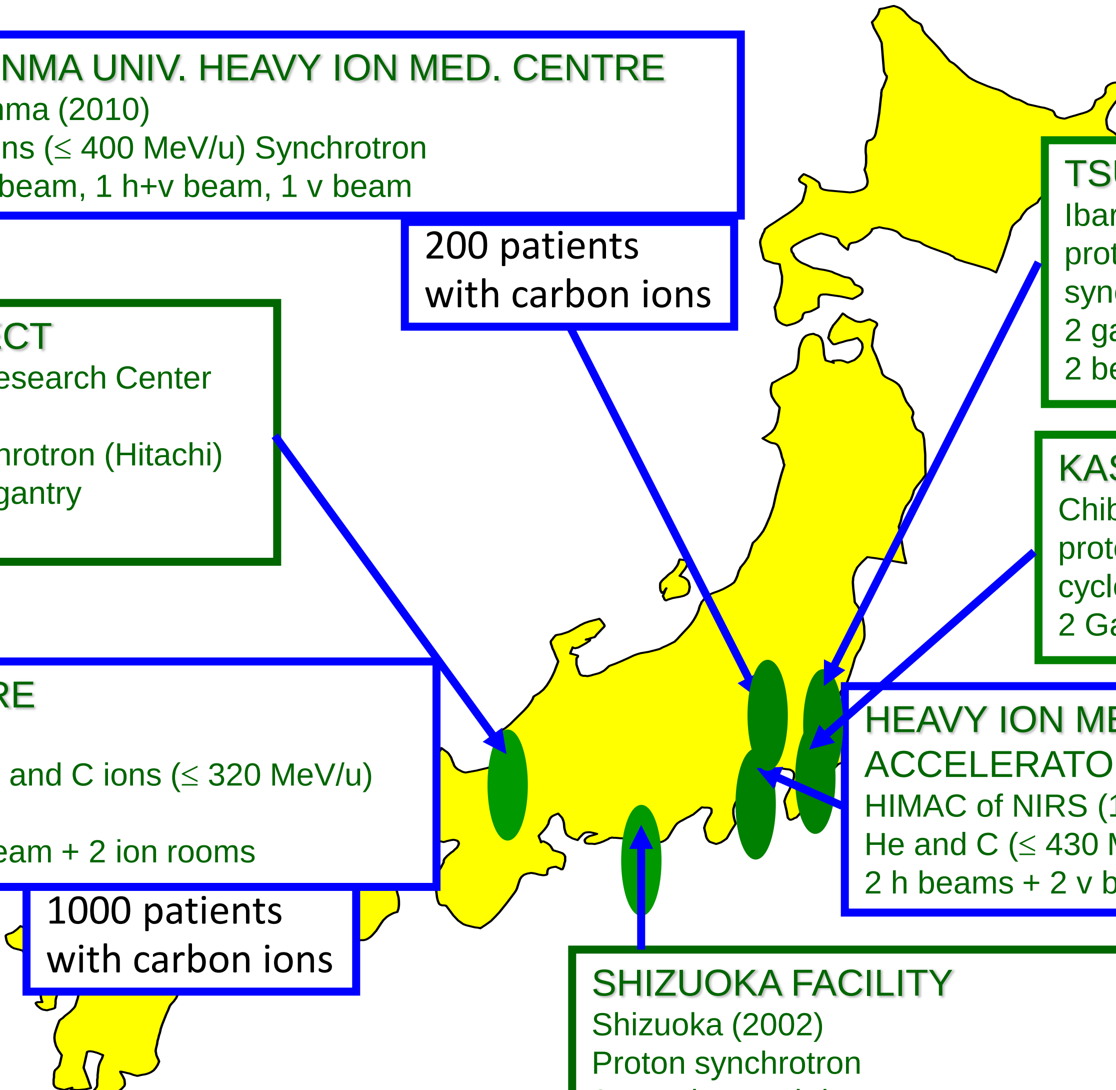


Hirohiko Tsujii
5000 pts 1994-2010

Since the cells do not repair. less fractions are possible

HIMAC: 4-9 fractions!

Japan is the best equipped region



GUNMA UNIV. HEAVY ION MED. CENTRE
Gunma (2010)
C ions (≤ 400 MeV/u) Synchrotron
1 h beam, 1 h+v beam, 1 v beam

200 patients
with carbon ions

TSUKUBA CENTRE
Ibaraki (2001)
protons (≤ 270 MeV)
synchrotron (Hitachi)
2 gantries
2 beam for research

WAKASA BAY PROJECT
by Wakasa-Bay Energy Research Center
Fukui (2002)
protons (≤ 200 MeV) synchrotron (Hitachi)
1 h beam + 1 v beam + 1 gantry

KASHIWA CENTER
Chiba (1998)
protons (≤ 235 MeV)
cyclotron (IBA – SHI)
2 Gantries + 1 hor. beam

HYOGO MED CENTRE
Hyogo (2001)
protons (≤ 230 MeV) - He and C ions (≤ 320 MeV/u)
Mitsubishi synchrotron
2 p gantries + 2 fixed p beam + 2 ion rooms

1000 patients
with carbon ions

HEAVY ION MEDICAL ACCELERATOR
HIMAC of NIRS (1995)
He and C (≤ 430 MeV/u) 2 synchrotrons
2 h beams + 2 v beams

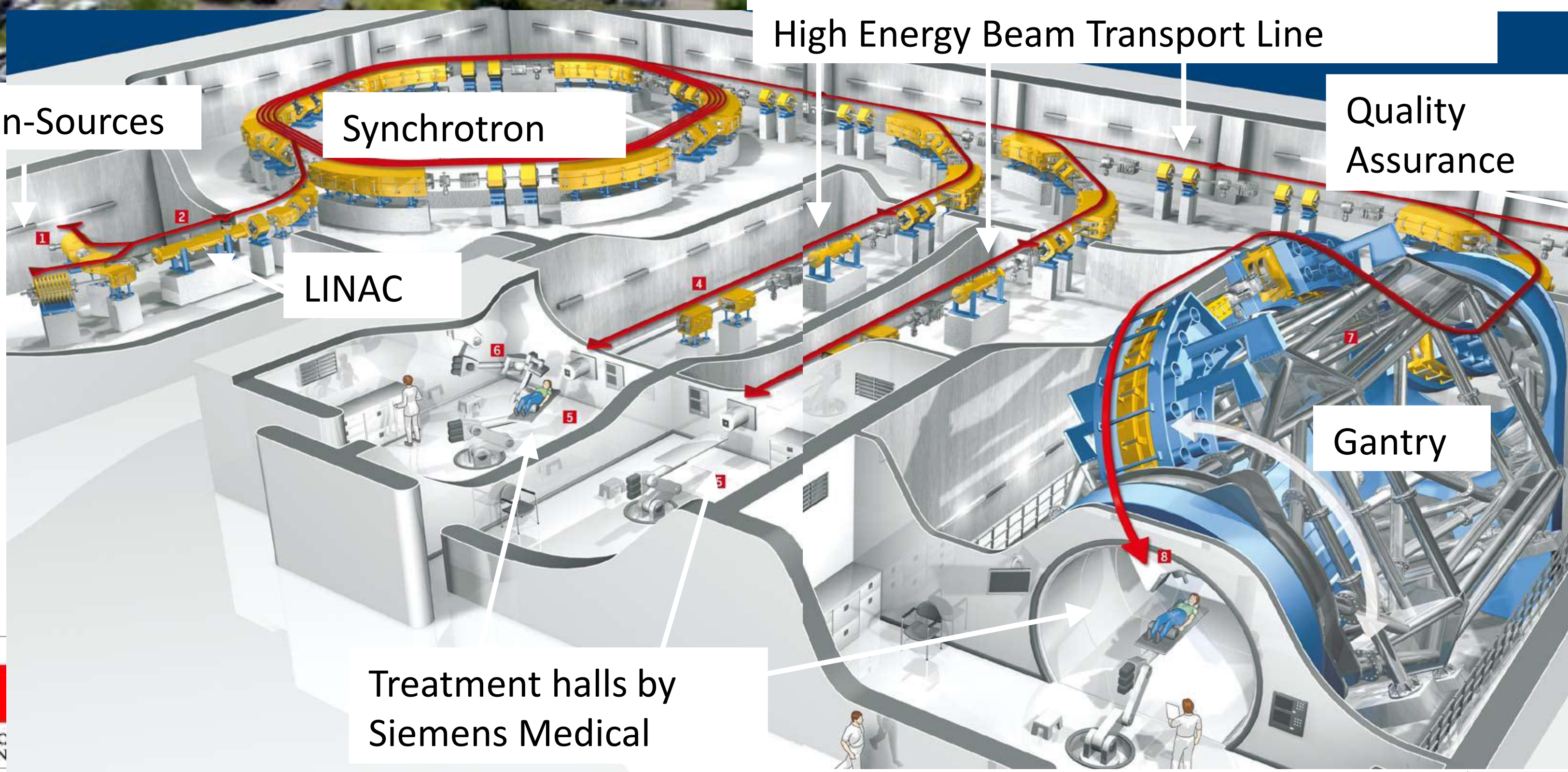
6500 patients
with carbon ions

SHIZUOKA FACILITY
Shizuoka (2002)
Proton synchrotron
2 gantries + 1 h beam

HIT at Heidelberg

Medical Director: J. Debus
Technical Director: T. Haberer

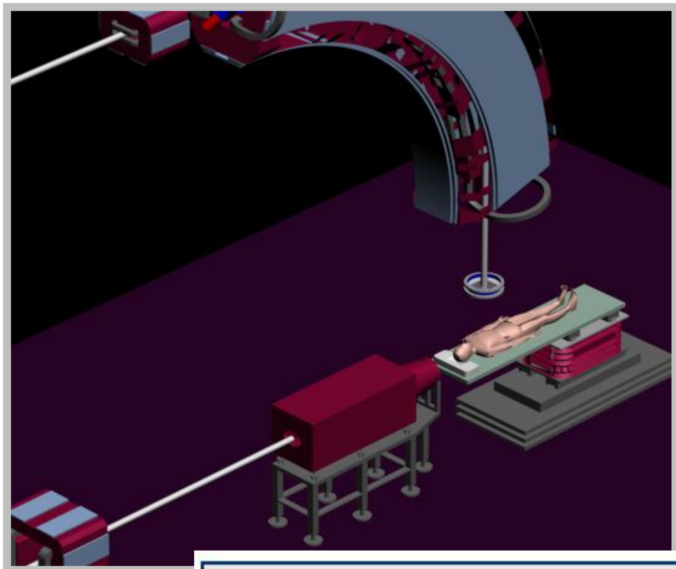
First patient: September 2009
At present: about 600 patients

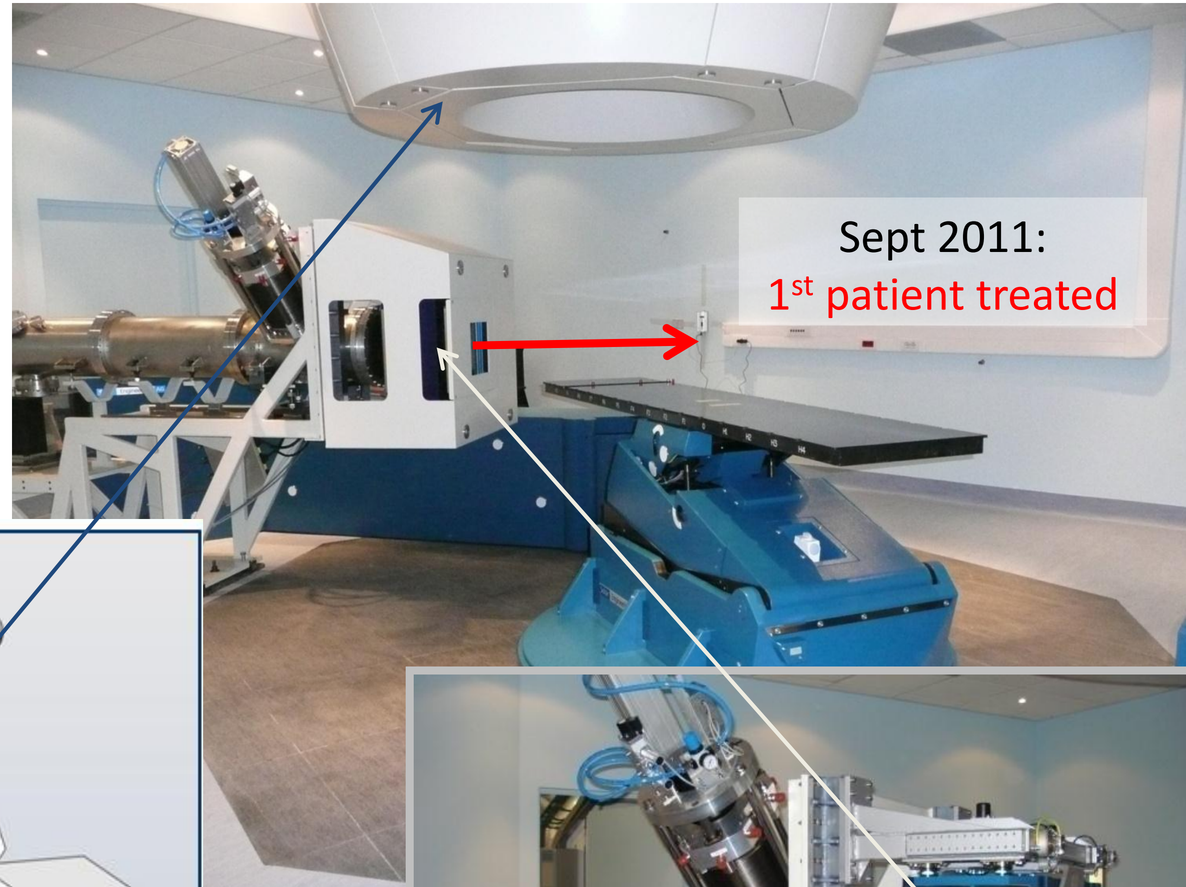


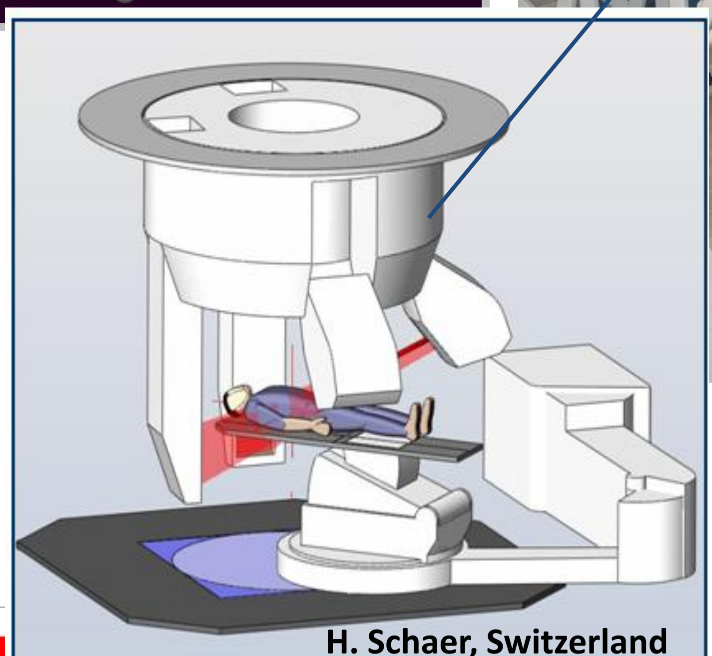
CNAO: Centro Nazionale Adroterapia Oncologica at Pavia

The CNAO Synchrotron for protons and carbon ions

CNAO: the treatment room







Sept 2011:
1st patient treated

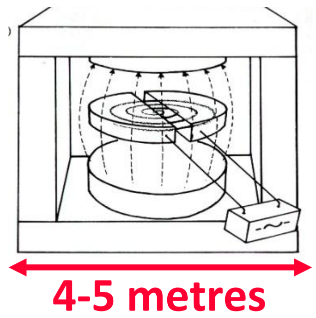
Part 2: Accelerators and technology

Treatment modalities

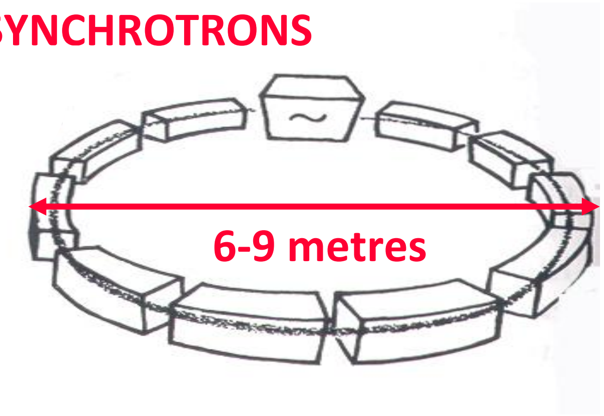
The accelerators used today in hadrotherapy are "circular"

Teletherapy with protons (200-250 MeV)

CYCLOTRONS (*) (Normal or SC)



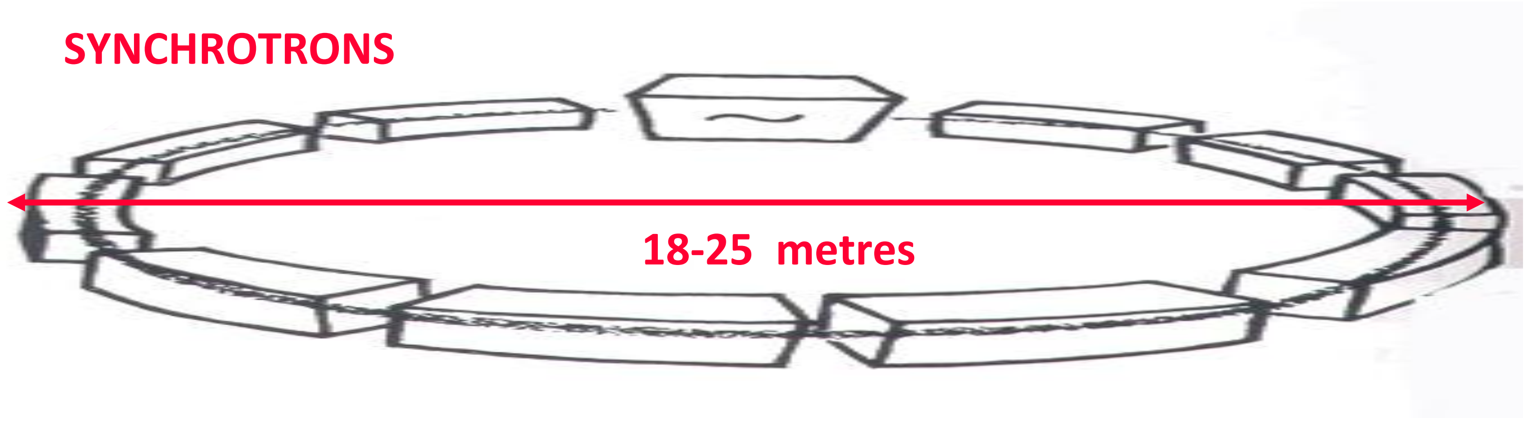
SYNCHROTRONS



(*) also synchrocyclotrons

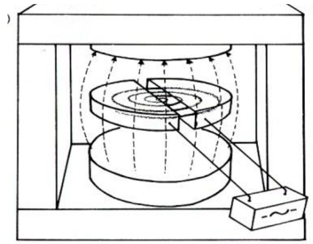
Teletherapy with carbon ions (4800 MeV = 400 MeV/u)

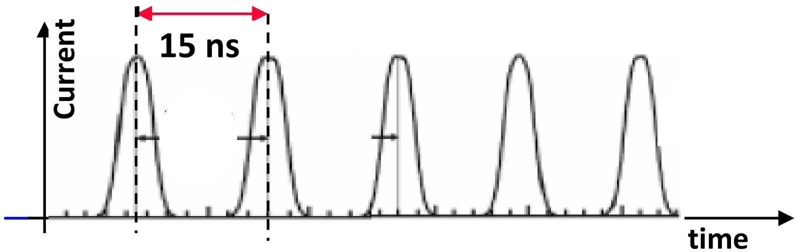
SYNCHROTRONS



The beam time structures are very different

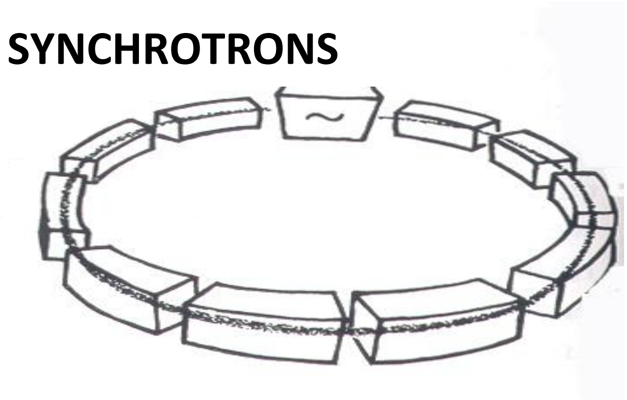
CYCLOTRONS (*) (Normal or SC)

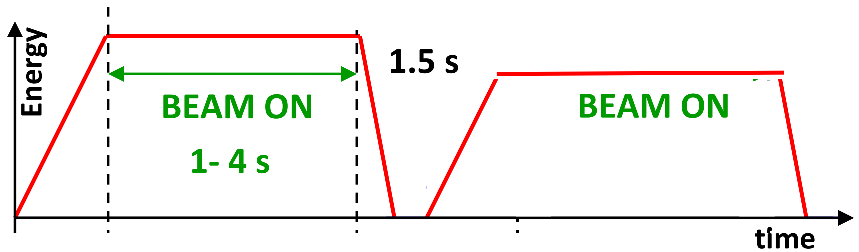




The pulsed beam of fixed energy
is always present

SYNCHROTRONS





A cycling beam of variable energy
has 1 second gaps

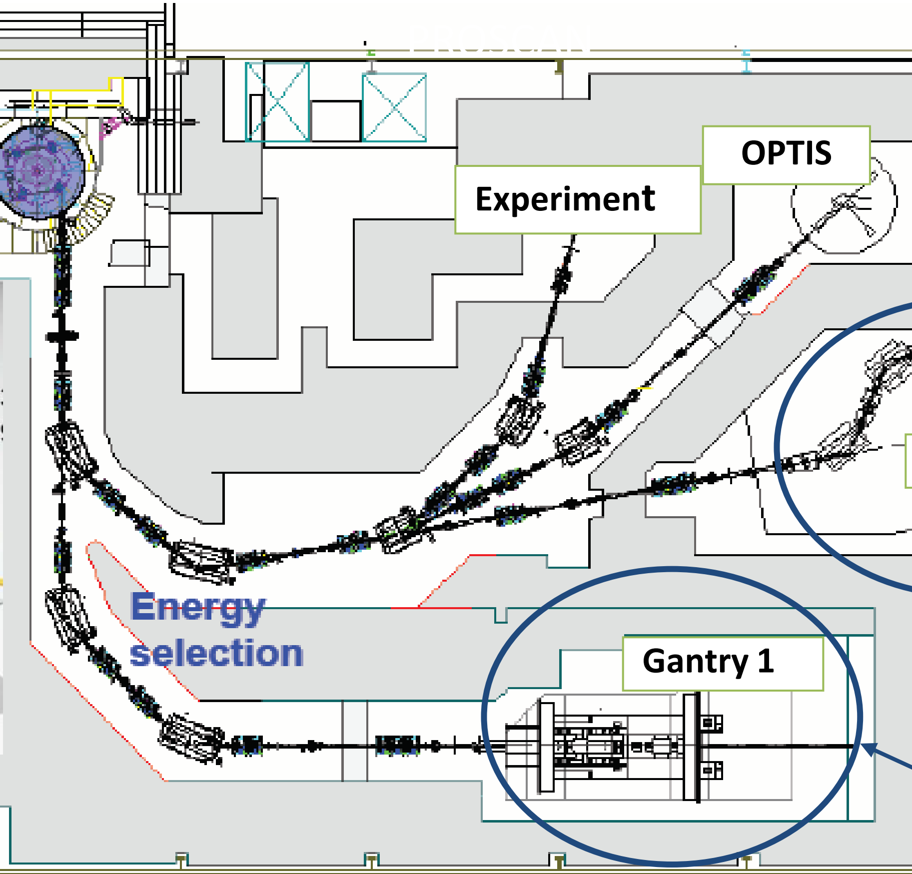
(*) A synchrocyclotron cycles at hundreds Hertz

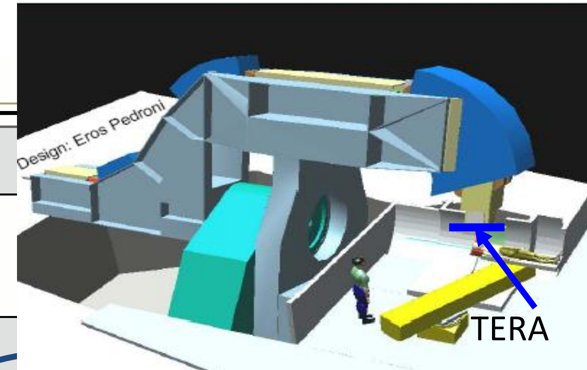
Properties of the beams of different accelerators

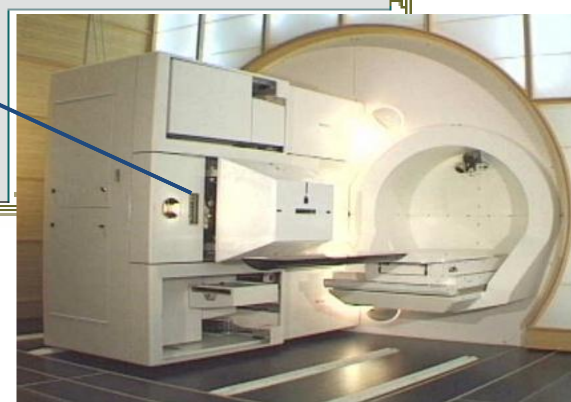
Accelerator type	Beam always present during treatment ?	Energy variation by electronic means	Time needed for varying the energy
Cyclotron	Yes	No	80-100 ms (*)
Synchrotron	No	Yes	1-2 second

(*) With advanced movable absorbers

Two methods for imparting the dose: "passive" system and "active" scanning

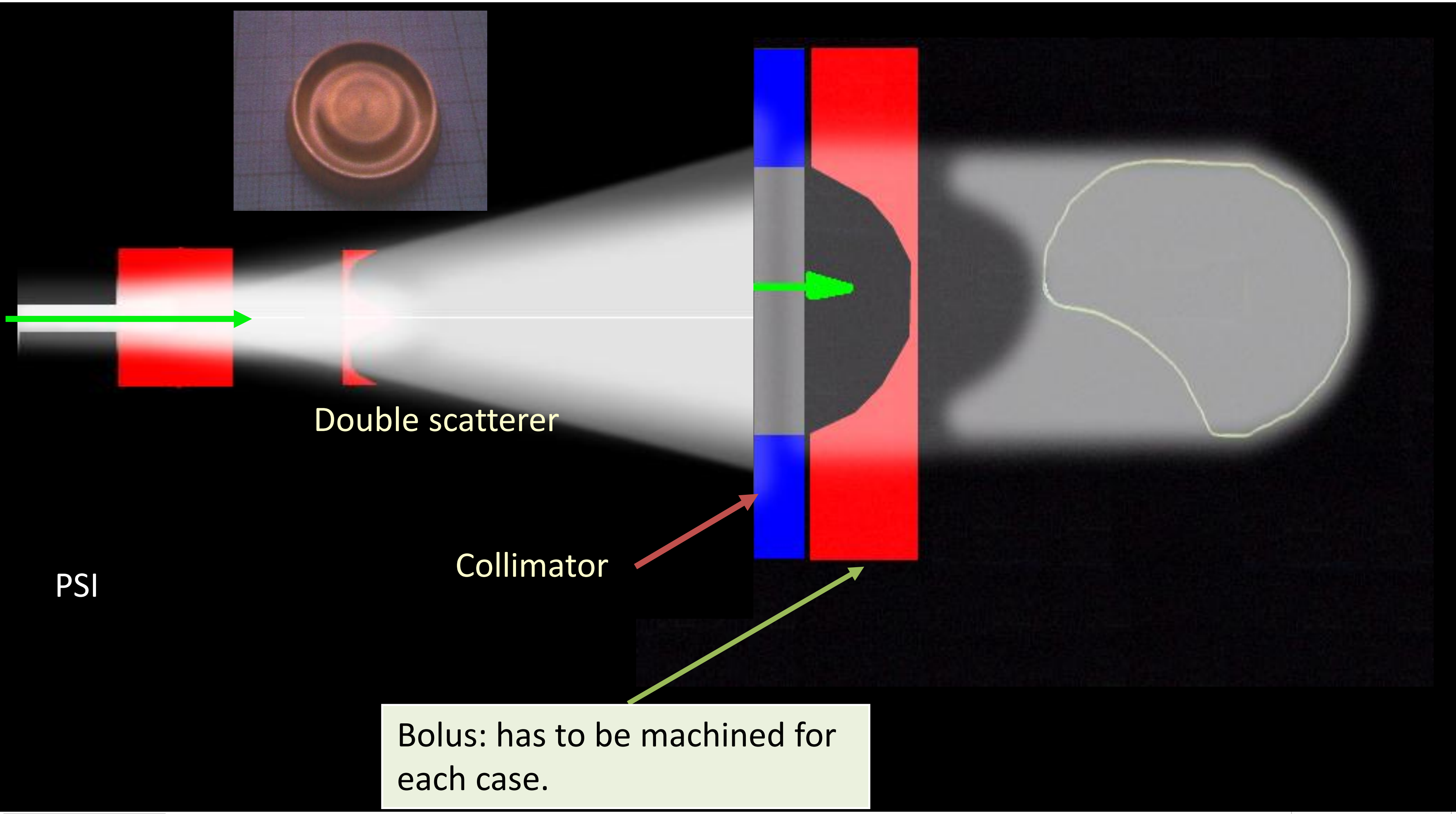




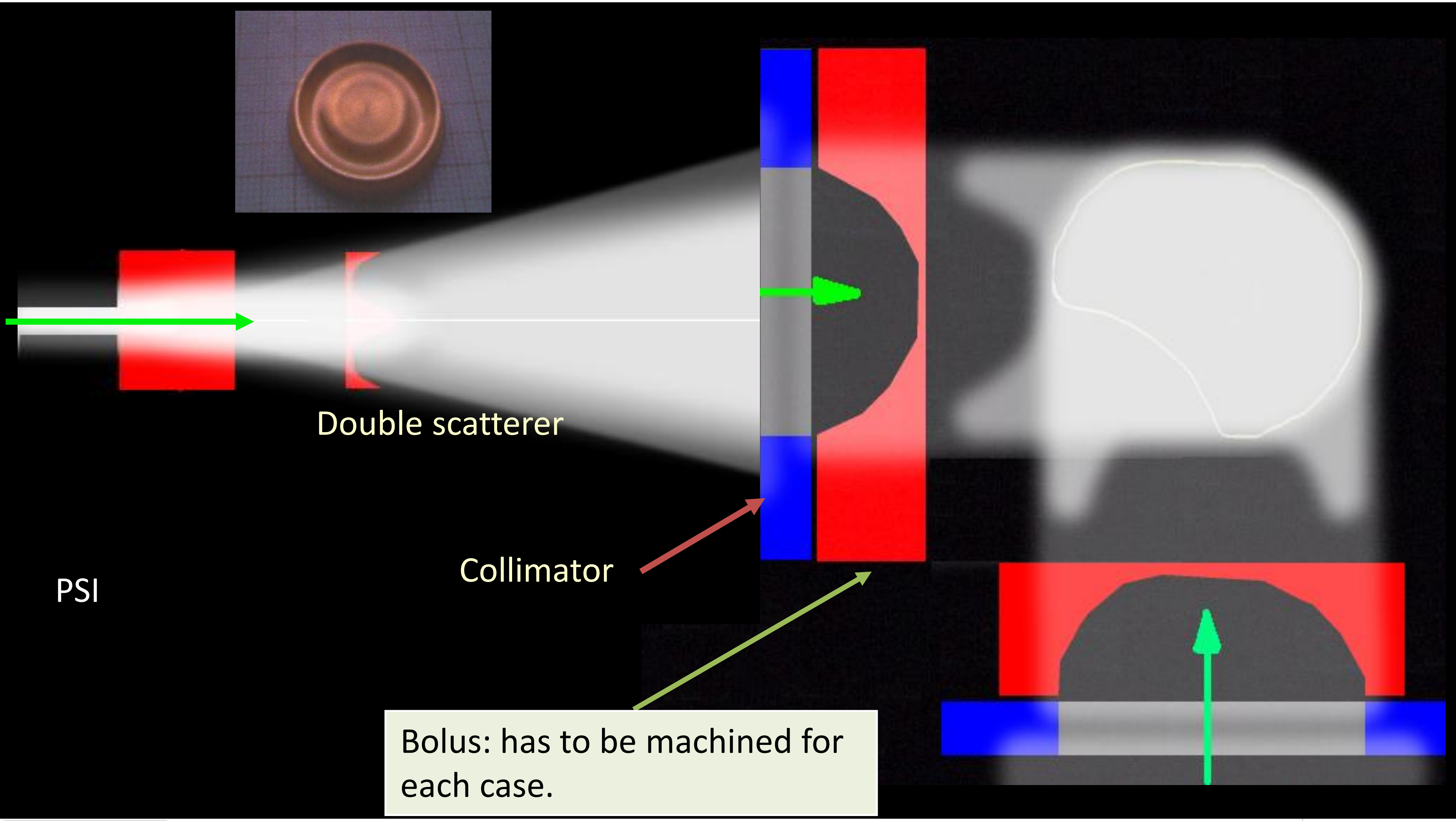


PROSCAN at PSI (Villigen):
with Gantry 1 and Gantry 2

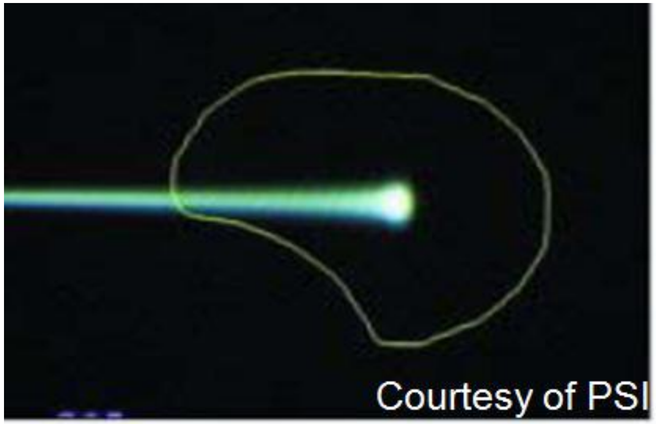
1A. Standard procedure: Passive beam spreading with respiratory gating



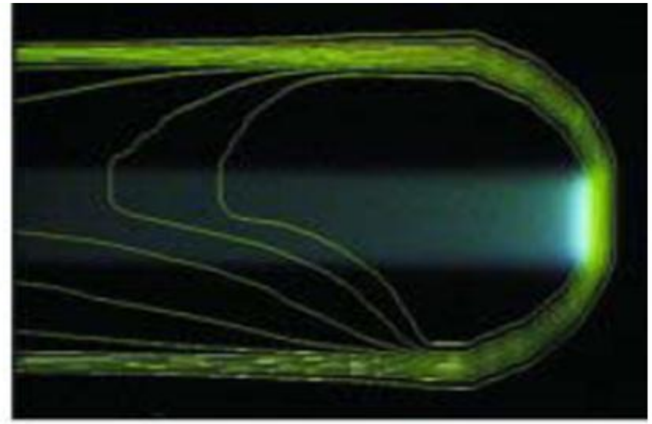
1A. Standard procedure: Passive beam spreading with respiratory gating



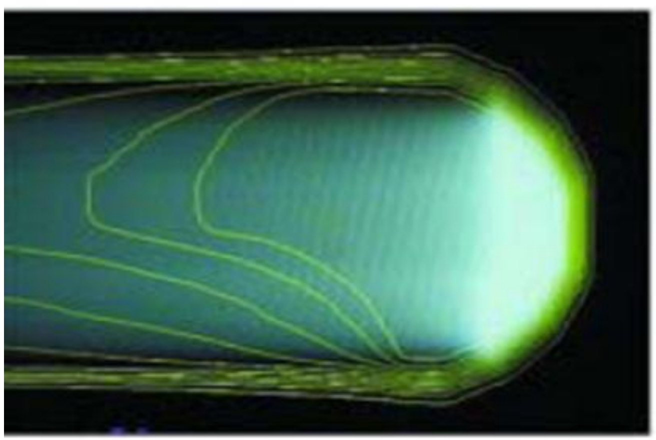
2A. Active “spot scanning” technique by PSI with respiratory gating (Villigen)



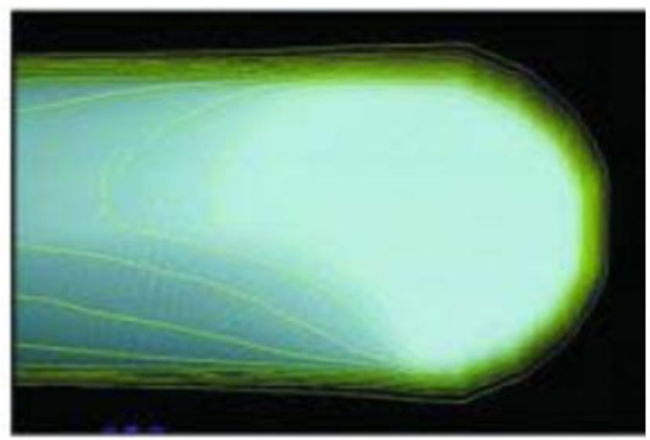
Single ‘spot’ pencil beam



Lateral scanning with magnets: 2 ms/step



Depth scanning: ENERGY MODULATION



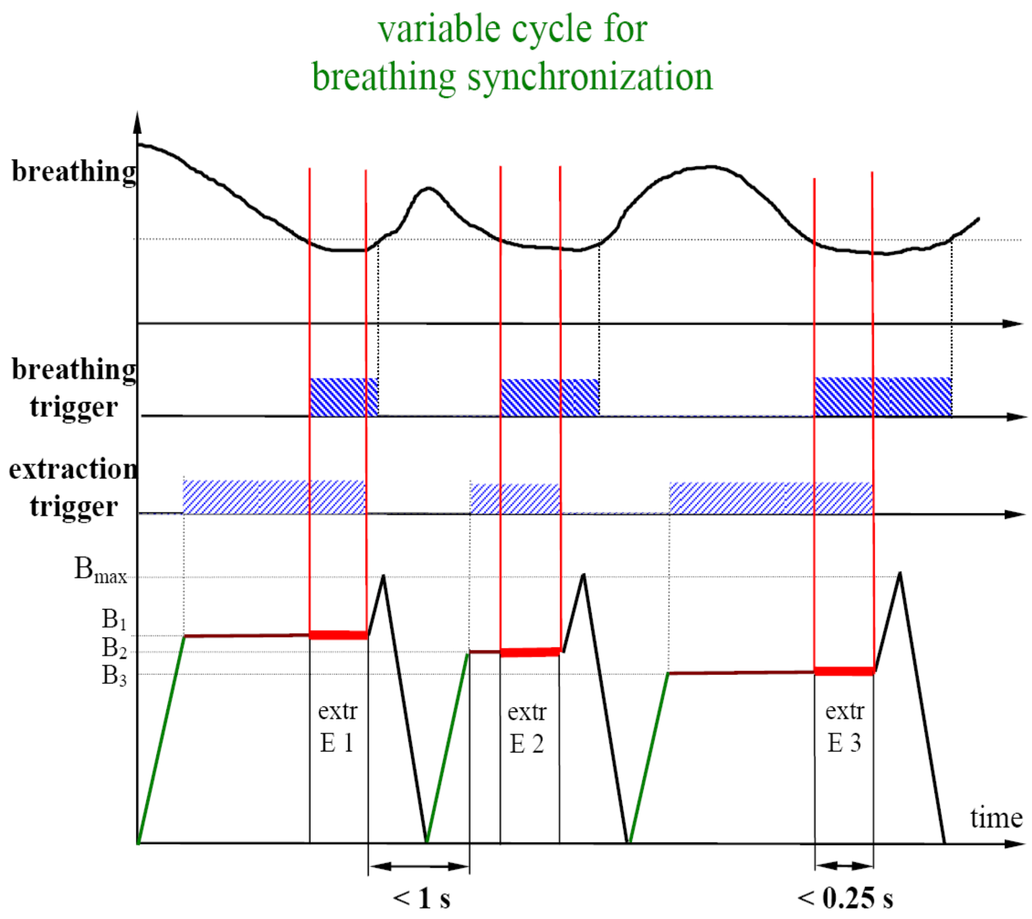
<u>3D conformal treament</u>

Part 2: Accelerators and technology

Future challanges in hadrontherapy: Moving organs and single room facilities

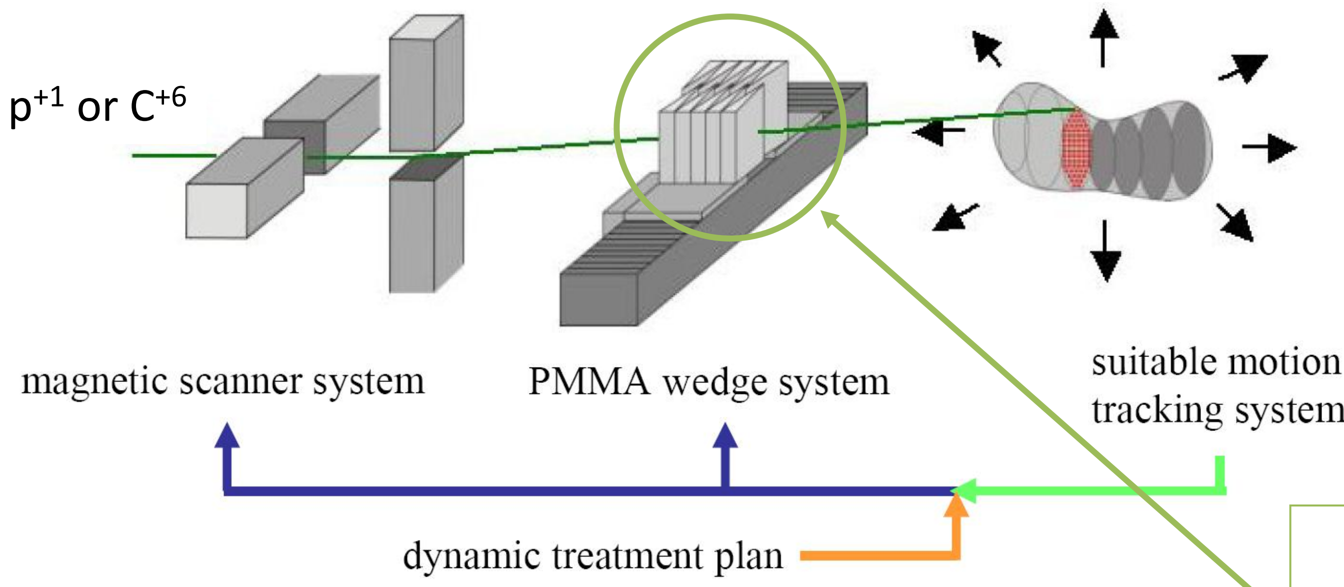
Respiratory gating with a synchrotron

- The beam reaches the patient only when the Target "gate" is ON
- Synchrotrons: synchronization of the respiration of the patient with the cycle of the accelerator
- Technique already in use in Japan (Tsukuba)



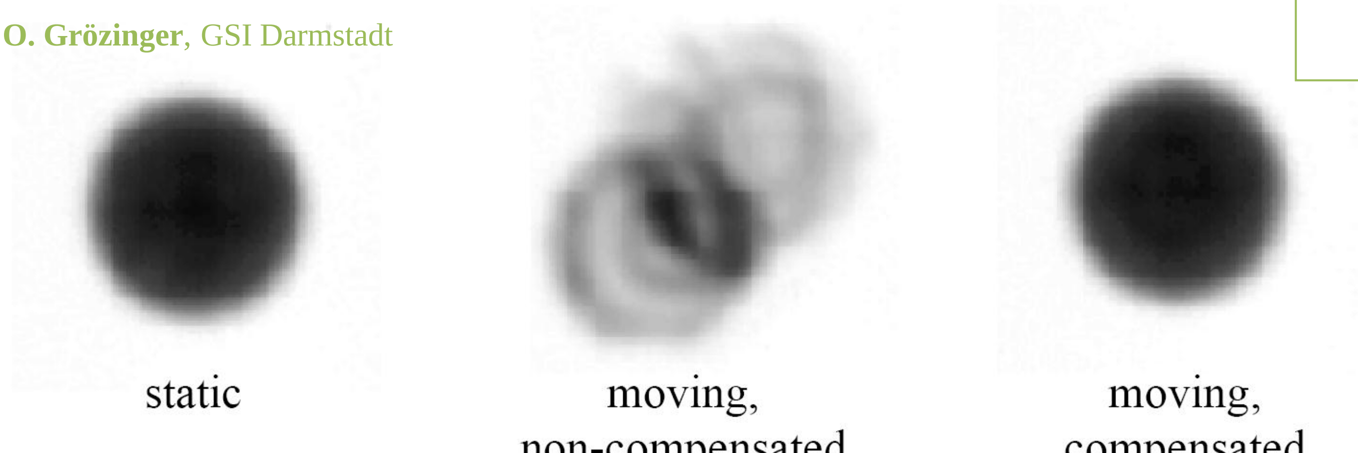
Cyclotrons are better because the beam is always present

GSI approach to treat moving organs: depth with fast absorbers



BETTER SOLUTION: energy variation by electronics and not mechanics

Sven O. Grözinger, GSI Darmstadt



2^{nd} challenge: proton single room-facilities

The reasons for proton single room-facilities*:

Radiation treatment	Patients per year in 10^7	Number of session per patient	Sessions/d in 1 room (d = 12 h)	Patients/y in 1 room (y=230 d)	Rooms per 10 million people (1)	Relative ratio ≈
Photons (1)	20'000	30	48	370	54	8^2
Protons (12%)	2'400	20	36	380	6.3	8
C ions (3%)	600	10	36	760	0.8	1

ENLIGHT results

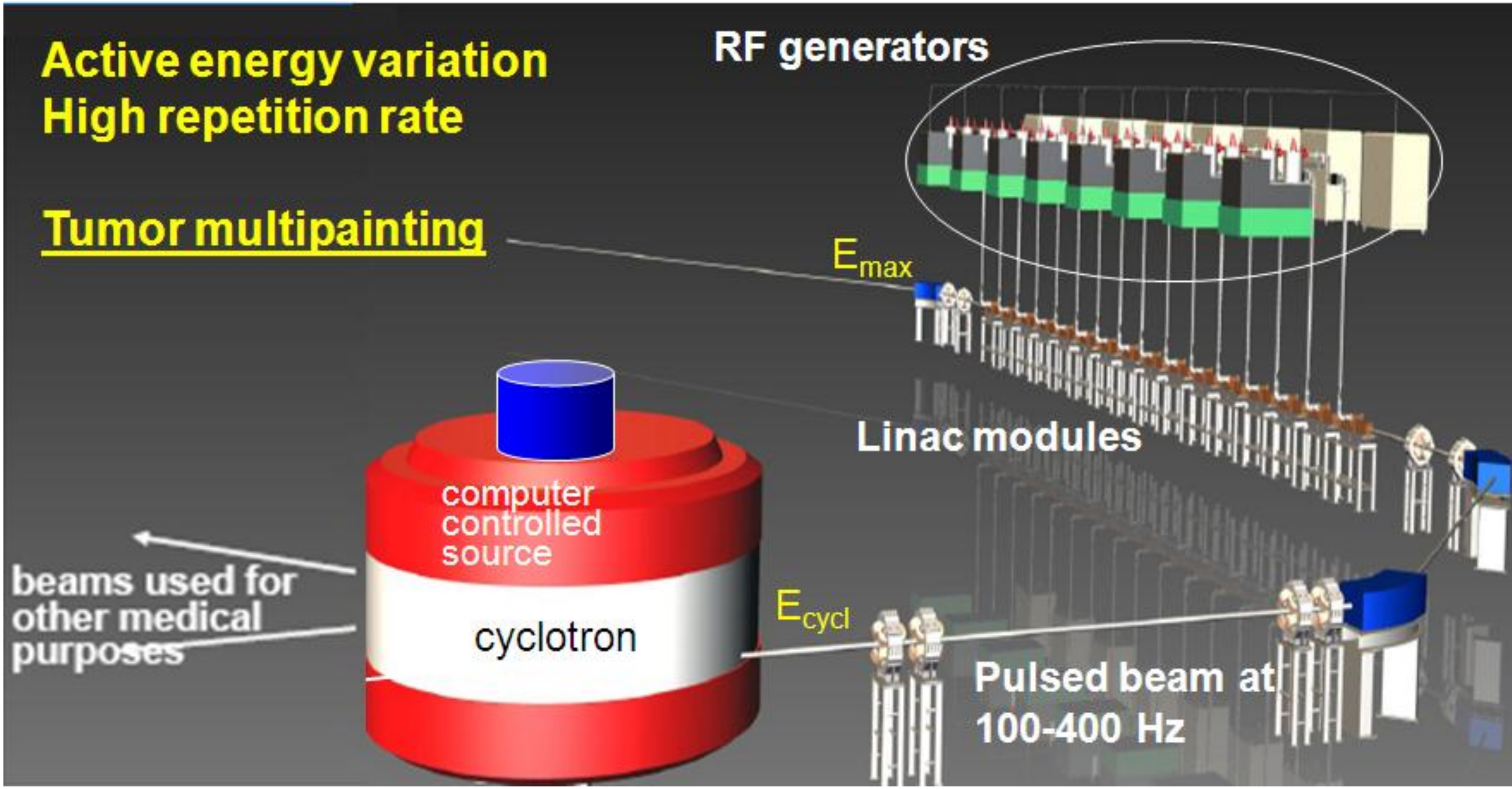
1 Proton single-room facility
every 8 X-ray rooms
in 3-4 close-by hospitals
serving ≤2 million people

* U. Amaldi et. al, NIM A 620 (2010), 563-577

TERA approach to treat moving organs and
for single room facilities:

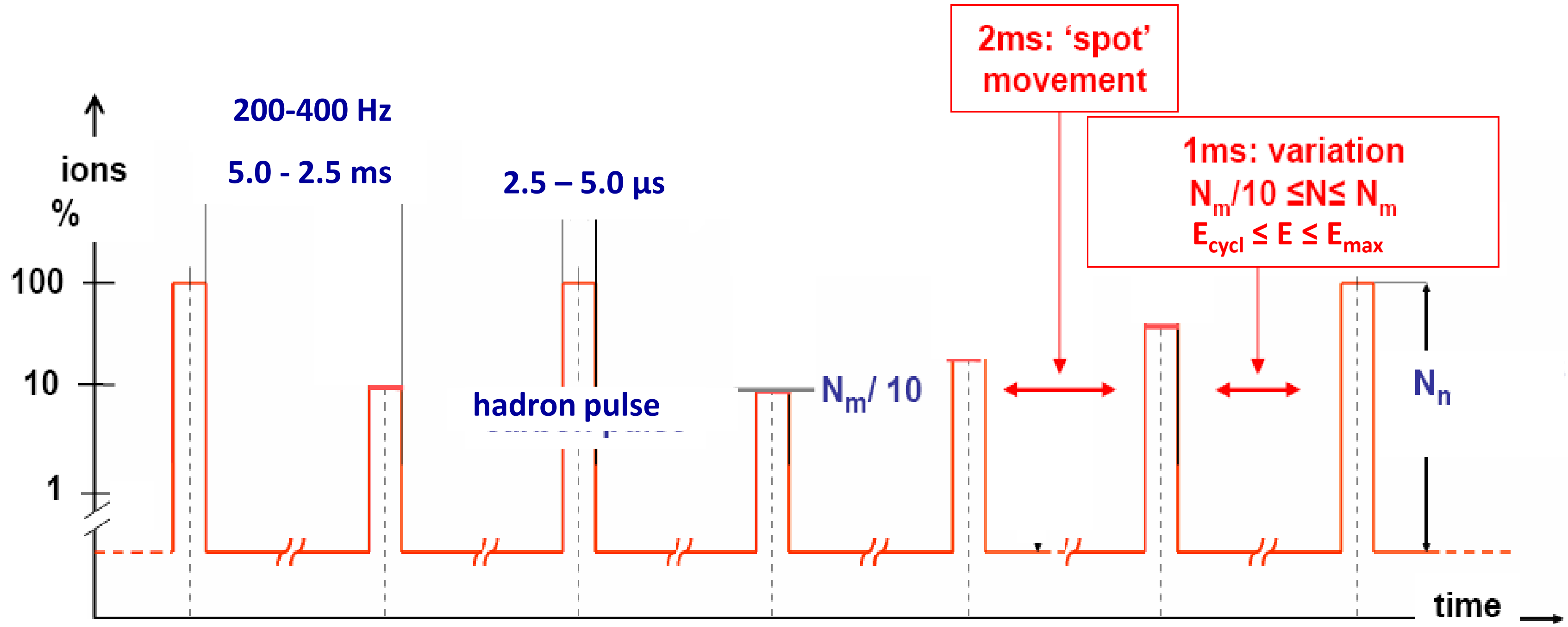
high-current cyclotron + fast-cycling high gradient linac
=
"cyclinac"

General concept of a Cyclinac



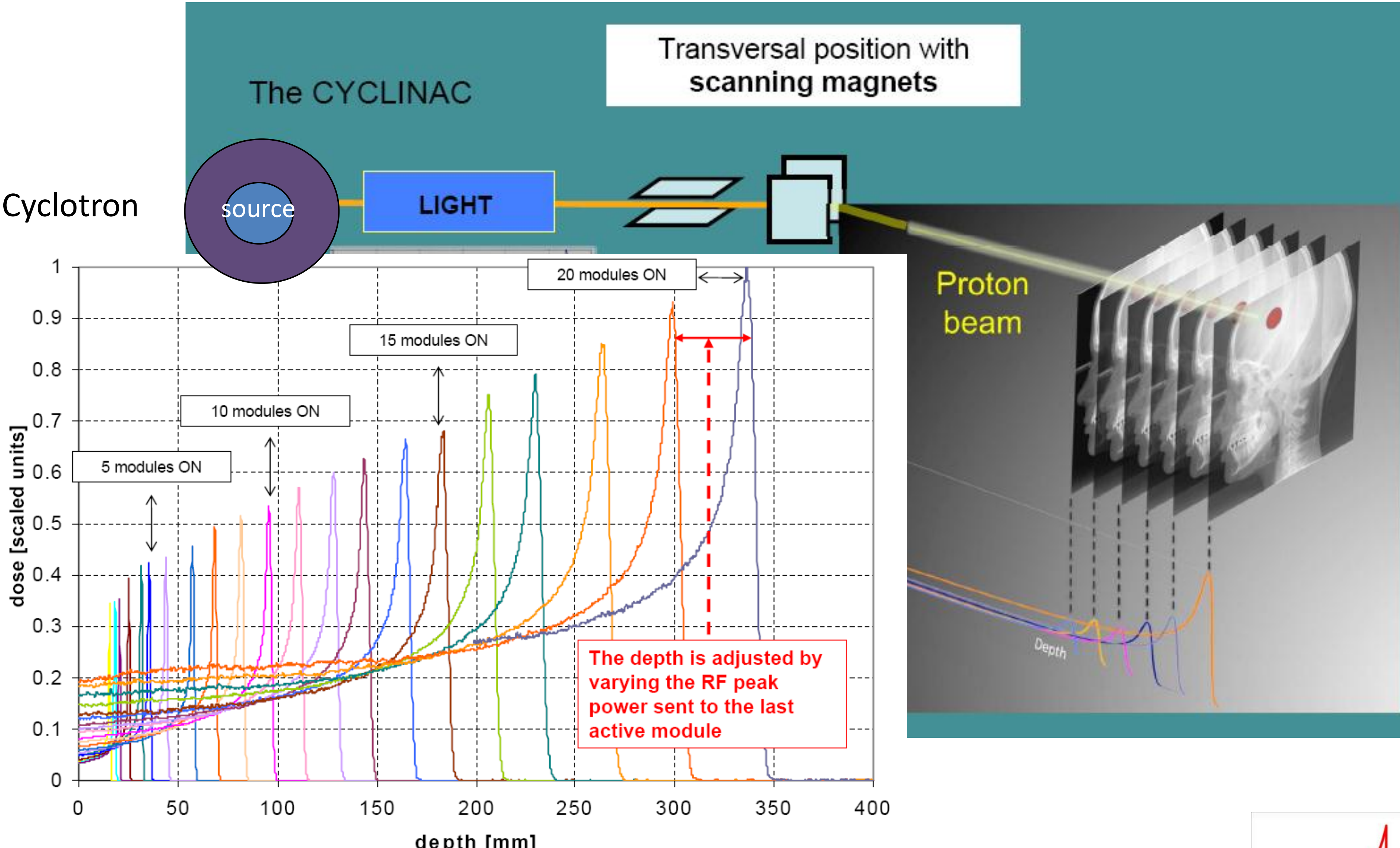
Beam suitable for the 4D spot scanning technique

The cyclinac beam is ideal for spot-scanning with many paintings and position feedbacks



The number of hadrons N, the two transverse positions and the depth of the spot can be varied every pulse, because the linac energy E can be adjusted every 1-2 ms

The energy of a cyclinac can be varied in 1-2 ms



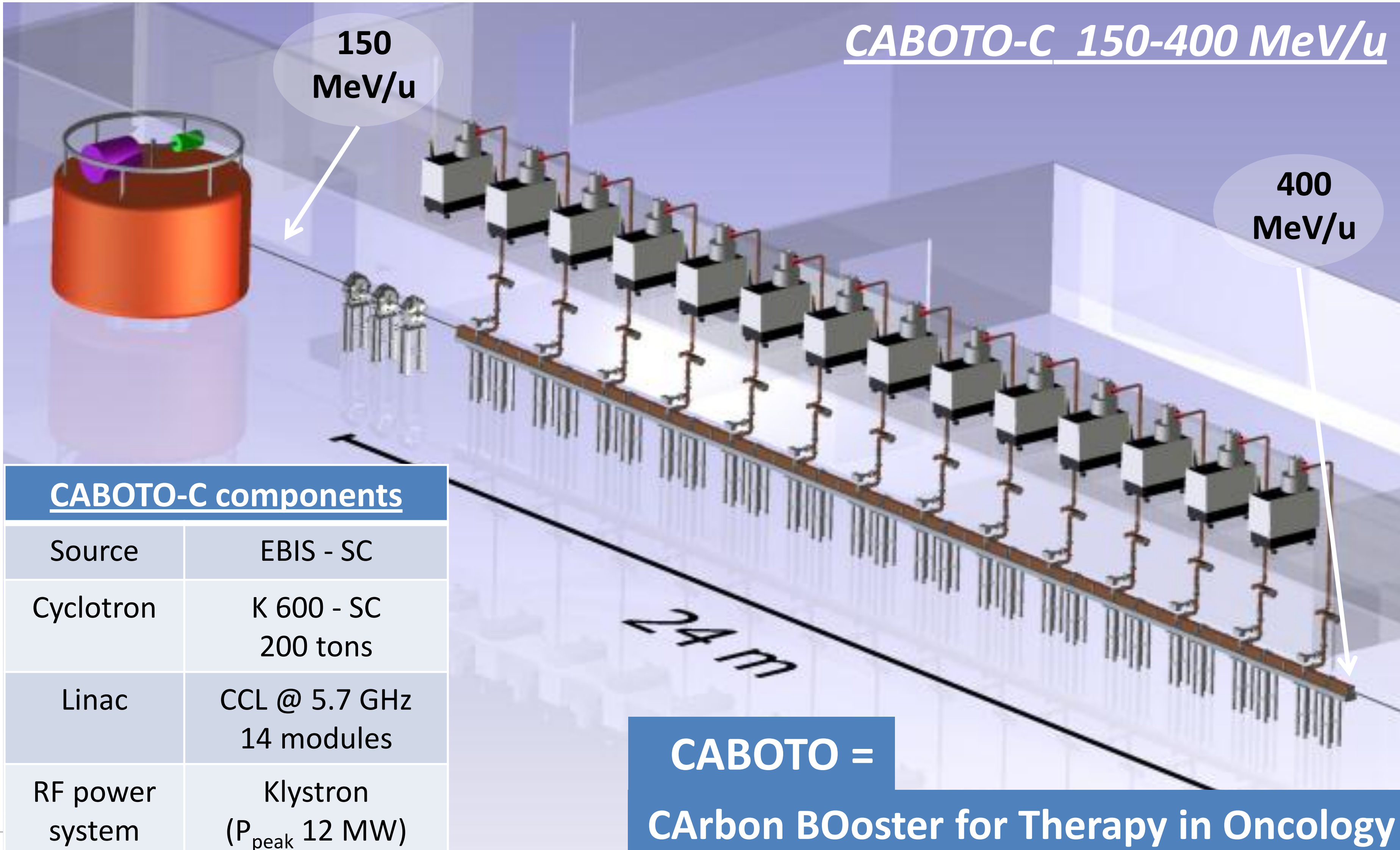
Properties of the beams of different accelerators

Accelerator type	Beam always present during treatment ?	Energy variation by electronic means	Time needed for varying the energy
Cyclotron	Yes	No	80-100 ms (*)
Synchrotron	No	Yes	1-2 second
Cyclinac	Yes	Yes	1-2 ms

The energy is varied by adjusting the RF pulses to the modules and allows 10 paintings

(*) With advanced movable absorbers

CABOTO-C: a cyclinac for a compact 'dual' machine

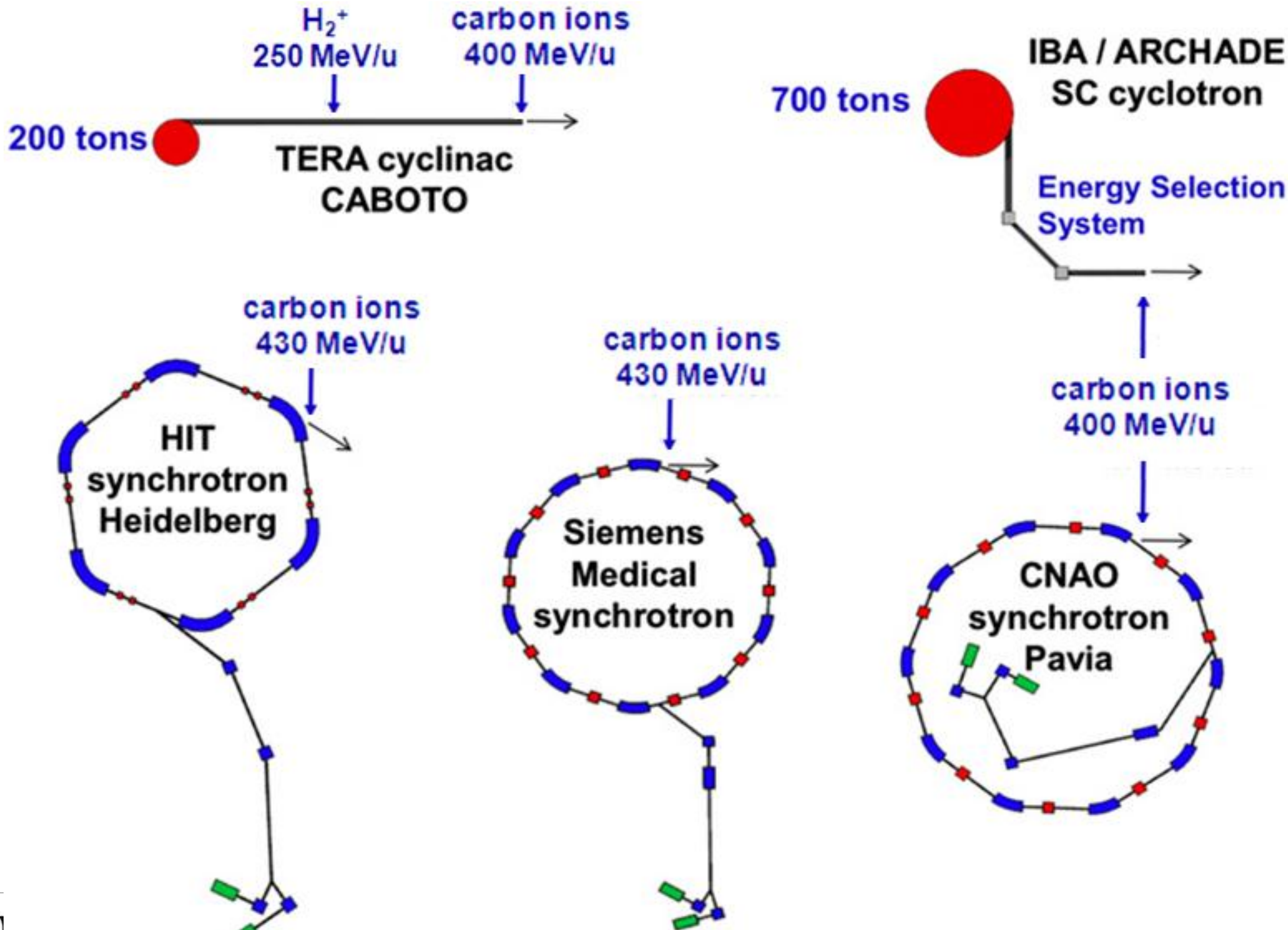


CABOTO-C components	
Source	EBIS - SC
Cyclotron	K 600 - SC 200 tons
Linac	CCL @ 5.7 GHz 14 modules
RF power system	Klystron (P_{peak} 12 MW)

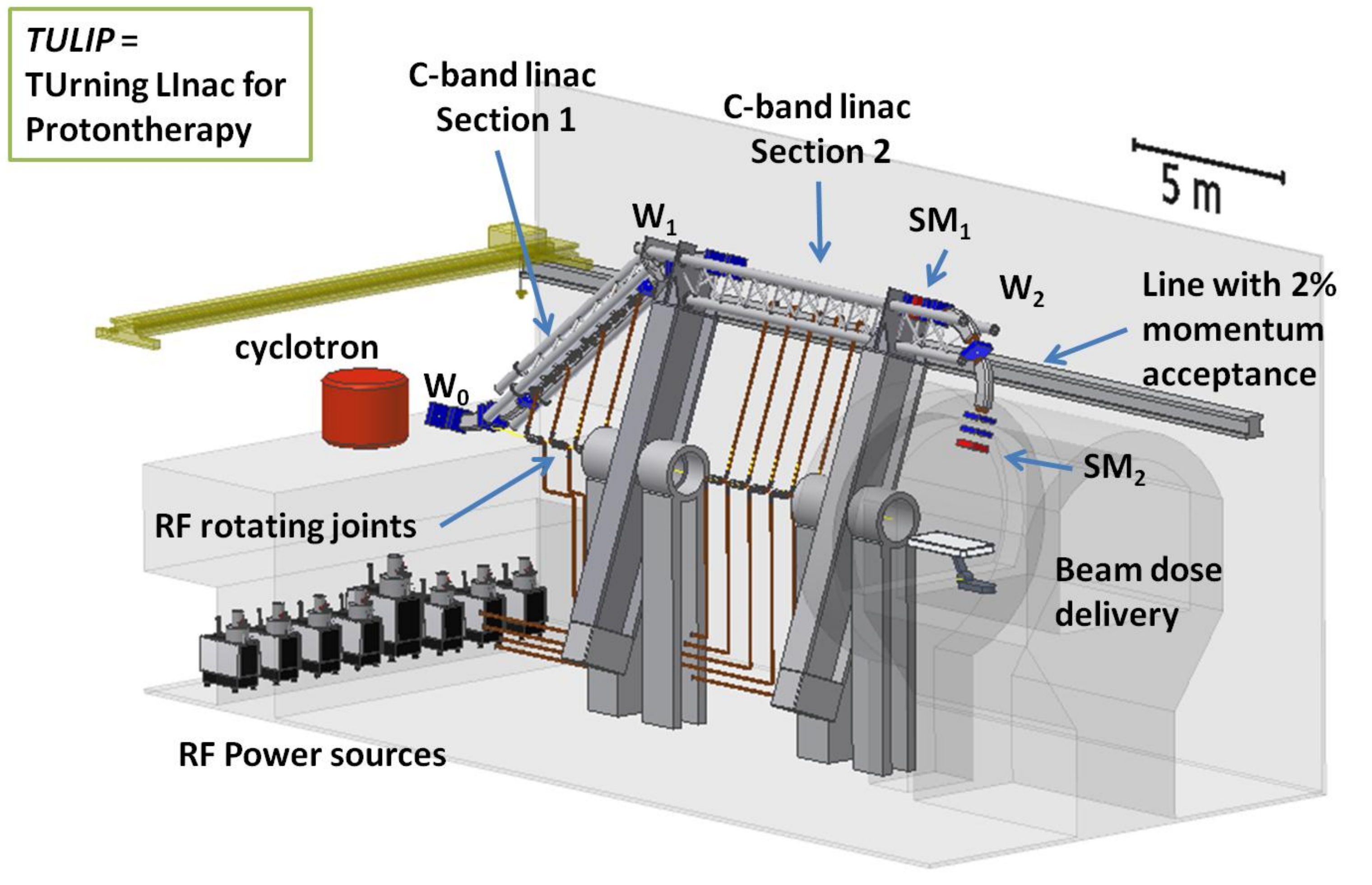
CABOTO =

CArbon BOoster for Therapy in Oncology

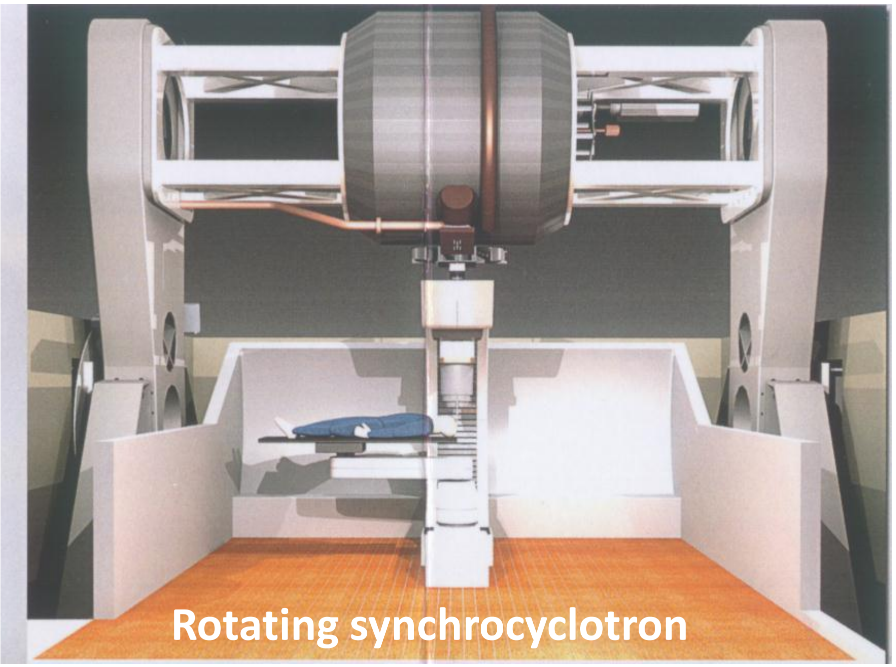
Dimensional comparison among carbon ion accelerators

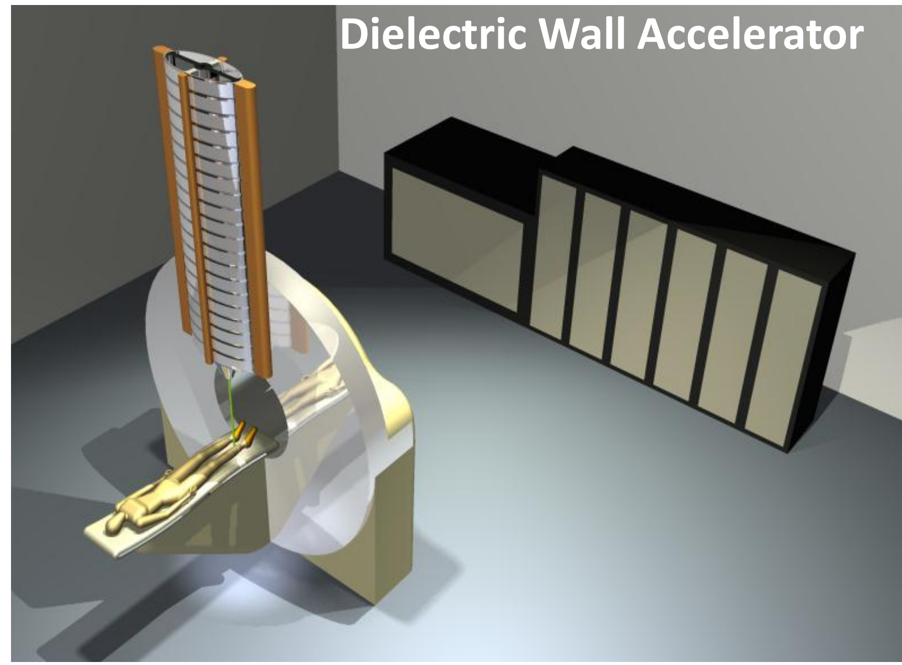


TERA solution: TUrning LInac for Protontherapy (TULIP) at 5.7 GHz, 35 MV/m



Single room facilities: ongoing projects





→ Still River Systems (Littleton, MA)

→ Los Alamos lab. (G. Caporaso et. al) with CPAC.Co (Livermore,CA)

Summary 2nd part

Accelerators and technology for hadrontherapy : Status and future perspective

- ***Hadrontherapy is booming worldwide***
  - > 50 centers in the next few years
- ***Circular machines for hadrontherapy***
  - time characteristics of the beam
  - treatment modalities (passive spreading vs. active scanning)
- ***Future challanges in hadrontherapy***
  - Treatment of moving organs
  - Compact and cost effective machines (single room facilities)
- ***New technolgies are under development (see ref.)***
  - Cyclinacs
  - Fixed Field Accelerating Gradients (FFAG)
  - Laser-plasma accelerators
  - Dielectric Wall Accelerators (DWA)

Conclusion

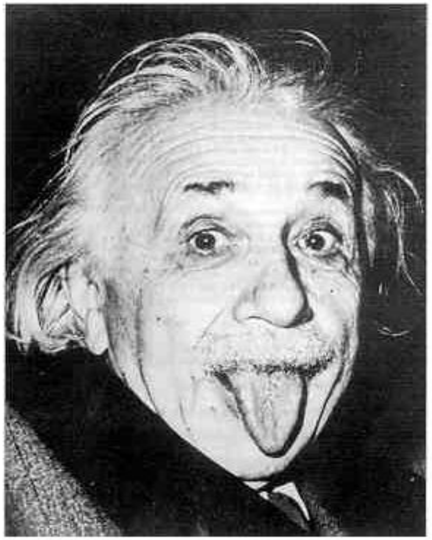
Conclusion

- ***Hadrontherapy is booming worldwide***
  - ~ 30 centres in operation
  - same number under construction
- ***Hadrontherapy is a multidisciplinary research field***
  - physics (not only accelerators, also detectors for diagnostics!)
  - radiobiology
  - engineering
  - clinical trials
  - IT technology (GRID for hadrontherapy centres)
- ***New developments are needed***
  - improve treatment modalities
  - reduce size and cost of the machines!

General Summary

- What is the main difference between **protons** and **photons** in terms of dose deposition?
- Why **carbon ions** are *'qualitatively'* better than photons ?
- How the **therapeutic window** can be increased ?
- How many **patients per year** undergo radiotherapy/hadrontherapy treatments ?
- What is the typical **cost** of a multi-room hadrontherapy centre ?
- Where are most of the dual centers for hadrontherapy concentrated ?
- What are two of the main **challenges of hadrontherapy** ?
- What are the **beam characteristics** needed for proton therapy with active scanning techniques?
  - beam currents /energies?
  - beam time characteristics ?
- What does **cyclinac** mean ?

More questions ???



THANK YOU for your ATTENTION!

General Summary

- Protons have finite range in matter and the dose deposition is concentrated in the **Bragg peak**, while photons show an exponential depth dose profile.
- Carbon ions are densely ionizing radiations and produce not reparable **multiple close-by double strand breaks** in the DNA of the tumoral cells.
- By a better **dose conformity**, by the **fractionation** of the treatment, etc.
- In developed countries about 20,000 patients/year every 10 Million inhabitants undergo radiotherapy. About 12-15% of them would benefit from proton and carbon ion treatments (**paediatric tumours, radioresistant tumours**).
- A multi-room centre for hadrontherapy costs about **150-180 MEUR**. The accelerator counts for about 20% of the total cost.
- Japan is the best equipped country in terms of dual centres.
- Two of the main challanges of hadrontherapy are the treatment of **moving organs** and the development of compact accelerators for **single room facilities**.
- Typical beam for proton therapy should have a variable energy between **70-230 MeV** and average currents up to **1 nA**. A fast active energy variation in few ms timescale is best suited for the treatment of moving organs.
- The cyclinac is the combination of a cyclotron (used as injector) and a linear accelerator (used as booster).

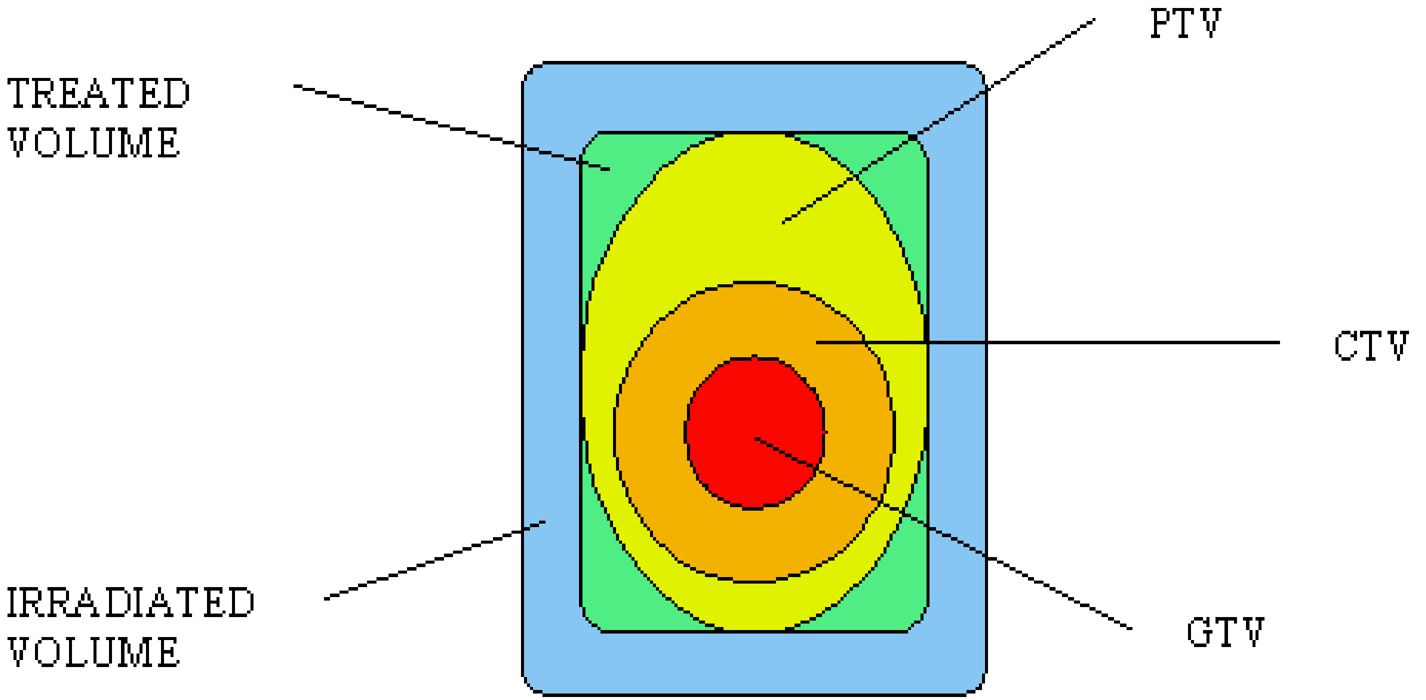
References

- R. R. Wilson, *Radiological use of fast protons, Radiology 1946, 47: 487-491*
- U. Amaldi, *Cancer therapy with particle accelerators, Nucl. Phys. A654, pp. 375c*-399c, 1999
- G. Kraft, *Tumor therapy with heavy charged particles,* Progress in Particle and Nuclear Physics, Volume 45, Supplement 2, S473-S544, 2000
- U. Amaldi, G. Kraft, *Radiotherapy with beam of carbon ions,* Rep. Prog. Phys. 68, 1861-1882, 2005

- Particle Therapy Co-Operative Group (http://ptcog.web.psi.ch/)
- ENLIGHT++ (http://enlight.web.cern.ch/enlight/cms/index.php?file=home)
- Review of Accelerators Science and Technology – RAST II on "Medical Applications of Accelerators" (http://www.worldscinet.com/rast/02/0201/S17936268090201.html)

Back-up material

The target volumes



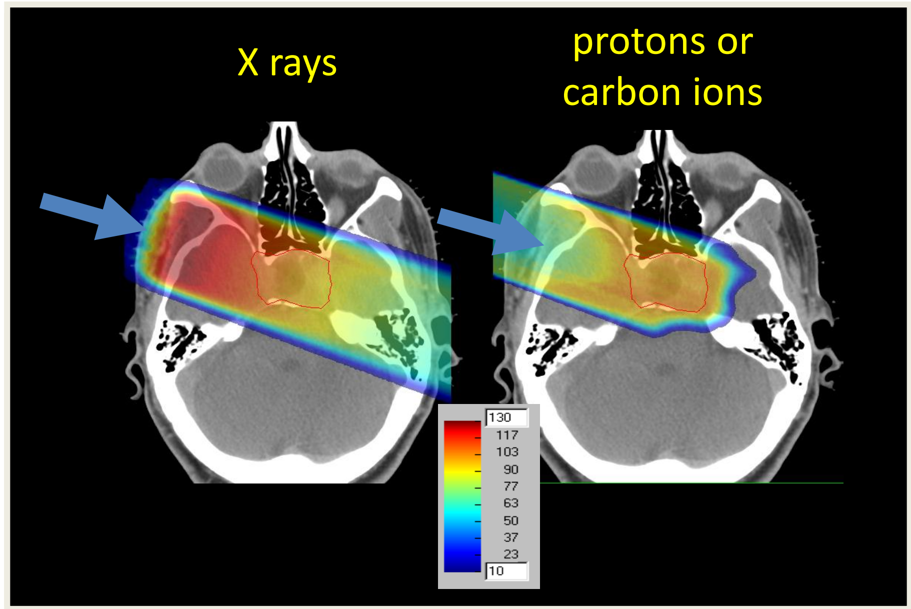
GTV: <u>Gross Target Volume</u> as determined by CT, MRI, SPECT ad PET

CTV: the <u>Clinical Target Volume</u> takes into account invisible infiltrations

PTV: the <u>Planning Treatment Volume</u> takes into account mouvements and misalignments

CHALLENGE: Conform the dose to the tumour !

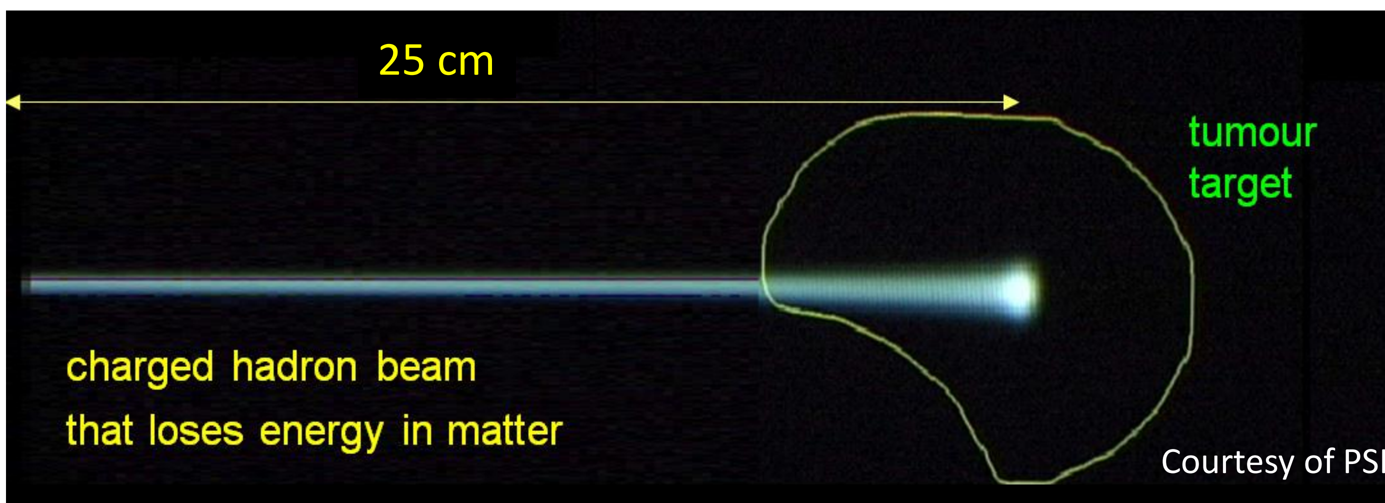
Protons and ions spare healthy tissues



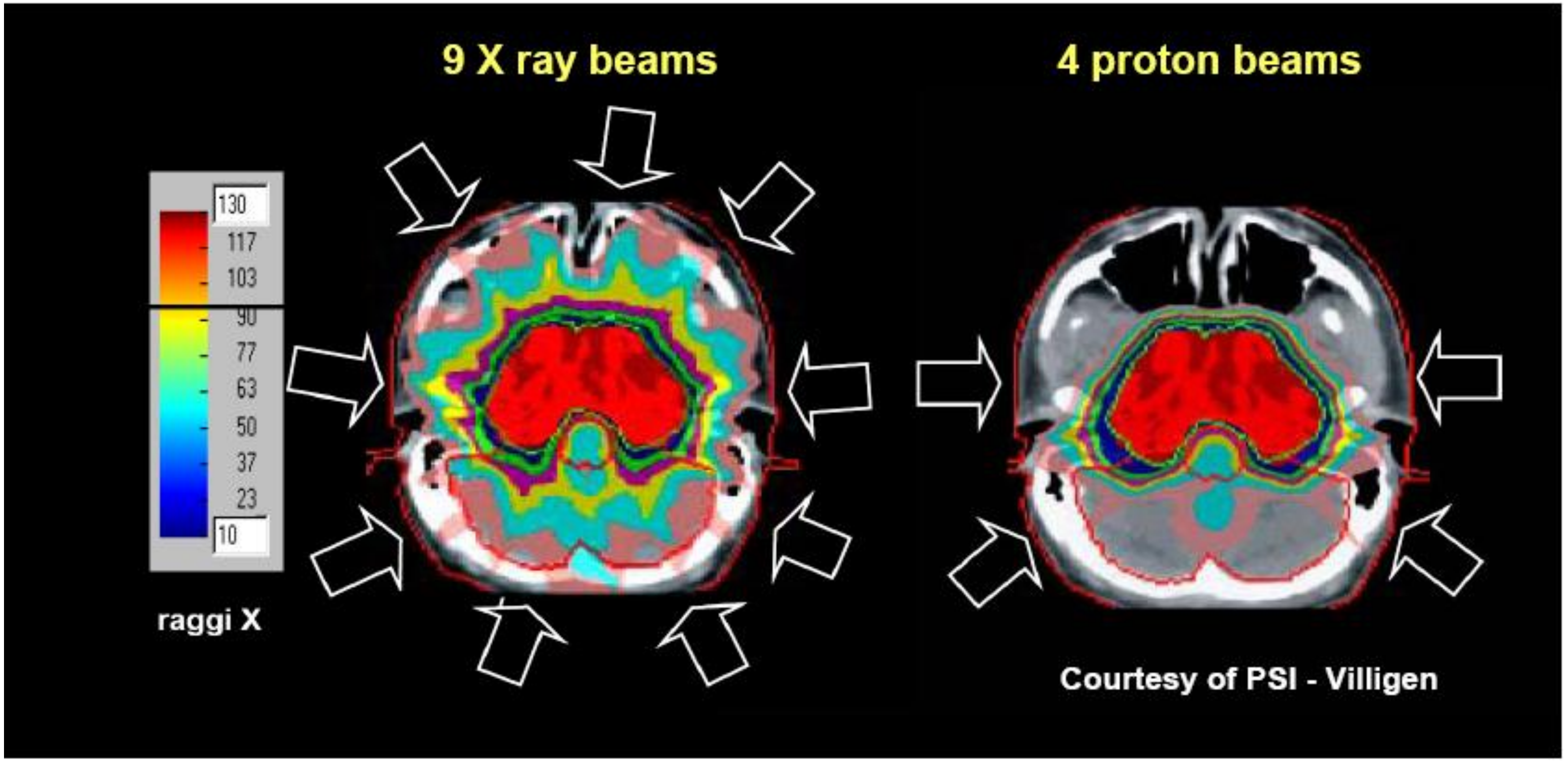
200 MeV - 1 nA protons

4800 MeV – 0.1 nA carbon ions

(radioresistant tumours)

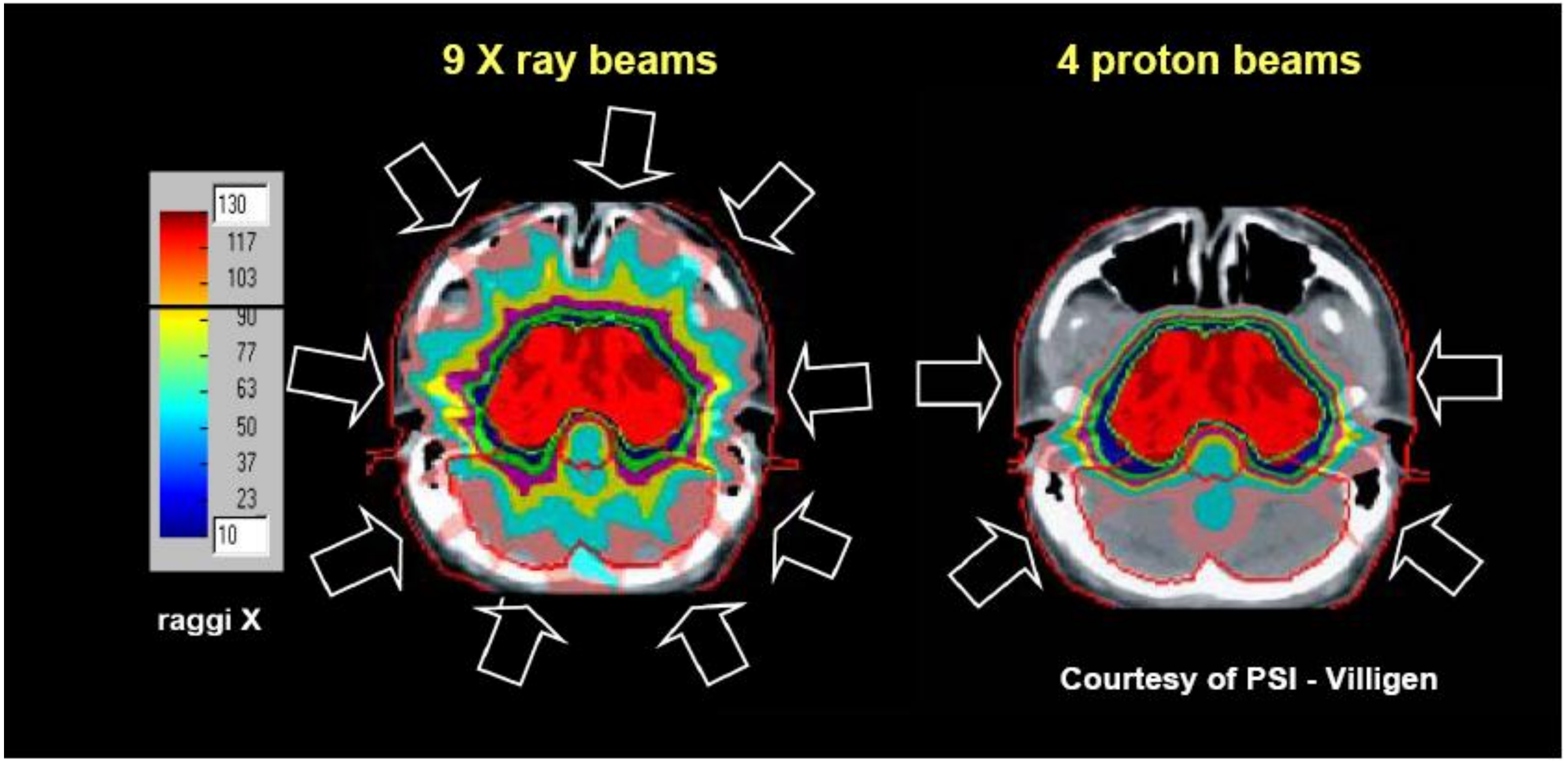


Protons are quantitatively different from X-rays



- The main difference is in the Bragg Peak.
- At the microscopic level both are **sparsely ionizing radiations**.

Carbon ions are qualitatively different from X-rays



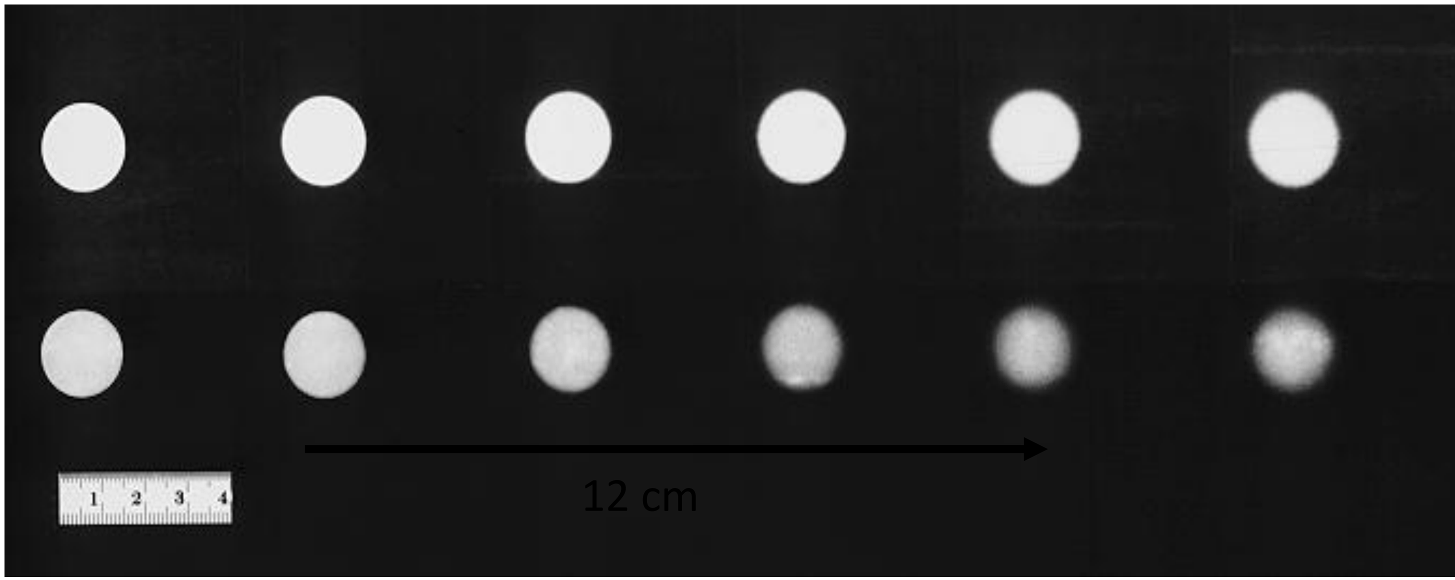
- Carbon ions deposit in a cell 22 times more energy than a proton producing not reparable **multiple close-by Double Strand Breaks**

- Carbon ions can control **radioresistant tumours**

Carbon ions have less multiple scattering than protons : higher lateral precision

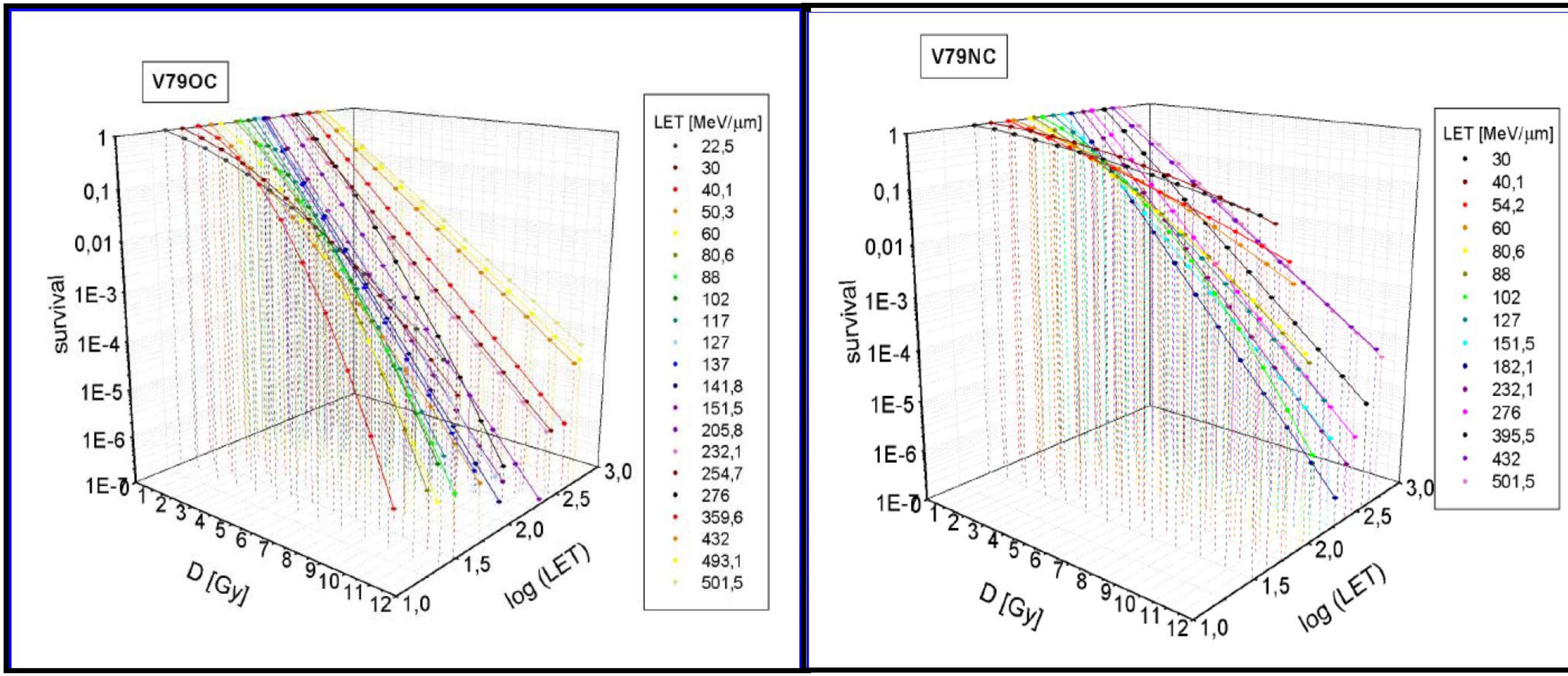
carbon beam

proton beam



Depth in tissue

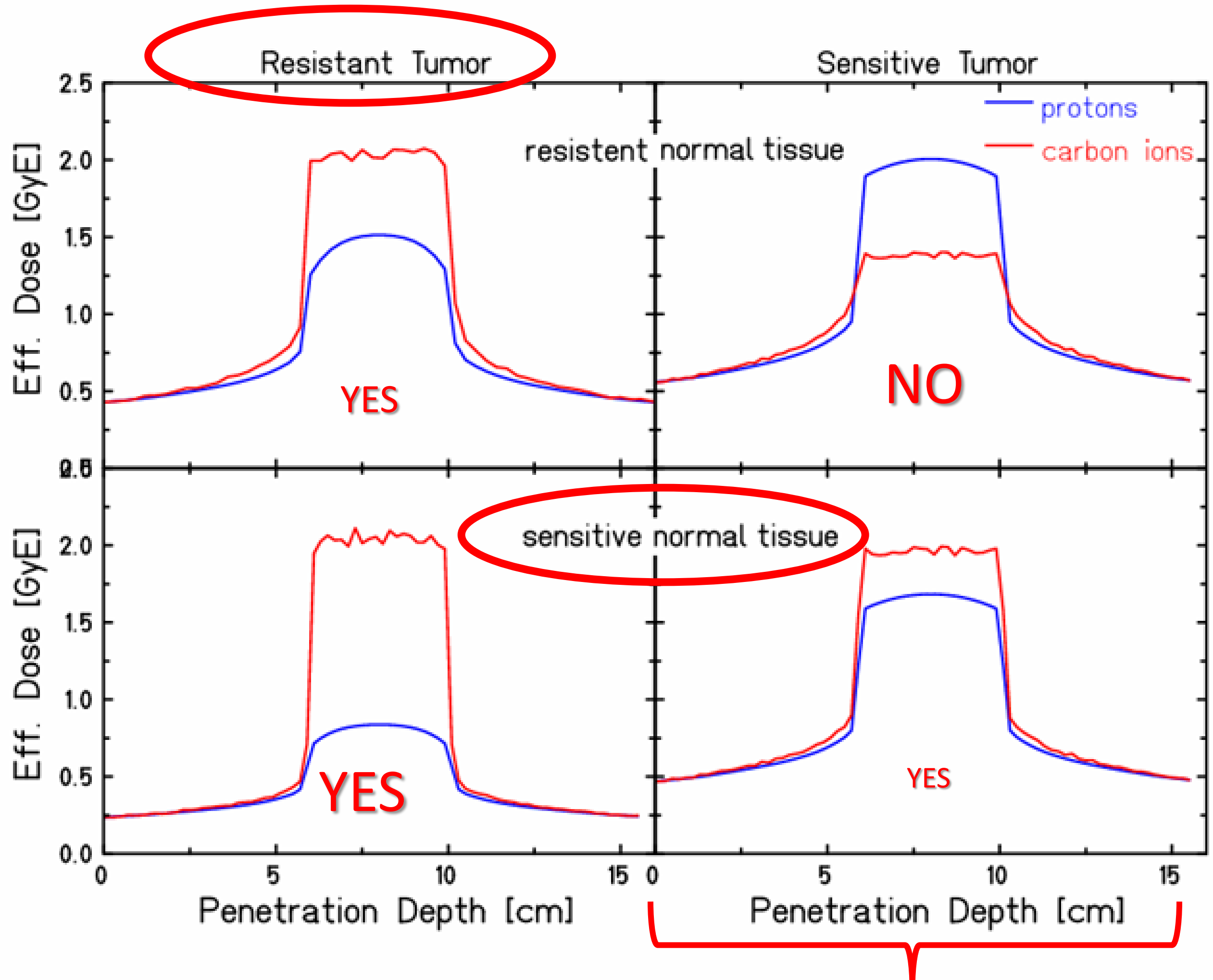
Response of different cells to high-LET radiations



Survival of V79 aerated and anoxic cells versus LET of carbon-12 ions

Data: Furusawa *et al.* *Radiat. Res.* **154**, 485-496 (2000)

Elective indications of carbon ions calculated with LEM



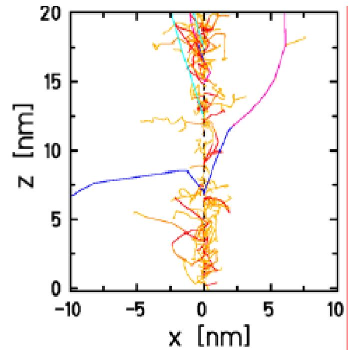
About 80% of all solid tumours

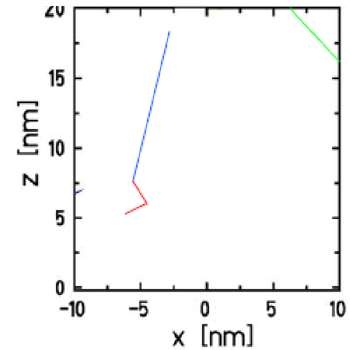
M. Scholz, GSI

Two qualitatively different microscopic dose distributions

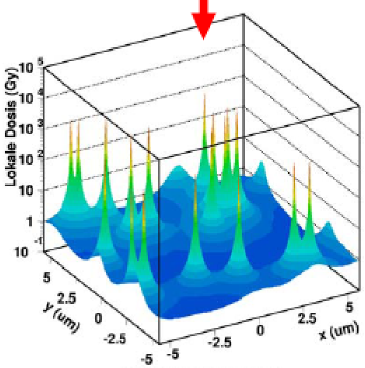
densely ionizing radiation

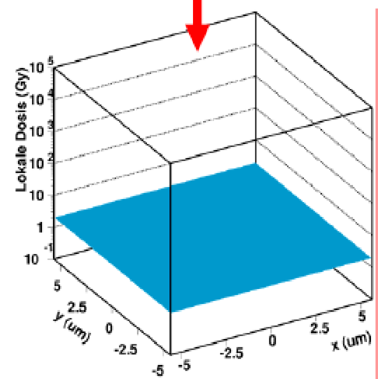
sparsely ionizing radiation

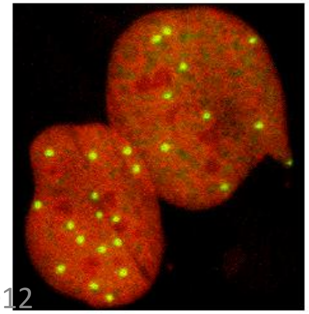




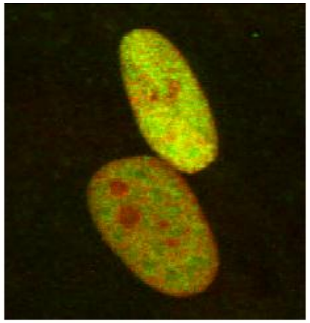
M. Scholz







Visualization of repair proteins



B.Jakob

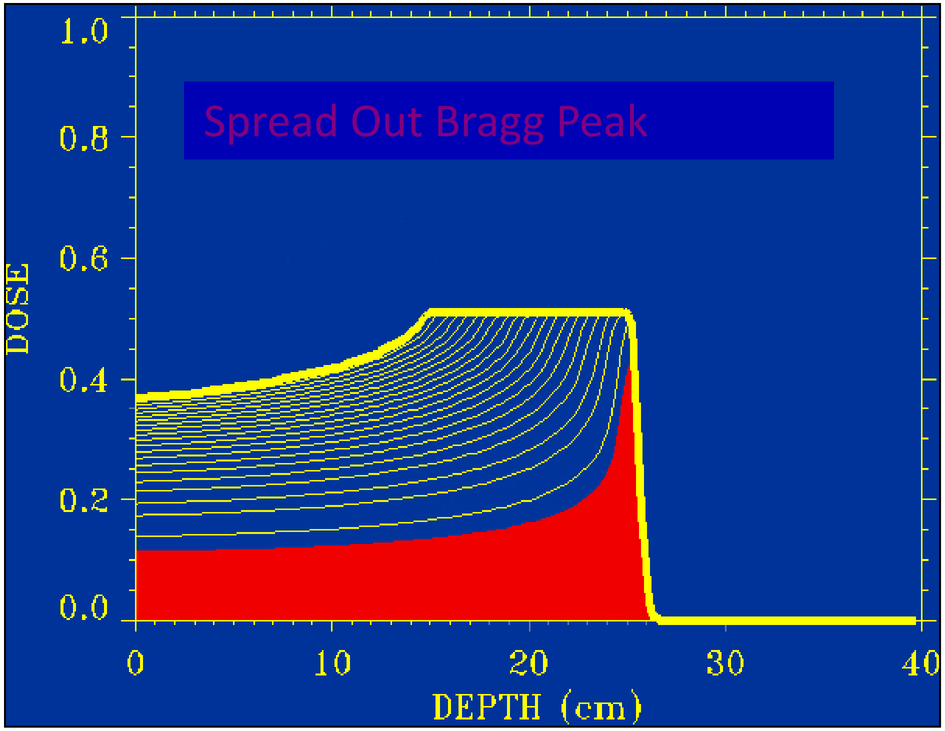
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

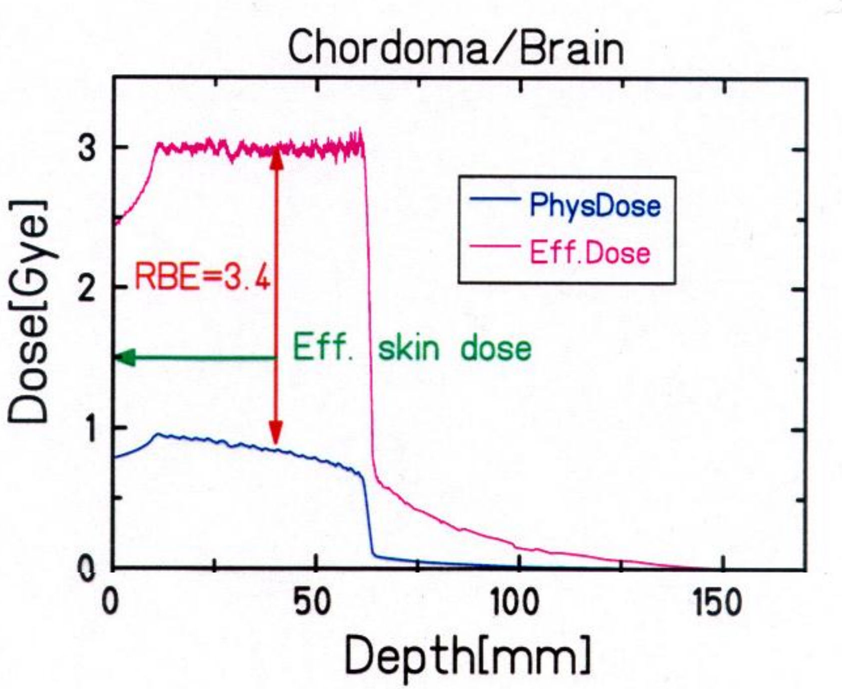
TERA Fondazione per Adroterapia Oncologica

The "effective dose" in Gye is defined as Gy x RBE

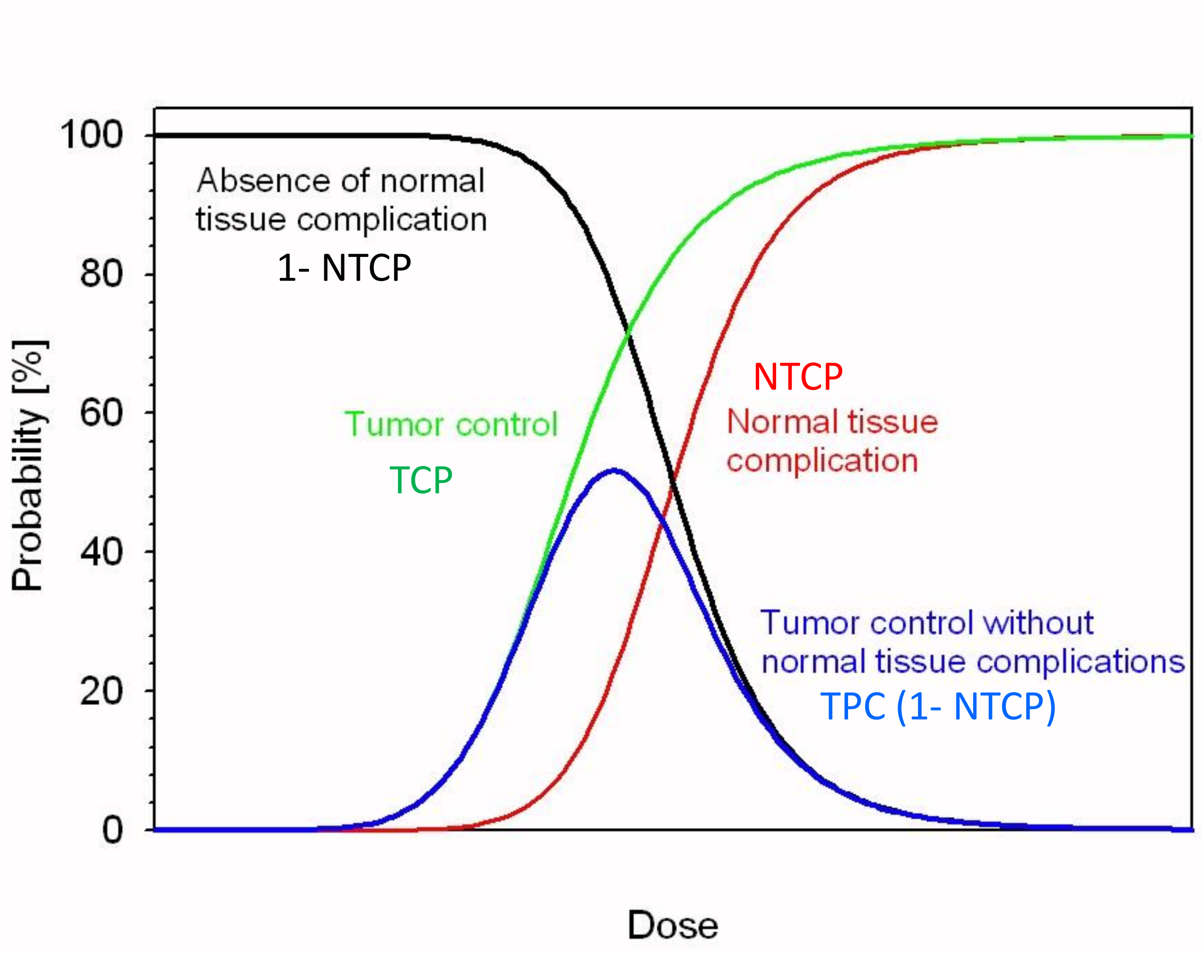
At GSI the values of RBE are computed with X-ray cell survival data by using the Local Effect Model (LEM) by G. Kraft el al.

To obtain a 'flat' dose in Gye the "physical dose" is not 'flat'

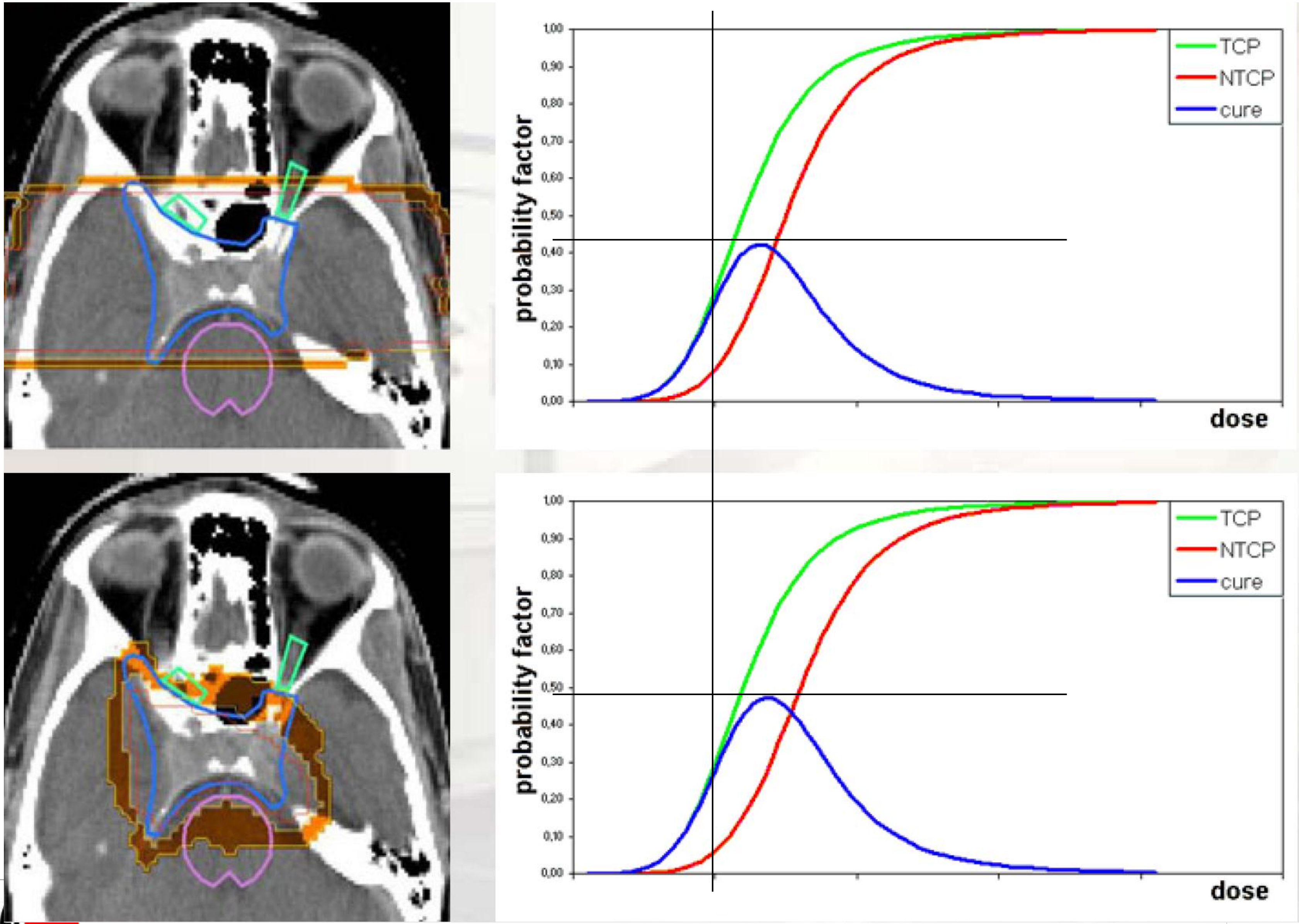




Quantification of the control without complications



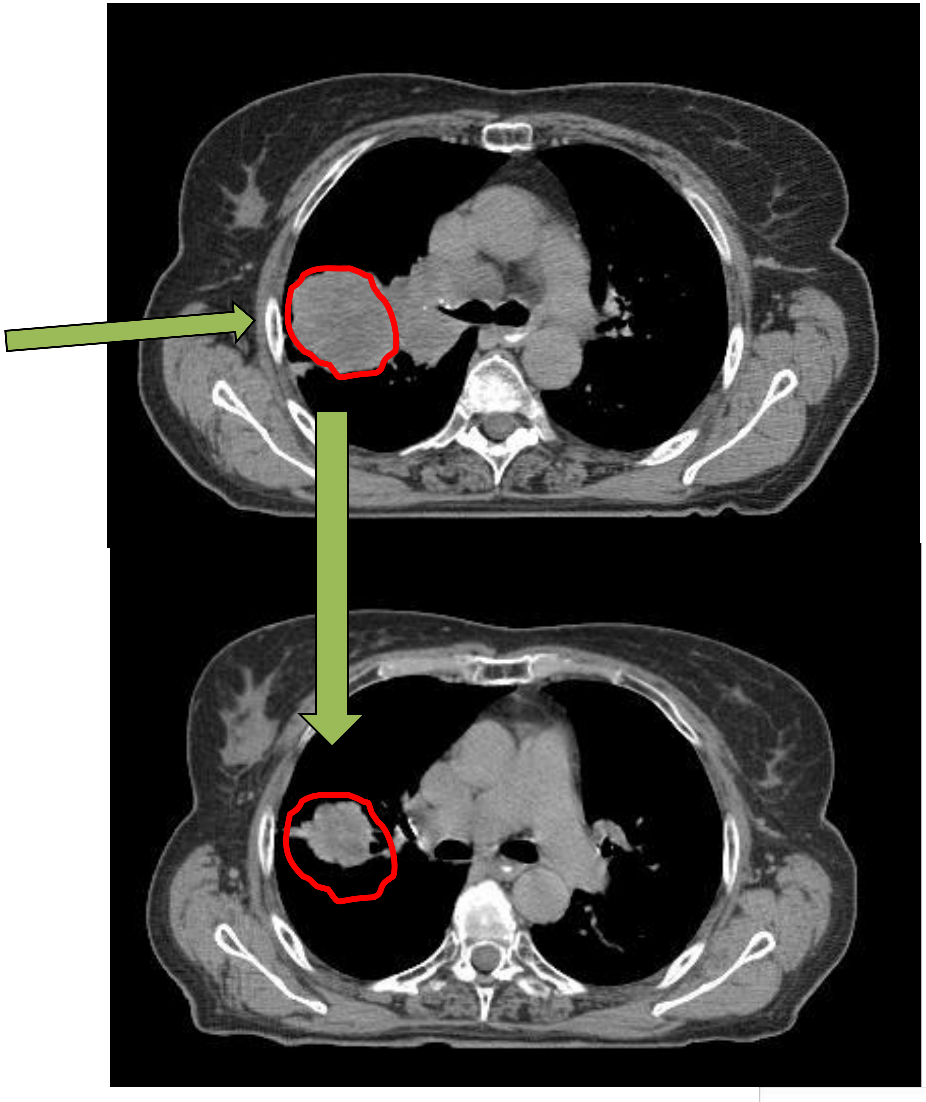
Tumour conformation to open the therapeutic window



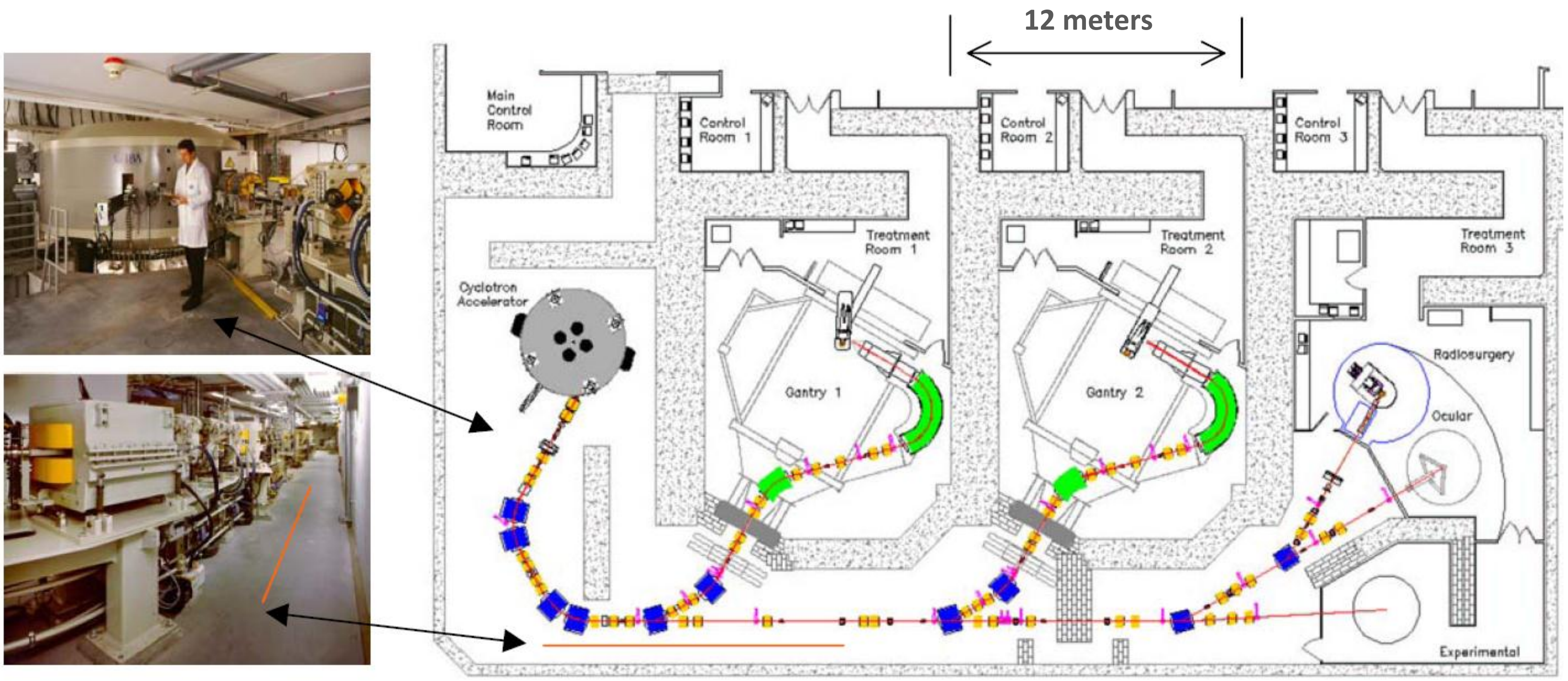
Example: lung tumours change with time

- Intra-patient daily variations
- Measure every few sessions and replan

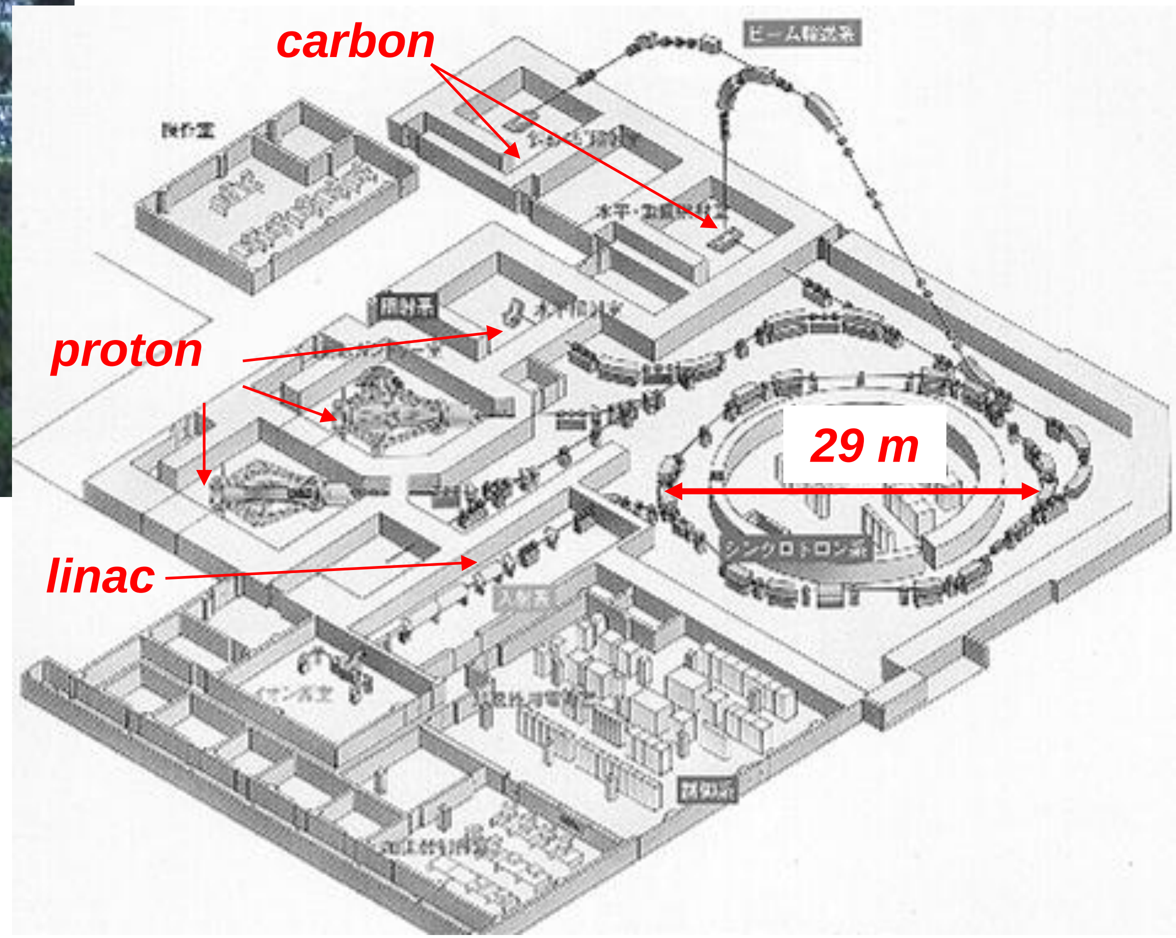
- Movements during irradiation
- Measurement with feedback and correction



Cyclotron solution for protons for MGH (Boston) by IBA



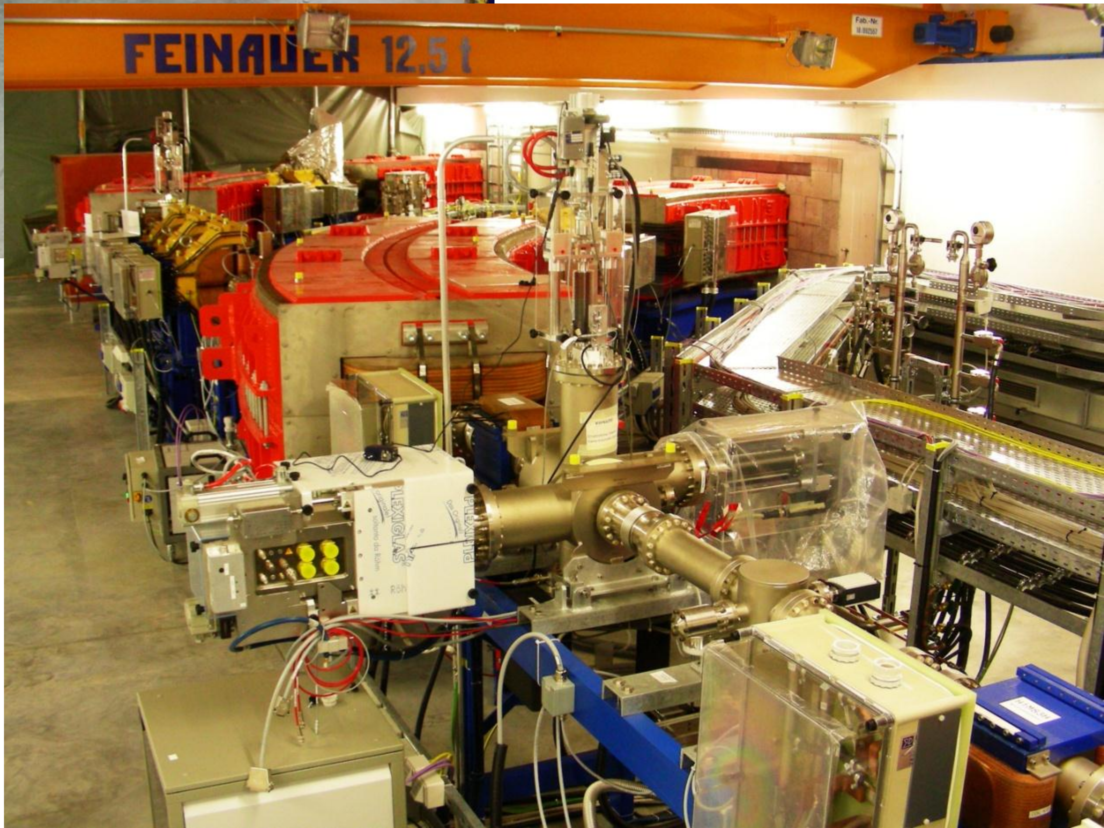
The Hyogo 'dual' Centre



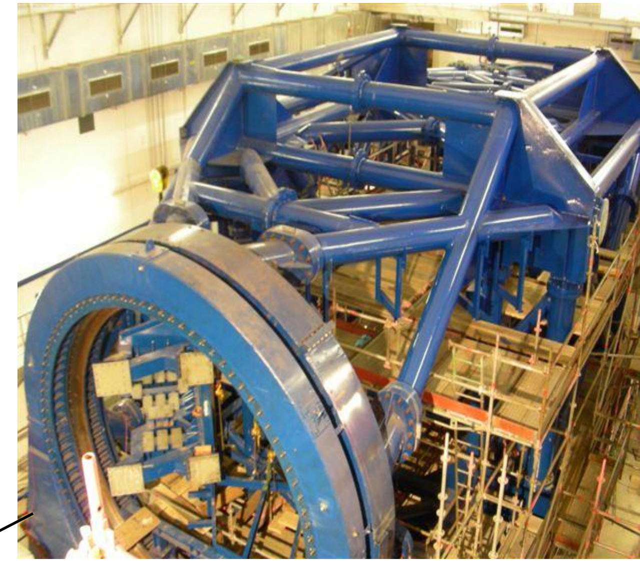
HIT at Heidelberg

synchrotron

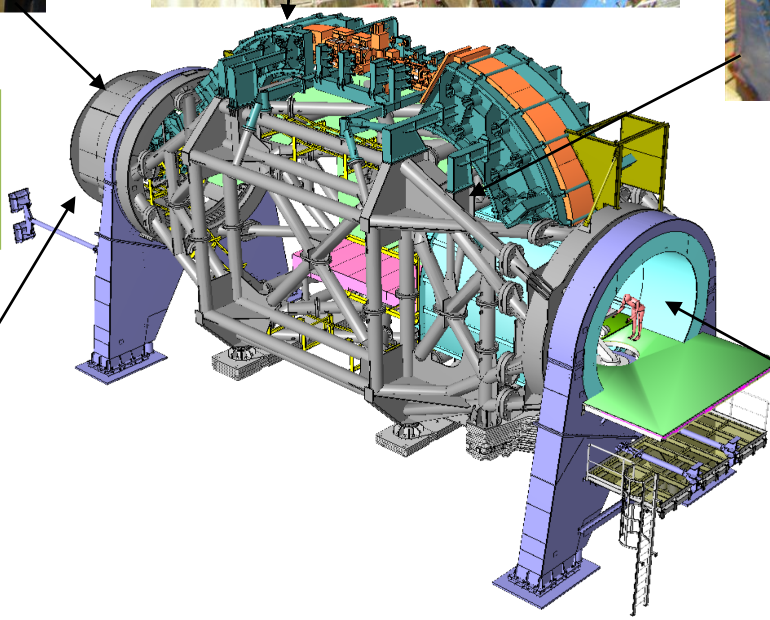
high energy
beam transport

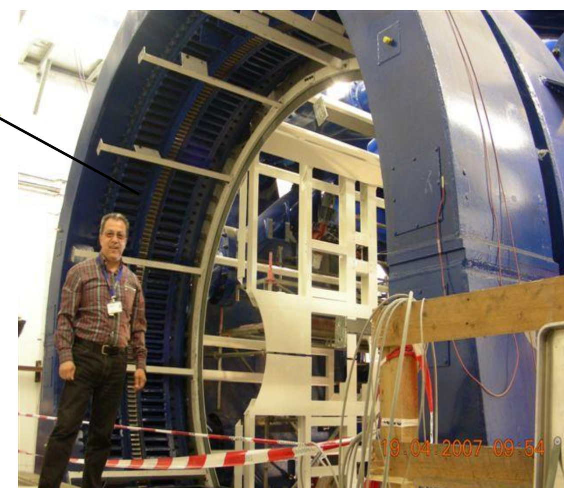


Heidelberg ion gantry: 600 tons and 400 kW



1st Rotation at
21.04.2007





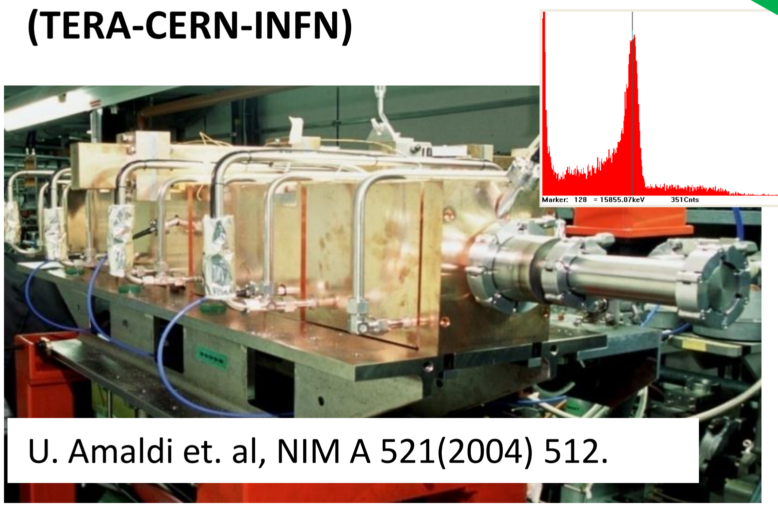
MT AEROSPACE

The Cyclinac solution

1993: first Cyclinac proposal

2001: first IDRA-design

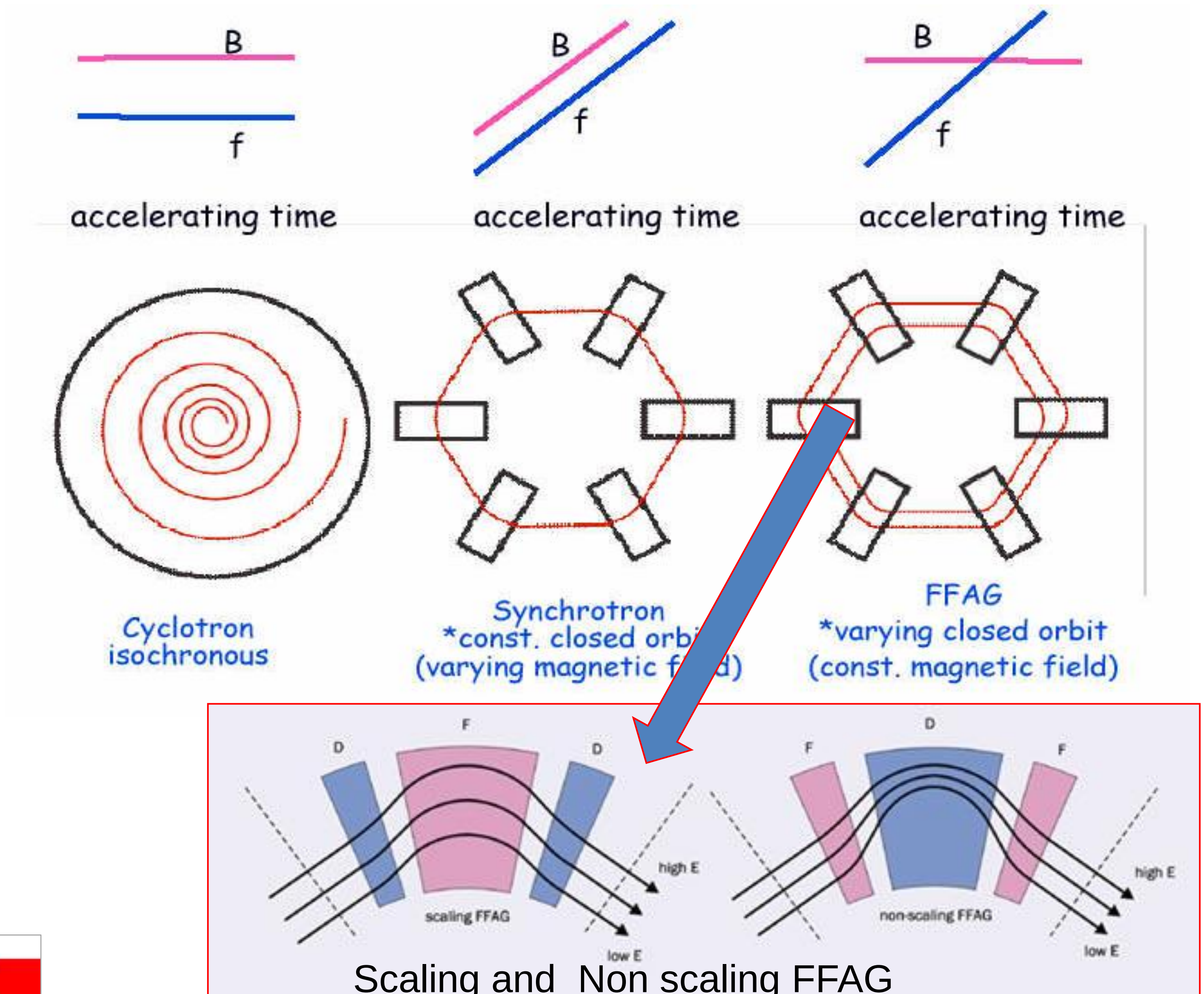
2003: test on LIBO-62 MeV (TERA-CERN-INFN)



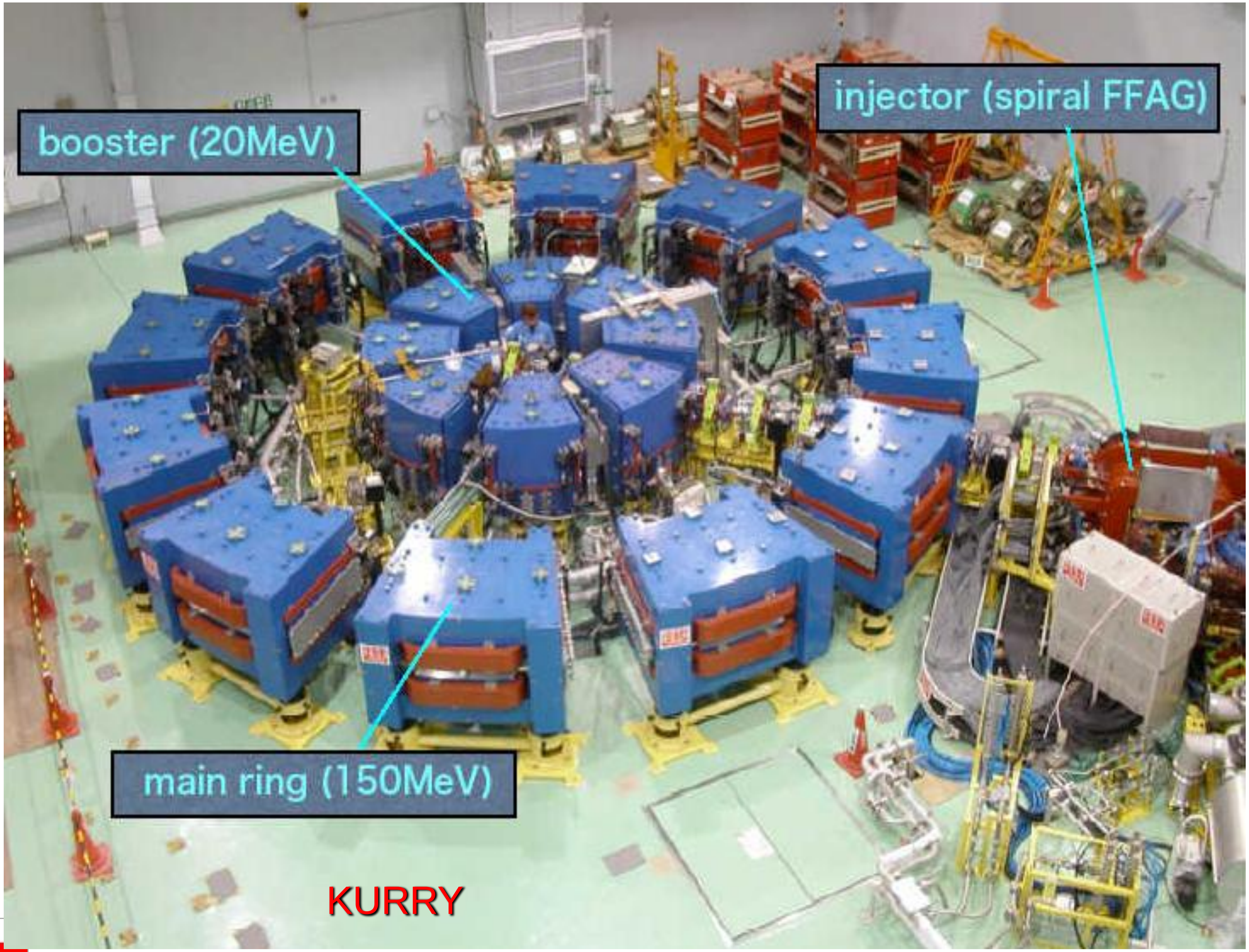
U. Amaldi et. al, NIM A 521(2004) 512.

2009-2010: First Unit of LIGHT (A.D.A.M.=Application of Detectors and Accelerators to Medicine)

An old-new solution: Fixed Field Alternating Gradient



The Japanese scaling 150 MeV proton FFAG



A non-scaling Fixed Field Alternating Gradient

DESIGN OF A NON-SCALING FFAG ACCELERATOR FOR PROTON THERAPY*

D. Trbojevic, A. G. Ruggiero, BNL, Upton, NY, USA, E Keil, CERN, Geneva, Switzerland, N. Neskovic, Vinca, Belgrade, and A. Sessler, LBL, Berkeley, CA, USA

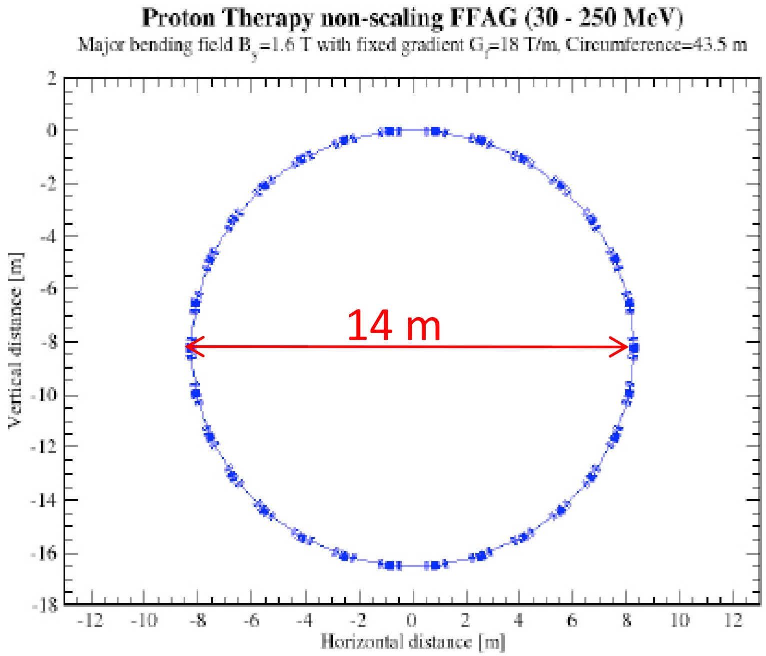


Figure 2. The whole ring of the fixed gradient lattice with 35 cells, C=43.5 m.

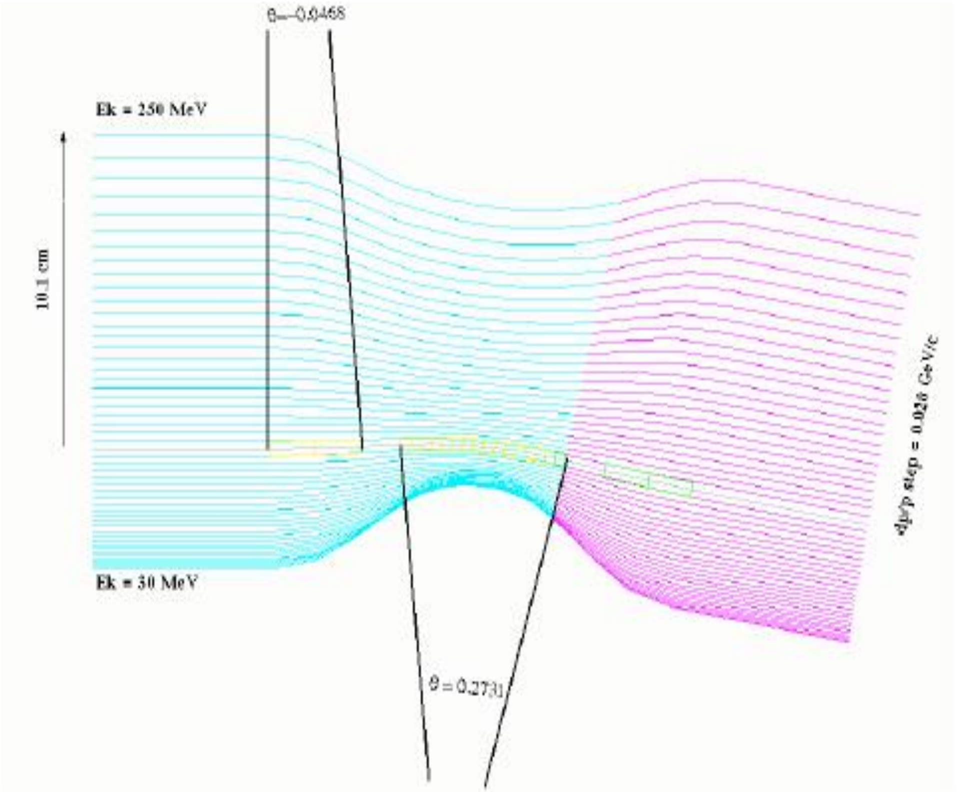
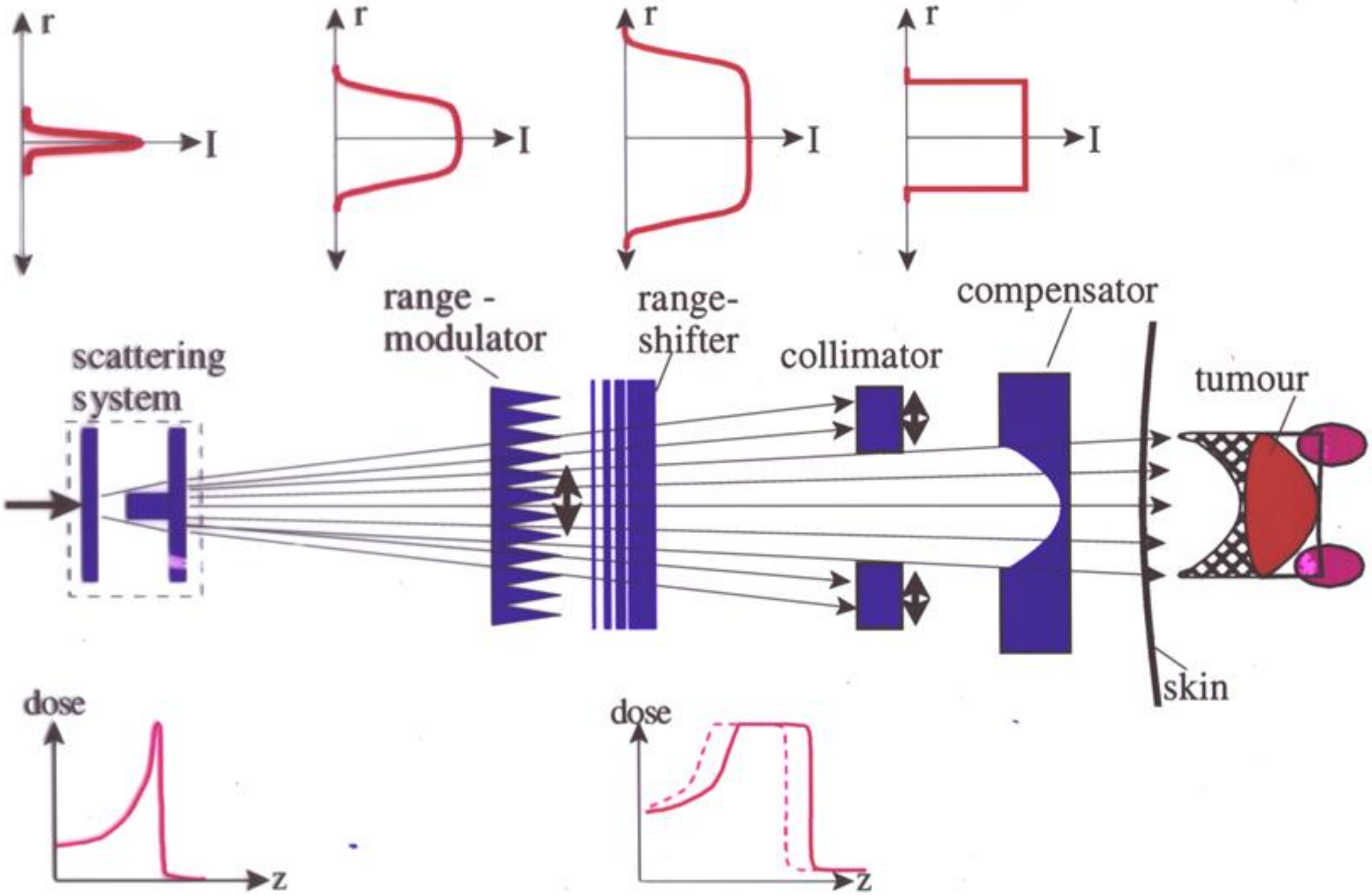


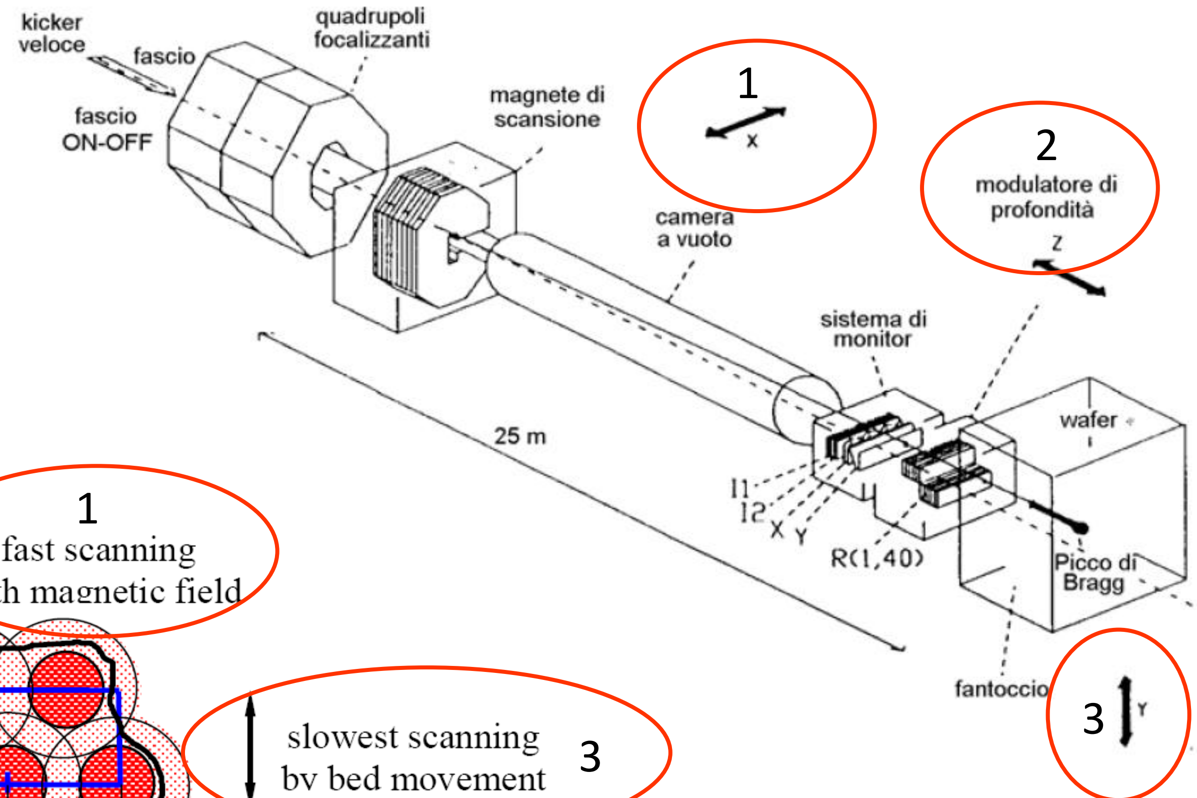
Figure 3. Orbits of particles during acceleration.

Two methods for imparting the dose: “passive” system

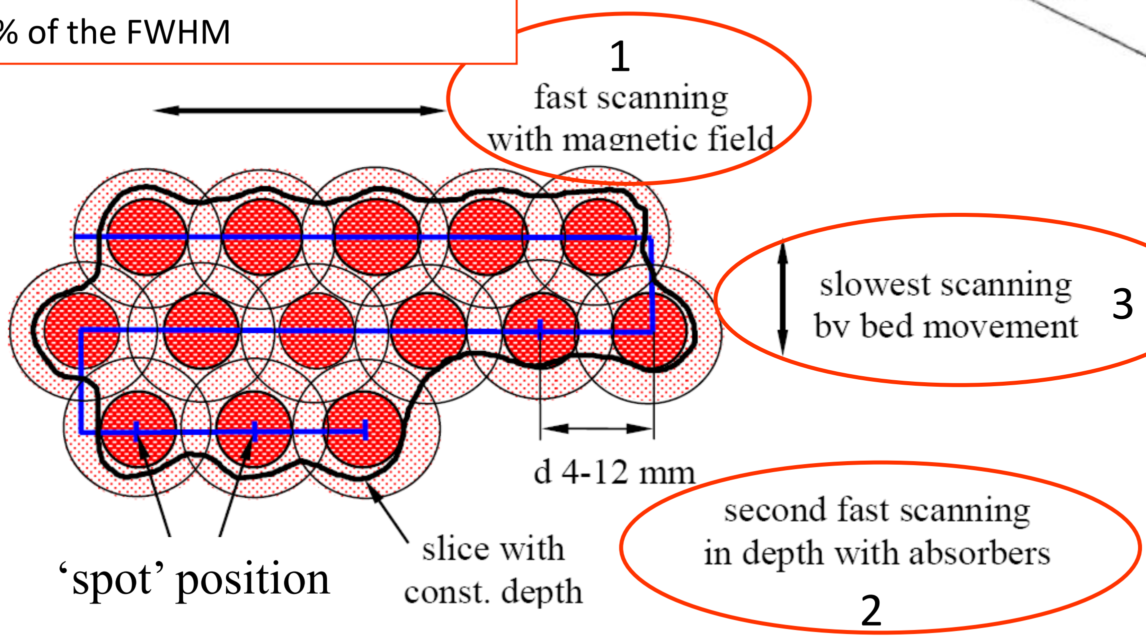


2A. Active “spot scanning” technique by PSI (Villigen)

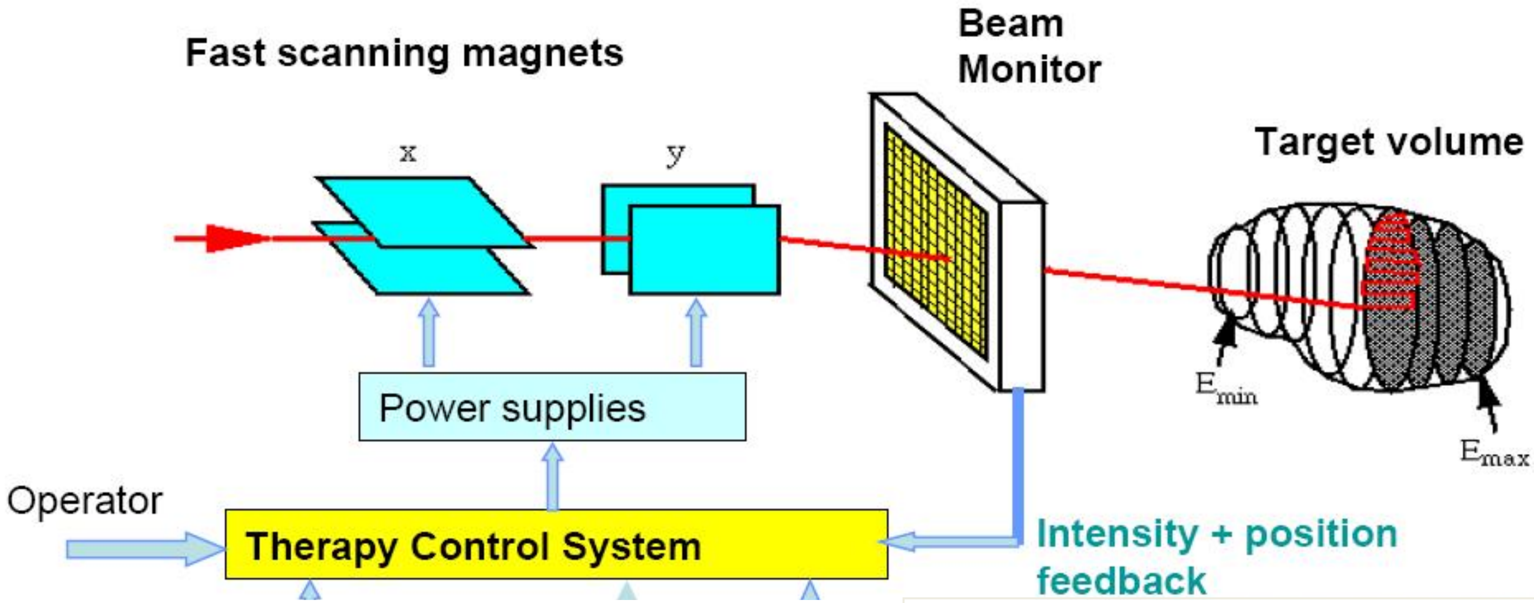
During the displacement the cyclotron beam is switched off for 5 ms



Distance between the centers is 75% of the FWHM



2B. Active “raster scanning” technique by GSI (Darmstadt)



Distance between the centers of the mini-voxels is 30% of the FWHM.
The beam is always on.