Accelerators for hadrontherapy

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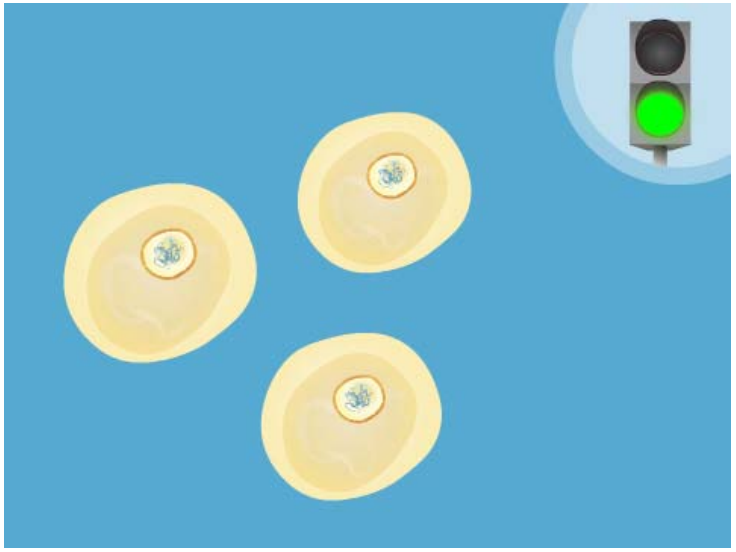
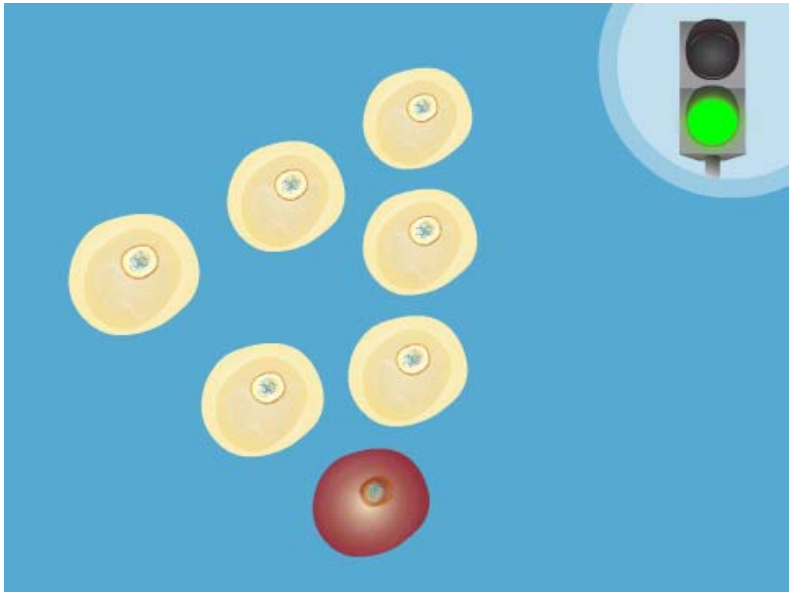
Giornatedi studio sui rivelatori, Cogne 2019

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

Tumours and radiotherapy



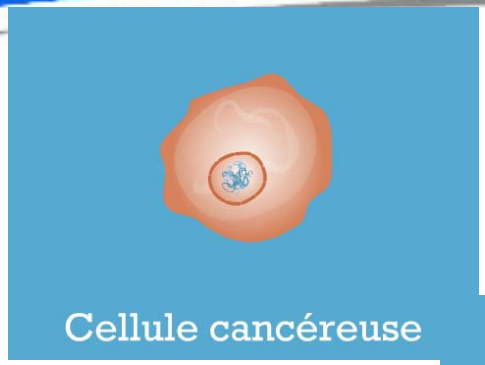
Normally cells multiply only when they are told so



If there is a mutation (DNA error)…

…the cell is told to suicide (apoptosis)

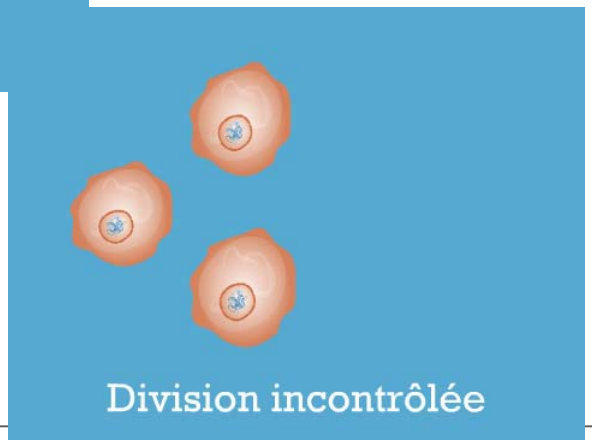
Something (else) goes wrong
and the mutant cell refuses to die …



No more response to control signals

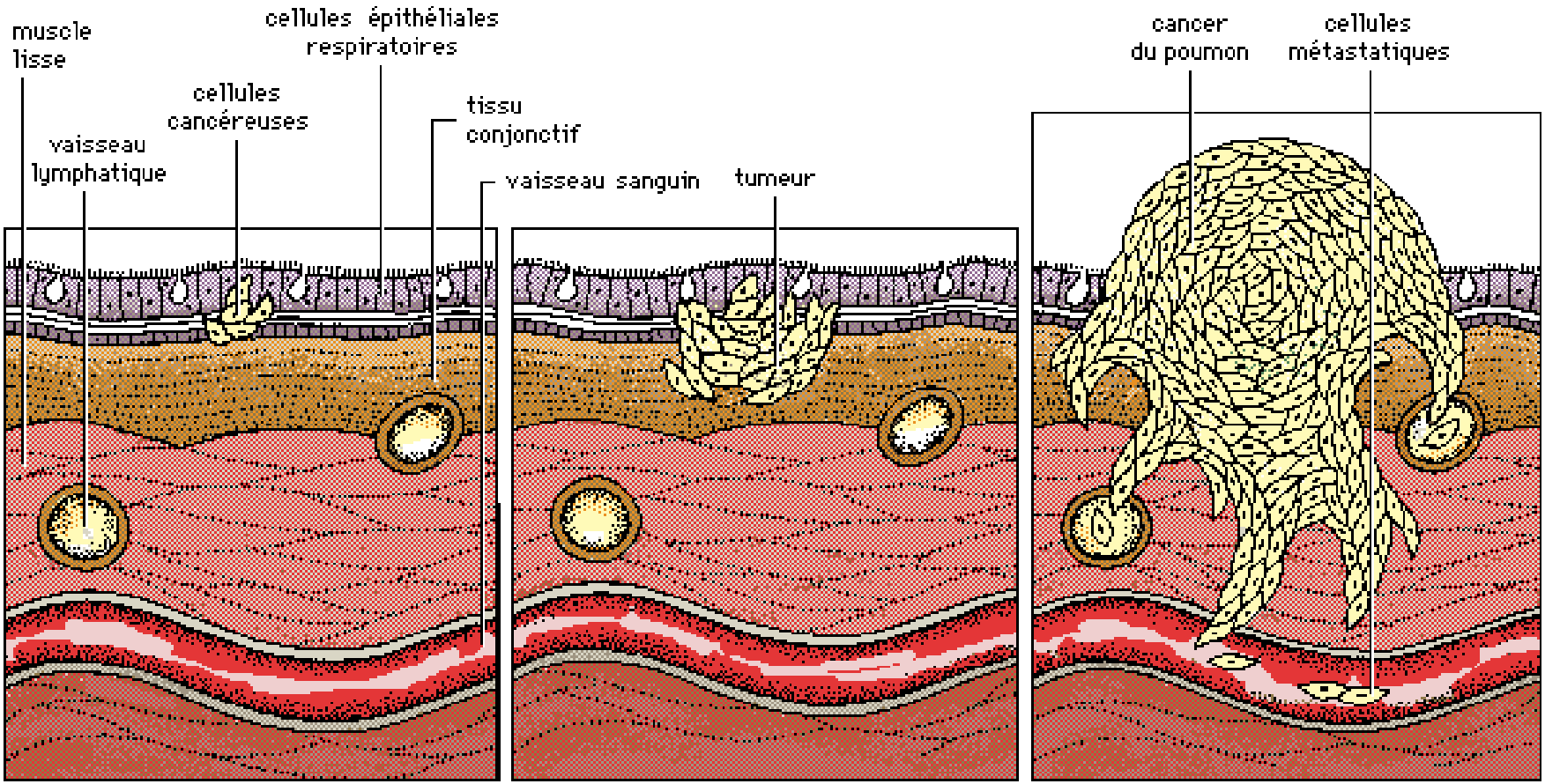
No apoptosis

… and begins to multply in an uncontrolled way



TUMOUR

If we don’t stop it…



Cellules saines avec peu de cellules cancéreuses

Multiplication des cellules cancéreuses

Cellules métastasées

Tumours

- They grow in an uncontrolled way
- They infiltrate the surrounding tissues and can originate metastasis (malignant)
- When metastatic, only chemotherapy is possible
- If localised, surgery or **radiotherapy**

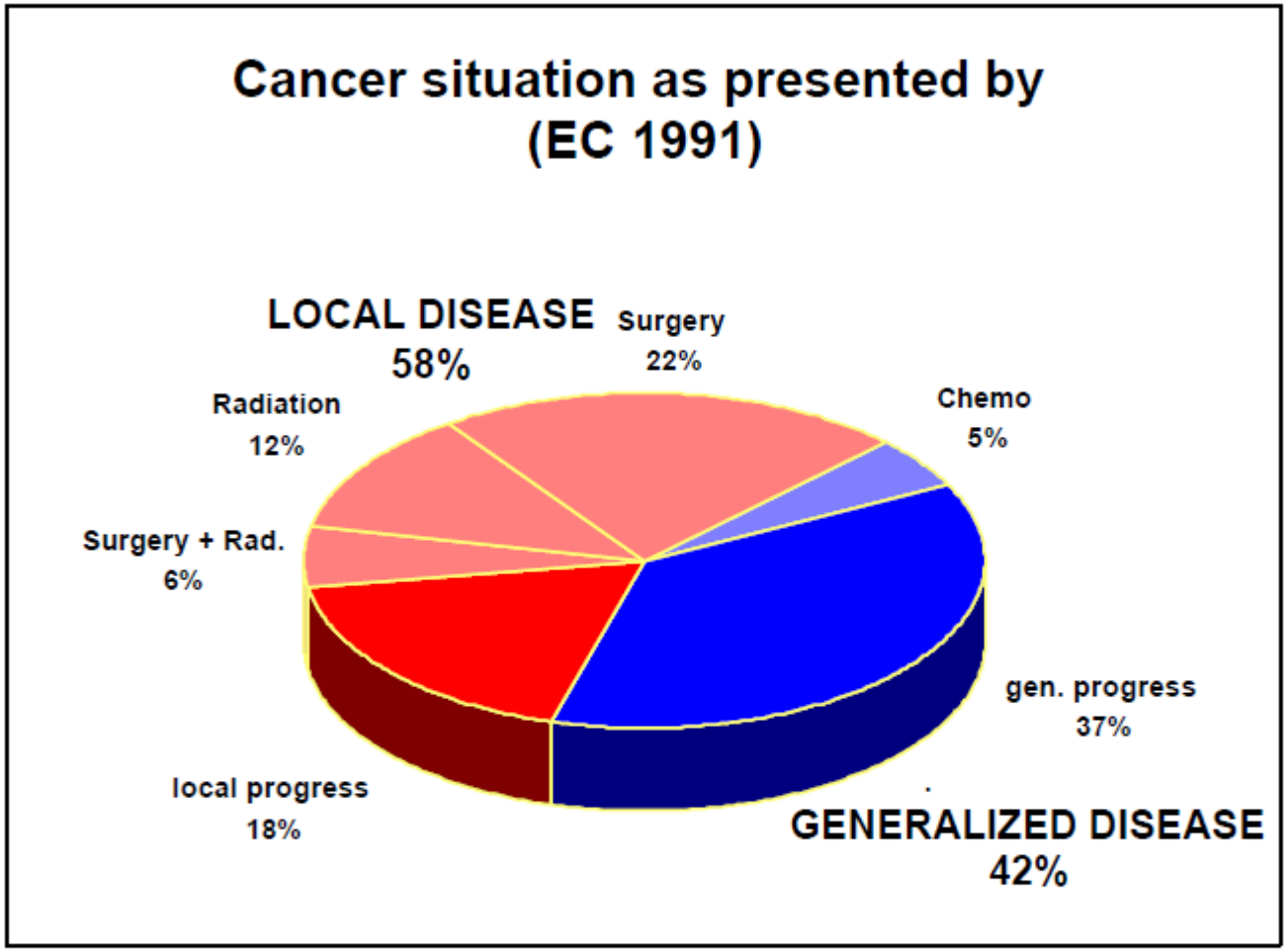


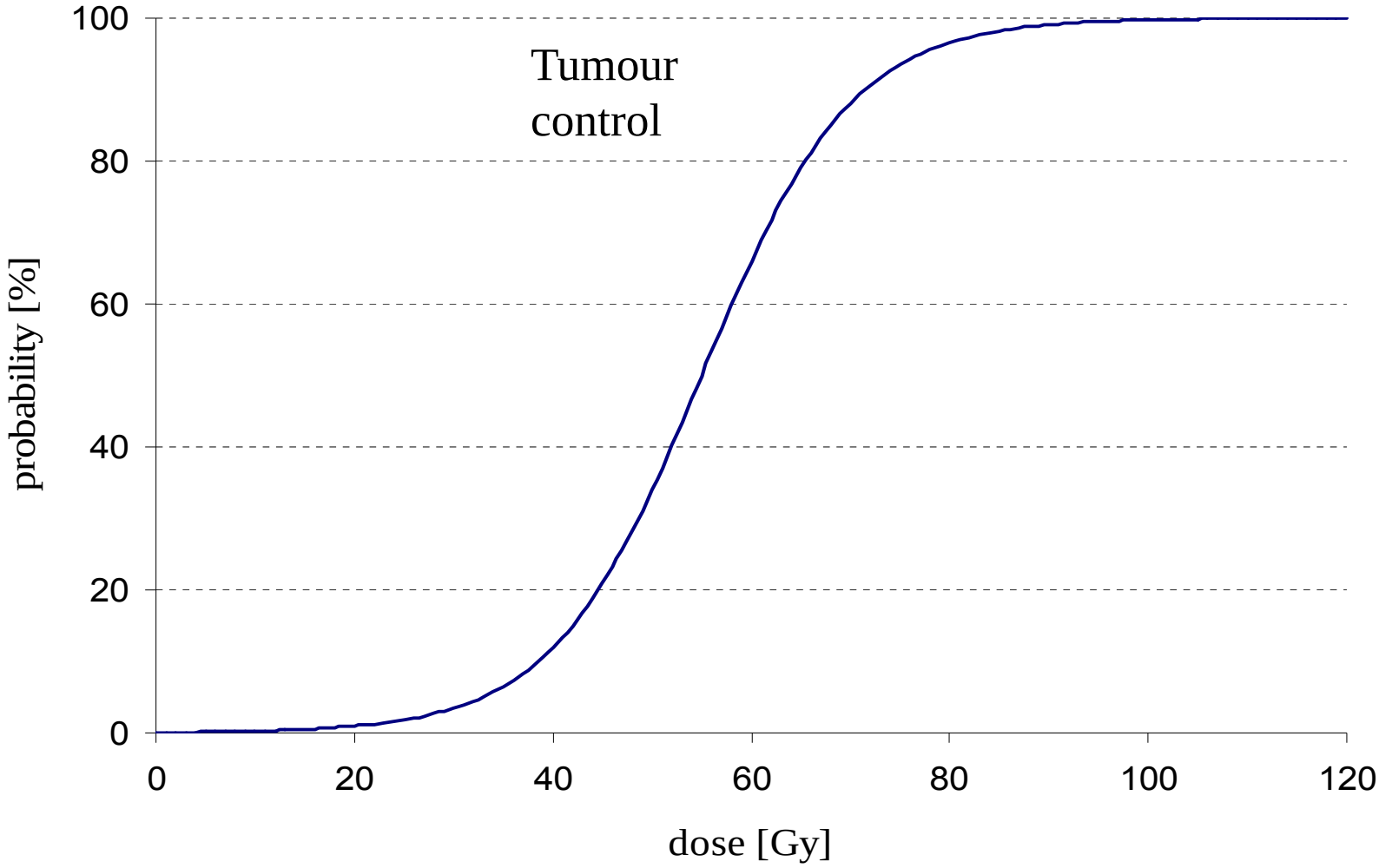
Figure 1: Distribution of the more than one million new cancer patients in Europe: Local disease (red fraction) are patients with only one well-defined tumor in the beginning. Generalized i.e. more than on tumor are given in blue. Nearly 50 % of the patients yielded a 5 year tumor free survival by the different treatment modalities but 18 % of patients with local deseases in the beginning cannot be curied. These are the candidates for particle therapy.

Energy and Efficacy

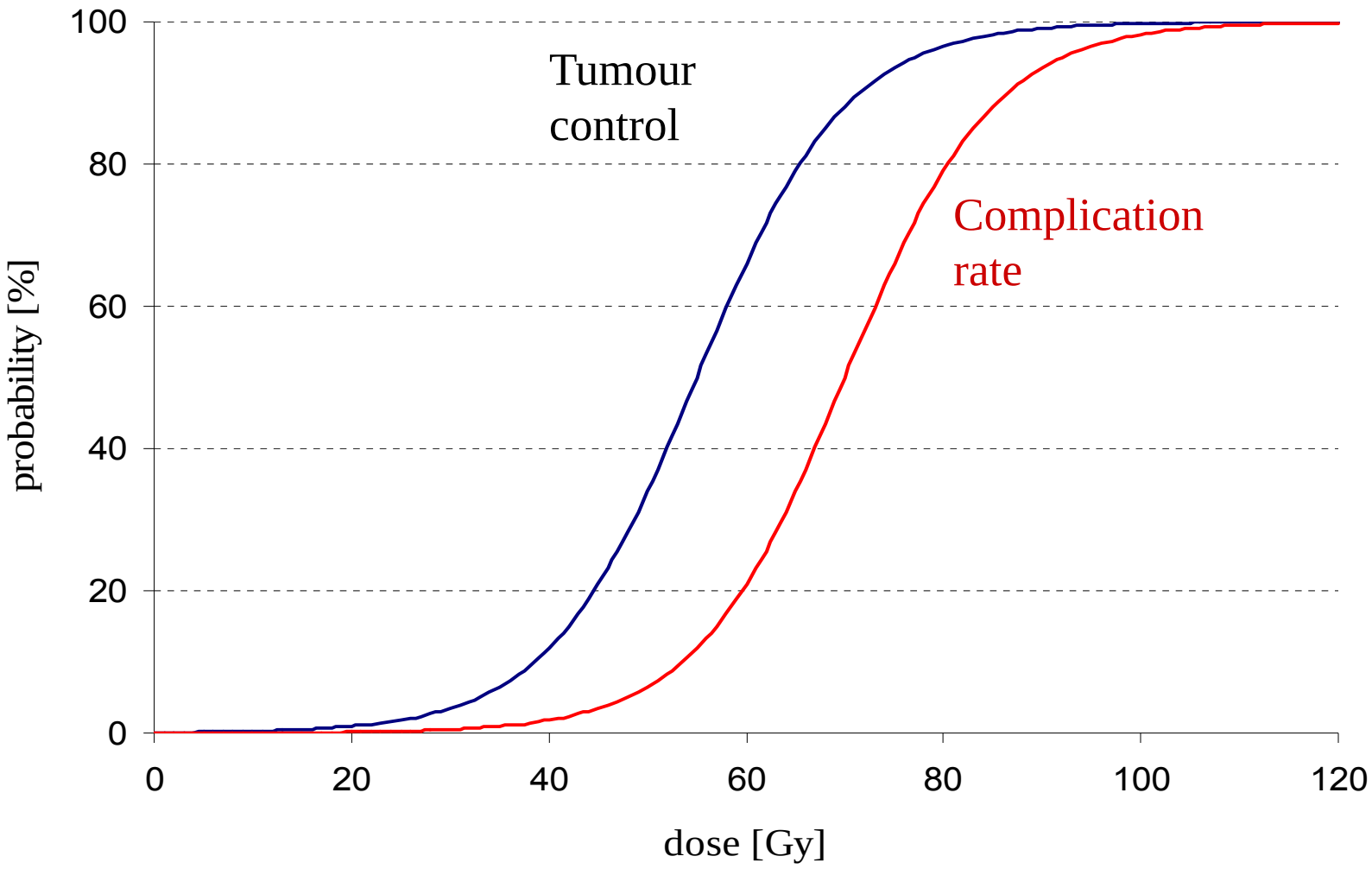
- Administered dose
  - 1 Gy = 1 J / 1Kg
  - (typical dose in radiotherapy 35 X 2 Gy)

- How many cells do I kill?
  - Potential energy (1 m fall = 10 Gy)
  - Heat (fever 38° = 4185 Gy)
  - Ionizing radiation (little energy, many damages)

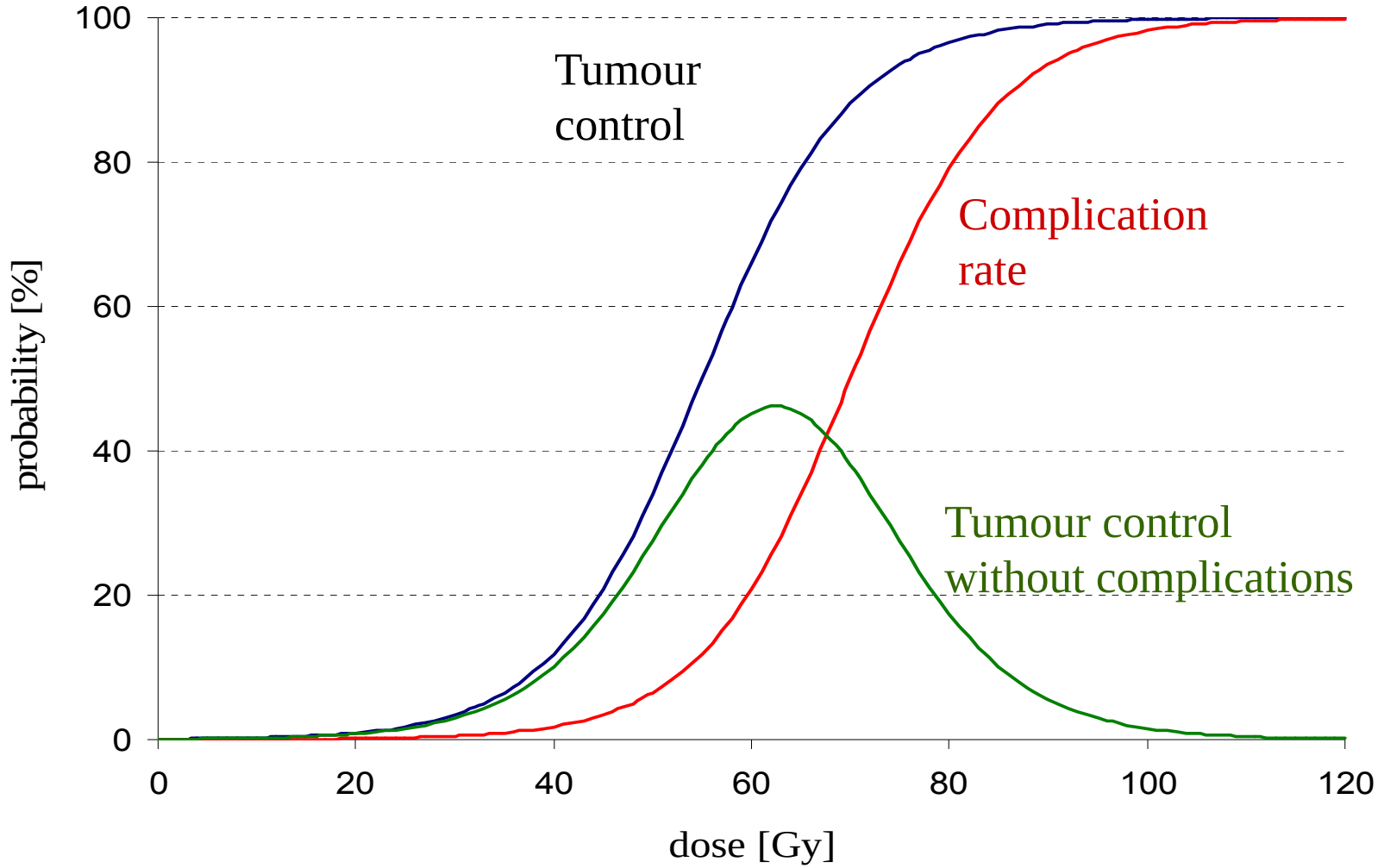
General principle of radiation therapy



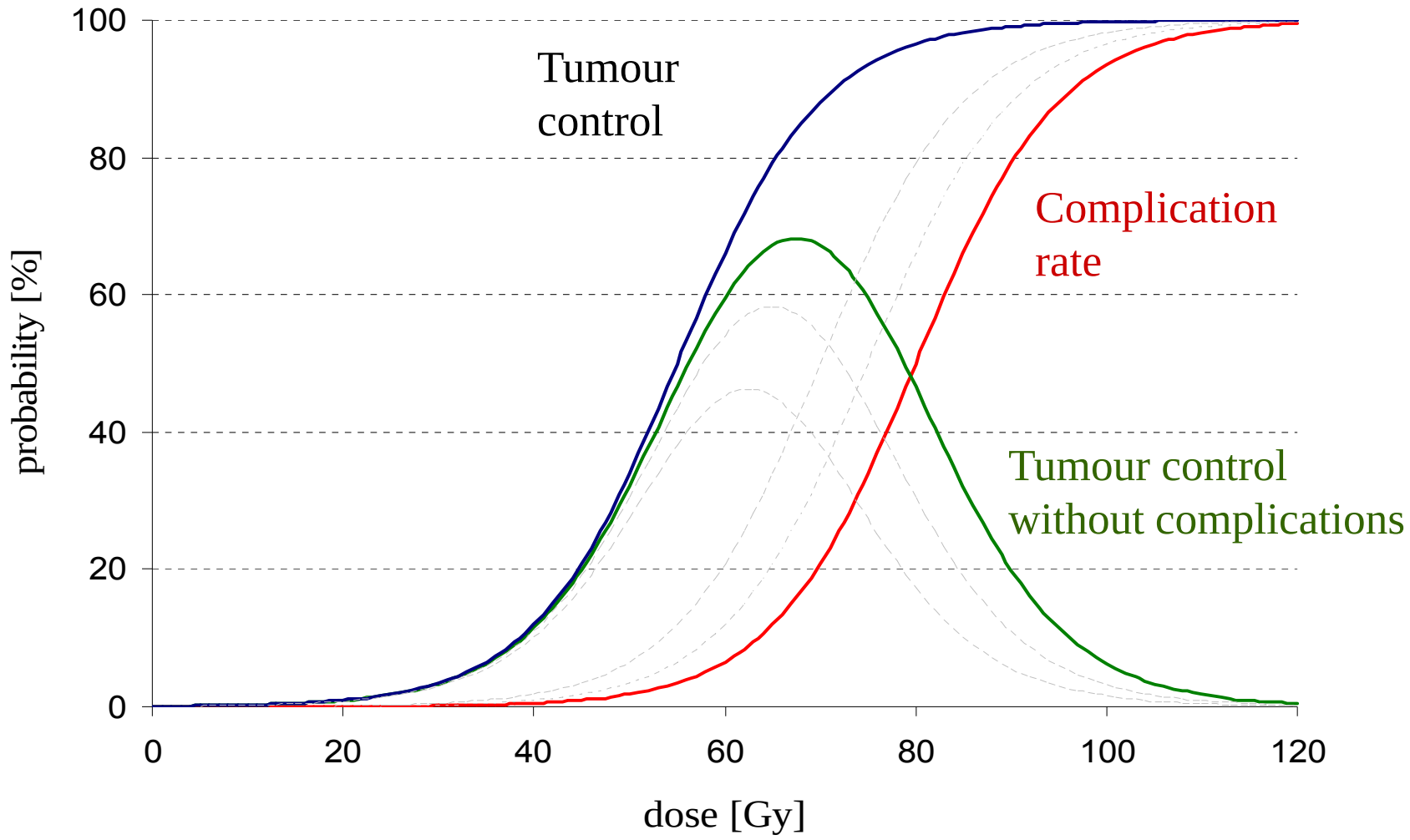
General principle of radiation therapy



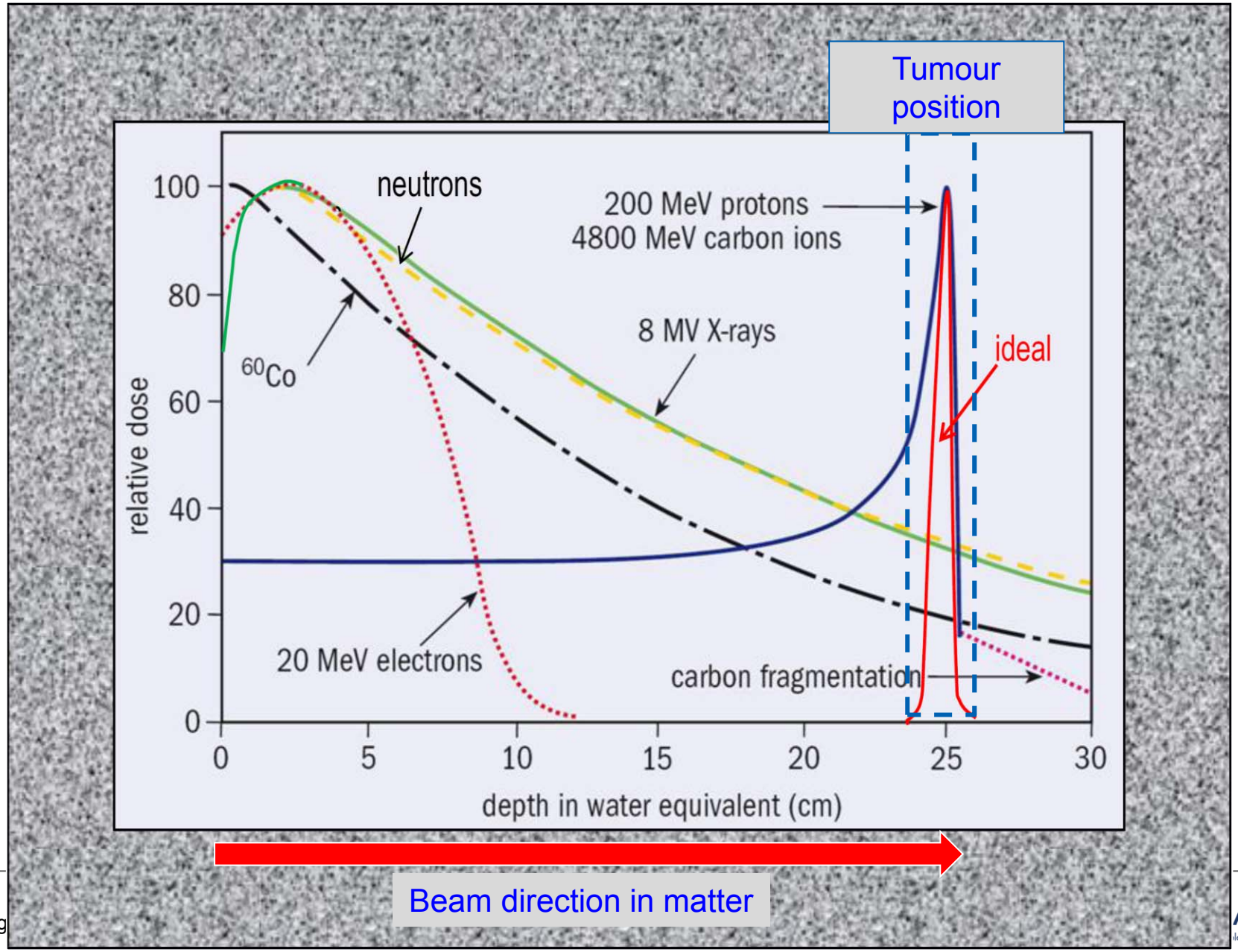
General principle of radiation therapy



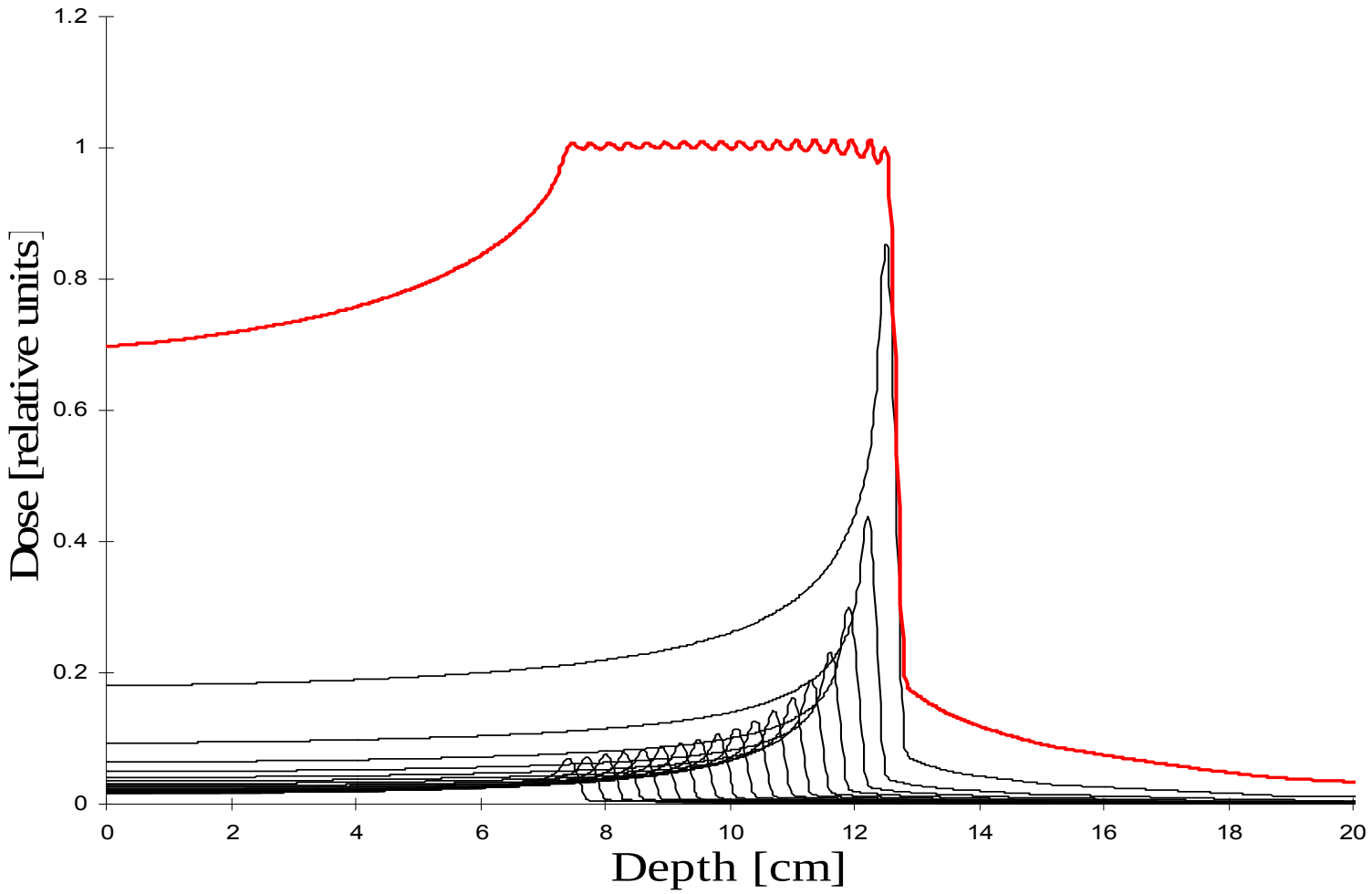
General principle of radiation therapy



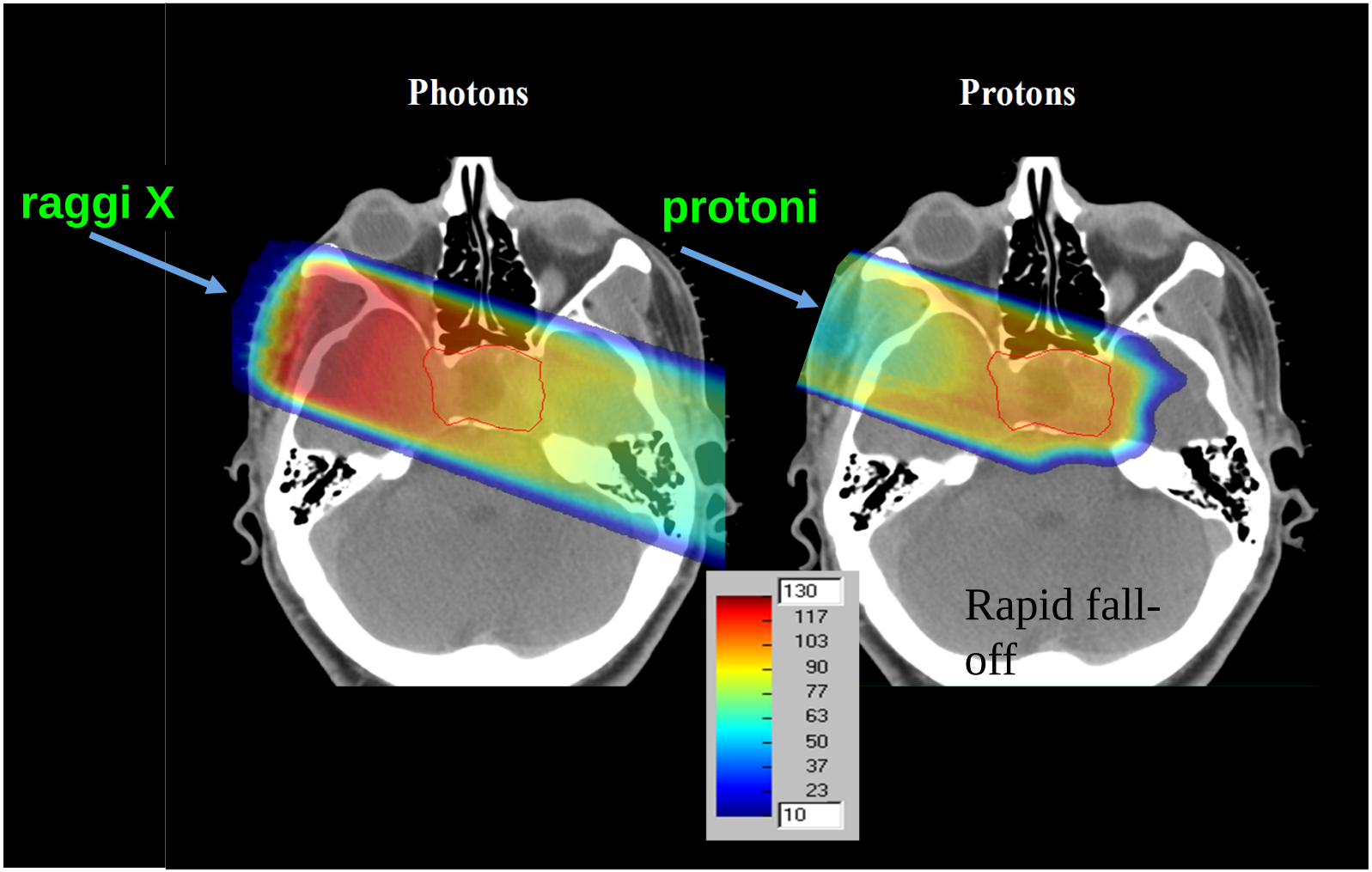
Hadrontherapy geometrical advantage



Longitudinal - Spread Out Bragg Peak

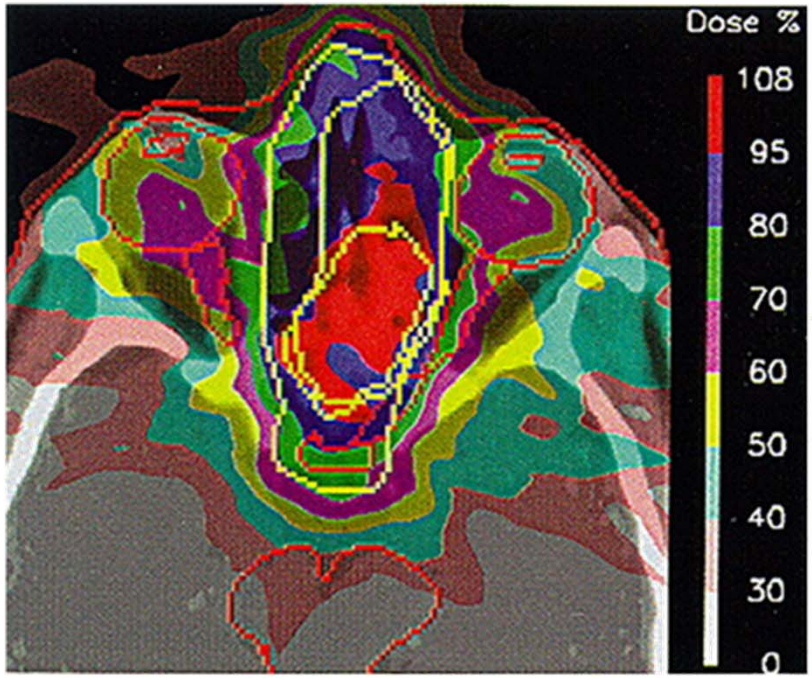


Macroscopic/geometric advantage

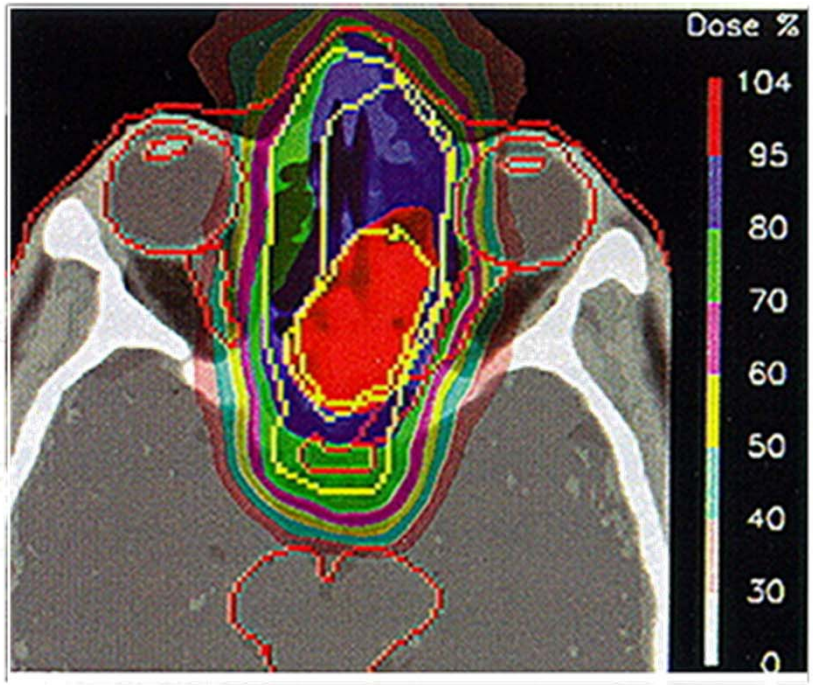


Better dose distribution

9 X beams



1 proton beam



tumor between eyes

Ionization density effects

Radiation damage

- Ionization breaks chemical bonds
- **Free radicals** creation (mainly hydroxyl radical, OH^-, and superoxide, O_2^- . Poison for the cell!)
- The target is DNA, ionization distribution is relevant

3 different cases

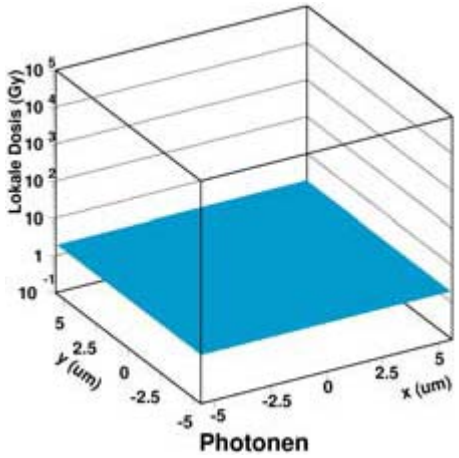
LET = Linear Energy Transfer

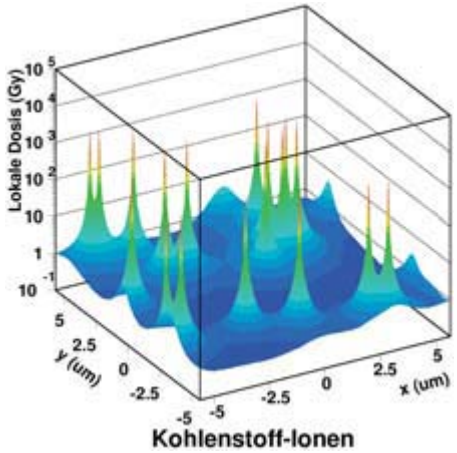
-1 Low LET(<20 keV/micron)
Distance between ionizations larger than DNA diameter. Classical radiotherapy; Fractionation very important.

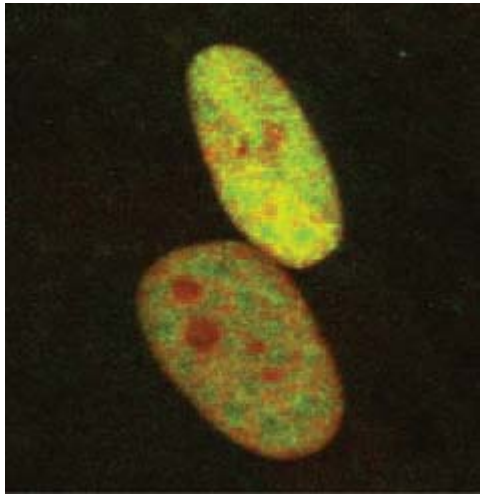
-2 High LET(50 – 200 keV/micron)
Distance between ionizations comparable with DNA diameter. C-ion therapy; Fractionation less important.

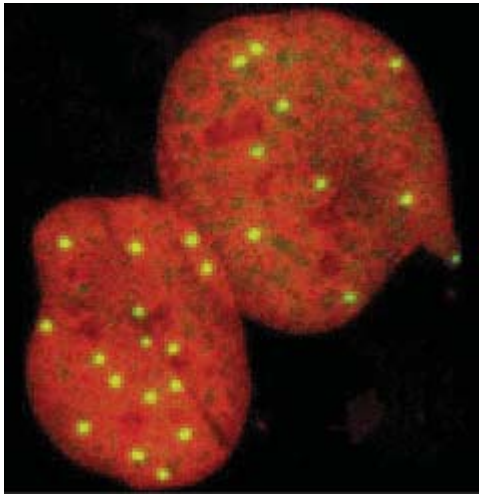
-3 Very high LET(> 1000 keV/micron)
Distance between ionizations smaller than DNA diameter; energy in excess in ionizations (overkill).

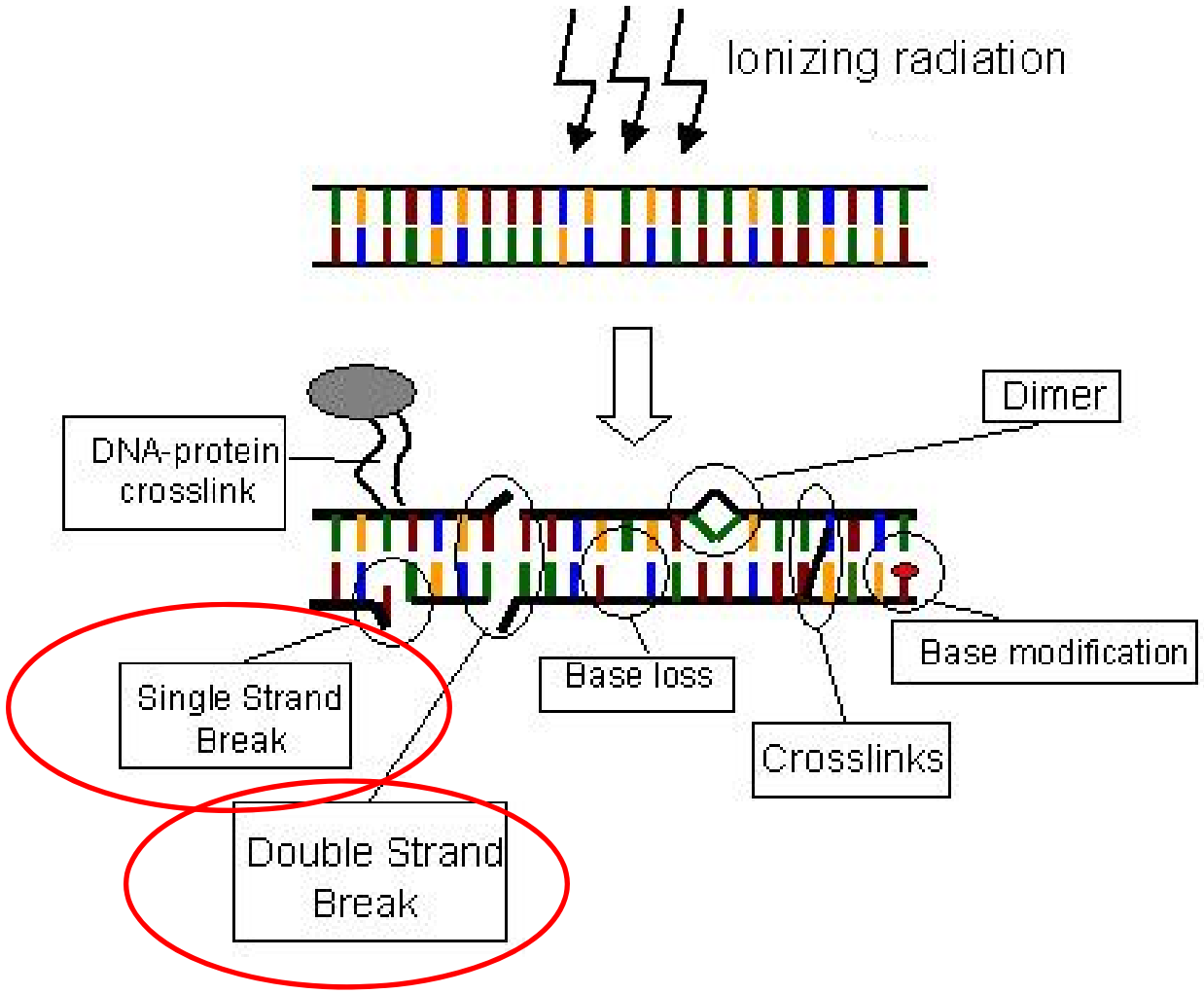
Distribution of dose and of damage (yellow) on the cell nucleus scale (microns) for photons and carbon ions











(courtesy of A Facoetti)

If cells are irradiated with x-rays, many breaks of a single strand occur. In intact DNA however single strand breaks are of little biological consequence because they are repaired readily using the opposite strand as template.

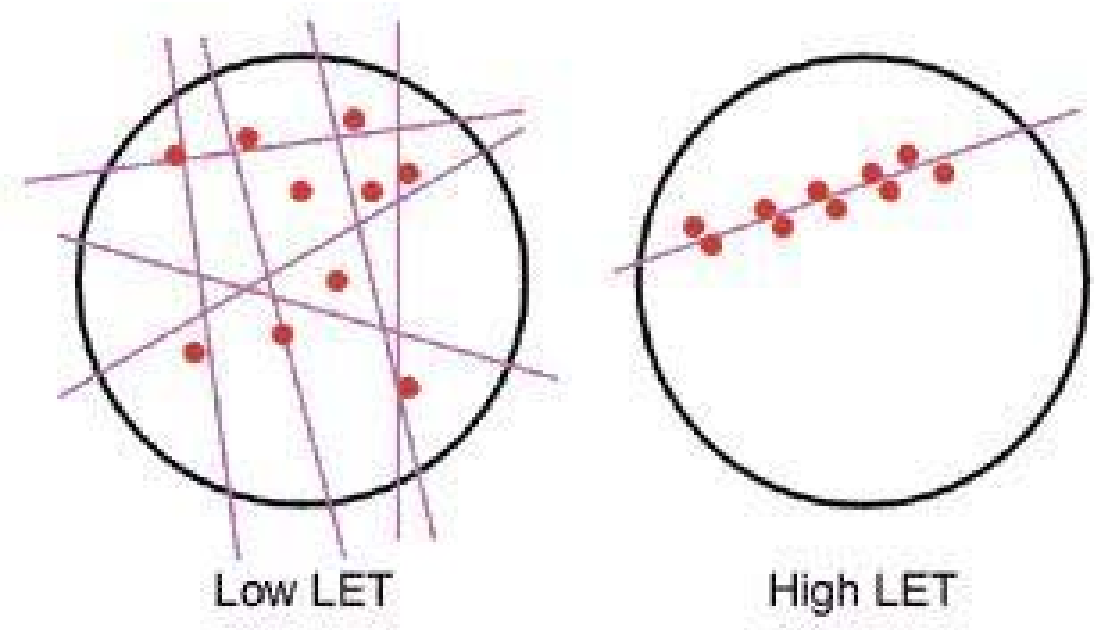
If the repair is incorrect (misrepair), it may result in a mutation.

If both strands of the DNA are broken, and the breaks are well separated, repair again occurs readily because the two breaks are handled separately.

By contrast, if the breaks in the two strands are opposite one another, or separated by only a few base pairs, this may lead to a double strand break (DSB).

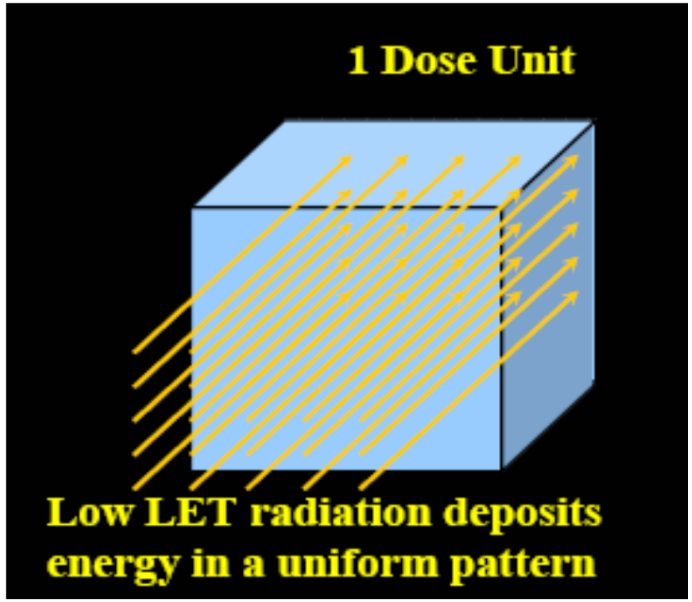
A DSB is believed to be the most important lesion produced in chromosomes by radiation.

(courtesy of A Facoetti)

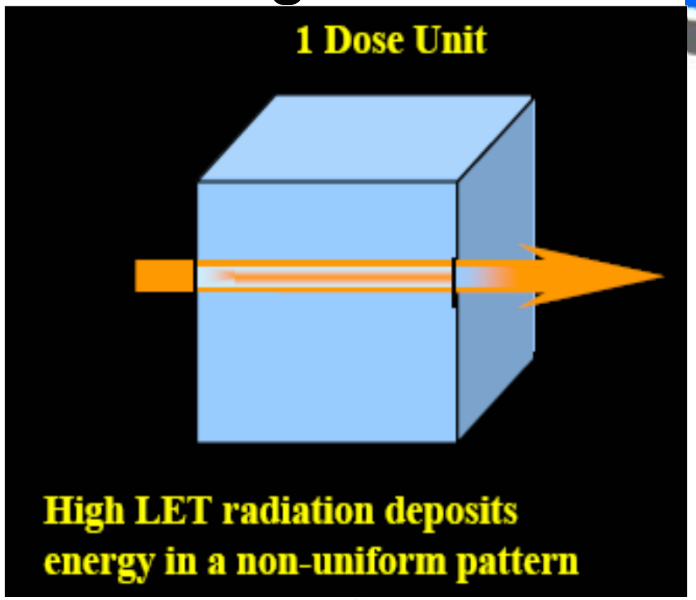


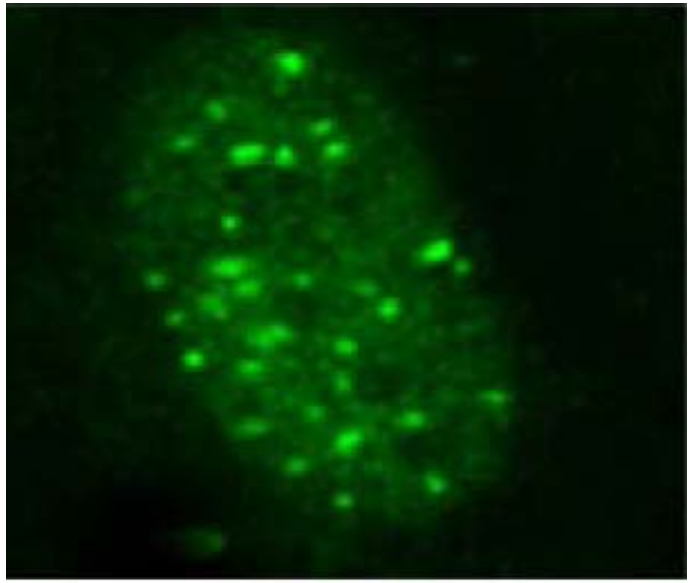
Both examples produce the same total number of ionizations, thus represent the same dose, but with different effects by Low LET and High LET

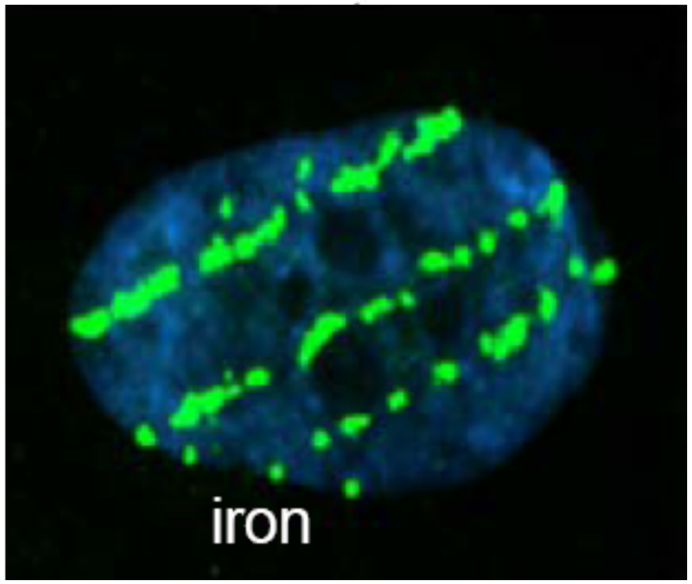
Low LET



High LET



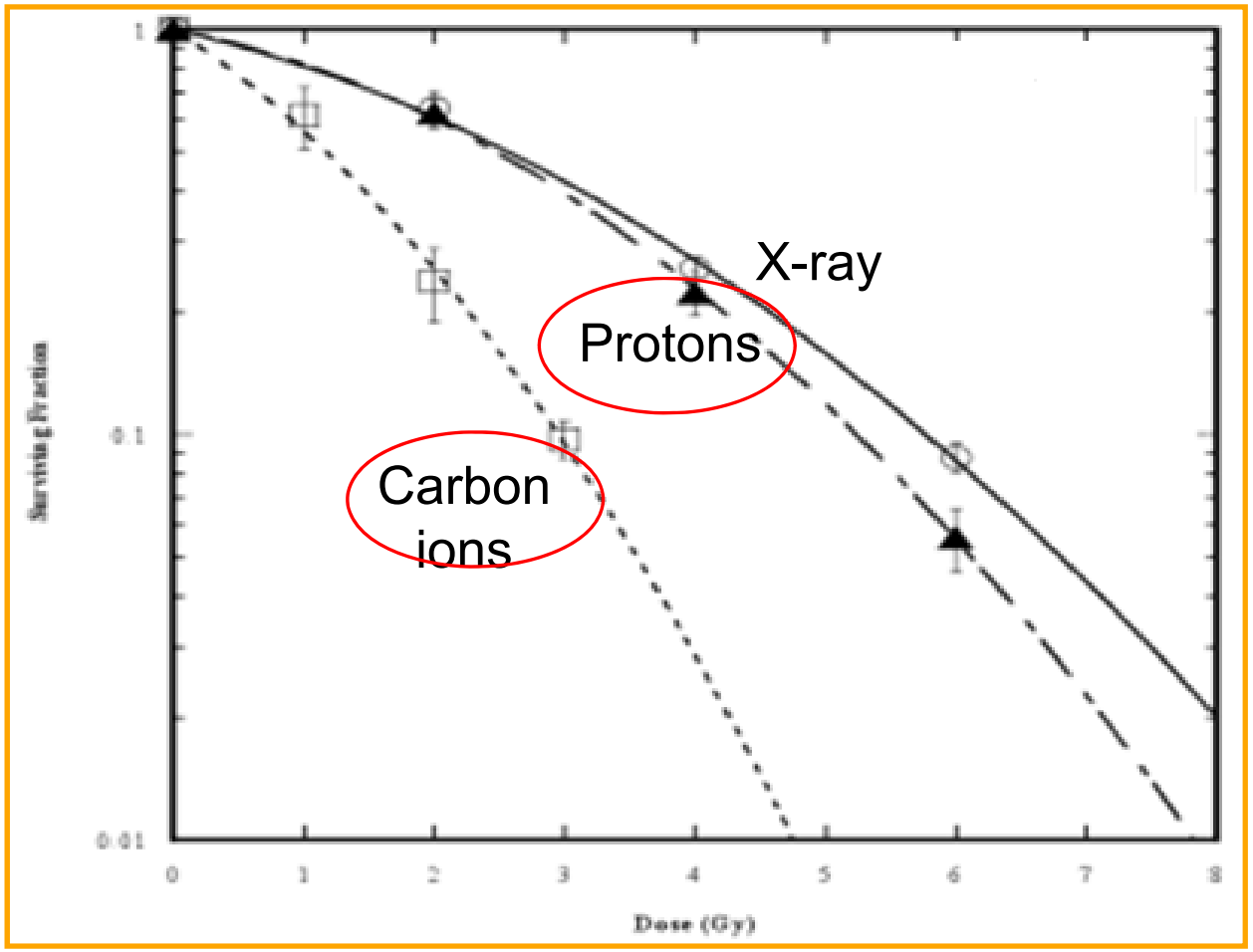




Formation of fluorescent g-H2AX clusters in irradiated human fibroblasts at 10 min postirradiation with 2 Gy of gamma rays or 0.5 Gy of 176 keV/mm iron ions

Modificato da: JAEA R&D, 2007; Cucinotta and Durante, 2006

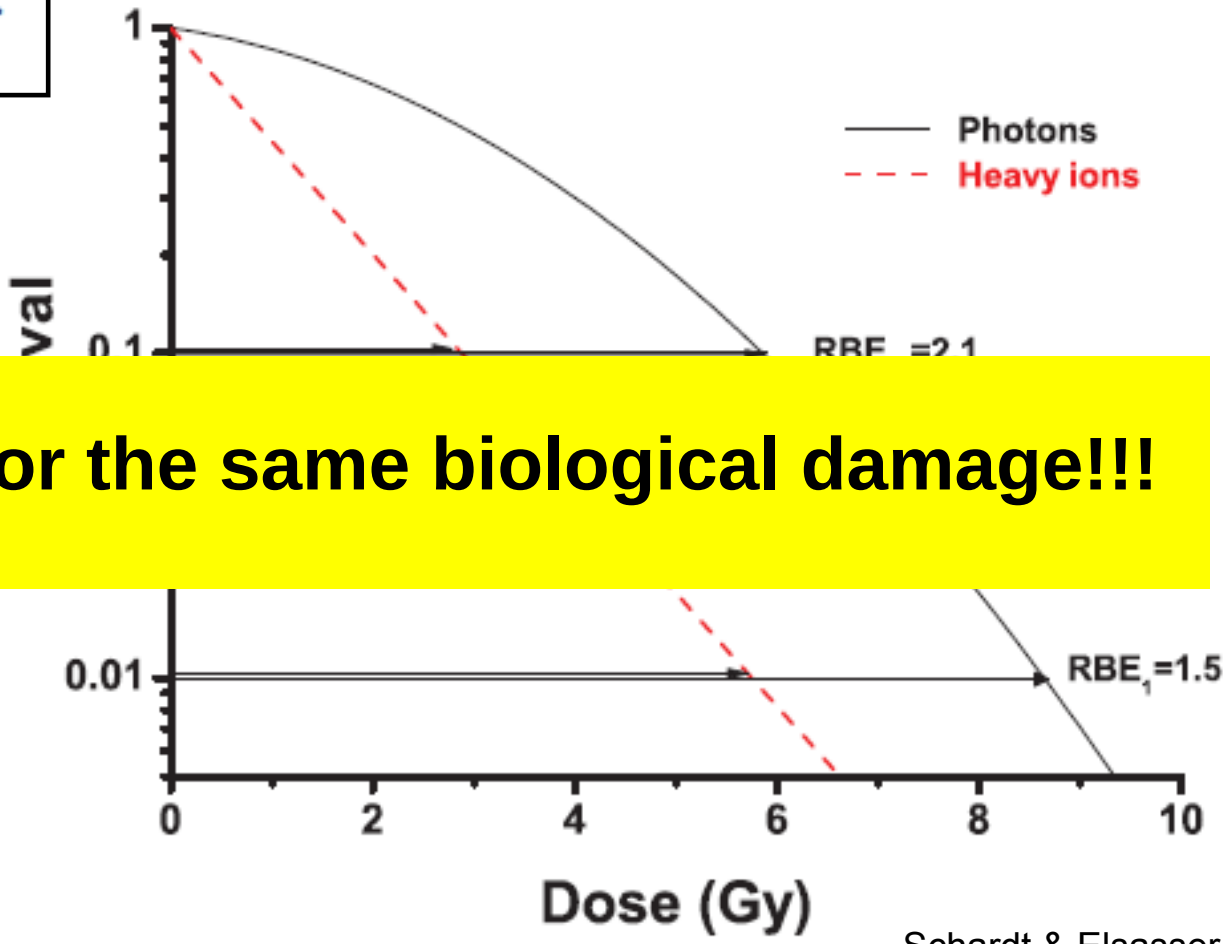
Survival curves



(courtesy of A Facoetti)

RBE (Relative biological effectiveness)

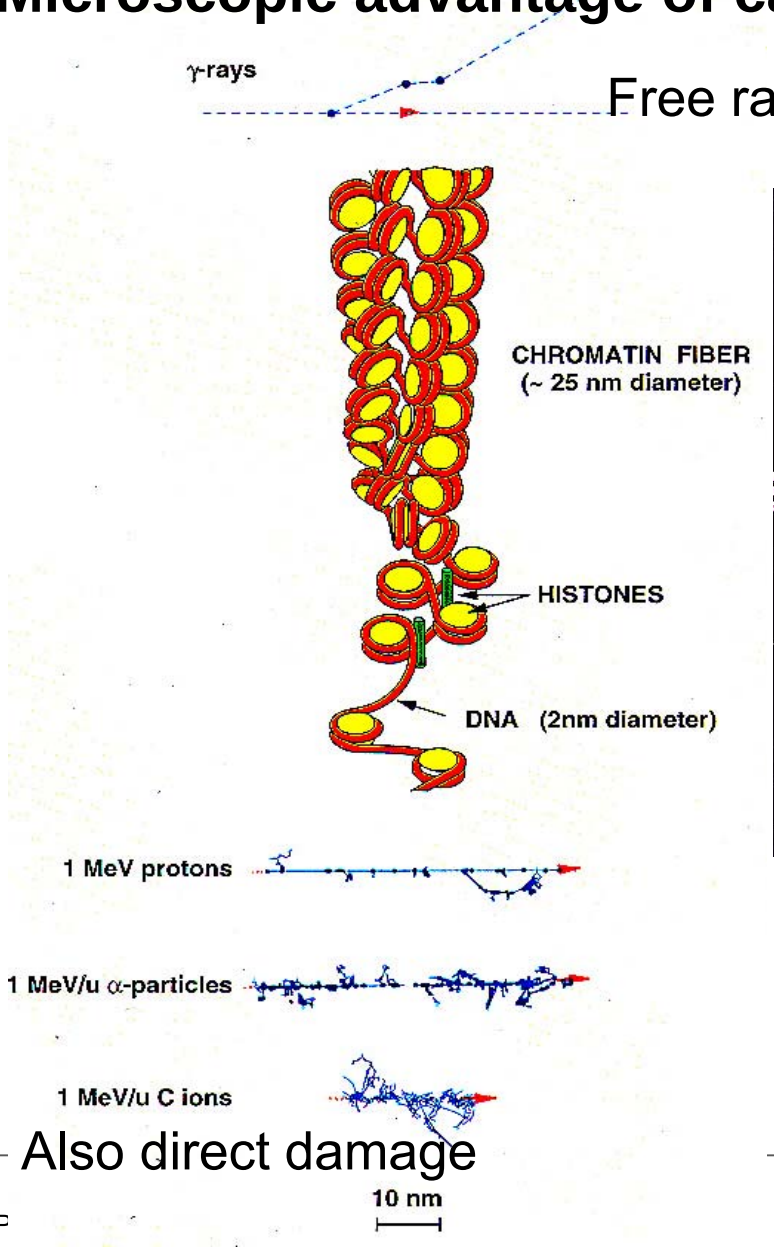
$$\mathrm{RBE}_{\mathrm{iso}} = \frac{D_{\mathrm{ref}}}{D_{\mathrm{ion}}}.$$



N.B.: for the same biological damage!!!

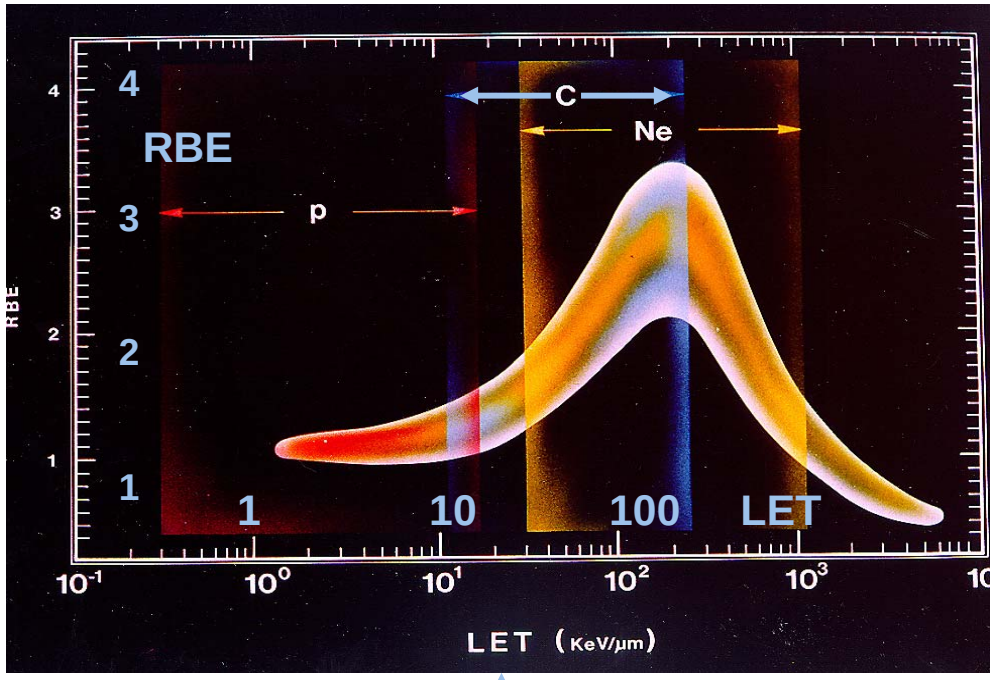
Schardt & Elsasser, 2010

Microscopic advantage of carbon ions



Free radicals

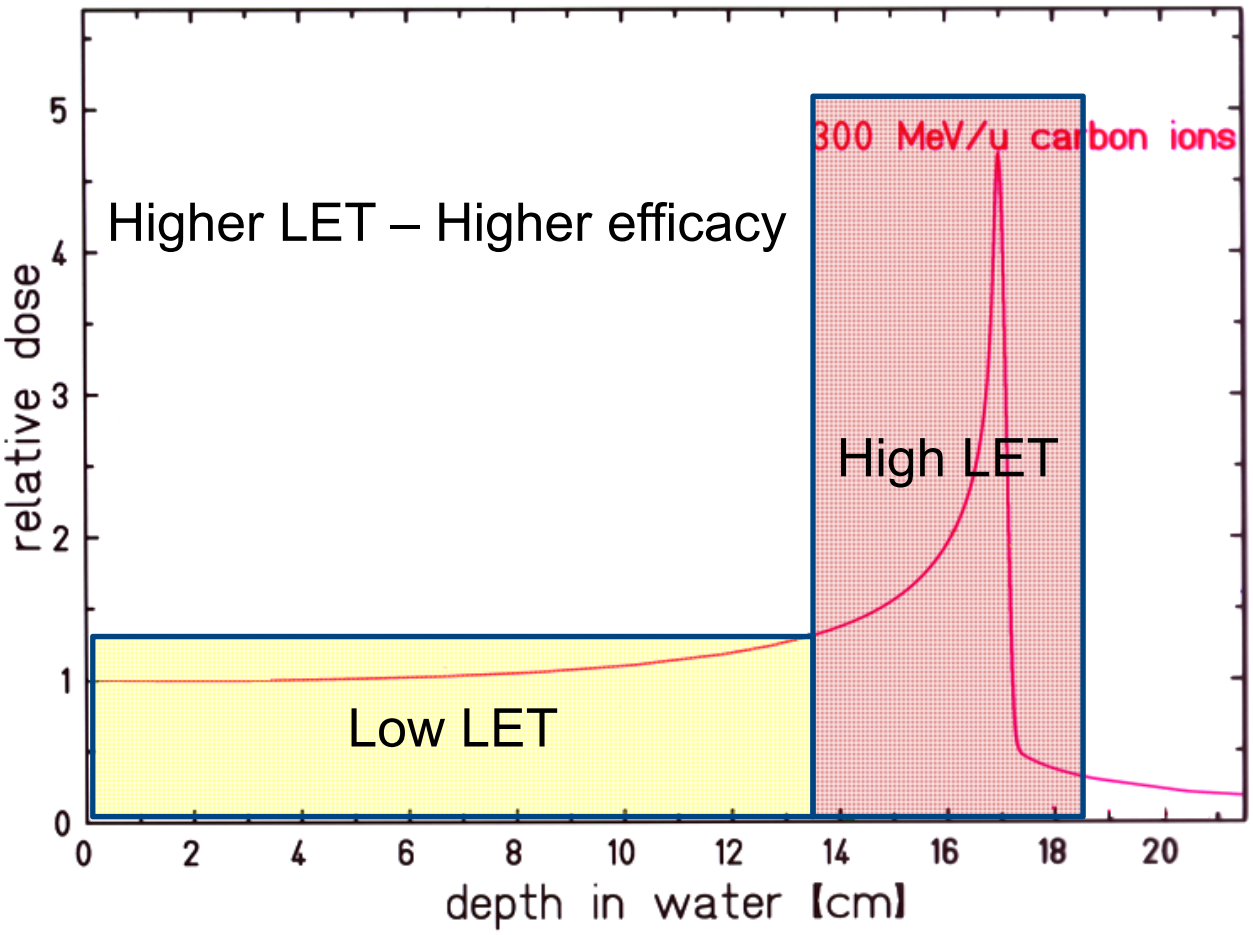
Also direct damage



10 – 20 keV/mm = 100 – 200 MeV/cm =

20 – 40 eV/(2 nm)

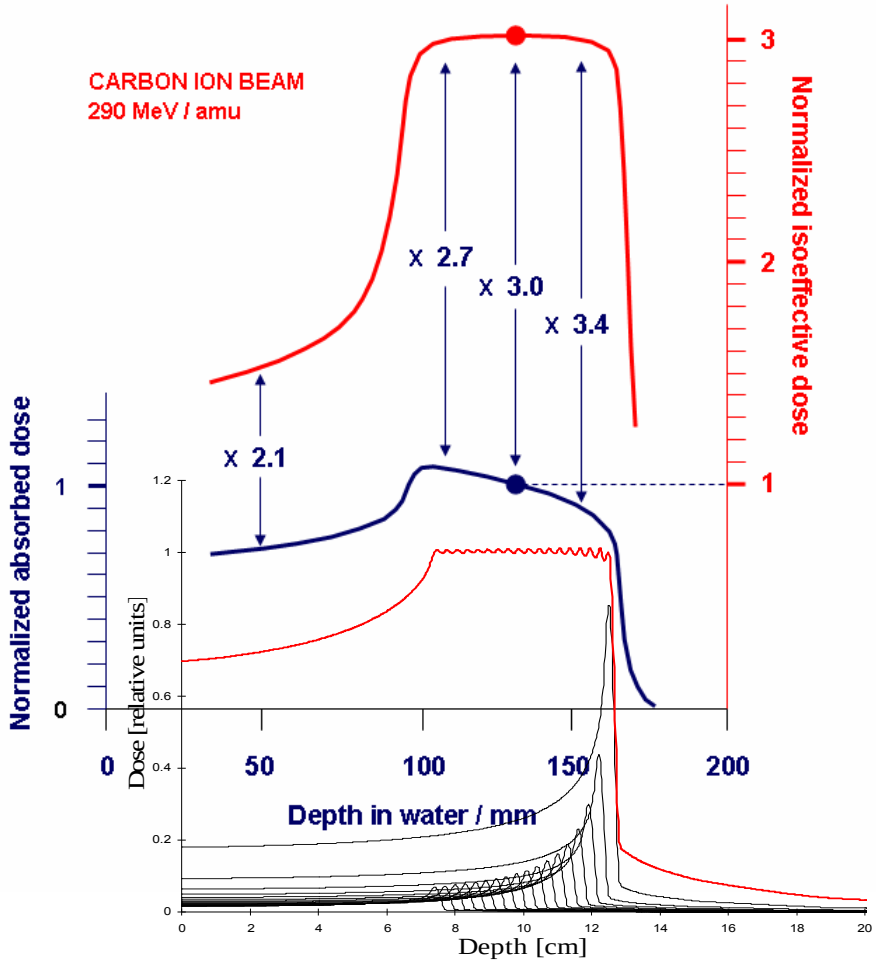
Carbon ions: high LET where needed



Physical and biological dose

Complicated treatment planning (even worse when beam delivery is taken into account)

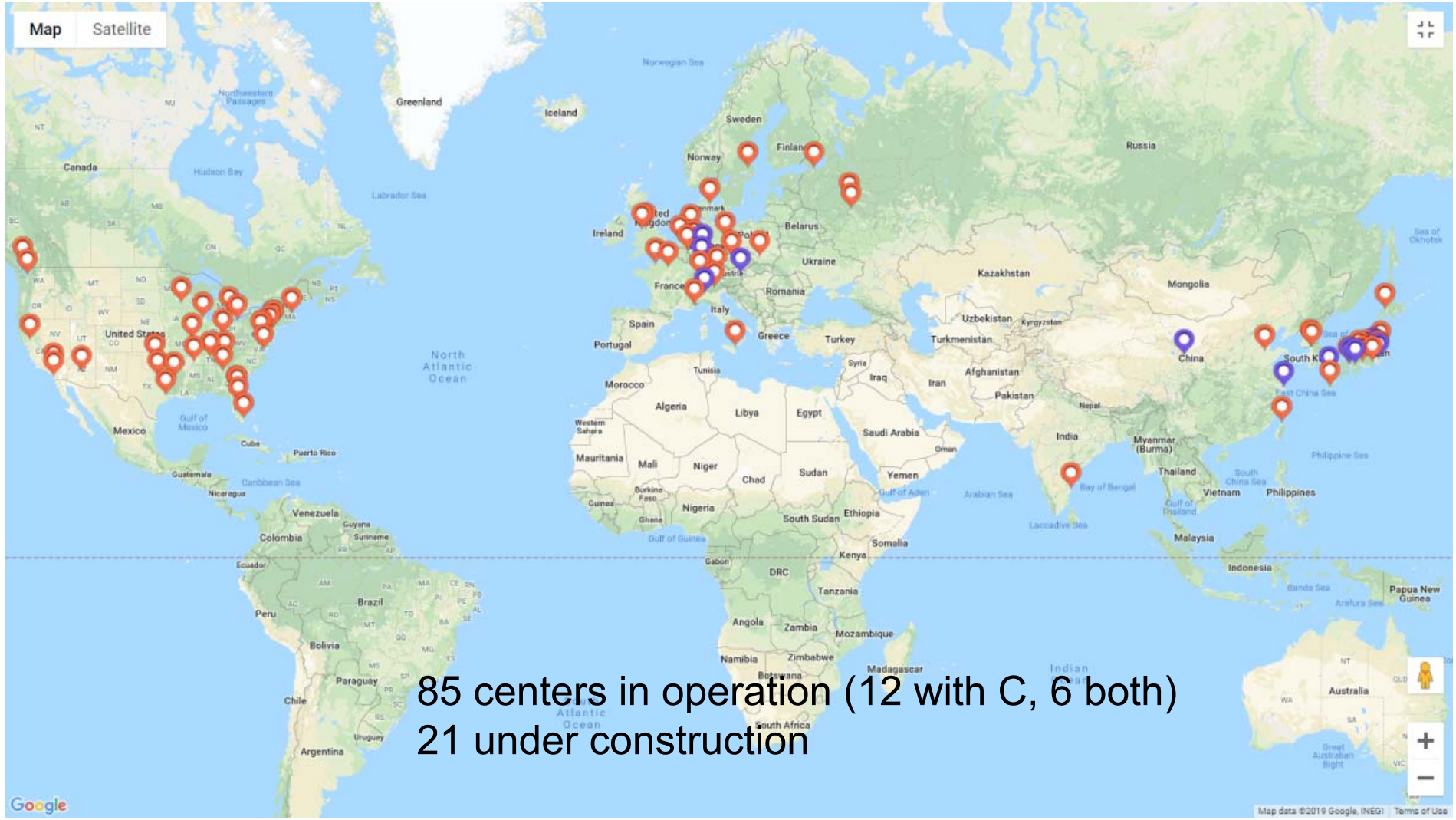
Different sharing of High and Low LET doses along the SOBP



RBE depends on many parameters

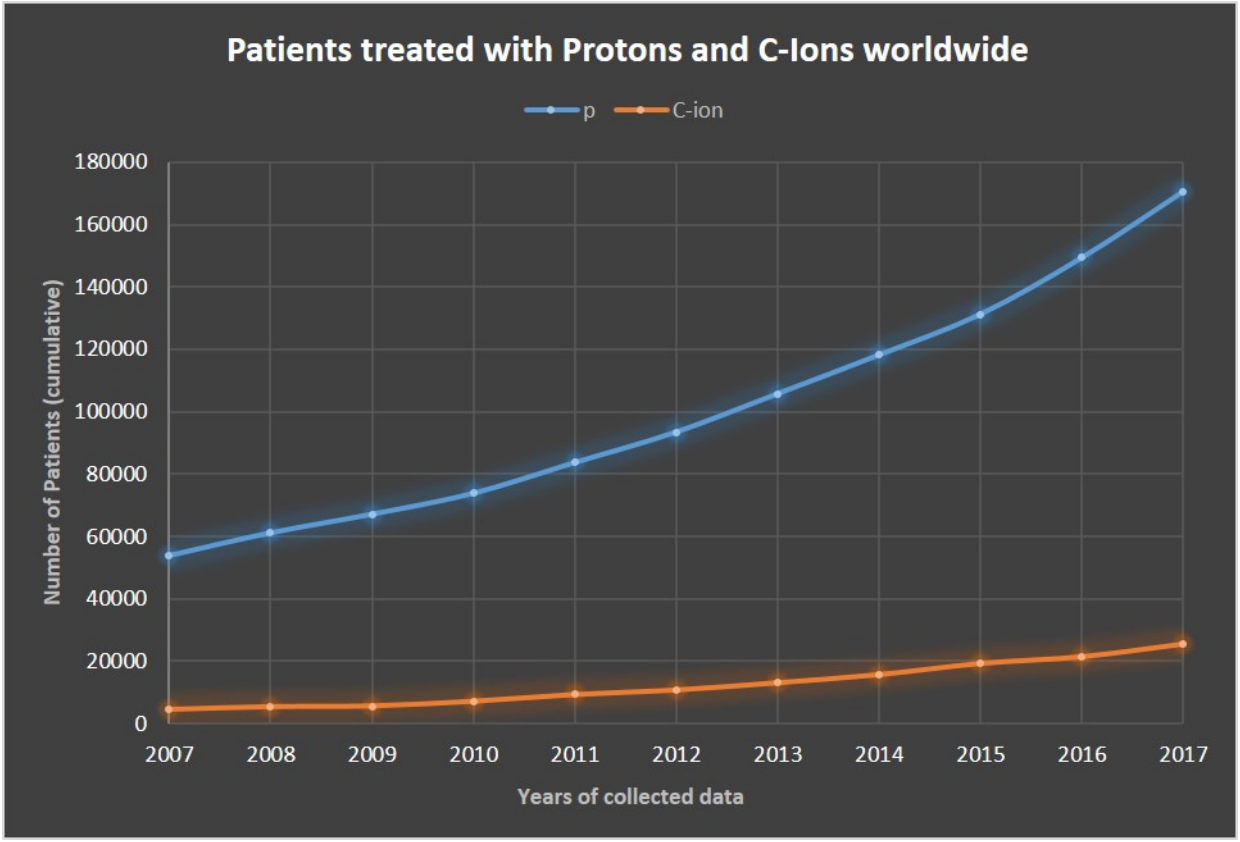
- Dose level
- Measured endpoint
- Particle charge and velocity
- Dose rate or fractionation
- Energy/LET of the particle
- Cell/tissue type
- Oxygen concentration
- Cell cycle phase
- **Etc…**

Hadrontherapy in the world



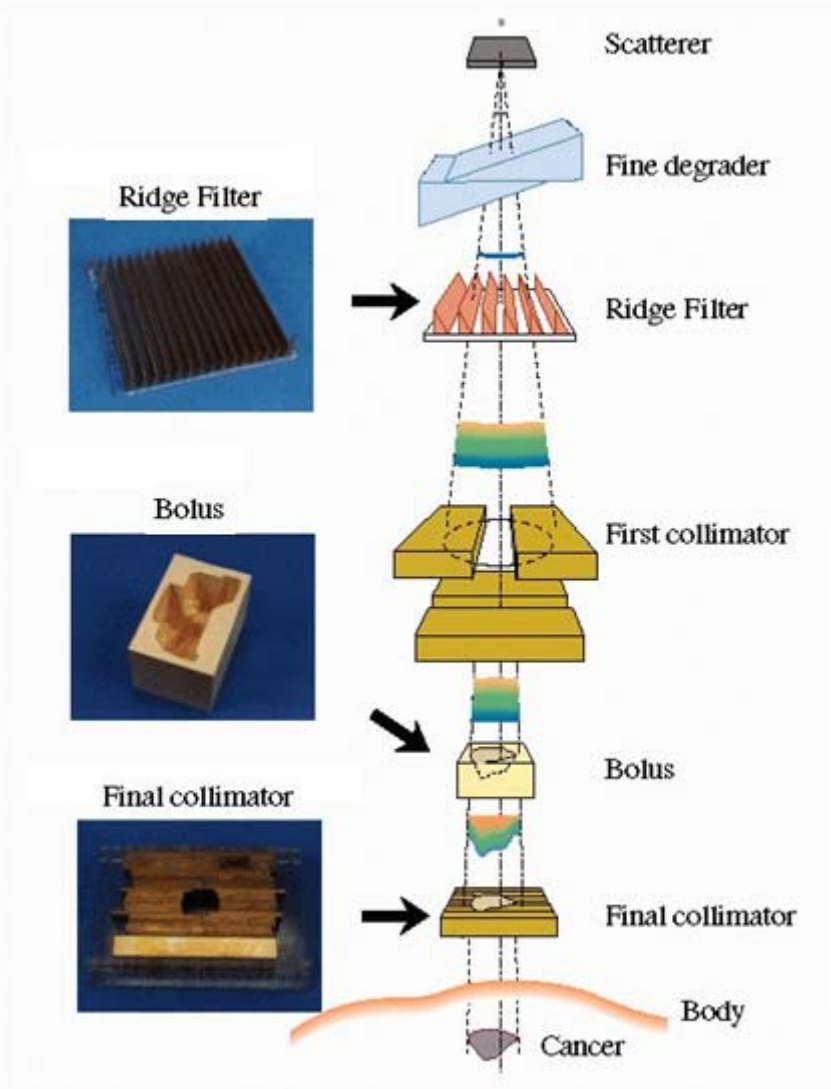
85 centers in operation (12 with C, 6 both)
21 under construction

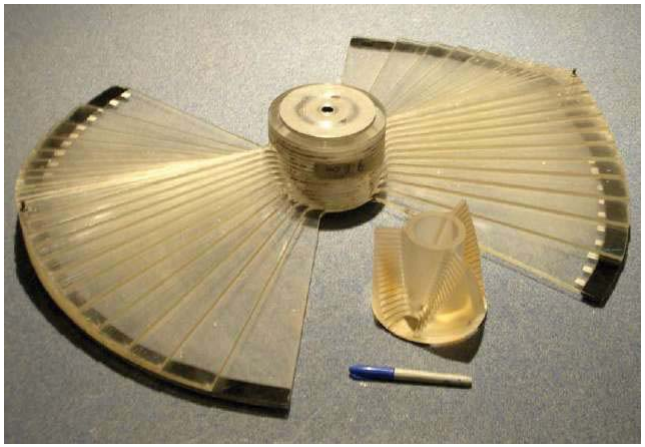
Patients treated (until 2017)

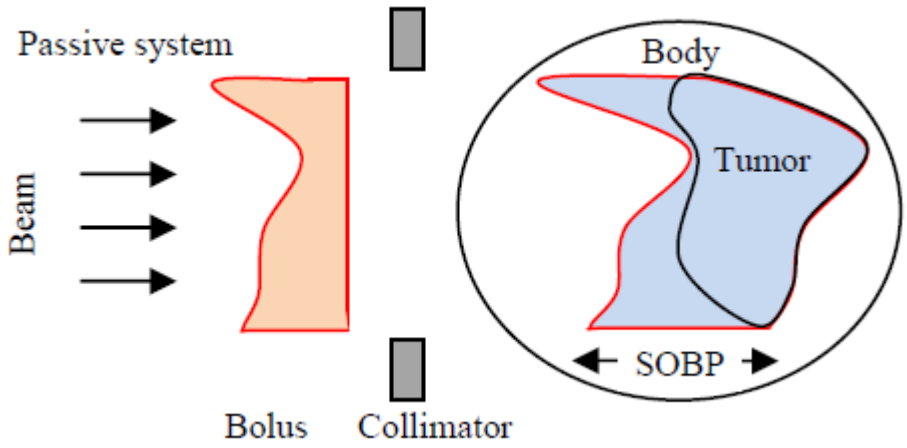


Beam delivery

Beam delivery: passive systems







Passive systems for Carbon

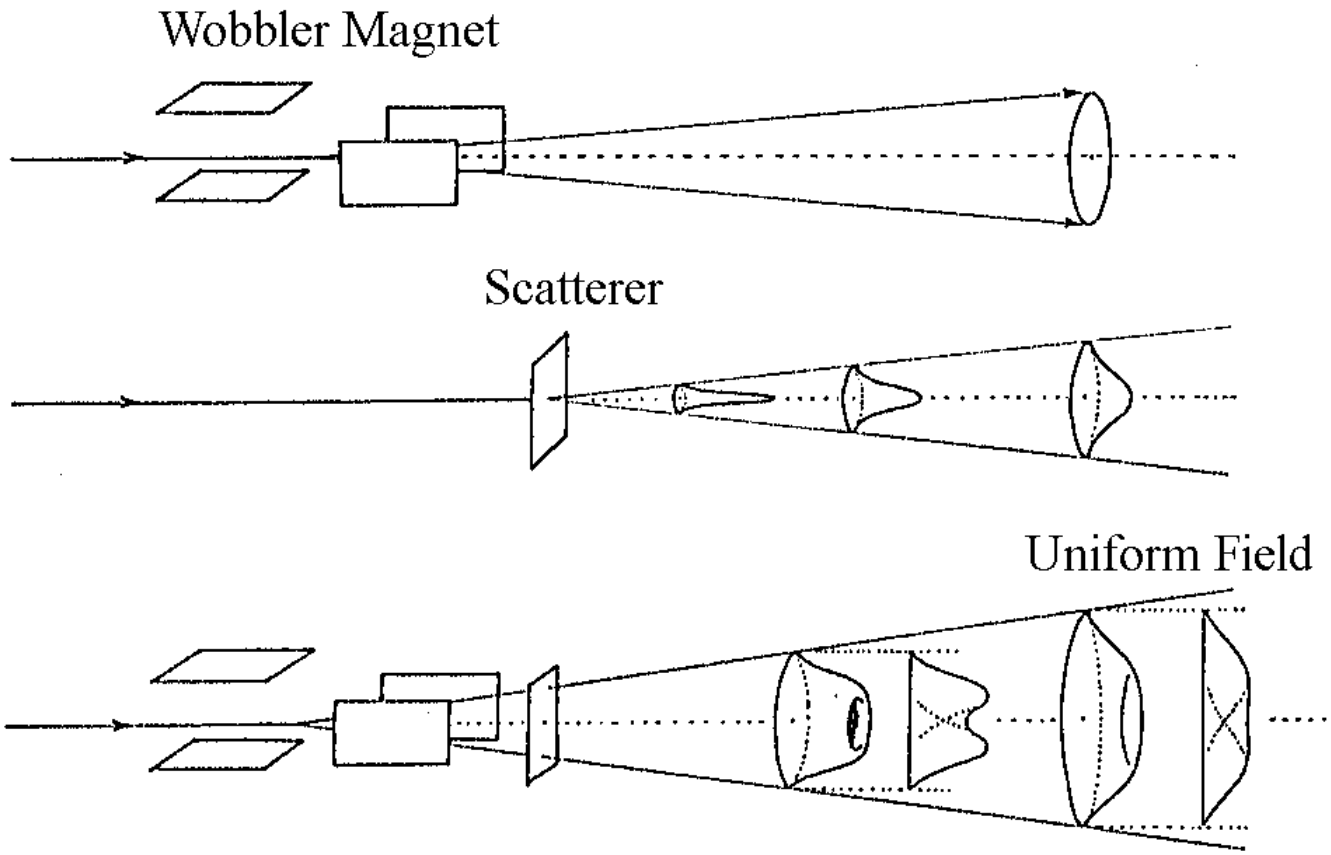
Completely passive system not advisable:

-Smaller scattering implies larger thicknesses and distances and thus larger energy loss and beam loss which implies larger energy and current from the accelerator

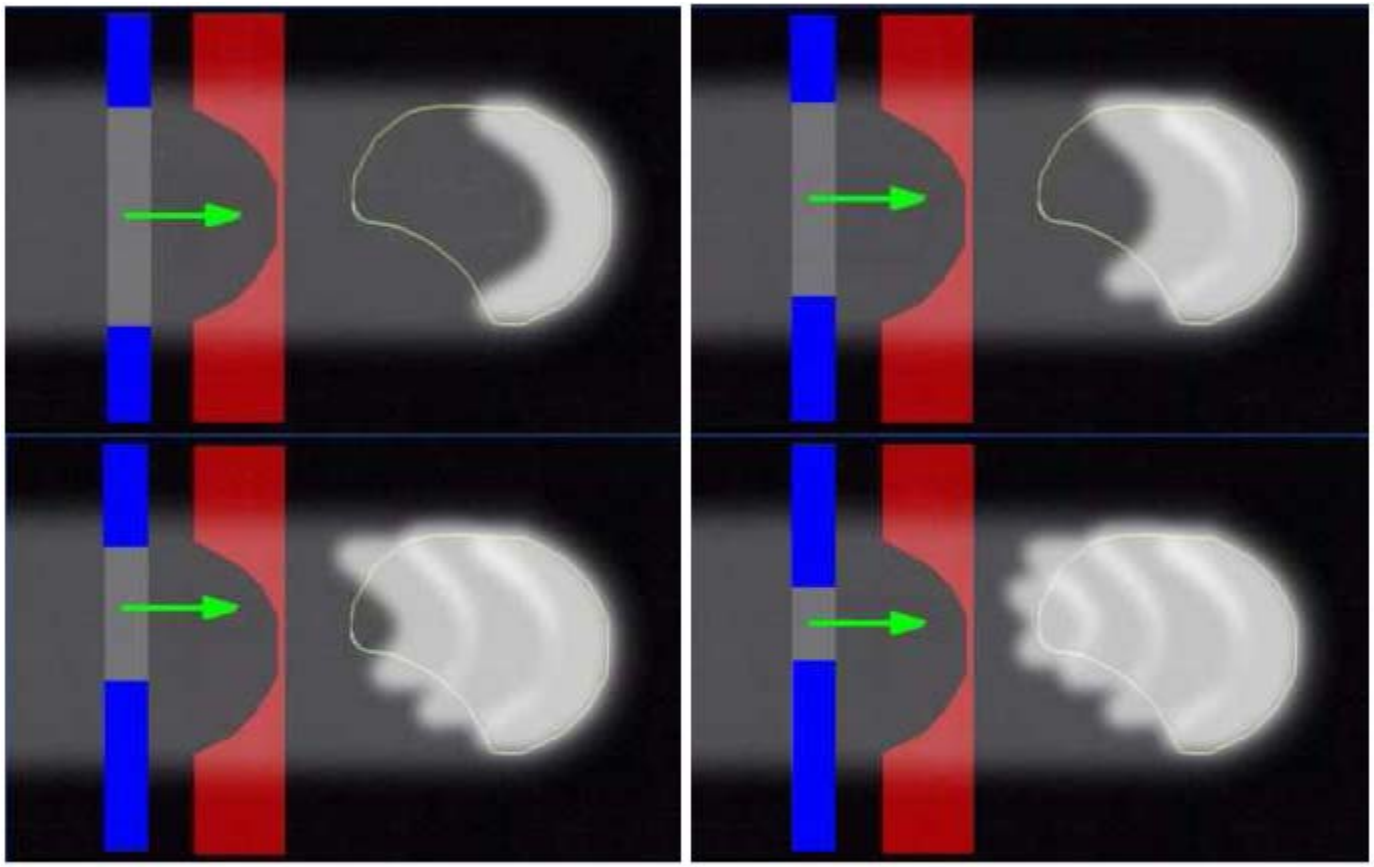
-Fragmentation of impinging ions causes a higher dose delivered after the tumor and larger production of neutrons.

-The amount of material in the beam line is considerable, leading to an increase in nuclear fragments produced by nuclear interactions with the material of the beam modifiers. These nuclear fragments have lower energies and lead to a higher LET and thus an increased biological effective dose of the beam already in the entrance region.

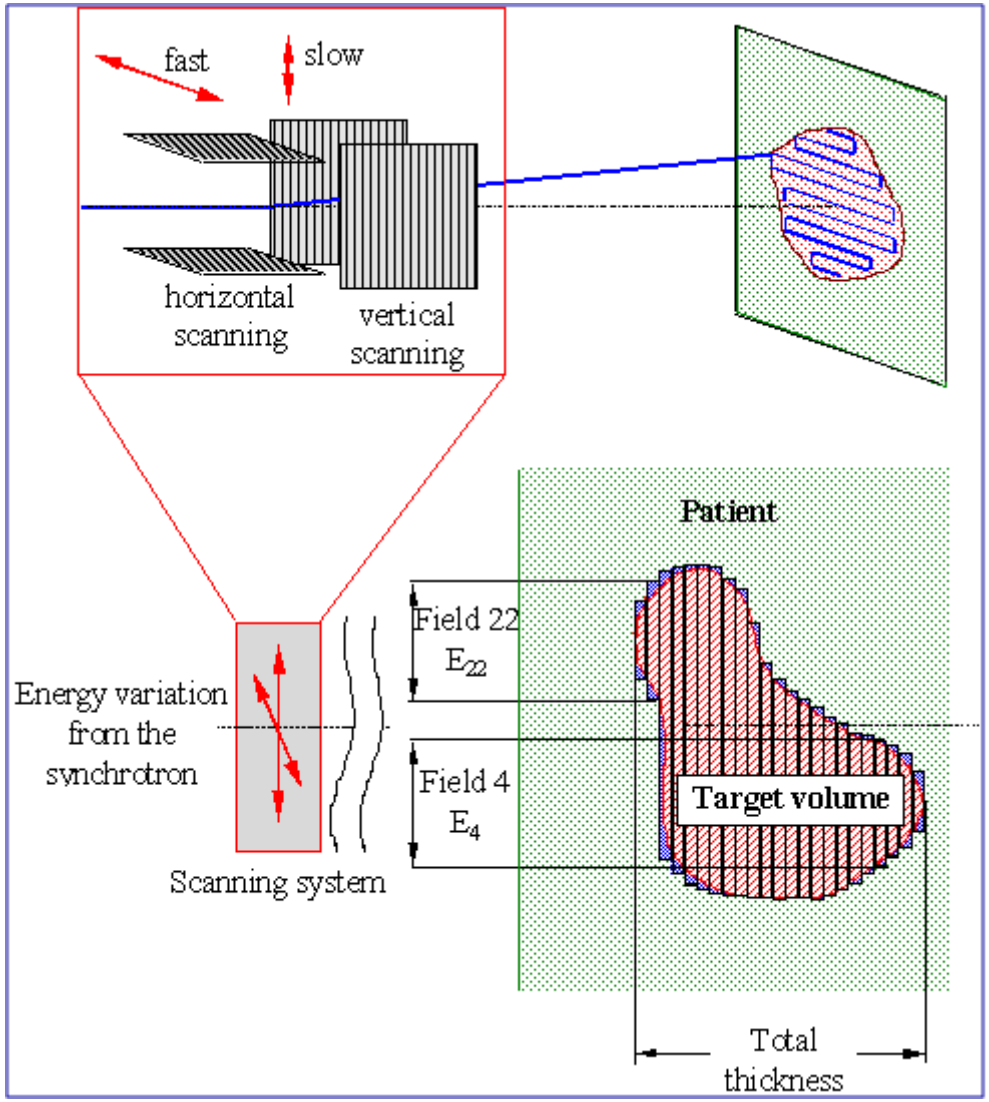
Wobbling



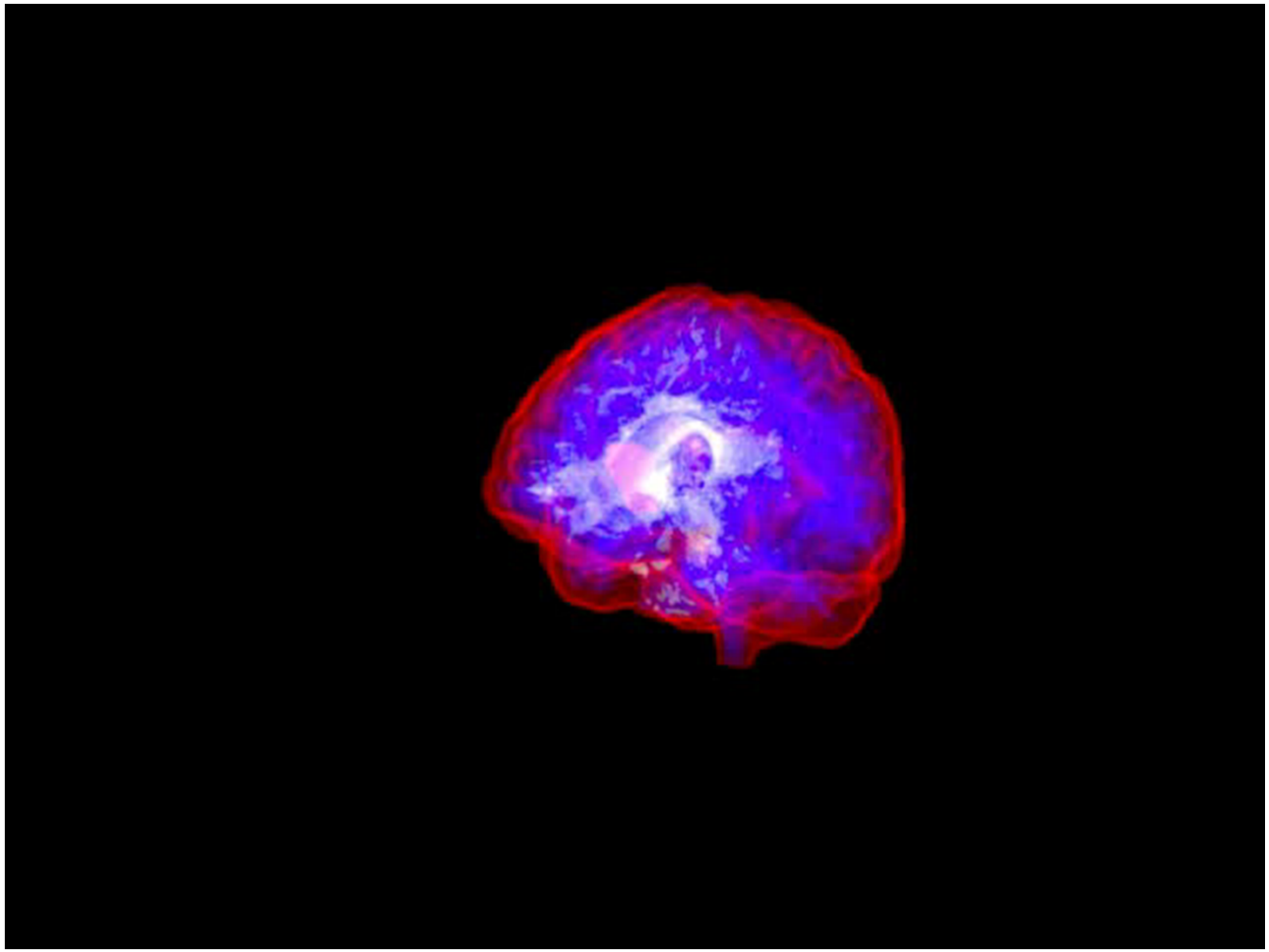
Layer stacking



Active systems

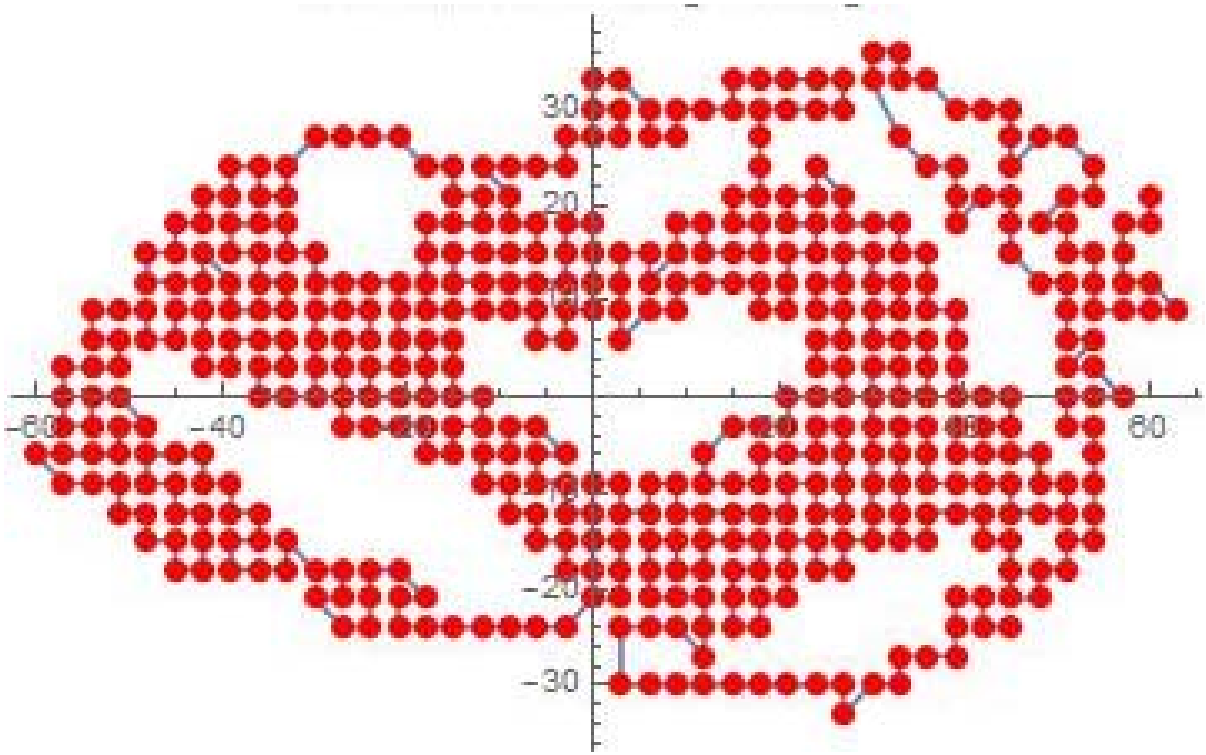


Scanning Beam

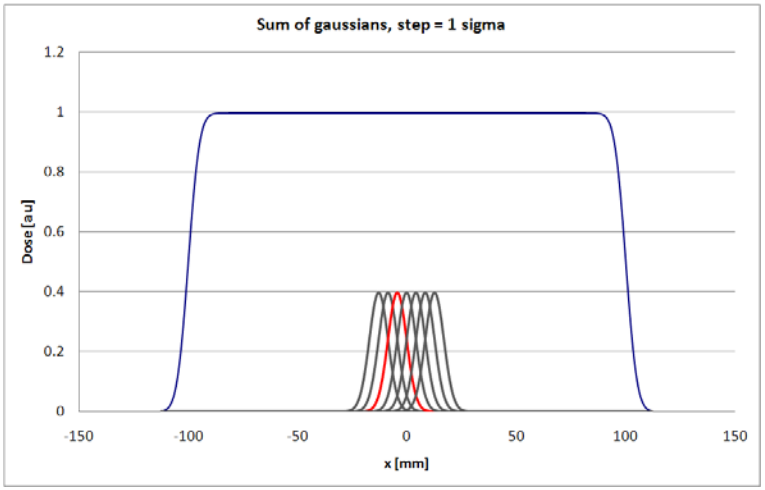


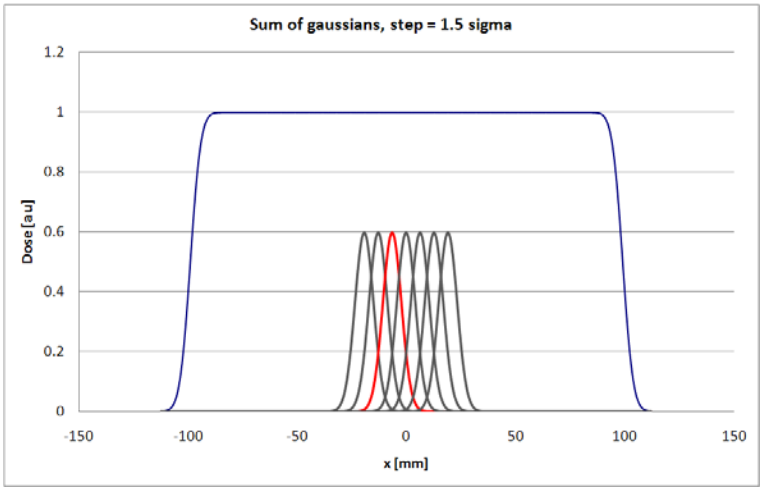
(Courtesy of A. Attili)

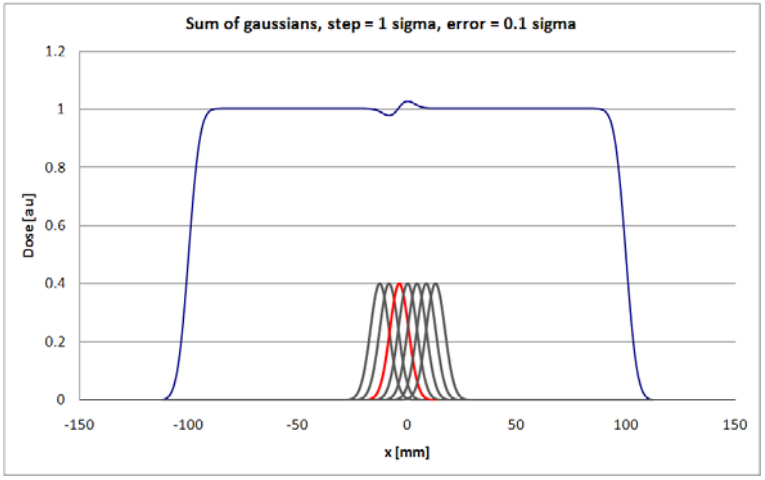
Slices can have complex shapes

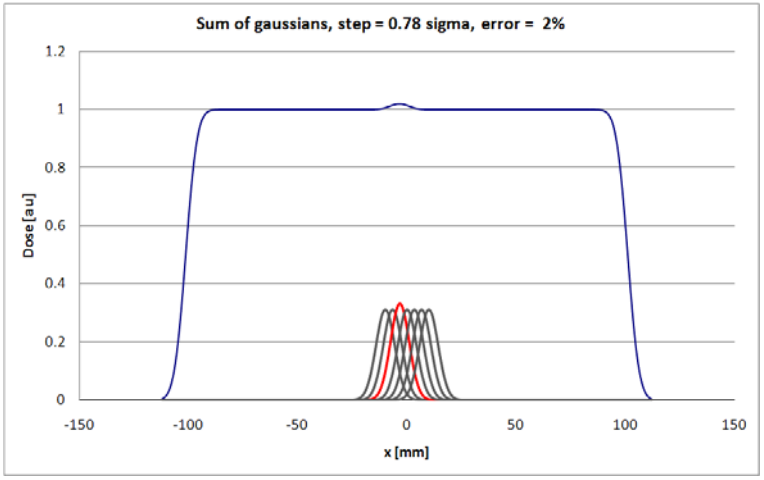


Beam position precision

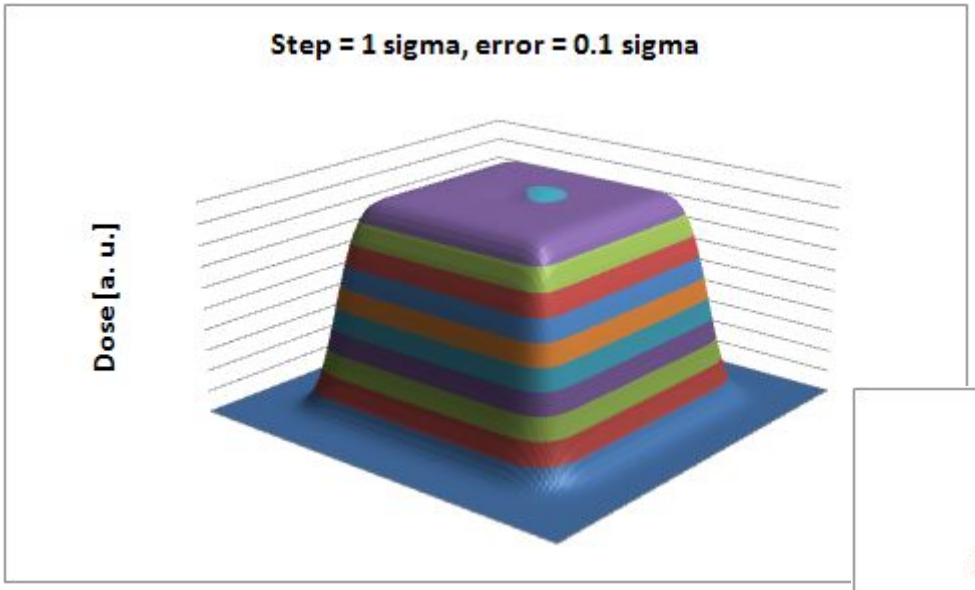


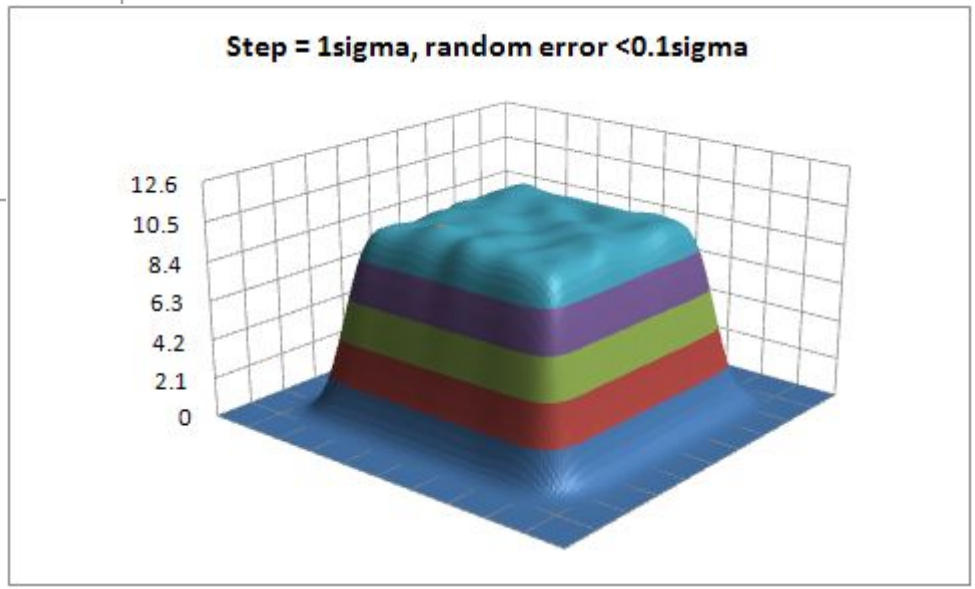






2D

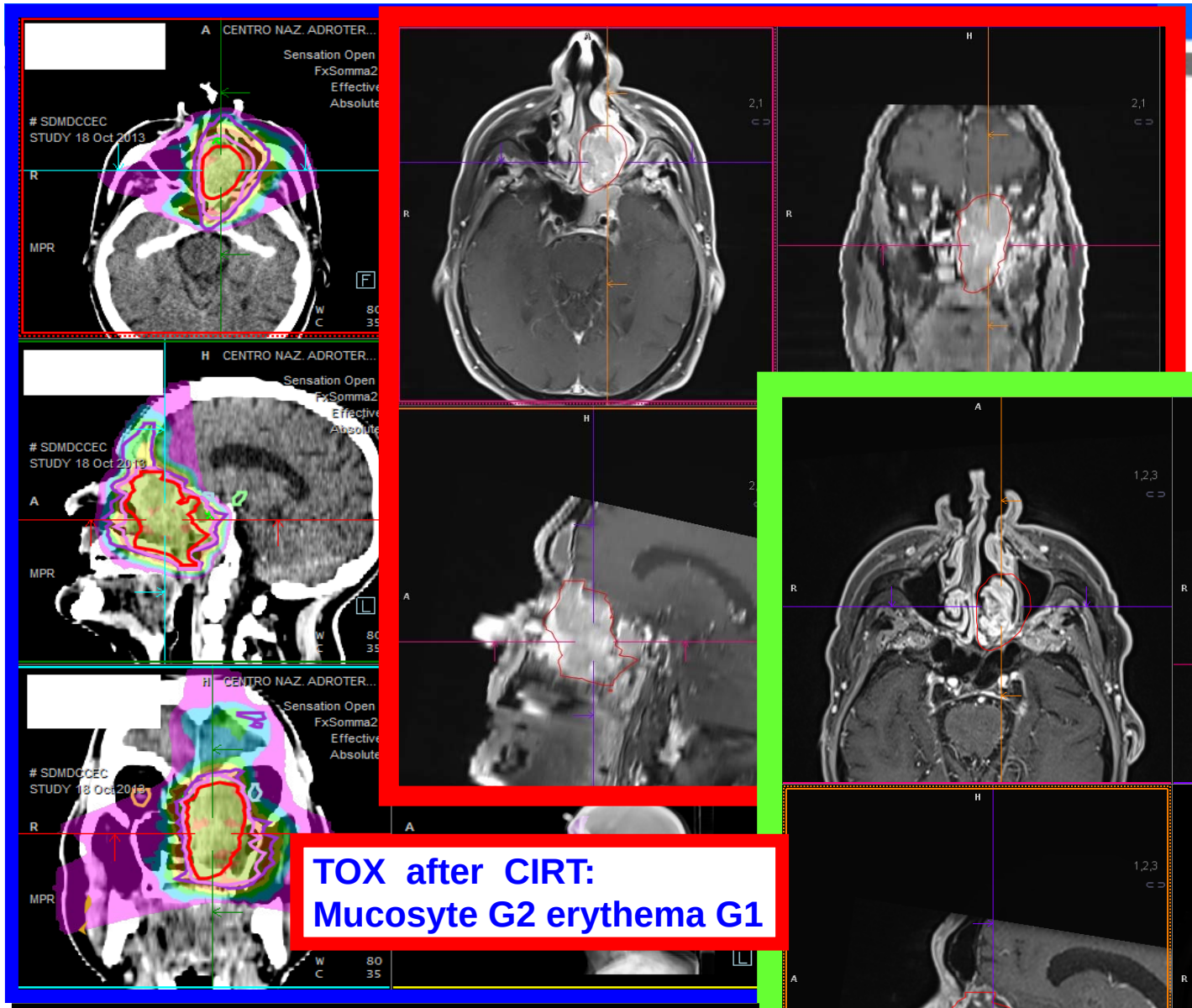




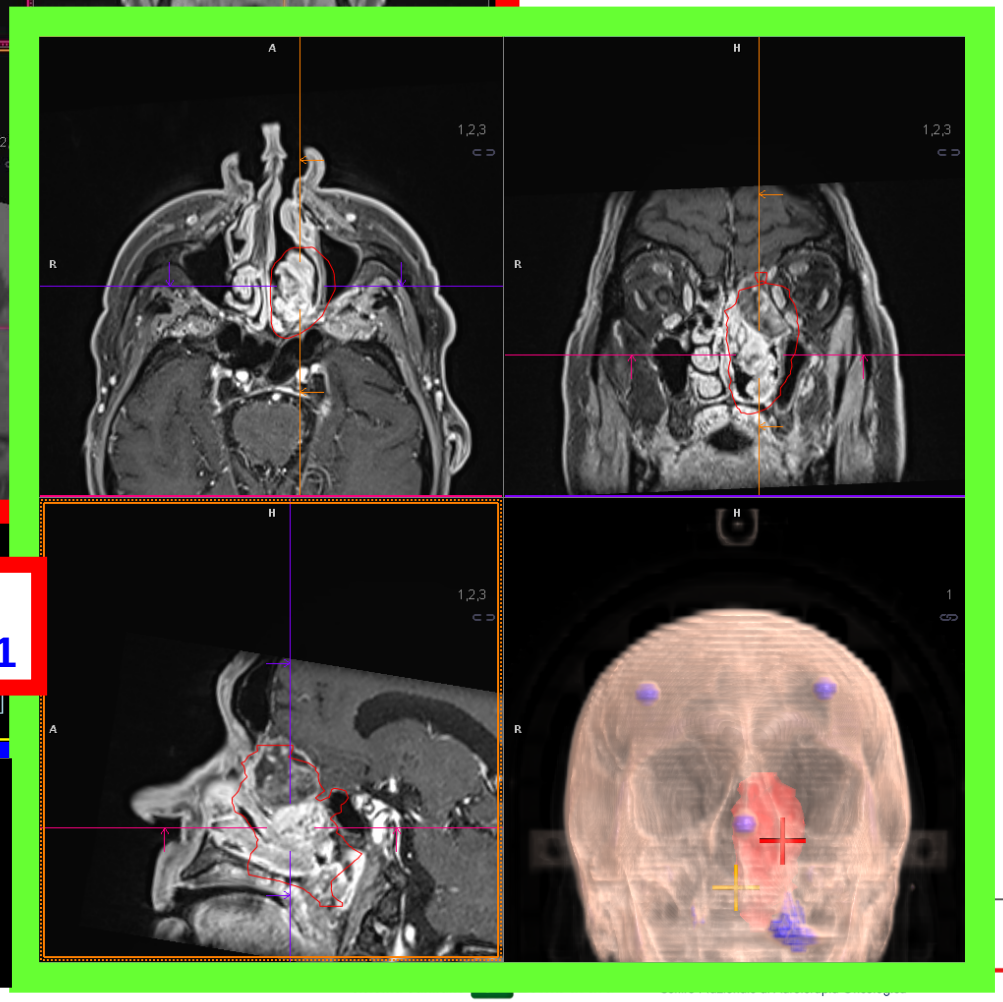
Local control is not the only aspect to consider

Mucosal Melanoma treatment by Carbon vs Surgery

Warning Heavy Pictures



3 months
Partial responce



TOX after CIRT:
Mucosyte G2 erythema G1

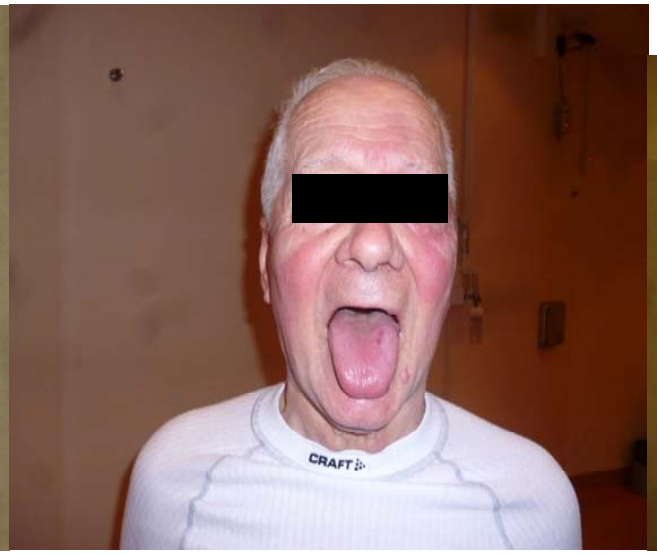
83 year old patient
Mucosal Melanoma
Unfit for surgery

During CIRT

At the end of CIRT

Mucosyte G2

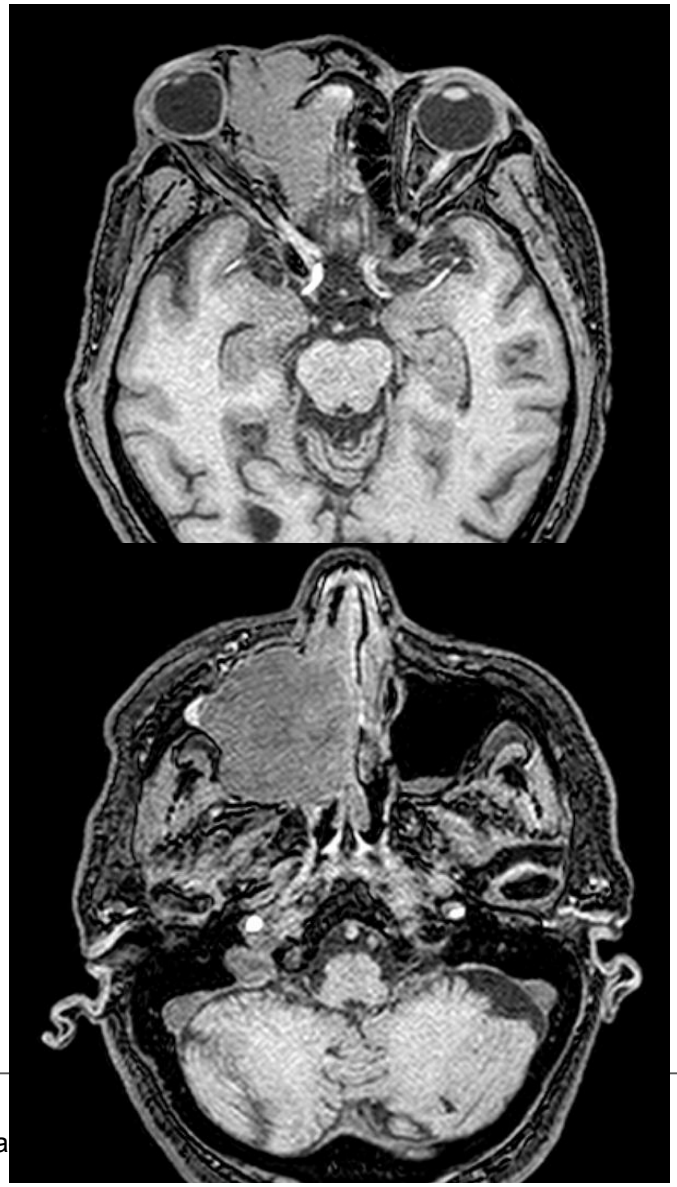
Erythema G1



Fup 12 months

- WARNING a bit impressive pictures

60 year old male with Mucosal Melanoma
preop RNM after surgery



Particle accelerators

Accelerators

Not necessarily a good name… for an electron:

	T [MeV]			
	1	10	100	1000
β	0.941	0.999	1.000	1.000
γ	3.0	20.6	196.7	1957.9

Ginzton, Hansen and Kennedy* suggested,
"Ponderator" o
"Mass Agrandiser",
But it did not become fashionable and we are left with
'Accelerator'.

*** Rev. Sci. Instr., Vol.19, No.2, Feb. 1948.**

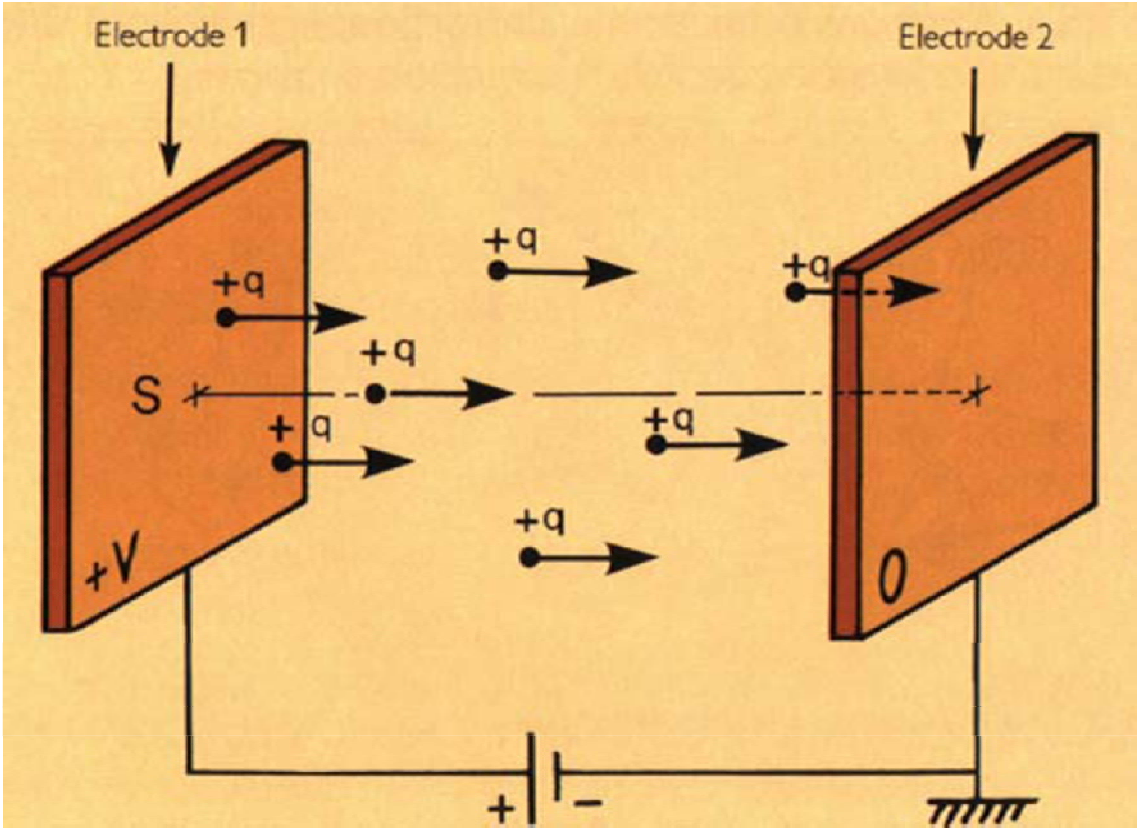
Electrostatic accelerators

Energy gained

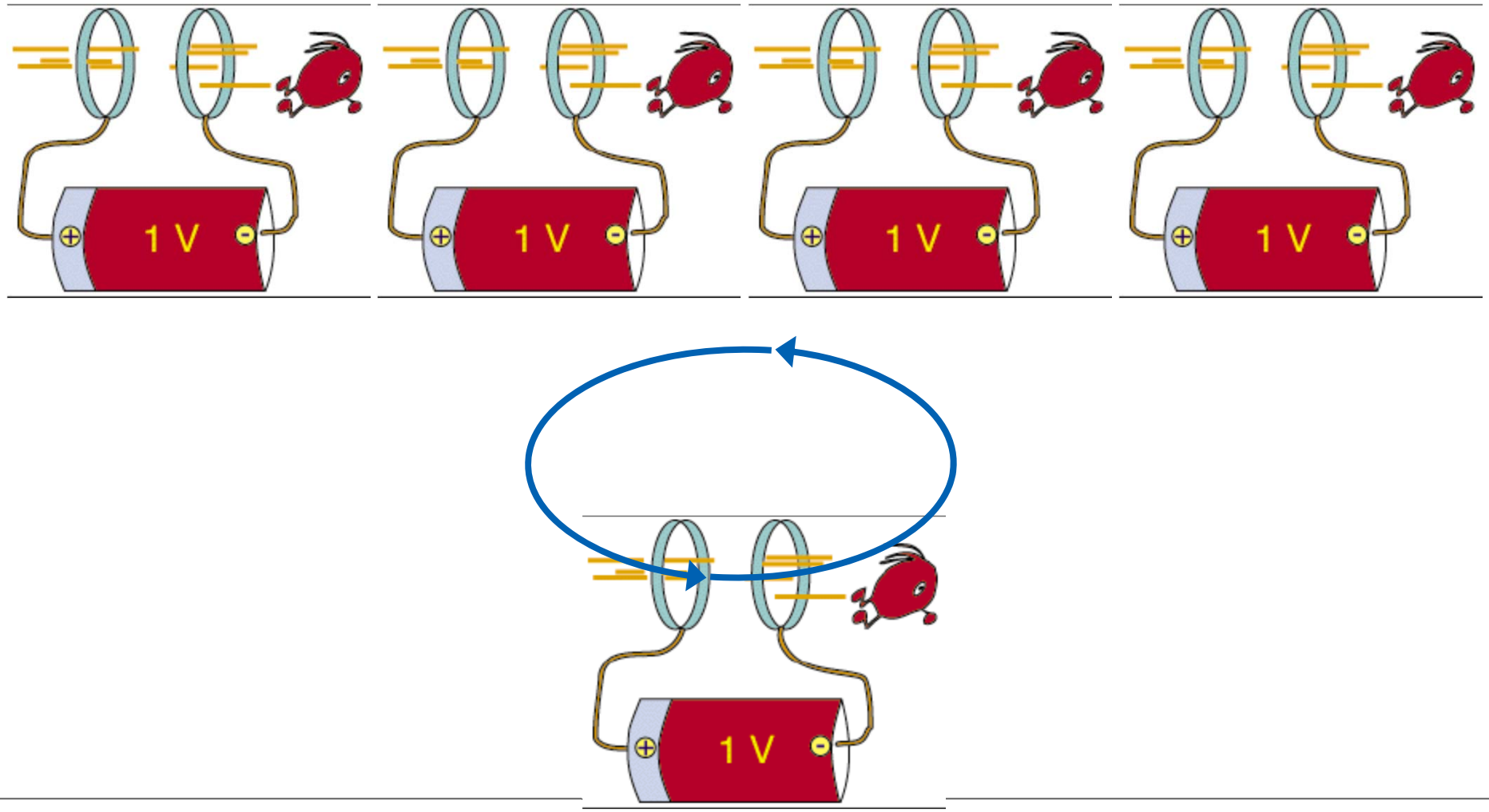
$K = q\,V$

Measured in

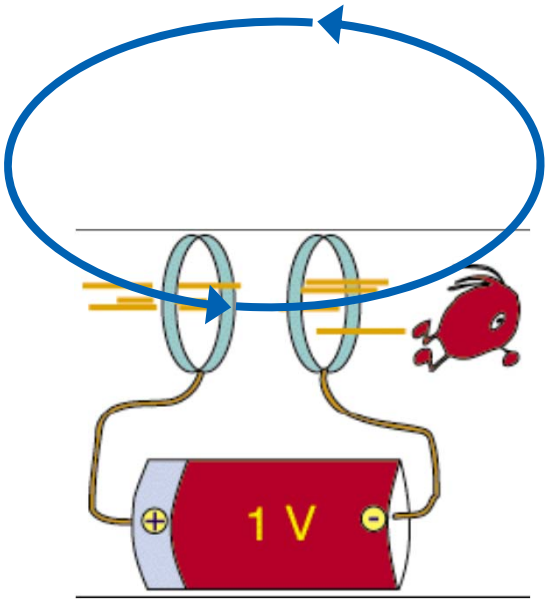
eV

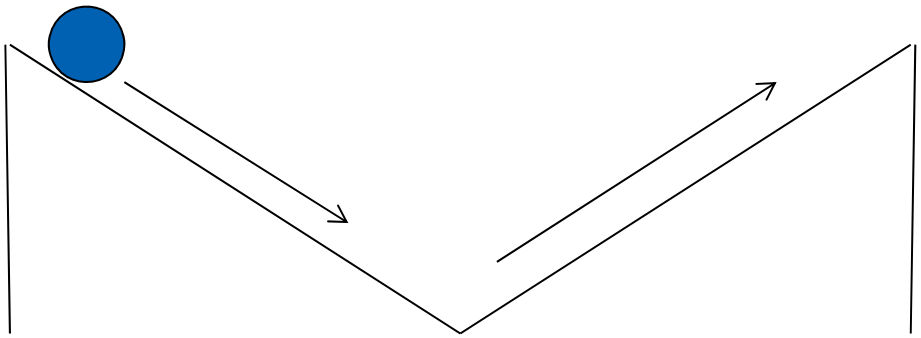


LINACs vs Circular machines



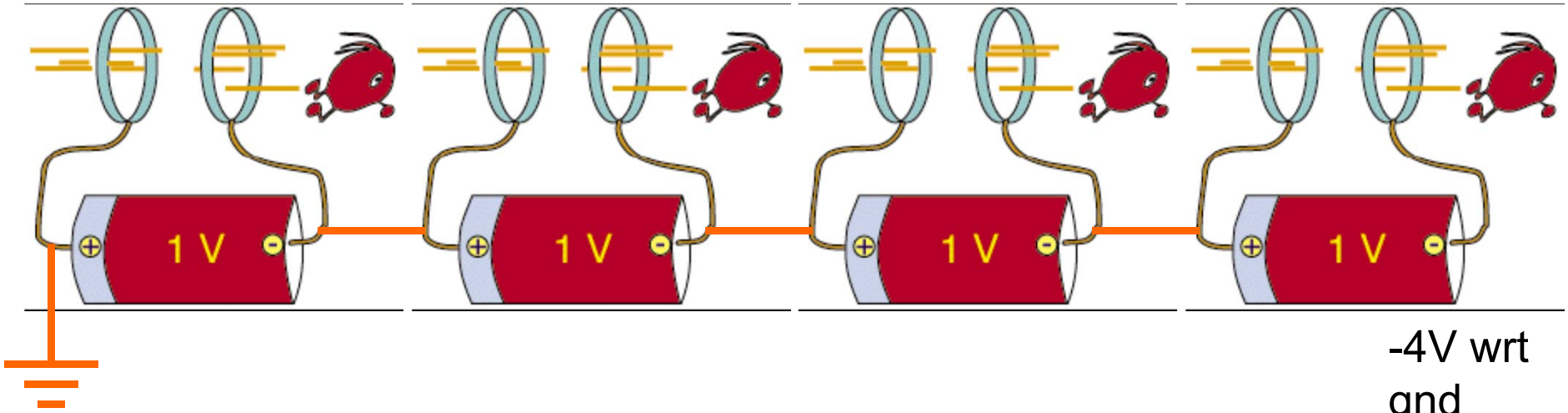
Circular accelerators





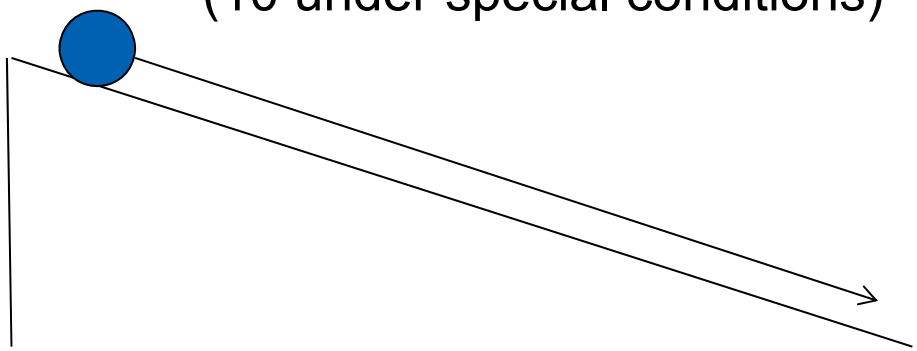
The electrostatic field is conservative, thus a circular electrostatic accelerator DOES NOT WORK

Electrostatic accelerators

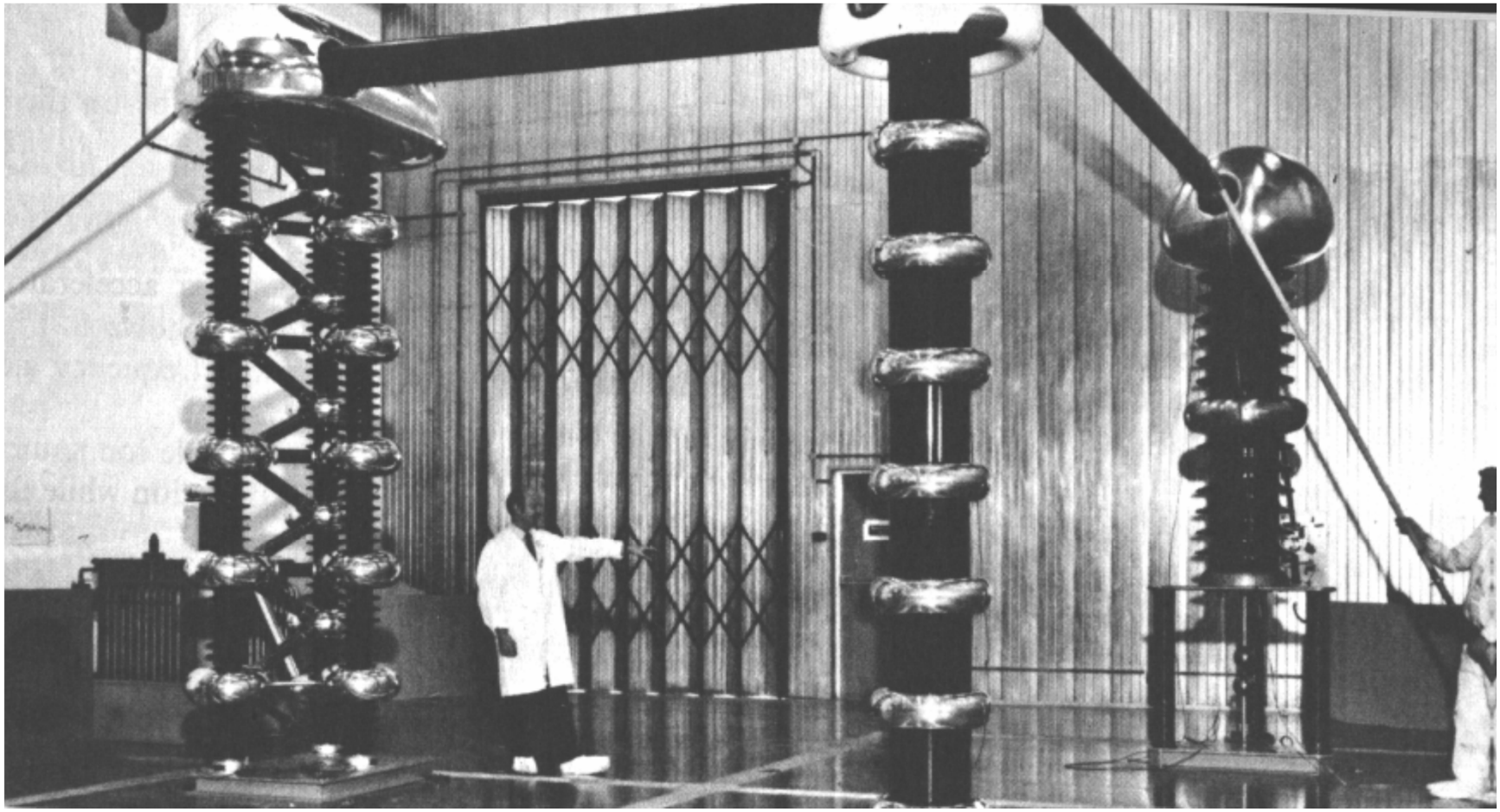


Maximum electrostatic field ~ 3 MV/m

(10 under special conditions)

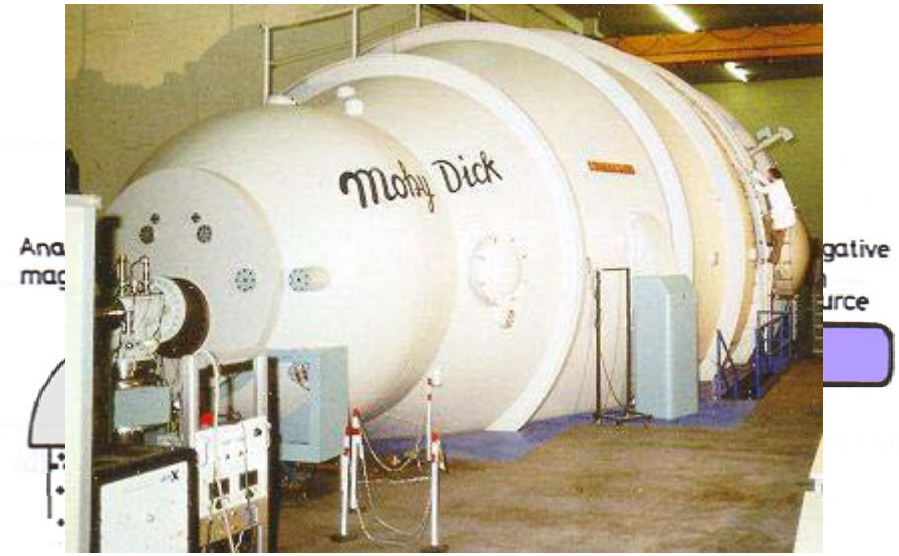


Electrostatic accelerators



70 MeV Cockcroft-Walton generator supplying the ion source which injected protons into NIMROD, the 7 GeV synchrotron at Rutherford laboratory.

The Tandem



INFN-LNL

Use the accelerating voltage twice.

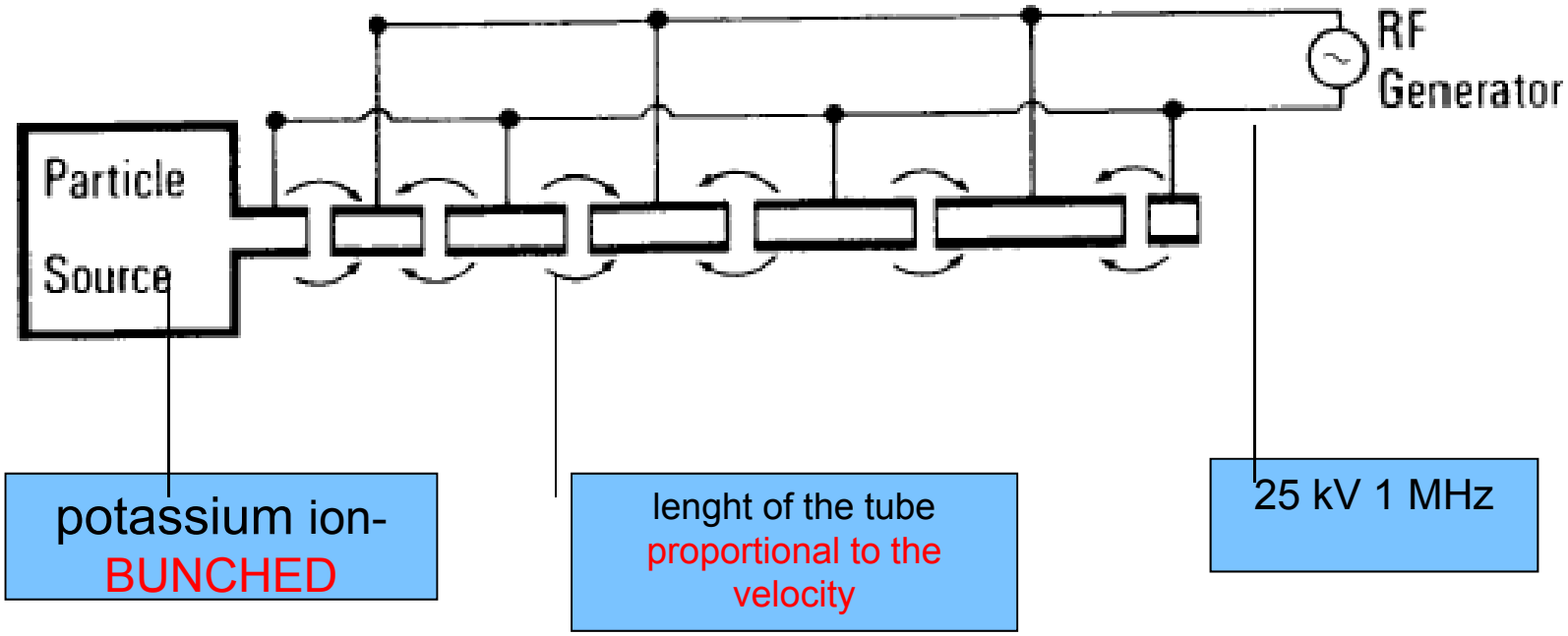
First an extra electron is attached to the neutral atoms to create negative ions.
The negative ion beam is injected at ground potential into the Tandem and accelerated up to the high-voltage terminal where it passes through a thin foil which strips at least two electrons from each negative ion converting them to positive ions. They are then accelerated a second time back to earth potential.

The right idea

- **1924 Ising proposes time-varying fields across drift tubes. This is a 'true' accelerator that can achieve energies above that given by the highest voltage in the system.**

- **1928 Wideröe demonstrates Ising's principle with a 1 MHz, 25 kV oscillator to make 50 keV potassium ions; the first linac.**

Wideroe linac



- **the energy gained by the beam (50 keV) is twice the applied voltage (25 keV at 1 MHz)**

(courtesy of A Lombardi)

from Wideroe to Alvarez linac

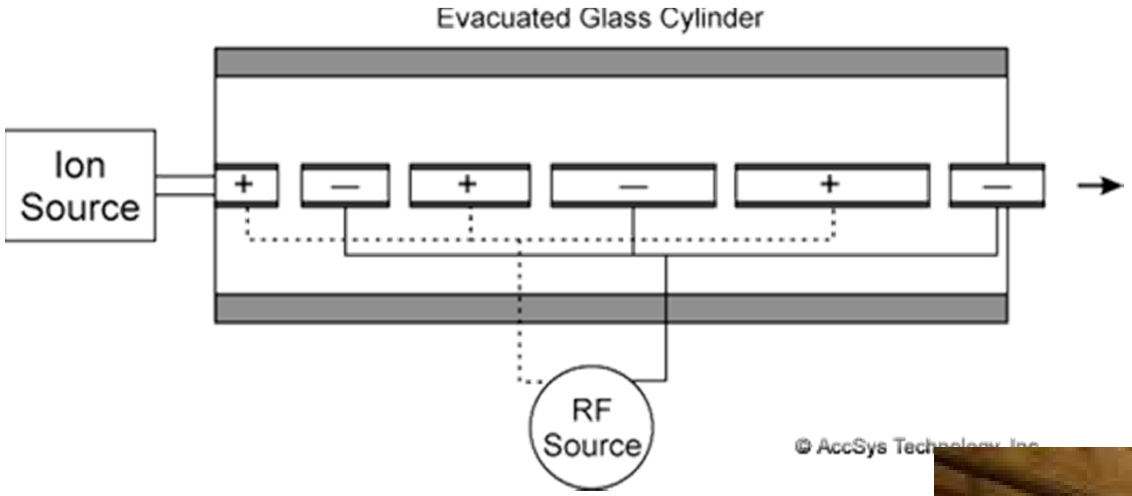
- **to proceed to higher energies it was necessary to increase by order of magnitude the frequency and to enclose the drift tubes in a cavity (resonator)**

- **this concept was proposed and realized by Luis Alvarez at University of California in 1955 : A 200 MHz 12 m long Drift Tube Linac accelerated protons from 4 to 32 MeV.**

- **the realization of the first linac was made possible by the availability of high-frequency power generators developed for radar application during World War II**

(courtesy of A Lombardi)

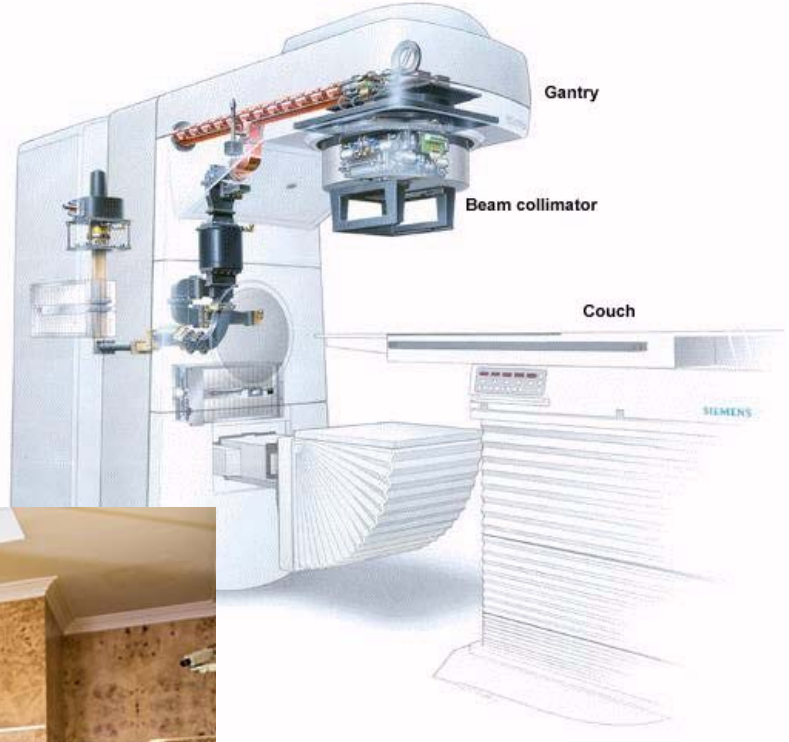
From Wideroe to Alvarez



(courtesy of A Lombardi)

Radiotherapy linac

3 GHz RF frequency



collimator

Thank you for your attention

“Physics is like sex: sure, it may give some practical results, but that's not why we do it. ”

R. Feynmann

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica