Treating Tumours with particle beams: status and perspectives

Outline

- **Cancer: the problem!**
- **Different ways to face it**
  - Radiotherapy
  - Hadrontherapy
  - Boron Neutron Capture Therapy
- **New development**
  - Teragnostic
  - Flash therapy

books:

- AA.VV. **"Proton Therapy Physics",** edited by Herald Paganetti
- AA.VV. ***"Radiation Oncology Physics"***, Edited by E.B. Podgorsak
- AA.VV "***Ion Beam Therapy***", edited by Ute Linz, Springer

Bologna, July, 10, 2024 *spighi@bo.infn.it*

Tumor in the world

Cancer definition: cellular mutation that indefinitely proliferates

In 2008 in the world were registered **14.1 millions** of tumors and **8.2 led to the patient's death**

~2‰ of the world population
each year get cancer

L.A. Torre, R.L. Siegel, E.M. Ward, and A.Jemal,
Global Cancer Incidence and Mortality Rates and Trends|An Update,
Cancer Epidemiol Biomarkers Prev; 25 (2016),
16 DOI: 10.1158/1055-9965.EPI-15-0578 Published January 2016

2018: **18.1 millions** of tumors and **9.6 led to the patient's death**

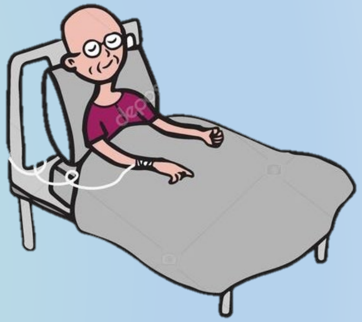
F. Bray, J. Ferlay,I. Soerjomataram, L. Siegel, L.A. Torre, A. Jemal,
"*Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries*"
CA CANCER J CLIN 2018;68:394–424 A Cancer Journal for Clinicians

Involved persons:

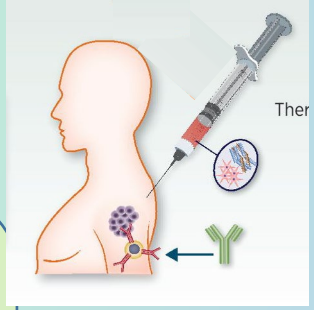
- Population increase:
  - 2020: 8 billions in the world
  - 16 millions cancers per year (2‰), one out of two needs RXT
    - **8 millions RXT**
- Population aging 2010-2030
  - People over 65 years x 2
  - People over 80 years x 3 (surgery ↘)

Cancer therapies:

- **Surgery**: removal part of the body containing the diseased cells



- **Chemotherapy**: non localized or localized somministration of medication to destroy or to prevent the cell reproduction

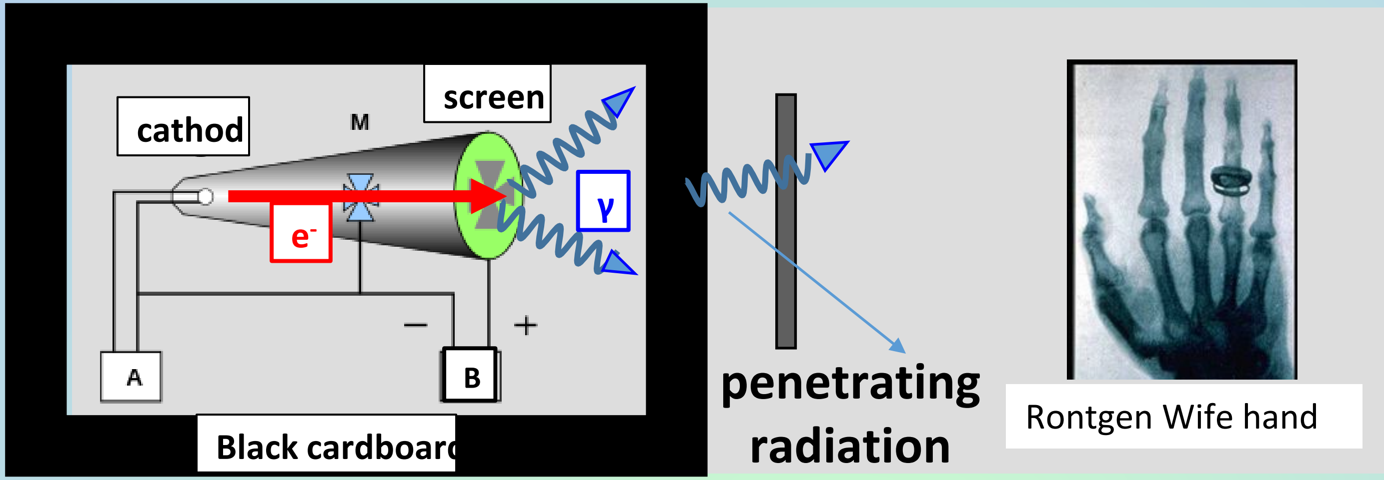


- **Immunotherapy**: instructs the immune system to recognize and eliminate diseased cells

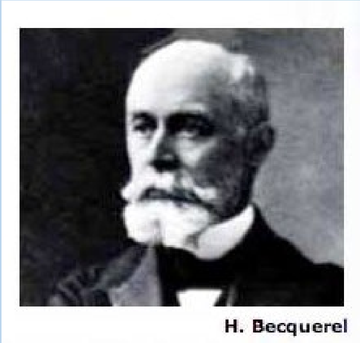
- **Radiotherapy**: e.m. irradiation (gammas and electrons) of cancer region to destroy or to prevent the cell reproduction

- **Hadrotherapy**: hadron (protons, neutrons an ions) irradiation of cancer region to destroy or to prevent the cell reproduction

RXT: a brief history,1



11/1895 RX discovery by Wilhelm Conrad von Röntgen, Nobel Prize in 1901



3/1896 Bequerel discovers the natural radioactivity of Uranium


Marya and Pierre Curie

1898 Marya Sklodowska discovered the Radium → α and γ emitter (she did not know !!)

$$^{226}_{88}Ra \xrightarrow{94\%} {}^{222}_{86}Rn \text{ (ground state)} + \alpha \text{ (4.7843 MeV)}$$ **α decay**

$$\xrightarrow{6\%} {}^{222}_{86}Rn \text{ (excited)} + \alpha \text{ (4.601 MeV)} \rightarrow {}^{222}_{86}Rn \text{ (ground state)} + \gamma \text{ (0.18 MeV)}$$

α decay and γ decay (Energy ~ MeV)

RXT: a brief history, 2

Use of radium for cosmetics and skin treatments

1904 Marya and Pierre Curie use radium-226 for cancer treatment

Satisfactory results on the “lupus eritematoso” (skin infection)

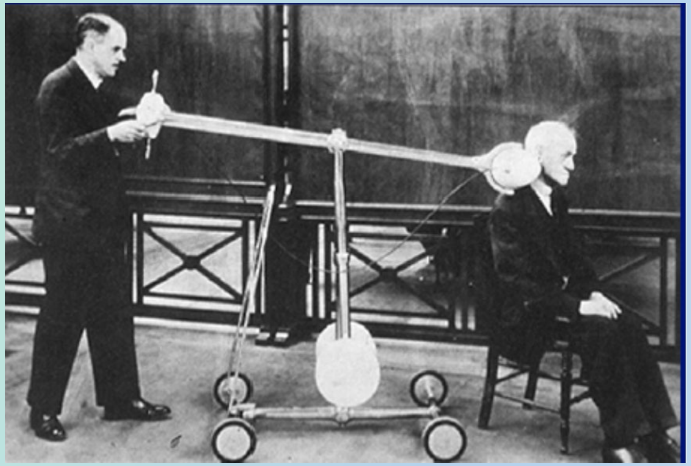
Begin 1900 phototherapy:Finsen (Nobel) healed 50% of skin infection

~ 1930 Brachytherapy (inside body) starting with ^{226}Ra (Z=88) needles and tubes

1934 Coutard: dose splitting (basis of current Radiotherapy): healed 23% of neck cancer

1936 Paterson publishes results on the treatment of cancer with X-rays


Finsen (Nobel Prize) Lamp



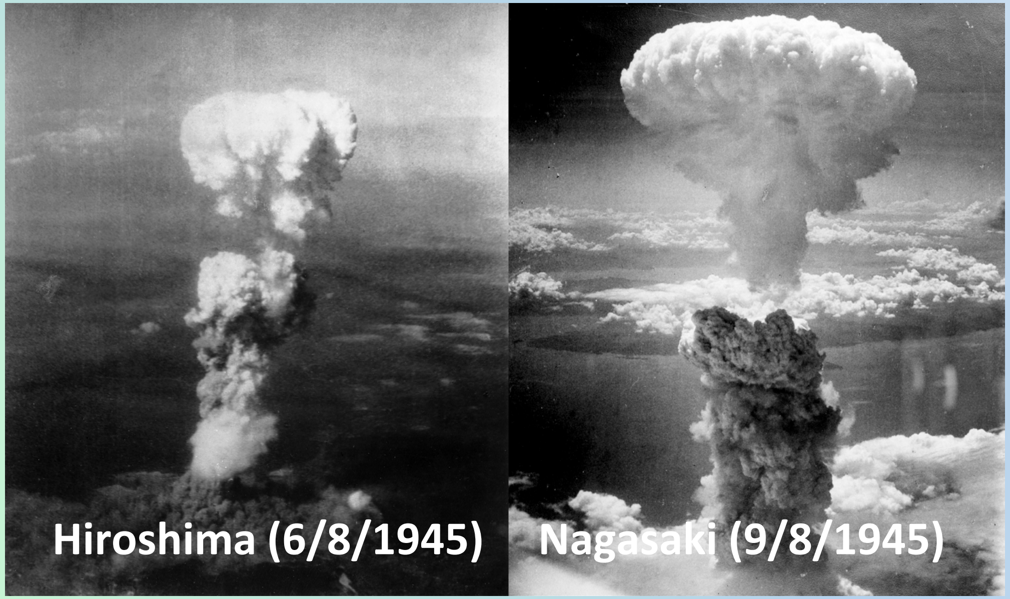
The second world war

1935 – 1945 war period → discovery of nuclear fission

Nuclear reactors

Atomic bomb

Energy production , medicine, …



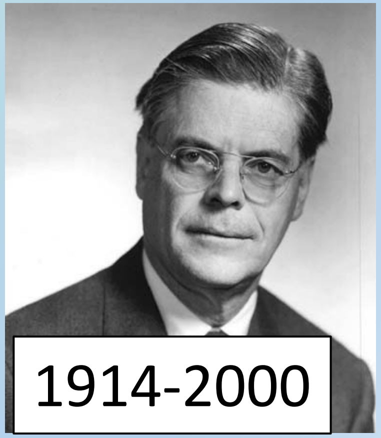
If you split the atomic nucleus, you can releas a lot of energy

Can kill people

Can save people

1945 Robert Wilson (one founder of Fermilab) proposed to use hadrons for radiotherapy

Proton, neutron, pions against human body



Hadrontherapy development

1954 Berkeley treats the first patient

1957 first patient treated with p in Europe (Uppsala -Sweden)

1975 Harvard pioneers the first eye treatment with protons

1976 Fermilab begin neutron therapy

1977 Chiba (Japan) opens with proton therapy

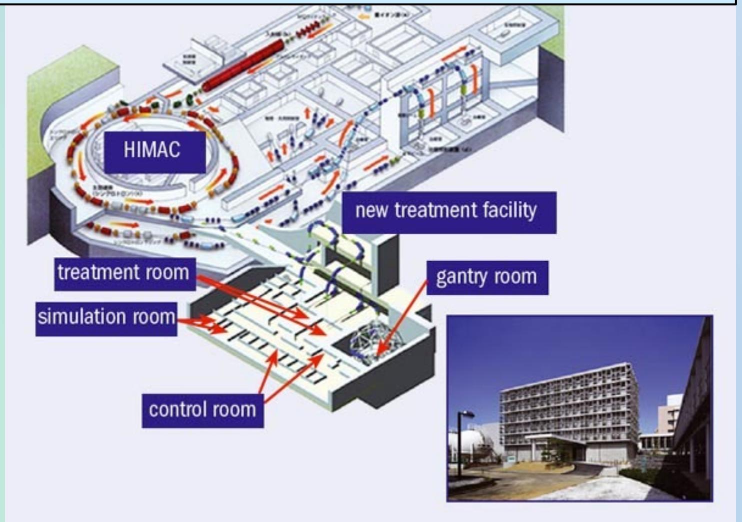
1994 first facility for carbon ions operational at HIMAC, Japan

2009 first European proton-carbon ion facility in Heidelberg

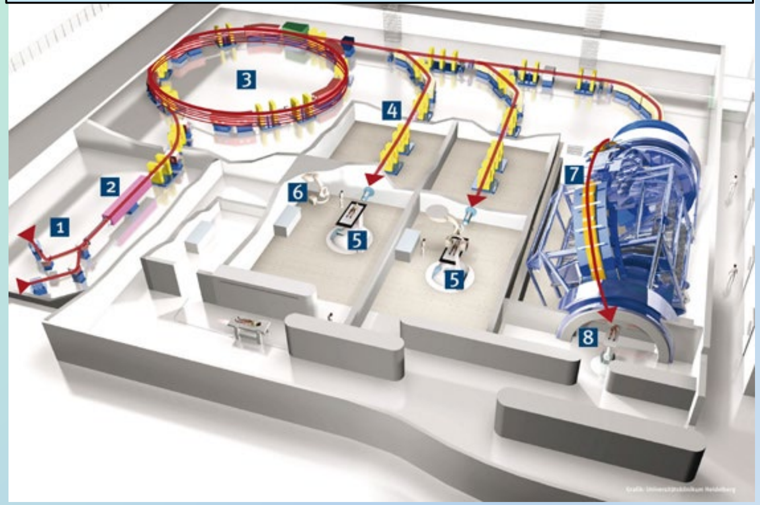
> 2009 also Italy is protagonist!!!

Catania
Pavia
Trento
Aviano, Milan

Heavy Ion Medical Accelerator in Chiba (Tokyo)



Proton and Carbon Ion Therapy (Heidelberg)



Radio and particle therapy

Radiotherapy: medical use of radiations and particles for the cancer treatment

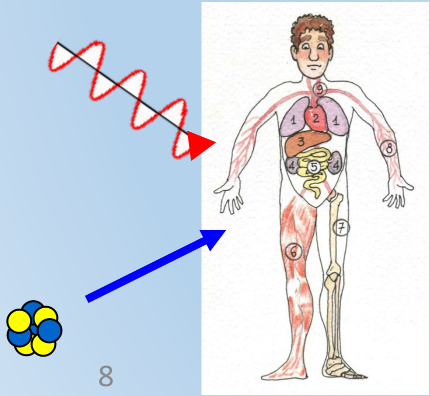
Conventional: Gammas and electrons

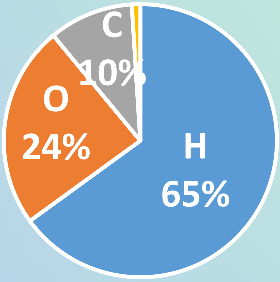
Energy range MeV

Particle Therapy: protons and light ions (typically Z≤6, under study neutrons and ≠ charge) **p & C**

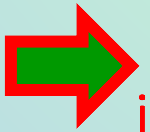
Energy range hundred MeV/u

GOAL: to kill the cancer, sparing healthy areas

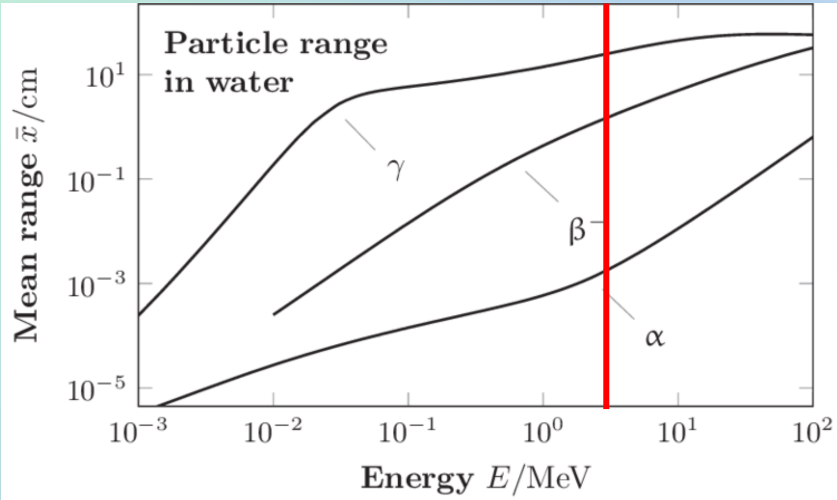




Human body



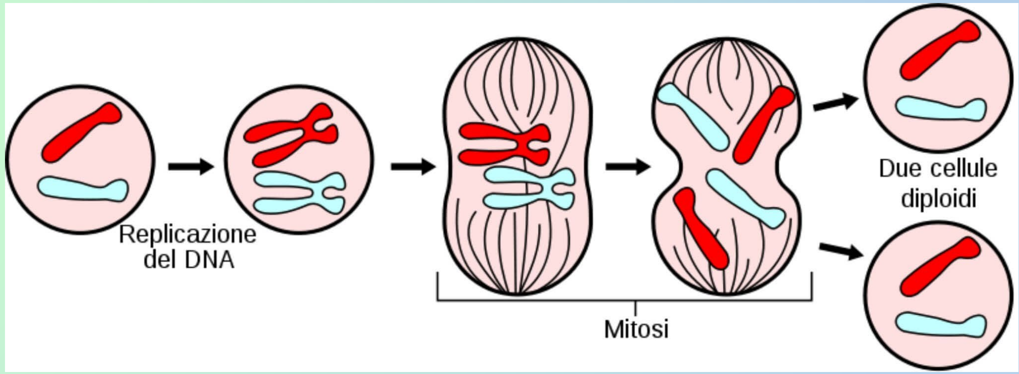
Differences
interactions with human body



Tumor: the goal

Tumor, cancer, neoplasia is a **mutated cell** that loose control and proliferates in a disorded way. Some tumor cells can migrate and form **metastases**.

Normal cell reproduction: **mitosis** (all cells) **or meiosis** (spermatozoa and ovum)



Defeat a tumour

to prevent the indefinite proliferation

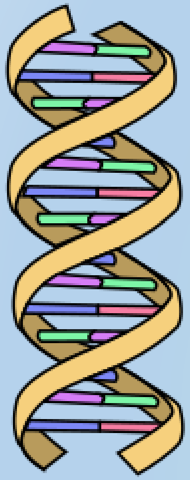
Hit the DNA

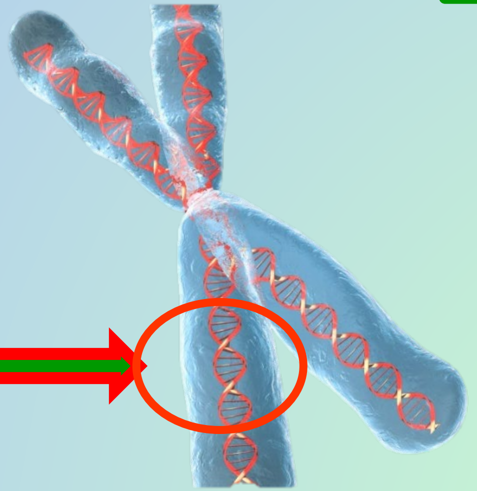
Cell that lost capability to reproduce indefinitely

is considered under control (**no effect = killed**)

To kill the DNA with radiation

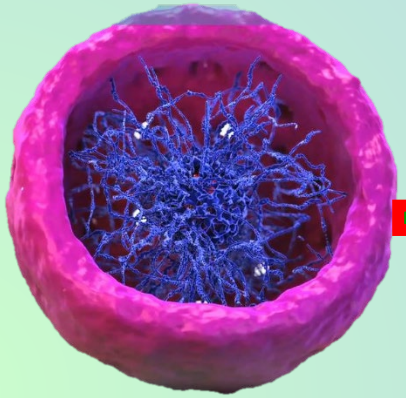
DNA

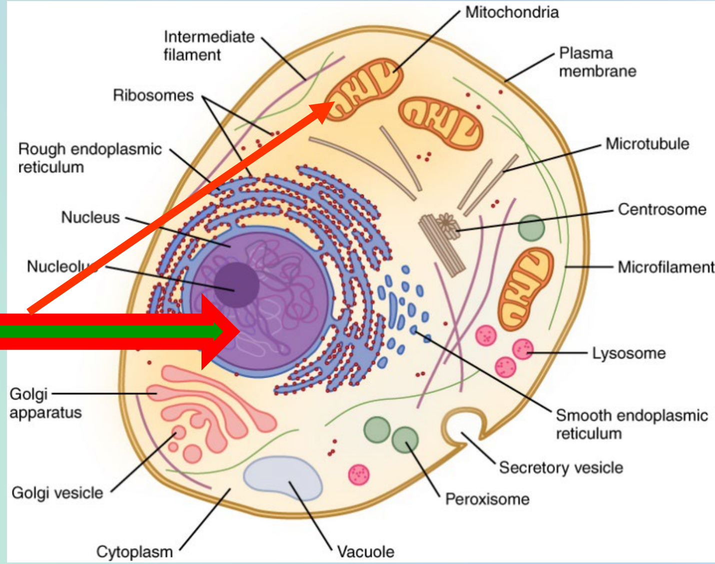




CROMOSOMA
(in man are 23 couples)

NUCLEUS





DNA Volume ~ 2-3% of the cell

2 possibile ways

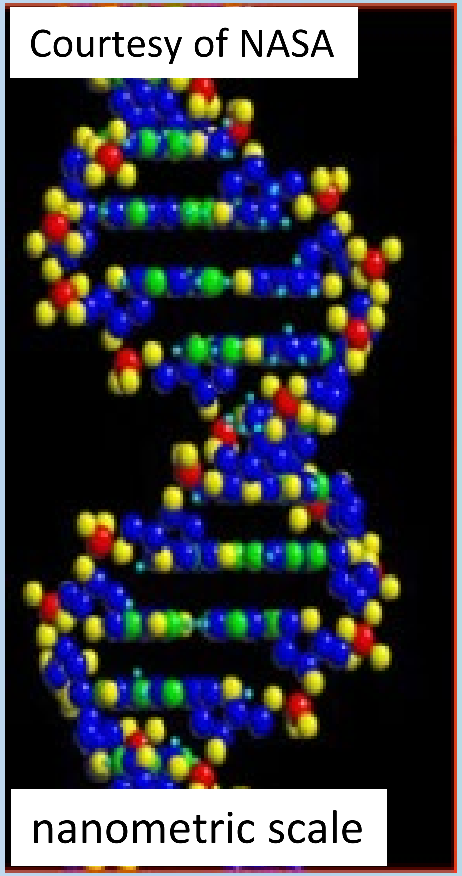
Indirect way: radiation hit the water copiously present in the cell → production of free radicals (very reactive neutral atoms or molecules with an odd electron) → damage the DNA

Direct way: radiation hit the strand of the DNA

Direct way

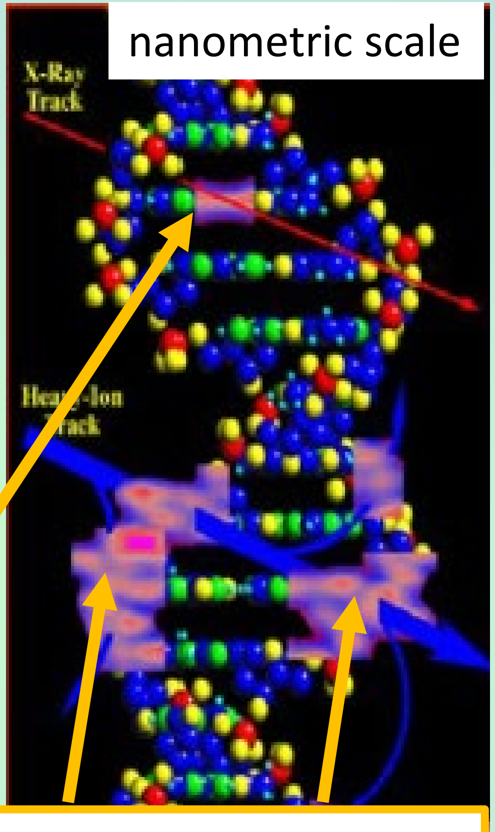
Double and single strand break (DSB and SSB)

DNA helixes



Ionization from
Radiation em/hadron

SSB	**1000**
DSB	**30-40**



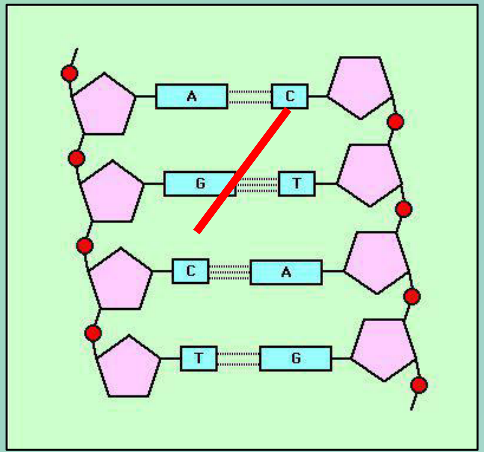
Reparable damage

NOT Reparable damage

Reproduction forbidden

Chemiotherapy: insert chemical agent to change the nitrogen bases

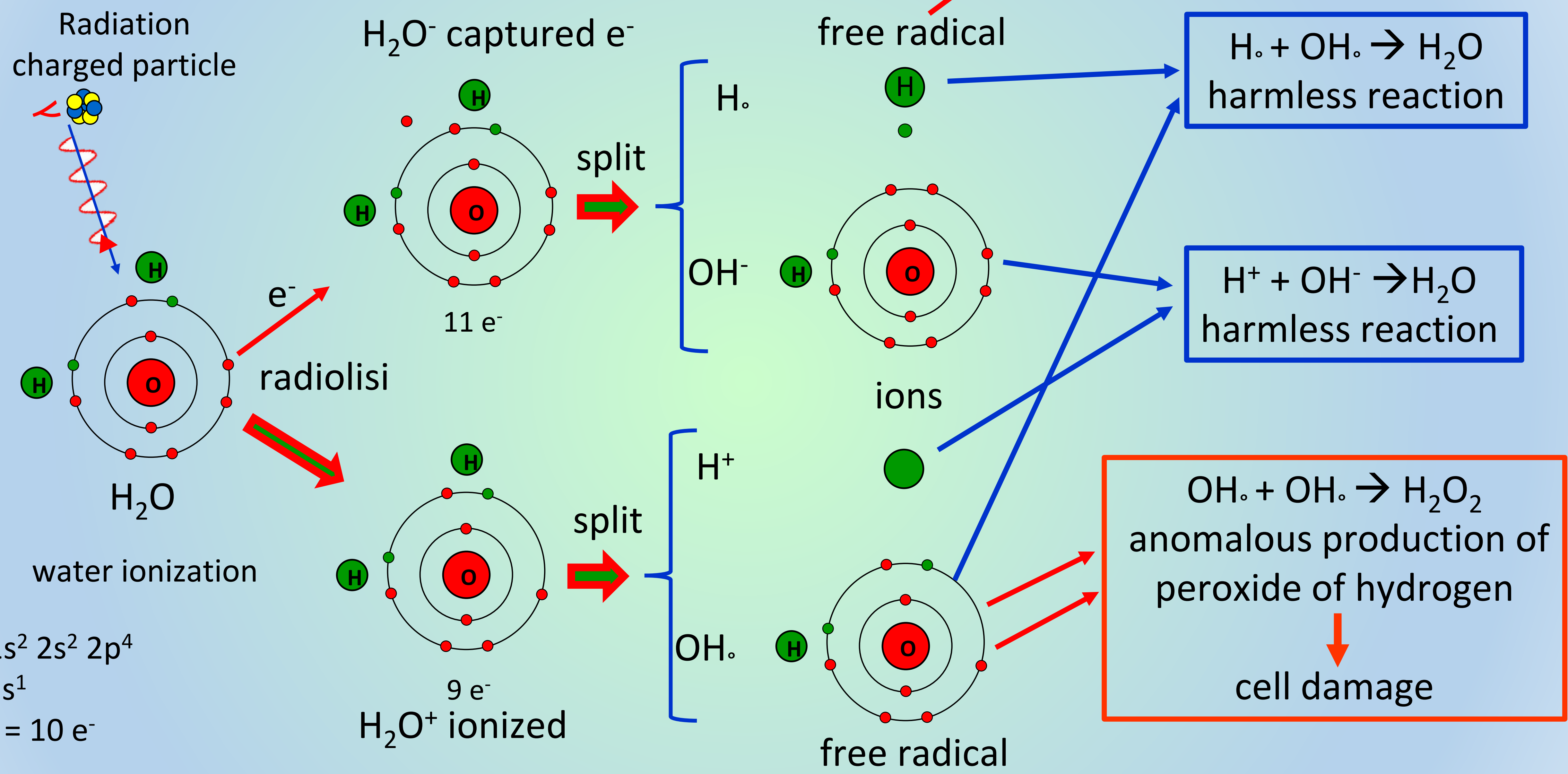
Prevent the reproduction



Goal: make a DSB of DNA

Indirect way (one possibility)

reactive neutral atoms/molecules due to a odd electron



Oxygen concentration increases the free radicals activity

TCP & NTCP

Tumor Treatment:

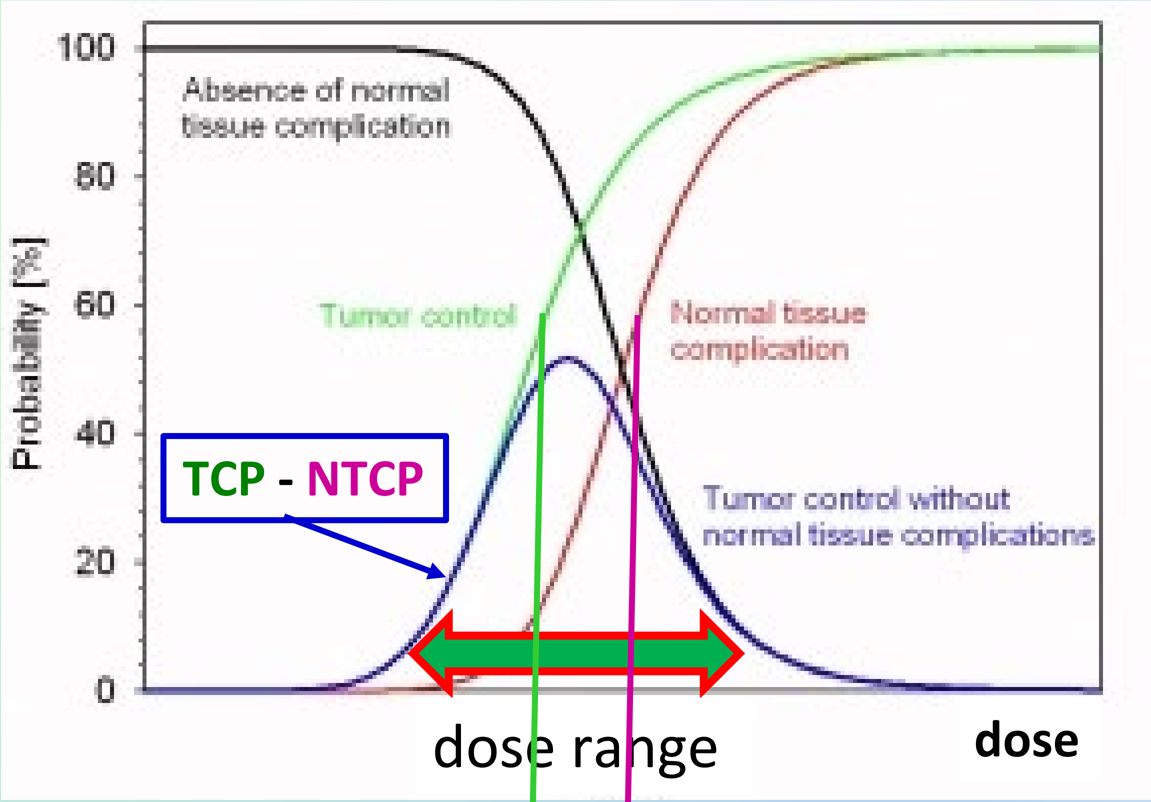
- **TCP** (Tumor Control Probability): probability to control the tumor → MAXIMIZE
- **NTCP** (Normal Tissue Complication Probability): probability to have complication in the healthy tissue → MINIMIZE

TCP & NTCP increase with the dose

↓

Find the dose range to maximize the TCP - NTCP

The quantity of dose depends on the tumor type and stage → typical range: 20-80 Gy (LETHAL DOSE if given in one shot!)



Healty tissue better repair damages

Gamma: interactions with matter

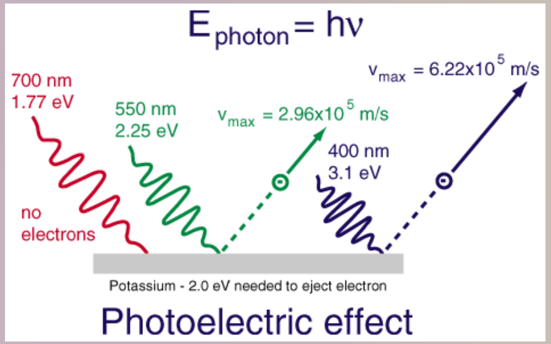
Photon interaction with matter

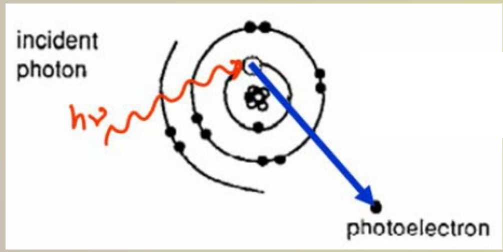
γ Interacts with matter essentially for

- **Rayleigh and Thomson**: negligible at this energy
- **Photoelectric effect**: photon with bound electron
- **Compton scattering**: photon with “free” electron
- **Pair production**: photon with nucleus
- **Photonuclear reaction**: negligible at this energy

Rayleigh and Thomson → elastic scattering with “free” e^- operating at very low energy

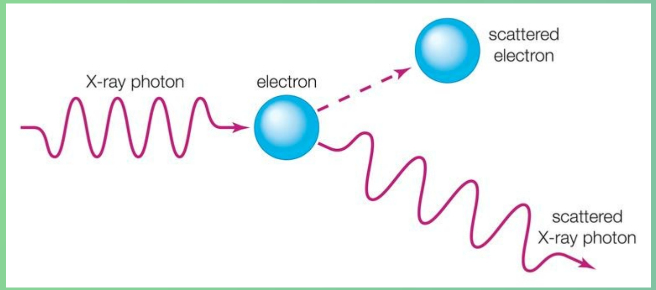
Photoelectric effect: photon absorbed, not present in the final state



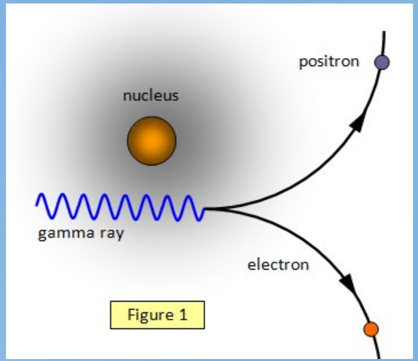


Inelastic Collision

Compton scattering: photon scattered (looses energy, change direction) , present in the final

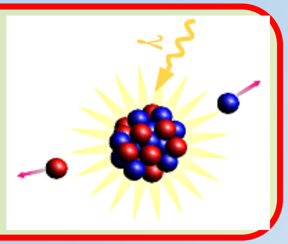


Elastic Collision

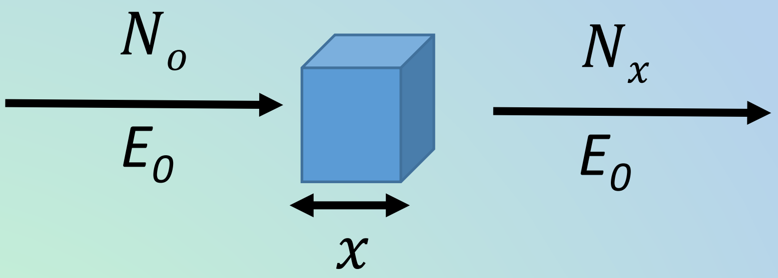


Pair Production: γ disappears → e^+e^- couple (necessity of a nucleus or a e^-)

Photonuclear reaction → γ hit a nucleus → ejection of p, n, ions (Eγ > 10 MeV)



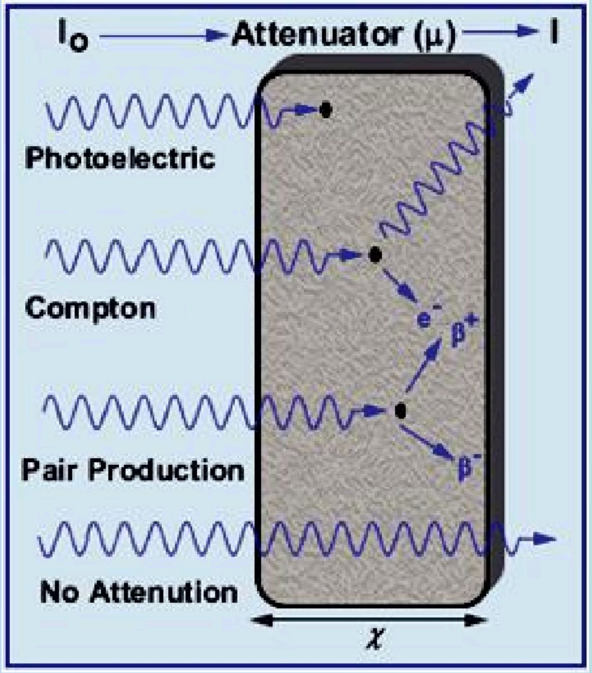
γ: the most probable interactions



$$N(x) = N_0\, e^{-\mu x}$$

***μ**:* Attenuation (absorption) coefficient [1/L]

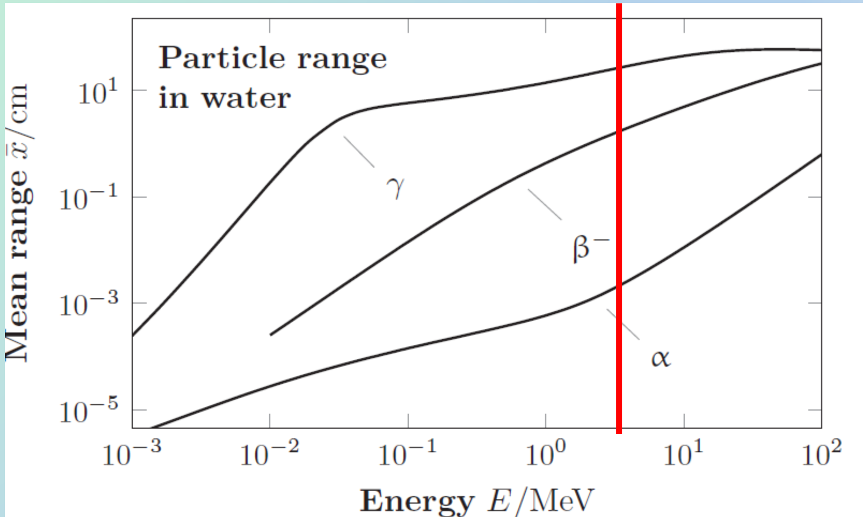
$$\mu = n\sigma_{tot} \quad \text{with} \quad n = \frac{N_A \cdot \rho}{M_{mol}}$$



Photoelectric effect: after 1 interaction γ disappears

Compton effect: after 1 interaction γ survives, but looses almost half energy → very few interactions

Pair production: after 1 interaction γ disappears

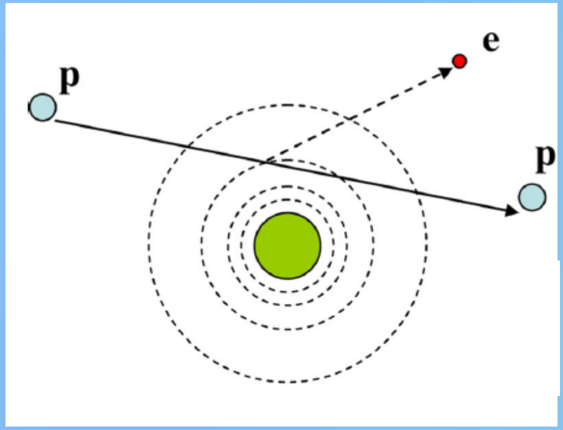
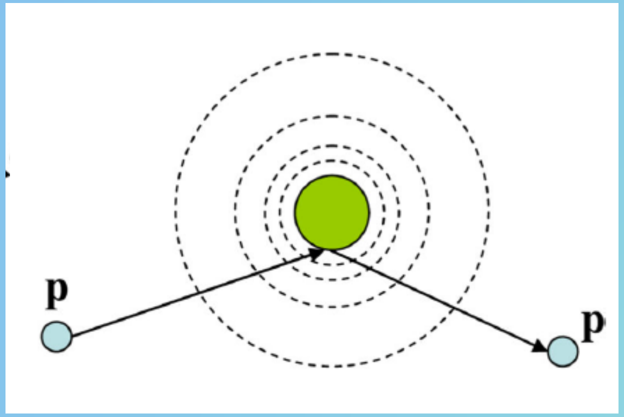
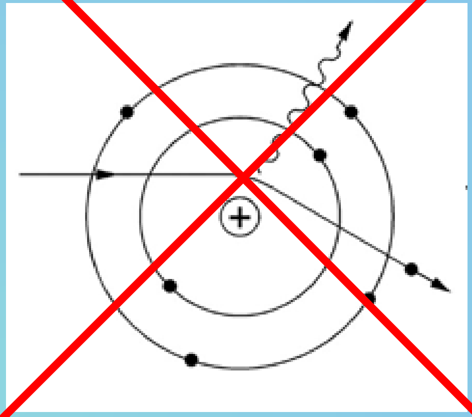
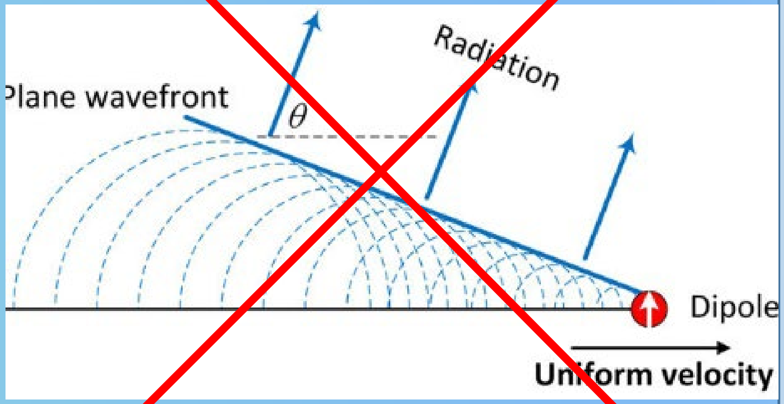


γ has few interactions with matter

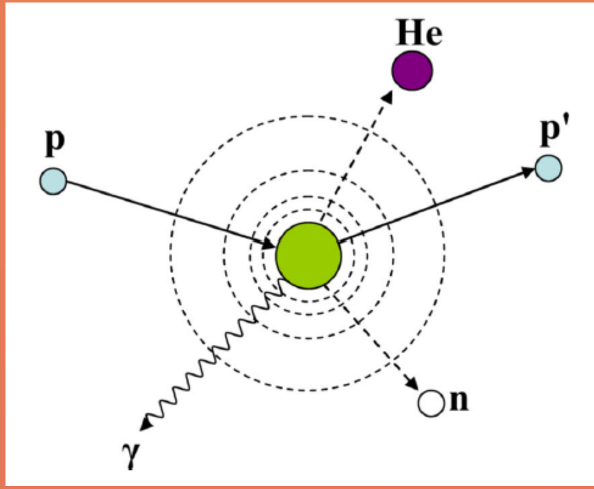
Charged particles: em interactions with matter

Charged Particle: interaction with matter

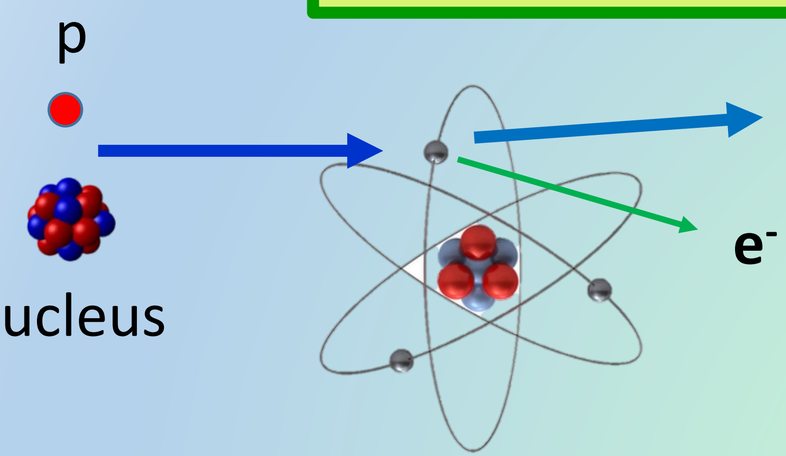
Em interaction with:

atomic electrons	nucleus	nucleus	electrons & nucleus
			
Bethe - Bloch	Rutherford (or Multiple Coulomb Scattering)	Bremsstrahlung	Cherenkov

Nuclear interaction

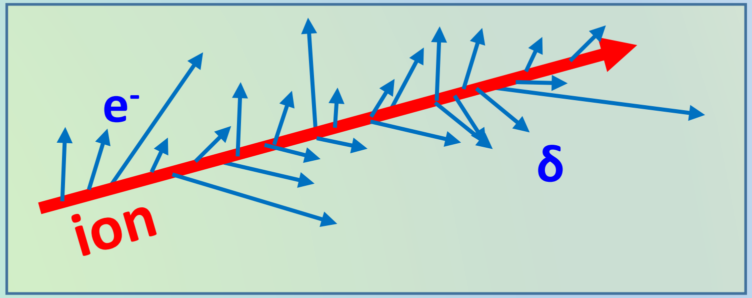


Charged particles: EM interaction on atomic electrons



energy loss, negligible deviation (mass projectile >> electron mass)

e^- can ionize if enough energy



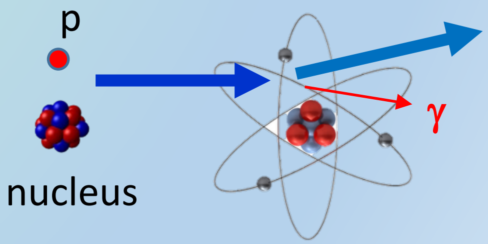
Inelastic Collision: not conservation of kinetic energy (part of the energy loss by proton is to free the electron)

This is the dominant process ($\sigma \sim 10^6$ barns!) [Leo, "***Techniques for Nuclear and Particle Physics Experiments***"]

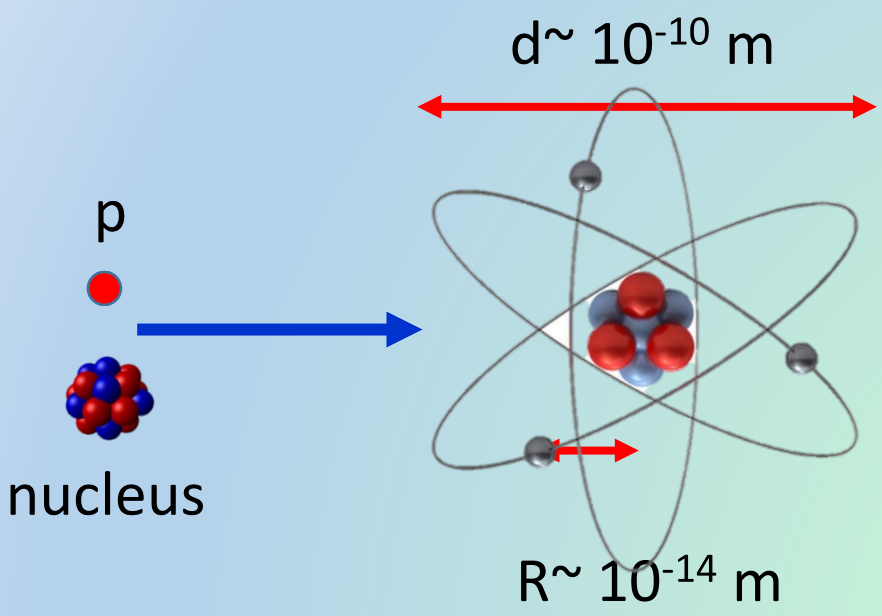
next slide

Hundreds of collisions, it makes no sense to speak of cross section, but of energy loss of the all processes

- Soft collision: Atom excitation → disexcitation emitting photons
- Hard collision: Atom ionization → electron emission (δ ray)



Charged particle: EM interaction with matter



$R = r_o A^{1/3}$ (r_o= nucleus radius)

$r_o = 1.25 \times 10^{-15}$ m = 1.25 fm

Cross section (interaction probability) ~ geometrical surface

$$\sigma \sim \pi(R_1+R_2)^2$$

Unit: barn → 1barn = 10^{-24} cm^2

$$\frac{\sigma_{atom}}{\sigma_{nucleus}} = \frac{S_{atom}}{S_{nucleus}} = 10^{8-10}$$

interaction with atomic e^- >> nuclei

$\sigma_{ATOM} \sim \pi(10^{-8})^2 = 10^{-16}$ cm^2 = 100 Mbarn

$\sigma_{NUCL} \sim \pi(10^{-12})^2 = 10^{-24}$ cm^2 = 1 barn

$\sigma_{pp} \sim \pi(1.25\times10^{-13})^2 = 10^{-26}$ cm^2 = 10-100 mbarn

Make no sense to speak of cross section → dE/dx

Bethe-Bloch formula or Stopping Power

$$-\frac{dE}{dx} = \frac{\rho Z}{A} \frac{4\pi N_A m_e c^2}{M_U} \left(\frac{e^2}{4\pi\epsilon_0 m_e c^2}\right)^2 \frac{z^2}{\beta^2}\left[ln\left(\frac{2m_e c^2\beta^2}{I(1-\beta^2)}\right) - \beta^2 - \frac{\delta}{2} - \frac{C}{Z}\right]$$

Medium properties

- ρ material density
- Z: atomic number
- A: mass number
- I: ionization potential

Z/A ~ 0.5

General constants

- N_A Avogadro number
- m_e: electron mass
- M_U: molar mass 1/12 C mass
- ε_0: empty dielectric constant
- e : electric charge

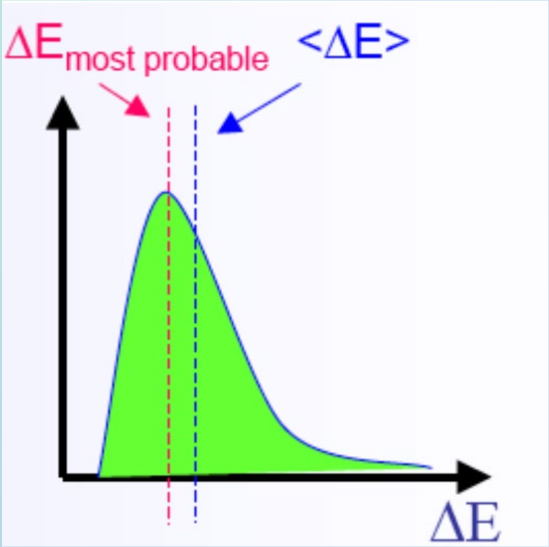
Beam characteristics (z, β)

- z (lower case): beam atomic number
- β: beam velocity

Corrections

- δ: density correction , important at high energy
- C: shell correction, important for low energy

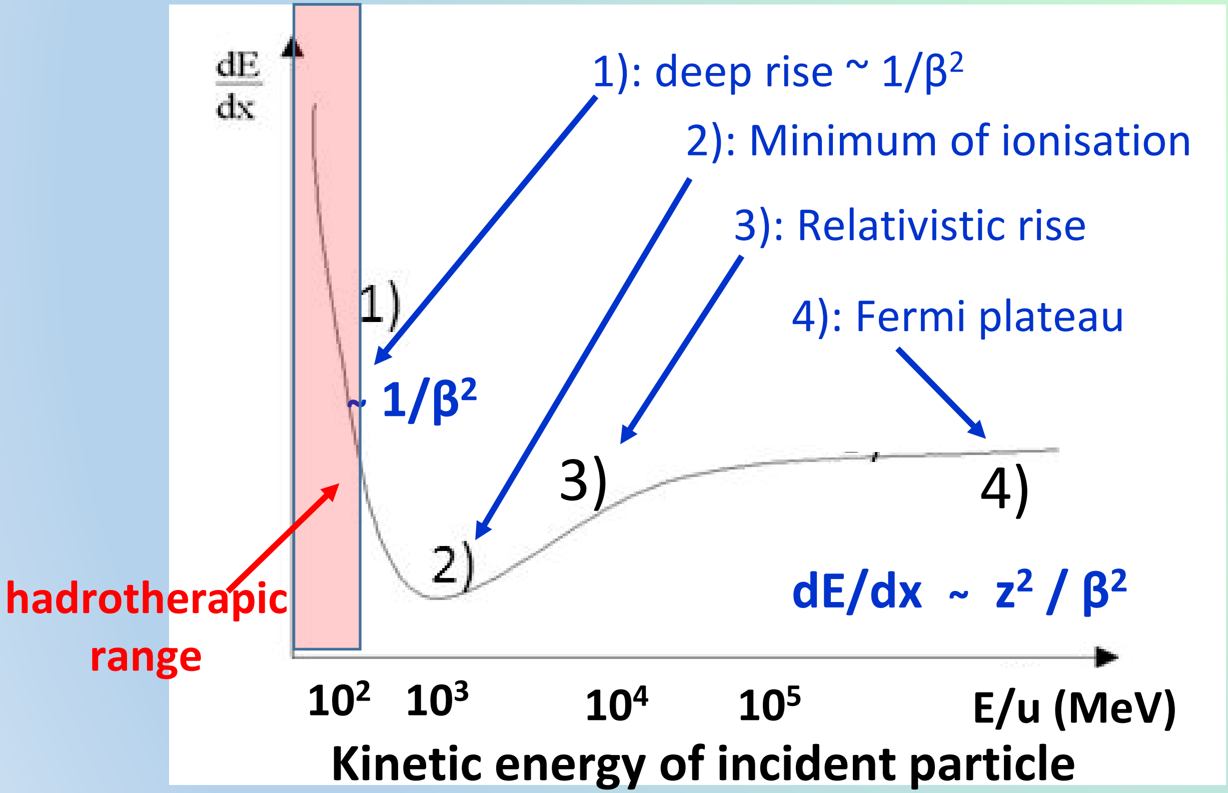
A particle interacting with matter is a stochastic process: if n identical particles (with same energy) cross the same depth of material → suffer different energy losses → Bethe-Bloch gives the average value of those energy losses → fluctuation around the average is described by the Landau distribution



Bethe-Bloch formula or Stopping Power

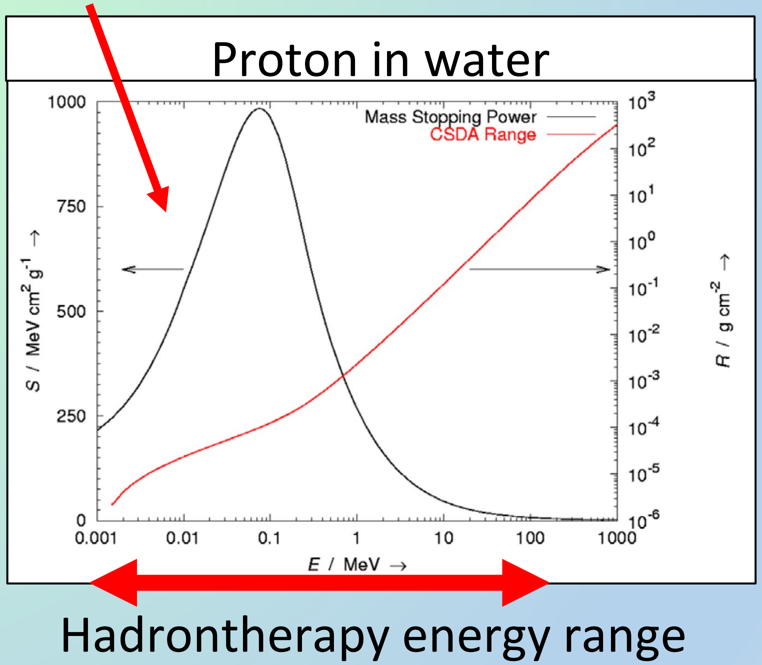
$$-\frac{dE}{dx} = \frac{\rho Z}{A} \; \frac{4\pi N_A m_e c^2}{M_U} \left(\frac{e^2}{4\pi\epsilon_0 m_e c^2}\right)^2 \; \frac{z^2}{\beta^2}\left[ln\left(\frac{2m_e c^2\beta^2}{I(1-\beta^2)}\right) - \beta^2 - \frac{\delta}{2} - \frac{C}{Z}\right]$$

Medium properties **General constants** **Beam characteristics (z, β)** **Corrections**



As lower is the energy as larger is dE/dx

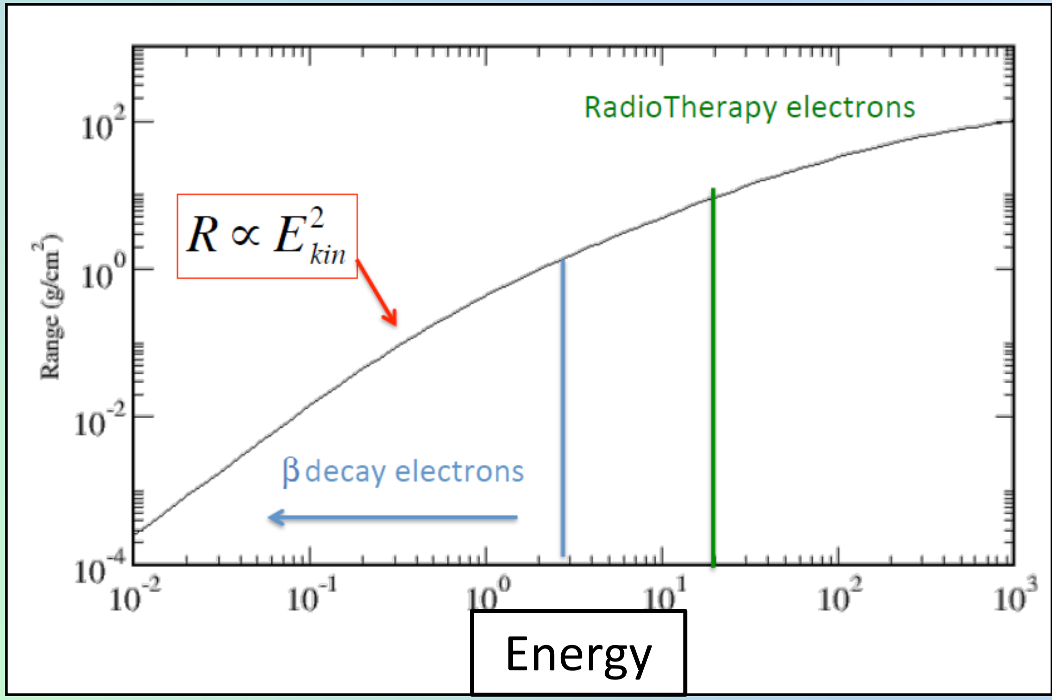
- δ: density correction , important at high energy
- C: shell correction, important for low energy (stop the $1/\beta^2$ increase)



Range

Range :
depth at which half of protons-ions come to rest

$$R = \int_0^R dx = \int_0^{E_0} \frac{dE}{\frac{dE}{dx}} = \ \dots \ \approx E_0^2 \ or \ better = \ E_0^{1.75}$$



In general $R(E) = \alpha E^p$ α depends on material, p on Energy

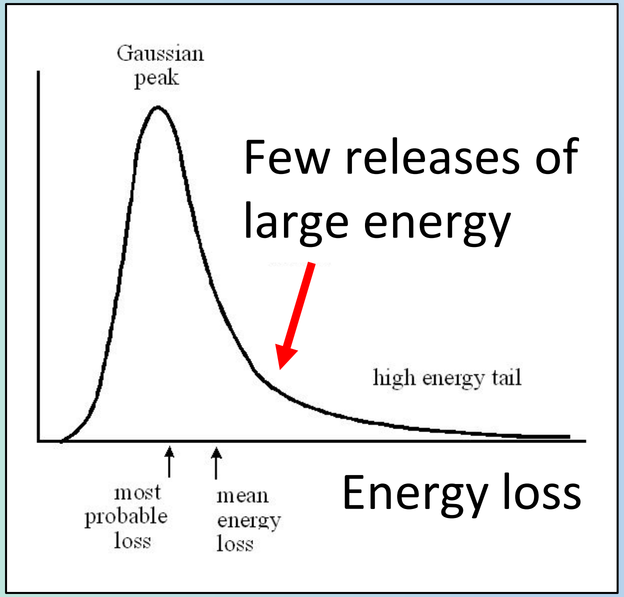
Range of charged particles depends on their kinetic Energy → very useful in hadrontherapy

Energy loss and range fluctuations

dE/dx is a stochastic process (hundreds of interactions)

A beam of the same particles of the same kinetic energy does not release the same dE

Energy loss distribution is not a Gaussian around a peak, but it is a Landau



dE/dx Fluctuation ⇒ Range fluctuation

Width depends on projectile and on material

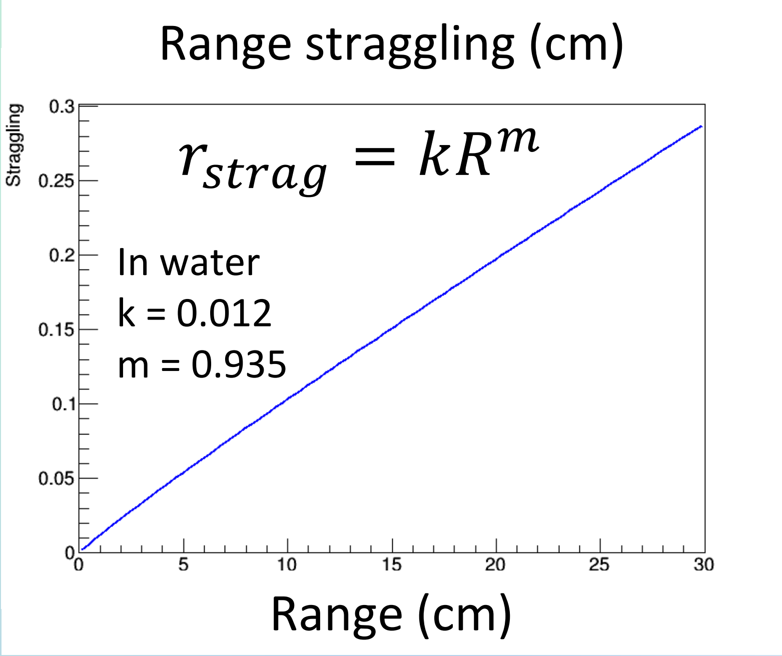
Example proton 200 MeV in water

- Range = 25.8 cm
- Range fluctuation (RMS) = 2.5 mm (1%)

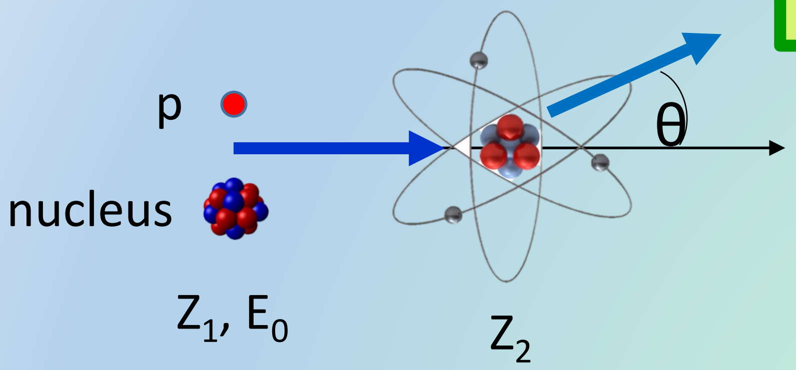
Range straggling important in hadrontherapy

⇓

Different depth of the treatment



Charged particle:EM interaction with nuclei of matter

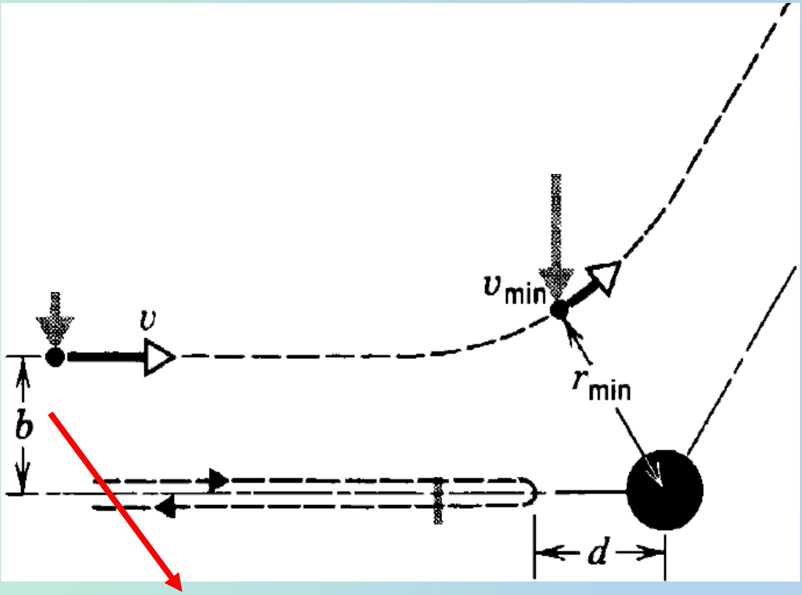


depending on impact parameter → Collision with nuclei
→ **Elastic collision** (kinetic energy conservation)

$$\frac{d\sigma}{d\Omega} = \left(\frac{1}{4\pi\epsilon_0}\frac{Z_1 Z_2 e^2}{4E_0}\right)^2 \frac{1}{\sin^4\left(\frac{\theta}{2}\right)}$$

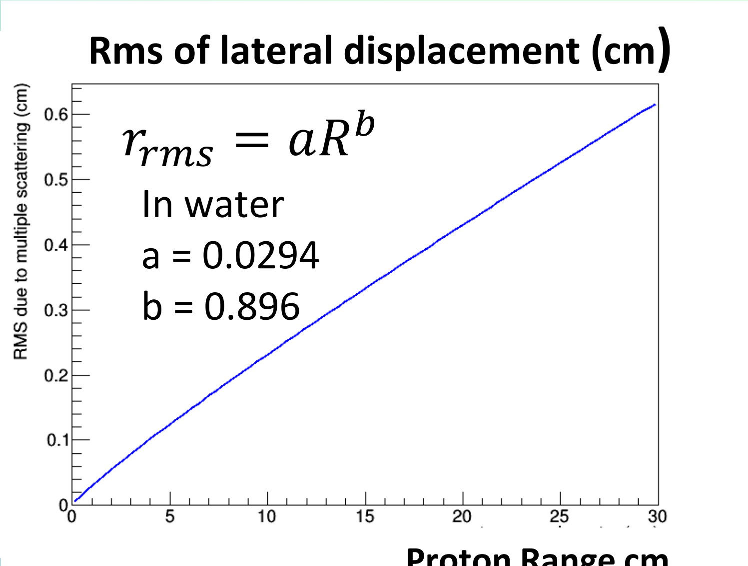
$\sigma = f(E, Z_1, Z_2, \theta)$

Rutherford formula (or multiple Coulomb scattering)



Impact parameter
If b <~ r_{nucl} → Nuclear interaction

- Large Deviation angle
- Low energy variation



Charged particles: uncertaintes in the position

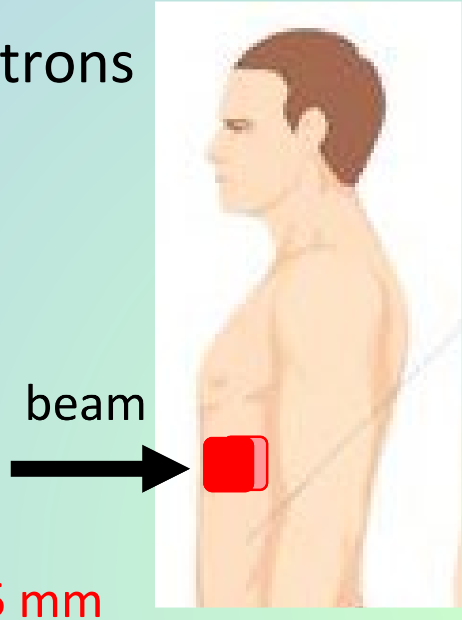
Interaction with atomic electrons

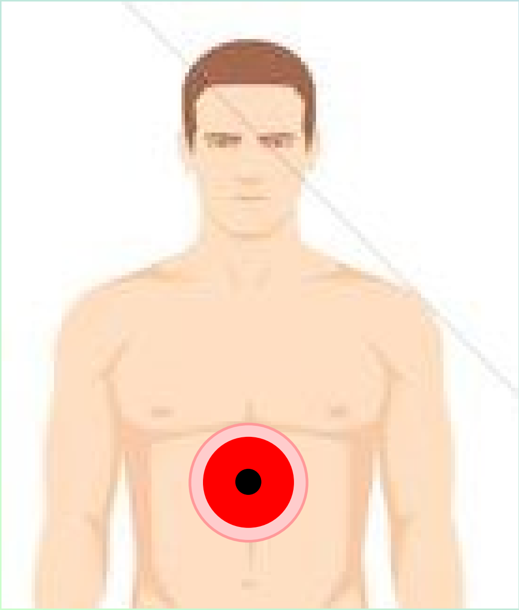
↓

range straggling

proton 200 MeV in water

- Range = 25.8 cm
- Range fluctuation (RMS) = 2.5 mm





Interaction with nuclei

↓

lateral displacement

proton 200 MeV in water

- Range = 25.8 cm
- Lateral displacement = 5 mm

Longitudinal displacement in hadrontherapy

↓

Different z position of treatment

Lateral displacement in hadrontherapy

↓

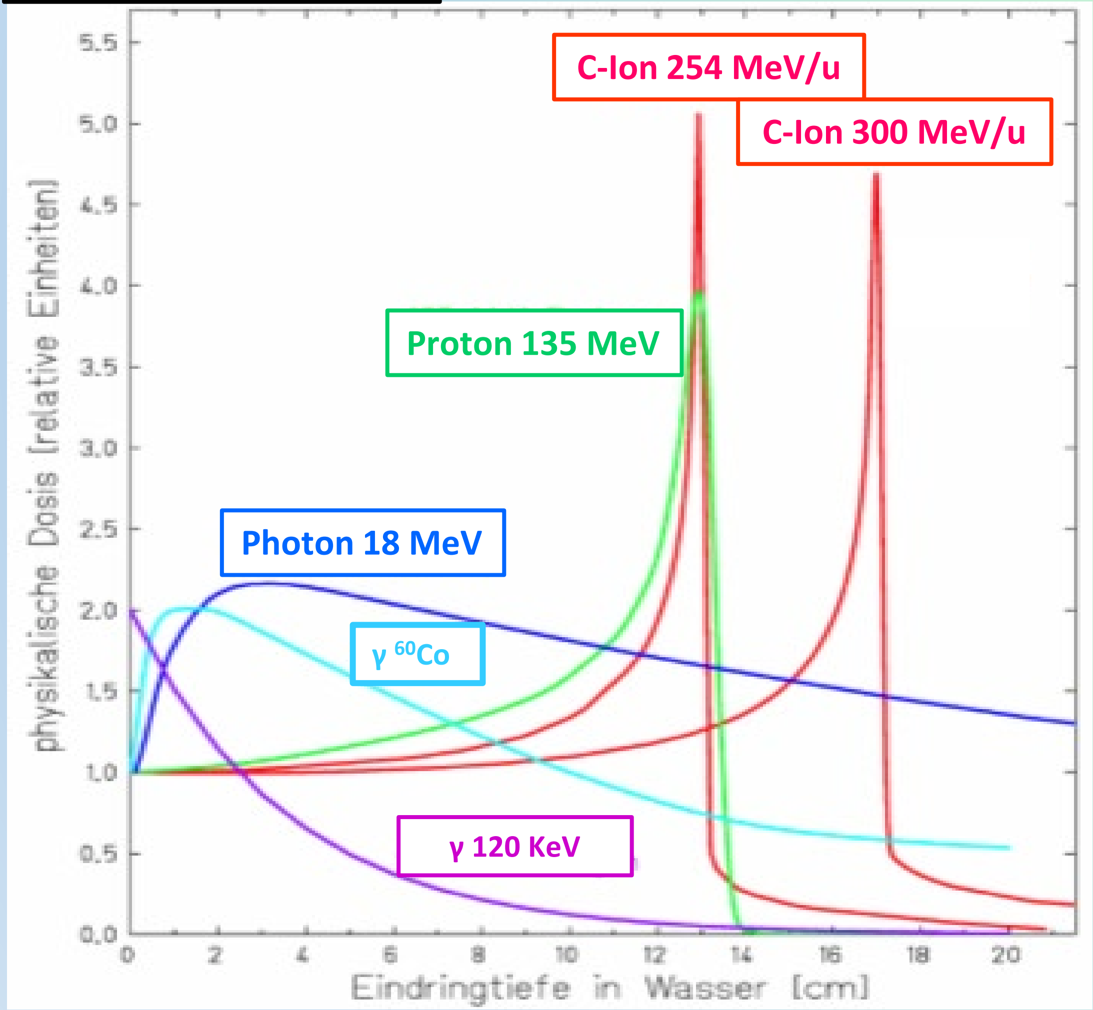
Different xy position of treatment

To consider in the treatment

Bragg Peak, 1

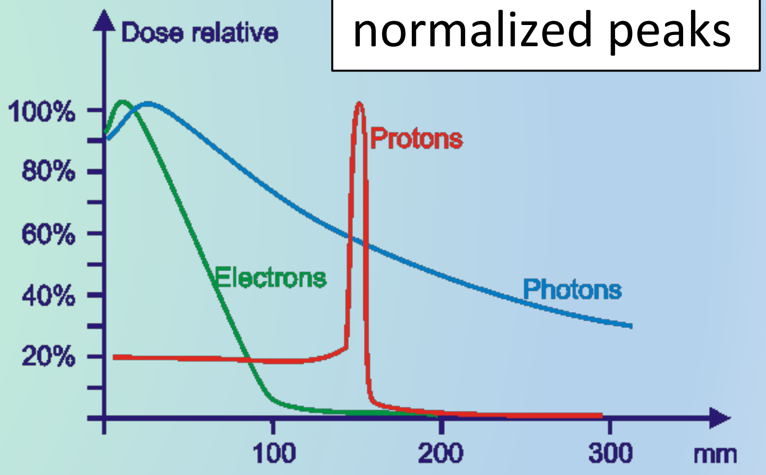
Different interaction γ-matter and charged particle-matter ⇒ Different dE/dx vs depth

dE/dx vs depth



- $e^{\pm}$ and γ loose energy exponentialy vs depth
- charged particle loose the big part of energy ~ at rest

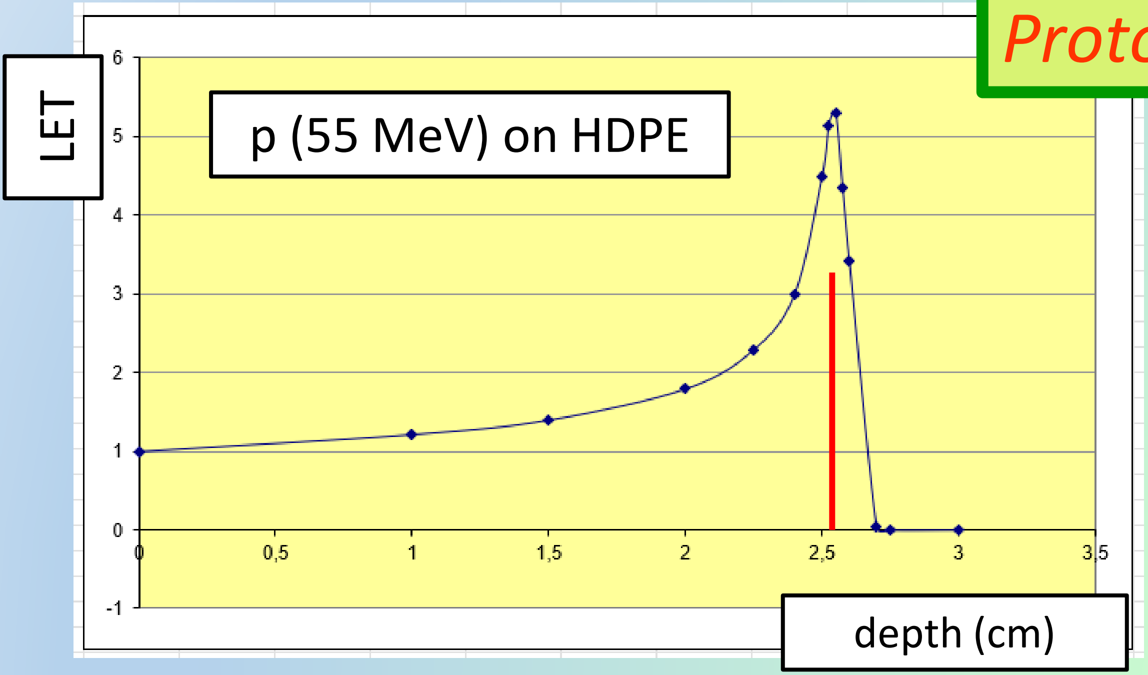
normalized peaks

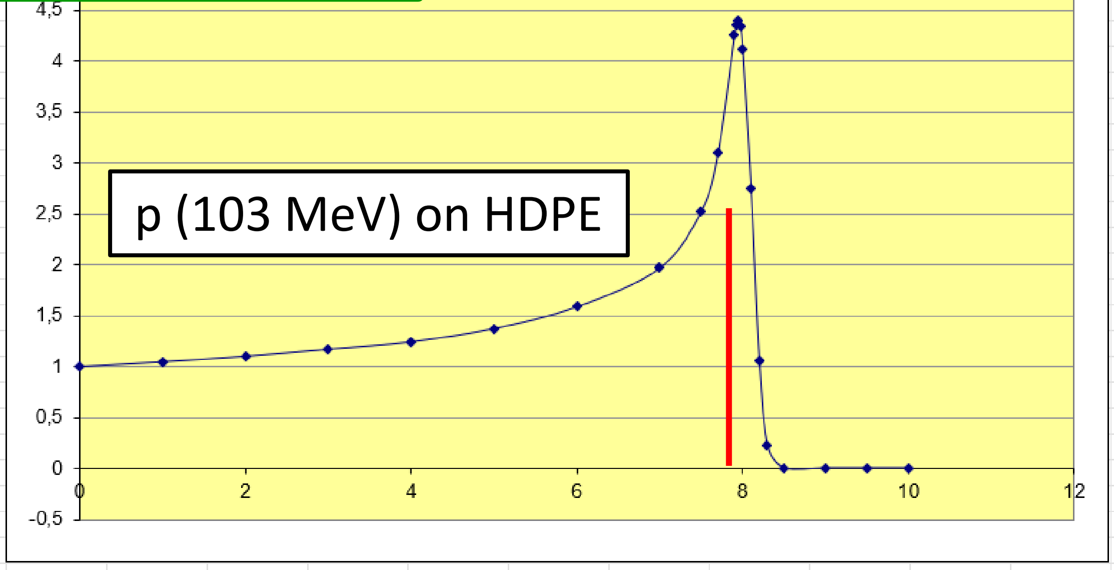


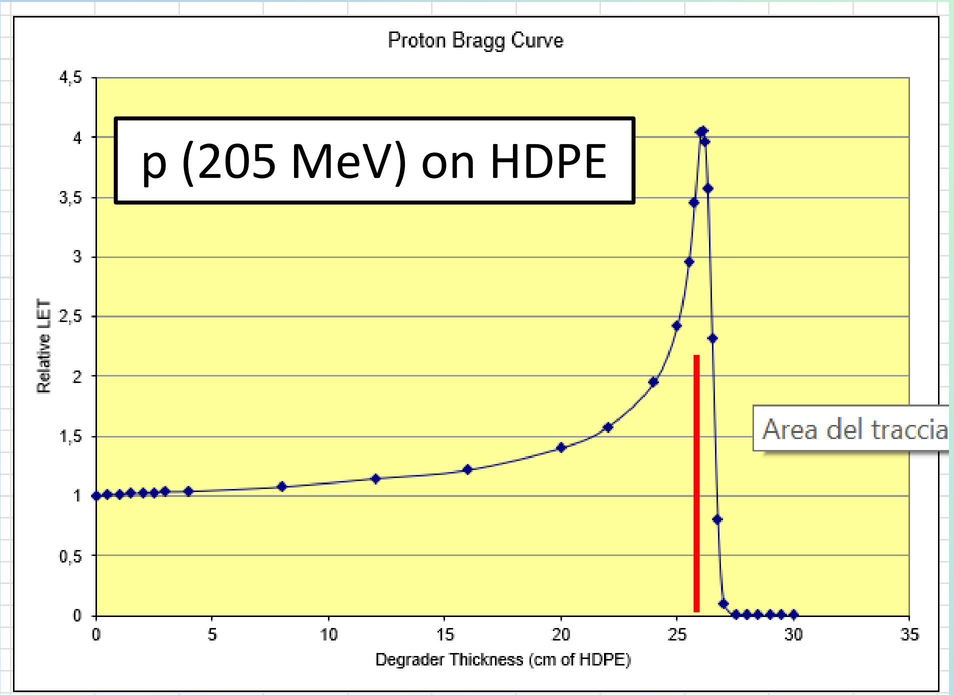
Hadrontherapy vs radiotherapy:

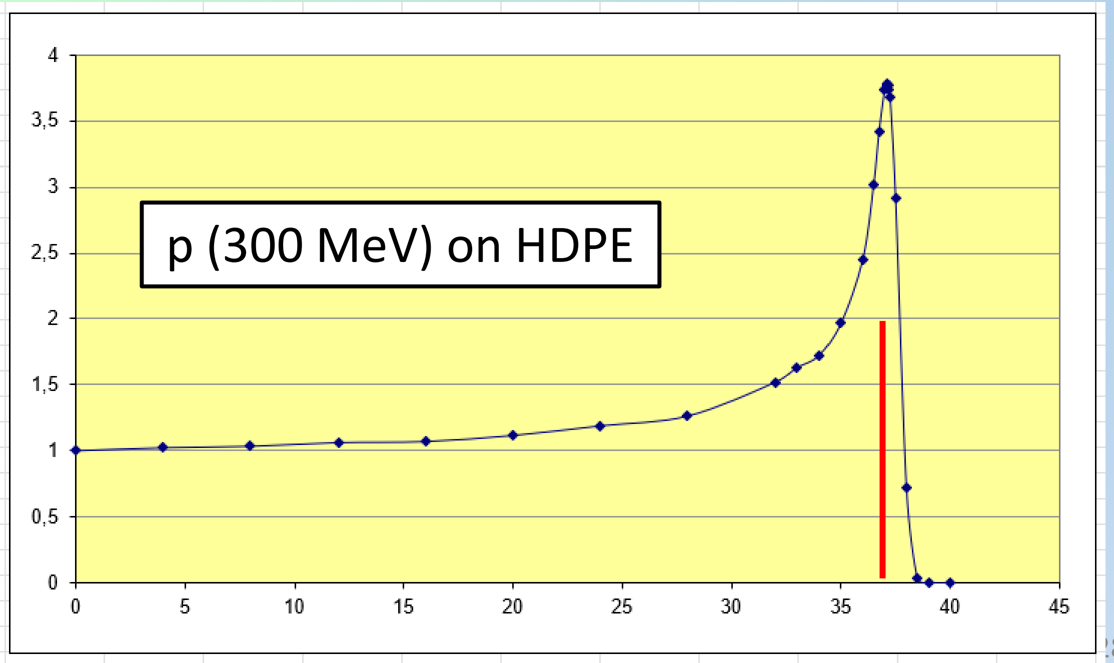
- Advantage in the dose deposition on cancer
- Advantage of heavy ions with respect protons
- Peak position depends on the beam energy
- Disadvantage: costs and not known aspects

Proton dE/dx versus depth





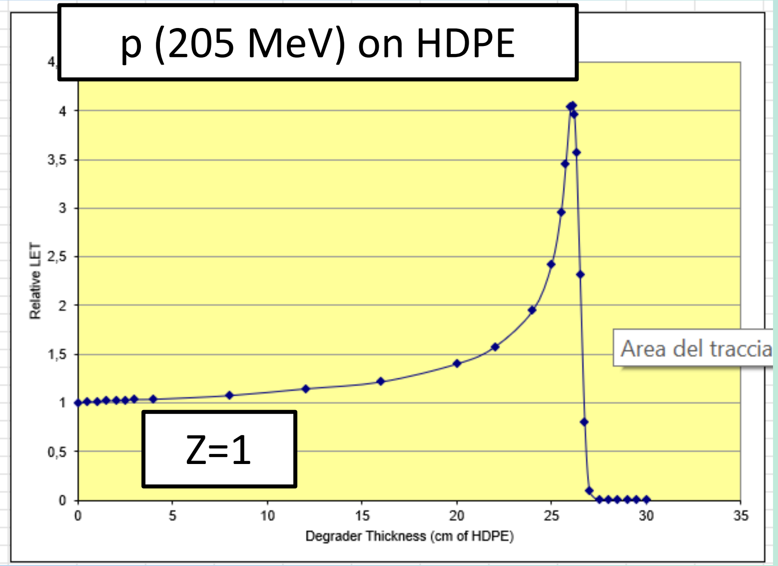


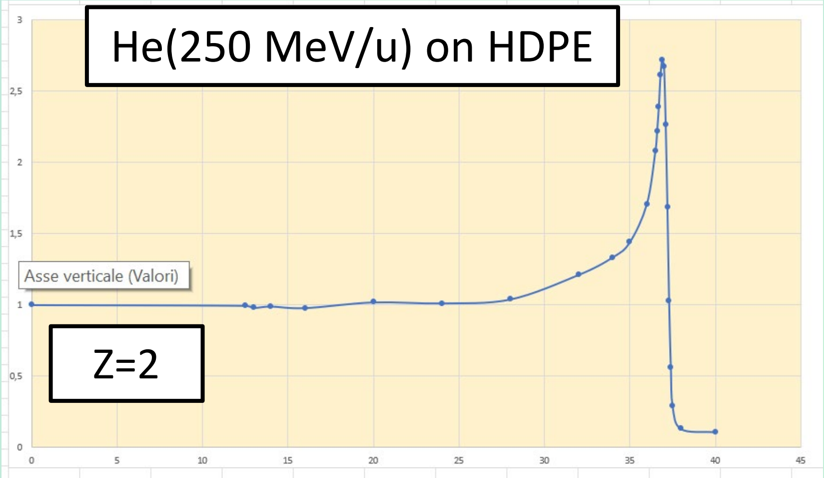


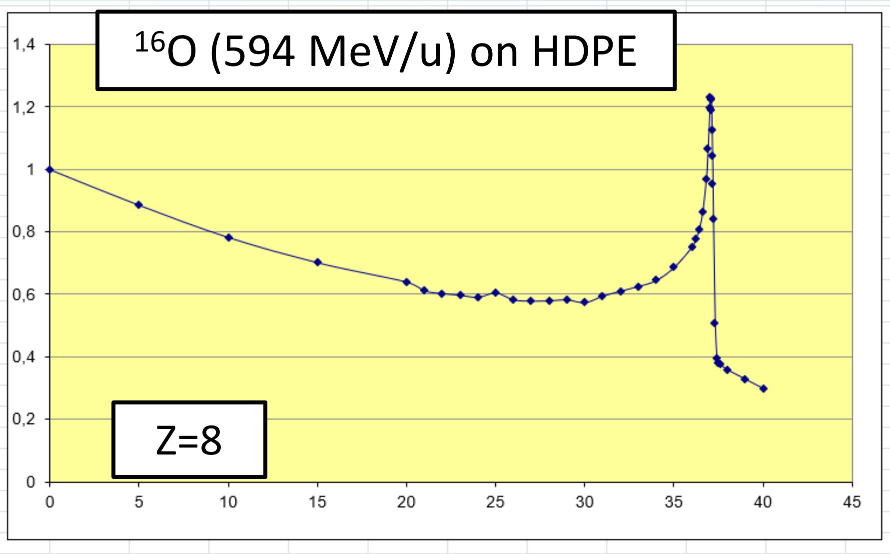
Bragg Peak: encreasing Z of the beam (~same range)

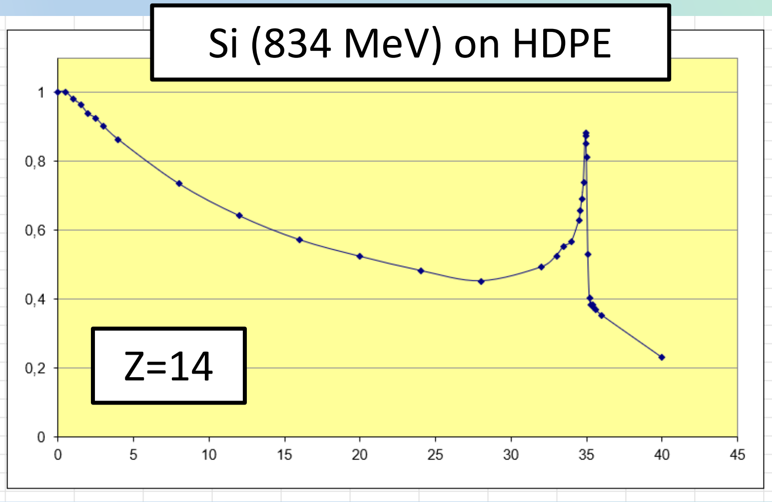
$$-\frac{dE}{dx} = \frac{\rho Z}{A} \frac{4\pi N_A m_e c^2}{M_U} \left(\frac{e^2}{4\pi\epsilon_0 m_e c^2}\right)^2 \frac{z^2}{\beta^2} \left[ln\left(\frac{2m_e c^2 \beta^2}{I(1-\beta^2)}\right) - \beta^2 - \frac{\delta}{2} - \frac{C}{Z}\right]$$

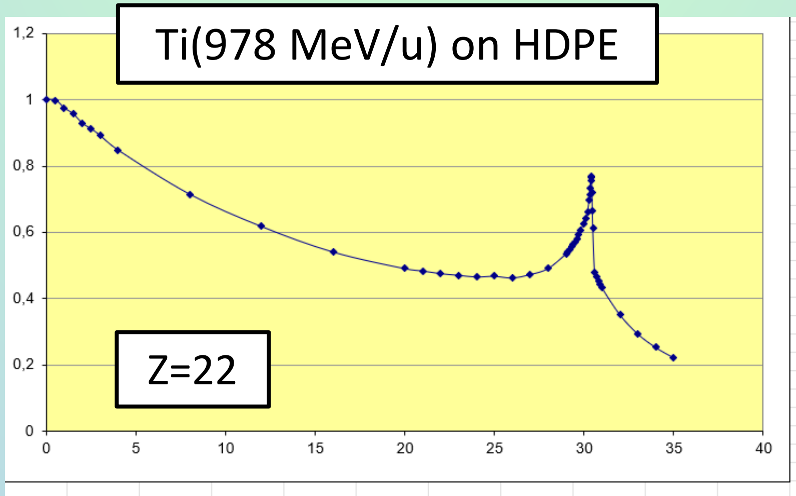
As large is Z as better is it?

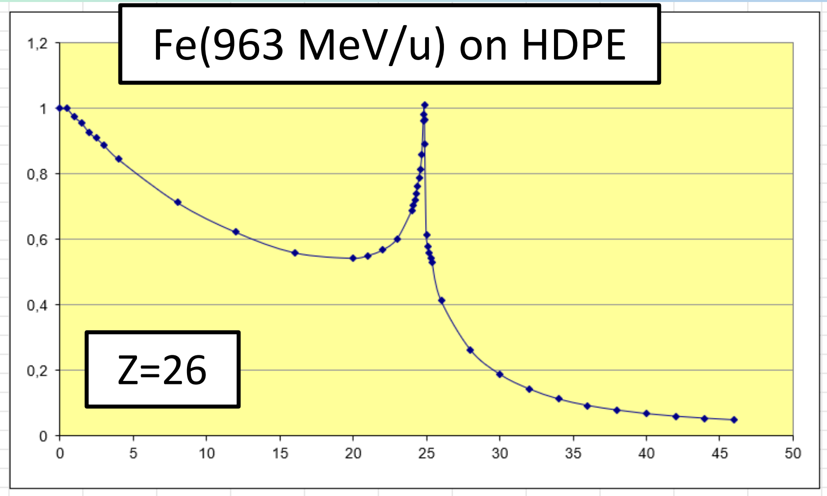




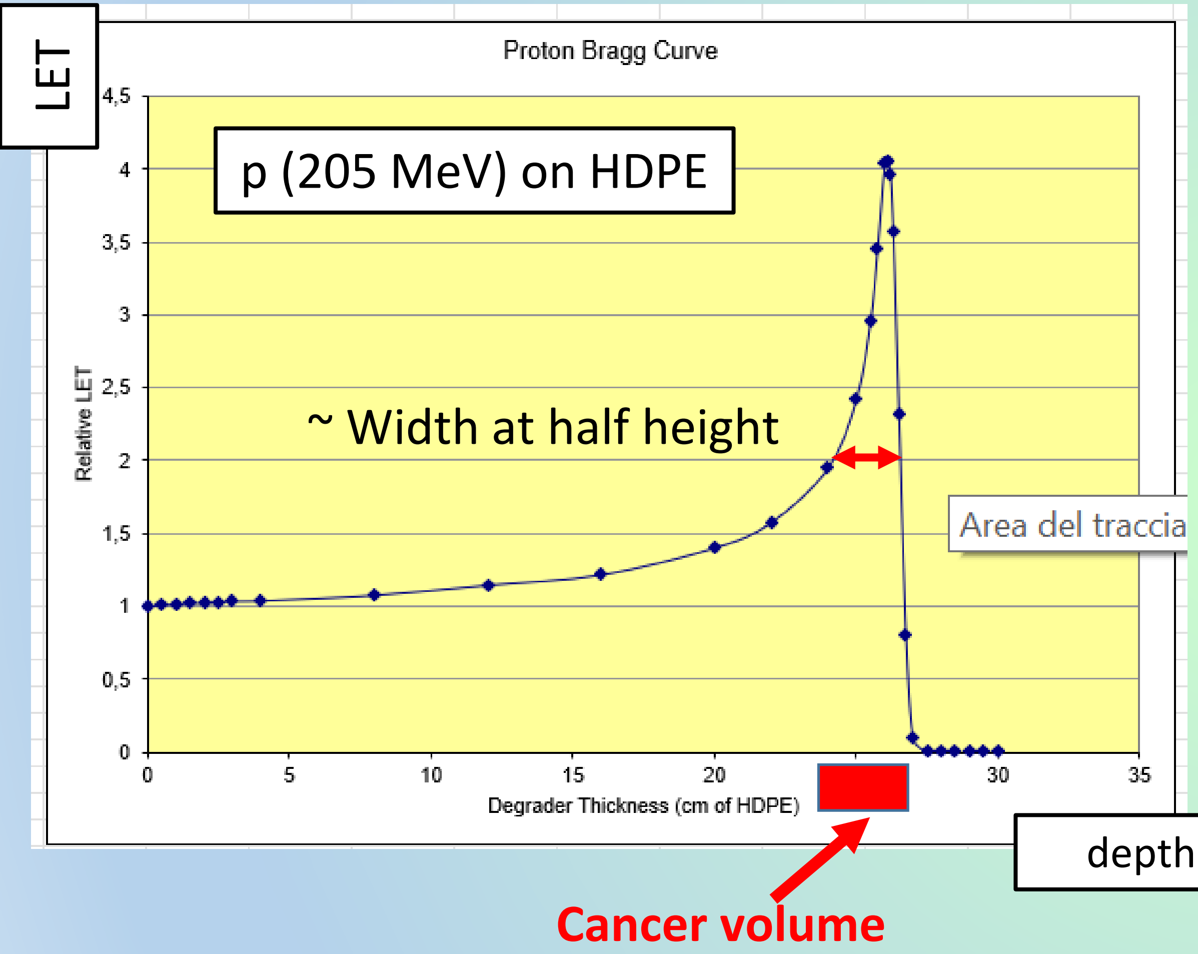


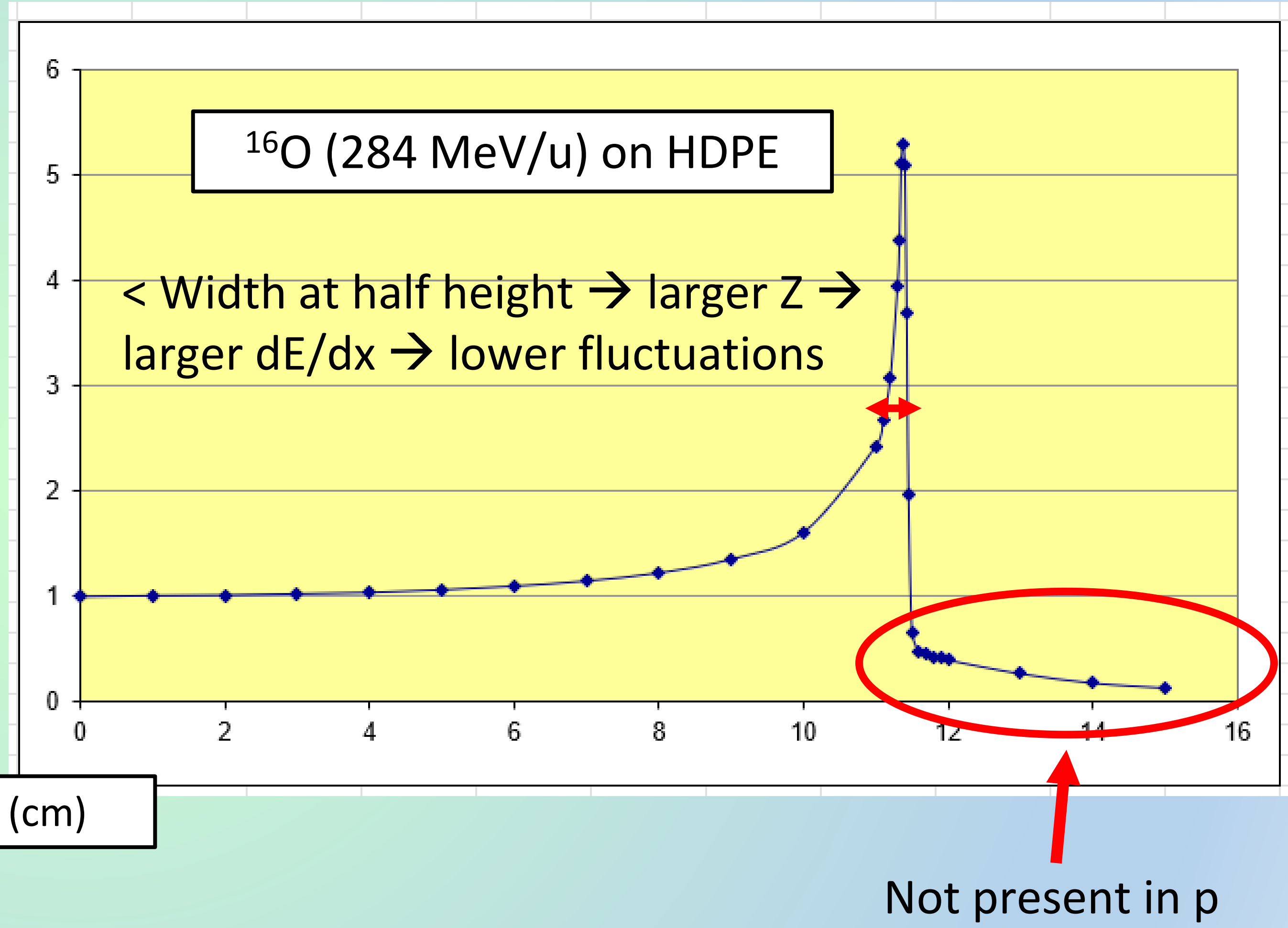






Proton and Oxygen dE/dx versus depth





depth (cm)

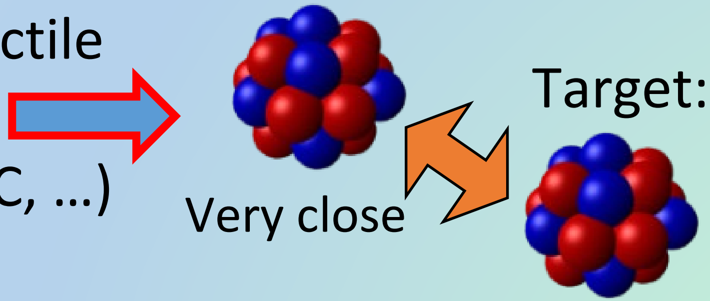
Remind:

- ^{16}O lower range than proton (obviously)
- Total kinetic energy of protons = 205 MeV, Oxygen = 284x16 MeV

Nuclear Interaction

Projectile

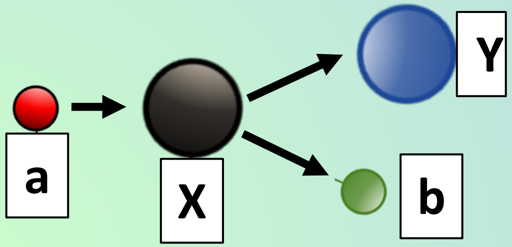
(p, ^{12}C, …)



Target: H, C, O

Nuclear force:

- ❑ **Short range~ 1 fm (~ nucleon)**
- ❑ **Independent of the charge**
- ❑ **Dependent on the spin**



Nuclear reaction **a + X → Y + b**

projectile — Target (usually stationary in Lab)

Conservation:

- ❑ **E (Energy)**
- ❑ **p (momentum)**
- ❑ **L (ang momentum)**
- ❑ **P (parity)**
- ❑ **I (isospin)**

To these energies (no meson or quark rearrangement)

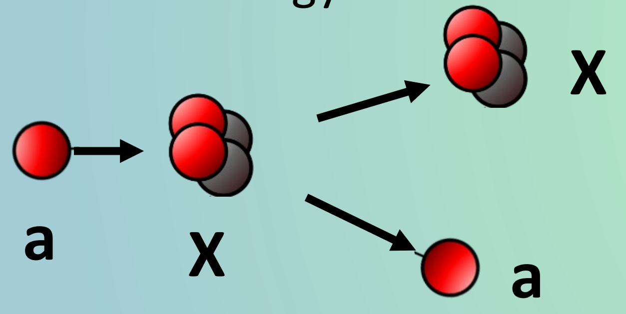
- ❑ **∑p and ∑n must be the same in initial and final state**

Elastic and inelastic Nuclear Interaction

ELASTIC

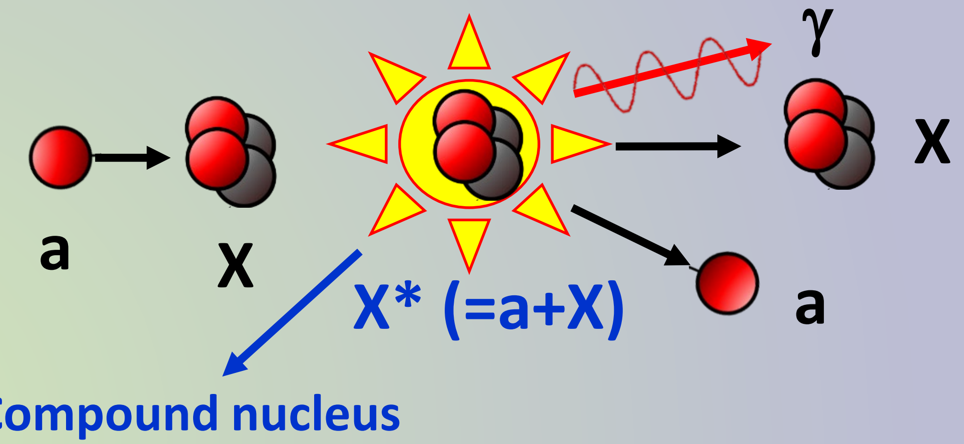
a + X → a + X

Energy from Nucleus de-excitation distributed to the kinetic energy of final state

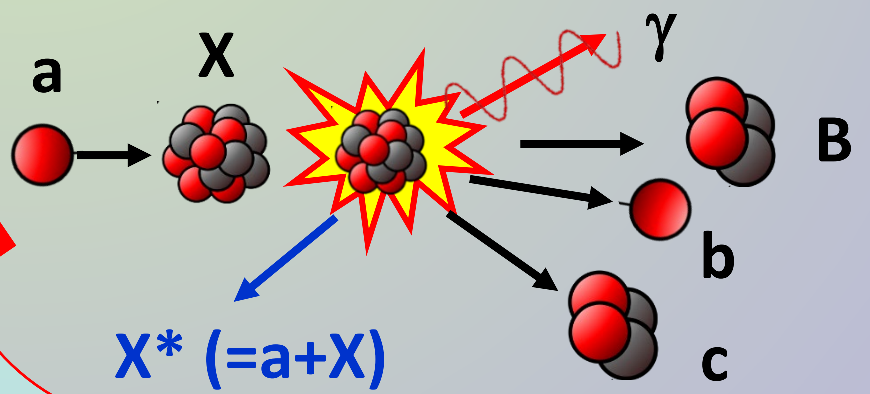


INELASTIC

a + X → X* → a + X + γ



a + X → b + B + c + …

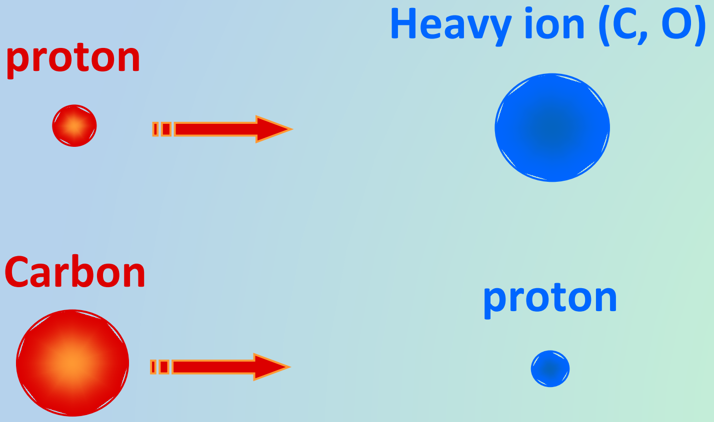


Particle beam disappears and it appears different fragments → all changes

Kinematics of Fragmentation

Projectile ~ 200 MeV/u | **Target at rest**

At the hadrontherapy energiy proton doesn't fragment

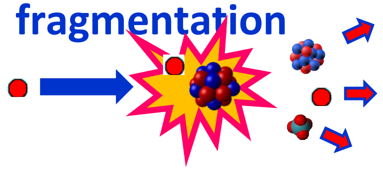


Only Target fragmentation → target fragments ~ **at rest**

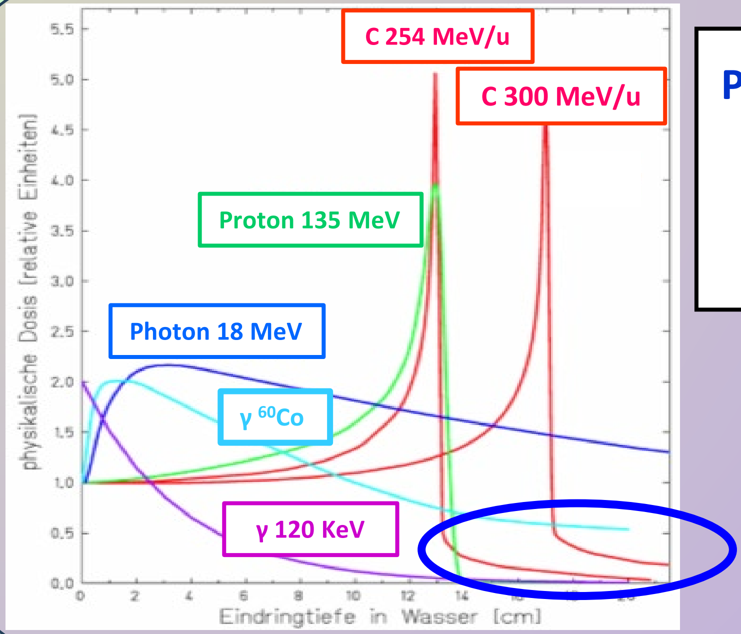
Projectile fragmentation → Projectile fragments **~beam energy**

Nuclear interaction is a side effect

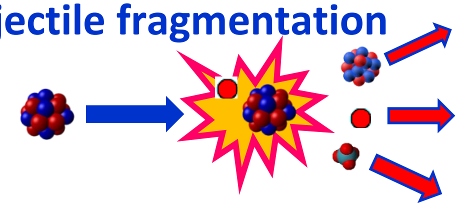
Target fragmentation



Fragment	E (MeV)	LET (keV/μm)	Range (μm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

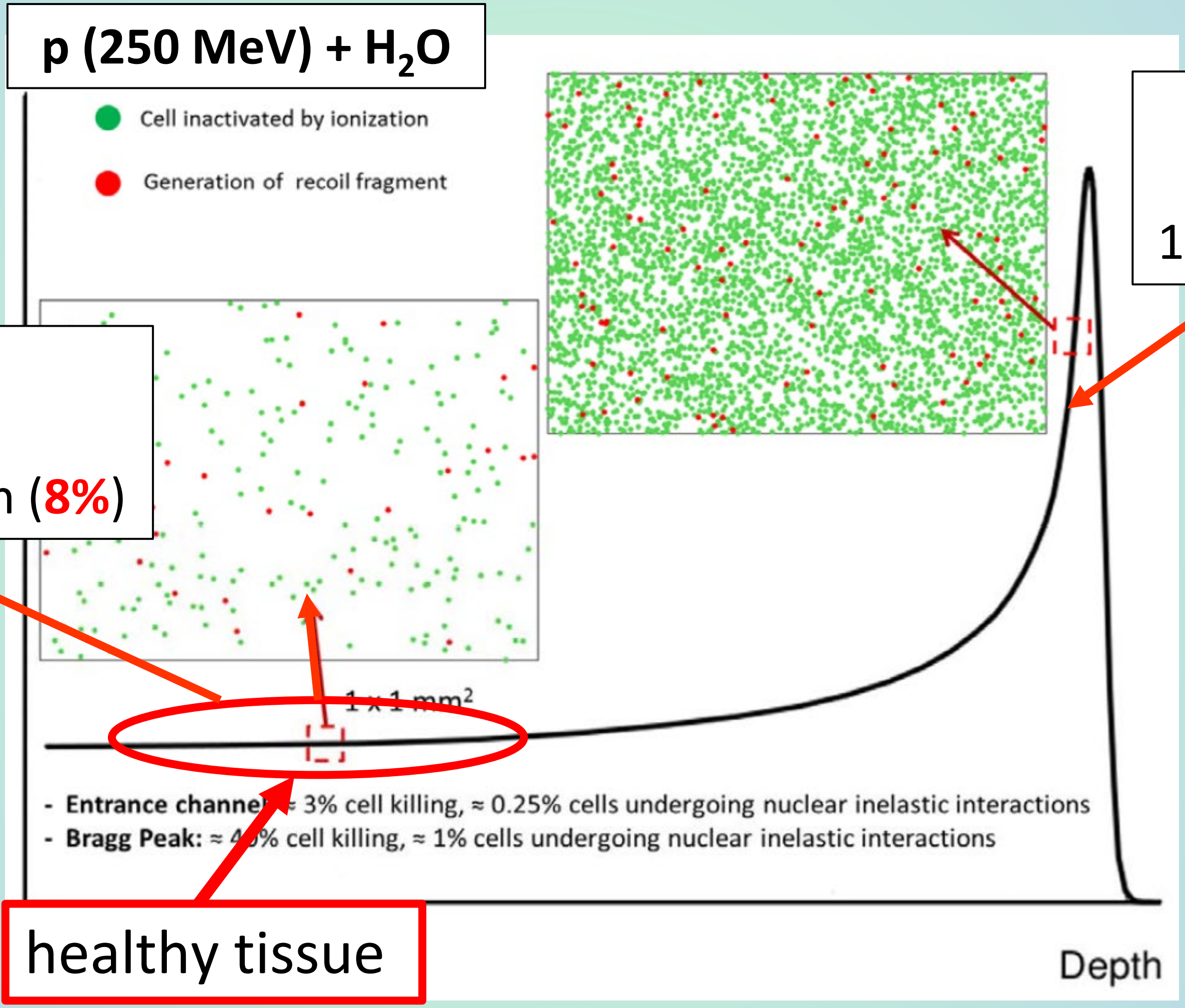


Projectile fragmentation



$$-\frac{dE}{dx} \sim \frac{z^2}{\beta^2}$$

Quntification of nuclear interaction



Bragg Peak:
40% cell killing
1% from nuclear reaction (**2%**)

Entrance channel:
3% cell killing
0.25% from nuclear reaction (**8%**)

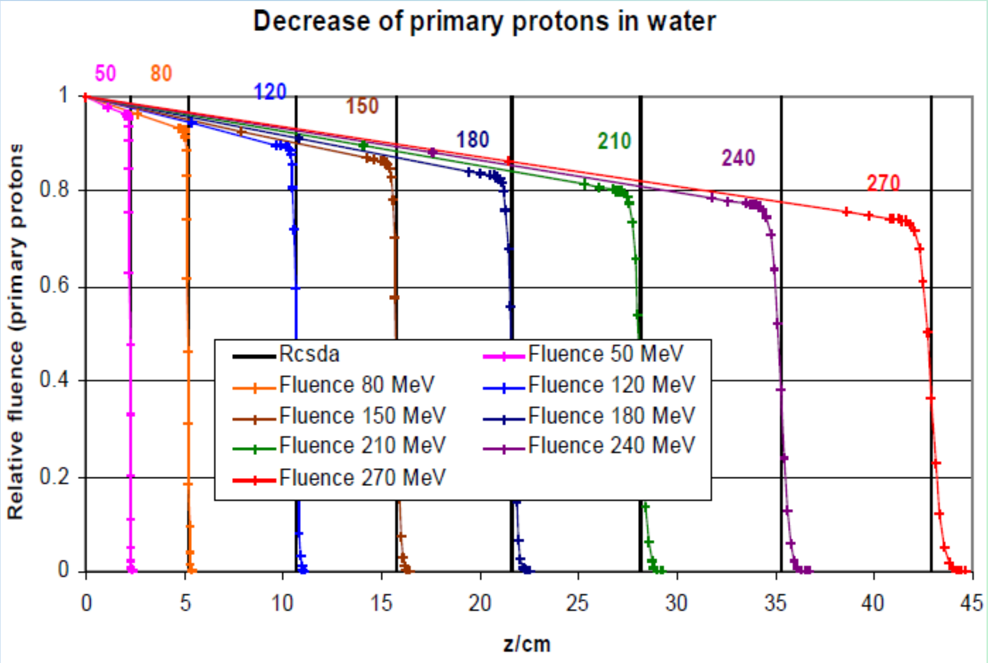
healthy tissue

Tommasino, Durante, "Proton Radiobiology"
Cancers **2015**, *7*, 353-381;
doi:10.3390/cancers7010353

^{12}C absorption in water

Carbon interaction

protoin interaction



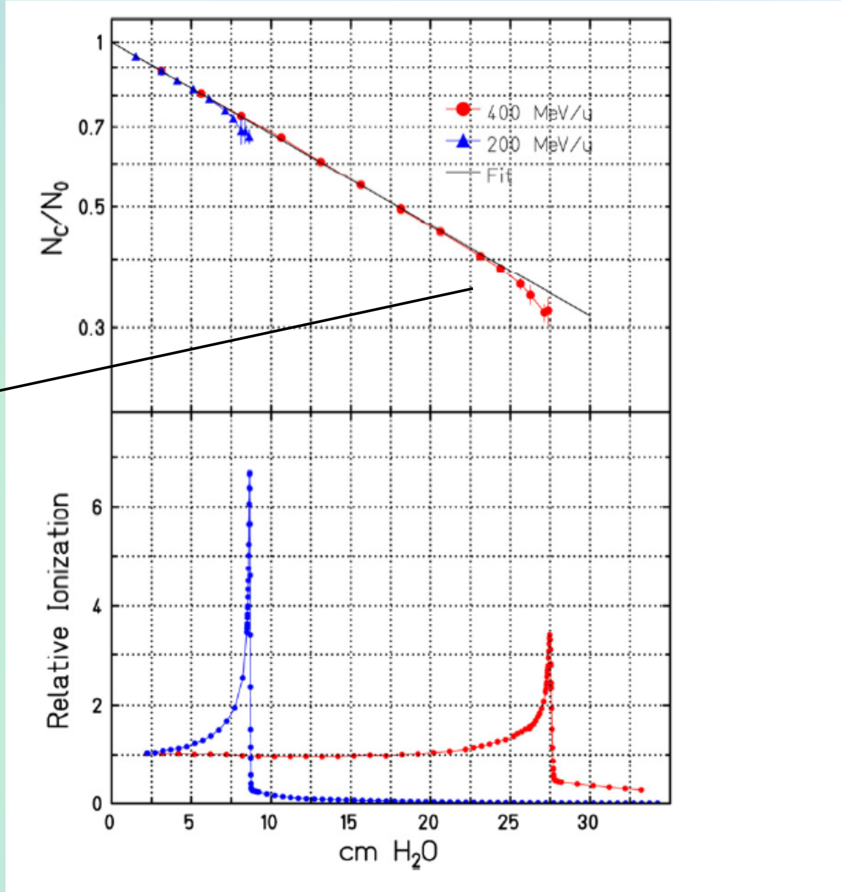


Figure 5. Measured attenuation of a carbon beam in a thick water absorber (upper part) and measured Bragg curves of ^{12}C ion beams of 200 MeV/*u* and 400 MeV/*u* (lower part).

70% of ^{12}C had nuclear interaction

p (50 MeV) decrease 5%
p(270 MeV) decrease 25%

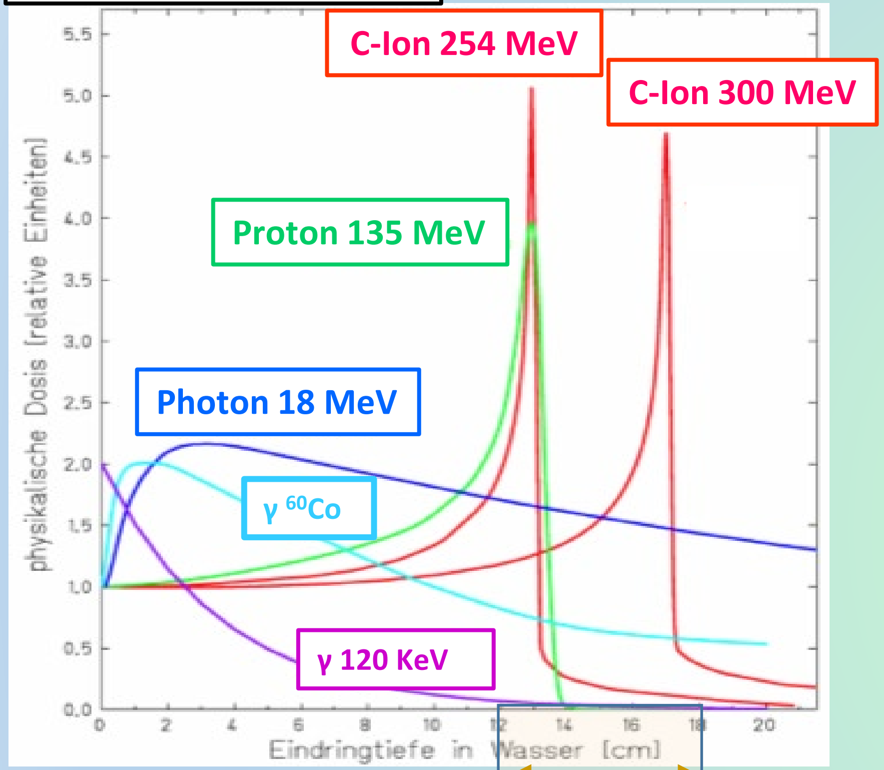
Journal of Nuclear and Particle Physics 2012, 2(3): 42-56 DOI: 10.5923/j.jnpp.20120203.04

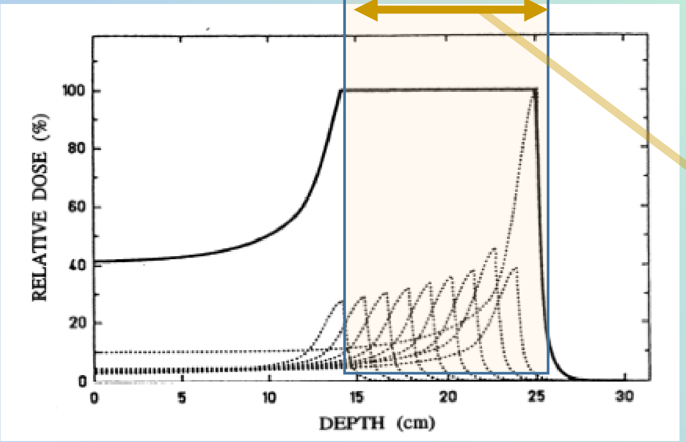
E Haettner, H Iwase, M Kramer, G Kraft and D Schardt,
"Experimental study of nuclear fragmentation of 200 and 400 MeV/*u* 12C ions in water for applications in particle therapy"
Phys. Med. Biol. **58** (2013) 8265–8279 doi:10.1088/0031-9155/58/23/8265

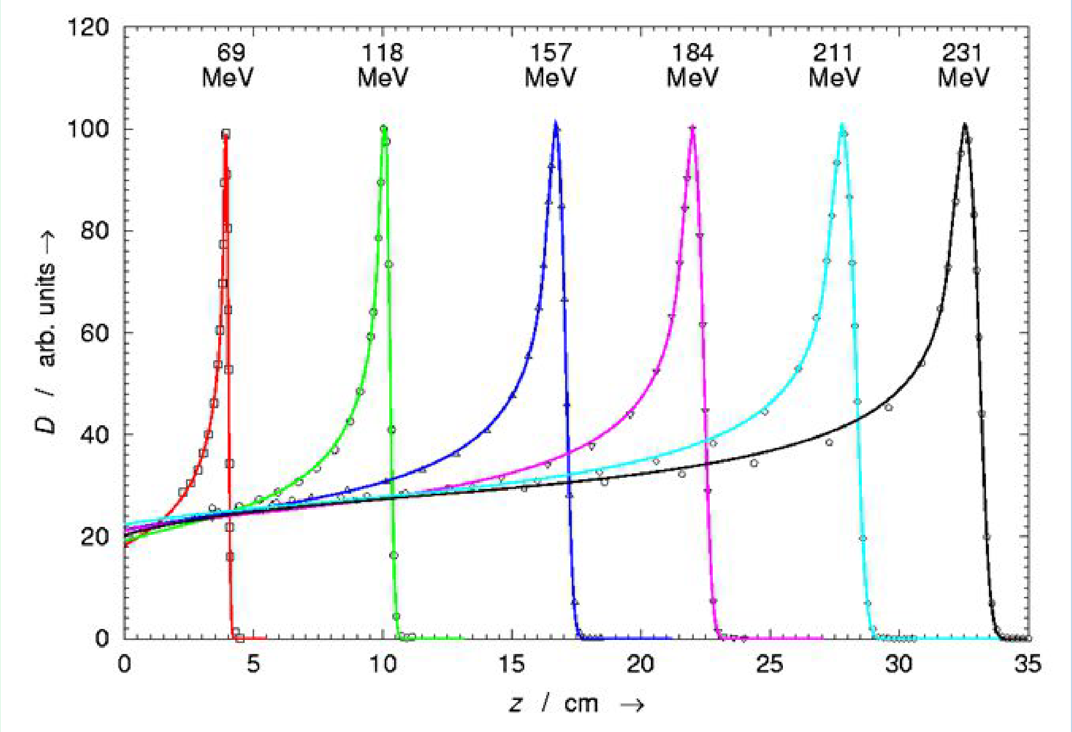
Spread Out Bragg Peak (SOBP)

Cover the tumor region scanning in energy (z) and position (x,y)

dE/dx vs depth



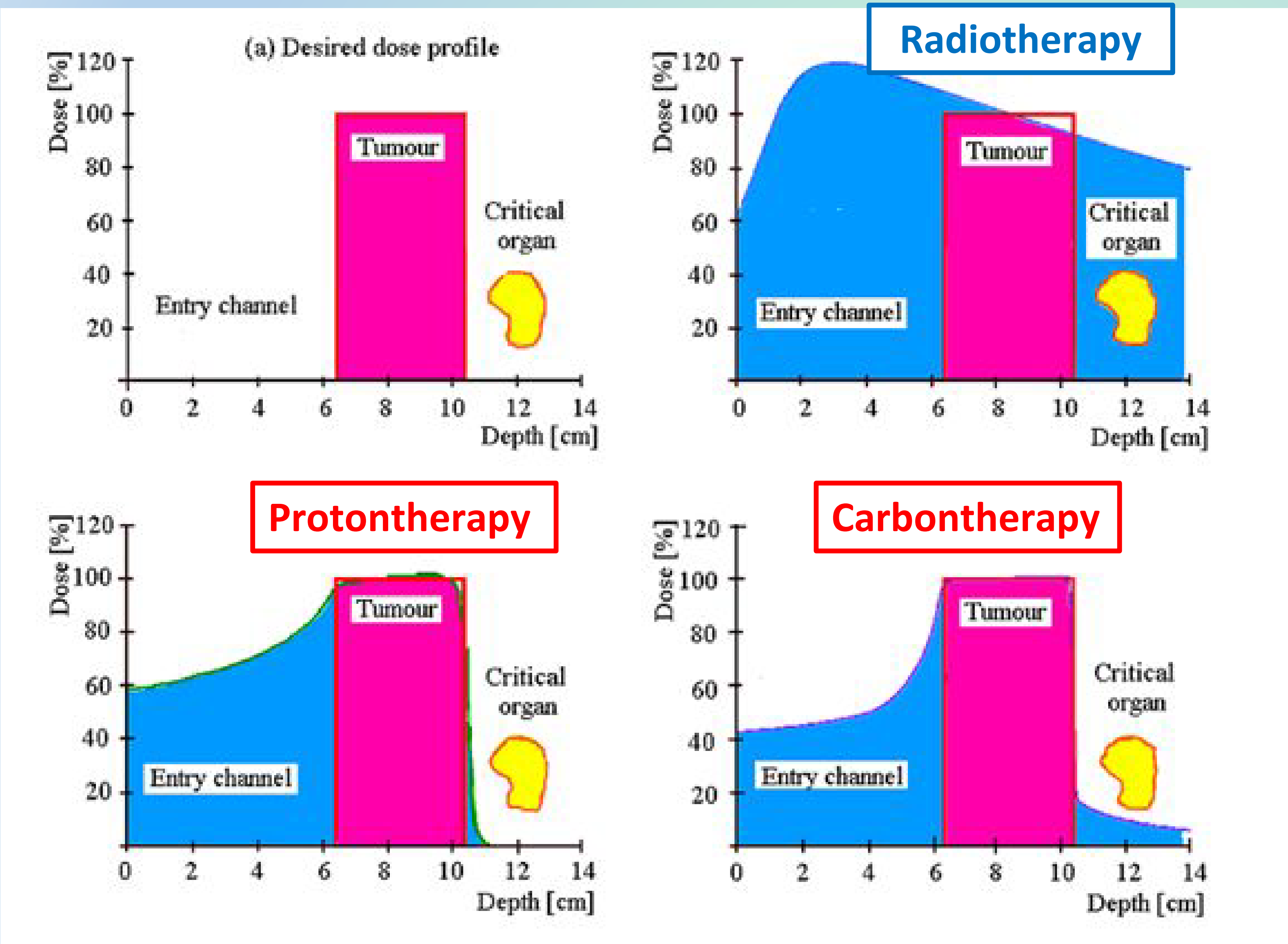


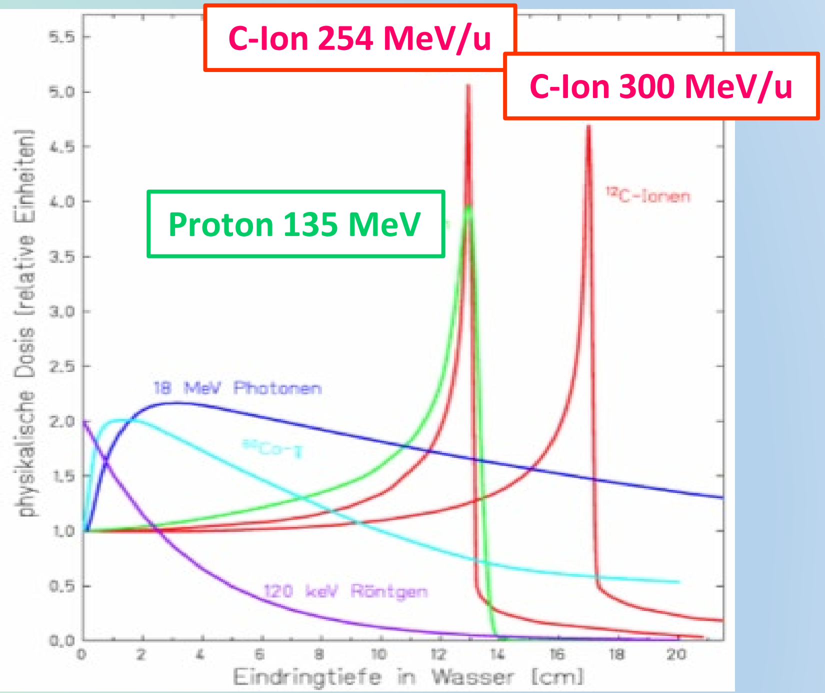


Energy spread for a longitudinal dimension of 5 cm → ~ 20 MeV

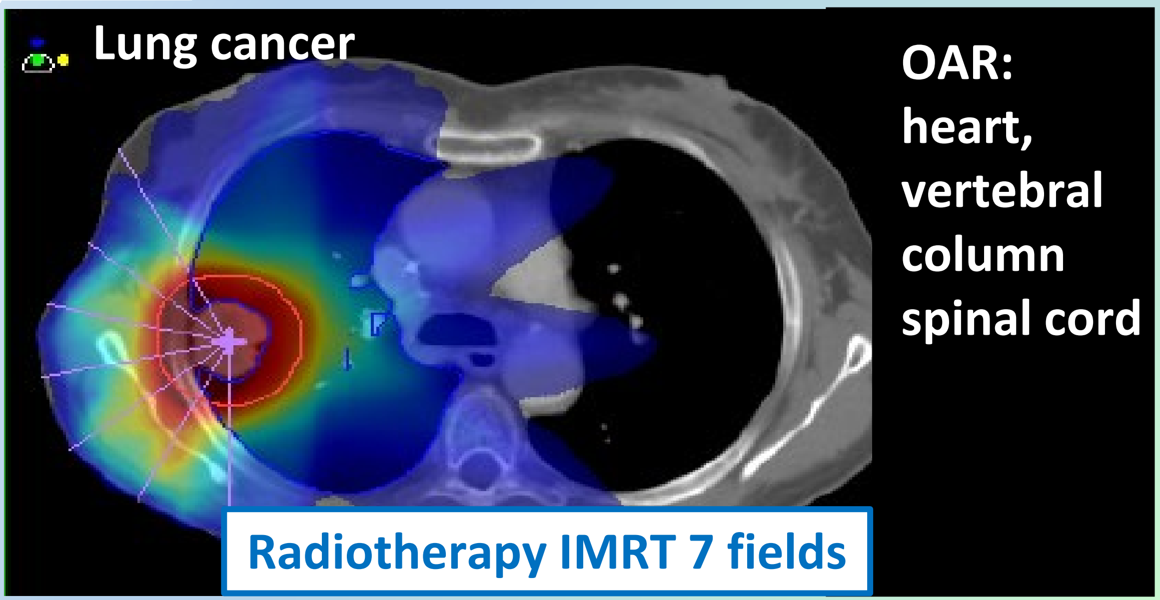
Size of the tumor region

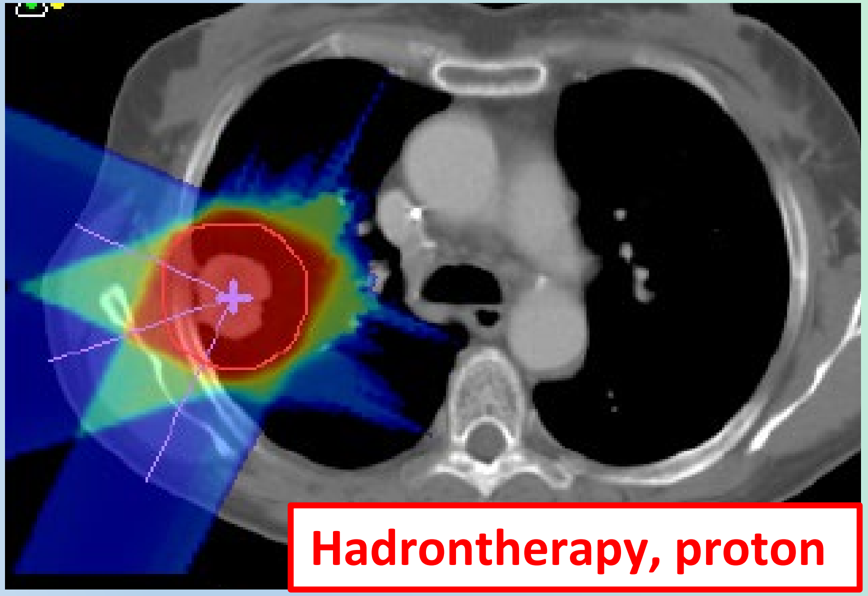
Critical organ

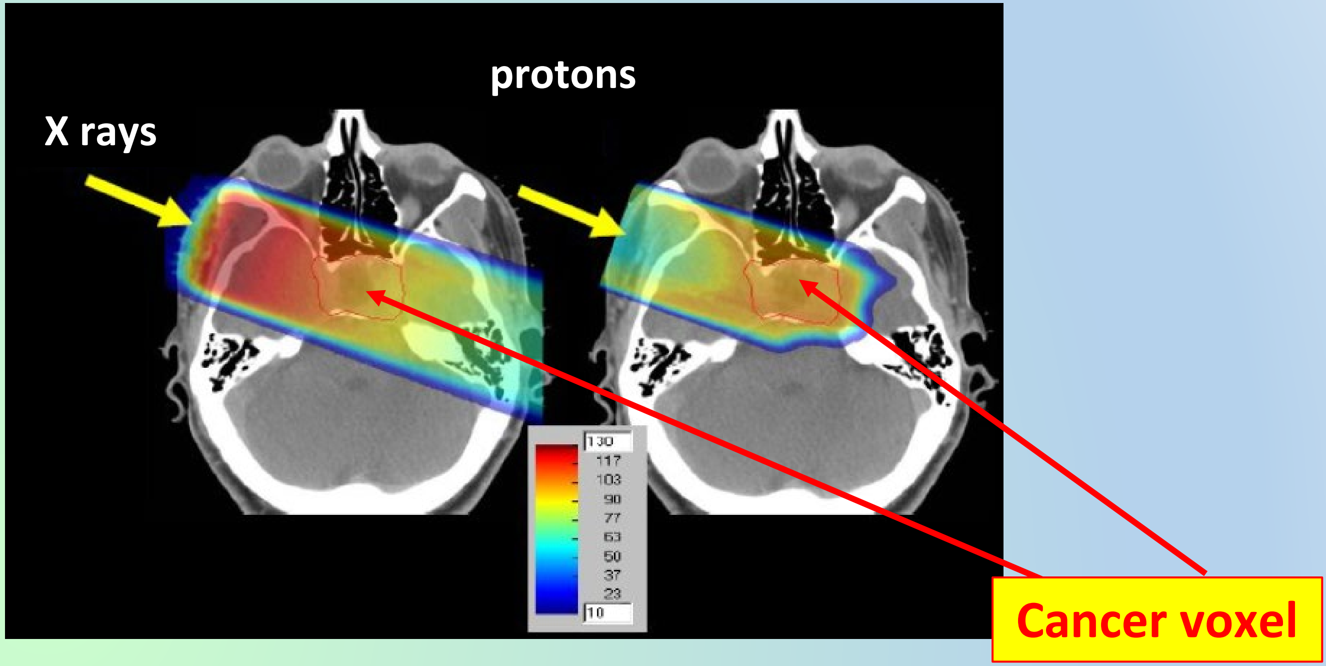




Hadrontherapy vs radiotherapy, 1







Pro and contra

- Hadrontherapy: the released dose is better focused;
- Hadrontherapy: less dose before and after tumor region
- Costs:
  - accelerator for Hadrontherapy ~15-250 millions euros
  - Machine for radioterapy: units of milion euros
  - Treatment more expensive than radiotherapy

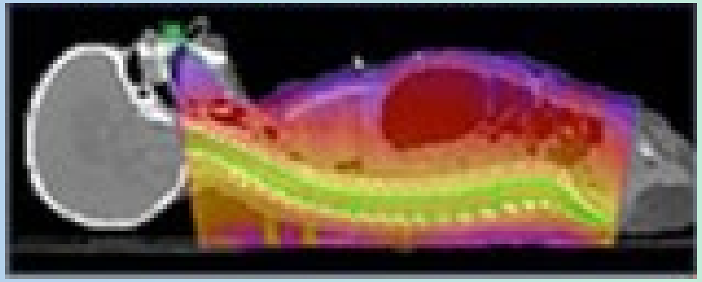
Different fields to decrease the energy deposition in the same region before cancer

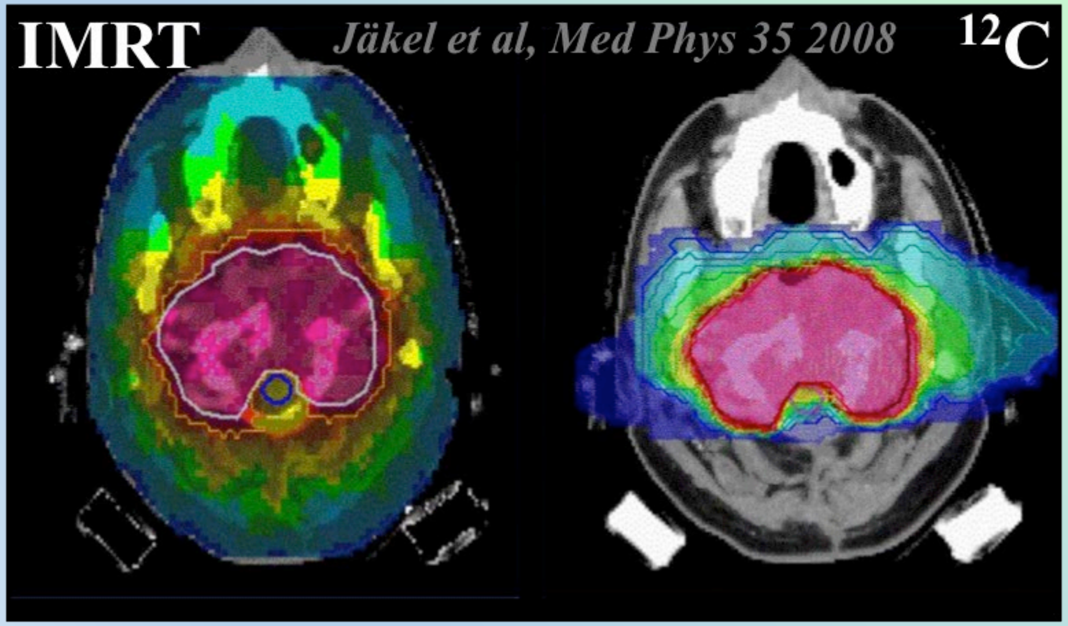
Hadrontherapy vs radiotherapy, 2

Cancer on vertebral column

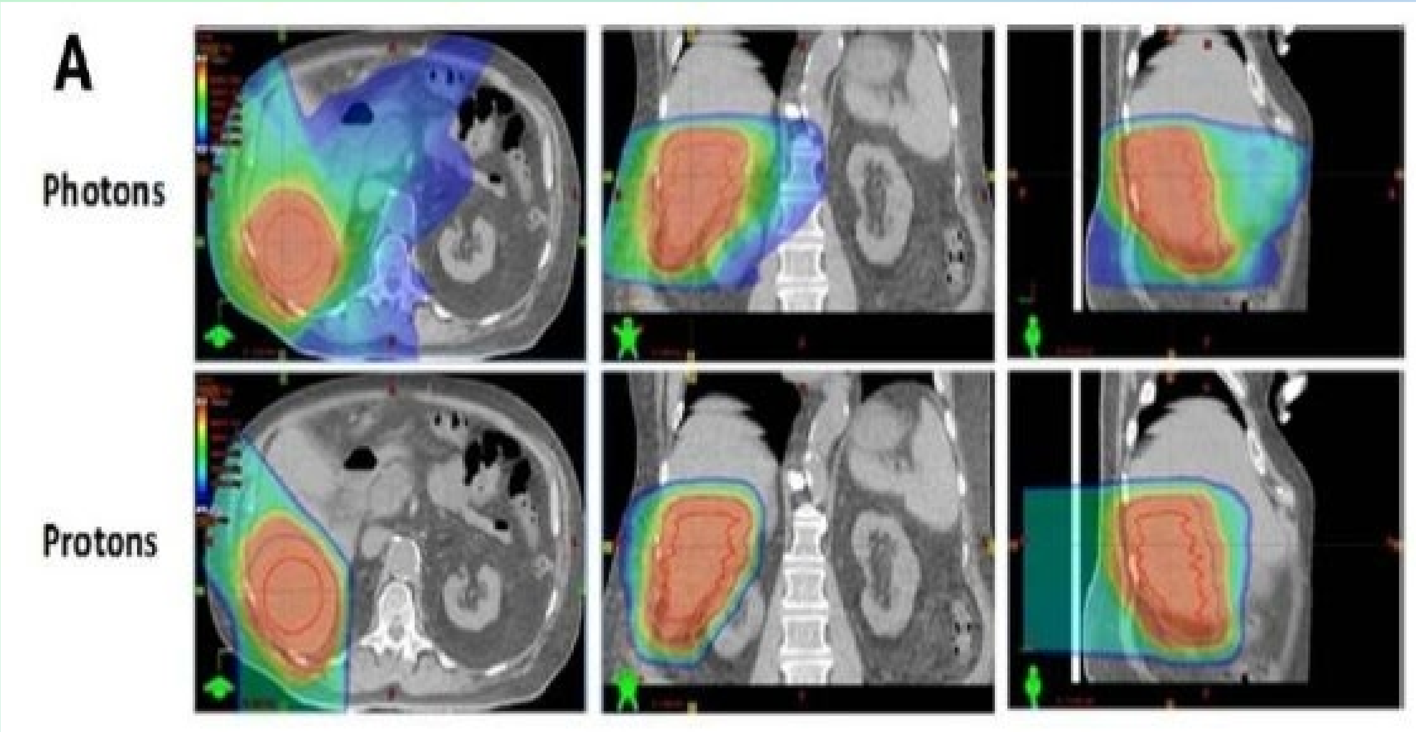
HADRONTHERAPY

CONVENTIONAL RADIOTHERAPY



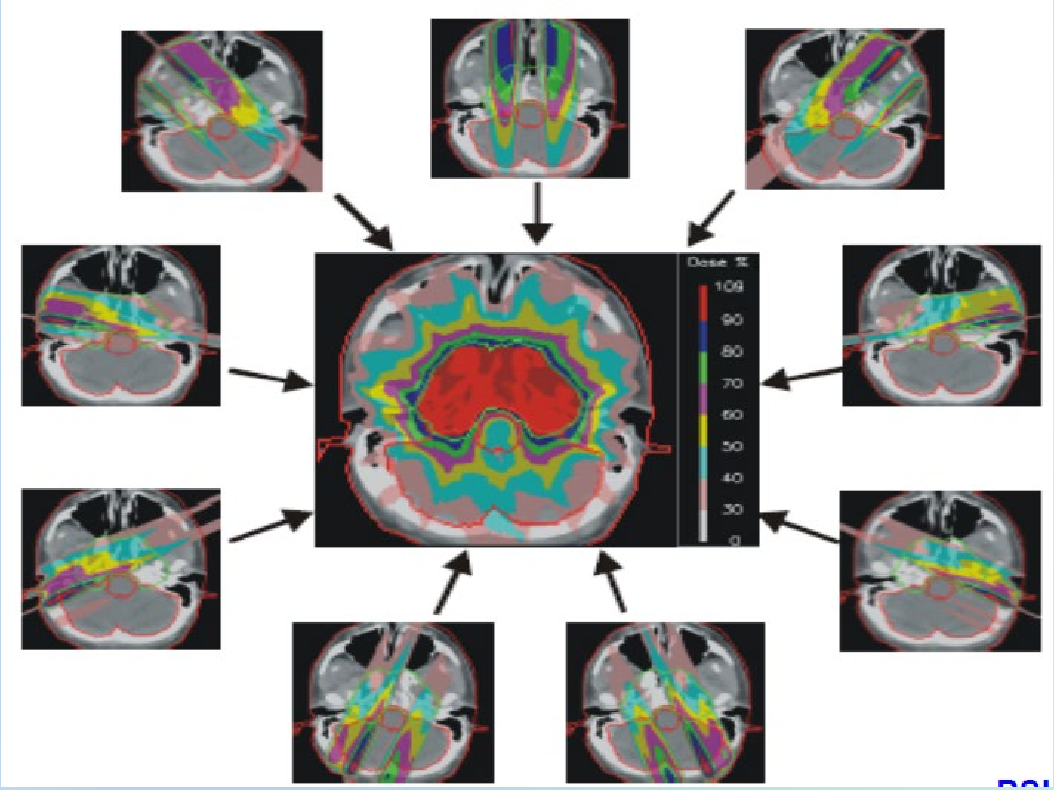


Cancer on lung (organ at risk: heart, vertebral column, spinal cord)



Photon, proton, Carbon Ionization inside human body

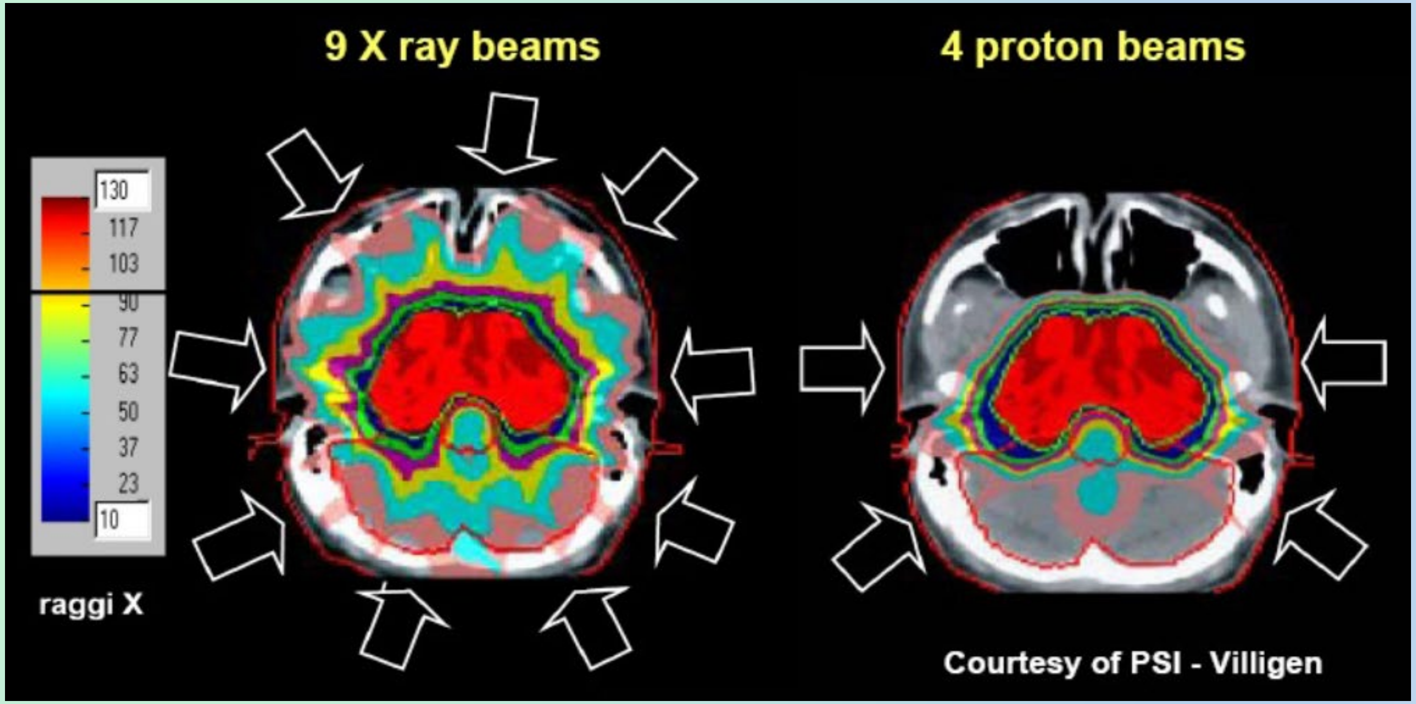
IMRT (Intensity Modulated Radiation Therapy) with photons with 9 non uniform fields



60-75 Gy given in 30-35 fractions (6-7 weeks)

X rays

Protons 200 MeV



Normalized to the same deposited energy on cancer volume.
Protons better spare healthy tissues

Do you want some number? Here it is

Local control rate → to keep the tumor under control

bones
cartilage
Nose pharynx
Nervous system
eye
nose cavity
pancreas
hepato
salivary gland
soft tissue

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

Geneva - 16.10.13 - UA

Radiobiology

Radiobiology, Dosimetry

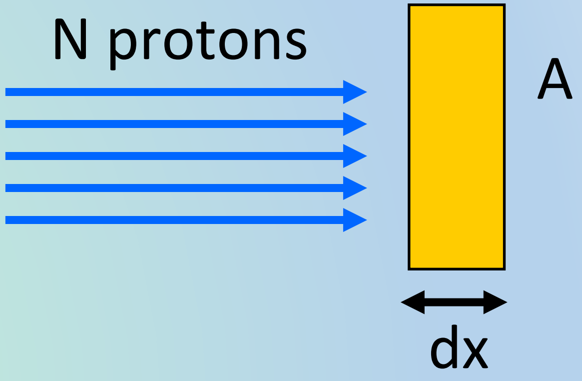
Goal: quantify the given radiation → quantify the given energy → evaluate the effect

Fluence

Protons/cm^2

$$\Phi = \frac{dN}{dA}$$

- dN → Number of particles (ad ex. protons in a beam)
- dA → Infinitesimal area ⊥ to the beam



Fluence rate

Protons/cm^{2}s

$$\dot{\Phi} = \frac{d\Phi}{dt}$$

Dose

$$D = \frac{dE}{dm}$$

absorbed energy dE (given by radiation) per mass unit dm (it does not take into account the biological effects)

In SI the unit is **Gray** = 1 J kg^{-1}

$$D = \frac{dE}{dm} = \frac{\left(\frac{dE}{dx}\right) \times \Delta x \times N}{\rho \times \Delta x \times A} = \Phi \frac{\left(\frac{dE}{dx}\right)}{\rho}$$

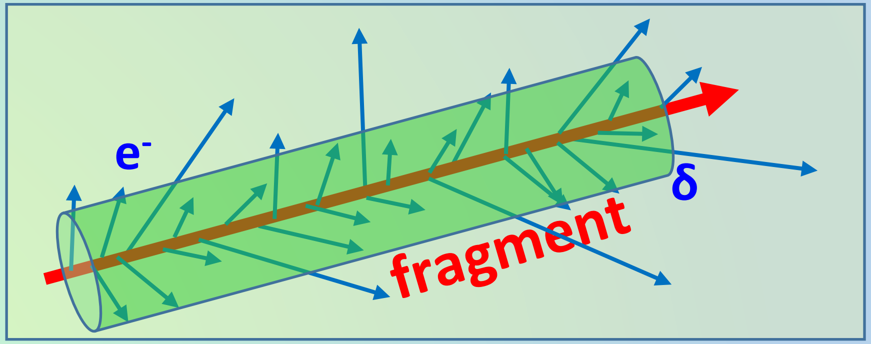
Link between the number of particles and the released dose

Linear Energy Transfer L.E.T.

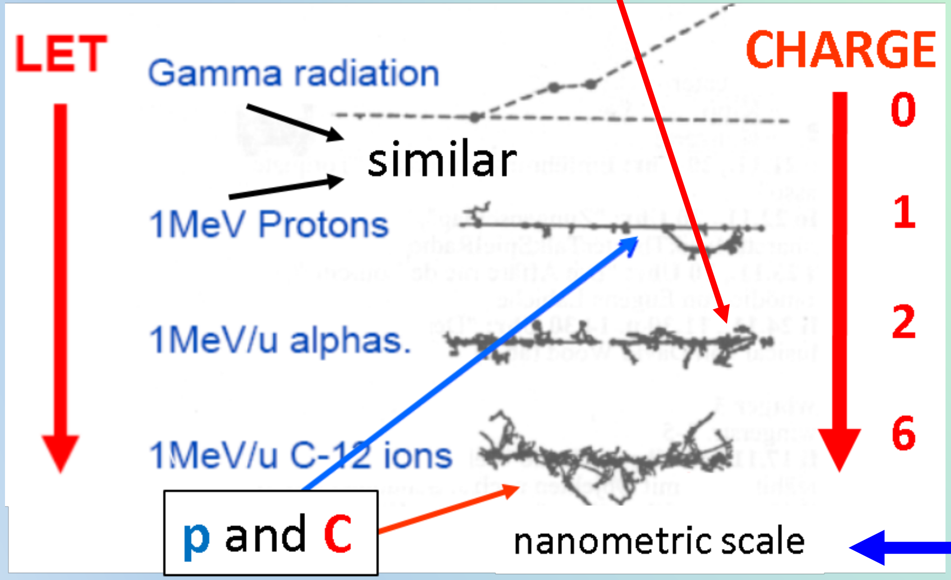
$$L.E.T = -\frac{dE}{dx}$$

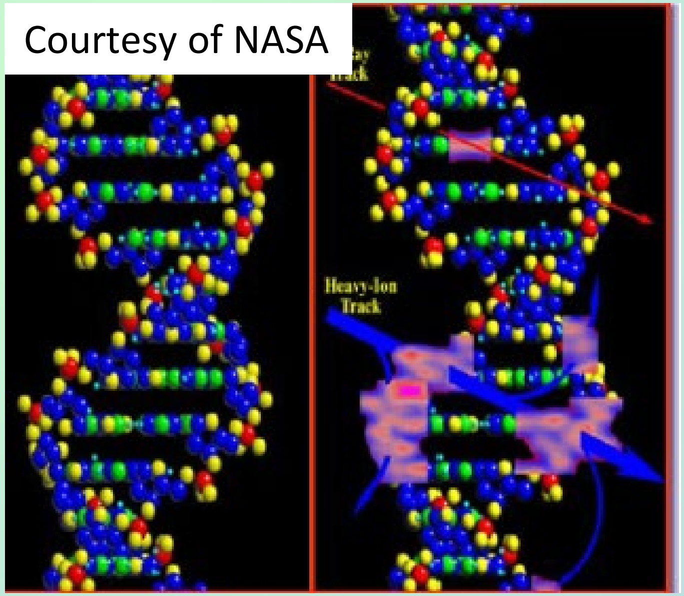
Energy lost by radiation

= Bethe Bloch, but exclude the secondary electrons with long range



crucial the density of the energy deposit





nanometric scale

Higher projectile charge

Higher damage

But

know nuclear interaction at medical energies

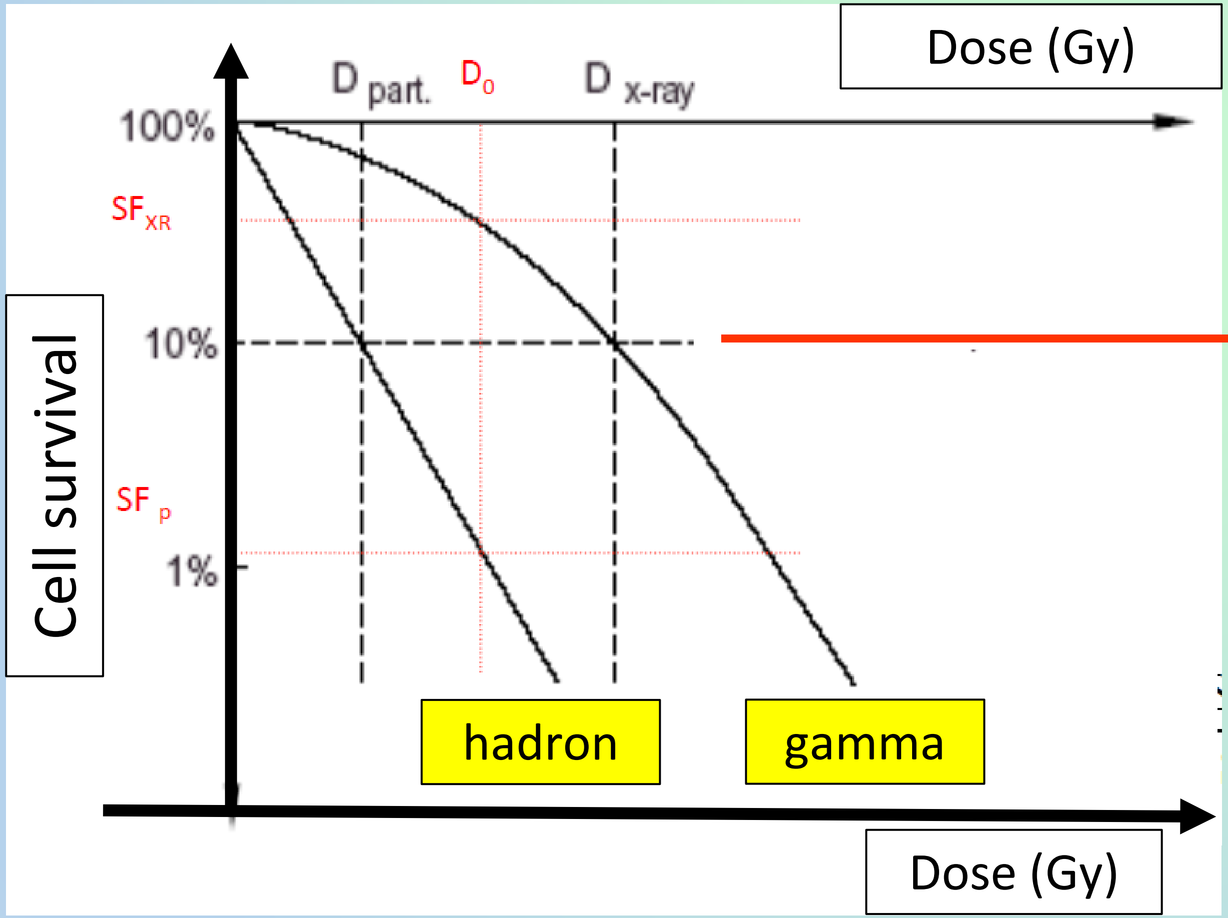
Double strand break → probable irreparable damage

Relative Biological effectiveness: RBE

$$R.B.E = \left(\frac{D_{X-ray}}{D_H}\right)_{Same\ effect}$$

pure number

The ratio between dose provided by gamma and the one provided by hadrons to obtain the same effect (at a particular % of survival cells)



If RBE > 1 → hadrons more effective than Gamma

for example fixing 10% of survival cell, $D_{hadron} < D_{gamma}$

In general for hadrons RBE > 1

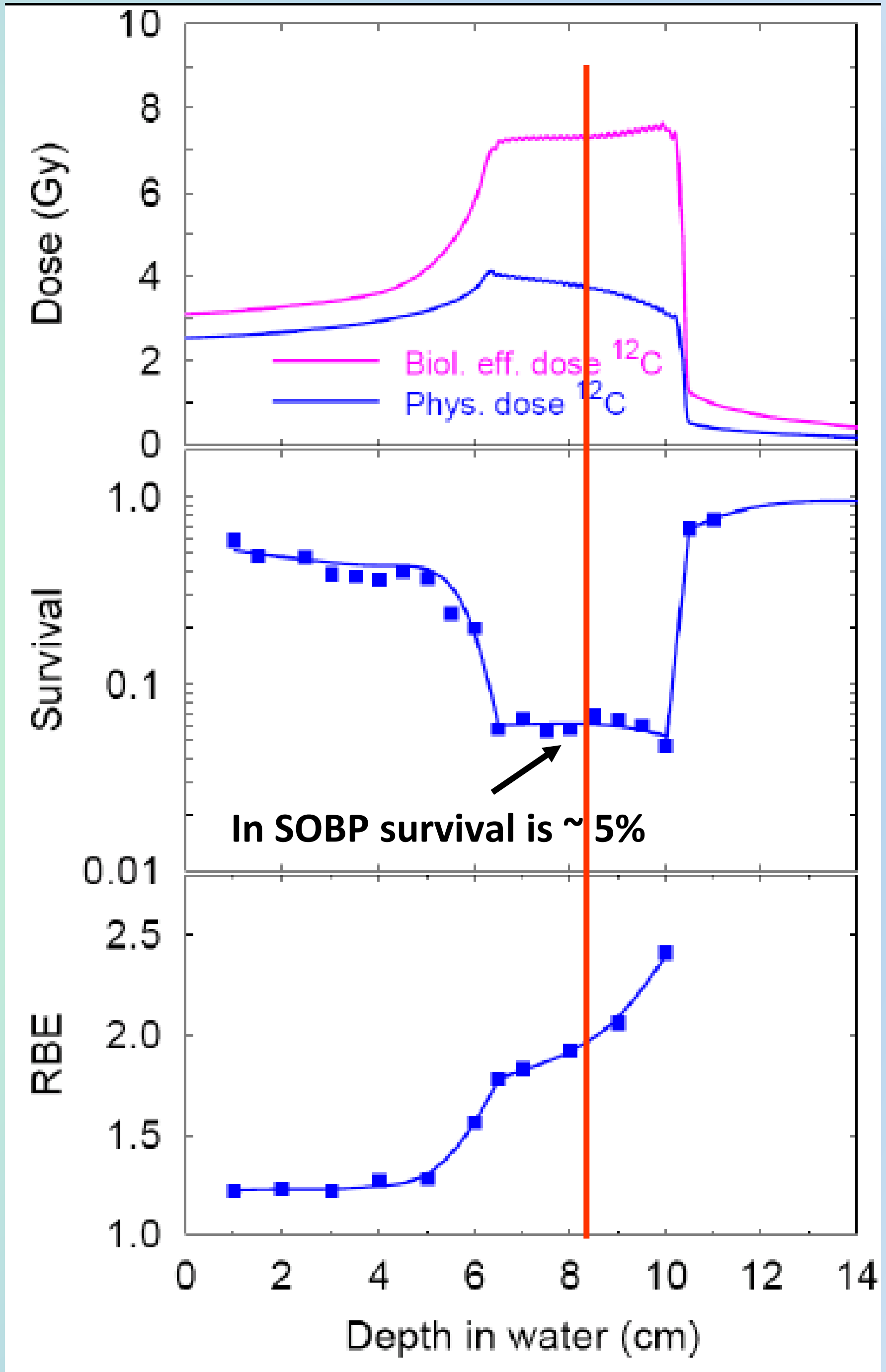
RBE for hadrons

Particle	RBE
Gamma	1
Protons	~ 1.1
^{12}C	3 - 4
^{20}Ne	3 - 4

To be investigated (for example it does not consider the target fragmentation

Not so different from γ

Hadrontherapy has an effect 3-4 times than radiotherapy



Biologic damage proportional to

RBE x deposited energy

Not so easy to evaluate RBE, it depende on:

- type of radiation, energy, LET, cell, definition of survival …

OER: Oxygen Enhancement Ratio

Biological effect of radiation depends on the oxygen concentration:

- **Anoxia** (absence of oxygen)
- **Normal** oxygen concentration
- **Hyperoxia** (abnormal presence of oxygen)

To quantify this effect

↓

Oxygen Enhancement Ratio

$$\mathrm{O}.E.R = \left(\frac{D_{anoxia}}{D_{normal}}\right)_{Same\ effect}$$

adding Oxygen in the cancer voxel, the treatment effect increases

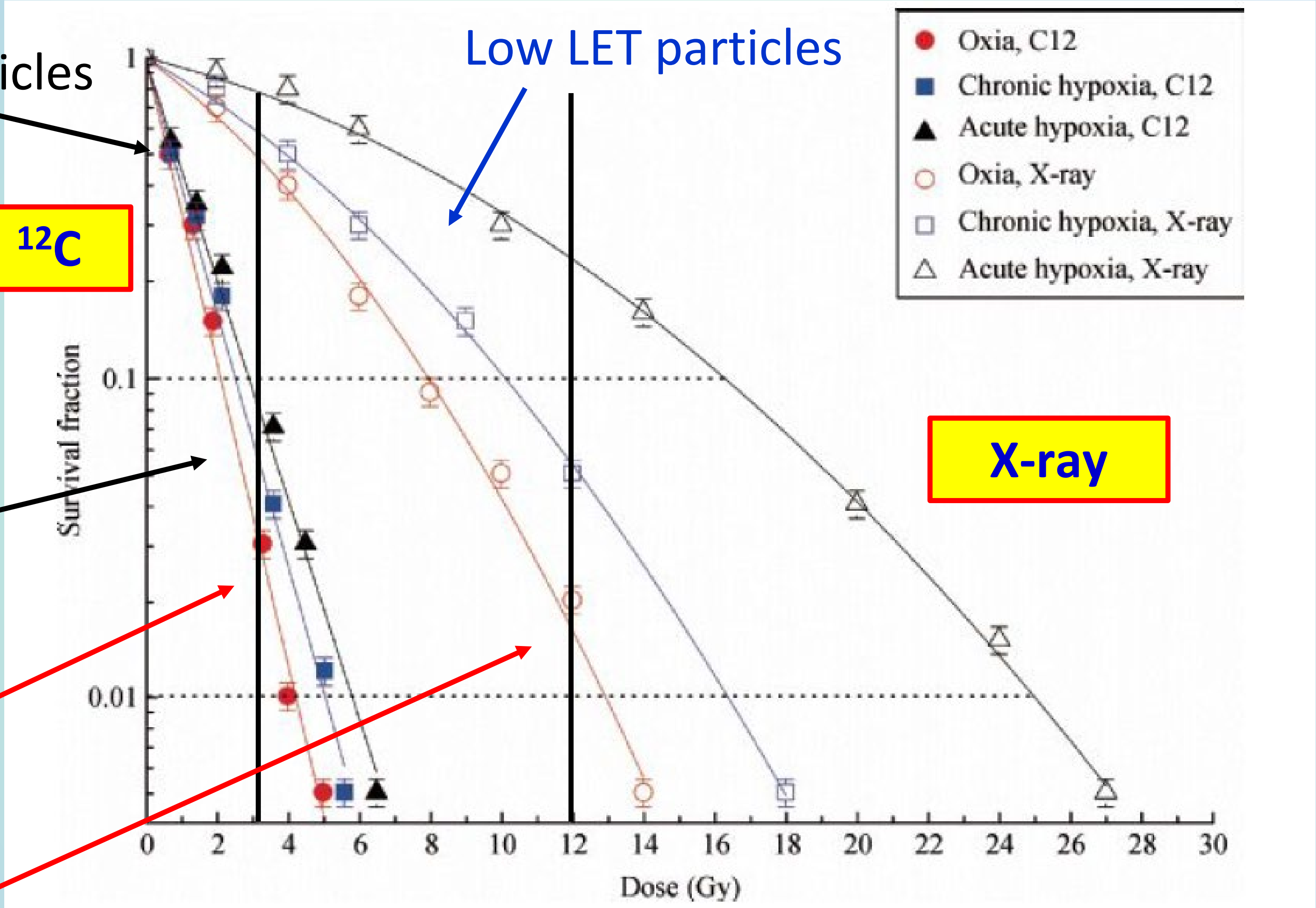
pure number

Linear quadratic model,experimental data

High LET particles

Low LET particles

hypoxia:
lack of oxygen



^{12}C

X-ray

Survival curve
~ single exponential: $Ae^{-\alpha D}$

Link free radical

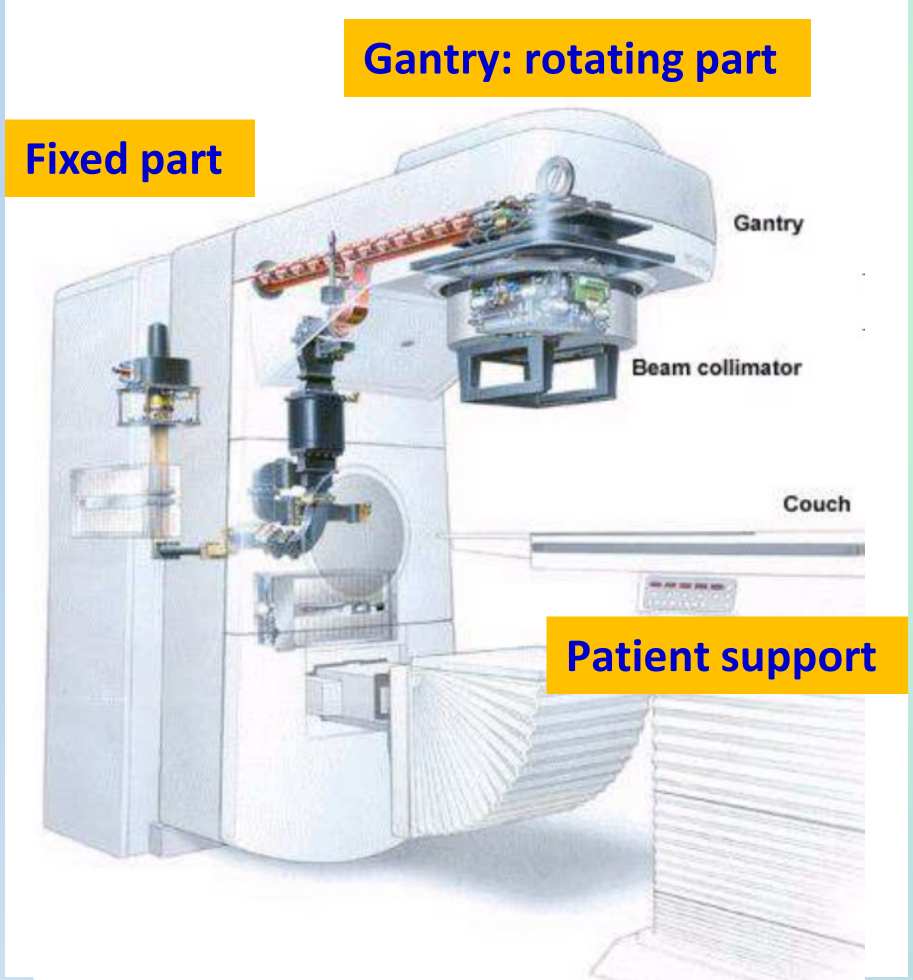
Higher the Oxygen, higher the damage

Larger Effect with low LET radiation:
high LET ionization is high → Oxigen effect smaller

Radiotherapy machine: linear accelerator

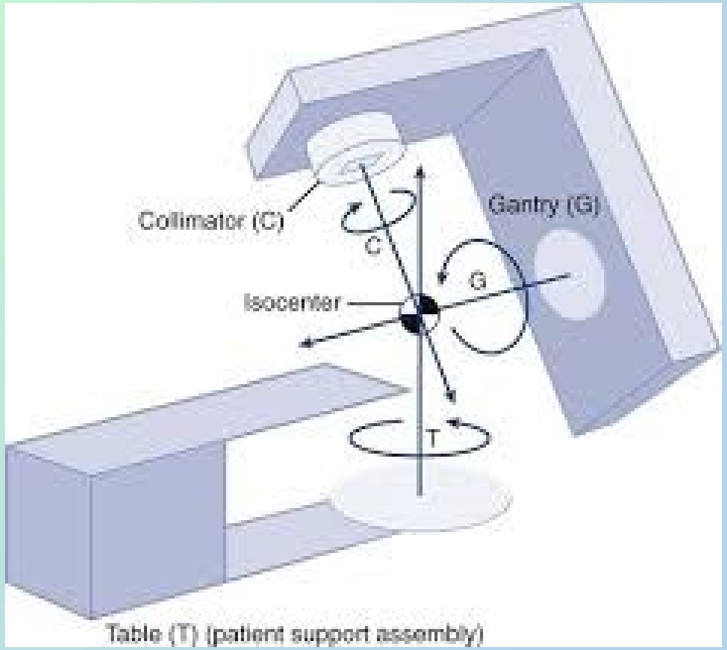
Provide e^- **beam** of various energy [4-25 MeV] or a **gamma** beam with max energy = e^-

Composed by 2 main parts



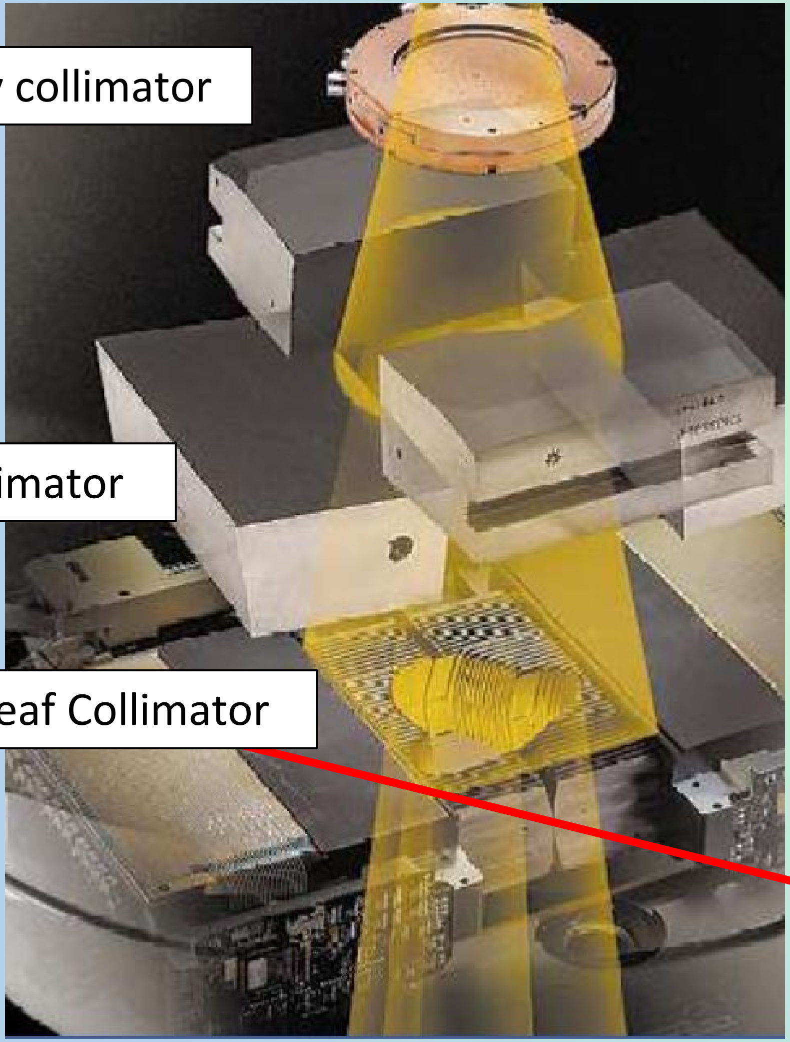
Isocenter: reference point for treatment, intersection between

- horizonthal rotation axis of the gantry
- Beam direction

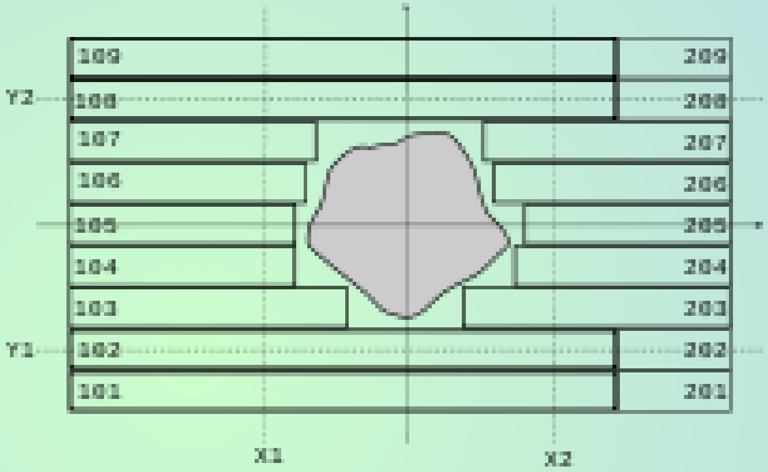


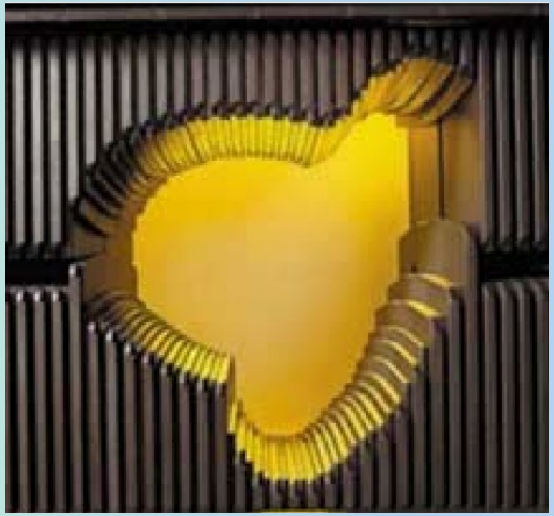
Gamma beam collimators

Collimator: high Z materials (Tungsten or Lead): they absorb the beam if they are crossed



They create the intensity modulated (IMRT)

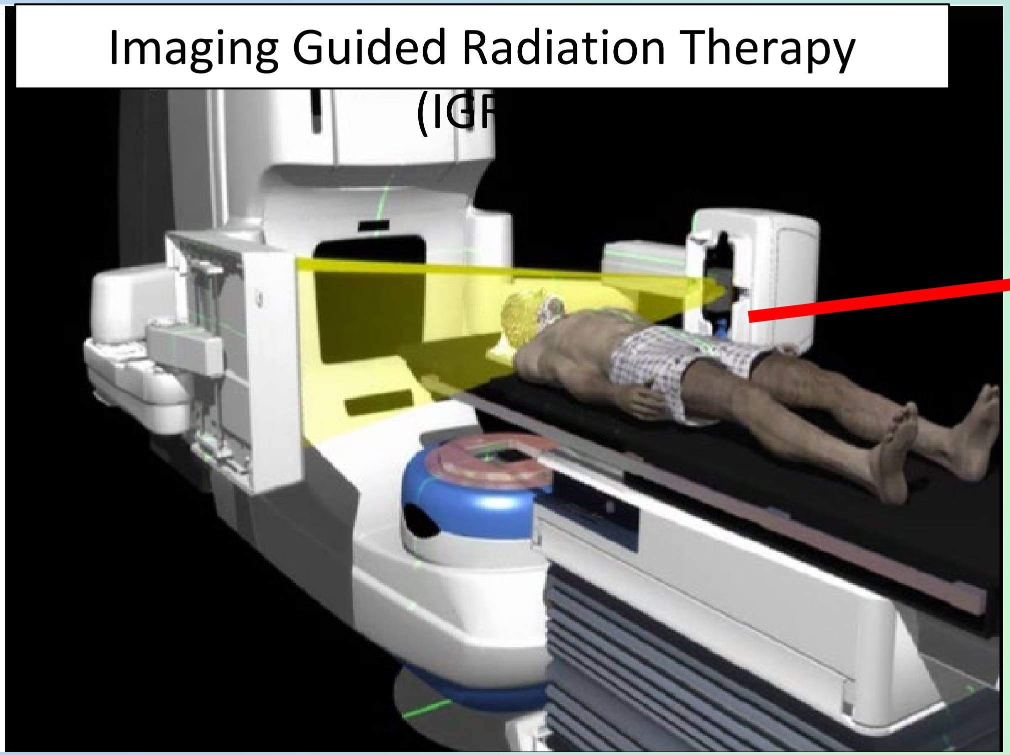


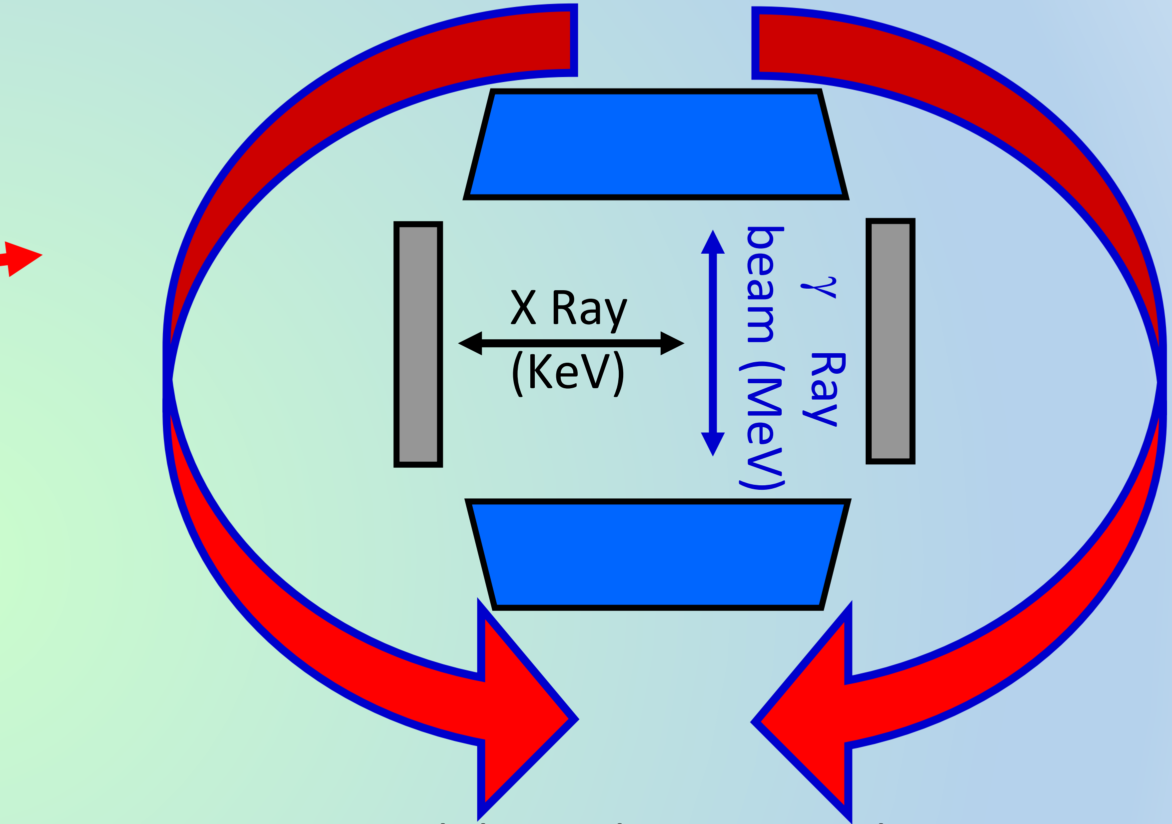


Heavy metal little plates (~120 leaves) with independent moving mechanism (120 computer controlled motors)

Crucial in IMRT: define the cancer shape (optimized for each patient)

IGRT Imaging Guided Radiation Therapy





Possibility to have 2 Simultaneous orthogonal slices from X Ray and beam

Sequence of treatment:

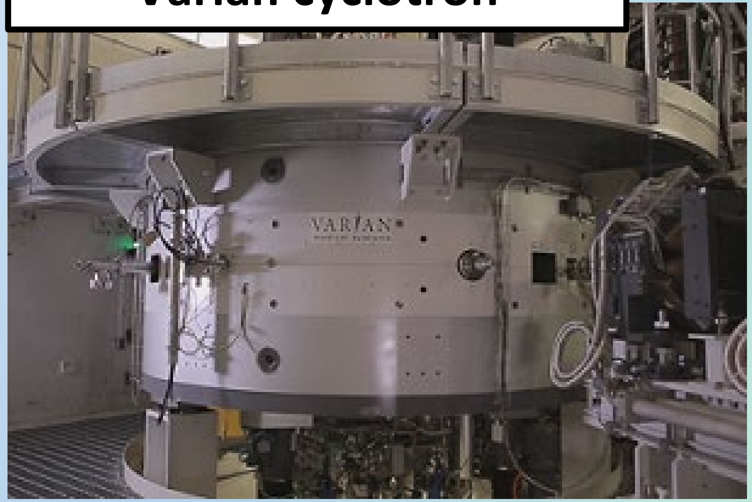
- X ray to scanning to have the patient position (TAC)
- Comparison of current position with the one in memory
- Correct the treatment considering the new position
- Treatment

< 2'

disadvantage: more dose on patient

Video

Varian cyclotron



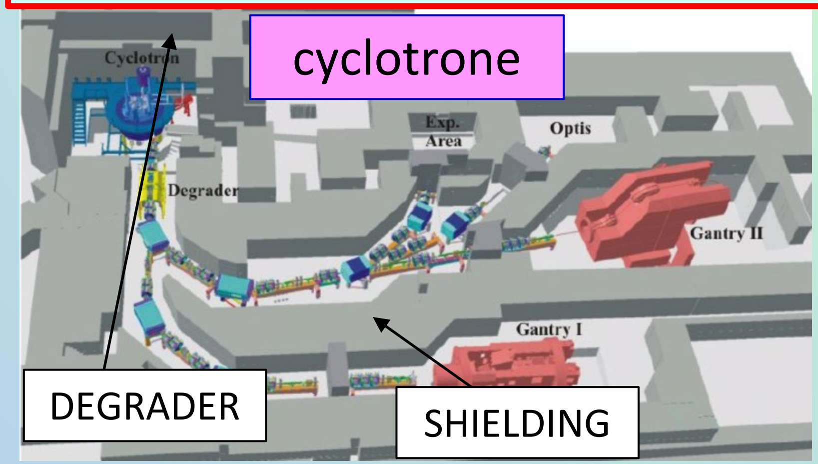
Hadrontherapy machines: Cyclotron & Synchrotron

Synchrotron at CNAO

cyclotron:

- Produce a monochromatic proton beam
  - Energy degrader → less precise and radiation
  - Different intensity independent of energy
- Low dimension
- Low cost

PROSCAN at PSI, Villigen (Zurich) Switzerland



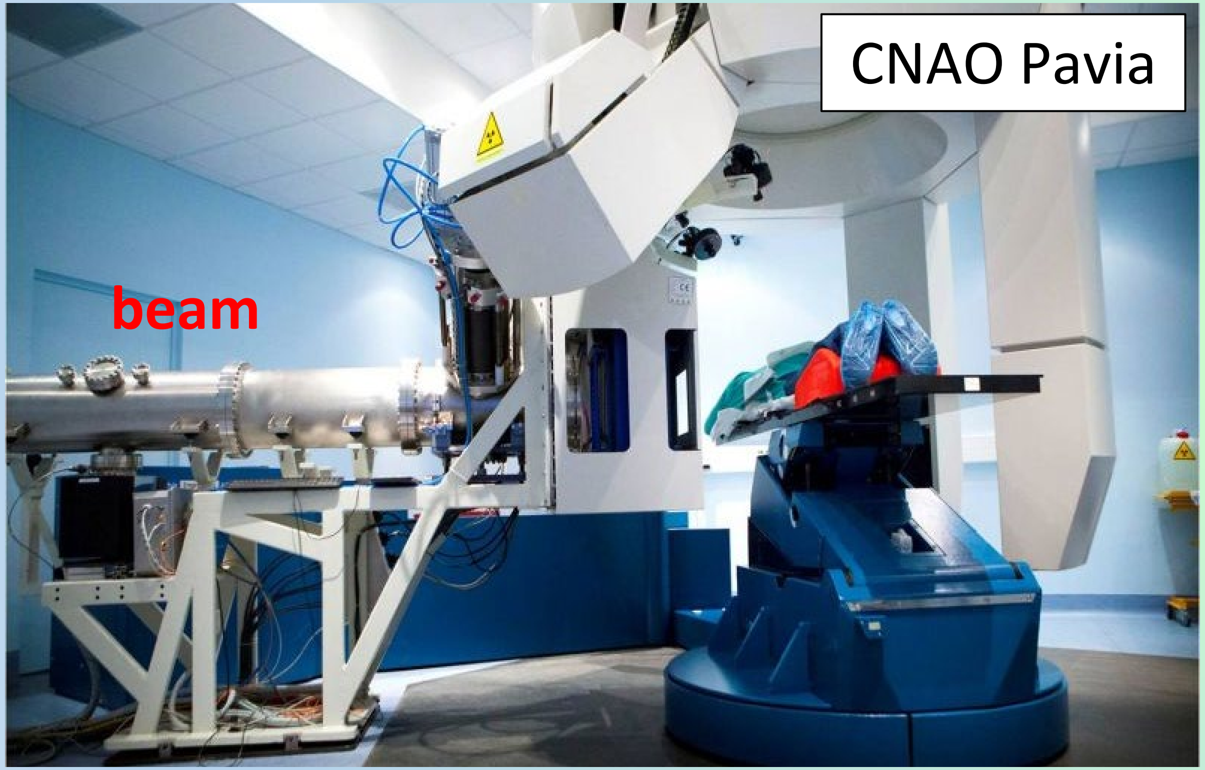
Synchrotron

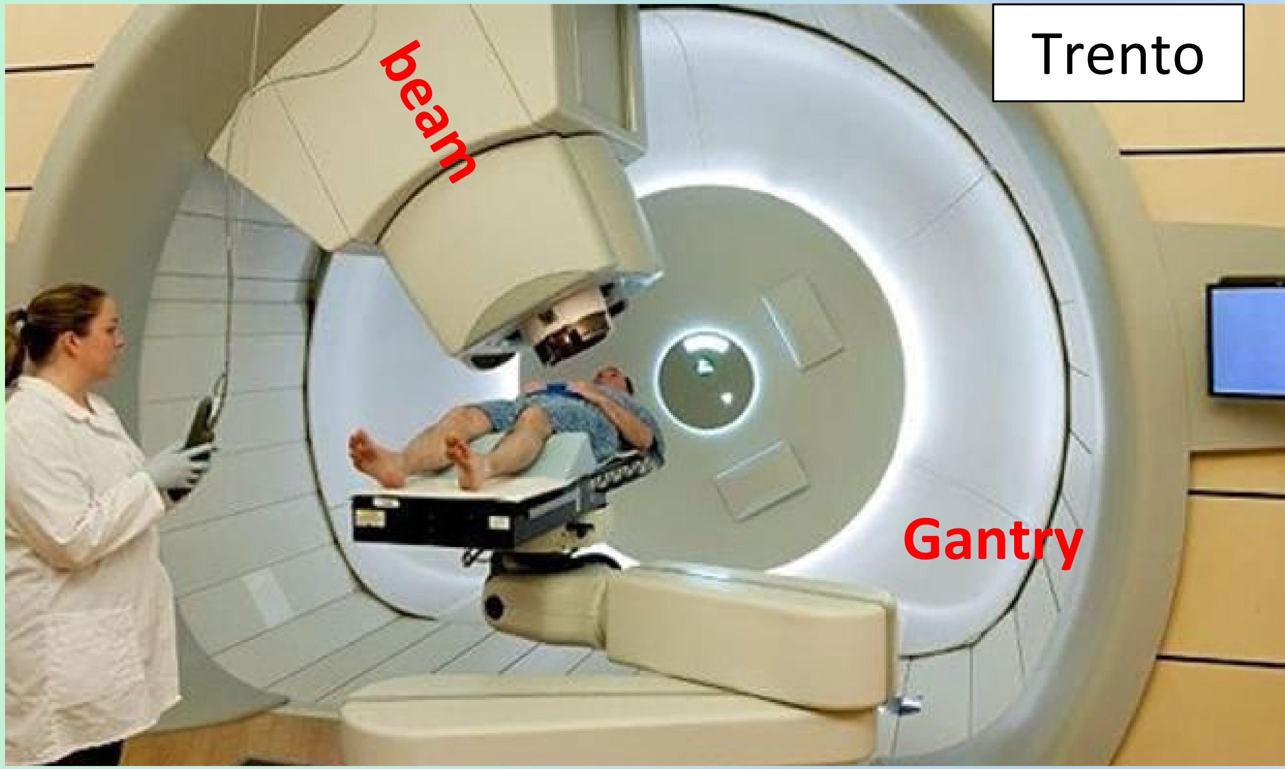
- Only machines in operation for heavy ions
- Beam of desired energy (till a limit)
- beam intensity independent of energy
- No radiation because no energy degrader
- Larger dimension
- Expensive

Video scanning path

Hadrontherapy in Italy

- CNAO: they use synchrotron with no gantry (construction synchrotron with gantry)
- TRENTO: they use cyclotron plus Gantry





CNAO till 2022: > 4000 patients

TRENTO till 2022: > 2000 patients

Italy till 2022: > 6000 patients

BNCT: Boron Neutron Capture therapies

Why Boron?:

- neutron capture cross section on ^{10}B **σ = 3.84 x 10^3 barn**

n; 5n+5p 2n+2p; 4n+3p

$n + {}^{10}B \rightarrow {}^{11}B^* \rightarrow \alpha + {}^{7}Li + \gamma$ (94%)

$\rightarrow {}^{11}B^* \rightarrow \alpha + {}^{7}Li$ (6%)

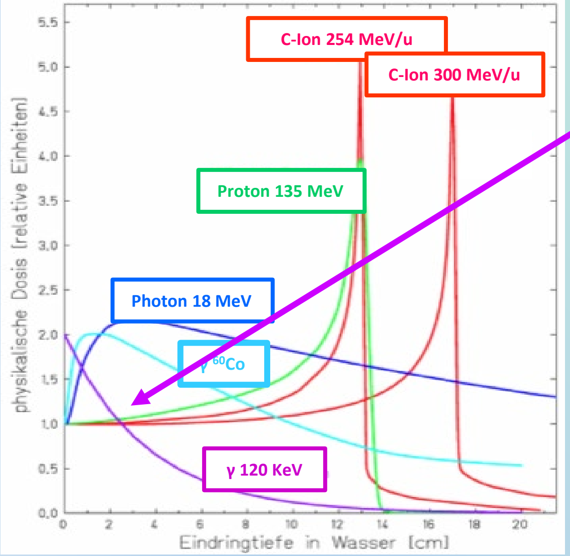
High ionization fragments

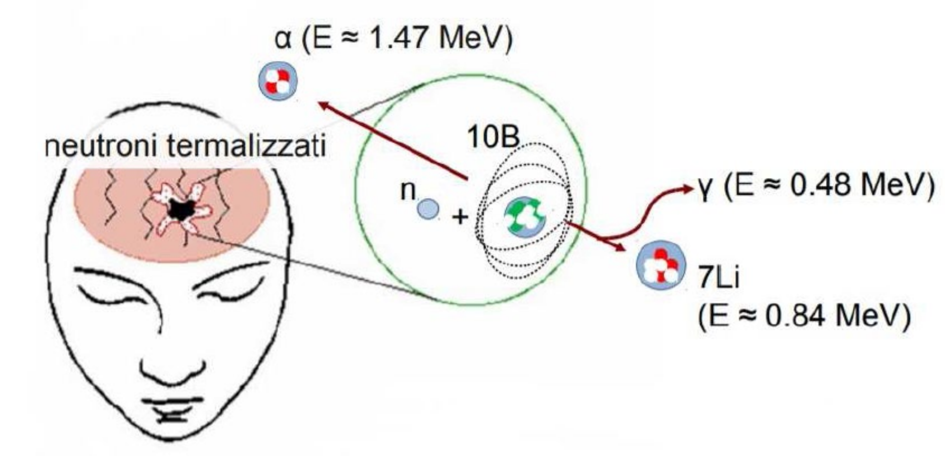
Undesired effect

E(α) = 1.47 *MeV*
E(^{7}Li) = 0.84 *MeV*
E(γ) = 0.48 *MeV*

E(α) = 1.78 *MeV*
E(^{7}Li) = 1.01 *MeV*

Range → 0
damage where they are produced

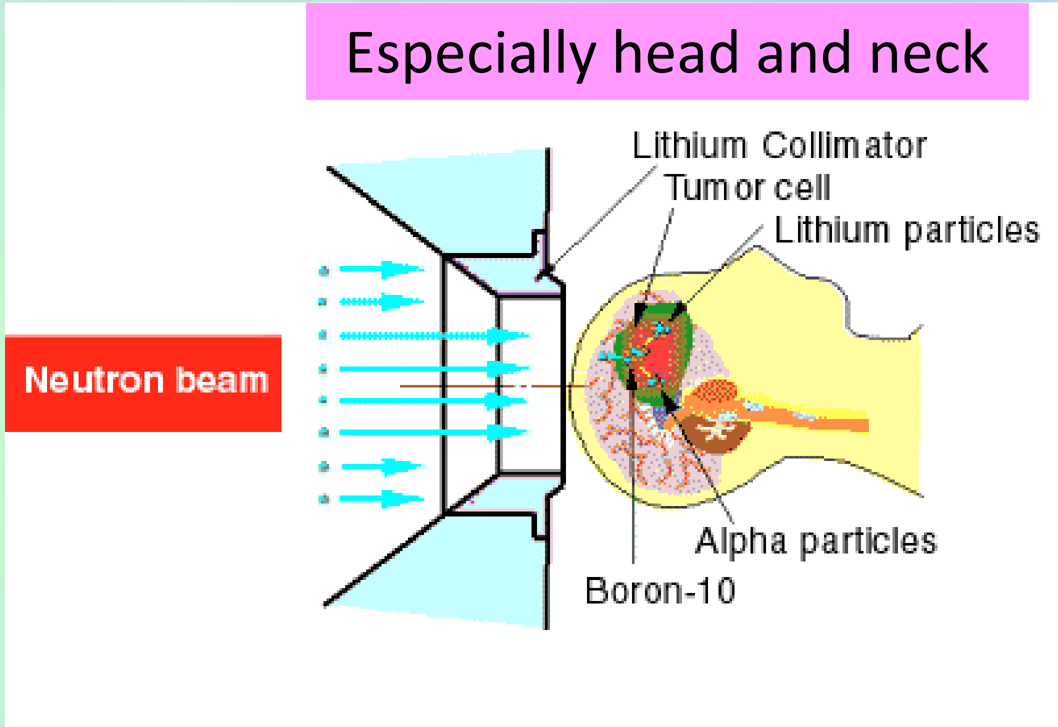




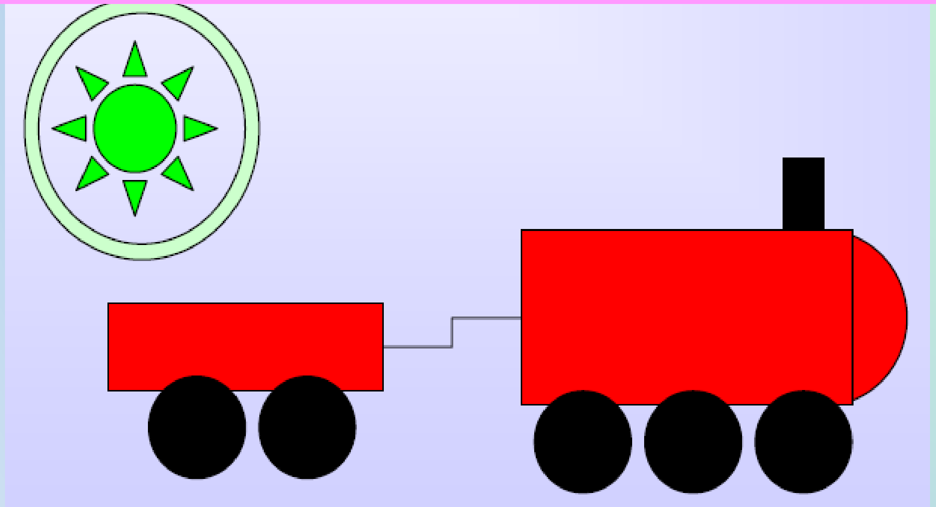
BNCT: Boron Neutron Capture therapy

Beam procedure:

- Thermal neutron (0.025 eV) provided by proton accelerator, heavy target and a degrader



(Boro)Fenilanina Vector aminoacid molecule



Target procedure:

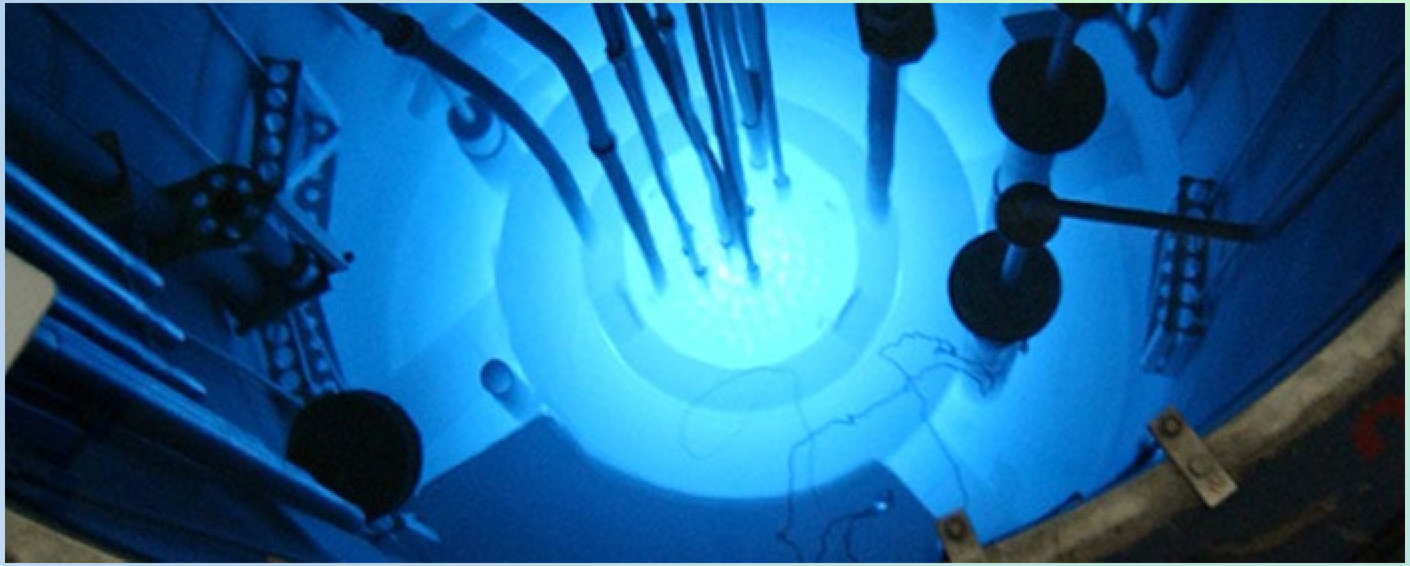
- ^{10}B inserted in aminoacid molecules
- Tumor enriched of ^{10}B
- tumor absorb > ^{10}B than healty tissues

A world premiere

In the early 2000s, at the Pavia hospital, to a man of 49 years old with colon cancer and many liver metastases, they enriched the liver with boron, explanted it, transported it to the LENA center (where there is a reactor for the production of neutrons), they irradiated it for 10 minutes and re-implanted it in the body. He lived for several years.

Another 40 years old man was treated in the same way, he died for other problems

<u>L.E.N.A. - Laboratorio Energia Nucleare Applicata</u>

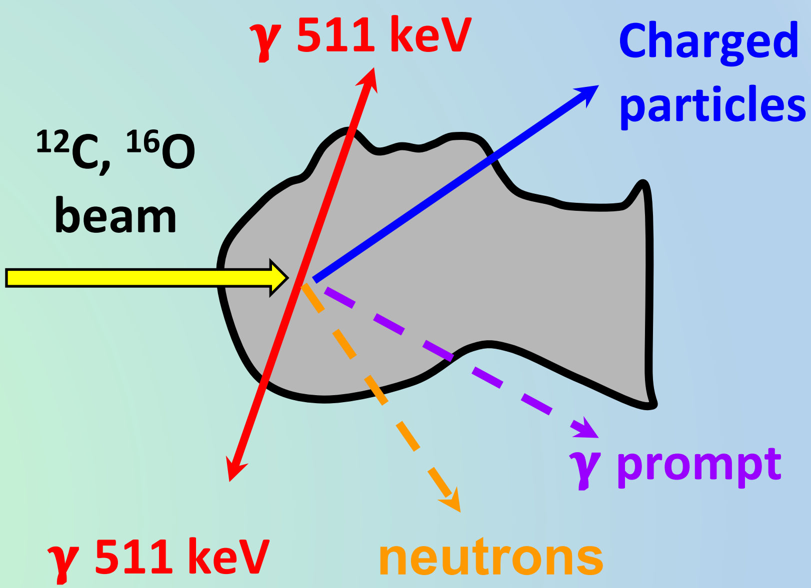


Teragnostic:
New developments in hadrontherapy treatment

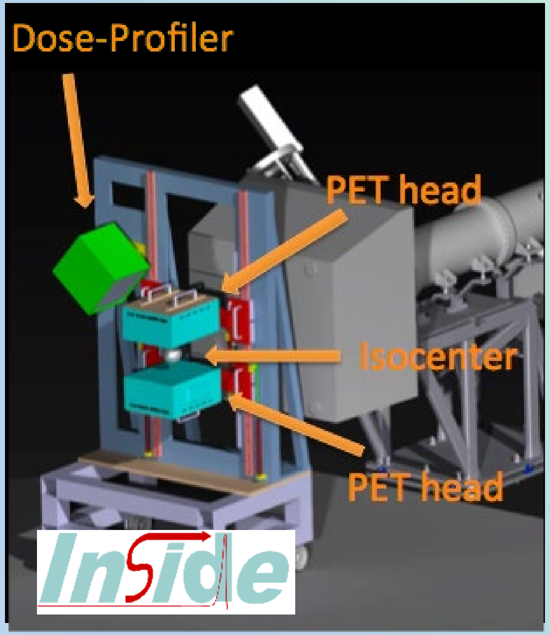
INSIDE: INnovative Solutions for In-beam DosimEtry in Hadrontherapy

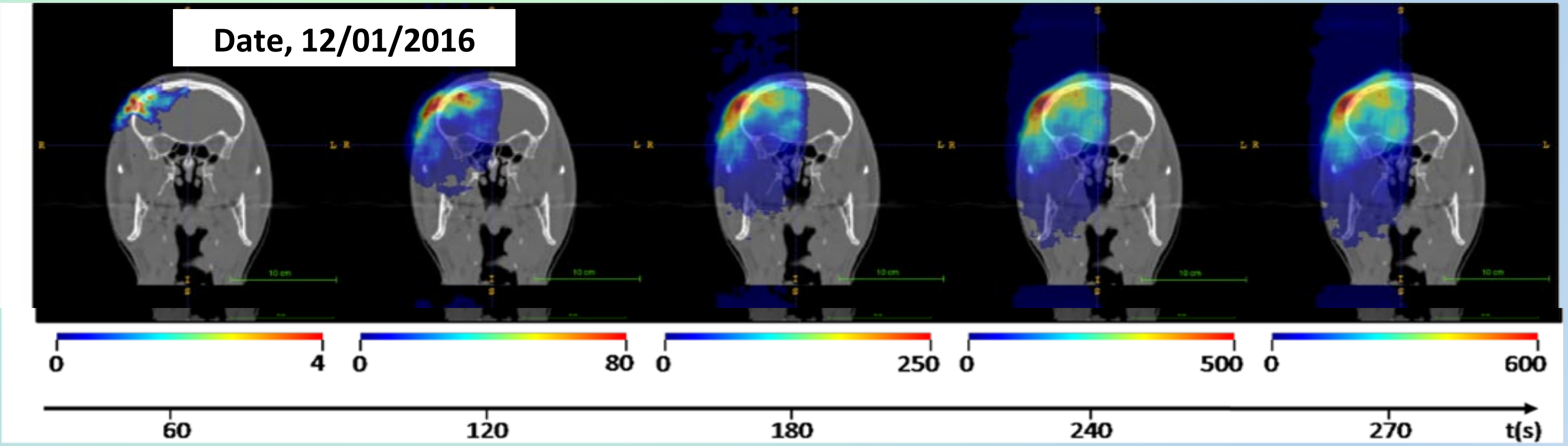
Therapy and diagnostic simultaneously

Goal: measure the effective position of the dose released



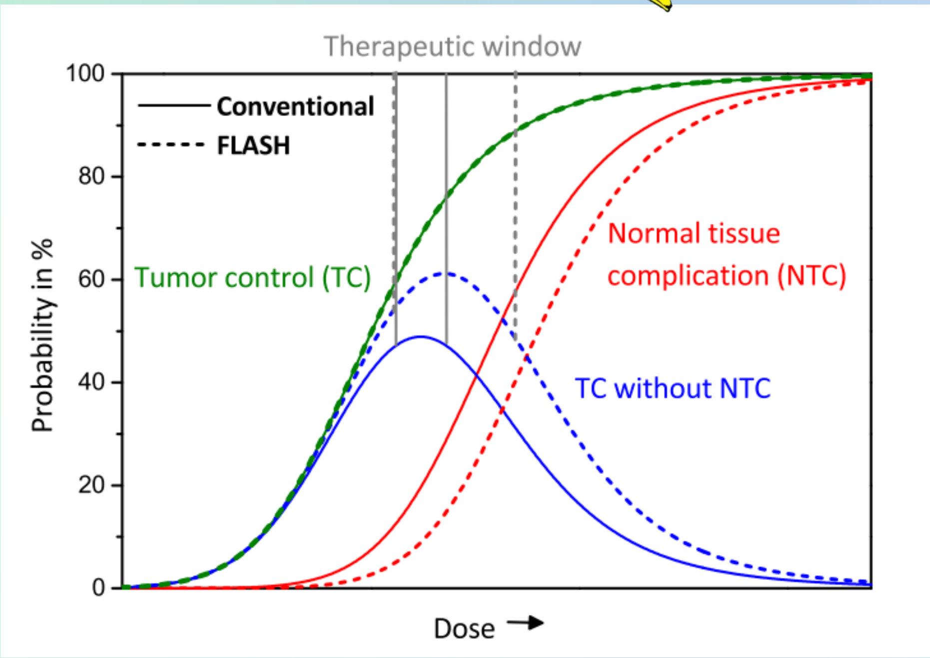
^{12}C beam make nuclear interaction and produce charged particles and β+ emitters)





THE FLASH THERAPY

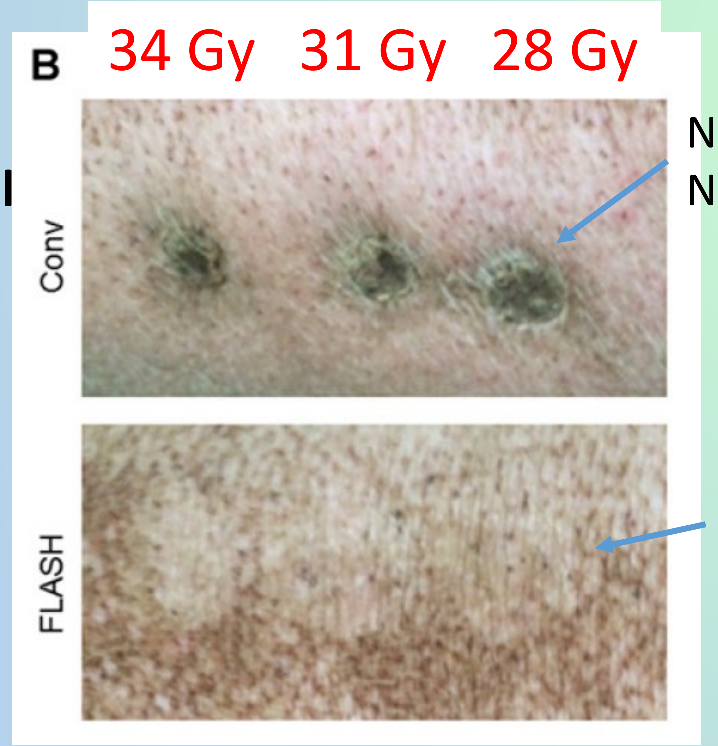
It has been discovered that the **irradiation rate** has an effect on cell survival probability
Conventional: 2 Gy delivered in minutes
Flash: 2 Gy delivered in milliseconds or microseconds



Initially healty pig skin

Conventional
5 Gy/min
0.08 Gy/s

FLASH
18 kGy/min
300 Gy/s



NecroticTissue after treatment
No recovery after months

Minimal visible damage

(Vozenin et al. 2019, Clin. Canc. Res.)

Advantages (choose one only):
- lower number of treatments (increasing doses)
- lower complicances probabilities (same dose)
- treatment of moving tumors (lung, abdomen)

This is the end

Thanks

hoping to have been useful