



UNIVERSITÀ
DEGLI STUDI
DI TORINO



New Detectors for Beam Monitoring in Particle Therapy

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Giornate di Studio sui Rivelatori - Scuola F. Bonaudi

February 10-14, 2020 Cogne



Outline

Physics for cancer

- Basic principles of Radiation Therapy
- Basic principles of Charged Particle Therapy

Instrumentation

- Accelerators
- Beam delivery system

Beam monitors

- Gas ionization chambers

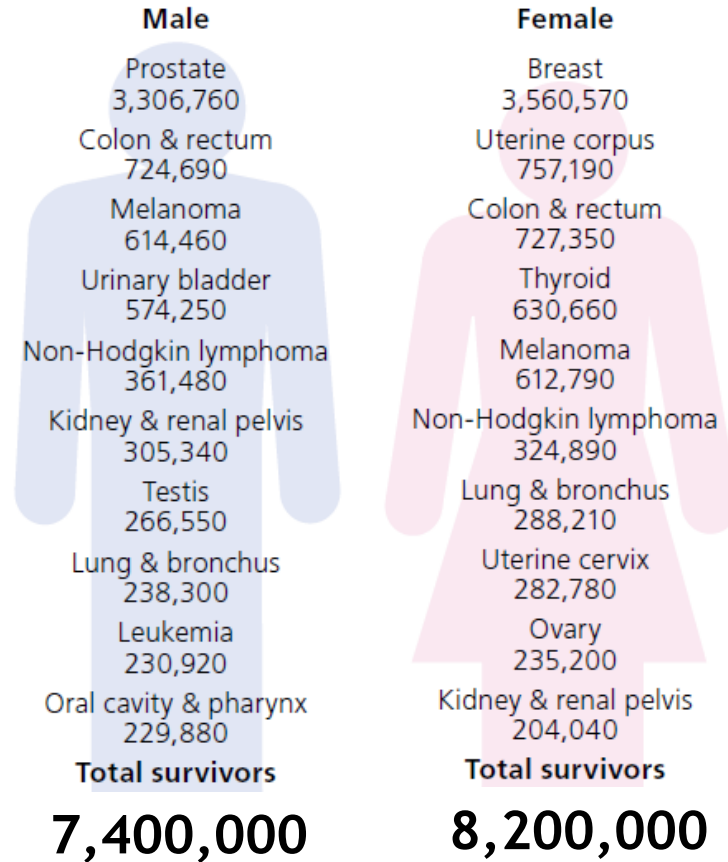
What's next?

The number of cancer survivors is increasing

Estimated US cancer survivors

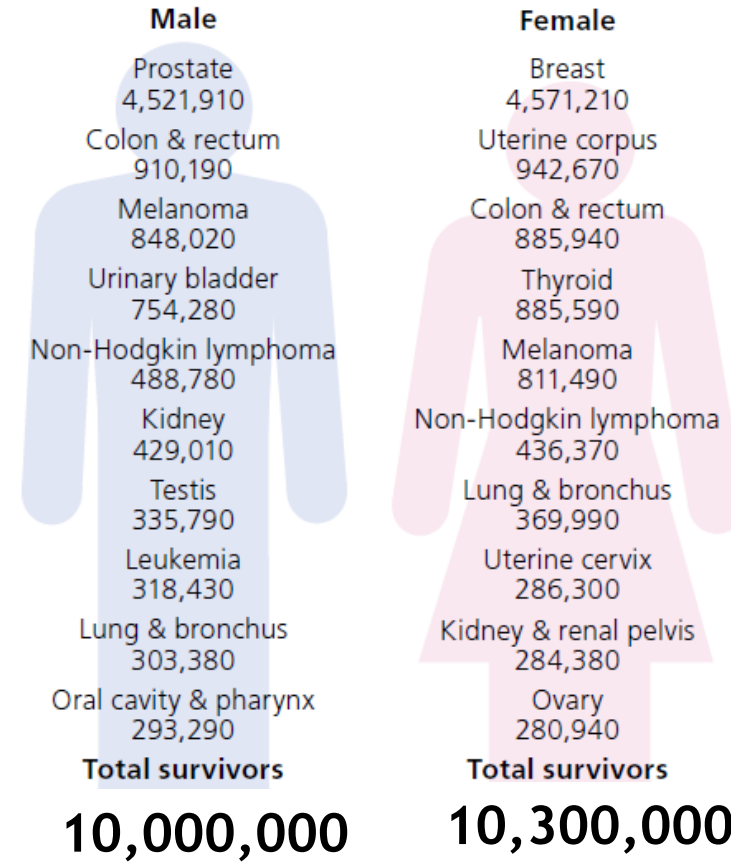
~19 million new cancers/year

As of January 2016



As of January 2026

~24 million new cancers/year



Reference [1]

+53% survivors in Italy

LA STAMPA

4 Febbraio 2020

Tumori: in 10 anni in Italia +53% di pazienti vivi dopo la diagnosi. Ma l'accesso a test e cure non è uguale per tutti

Fra i prossimi obiettivi della comunità scientifica l'abbattimento delle differenze regionali nel trattamento dei pazienti. Da AIOM appello alle Istituzioni perché venga seguito l'esempio delle Regioni più virtuose



Reference [2]

Clinical strategies for Cancer Treatment

- Surgery
- Chemotherapy
- Radiotherapy
- Immunotherapy
- Biological and targeted-therapy
- Combined and personalized therapy

Clinical strategies for Cancer Treatment

- Surgery
- Chemotherapy
- Radiotherapy
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Radiation therapy after Marie Curie



REVIEW ARTICLE

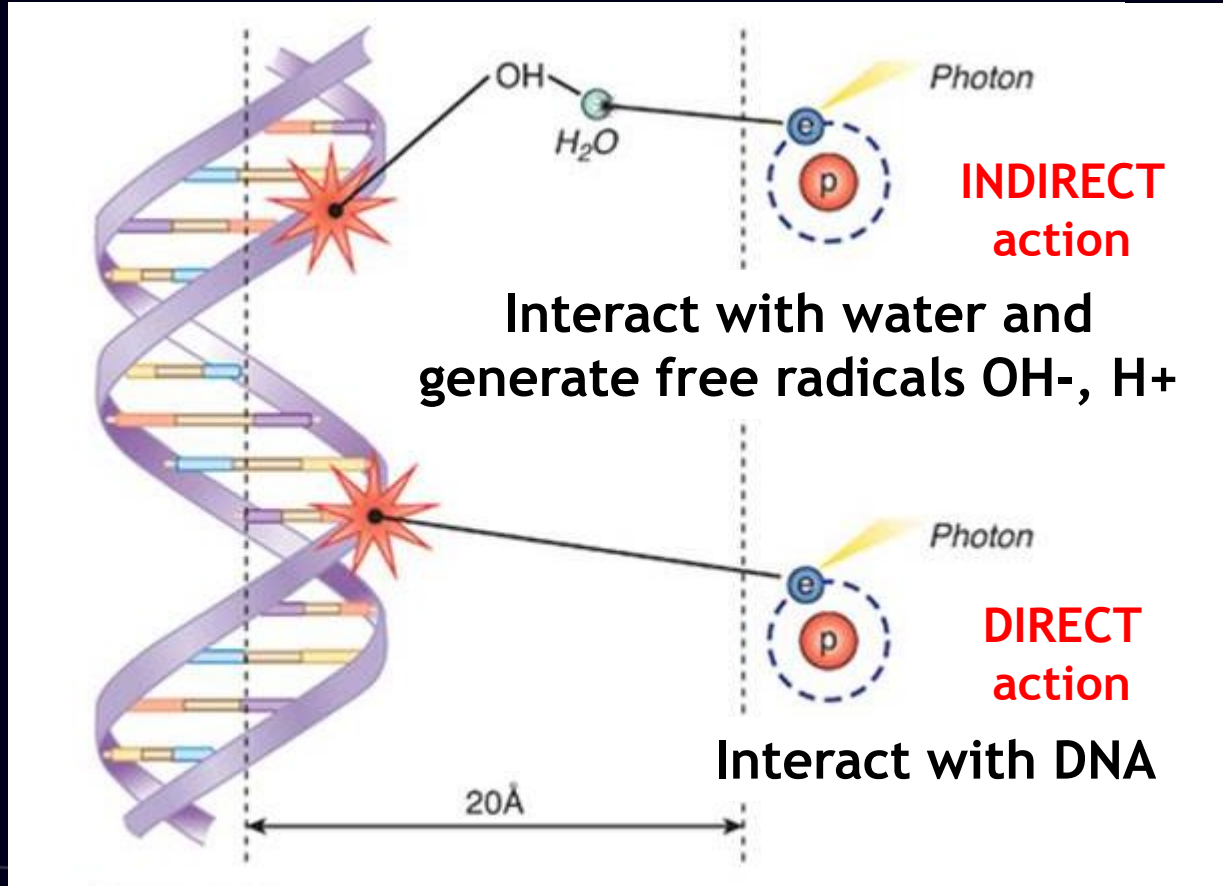
Practice-changing radiation therapy trials for the treatment of cancer: where are we 150 years after the birth of Marie Curie?

Mareike K. Thompson¹, Philip Poortmans², Anthony J. Chalmers³, Corinne Faivre-Finn⁴, Emma Hall⁵, Robert A. Huddart⁶, Yolande Lievens⁷, David Sebag-Montefiore⁸ and Charlotte E. Coles⁹

Reference [3]

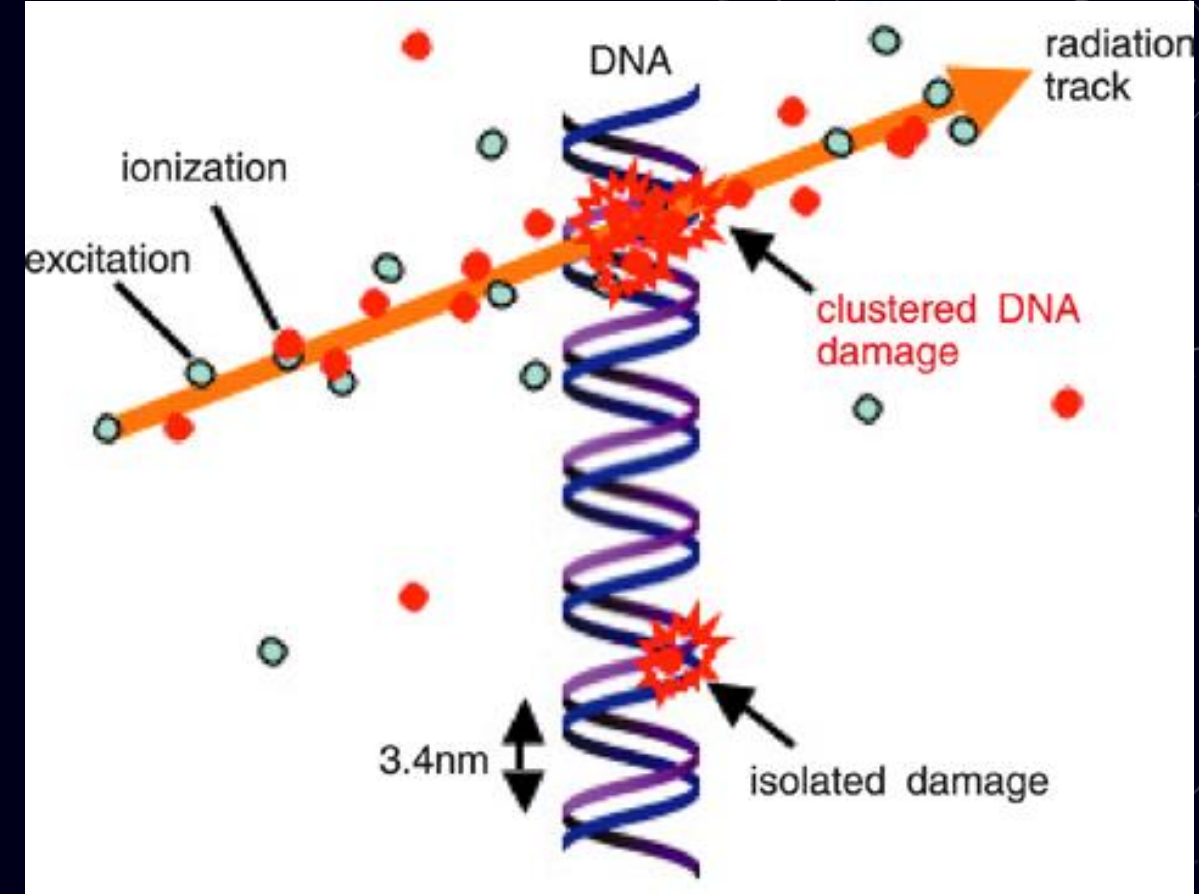
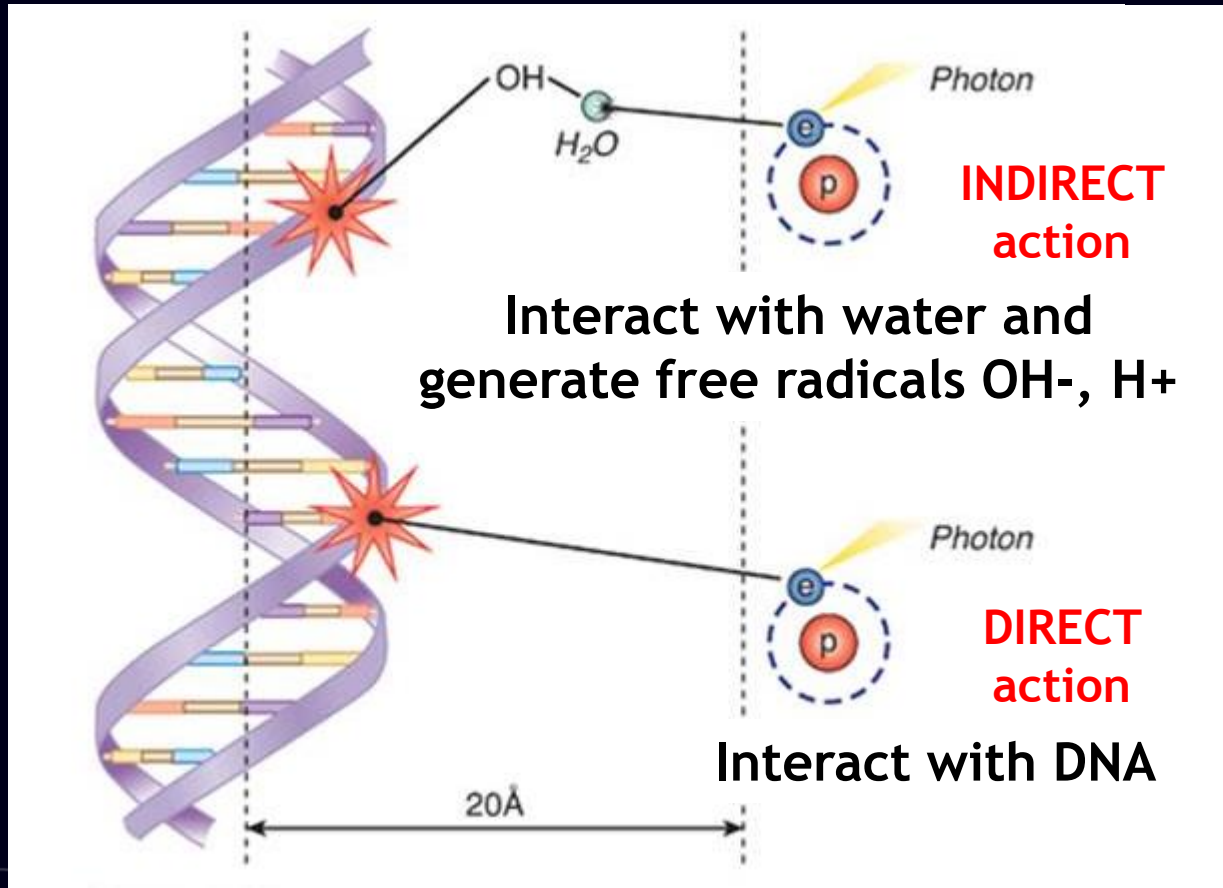
Ionizing radiations damage and kill our cells

The target is the DNA

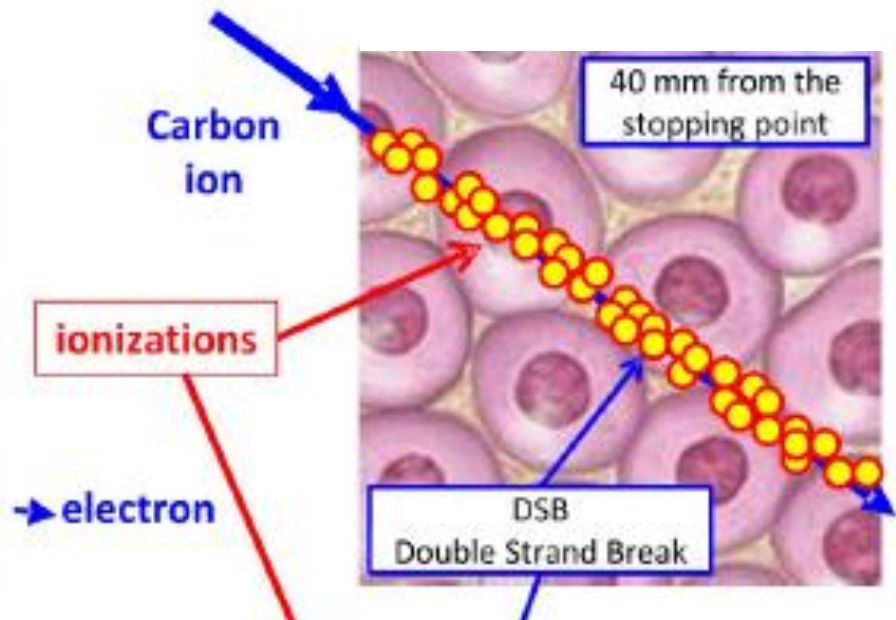
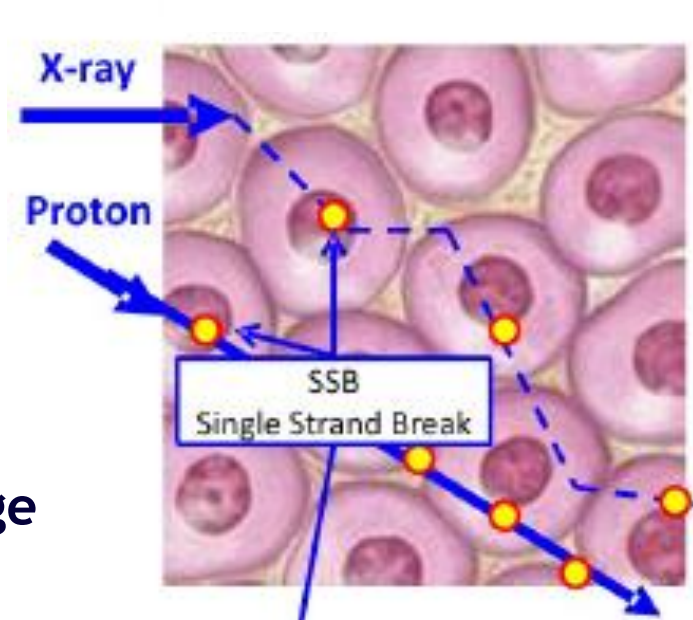


Ionizing radiations damage and kill our cells

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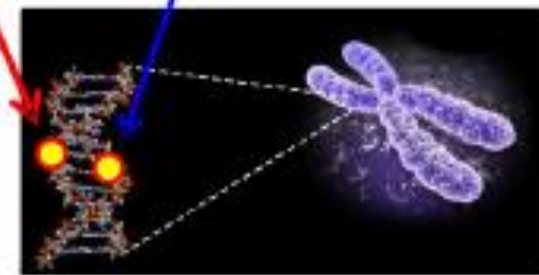
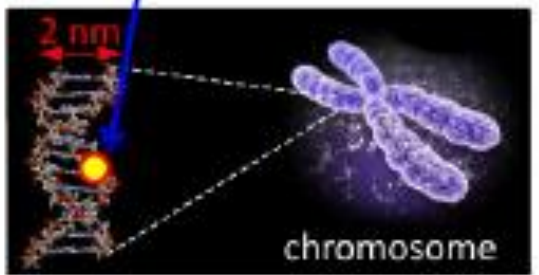


Single and Double Strand Breaks



Isolated damage
SSB
Single Strand Break
Sublethal effects

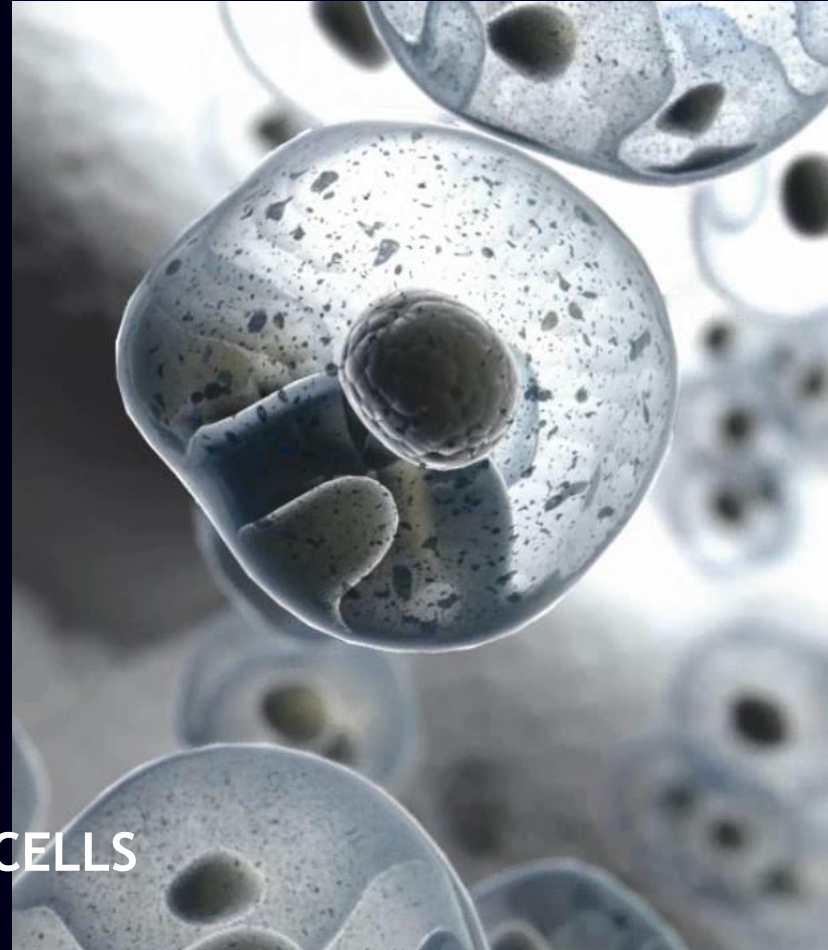
Clustered damage
DSB
Double Strand Break
Lethal effects



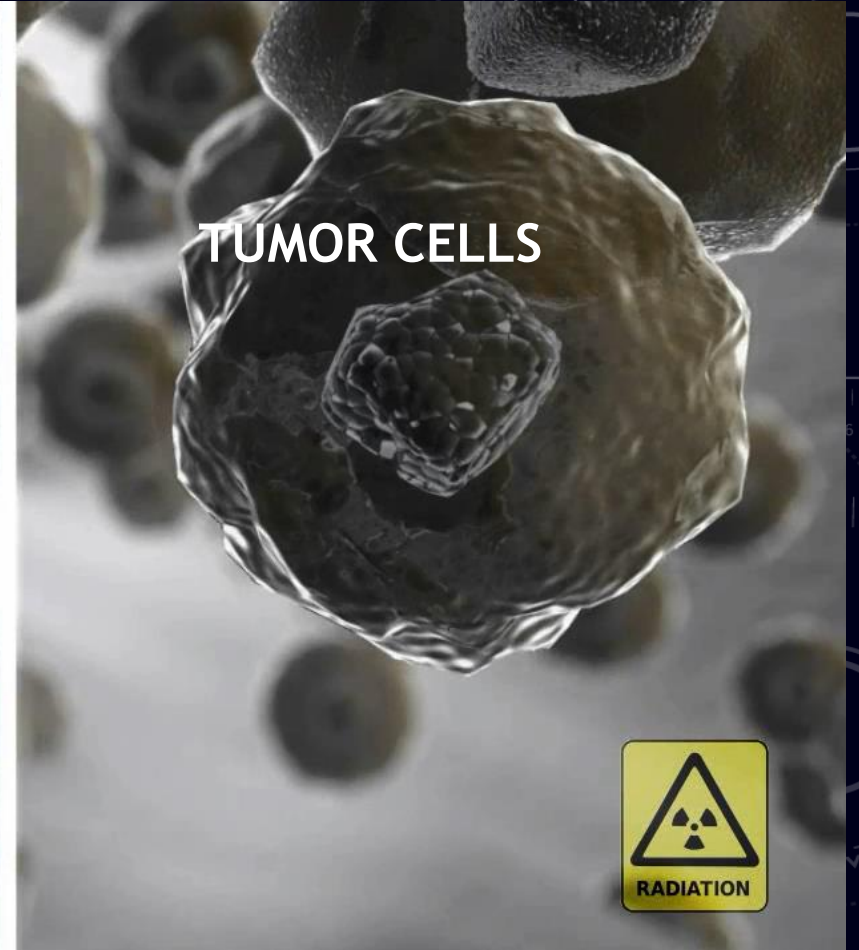
Radiation therapy

Tumor cells are more sensitive to ionizing radiation than normal cells

→ Healthy cells repair themselves more easily



NORMAL CELLS



TUMOR CELLS



Ref 4

The killer amount of Energy

$$Dose = \frac{dE}{dm} [Gy = J/kg]$$

The effects DEPEND ON DOSE

Typical killer dose 60-80 Gy

The effects DEPEND ON DOSE RATE

Delivered in 30-35 days \rightarrow \sim 2 Gy/day

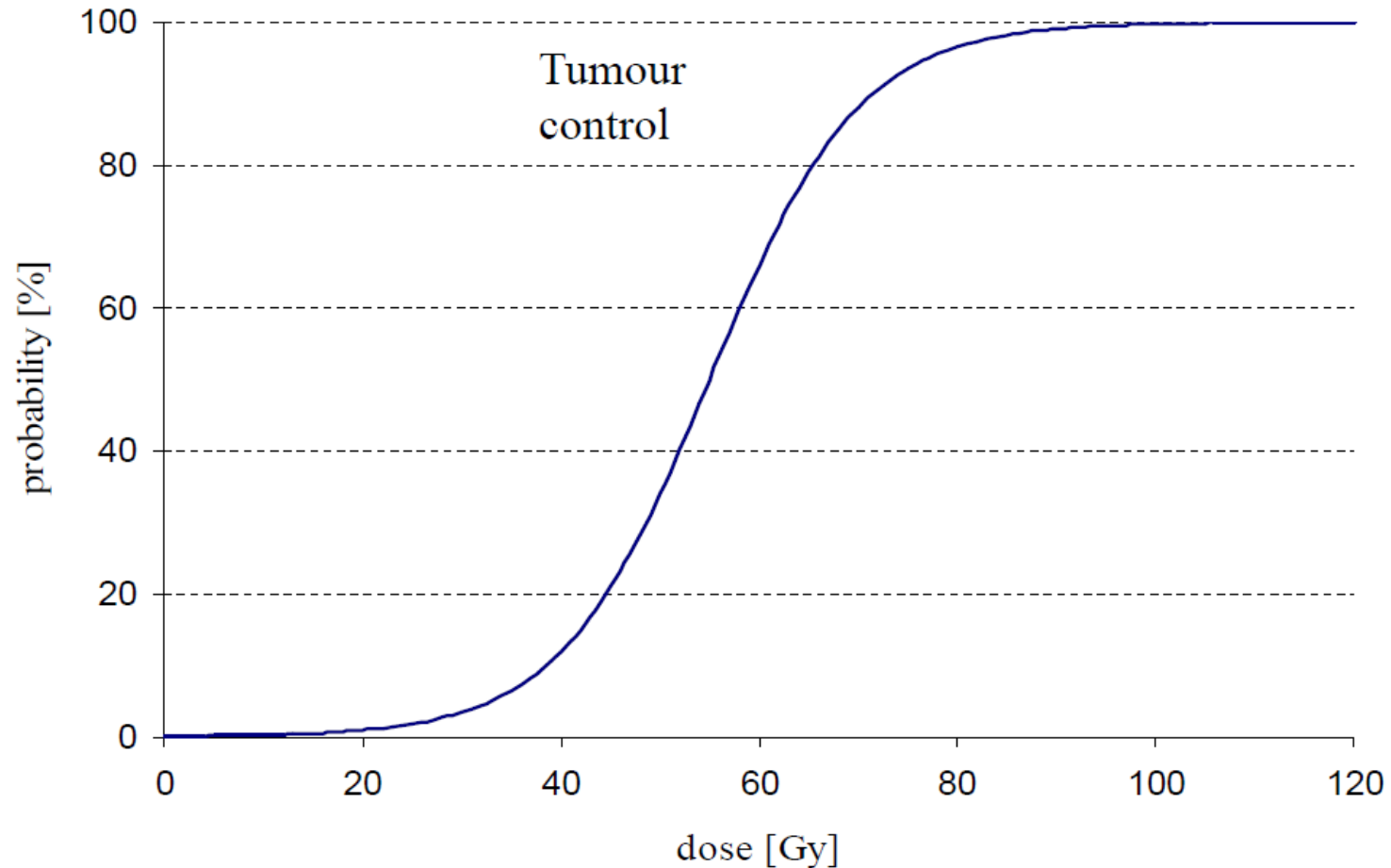
2 Gy delivered in 1-2 minute (averaged dose rate 2-1 Gy/min)

The effects DEPEND ON several other parameters like radiation type, tissue type, beam characteristics,...



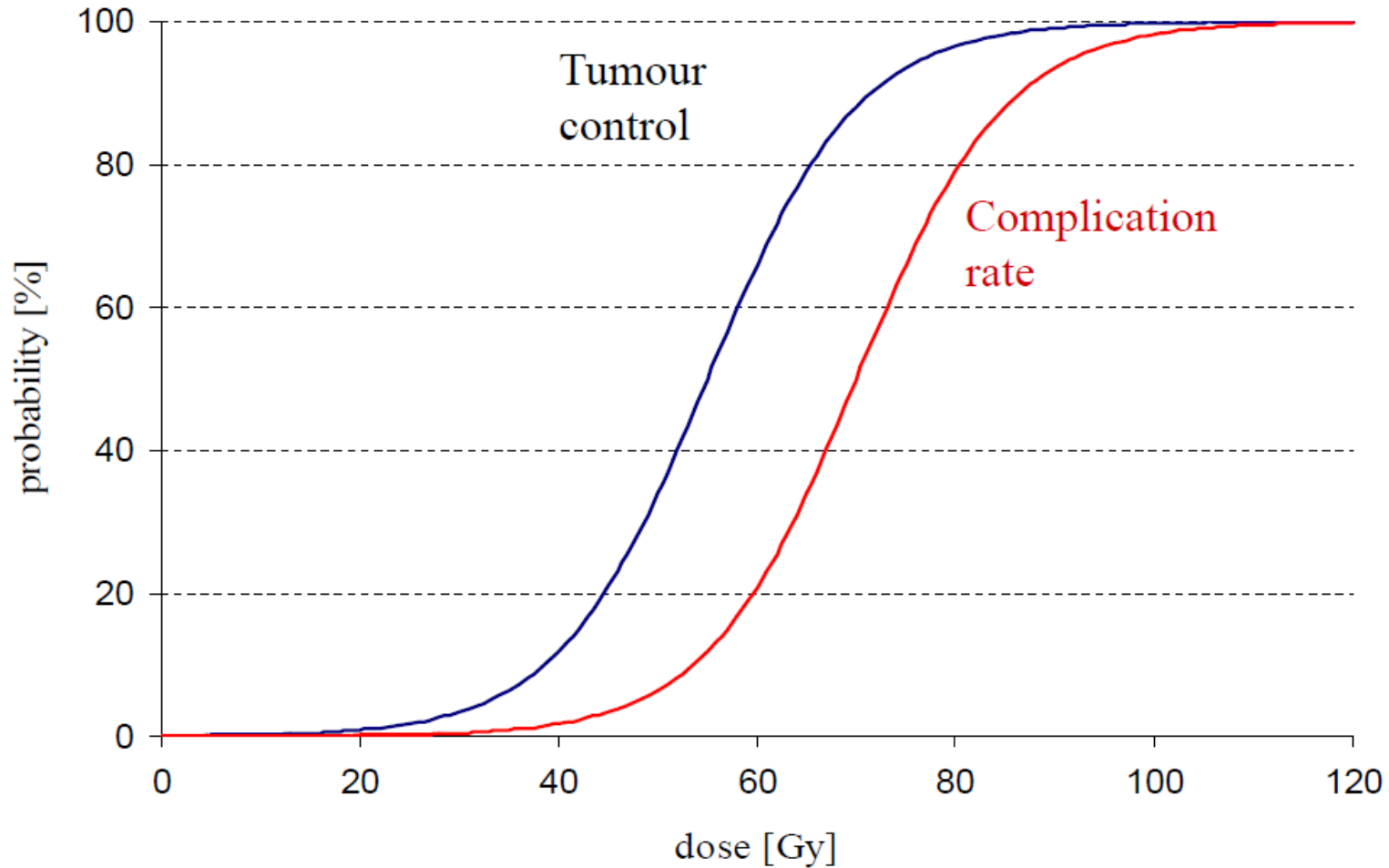
Tumor control vs dose

General principle to select the best dose

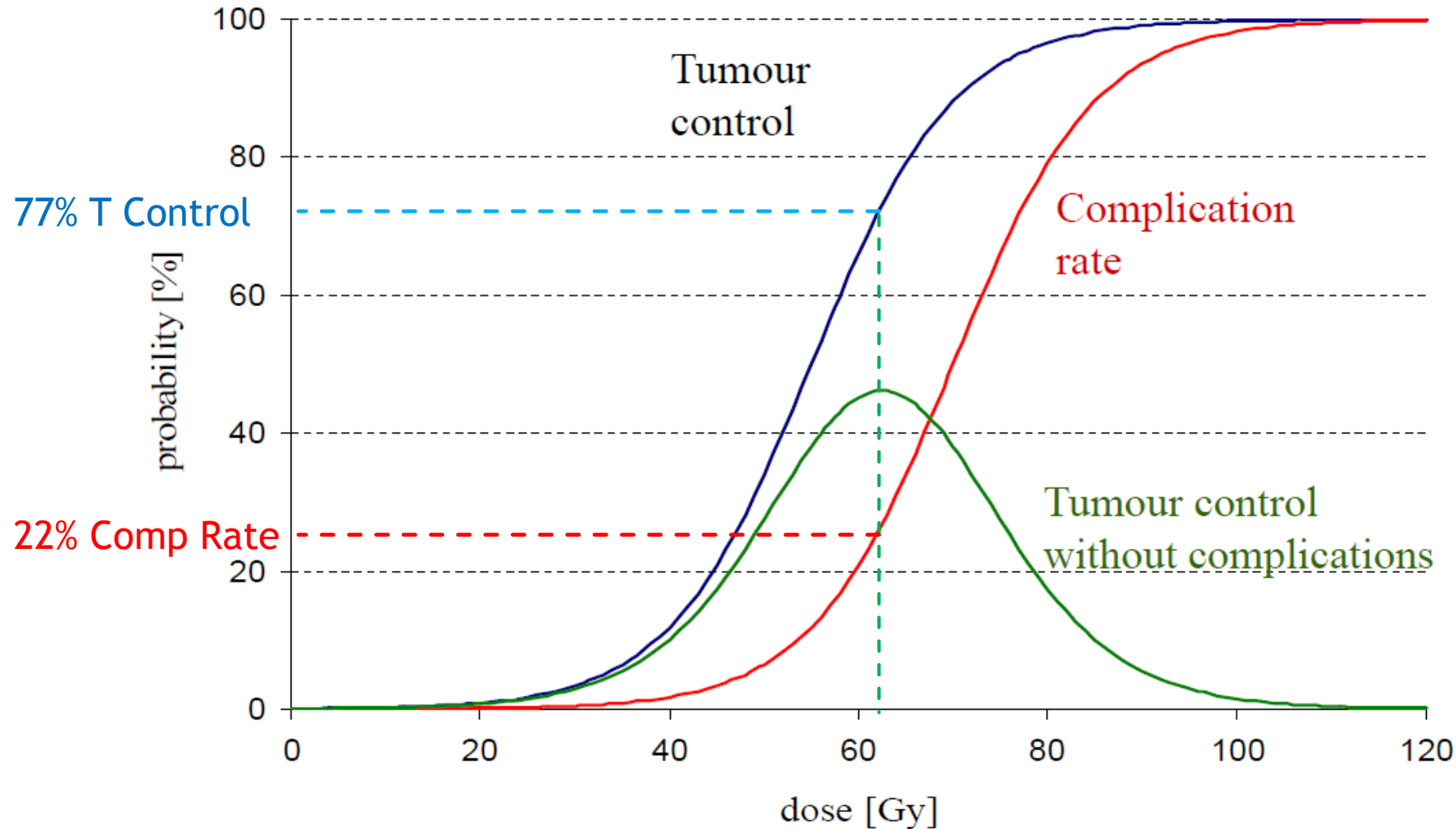


Complication rate vs dose

General principle to select the best dose that minimize the complication rate

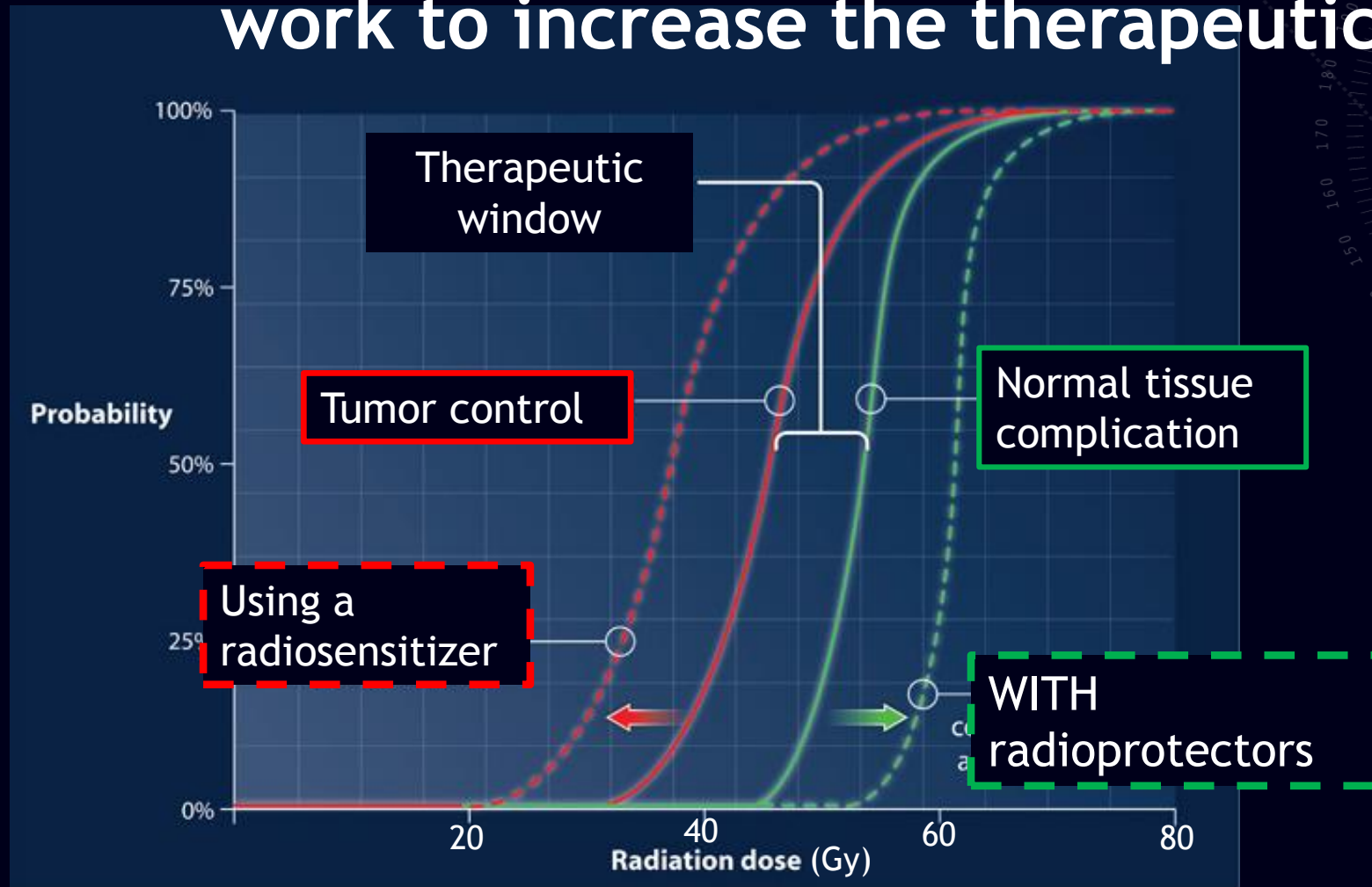


Clinical goal : tumor control without complications



Radiation oncology research and technological improvements

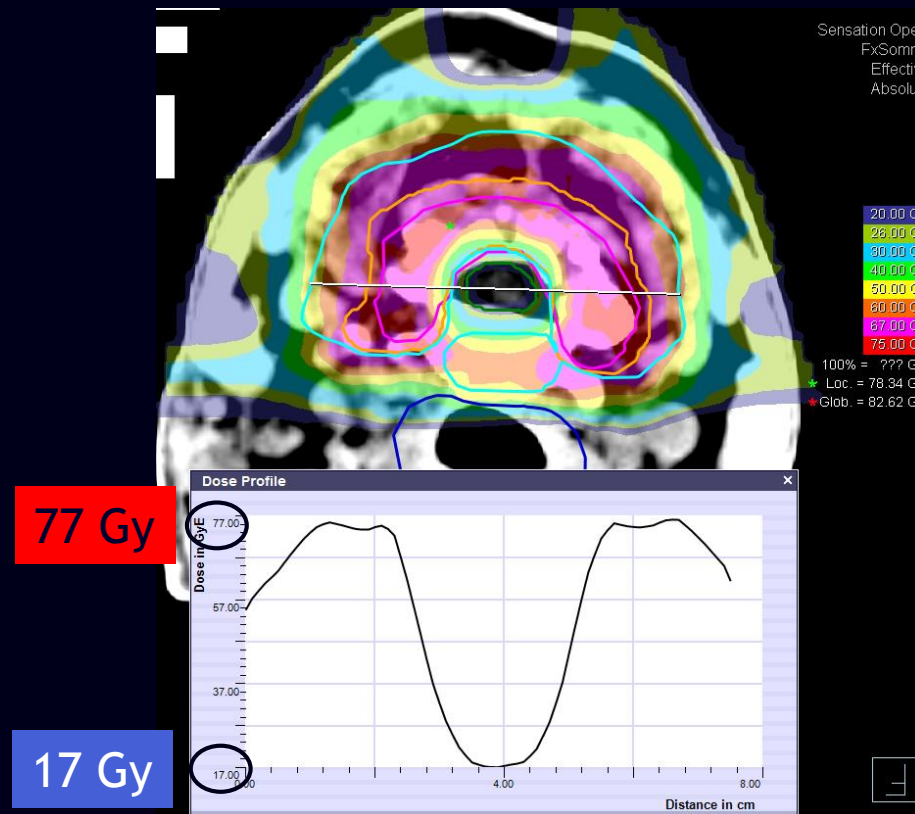
work to increase the therapeutic window



Radiotherapy clinical goal

Kill efficiently the tumor cells while minimizing toxicity to normal tissues

Clinical goal

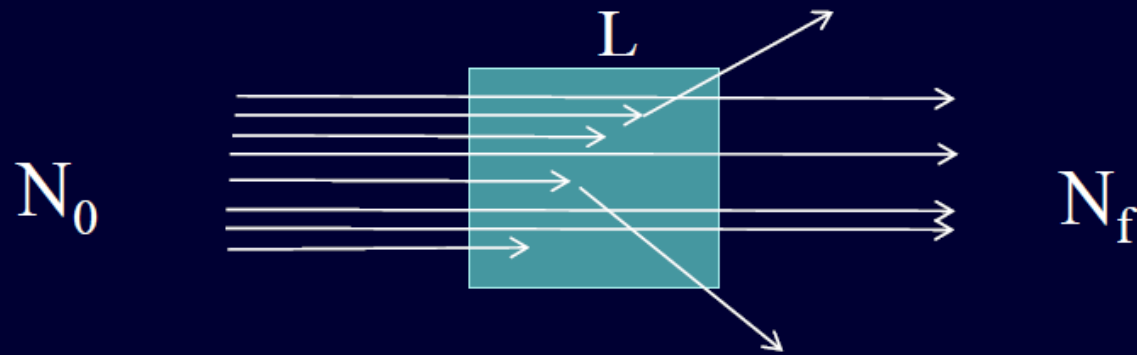


X-rays, protons and carbon ions

Interact differently with matter

Leading to different Depth Dose Distributions

Photon attenuation

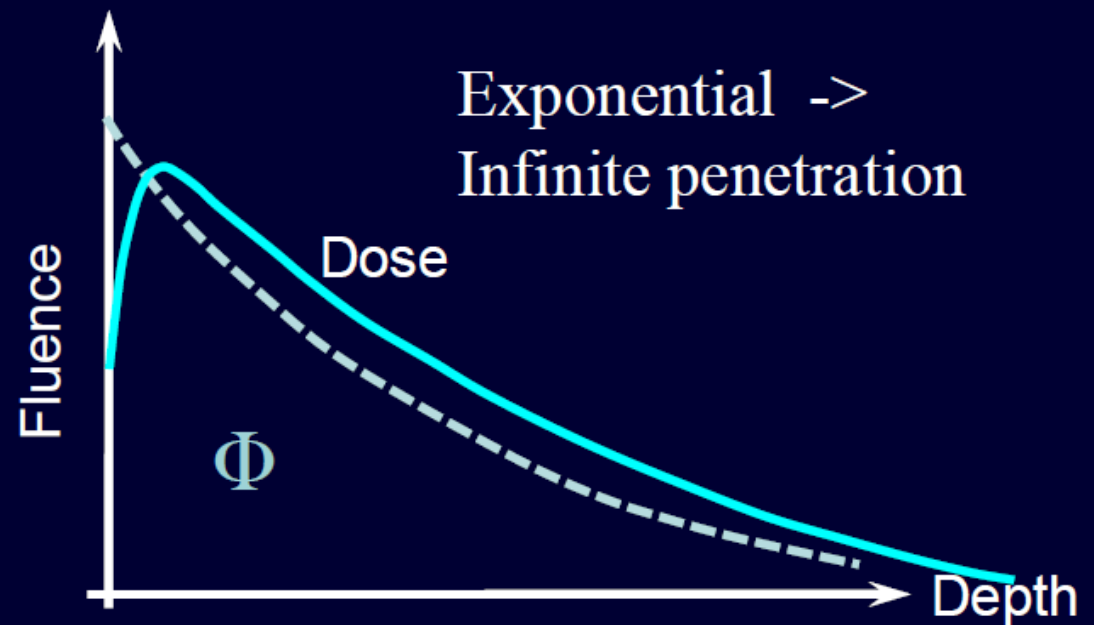


Number of photons
decreases exponentially

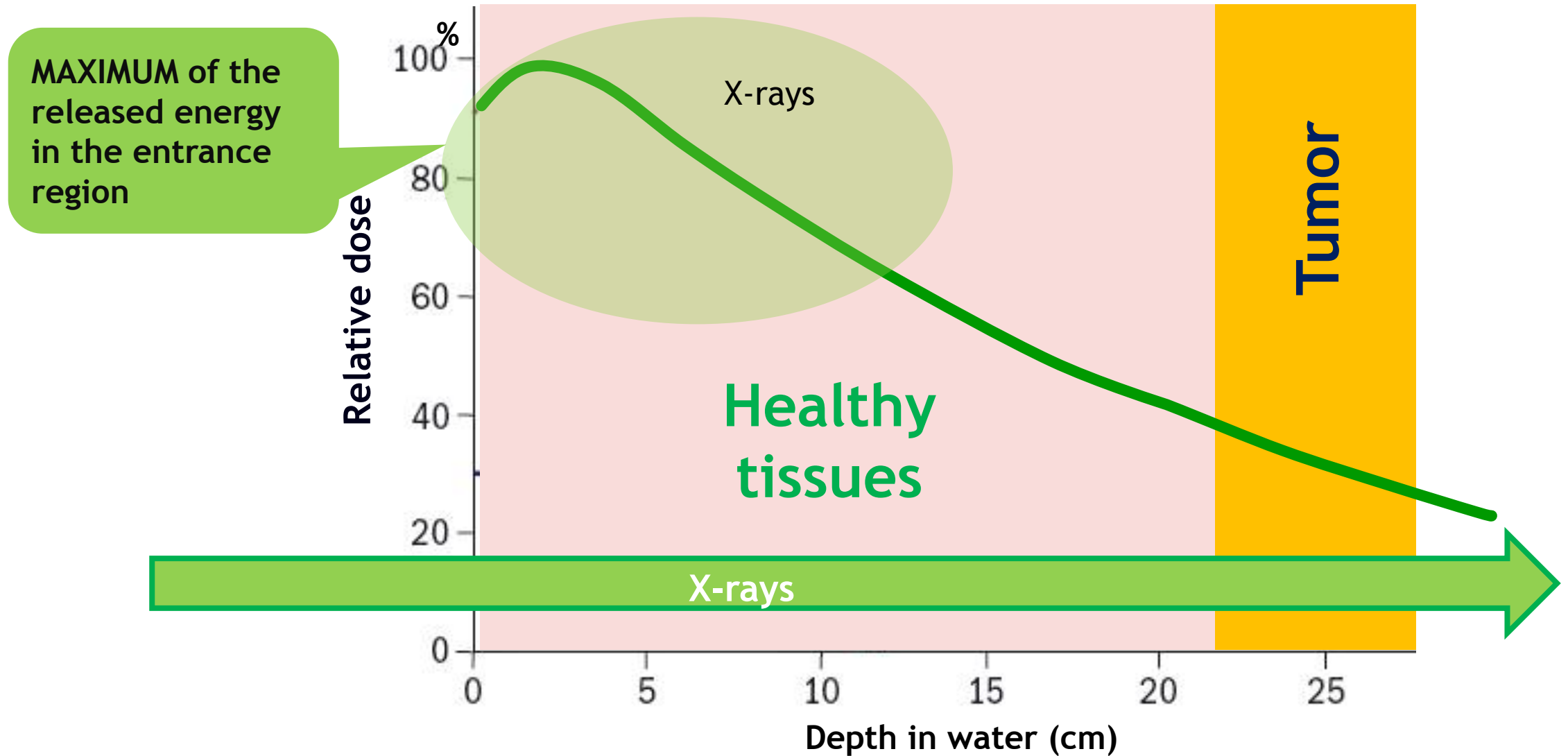
$$N_f = N_0 e^{-\mu L}$$

Fluence:

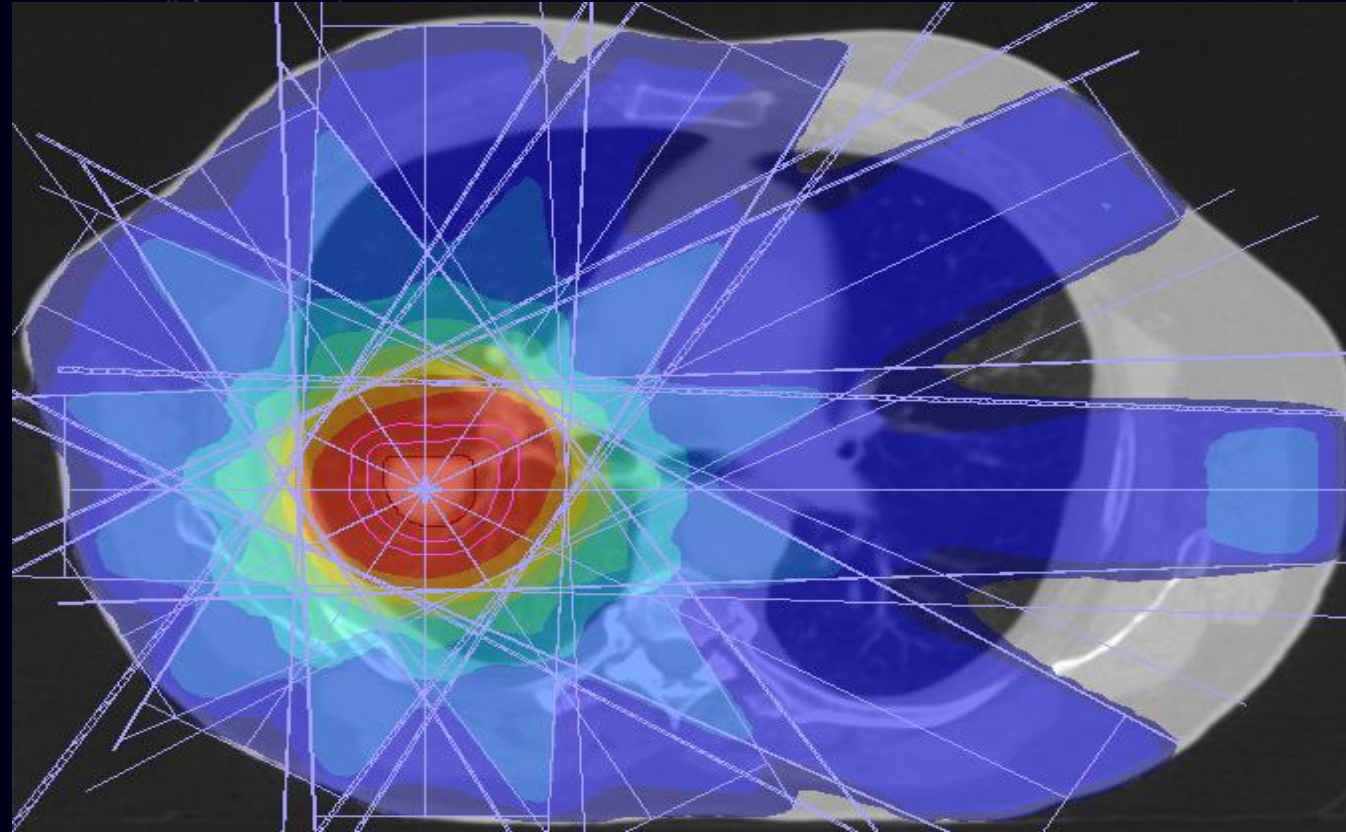
$$\Phi = N / A$$



X-rays Depth Dose Distributions



X-rays come from several directions



To save healthy tissues, several beams coming from different directions around the patient are used. They are arranged to maximize their overlap into the region to be treated.

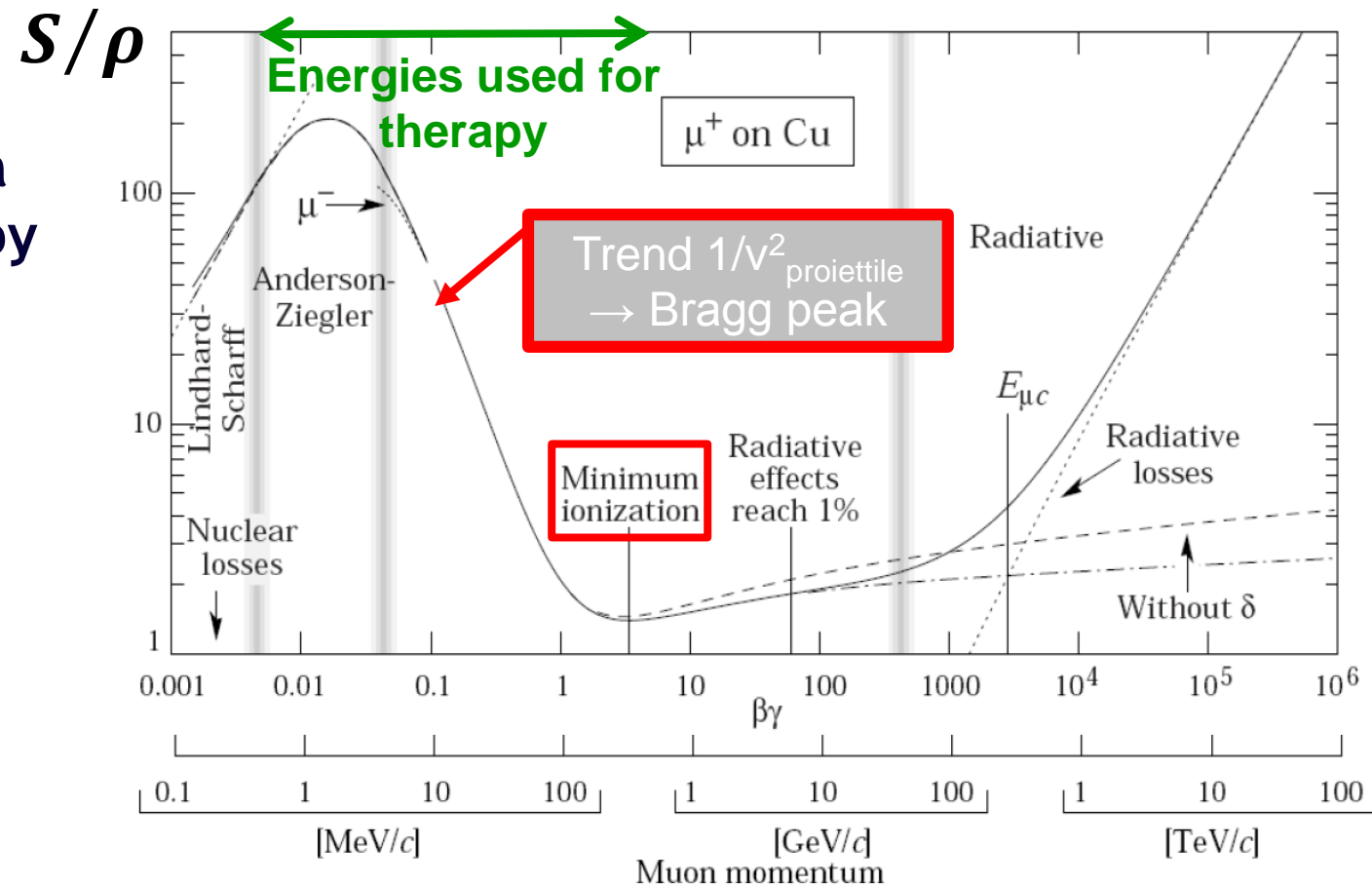
Charged particle Stopping power

Represents the mean kinetic energy K_p loss per distance travelled by charged particles traversing matter
 $(S = -dK_p/dx)$

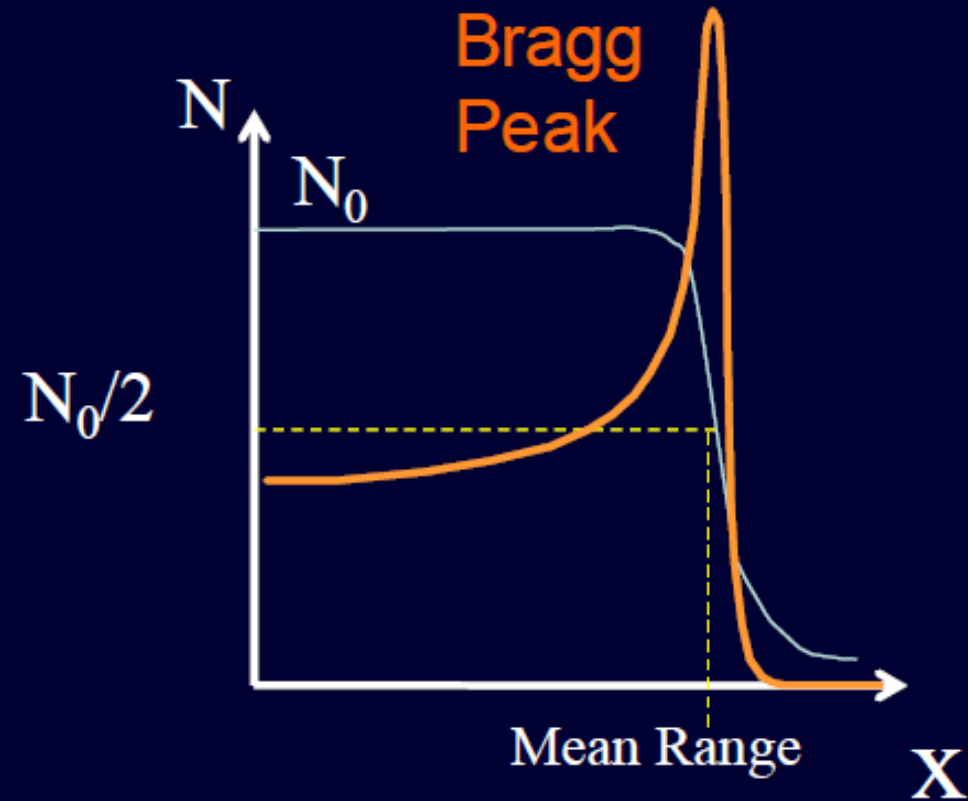
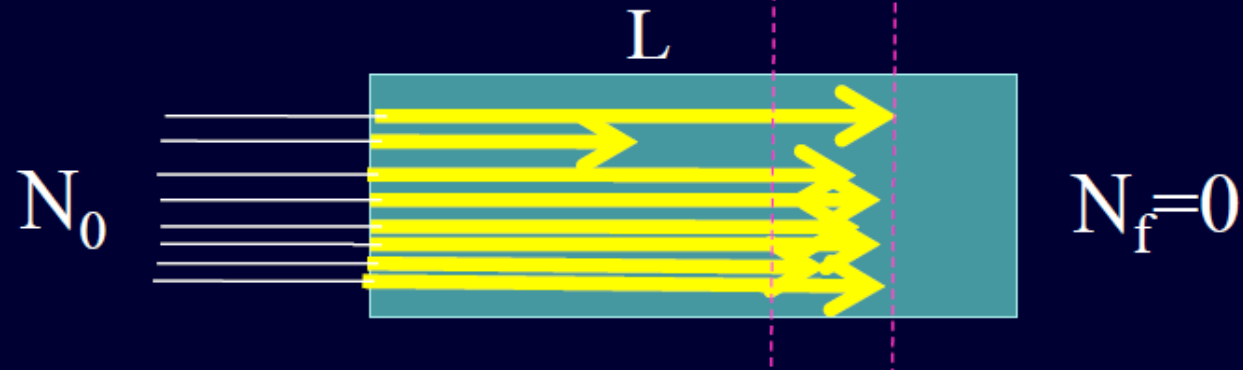
It is described by di Bethe Bloch formula in the range of energies used for therapy

$$S = C \rho \frac{Z}{A} \frac{Z_p^2}{v_p^2} \ln \left(\frac{2 m_e v_p^2}{I} \right)$$

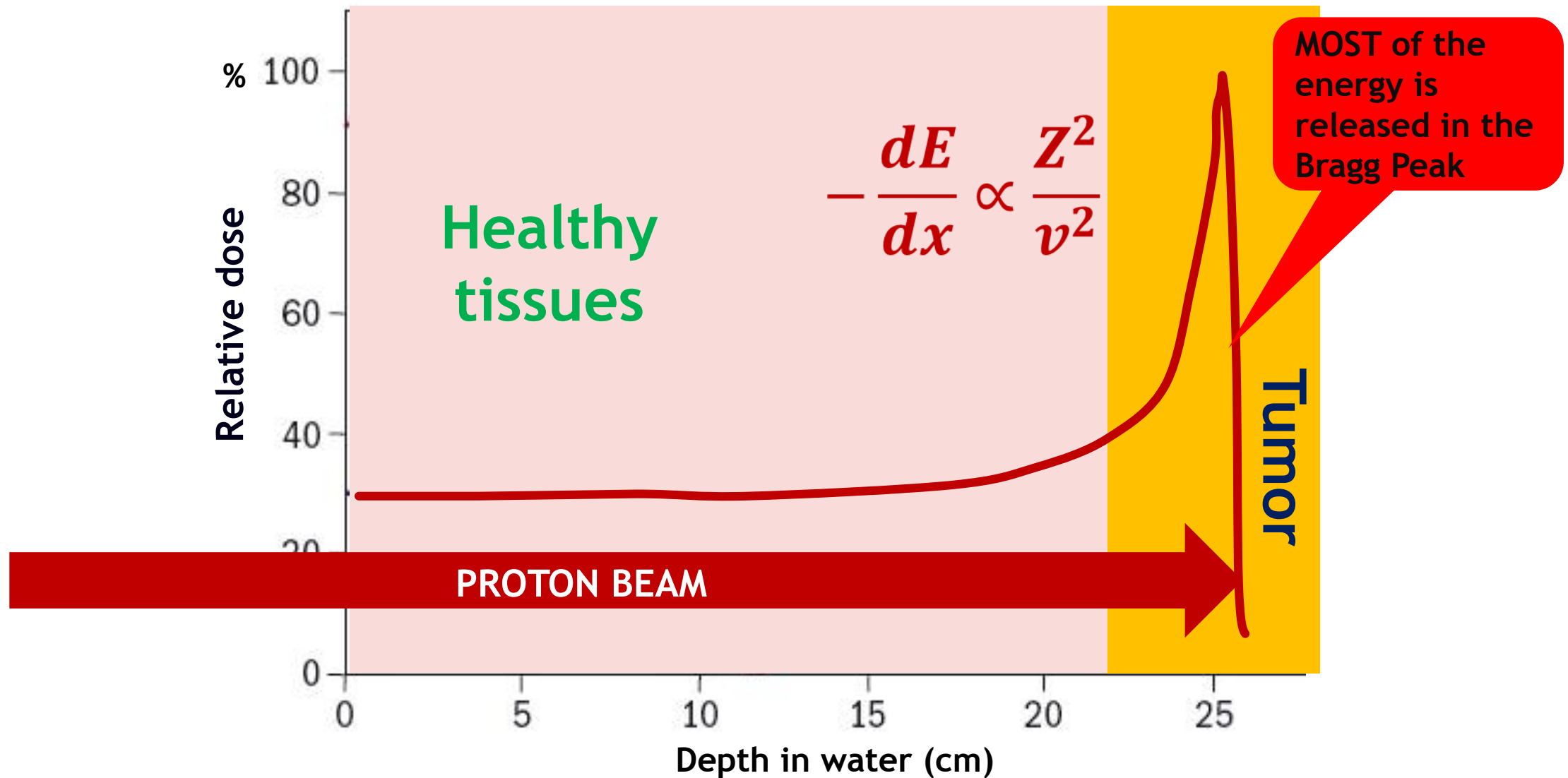
$$K_p = \frac{1}{2} m_p v_p^2 \quad \Rightarrow \quad S \approx \frac{Z_p^2}{K_p} \ln(K_p)$$



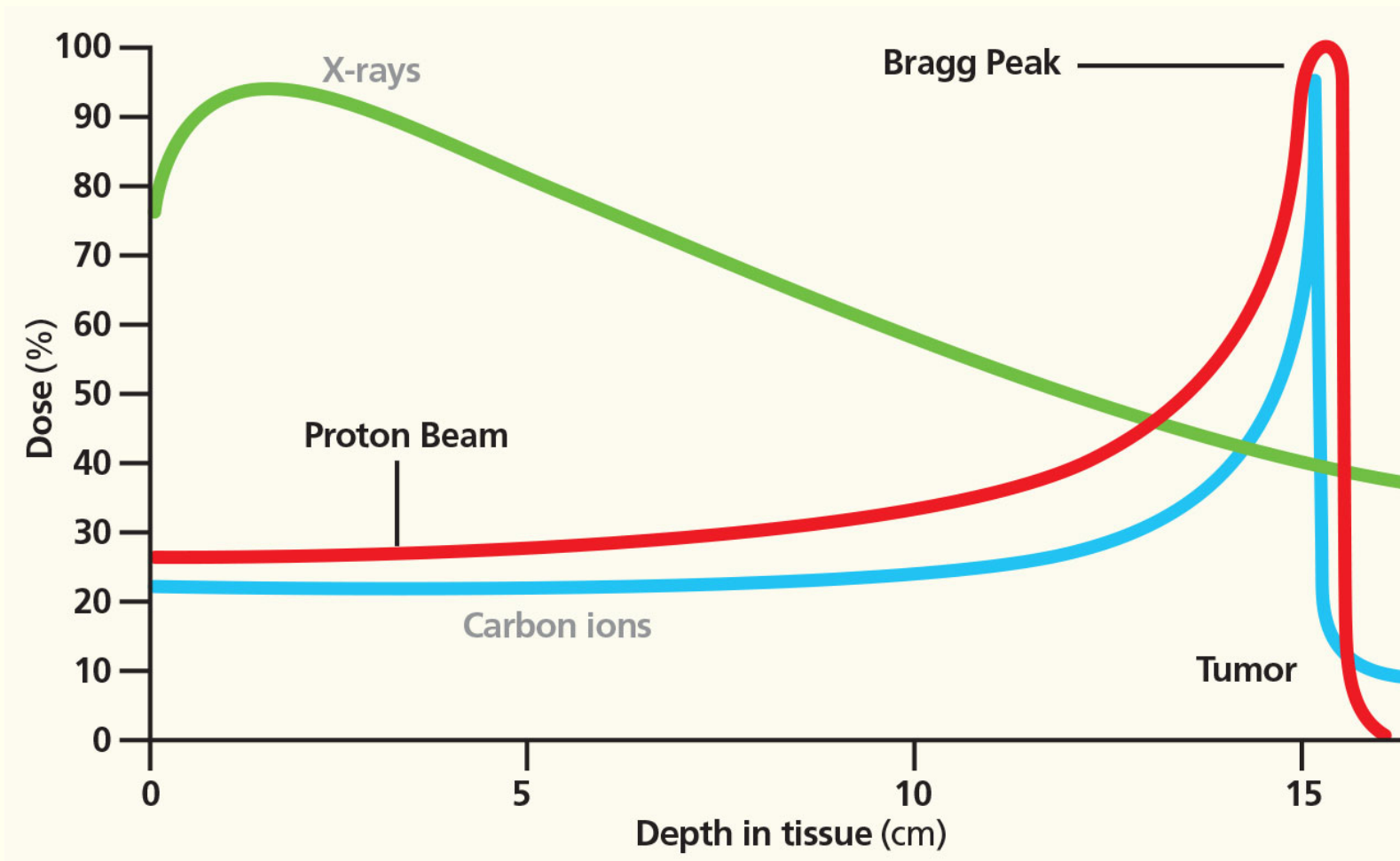
Heavy charged particles do not attenuate



Protons and ions depth dose distribution



Average dE/dx variation over a wide energy range



$$-\frac{dE}{dx} \propto \frac{Z^2}{v^2}$$

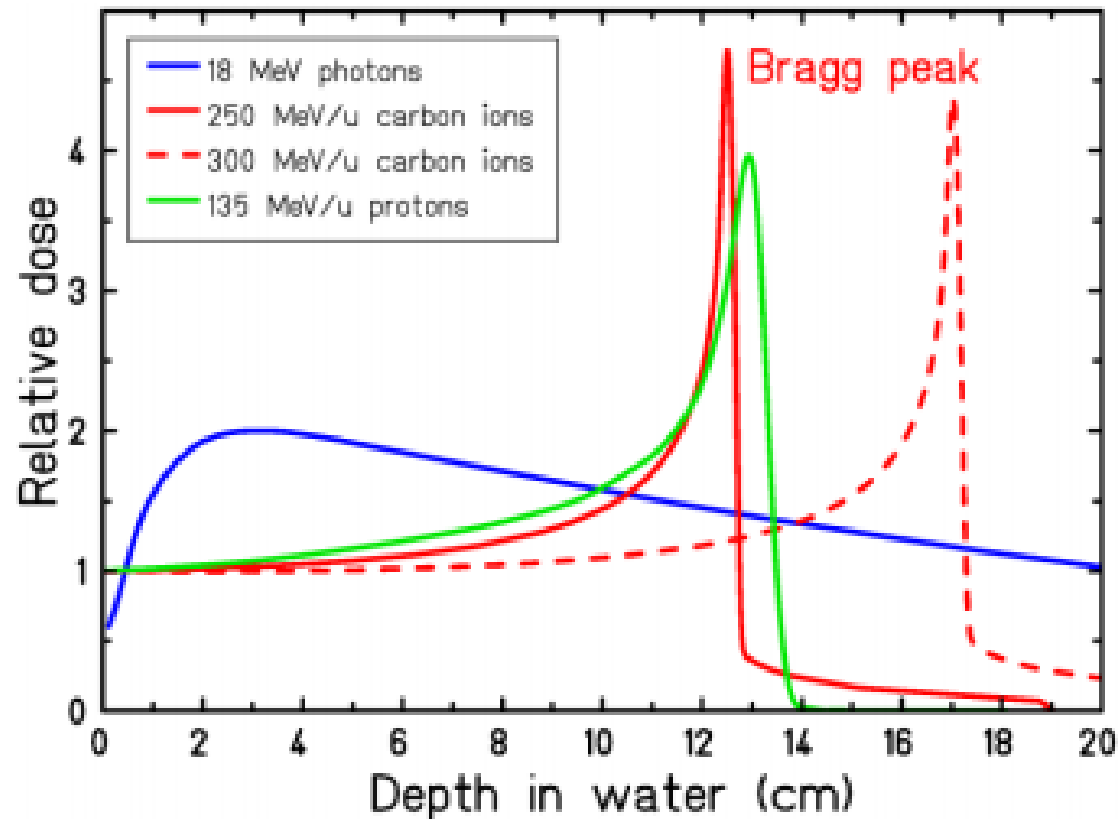
Carbon ions (Z=6)

^{12}C

- Narrow Bragg Peak
- Dose in the Peak tail due to fragmentation

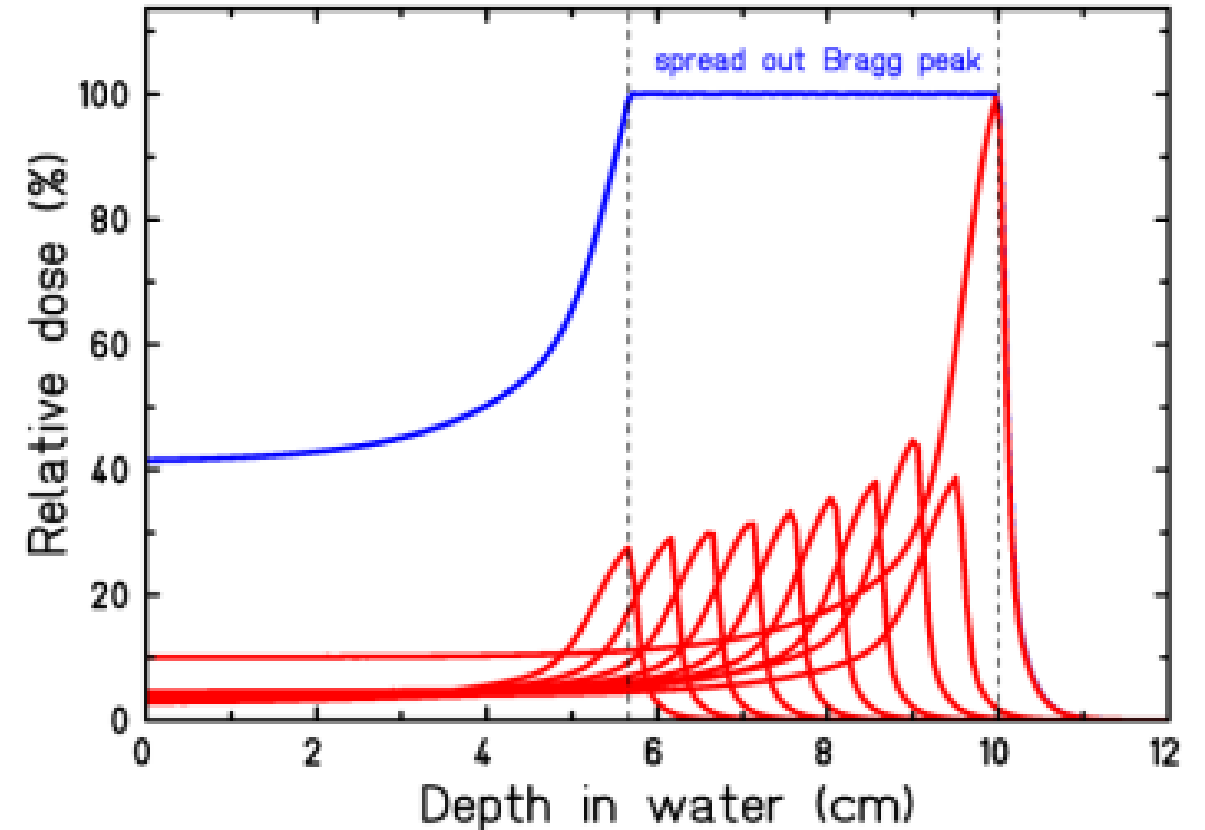
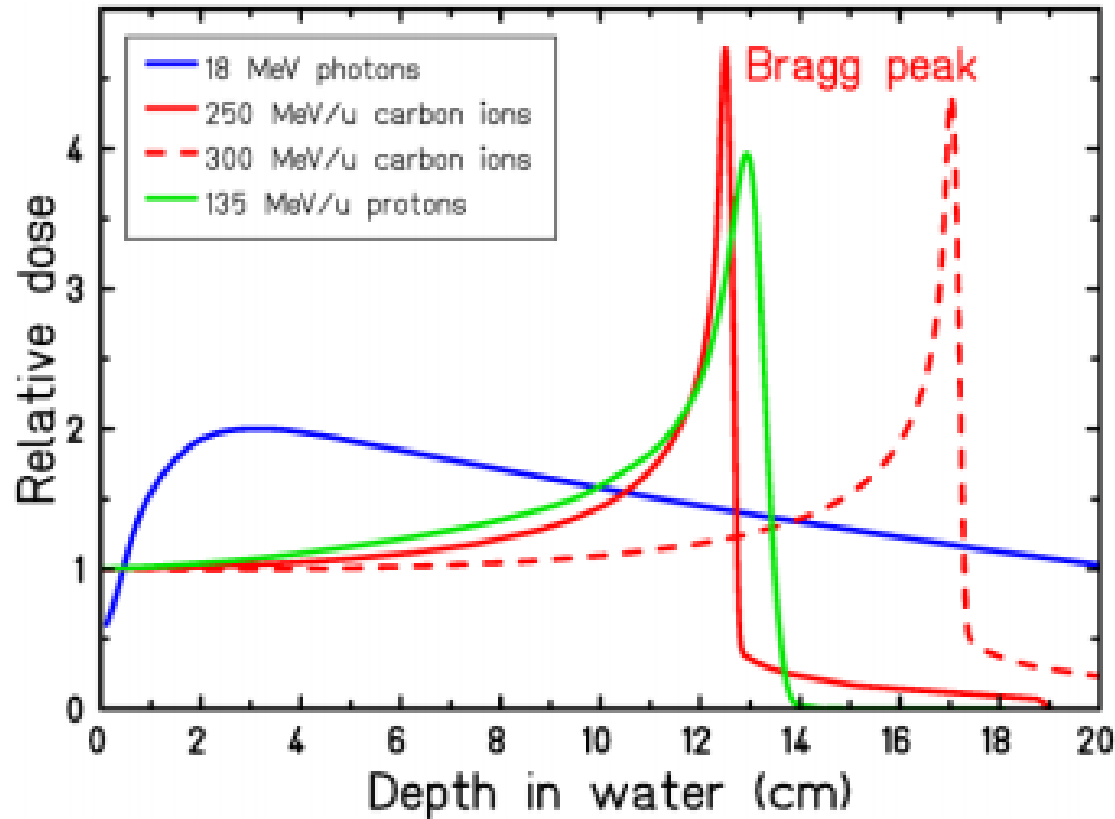
Beam energy and range modulation

Spread Out Bragg Peak for dose modulation in depth



Beam energy and range modulation

Spread Out Bragg Peak for dose modulation in depth



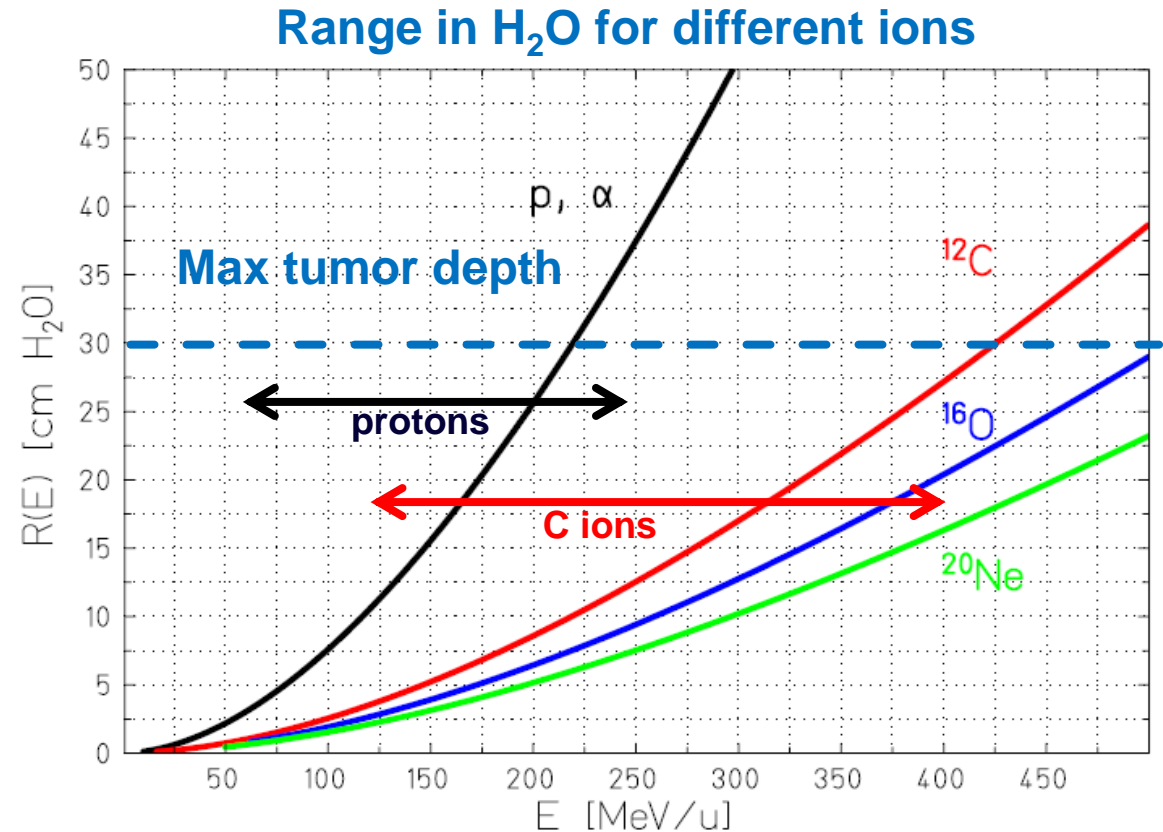
Range in water vs energy for different ions

$$R = \int_{K_i}^0 \frac{dx}{dK_p} dK_p = \int_0^{K_i} \frac{1}{S} dK_p$$

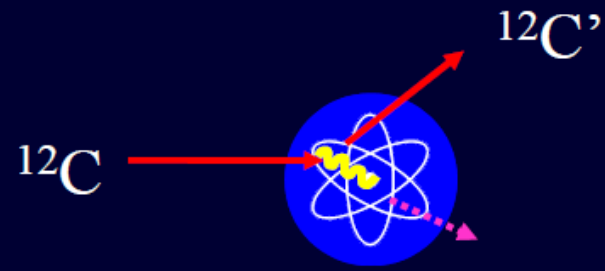
$$S \sim \frac{Z_p^2}{K_p}$$



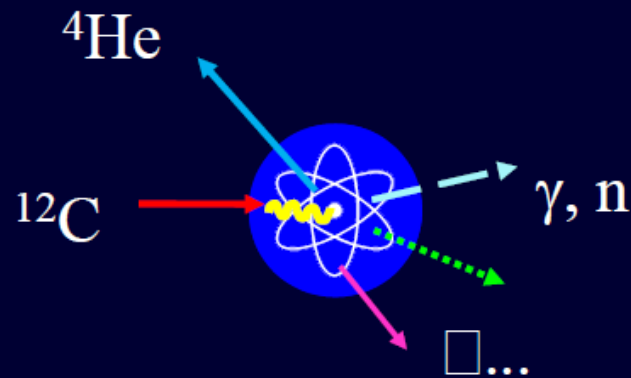
$$R \sim \int_0^{K_i} \frac{K_p}{Z_p^2} dK_p = \frac{K_p^2}{Z_p^2}$$



Nuclear interactions of heavy ions

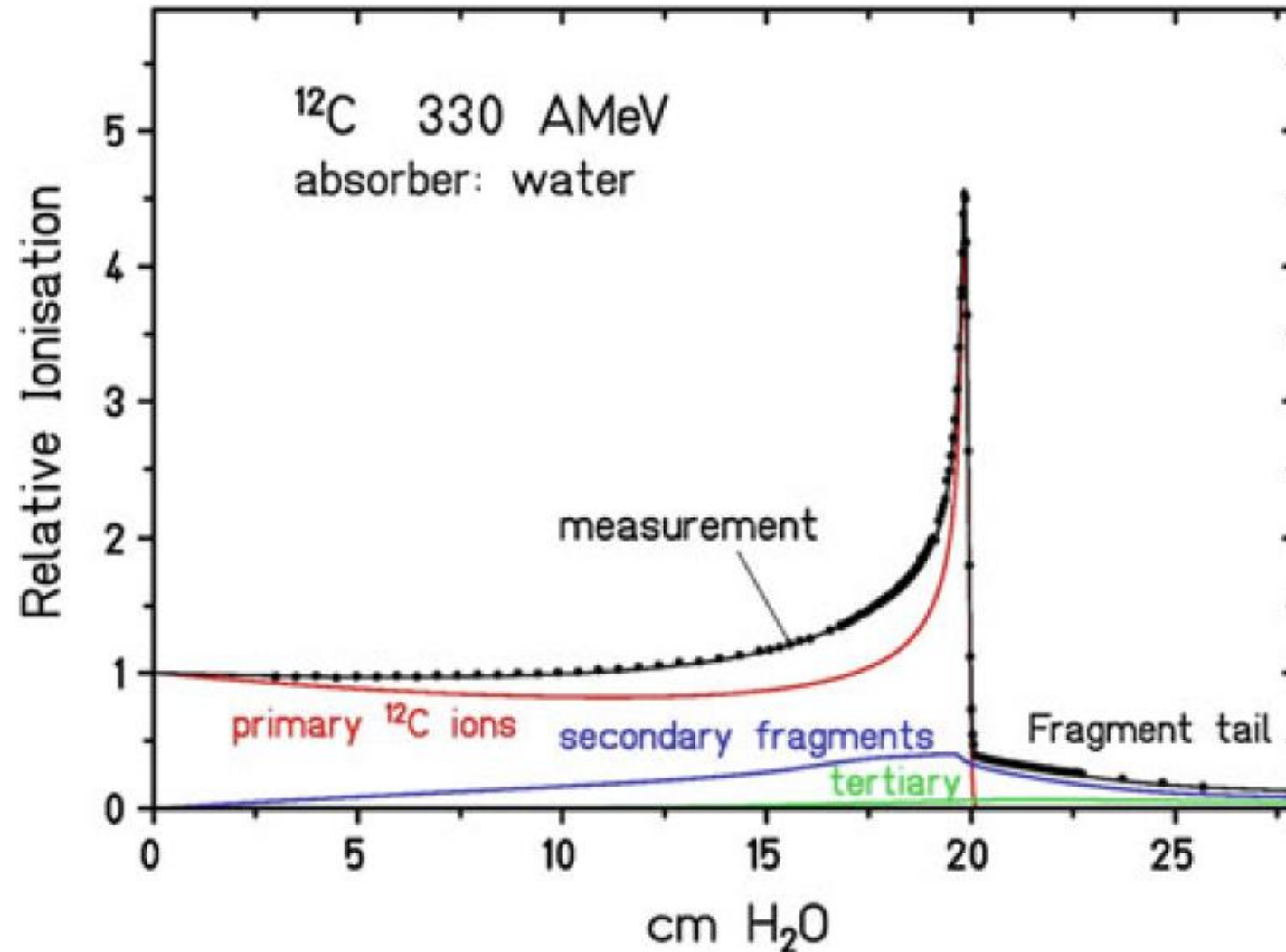


Elastic nuclear collision (large θ)

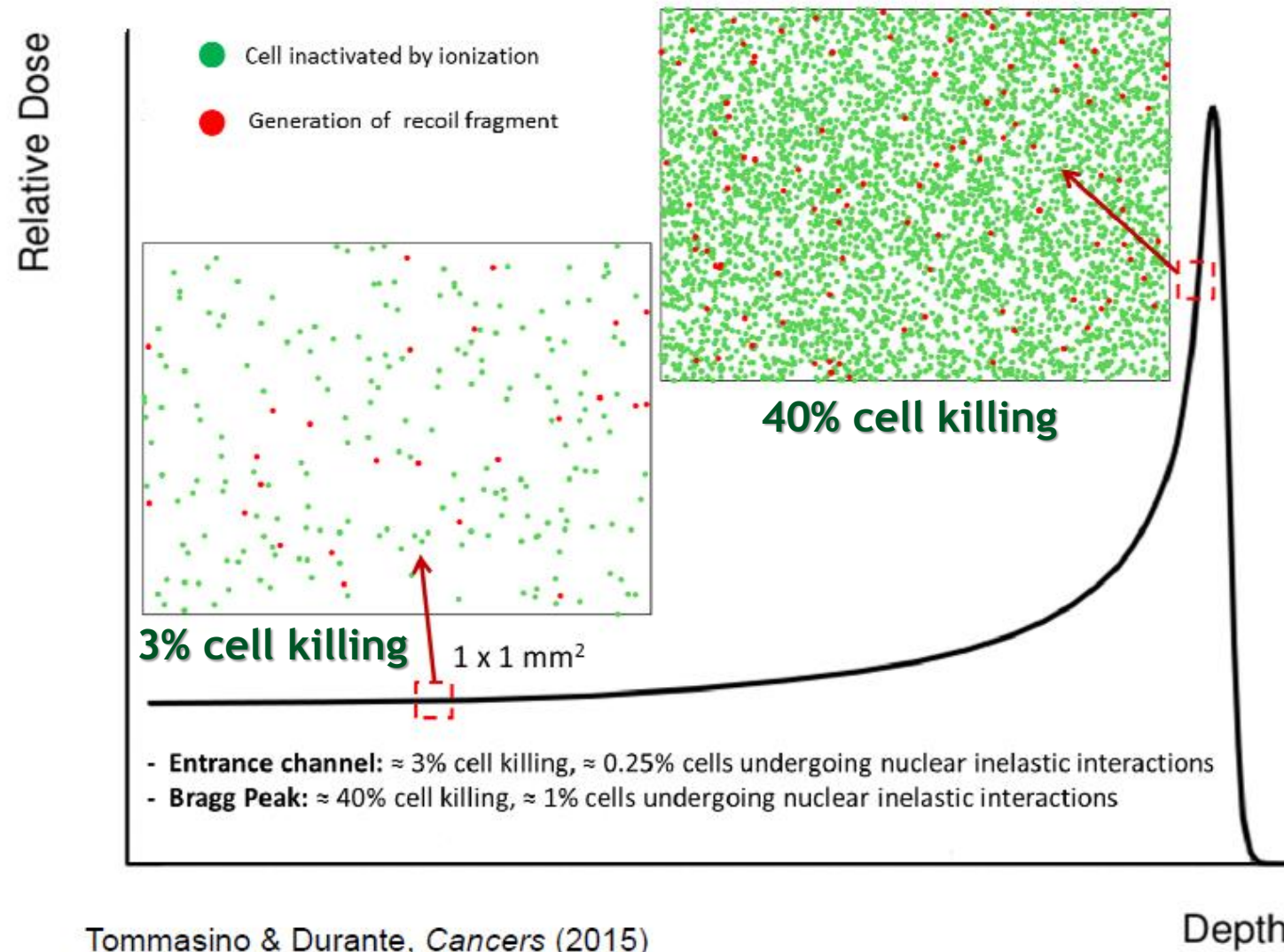


Nuclear interaction (fragmentation)

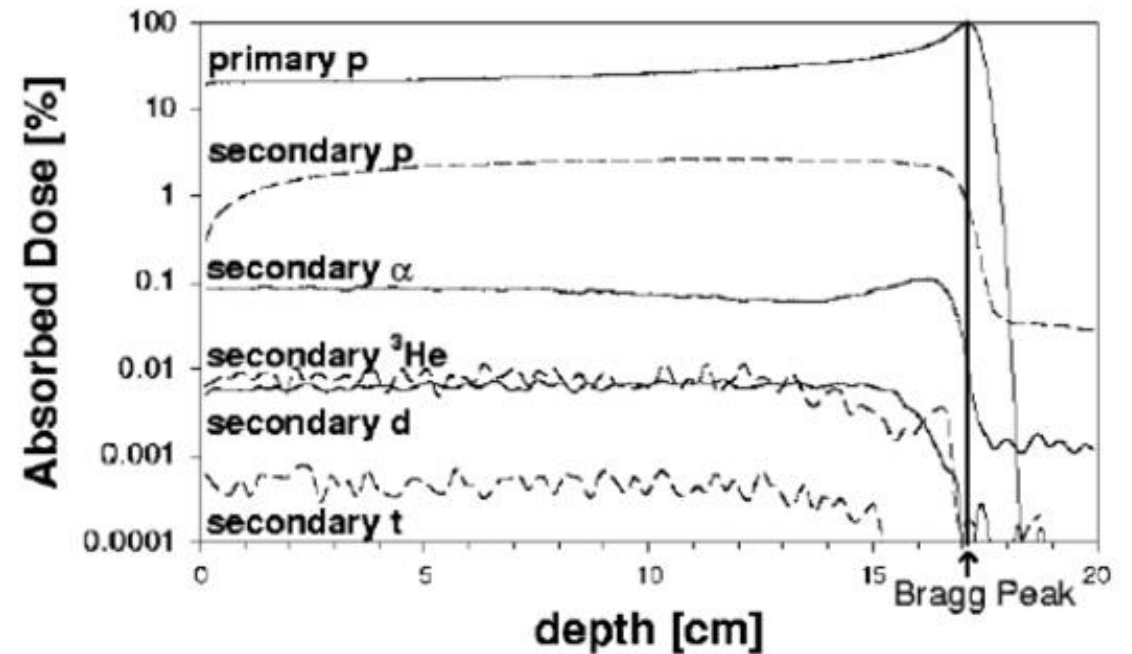
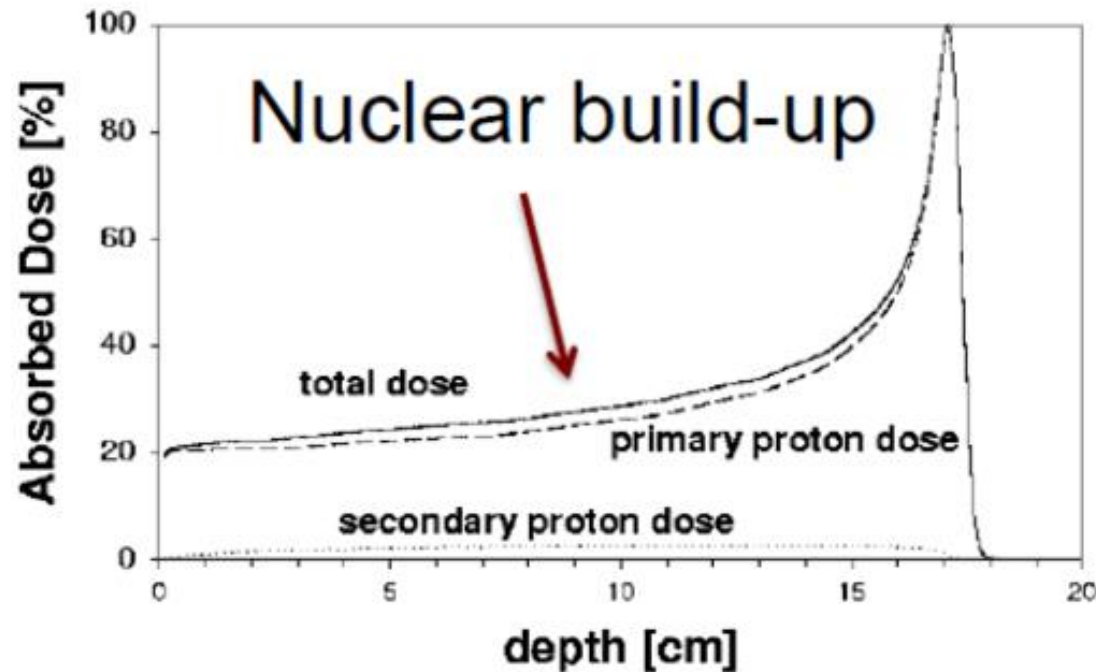
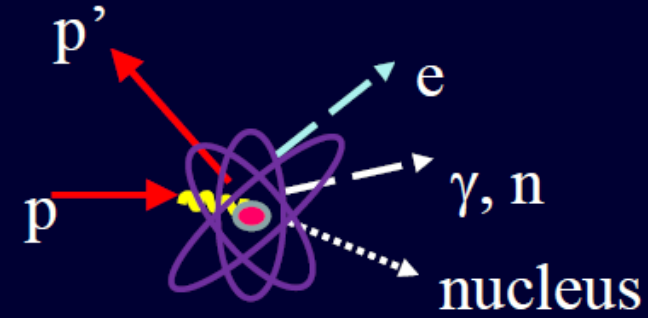
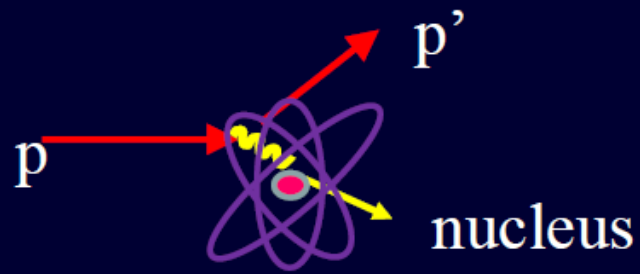
Dose from fragments with carbon ions



Impact of target fragmentation

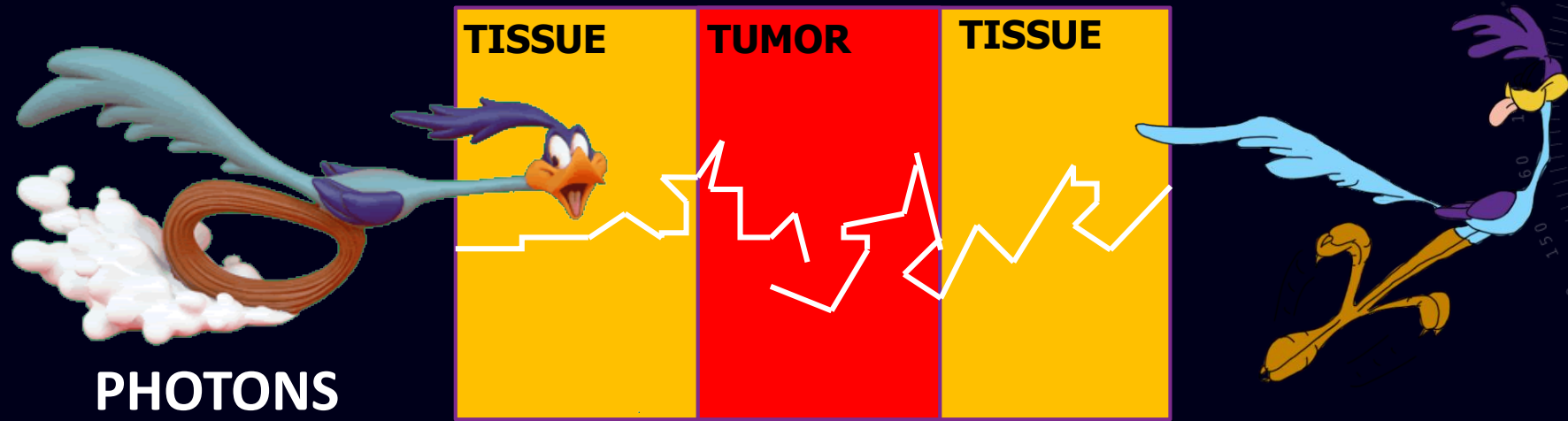


Nuclear interactions of protons



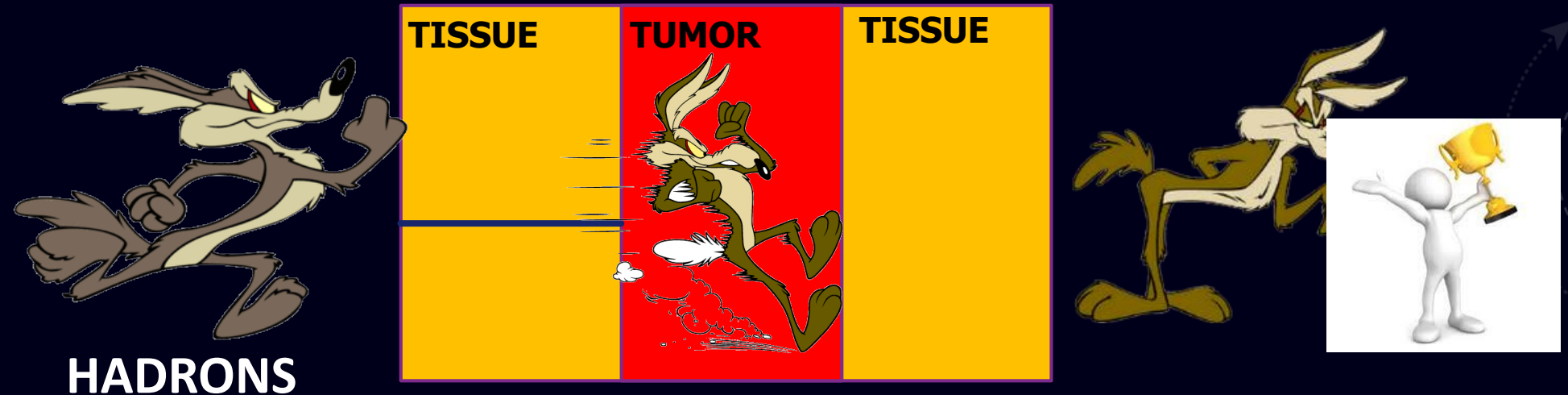
Summary

The physical strength of ions is...



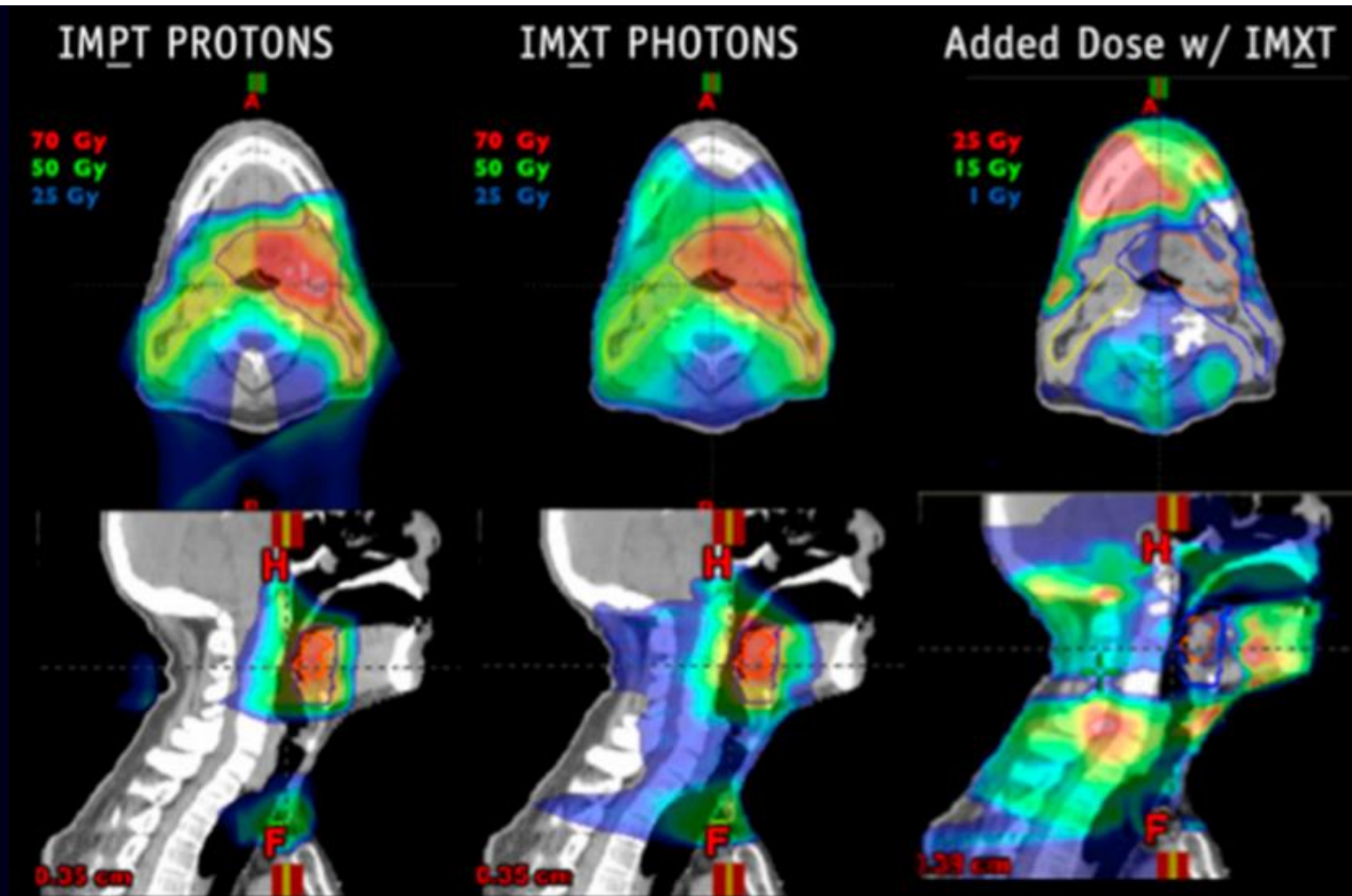
PHOTONS

...the ability to stop!!



HADRONS

Protons vs photons for head&neck tumors

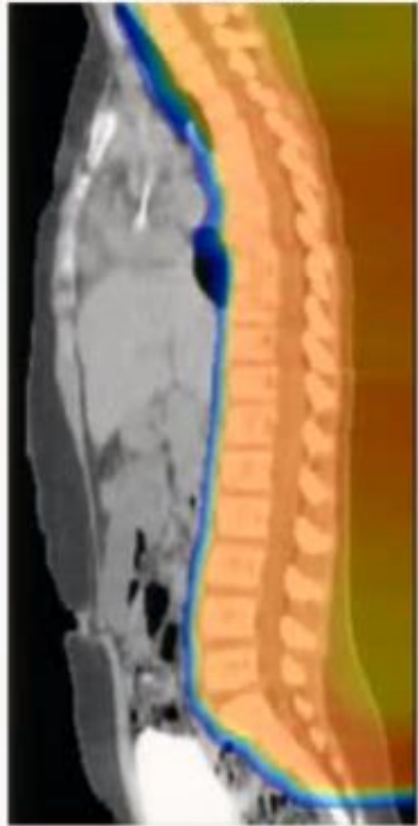


RED is high dose, GREEN is intermediate dose, BLUE is Lower dose

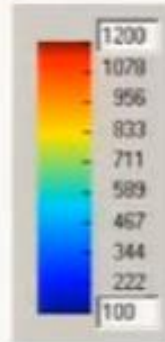
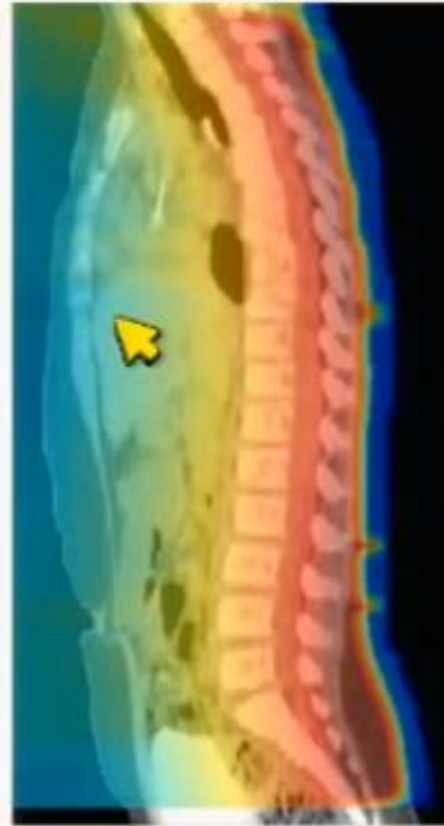
Protons vs photons for pediatric tumors

Medulloblastoma

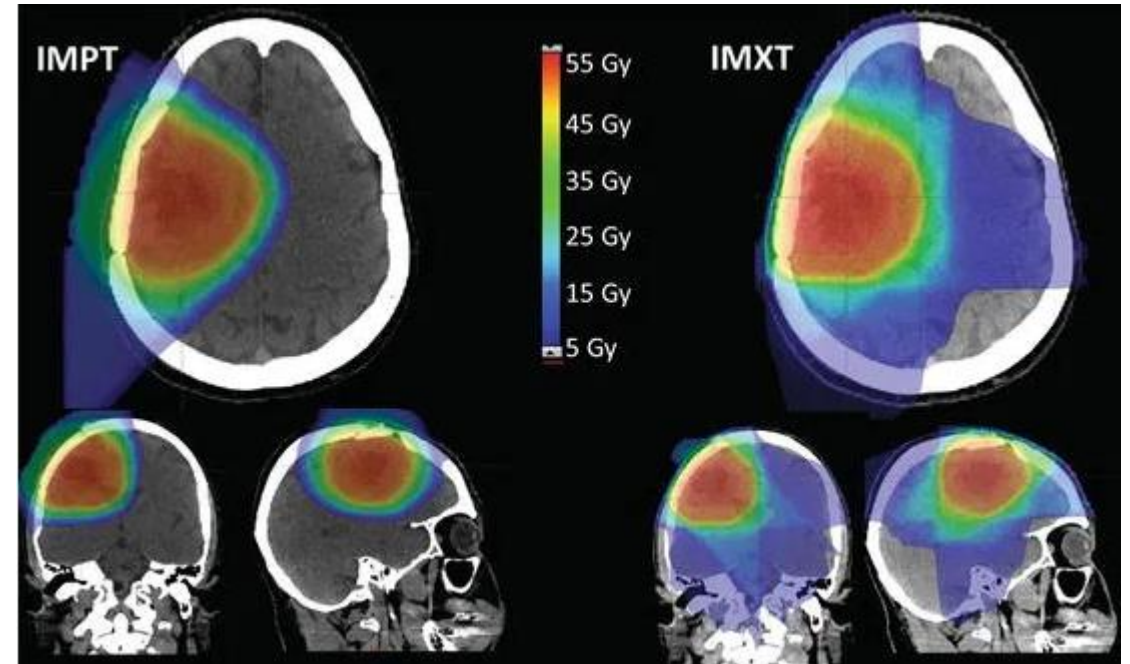
Protons



Photons



Pediatric brain tumors



X-rays, protons and carbon ions

Show different Linear Energy Transfer

Leading to different radiobiological effectiveness

The relative biological effectiveness - RBE

$$RBE_n = \frac{D_X}{D_{\text{Ion}}} \Big|_{S_X = S_{\text{Ion}} = n}$$

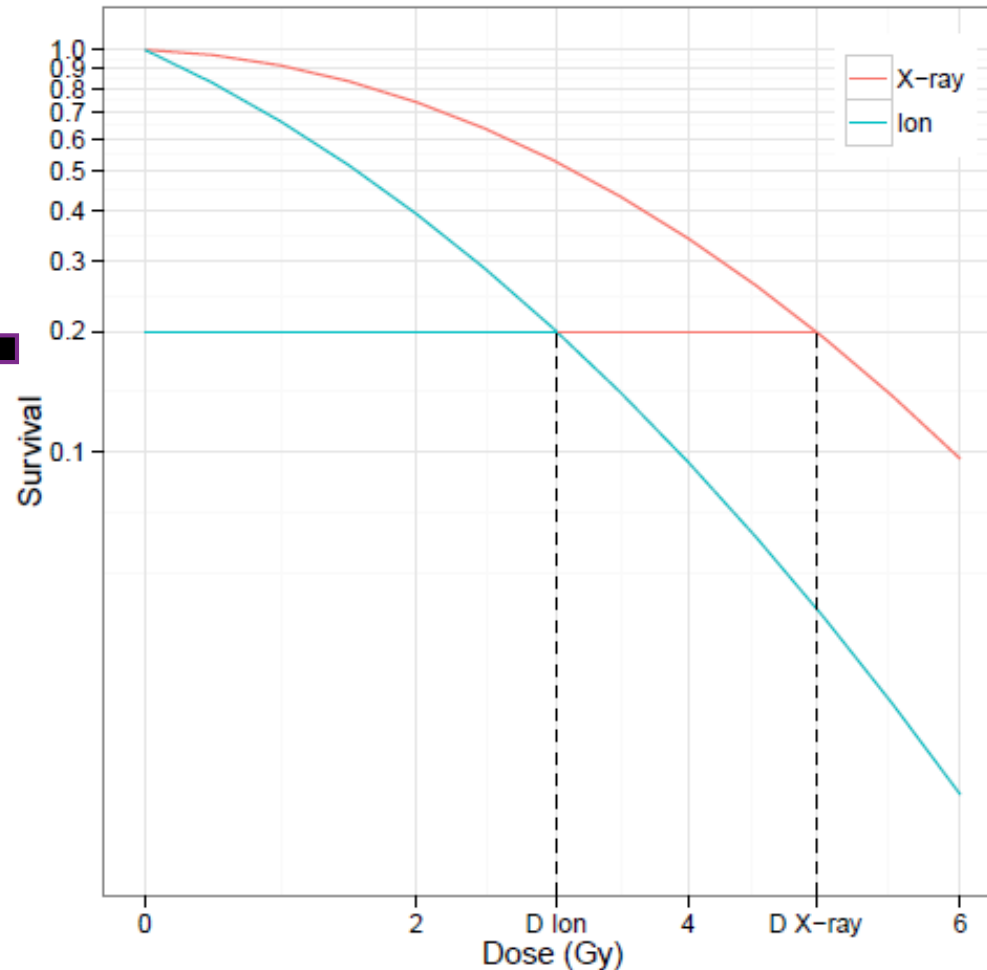
RBE is a function used to describe the biological effect of a radiation compared with X-rays effect

Survival curve and RBE

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

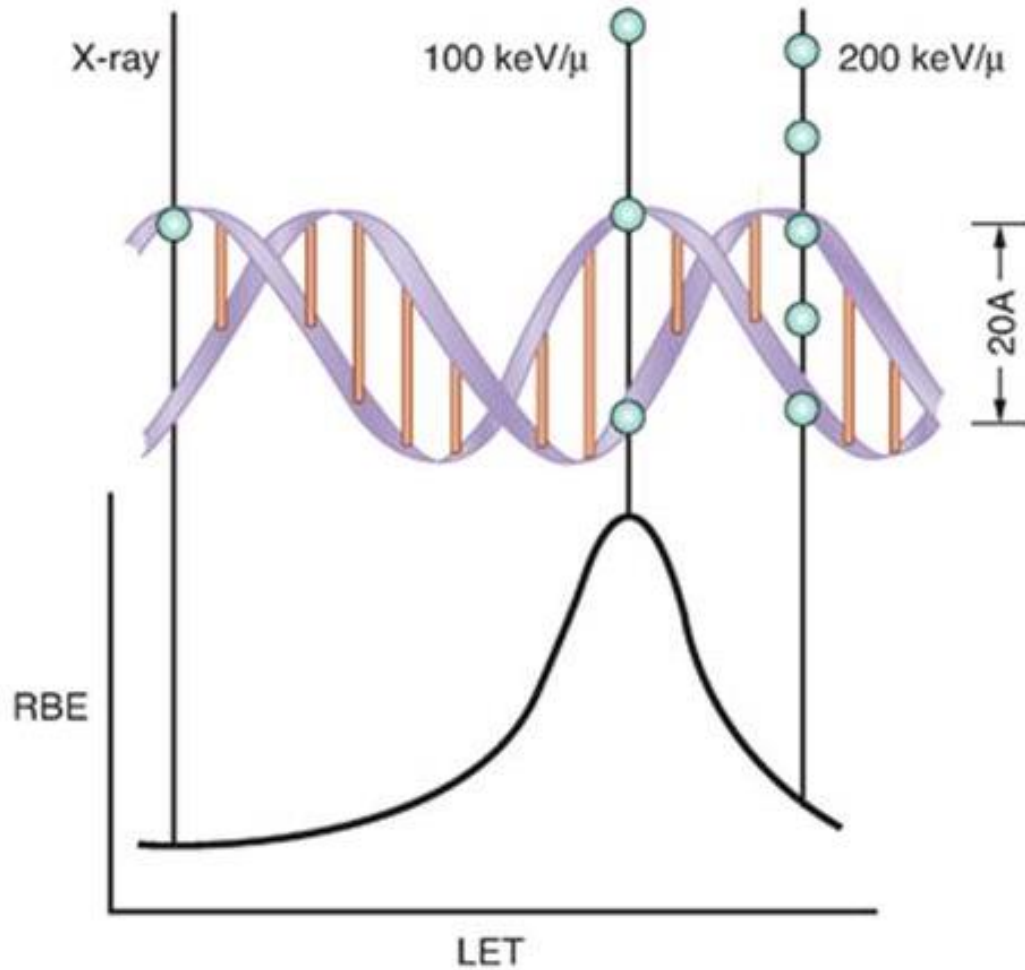
Same Biological Damage ←

$$D_{\text{bio}} = D \cdot RBE$$

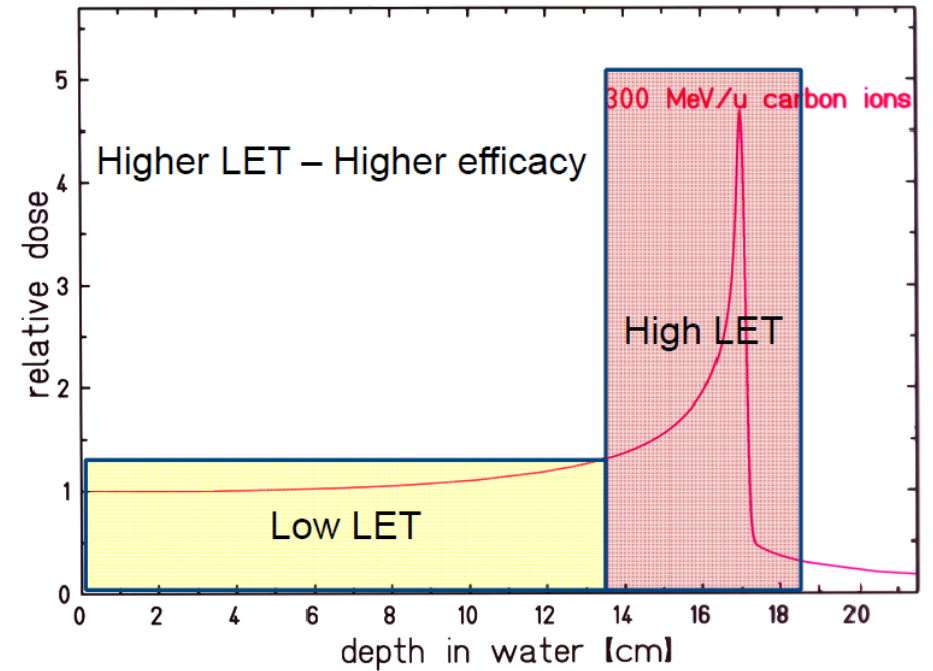


$$RBE_n = \frac{D_X}{D_{\text{Ion}}} \Big|_{S_X = S_{\text{Ion}} = n}$$

Relative Biologic Effectiveness (RBE) depends on Linear Energy Transfer (LET)

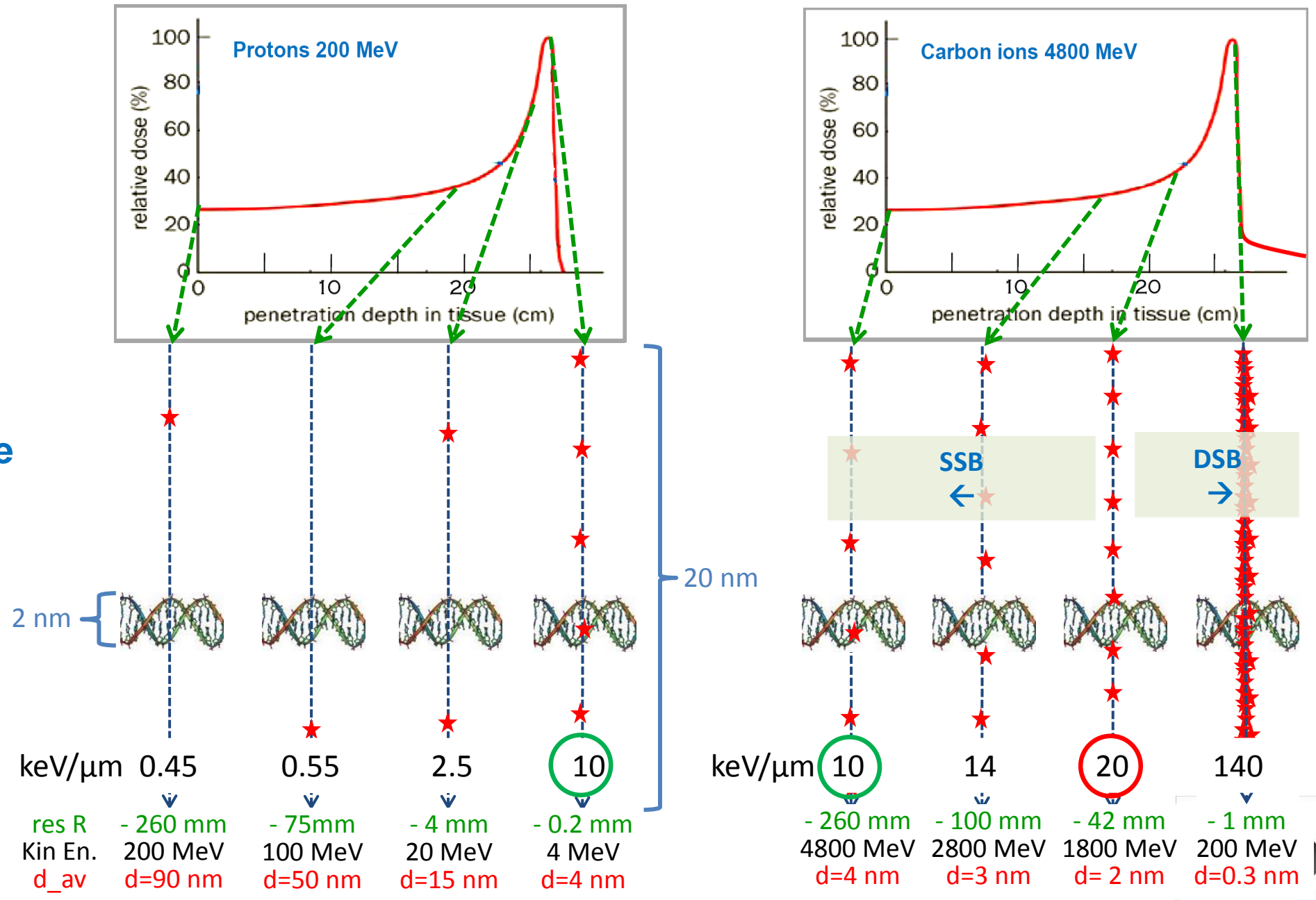


Carbon ions: high LET where needed



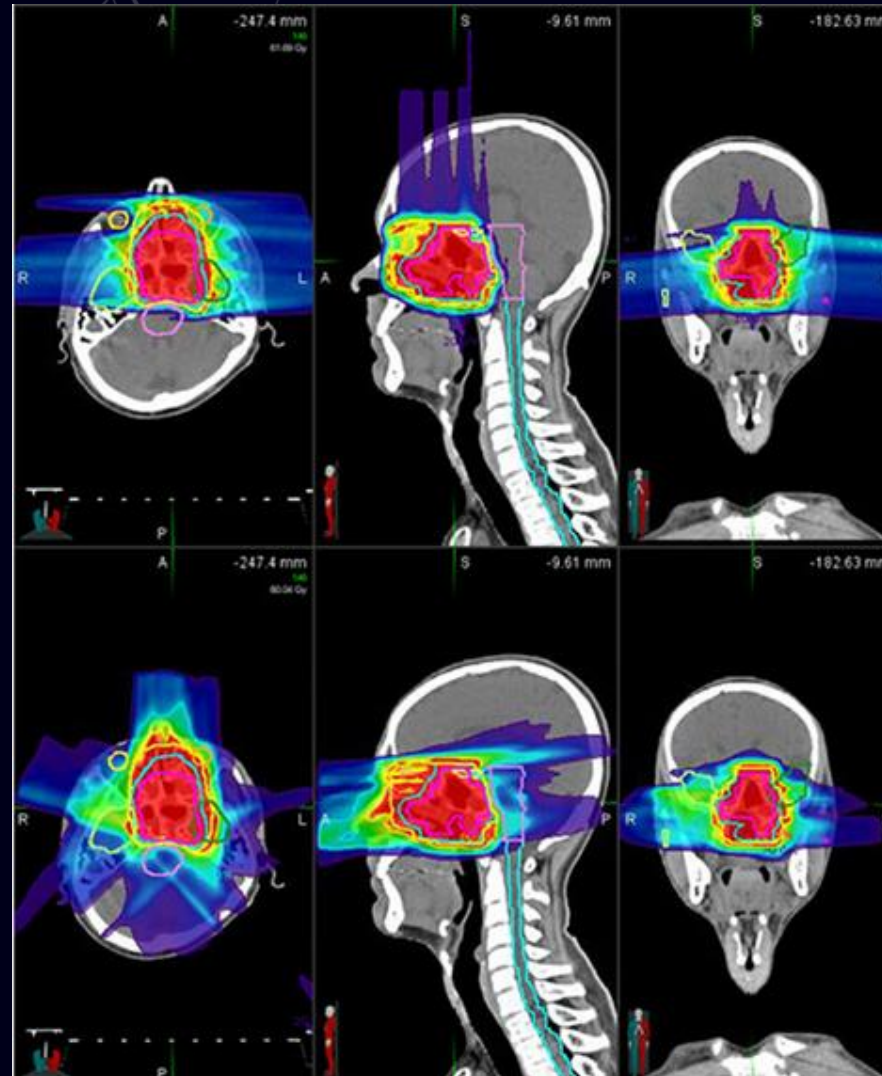
RBE

- RBE for protons is costante (~ 1,1)
- RBE for carbon ions Change along the path with a maximum in the Bragg peak



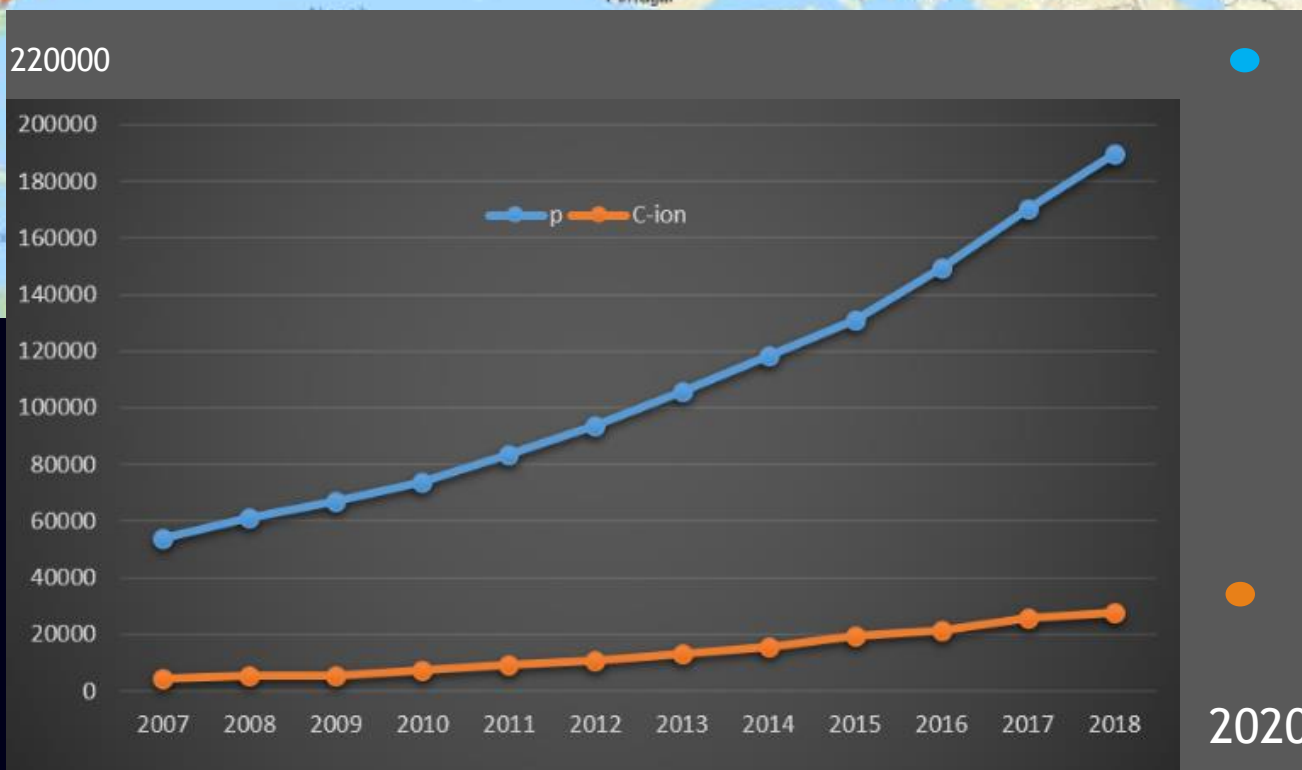
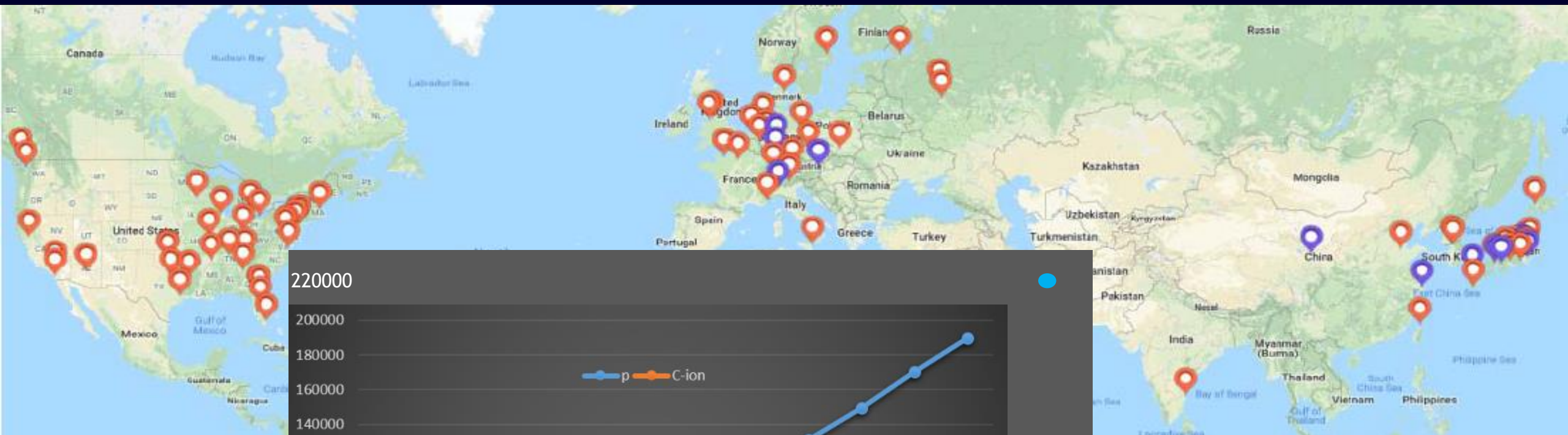
Carbon ions vs X-rays

Carbon ions



X-rays

Centers worldwide and patients treated



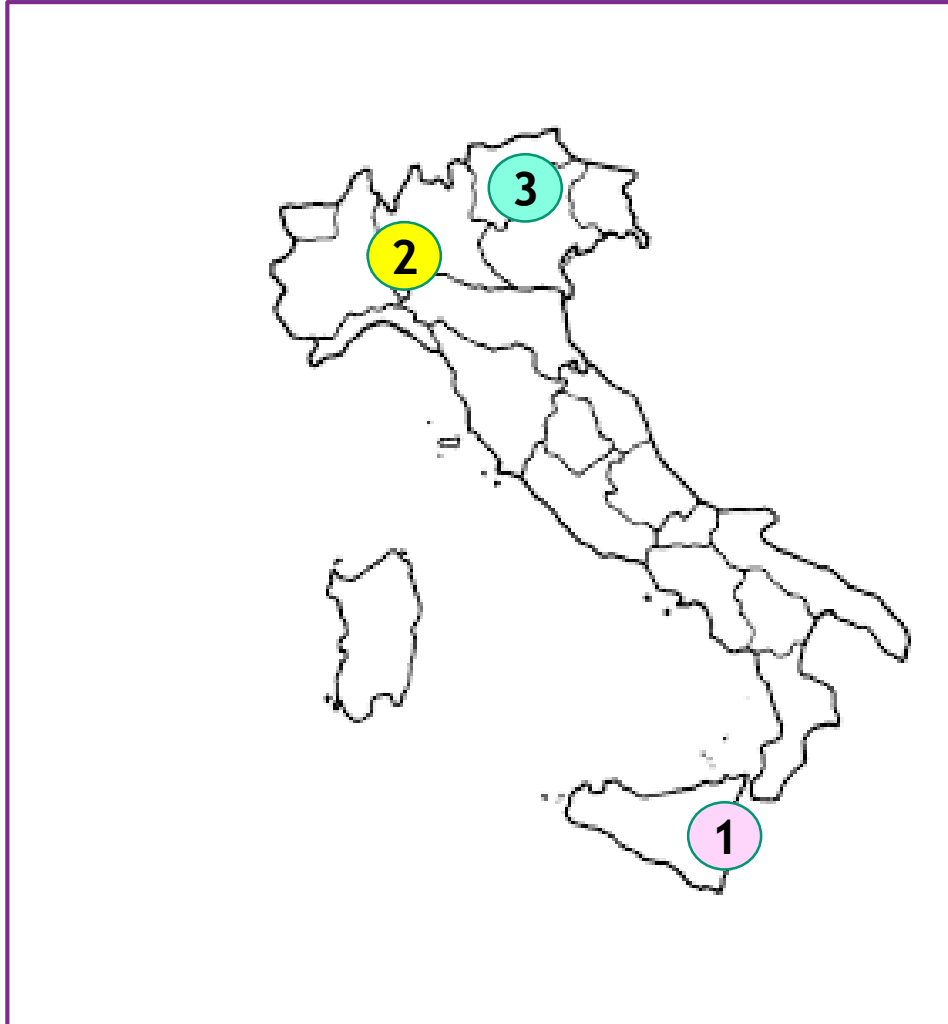
January 2020

217400

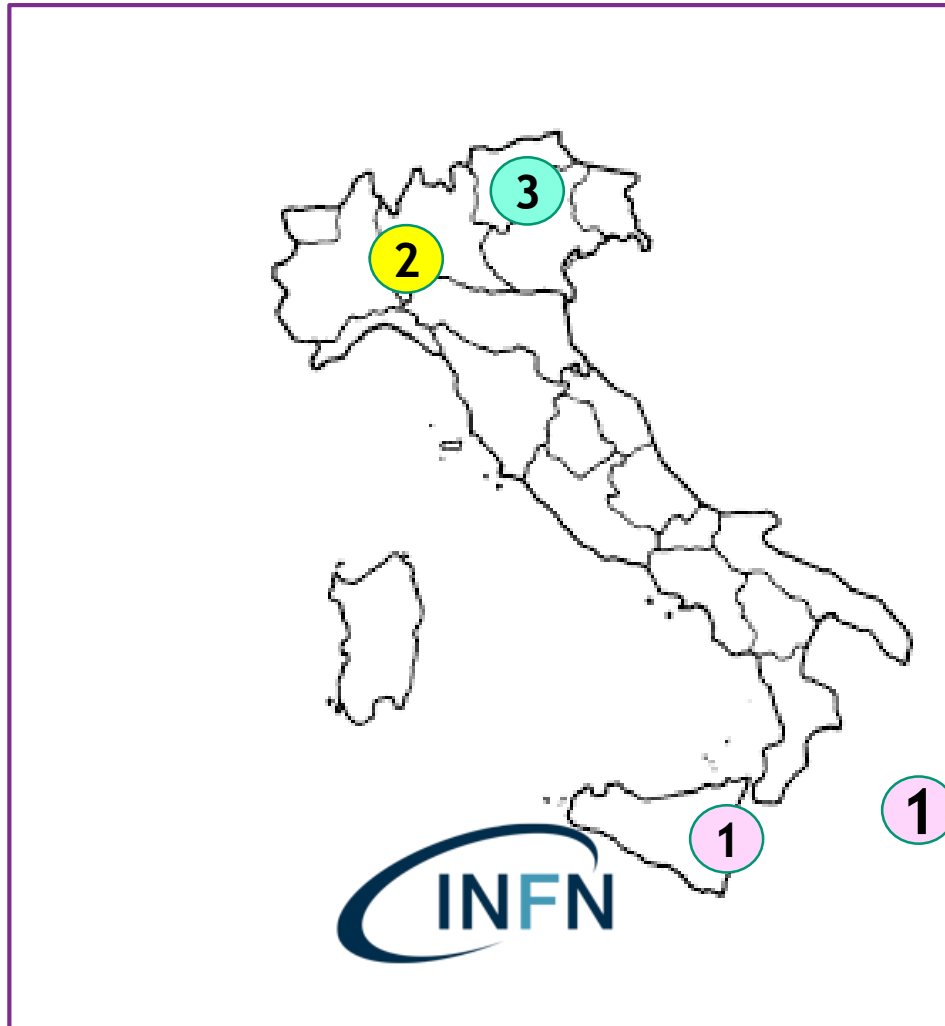
30000

[Ref 5]

Italian particle therapy centers



Italian particle therapy centers



Beam line in the INFN Physics laboratory

CATANA - Catania

1st patient 2002

400 patients

CATANA in Catania



First center to treat with protons
eye tumors

1st patient in 2002

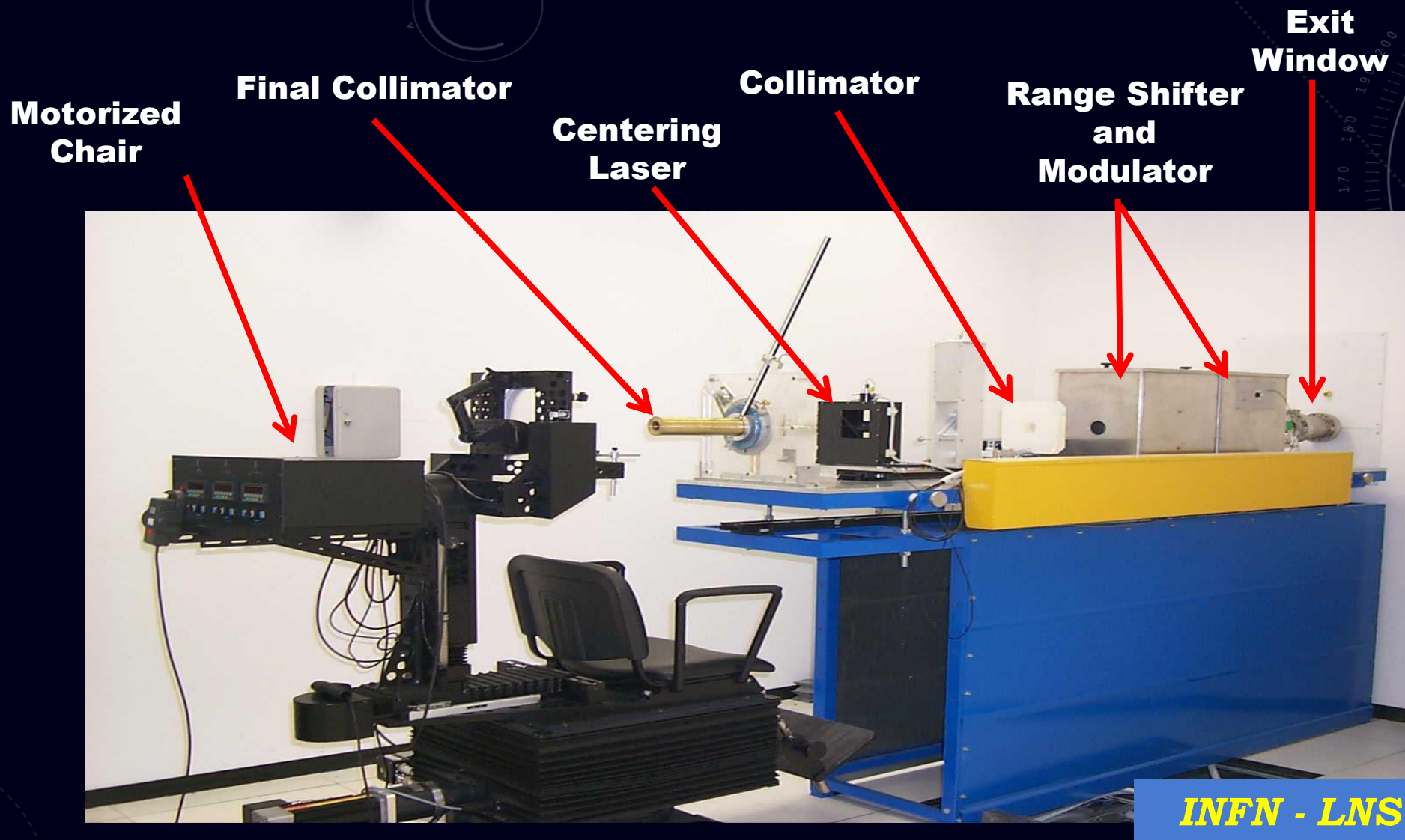
~200 treated patients



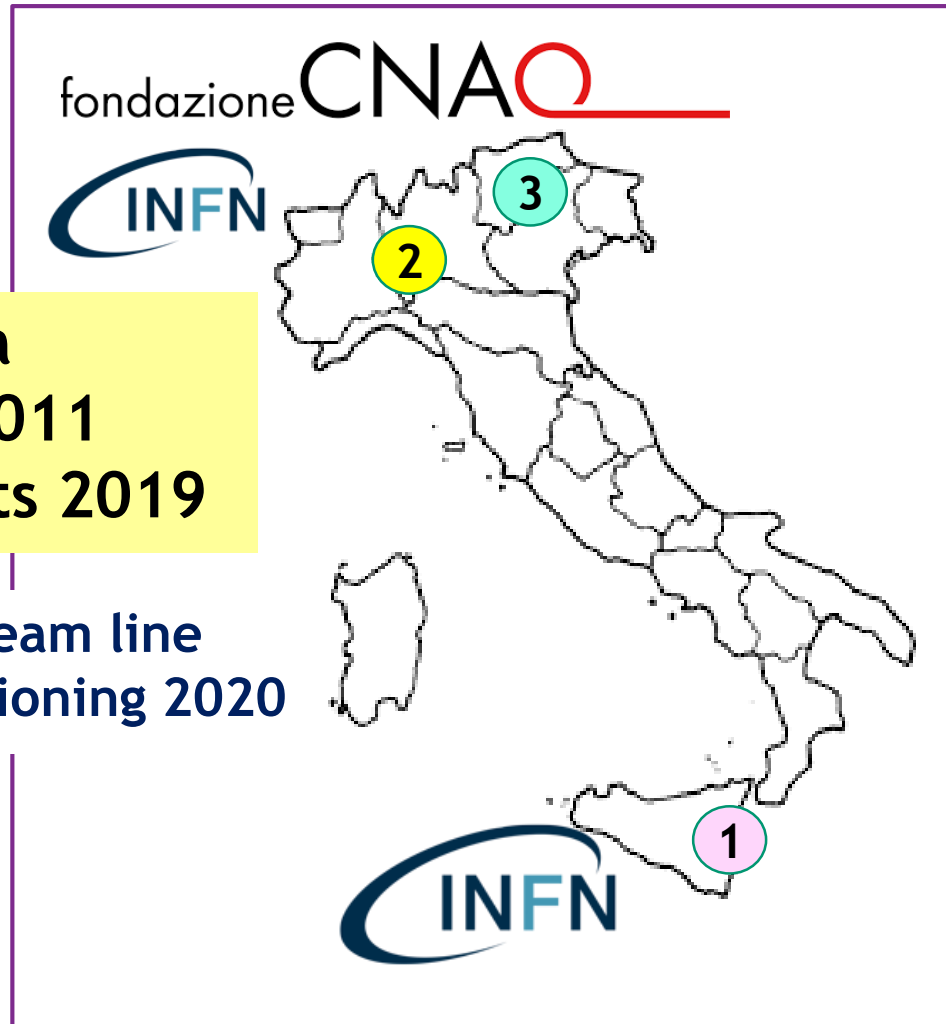
Centro di **A**droTerapia e
Applicazioni **N**ucleari **A**vanzate



CATANA BEAM LINE



Italian particle therapy centers



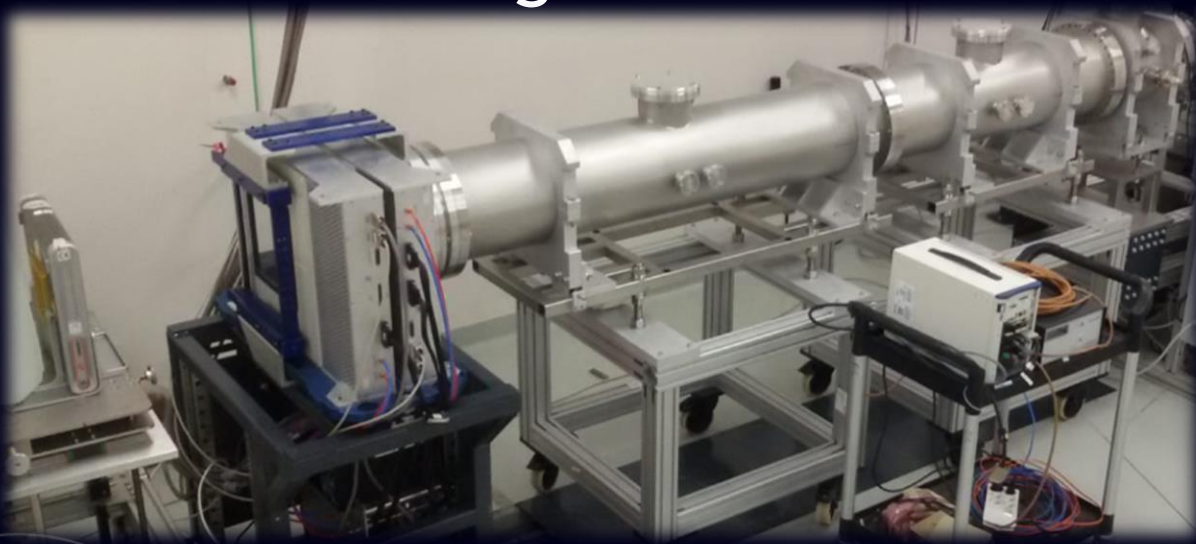
CNAO - Pavia
1st patient 2011
2500 patients 2019

Experimental beam line
End of commissioning 2020

Centro Nazionale di Adroterapia Oncologica - CNAO

One of the 6 facilities in the world
with both Proton and carbon ions beams

- 1 experimental room under
commissioning



<https://fondazionecnao.it/it/>

1991 the idea → 2011 first patient

1991 : Ugo Amaldi (CERN) proposed a center for teletherapy with hadrons



First Italian center built for:

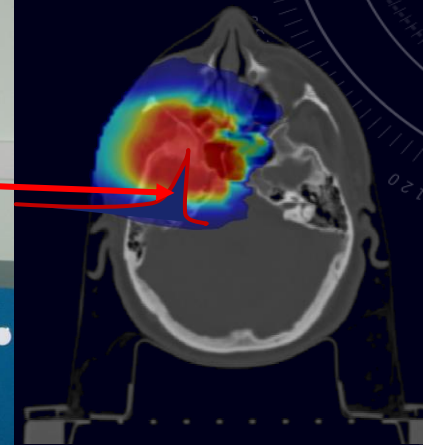
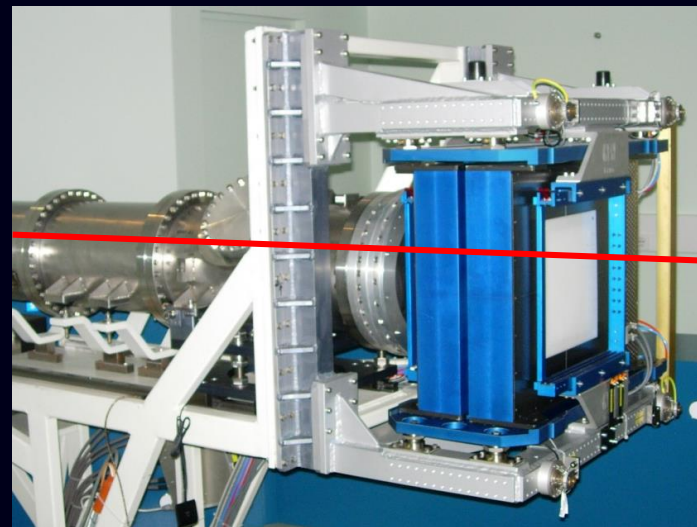
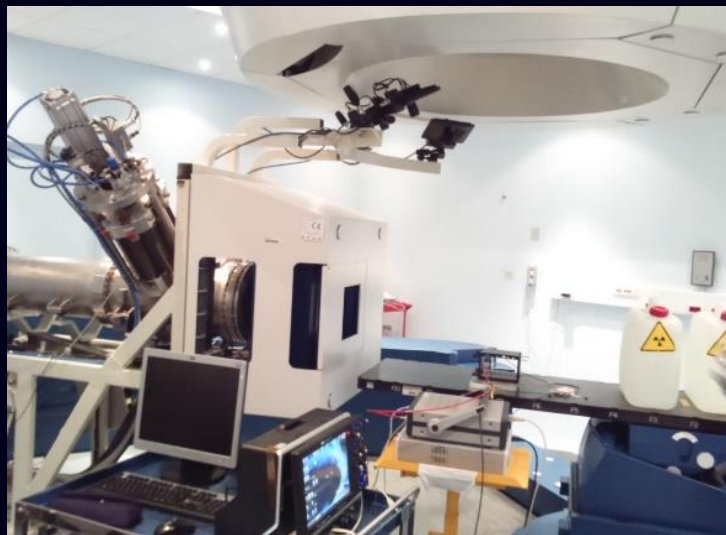
- Patients' treatment with carbon ions and protons
- Clinical and radiobiological research

2011, September: beginning of the treatments with protons

2012, October: beginning of the treatments with carbon ions



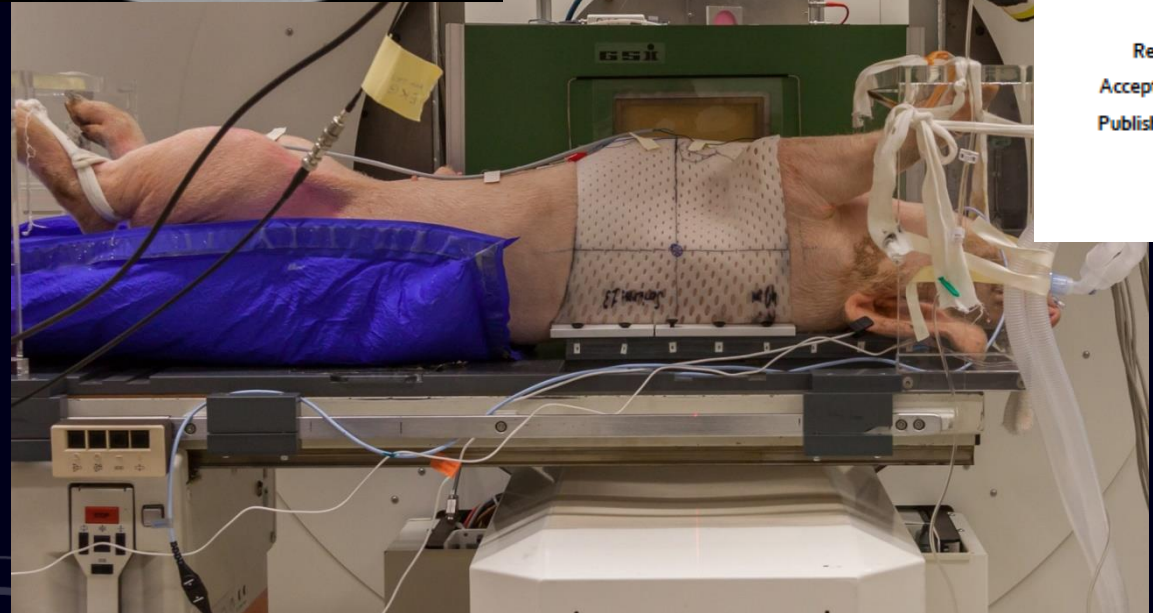
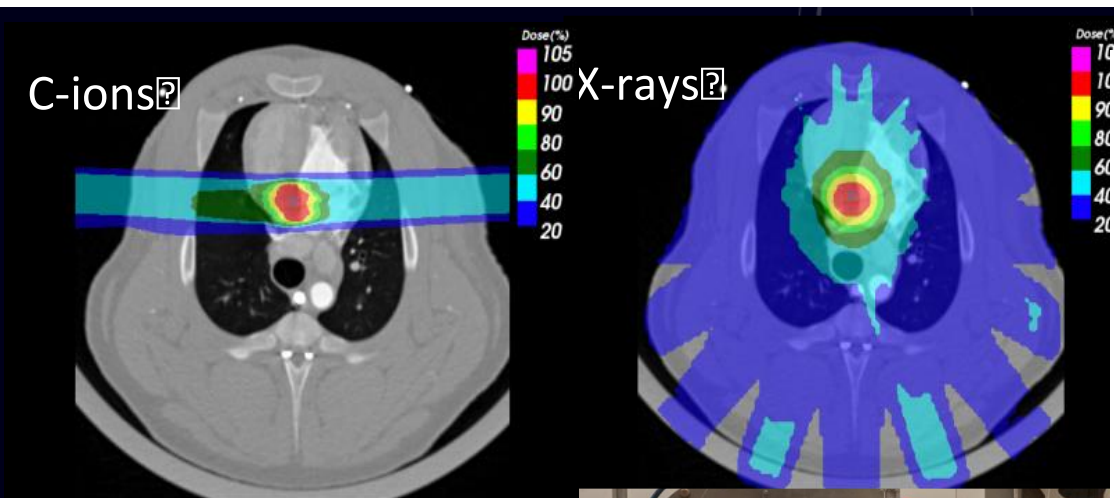
Developed by Fondazione CNAO, INFN and University of Torino



Reference [6]

CNAO Dose Delivery System: Particle detectors integrated with the synchrotron to guide and monitor the beam in real time

Particle therapy: beyond cancer



SCIENTIFIC REPORTS

OPEN 2016

Feasibility Study on Cardiac Arrhythmia Ablation Using High-Energy Heavy Ion Beams

Received: 08 August 2016
Accepted: 09 November 2016
Published: 20 December 2016

H. Immo Lehmann^{1,*}, Christian Graeff^{2,*}, Palma Simoniello², Anna Constantinescu², Mitsuru Takami¹, Patrick Lugenbiel³, Daniel Richter^{2,4}, Anna Eichhorn², Matthias Prall², Robert Kaderka², Fine Fiedler⁵, Stephan Helmbrecht⁵, Claudia Fournier², Nadine Erbedinger², Ann-Kathrin Rahm³, Rasmus Rivinius³, Dierk Thomas³, Hugo A. Katus³, Susan B. Johnson², Kay D. Parker², Jürgen Debus⁶, Samuel J. Asirvatham¹, Christoph Bert^{2,4}, Marco Durante^{2,7} & Douglas L. Packer¹



Courtesy of M. Durante

Not only cancer

January 22, 2020

CULTURE 22/01/2020 14:14 CET | Aggiornato 15 ore fa

Aritmia ventricolare trattata con un fascio di protoni, prima volta al mondo

L'intervento, messo a punto in collaborazione con la Fondazione Irccs Policlinico San Matteo, è stato eseguito al Cnao di Pavia

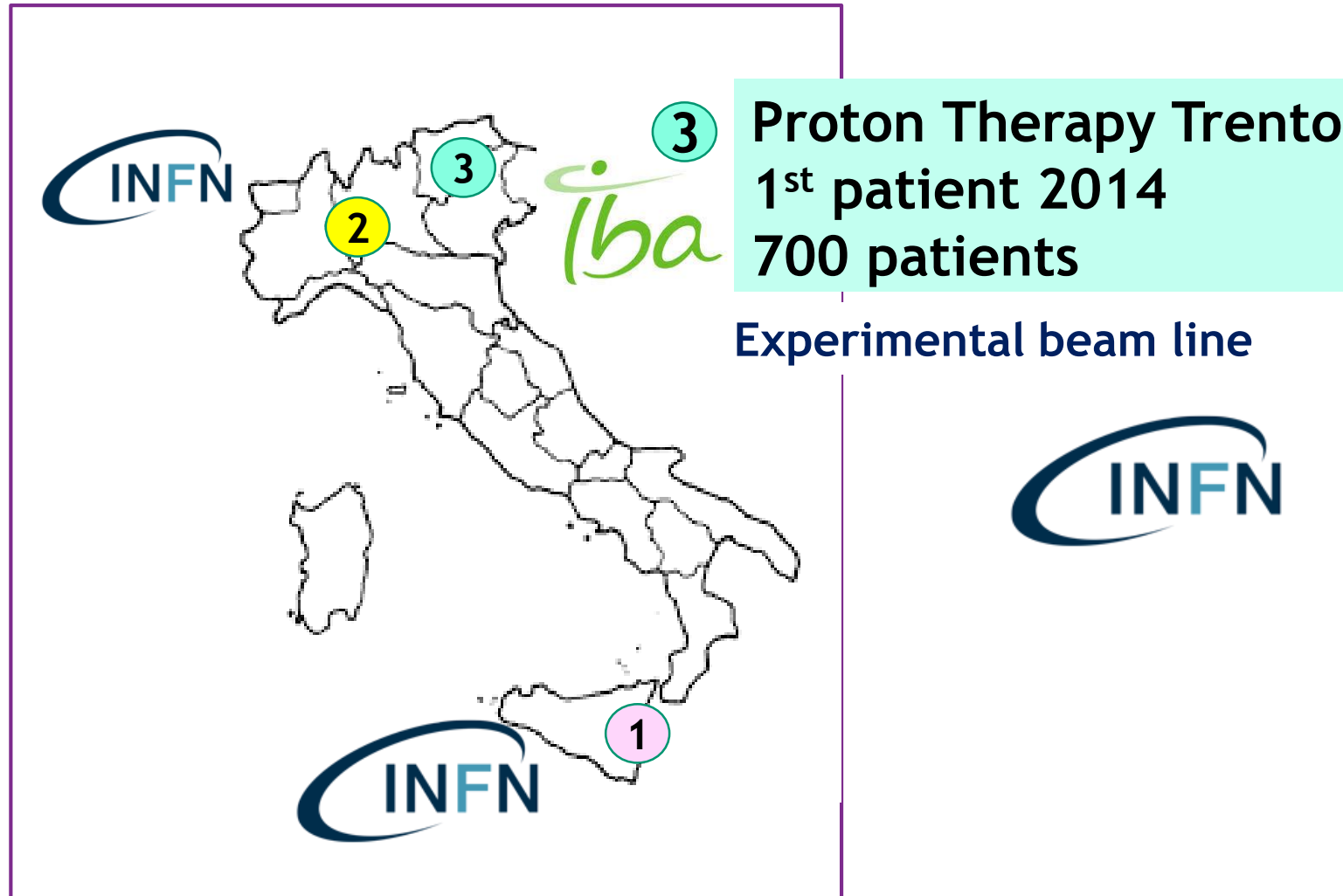
ANSA



SCIENCE/SCIENCE PHOTO LIBRARY VIA GETTY IMAGES

Illustration of a man's heart.

Italian particle therapy centers



PROTONTERAPIA TRENTO and TIFPA

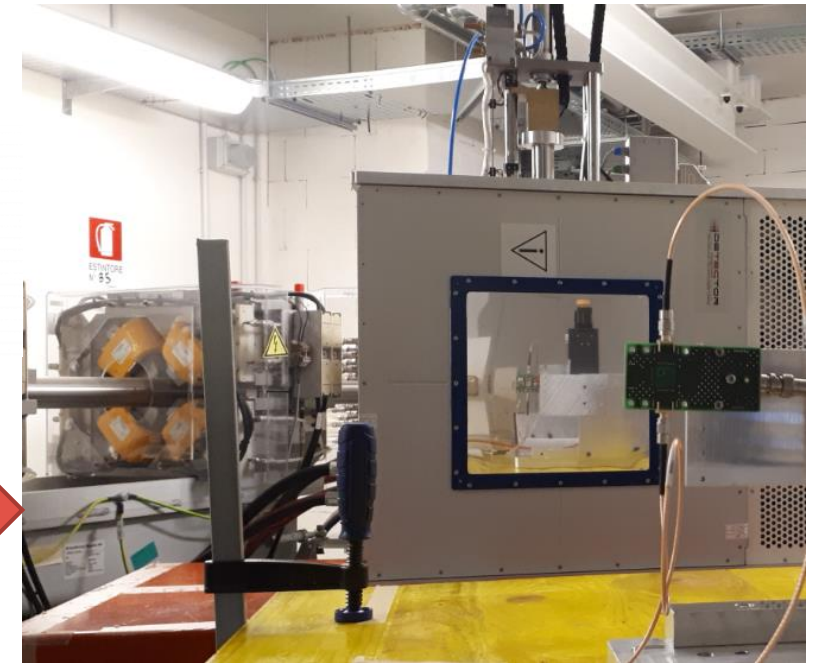


PROTONTERAPIA
TRENTO

<https://protonterapia.provincia.tn.it/>



Trento Institute for
Fundamental Physics
and Applications



Two treatment rooms with gantry

One experimental room for research

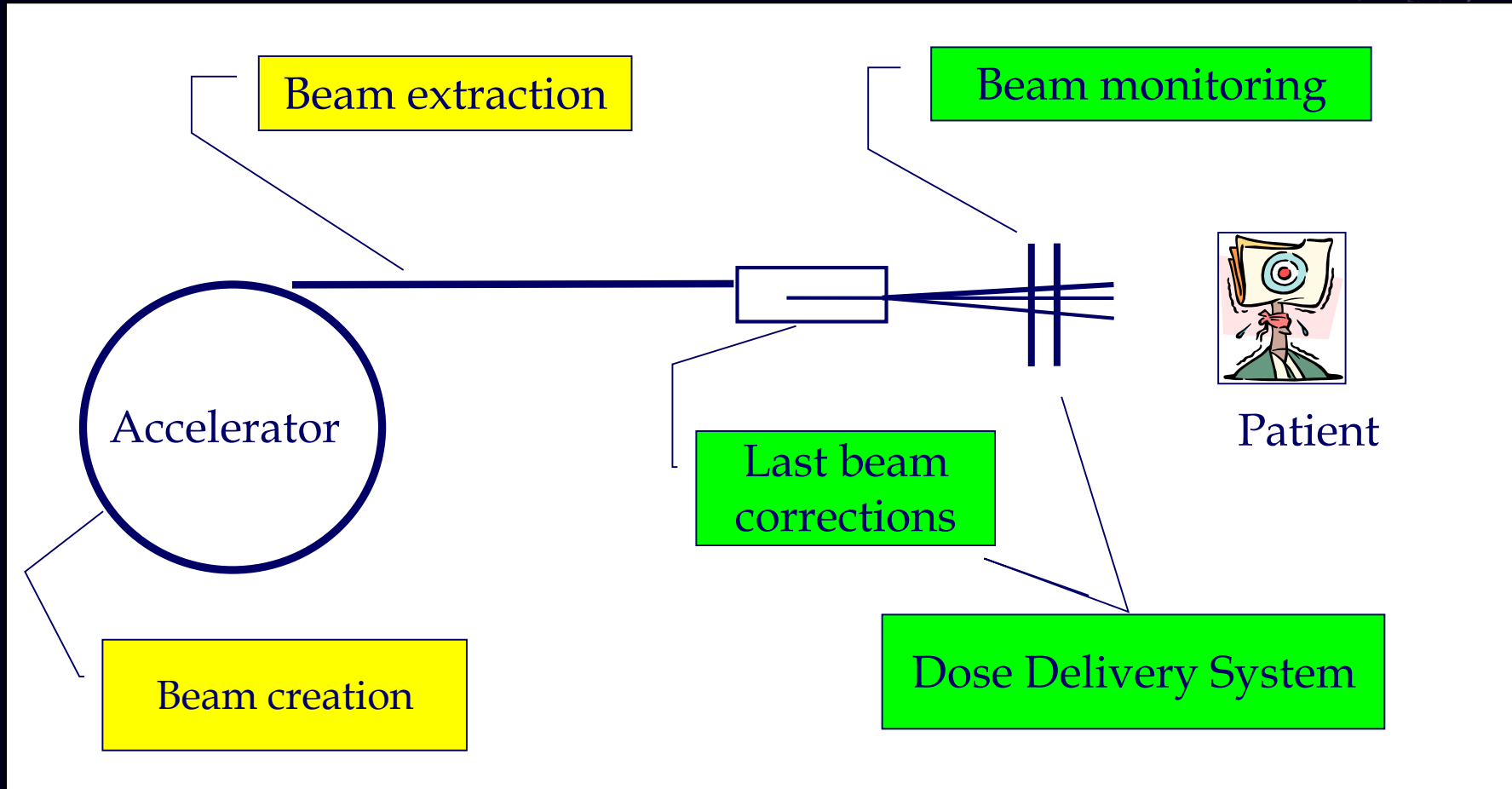
First treatments → end of 2014

1000 patients → end of 2019

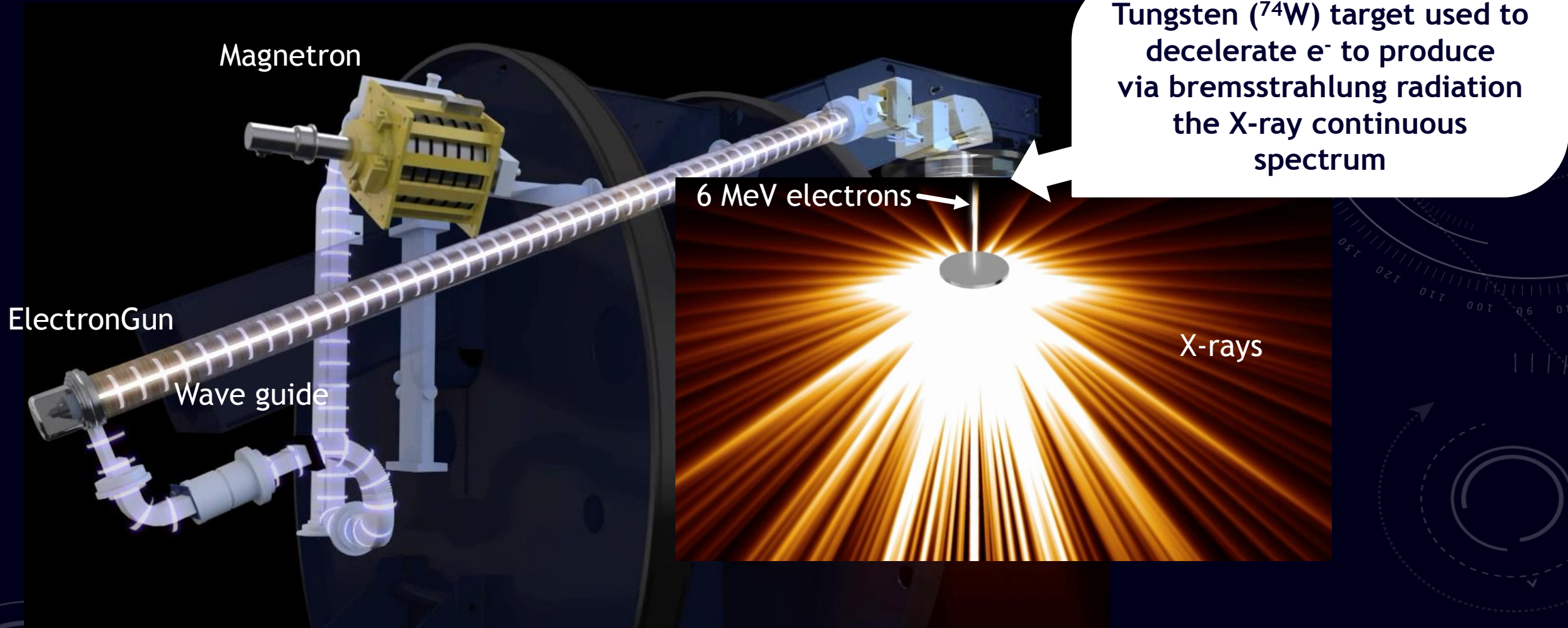
Radiotherapy Instrumentation



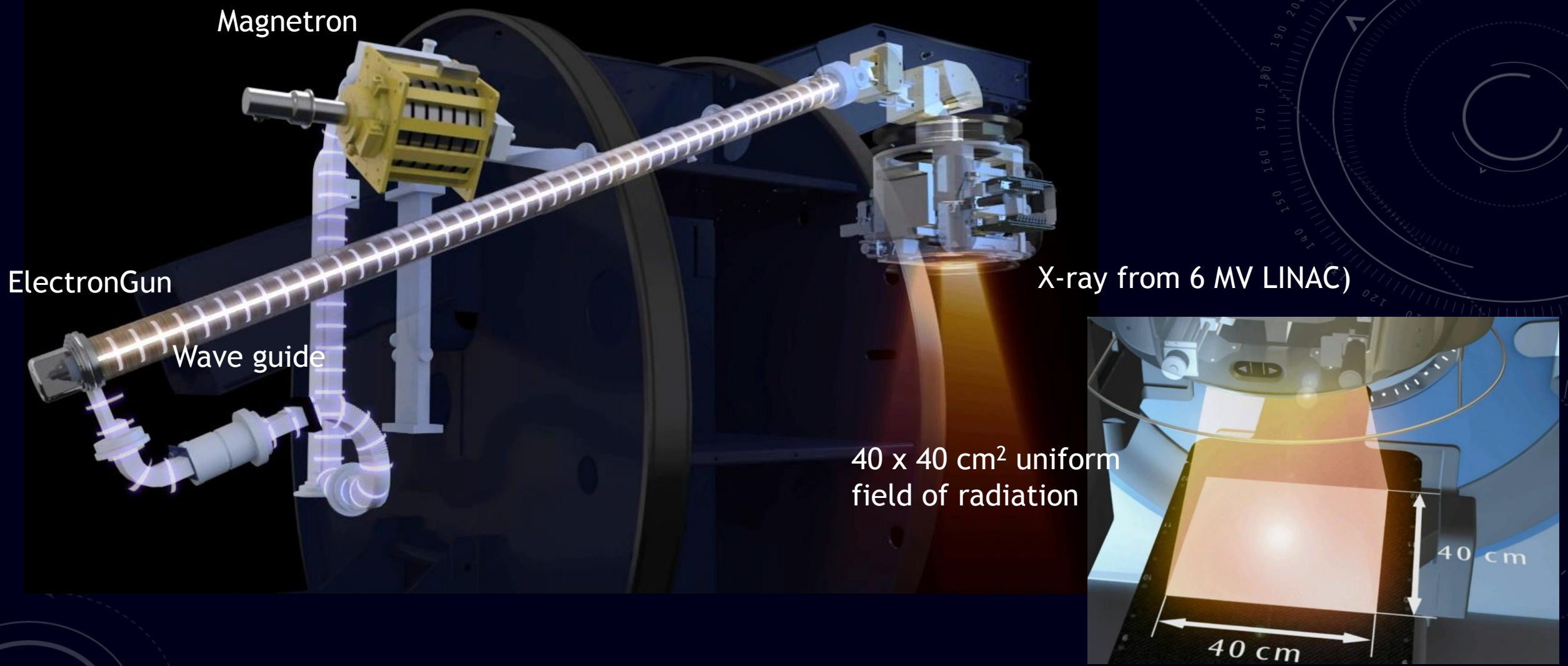
Radiotherapy Instrumentation



LINAC for radiotherapy



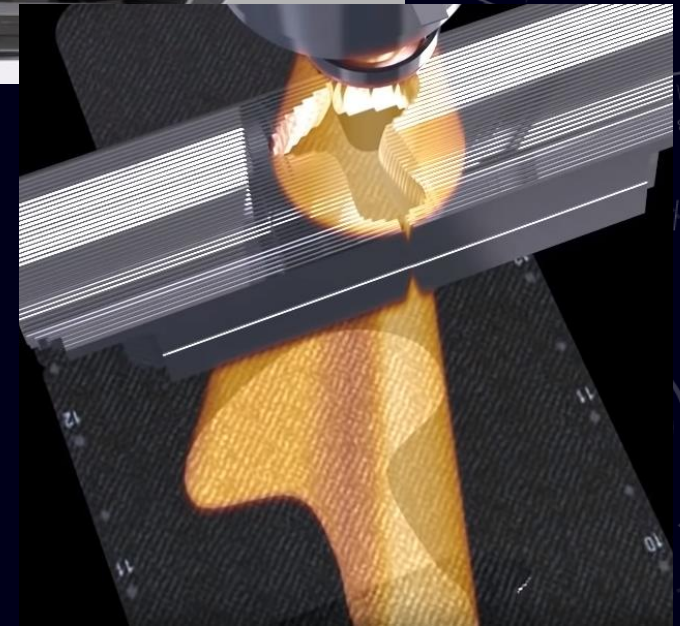
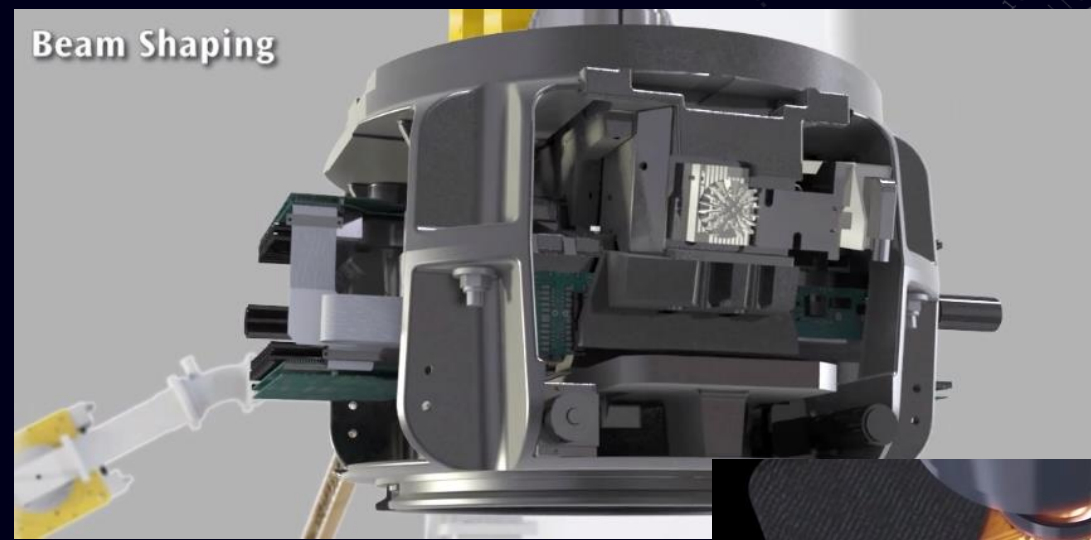
LINAC for radiotherapy

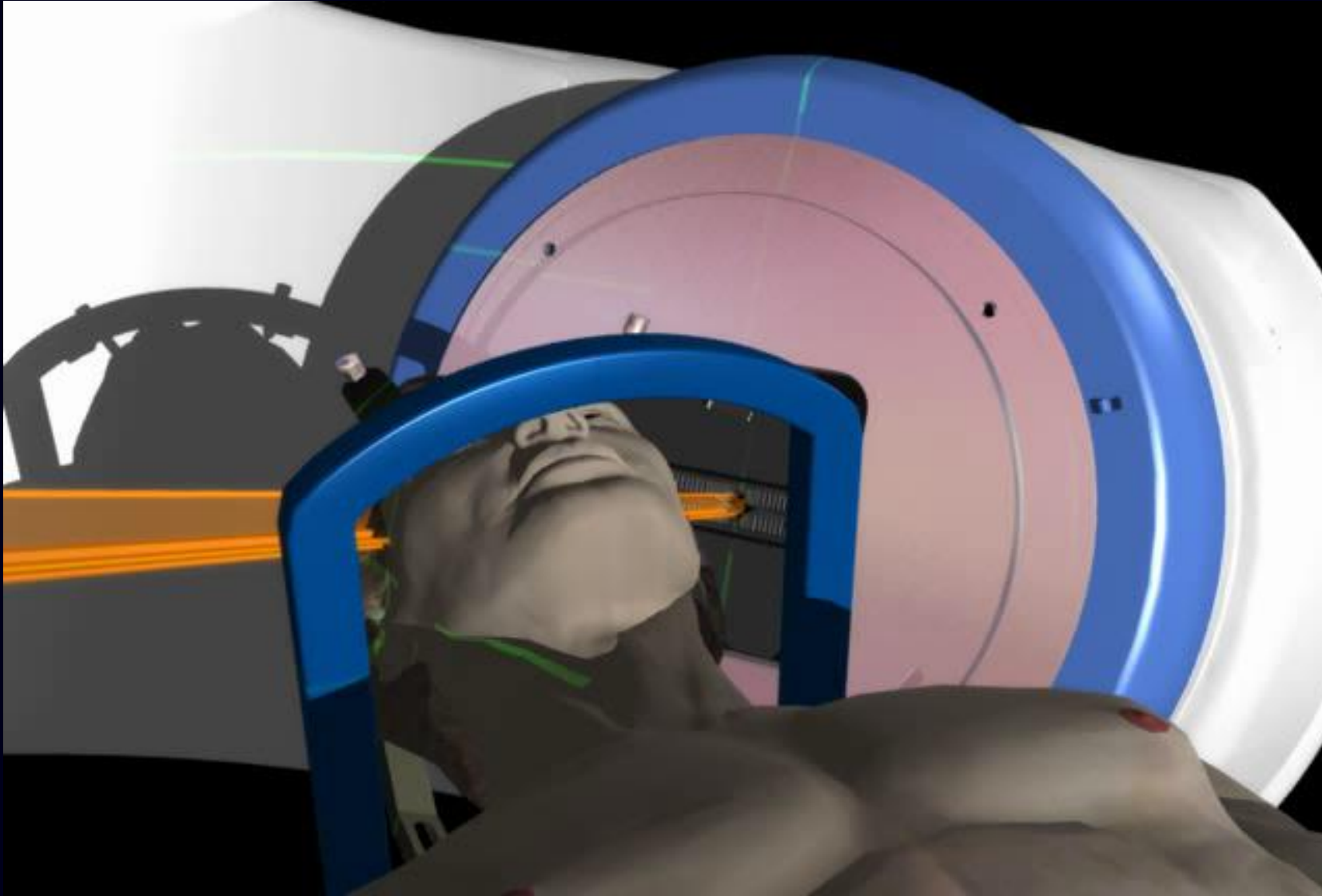


Dose Delivery to shape the X-ray beam

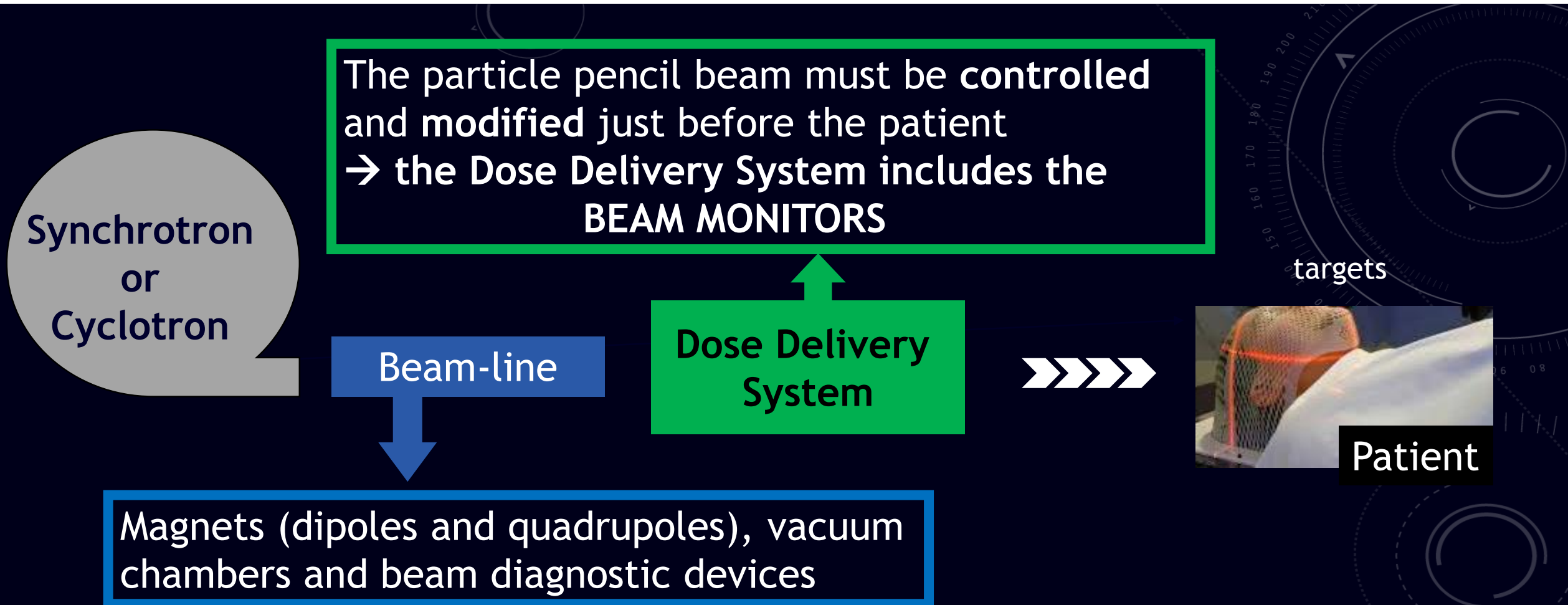


Dynamic multileaf collimator to shape the beam (up to 160 individual leaves)

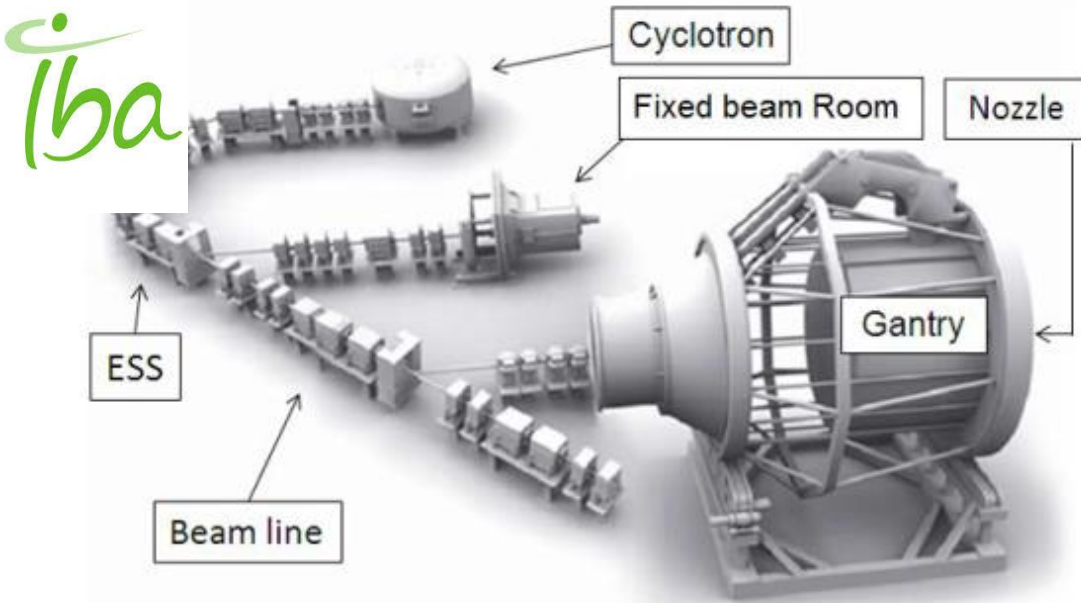
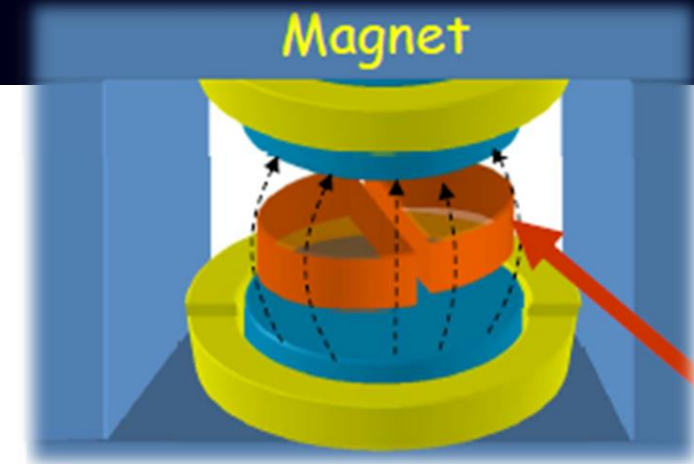




Particle Therapy Instrumentation



Cyclotron for proton therapy



The cyclotron provides proton therapy reliably and at low cost (Main vendors on the market: IBA, Varian, Mevion, Hitachi).

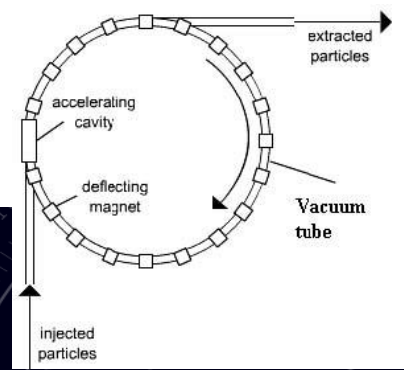
ProteusOne and ProteusPlus turn-key proton therapy solutions from IBA (Belgium)

TIME STRUCTURE → CONTINUOUS BEAM

Critical issues with cyclotrons:

1. Energy modulation (required to adjust the depth and scan the tumour) is obtained with degraders (sliding plates) that are slow and remain activated.
2. Large shielding

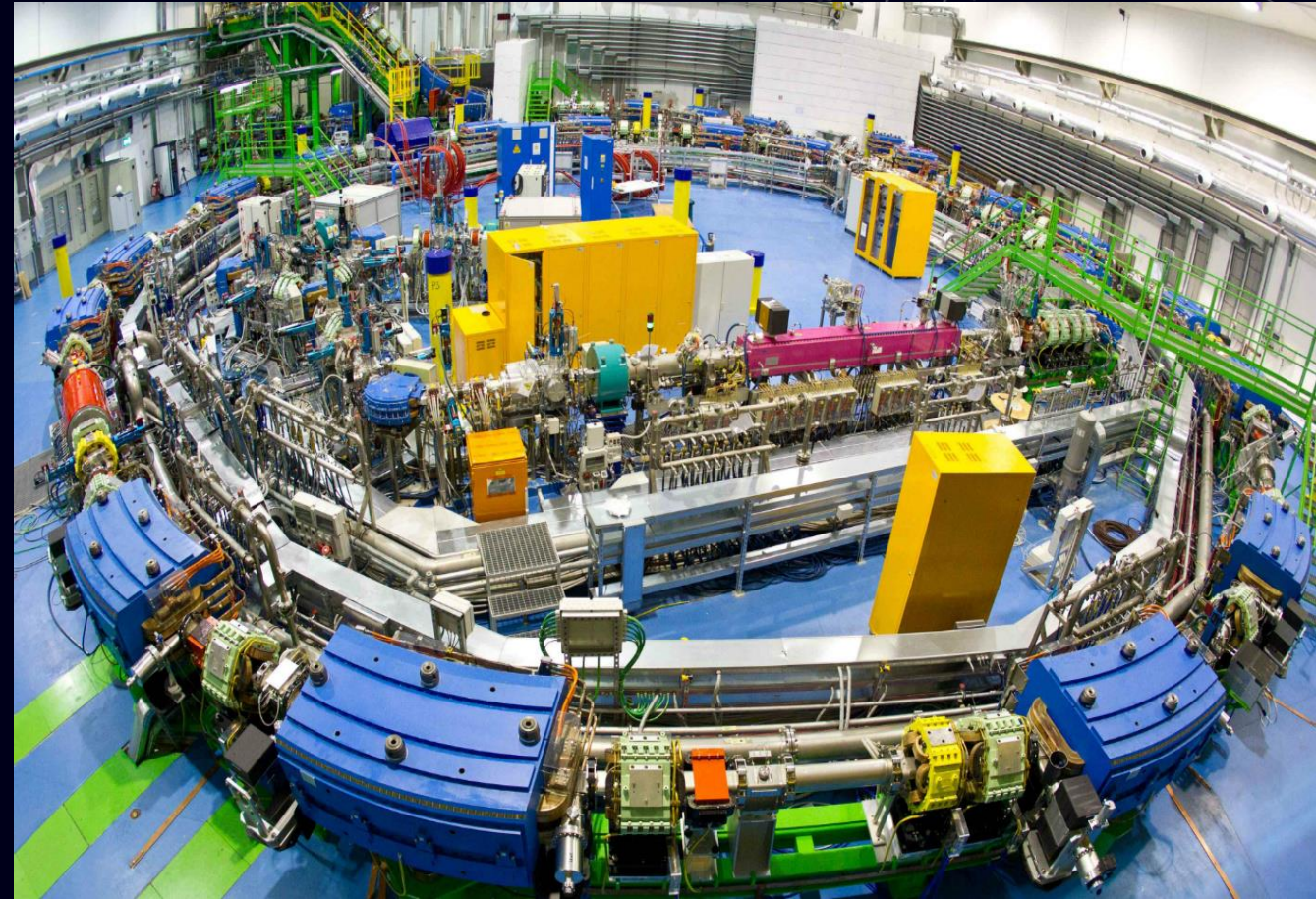
Synchrotron for heavy ion therapy



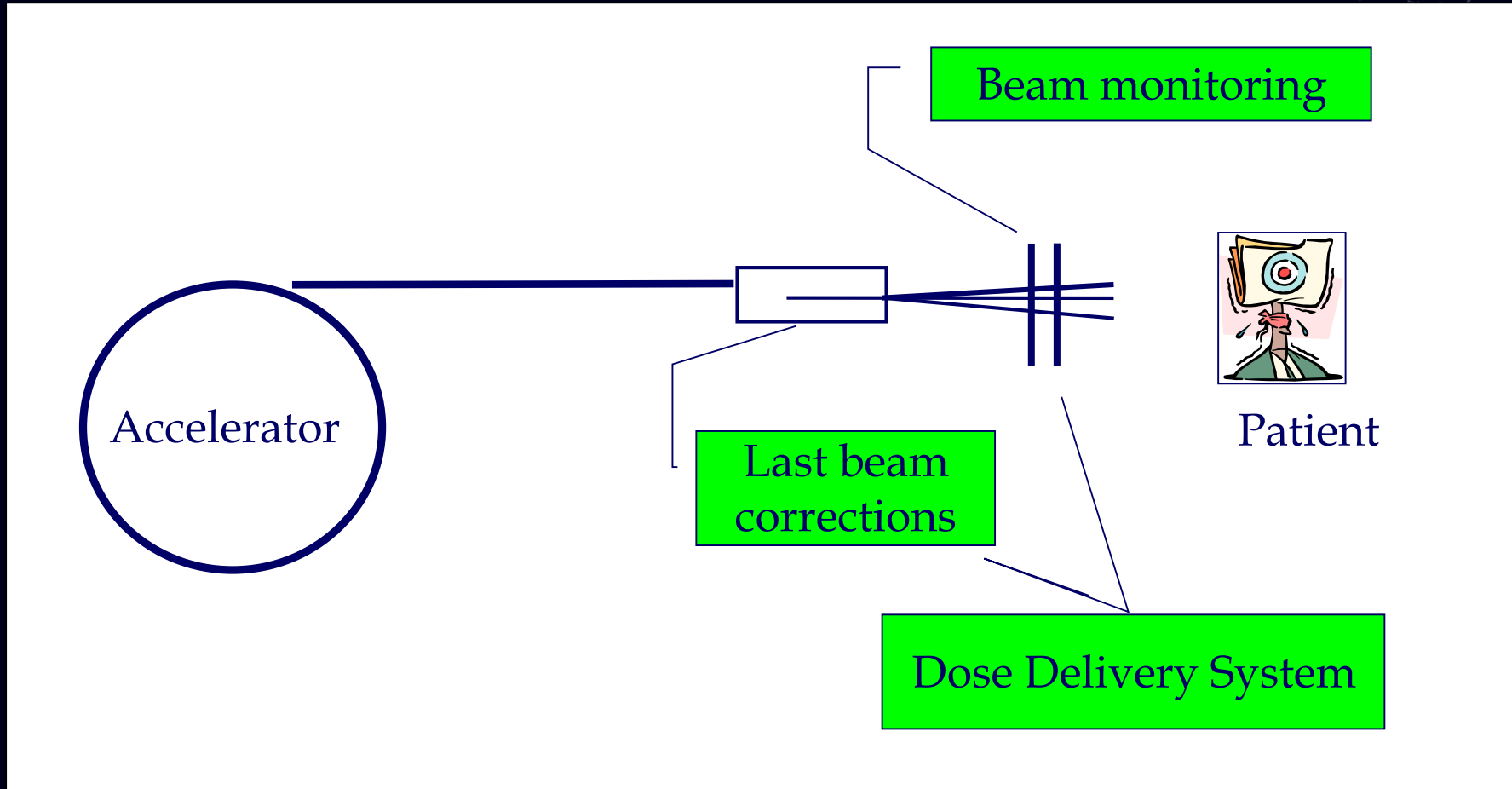
Accelerate different ion species
Modulate the beam energy

TIME STRUCTURE → beam delivered
in spill
Duty cycle < 50 %

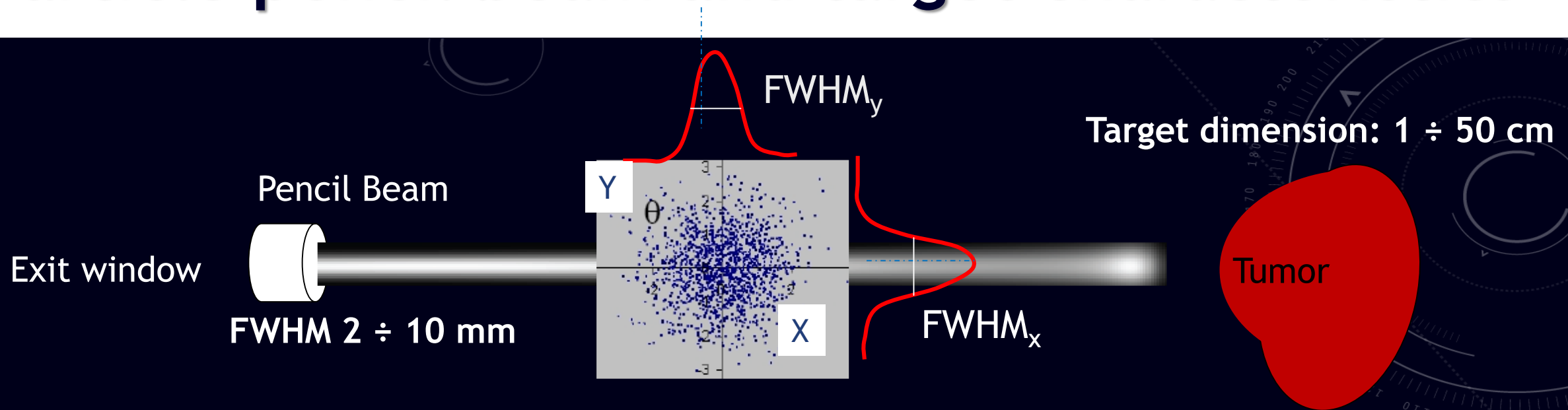
Very big (25 m Ø)
Complex
Expensive (construction and
maintenance)



Radiotherapy instrumentation

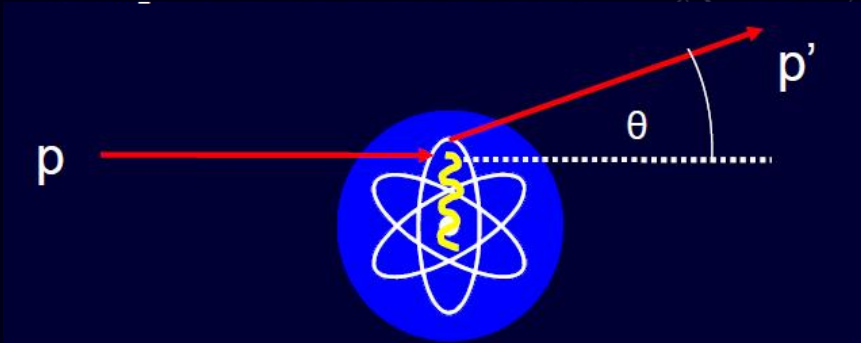


Particle pencil beam and target characteristics

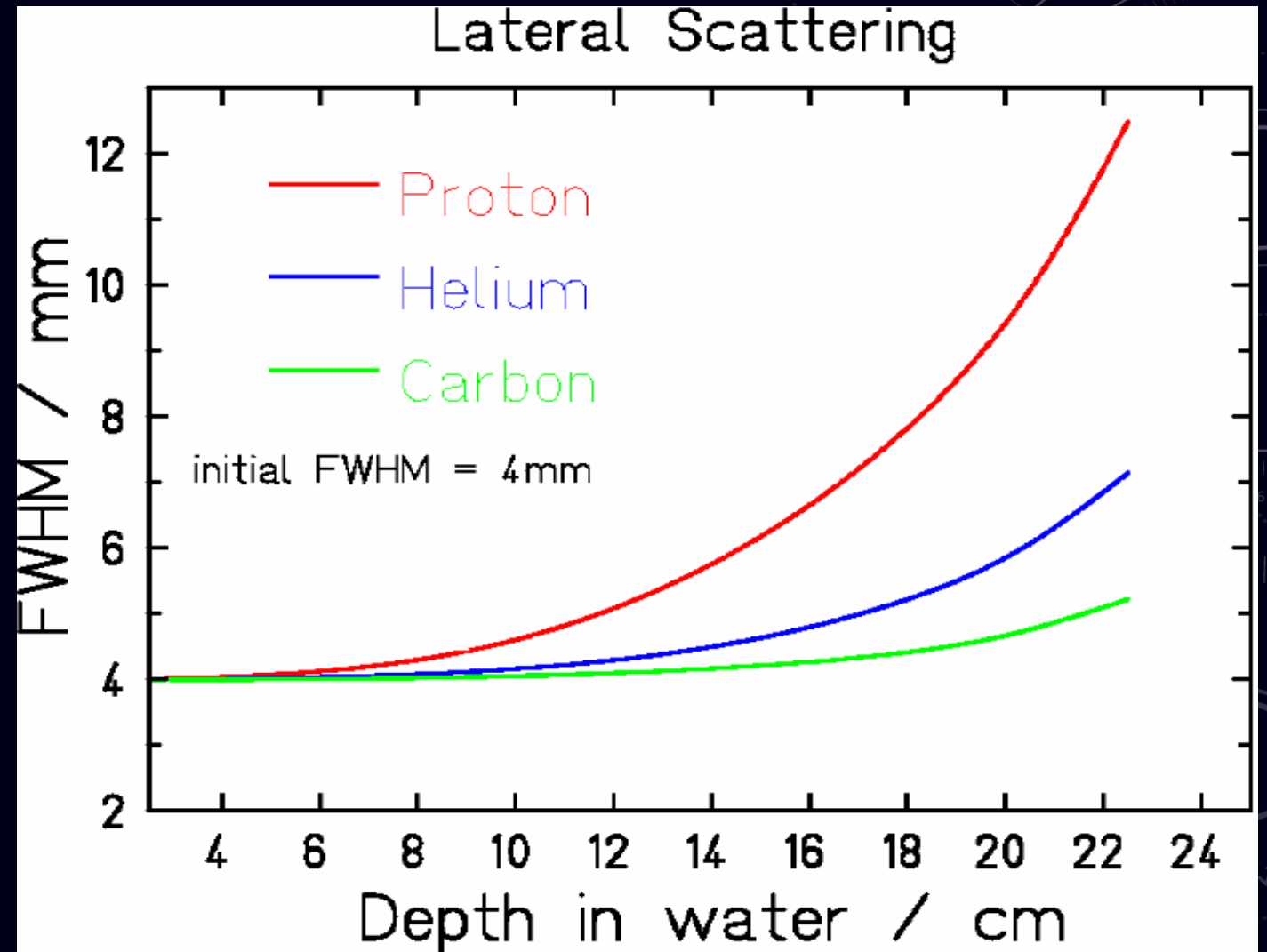
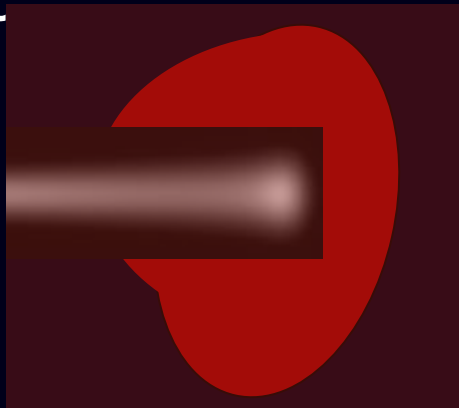


Beam range for protons/carbon ions	→ 3 ÷ 30 cm
Beam energy range for protons/carbon ions	→ 60 ÷ 250 MeV / 120 ÷ 400 MeV/u
Beam intensity for protons/carbon ions	→ $10^8 \div 10^{10}$ / $4 \times 10^7 \div 4 \times 10^8$ /sec
Spot size (FWHM in air at the isocenter) protons/carbon ions	→ 7 ÷ 20 / 4 ÷ 8 mm from highest to lowest energies
Field size (min/max) at the isocenter	→ 20x20/40x40 cm ²

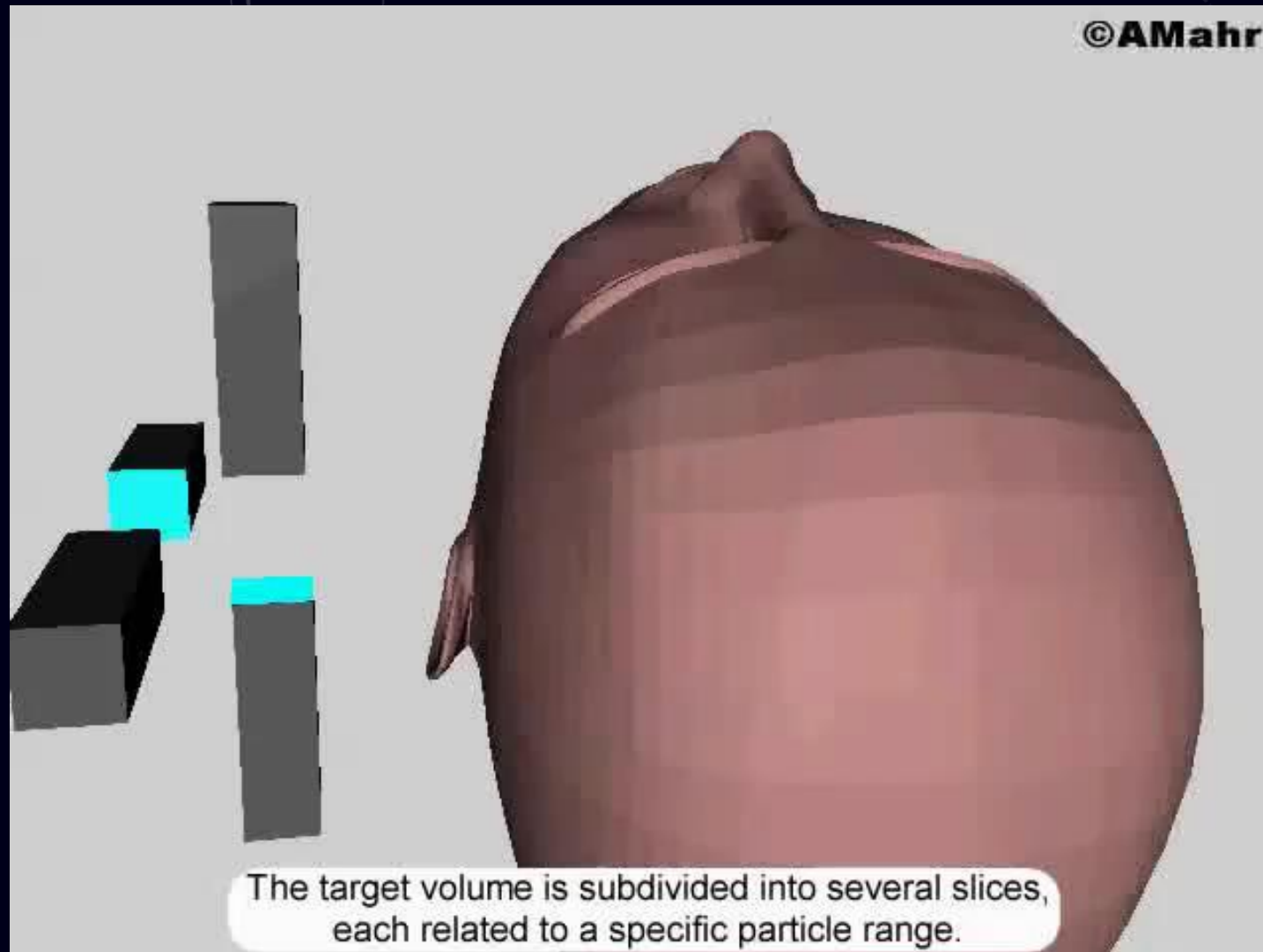
Effect of Multiple Coulomb Scattering



Scattering in air and in the body is not enough to cover the whole target



3D dose modulation with pencil beams



3D dose modulation with pencil beams

1000 - 50000
pencil beams for field

Thousands of pencil
beams (or spots)
deliver dose into
thousands of voxels

512 x 512 x 250 voxels

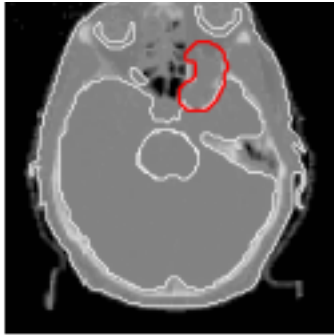
Pencil beam

Energy

Treatment Planning System

calculate the dose distributions delivered by particle beams

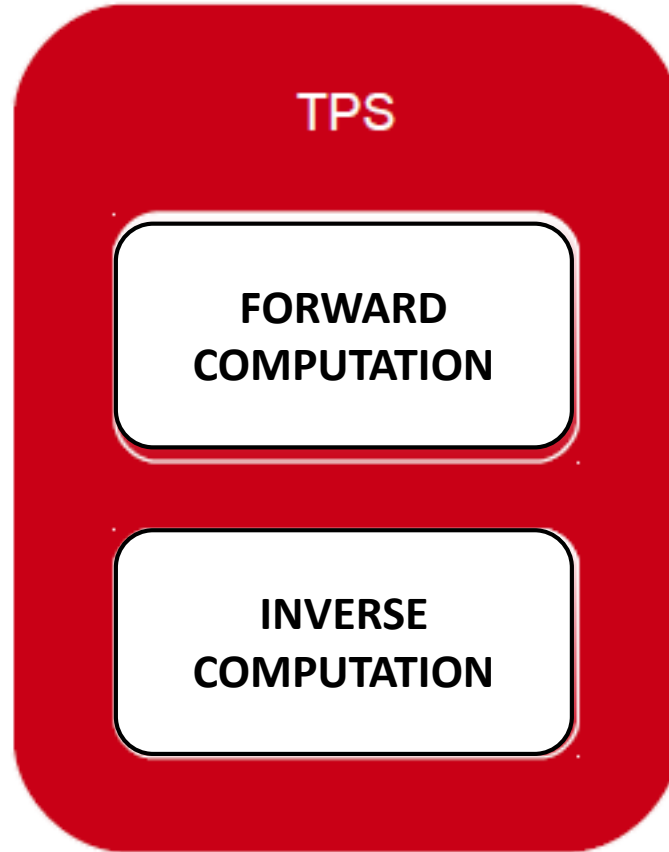
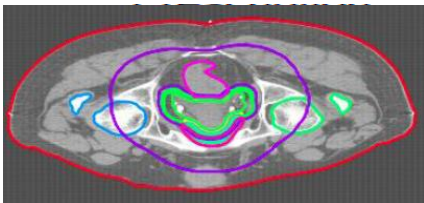
CT image : anatomical description



Irradiation set-up

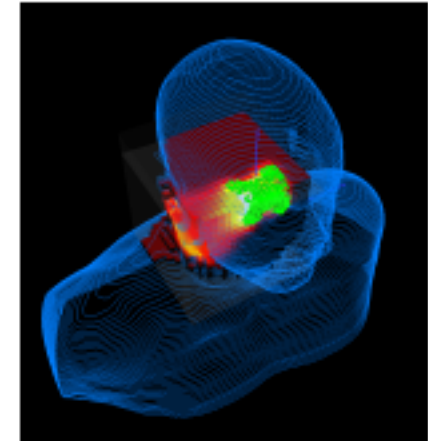
(chosen beam line, number and direction of fields, beams energies, spot inter-distance. ...)

Prescription



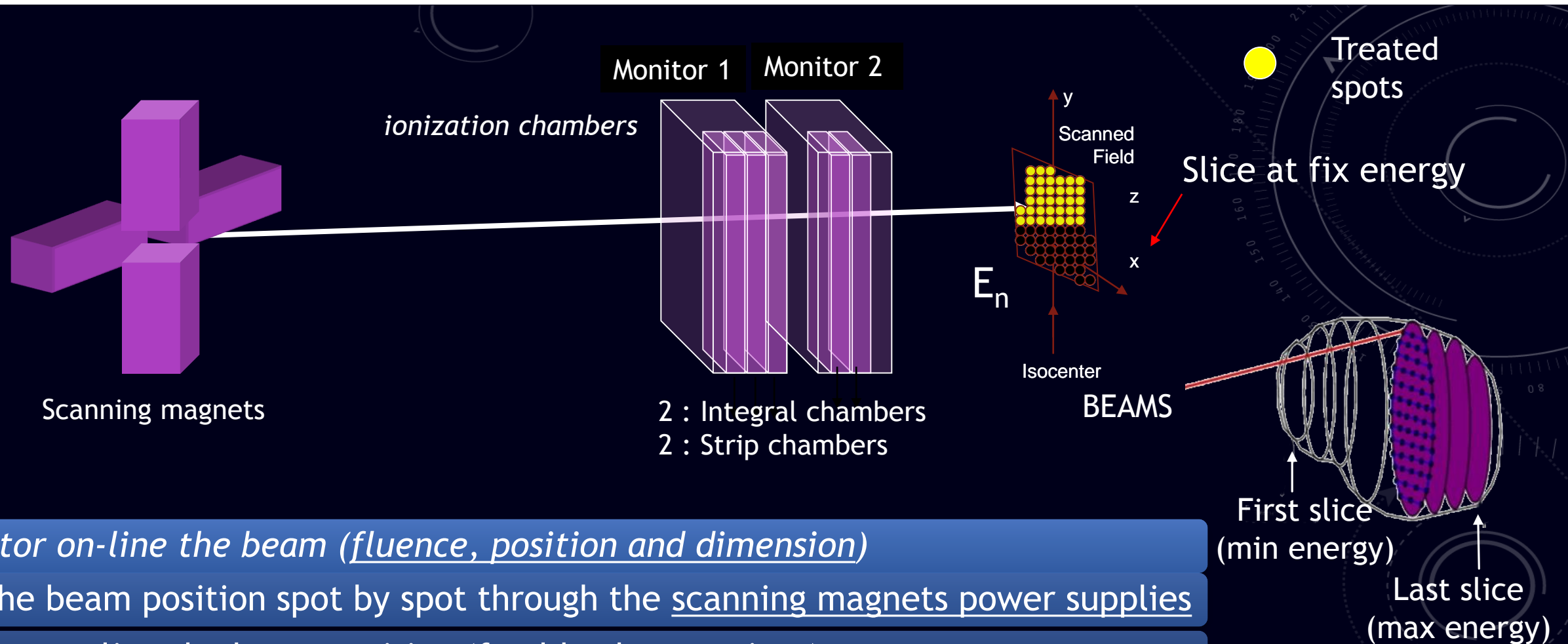
3D effects distributions

(dose, biological dose, LET, survival, ...)



**OPTIMIZED
SPOT
FLUENCE**

Modulated scanning technique driven by beam monitors



[Ref 7]

- Monitor on-line the beam (fluence, position and dimension)
- Set the beam position spot by spot through the scanning magnets power supplies
- Correct on-line the beam position (feed-back operations)
- Stop the beam slice by slice or when something is wrong

Main tasks of beam monitors

To measure during treatment and before the patient ...

Beam flux and fluence (beam Intensity - dose rate)

→ Accepted uncertainty 1-2 %

Transversal Beam positions

→ Accepted uncertainty 0.5 mm

Transversal Beam shape (FWHMs - symmetry)

→ Accepted uncertainty 1 mm

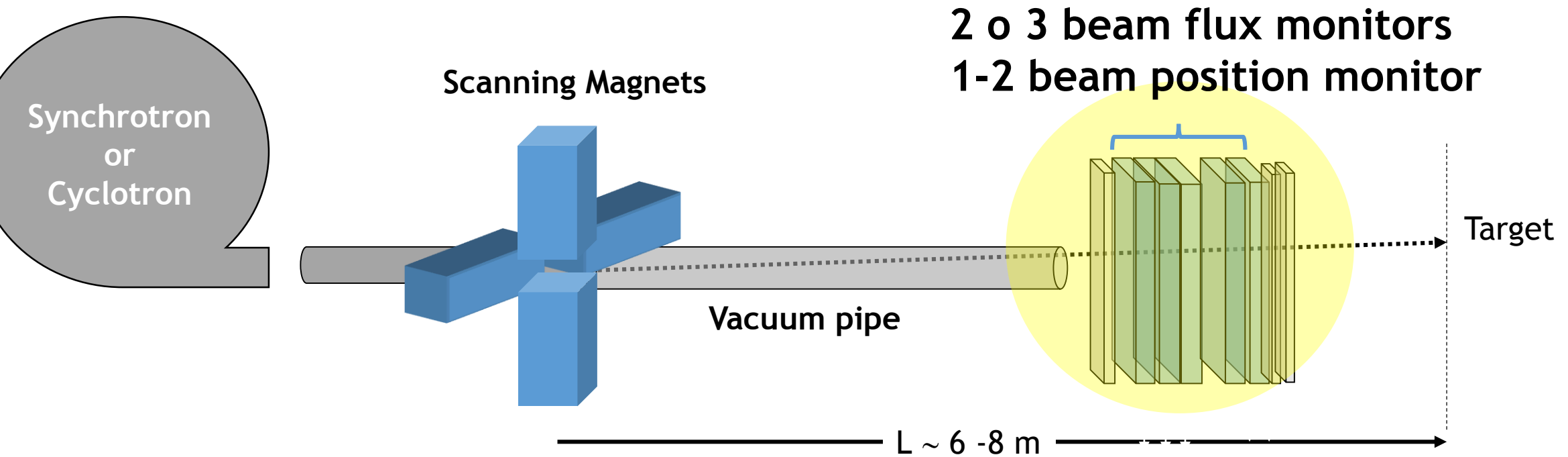
Beam range or absolute energy

→ Accepted uncertainty 1 mm (0.5 - 1 MeV)

Currently not online!!

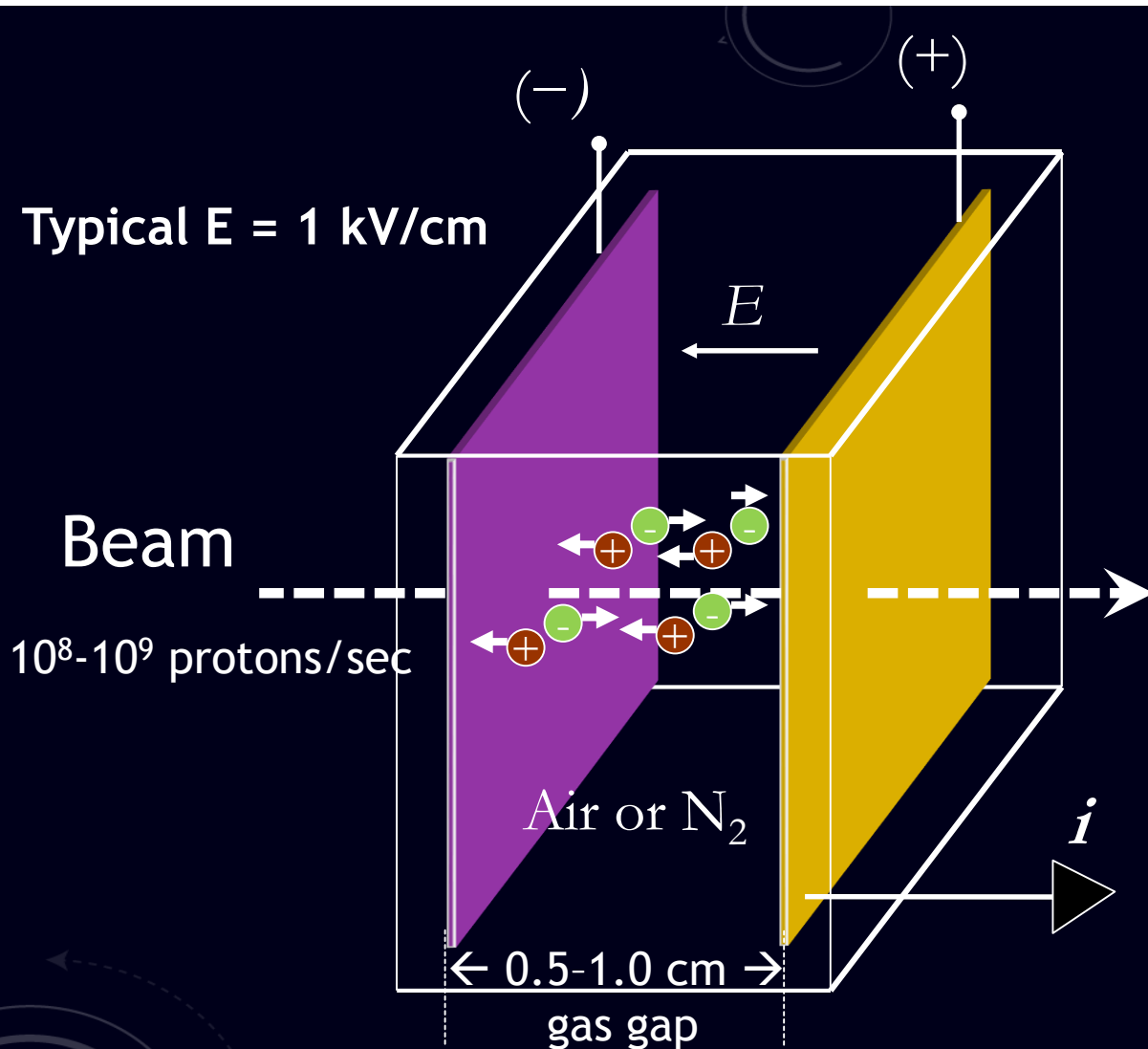
State of the art for beam monitoring

Worldwide the beam monitors are based on gas ionization chambers...

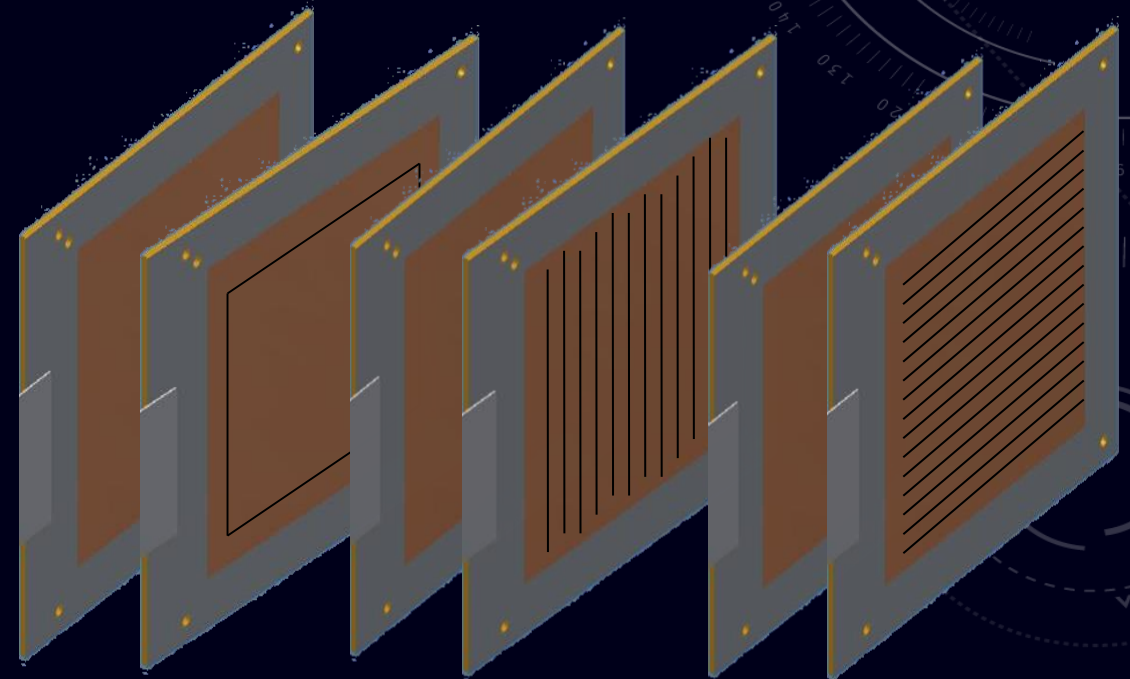


[Ref 8]

Beam monitors → Gas ionization chambers



Sequence of Parallel Plate ICs:
→ single large electrode for FLUX measurement
→ electrodes segmented in strips for BEAM POSITION measurement



Ionization chambers

IC measure a charge proportional to the number of particles sent to the patient

$$Q = \frac{S \cdot d \cdot e}{W} N$$

S = stopping power gas [keV/ μm = MeV/mm]

d = distance between electrodes [mm]

e = elementary charge $1,6 \cdot 10^{-19}$ C

W = mean energy to create a e^- /ion pair

(~ 30 eV = $3 \cdot 10^{-5}$ MeV)

Collection time depends on the position of pair produced within the chamber

$$t_- \sim d / (\mu_- \cdot E) = 500 \text{ ns} \quad (e^-)$$

$$t_+ \sim d / (\mu_+ \cdot E) = 400 \mu\text{s} \quad (\text{ions})$$

• Ion mobility in N_2

$$\mu_+ = 1,3 \text{ cm}^2 \text{s}^{-1} \text{V}^{-1}$$

$$\mu_- \approx 10^3 \text{ cm}^2 \text{s}^{-1} \text{V}^{-1} \text{ 1000 times faster!}$$

→ Long collection times compared with the average time between two particles in clinical beams (1 ns)

Some numbers about IC

Assuming:

- Beam intensity 10^9 prot/s
(1 prot/ns)
- $E_p = 120 \text{ MeV}$
- Gas N_2 in standard T e p
- $d = 0,5 \text{ cm}$, $\Delta V = 500 \text{ V}$
 $\rightarrow E = 1 \text{ kV/cm}$

From letterature:

- In N_2 $S = 7,0 \cdot 10^{-4} \frac{\text{MeV}}{\text{mm}}$
 $W = 3,5 \cdot 10^{-5} \text{ MeV}$
- Ion mobility $\mu_+ = 1,3 \text{ cm}^2 \text{ s}^{-1} \text{ V}^{-1}$
- e^- 1000 times faster!
 $\mu_- \approx 10^3 \text{ cm}^2 \text{ s}^{-1} \text{ V}^{-1}$

Energy loss by a proton through the chamber:

$$S \cdot d = 3,5 \text{ keV} \rightarrow \text{negligible}$$

Number of pair e^- - ion

$$S \cdot d/W = 100$$

Collected charge very small!

$$100 \times 1,6 \cdot 10^{-19} \text{ C} = \boxed{0,016 \text{ fC}}$$

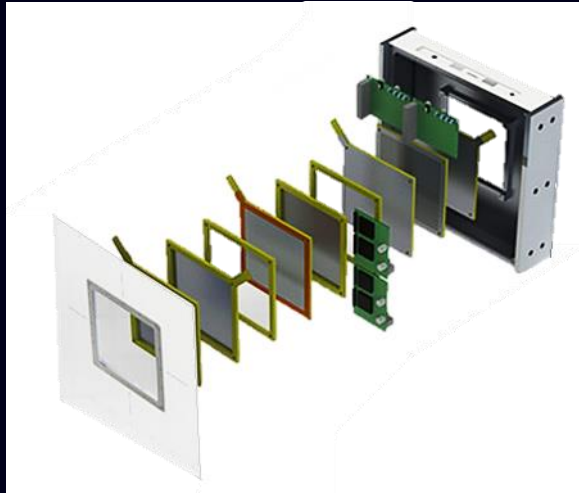
Collection time depends on the position of pair produced within the chamber

$$t_- \sim d/(\mu_- \cdot E) = 500 \text{ ns} \quad (e^-)$$

$$t_+ \sim d/(\mu_+ \cdot E) = \boxed{400 \mu\text{s}} \quad (\text{ioni})$$

\rightarrow Long collection times compared with the average time between two particles in clinical beams (1 ns)

From IC Monitor Units to Dose



Integrator $V_{out} \propto \int i(t)dt = Q$

i (μA)



Monitor counts

Calibration

N particles

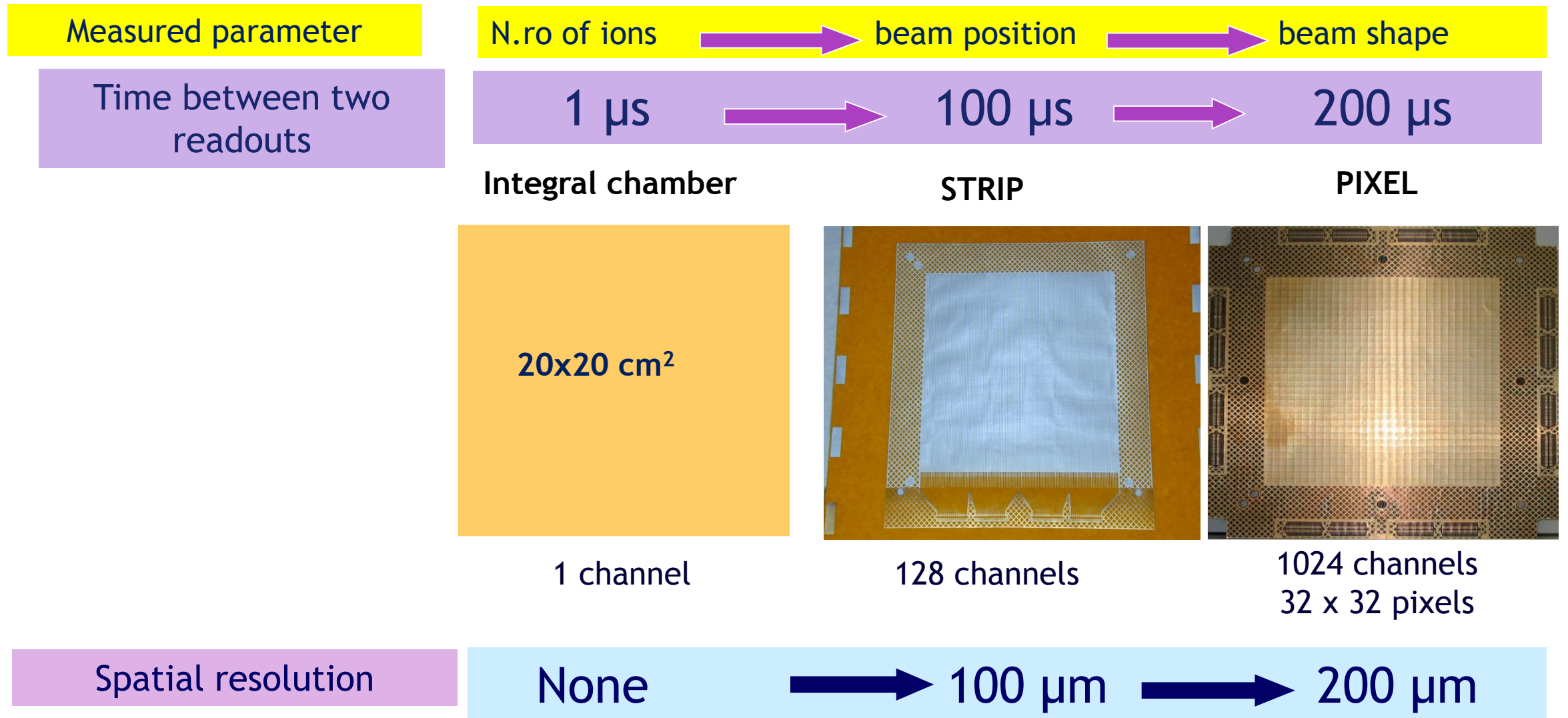
Dose Planning

Dose (Gy)

LOW SENSITIVITY

- 1 MU ~ 200 fC ~
- 7.2×10^3 protons (62 MeV)
 - 1.9×10^4 protons (226 MeV)
 - 341 carbon ions (115 MeV/u)
 - 767 carbon ions (399 MeV/u)

IC with segmented anodes



Advantages of gas ionization chambers

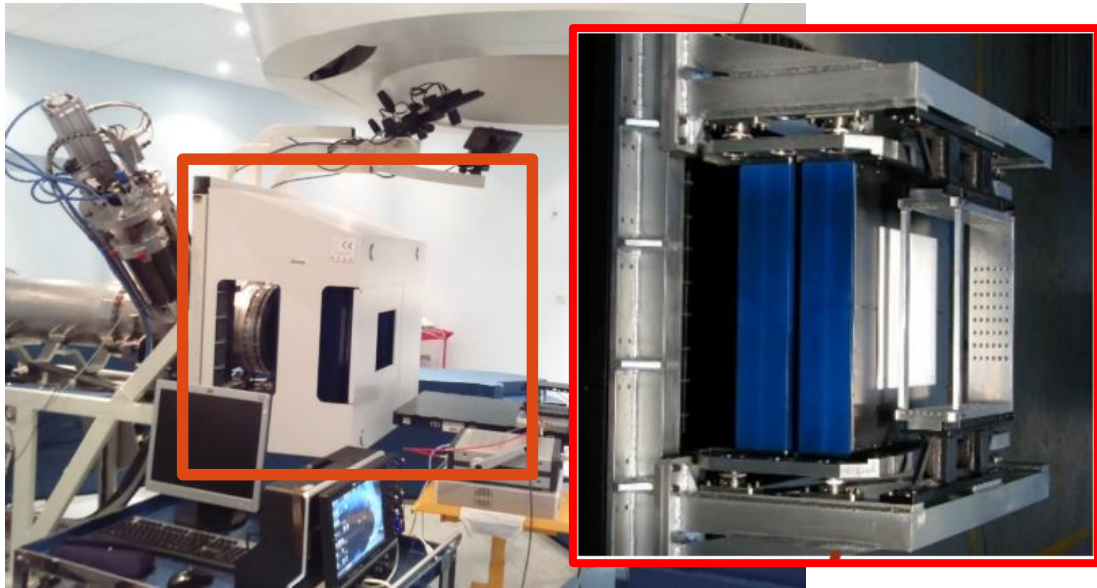
- Reliability & long term (years) stability
- Large (30x30 cm²) sensitive area allowed
- Simple to use
- Deeply studied manufacture
- A few mm water equivalent thickness
- Radiation resistant



The best choice for current clinical requirements and existing accelerators

CNAO parallel plate ionization chambers

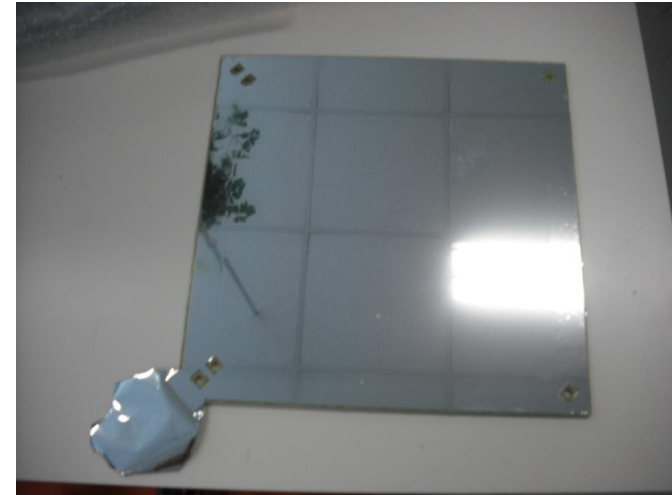
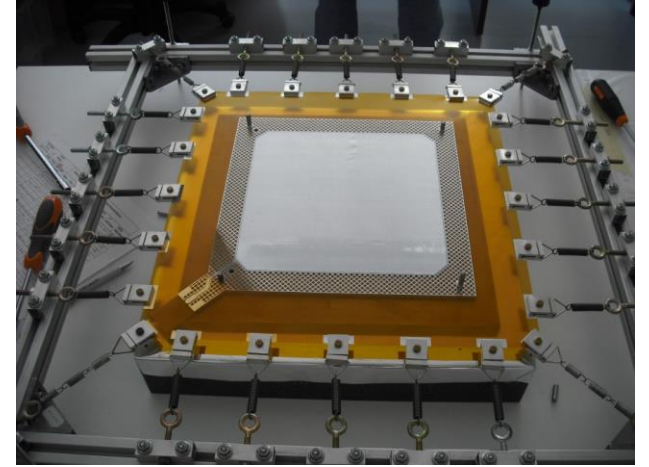
Thin electrodes “transparent” to the beam



Anode

CNAO: chamber filled with $N_2 \rightarrow HV = 400 V$
 $d = 0.5 \text{ cm}$

Cathode



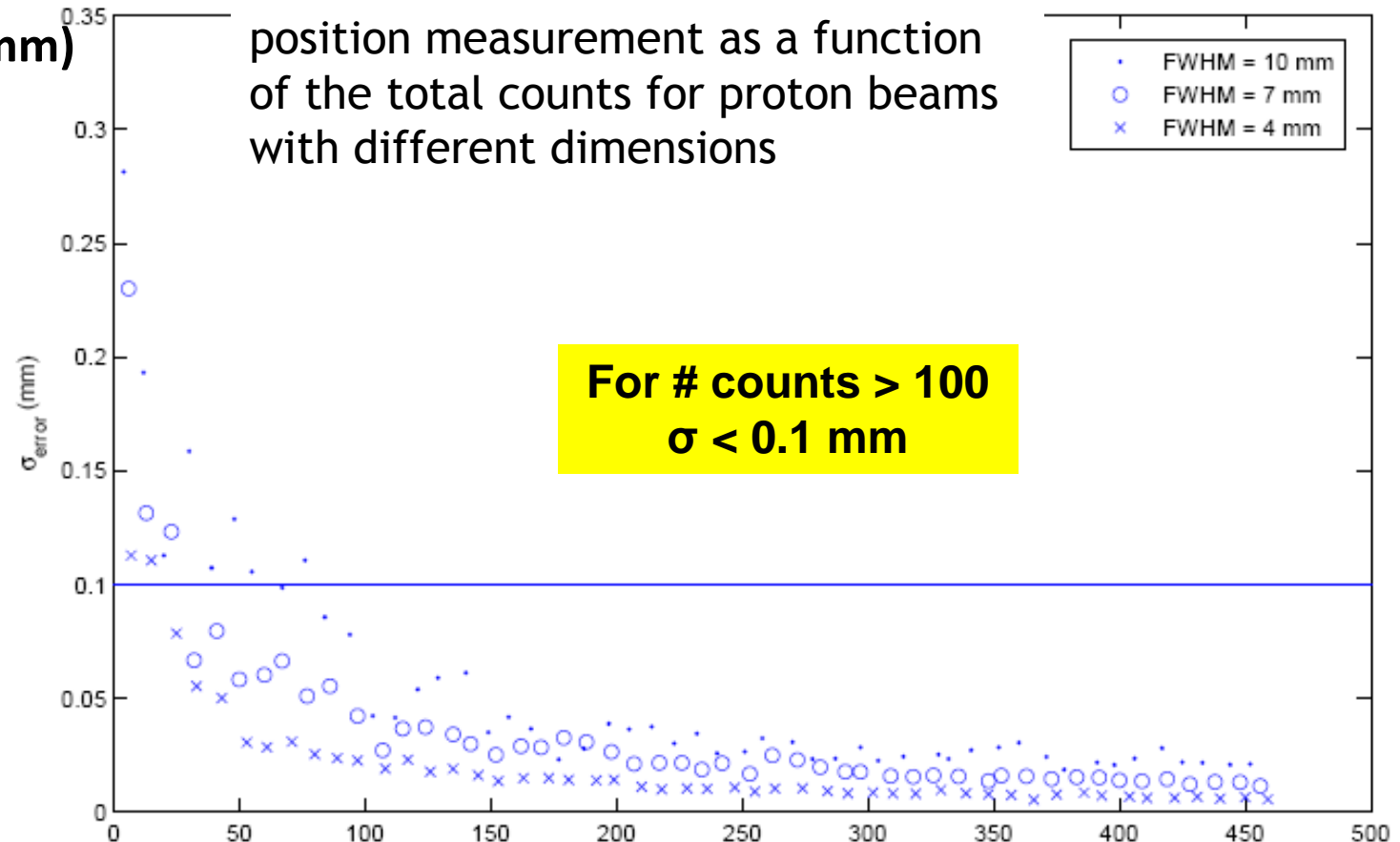
Position accuracy depends on readout counts

$$Error \propto \frac{1}{\sqrt{S_i}}$$

Minimum time to collect 100 counts:
100 μ s
→ Beam intensity of 10^{10} protoni e
 $4 \cdot 10^8$ carbon ions

100 counts = 20 pC

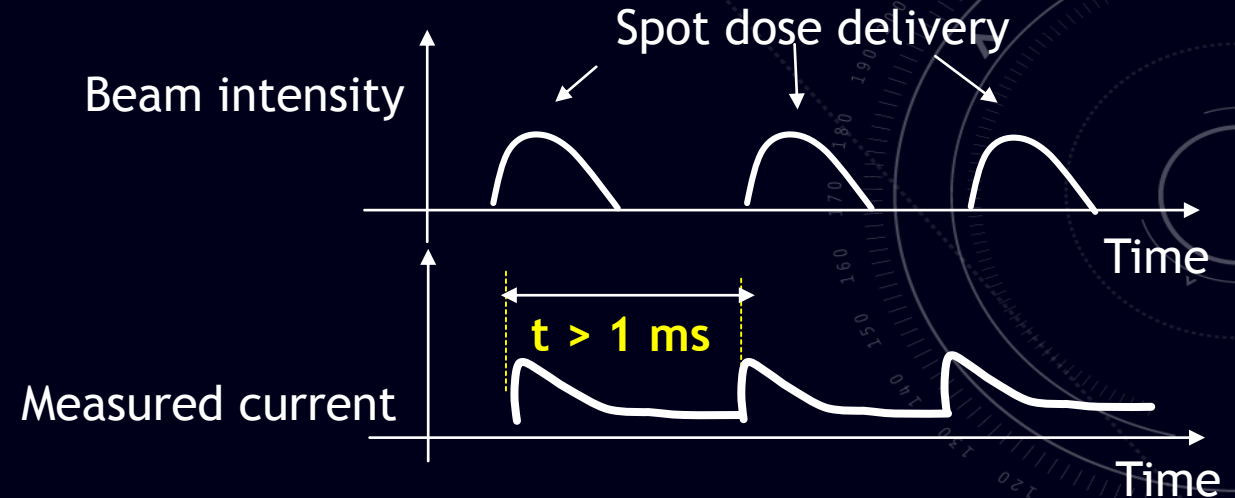
σ_{err} (mm)



Total readout counts per channel

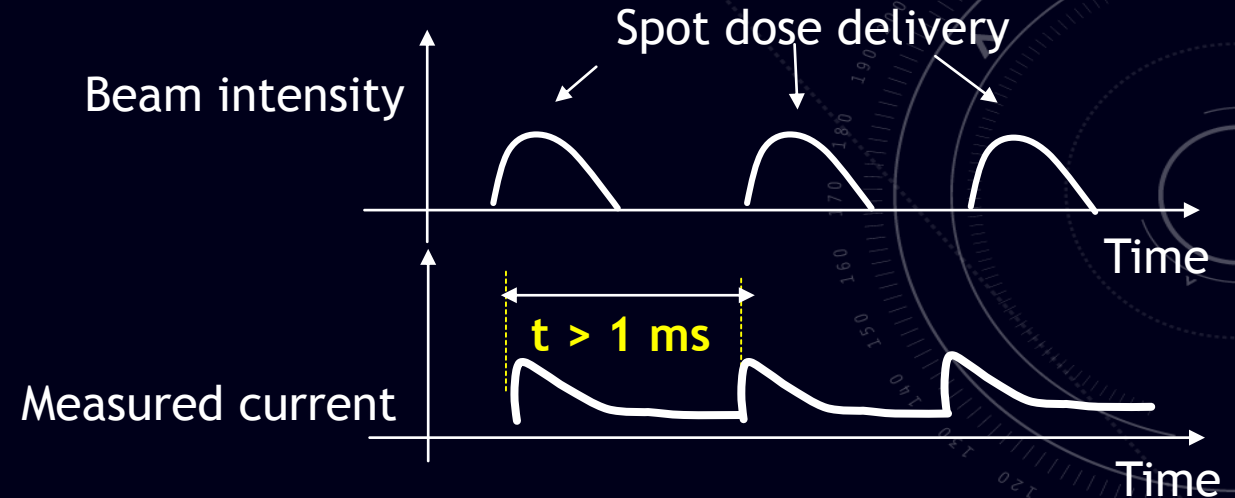
CONSTRAINTS of gas IC

- Slow collection time
(400 μs for 0.5 cm gap)



CONSTRAINTS of gas IC

- **Slow collection time**
(400 μ s for 0.5 cm gap)



- Collected charge dependent on T, P, beam E
→ **Calibration needed**
- Low sensitivity (Q = 0.2-2 pC charge resolution)
→ **Threshold needed on the minimum number of particles per spot**
- Charge recombination with high intensity and pulsed beams

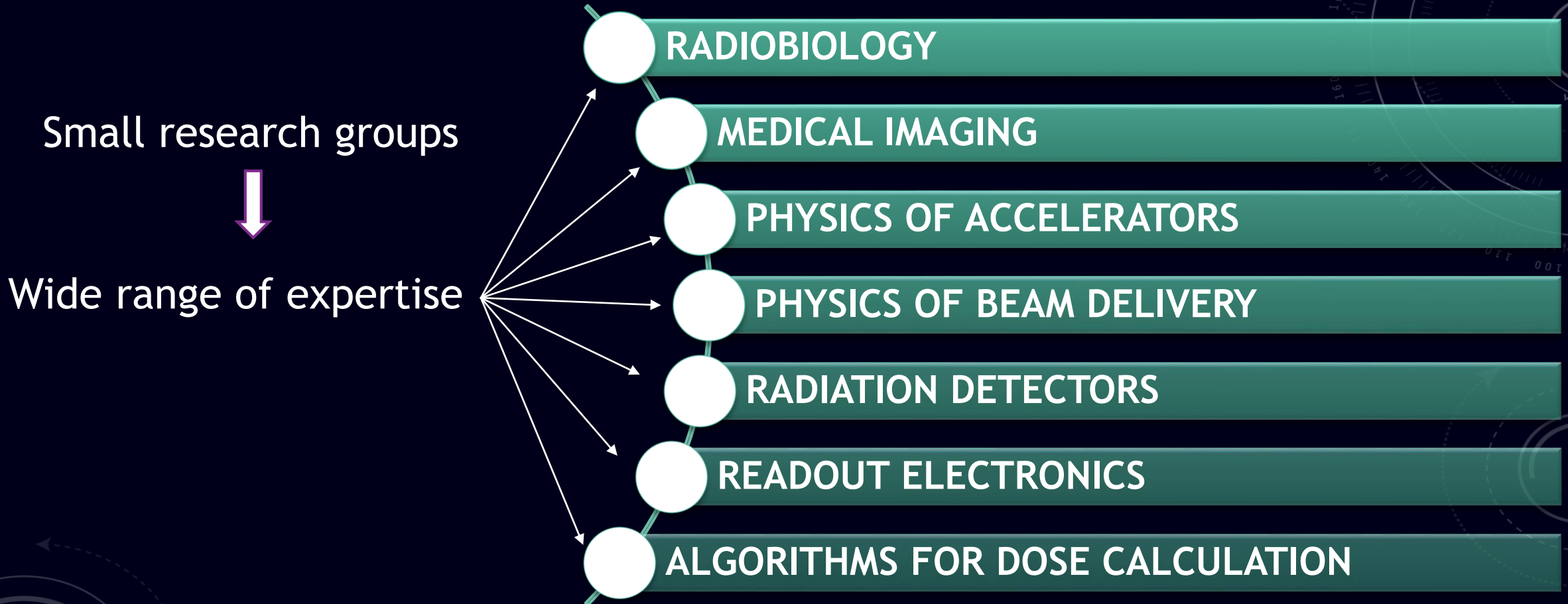
What's next?

MUCH LOWER and MUCH HIGHER DOSE RATES
are required to deal with

-
- New treatment modalities
- New accelerators
- New delivery techniques
- New dose fractionation
-

Take home messages (I)

PHYSICS APPLIED TO MEDICINE INCLUDE SEVERAL TOPICS



Take home messages (II)

**CHARGED PARTICLE THERAPY IS NOW
ACCEPTED AS BEING SELF-EVIDENT**

**WORLDWIDE THE BEAM MONITORS ARE GAS
IONIZATION CHAMBERS**

**FOR NEW and IMPROVED TREATMENTS NEW RESEARCH AND
TECHNOLOGIES are NEEDED**

Take home messages (III)

WORLDWIDE THE CANCER SURVIVORS ARE INCREASING

PHYSICS APPLIED TO MEDICINE HAS CONTRIBUTED TO CANCER CURE SINCE THE DISCOVERY OF X-RAYS AND RADIOACTIVITY



UNIVERSITÀ
DEGLI STUDI
DI TORINO



SCUOLA
ALTA
FORMAZIONE



**Thanks for your
attention!**

*Simona Giordanengo
INFN Torino*

Giornate di Studio sui Rivelatori - Scuola F. Bonaudi

February 10-14, 2020 Cogne



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