radiotherapy, FLASH effect and laser-driven beams

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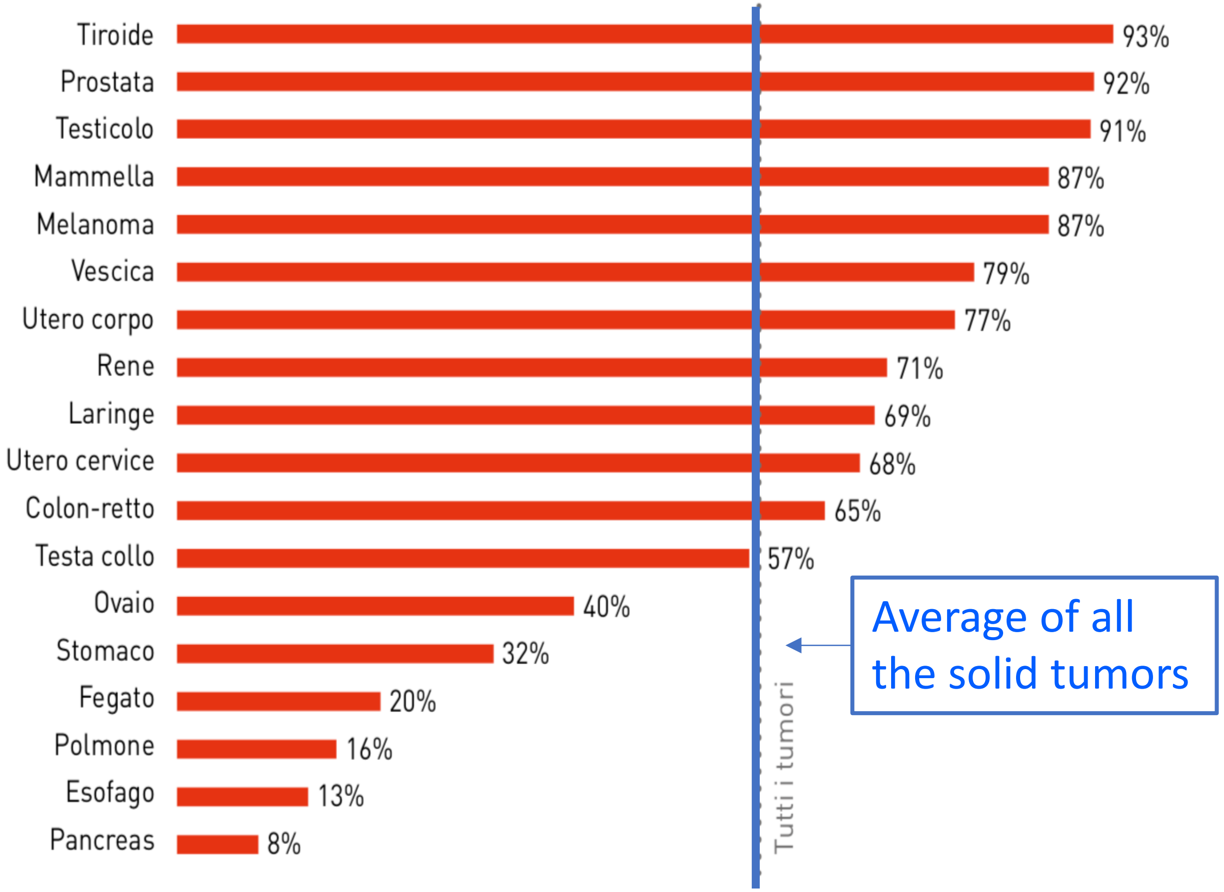
Summary

I will try to give a flavor of the interconnections among radiotherapy, medical physics, biomedical engineering and particle/nuclear physics:

- Standard photon radio therapy
- Particle (hadron) therapy
- Very High Energy Electron Radio Therapy
- FLASH effect
- Laser-Plasma vs FLASH effect

All this keeping in mind that in such an interdisciplinary subject my klnowledge is far from sufficient in any aspect of this wide topic!!!

Tumors and numbers….



Survival percentage after 5 years from disgnosys (2005-2009)

Survival increased in the last 20 years: now is' ~ 60%.

Two main reasons:

- ➢High tech Imaging provides more prompt diagnosys
- ➢Improvement of the treatment technology

Dati 2019 : AIOM (Associazione Italiana di Oncologia Medica) ed AIRTUM (Associazione Italiana dei Registri Tumori)

Cancer treatment

Cancer therapy needs always a multimodal approach in which radiotherapy plays a fundamental role (>50% of cases)

Chemical

Goal: stopping or slowing the growth of cancer cells using drugs (chemotherapy, immunotherapy)

Surgery

Goal: mechanical removal of the tumor mass (open surgery, laparoscopic)

Radiotherapy

Goal: kill cancerous cells by damaging the DNA chemical bounds using radiations

External beam Radiotherapy and Brachitherapy

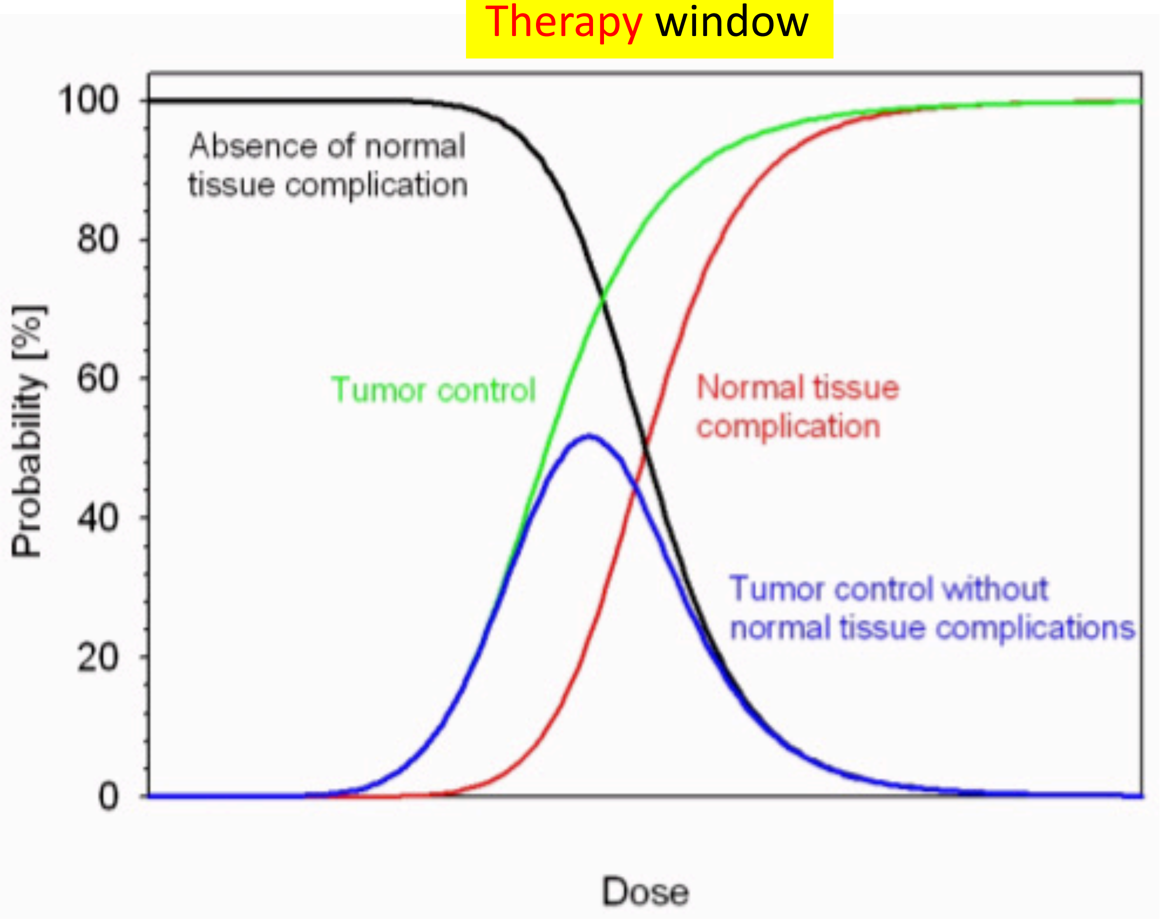
Radiotherapy (general)

- Part of multi-disciplinary approach to cancer care
- Useful for 50-60% of all cancer patients (also together surgery)
- Can be given for cure or palliation

- Mainly used for loco-regional treatment
- Benefits and side-effects are usually limited to the area(s) being treated
- The driving quantity is the Dose:

$$D = \frac{d\bar{\epsilon}}{dm}$$ [Gy]

Therapy window

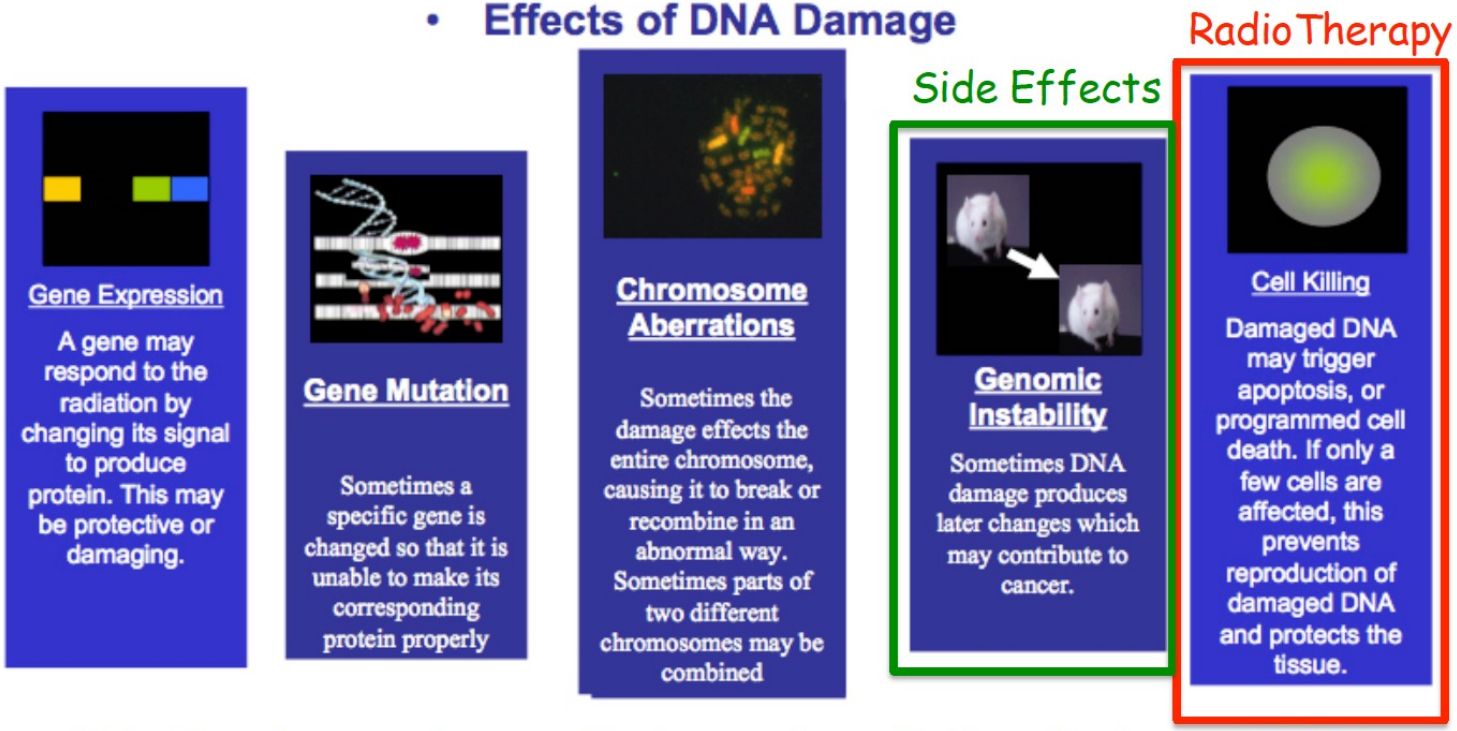


Trade off between high probability of killing the tumor and Normal Tissue Complication Probability

Effect of radiations

DNA is the most important molecule that can be changed by radiation

- Effects of DNA Damage

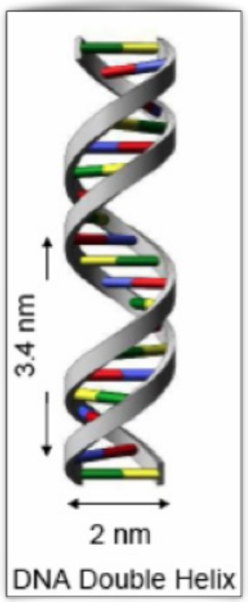


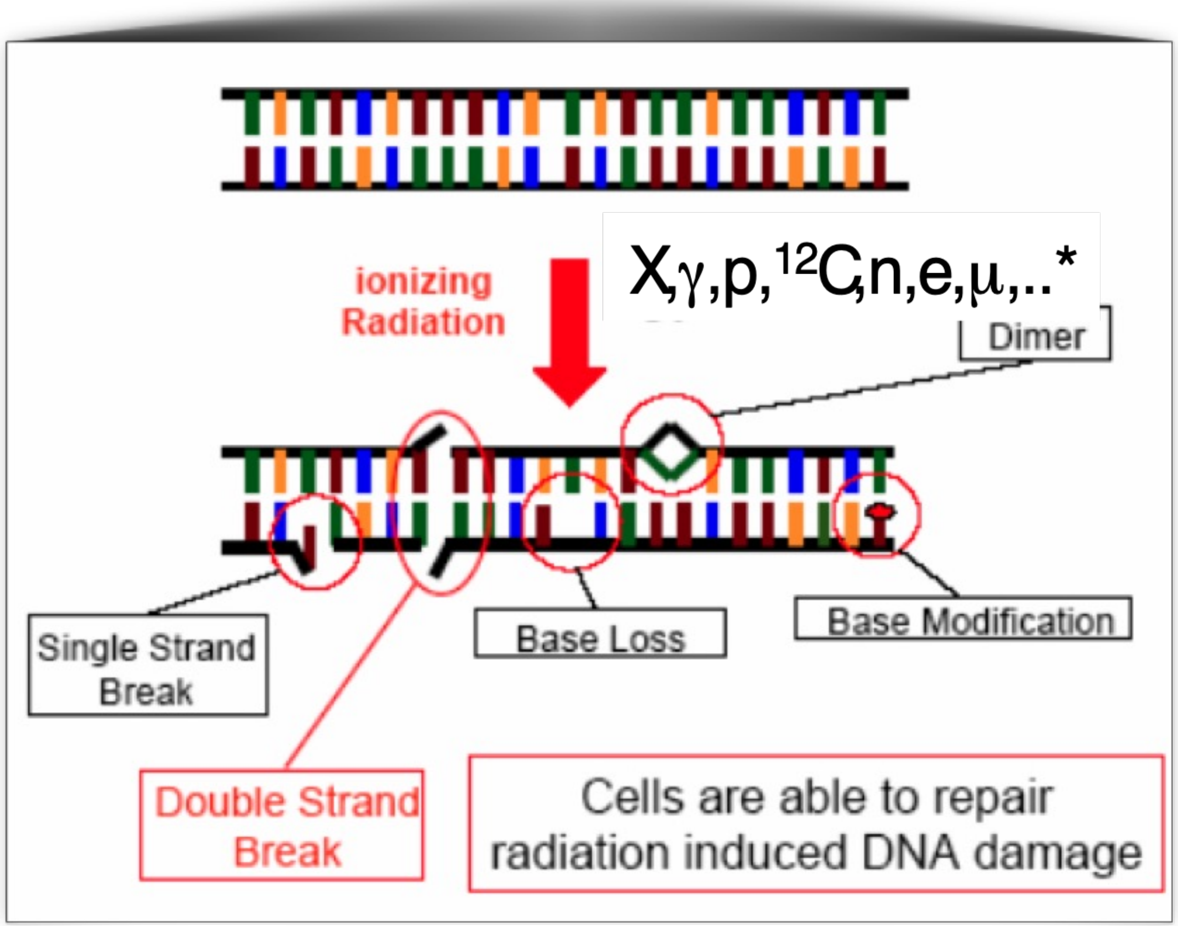
Studies have shown that most radiation-induced DNA damage is normally repaired by the body

Radiobiological effects

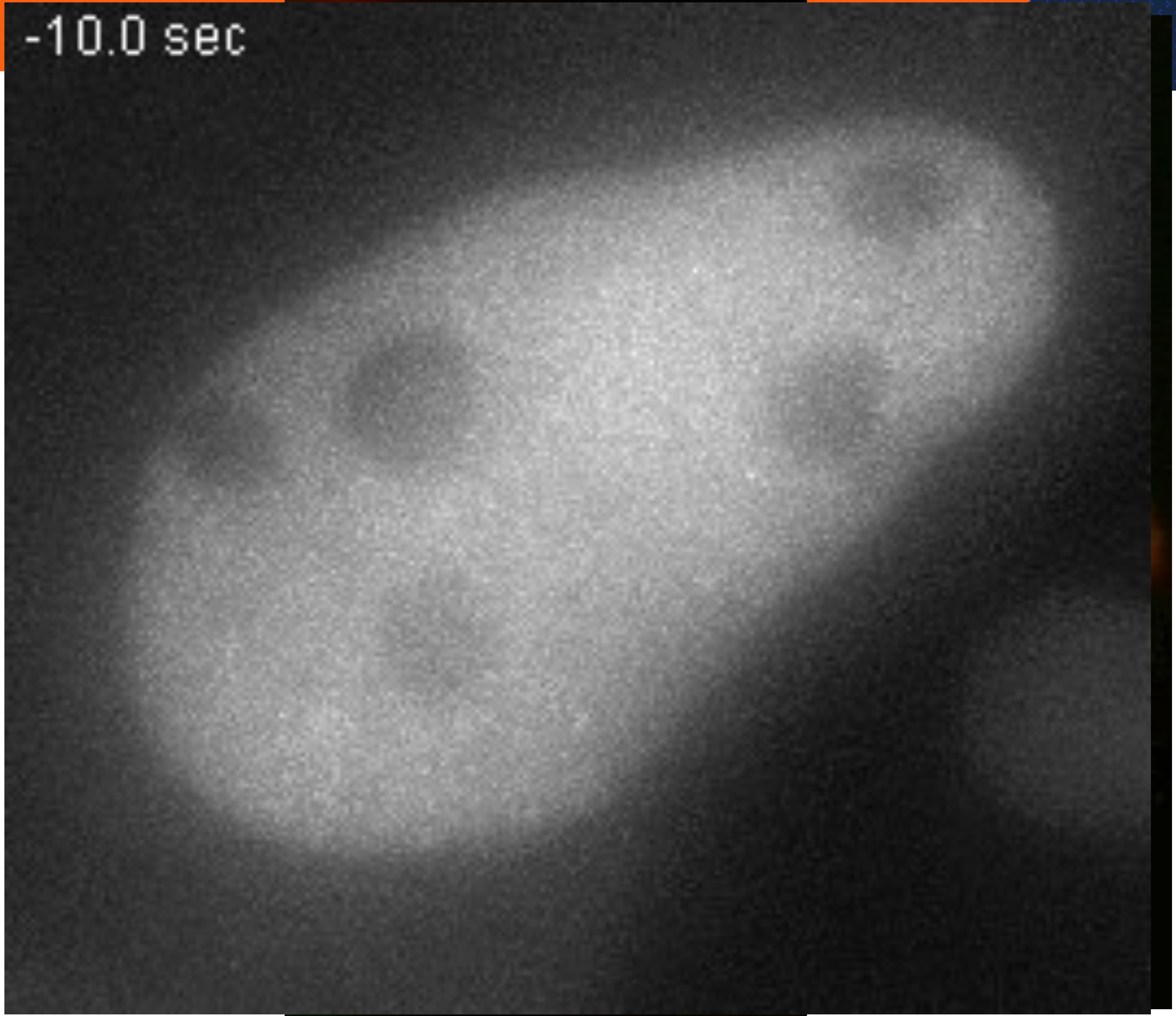
- **Indirect damage: the radiation produces (mainly in water) free radicals that break the cells**

- **Direct damage: the radiation directly breaks the DNA helix**





Live cell imaging of heavy ion traversals in euchromatin and heterochromatin



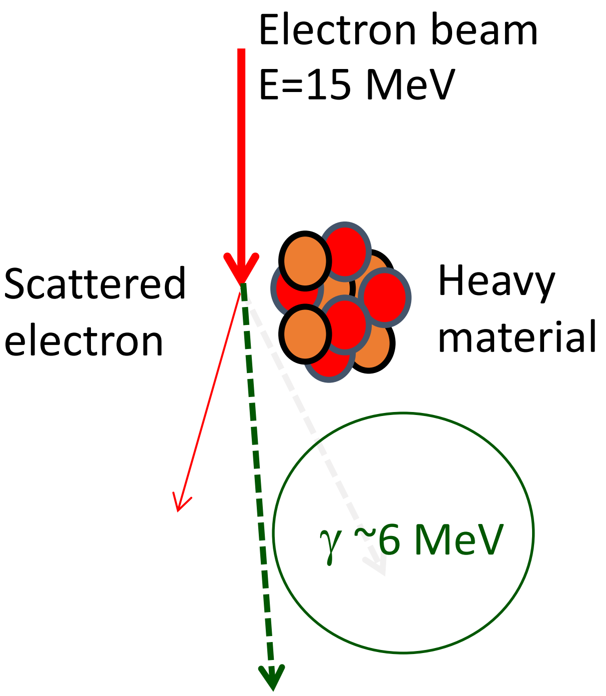
Sci. USA 2009; *Nucl. Acids Res*. 2011

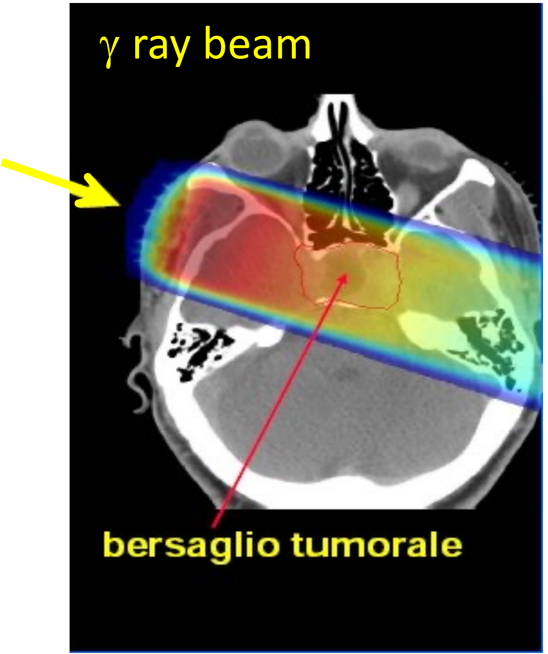
Conventional RadioTherapy

Conventional RT uses γ rays, both emitted from nuclear decays or from electron interaction.

Electron are accelerated in a LINAC before interacting and producing photon beam.

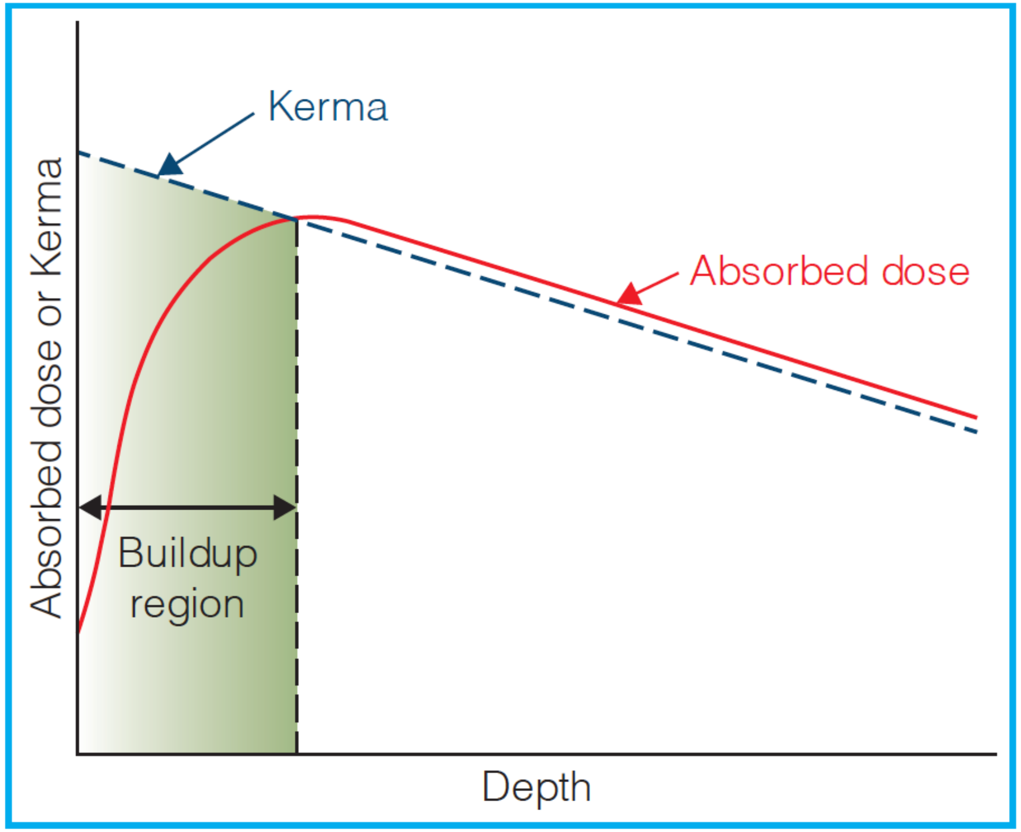
More than 50 years of R&D made photon RT a very optimized, compact, effective technology (IMRT, radio surgery, etc)





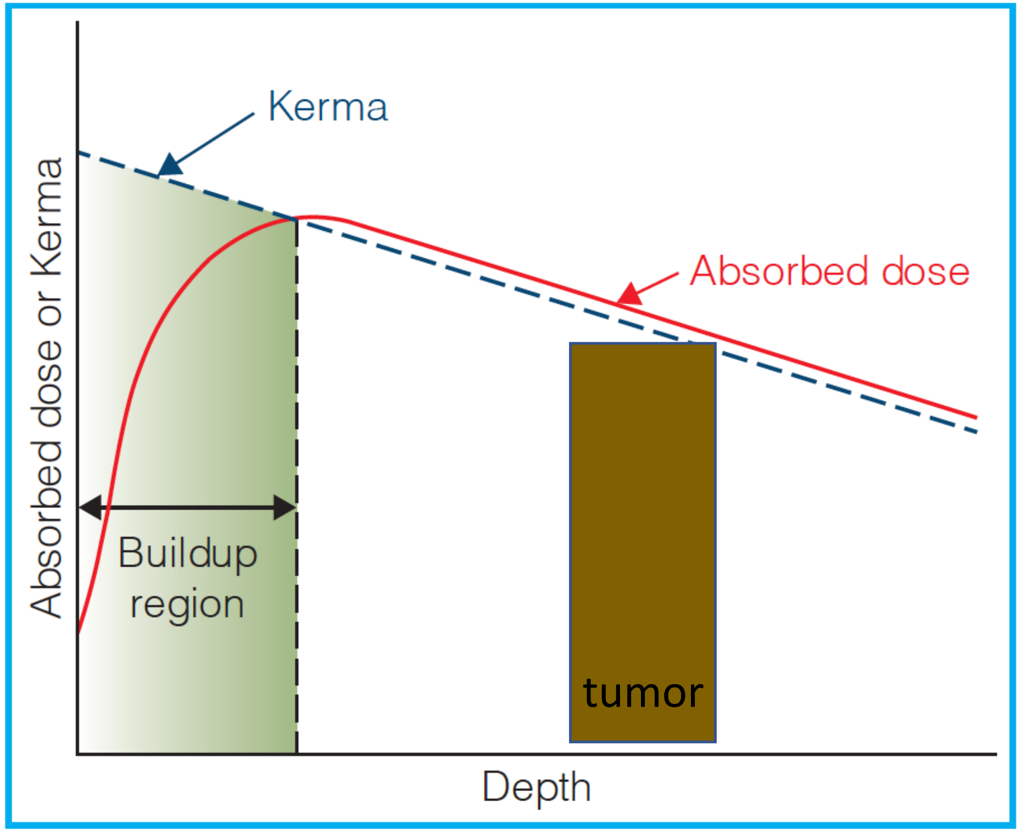
Approximatively half of the tumor are treated with γ RT.
In Italy ~ 300000 patients/year

X-rays dose



- Kerma is the kinetic energy released
- Dose is the energy absorbed
- Build-up region produced by forward-scattered low e engy electrons that stop at deeper depths

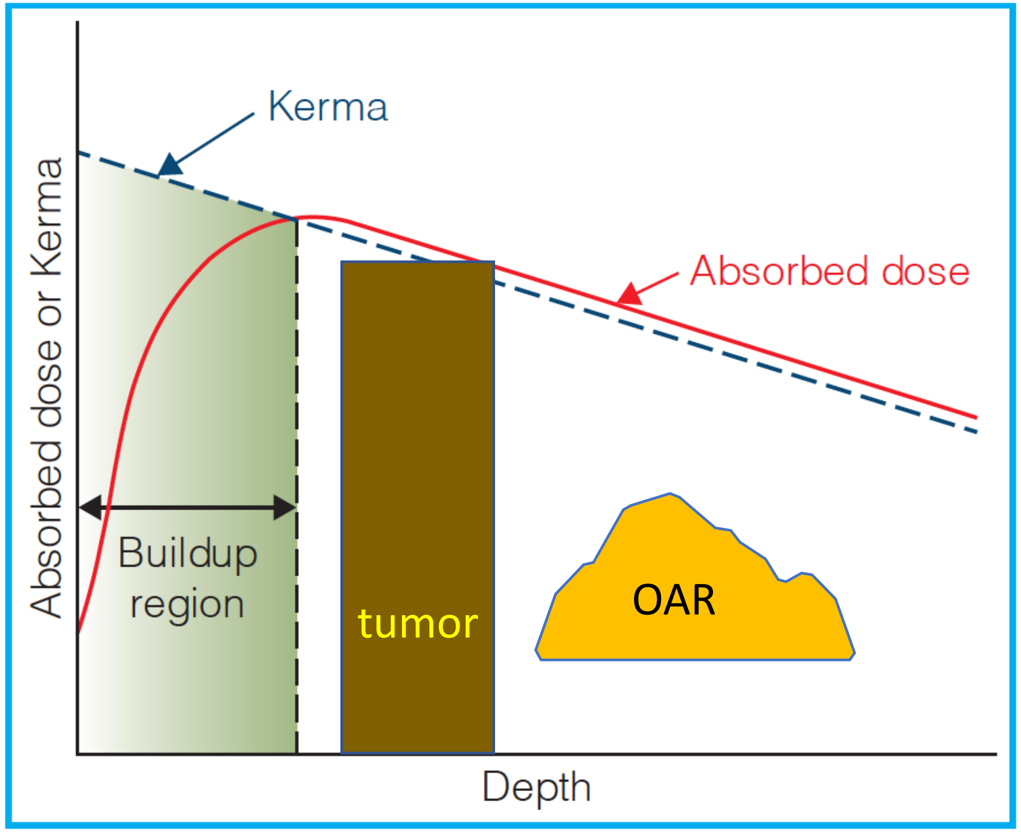
X-rays dose



- Kerma is the kinetic energy released
- Dose is the energy absorbed
- Build-up region produced by forward-scattered electrons that stop at deeper depths

It seems not so efficient for deep-sited tumors…

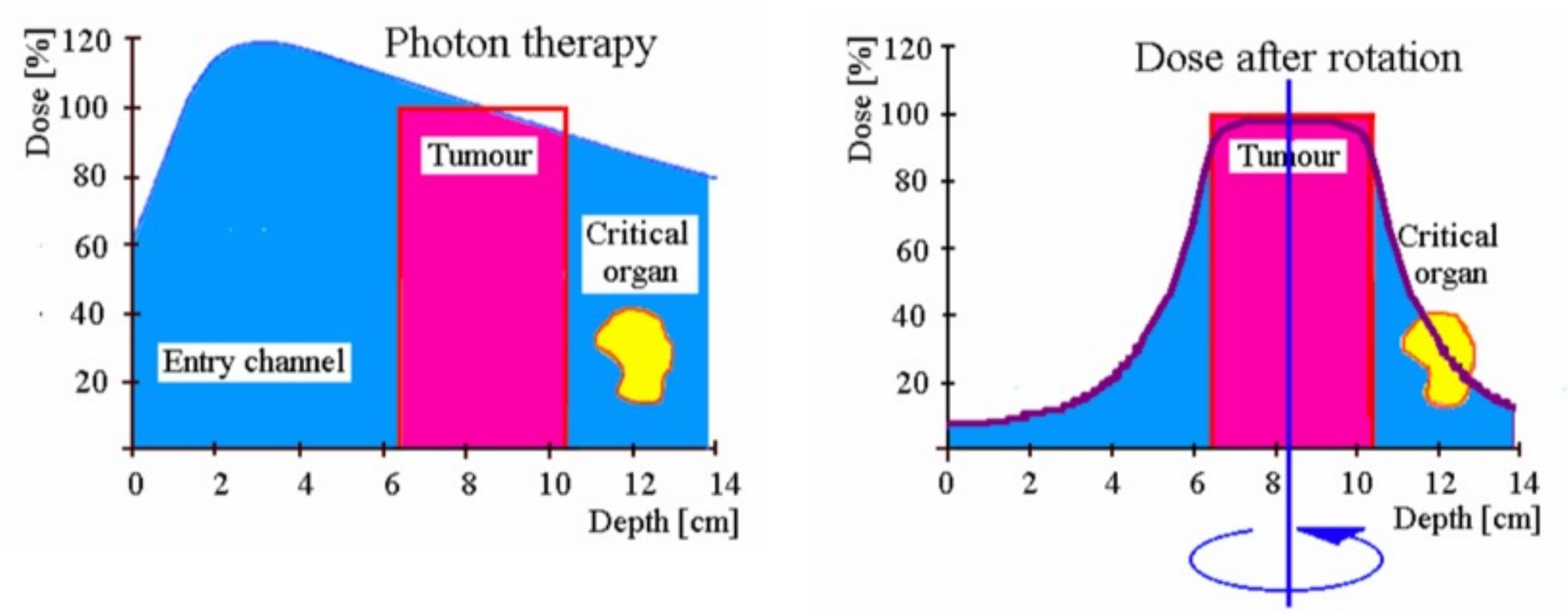
X-rays dose



- Kerma is the kinetic energy released
- Dose is the energy absorbed
- Build-up region produced by forward-scattered electrons that stop at deeper depths

Painting the tumor:IMRT

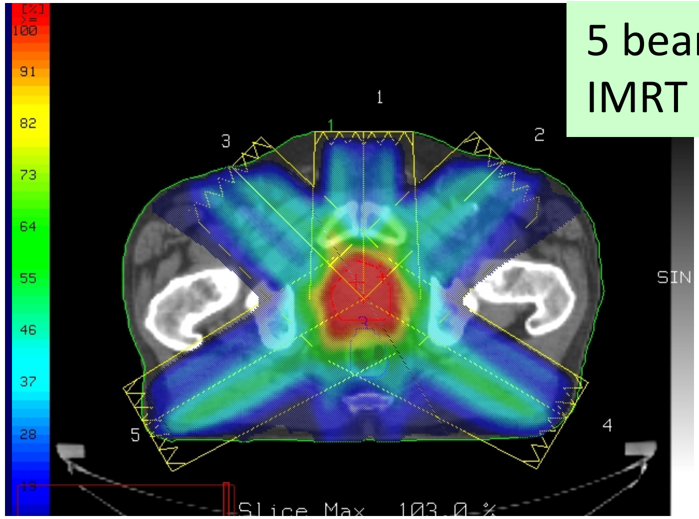
- The use of the superposition of different beams and multi-leaf collimators makes the difference! →IMRT (Intensity modulated Radio Therapy)



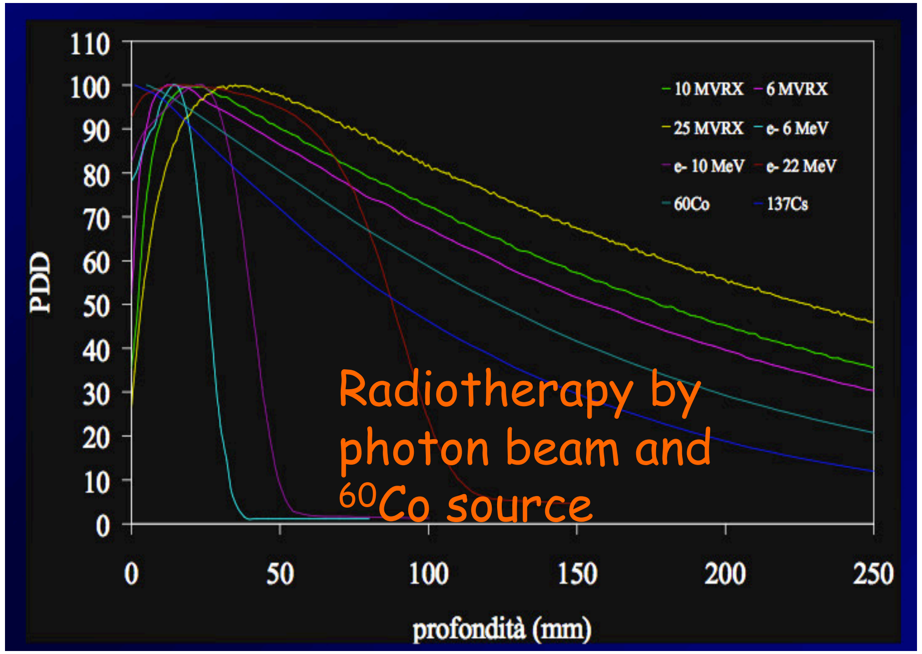
Conventional RT, Archimede and photon physics..

The photon beam has an exponential energy release with the depth inside the patient: not optimal to treat deep tumors

Concentrating more beams with the aid of imaging and complex software (TPS), the dose given on the tumor is maximized with respect to that given to healthy tissues.

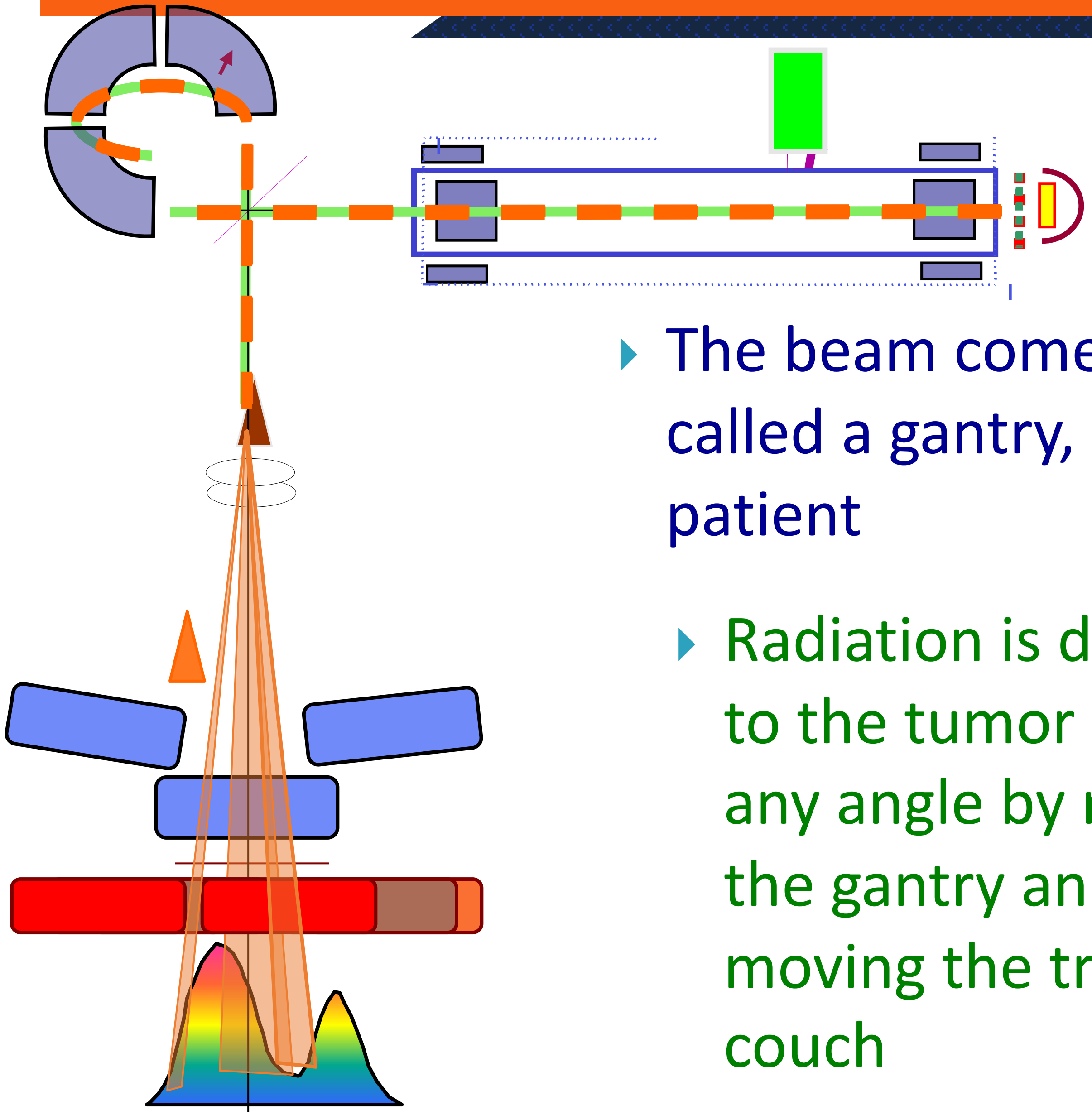


5 beams IMRT

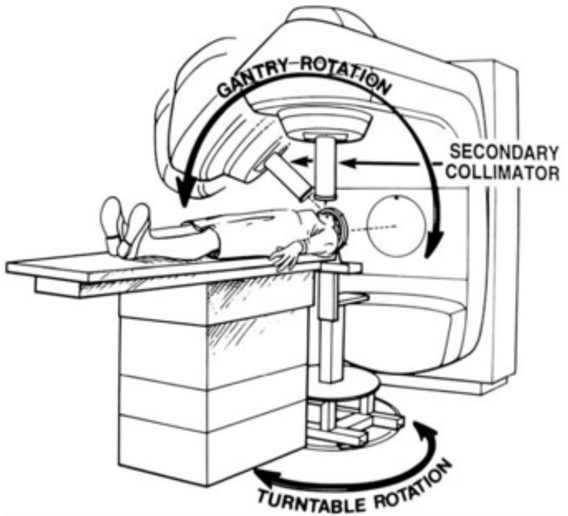


Archimedes did it with solar rays and Roman ships ...

LINear ACcelerator



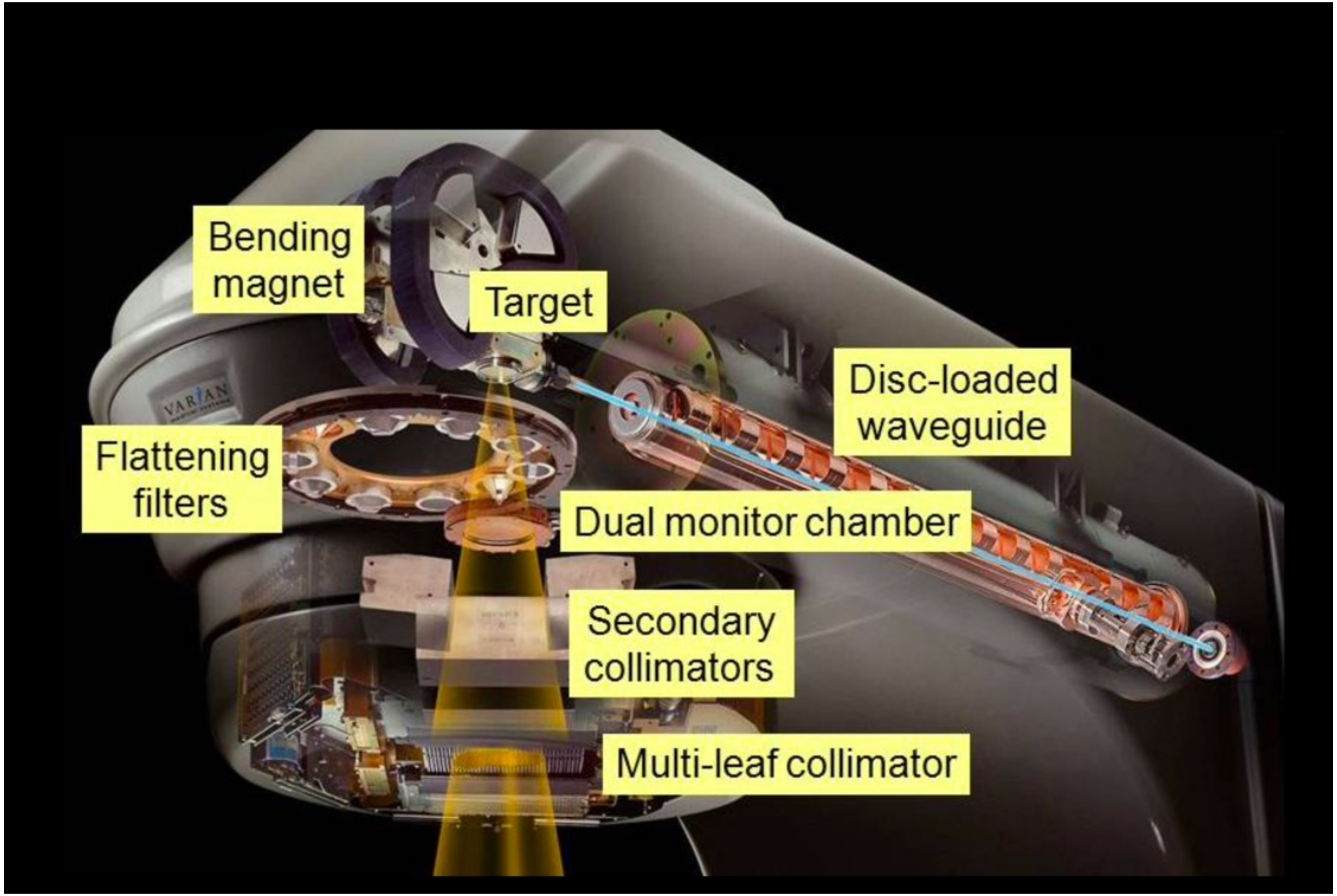
- Patient lies on a moveable treatment couch which can move in any direction
- The beam comes out of a part of the accelerator called a gantry, which can be rotated around the patient
  - Radiation is delivered to the tumor from any angle by rotating the gantry and moving the treatment couch



The LINAC Head

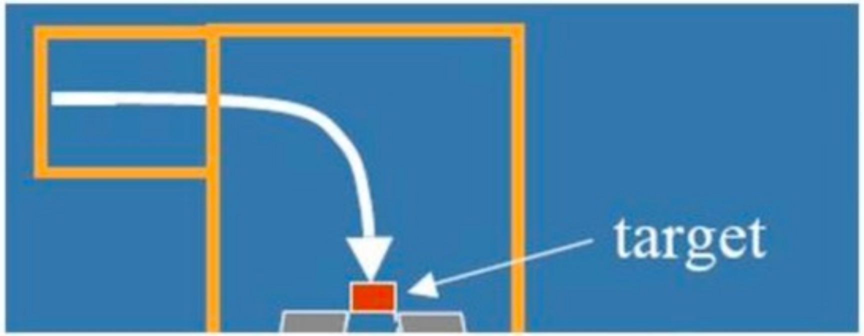
The head rotanting on a gantry hosts fundamental components:

- Bending magnets
- Target
- Flattening filters
- Monitor chambers
- collimators



Finally… the photons!

- ✓ The photon beam is produced via Bremms on high Z materials (Tungsten)
- ✓ Typical energy spectra are 6-10 MeV photons from 15-20 MeV electrons
- ✓ The target conversion efficiency is few %



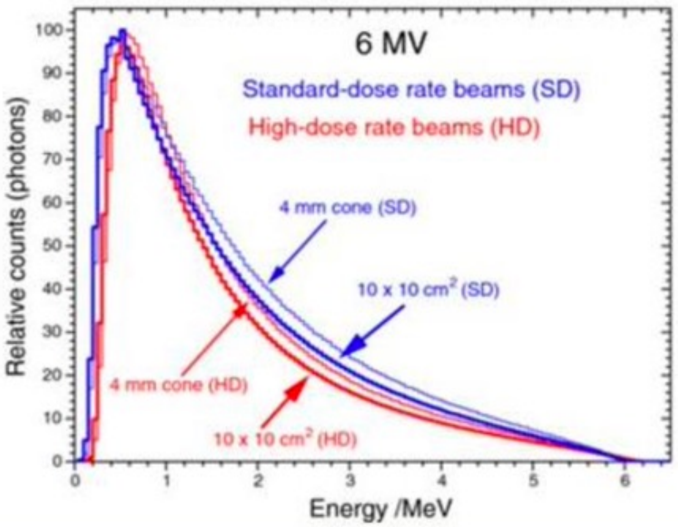
X-ray target:

- Located inside vacuum
- Conversion of electron beam to bremsstrahlung (x-ray) ⇒ X-ray treatment

Target materials:

- Target materials affects x-ray yield and spectrum
- Copper/water for cooling

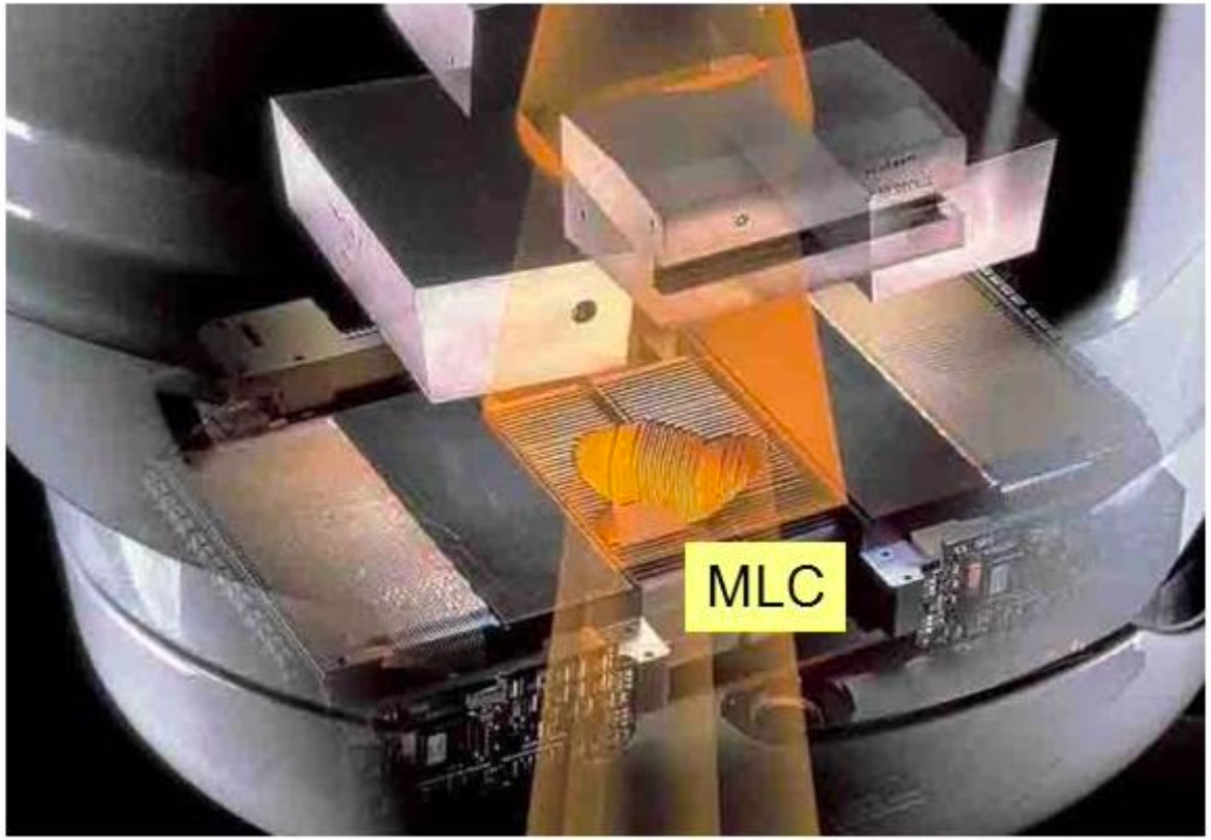
6 MeV bremsstrahlung spectrum:

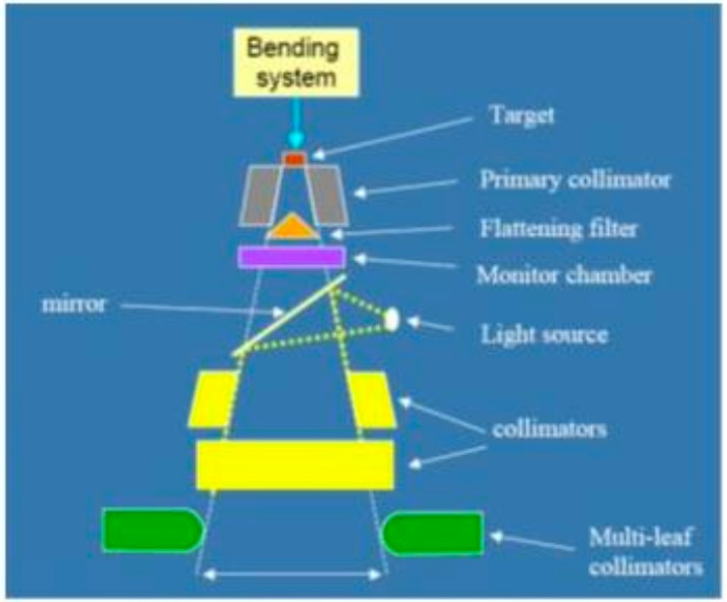


Beam Collimation

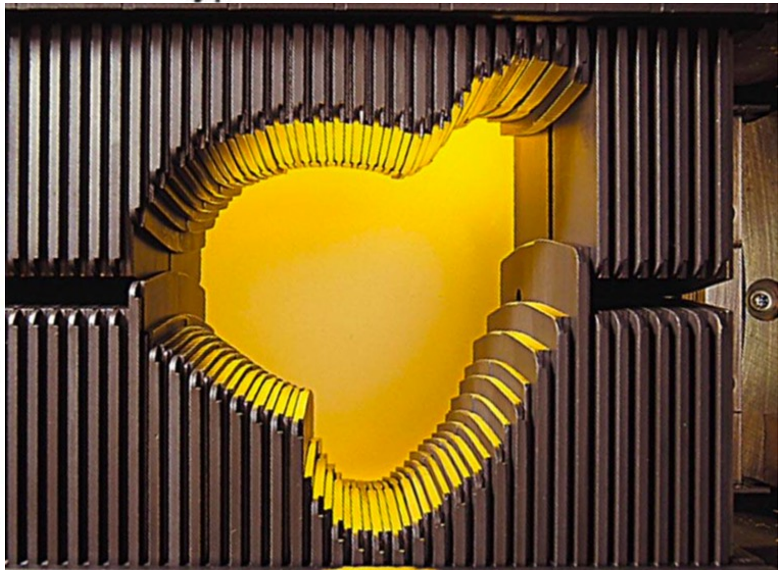
Multi leaf collimators

- 2 rows of thin tungsten blades
- **Detailed shaping** of the treatment field



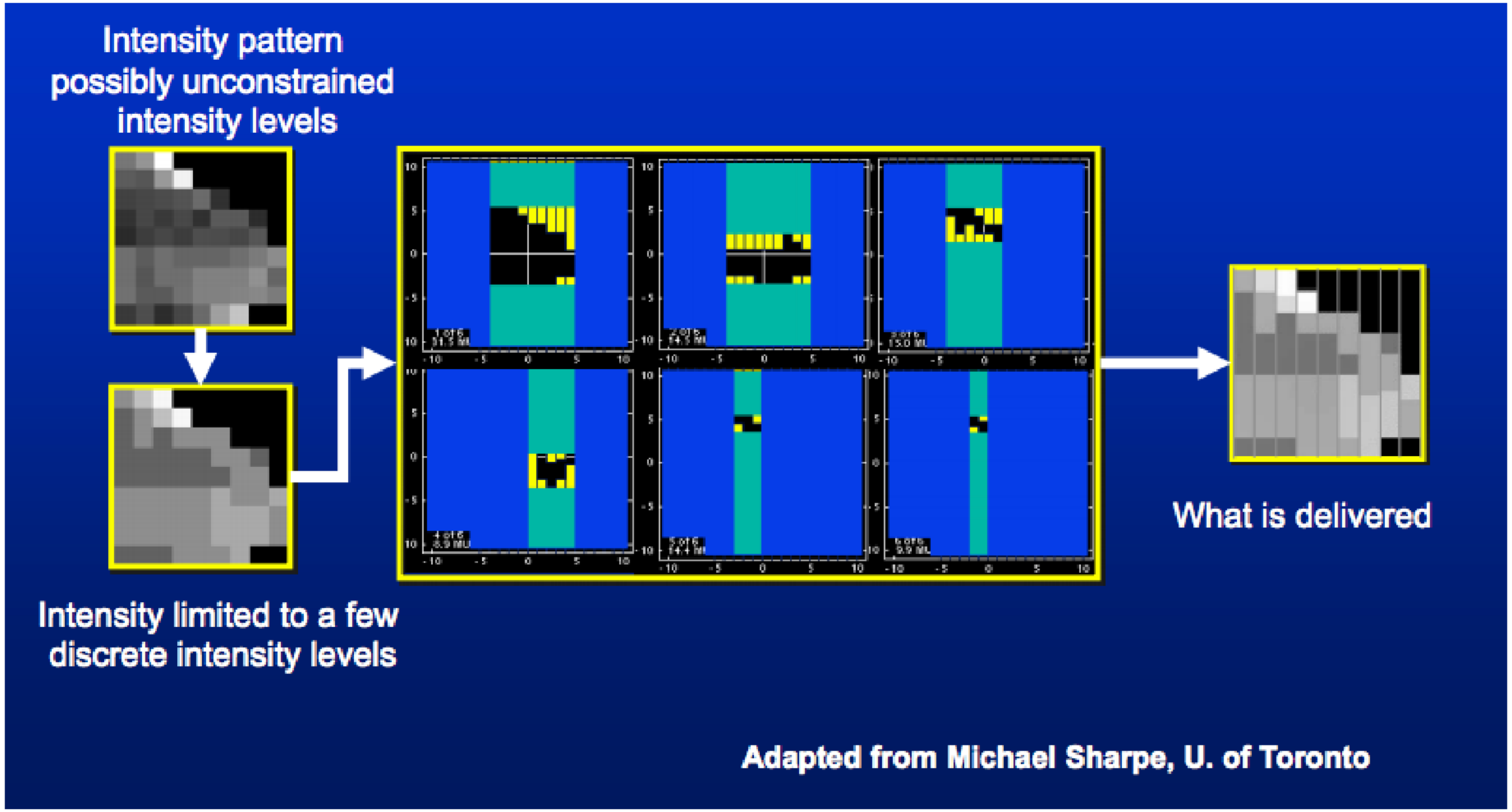


Typical leaf width: 5 mm



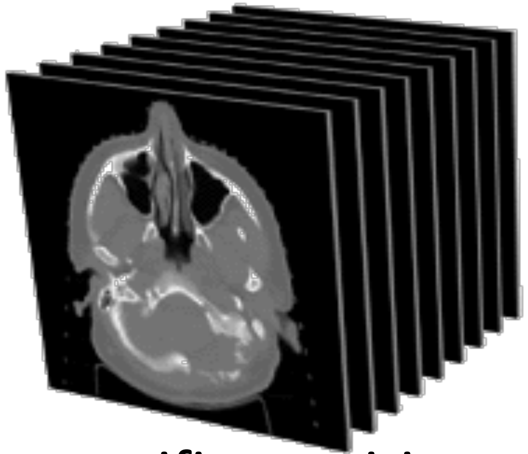
MLC as intensity modulator

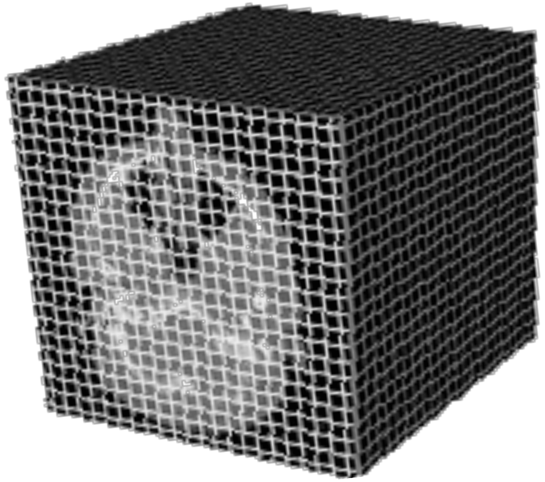
Step and Shoot IMRT Leaf Sequencing

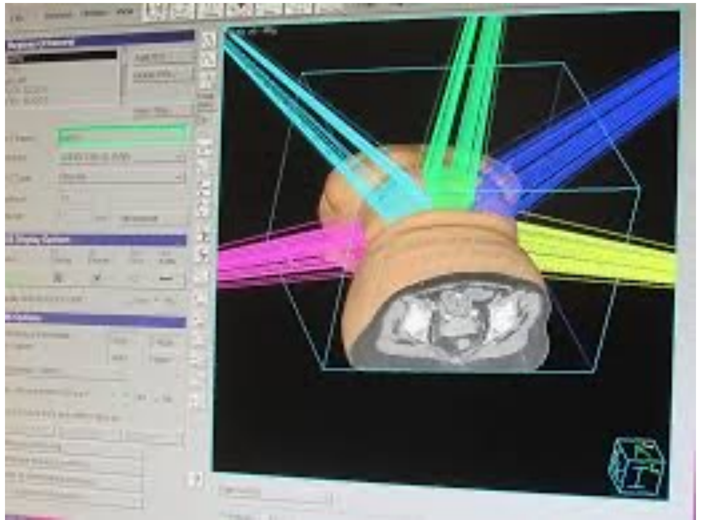


Slide by Rock Mackie, available on aapm.org

Treatment Planning System (TPS)







- The patient is placed in a specific position, reference points are taken with laser and the mask is fixed.
- Imaging (CT) provides the tumor position and the 3D density map of the patient tissues
- A Treatment Planning System is used to optimize the photon beam intensity and directions

TPS: building blocks

(required) Kinetic Energy (MeV)	Stopping Power (MeV cm^2/g)			Range		
	Electronic	Nuclear	Total	CSDA (g/cm^2)	Projected (g/cm^2)	Detour Factor Projected / CSDA
1.000E-03	1.337E+02	4.315E+01	1.769E+02	6.319E-06		
1.500E-03	1.638E+02	3.460E+01	1.984E+02	8.969E-06		
2.000E-03	1.891E+02	2.927E+01	2.184E+02	1.137E-05		
2.500E-03	2.114E+02	2.557E+01	2.370E+02	1.357E-05		
3.000E-03	2.316E+02	2.281E+01	2.544E+02	1.560E-05		
4.000E-03	2.675E+02	1.894E+01	2.864E+02	1.930E-05		
5.000E-03	2.990E+02	1.631E+01	3.153E+02	2.262E-05		
6.000E-03	3.276E+02	1.439E+01	3.420E+02	2.567E-05		
7.000E-03	3.538E+02	1.292E+01	3.667E+02	2.849E-05		
8.000E-03	3.782E+02	1.175E+01	3.900E+02	3.113E-05		
9.000E-03	4.012E+02	1.080E+01	4.120E+02	3.363E-05		
1.000E-02	4.229E+02	1.000E+01	4.329E+02	3.599E-05	[illegible]	[illegible]
1.250E-02	4.660E+02	8.485E+00	4.745E+02	4.150E-05	3.037E-05	0.7318
1.500E-02	5.036E+02	7.400E+00	5.110E+02	4.657E-05	3.499E-05	0.7514
						0.7674
						0.7808
						0.7923
						0.8022
						0.8109
						0.8187
						0.8319
						0.8429
						0.8522

Patient anatomic data (CT, MRI, PET)

Volume of interest	% of Volume	Prescription/tolerance dose (Gy)	Relative importance
Prostate PTV	100	74.0	1.0
Prostate PTV	5.0	72.0	1.0
Prostate PTV	10.0	76.0	1.0
Rectum	90.0	10.0	0.5
Rectum	50.0	20.0	0.5
Rectum	10.0	30.0	0.5
Bladder	90.0	10.0	0.2
		20.0	0.2
		30.0	0.2
		10.0	0.2
		20.0	0.2
Femoral heads	10.0	40.0	0.2

Table of:

- dE vs Ebeam , x, y, z
- RBE vs Ebeam, dE, x, y, z

TPS

Physician Prescription On Tumor and OAR

Dose calculation

Accelerators Parameters: Fluences for each beam spot

The **TPS** provides information to the beam control system:

- **Position**
- **Intensity**
- **Direction**

TPS: dose engine

ANALYTICAL ALGORITHMS

- Reasonable times for calculating the TPS
- Simplified representation of the tissue: the geometry of the patient is represented in an equivalent volume of water, neglecting the real atomic composition of the tissues.
- **Not high accuracy**

Ex. Proton TPS ~ 1 h/core

MONTE CARLO

- Realistic assessment of body composition
- Extracts accuracy in the description of the transport and the interaction of the particles with matter
- **Long times for calculating the TPS**

Ex. Proton TPS ~ days/core

FAST MONTE CARLO

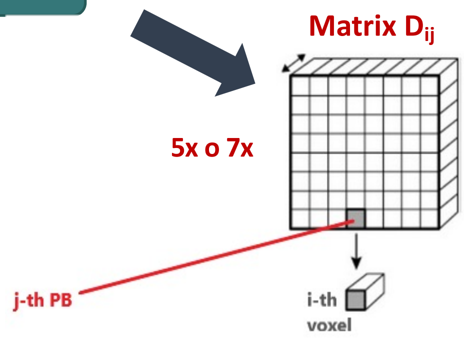
- High accuracy in the description of the transport and of the interaction of particles with matter
- Realistic assessment of body composition
- **Very fast calculation of TPS**

Ex. Proton TPS ~ minutes

TPS: optimization

Dose Engine

The dose of the j-th elemental beamlet on the i-th voxel is provided by the Dose Engine



multiple beamss contribute to dose release in the i-th voxel:

$$d_i = \sum_{j=1}^{N_j} N_j D_{ij}$$

In a naive form the TPS varies the beams parameter (direction, intensity, MLC position) searching the **global minimum** of the cost function:

$$\chi^2 = \sum_{i \in PTV} w_i \frac{(d_i - D_{PTV})^2}{d_i^2} + \sum_{i \in OAR} w_i \frac{(d_i - D_{OAR})^2}{d_i^2} * g(d_i - D_{OAR})$$

$$\begin{cases} 1 \; per \; d_i > D_{OAR} \\ 0 \; per \; d_i < D_{OAR} \end{cases}$$

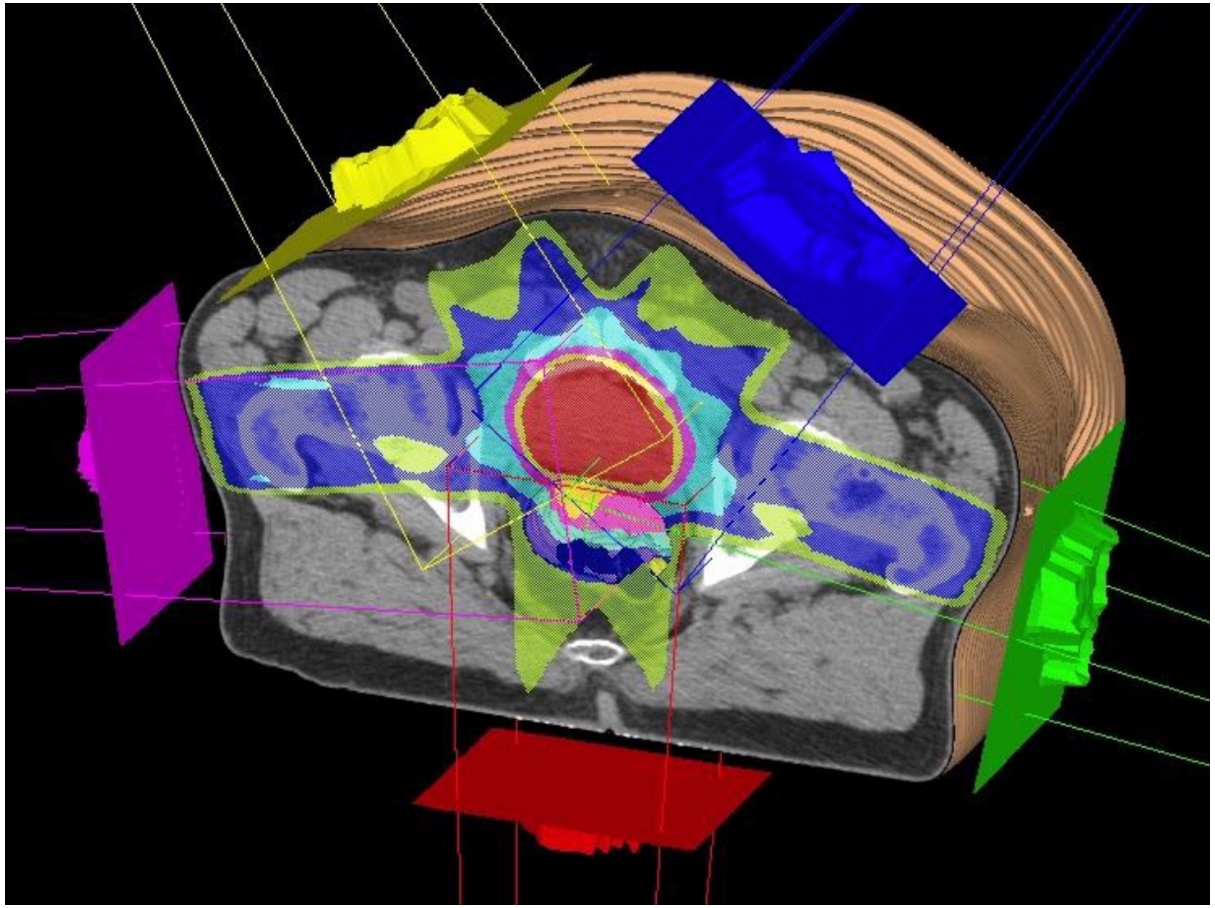
Algorithms:
Steepest descends
Simulated Annhealing
Genetic Algorithms
Quantum tunnelling

- **d_i**, dose of i-th voxel
- **w_i**, weight of i-th voxel
- **D_{PTV}**, prescribed dose to PTV
- **D_{OAR}**, maximum allowable organ dose
- **threshold** of voxel in NoT
- **red** reduction voxel of NoT

It’s almost magic!

The results are impressive!!!

3D view of a Imaging Modulated Radio Therapy (IMRT) treatment



Summary of Standard RT

- RadioTherapy standard technology : 6-20 MeV multiple photon beams, provided by compact, light weight electron linac with photon production on tungsten target
- Multiple fractions treatment: up to 30 (2 Gy each) delivered within 1-2 month
- Each fraction delivered in ~ minutes providing order of Gy to the tumor region-> Dose rate ~ Gy/minute
- Dose (beam intensity) controlled at few % accuracy !!

Main limitations of standard RT:

- Radioresistant, bulky tumors (es glioblastoma)
- Diffuse tumors->metastases

Dose escalation prevented by toxicity on healthy tissue

Hidden problem: secondary cancers

Carcer survivivors represent about 3.5% of US population. Second primary malignants in this high risk group account for 16% of all cancers

Three main causes:

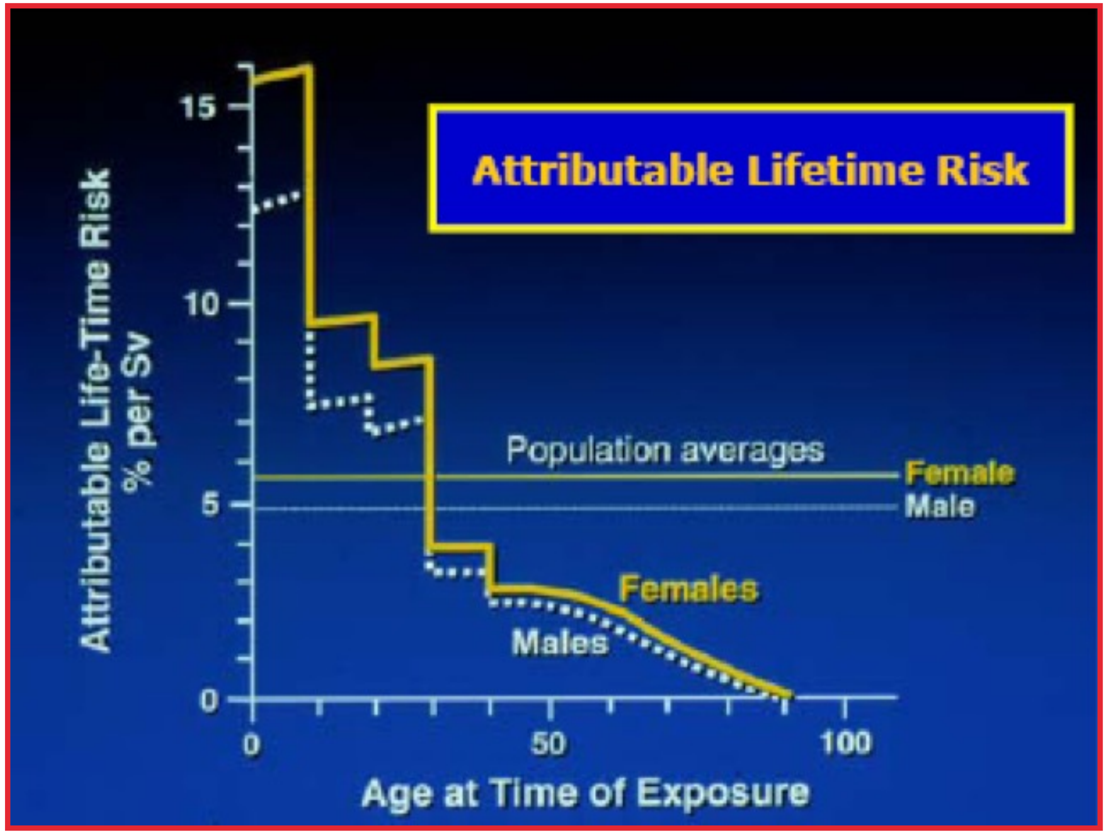
Continuing risky lifestyle

Genetic predisposition

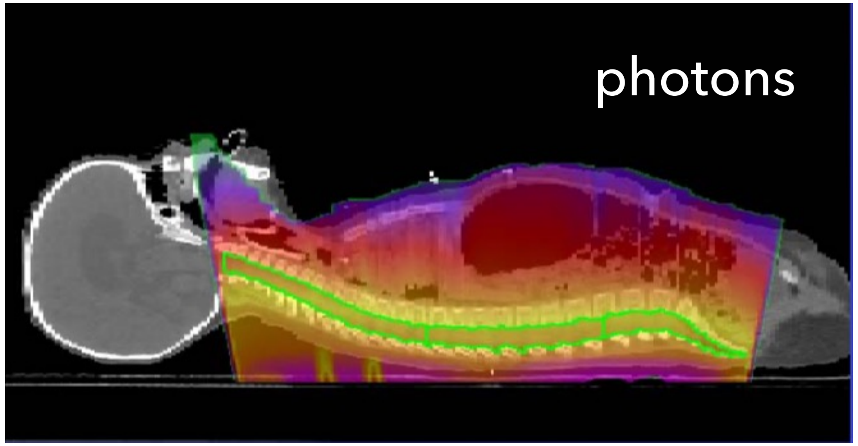
Treatment of the primary cancer

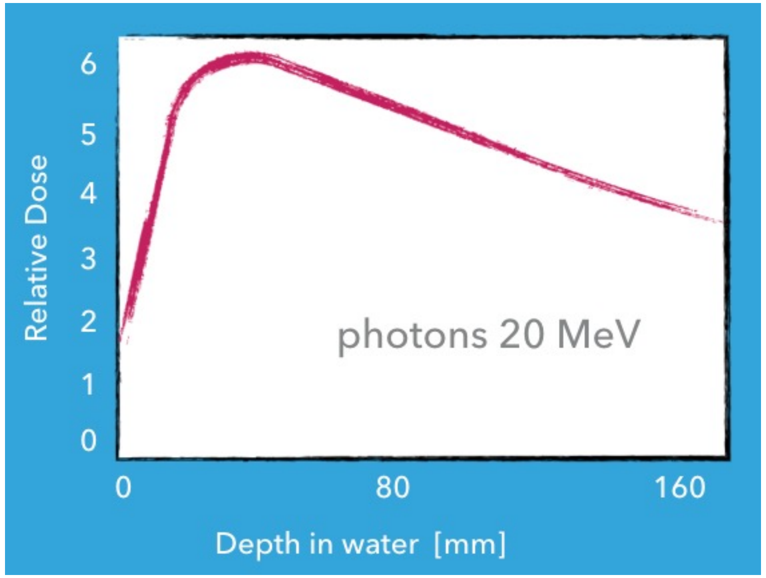
Radiation induced secondary cancers are mostly carcinomas, but sarcomas in heavily irradiated sites are also observed

Particularly important is the normal tissue stray dose



Pediatric case



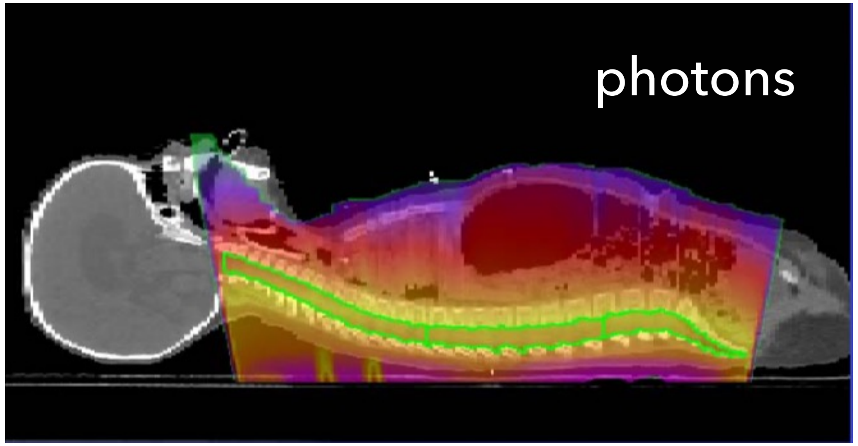


	X-ray	IMRT
CTV	90%	90%
Heart	18.2	17.4
Right lung	3.5	21.9
Esophagous	11.9	32.1
Stomach	3.7	20.6
Right kidney	3.3	29.8
Transvers colon	2.6	18.0

In pediatric treatments the occurrence of secondary cancer is particularly crucial:

1. quality of life
2. expectation of life
3. organs closeness

Pediatric case



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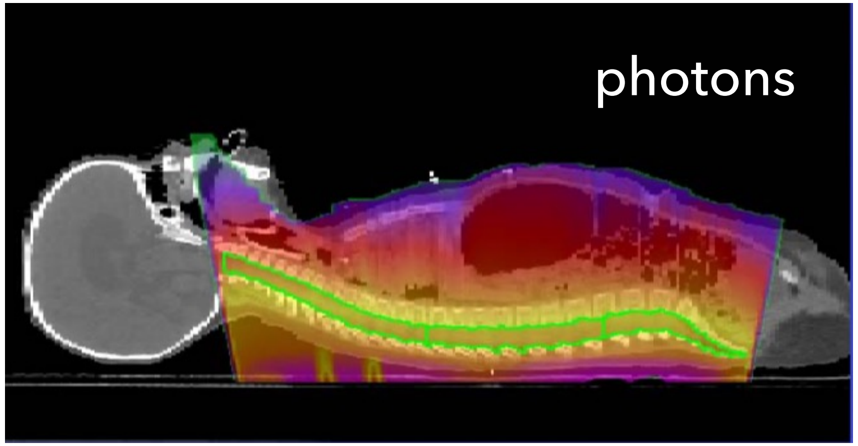
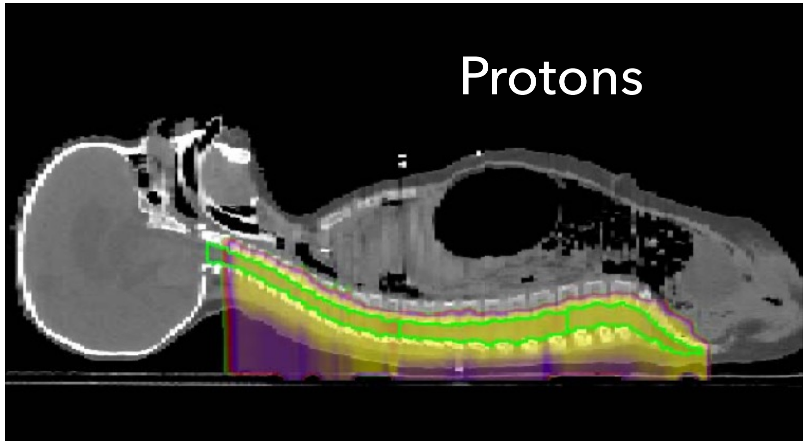
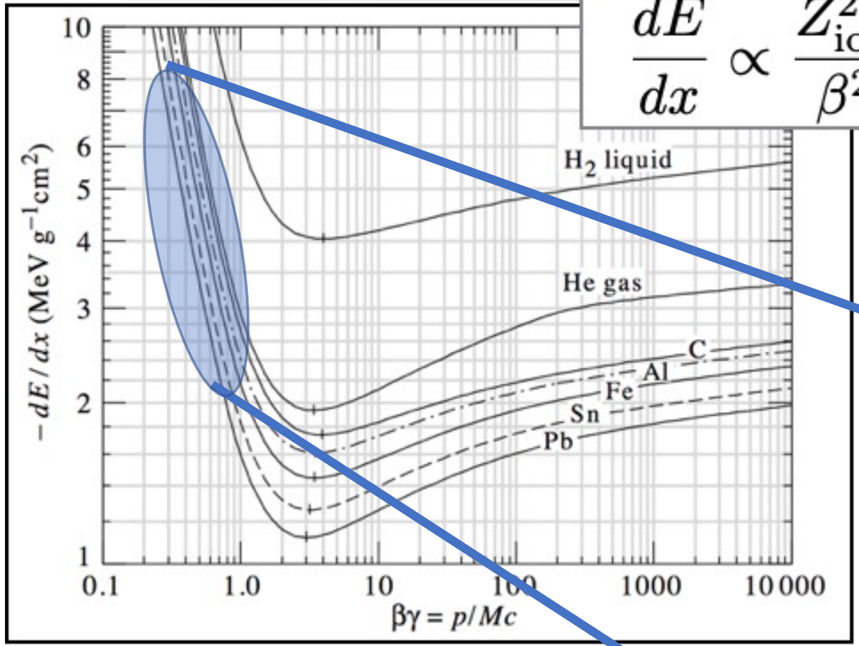




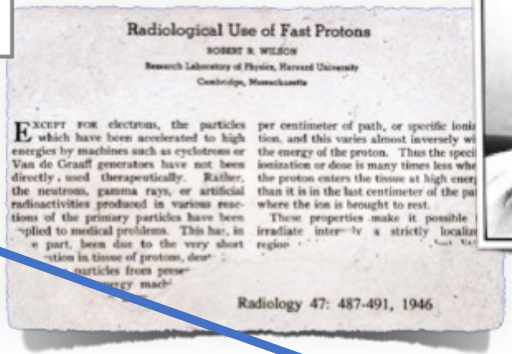
	X-ray	IMRT	Proton
CTV	90%	90%	90%
Heart	18.2	17.4	0.1
Right lung	3.5	21.9	0.1
Esophagous	11.9	32.1	10.2
Stomach	3.7	20.6	0.1
Right kidney	3.3	29.8	0.1
Transvers colon	2.6	18.0	0.1

physics can help!!

A different approach: charged particles



$$\frac{dE}{dx} \propto \frac{Z_{\mathrm{ion}}^2}{\beta^2}$$



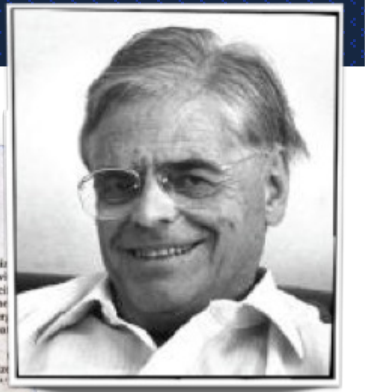
Radiological Use of Fast Protons

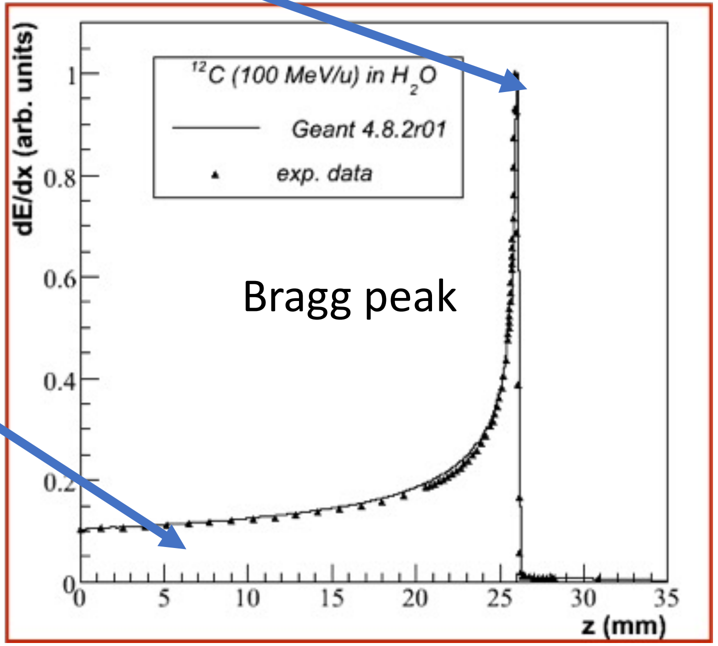
ROBERT R. WILSON

Research Laboratory of Physics, Harvard University

Cambridge, Massachusetts

Radiology 47: 487-491, 1946





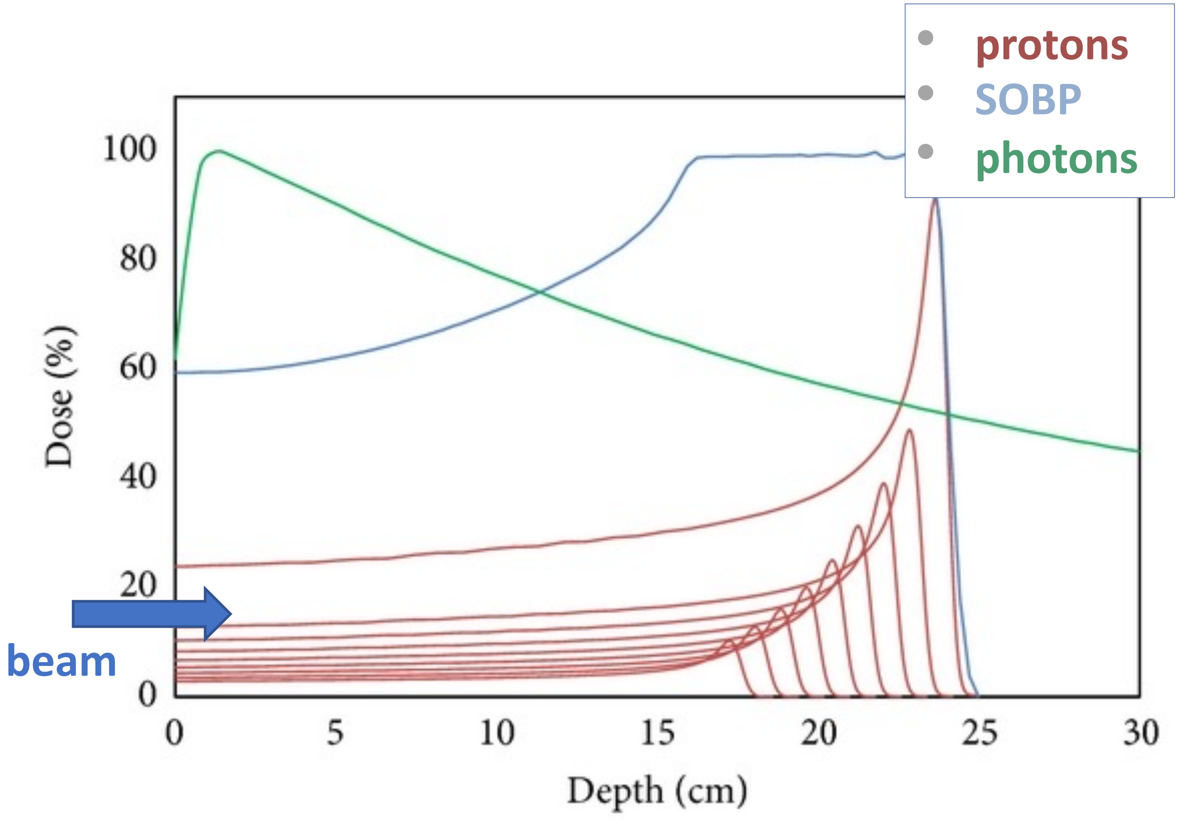
- Rapidly increasing stopping power with the particle speed decreasing
- Protons (50-250 MeV), ^{12}C (100-400 MeV/u)

Particle therapy

- The **Particle Therapy** (PT) Proposed for the first time in 1946 (R. Wilson) but has mainly spread in the last decades thanks to the development of accelerators

- Better efficacy wrt photons in covering the tumor volume due to the peaked dose-depth profile (**Bragg Peak**)

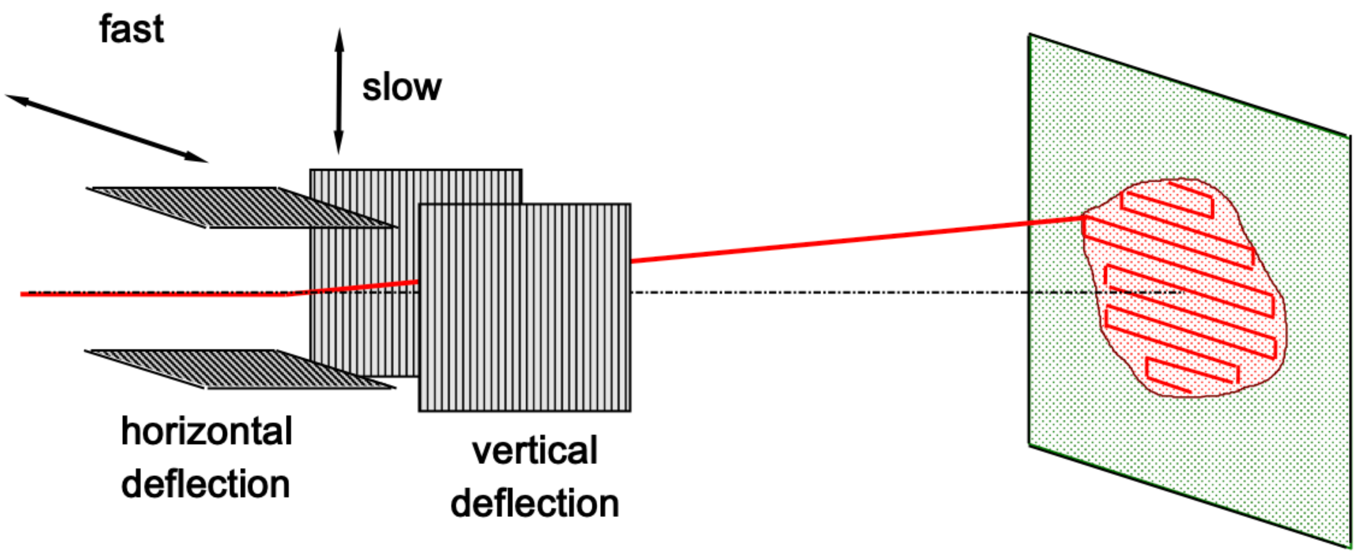
- **Modulating the beam energy and deflecting the beam a uniform dose can be delivered to the whole tumor volume (<u>Spread-out Bragg Peak</u>)**



- **p (50-250 MeV) or ^{12}C ions (100-400 MeV/u) are currently used in PT**

Active scanning

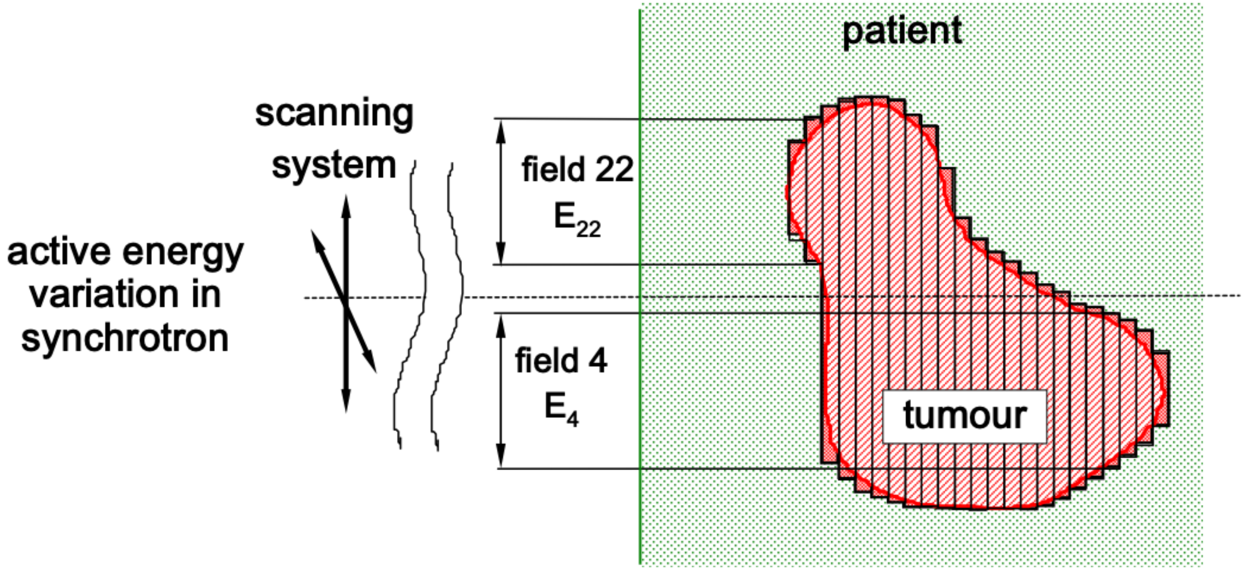
- Transverse scanning with a small “pencil” beam.
- Fast magnetic deflection (≤ 10m/s).
- Transverse beam size adjustable from 4 to 10 mm.



- No beam losses.
- No patient specific hardware.
- Requires sufficient time (~1s per slice) for online dosimetry.
  - Slow resonant extraction if a synchrotron is used.

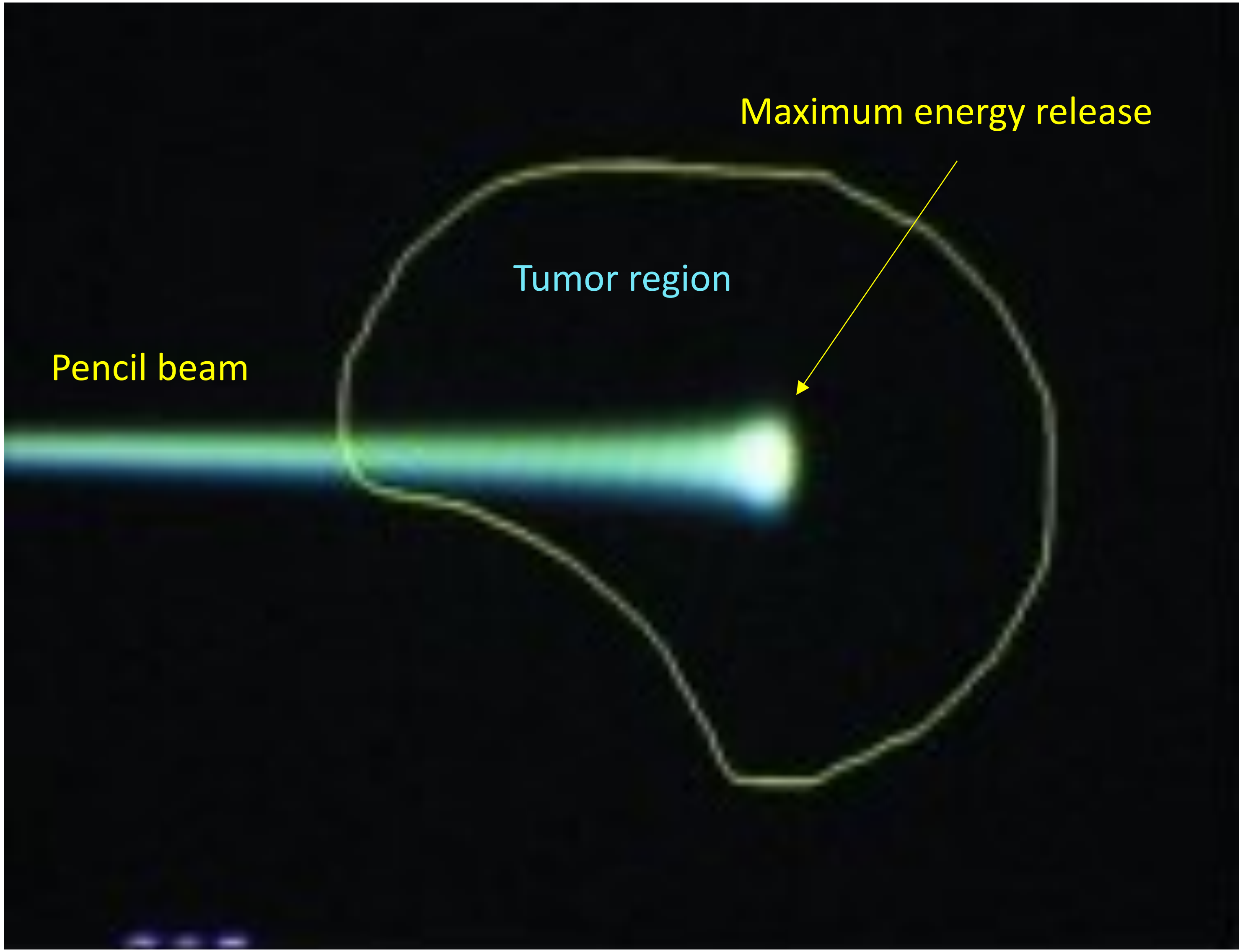
Active scanning

- Cut tumour into many slices with different depth.
- Transverse scanning, slice by slice, with corresponding energy.
- Intensity and beam size adjustable from slice to slice.

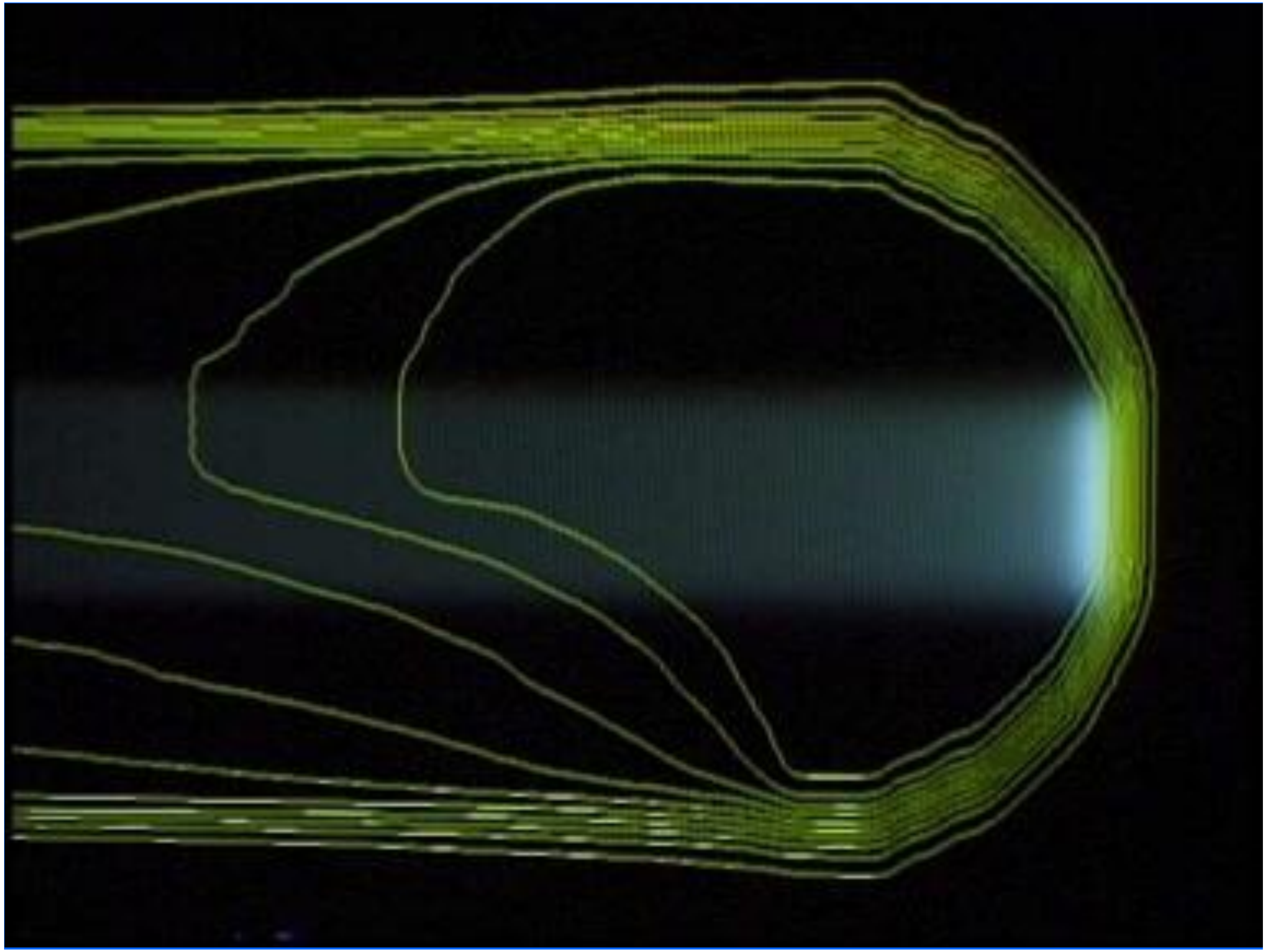


- Best achievable dose distribution.
- Strong time-position correlation, problematic for tumour movements.

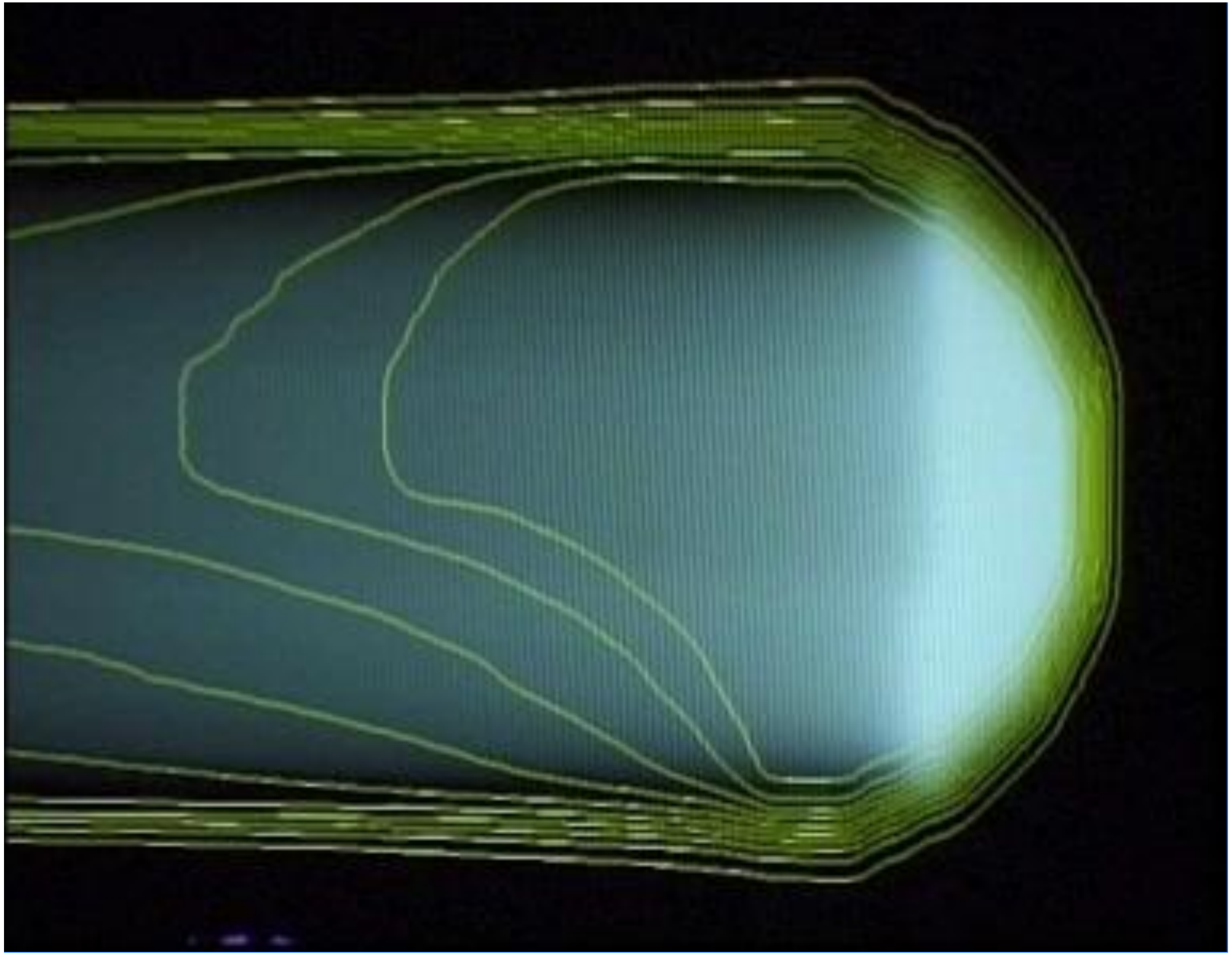
Painting the tumor…



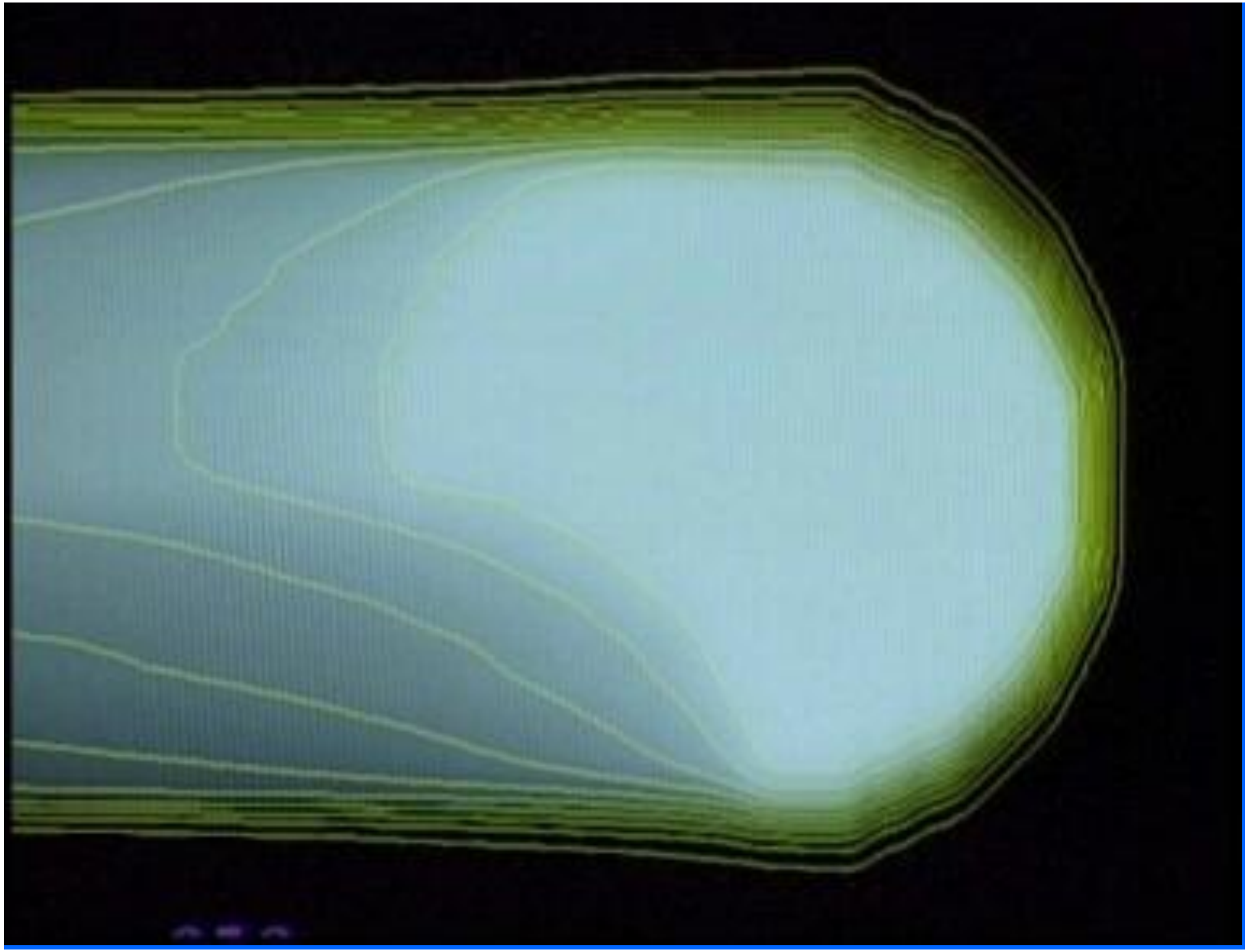
Conformal dose by beam painting...



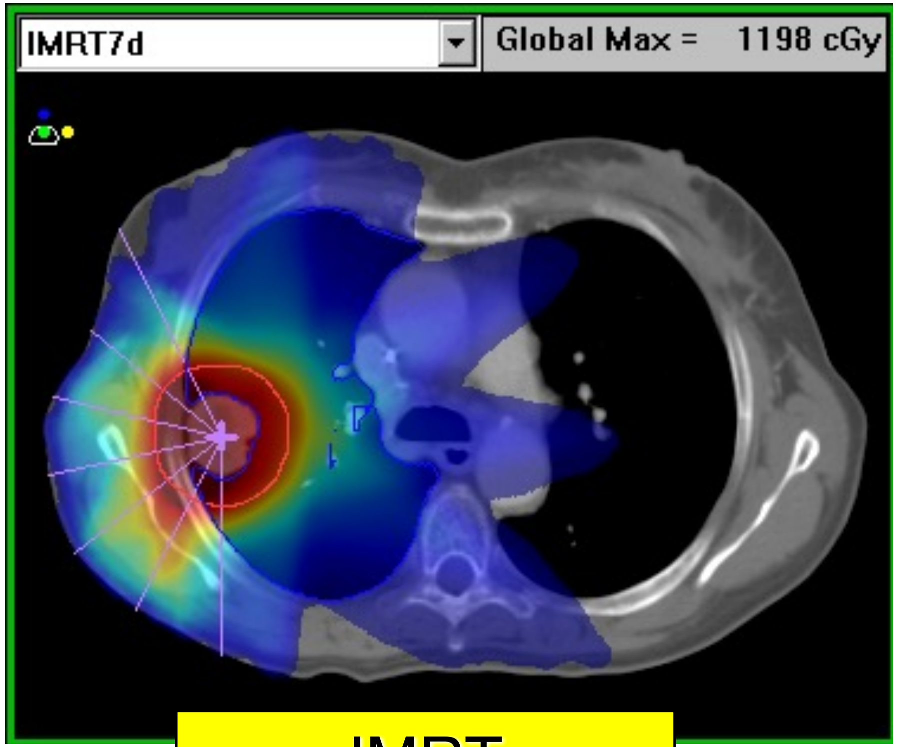
Conformal dose by beam painting...



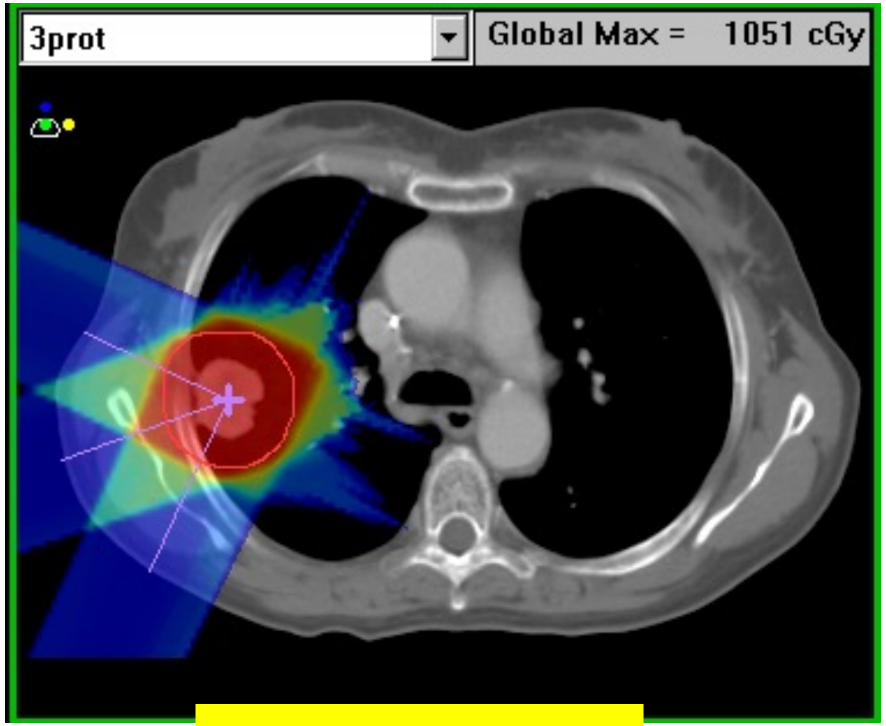
Conformal dose by beam painting…



PT vs RT



IMRT

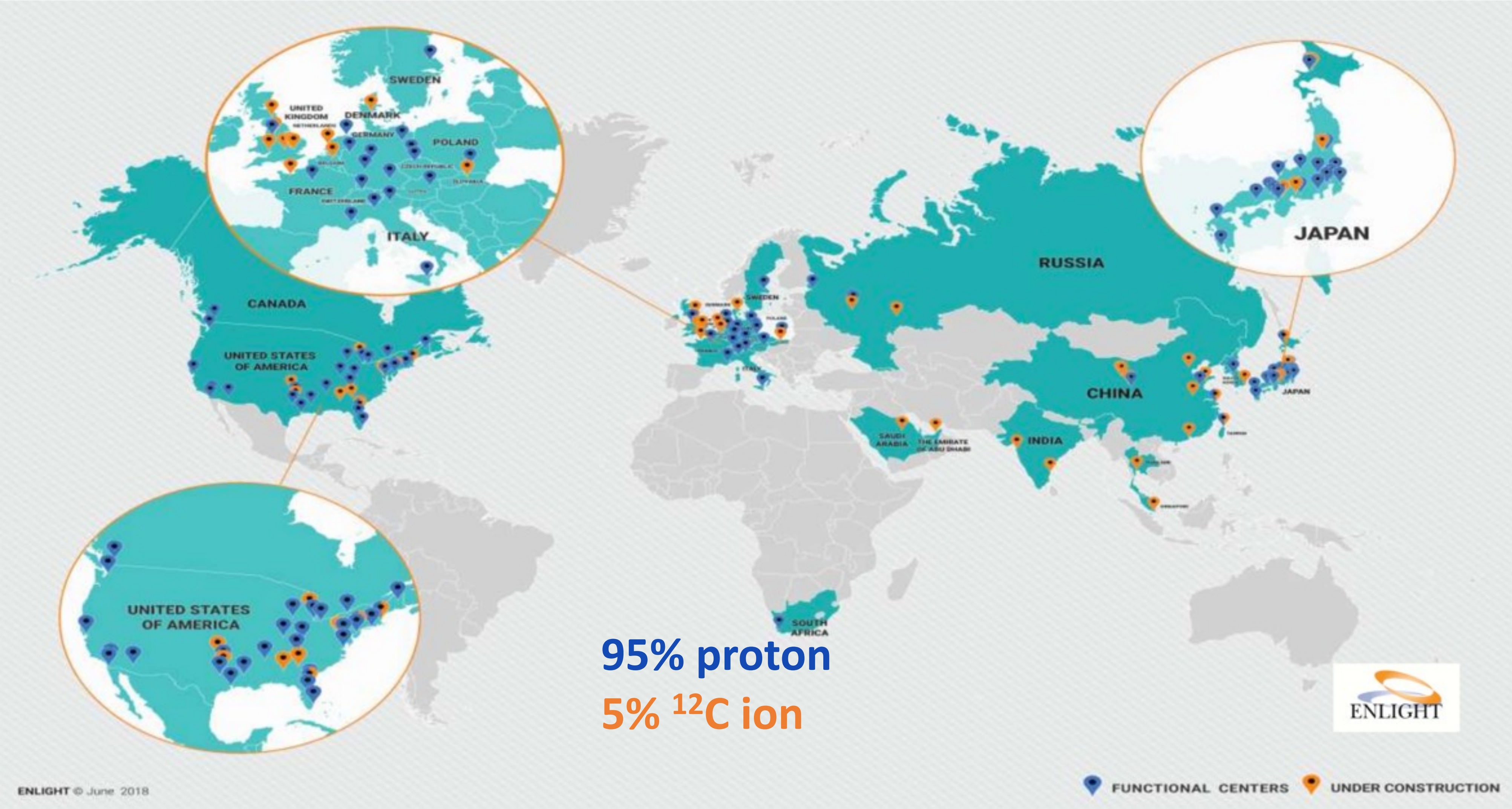


Hadrontherapy

PT has a greater potential in sparing healthy tissues!

Particle therapy in the world

- 95 facilities currently in clinical operation in the world , 25 in Europe, ~40 under construction



95% proton

5% ^{12}C ion

Accelerators for PT

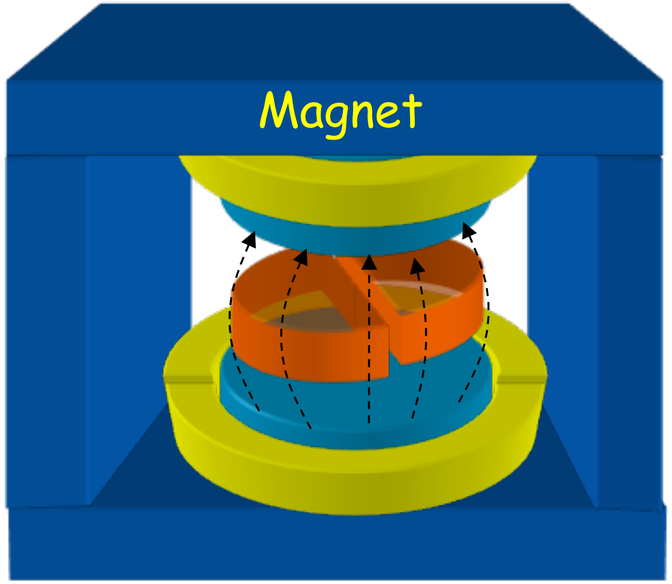
- **Cyclotron:**
  - Protons only.
  - Beam radius ~cm.
  - Fixed extraction energy.
  - $\Delta p/p \sim 10^{-3}$ (sharp B-Peak)
- **Synchrotron:**
  - Protons and C-ions.
  - Beam radius ~cm.
  - Energy variable, cycle to cycle.
  - $\Delta p/p \sim 10^{-3}$ (sharp Bragg peak)

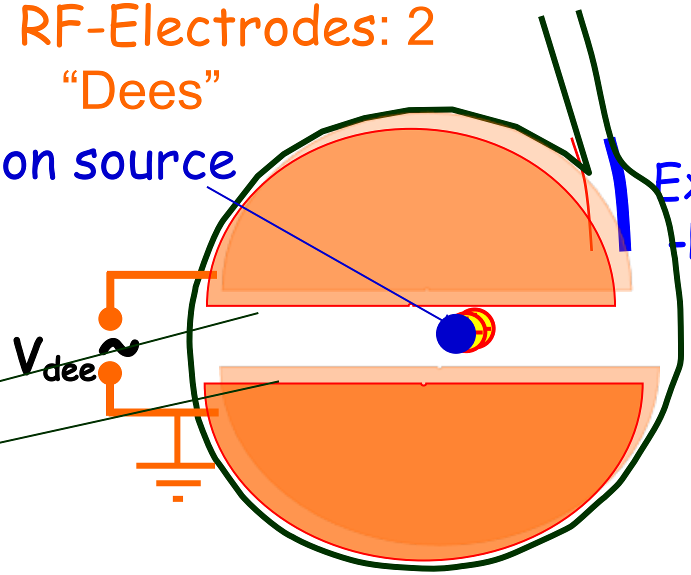
The Cyclotron

The PT proton beam are mostly provided by commercial cyclotrons

- The magnetic field keeps the particles on a circular orbit
- The alternate electric field accelerates the particle at each turn
- Increasing the energy the particle increases the orbit radius and is extracted from the the dee

Ernest Lawrence
(1901-1958)





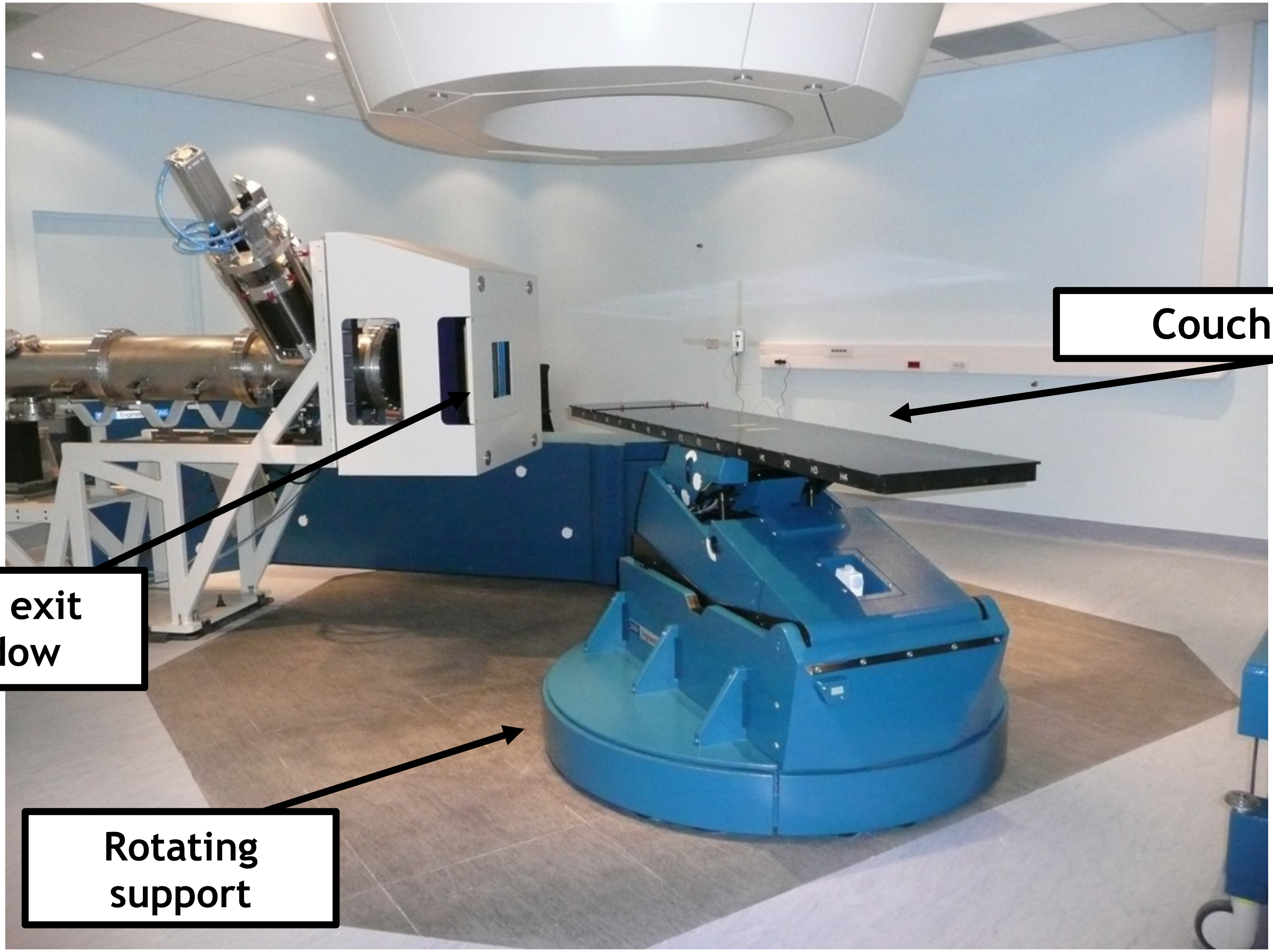
oscillating high voltage on "Dee" electrode

At each electrode border:
Energy gain $\Delta E = V_{dee}$

PT cyclotron

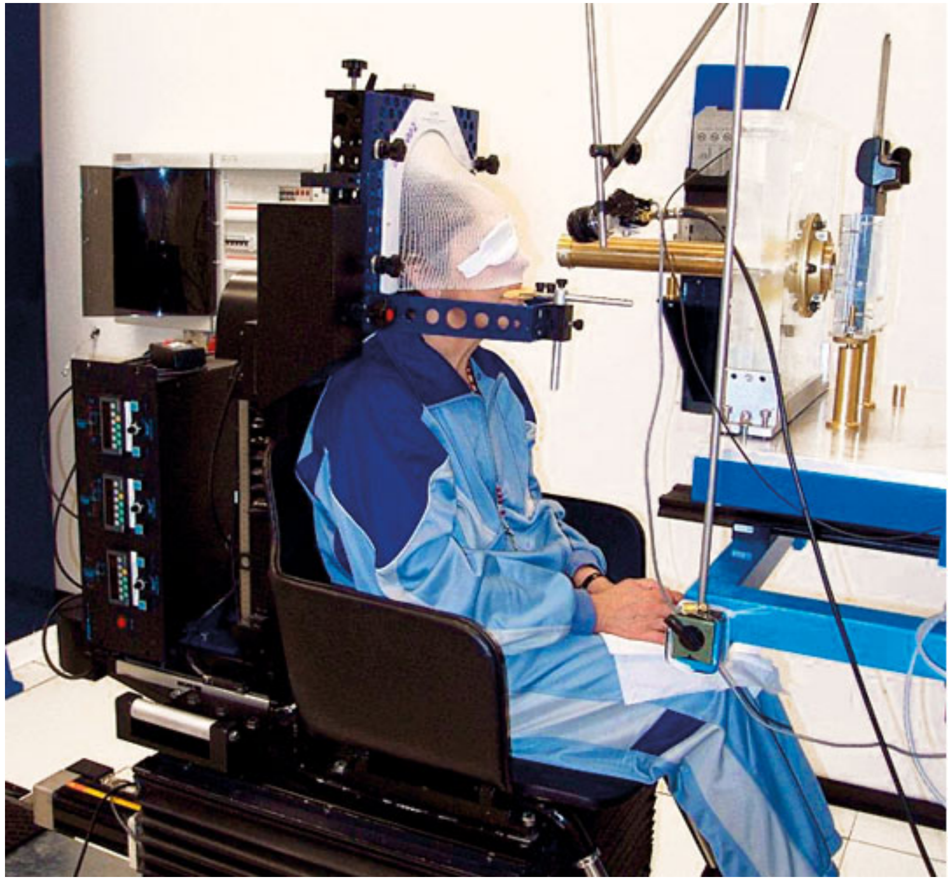
It is a huge equipment to be embedded in a standard hospital…
And is quite expensive!

Treatment room



PT and ocular tumor

62 MeV proton beam from cyclotron



At LNS of INFN more than 300 patients have been cured since 2022 (average age 48), with 98% of survival probability and 95% probability of local control

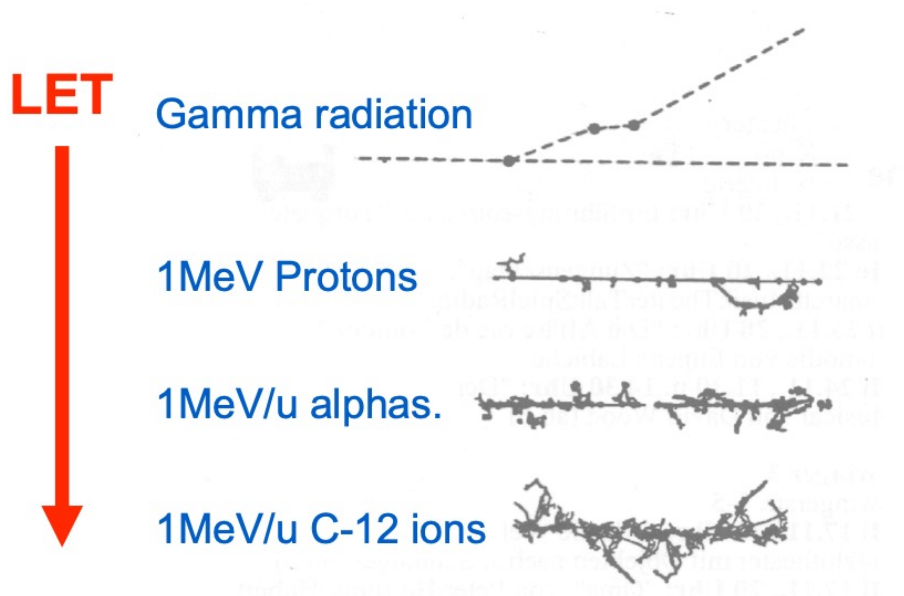
Are the protons enough?

In spite fo the great conformality of the proton beams, some hypoxic radioresistant tumors would need more dose to be eradicated.

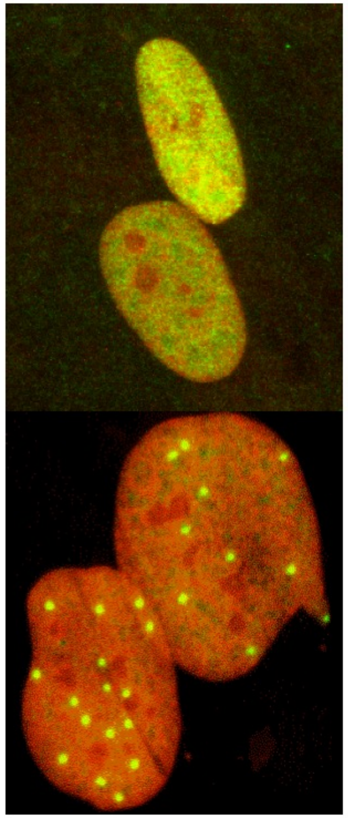
But the surrounding normal tissue does not allow a dose escalation..

And here comes into the game the carbon beam!!

Ionisation tracks



Damage in nucleus



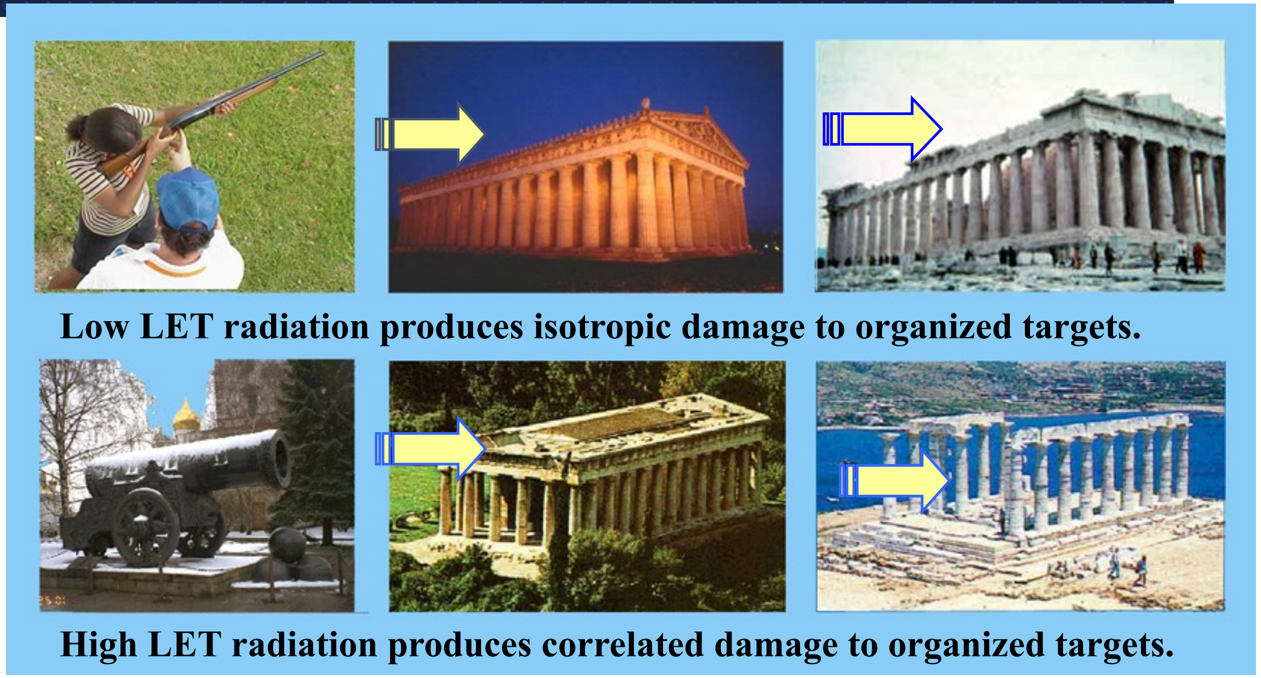
M. Scholz et al. Rad. Res. 2001 Immunoflourescence image of the repair protein p21;

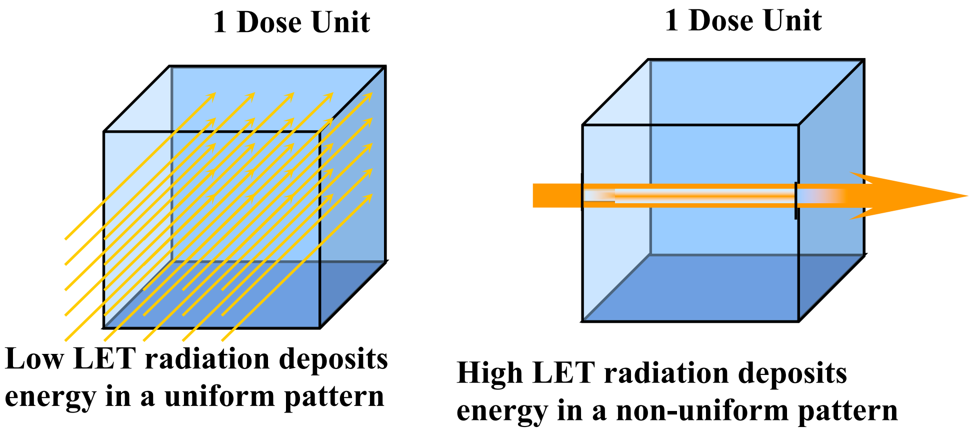
Increase of **direct radiation damage & RBE** for high-LET

Cell damage vs radiation Charge

The “physical” dose= ΔE/Δm is not enough to describe damage of human tissue by ions.

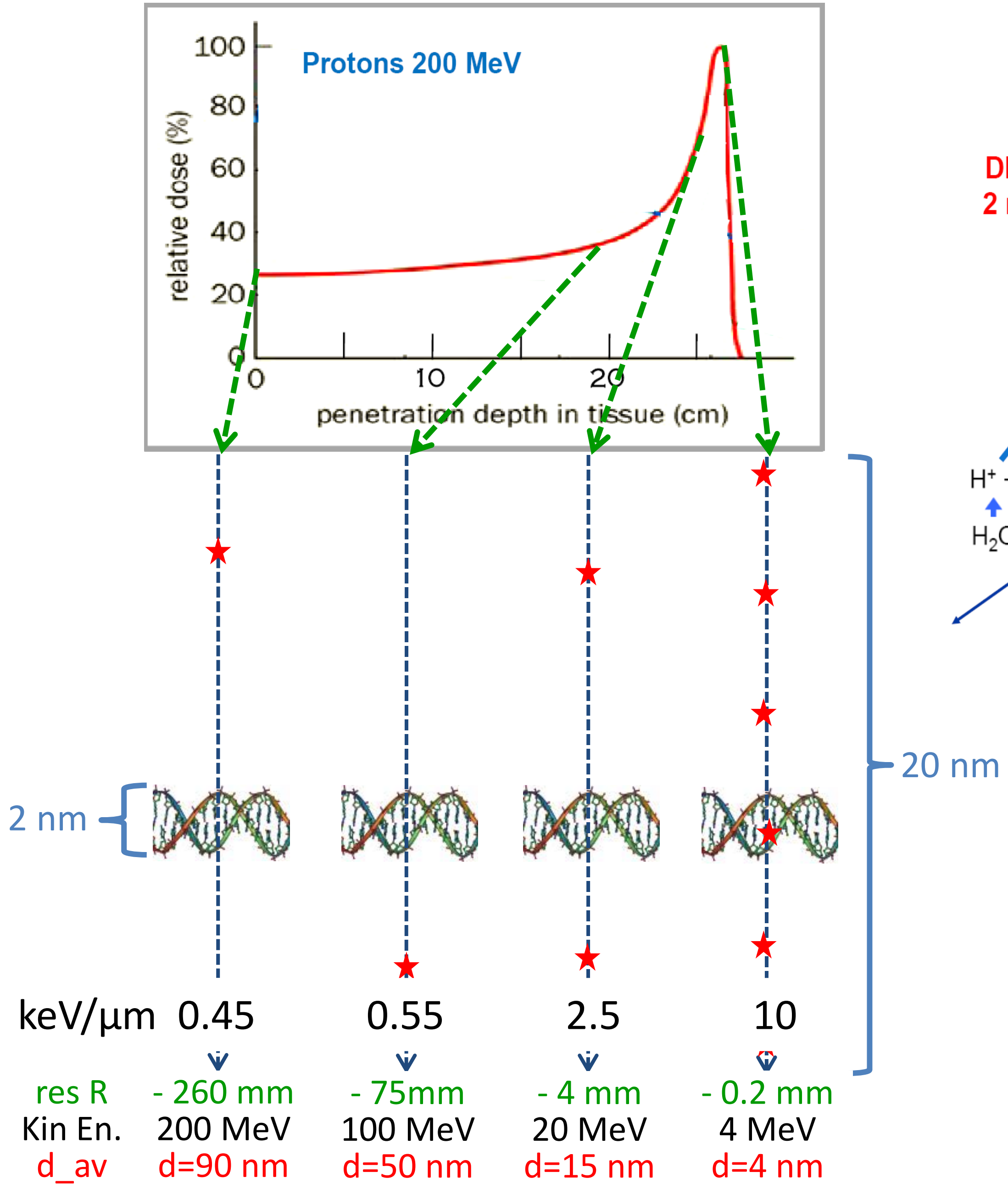
If we look at the LET = Linear Energy Transfer, the ions has different pattern wrt photons or protons

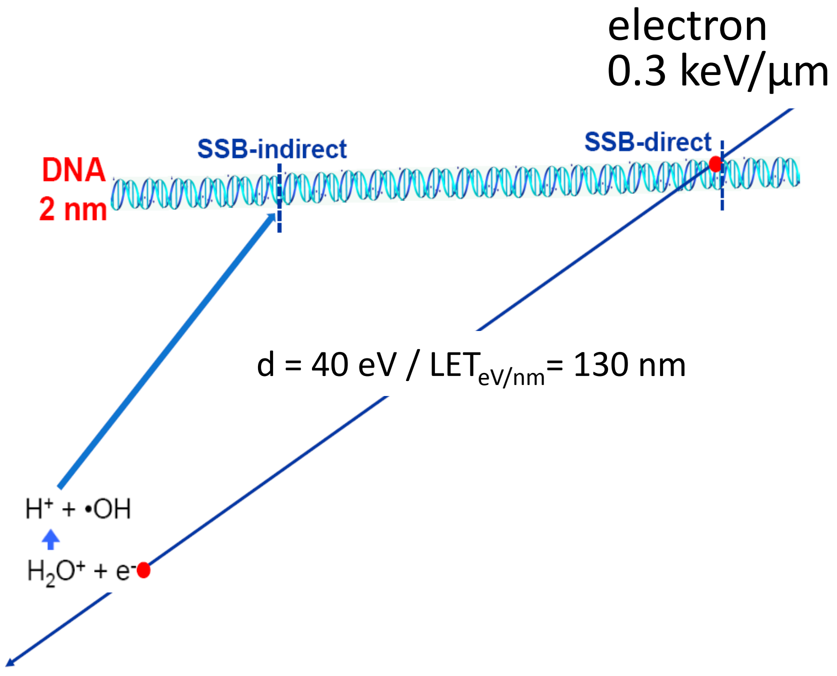




The same density of released energy may result in different damage to the target depending on the release structure -> different Relative Biological Effectiveness and equivalent (biological) dose

Microscopic distribution of the hadronic ionizations



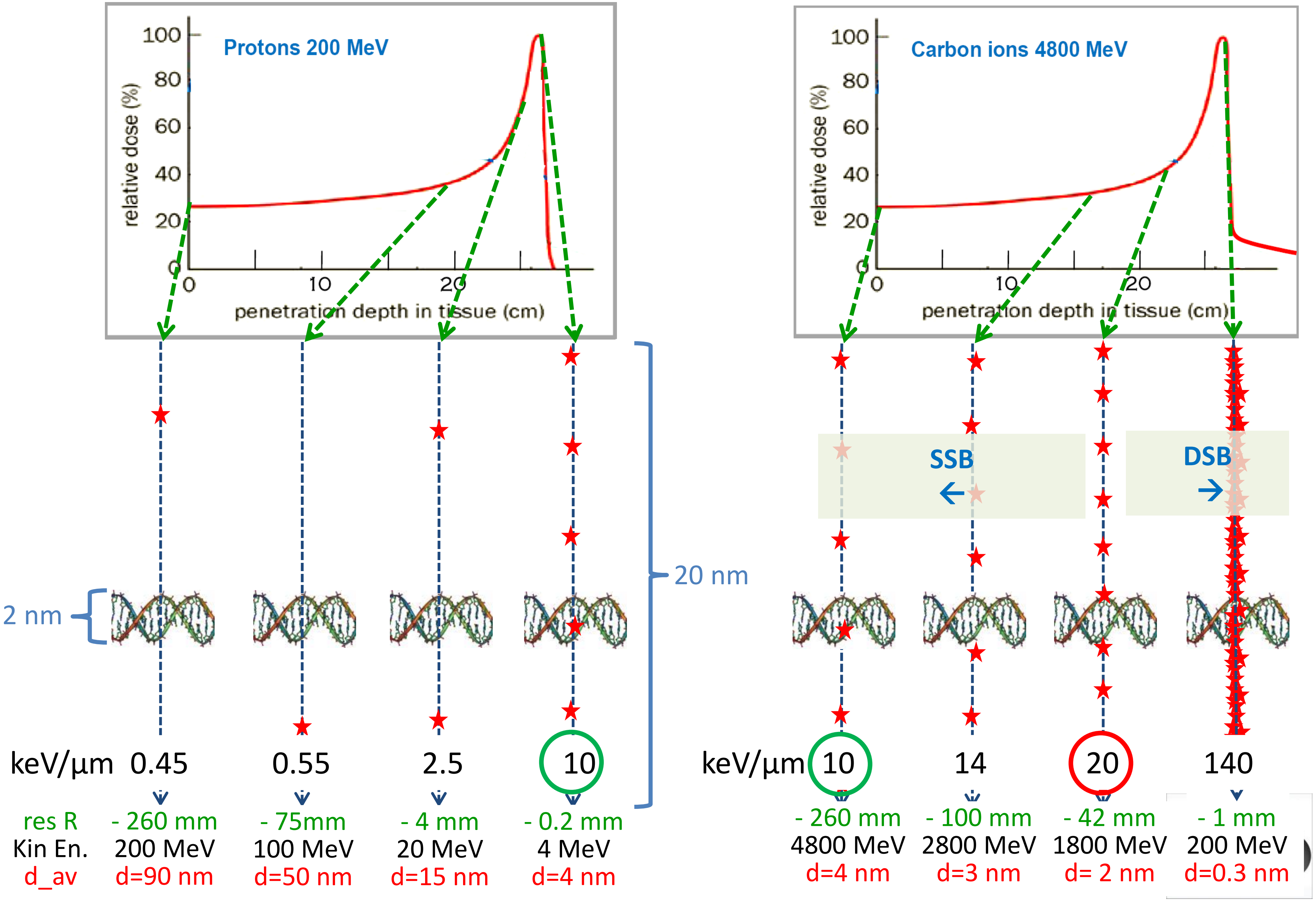


Protons are
SPARSELY IONIZING

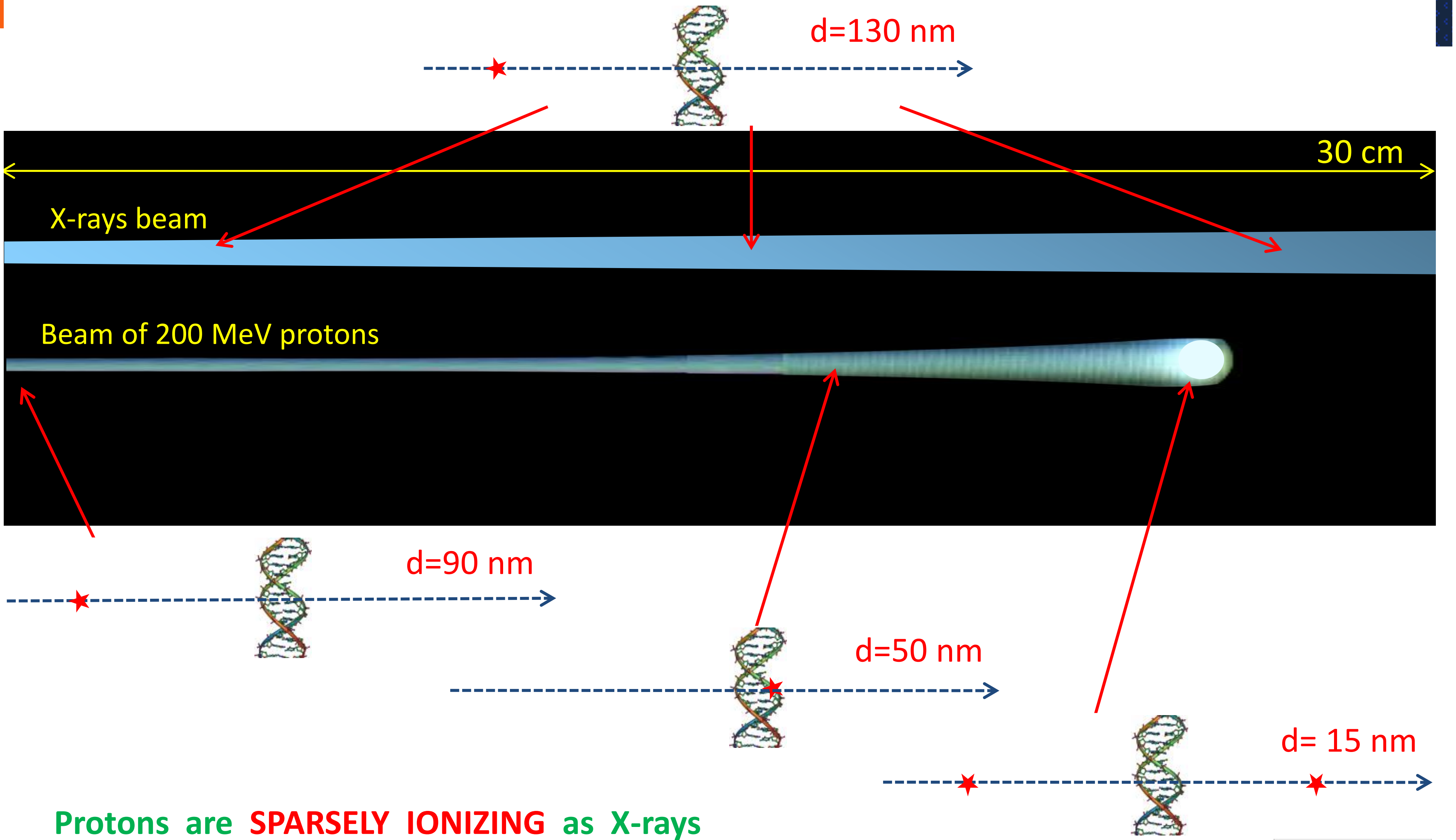
Protons are quantitatively different from X-rays

Courtesy U.Amaldi

Microscopic distribution of the hadronic ionizations



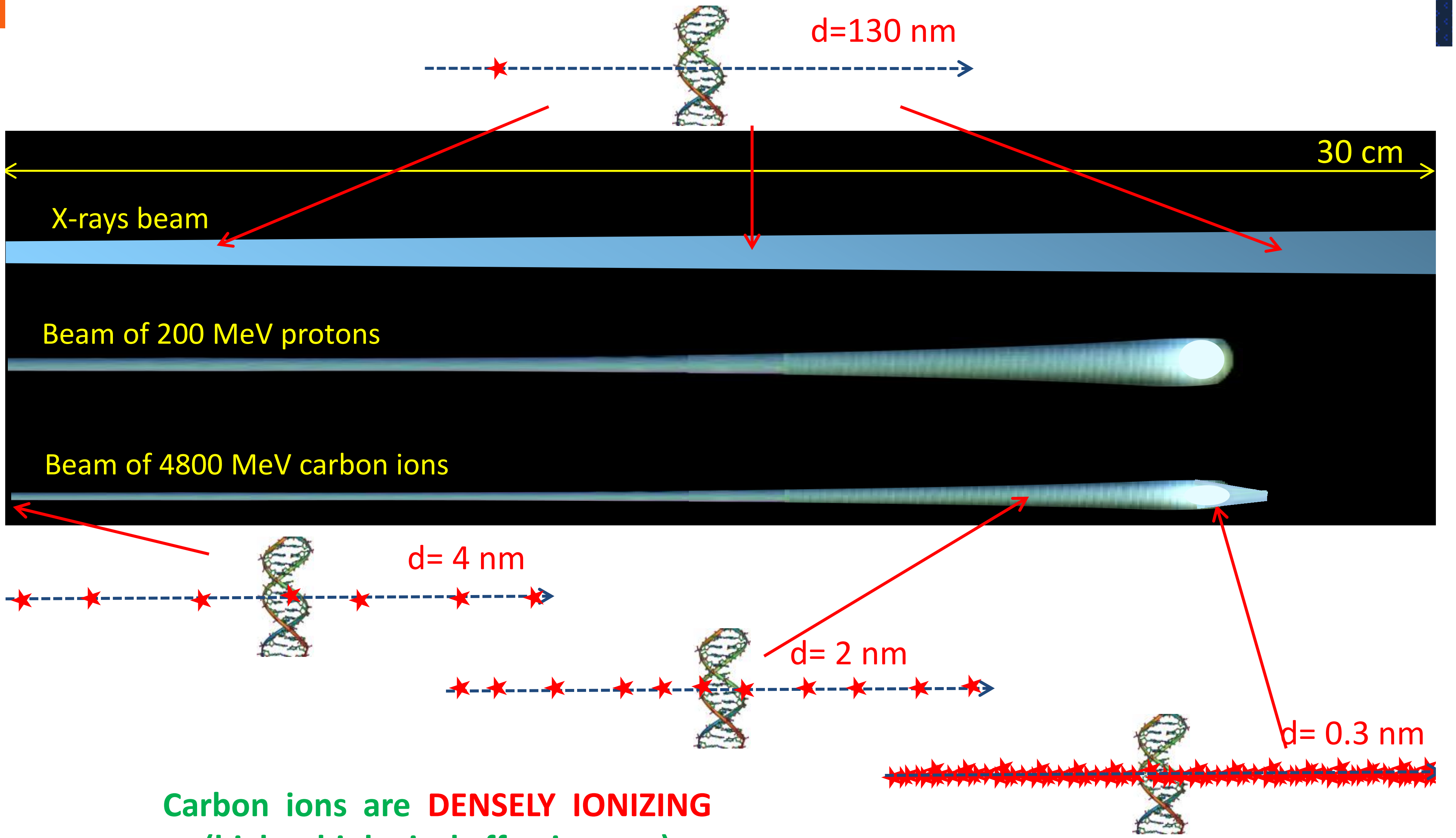
Protons: 1. more favorable dose 2. same '**indirect effects**'



Protons are SPARSELY IONIZING as X-rays

Courtesy U.Amaldi

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



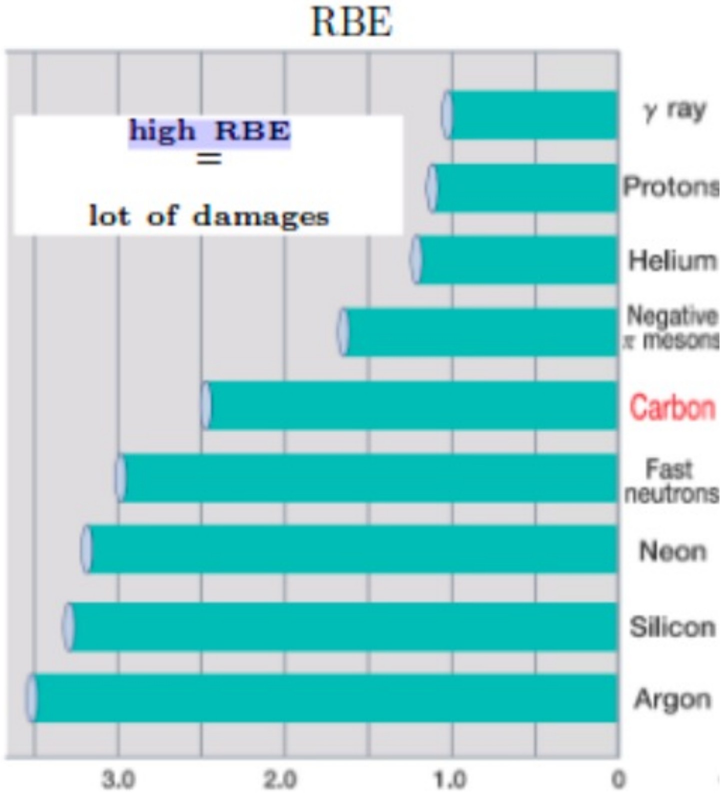
Carbon ions are DENSELY IONIZING
(higher biological effectiveness)

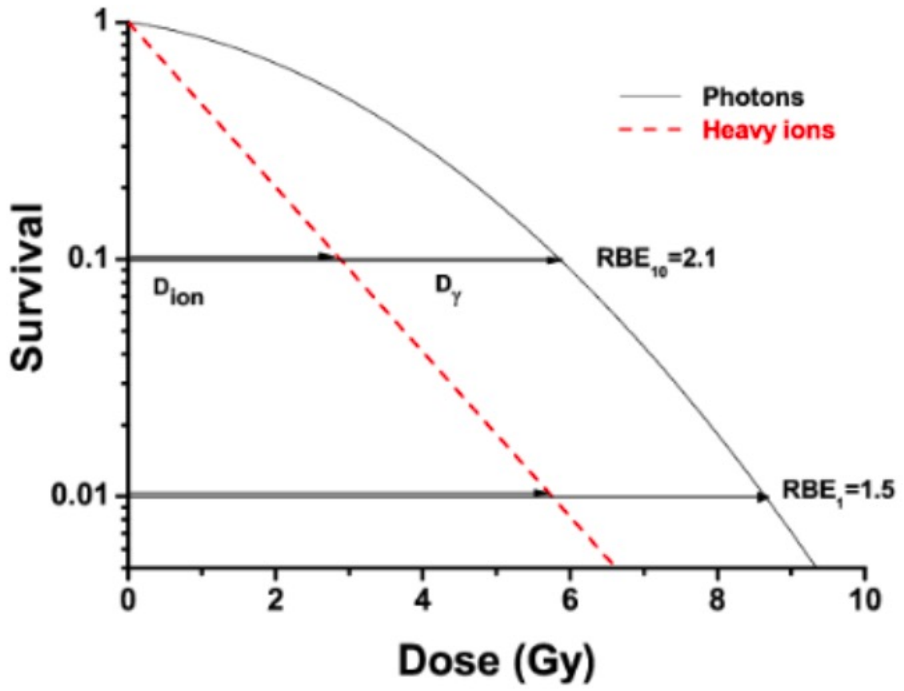
Courtesy U.Amaldi

Relative Biological effectiveness (RBE)

Higher LET means -> **higher Relative Biological Effectiveness**!

$$RBE = \left[\frac{D_\gamma}{D_{ion}}\right]_{Isoeffect}$$



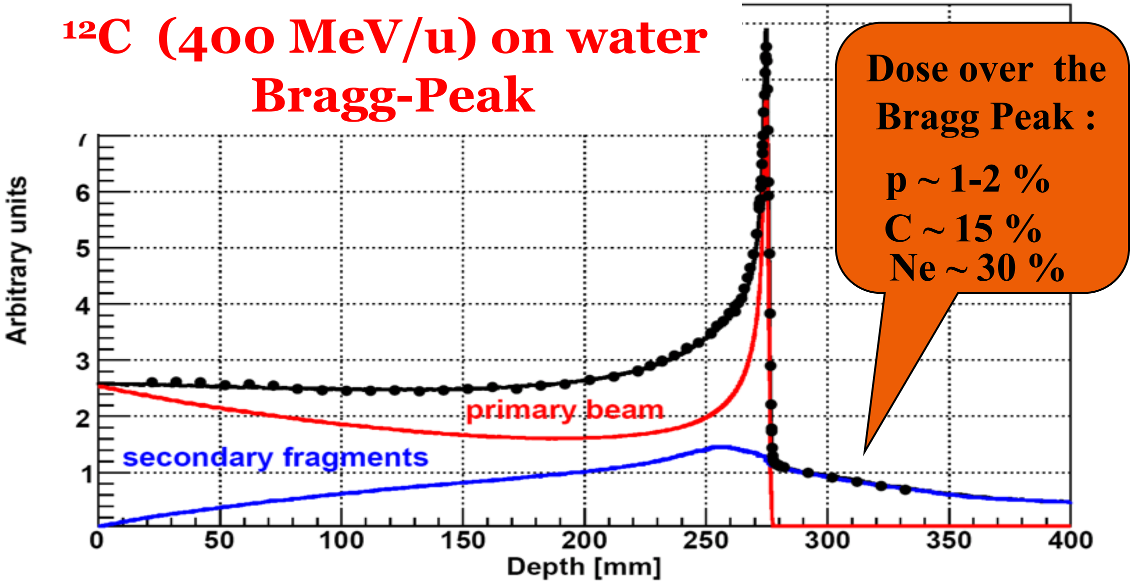


Heavier is better? -> Fragmentation!

Dose release in healthy tissues with possible long term side effects, in particular in treatment of young patients ➔ must be carefully taken into account in the Treatment Planning System

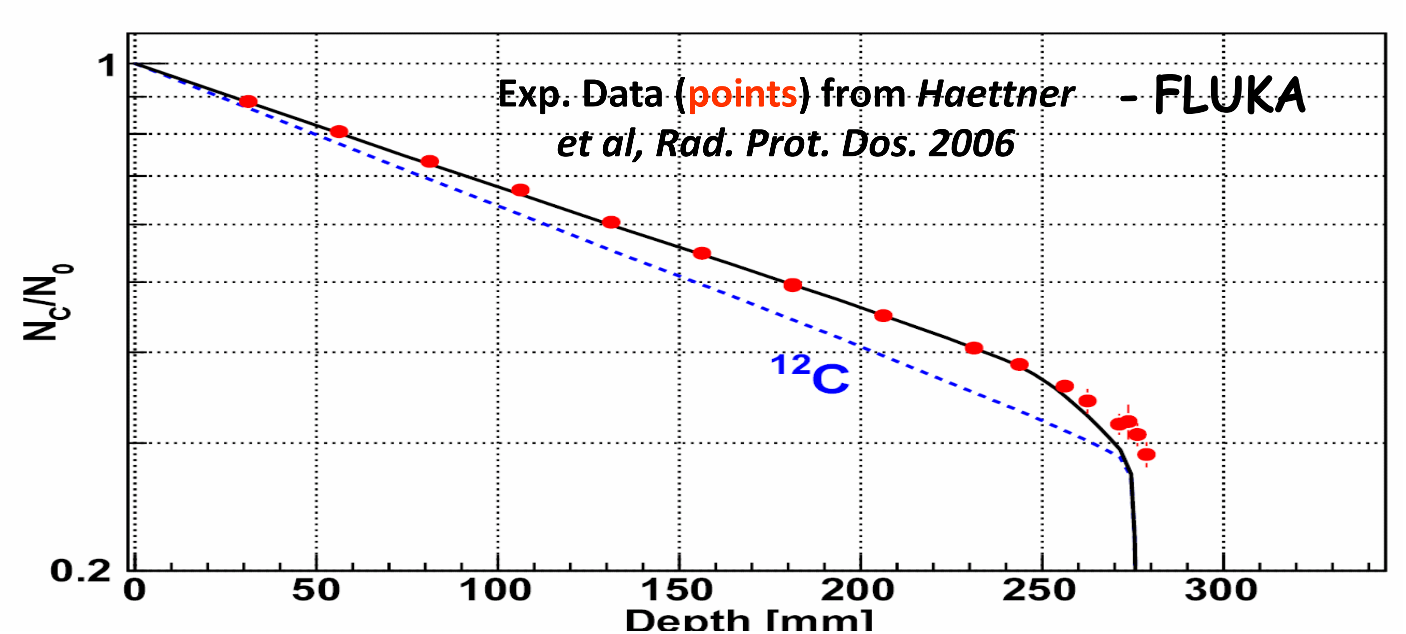
- ✓ Production of fragments with higher range vs primary ions
- ✓ Production of fragment with different direction vs primary ions

- ✓ *Mitigation and attenuation of the primary beam*
- ✓ *Different biological effectiveness of the fragments wrt the beam*



Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006
Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

400 MeV/n ^{12}C on water: Attenuation of the primary beams



The 70 % of the carbon ions undergo nuclear reactions altering considerably the radiation field

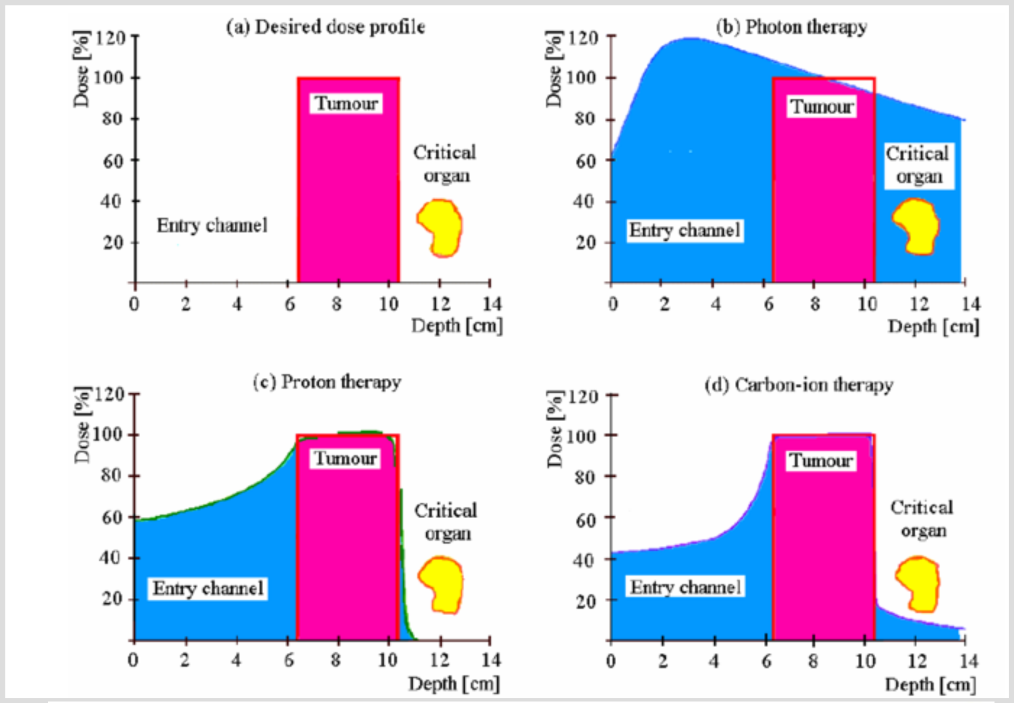
Fragmentation rules out beams heavier than Oxygen and must be carefully taken into account in TPS even for ^{12}C

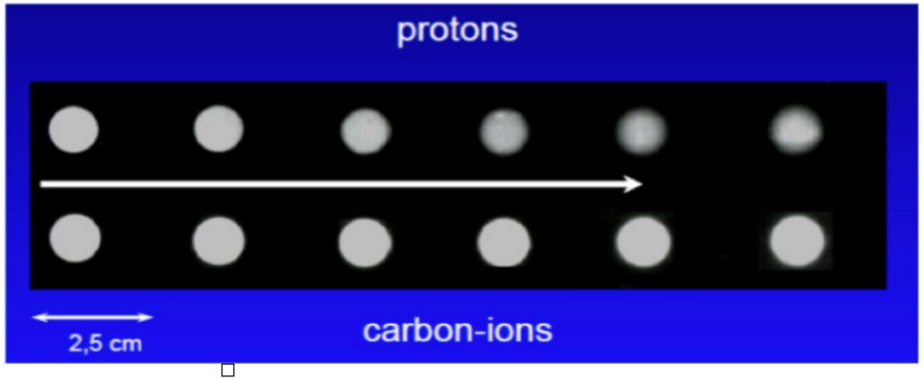
Protons & carbon RT

Pro’s and Con’s of proton beam vs carbon beam

- Carbon has better peak to plateau ratio
- Carbon has less multiple scattering

- Carbon has dose tail after the Bragg Peak
- Proton are less expensive



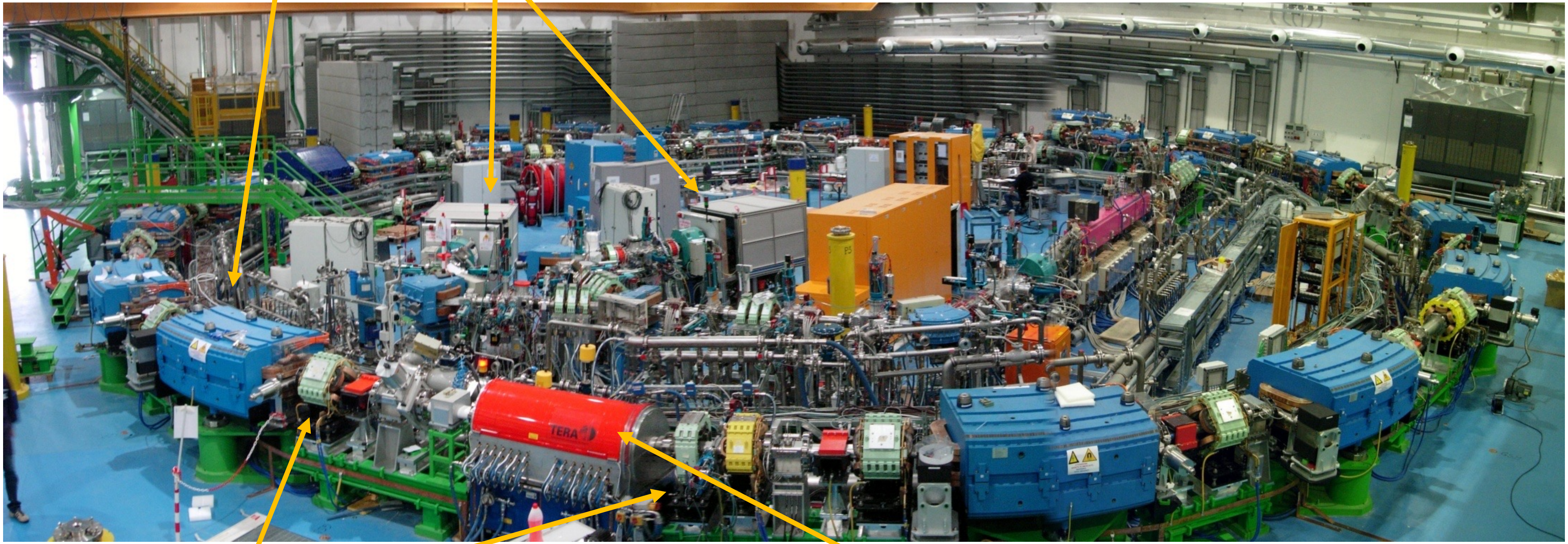


CNAO (pv, Italy) synchrotron

Bending magnets

Sources

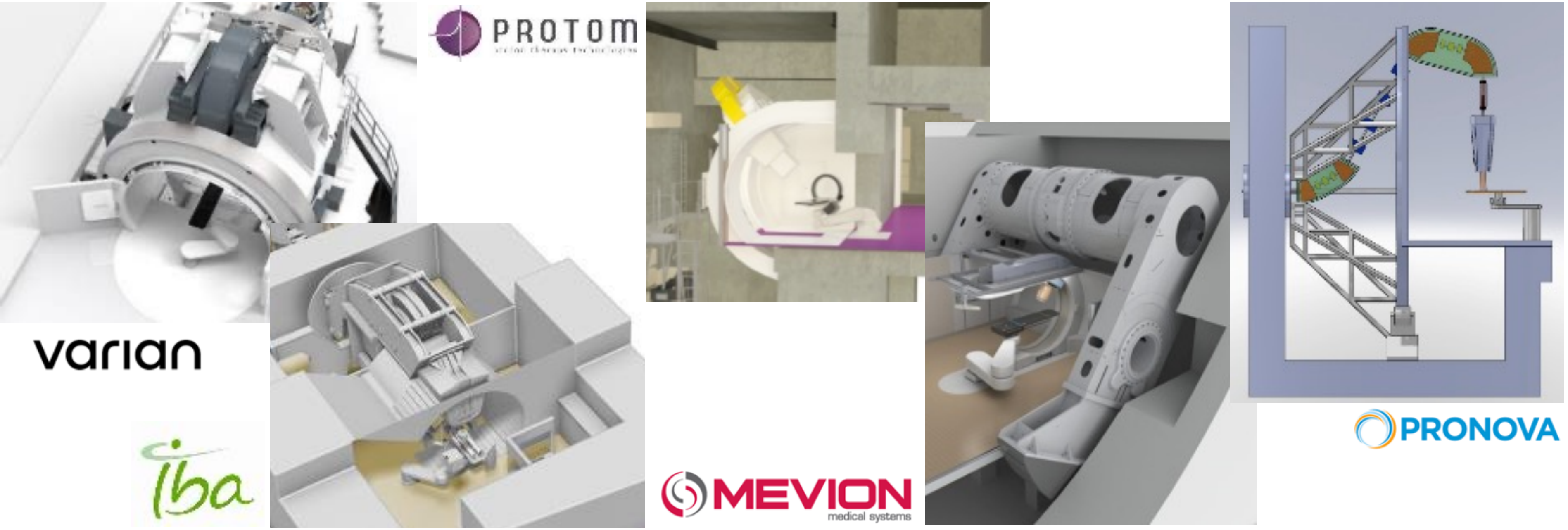
Accelerator ring: 25 meters radius



Focusing magnets

Radio Frequency cavity

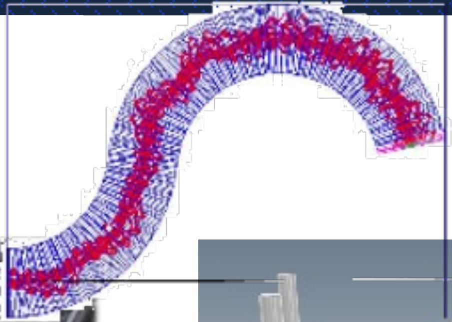
Proton Gantries



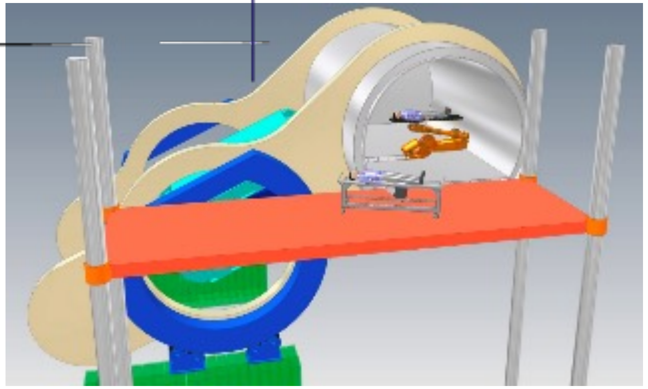
Parameter		Pro Beam	Proteus One	R330	S250i	Hitachi	SC360
Radius	[m]	5.5	3.6	≈ 4	4.3	4	4
Length	[m]	≈ 9.5	9.5	≈ 10	4.3	≈ 8	≈ 8
Weight	[tons]	270	110		17	125	25
Rot. angle	[deg]	360	220	180	190	360	360

Ion Gantries

NIRS HIMAC



BROOKHAVEN NATIONAL LABORATORY



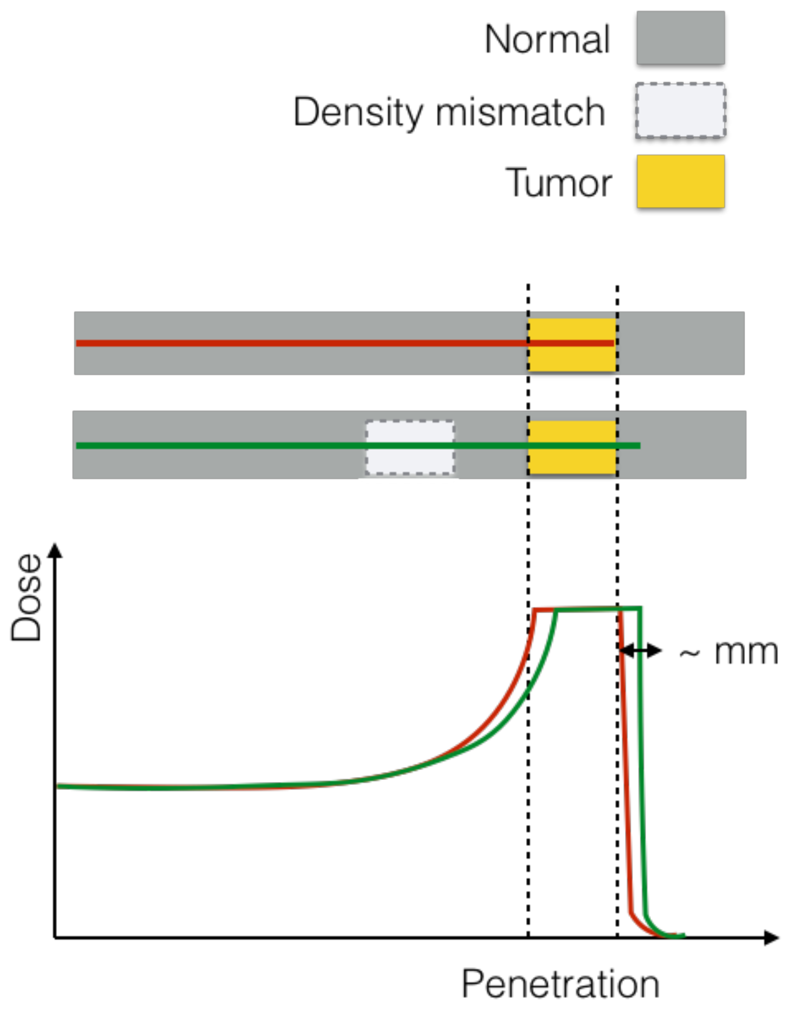
HIT Heidelberger Ionenstrahl-Therapiezentrum

ULICE

Parameter		HIT	HIMAC	FFAG	Riesen-rad
Radius	[m]	6.5	5.5	4.2	8.5
Length	[m]	25	13	8	16
Weight	**[tons]**	**670**	**350**		**350**
Rot. angle	[deg]	360	360	360	360

Everything ok ? Range uncertainties

- PT is extremely sensible to range variations wrt what predicted at planning stage
- Planning rationale: **avoid tumor under-dosage** by using **safety margins** (3.5% range + 3 mm)
- Possible causes: patient mispositioning, uncertainties on the CT Hounsfield number conversion, **anatomical density variation**
- **At present, a monitoring system is missing in clinical routine**



Photons, adrons..what about electrons?

To reach deep seated tumors (10-15 cm) Very High Energy Electrons (E>60 MeV) must be considered. Never introduced in clinical RT till now!

The electron beams with E>50 MeV has peculiar features

✓ Dose depth distribution with a broad peak whose downstream position increase with beam energy

✓ Dose depth distribution with tail after the peak increasing with energy

✓ Lateral dose dominated by Multiple Scattering inside the patient (~insensitive to beam features!) and decreases with energy

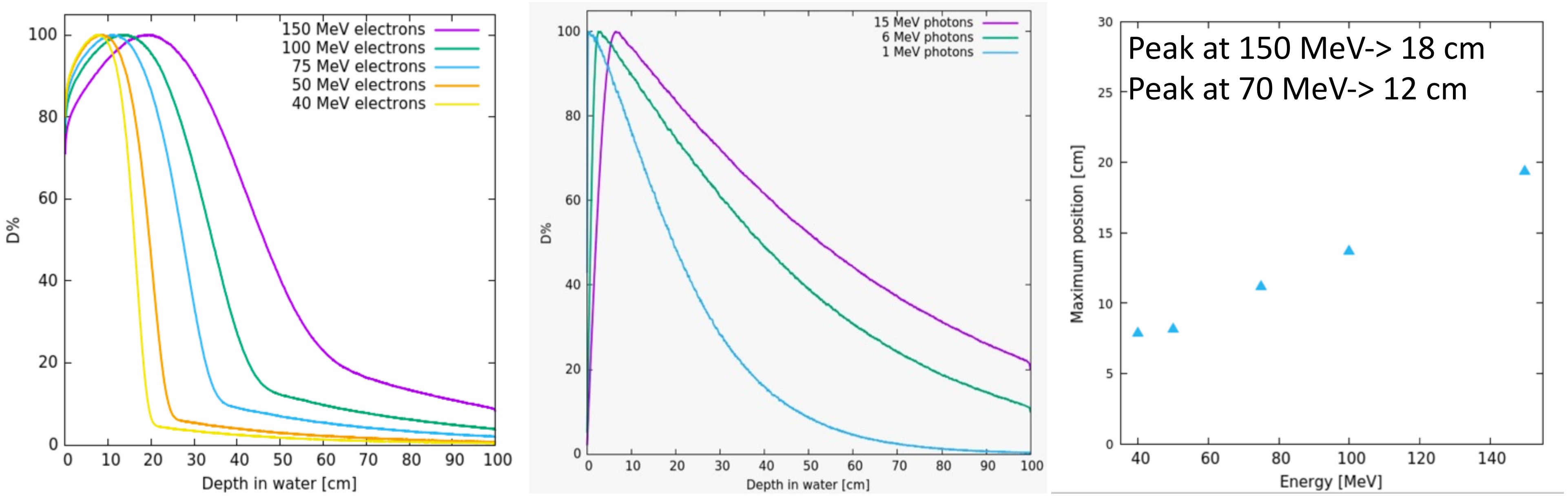
Standard LINACs can easily provide the needed beam: transverse spot size of ~ mm and angular divergence below tenth of degree.

Electrons longitudinal dose

Electron beams with E>50 MeV has a behaviour that is in between the photons and the protons

- The DDD peak slowly moves downstream with energy. (es: 70 MeV-> peak at 12 cm, 150 MeV-> peak at 18 cm)

➢The tails beyond peak largely increase with beam energy



FLUKA 2020: pencil beam simulation in water

Electrons longitudinal dose

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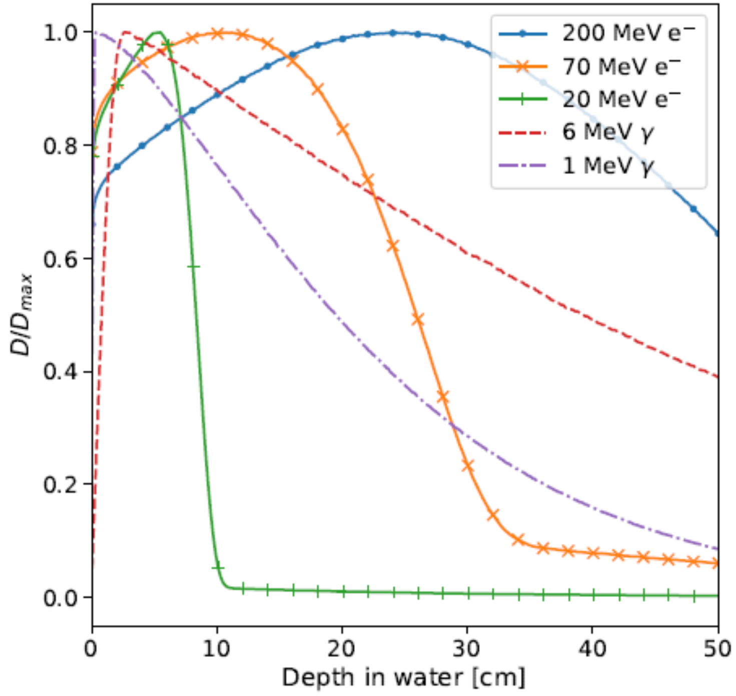
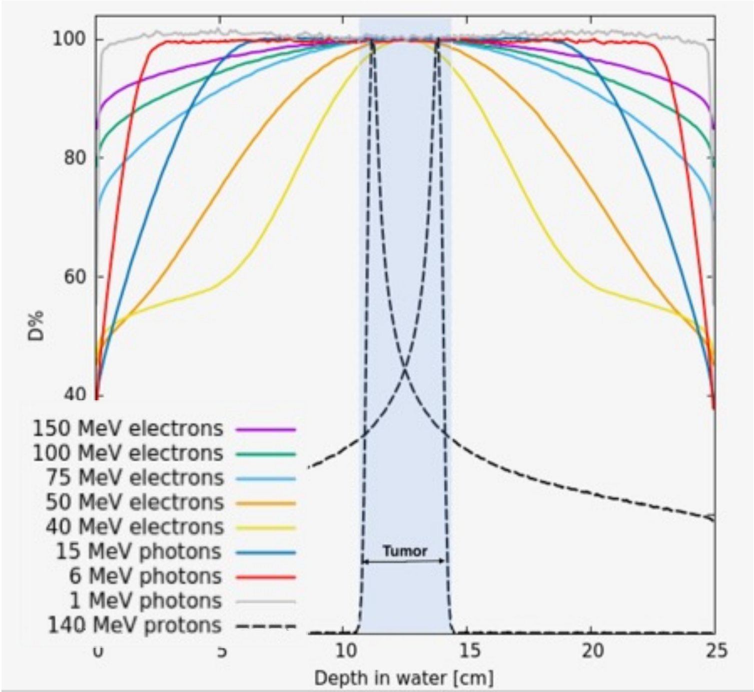


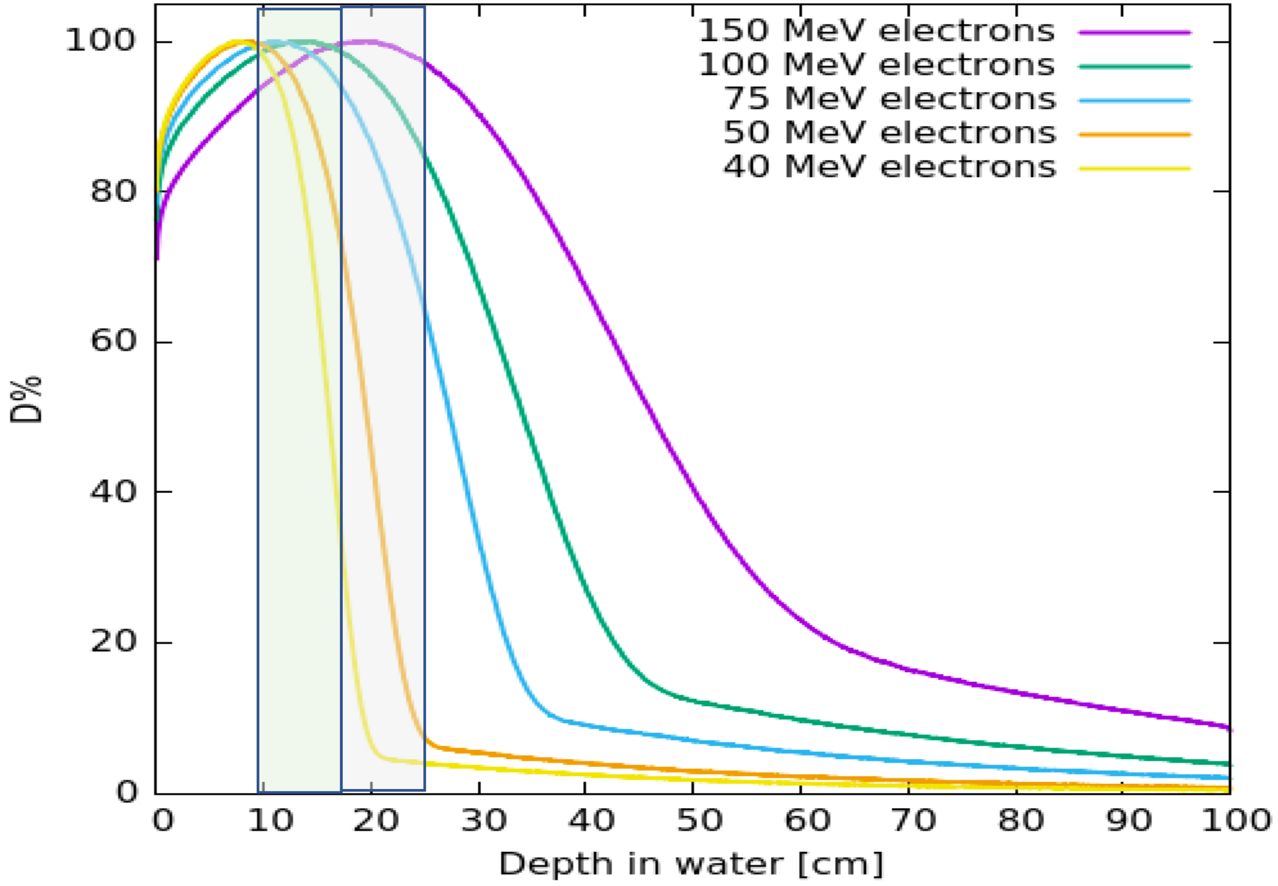
The dose distribution has much better behaviour than photons in entrance channel



FLUKA 2020: pencil beam simulation in water

Electrons longitudinal dose

- The DDD nicely covers a 10-15 cm deep tumor if E>50 MeV
- The DDD covers quite well a 15-25 cm deep tumor if E>75 MeV

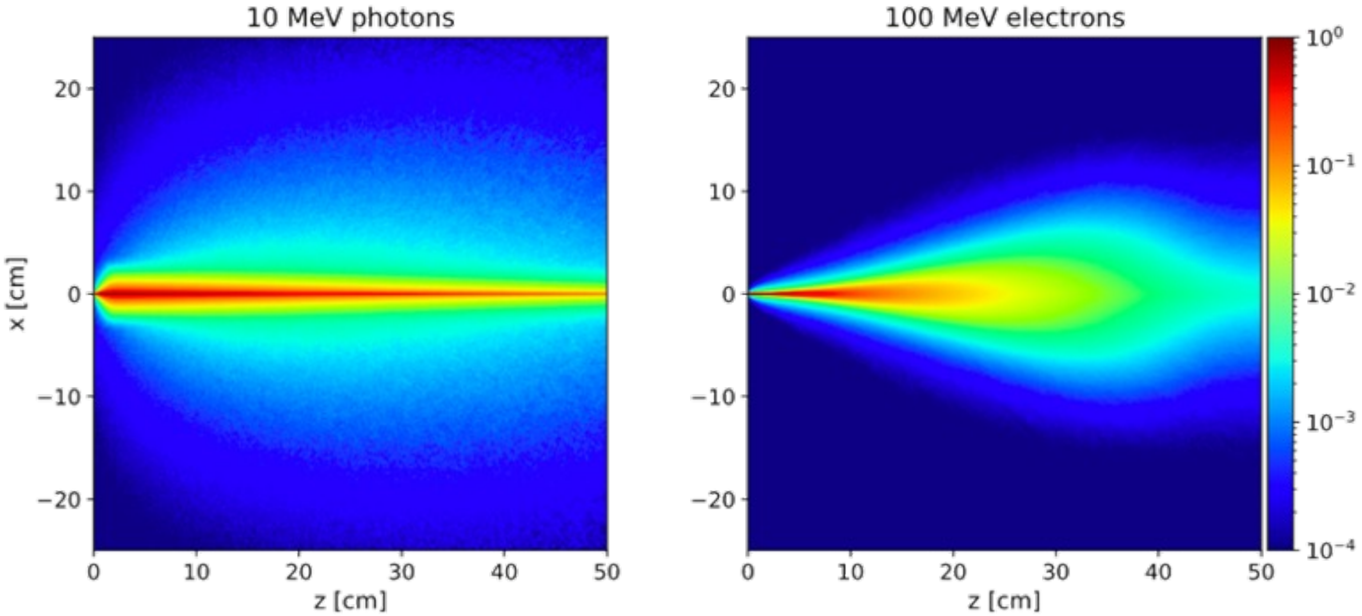


- The lower the energy, the smaller the tails beyond the PTV
- The DDD has much better behaviour than photons in entrance channel

FLUKA 2020: pencil beam simulation in water

Lateral Distribution… the pitfall!!

- Even if the electron beam is pencil like, it «explodes» inside the patient in a rigid (but predictable) behaviour due to MS
- To overcome MS energy must be increased (>100 MeV): high cost, large and expensive machines. This mainly prevented in the past the use of electrons in clinical practice.
- Two conditions changed this situation: R&D in e- LINAC and FLASH effect

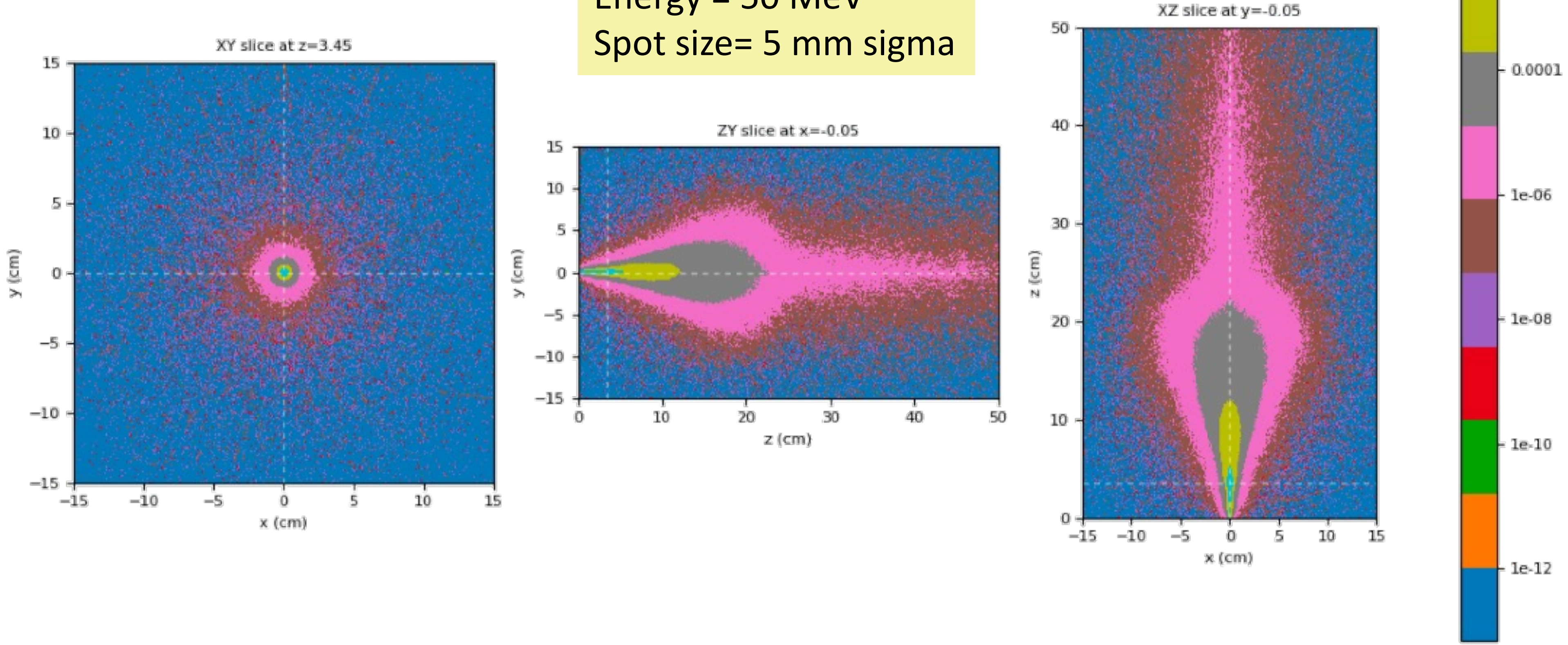


The FLASH effect reduces the "effective" dose seen by the healthy tissue….. Less problems from dose leakage in healty tissue

Electrons 2D dose distribution

The electron beams with E>50 MeV has a 2-dimesional dose with a penumbra that increases with the penetration in tissue and decreases with the beam energy.

Energy = 50 MeV
Spot size= 5 mm sigma

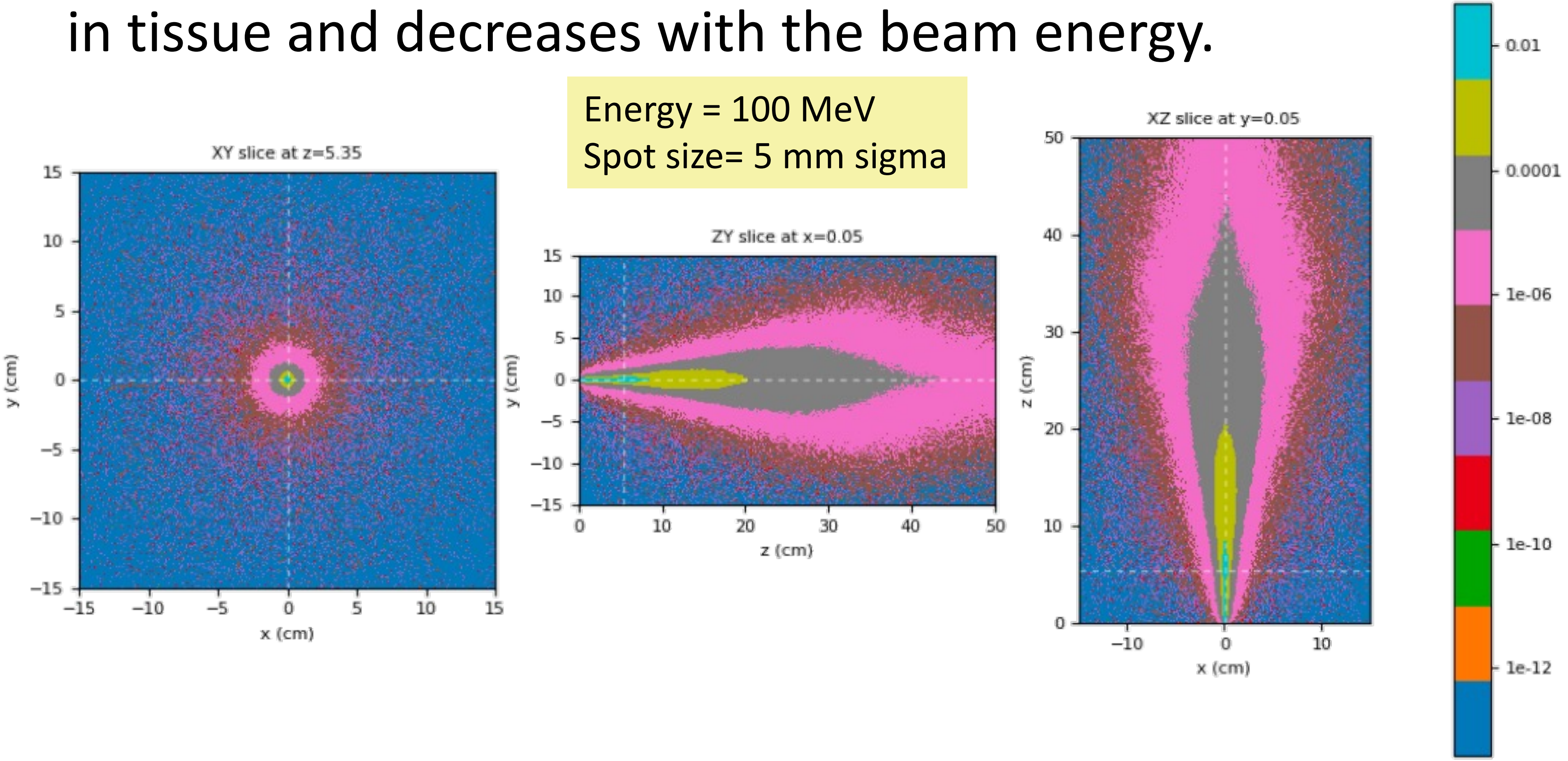


FLUKA 2020 simulation in water of a 0.5 cm sigma trasverse size pencil beam

Electrons 2D dose distribution

The electron beams with E>50 MeV has a 2-dimesional dose with a penumbra that increases with the penetration in tissue and decreases with the beam energy.

Energy = 100 MeV
Spot size= 5 mm sigma

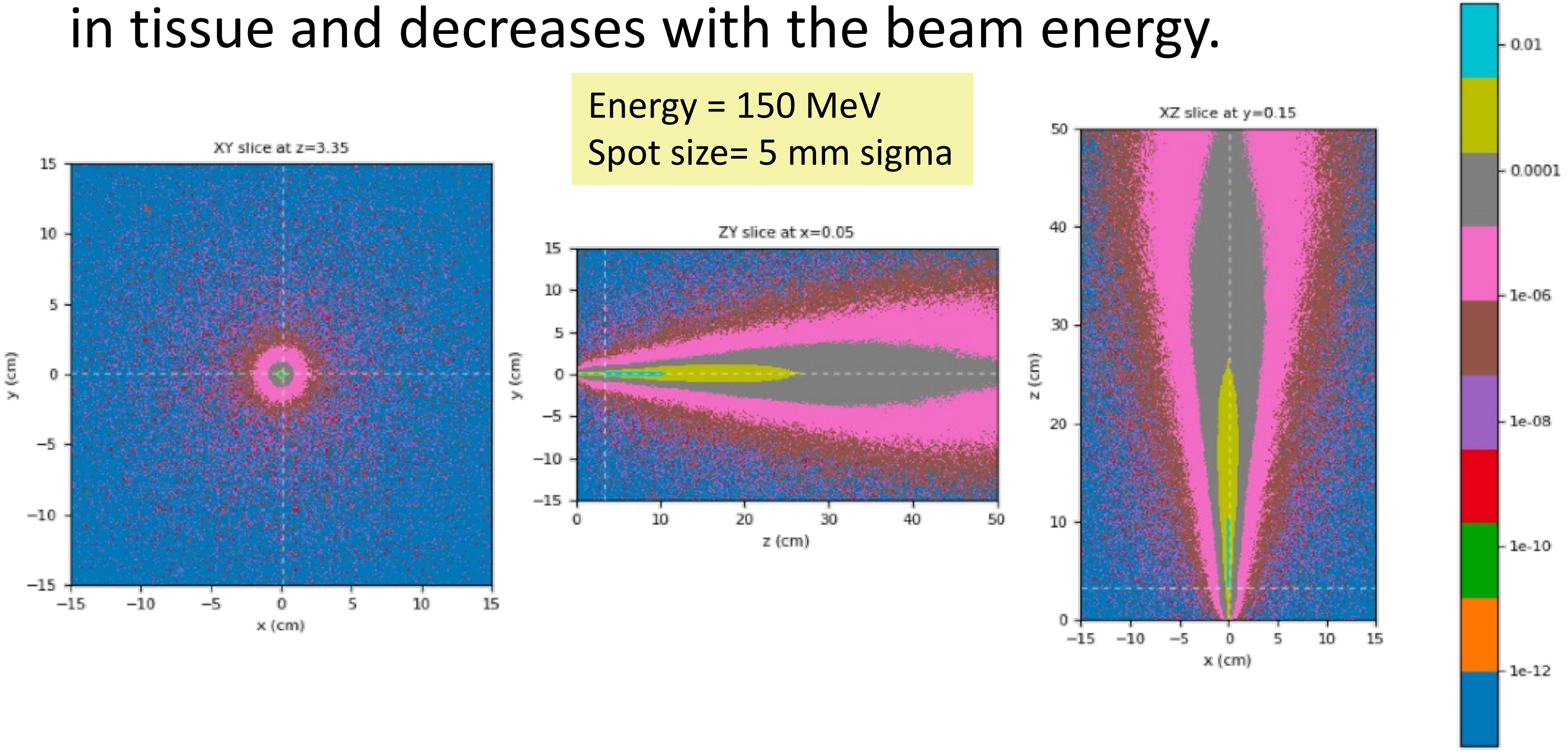


FLUKA 2020 simulation in water of a 0.5 cm sigma trasverse size pencil beam

Electrons 2D dose distribution

The electron beams with E>50 MeV has a 2-dimesional dose with a penumbra that increases with the penetration in tissue and decreases with the beam energy.

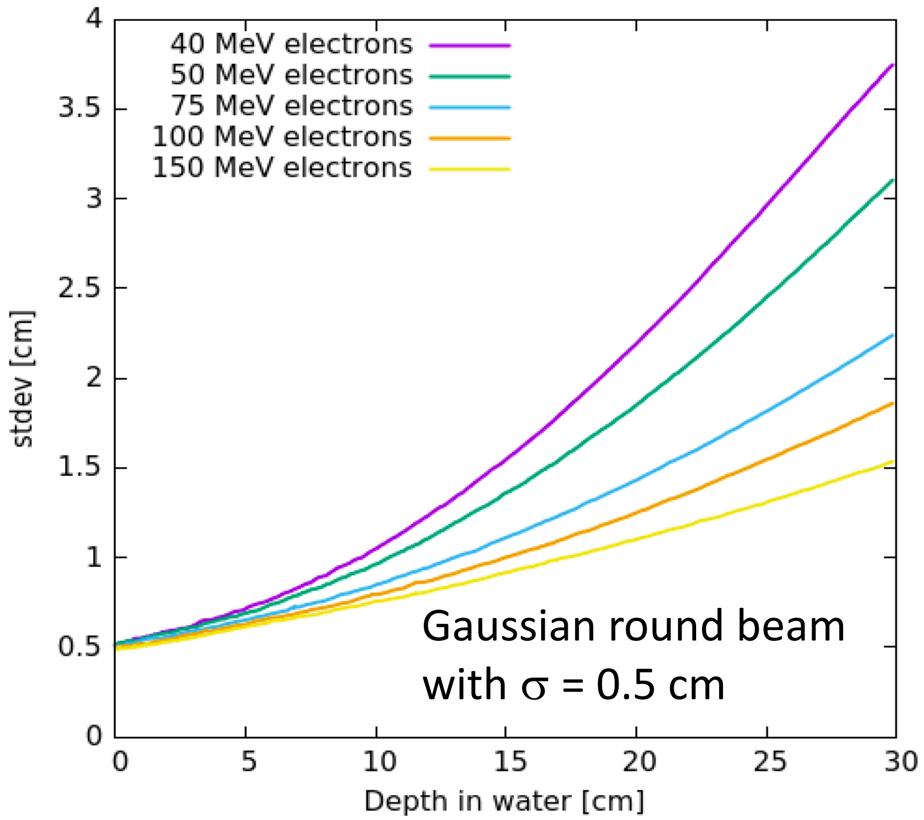
Energy = 150 MeV
Spot size= 5 mm sigma



FLUKA 2020 simulation in water of a 0.5 cm sigma trasverse size pencil beam

Lateral Dose distribution & Penumbra

- The transverse size of the beam at tumor depth is dominated by the MS.
- Starting with 0.5 cm sigma after 10 cm in water the MS drives the lateral size of the dose release.
- The penumbra of VHEE electrons can match the photons sharpness as energy increase.

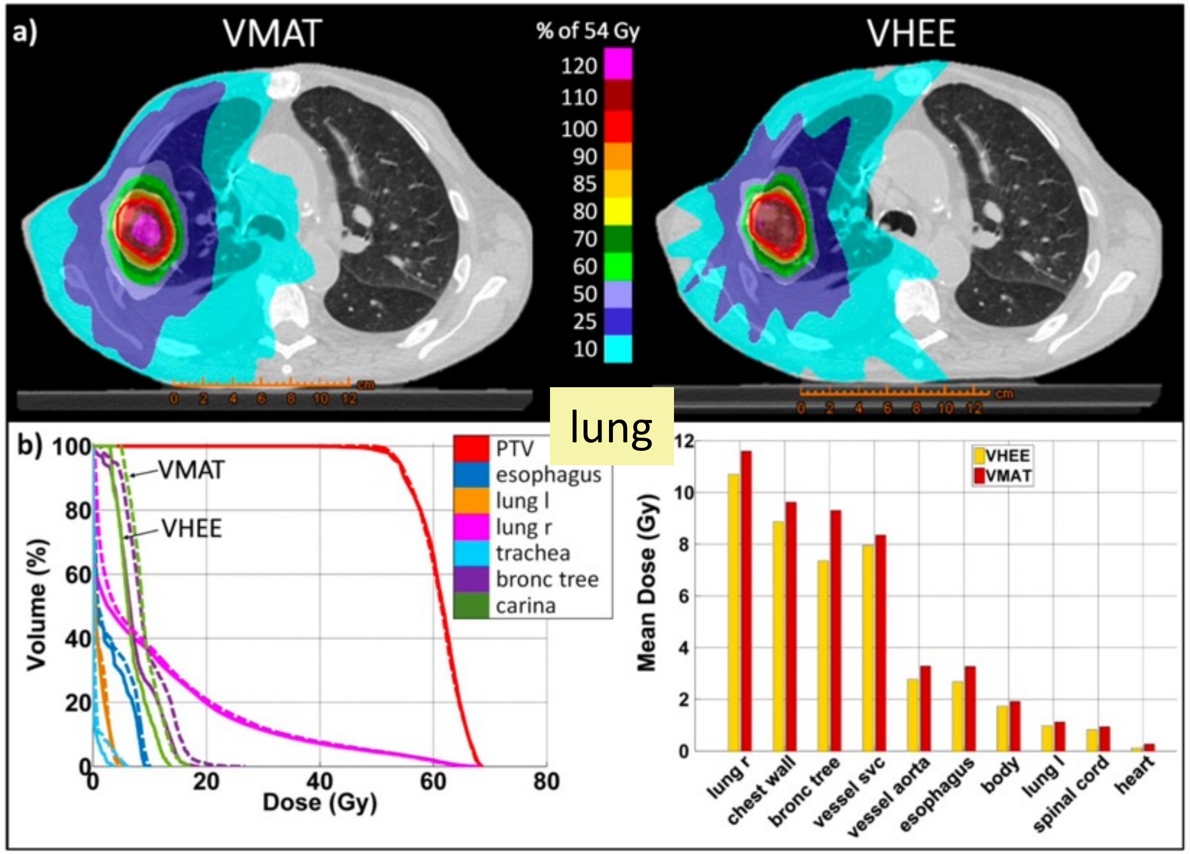


Energy (MeV)	Mode	Penumbra
10	Photons	0.7 cm
100	Electrons	1.4 cm
150	Electrons	0.9 cm
200	Electrons	0.8 cm

Penumbra (distance between 10% and 90% isolines) at 15 cm of depth of water for photon and electron pencil beams

VHEE and RT in literature

In the last years few research groups studied the possibility to use VHEE electron beam with 100 MeV < E < 250MeV in RT. Some papers reported a superiority VHEE RT vs standard VMAT in the treatment of some tumors.



Palma, B. *et al. Radiother Oncol* **119**, 154–158, (2016)

Almost all studies in literature about Electron RT for deep tumors considered system made of:

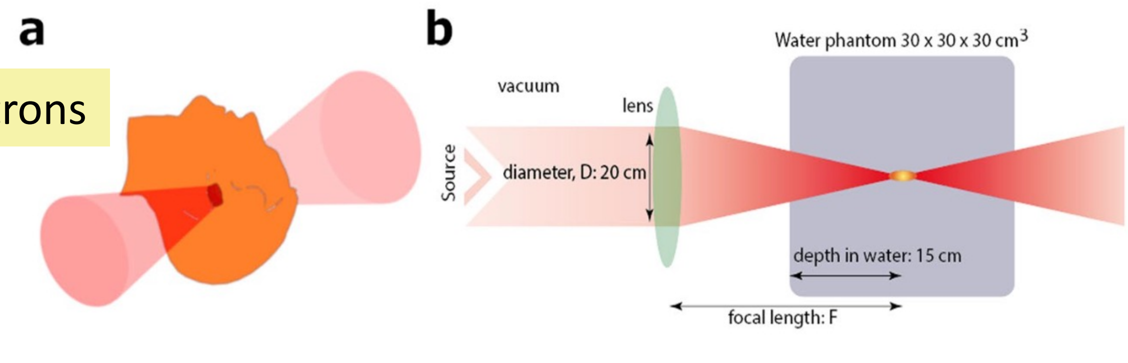
- ✓ High energy beams (E>100 MeV)
- ✓ Many fields (>16)
- ✓ Only one energy for all fields

VHEE and RT in literature

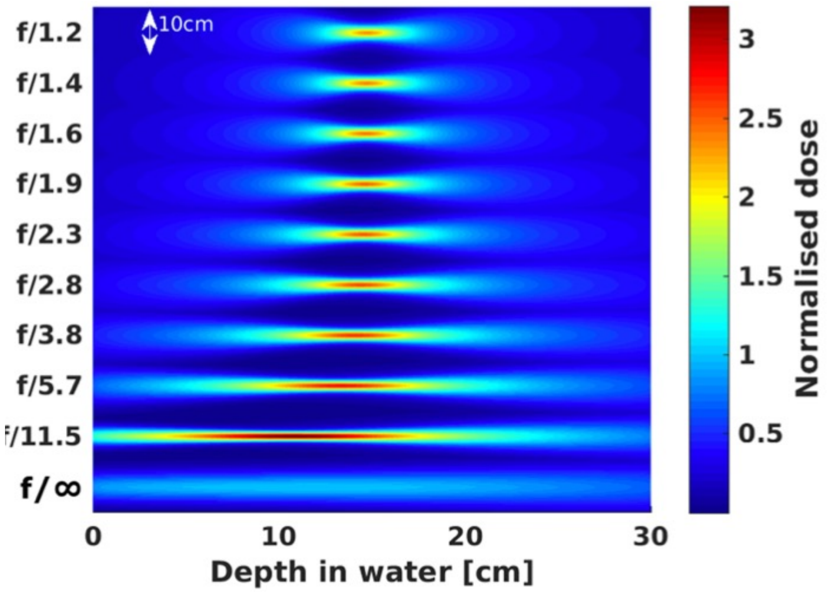
Several innovative technology solutions have been studied, some exploit magnetic focusing of the VHEE to beat the MS in the patient.

Solution mutuated from particle physics R&D, sometimes quite difficult to be implemented in a commercial system

200 MeV electrons



Dose distribution vs magnetic lens focus



The approach works perfectly, but at cost of a huge complexity of the system

Kokurevic, K. et al. *9:10837* Scientific Reports (2019)

VHEE is gaining momentum

The discovery of FLASH effect and the technology innovation in accelerator physics are freeing the VHEE RT from the limbo.

Very High Energy Electron Radiotherapy Workshop (VHEE'2020)

5-7 October 2020
CERN
Europe/Zurich timezone

Search...

Overview
Timetable
Contribution List
Registration
Scientific Advisory Committee
Local Organising Committee
Videoconference instructions
VHEE 2017

CLIC Project Office
clic.project.office@cern.ch

VHEE2020

Establishing innovative treatment modalities for cancer is a major 21st century health challenge. Although accelerated electrons are widely used to generate X-rays for radiotherapy, electrons are less frequently used directly because low energy electrons have limited penetration range and are mostly for the treatment of superficial tumours and thus limiting their clinical applicability.

The investment (man power, funding, infrastructure) in the field are mainly driven by the fundamental research (but also companies are active) and a clear example is a new initiative is starting at CERN (CLEAR)

VHEE and RT in real life

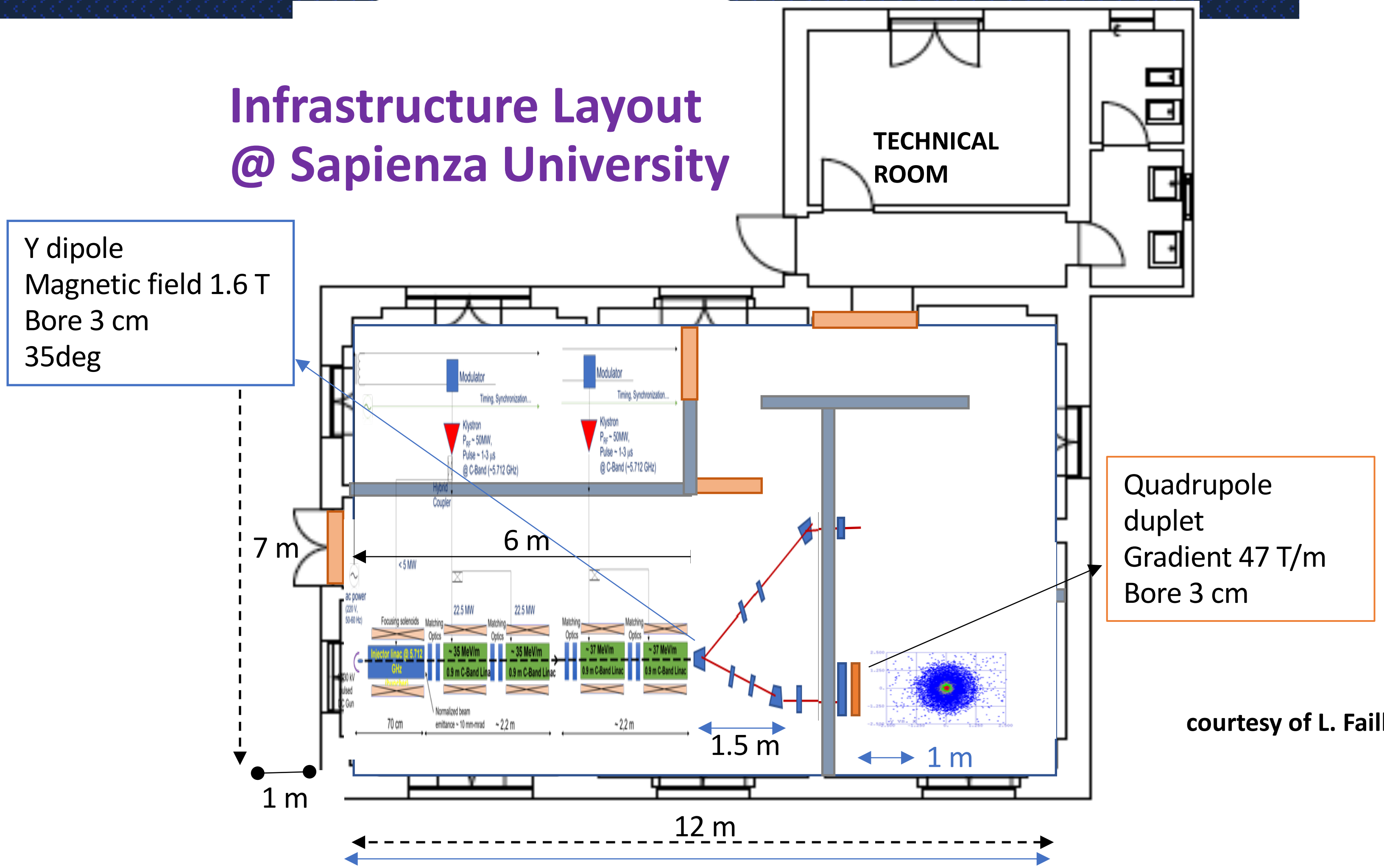
Why the VHEE technology has not spread out in hospitals in spite of the reported results, obtained using simulation?

- ✓Main motivation: cost, complexity and the space needed, up to now, by a 100-200 MeV electron beam. All these items grow more then linearly wrt beam energy
- ✓Radioprotection issues (at least in Italy, but it's similar all over the Europe) for electron beams with E>25 MeV
- ✓Some/all simulated results are obtained with a very ideal, complex setup with a lot of fields and high energy.
- ✓Unavailability of commercial TPS (no machine available) to compare standard RT treatment with VHEE
- ✓Radiobiology (?) My personal feeling is that 100 MeV e- are relativistic particle as 10 MeV e- and that the two electrons have the same interaction with tissue…. But it' my opinion

VHEE: something is changing

The landscape is rapidly changing: non superconductive, high gradient electron linac are now possible

Several test facility are aiming to achieve a VHEE clinical machine!



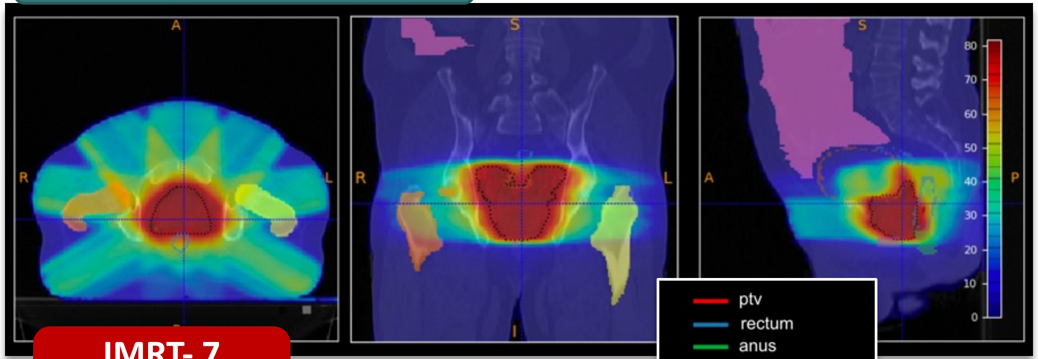
courtesy of L. Faillace

Compact machine, limited energy <130 MeV, likely magnetic delivery (magnetic rigidity much less than proton, smaller and cheaper gantry). Not yet optimizied for space occupancy

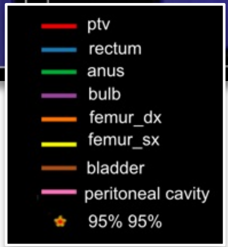
A study case: prostate cancer

IMRT | PROTONS | VHEE | RESULTS

Pinnacle TPS optimized dose map



IMRT- 7 fields



Dosimetric constraints

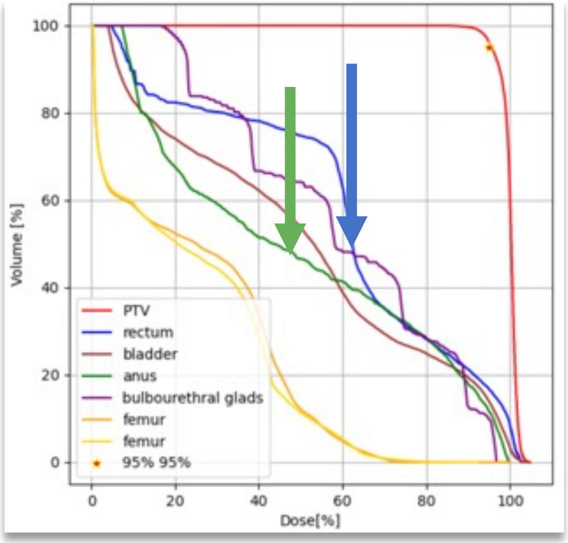
Organ	dosimetric constraints
Target volume	$V_{95\%} > 95\%$, never above 107%
Rectum	$V_{50} < 50\%$, $V_{60} < 35\%$, $V_{65} < 25\%$, $V_{70} < 20\%$, $V_{75} < 15\%$
Anus	$V_{30} < 50\%$
Bulbourethral Glands	$\overline{D} < 50$ Gy
Femurs	$\overline{D} < 52$ Gy, $V_{60} < 5\%$
Bladder	$\overline{D} < 65$ Gy, $V_{65} < 50\%$, $V_{70} < 35\%$, $V_{75} < 25\%$, $V_{80} < 15\%$

V_{xx} <YY%: YY% of the referred organ or region must absorb less than XX Gy

$\overline{D}$ is the mean dose absorbed by a given organ

Real IMRT prostate treatment at Policlinico Umberto I hospital, Rome

- Patient with intermediate-risk prostate cancer, was treated with conventionally fractionated IMRT of **78 Gy** in **39 fractions**;
- **7** photons **fields** (6 MV-ONCOR Linear Accelerator);



Dose Volume Histograms (DVH)

A study case: prostate cancer

IMRT | **PROTONS** | VHEE | RESULTS

- The same CT has been used by the **APSS Hospital** (Trento, Italy) to plan and optimise the **protons treatment** for a preliminary assessment of PT potential.
- In this case only **2 fields** have been used to treat the patient and ensure the needed PTV coverage.
- The same cost function used to plan the RT treatment has been implemented, trying to achieve a 100% of the PTV coverage.

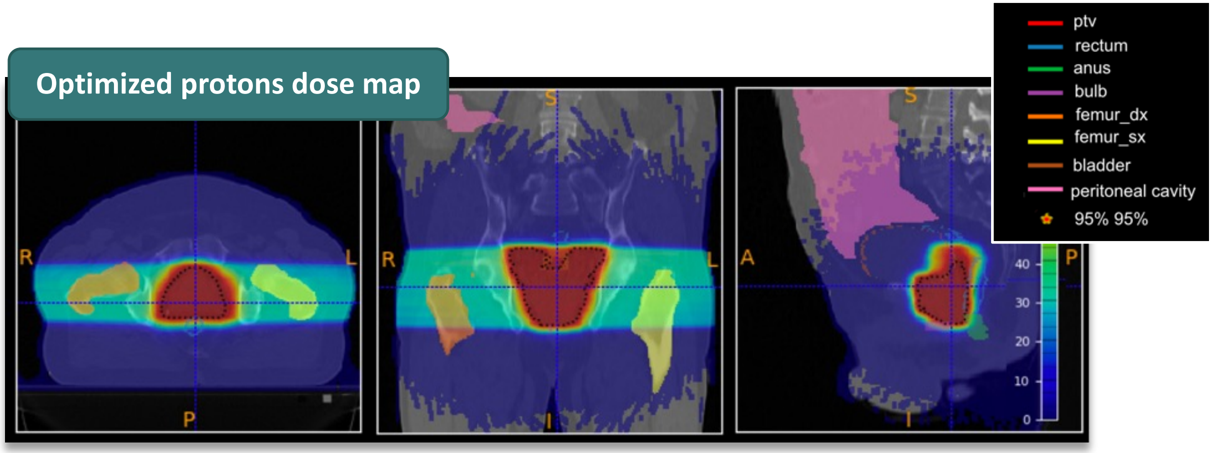
Target volume	$V_{95\%}$ 100%, $V_{100\%}$ 99.79%, $V_{105\%}$ 0.12%
Rectum	V_{75} 13.34%, V_{50} 33.97%
Anus	V_{30} 24.87%
Bulbourethral Glands	$\bar{D}$ 45.15 Gy
Femurs	$\bar{D}$ 16.75 Gy, V_{60} 0%
Bladder	$\bar{D}$ 21.75 Gy, V_{70} 21.29%, V_{65} 22.46%

All dosimetric constraints are respected

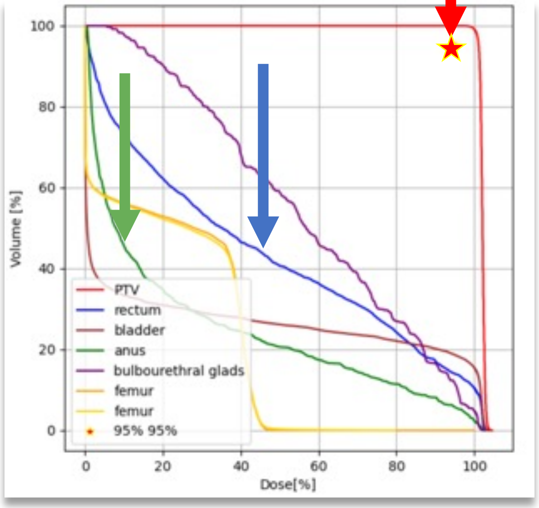
Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

The exercise performed using protons and a fairly standard approach (two opposite fields) gives already promising results, as expected when exploiting the PT high conformity.

Optimized protons dose map



DVH



A study case: prostate cancer

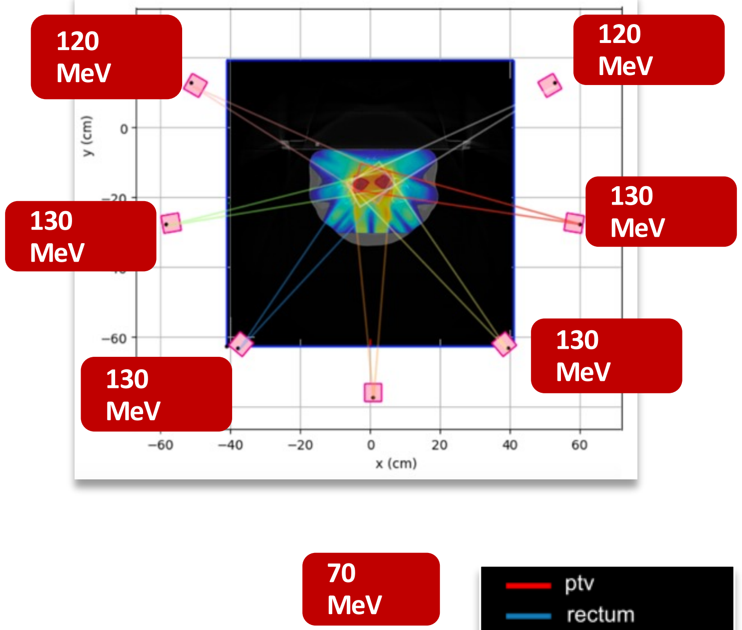
IMRT | PROTONS | **VHEE** | RESULTS

FLUKA MC SIMULATION

To put on a solid ground the comparison in this first attempt focused on evaluating the impact of a VHEE FLASH RT:

- the same 7 equidistant fields have been used for IMRT and VHEE planning. Each field can have different energy;
- VHEE beams transverse size $O \sim$ mm and divergence $O \sim$ 10mrad;
- the electron "pencil beam" paints each irradiation field like in active PB scanning techniques.

Simulation parameters: **70**, **120** and **130 MeV** electron beams (BP on the PTV), Gaussian profile with **σ = 4 mm.**



FLASH EFFECT

The FLASH effect is modelled using the Dose Modifying Factor (**DMF**) to account for the reduced normal tissue damage

$$DMF = \frac{D_R}{D_T}$$

Conventional

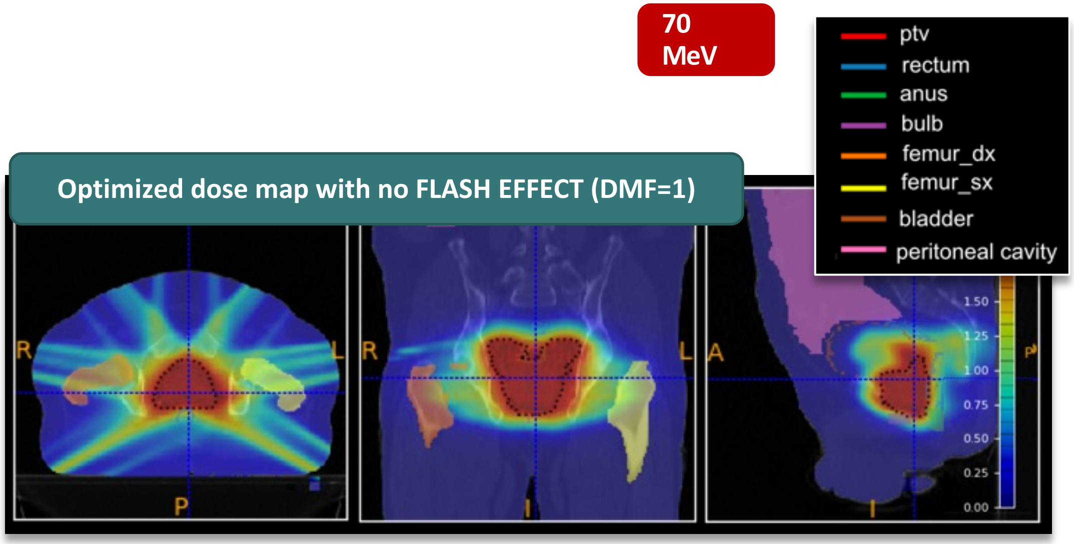
FLASH RT

We have implemented DMF=1, 0.9 and 0.8

TREATMENT OPTIMIZATION

The fluence of each PB is then optimized to ensure the required PTV coverage while sparing the OARs

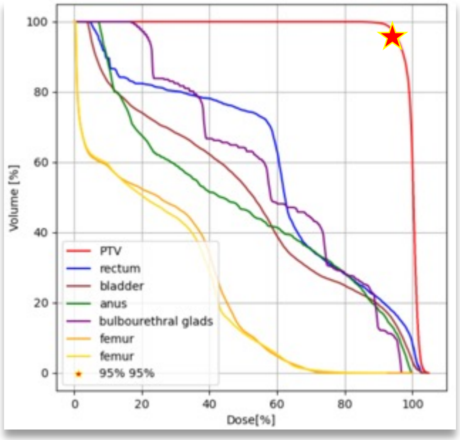
Optimized dose map with no FLASH EFFECT (DMF=1)



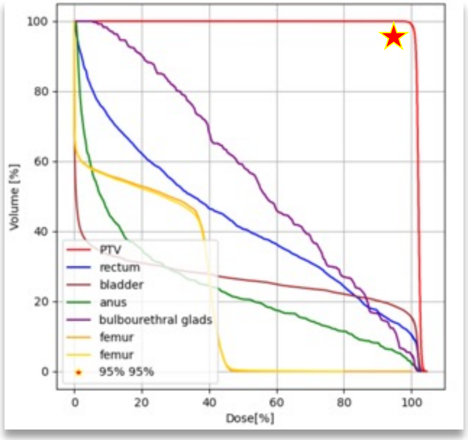
Prostate vs γ, p, e^- and FLASH e^-

IMRT | PROTONS | VHEE | **RESULTS**

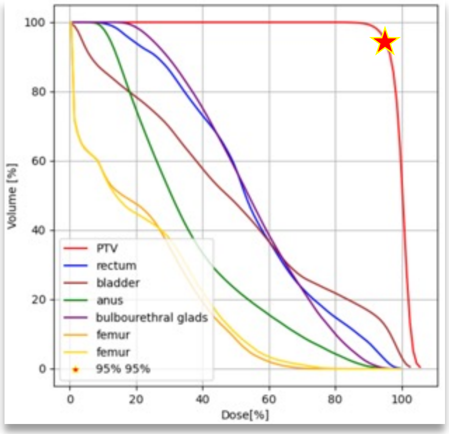
IMRT



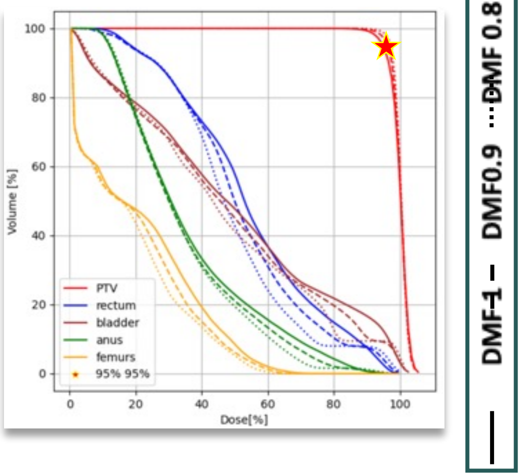
PROTONS



VHEE with DMF=1



VHEE with DMF=1, 0.9 and 0.8



VHEE

Organ	DMF=1	DMF=0.9	DMF=0.8
Target volume	$V_{95\%}$96% $V_{105\%}$0.2%	$V_{95\%}$98% $V_{105\%}$0.03%	$V_{95\%}$99% $V_{105\%}$0.04%
Rectum	V_{50} 30% V_{75} 0.9%	V_{50} 24% V_{75} 2.6%	V_{50} 18% V_{75} 4.1%
Anus	V_{30} 35%	V_{30} 34%	V_{30} 33%
Bulbourethral Glands	$\bar{D}$ 42 Gy	$\bar{D}$ 41 Gy	$\bar{D}$ 39 Gy
Femurs	$\bar{D}$ 16 Gy	$\bar{D}$ 14 Gy	$\bar{D}$ 14 Gy
Bladder	$\bar{D}$ 38 Gy V_{70} 17% V_{65} 20%	$\bar{D}$ 37 Gy V_{70} 11% V_{65} 17%	$\bar{D}$ 36 Gy V_{70} 9% V_{65} 9%

All dosimetric constraints are respected with VHEE even without FLASH effect

Const minimal FMF

- **Without FLASH EFFECT we obtain the needed PTV coverage and a better sparing of the OARs with respect to conventional RT;**
- **If a FLASH EFFECT is taken into account, even in the case of a small DMF, the treatment becomes competitive even with the PT one**

A. Sarti Front. Oncol. 11:777852. doi: 10.3389/fonc.2021.777852

FLASH effect

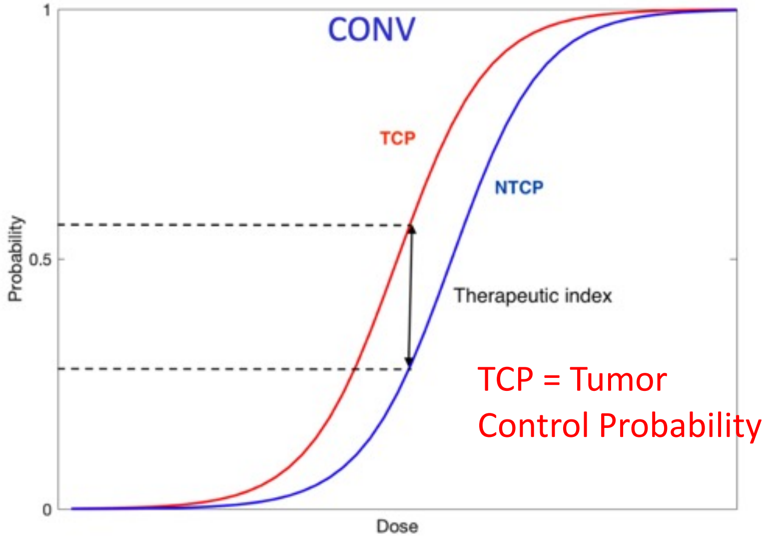
Lately has been reported evidence for a sparing effect on healthy tissue if the dose is delivered at very high rate (>40 Gy/s overall dose rate, for a total irradiation time <100 ms , but much higher rates (up to 10^9 Gy/s) during each pulse)

More interesting the sparing ewffect does not happen on tumors

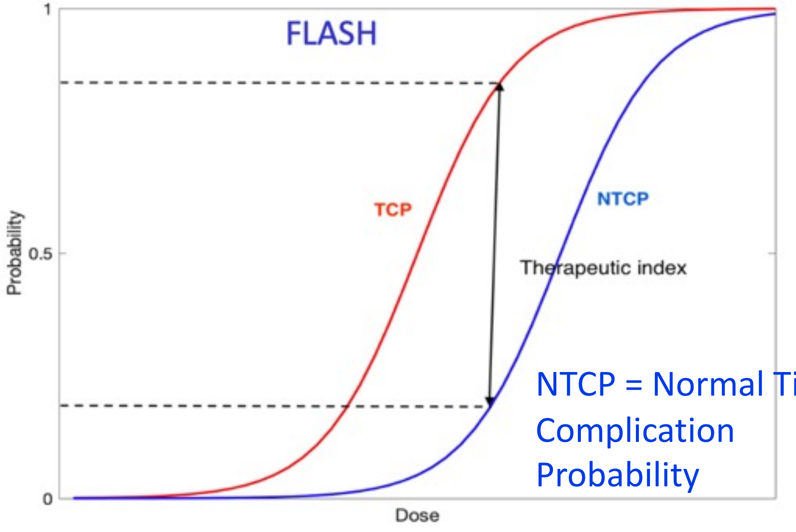
The effect has been reported (many times) on organs and on animals. Not yet seen on cells

Not final assesement on res[onsible mechanism yet found

Many model proposed

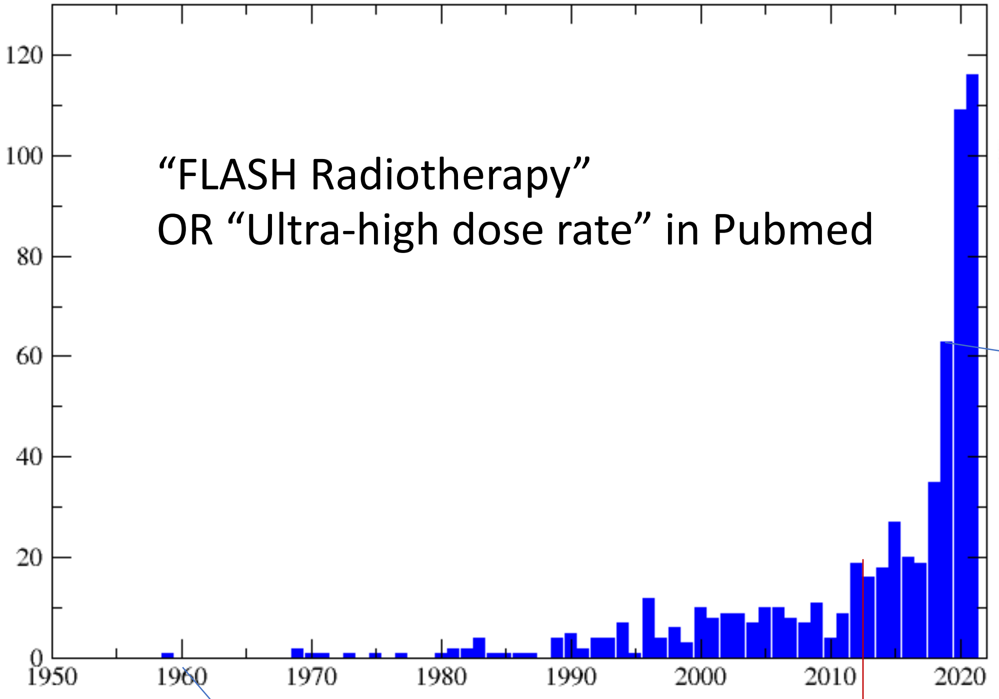


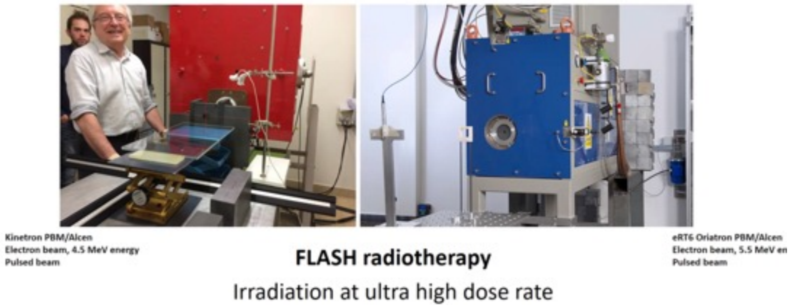
TCP = Tumor Control Probability



NTCP = Normal Tissue Complication Probability

FLASH: an exploding history





Clinical Oncology 31 (2019) 407–415

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journal homepage: www.clinicaloncologyonline.net

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/erview

ological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: eeping Beauty Awoken

-C. Vozenin *†, J.H. Hendry ‡, C.L. Limoli §

- Dewey an Boag’59

Science Translational Medicine AAAS

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice
Vincent Favaudon *et al.*
Sci Transl Med **6**, 245ra93 (2014);
DOI: 10.1126/scitranslmed.3008973

FLASH: an exploding history

The Hottest Topic in Radiation Oncology!

ARTICLE IN PRESS

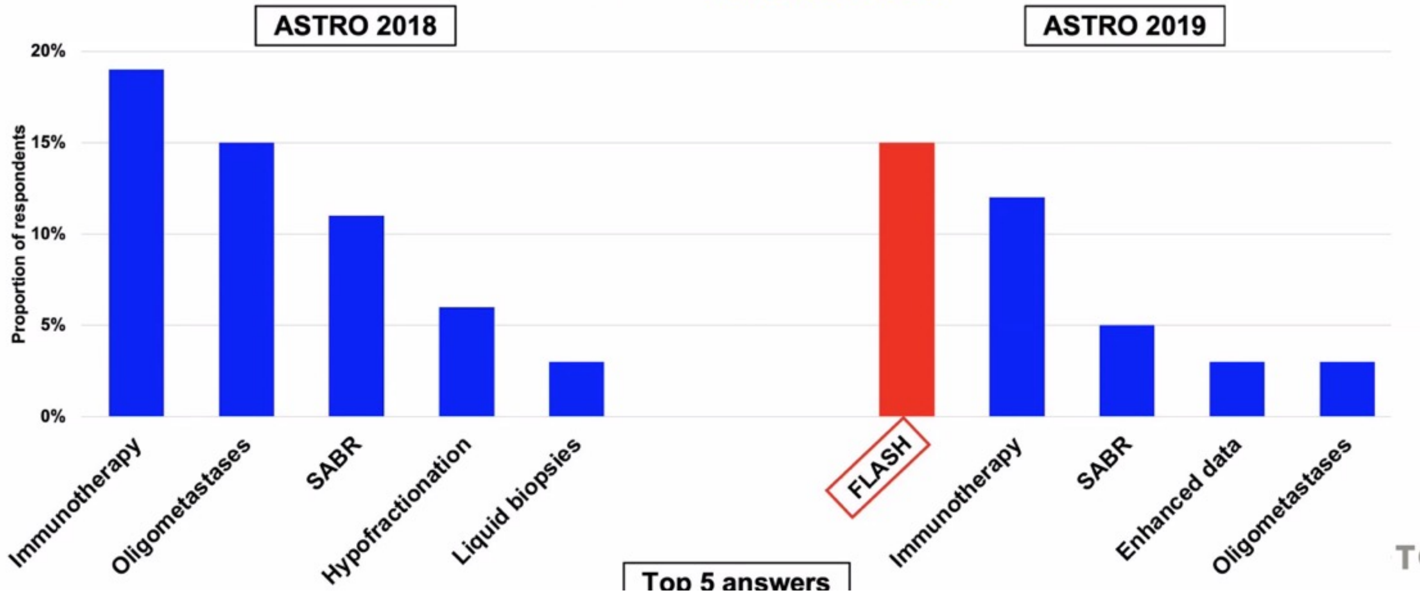
International Journal of Radiation Oncology biology • physics

www.redjournal.org

EDITORIAL

Responses to the 2018 and 2019 "One Big Discovery" Question: ASTRO Membership's Opinions on the Most Important Research Question Facing Radiation Oncology...Where Are We Headed?

ASTRO Meeting Survey:
What is the One Big Discovery that needs to be translated into the clinic RIGHT NOW?

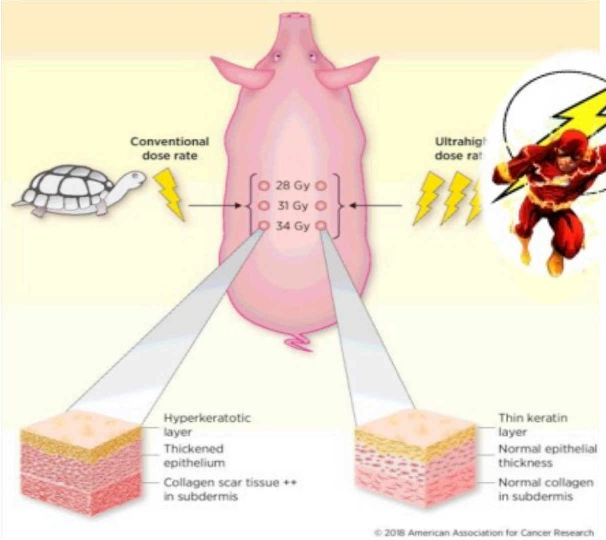


TON CENTER

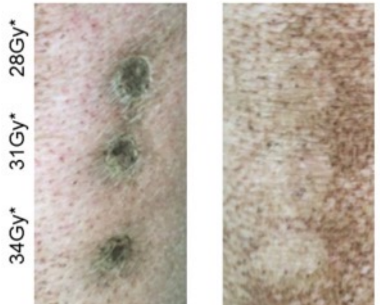
The FLASH Effect

Irradiation with **ultra-high dose rate**

- Decreasing of the normal tissue response

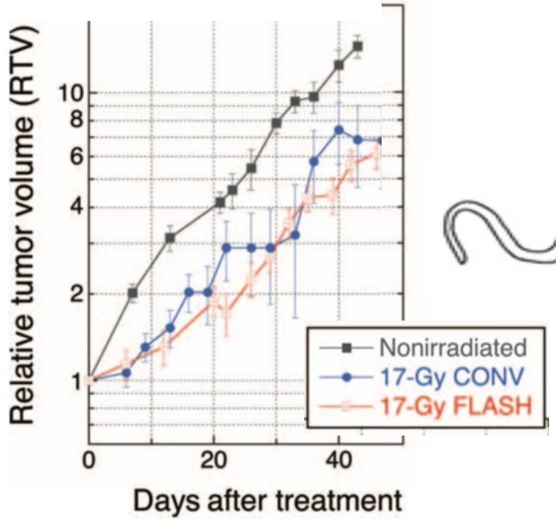


Vozenin et al. 2019, Clin. Canc. Res.



CONV FLASH

- Preservation of the tumor responses



V. Favaudon et al. 2014, Sci. Transl. Med.

Is the evidence robust?

RESEARCH ARTICLE

RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5†] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2§] Charles Fouillade,[1,2] Marie-France Poupon,[1,2‖] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s

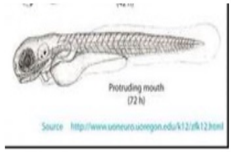
Pierre Montay-Gruel[a,b,1], Kristoffer Petersson[c,1], Maud Jaccard[c], Gaël Boivin[a], Jean-François Germond[c], Benoit Petit[a], Raphaël Doenlen[d], Vincent Favaudon[b], François Bochud[c], Claude Bailat[c], Jean Bourhis[a,1], Marie-Catherine Vozenin[a,e,1]

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Original article

X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice

Pierre Montay-Gruel[a], Audrey Bouchet[b], Maud Jaccard[c], David Patin[c], Raphael Serduc[b,e], Warren Aim[b], Kristoffer Petersson[a,c], Benoit Petit[a], Claude Bailat[c], Jean Bourhis[a], Elke Bräuer-Krisch[d,1], Marie-Catherine Vozenin[a,1]



PNAS

Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species

Pierre Montay-Gruel[a,b,1], Munjal M. Acharya[c,1], Kristoffer Petersson[a,b,d], Leila Alikhani[c], Chakradhar Yakkala[a,b], Barrett D. Allen[c], Jonathan Ollivier[a,b], Benoit Petit[a,b], Patrik Gonçalves Jorge[a,b,d], Amber R. Syage[c], Thuan A. Nguyen[c], Al Anoud D. Baddour[c], Celine Lu[c], Paramvir Singh[c], Raphael Moeckli[d], François Bochud[d], Jean-François Germond[d], Pascal Froidevaux[d], Claude Bailat[d], Jean Bourhis[a,b], Marie-Catherine Vozenin[a,b,2,3], and Charles L. Limoli[c,2,3]

[a]Laboratory of Radiation Oncology, Lausanne University Hospital, University of Lausanne, Lausanne VD-1011, Switzerland; [b]Department of Radiation Oncology, Lausanne University Hospital, University of Lausanne, Lausanne VD-1011, Switzerland; [c]Department of Radiation Oncology, University of California, Irvine, CA 92697-2695; and [d]Institute of Radiation Physics, Lausanne University Hospital, University of Lausanne, Lausanne VD-1011, Switzerland

Edited by James E. Cleaver, University of California, San Francisco, CA, and approved April 18, 2019 (received for review February 12, 2019)

Clinical Trial Brief Report
Clinical Cancer Research

The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients

Marie-Catherine Vozenin[1], Pauline De Fornel[2], Kristoffer Petersson[1,3], Vincent Favaudon[4], Maud Jaccard[1,3], Jean-François Germond[3], Benoit Petit[1], Marco Burki[5], Gisèle Ferrand[6], David Patin[3], Hanan Bouchaab[1], Mahmut Ozsahin[1,6], François Bochud[3], Claude Bailat[3], Patrick Devauchelle[2], and Jean Bourhis[1,6]

(P003) Delivery of Ultra-Rapid Flash Radiation Therapy and Demonstration of Normal Tissue Sparing After Abdominal Irradiation of Mice

Billy W. Loo, MD, PhD, Emil Schuler, PhD, Frederick M. Lartey, PhD, Marjan Rafat, PhD, Gregory J. King, PhD, Stefania Trovati, PhD, Albert C. Koong, MD, PhD, and Peter G. Maxim, PhD; *Stanford University*

CCR Translations
Clinical Cancer Research

Ultrahigh Dose-rate Radiotherapy: Next Steps for FLASH-RT

Kevin J. Harrington

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Original Article

Reduced cognitive deficits after FLASH irradiation of whole mouse brain are associated with less hippocampal dendritic spine loss and neuroinflammation

Danielle A. Simmons[a,#], Frederick M. Lartey[b,c,#], Emil Schüler[b], Marjan Rafat[b,d], Gregory King[b], Anna Kim[b], Ryan Ko[b], Sarah Semaan[a], Selena Gonzalez[a], Melissa Jenkins[b], Pooja Pradhan[b], Zion Shih[b], Jinghui Wang[b], Rie von Eyben[b], Edward E. Graves[b,c], Peter G. Maxim[b,c,e], Frank M. Longo[a,*], Billy W. Loo Jr.[b,c,*]

The first clinical result

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journal homepage: www.thegreenjournal.com

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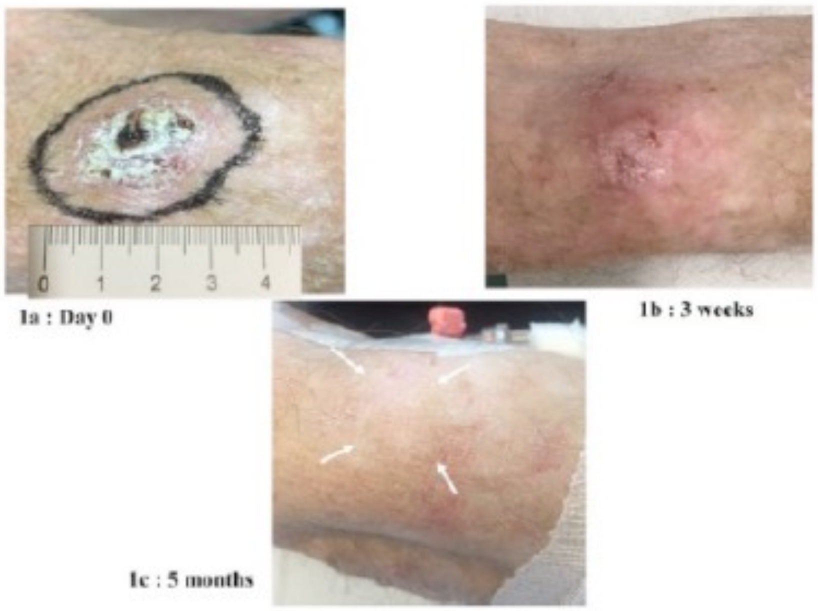
Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and [d] Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland



•multiresistant CD30+ T-cell cutaneous lymphoma disseminated throughout the whole skin surface.

•Localized skin RT previously used over 110 times for various ulcerative and/or painful cutaneous lesions progressing despite systemic treatments.

•Treatment given to a 3.5-cm diameter skin tumor with a 5.6-MeV linac specifically designed for FLASH-RT.

•Prescribed dose to the PTV = 15 Gy, in 90 ms.

•Results: At 3 weeks, i.e. at the peak of the reactions, a grade 1 epithelitis (CTCAE v 5.0) along with a transient grade 1 oedema (CTCAE v5.0) in soft tissues surrounding the tumor were observed.

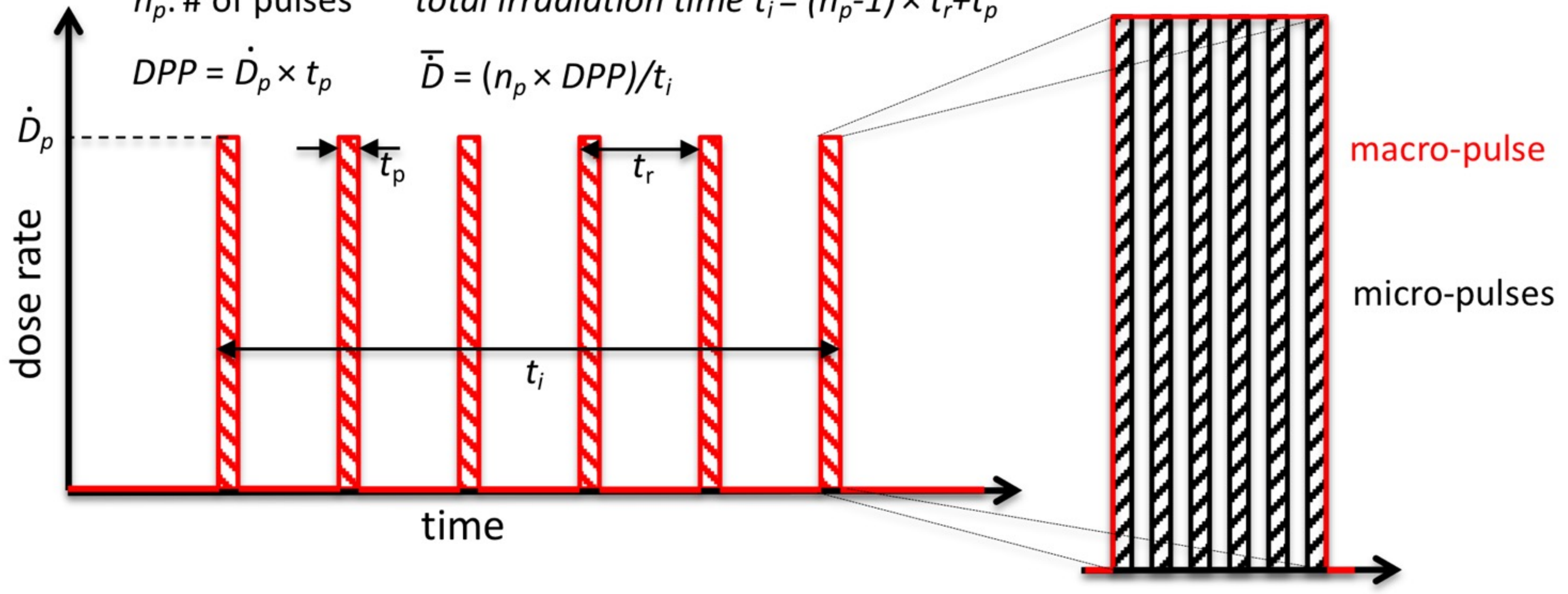
•In parallel, the tumor response was rapid, complete, and durable with a short follow-up of 5 months

Dose Delivery time structure

t_p: pulse width — time between pulses $t_r = 1/PRF$

n_p: # of pulses — *total irradiation time* $t_i = (n_p - 1) \times t_r + t_p$

$DPP = \dot{D}_p \times t_p$ — $\bar{\dot{D}} = (n_p \times DPP)/t_i$

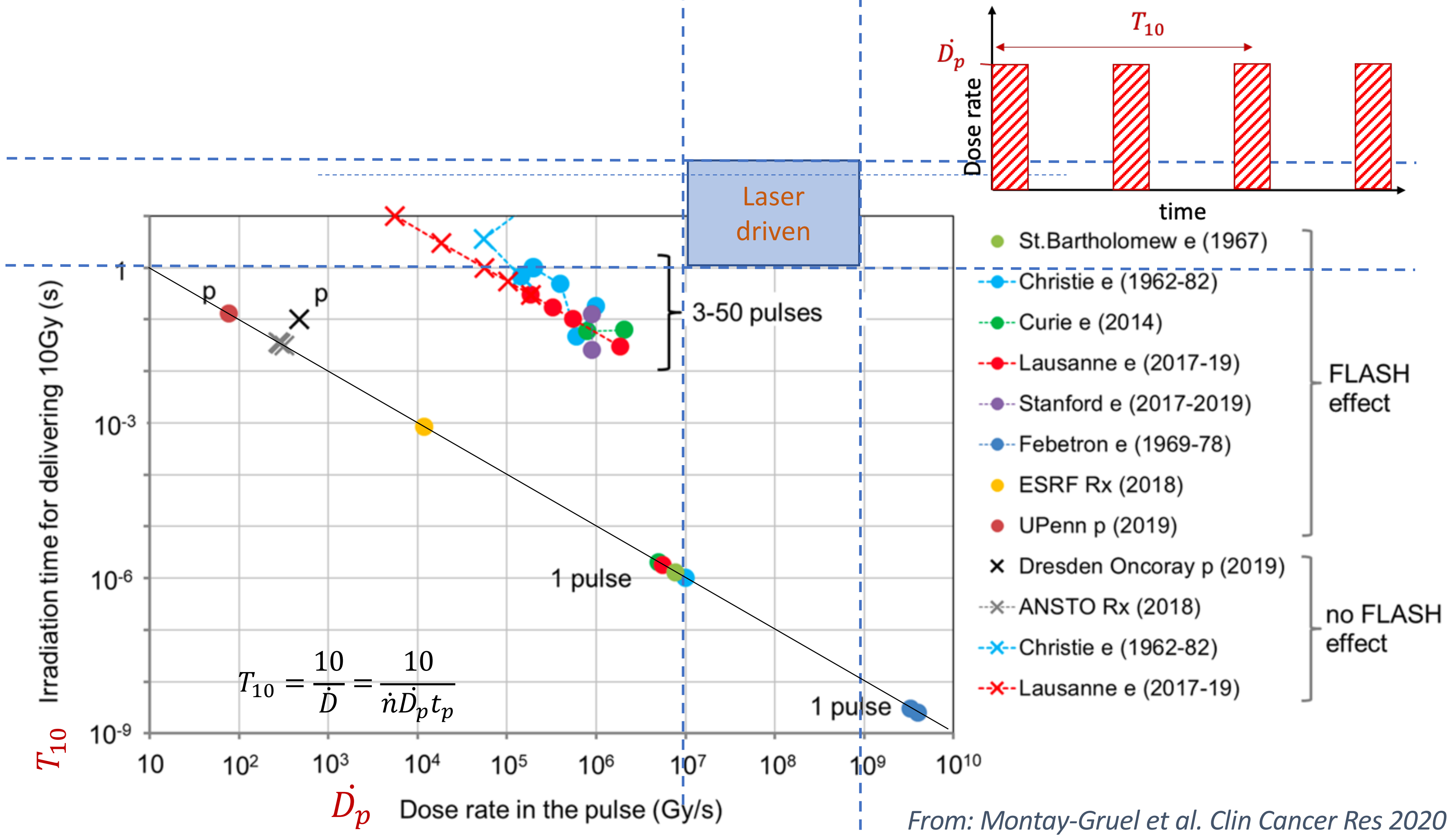


Pulse frequency

$$\dot{n} = \frac{n_p}{t_i}$$

Esplen et al. PMB 2020

Parameters for observing FLASH/noFLASH



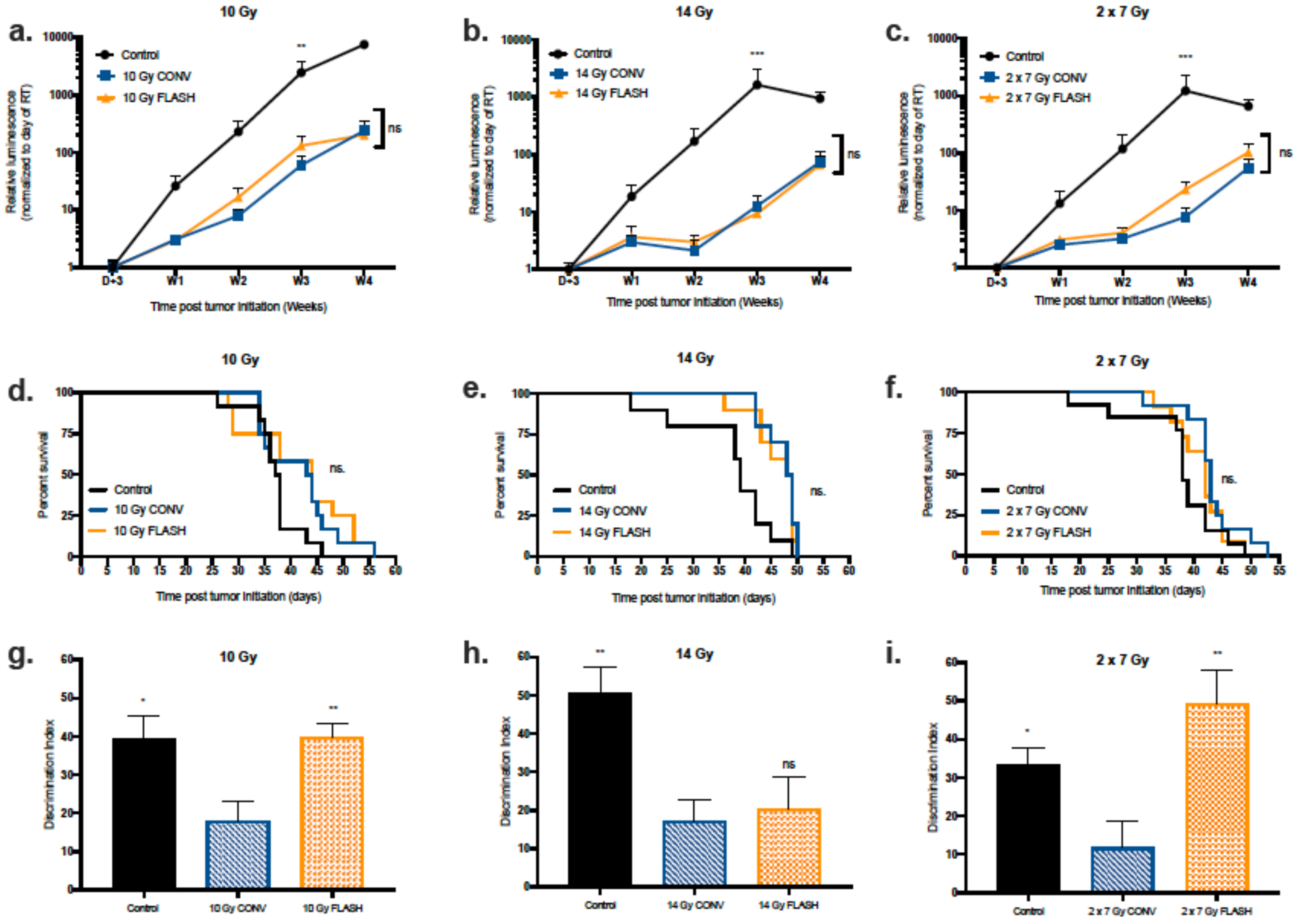
From: Montay-Gruel et al. Clin Cancer Res 2020

Impact of Fractionation

Tumor growth delay

Survival

Cognition (Novel Object Recognition)



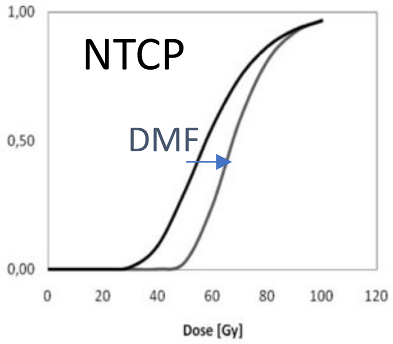
Dose modifying factor

Wilson `Front Oncol 2020

Let's be quantitative

DMF_{NT}= ratio between the two values of dose (flash and conv) to obtain the same effect

In vivo studies			Irradiation delivery technique			
Model	**Assay**	**FLASH dose modification factor (Bold if > 1)**	**Total dose (Gy)**	**Dose rate (Gy/s)**	**Pulse rate (Hz)**	**Modality of radiation**
Zebrafish embryo (16)	Fish length	**1.2–1.5**	10–12	10^6–10^7	Single pulse	Electron
Zebrafish embryo (29)	Fish length, survival, and rate of oedema	1	0–43	100	0.106 × 10^9	Proton
Whole body irradiation of mice (34)	LD50	**1.1**	8–40	17–83	400	Electron
Thoracic irradiation of mice (10)	TGFβ signaling induction	**1.8**	17	40–60	100–150	Electron
Thoracic irradiation of mice (18)	Number of proliferating cells, DNA damage, expression of inflammatory genes	**>1 Significant Differences**	17	40–60	100–150	Electron
Abdominal irradiation of mice (33)	Survival	<1 Significant Difference	16	35	Likely 300	Electron
Abdominal irradiation of mice (12)	LD50	**1.2**	22	70–210	100–300	Electron
Abdominal irradiation of mice (17)	Survival, stool formation, regeneration in crypts, apoptosis, and DNA damage in crypt cells	**>1 Significant Differences**	12–16	216	108	Electron
Whole brain irradiation of mice (25)	Novel object recognition and object location tests	**>1 Significant Differences**	30	200, 300	108, 180	Electron
Whole brain irradiation of mice (13)	Variety of neurocognitive tests	**>1 Significant Differences**	10	5.6·10^6	Single pulse	Electron
Whole brain irradiation of mice (14)	Novel object recognition test	**>1 Significant Differences**	10	30–5.6·10^6	100 or single pulse	Electron
Whole brain irradiation of mice (8)	Novel object recognition test	**≥1.4**	10	5.6–7.8·10^6	single pulse	Electron
Whole brain irradiation of mice (24)	Novel object recognition test	**>1 Significant Difference**	10	37	1,300	X-ray
Total body and partial body irradiation of mice (32)	TD50	1	3.6–28	37–41	1,388	X-ray
Thoracic irradiation of mice (11)	lung fibrosis, skin dermatitis, and survival	**>1 Significant Difference**	15, 17.5, 20	40	?	Proton
Irradiation of mouse tail skin (49)	Necrosis ND50	**1.4**	30 and 50	17–170	50	Electron
Irradiation of mouse skin (27)	Early skin reaction score	**1.1–1.6**	50–75	2.5 mean, 3 × 10^4 in the pulse	23–80	Electron
Irradiation of rat skin (26)	Early skin reaction score	**1.4–1.8**	25–35	67	400	Electron
Irradiation of mini-pig skin (15)	Skin toxicity	**≥1.4**	22–34	300	100	Electron



The sparing factor ranges between 20% and 50%

$$DMF_{NT} = \frac{TD_{50}^{FLASH}}{TD_{50}^{CONV}}$$

$$1.2 < DMF_{NT} < 1.5$$

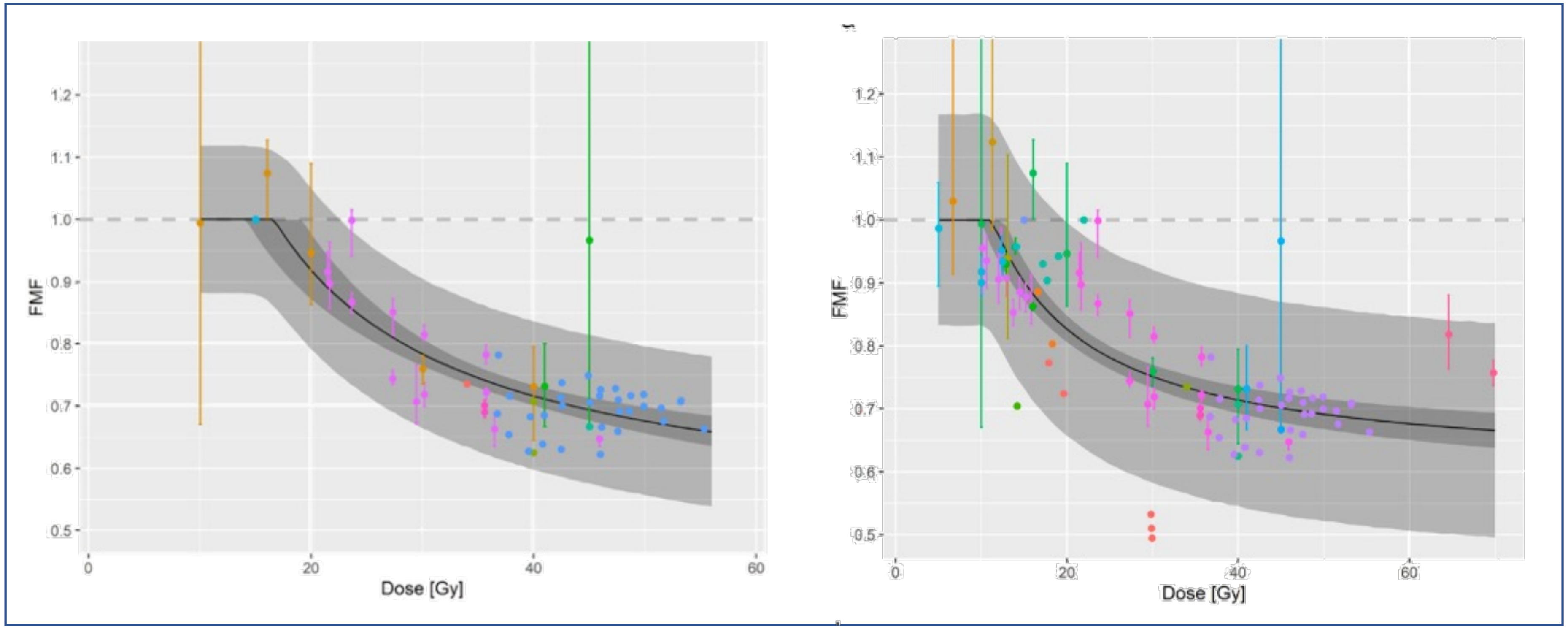
Some authors use FMF = 1/DMF

$$FMF_{NT} = \frac{TD_{50}^{CONV}}{TD_{50}^{FLASH}}$$

FMF and threshod dose

There is a minimum threshold to switch on the FLASH effect!! Order of 5 Gy !!!

Mammalian skin data | Mammalian non skin data



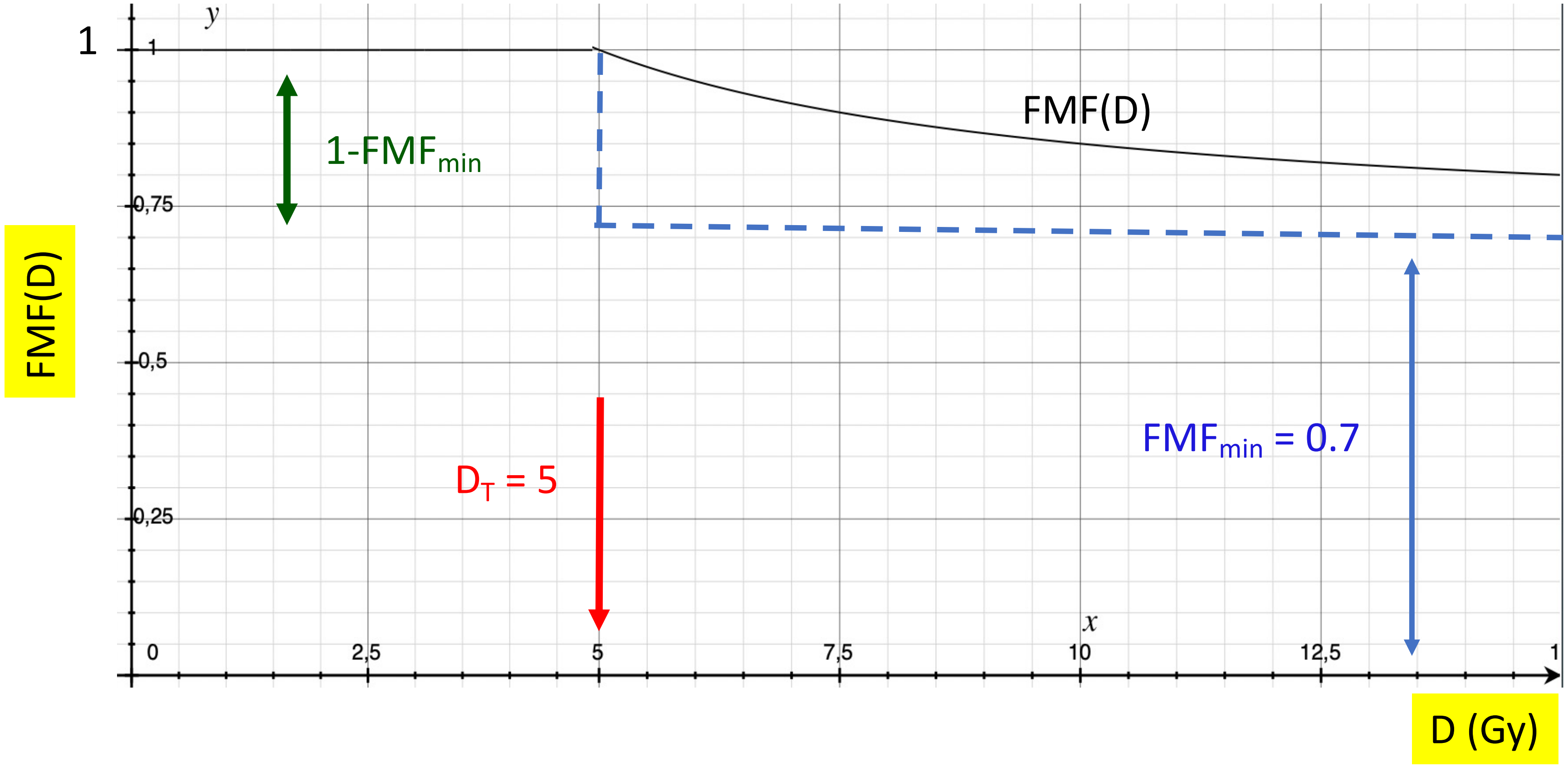
Böhlen, T. T.,. (2022). International Journal of Radiation Oncology, Biology, Physics

All the parameters (FMF_{min}, DT) can be (are) tissue specific and must be extracted from fit to the data. Currently the error bars are really huge: radiobiological data are badly needed (you will hear this many times…)

FLASH modifying factor: FMF

Assuming DR> 40Gy/s the FMF can be parametrized WRT the dose fitting the data

$$\text{FMF} = \begin{cases} 1 \text{ for } D \leq D_T \\ (1 - \text{FMF}^{\min}) \dfrac{D_T}{D} + \text{FMF}^{\min} \text{ for } D > D_T \end{cases}$$



A naïve approximation of the FLASH effect : FMF = 1 below threshold and FMF = FMF_{min} if $D>D_T$ provides a more than optimistic evaluation of the FLASH effect

It is easy to say: “Dose Rate”

The Dose Rate is uniquely defined in case of continuous and short irradiation time (i.e. LINAC shoot 1 μs pulse at high dose). This is the case of IORT, that is the best candidate for a FLASH introduction in clinical practice.

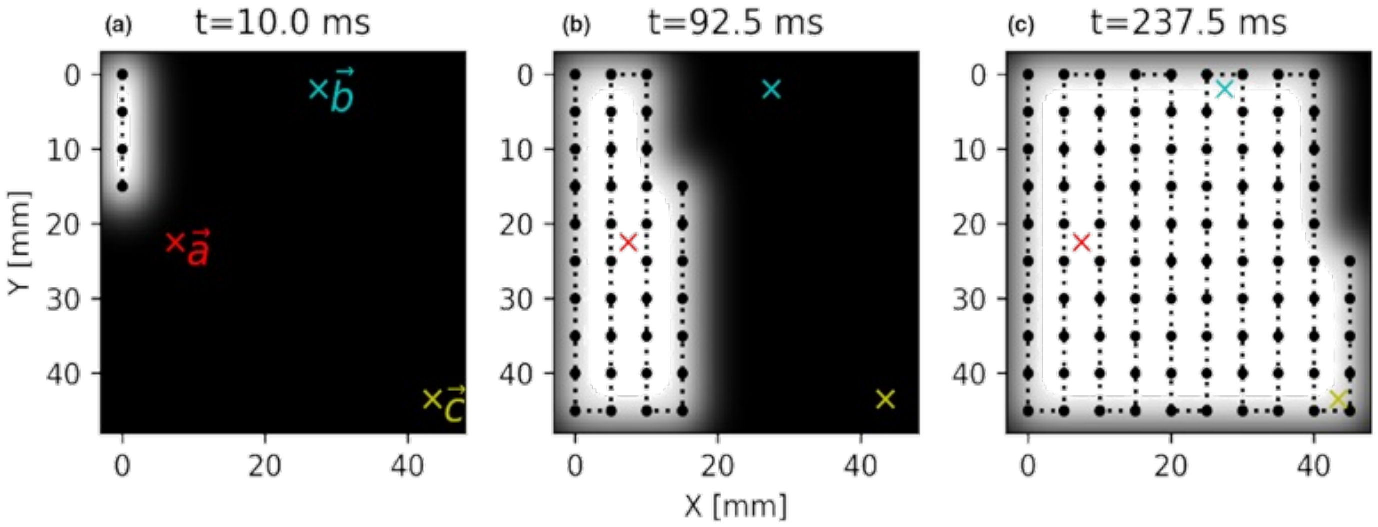
If the irradiation is more complex as in the case of many pencil beams in active scanning or multiple fields the time structure of the beam, and of the released dose can be parametrized differently with different numerical results.

In this complex case there is more than a single “time” to be taken into account, and to be compared with a typical FLASH coherence time ~100-200 ms. For instance, the irradiation pulse duration and the time to change position of the pencil beam

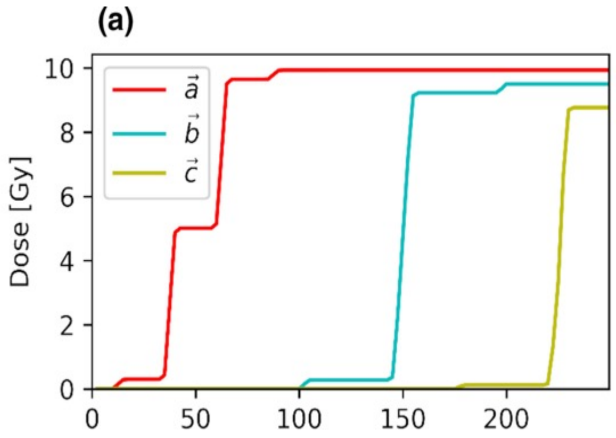
DR and spot scanning

Let's take a proton terapy spot scanning as use case…

The time for a voxel to accumulate the max dose is a **fraction** of the total time of irradiation.

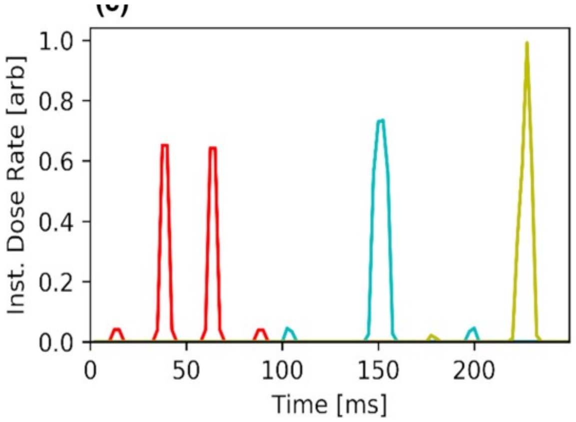


Cumulative dose



The dose rate depends on the **scanning pattern** and the **relative position** between the spots.

Instantaneous dose rate



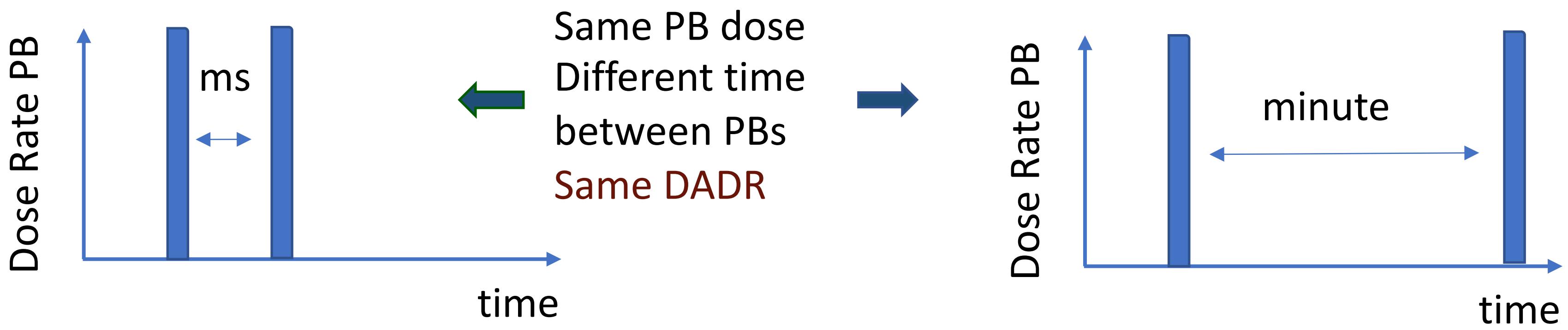
Medical Physics, Volume: 47, Issue: 12, Pages: 6396-6404, First published: 10 September 2020, DOI: (10.1002/mp.14456)

DADR: Dose averaged Dose Rate

Assume $D_{i,j}$ is the dose deposited by the i-th PB to the j-th voxel and $\dot{D}_{i,j}$ is the i-th PB dose rate in the j-th voxel, DR is a combination of the particle flux rate and particle dose contribution to the j-th voxel.

$$\dot{D}_j^{DADR} = \sum_{i=1}^{N} \frac{D_{j,i}}{\sum_{i=1}^{N} D_{j.i}} \dot{D}_{j.i}$$

This method **does not account for the temporal separation between spots**. Therefore, it will provide the same dose rate estimate from an array of spots, regardless of the duration required to accumulate the dose.



DTDR: Dose Threshold Dose Rate

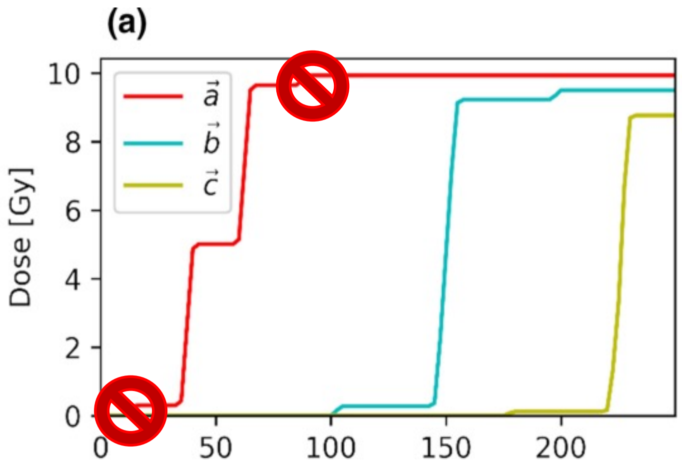
This approach is a spin-off of the DTDR, that aims to get rid of the small dose release due to the far PBs (a kind of noise filter).

The dose-threshold dose rate (DTDR) is defined by the minimum instantaneous dose rate of all the spots that deposit dose to the voxel above a predefined dose-threshold $d*$

$$\dot{D}_j^{DTDR} = \min(\dot{D}_{j,i}), \text{ if } D_{j,i} > d^*, \ i = 1, 2 \ldots n$$

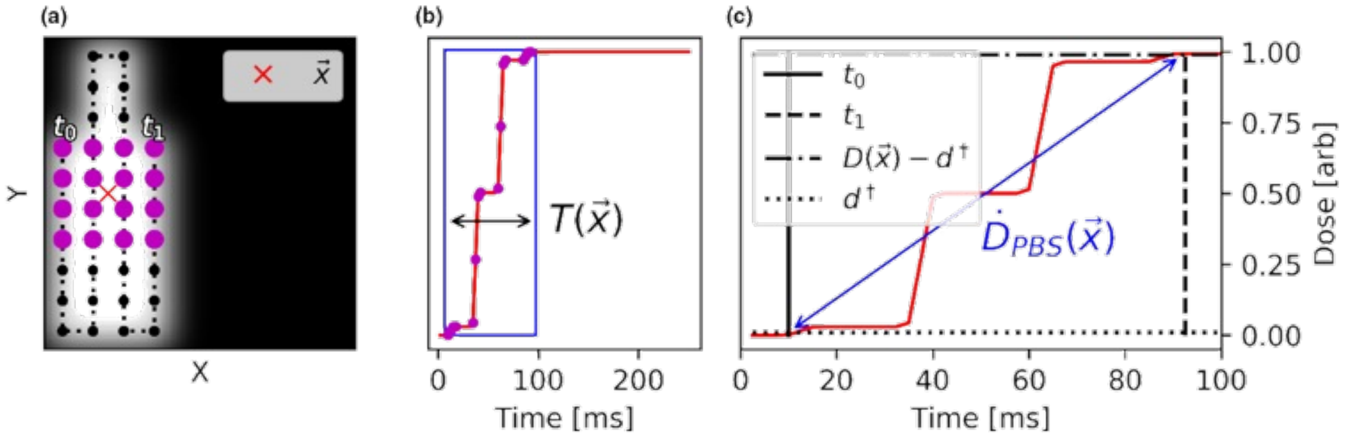
Also this method **does not account for the temporal separation between spots**.

Cumulative dose



ADR: Averaged Dose Rate

The ADR consider the bulk of the dose release (from the very near PBs) to evaluate a "robust"dose rate



$$\dot{D}_j^{ADR} = \frac{D_j - 2d^*}{T_j}$$

$$d_j(t_0) = d^* \qquad d_j(t_1) = D_j - d^*$$

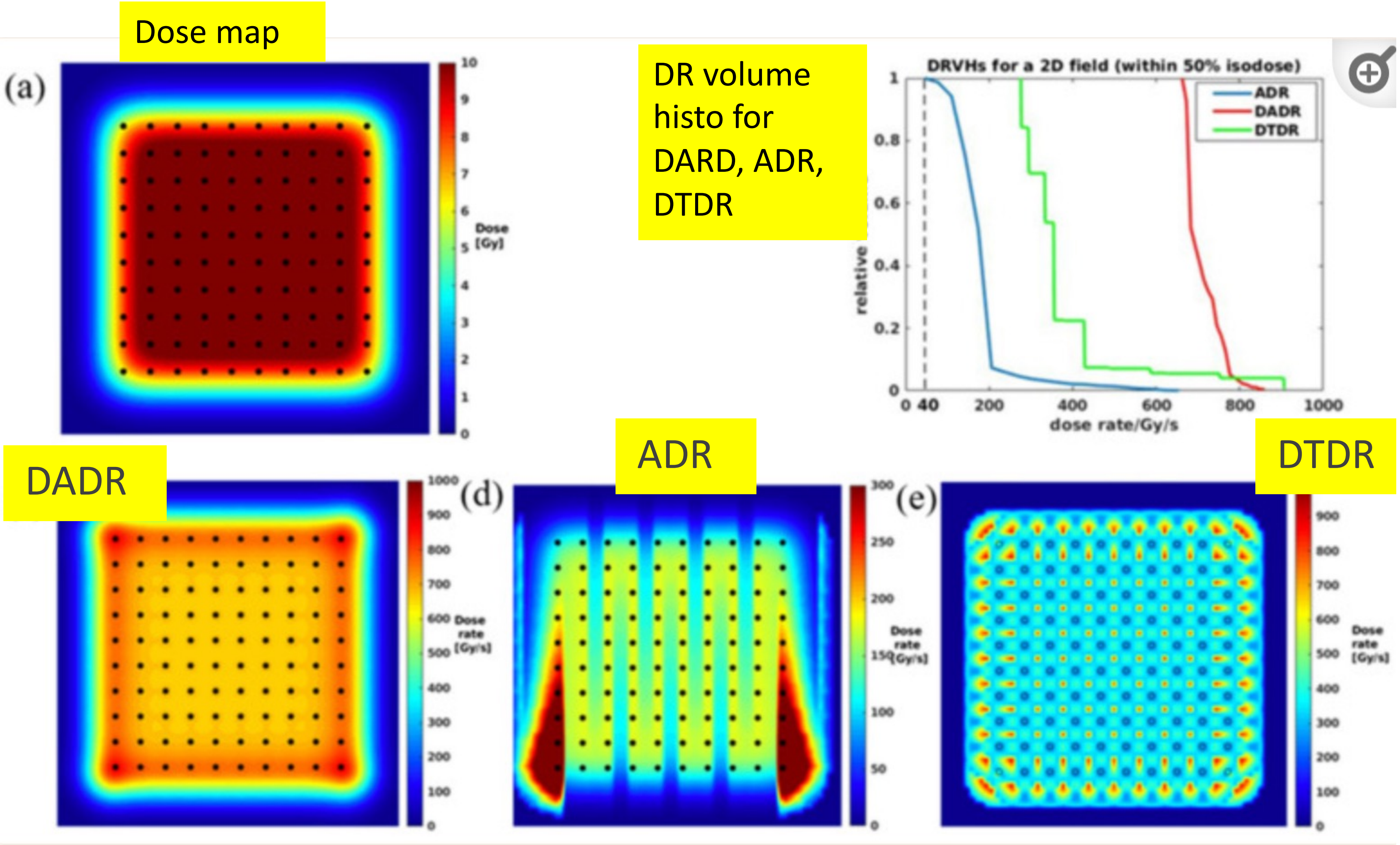
$$T_j = t_1 - t_0$$

d* preset dose-threshold that determines the effective irradiation time

Both duration of individual PB delivery and scanning from one PB to the next are considered for the dose rate calculations.

All the same? NO !!

Assuming the features of a proton beam scanning a 5x5x5 cm3 water cube with very fast delivery, all these DR definitions on a 5 × 5 cm^2 water phantom surface we obtain very different absolute values



So what???

Each Dose Rate methodology presented in literature is not based on first principles but is phenomenology driven.

The choice of the DR metric has an huge impact on an eventual FLASH Treatment planning system. The choice of the metric will determine the results!

The choice can only be driven by experiments! From a phenomenological point of view the correct metric is that one that provides the best parametrization of the radiobiological data.

Radiobiology data badly needed!! (again)

SPOILER: the design (and eventual the costs) of future flash machines depends also by the FLASH TPS outcome..

Dropping FMF on the stage

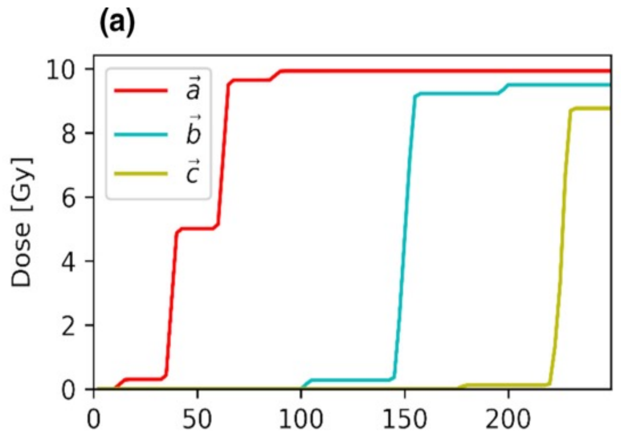
To introduce the FLASH effect we have to embed the FMF as modifying factor of the voxel dose only in the Organ at Risk in the TPS optimization:

$$\chi^2 = \sum_{i \in PTV} \in \omega_i \frac{(d_i - D_{PTV})^2}{d_i^2} +$$

$$+\sum_{i \in AR} \in \omega_i \frac{(d_i - D_{OAR})^2}{d_i^2} \times g(d_i \times FMF(d_i, DR, D_T) - D_{OAR})$$

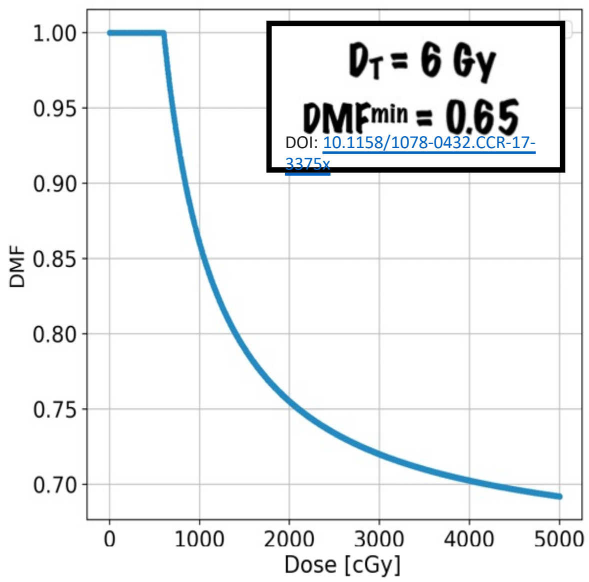
The evaluation of the DR can be very time comsuming. The ADR and Time Window methods ask to keep in memory and to update the time evolution of the dose of each voxel included in the optimization.

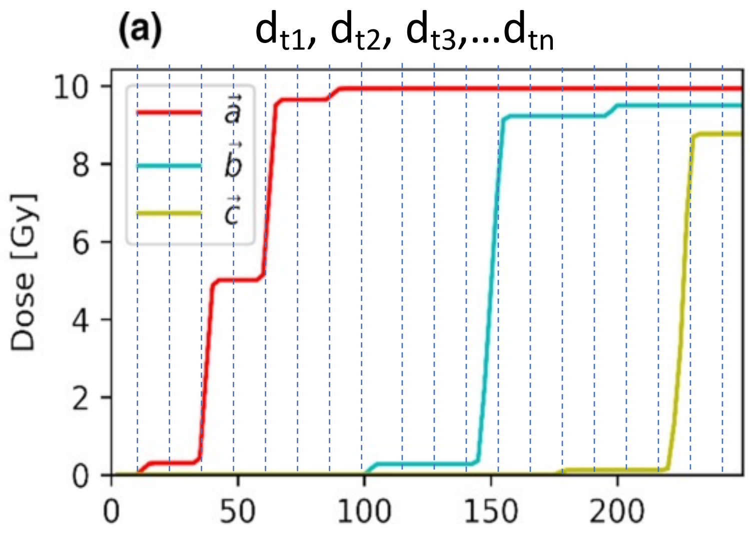
This has also a huge impact on the memory management of the optimization



A bit of techicality

The introduction of the $FMF(d_i, DR, D_T)$ function increase the CPU time and uncertainties in the optimization, in particular for algorithms based on the cost derivatives (T. Lomax) typical of PT





The DR evaluation needs the storage, for each voxel, of the dose time vector d_{tn}, that span on the irradiation time with thick< 100ms.

Several Gbytes of memory to read, write and handle

Which beam for FLASH?

- Photons: the efficiency of production of photon beam from electron beam is 3%: very huge power on electron LINAC needed AND the tungsten target must dissipate a LOT of power
- Hadrons: irradiate the same tissue with different energies(SOBP). The change of energy is too slow to deliver the dose at FLASH rate. The maximum rate is achieved at maximum energy: passive scatterer to regain conformality
- Electron: low energy electrons (IORT) are already on the market at FLASH rate. Very huge work of research on the VHEE that can be produced with the same high intensity of IORT

Laser acceleration? See in a moment..

Carbon-FLASH observed in vivo

Radiotherapy and Oncology
Available online 7 May 2022
In Press, Journal Pre-proof

Original Article

FLASH with carbon ions: tumor control, normal tissue sparing, and distal metastasis in a mouse osteosarcoma model

Walter Tinganelli [a], Uli Weber [a], Anggraeini Puspitasari [a], Palma Simoniello [b], Amir Abdollahi [c], Julius Oppermann [a], Christoph Schuy [a], Felix Horst [a], Alexander Helm [a], Claudia Fournier [a], Marco Durante [a, d]

Highlights

- FLASH radiotherapy with high-energy carbon ions demonstrated for the first time in an animal model (mouse osteosarcoma in the hind limb)
- FLASH (100 Gy/s) reduced normal tissue toxicity and tumour growth.
- The number of lung metastasis was greatly reduced by FLASH irradiation compared to controls and animals irradiated at conventional dose-rate.

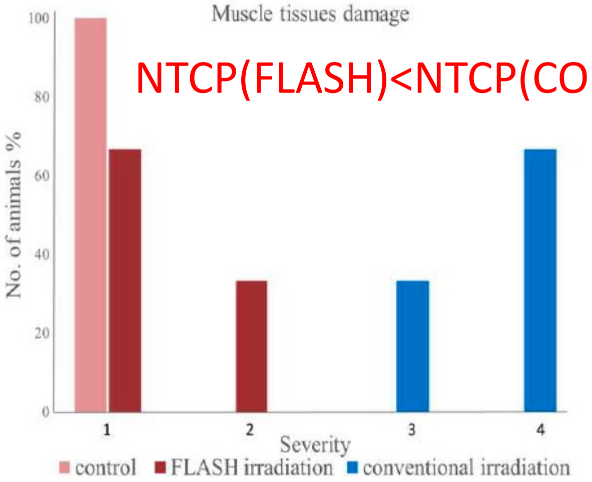
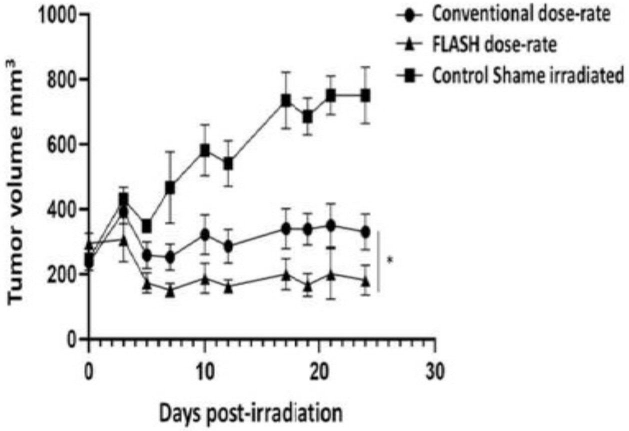
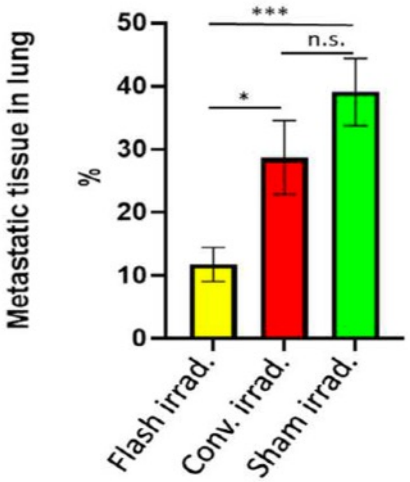


Figure 2

TCP(FLASH)>TCP(CONV)





Guess what? FLASH photons !!

Original Article

First demonstration of the FLASH effect with ultrahigh dose rate high-energy X-rays

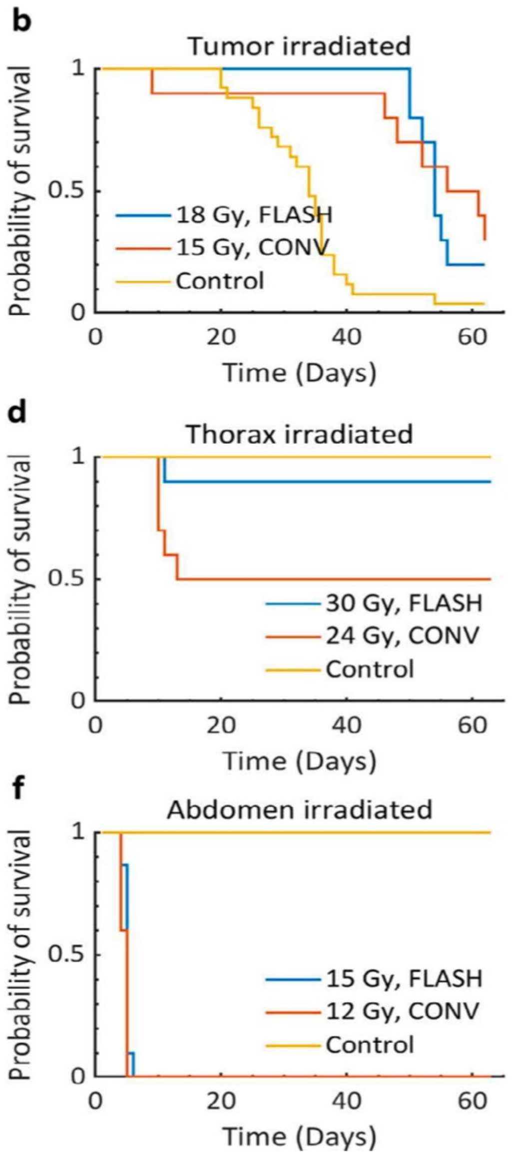
Feng Gao[a], Yiwei Yang[b,1], Hongyu Zhu[c,1], Jianxin Wang[d], Dexin Xiao[d], Zheng Zhou[d], Tangzhi Dai[a], Yu Zhang[a], Gang Feng[a], Jie Li[a], Binwei Lin[a], Gang Xie[e], Qi Ke[e], Kui Zhou[d], Peng Li[d], Xuming Shen[d], Hanbin Wang[d], Longgang Yan[d], Chenglong Lao[d], Lijun Shan[d], Ming Li[d], Yanhua Lu[d], Menxue Chen[d], Song Feng[f], Jianheng Zhao[d], Dai Wu[d,*], Xiaobo Du[a,*]

Radiotherapy and Oncology 166 (2022) 44–50

There are several attempts to produce a FLASH photon machine, even if the technical challenge is severe.

HEX-FLASH irradiation was performed using the PARTER platform at the Chengdu, China, at China Academy of Engineering Physics terahertz free electron laser. The superconducting LINAC can produce 6–8 MeV electrons with an adjustable mean current of up to 10 mA

BTW, this is not a clinical compliant equipment….



What about laser acceleration?

The laser acceleration is likely to be the next disruptive technology in this field.

It has FLASH native dose delivery: the time structure of the laser mechanism itself ensure the FLASH regime by itself.

Both ions, protons, electron are produced with such a mechanism: all the particles on which the research on FLASH has been successful till now.

The real point is the timeline of the needed technology evolution and the competition of the other technologies (in particular eLINAC and pLINAC)

A way to success: what is needed?

From a naïve point of view (mine) the laser based technology to be in business should achieve in the next (10?) years the following features:

- ✓Stability and control in beam delivery so to ensure the 3% accuracy in dose release during the treatment needed by the protocols
- ✓To achieve conformality high selectivity in energy and angle is requested: if the beam has energy and angular spread then very high intensity is needed to select energy and angle
- ✓Beam energy to treat deep seated tumor (P~200MeV, e- ~100 MeV)
- ✓Higher (100 Hz?) repetition rate
- ✓Compactness in the acceleration device. It should fit in a current treatmnet room for photon beam (5x5x5 m^3)
- ✓Non impossible cost (as oreder of magnitude: photon ~1-2 Meuro, Proton ~10-20 Meuro, carbon > 100 Meuro)

Conditio sine qua non!!

Which is the situation today?

Quoting the Snowmass 2021 White Paper about FLASH radiation therapy, about the use of Laser driven accelerator for FLASH:

"To summarize, current Laser-Driven LD particle source parameters are well below the requirements for their use as an alternative medical FLASH radiotherapy modality.
However, their comparatively low-cost and compact nature has earned LD particle sources increasing attention and the differential normal tissue sparing in vitro under LD proton irradiation was recently demonstrated.
Therefore, LD particle sources could soon complement conventional accelerators to increase and democratize access to particle sources for preclinical radiobiological research.. "

In spite of that.. First step are there!

Deliver of petawatt laser-driven proton pulses of 2 MeV energy at 0.2 Hz repetition rate by means of a compact, tunable active plasma lens beamline to biological samples.

Cell monolayers grown over a 10 mm diameter field were exposed to clinically relevant proton doses ranging from 7 to 35 Gy at ultra-high instantaneous dose rates of 10^7 Gy/s.

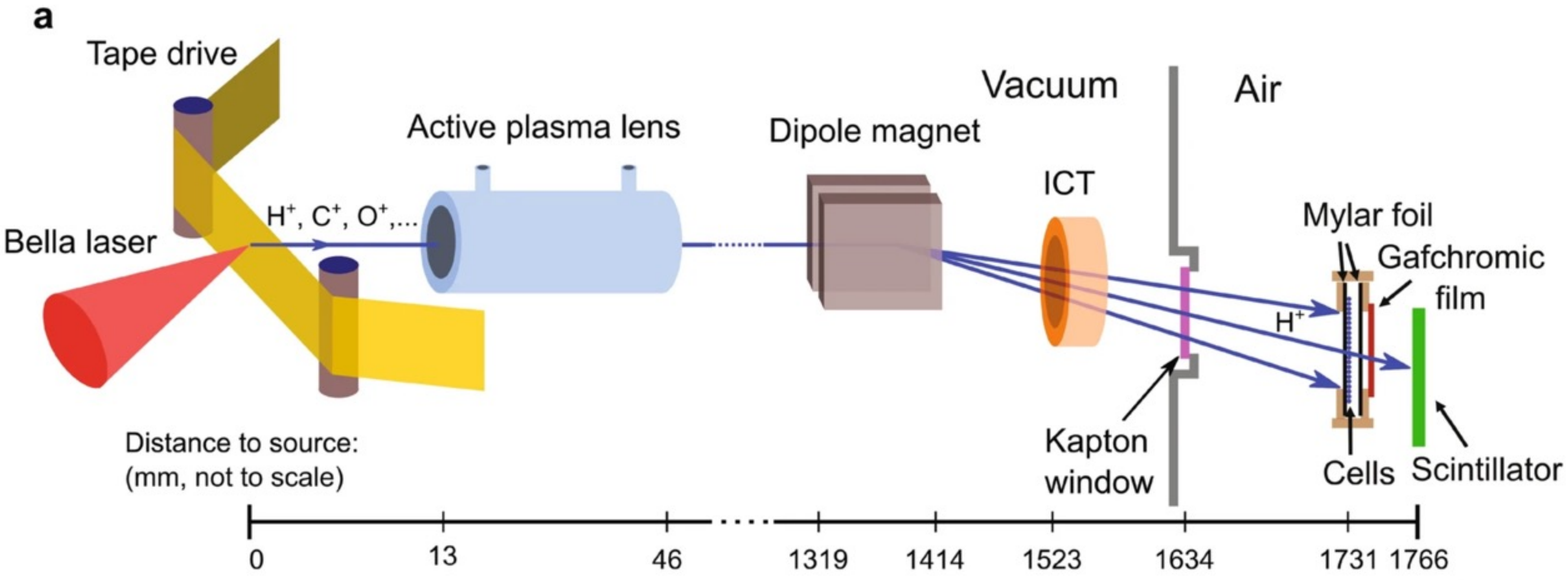
scientific reports

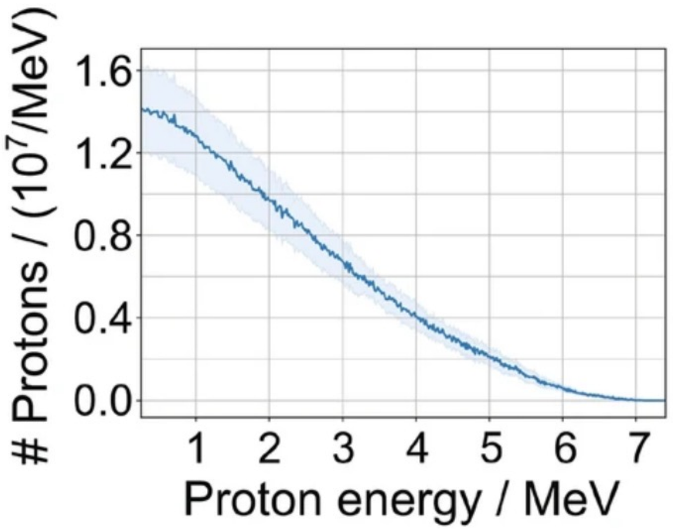
Check for updates

OPEN

A new platform for ultra-high dose rate radiobiological research using the BELLA PW laser proton beamline

Jianhui Bin[1,2,7], Lieselotte Obst-Huebl[1,7], Jian-Hua Mao[3], Kei Nakamura[1], Laura D. Geulig[1,4], Hang Chang[3], Qing Ji[1], Li He[3], Jared De Chant[1,5], Zachary Kober[1], Anthony J. Gonsalves[1], Stepan Bulanov[1], Susan E. Celniker[3], Carl B. Schroeder[1], Cameron G. R. Geddes[1], Eric Esarey[1], Blake A. Simmons[3], Thomas Schenkel[1], Eleanor A. Blakely[3], Sven Steinke[1,6] & Antoine M. Snijders[3]✉

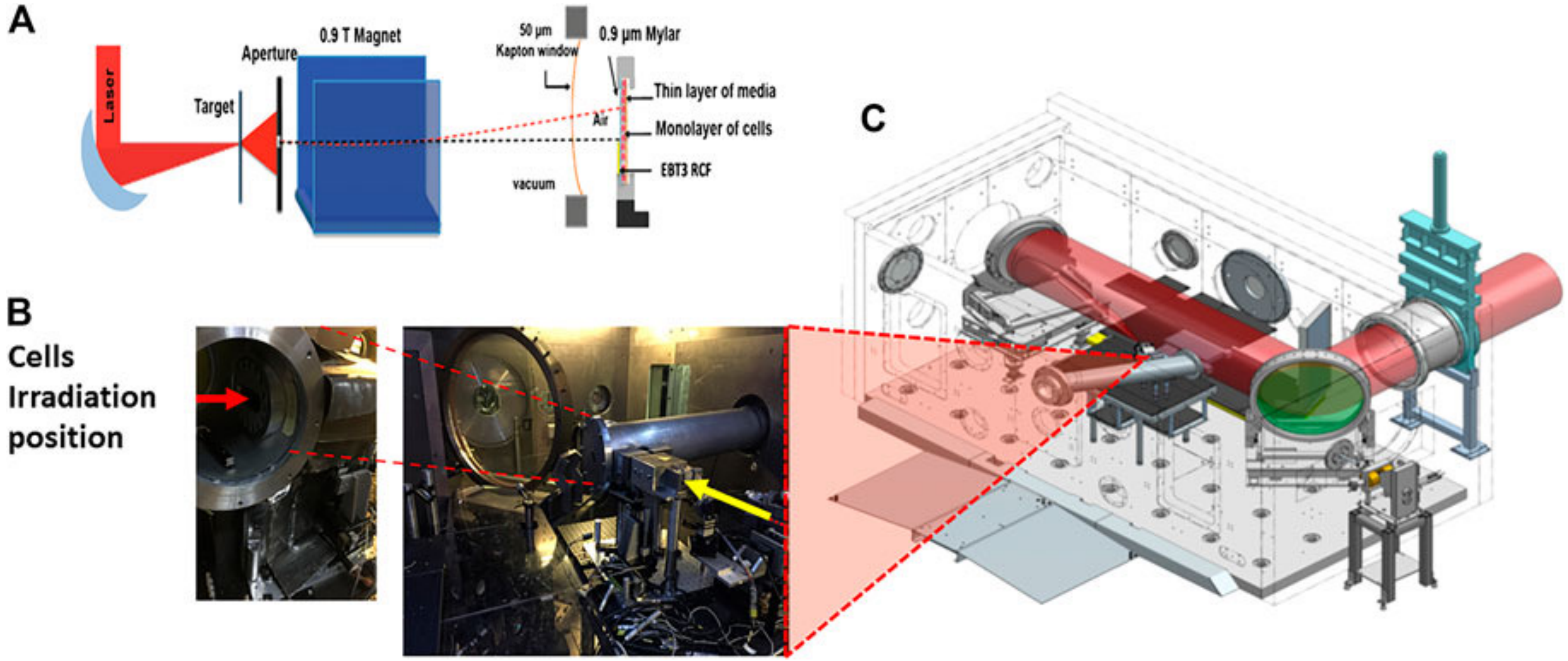




First step: let’s irradiate cells

LD proton beams for radiobiology irradiation are starting in several centers

Due to the high intensity and to the wide beam energy spectra the beam monitor and the dosimetry is extremely challenging



Overview of the Laser Interaction chamber of the Vulcan Target Area Pettawatt Laser of the Central Laser Facility at the Rutherford Appleton laboratory, Didcot, Oxford, England

ELI-Beamlines
Medical and
multidisciplinary
application
is born with this
specific target

Courtesy of P. Cirrone

ELIMED goals

Beam control

Answer to the question

can we use laser-ions for medical/multidisciplinary applications?

Try to fill this table

	Conventional beams	Laser-driven beams
Maximum energy	250 MeV 400 AMeV	?
Current	order of nA	?
Monochromaticity	$\Delta E/E \leq 10^{-2}$	?
Stability, reproducibility, control, absolute dosimetry	Less that 3%	?
Radiobiology	Almost known	?

ELI-MED and ELI-MAIA

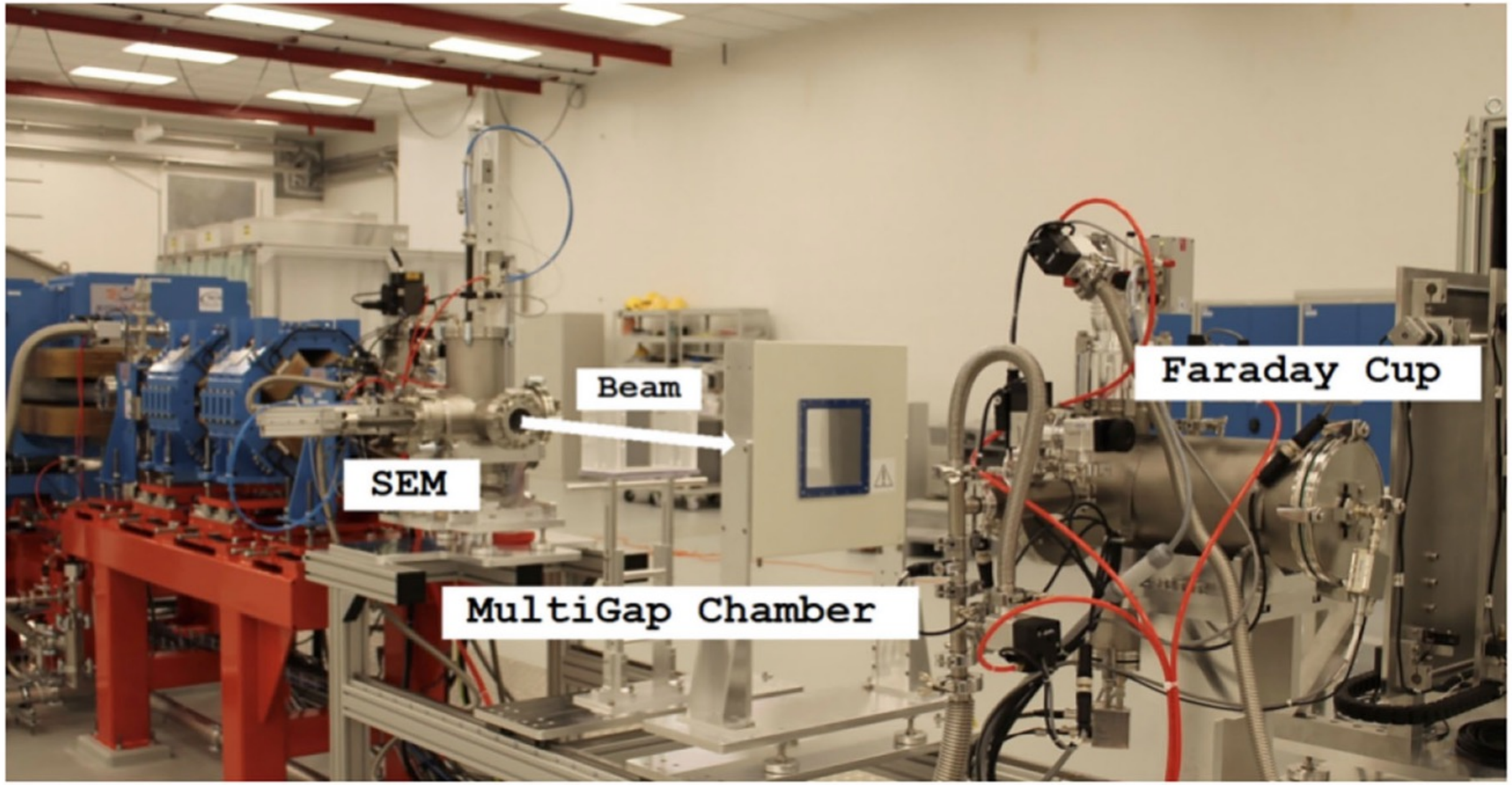
- Mixed laser driven + transfer line concept: proof of principle.
- Focused on the study of a medical quality beam
- Does not address topics as space, cost

frontiers in Physics

ORIGINAL RESEARCH
published: 13 November 2020
doi: 10.3389/fphy.2020.564907

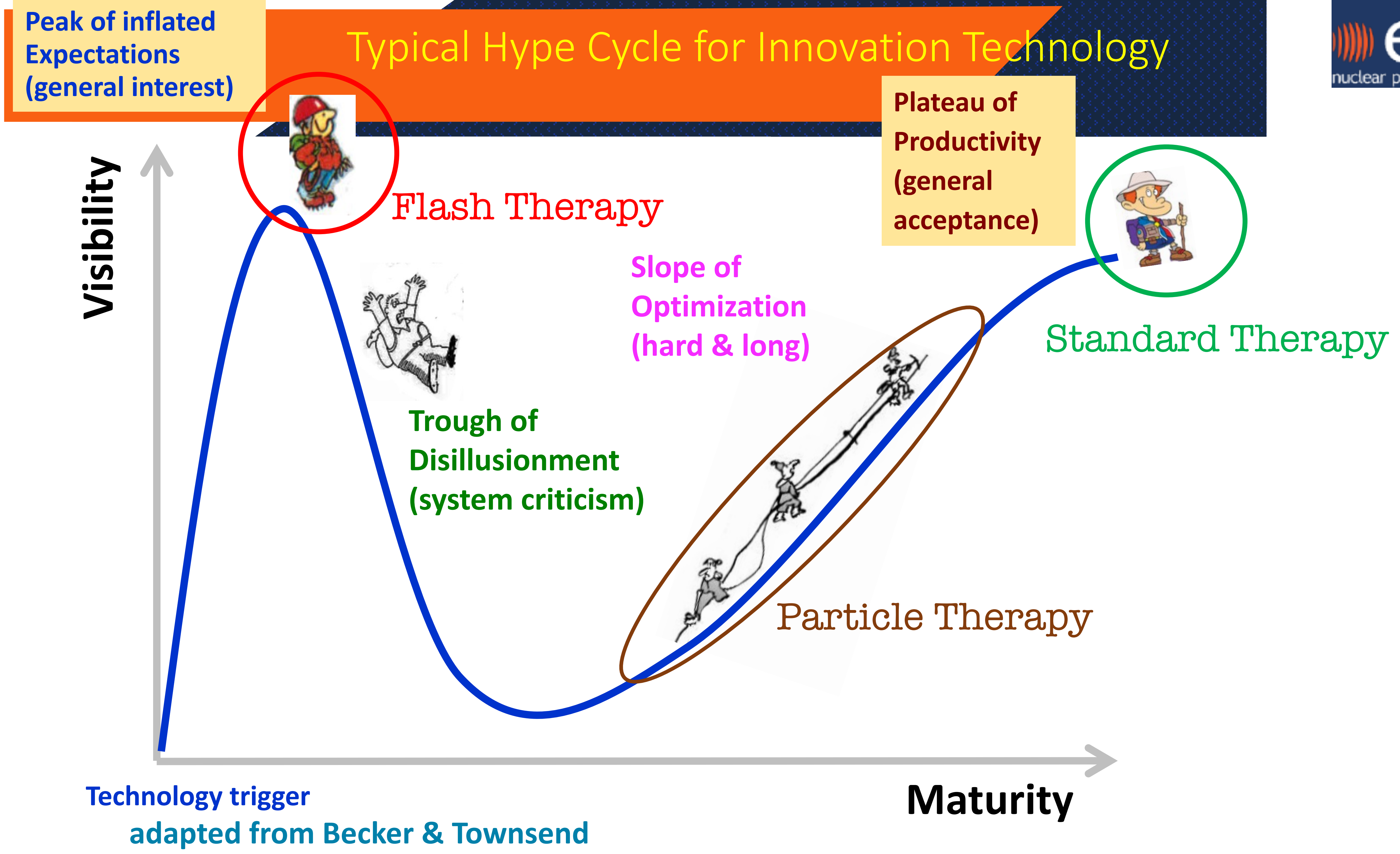
ELIMED-ELIMAIA: The First Open User Irradiation Beamline for Laser-Plasma-Accelerated Ion Beams

Giuseppe A. P. Cirrone[1], Giada Petringa[1], Roberto Catalano[1], Francesco Schillaci[2], Luciano Allegra[1], Antonino Amato[1], Renato Avolio[1], Michele Costa[1], Giacomo Cuttone[1], Antonin Fajstavr[2], Giuseppe Gallo[1], Lorenzo Giuffrida[2], Mariacristina Guarrera[1], Georg Korn[2], Giuseppina Larosa[1], Renata Leanza[1], Enzo Lo Vecchio[1], Gustavo Messina[1], Giuliana Milluzzo[1,3], Veronika Olsovcova[2], Salvatore Pulvirenti[1], Jan Pipek[1], Francesco Romano[1], Daniele Rizzo[1], Antonio D. Russo[1], S. Salamone[1], Valentina Scuderi[1], Andriy Velyhan[2], Salvatore Vinciguerra[1], Martina Zakova[2,4], Emilio Zappalà[1] and Daniele Margarone[2,3]*



- Huge activity to address dosimetric and beam monitor studies for Laser driven beam
- Beam line open to external user

Typical Hype Cycle for Innovation Technology



Summary & conclusions

- Radiotherapy has been beneficial in the last years from the technological improvement of accelerator technology
- Standard radiotherapy has gained full maturity and is an hard competitor to beat, but even to reach
- Particle therapy is gaining more and more momentum, but the equipment cost and size are limiting its diffusion
- FLASH therapy is the new deal, but we have still to understand mechanism, measure the radiobiology, take it to the clinic
- Laser driven beam are the future, but how far is this future is not yet clear

Thanks for the attention!