Proton Therapy Department
Trento Hospital
Trento(IT)

Trento Institute for
Fundamental Physics
and Applications

Overview of hadrontherapy

Marco Schwarz
marco.schwarz@apss.tn.it

Why hadrons?
From physics to biological effect
From physics to technology
Hadron-specific medical physics issues

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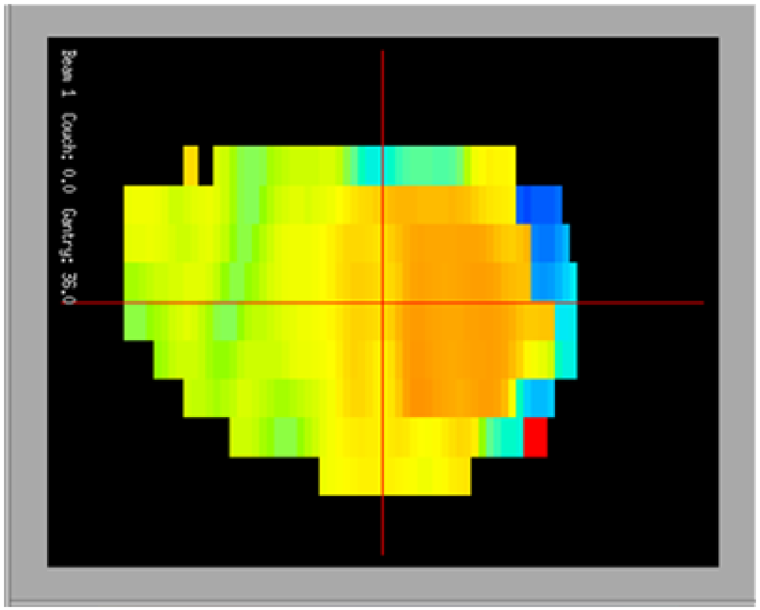
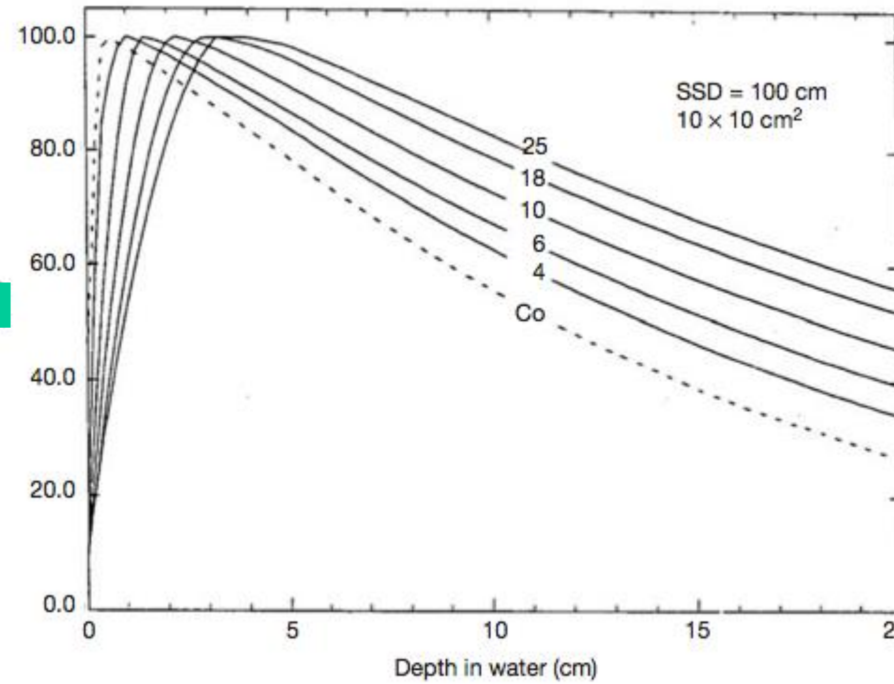
State of the art of XRT





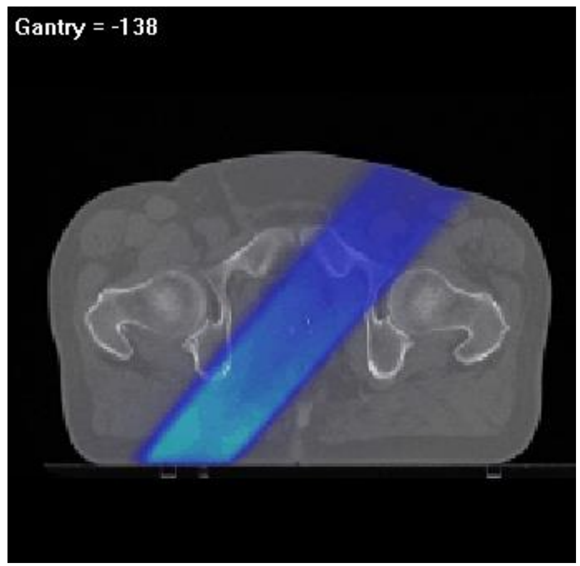
We learned how to modulate beam intensity in the transversal plane

Photons physics **does not** allow modulation along the beam direction

How do we solve the problem?
Spreading the unwanted dose around

Shape and intensity
Of a single field

Dose per field

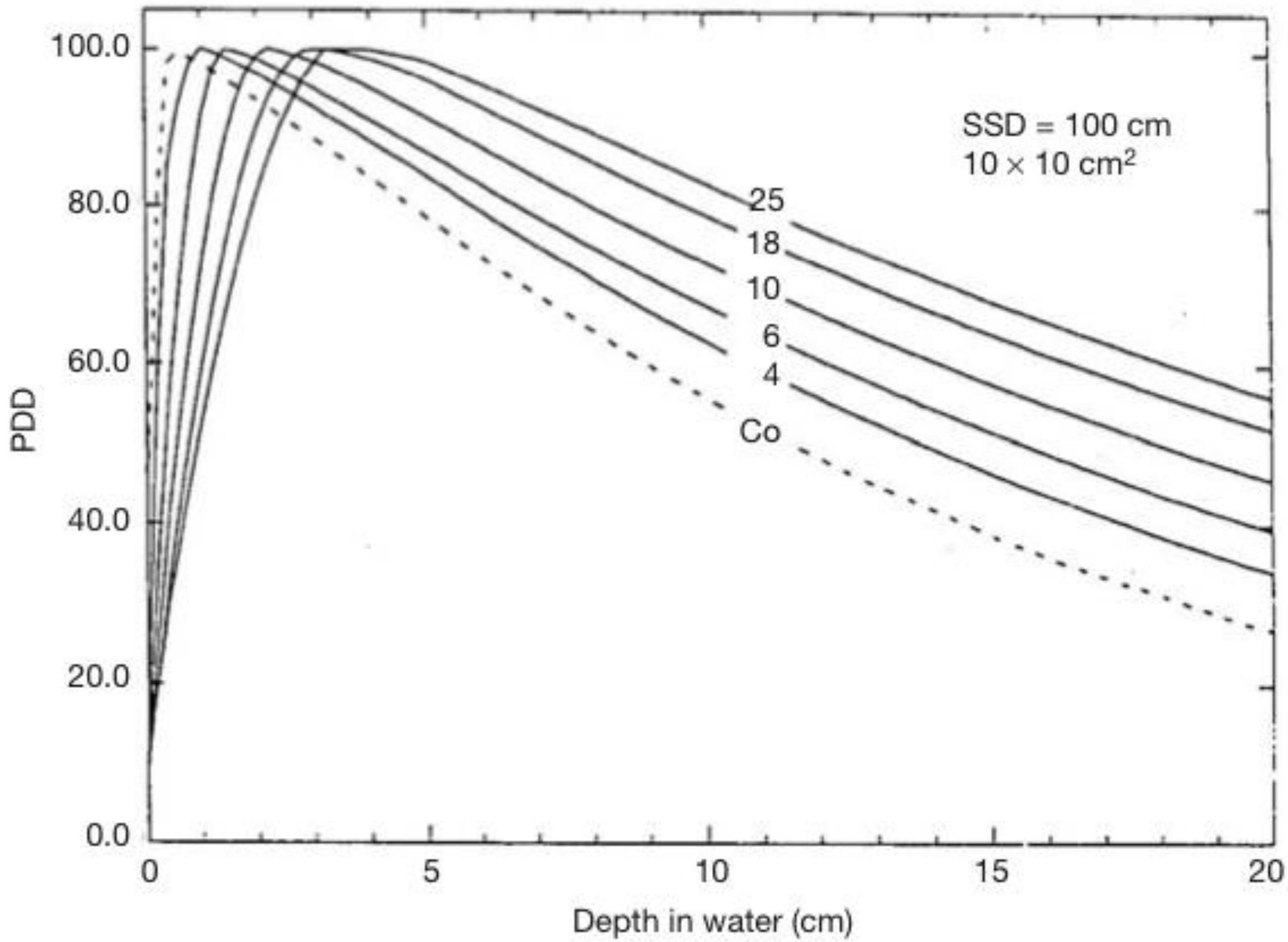


Cumulative dose

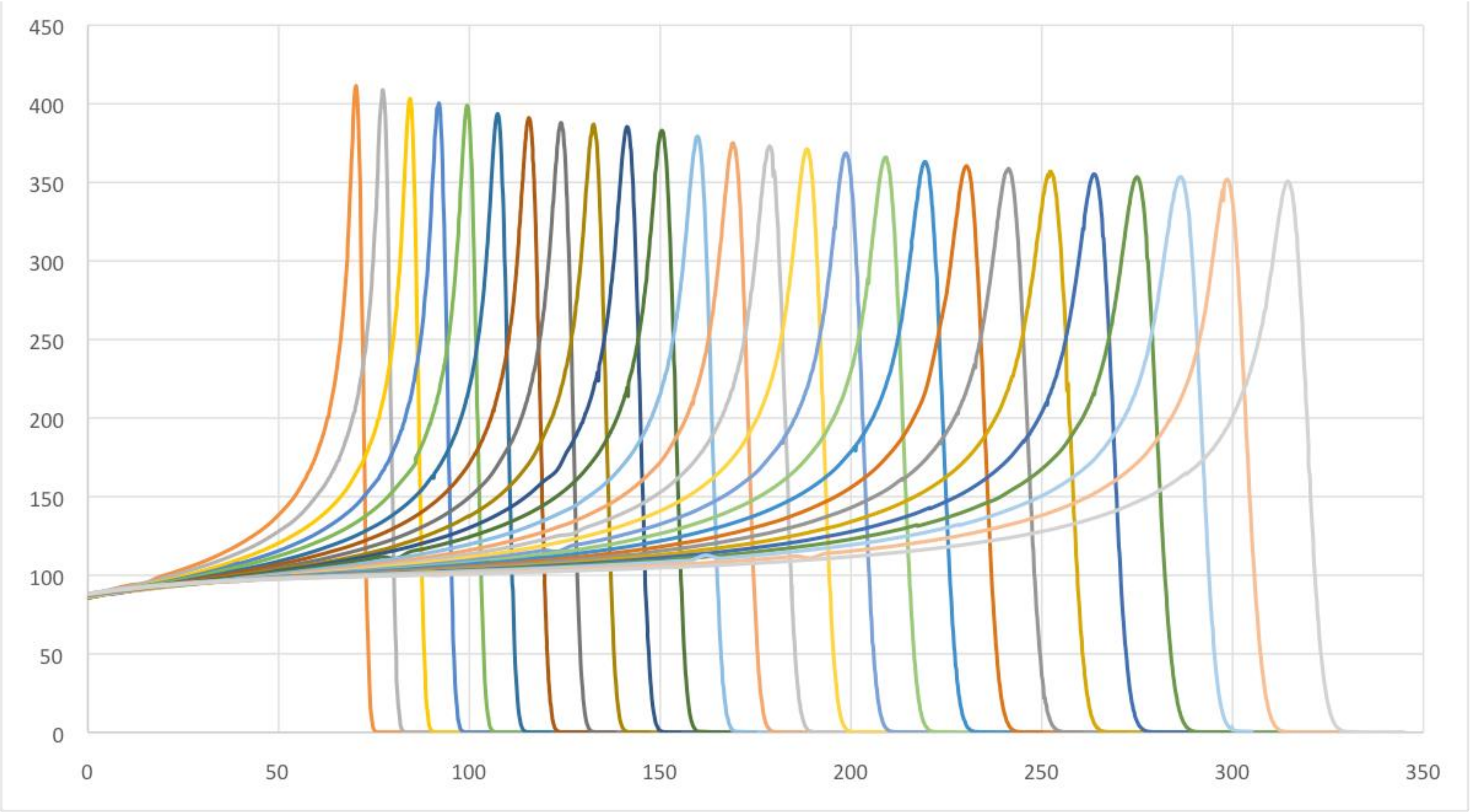
Pro: Good conformity
Con: large volume of tissues receving some dose

Courtesy B. Mijnheer

What if instead of this ...



… we could use this?



Dose shaping *in water* achievable continuosly from 0cm to 32cm

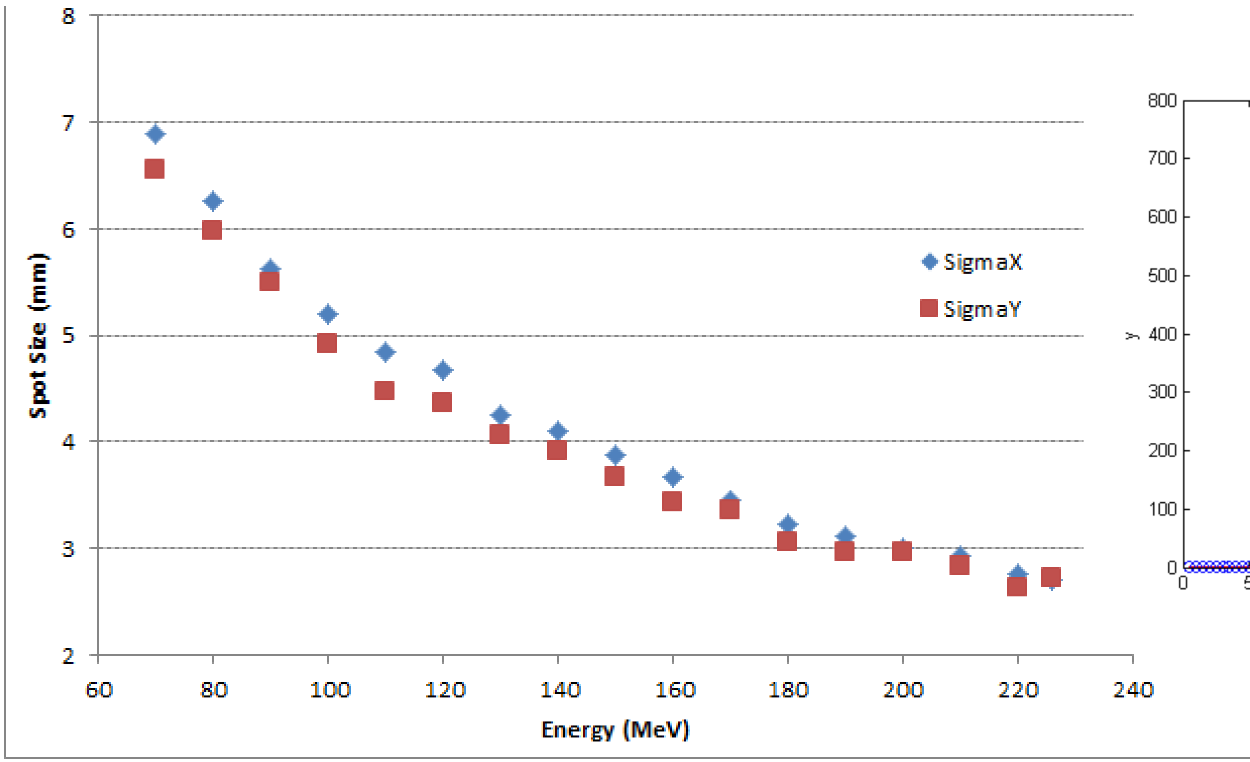
Accuracy and precision ≤ 1mm

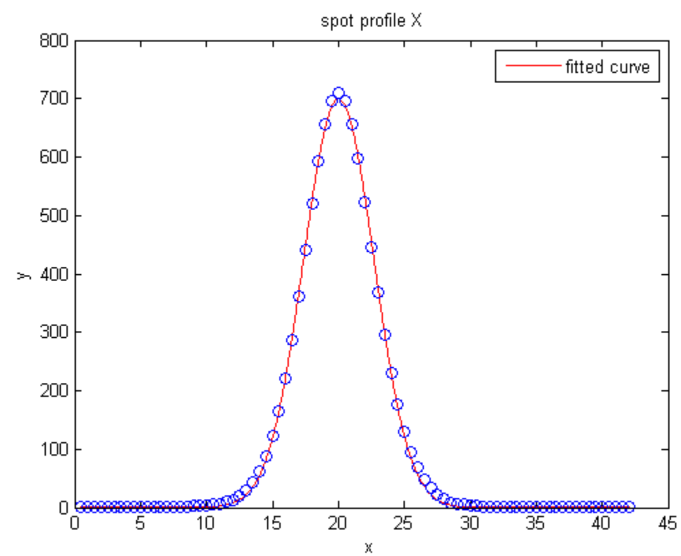
(Slightly) sharper dose falloff for lower energies/depth
Physical limit (falloff due to range straggling) ≈ 0.016*Range

... + this
(dose shaping in the transversal plane)?

Lower energies:
Larger beam size at patient entrance
Less scatter in the patient

Higher energies:
Smaller beam size at patient entrance
More scatter in the patient





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Energy loss of a "heavy charged particle"

Most energy losses are due to Coulomb interactions with orbital electrons.

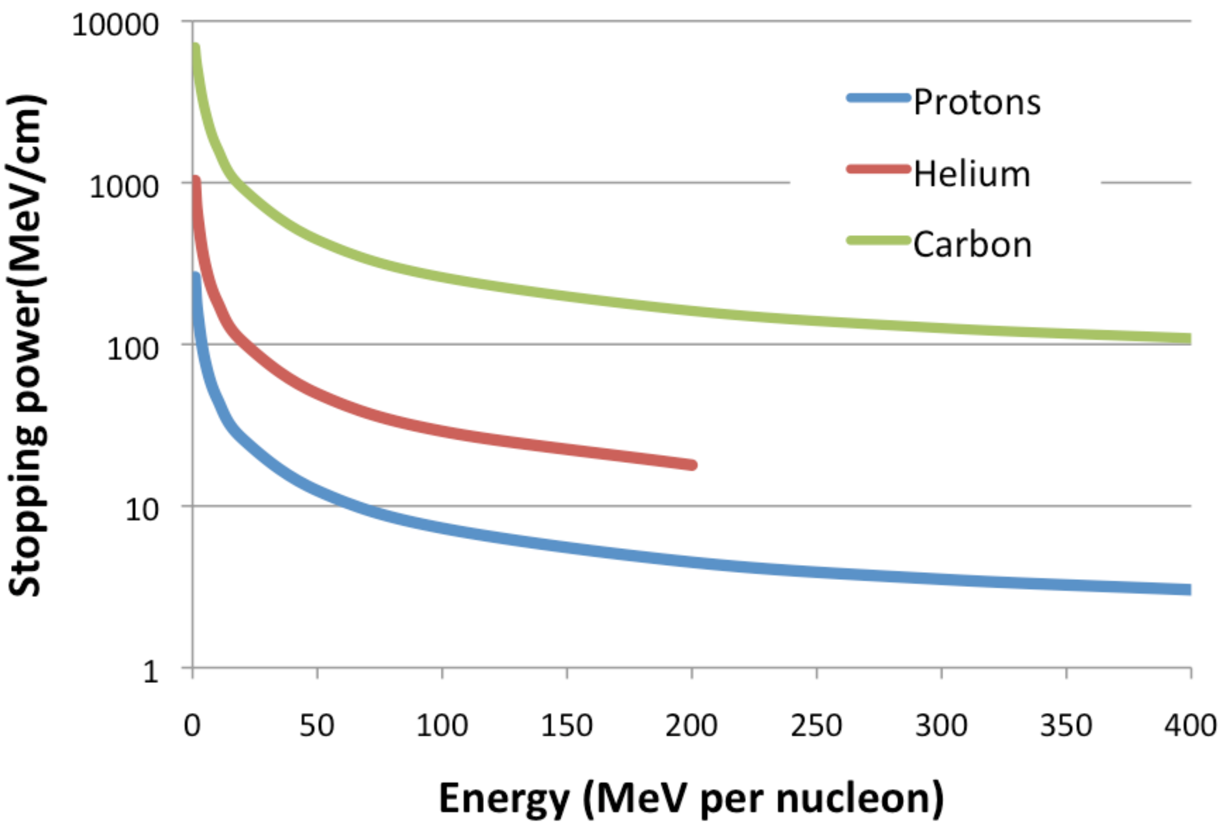
Analytical expression provided by the Bethe-Bloch equation

Property of the particle

$$-\frac{1}{\rho}\frac{dE}{dx} = K\frac{Z}{A}\frac{z^2}{v^2}\left[\ln\left(\frac{2m_e c^2}{I}\right)+\ln\beta^2-\ln\left(1-\beta^2\right)-\beta^2\right]$$

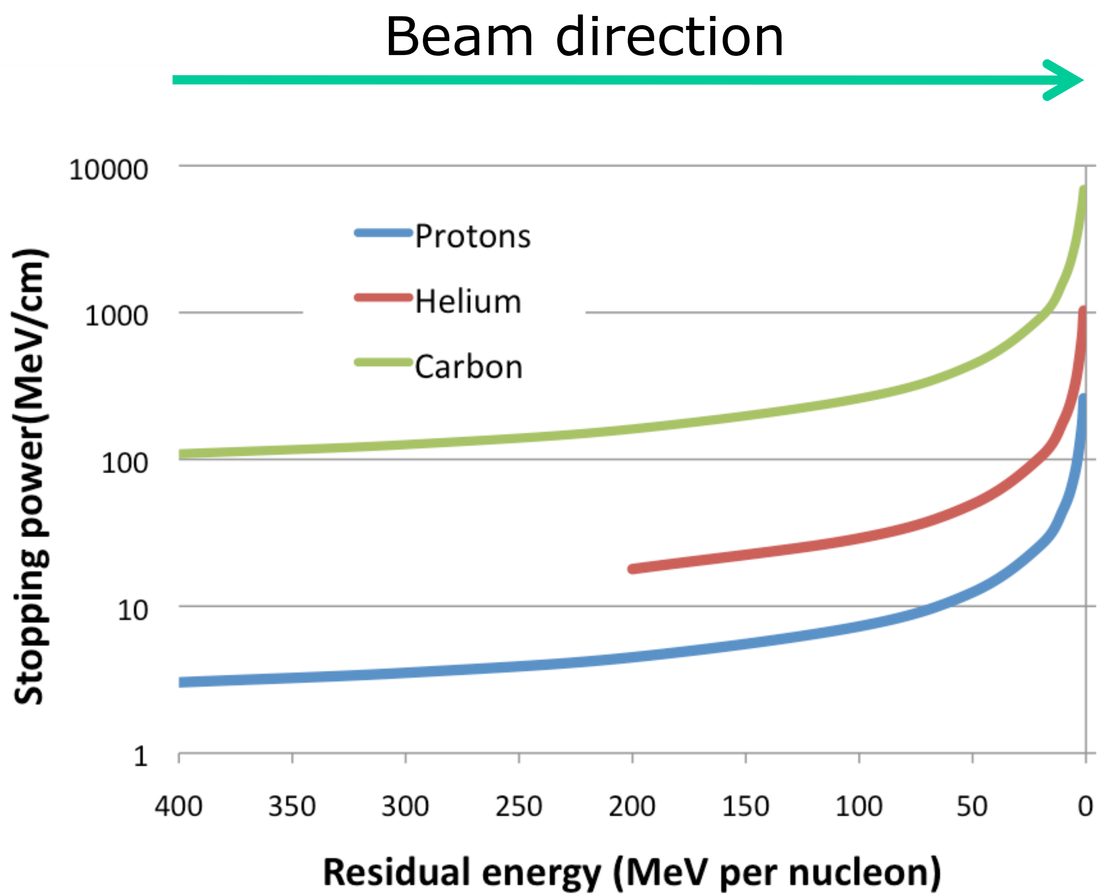
Property of the medium

Stopping power of therapeutic beams



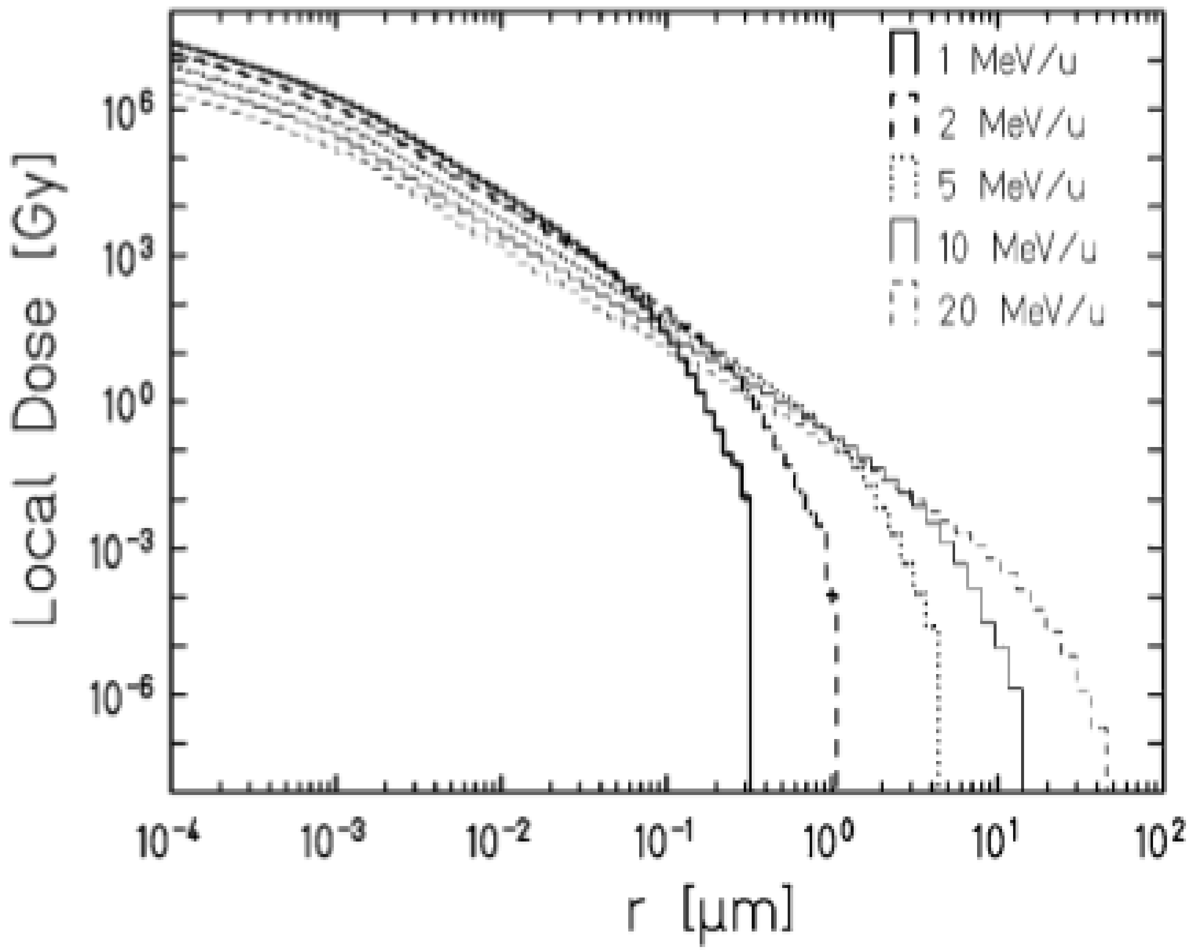
Different ions have different SP by *orders of magnitude*
Protons should not be considered high LET radiation

Stopping power of therapeutic beams

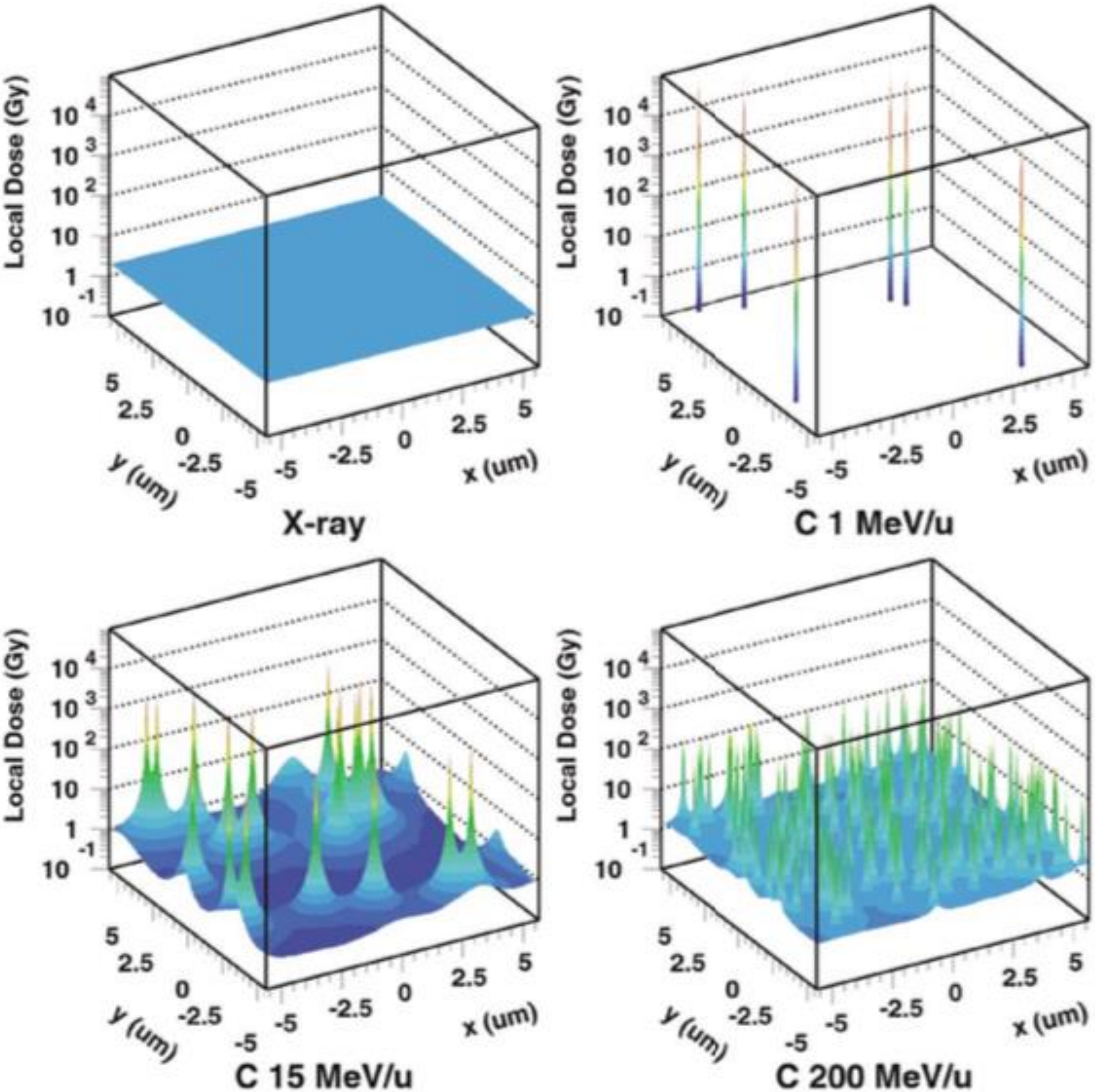


A dramatic increase in SP (only) happens at the very end

Carbon ion – radial track



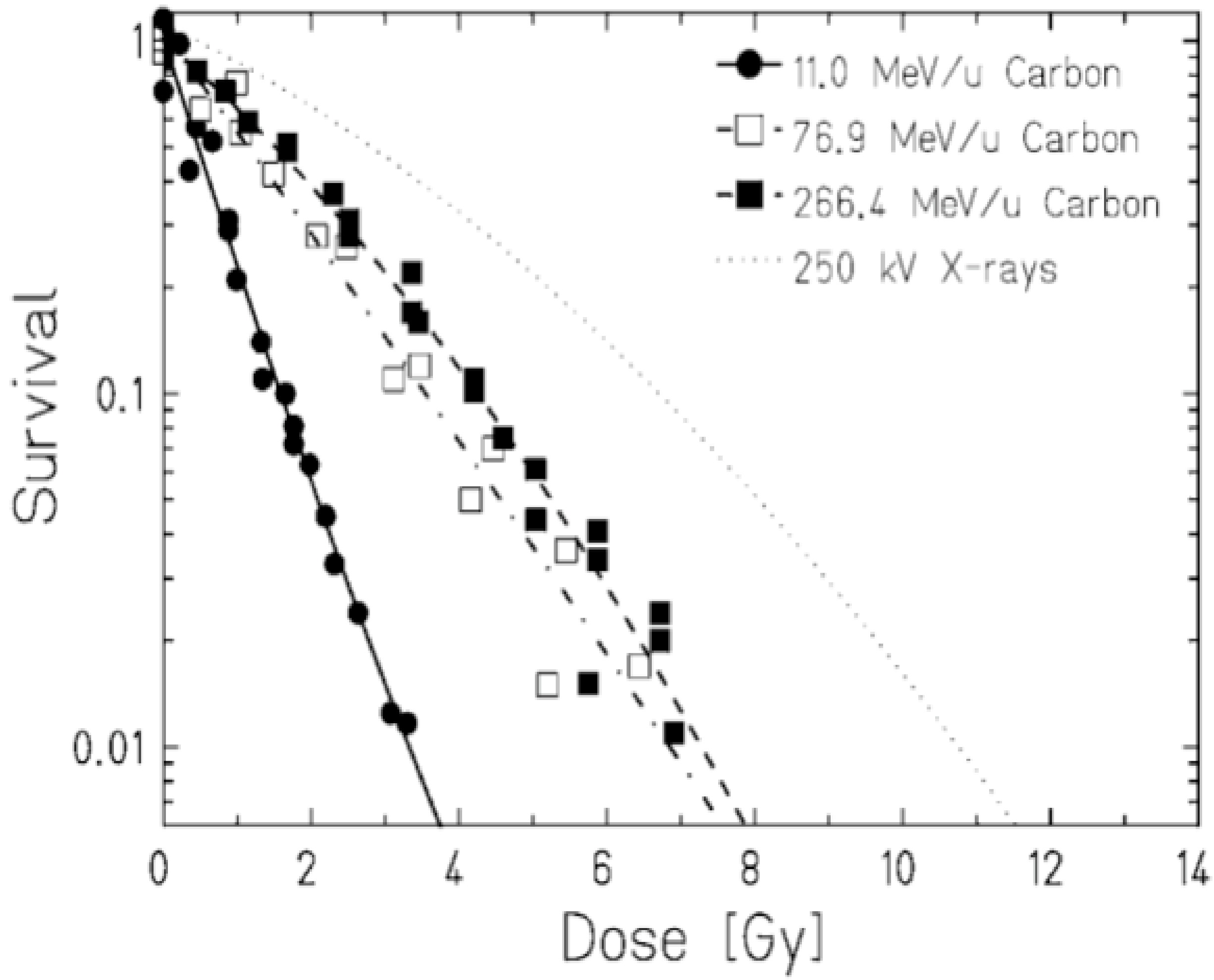
Scholz 2006



C vs X energy deposition @ microscopic scale

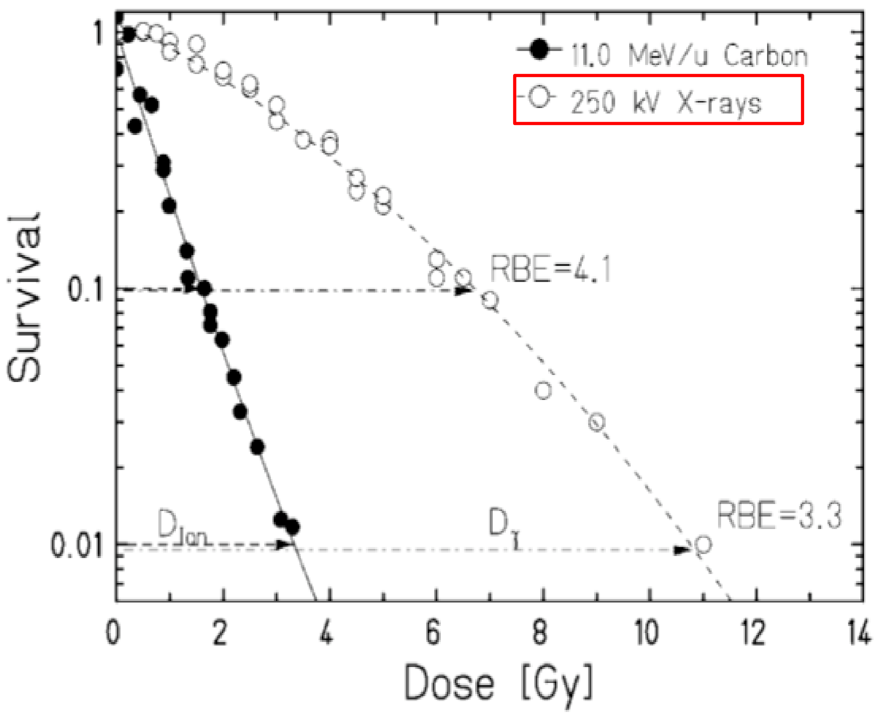
Kramer 2003

Differences in physics → differences in biological effect



Scholz 2006

Thus the concept of relative biological effectiveness (RBE)

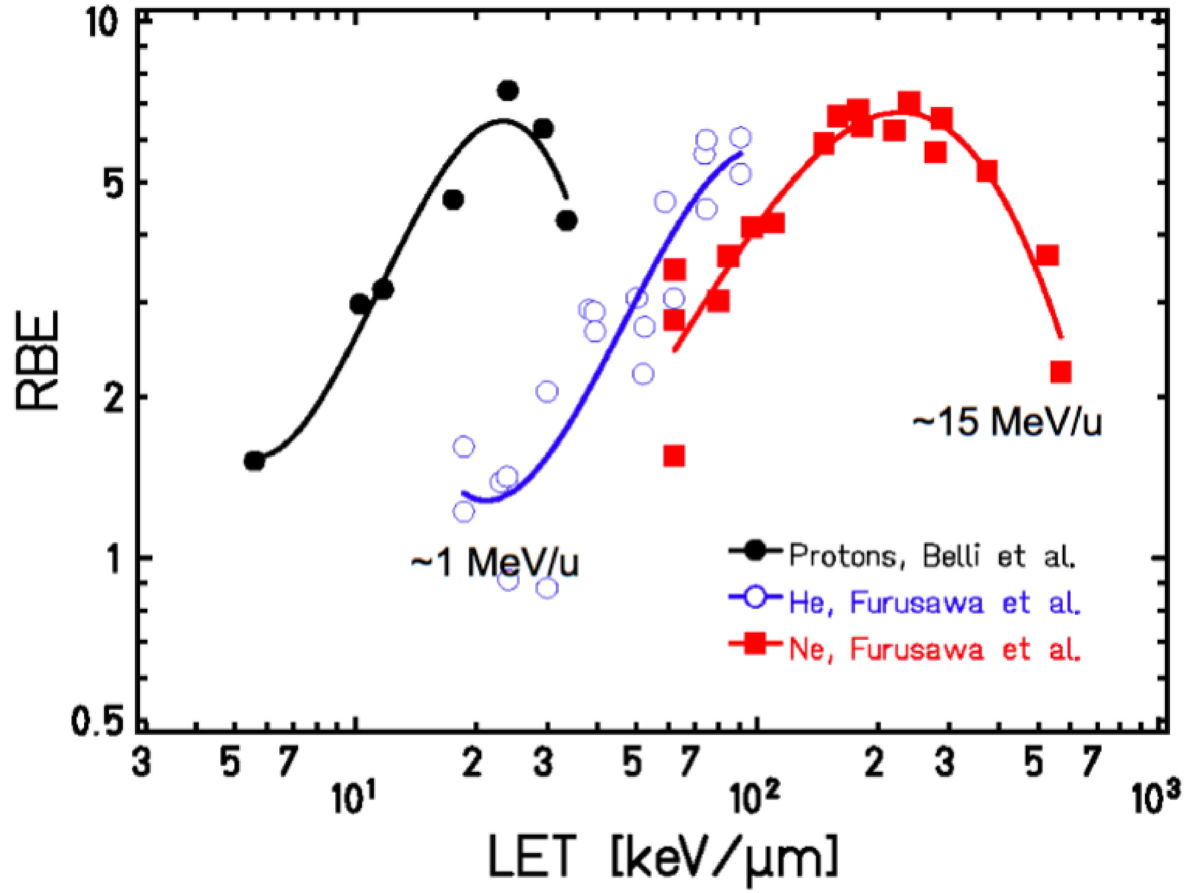


RBE is the response to a pragmatic need, but it’s a complication too, as it depends on endpoint, tissue type, dose per fraction, LET, type of particle.

NB1 Saying that “particle x has RBE y” is often a (gross) simplification.

NB2 RBE is a ratio, i.e. its variation may have to do also with variation in effect of the reference radiation

RBE variations between and within particles

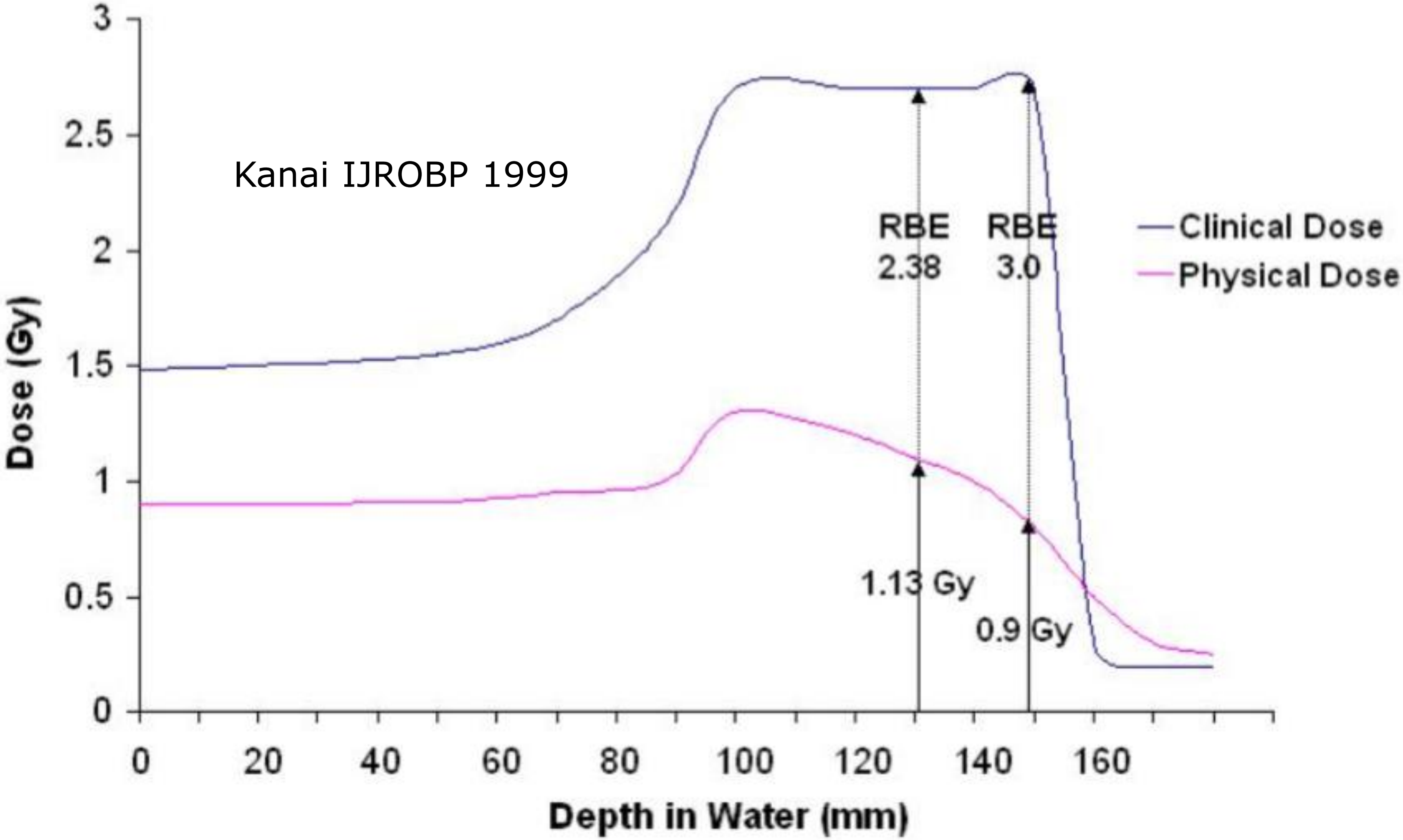


Paganetti

At higher LET, saturation effects → RBE decrease.

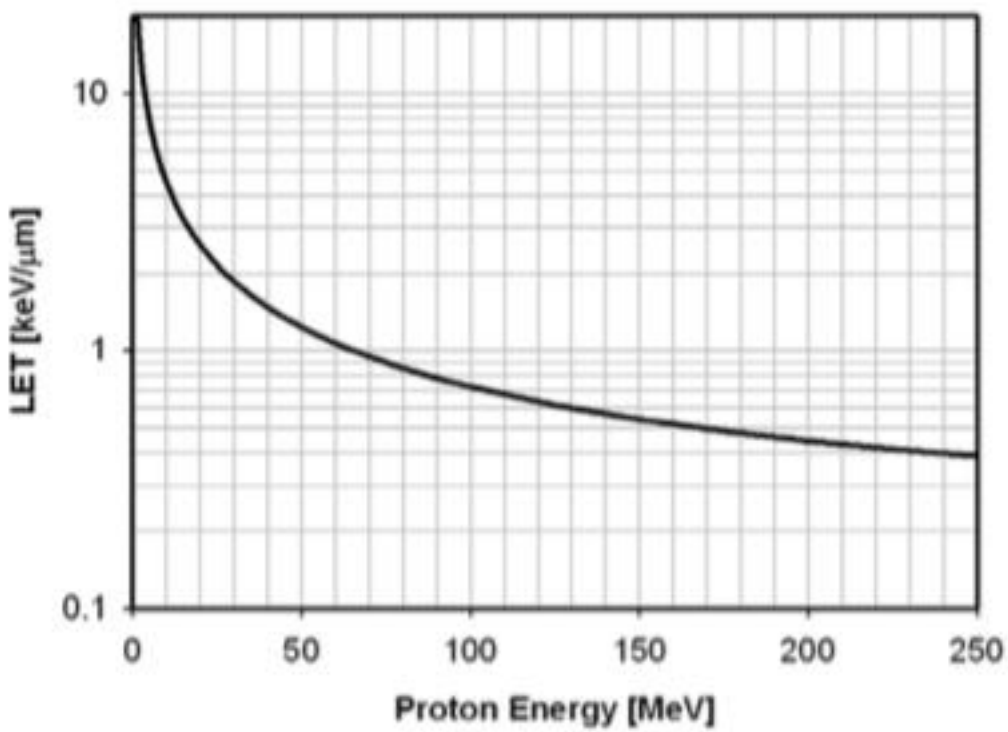
What matters is not high vs low RBE *per se*
but where the RBE peak is with respect to the dose peak

C ions – Example of physical vs biological dose



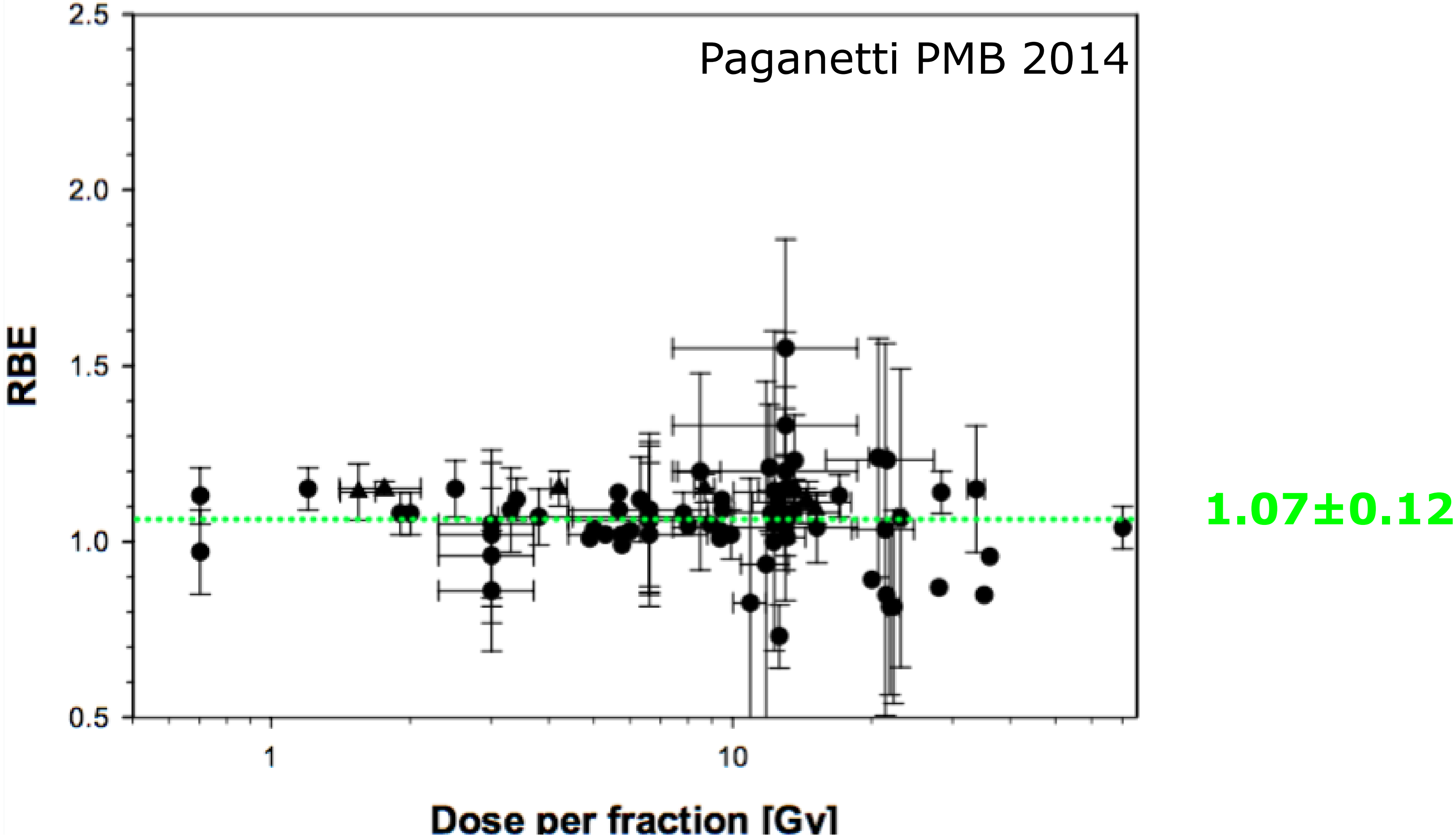
(One additional reason why particle therapy may seem (very) uncertain is that the biological effect is included in the prescription, unlike in XRT)

Protons - LET vs energy vs range



E (MeV)	dE/dx (keV/µm)	Range (mm)
50	1.24	22.2
20	2.61	4.2
10	4.56	1.3
5	7.91	0.36
1	26	0.024

Proton RBE vs dose per fraction – in vivo (animal studies)



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1946

Radiological Use of Fast Protons

ROBERT R. WILSON
Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reac-

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

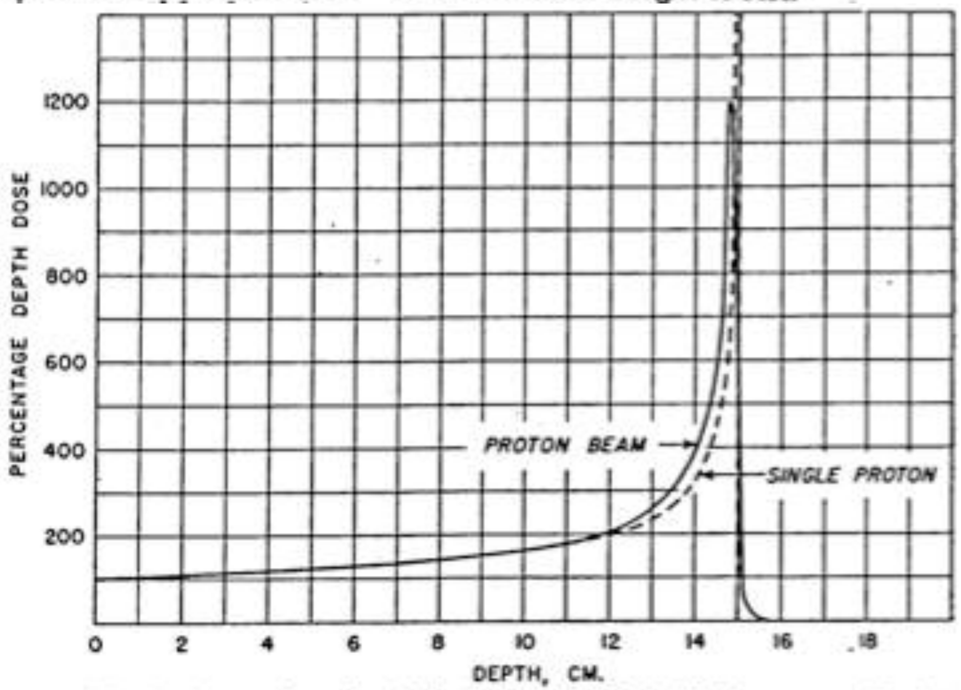
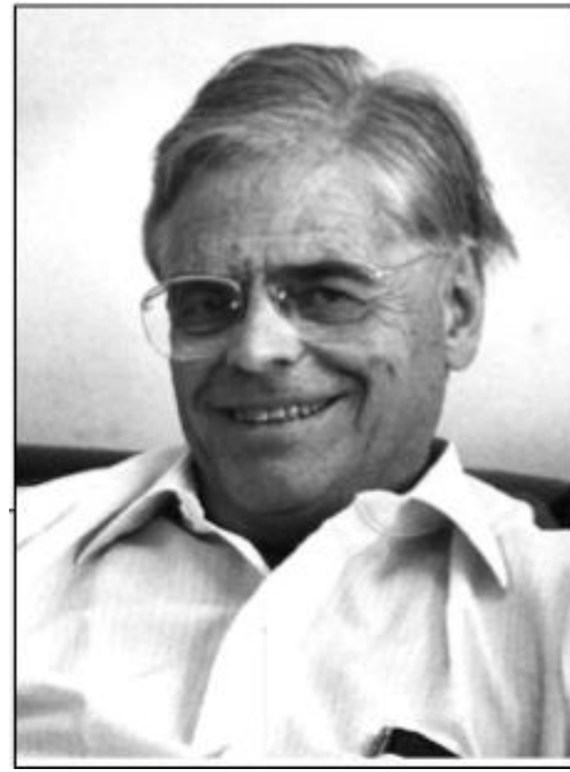
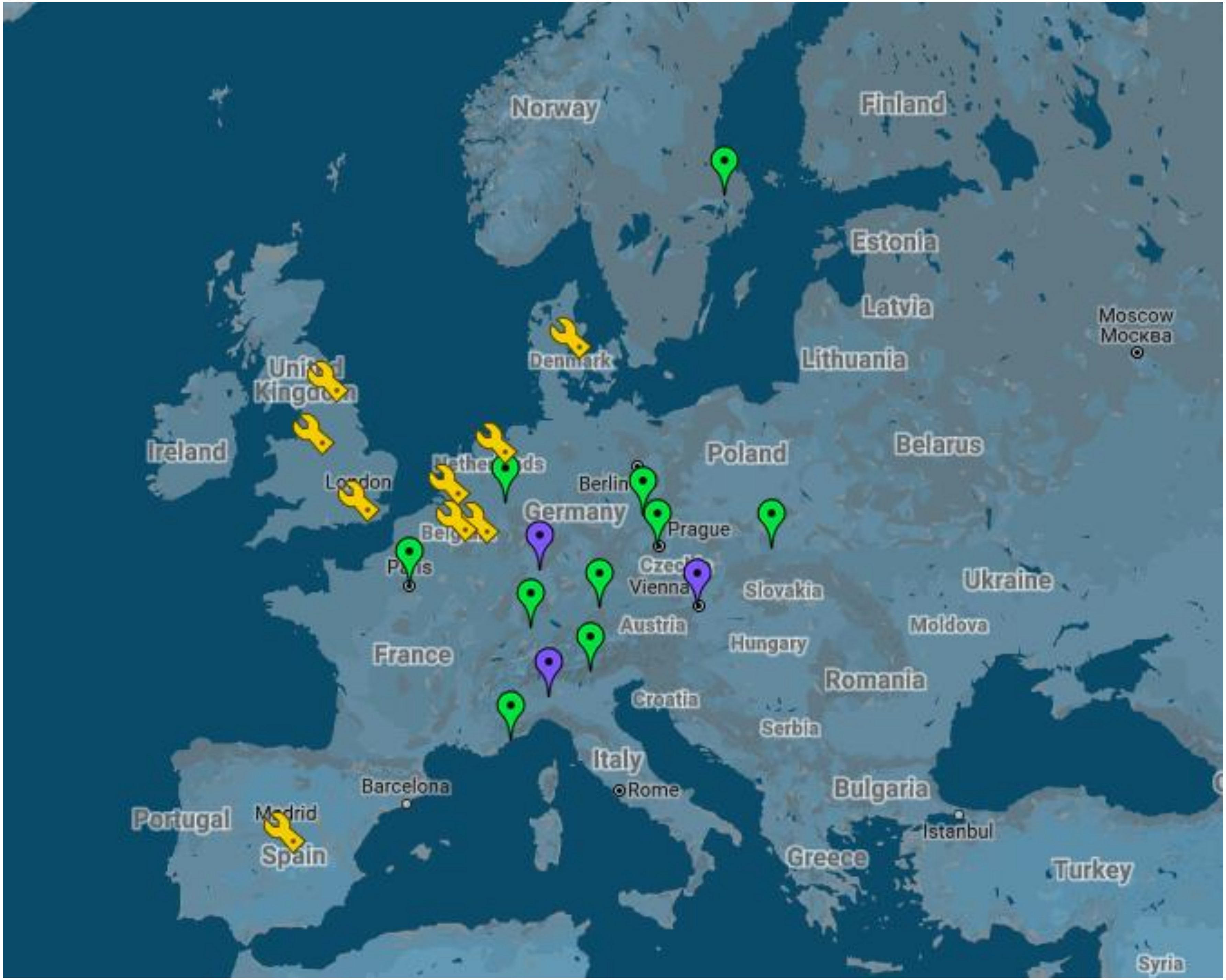


Fig. 2. The dotted curve shows the relative dose due to a single 140 Mev proton. The full curve shows qualitatively the depth dose curve for a beam of 140 Mev protons in tissue.

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Lithuania
Moscow
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Netherlands
London
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Germany
Prague
Paris
Czechia
Vienna
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Ukraine
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Hungary
France
Romania
Croatia
Serbia
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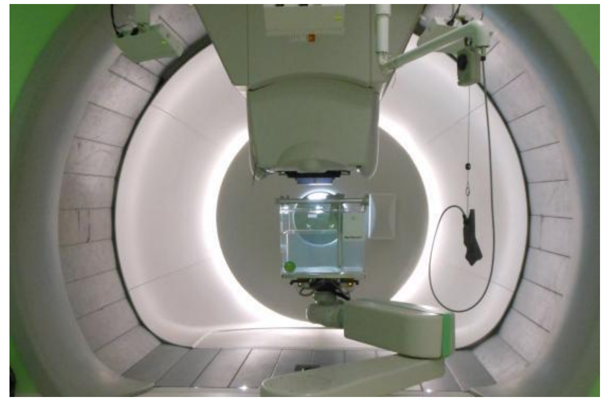
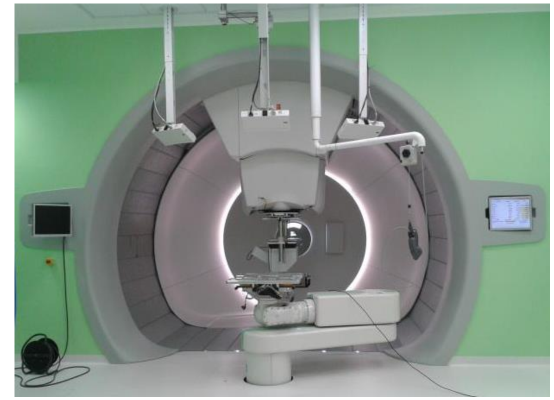
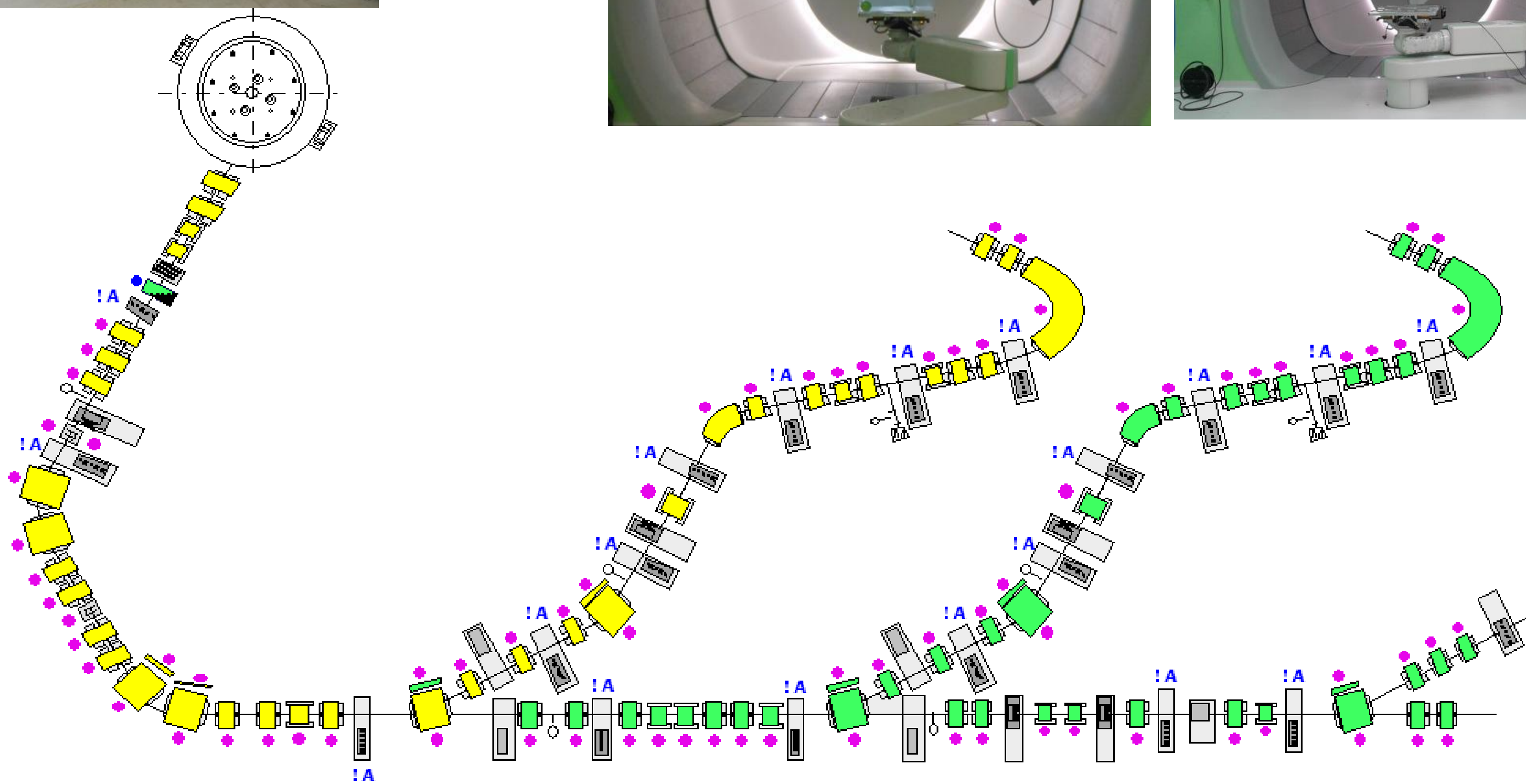
Bulgaria
Portugal
Madrid
Spain
Istanbul
Greece
Turkey
Syria

Layout of a PT centre (Trento, IT)







Layout of a Carbon ion centre (Heidelberg, GER)


CAUTION
NO
STEP
ATTENZIONE
1

Cyclo in Trento key specs

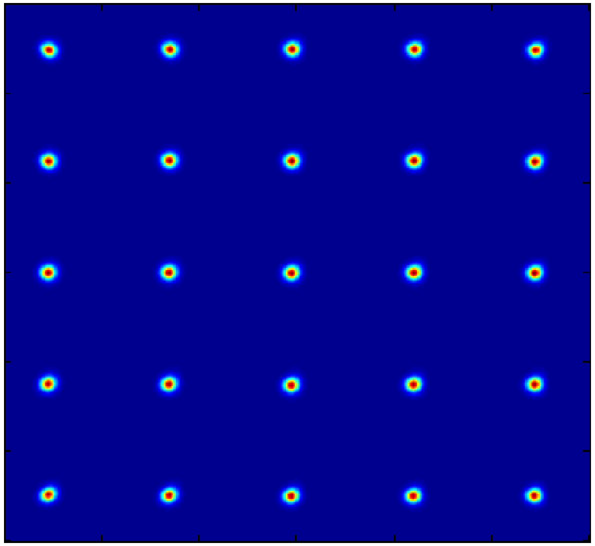
Isochronous cyclotron
235 MeV proton energy
300nA beam current
Typical efficiency:55%!*!

Conventional magnet coil:1.7-2.2T (fixed field)
RF frequency: 106 MHz (fixed frequency)
Dee voltage: 55 to 150kV peak

Approx weight: 220 tons
Diameter: 4.3m

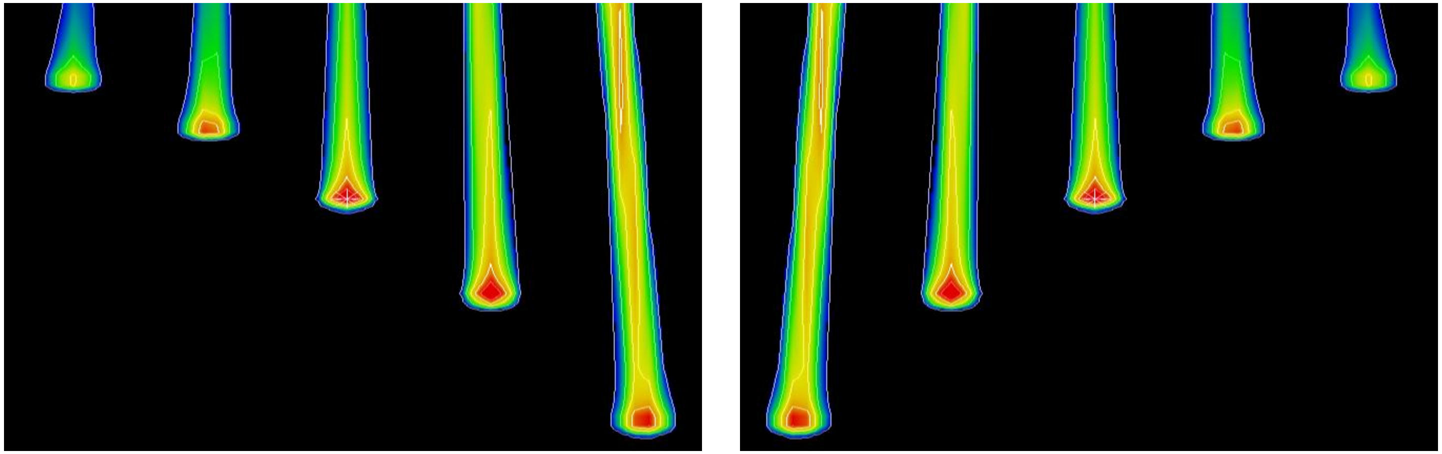

HA 15i
TUTTONOLEGGI

Pencil beam scanning (PBS)



Small pencil beams (a few mm)

Scanning magnets to position the beam in the transversal plane



Energy selection to control the peak depth

PBS is the gold standard for proton beam delivery

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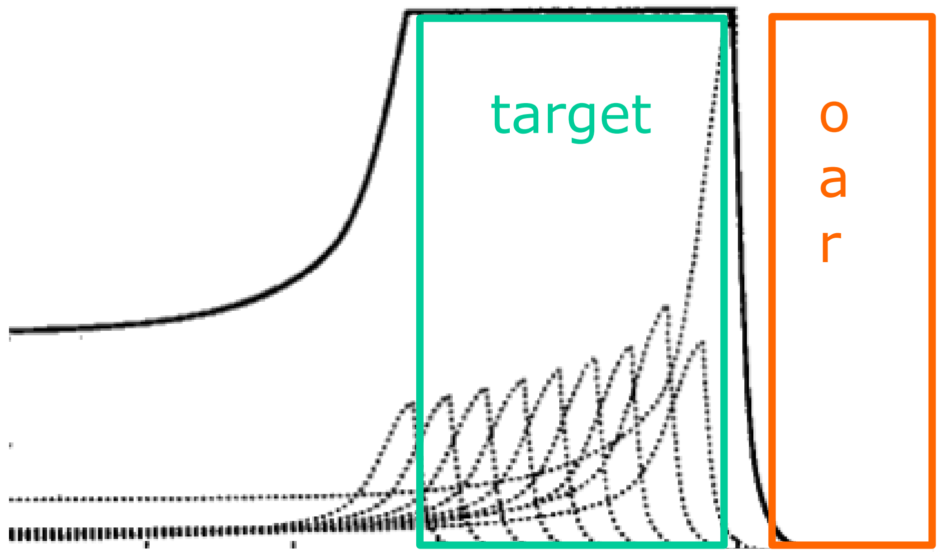
Ideal scenario



IF entrance dose is not a significant concern (e.g. target starts close to the surface)

IF we are confident about range *in the patient*

This is **the** solution

… Not so fast

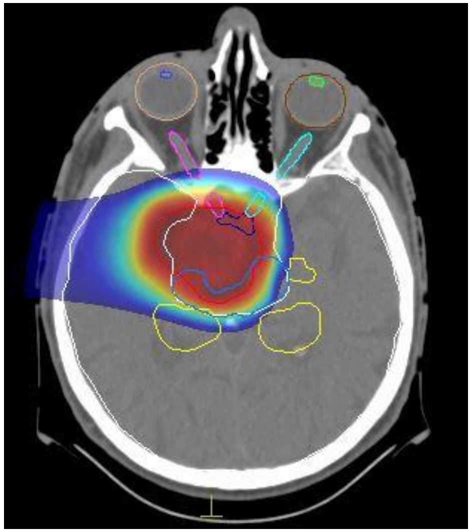
Range uncertainties are inherently part of proton therapy

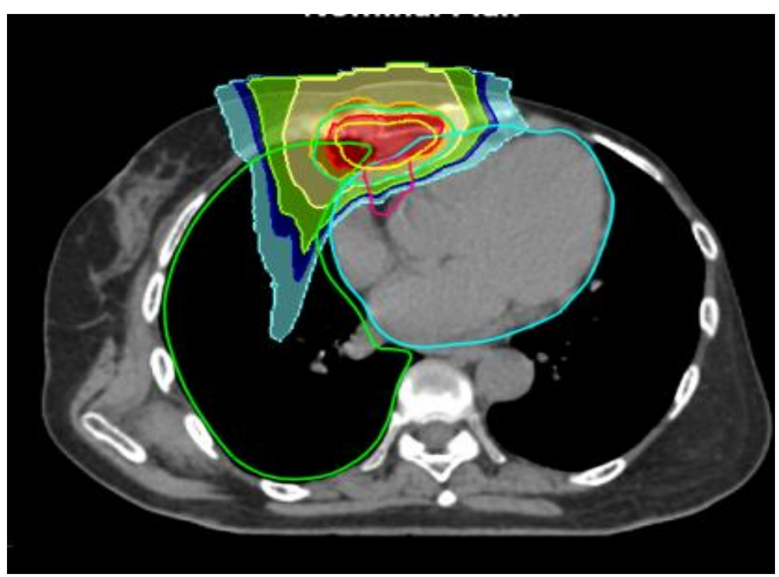
They **do not** have to do with fluctuations in beam energy at patient’s entrance (i.e. with proton range *in water)*.

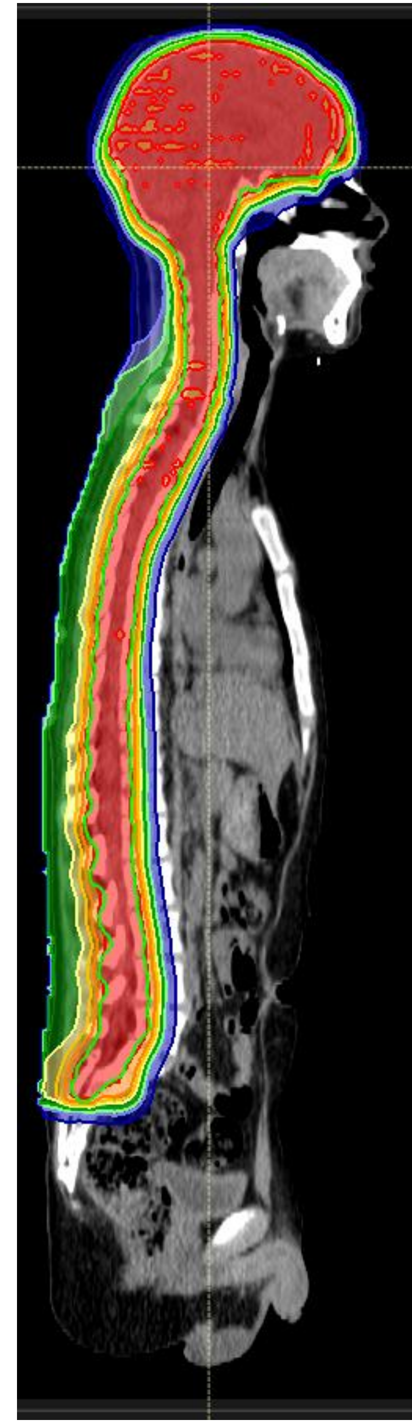
They **do** have to do with proton range *in the patient*, i.e. with differences between planned and actual anatomy density distribution due to

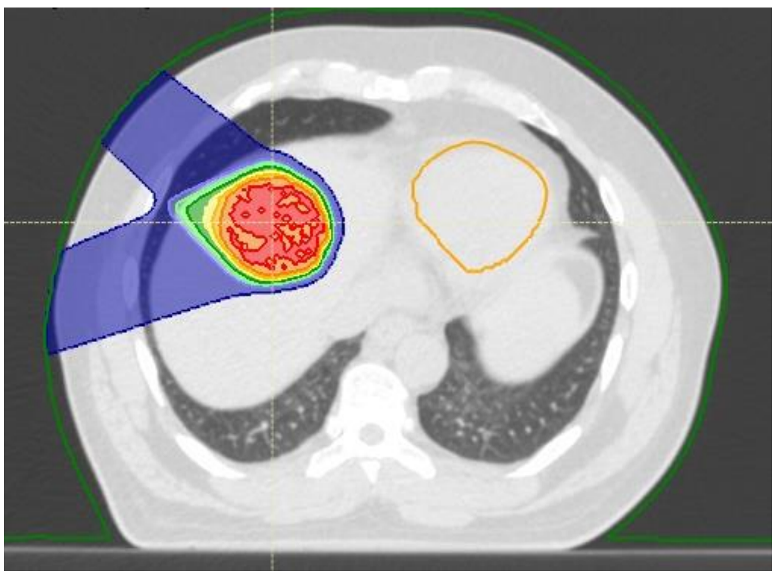
- ✓ Wrong range estimation at treatment planning and/or
- ✓ Set up errors and/or
- ✓ Organ motion and/or
- ✓ Anatomy changes and/or

The distal dose falloff is a powerful tool, but it must be used carefully



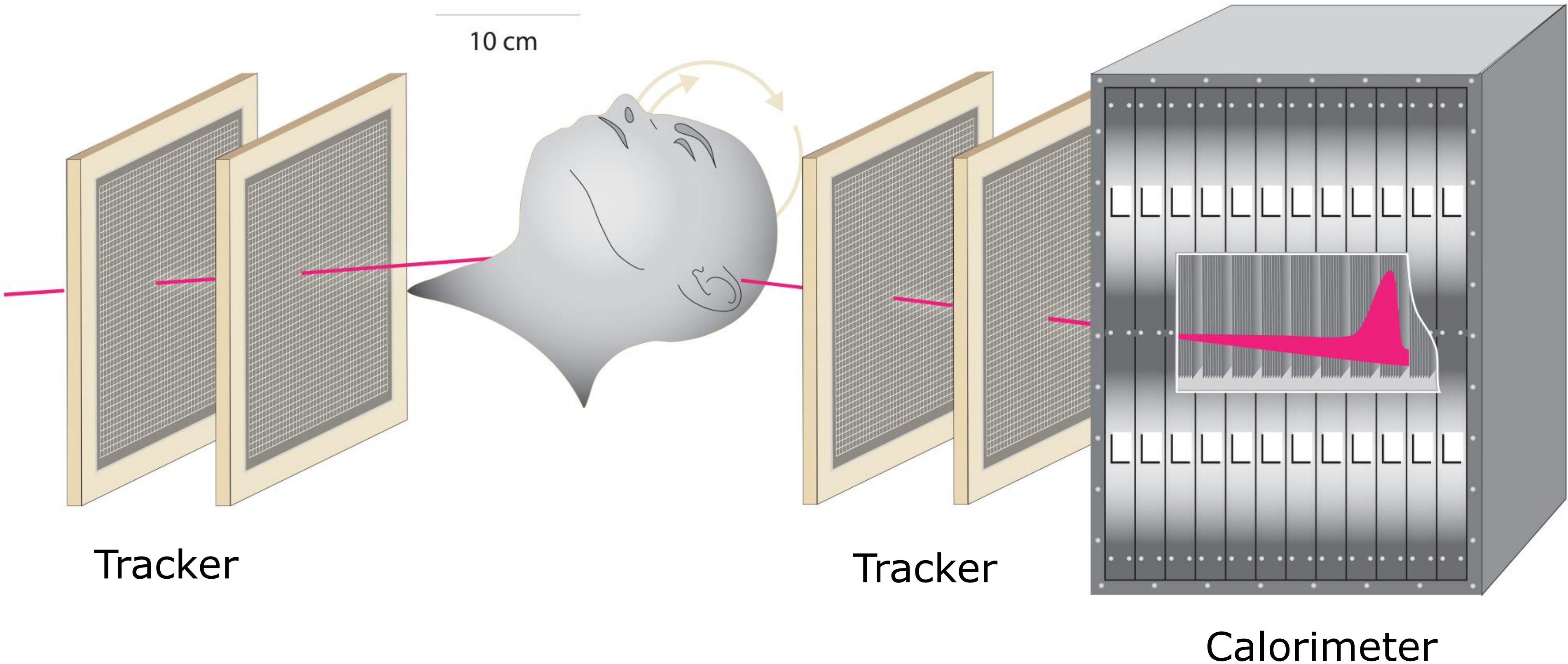






Model of the (static) patient for dose calculation

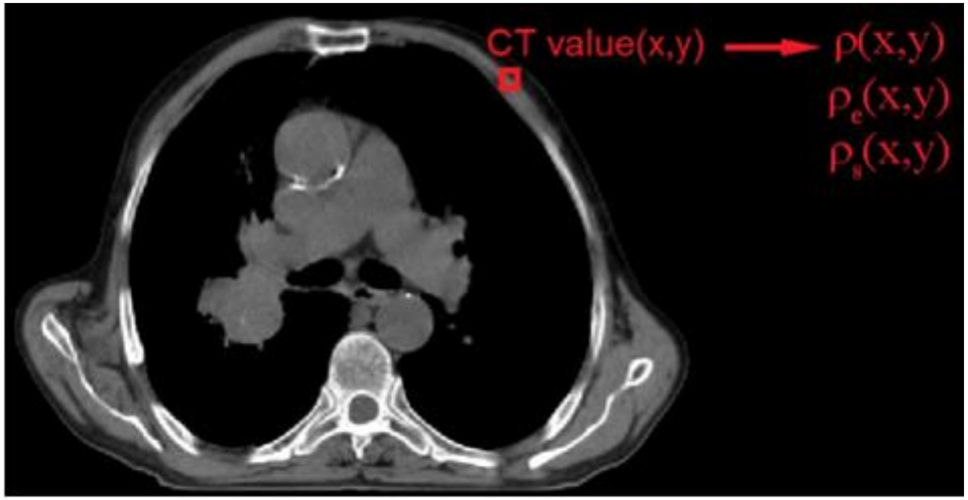
In theory, «proton CT» is what we'd like to have



Picture from fnal.gov

In practice, we start from CT scans

$$CT(x,y) = 1000\,\frac{\mu(x,y) - \mu_{water}}{\mu_{water}}$$



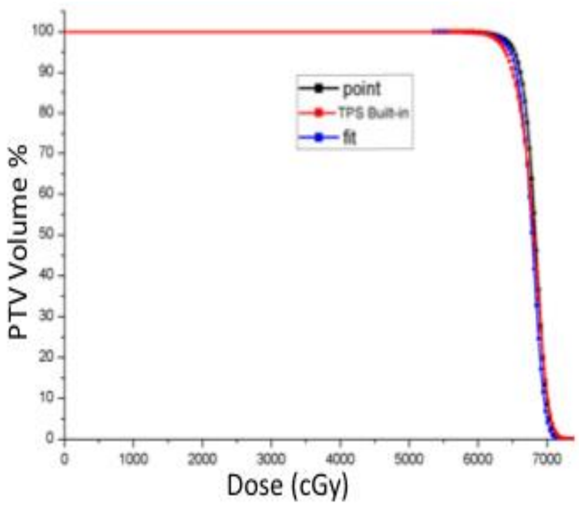
$$\rho_e = \frac{\rho N_e}{\rho_w N_e^w}$$

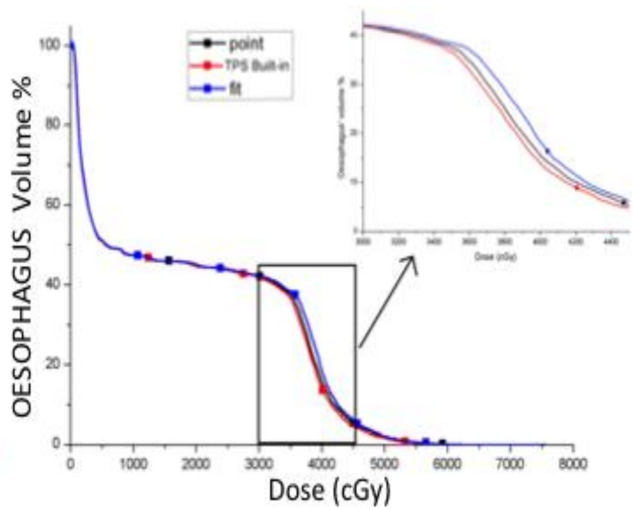
Photons

$$\rho_e = \frac{\rho N_e}{\rho_w N_e^w} \rightarrow SPR = \rho_e \frac{\log\left[2 m_e c^2 \beta^2 / I_m \left(1-\beta^2\right)\right] - \beta^2}{\log\left[2 m_e c^2 \beta^2 / I_w \left(1-\beta^2\right)\right] - \beta^2}$$

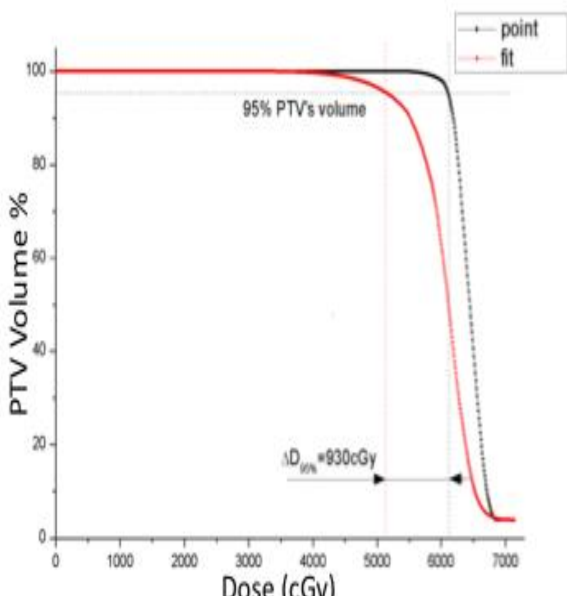
Protons

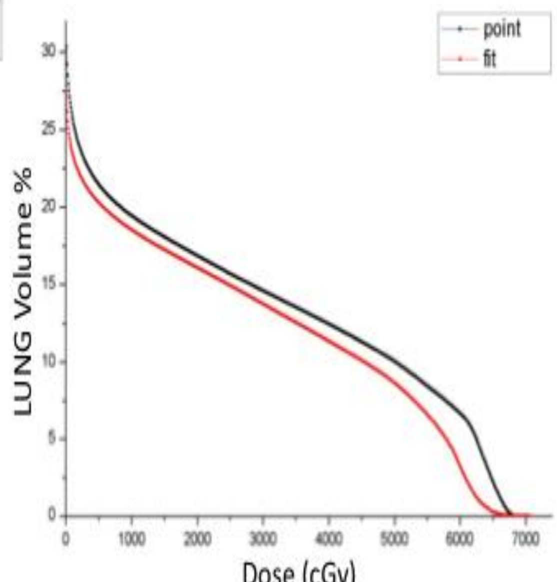
Impact of different calibration curves



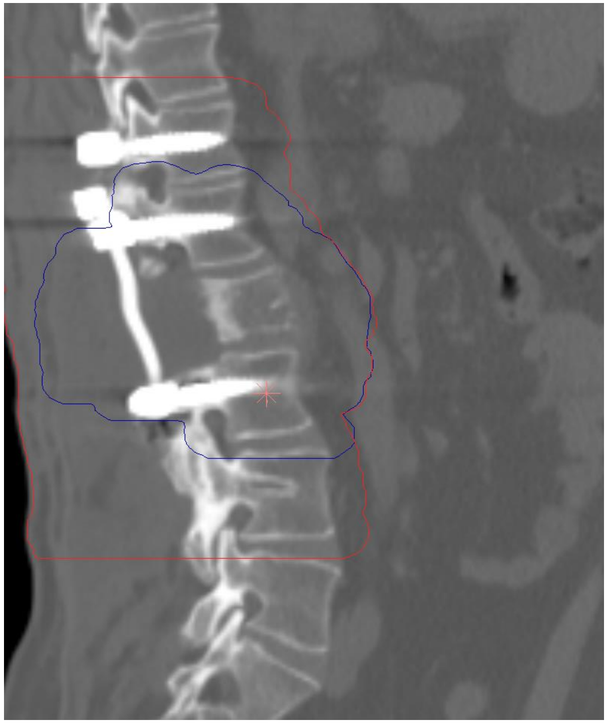


XRT





PT



(Large) surgical implants quite common in PT patients

Issues with image quality, SPR estimation and dose calculation

When possible, implants material should be characterized with phantoms

Different PT centers have different policies about what (not to) treat

Dental implants may be very problematic too

Dose calculation

X-rays vs p+ dose calc - source model

Photons

Broad energetic spectrum

The beam interacts with quite a few objects before reaching the patient

Beam (or segment)-specific beam modifiers

Protons (PBS)

(quasi) monoenergetic spectrum

Nice and gaussian at the nozzle exit

Steered by magnets, not shaped by iron

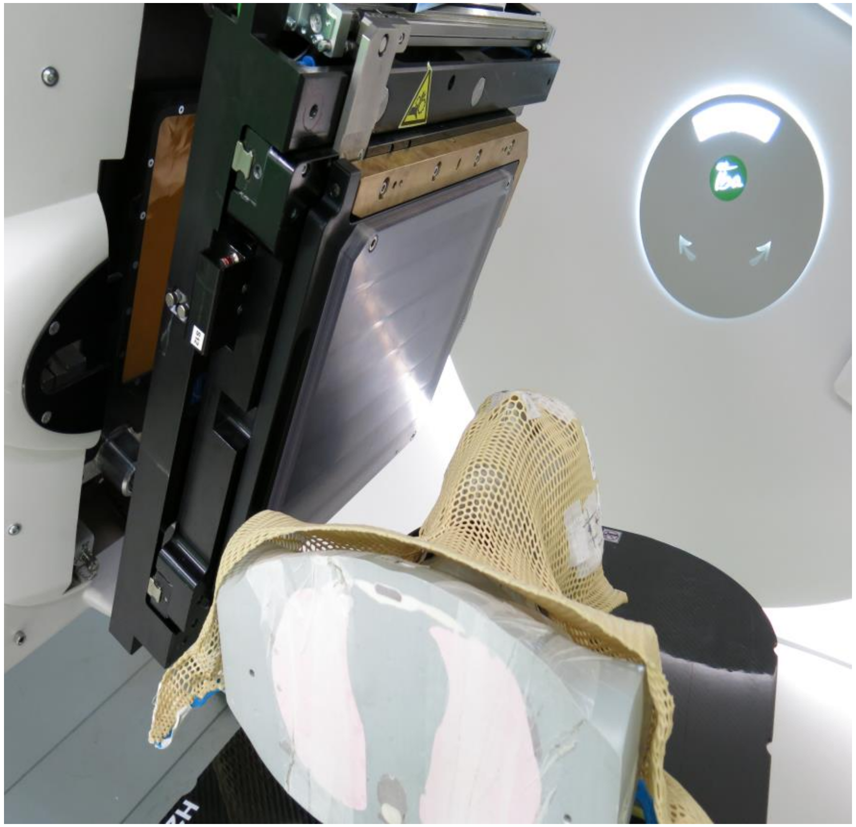
For deep seated targets, modeling a proton PBS beam is actually simpler than modeling a photon beam

Beam scanning & beam modifiers

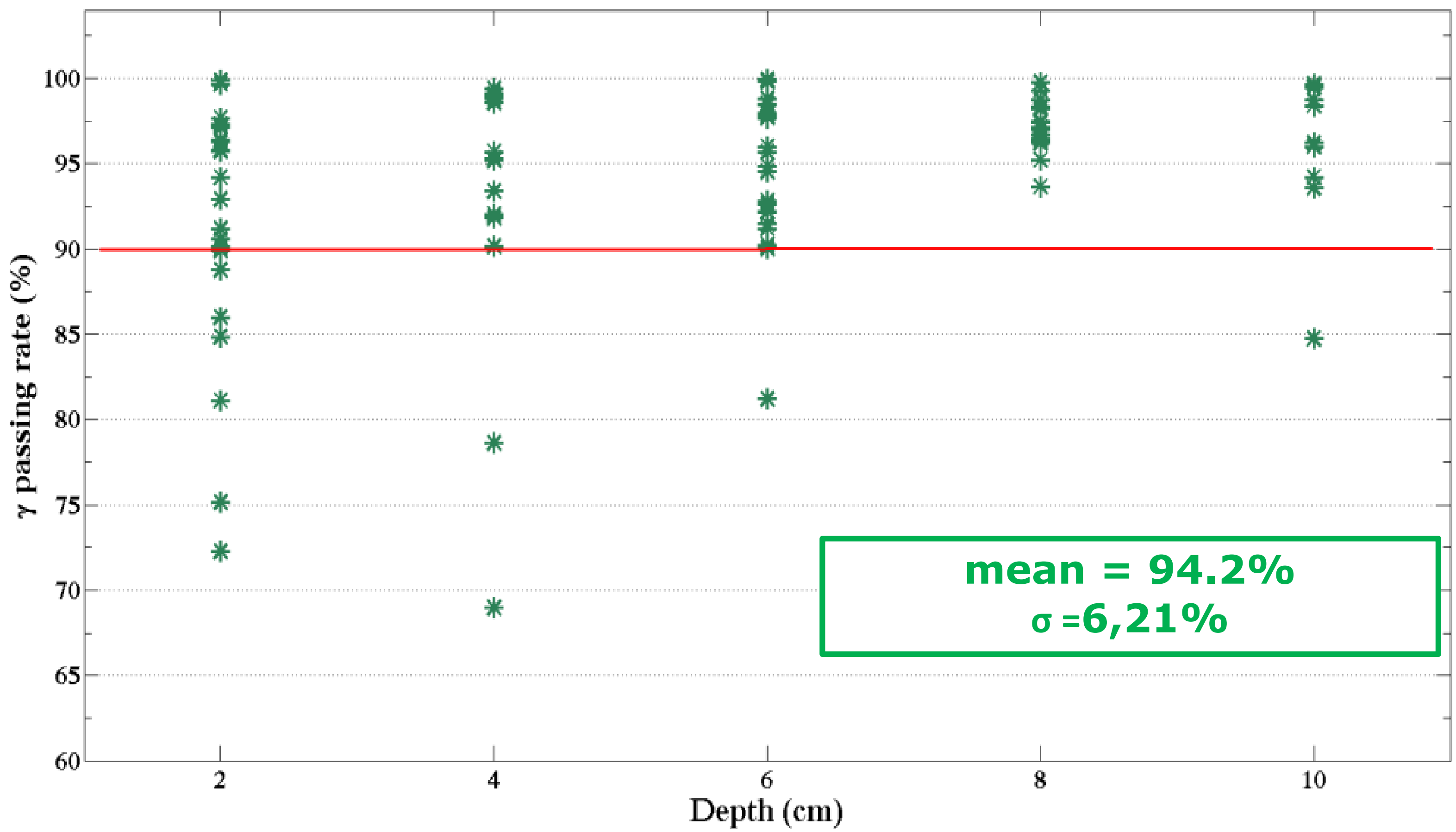
(PBS is not entirely patient-specific hardware free)

Any scattering material between the last focusing element and the patient makes dose calculation difficult

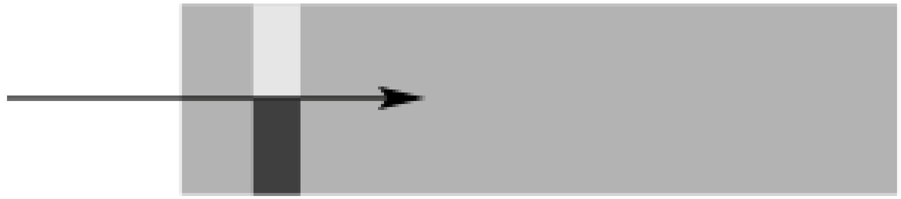
The thinner the preabsorber, and the smaller the airgap, the better.

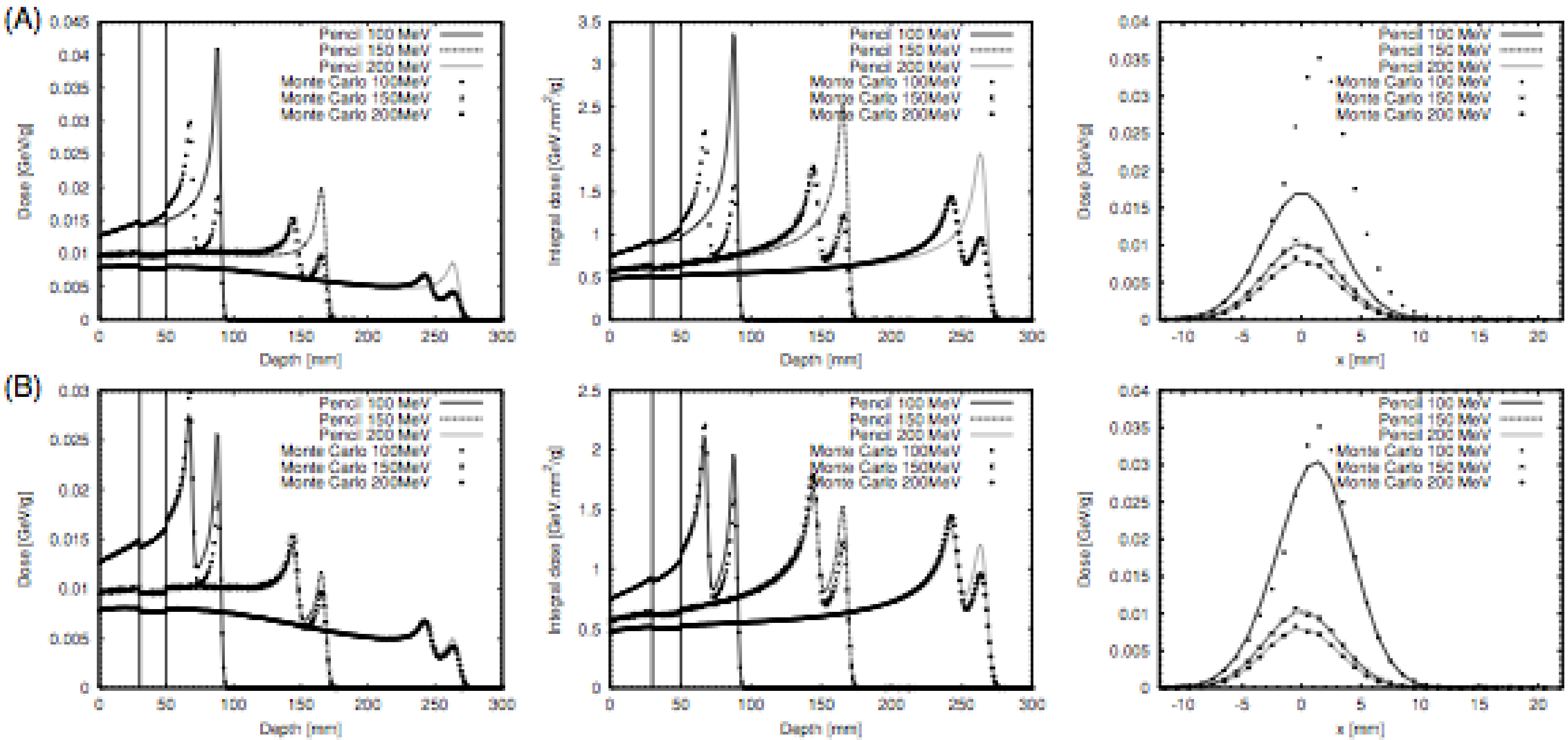


Gamma passing rates vs. depth in homogeneous medium (i.e. issues with the source model)



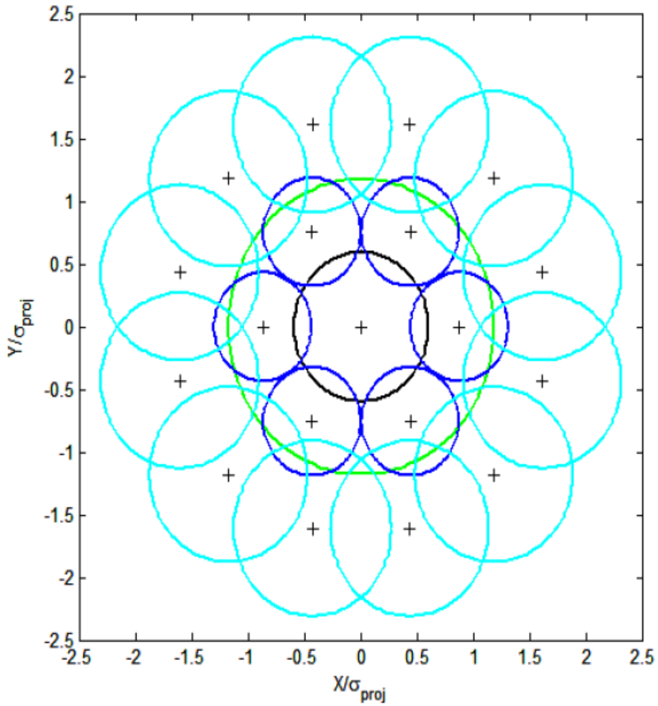
Dose calculation in heterogeneous medium

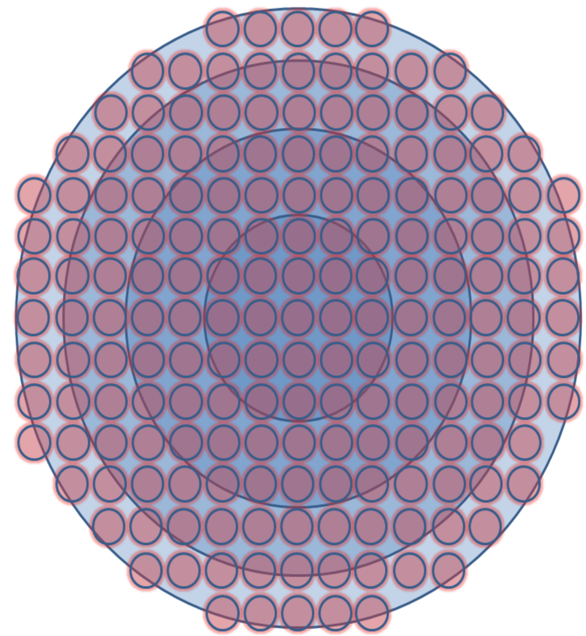




Soukup et al, PMB2005

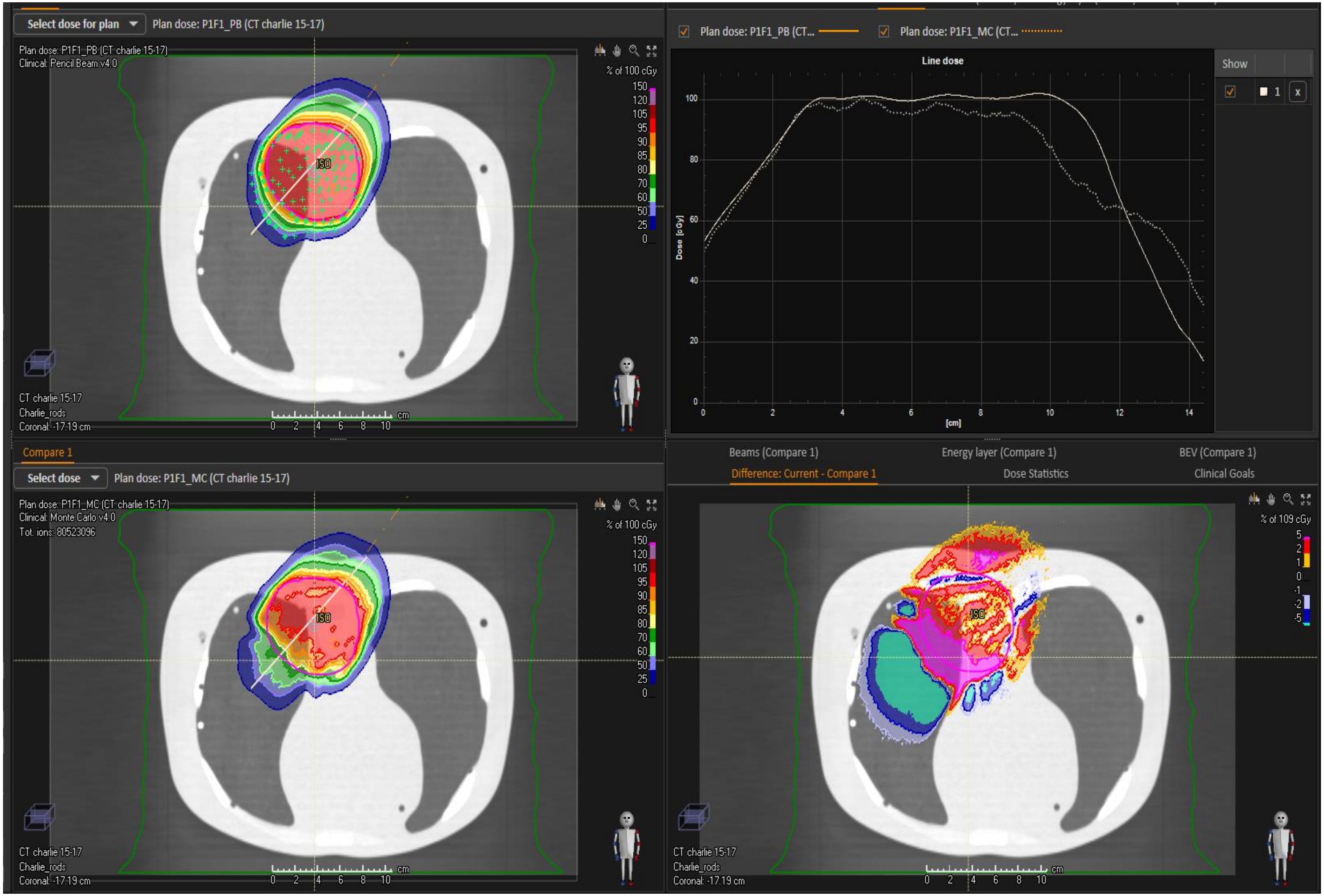
"Spot decomposition"





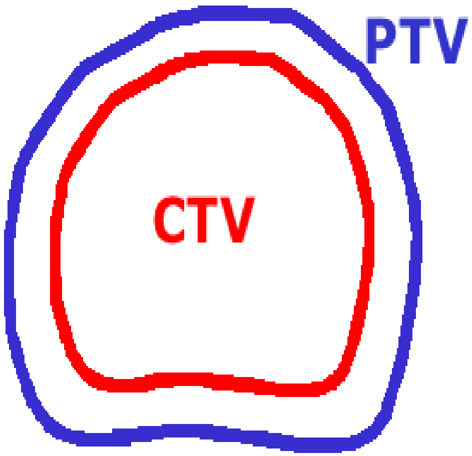
Accurate raytracing of the spot in the patient is crucial to achieve accurate dose calculation

PB vs MC in lung phantom



Charged particles planning & geometrical uncertainties

PTV and particles are not good friends



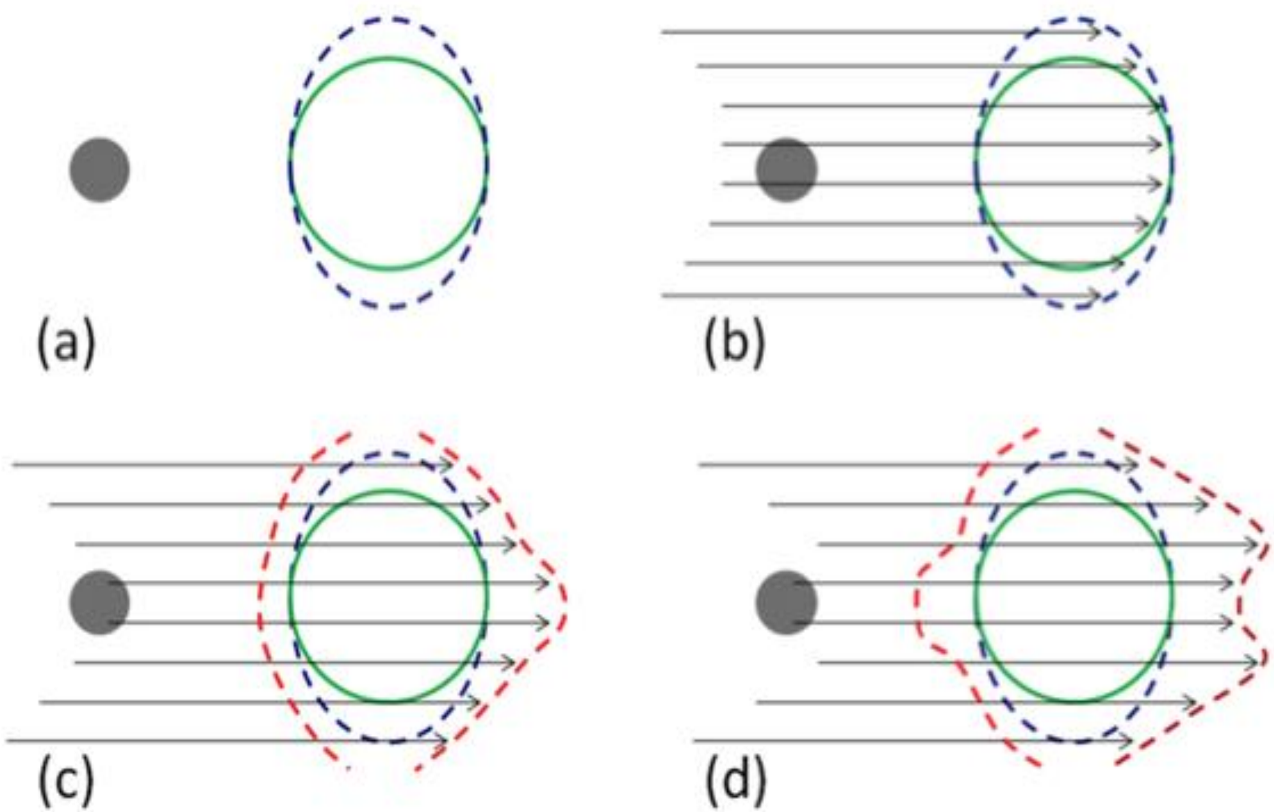
The Planning Target Volume approach works when

a) Margins are defined correctly vis à vis the geometrical uncertainties

b) The dose is as homogeneous as possible

c) *The dose is invariant after anatomy translations/rotations*

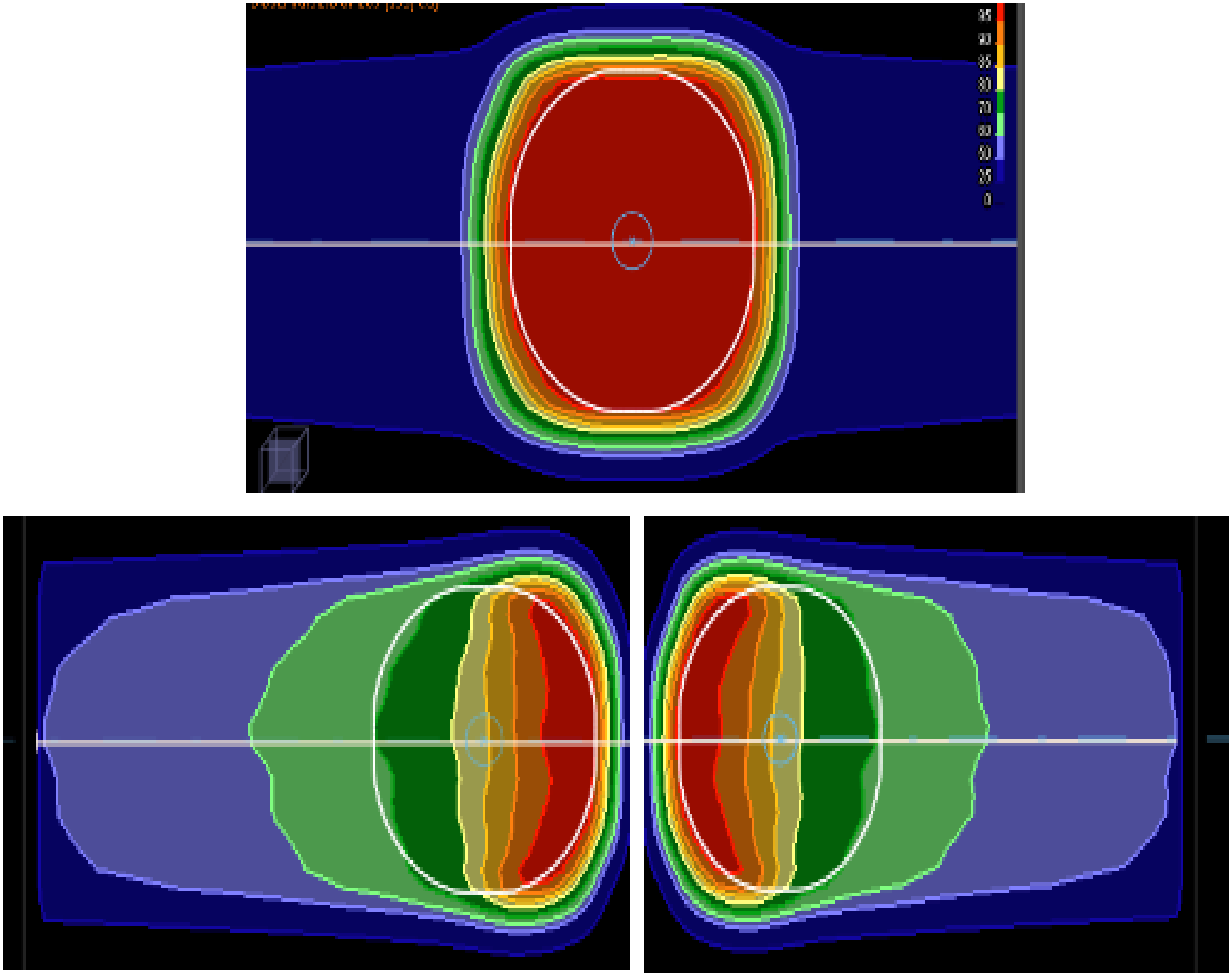
Margin-based approach in particles for single field optimization (SFO)



Park IJROBP 2012

Field-specific target volume taking into account the combined effect of range and setup uncertainties

Margins more problematic in MFO/IMPT



MFO & geometrical uncertainties

In MFO planning there isn't an *explicit* method to

- Handle geometrical&range uncertainties
- Place the dose gradients at specific positions
- Decide whether lateral penumbra or distal fall-off should be used

In theory there is no other way to explicitely include them in the optimization (a.k.a. 'robust optimization')

(As always) clinical practice does not match theory
(as always) because of a mix of good and bad reasons

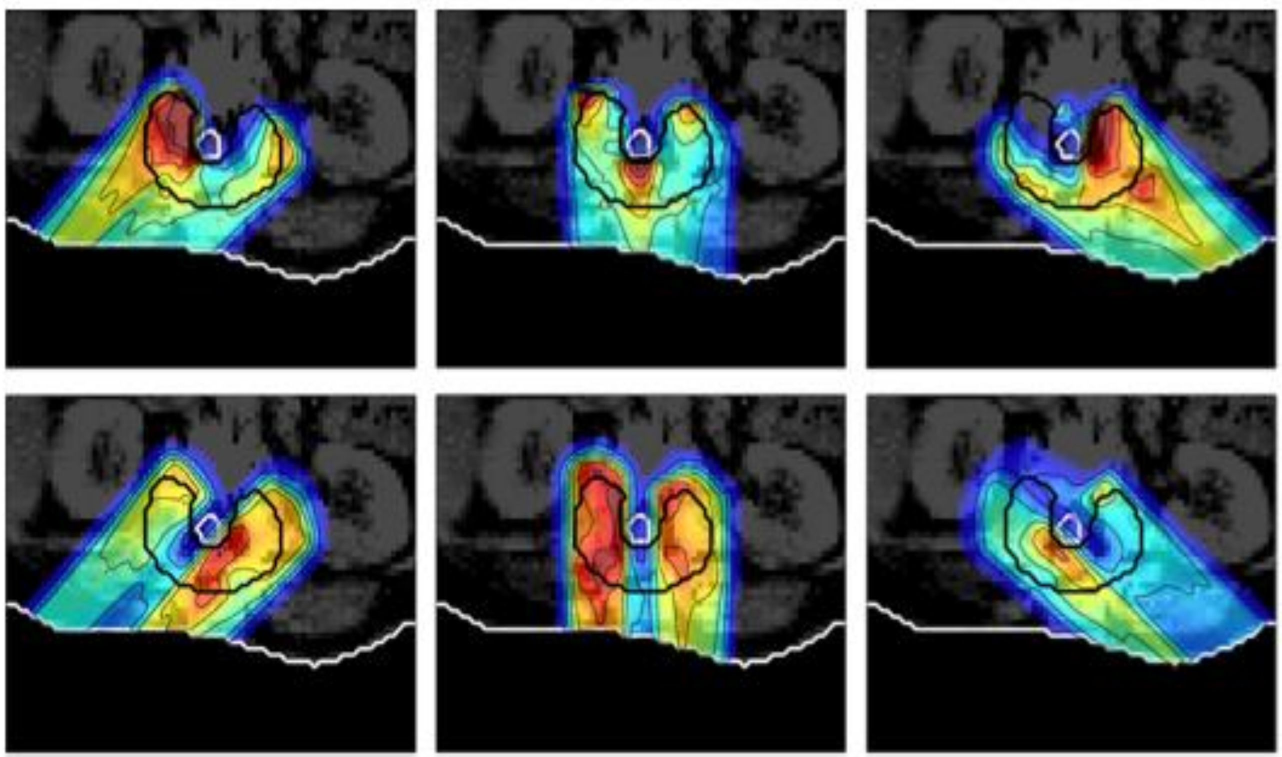
Worst case optimization

1) Calculate the worst case dose distribution D_w
2) Optimize

$$\widetilde{F}(\vec{w}) = F\left(D_{nom}(\vec{w})\right) + p_w F\left(D_w(\vec{w})\right)$$

p=0

P=1



5mm Range Uncert.

Pflugfelder PMB 2008

Min-max optimization

Set up errors and **range uncertainties** can be handled

Instead of optimizing the nominal scenario

$$\underset{x}{\text{minimize}} \quad f(d(x))$$

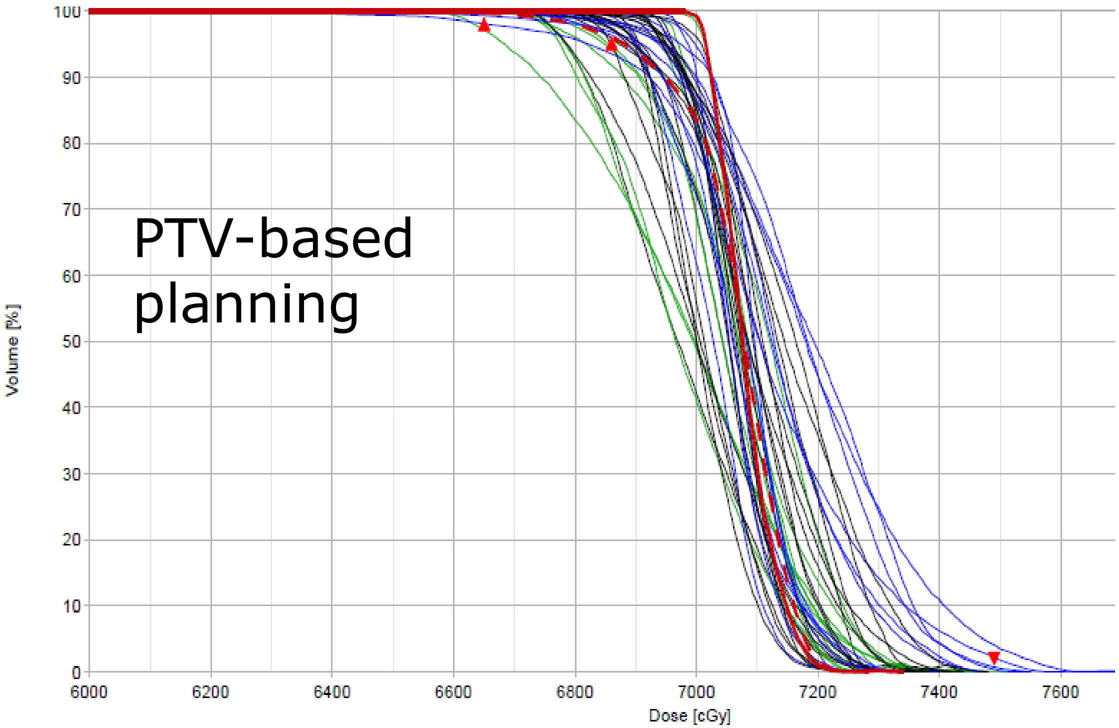
$$\text{subject to} \quad x \geq 0,$$

One 'minimizes the damage' in a realistic worst case scenarios

$$\underset{x}{\text{minimize}} \quad \max_{s \in S}\{f(d(x,s))\}$$

$$\text{subject to} \quad x \geq 0.$$

Fredriksson MedPhys 2011



Red: nominal
Black: 0% density variation
Blue: +3% density variation
Green: -3% density variation

MFO degeneracy helps in reducing the price of robustness

Robust optimization now implemented in commercial TPS

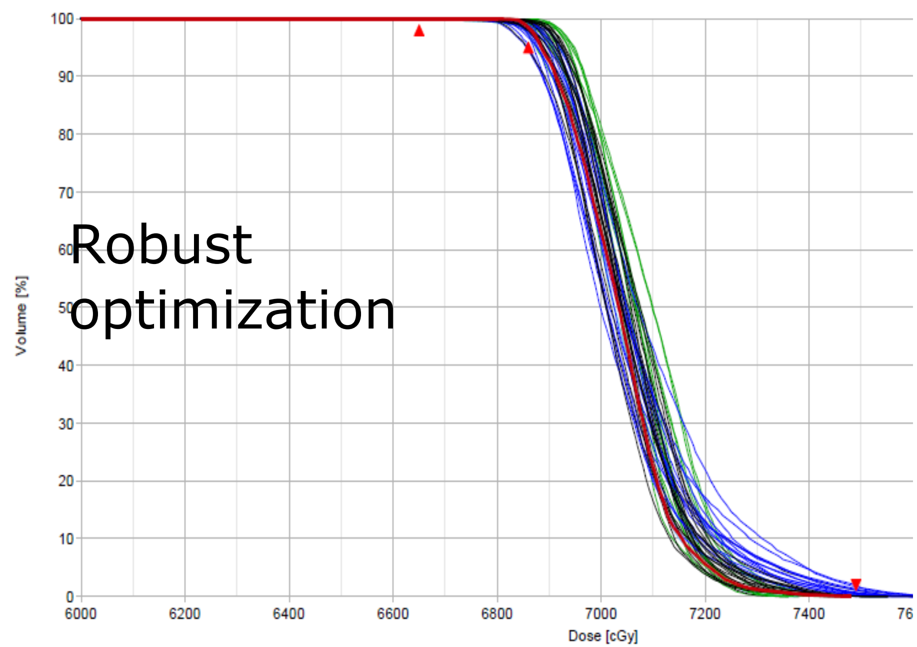
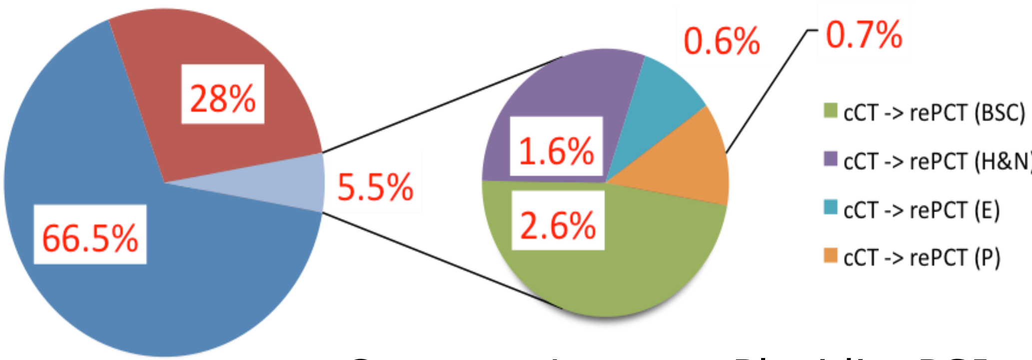


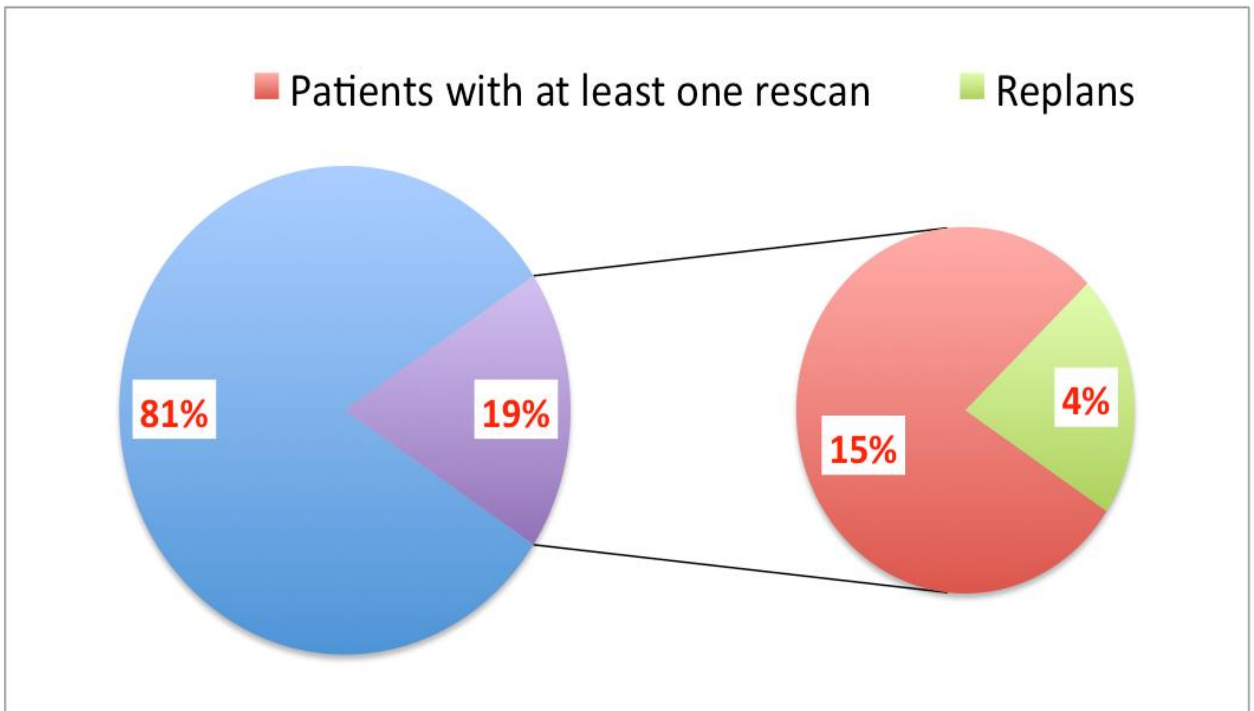
Image guidance and adaptive therapy

How much adaptive are we doing nowadays?



Courtesy Lorenzo Placidi - PSI

PSI
730 patients
66% BoS
14%H&N
Extracranial CNS 15%
Pelvis 3%

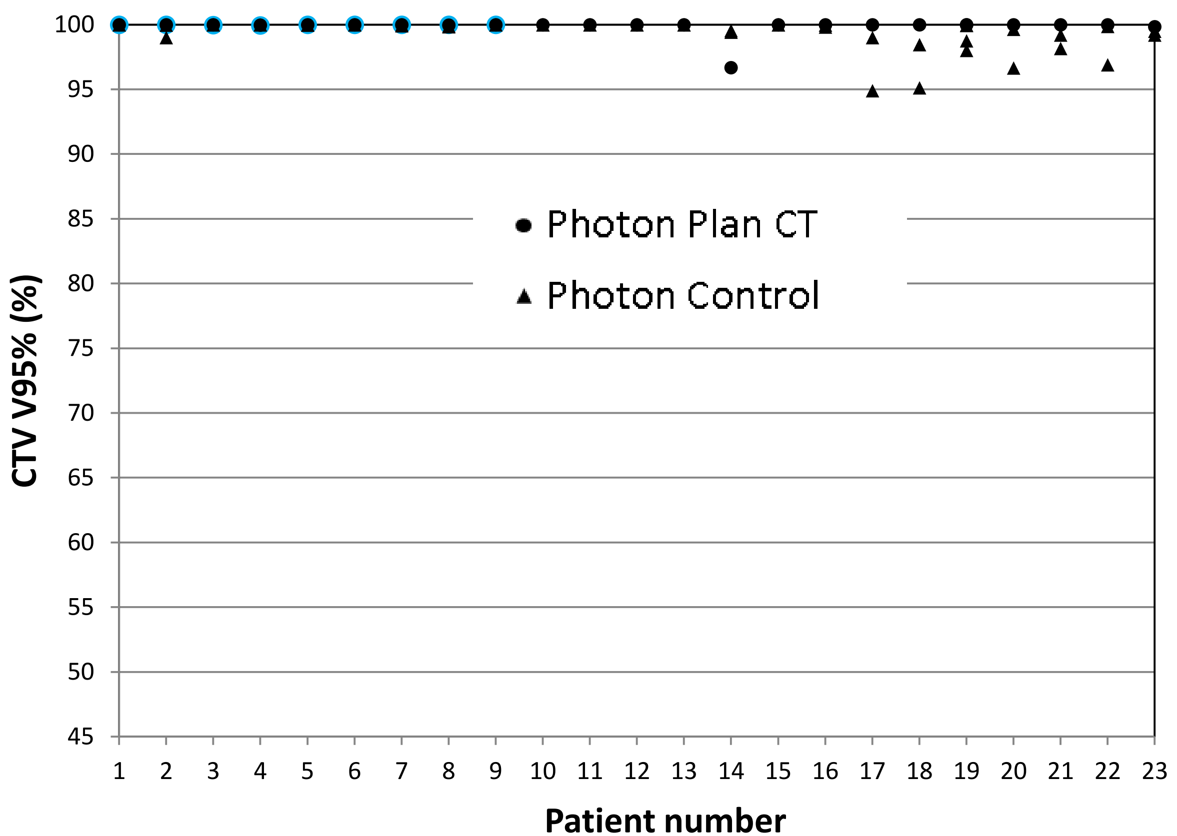


Trento
120 patients

About 50% intracranial and 50% extracranial

How much adaptive do we need? XRT vs PT

Lung XRT - Re-calculated at fx 10 and 20 on repeat CTs



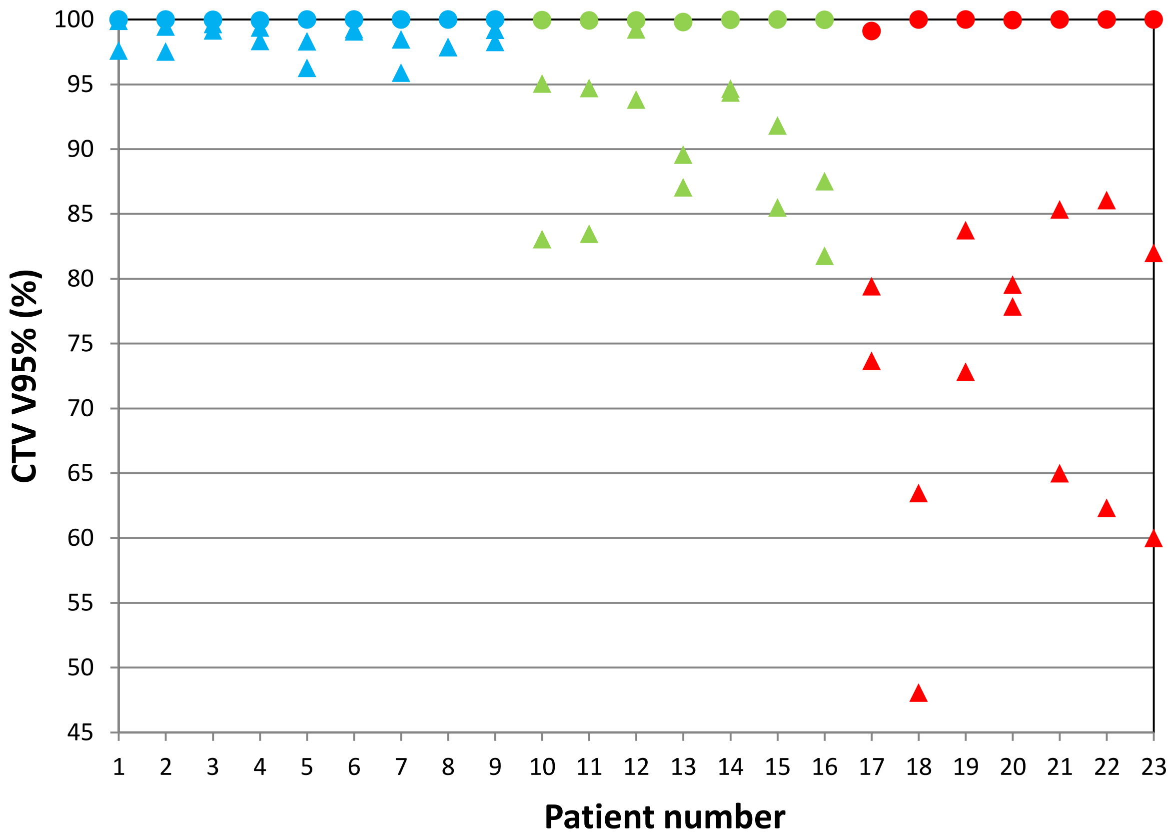
Hoffmann et al, R&O 2017

How much adaptive do we need? XRT vs PT

95 % of CTV covered

80 % of CTV covered

45 % of CTV covered



Hoffmann et al, R&O 2017

What imaging tools in the treatment room are available/needed?

CBCT
It’s coming for protons too, but nowhere near a standard yet.

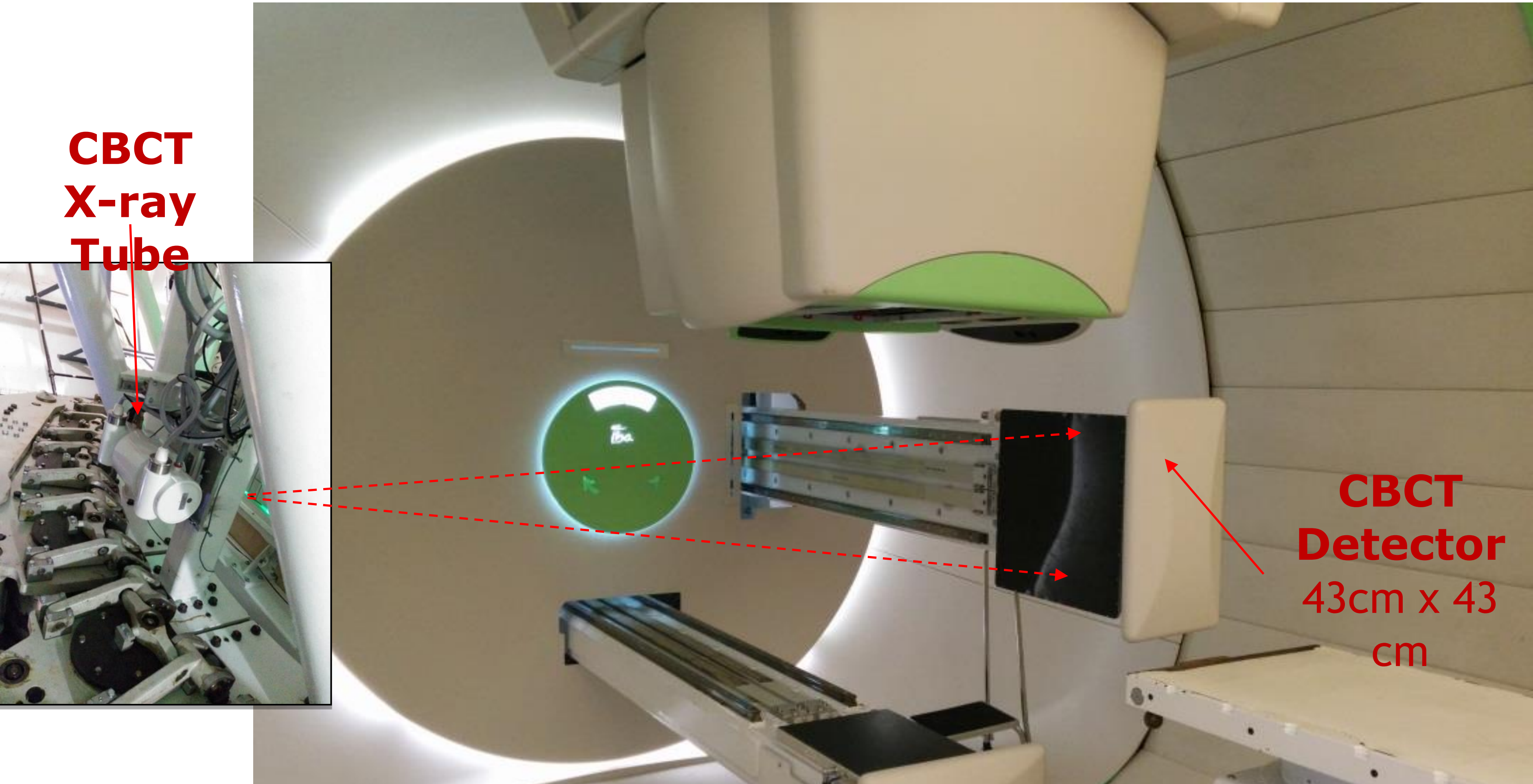
Is the compromise of image quality vs speed of intervention good?

CT on rail
Different compromises with respect to CBCT.
Worth evaluating.
It may remain a niche.

In vivo range measurements
Active area of developments
Not “ready for primetime”
Proton radiography
Proton CT
PET
Prompt Gamma

MRI
Don’t hold your breath

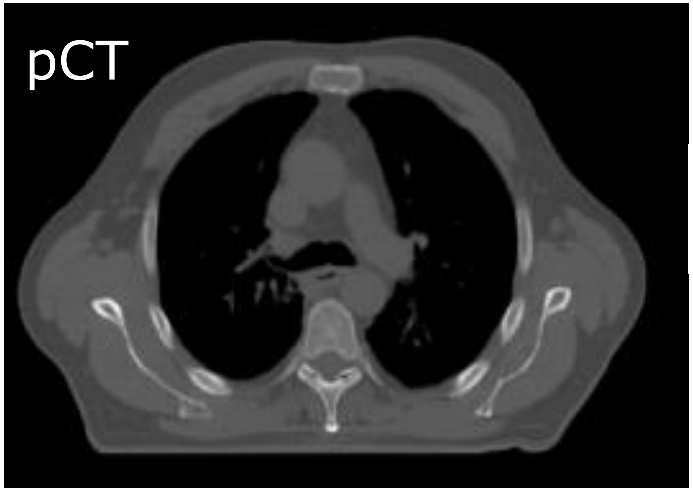
Gantry Mounted CBCT

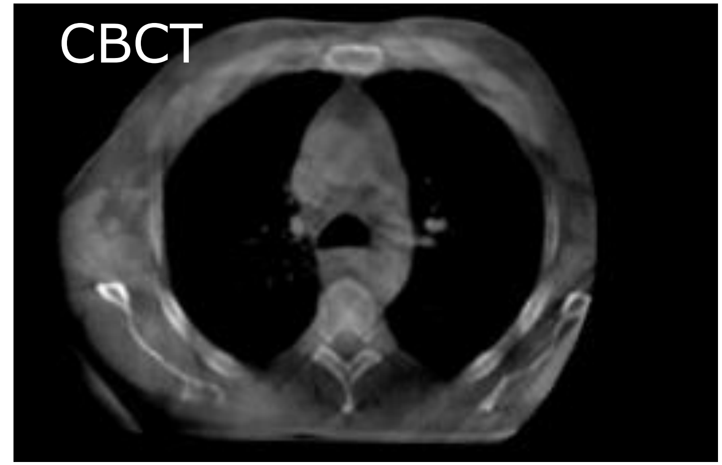


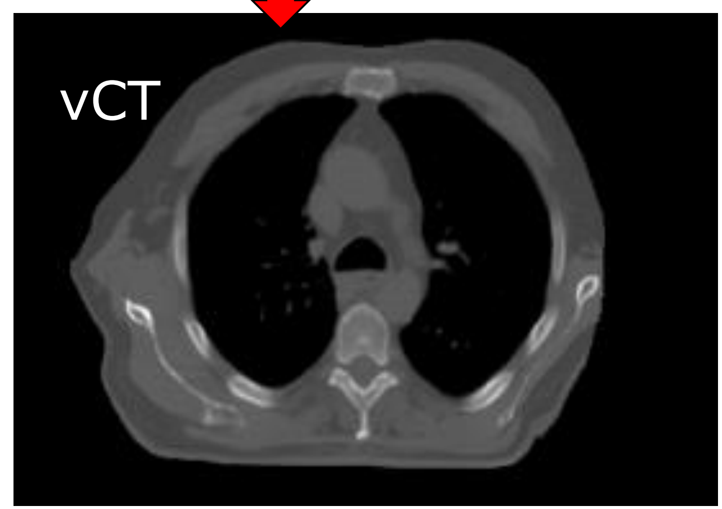
- **FOV: 34 cm axial and 34 cm longitudinal field of view**
- **Rotation speed of 0.5 or 1 RPM (full scan or half scan)**
- **First installation in UPenn room Sept 2014**

Courtesy Kevin Teo

From CBCT to Virtual CT (vCT)







Method works in most cases

Limitations:
(1) Complex anatomical change not handled correctly by deformable image registration (DIR) software
(2) Subtle changes in lung/tumor density not accounted for

C Veiga et al, IJROBP 95 549 (2016)

Courtesy Kevin Teo

CT on rail as a solution for image guidance in p+

High image quality needed for dose recalculation and adaptive regimes

Conclusion

It’s a good time to be a medical physicist in particle therapy.

There are many opportunities to make an impact, both as researchers and as clinical medical physicists.

We are ready to shift our focus away from the equipment *per se* and to focus on the interactions between technical tools and clinical outcomes.

Grazie