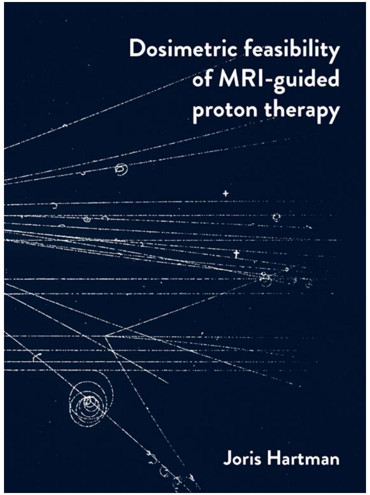
Proton therapy

Joris Hartman, MD, PhD

Nikhef colloquium, Friday 12 April 2019

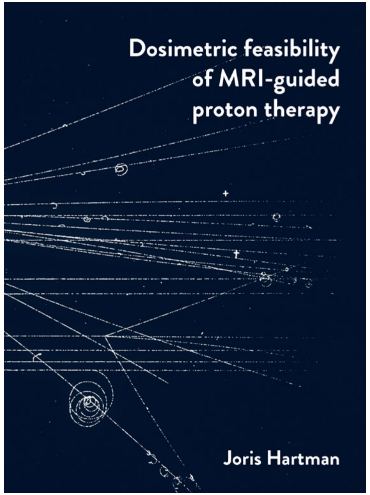
Personal background

- Physics 1999 – 2009
- Medicine 2002 – 2013
- Master Nikhef 2006 – 2009
- PhD student @ ANTARES, Nikhef 2009-2010
- PhD student @ UMC Utrecht 2013-2018
  - Feasibility of MRI-guided proton therapy



Personal background

- Physics 1999 – 2009
- Medicine 2002 – 2013
- Master Nikhef 2006 – 2009
- PhD student @ ANTARES, Nikhef 2009-2010
- PhD student @ UMC Utrecht 2013-2018
  - Feasibility of MRI-guided proton therapy



Currently working on MC validation (physics) and in psychiatry (medicine).

Overview

I. Radiotherapy: a short introduction

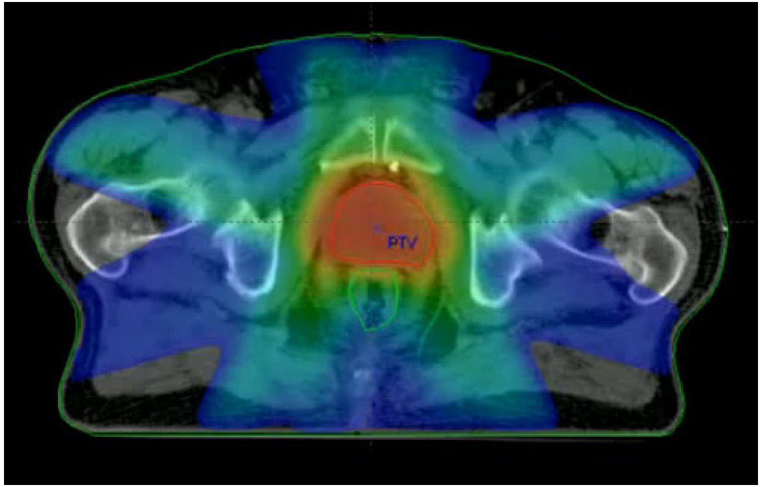
II. Proton therapy: what?

III. Proton therapy: why?

IV. Proton therapy: how?

V. Challenges and developments

I. Radiotherapy: a short introduction



What is radiotherapy

"In radiotherapy, ionizing radiation is used to treat cancer"[†]

[†]And some other, benign, conditions

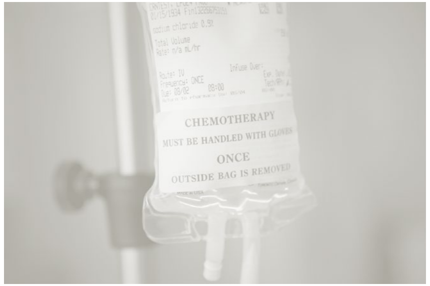
What is radiotherapy

"In radiotherapy, ionizing radiation is used to treat cancer"†

†And some other, benign, conditions

What is radiotherapy

"In radiotherapy, ionizing radiation is used to treat cancer"†



50% of patients treated with radiation therapy

†And some other, benign, conditions

Radiation treatment: dose

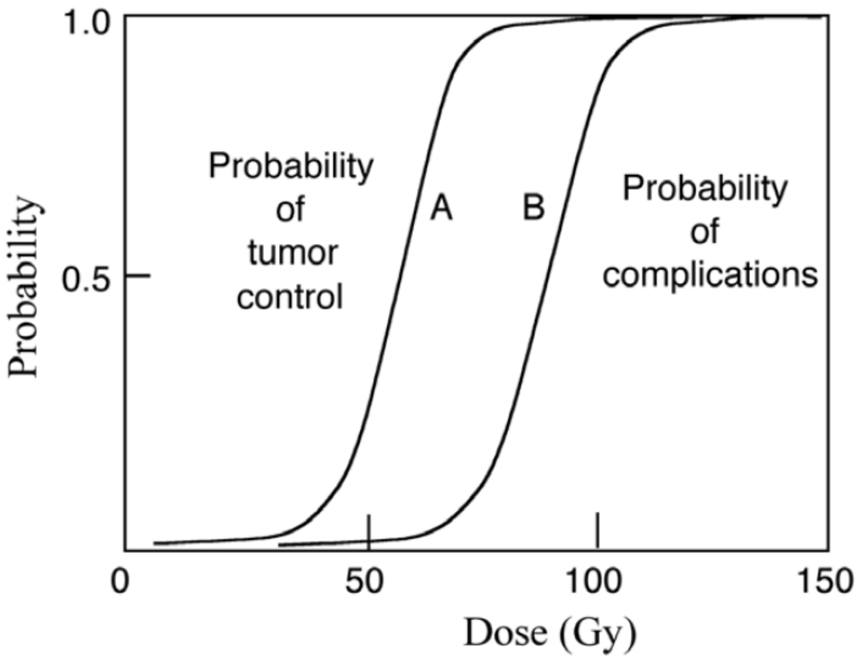
Dose $$D = \boldsymbol{\Phi}\frac{S}{\rho}$$

or $$D = 0.1602\,\boldsymbol{\Phi}\frac{S}{\rho}\;Gy\;\;(or\;\frac{J}{kg})$$

with $\boldsymbol{\Phi}$ in Gp/cm^2 and S/$\boldsymbol{\rho}$ in MeV/(g/cm^2)

Radiation treatment: dose

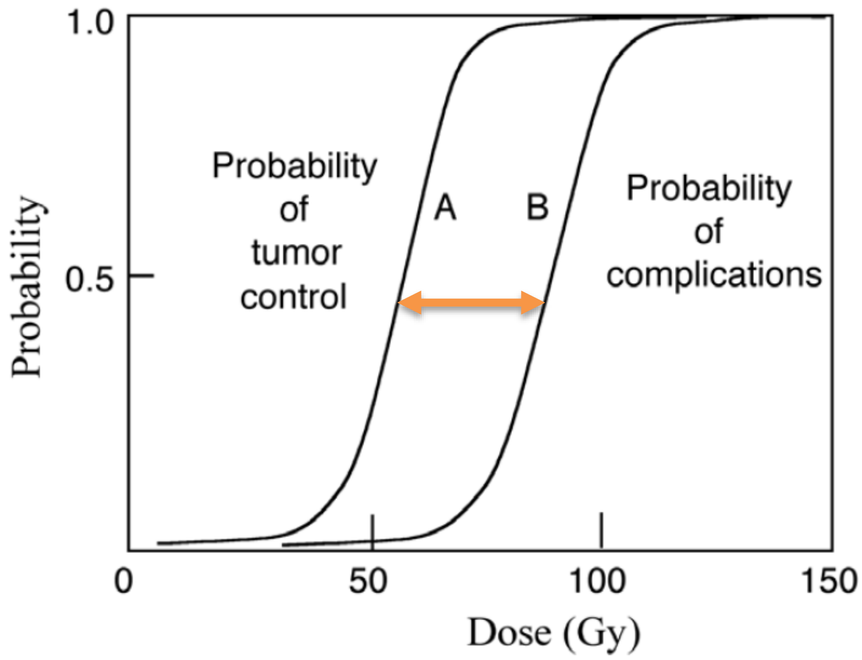
Based on tumor **type** and **location**



A. tumor control probability (TCP)
B. normal tissue complication probability (NTCP)

Radiation treatment: dose

Based on tumor **type** and **location**



A. tumor control probability (TCP)
B. normal tissue complication probability (NTCP)

Therapeutic window

Radiation treatment: dose

Example dose:

Prostate:	74 Gy (external) up to 200 Gy (internal, ^{125}I)
Glioblastoma:	50 Gy
Melanoma:	30 Gy
TBI:	12 Gy
Fatal:	4 Gy (50% of patients)

Radiation treatment: dose

Example dose:

Prostate:	74 Gy (external) up to 200 Gy (internal, ^{125}I)
Glioblastoma:	50 Gy
Melanoma:	30 Gy
TBI:	12 Gy
Fatal:	4 Gy (50% of patients)

Limit the toxic effects by **hyperfractionation**

Radiation treatment

DNA damage

Linear Energy Transfer (LET) dE/dl in keV/μm

→ Differs per particle type (higher in **heavy charged particles**)

Radiation treatment

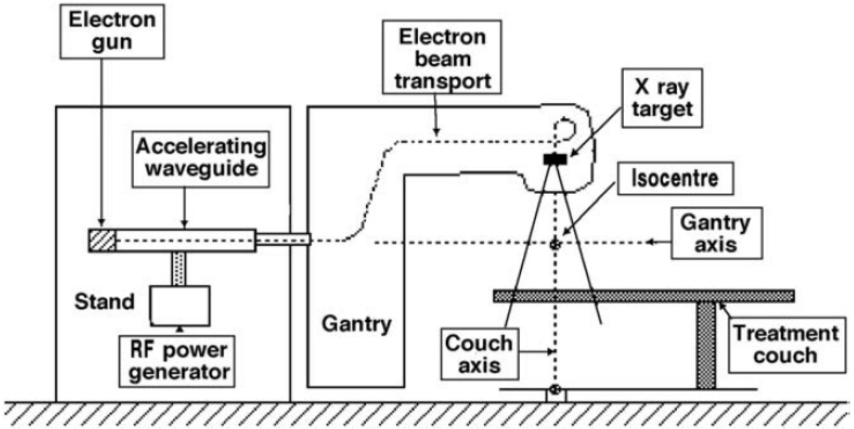
DNA damage

Linear Energy transfer (LET) dE/dl in keV/um

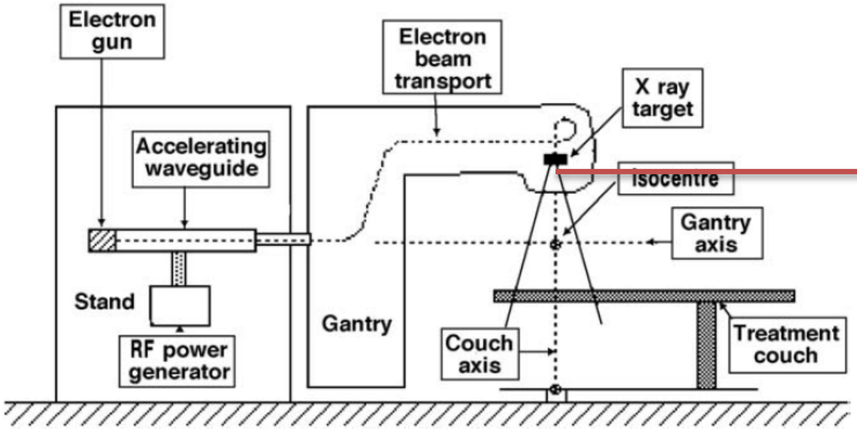
→ Differs per particle type (higher in **heavy charged particles**)

	Direct damage	vs	Indirect damage
	Direct ionization of target		Production of free radicals
γ/e^-	~ 1/3		~ 2/3
p^+/C/…	predominant		

‘Regular’ treatment: linac



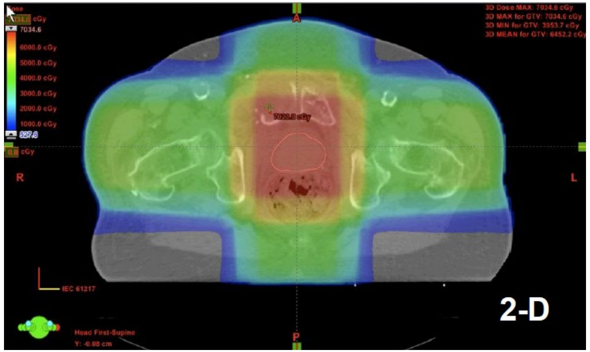
‘Regular’ treatment: linac

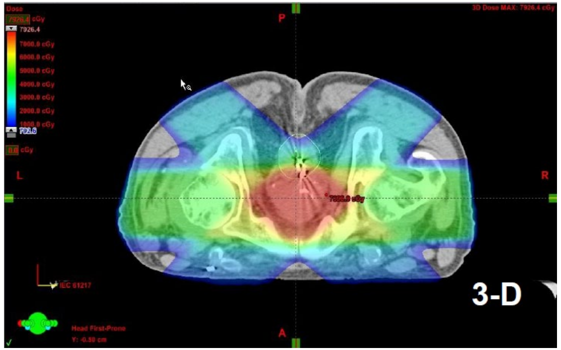


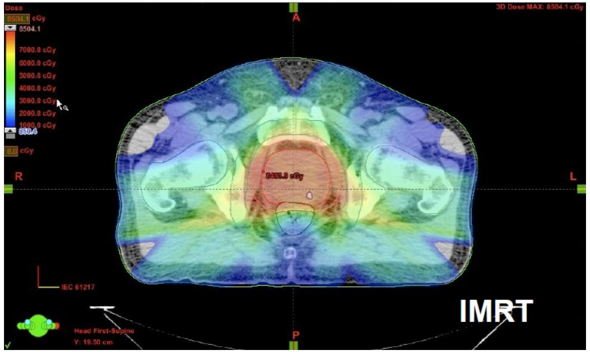
Multileaf collimator

‘Regular’ treatment: linac

‘Regular’ treatment: dose distributions



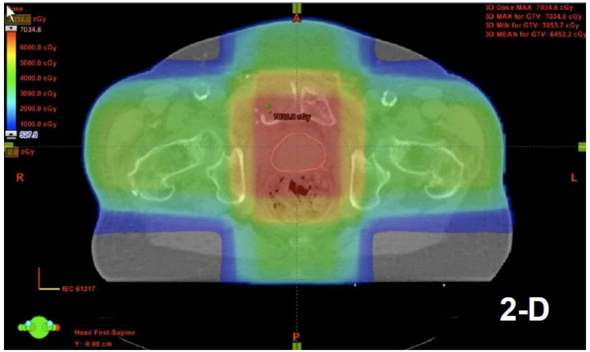


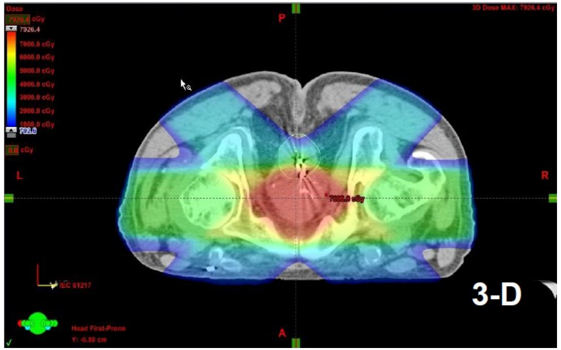


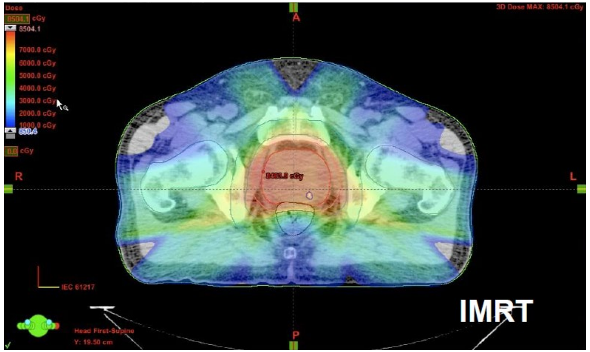
Intensity Modulated Radiotherapy

Zelig Tochner, PTCOG 57

‘Regular’ treatment: dose distributions





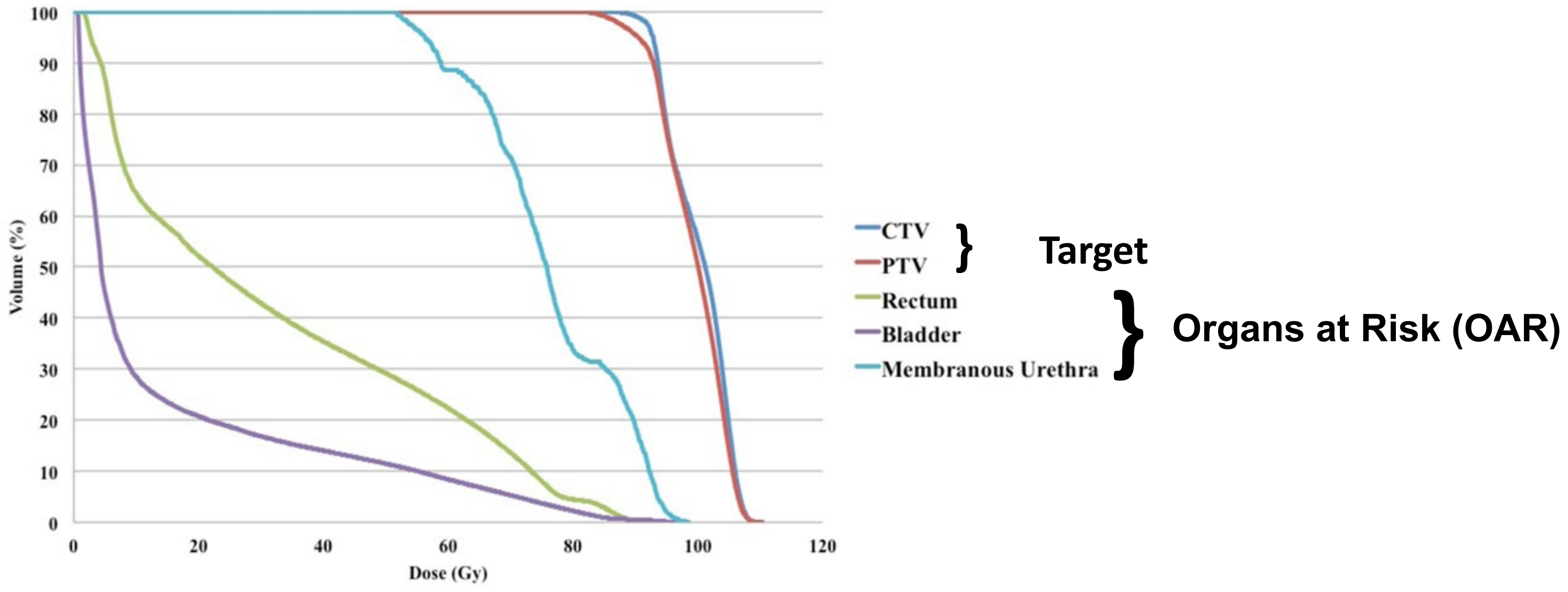


Intensity Modulated Radiotherapy

improvement

Zelig Tochner, PTCOG 57

Dose Volume Histogram



Imaging

Before treatment

Most used: Computed Tomography (CT)

Better: Magnetic Resonance Imaging (MRI)

Imaging

Before treatment

Most used: Computed Tomography (CT)

Better: Magnetic Resonance Imaging (MRI)

During treatment

Planar X-Ray: kilovolt or megavolt

Cone-beam CT

Imaging

Before treatment

Most used: Computed Tomography (CT)

Better: Magnetic Resonance Imaging (MRI)

During treatment

Planar X-Ray: kilovolt or megavolt

Cone-beam CT

CBCT

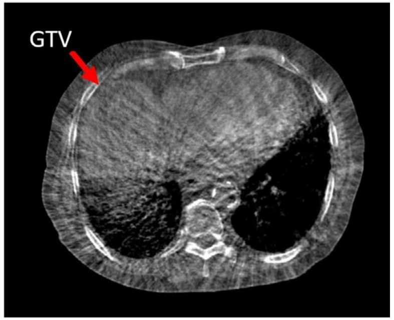
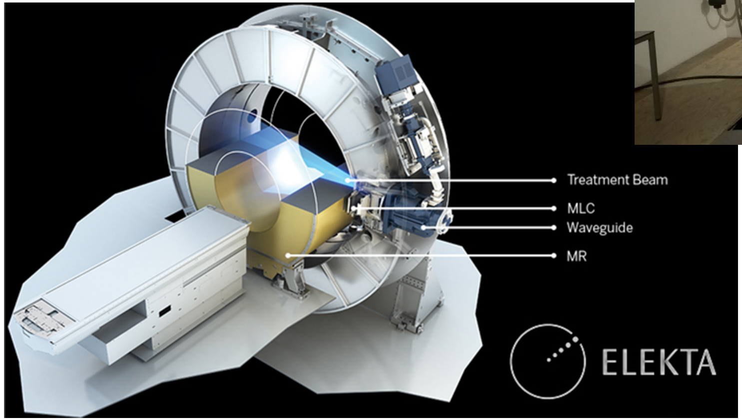
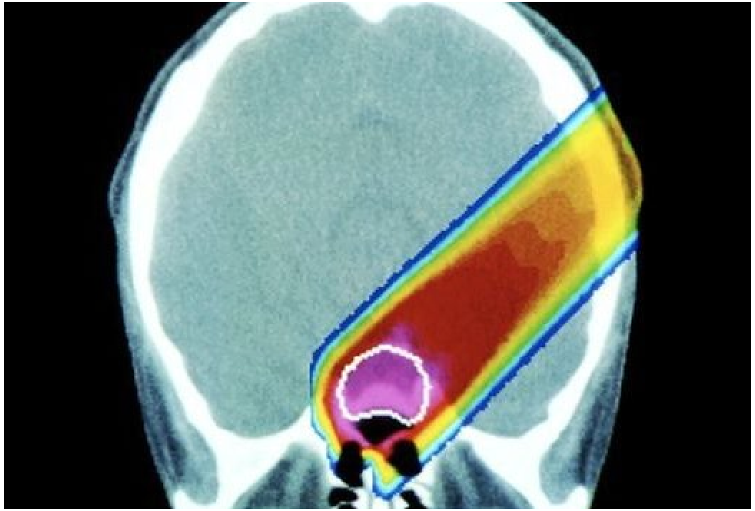


Image guided: MR-Linac

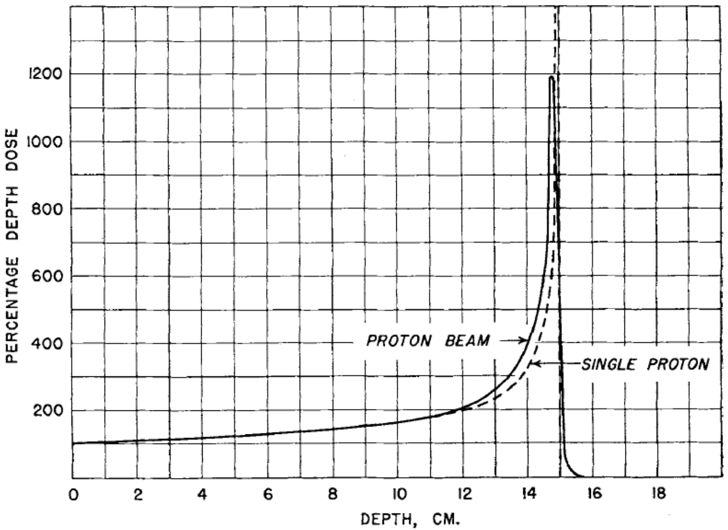
Integration of a 1.5T MRI with a linear accelerator

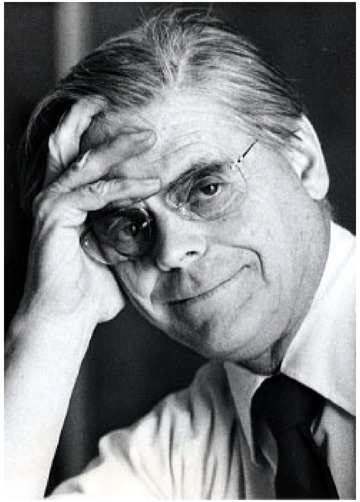


II. Proton therapy: what?



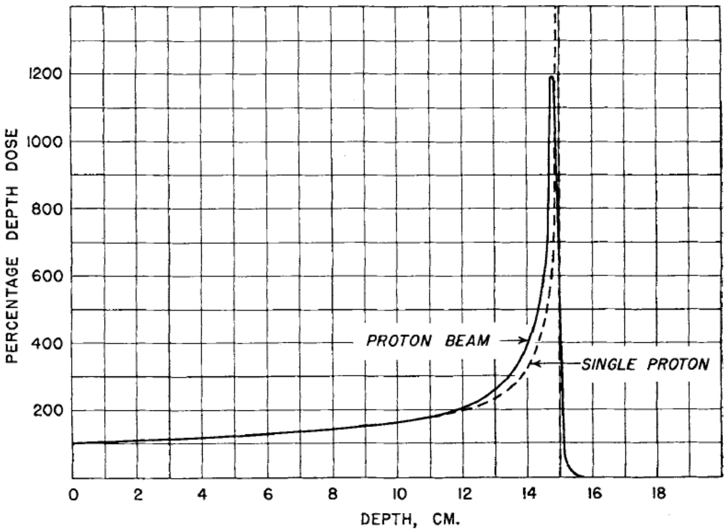
History

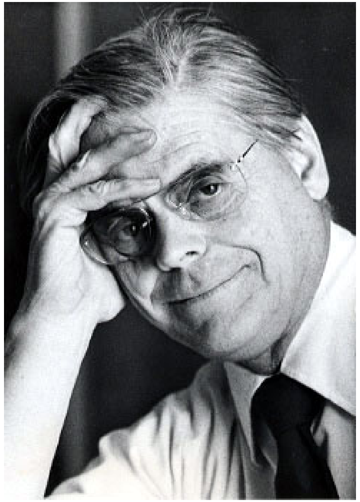




Wilson RR. **Radiological use of fast protons**. Radiology. 1946 Nov;47(5):487-91.

History

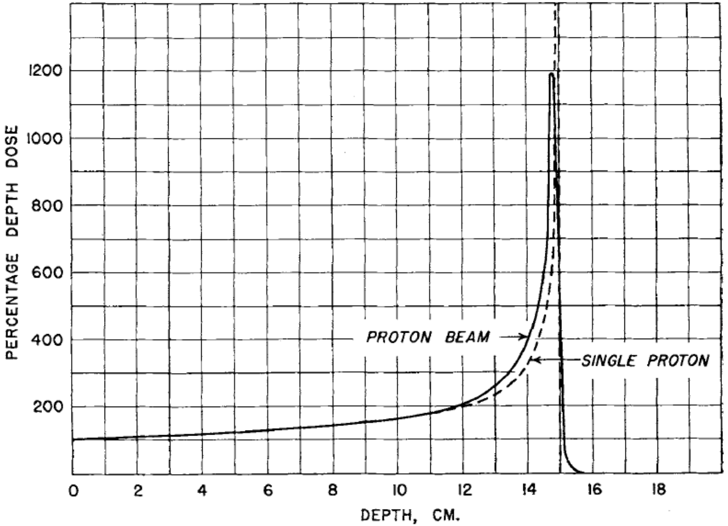


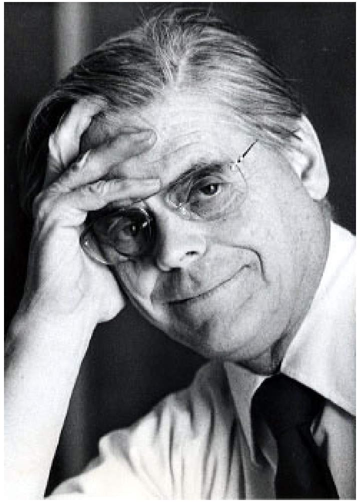


“These properties make it possible to irradiate intensely a strictly localized region within the body”

Wilson RR. **Radiological use of fast protons**. Radiology. 1946 Nov;47(5):487-91.

History





1946: Idea

1954: First treatment

2018: First in NL

"These properties make it possible to irradiate intensely a strictly localized region within the body"

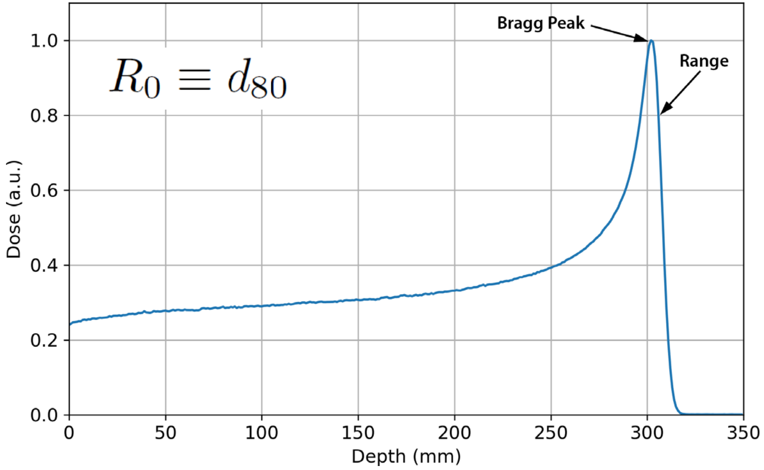
Wilson RR. **Radiological use of fast protons**. Radiology. 1946 Nov;47(5):487-91.

Stopping power

$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \frac{Z}{A} \frac{1}{\beta^2} \left(\ln \frac{C_2 \beta^2}{I(1-\beta^2)} - \beta^2 \right)$$

Stopping power

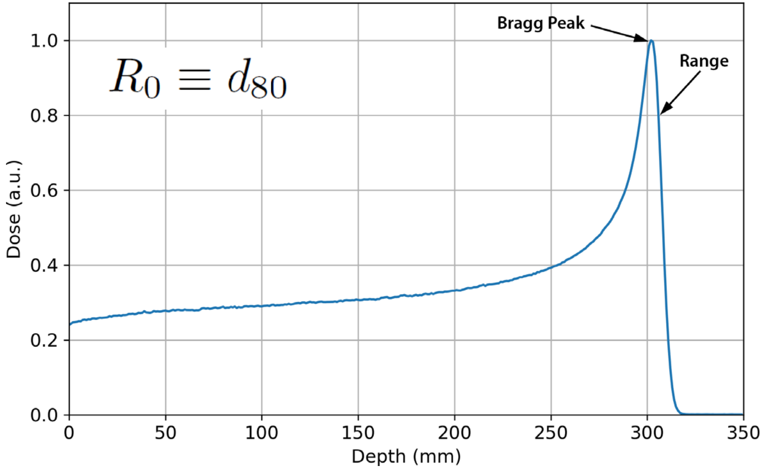
$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \frac{Z}{A}\frac{1}{\beta^2}\left(\ln \frac{C_2\beta^2}{I(1-\beta^2)} - \beta^2\right)$$



221.8 MeV in a water phantom (TOPAS/Geant4)

Stopping power

$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \frac{Z}{A}\frac{1}{\beta^2}\left(\ln\frac{C_2\beta^2}{I(1-\beta^2)} - \beta^2\right)$$



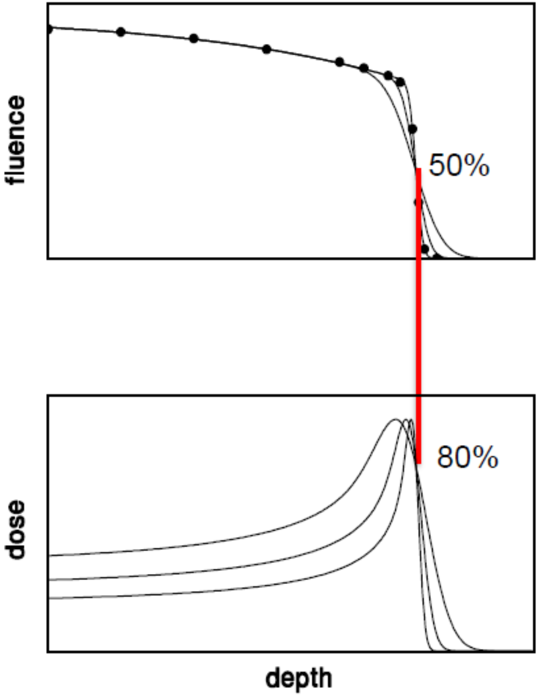
221.8 MeV in a water phantom (TOPAS/Geant4)

Bragg Kleeman rule

$$R_0 \approx \alpha E_0^p$$

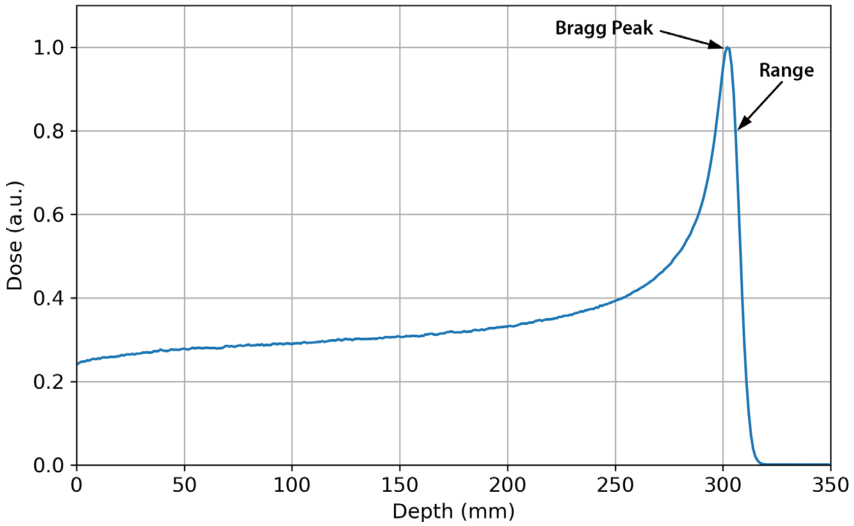
$p \approx 1.75$

$\alpha \approx 0.00244\ cm/MeV^p$



H. Paganetti “Proton Therapy Physics” Taylor & Francis / CRC Press

Pencil beams



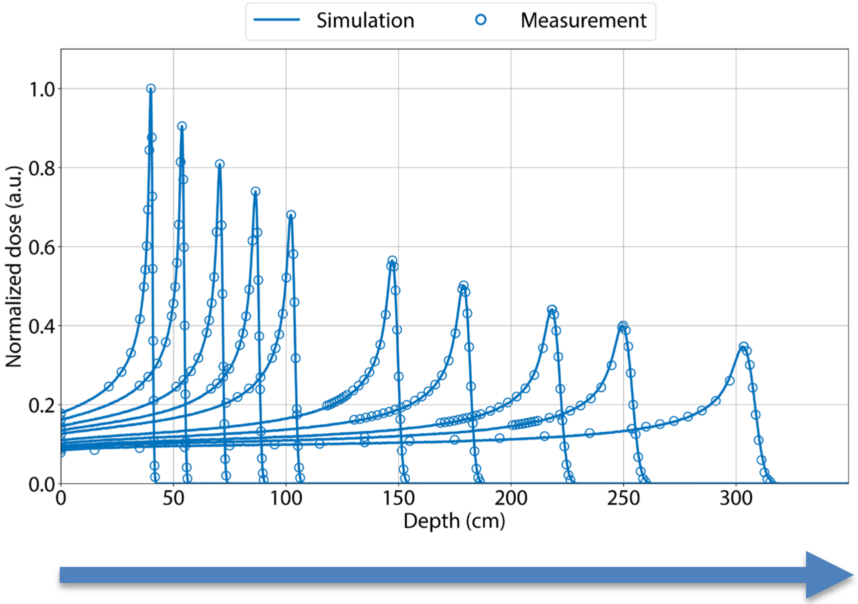
Single beam = **pencil beam**

Clinical energies: 70 – 250 MeV

Energy determines range, can only deliver high dose to small volume

Combination of 100’s to 1000’s of pencil beams used in a treatment plan

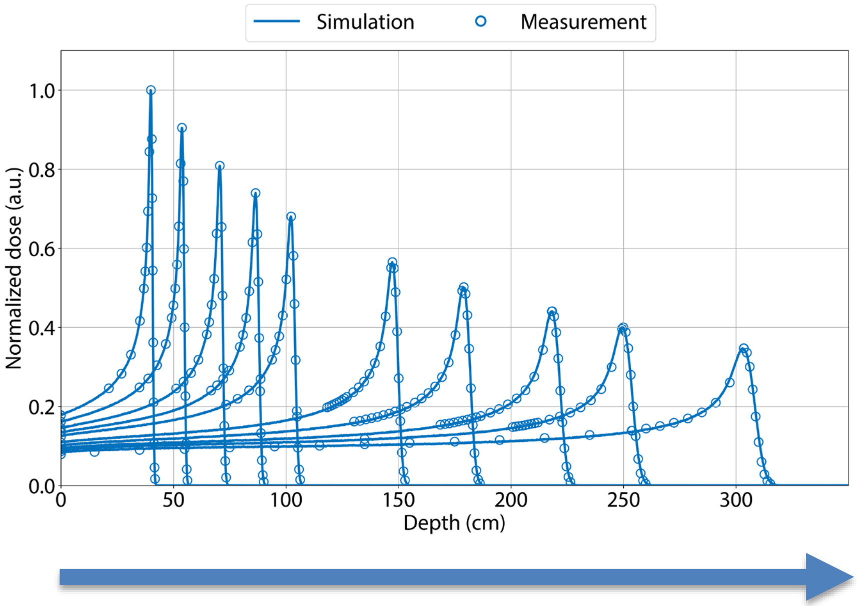
Pencil beams



Higher energy (range)

Increased range straggling

Pencil beams



Higher energy (range)

Increased range straggling

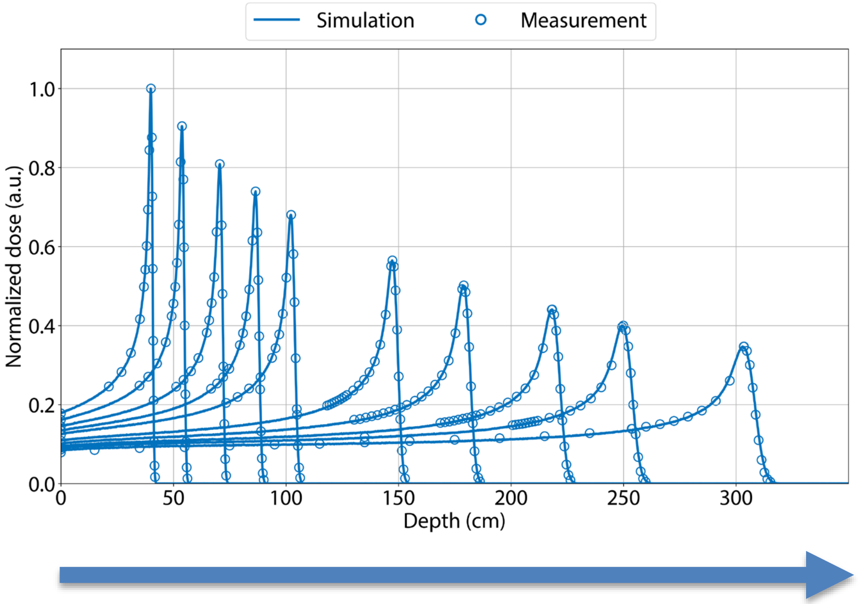
Range straggling

$$\sigma^2 \approx \alpha' \frac{p^3 \alpha^{2/p}}{3p-2} R_0^{3-2/p}$$

For water (in cm):

$$\sigma \approx 0.012 R_0^{0.935} \approx 4.31 \times 10^{-5} E_0^{1.636}$$

Pencil beams



Higher energy (range)
Increased range straggling

Range straggling

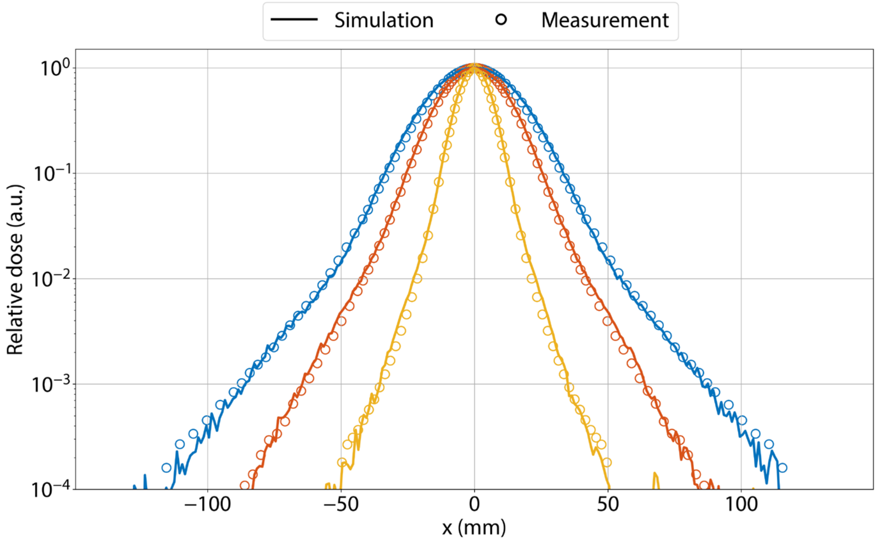
$$\sigma^2 \approx \alpha' \frac{p^3 \alpha^{2/p}}{3p-2} R_0^{3-2/p}$$

For water (in cm):

$$\sigma \approx 0.012 R_0^{0.935} \approx 4.31 \times 10^{-5} E_0^{1.636}$$

@ 200 MeV, σ = 2.5 mm

Pencil beams

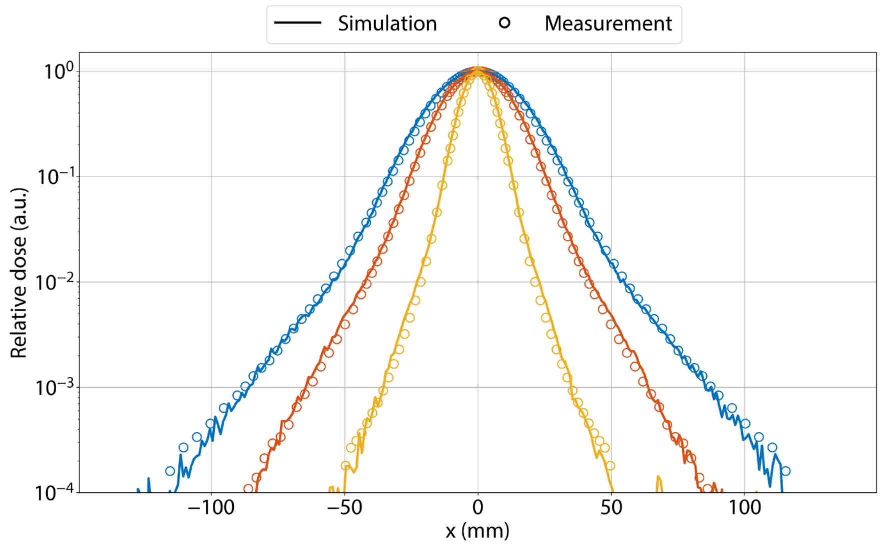


81.4 (outer blue), 100.9 (middle orange), and 219.3 (inner yellow) MeV in a water phantom at 2 cm depth

E (MeV)	σ (mm)	FWHM (mm)
72.5	14.91	35.12
151.0	7.60	17.90
221.8	5.57	13.11

For the MD Anderson Proton Therapy Center, Houston, Texas (Hitachi Synchrotron)

Pencil beams



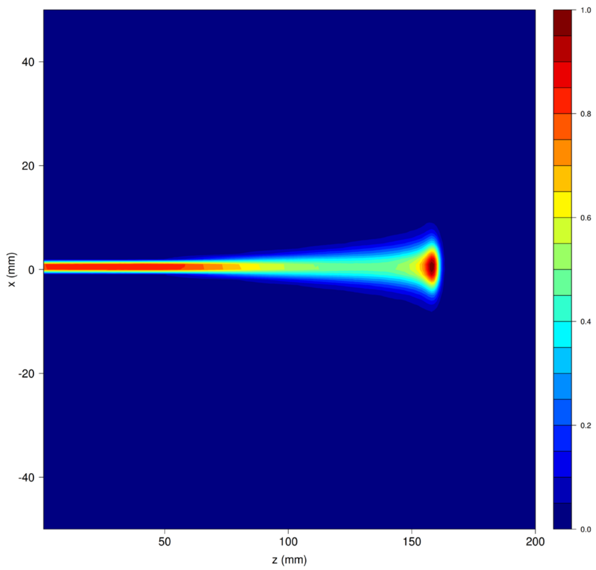
81.4 (outer blue), 100.9 (middle orange), and 219.3 (inner yellow) MeV in a water phantom at 2 cm depth

E (MeV)	σ (mm)	FWHM (mm)
72.5	14.91	35.12
151.0	7.60	17.90
221.8	5.57	13.11

For the MD Anderson Proton Therapy Center, Houston, Texas (Hitachi Synchrotron)

Not really small pencils

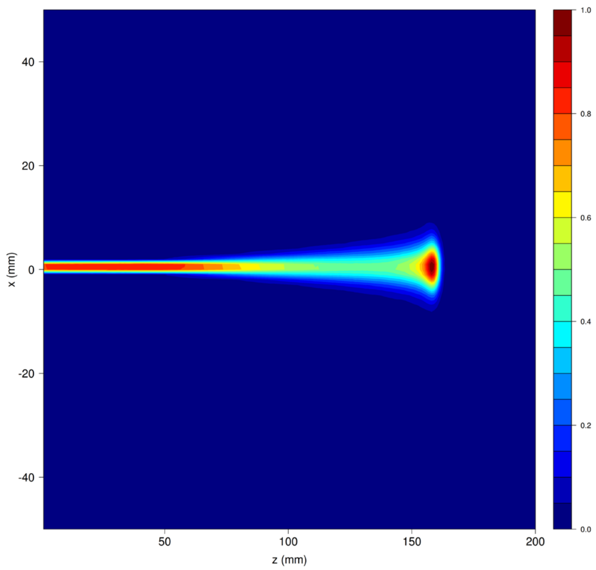
Pencil beams



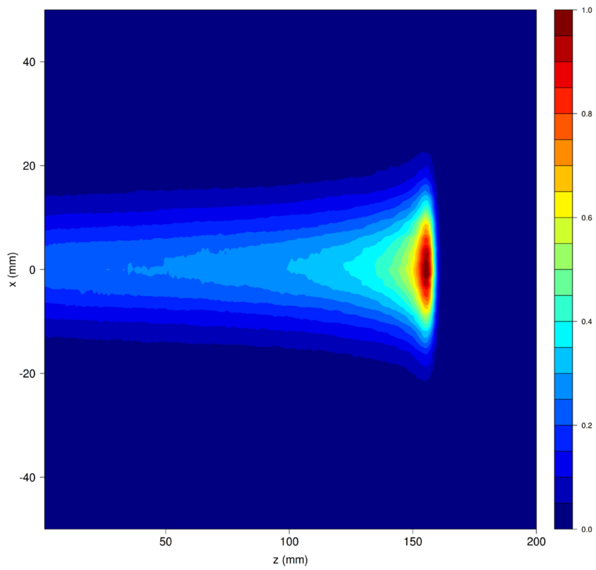
Ideal

E = 150 MeV, simulated in water phantom

Pencil beams



Ideal



Realistic

E = 150 MeV, simulated in water phantom

Stopping power

$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \frac{Z}{A} \frac{1}{\beta^2} \left(\ln \frac{C_2 \beta^2}{I(1-\beta^2)} - \beta^2 \right)$$

Stopping power

$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \frac{Z}{A} \frac{1}{\beta^2} \left(\ln \frac{C_2 \beta^2}{I(1-\beta^2)} - \beta^2 \right)$$

Stopping power

$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \frac{Z}{A} \frac{1}{\beta^2} \left(\ln \frac{C_2 \beta^2}{I(1-\beta^2)} - \beta^2 \right)$$

Material!

Stopping power

$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \boxed{\frac{Z}{A}} \frac{1}{\beta^2} \left(\ln \frac{C_2 \beta^2}{I(1-\beta^2)} - \beta^2 \right)$$

Material!

Large influence on stopping power

Lot of unknows…

Stopping power

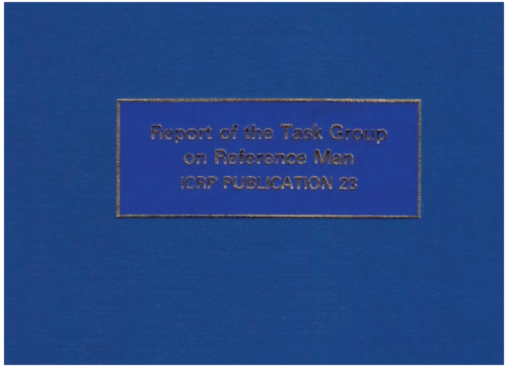
$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \frac{Z}{A} \frac{1}{\beta^2} \left(\ln \frac{C_2 \beta^2}{I(1-\beta^2)} - \beta^2 \right)$$

Material!

Large influence on stopping power

Lot of unknows…

What is the composition of human tissue?



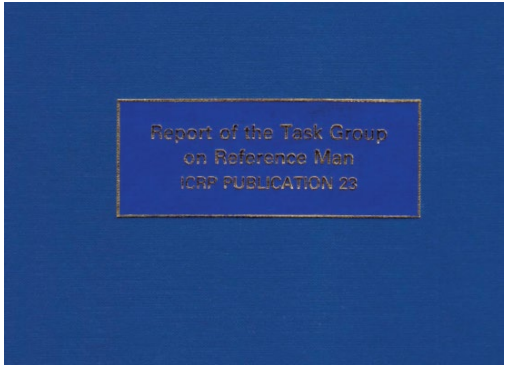
Stopping power

$$S \equiv -\frac{\mathrm{d}E}{\mathrm{d}x} = C_1 \frac{Z}{A} \frac{1}{\beta^2} \left(\ln \frac{C_2 \beta^2}{I(1-\beta^2)} - \beta^2 \right)$$

Material!

For water, we assume I = 75 eV… or 78 eV (at least between 68 and 82 eV)

What is the composition of human tissue?



Large influence on stopping power

Lot of unknows…

Proton therapy: what?

Use of protons to deliver radiation dose

Bragg peak: high dose in small volume

Pencil beams to deliver dose

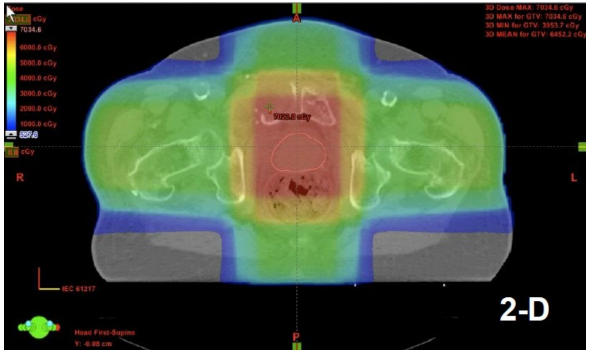
Size limited by physics

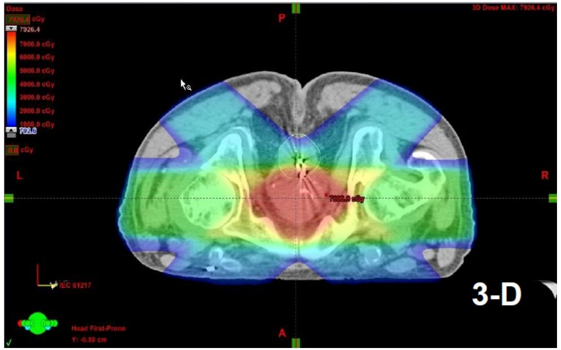
Knowlegde of body materials crucial

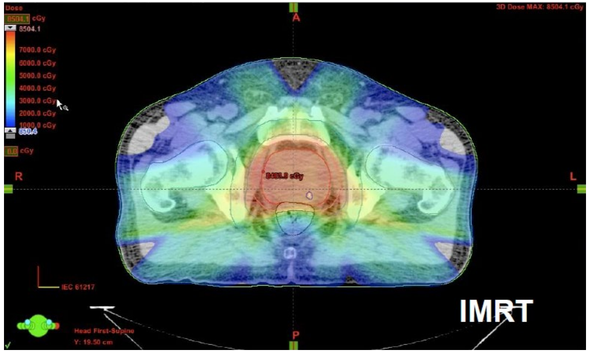
Lot of unknowns

III. Proton therapy: why?

Dose distributions

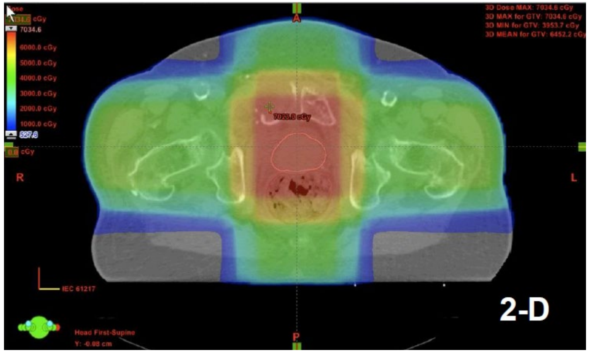


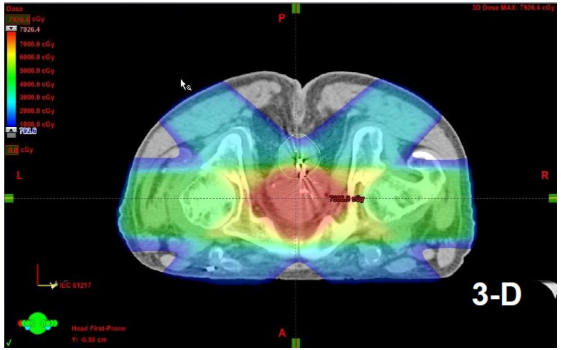


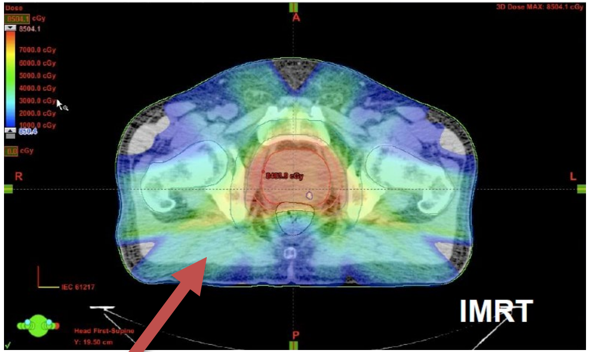


Zelig Tochner, PTCOG 57

Dose distributions



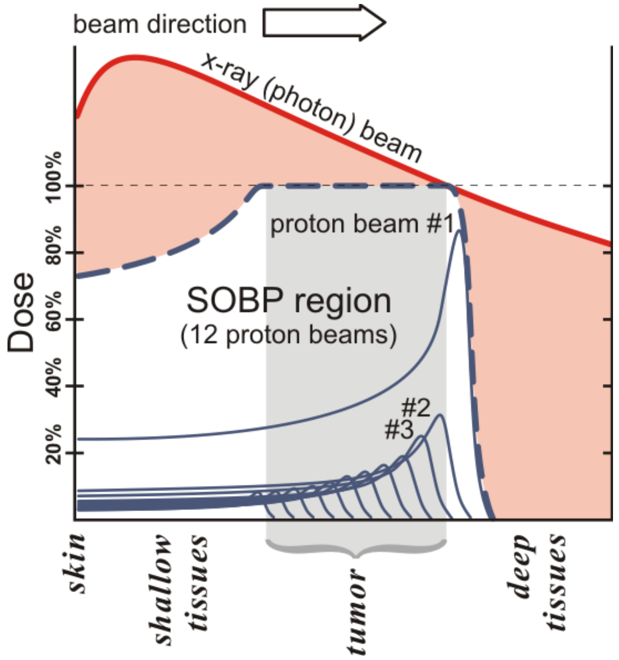




Lot of dose in healthy tissue
= BAD

Zelig Tochner, PTCOG 57

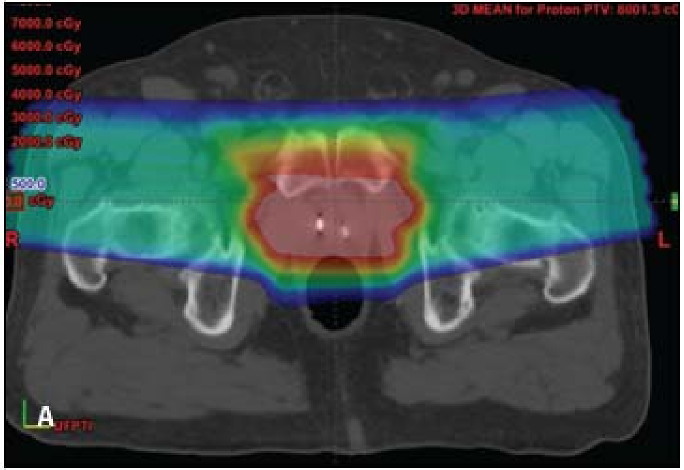
Dose distributions



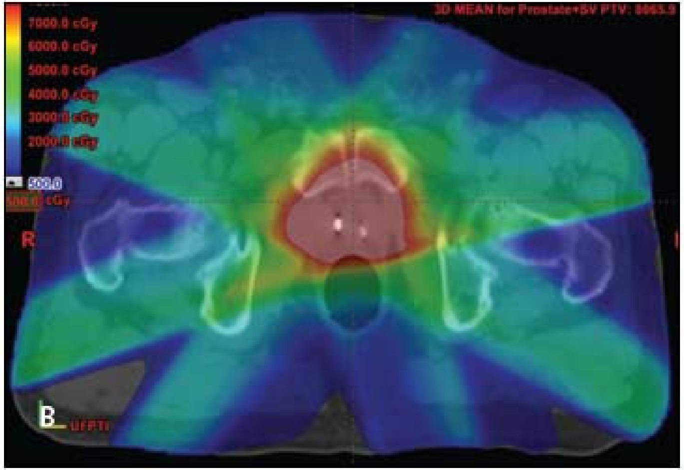
Protons: no exit dose!

Combine multiple pencil beams, create a Spread-out Bragg Peak (SOBP)

Dose distributions

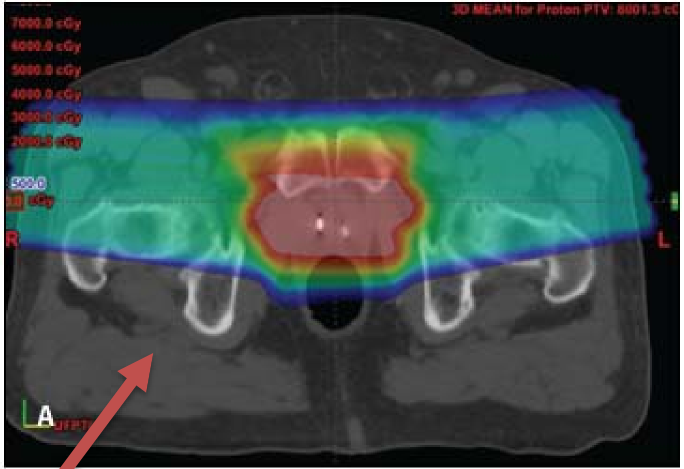


Protons

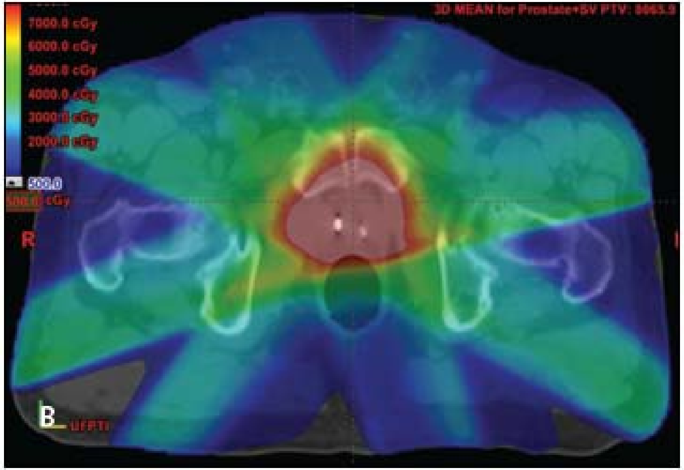


IMRT

Dose distributions



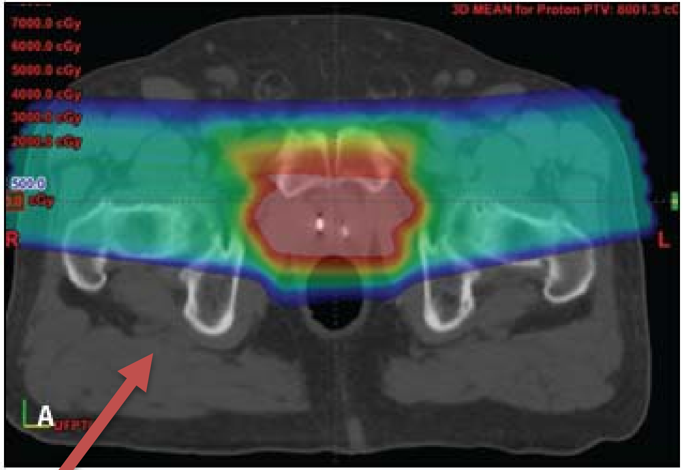
Protons



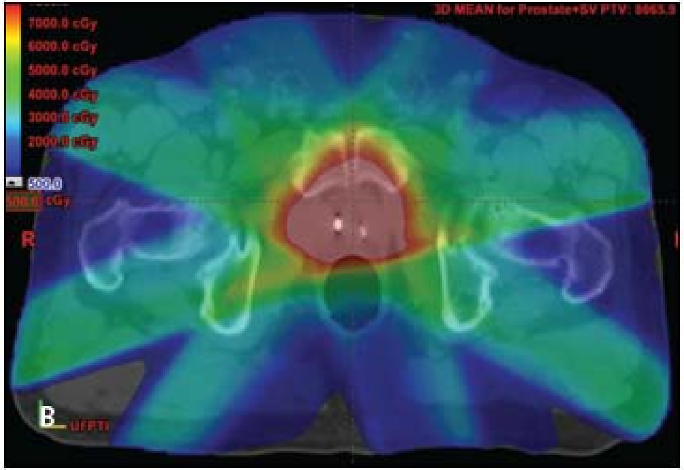
IMRT

Less dose in healthy tissue
= GOOD

Dose distributions



Protons

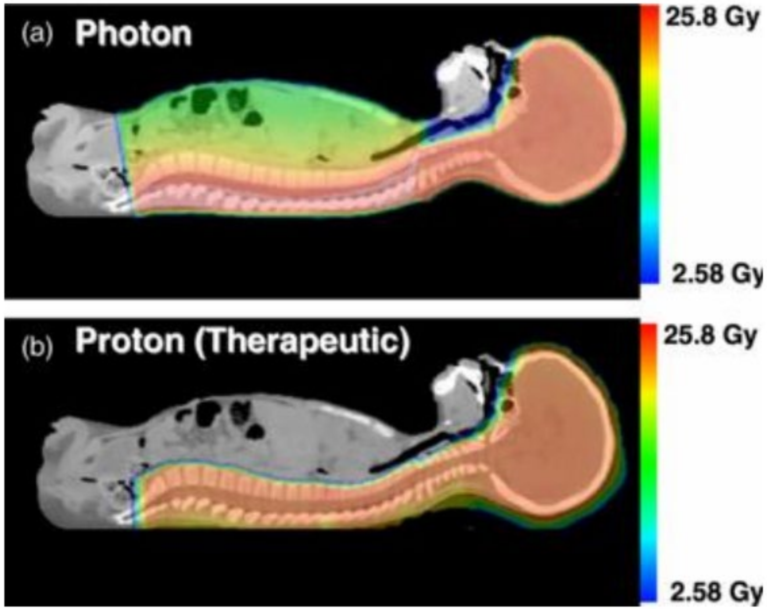


IMRT

Less dose in healthy tissue
= GOOD

(unfortunately, bad *clinical* example, don't do this)

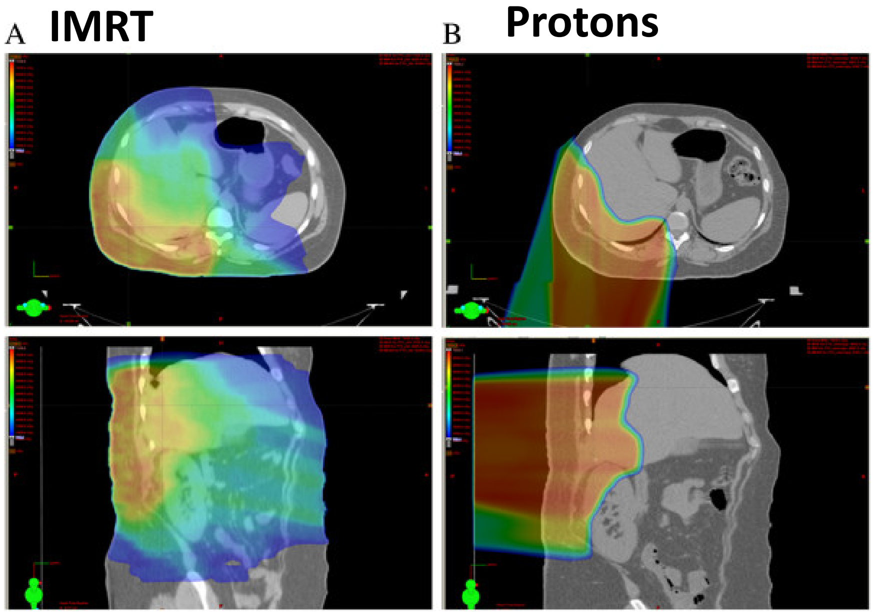
Lower integral dose

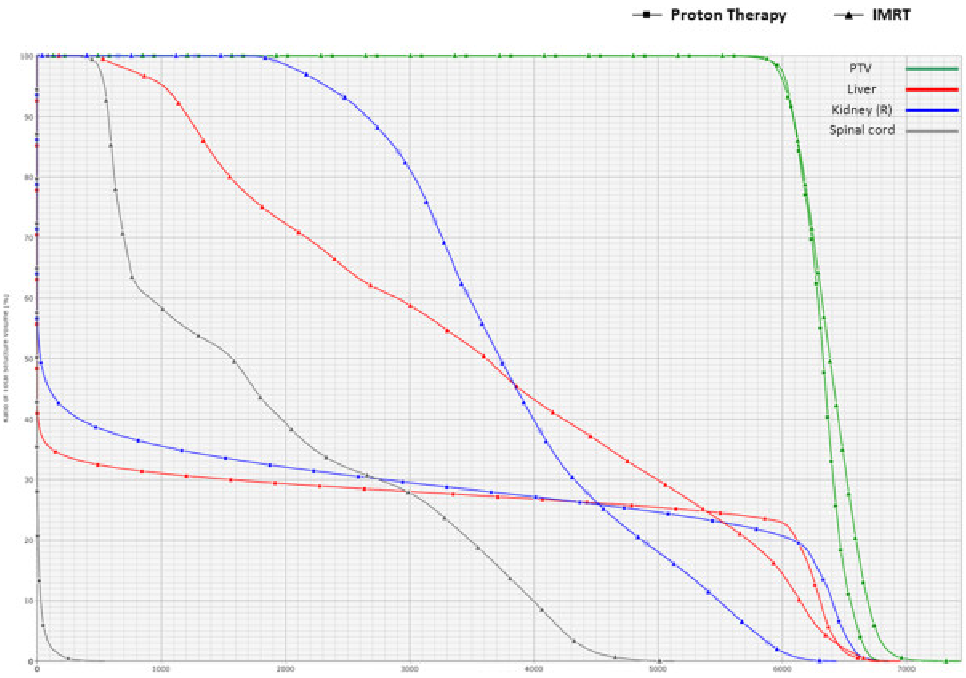


Better example: **pediatrics**

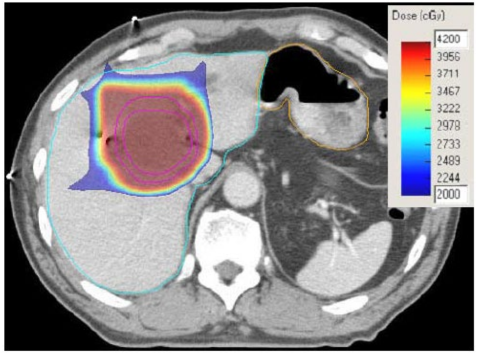
Lower integral dose, less toxicity and **less secondary cancer**

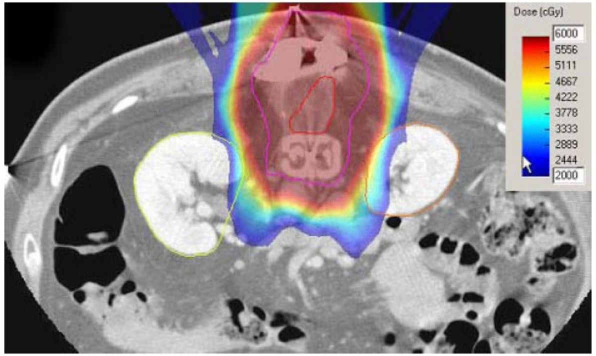
Lower integral dose

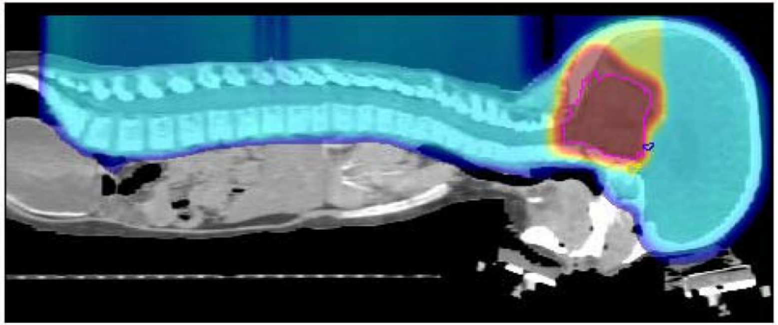


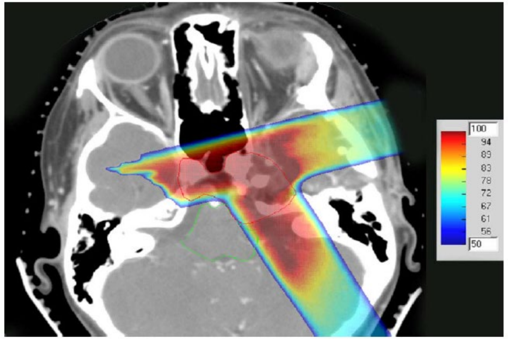


T. DeLaney and R. Haas, Innovative radiotherapy of sarcoma: Proton beam radiation



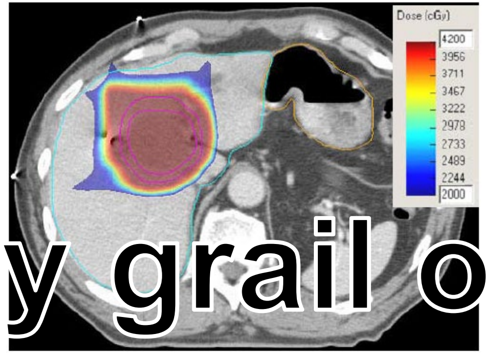


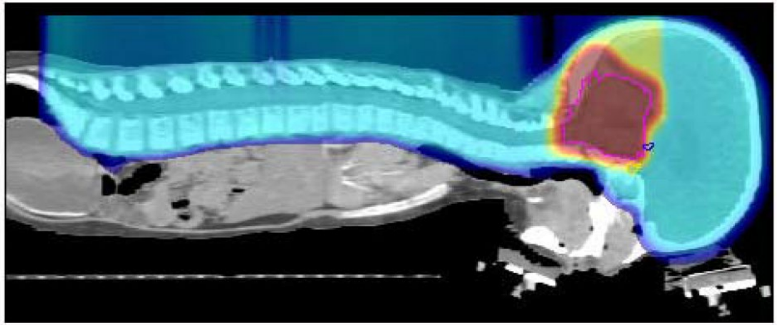


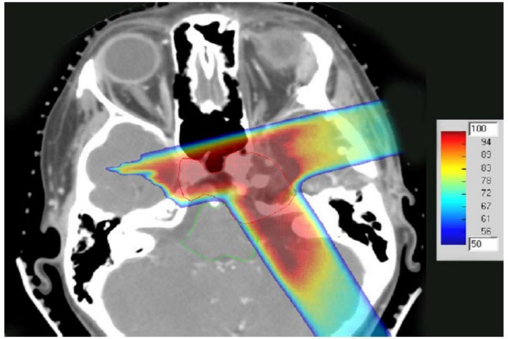


Bussiere MR, Adams JA. **Treatment planning for conformal proton radiation therapy.** Technology in Cancer Research & Treatment 2:389-399. 2003

Holy grail of radiotherapy?





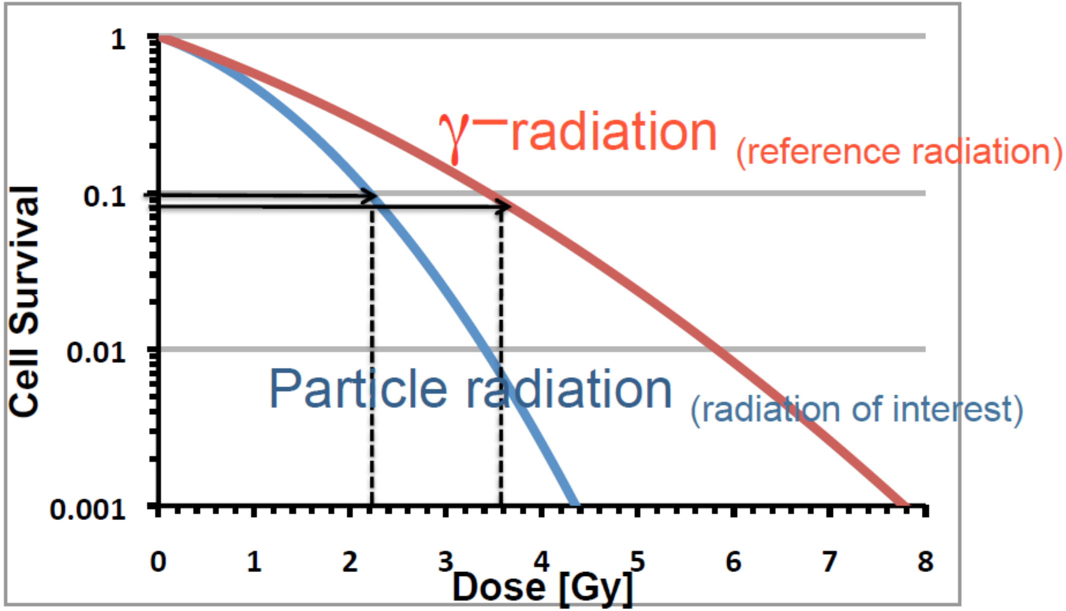


Bussiere MR, Adams JA. **Treatment planning for conformal proton radiation therapy.** Technology in Cancer Research & Treatment 2:389-399. 2003

Intensity Modulated Proton Therapy for Head and Neck Tumors:
Gilding the Lily or Holy Grail?

Quality of Life and Value Considerations in Head and Neck Proton Beam Therapy: ***The Holy Grail at Last, or the Quest Continues****?*

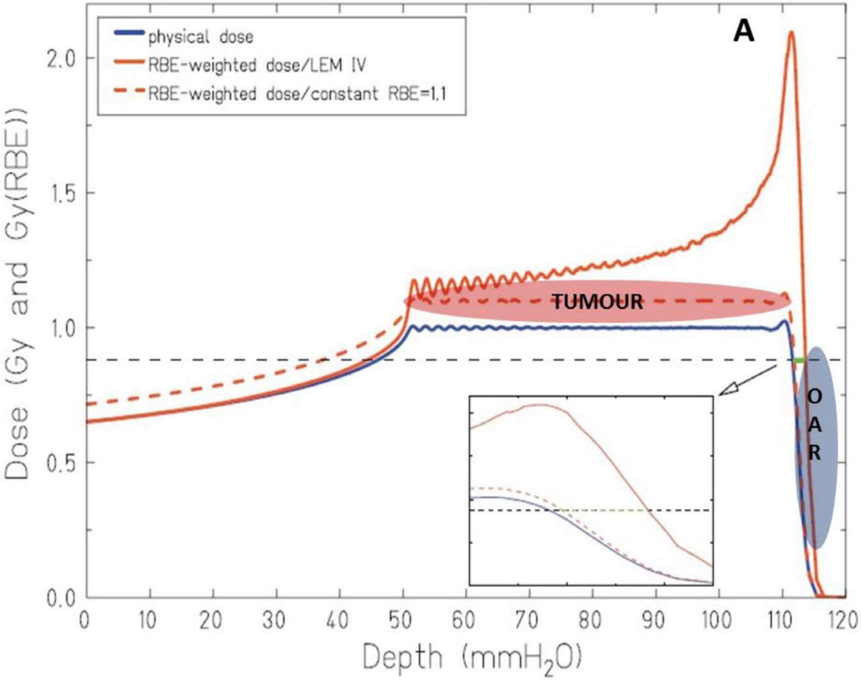
Relative Biological Effectiveness (RBE)



Higher RBE for protons

Usually, a value of
RBE = 1.1 is used

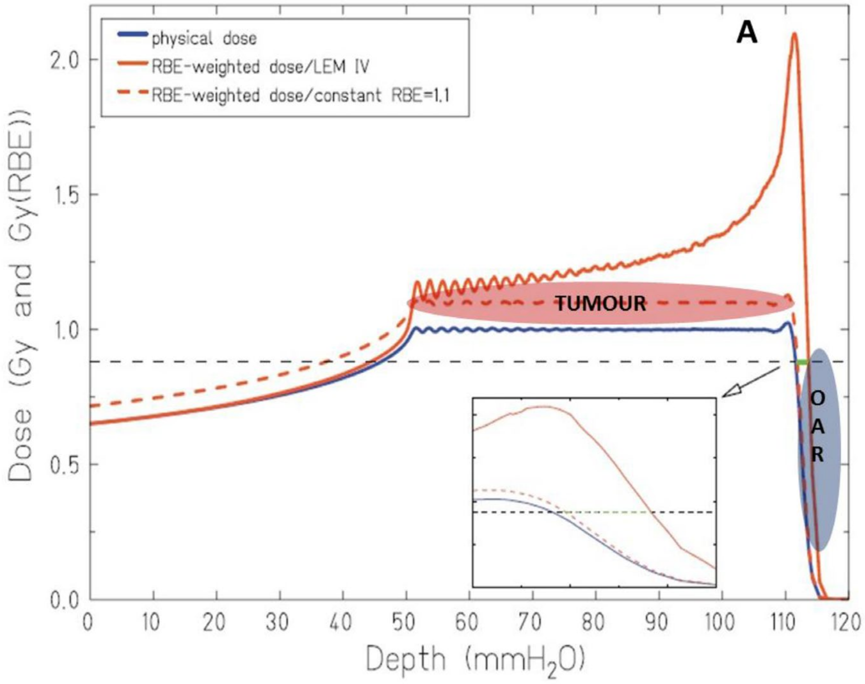
RBE



Francesco Tommasino and Marco Durante, Proton Radiobiology, Cancers 2015

… but this value is far from constant

RBE



oops…

… but this value is far from constant

Francesco Tommasino and Marco Durante, Proton Radiobiology, Cancers 2015

Proton therapy: why?

Less integral dose

but, not always best option

Less secondary cancers

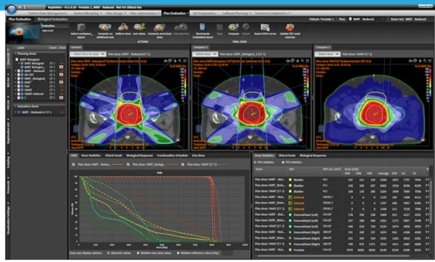
especially in, for example, pediatrics

Higher RBE

but not completely understood

IV. Proton therapy: how?

Proton therapy: how?

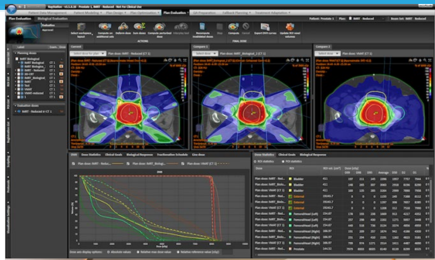


I. Planning

Proton therapy: how?

I. Planning

II. Production of protons

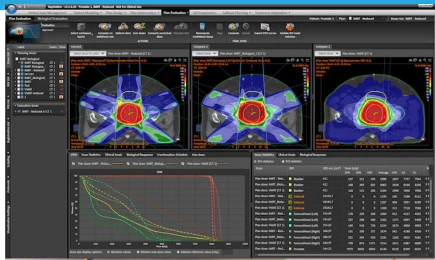


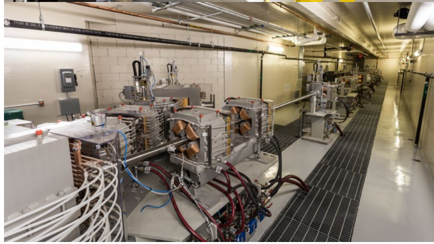
Proton therapy: how?

I. Planning

II. Production of protons

III. Transport of protons





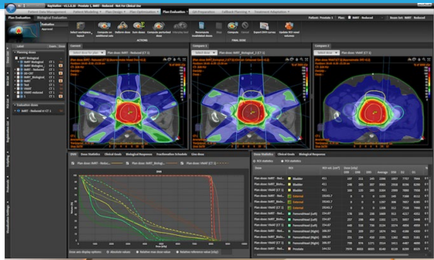
Proton therapy: how?

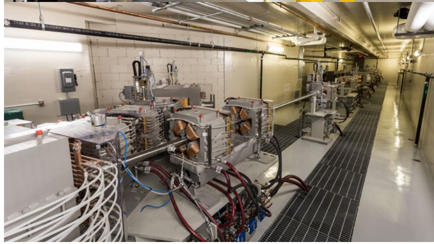
I. Planning

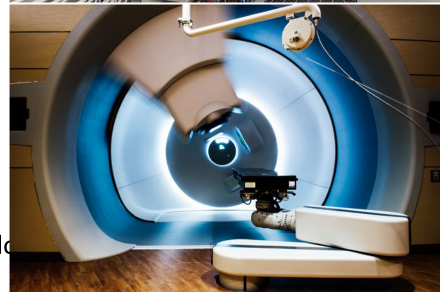
II. Production of protons

III. Transport of protons

IV. Delivery of protons to patient







Planning

Dedicated treatment planning software

Still mainly based on **analytical** beam models

Spots are determined, optimization based on goals:

a) High, uniform dose to target

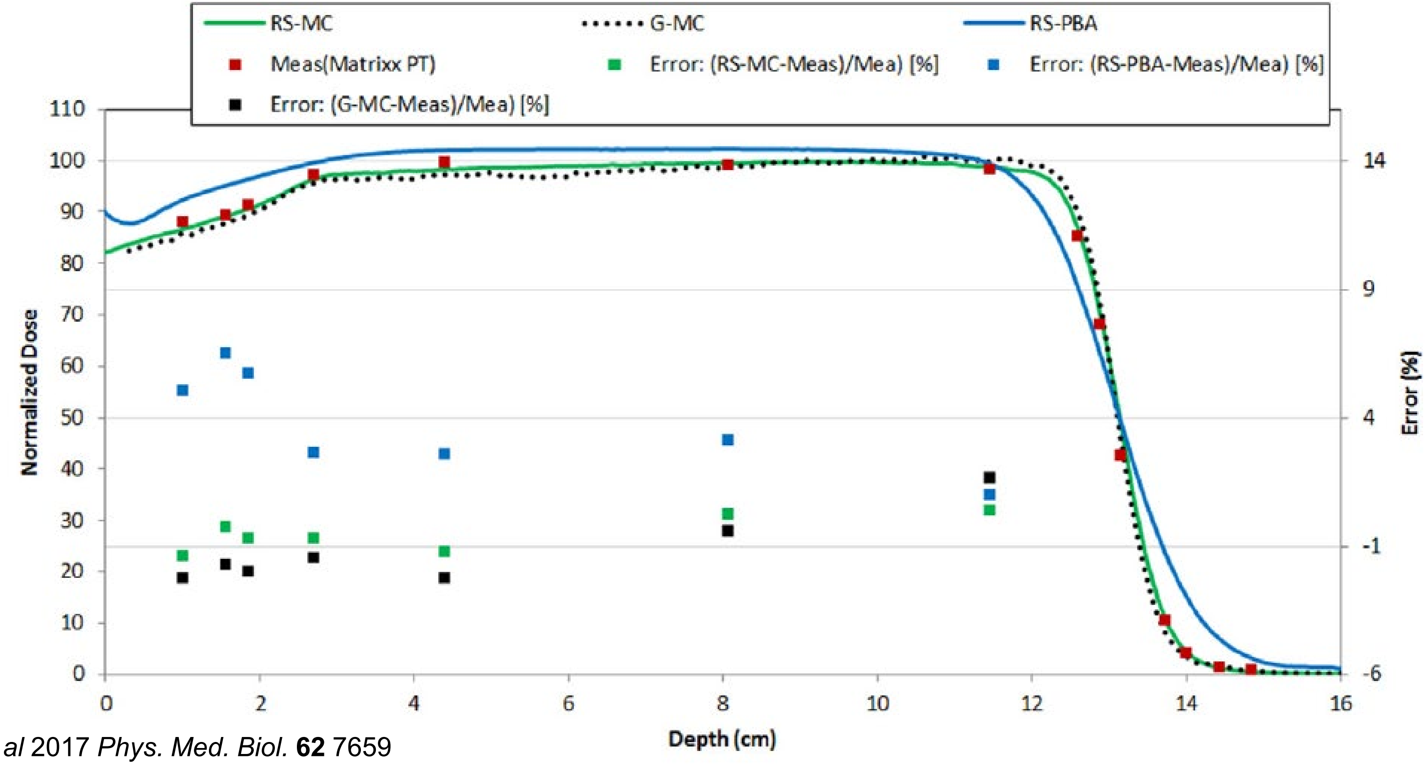
b) Low dose to organs at risk, based on sensitivity of OAR

Number of fields (and angles) usually not optimized

Usually 2-5 fields per treatment plan

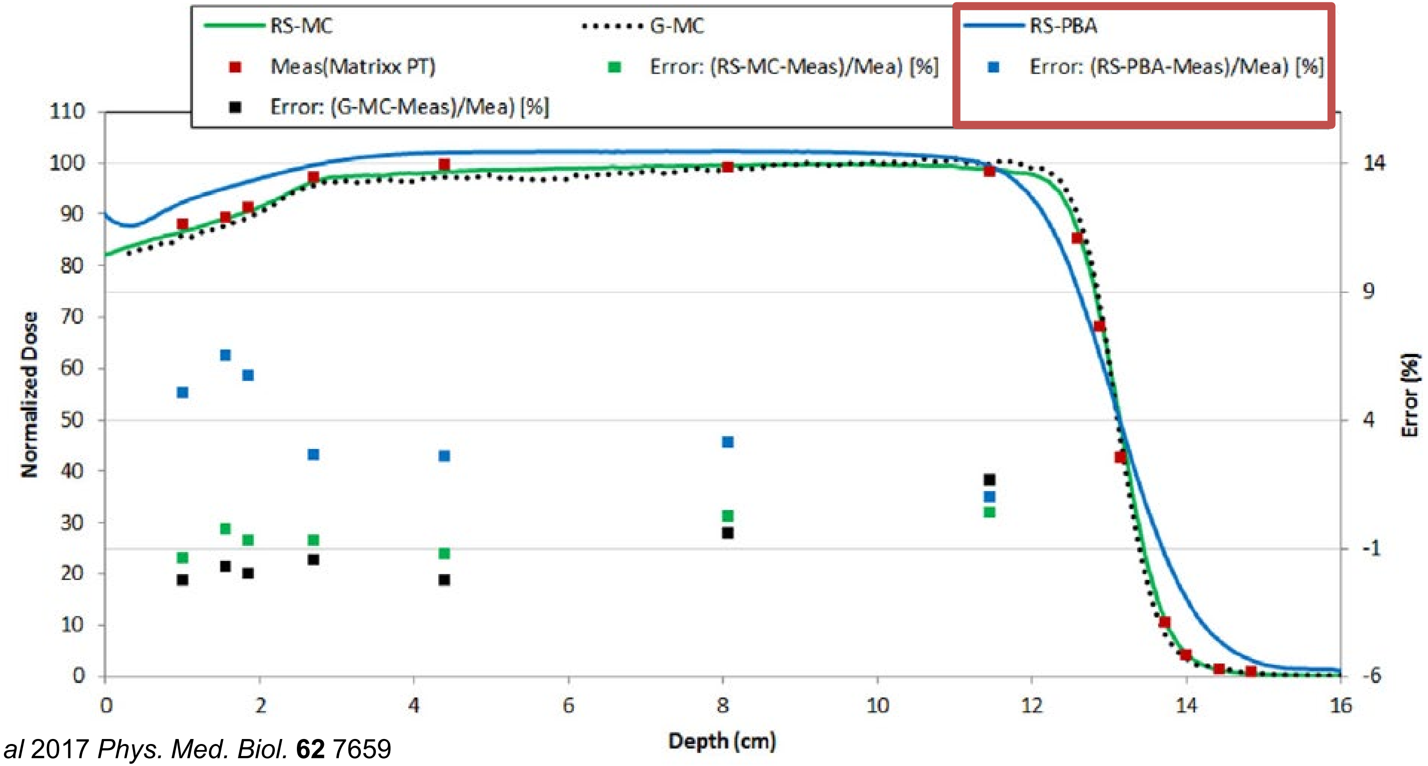
Based on **CT and/or MR imaging**

Planning



Jatinder Saini *et al* 2017 *Phys. Med. Biol.* **62** 7659

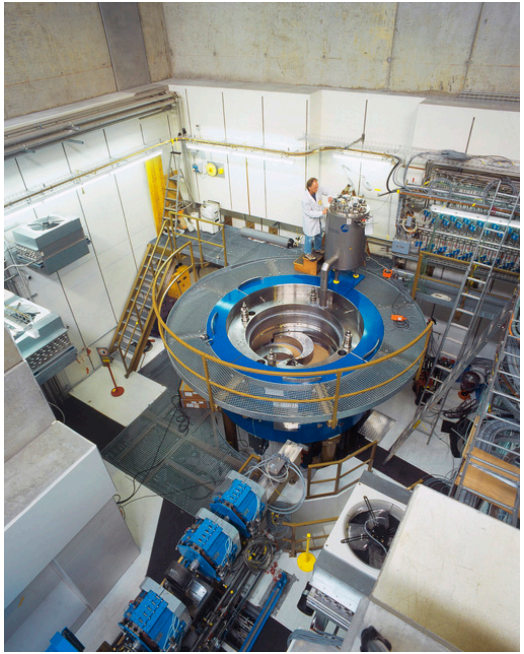
Planning



Jatinder Saini *et al* 2017 *Phys. Med. Biol.* **62** 7659

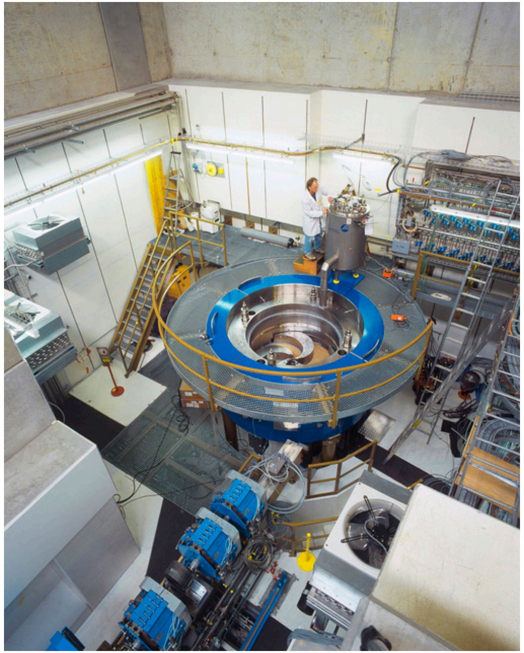
Production of protons

(Synchro)cyclotron



or synchrotron

Production of protons: cyclotron

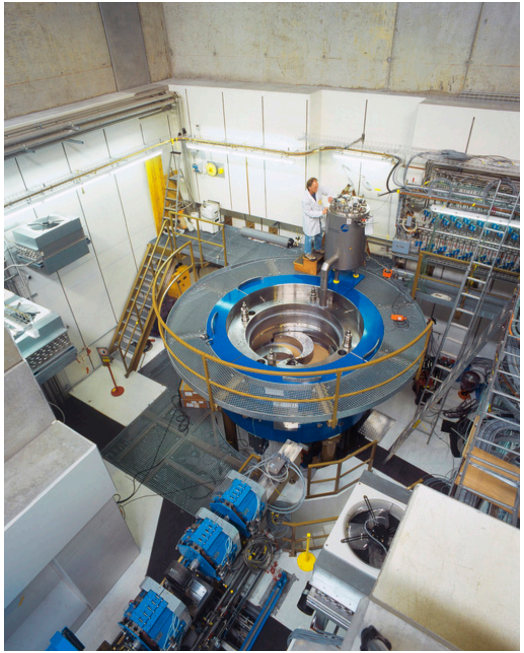


Energy usually around 250 MeV

Energy selection with degrader

Continuous beam

Production of protons: cyclotron



Energy usually around 250 MeV

Energy selection with degrader

Continuous beam

Activation

(no carbon yet)

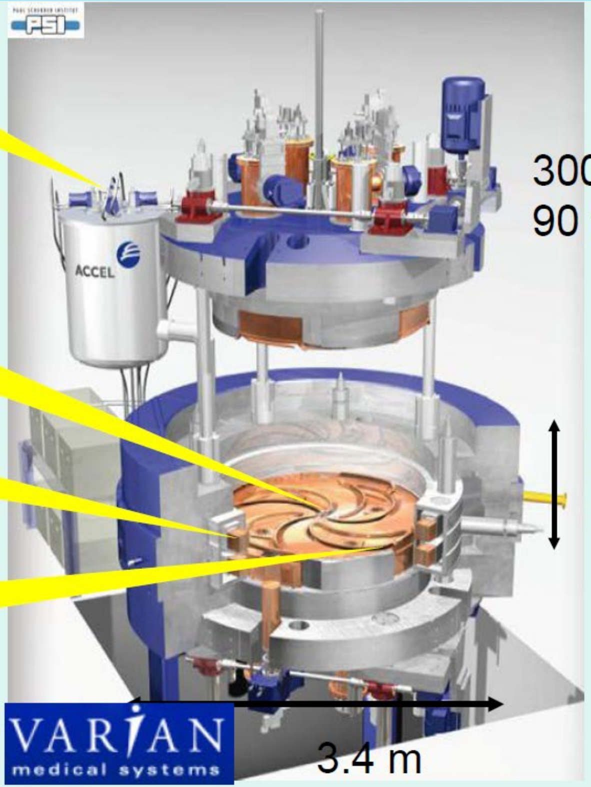
250 MeV proton cyclotron

Closed He system
4 cryocoolers

Proton source

superconducting coils
=> 3 T

4 RF-cavities:
~80 kV at 72 MHz



300 kW
90 tons

Production of protons: synchrotron

Adjustable energy

Low activation

(Carbon) ions

Limited intensity (average)

Large/expensive

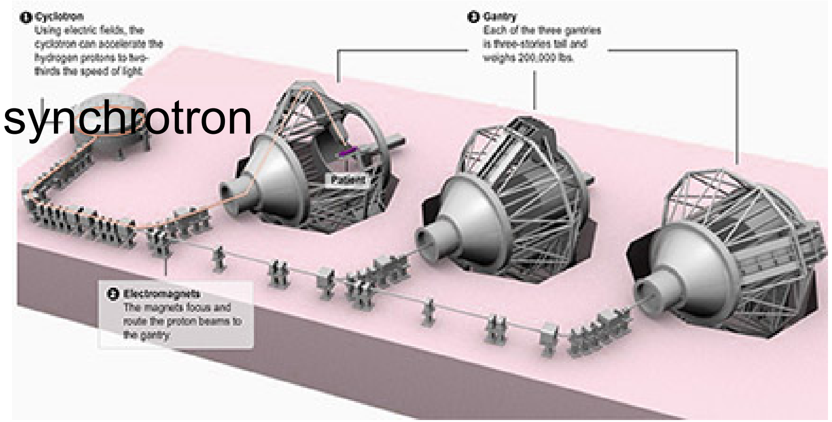
Production of protons

	Cyclotron	Synchrotron
Carbon	In development	Easy
Multiple particles	In development	Easy
Size (diameter)	3.5 – 5 m (SC < 2 m)	6 – 8 m (^{12}C: 25m)
Intensity	Adjustable (SC: low)	Limited (per spill)
Fast E scanning	Degrader (activation)	Next spill
Time structure	Cont (SC: pulsed)	Dead time
Spot scanning	Yes	Yes
– Continuous SS	– Yes (SC: no)	– Difficult

Transport of protons

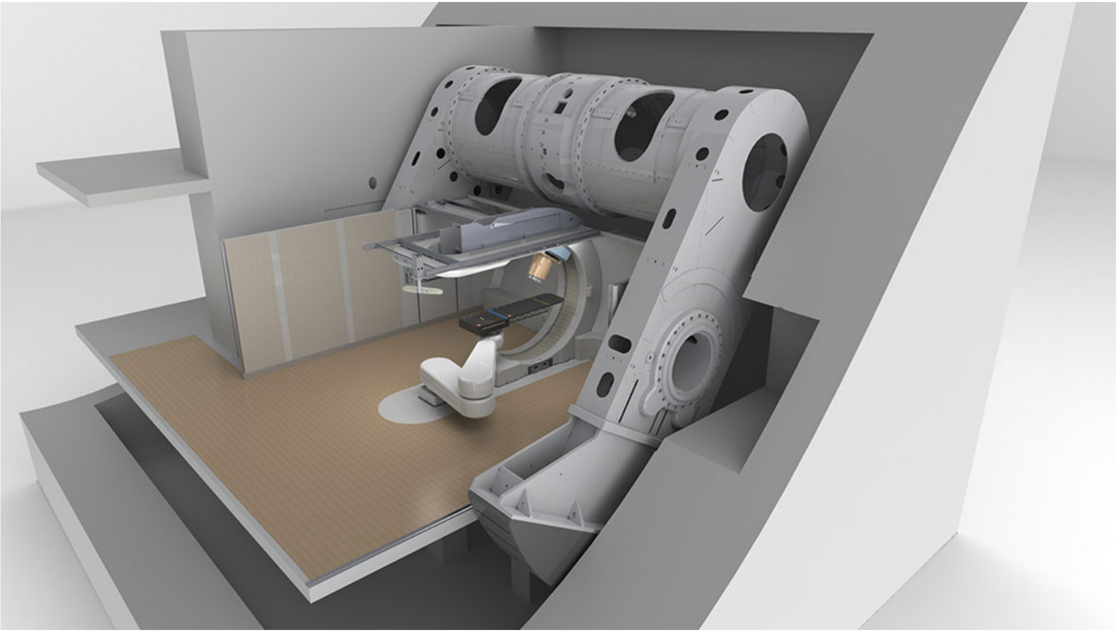
Usually a single accelerator, shared by several gantries

or synchrotron



Transport of protons

But systems with accelerator on gantry exist



Mevion S250

Delivery of protons

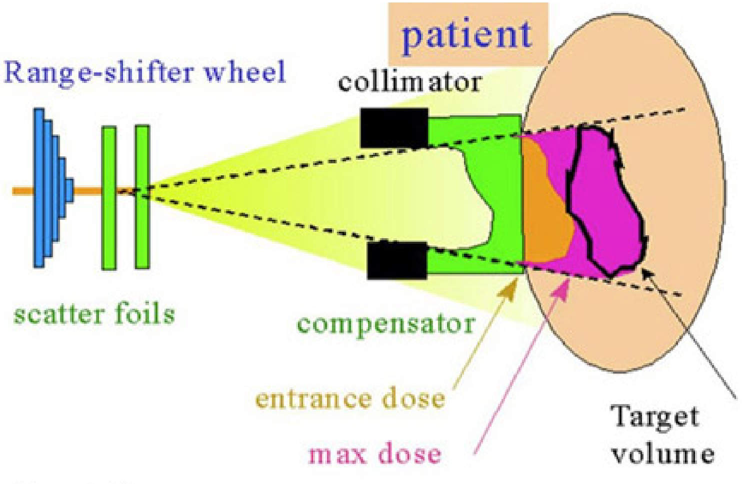
Delivery, per field, of planned dose to target

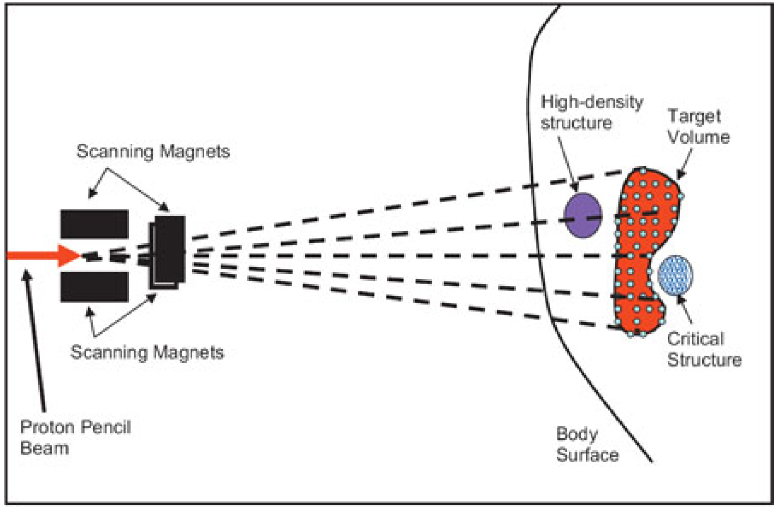
Timing is dependent on a lot of parameters

i. Target size
ii. Number of spots per field
iii. Dose to be delivered
iv. Proton current
v. …

In the order of a few Gy per minute

Delivery of protons

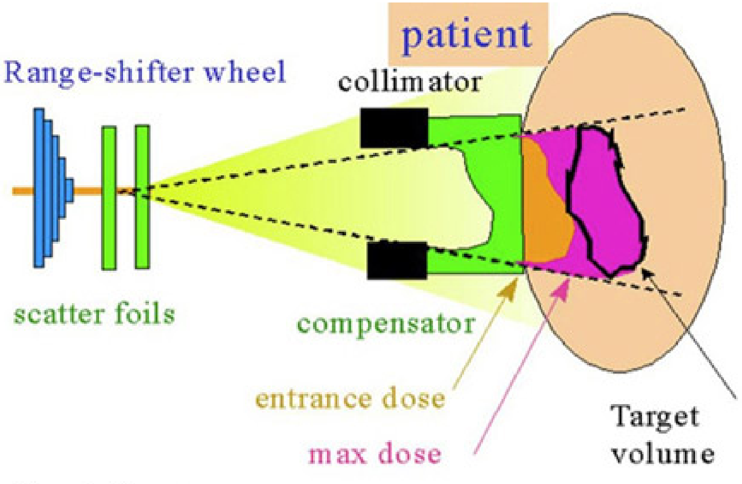


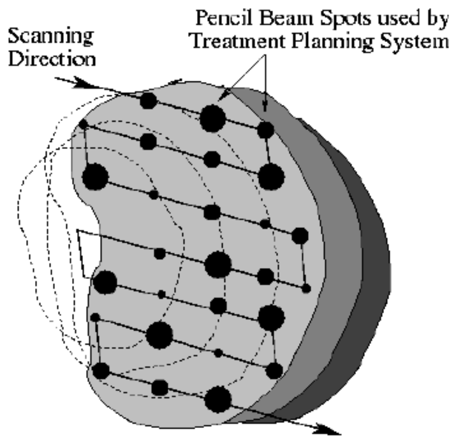


Dose distribution determined by **distal edge**.

Dose distribution determined by **individual Bragg Peaks**.

Delivery of protons

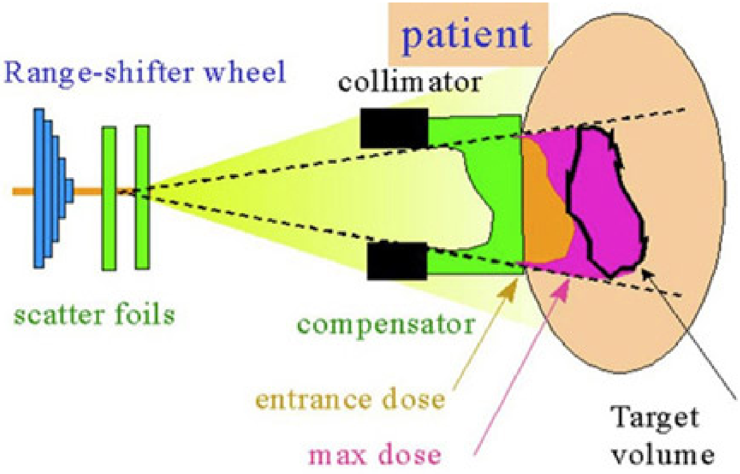


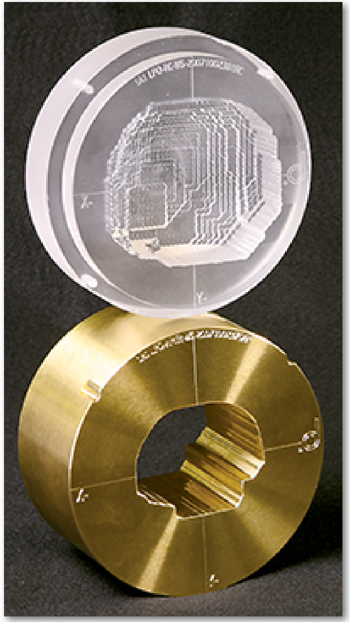


Dose distribution determined by **distal edge**.

Dose distribution determined by **individual Bragg Peaks**.

Delivery of protons: passive scattering





Time intensive

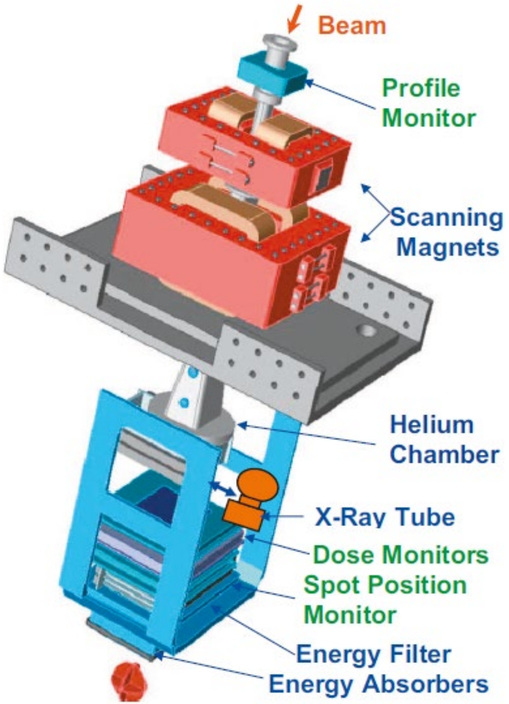
Patient specific

Activation

Non-optimal dose distribution

Becoming obsolete

Delivery of protons: scanning



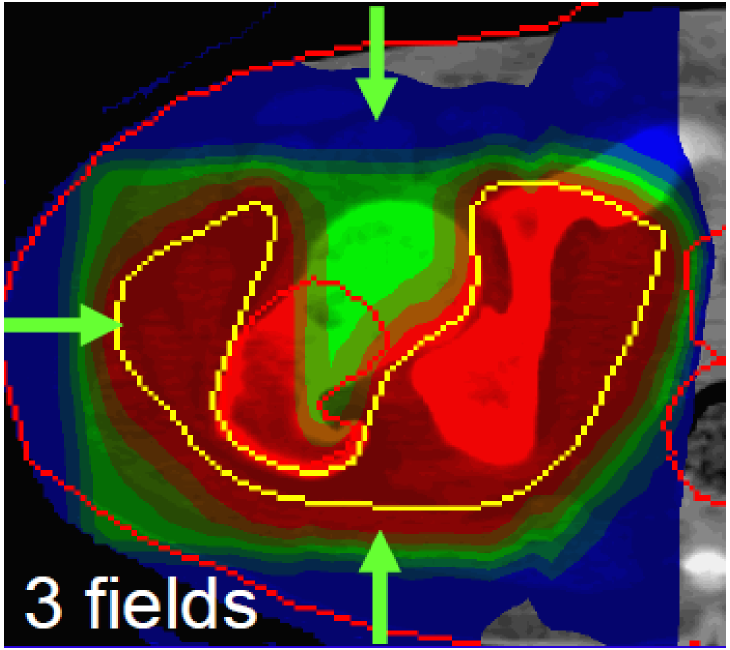
Less preparation

Not patient specific

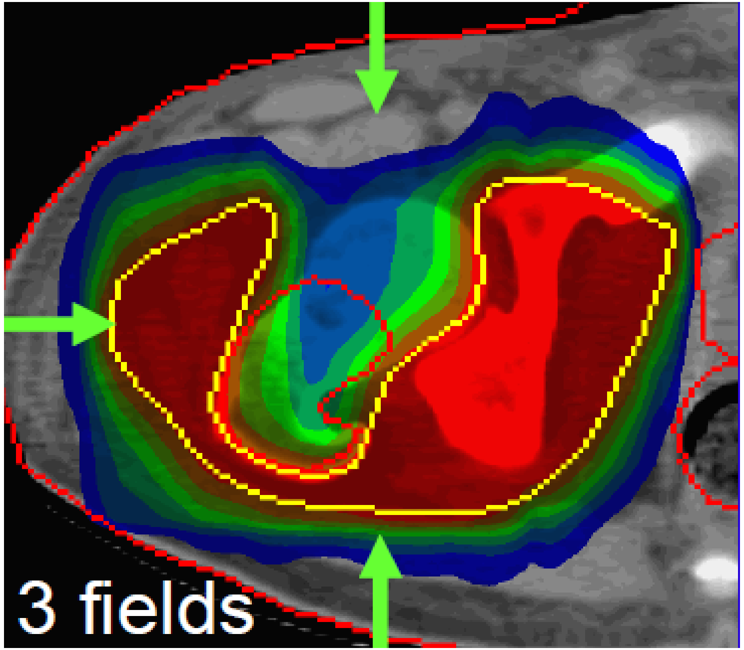
Best dose distribution

All new machines

Delivery of protons: scattering vs scanning



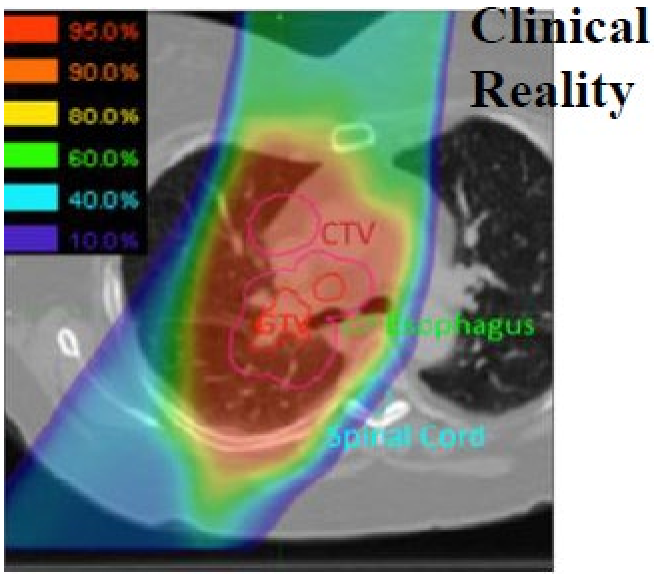
Passive scattering

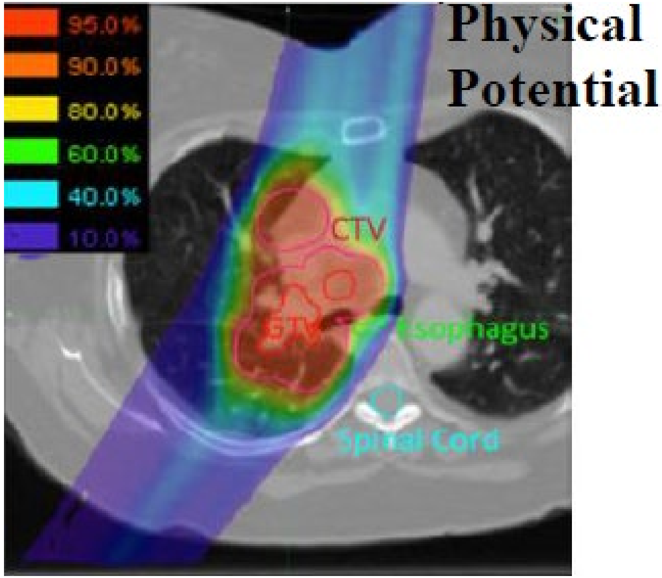


3-field pencil beam scanning

Tony Lomax

Delivery of protons: fields and optimization





Jay Flanz

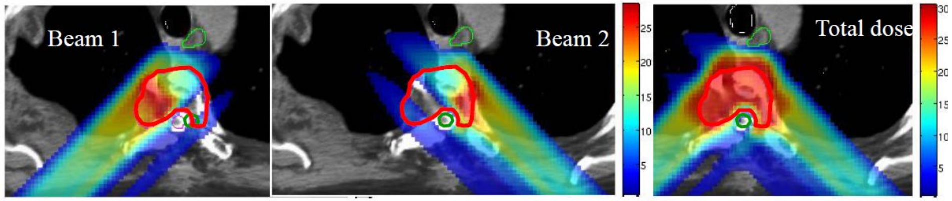
Delivery of protons: fields and optimization

i. Single Field Uniform Dose Optimization
   all fields deliver a uniform dose to the target

Delivery of protons: fields and optimization

i. Single Field Uniform Dose Optimization
 all fields deliver a uniform dose to the target

ii. Multi Field Optimization
 every field may not be uniform, combined dose is



Jay Flanz

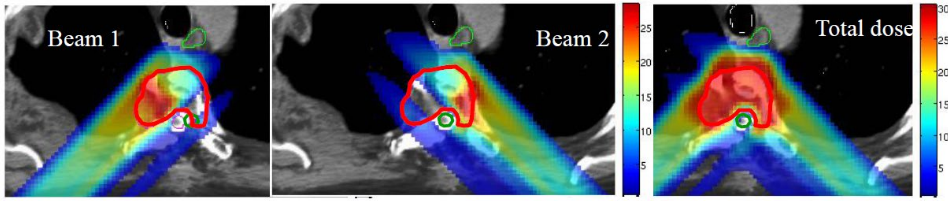
Delivery of protons: fields and optimization

i. Single Field Uniform Dose Optimization

all fields deliver a uniform dose to the target

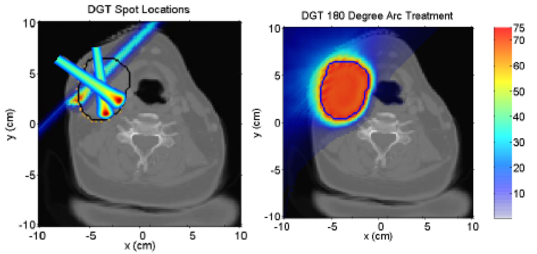
ii. Multi Field Optimization

every field may not be uniform, combined dose is



iii. Distal edge tracking

Delivery to distal edge



Proton therapy: how?

Planning can be improved

still analytical and not all parameters are optimized

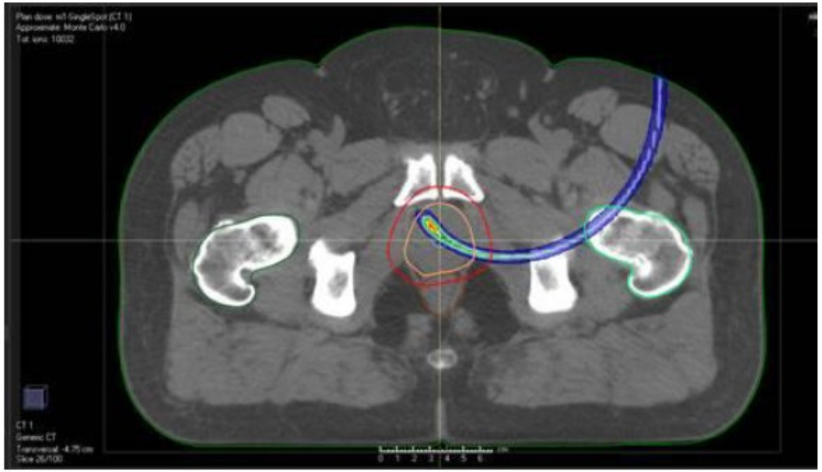
Cyclotron or synchrotron for protons

no ‘best’ option

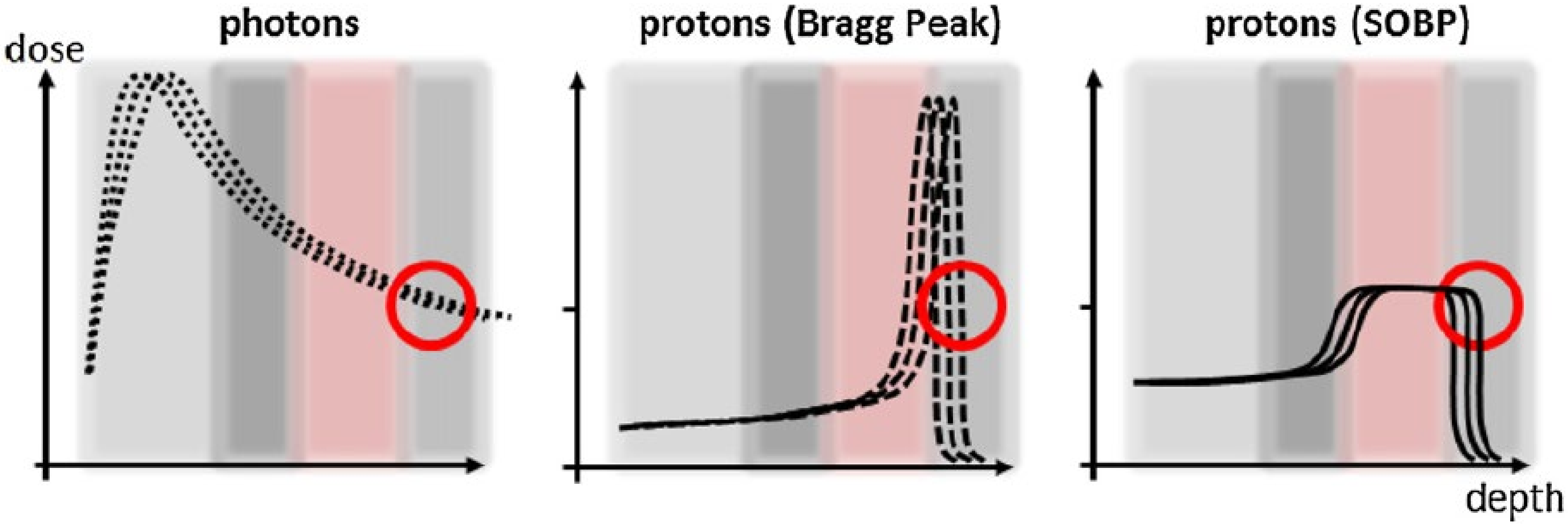
Different techniques for delivery

scanning is new standard

V. Challenges and developments



Uncertainties



Larger effect for protons

Knopf and Lomax

Uncertainties

I. What tissue? Composition? **Imaging**!

II. Motion

Compensation by breathold, repainting (‘averaging’), gating, robust planning, tracking, so **imaging**!

III. Anatomical changes (tumor shrinkage, cavity filling)

Compensation by replanning, **imaging**!

Current imaging

CT has problems

i. Low resolution
ii. Low soft-tissue contrast
iii. Ionizing radiation

Current imaging

CT has problems

i. Low resolution
ii. Low soft-tissue contrast
iii. Ionizing radiation

MRI had advantages

i. Superior contrast
ii. Good resolution
iii. No ionizing radiation

Current imaging

CT has problems

i. Low resolution
ii. Low soft-tissue contrast
iii. Ionizing radiation

MRI had advantages

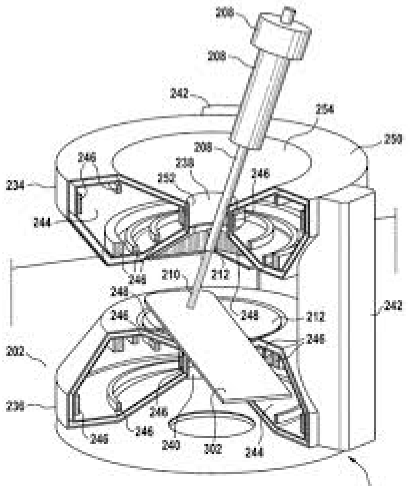
i. Superior contrast
ii. Good resolution
iii. No ionizing radiation

and problems

i. Relative values
ii. Not easy to get stopping powers
iii. Complicated technique

MRI-guidance

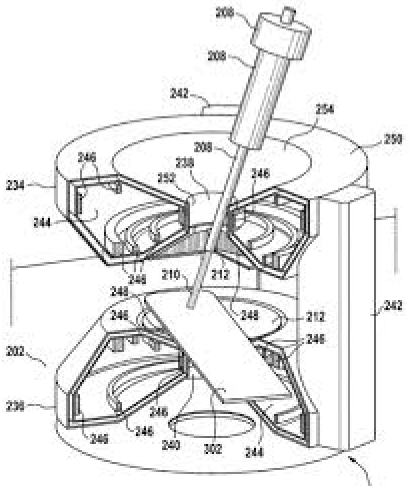
Based on MR-Linac, integrated MR - proton therapy system



Original philips design

MRI-guidance

Based on MR-Linac, integrated MR - proton therapy system



Original philips design

Problems:

A. Magnetic field effects on the Bragg Peak
   i. Inside MR
   ii. Fringe fields

B. Steering magnets close to MR magnet?

C. How do you get the protons inside MR?

MRI-guidance

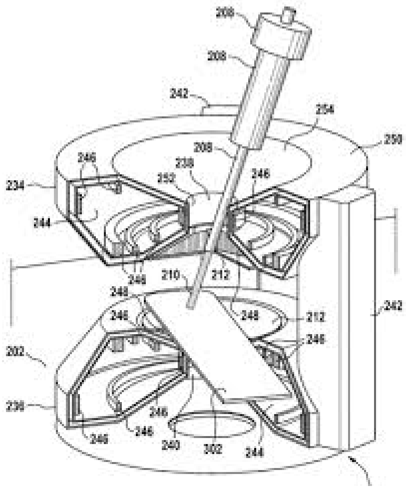
Based on MR-Linac, integrated MR - proton therapy system

Problems:

A. Magnetic field effects on the Bragg Peak
   i. Inside MR
   ii. Fringe fields

B. Steering magnets close to MR magnet?

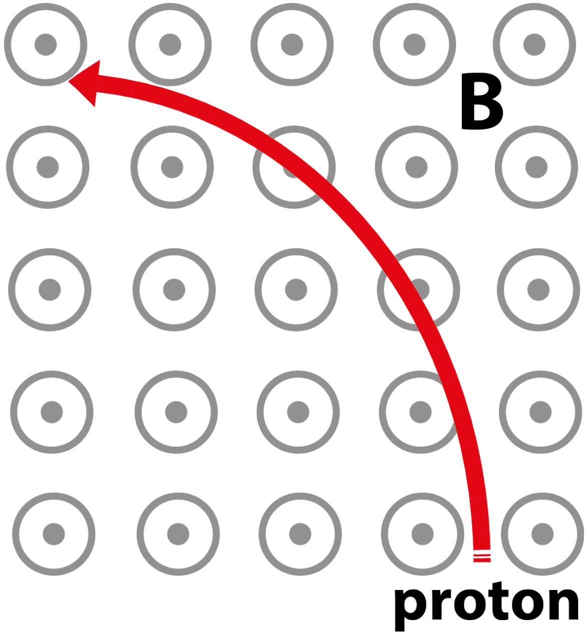
C. How do you get the protons inside MR?



Original philips design

MRI-guidance: field effects

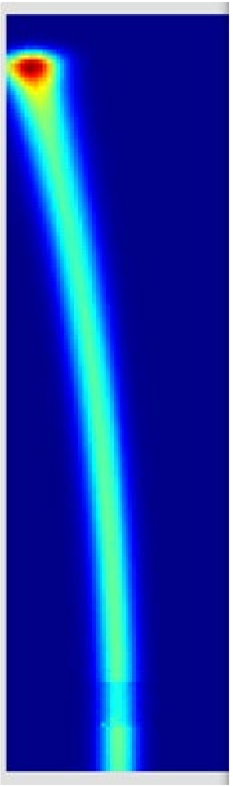
Curvature

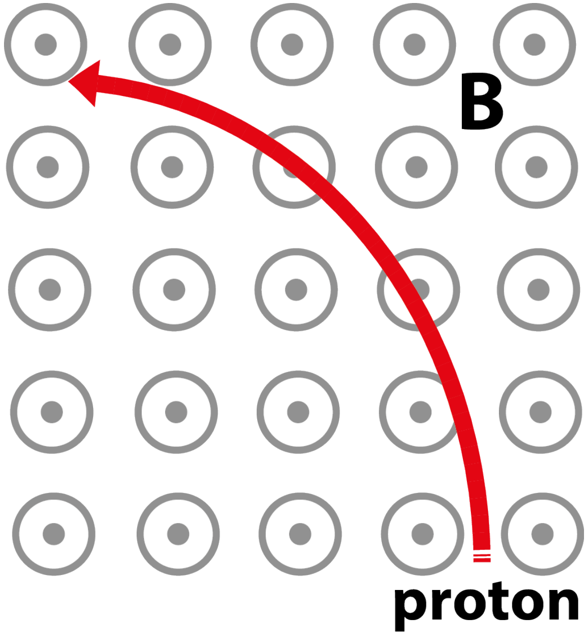


MRI-guidance: field effects

Curvature

So Bragg peak ends up at other location



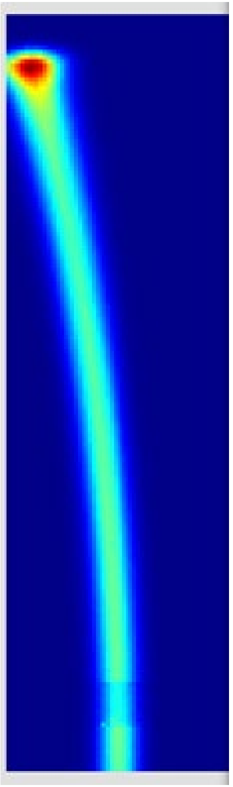


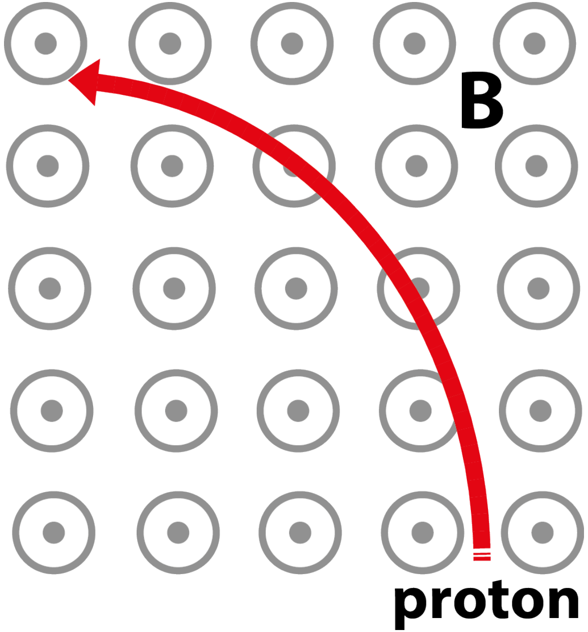
MRI-guidance: field effects

Curvature

So Bragg peak ends up at other location

Of course well known physics





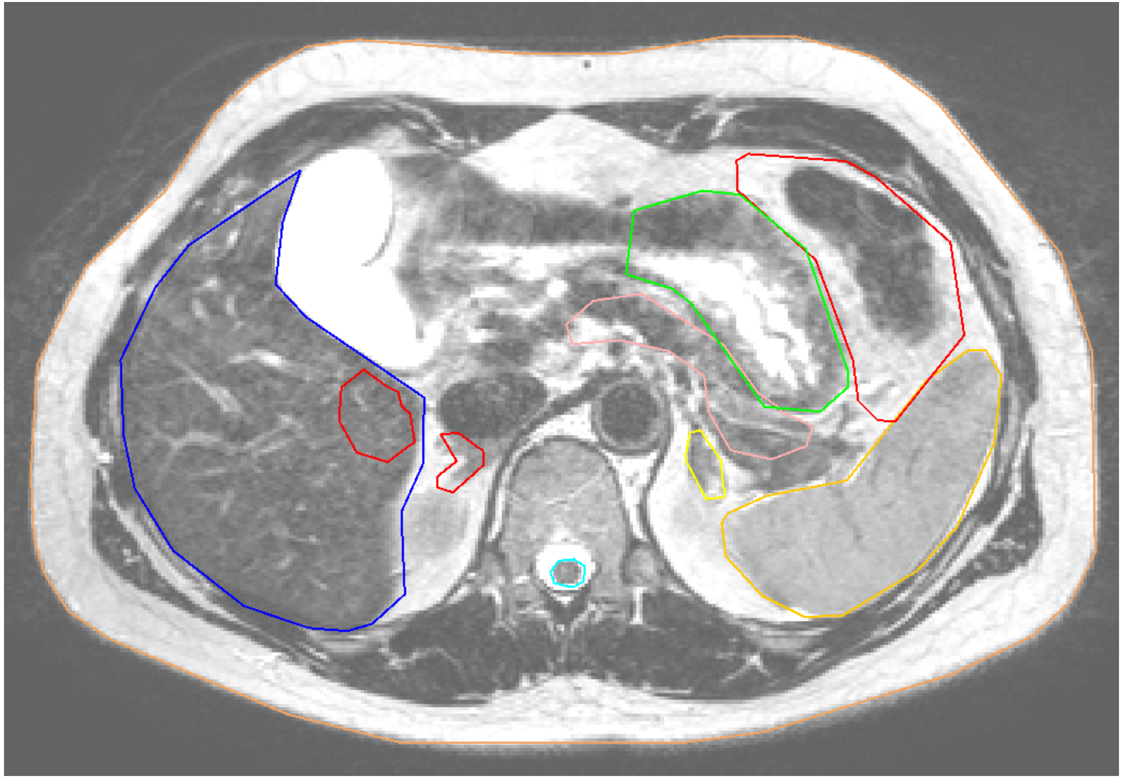
MRI-guidance: planning

But.. not straightforward to determine position in tissue, espescially with analytical methods

MRI-guidance: planning

But.. not straightforward to determine position in tissue, espescially with analytical methods

MRI-guidance: planning



MRI-guidance: planning

Image data

↓ 0T and 1.5T

Generate beamlets
(Low statistics)

↓

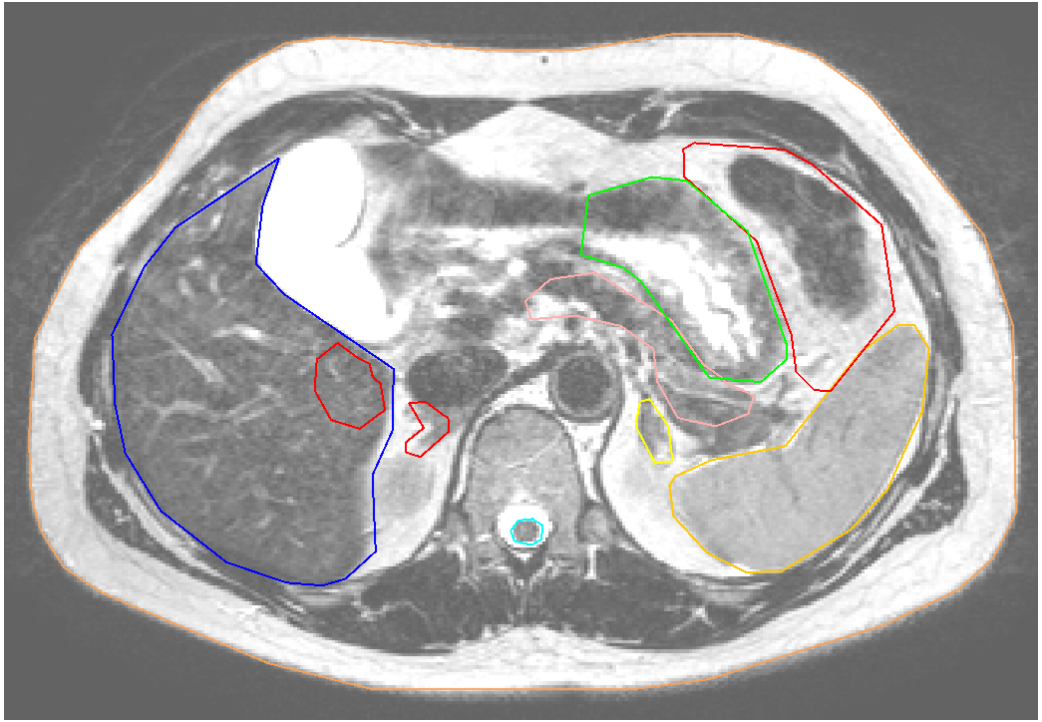
Select beamlets inside target

↓

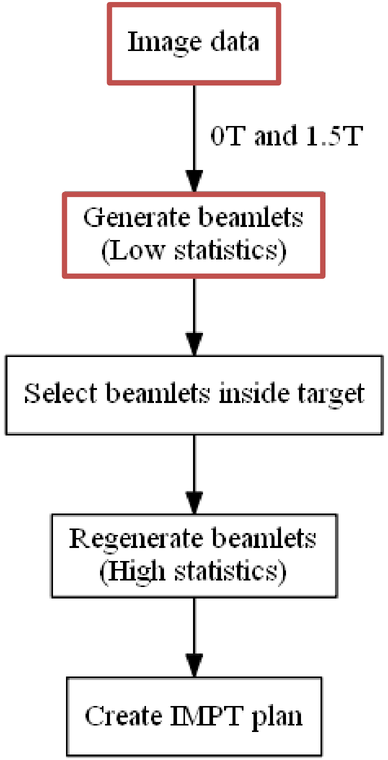
Regenerate beamlets
(High statistics)

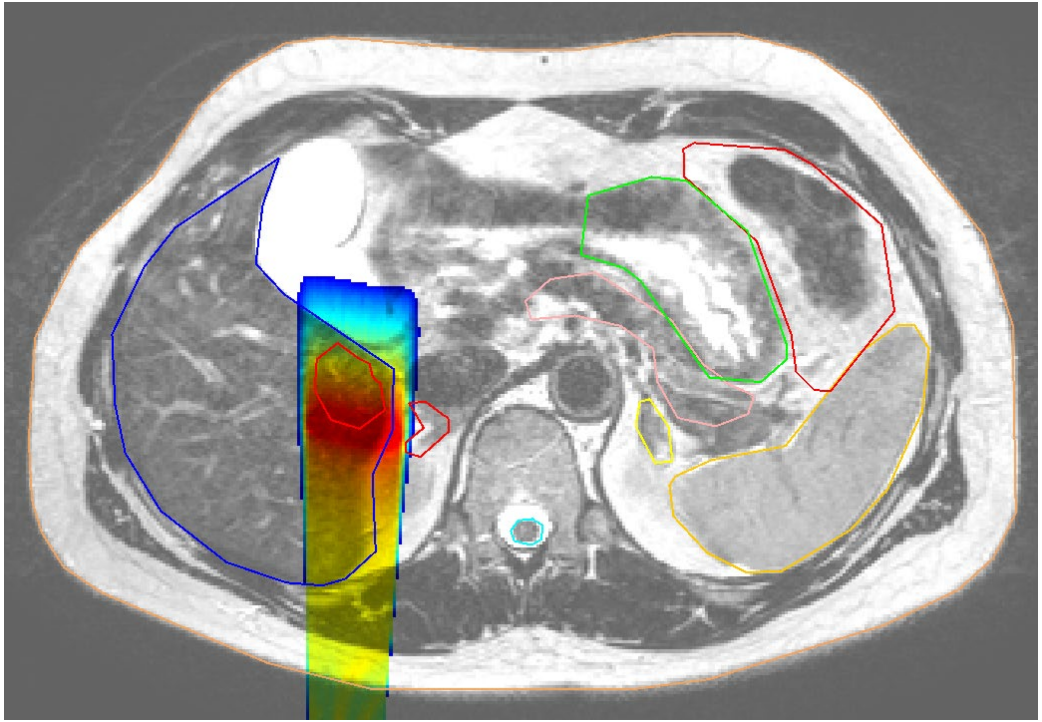
↓

Create IMPT plan

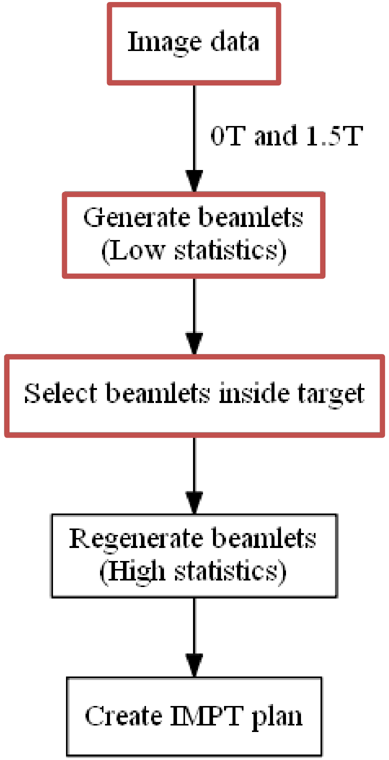


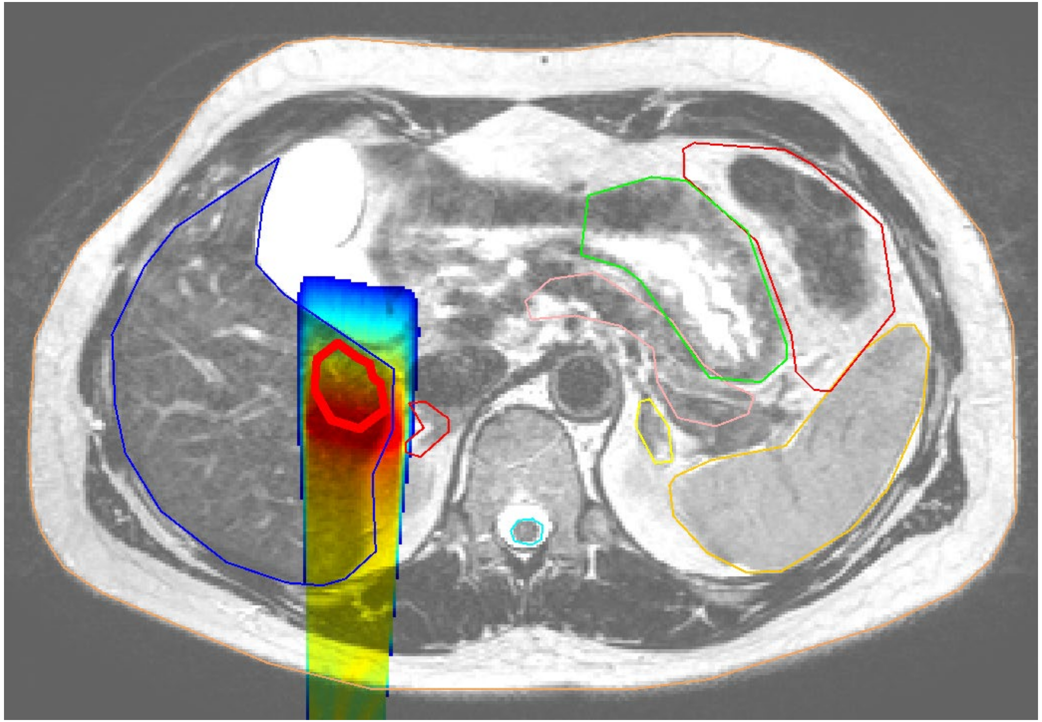
MRI-guidance: planning





MRI-guidance: planning





MRI-guidance: planning

Image data

↓ 0T and 1.5T

Generate beamlets
(Low statistics)

↓

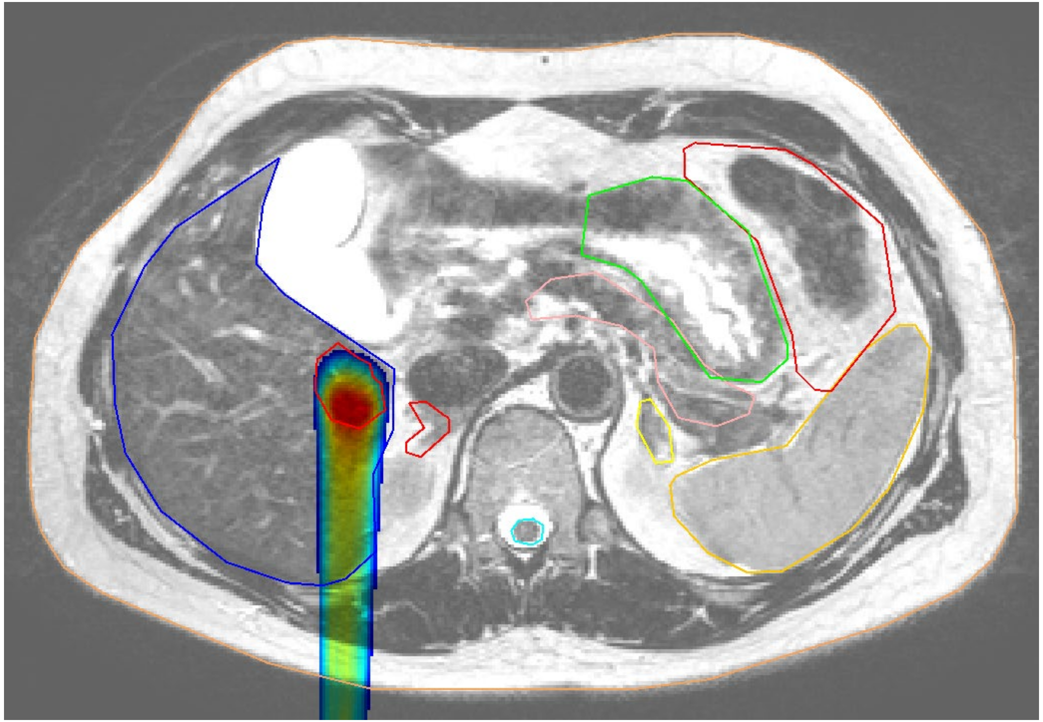
Select beamlets inside target

↓

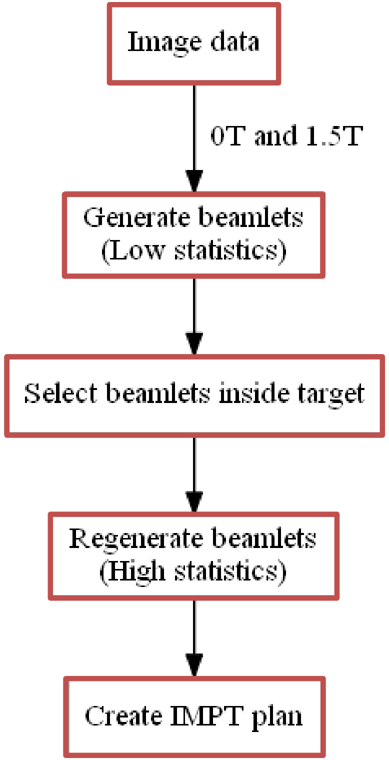
Regenerate beamlets
(High statistics)

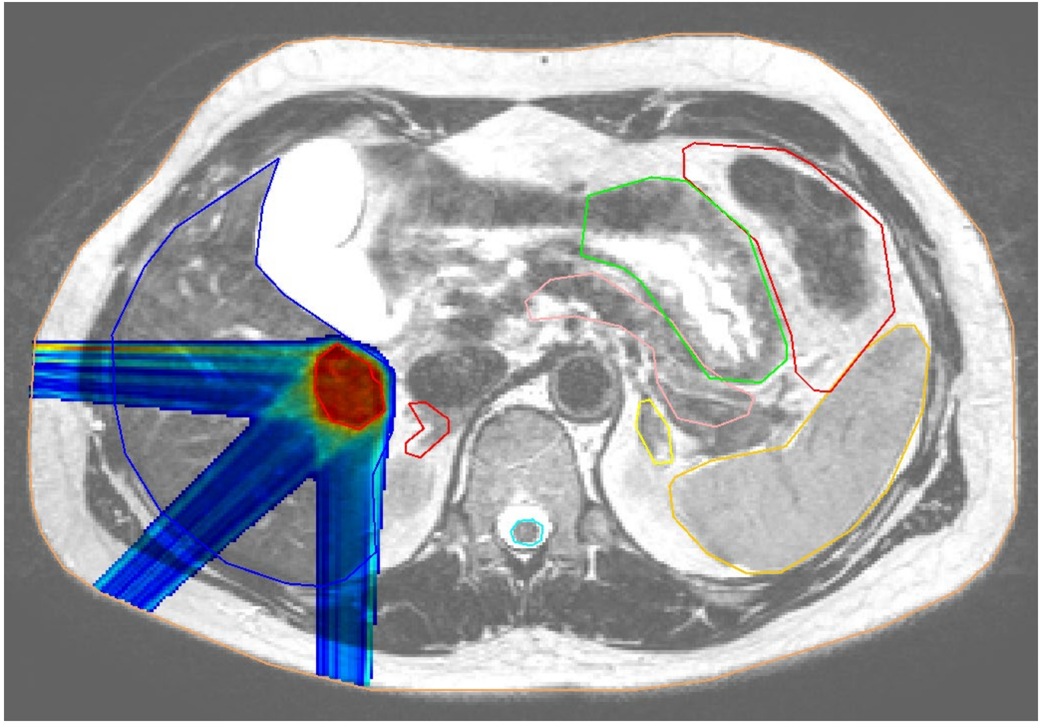
↓

Create IMPT plan



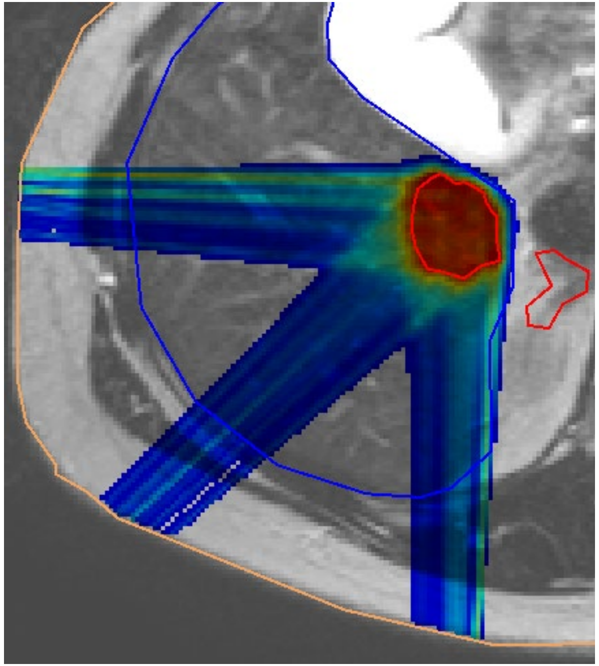
MRI-guidance: planning



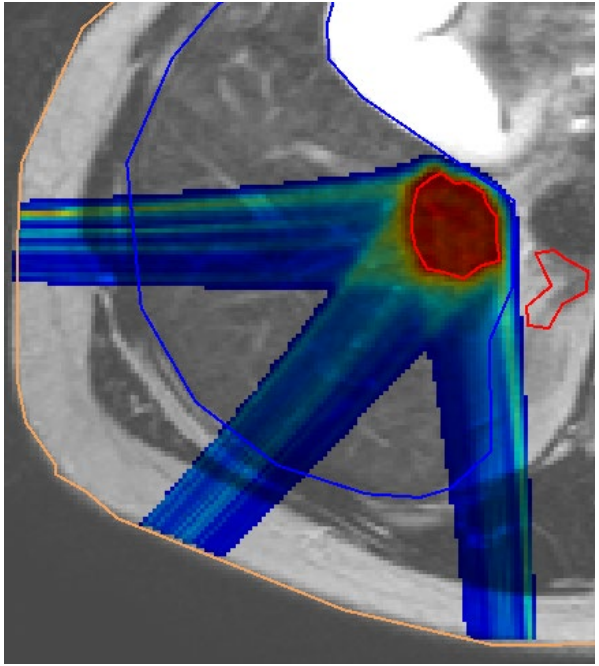


MRI-guidance: planning

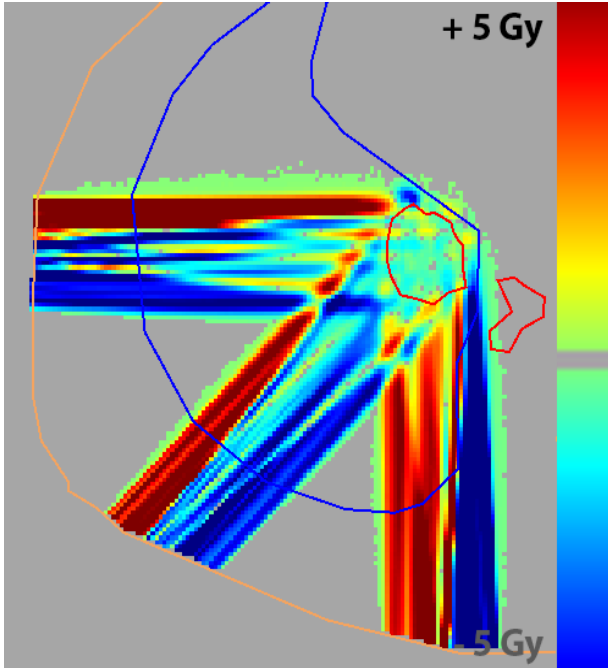
No field



1.5T



Difference



MRI-guidance: planning

Advantages

i. Monte Carlo gives highest precision

ii. You get magnetic field ‘for free’

MRI-guidance: planning

Advantages

i. Monte Carlo gives highest precision

ii. You get magnetic field ‘for free’

Disadvantage: slow…

MRI-guidance: planning

Advantages

i. Monte Carlo gives highest precision

ii. You get magnetic field ‘for free’

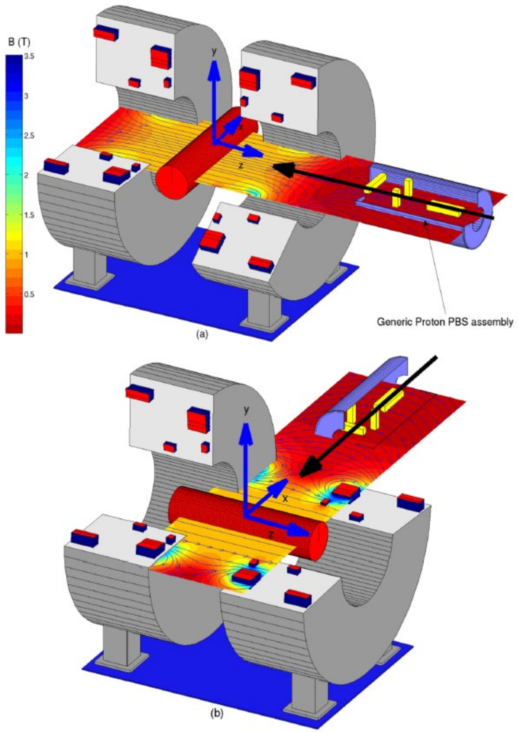
Disadvantage: slow…

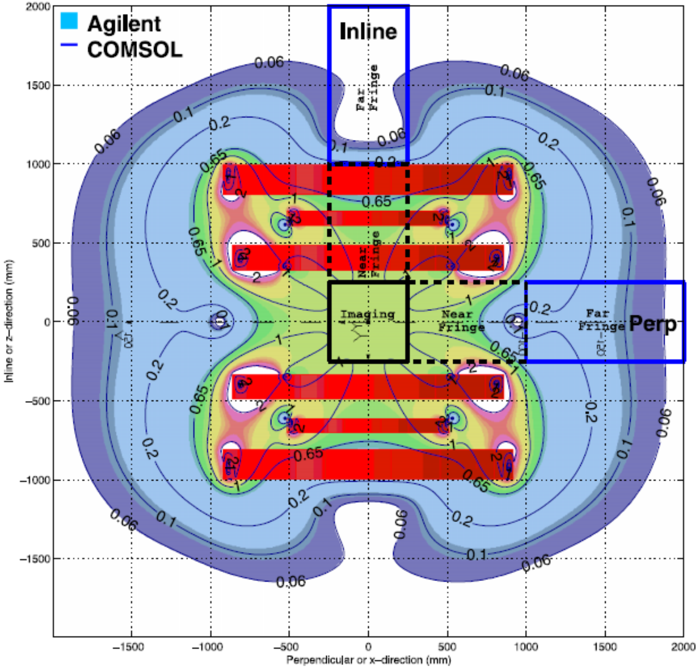
Solutions

i. GPU MC

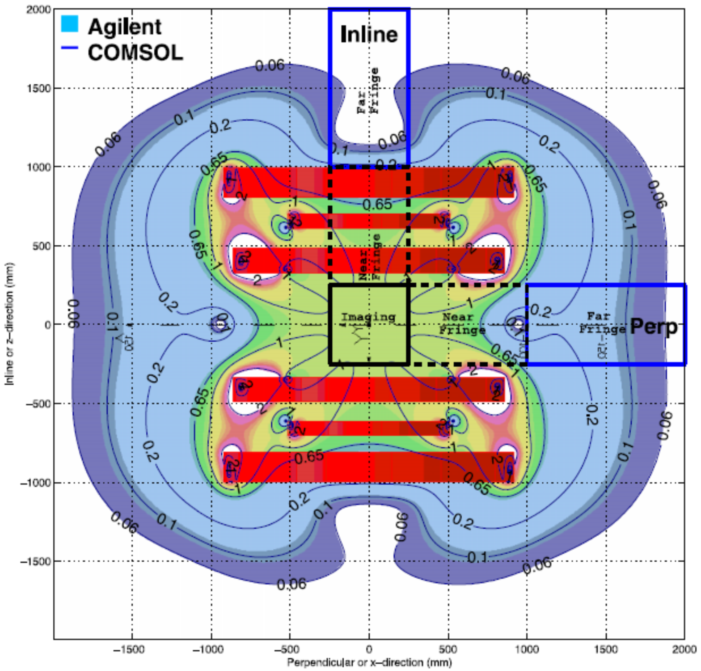
ii. Simplification

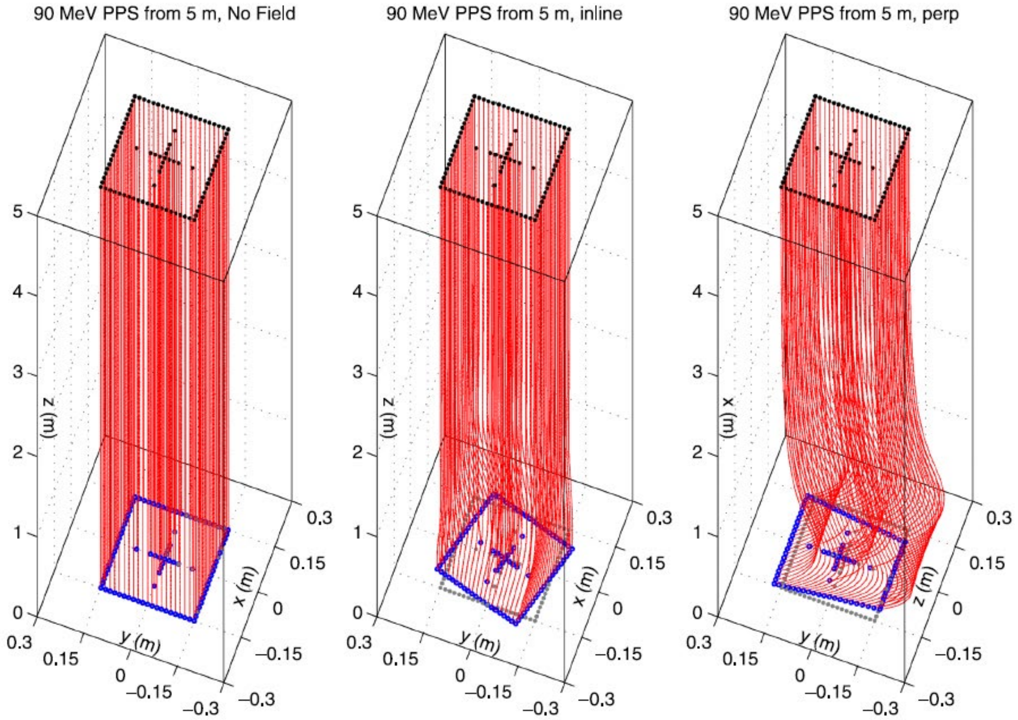
Magnetic fields: beam entrance



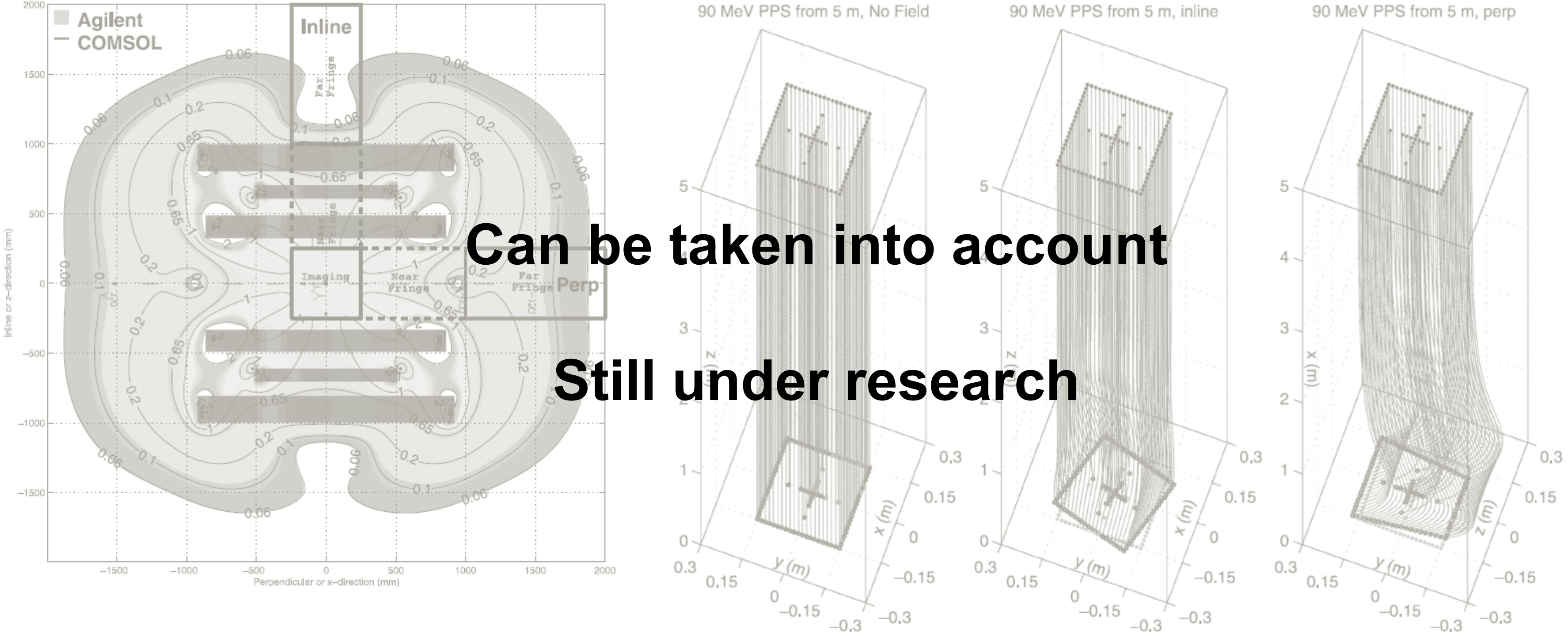


Magnetic fields: complicated





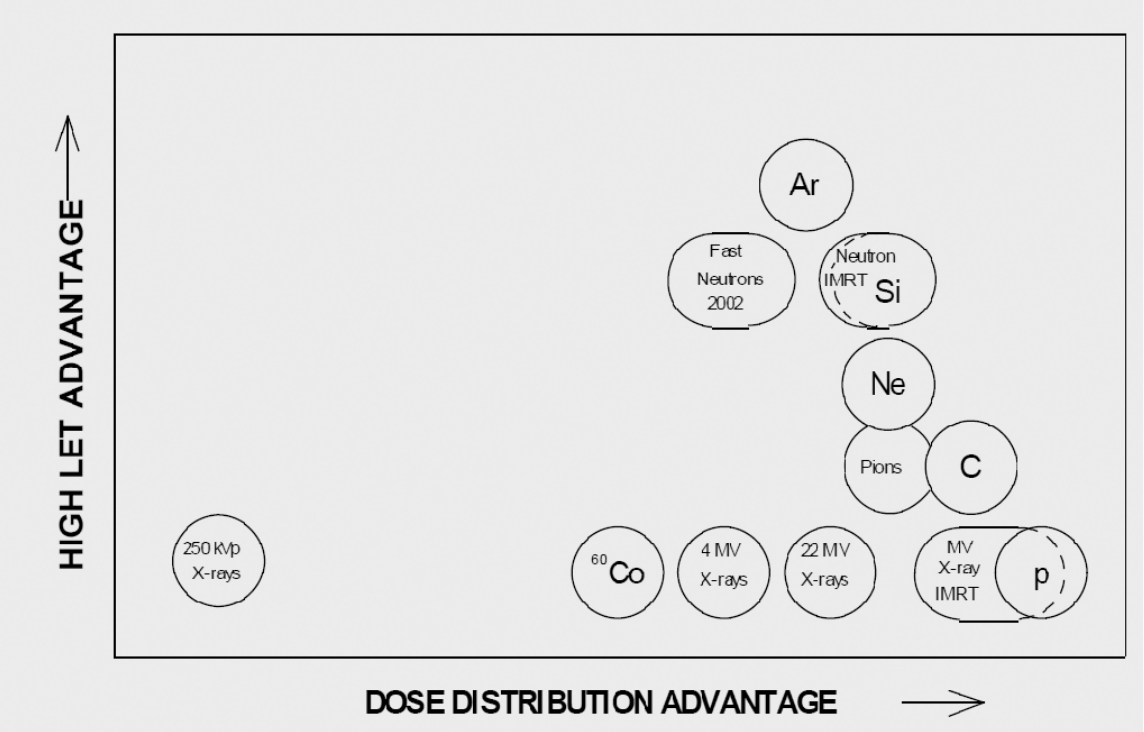
Magnetic fields: complicated



Can be taken into account

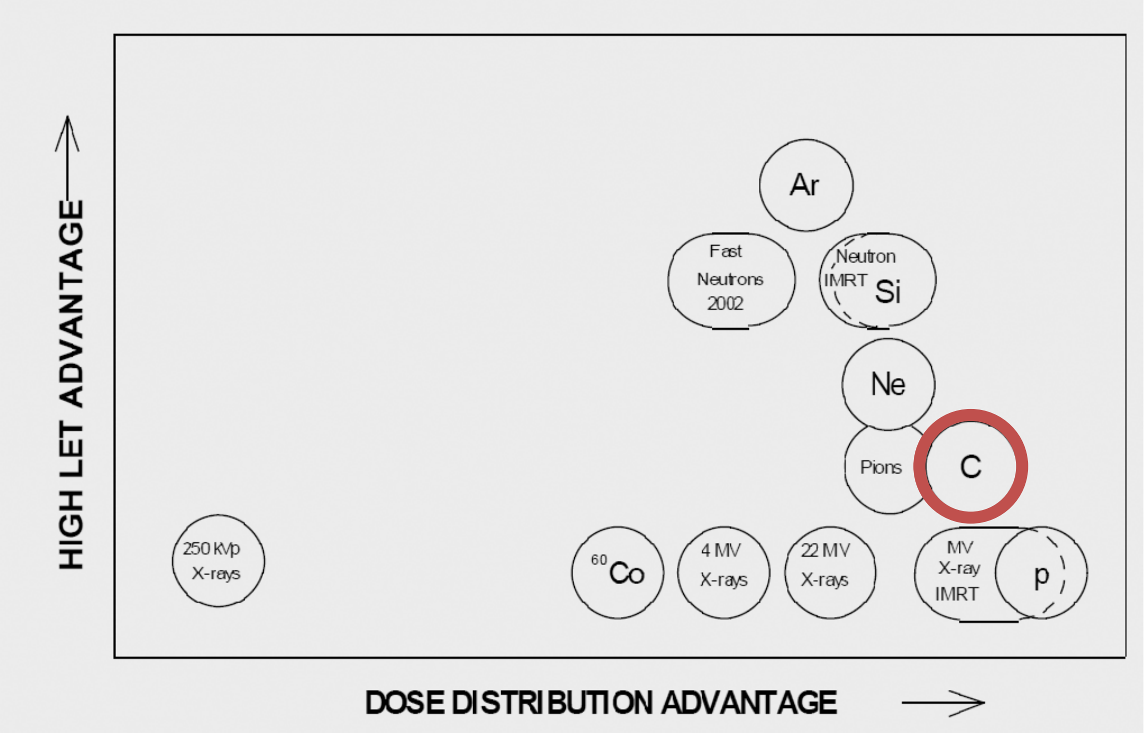
Still under research

Heavy particles



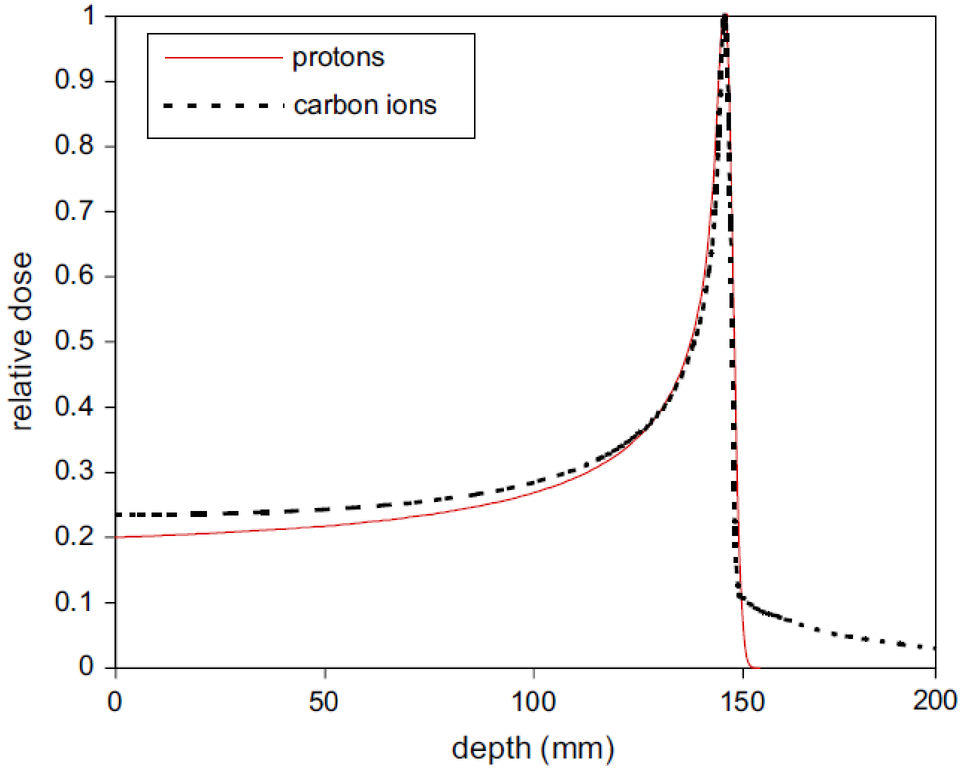
A. Kohler

Heavy particles



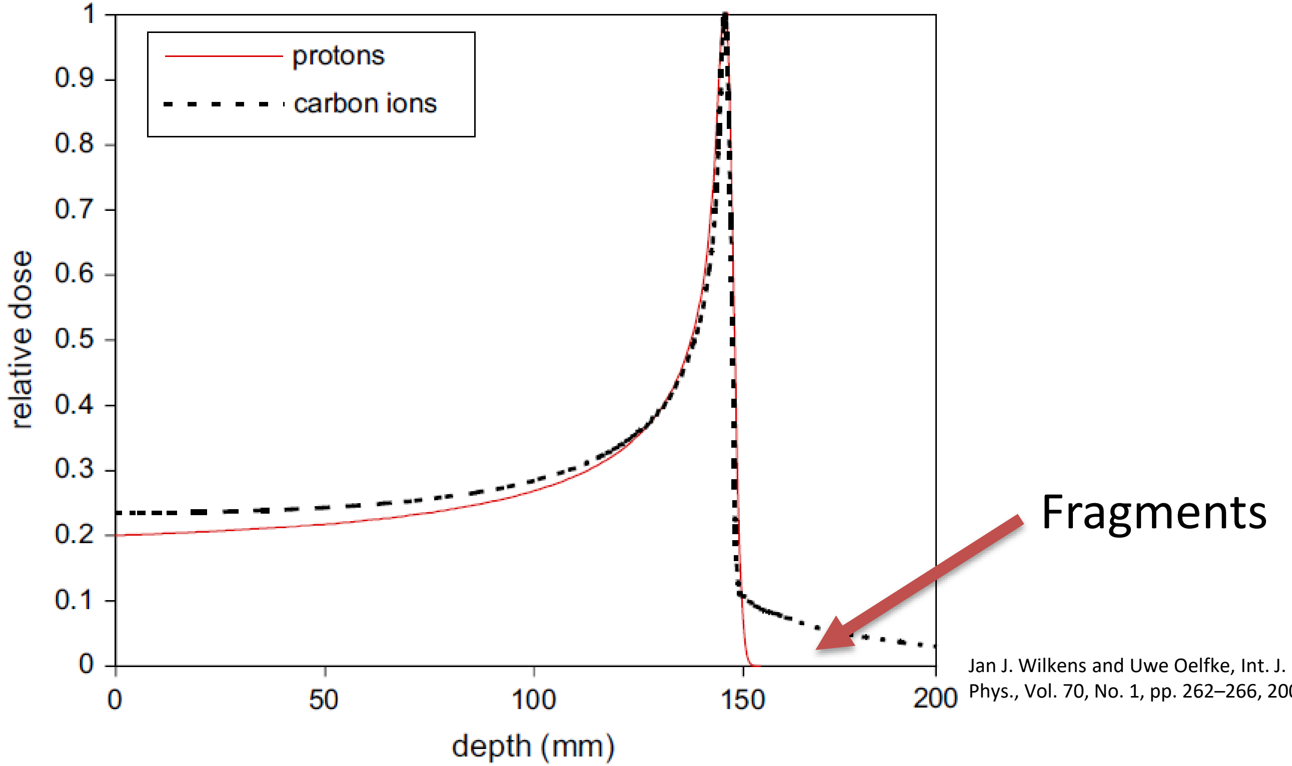
A. Kohler

Carbon



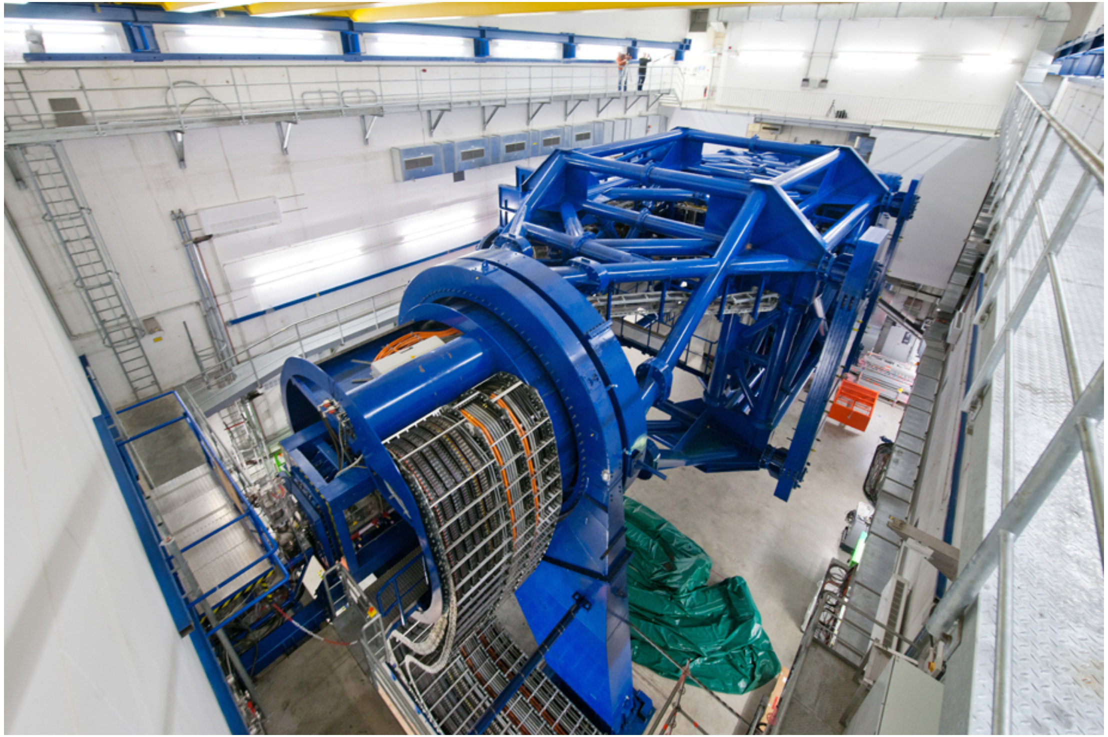
Jan J. Wilkens and Uwe Oelfke, Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 1, pp. 262–266, 2008

Carbon



Jan J. Wilkens and Uwe Oelfke, Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 1, pp. 262–266, 2008

Carbon



Carbon gantry HIT (Heidelberg)

- Only in the world
- 25 x 13 meters
- 670 tons
- 360° rotation
- 425 MeV/u

Carbon

Carbon gantry HIT (Heidelberg)

- Only in the world
- 25 x 13 meters
- 670 tons
- 360° rotation
- 425 MeV/u

Carbon

Carbon gantry HIT (Heidelberg)

- Only in the world
- 25 x 13 meters
- 670 tons
- 360○ rotation
- 425 MeV/u

Other developments

Proton imaging

In-vivo range verification

Further focus on particle therapy (with immunotherapy)

More compact accelerators

Other developments

Proton imaging

In-vivo range verification

Further focus on particle therapy (with immunotherapy)

More compact accelerators

And more… a lot of research is going on!

Questions?