DEPARTMENT OF PHYSICS AND ASTRONOMY

Calorimetry for Proton Beam Therapy: a technology transfer adventure

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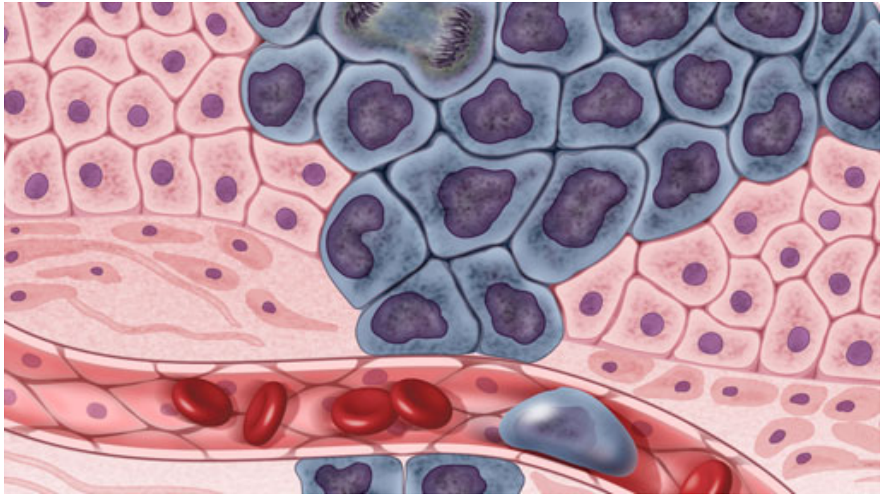
What is cancer?

- Cells reproduce through *mitosis* (cell division).
- All cells in the body have a pre-programmed lifespan.
- If the cell becomes abnormal it is programmed to die. This is called *apoptosis*.



https://www.genome.gov

- If a sequence of mutations occurs the cell begins to divide uncontrollably (tumour) and eventually spread to other parts of the body: cancer.

Cancer in Italy

Cases

363.000

New cases of cancer, 2015.

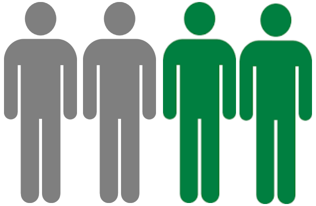
Deaths

178.232

Deaths from cancer, 2015.

Survival

54%

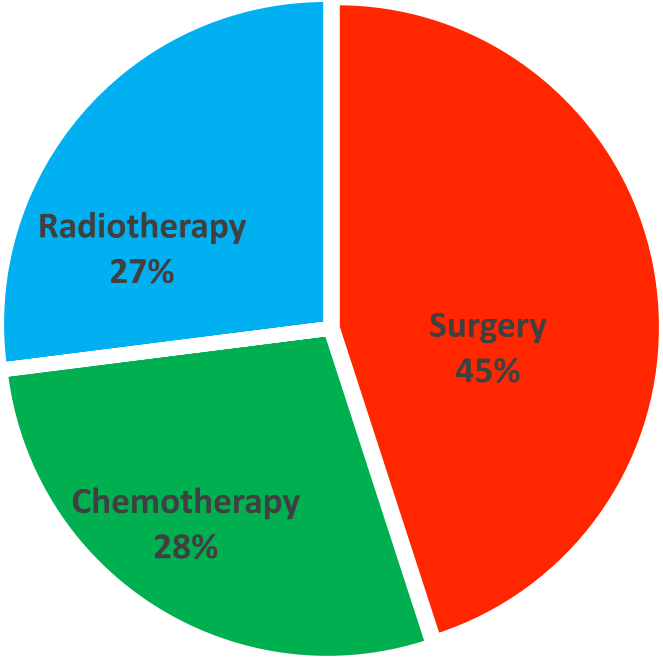


Survive cancer for 5 years, 2005-2009.

https://www.aiom.it

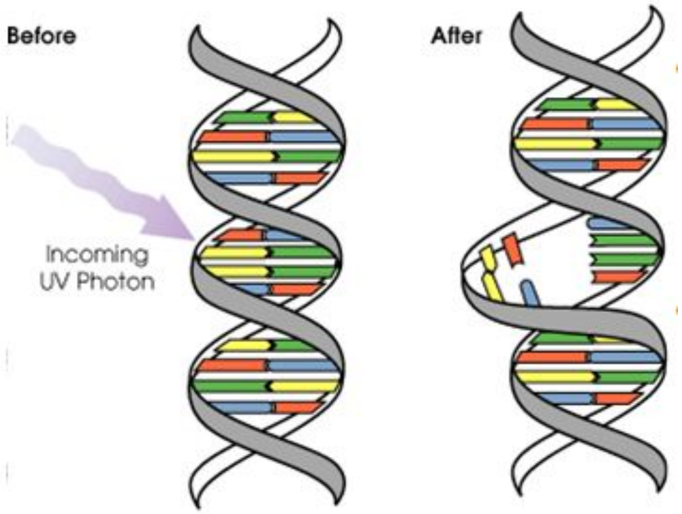
Cancer Treatment

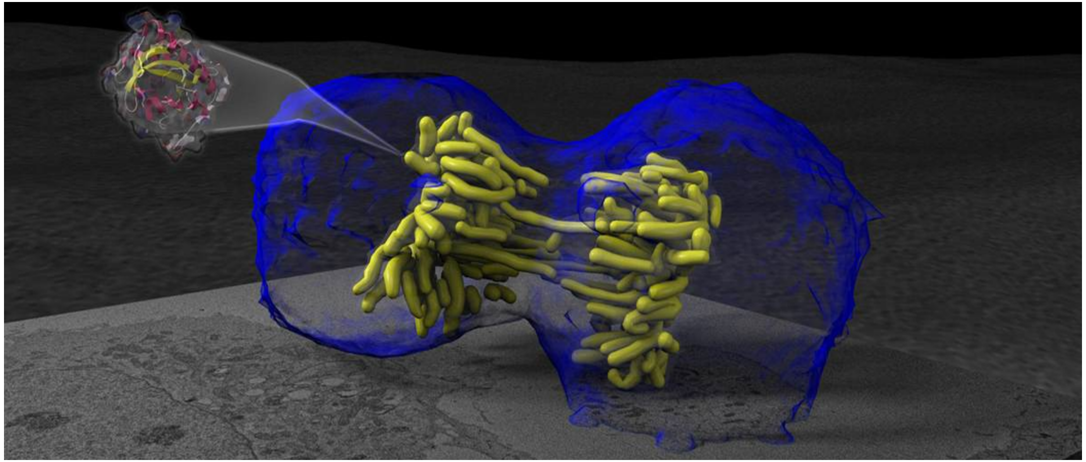
- Cancer treated with 3 different modalities:
  - Surgery
  - Chemotherapy
  - Radiotherapy
- Often used in combination
- If you can't remove cancer with surgery, radiotherapy is often the next best option



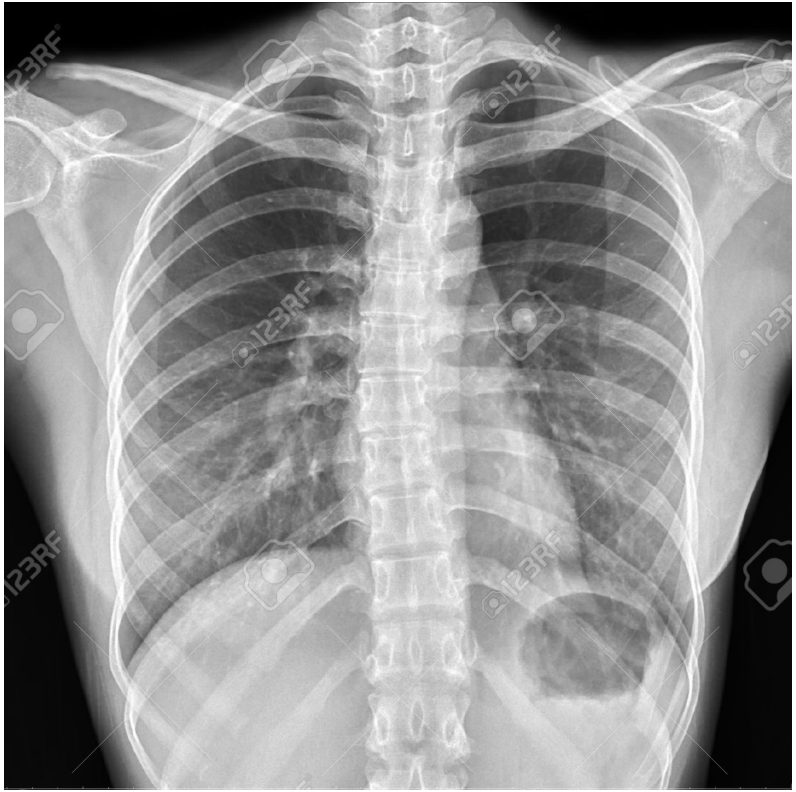
https://www.cancerresearchuk.org

Killing Cancer via DNA Damage



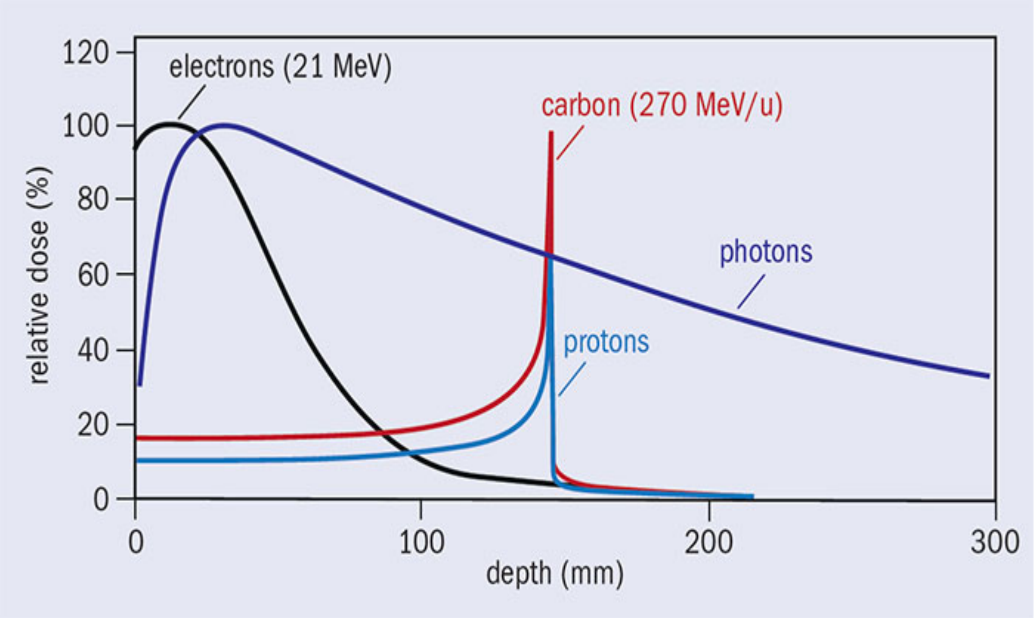


X-rays Pass Through The Body!

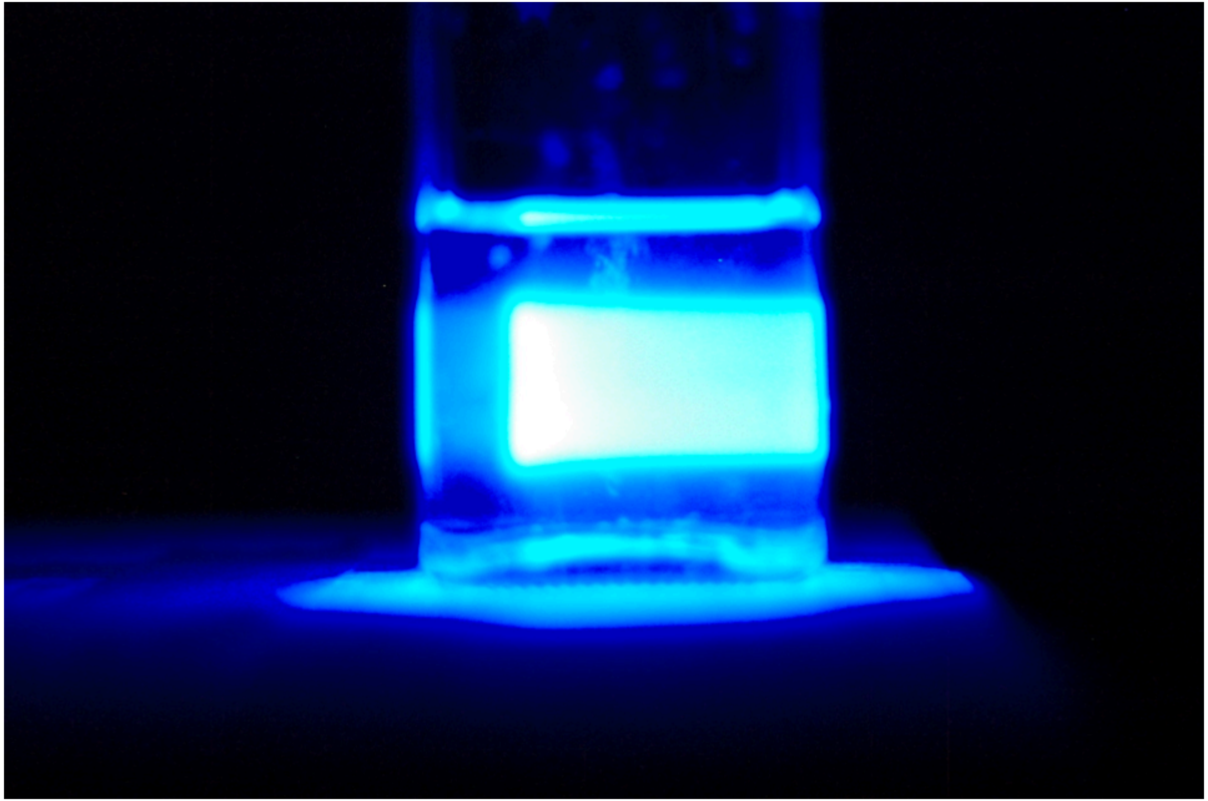


Particle Beam Therapy

- Unlike X-rays, charged particles stop!
- Electrons, being lighter, scatter and spread out.
- Protons deposit most dose at the *end* of their path: the ***Bragg Peak***.
- Protons stop, but you need to know where…

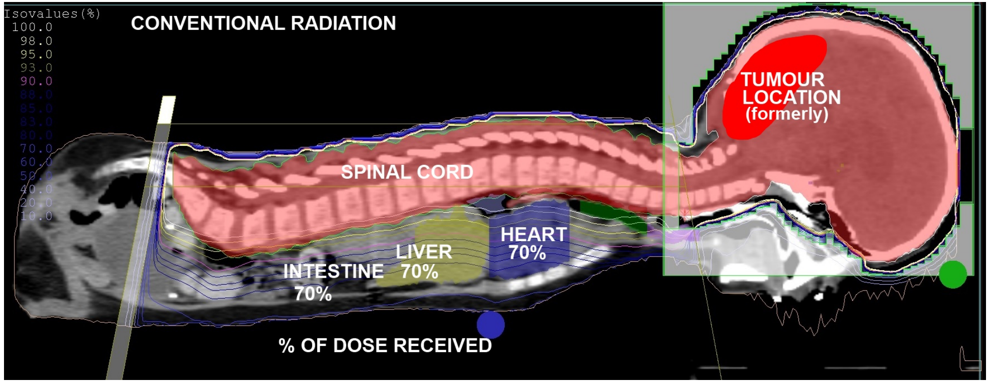


A Real Bragg Peak!

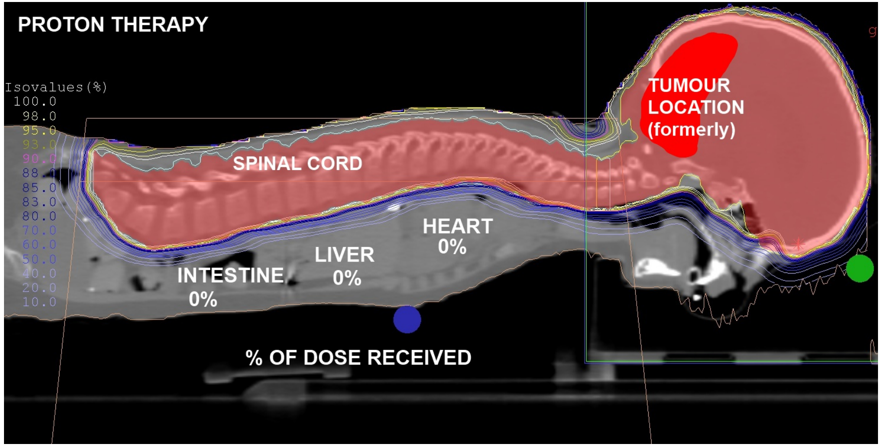


Medulloblastoma Comparison

X-rays



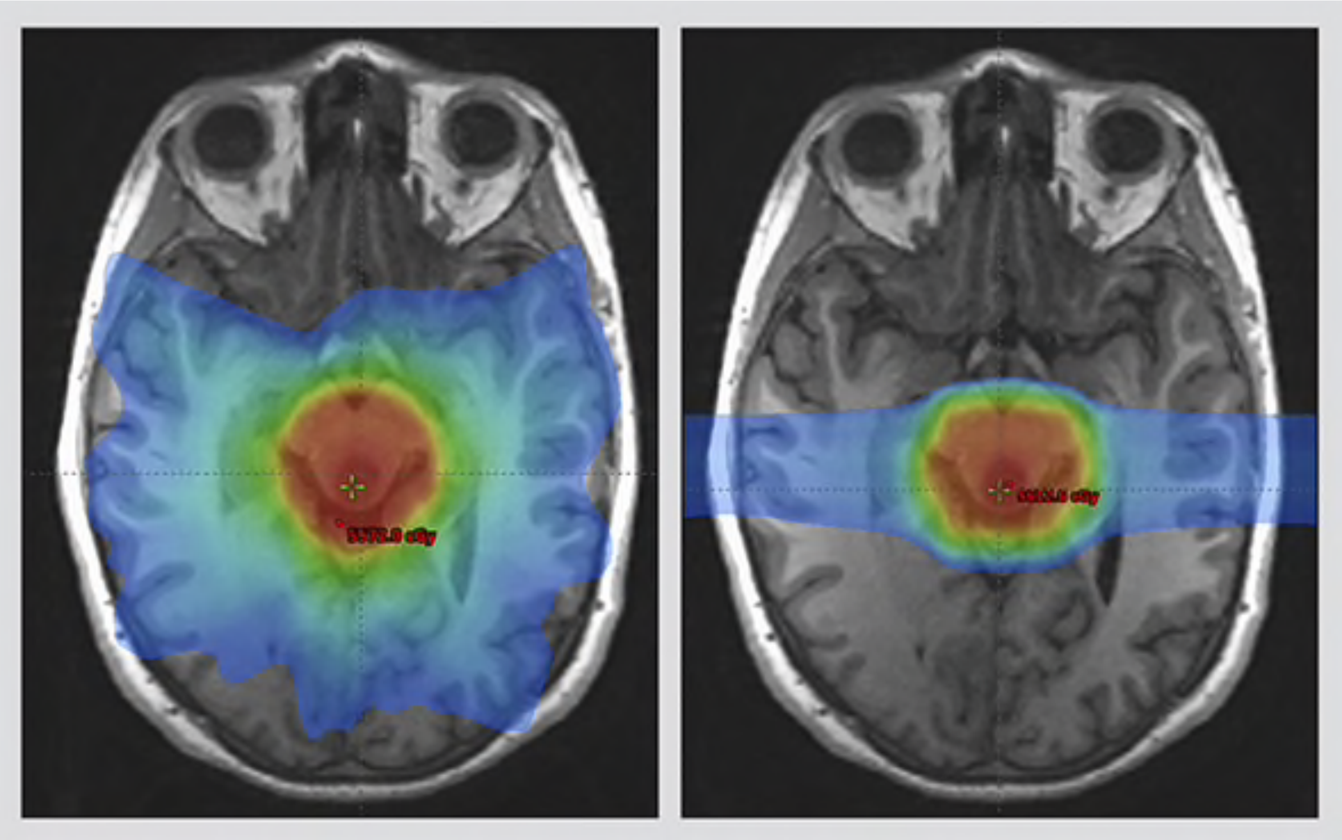
Protons



https://www.itnonline.com/content/pediatric-brain-tumor-patient-uk-undergoes-first-treatment-proton-therapy

Brain Comparison

X-rays



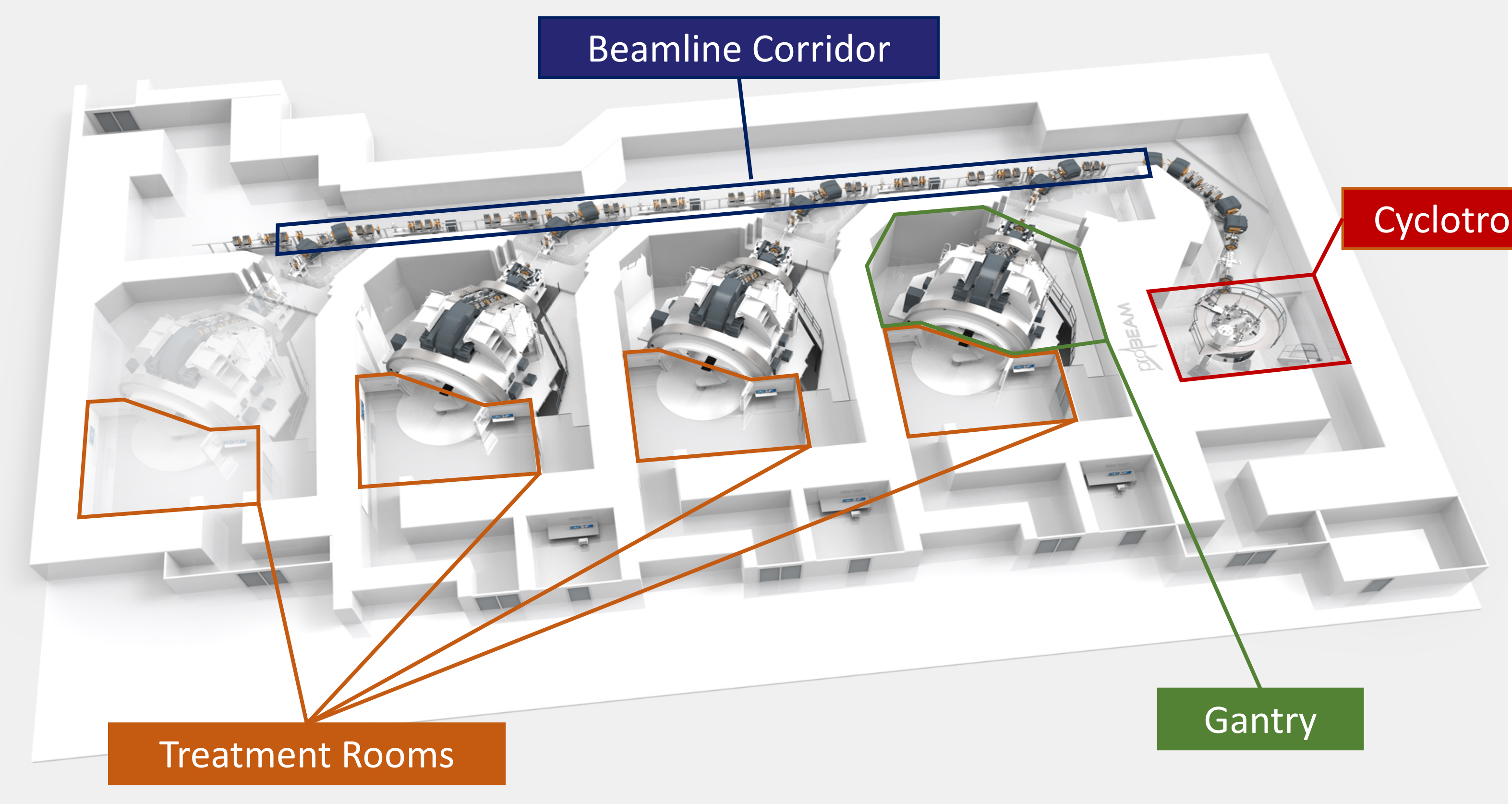
Protons

https://www.mayoclinic.org/medical-professionals/neurology-neurosurgery/news/proton-beam-therapy-in-minnesota-and-arizona/mac-20430872

Proton Therapy Around The World

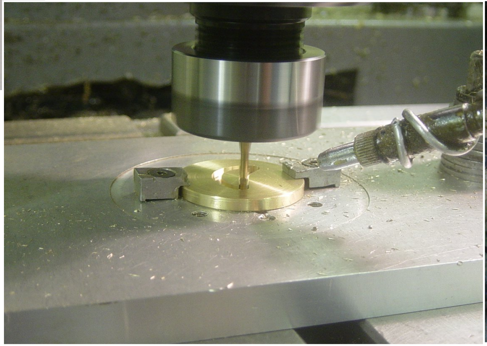
- Almost 100 particle therapy centres expected around the world by 2020, over 30 in Europe
- In Italy 3 operating centres (Catania, Pavia, Trento) and 1 planned (Milano)
- Clatterbridge Cancer Centre (UK) is the world's first hospital-based PBT centre: first two patients in June 1989

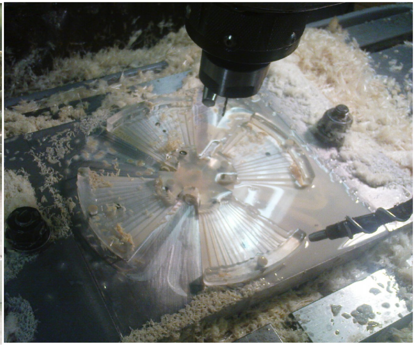
UCLH Proton Therapy Facility



Images courtesy of UCLH/Varian Inc. (not for reproduction)

Clatterbridge Cancer Centre





- 60 MeV cyclotron treats eyes with double scattering beamline.

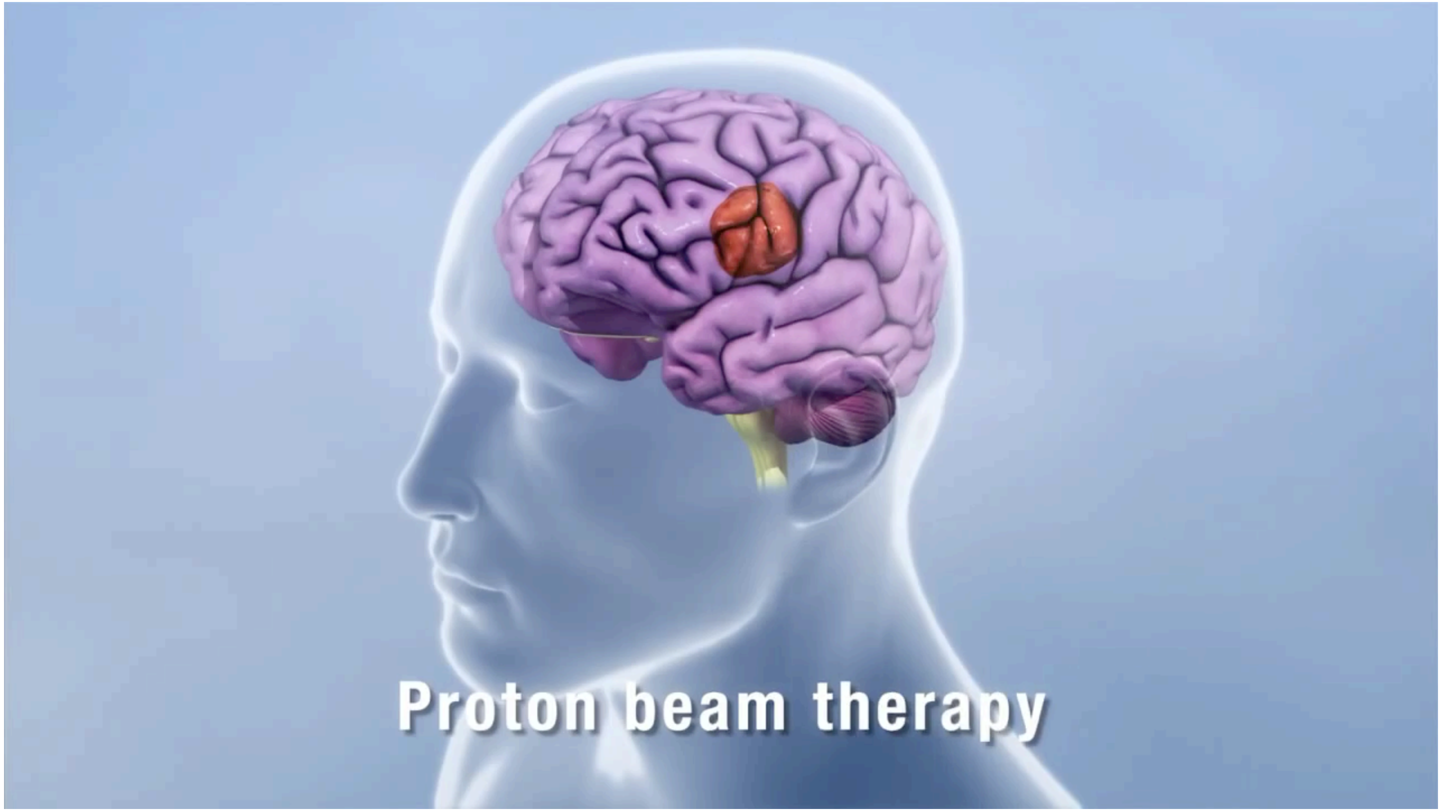
Heidelberg Gantry

Treatment Room

1. In-room monitor
2. Gantry
3. Scanning nozzle
4. Alcove
5. Hand pendant
6. Treatment table
7. Laser system

Images courtesy of Jan Timmer, Varian Inc. (not for reproduction)

Conformal Dose Delivery



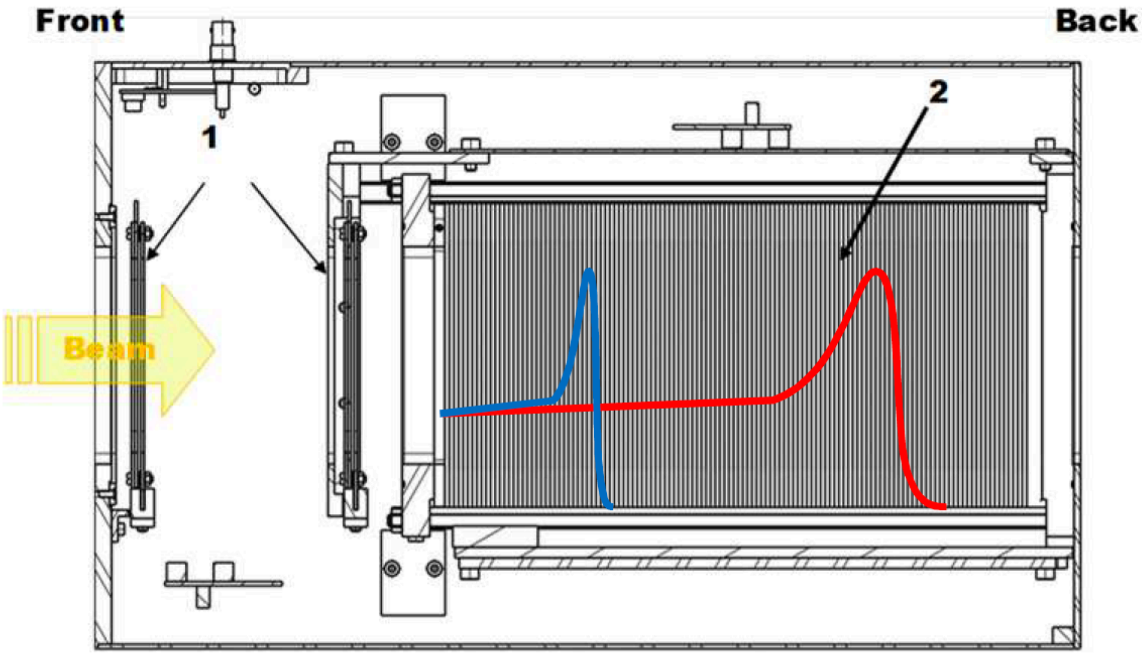
Proton Beam Quality Assurance

- A range of QA checks are necessary for safe PBT treatment:
  - Daily, Weekly, Monthly.
- Daily checks carried out before treatment:
  - Absolute dose, Pencil beam position and size, Range and Energy
- Average time per day per room: 44 min

Daily Range QA @PSI: MLIC

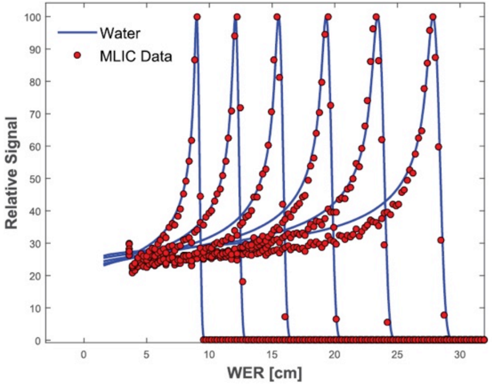
- Combination of ionization chambers are commonly used
- MLICs are expensive, have fast acquisition time but long setup time

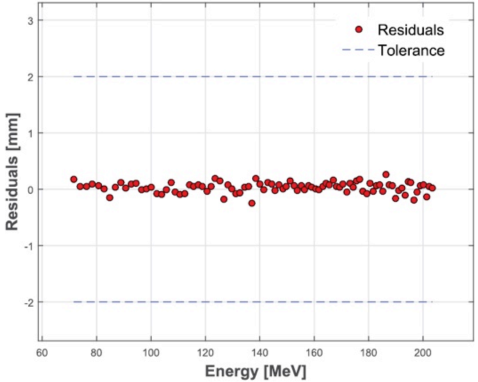
Multilayer ionization chambers (MLICs)



O. Actis *et al.* 2017 *Phys. Med Biol.* **62** 1661

Daily Range QA @PSI





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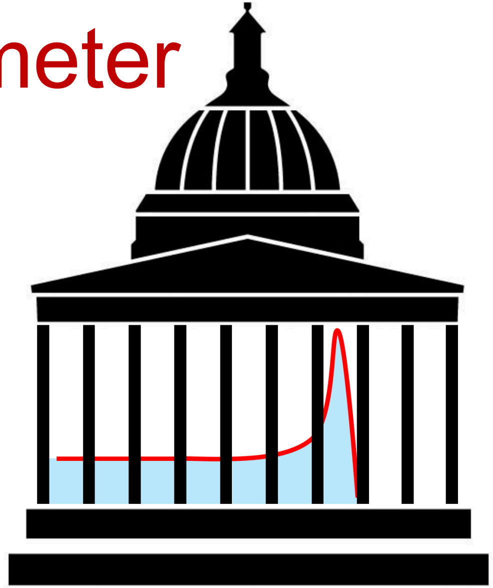
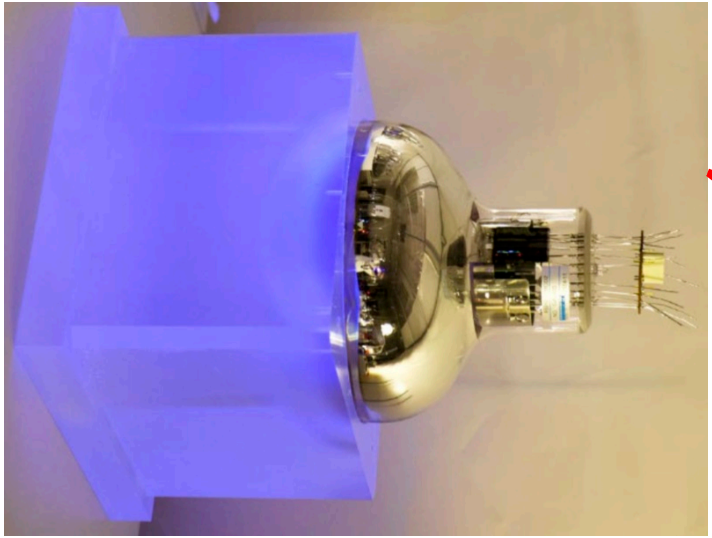
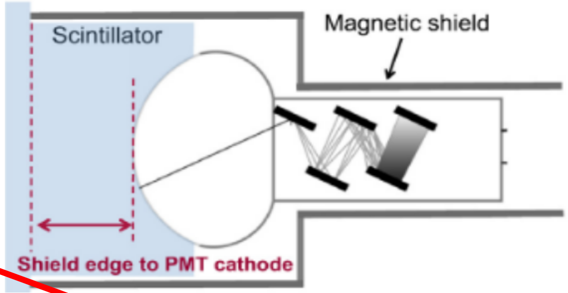
QuARC:

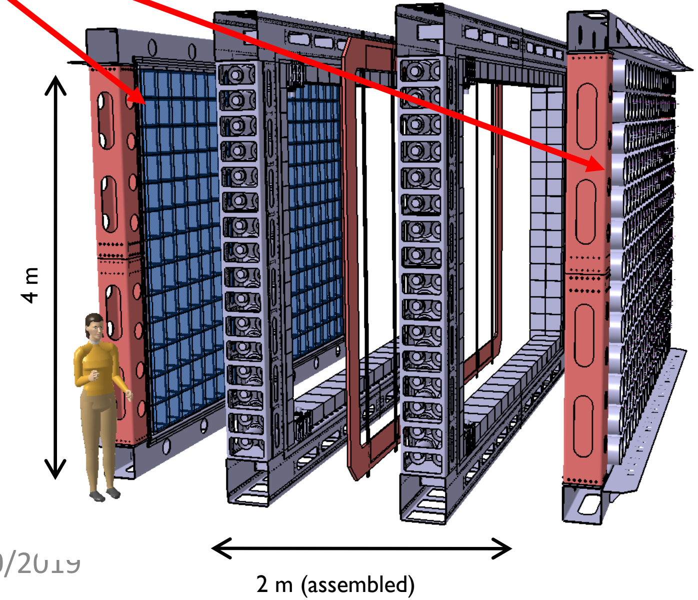
Quality Assurance Range Calorimeter



SuperNEMO Calorimeter



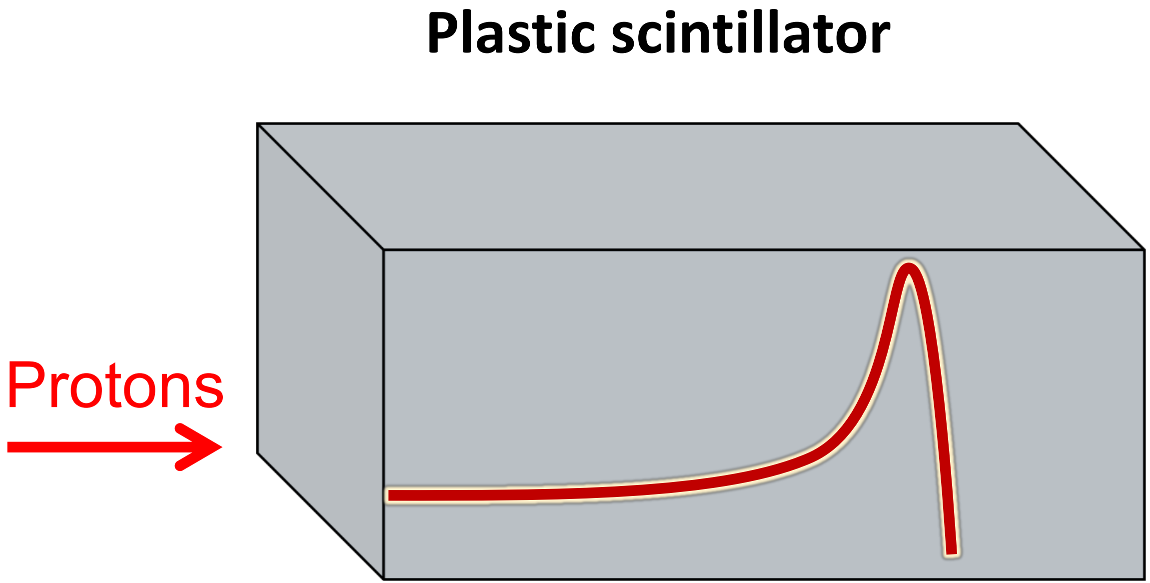




https://doi.org/10.1016/j.nima.2017.06.044

https://supernemo.org/about.html

Calorimeter for Range verification



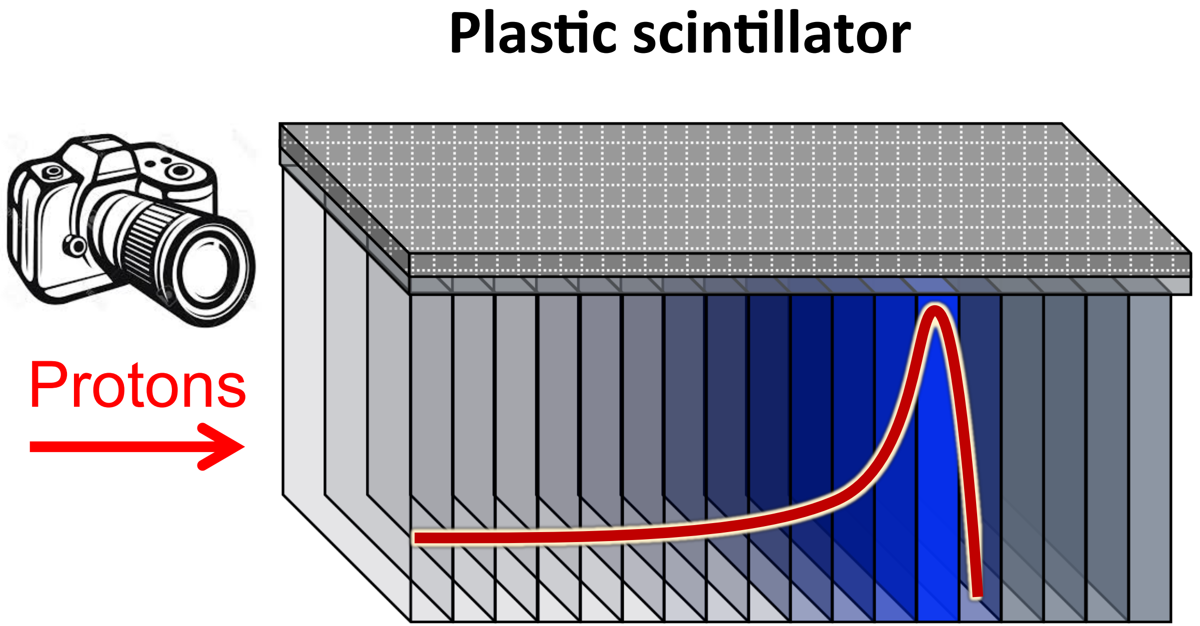
Advantages

- Price
- Light output
- Water equivalent material

Disadvantages

- Quenching
- Radiation hardness

Calorimeter for Range verification



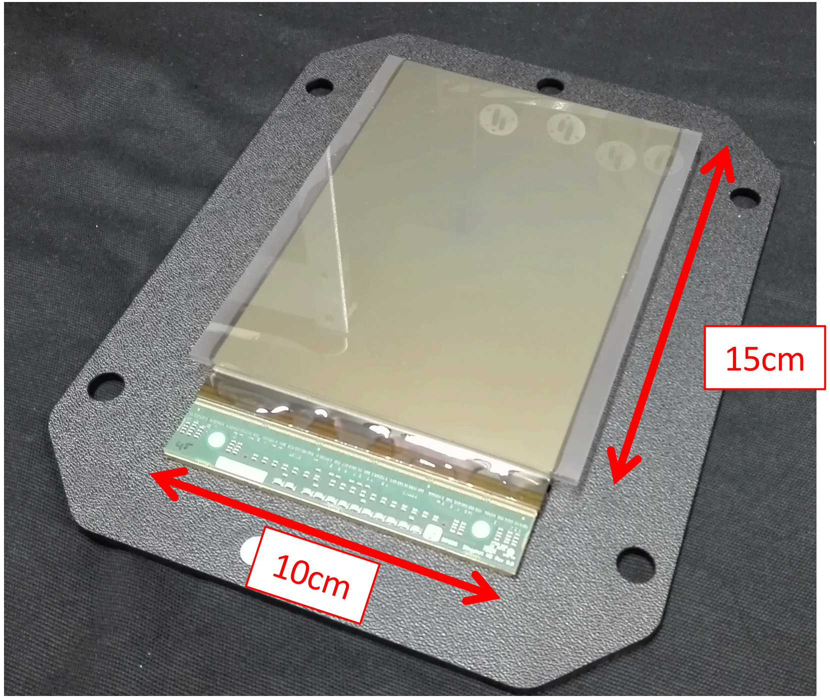
- Segment block into slices and read out light from each slice individually
- Current prototype uses simple, stable light detection: DSLR/pixel sensor

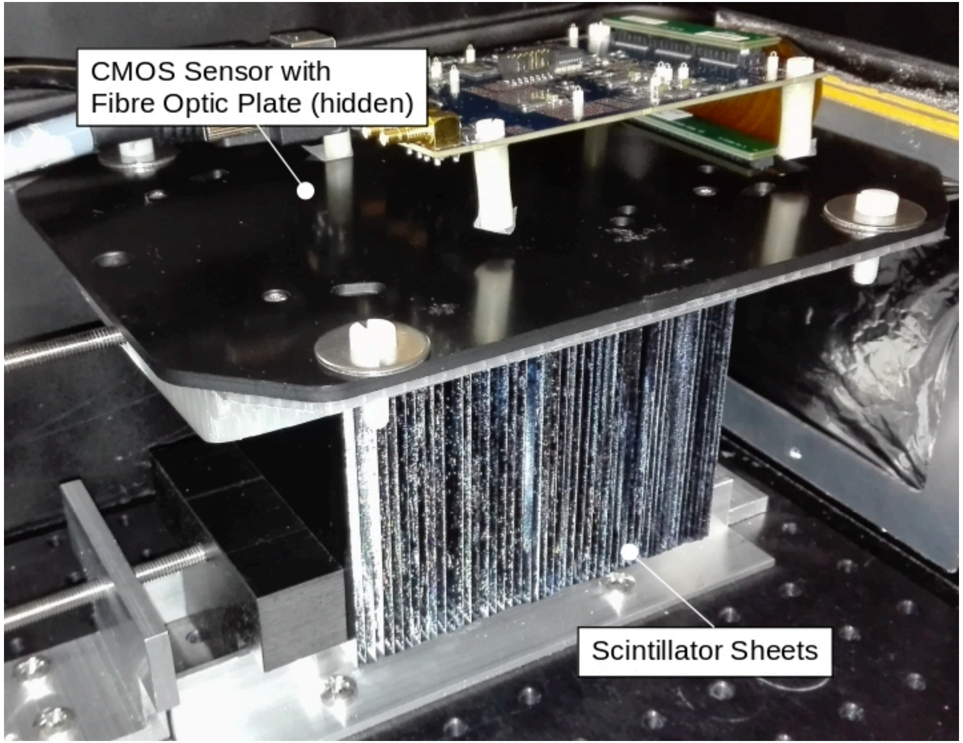
- Integrate signal from many protons: very large output from 10^{10}/s
- The proton beam range is estimated from the light-dose distribution

Scintillator Sheets

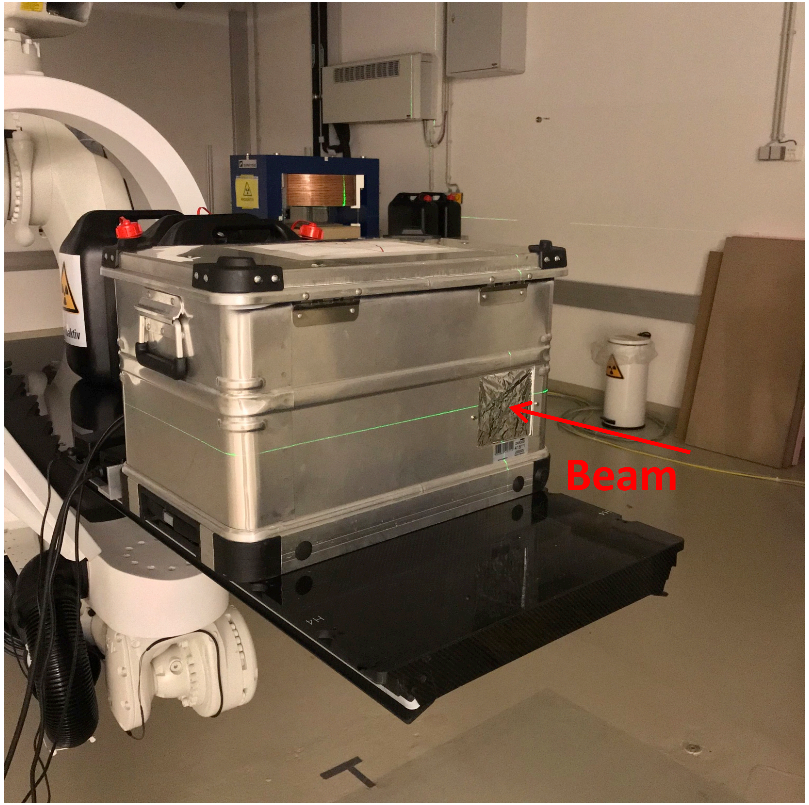
- Active area: 10 cm x 10 cm
- Thickness: 2- 3mm

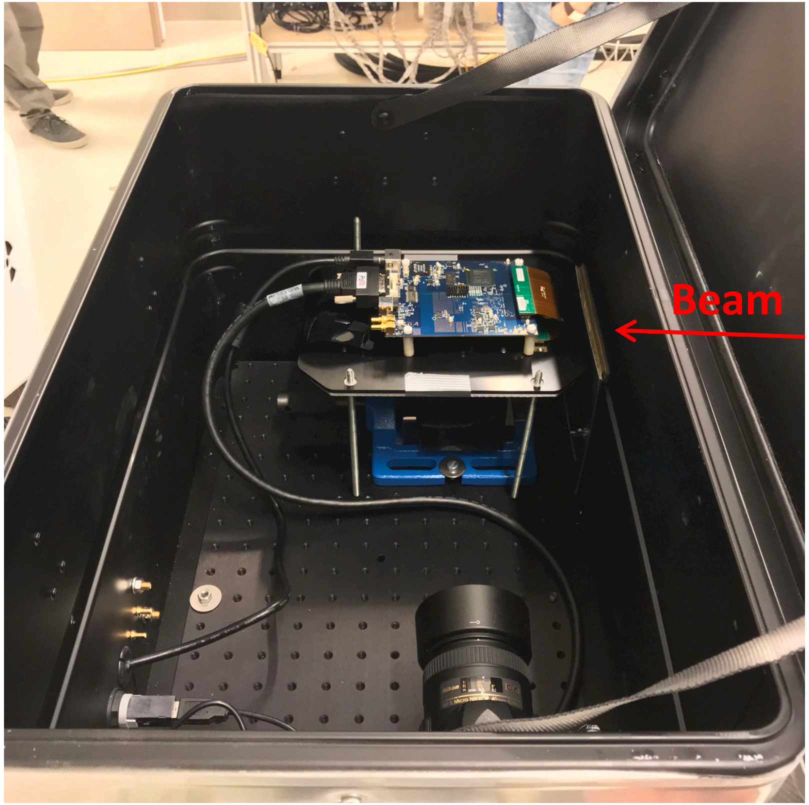
Readout: CMOS Pixel Sensor



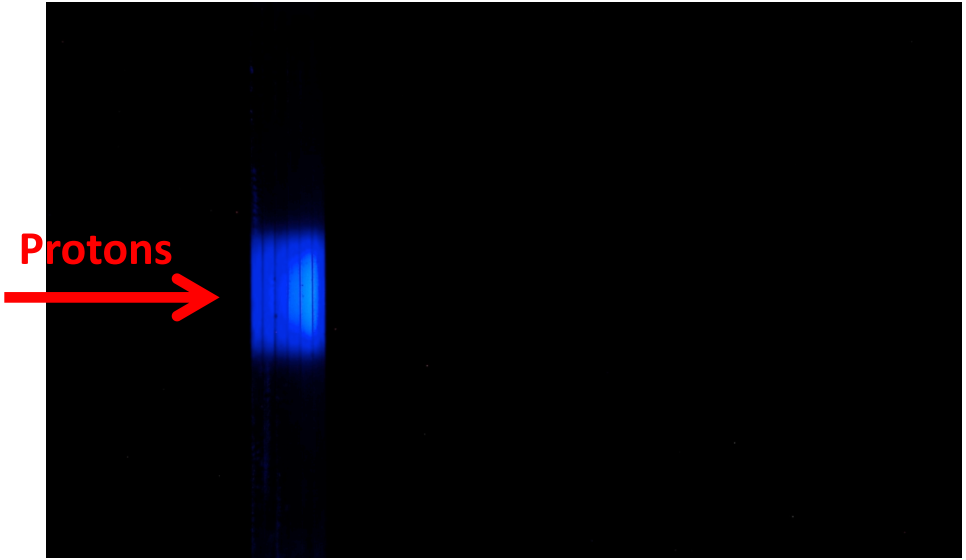


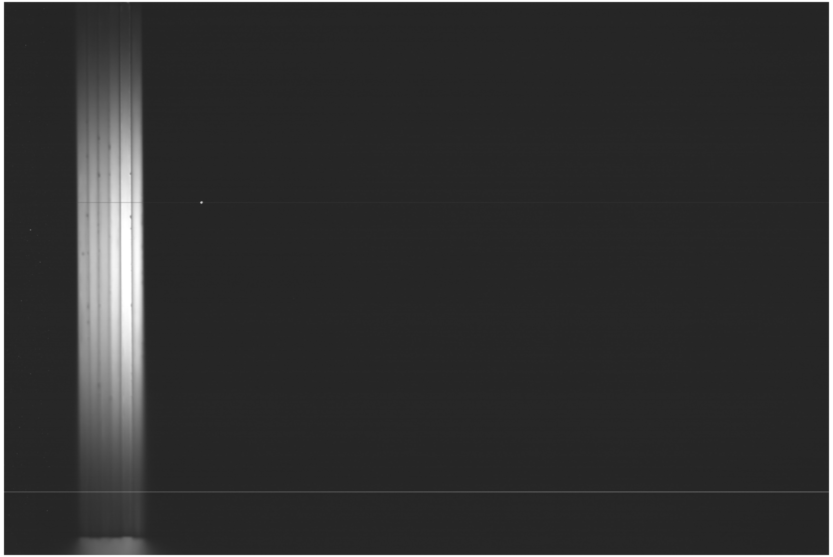
Experimental Setup



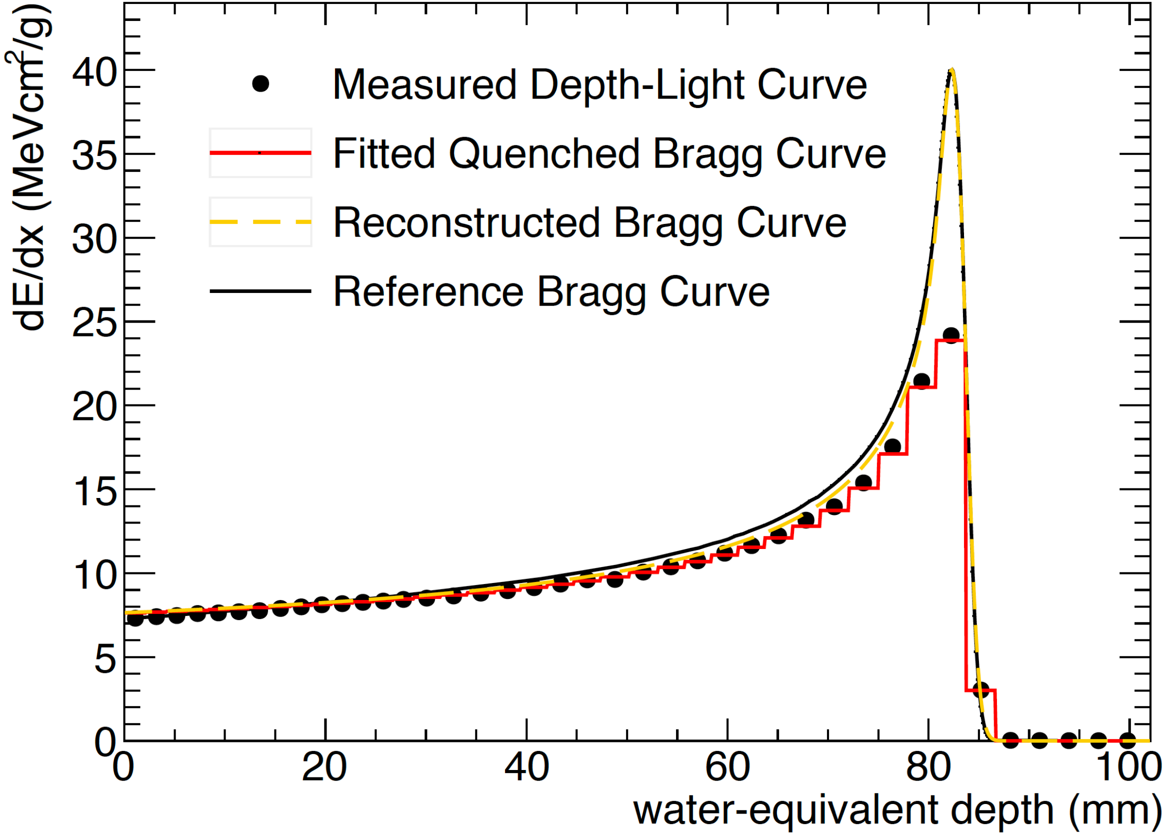


Proton Beam: DSLR vs Sensor

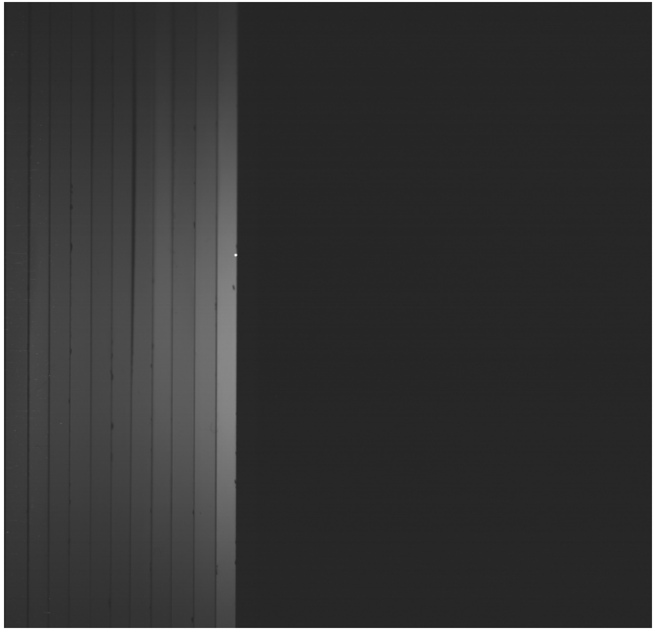


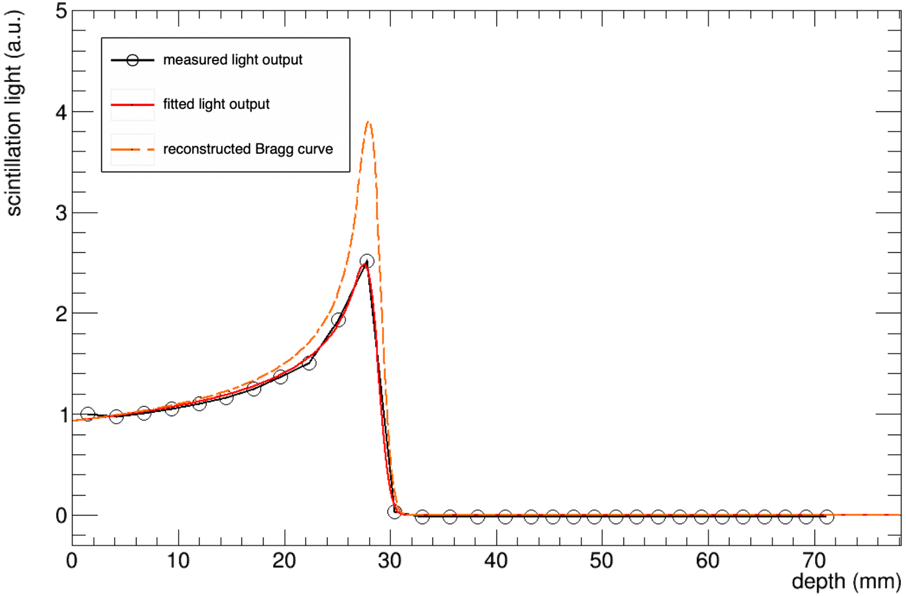


Analysed Data: 106.2 MeV



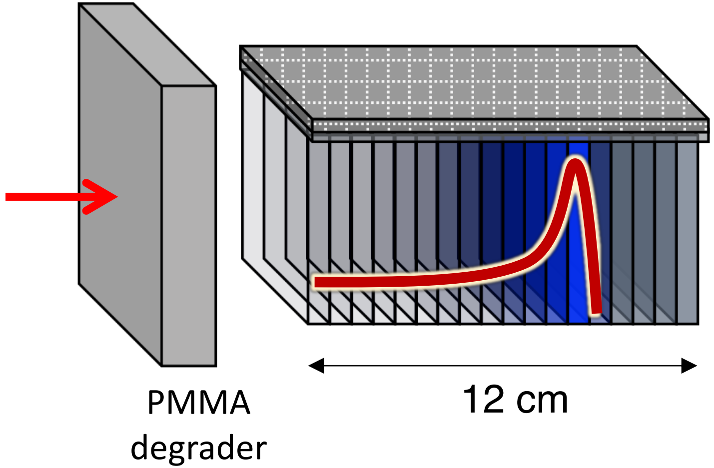
Range Scan

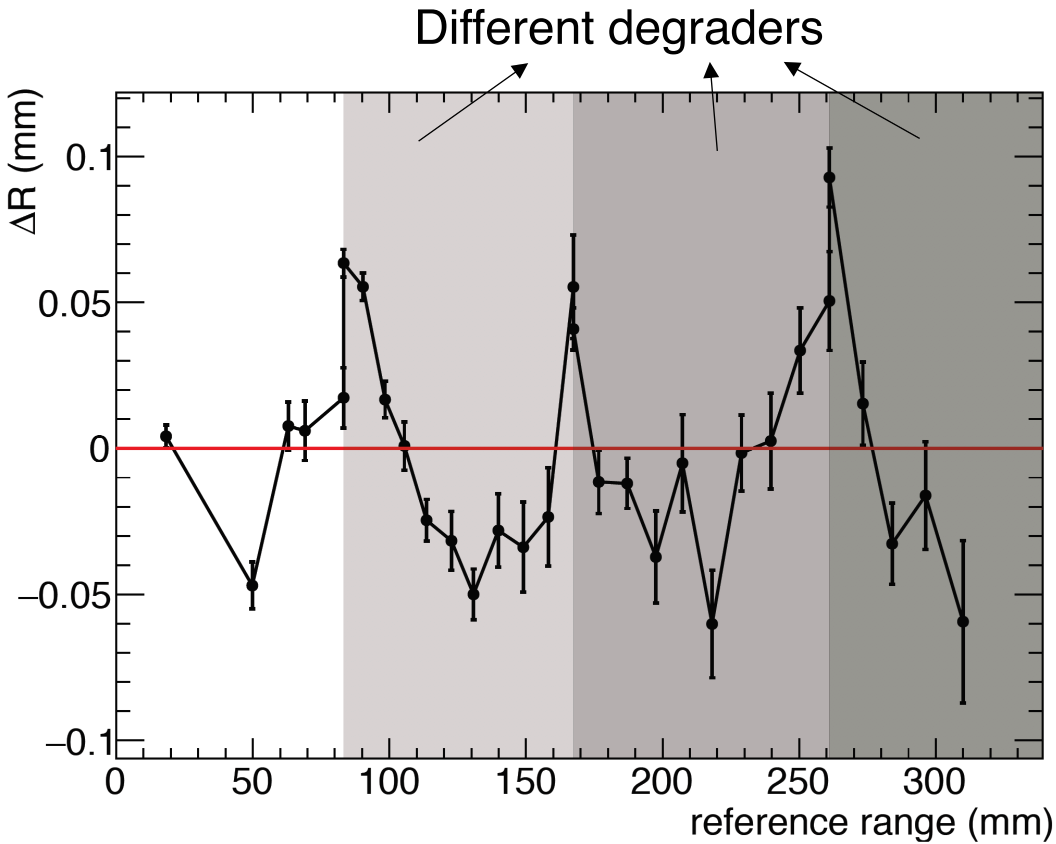




scintillation light (a.u.)
depth (mm)
measured light output
fitted light output
reconstructed Bragg curve
0
1
2
3
4
5
0
10
20
30
40
50
60
70

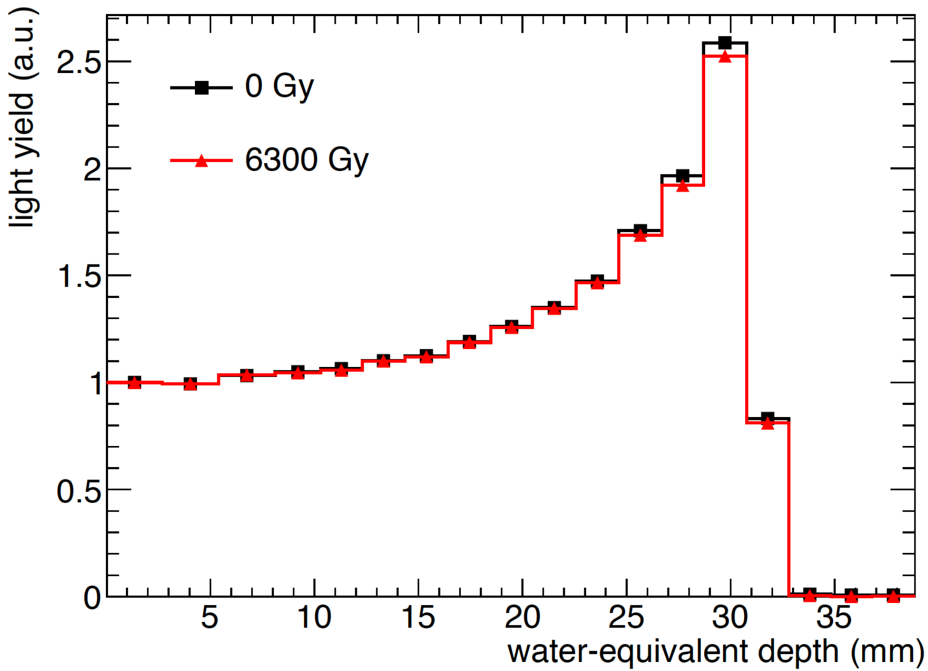
Range Measurement Accuracy

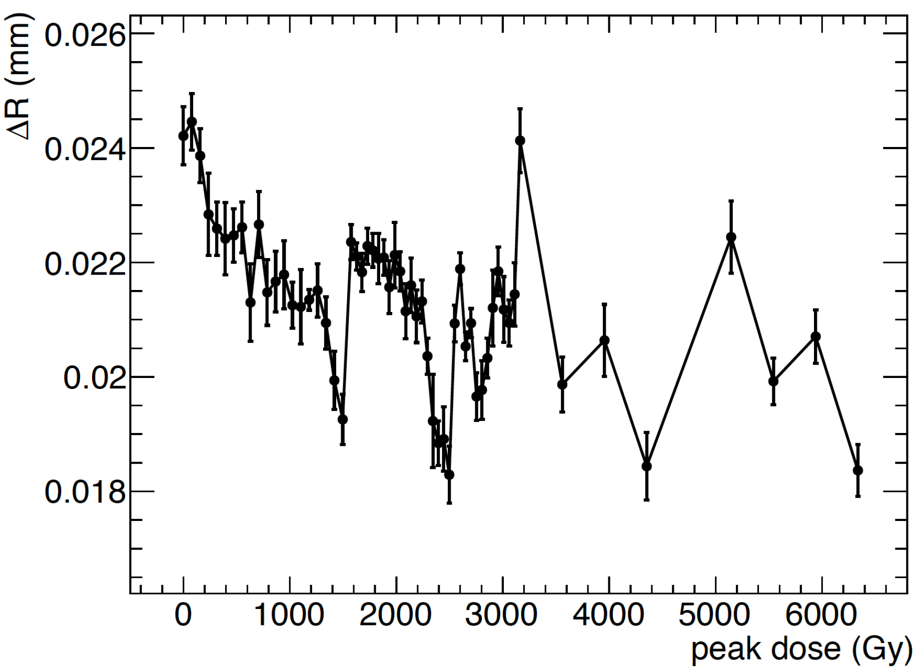




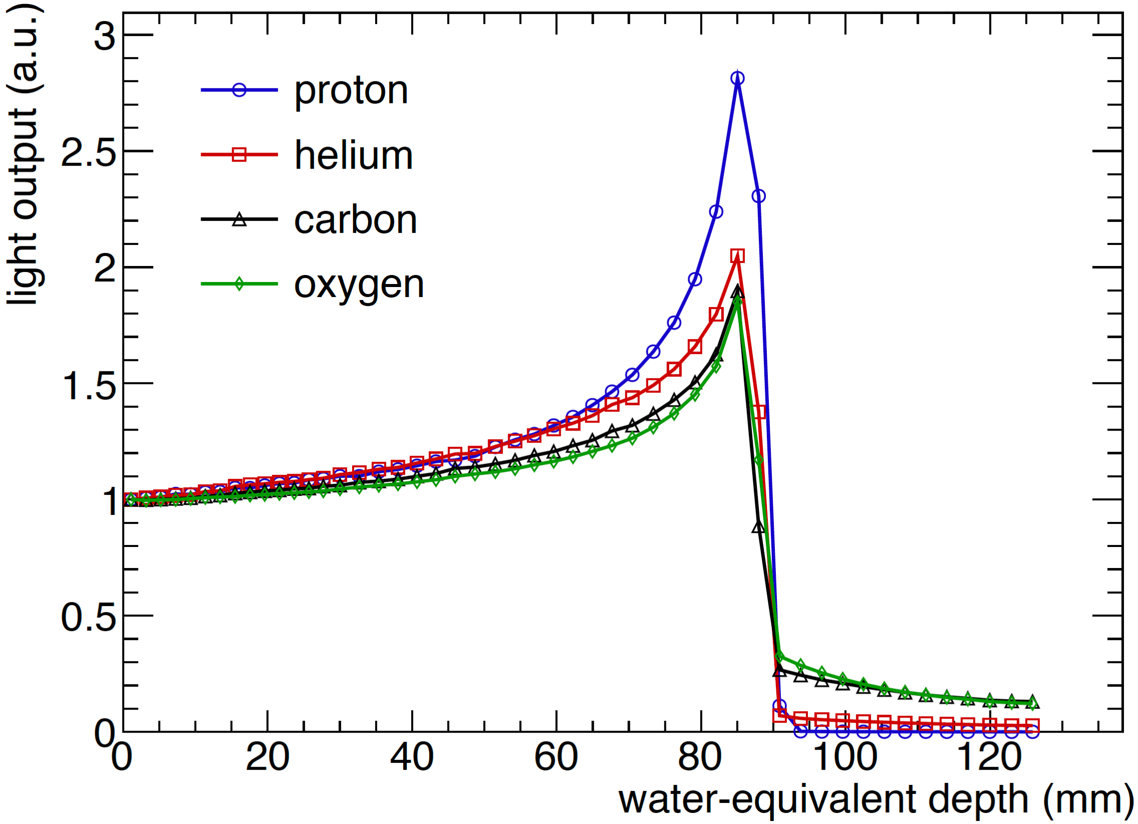
- max range difference is 0.08 mm
- mean deviation is 0.04 mm

Radiation Hardness



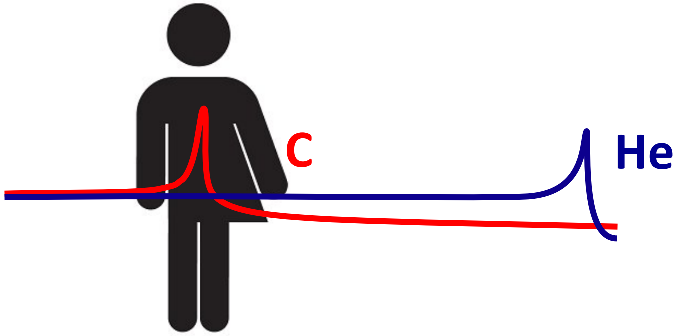


Ion beam test



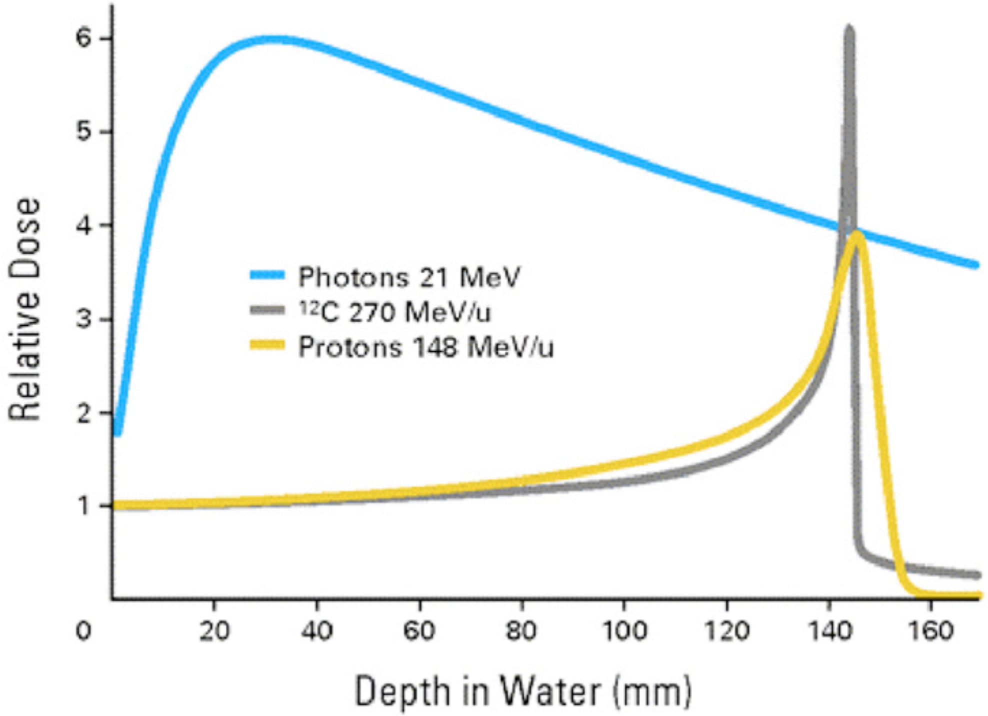
Additional Application:

Monitoring intra-fractional motion in a mixed He/C beam



Carbon beam therapy

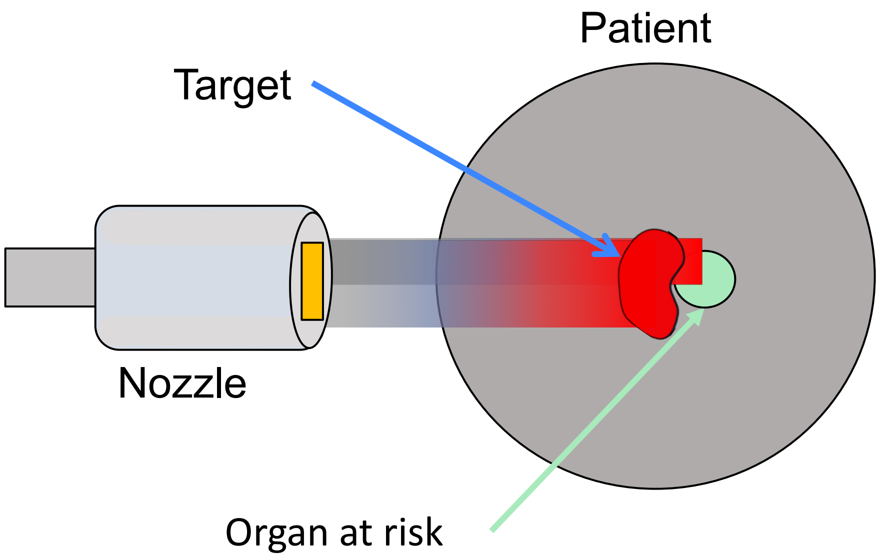
More conformal dose distributions

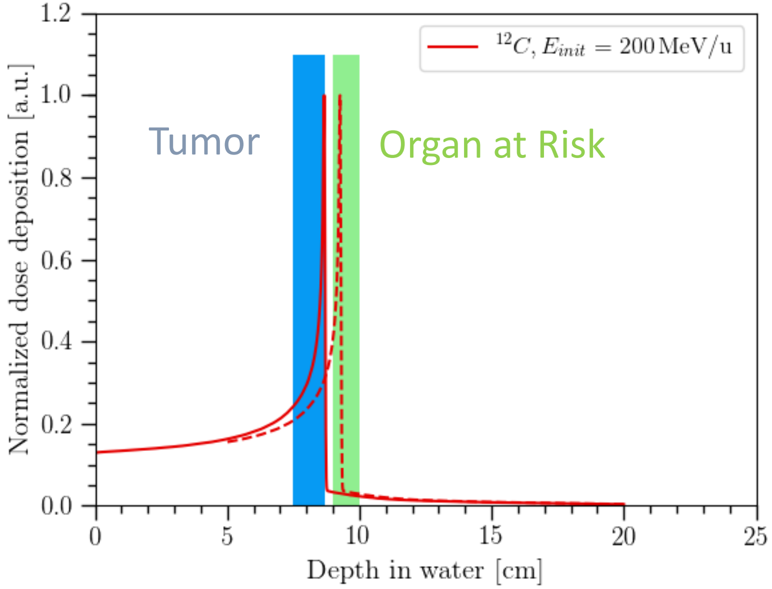


Patient/tumour motion

- Inter-fractional movements, e.g.
  - Patient misalignment
  - Tumour shrinking
  - Cavity filling
- Intra-fractional motion, e.g.
  - Breathing
  - Bowel movements
  - Rectal gassing

Range uncertainty

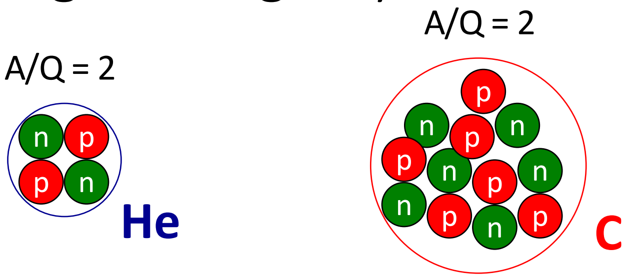




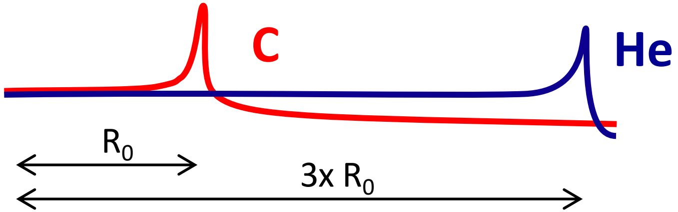
Needed: Online treatment monitoring

Helium/Carbon mixing

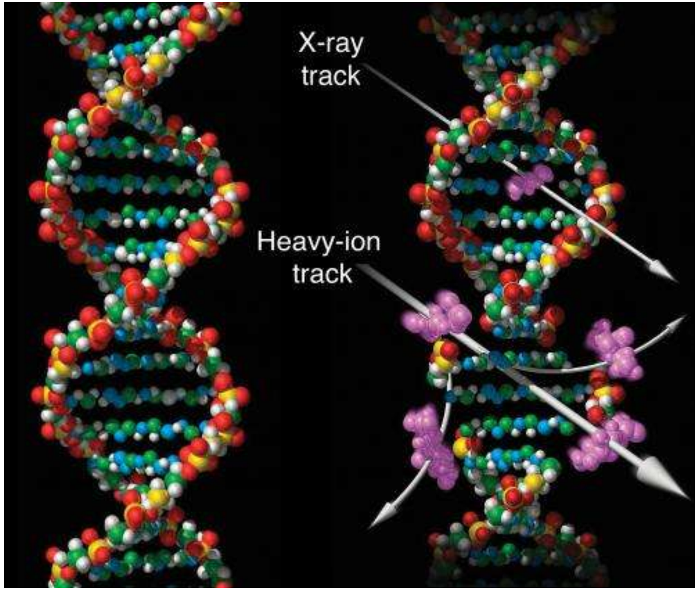
- Similar magnetic rigidity: Accelerate together



- $R_0(He) = 3 \times R_0(C)$: simultaneous treatment and imaging



Particle beam therapy

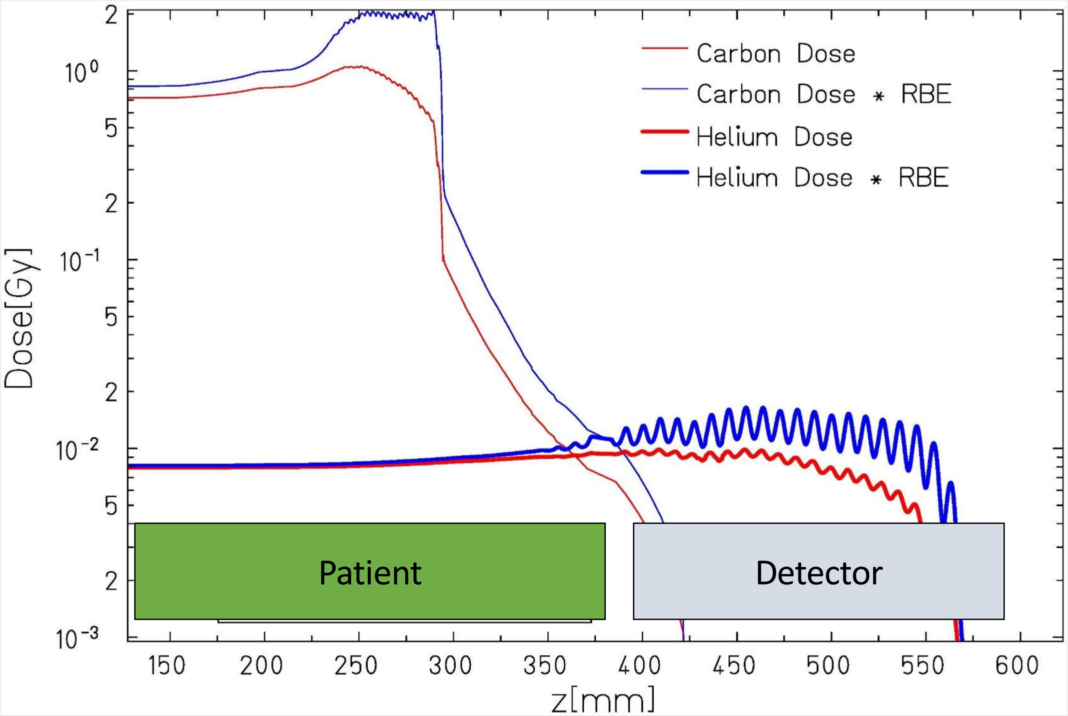


Relative biological effectiveness RBE

Different types of radiation treatment cause different kinds of damage to the DNA in a tumor →have different biological effectiveness

Helium/Carbon mixing

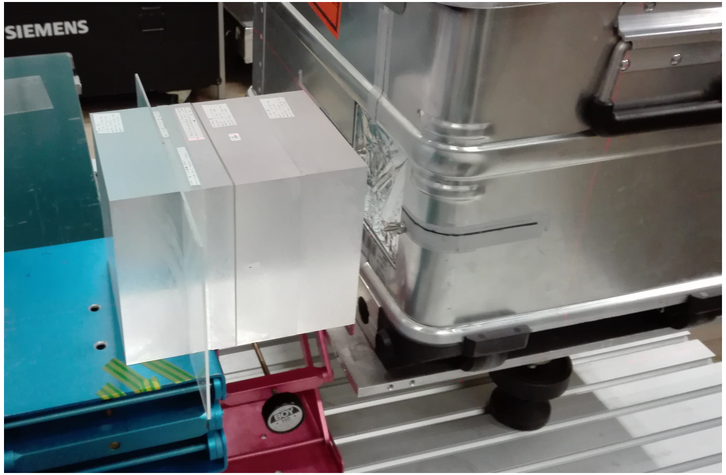
C beam treatment plan

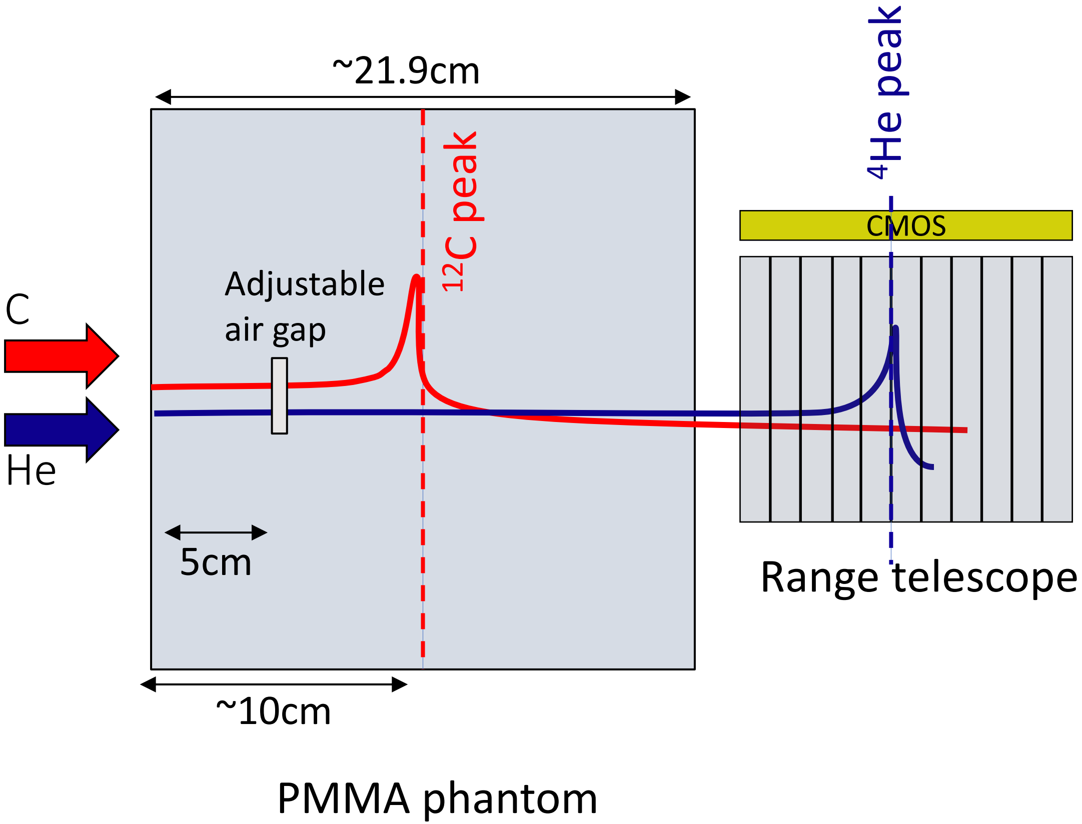


Courtesy C. Graeff

10% He contamination → <0.5% target RBE dose

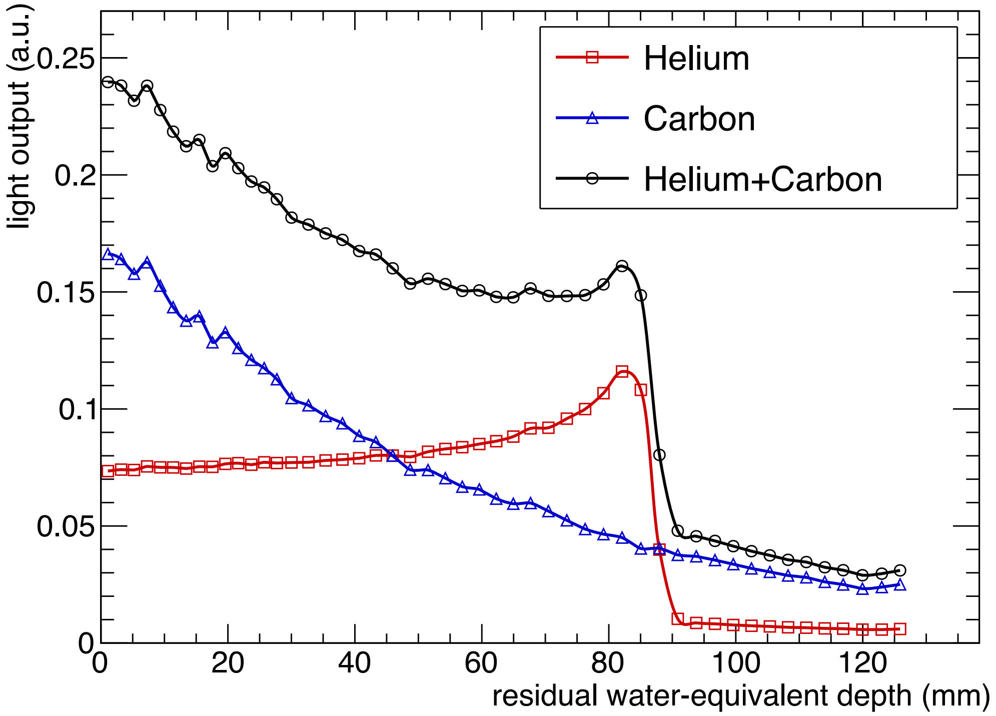
PMMA phantom: setup



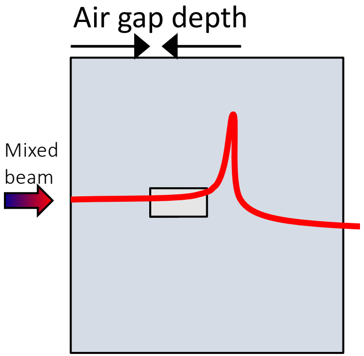


Off-line beam mixing

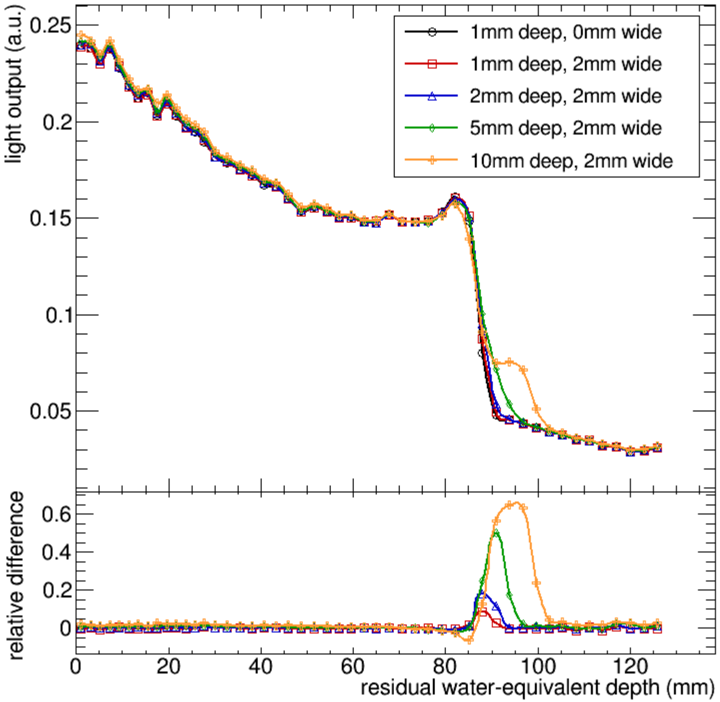
E=220MeV/u



PMMA phantom: results



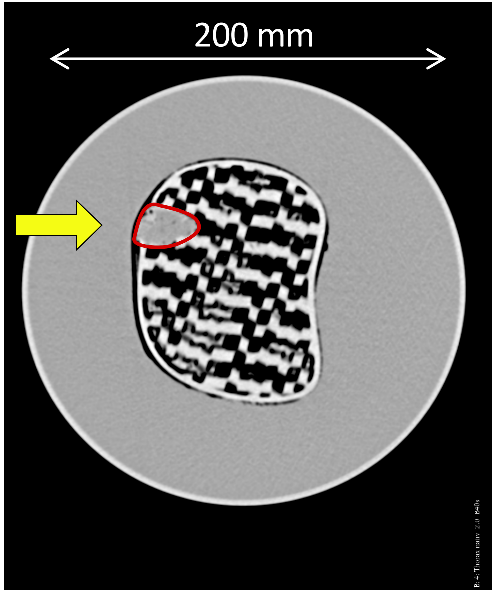
PMMA phantom

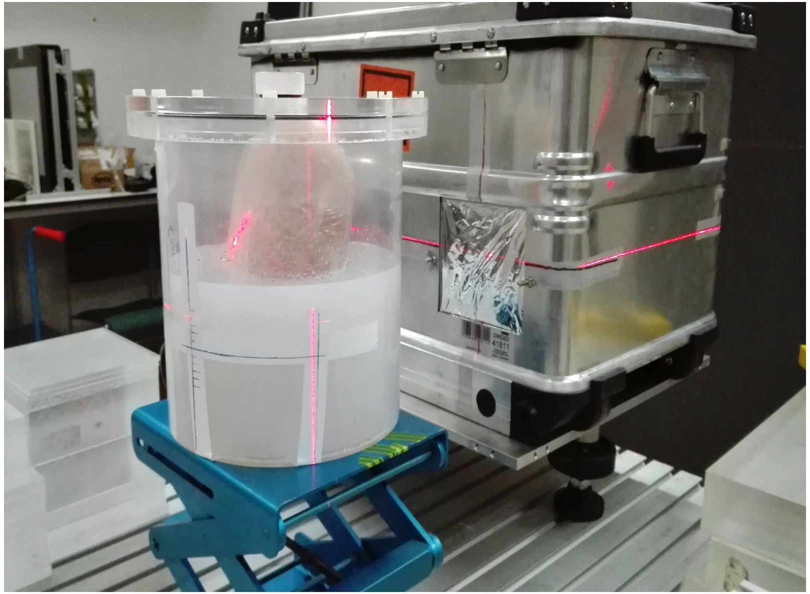


Range telescope

Lung phantom: setup

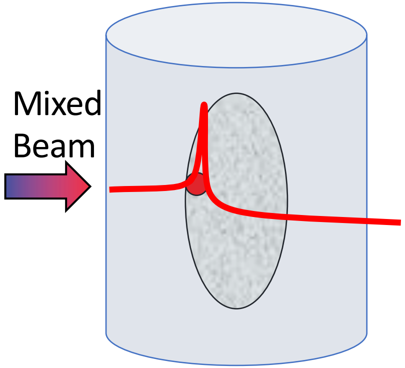
3D printed lung and lung tumour

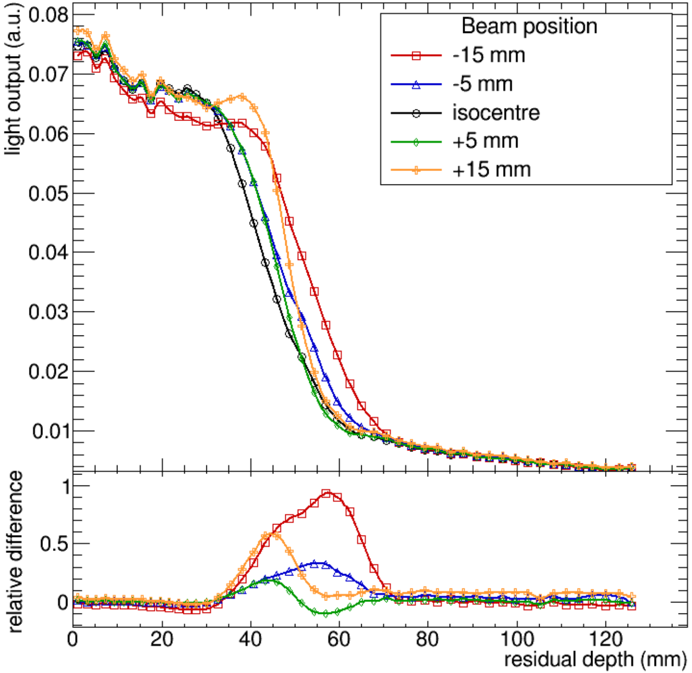




Lung phantom: results

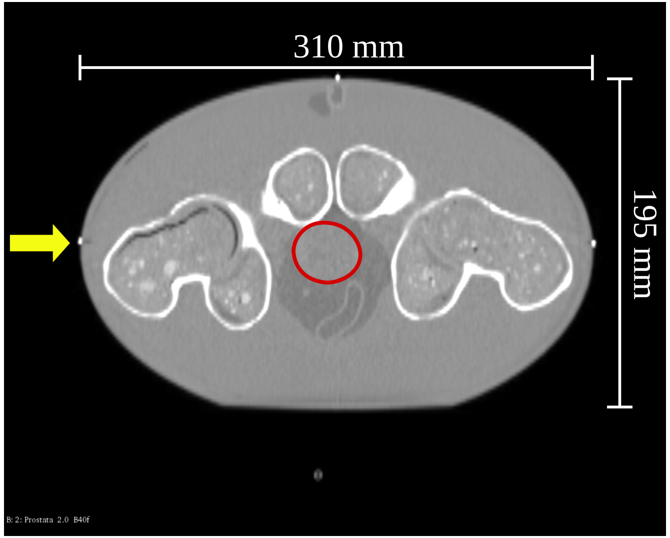
Simulate breathing motion

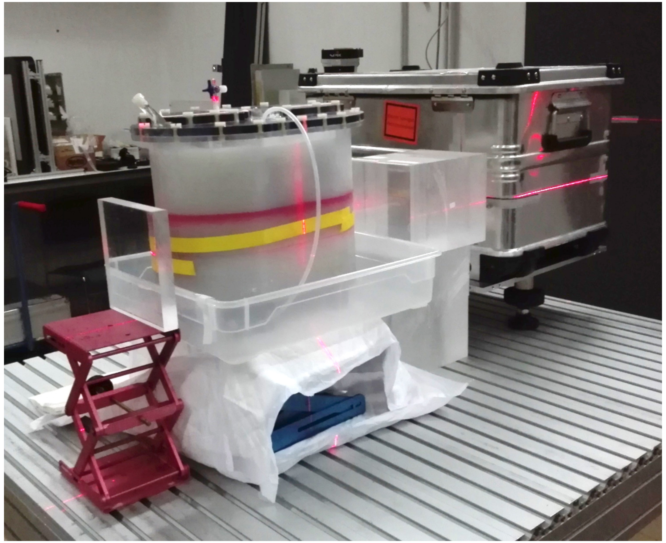




Pelvis phantom 1: setup

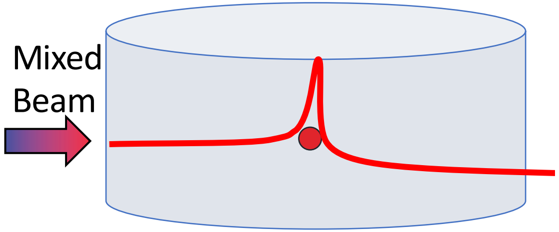
Pelvis/hip phantom and prostate cancer

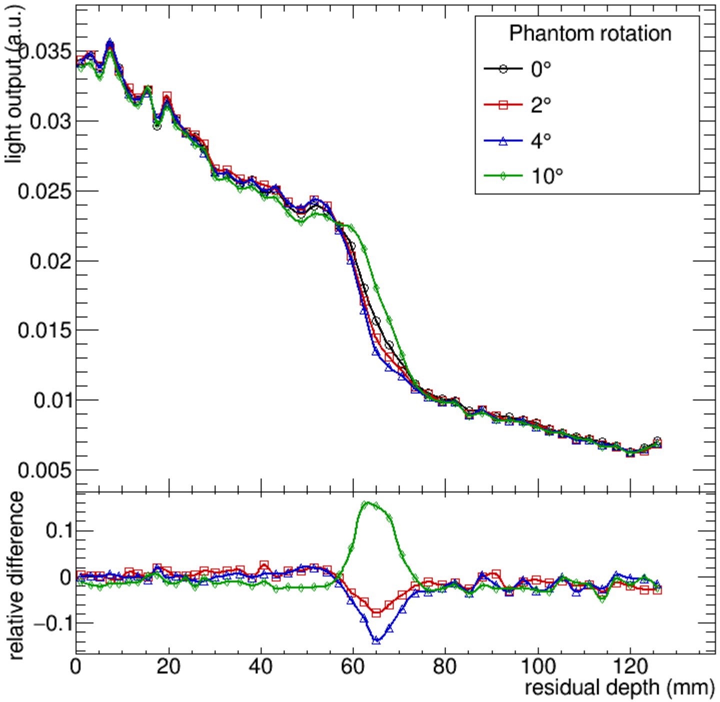




Pelvis phantom 1: rotation

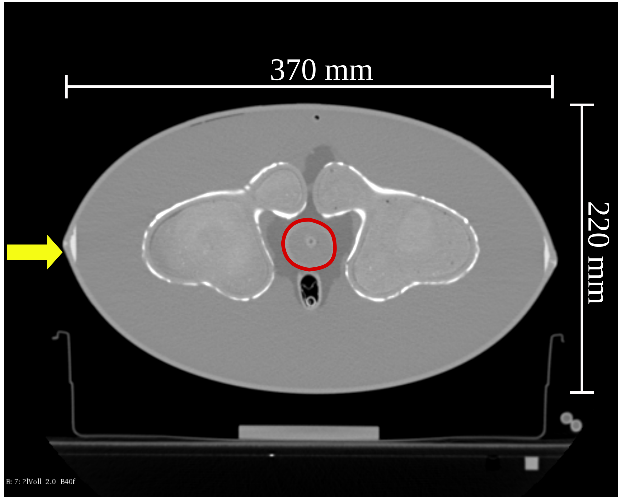
Simulate patient misalignment

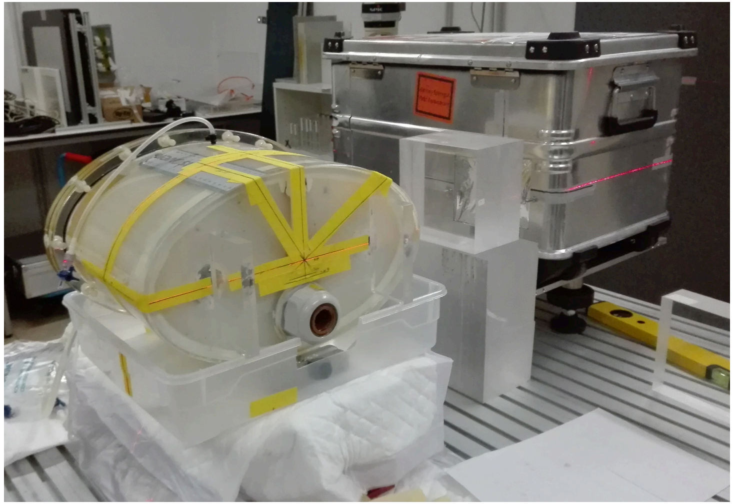




Pelvis phantom 2: setup

Pelvis/hip phantom and prostate cancer

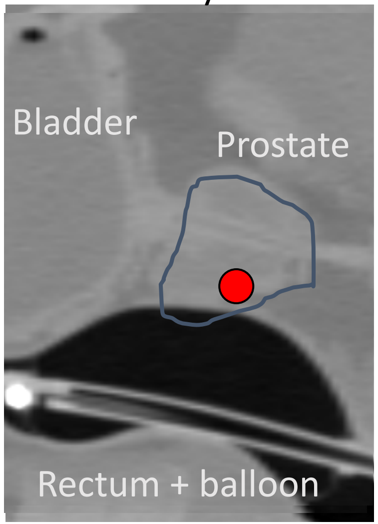




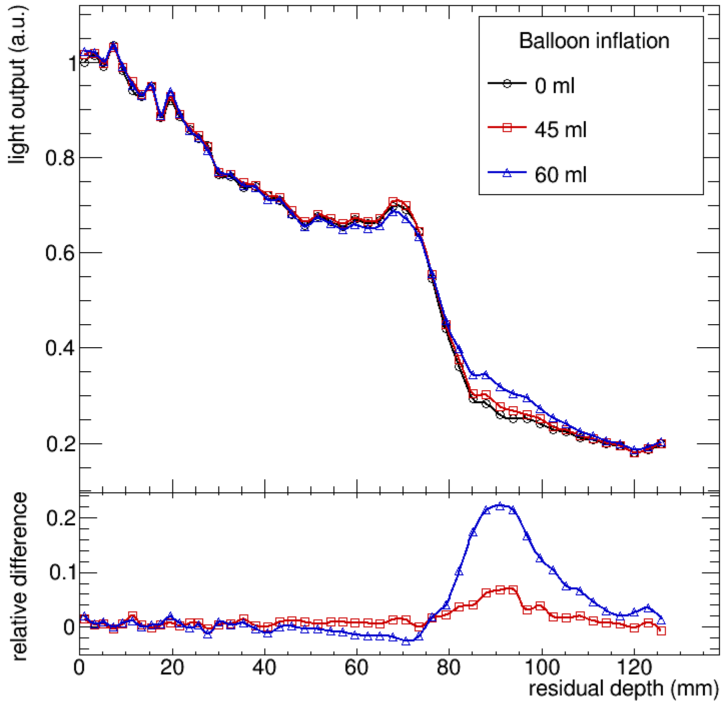
Pelvis phantom 2: results

Simulate rectal gassing

Beams eye view



60 ml



Summary

- Developed a prototype for fast proton range QA
  - Quenching effects considered in the analysis
  - Proton range reconstruction accuracy of 0.04 mm.
  - Robust results and radiation hardness
- Ongoing:
  - Build read-out based on photodiodes
  - Commercialisation

Summary

- He/C mixing offers online motion monitoring
- Extremely high sensitivity to range changes
- Submitted to Phys. Med. Biol
- Many open questions (technical, workflow…)

Thank you !

Additional Material

He/C mixing in clinics

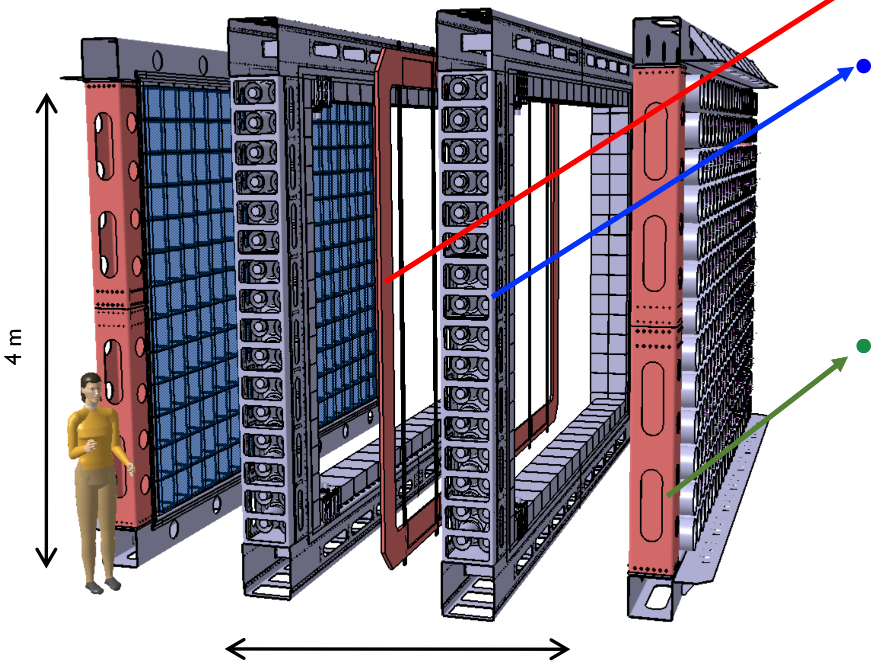
- Advantages:
  - High sensitivity
  - No extra room time
  - Negligible extra dose
- Disadvantages:
  - Not extendable to proton therapy
  - Changes behind C peak still affect He signal
  - Helium beam range might be too low to exit patient
- Open questions:
  - How to quantify changes?
  - How to generate a reference curve?
  - How to react if there is a change?
  - Which tumours can benefit?

Technical aspects of beam mixing

- Ion source: use e.g. methane as main gas and helium as support gas
- Several possibilities for beam generation:
  - Extract C6+ and He2+ (A/Q=2) but low current
  - Extract C3+ and He+ (A/Q=4) but Linac too weak
  - Extract one ion after another and mix in synchrotron
- Simulations needed to prove that mixed beam is stable in synchrotron

SuperNEMO

Neutrinoless double beta decay detector

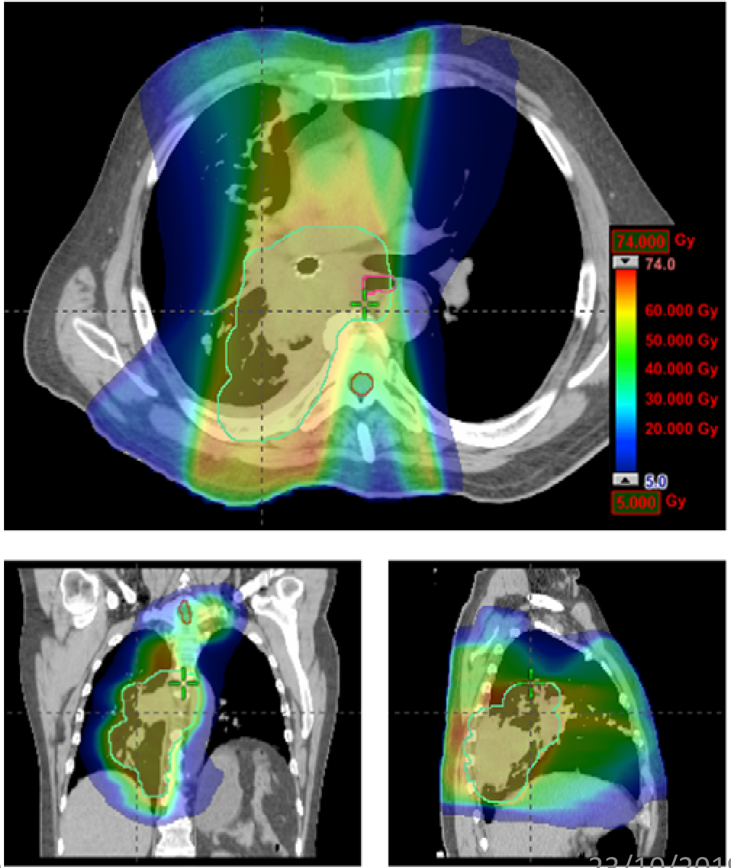


- Source foil: ββ decaying isotope
- Tracker: ~2000 drift cells in Geiger mode
→ particle identification (for background suppression)
- Calorimeter: ~550 scintillator blocks + PMTs
→ energy and time of flight measurements of particles

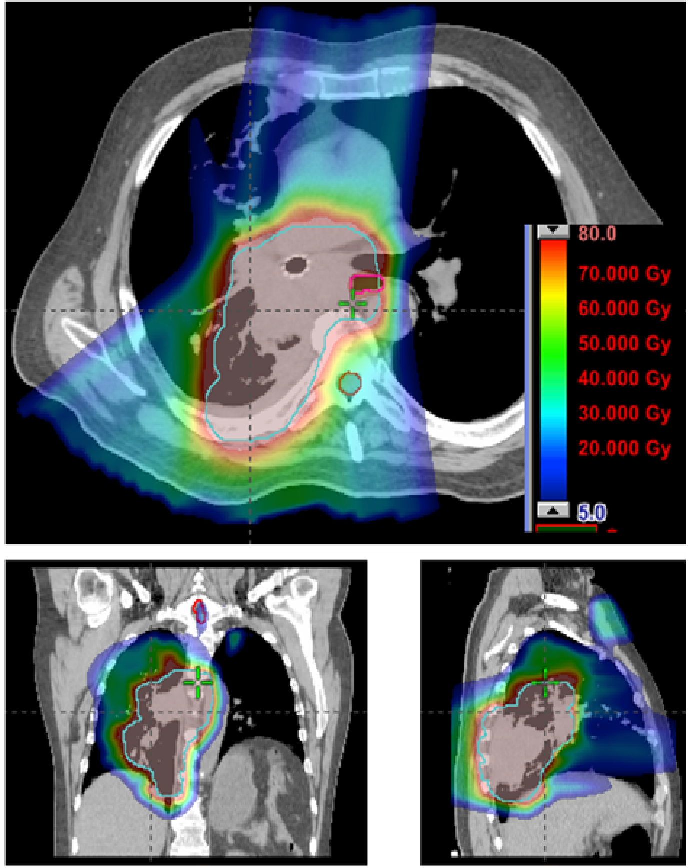
https://supernemo.org/about.html

Lung Comparison

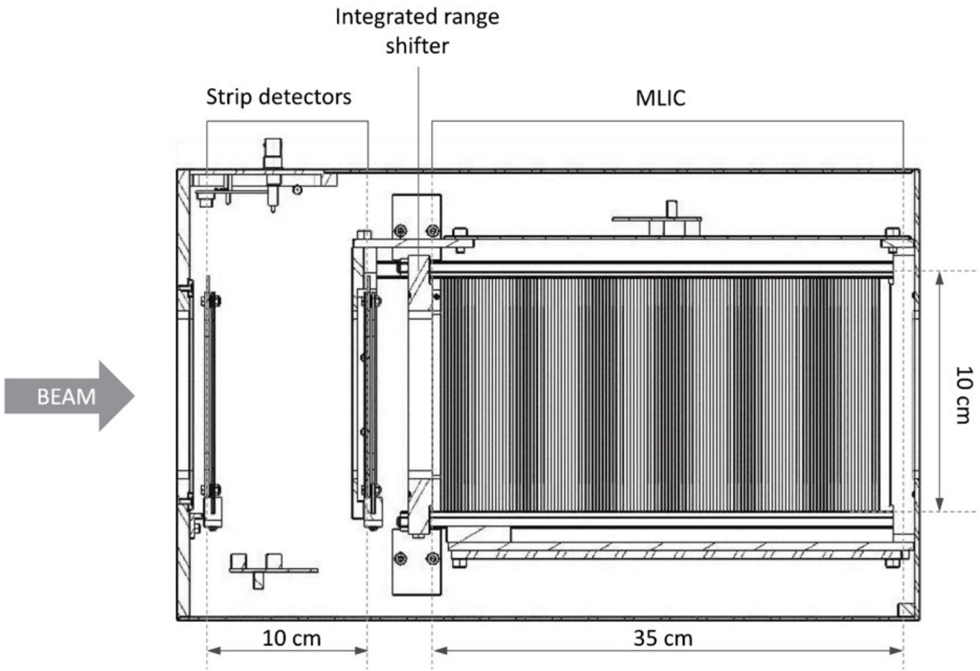
X-rays



Protons



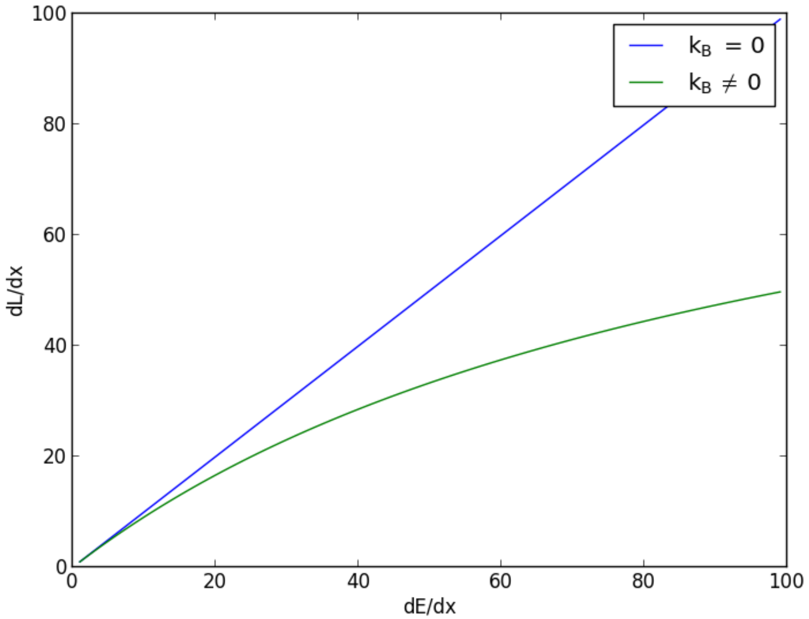
Zhang X, Li Y, Pan X, et al. *Int J Radiat Oncol Biol Phys.* 2009;77(2):357-366



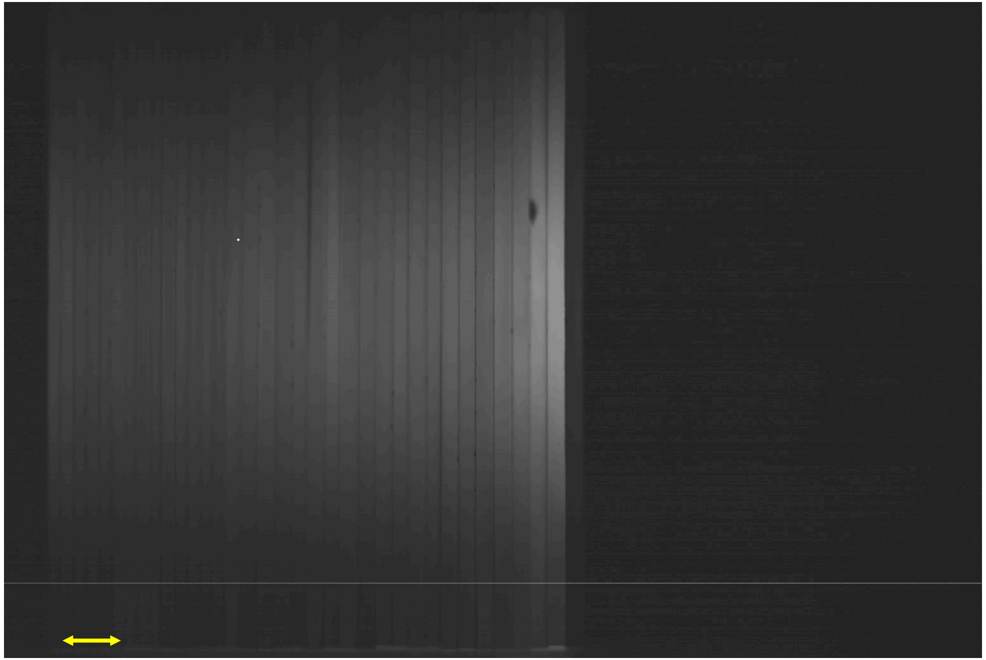
O. Actis *et al.* 2017 *Phys. Med Biol.* **62** 1661

Quenching: Birk's Law

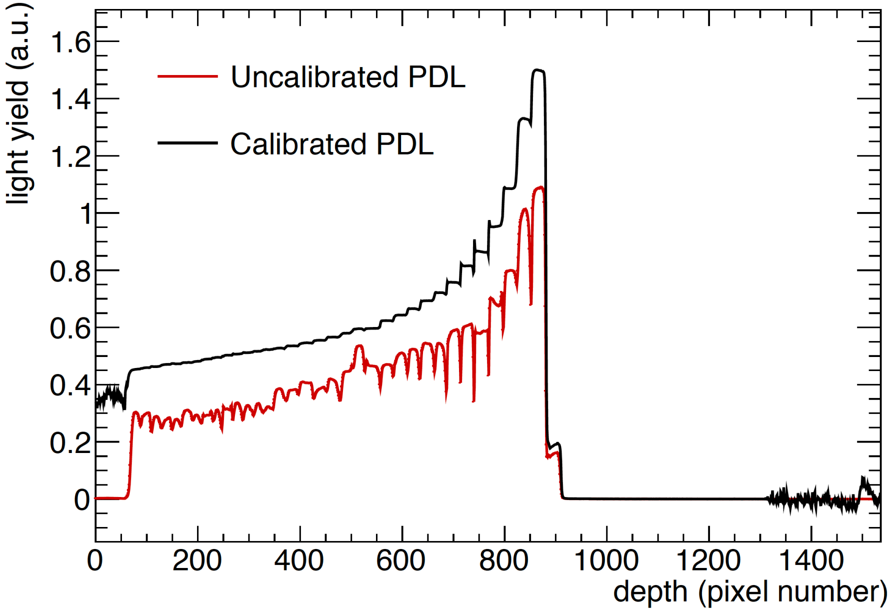
$$\frac{dL}{dx} = S\frac{\frac{dE}{dx}}{1 + k_B\frac{dE}{dx}}$$



Beam E 106.2 MeV

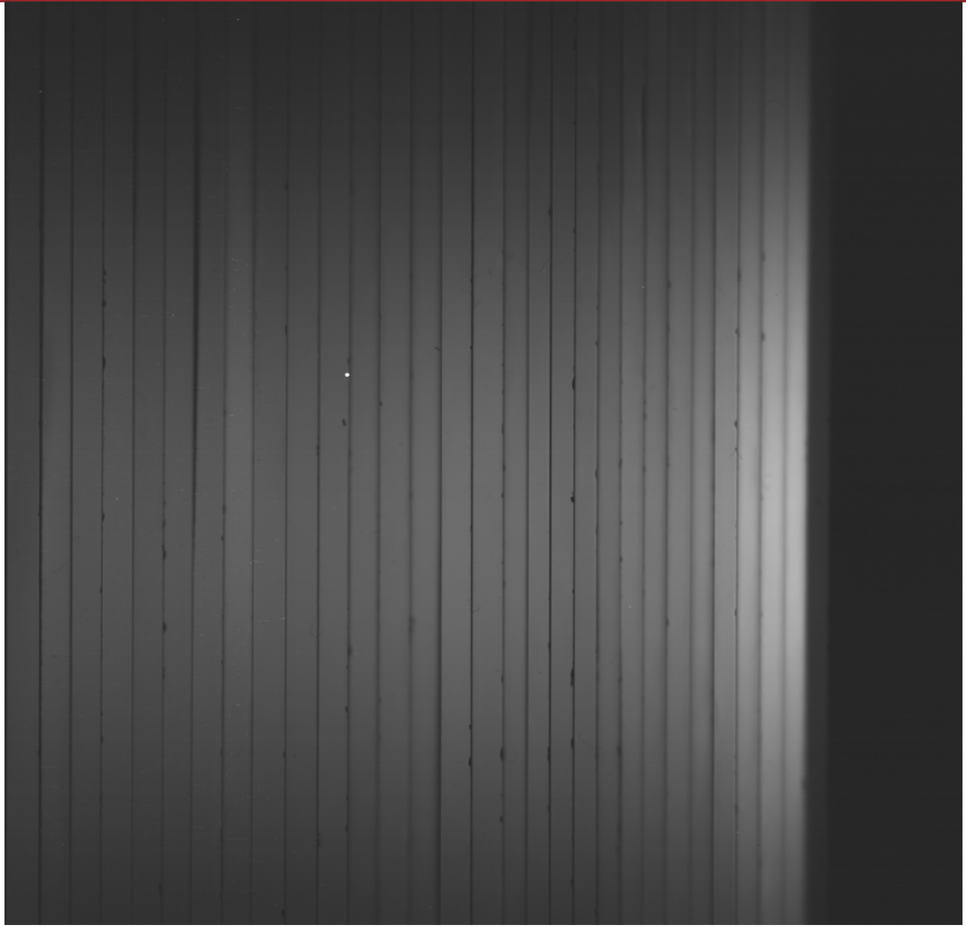


10 mm

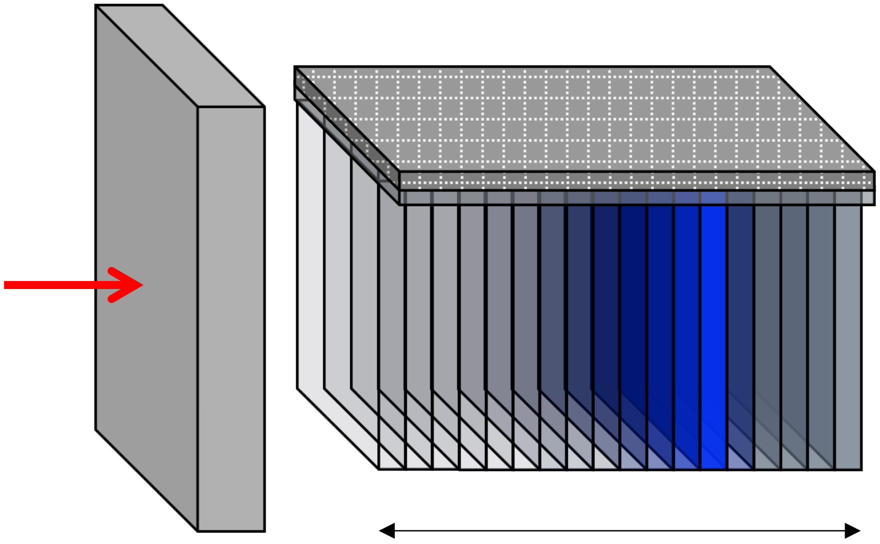


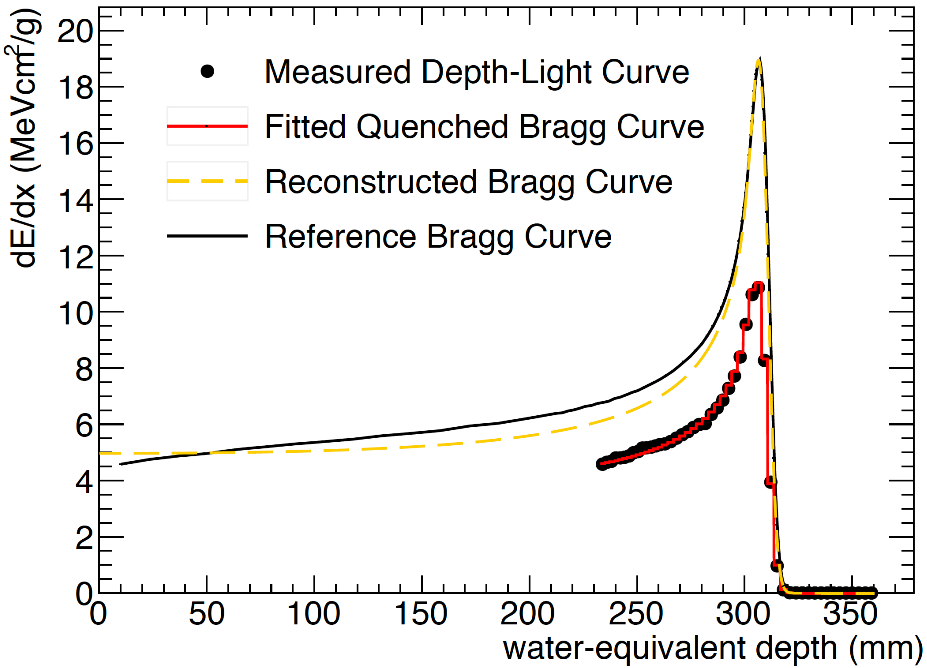
Raw data

Protons



Beam E 222.7 MeV

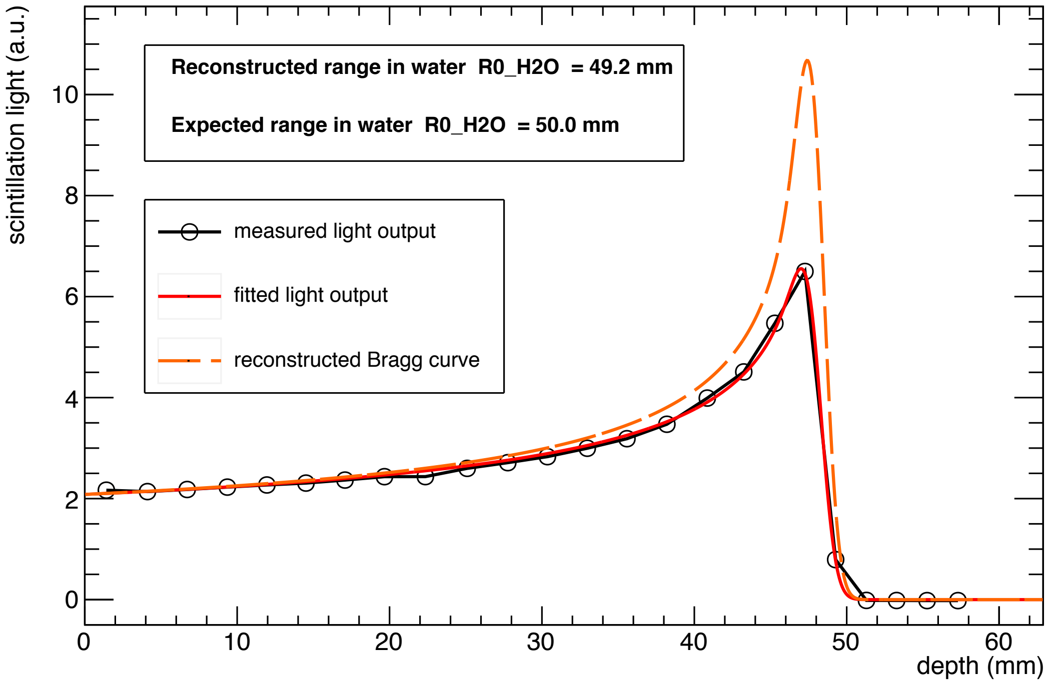




PMMA degraders needed to cover the full range of clinical proton energies

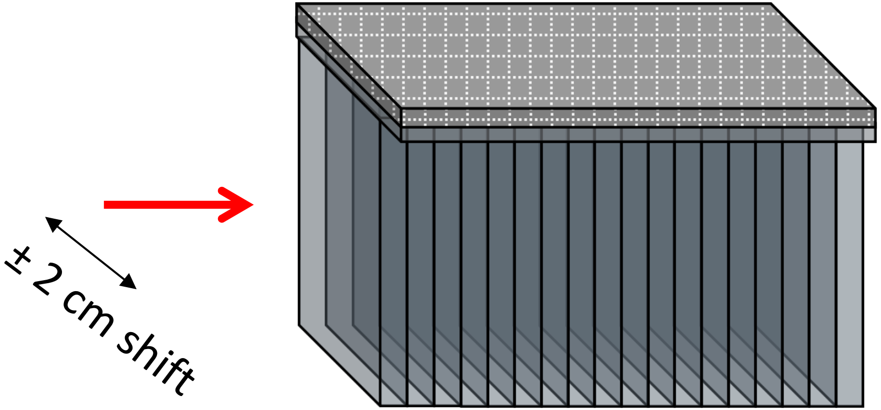
81.3 MeV Bragg Peak Fit

- Integrate down one column of pixels and calculate the average light intensity for each sheet.
- Fit quenched Bragg curve to this data.
- Reconstruct actual Bragg peak and Water Equivalent Path Length (WEPL).



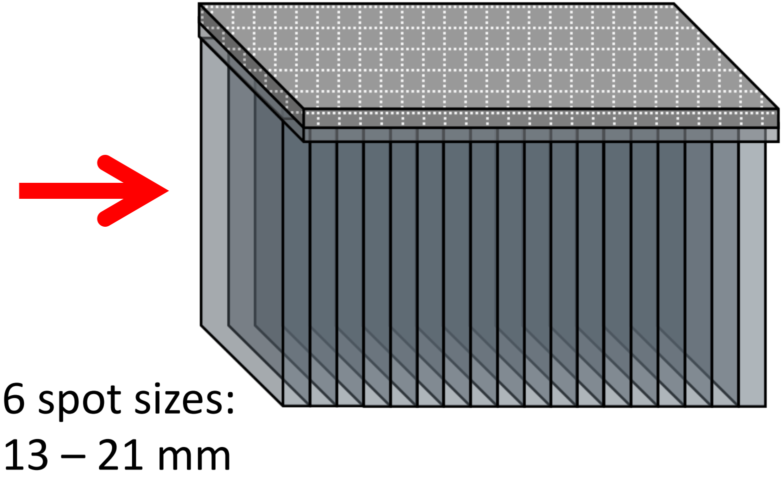
Robustness checks

Beam Spot Position



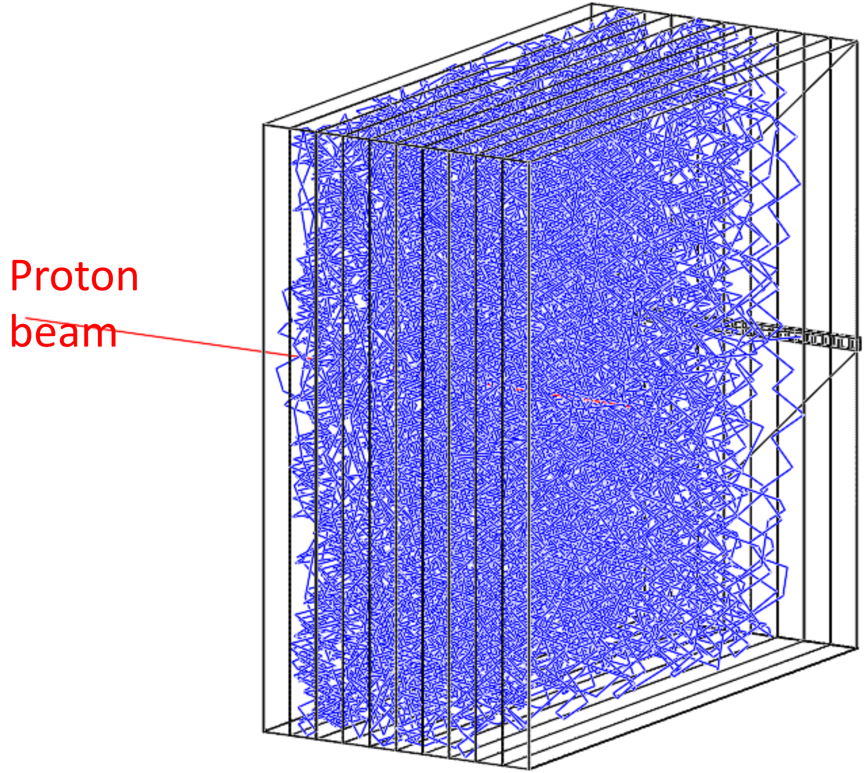
Range observed variation <0.05 mm

Beam Spot Size

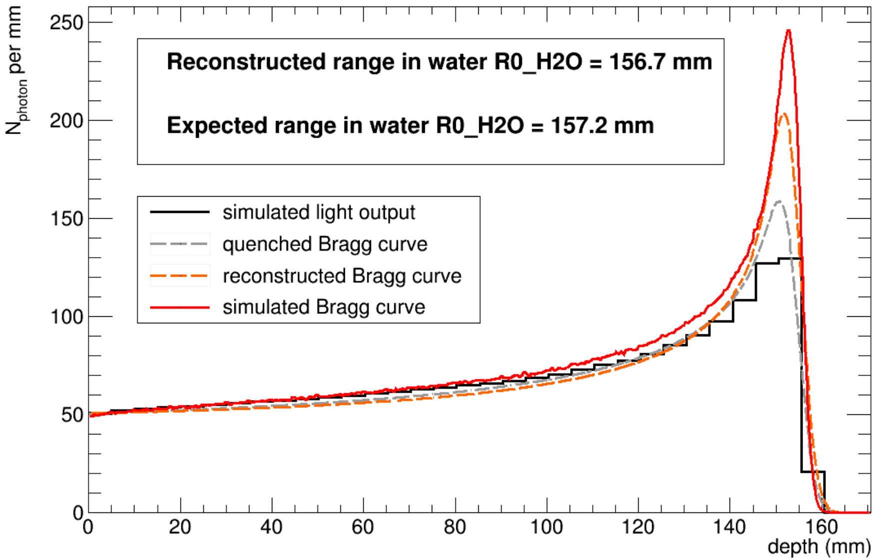


Range observed variation <0.03 mm

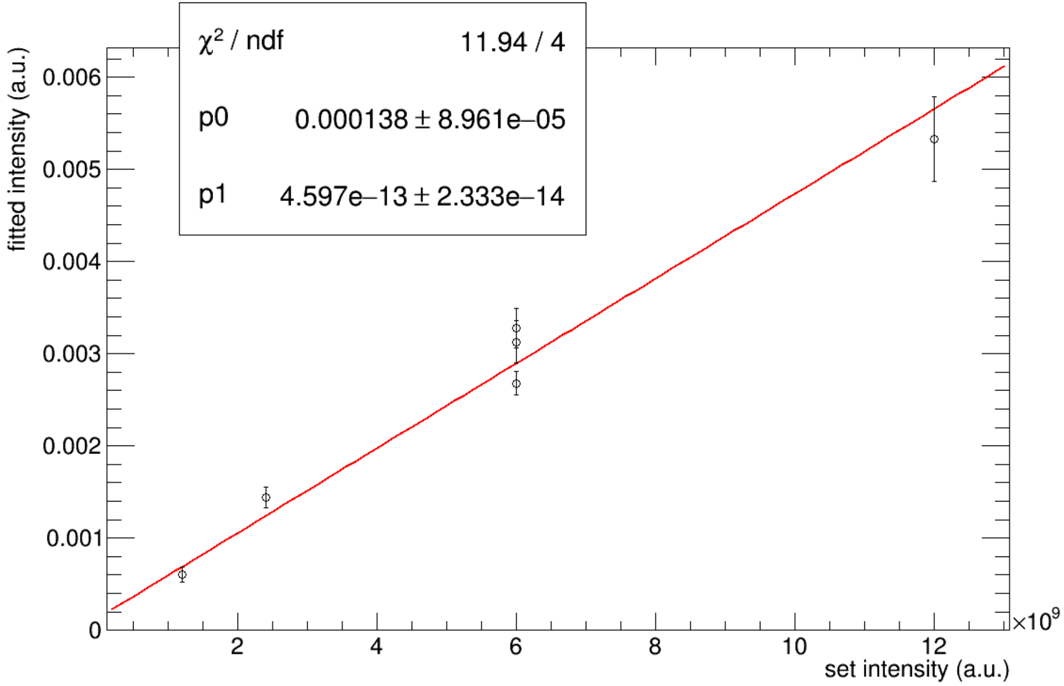
Detector Simulation (Geant4)



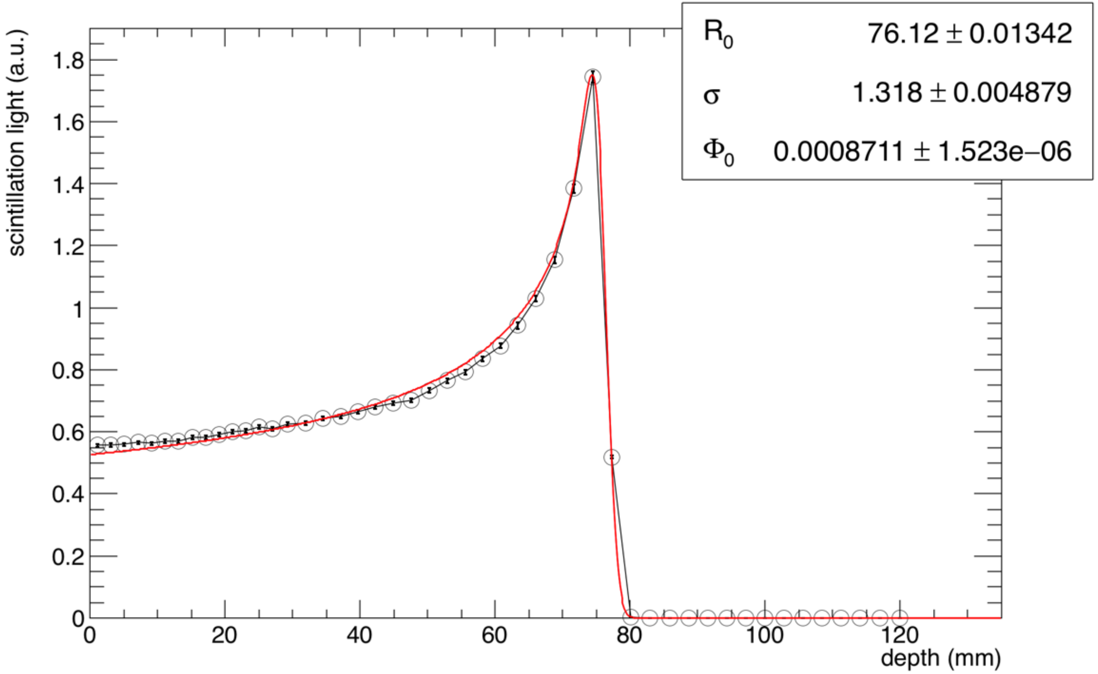
Reconstructed Range



Intensity Scan

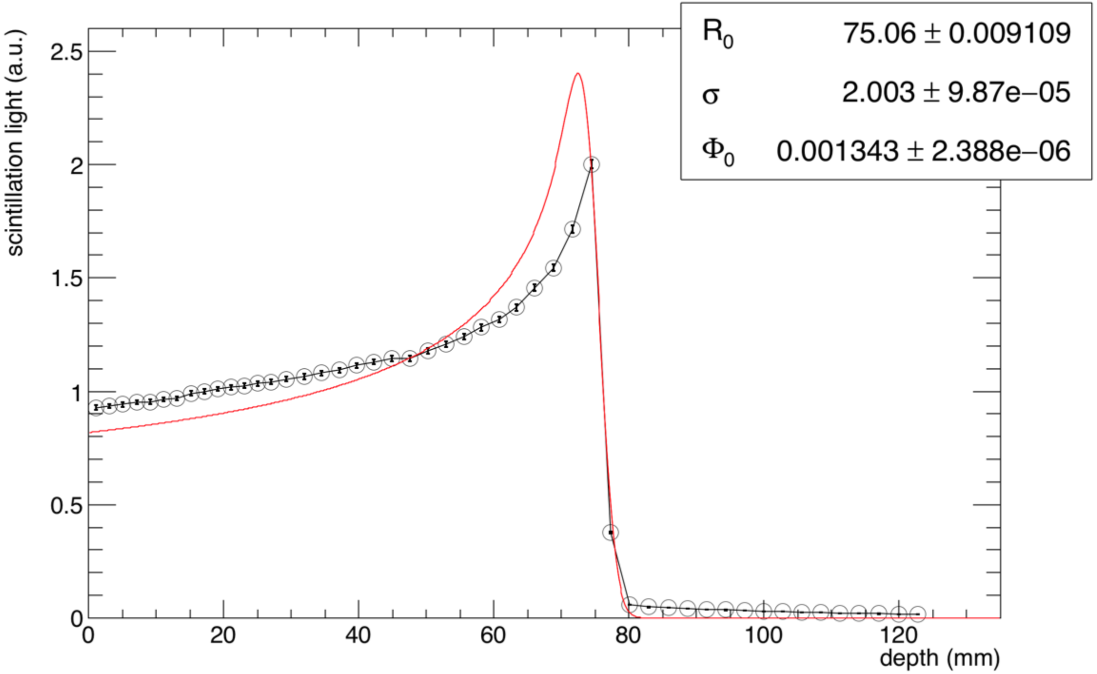


Proton Beam



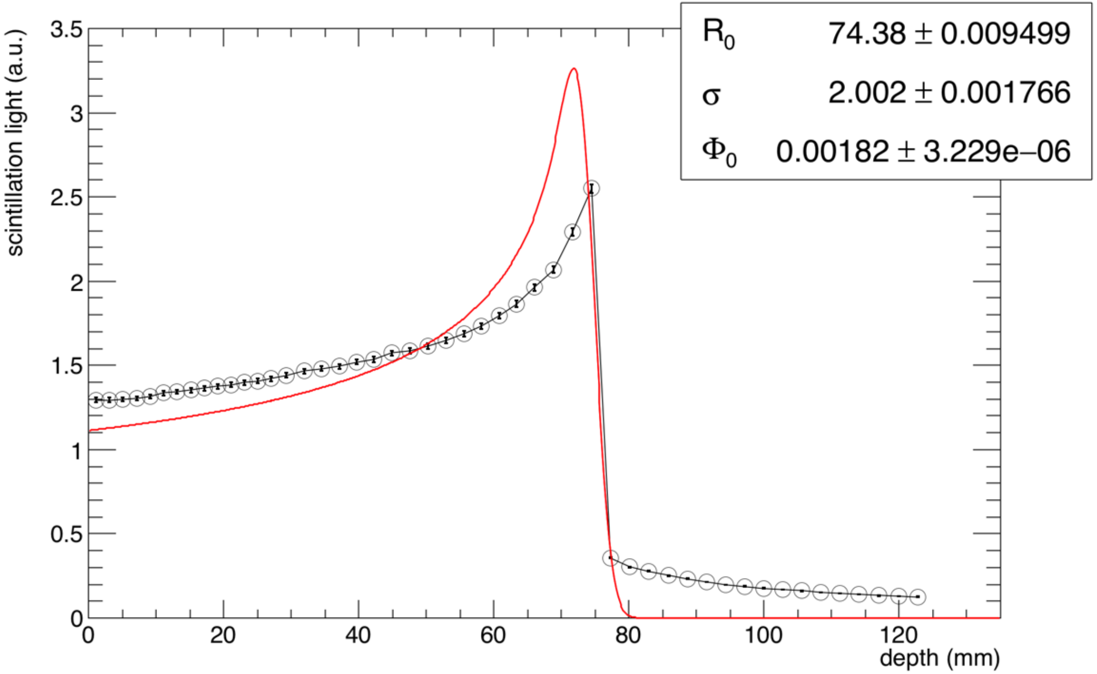
R_0 76.12 ± 0.01342
σ 1.318 ± 0.004879
Φ_0 0.0008711 ± 1.523e−06
scintillation light (a.u.)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
0
20
40
60
80
100
120
depth (mm)

Helium Beam



R_0 75.06 ± 0.009109
σ 2.003 ± 9.87e−05
Φ_0 0.001343 ± 2.388e−06
scintillation light (a.u.)
0
0.5
1
1.5
2
2.5
0
20
40
60
80
100
120
depth (mm)

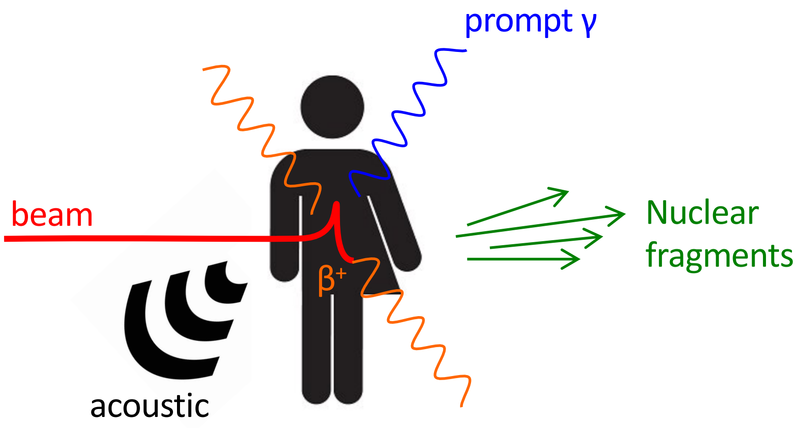
Carbon Beam



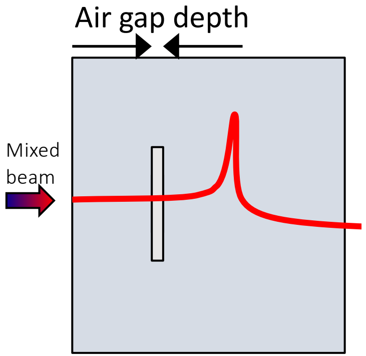
scintillation light (a.u.)
3.5
3
2.5
2
1.5
1
0.5
0
0
20
40
60
80
100
120
depth (mm)
R_0 74.38 ± 0.009499
σ 2.002 ± 0.001766
Φ_0 0.00182 ± 3.229e−06

Online treatment monitoring

- Prompt gamma
- In-beam PET
- Nuclear fragments
- Iono-acoustic

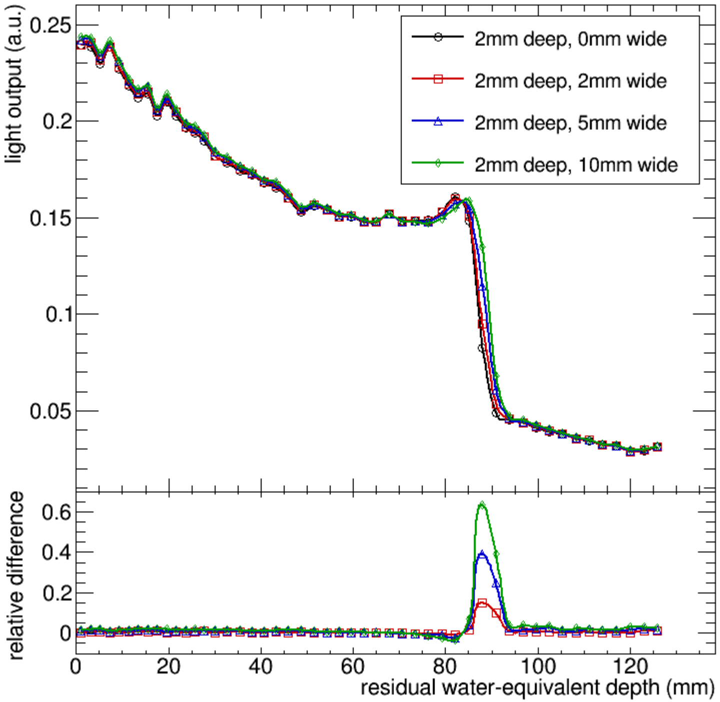


PMMA phantom: results



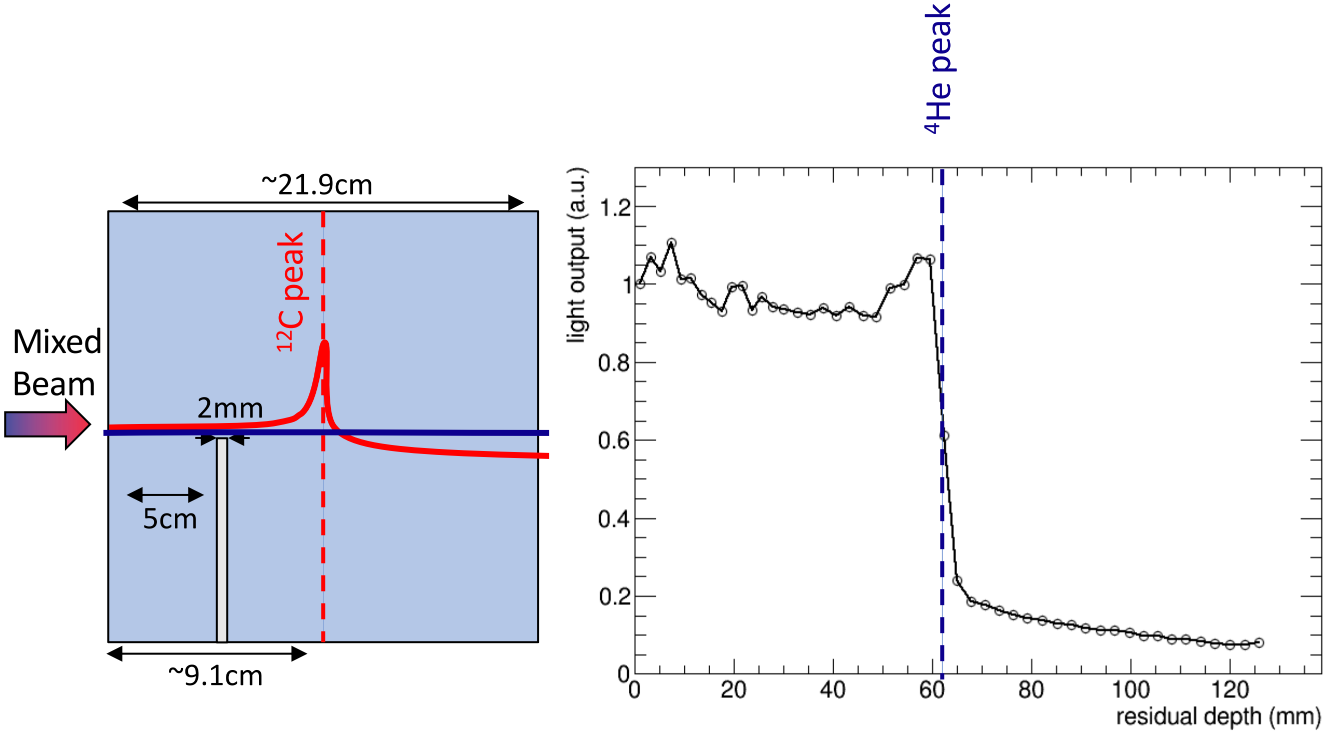
PMMA phantom

Beam size = 8mm FWHM



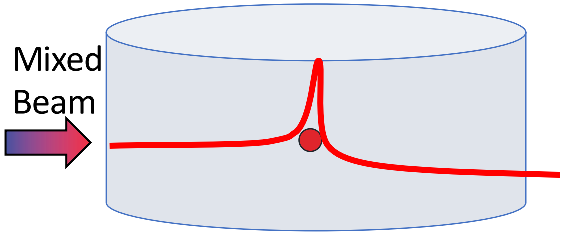
Range telescope

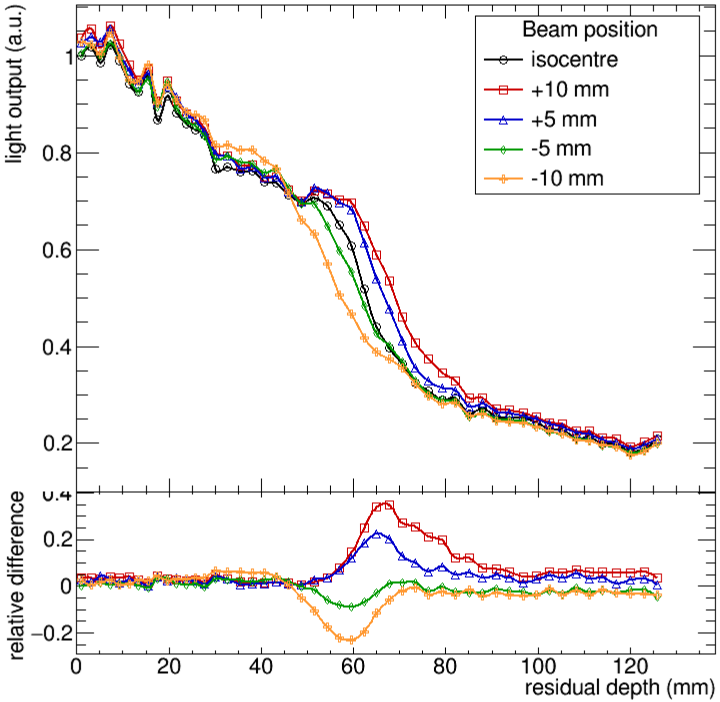
PMMA phantom: results



Pelvis phantom 1: translation

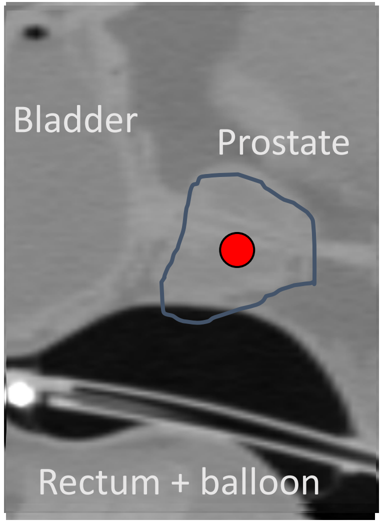
Simulate patient misalignment





Pelvis phantom 2: results

Beams eye view



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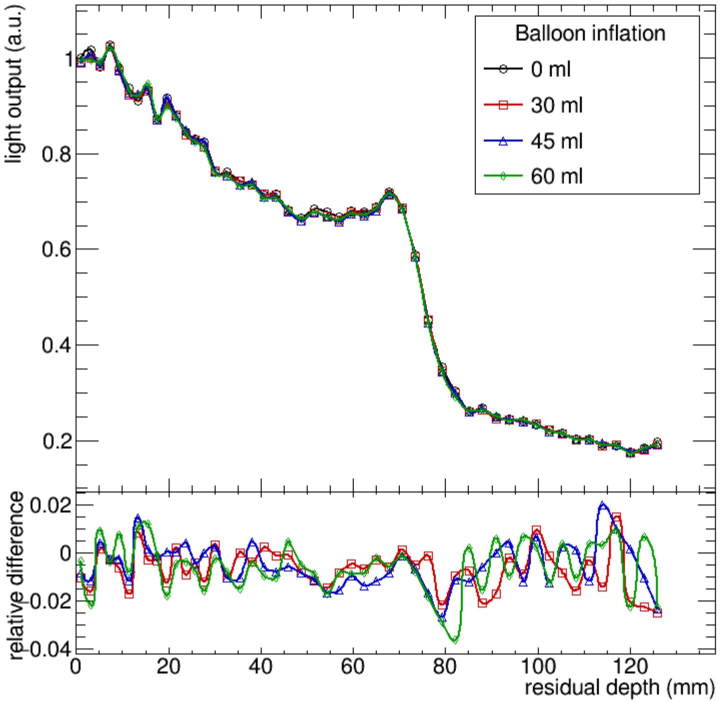
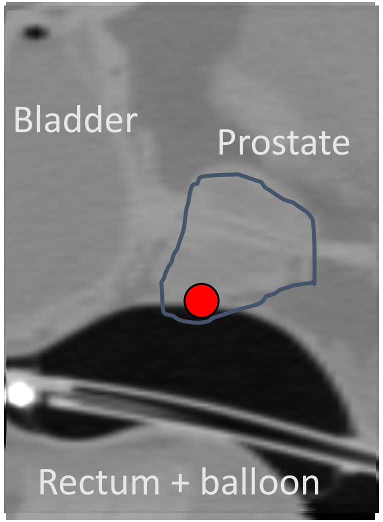
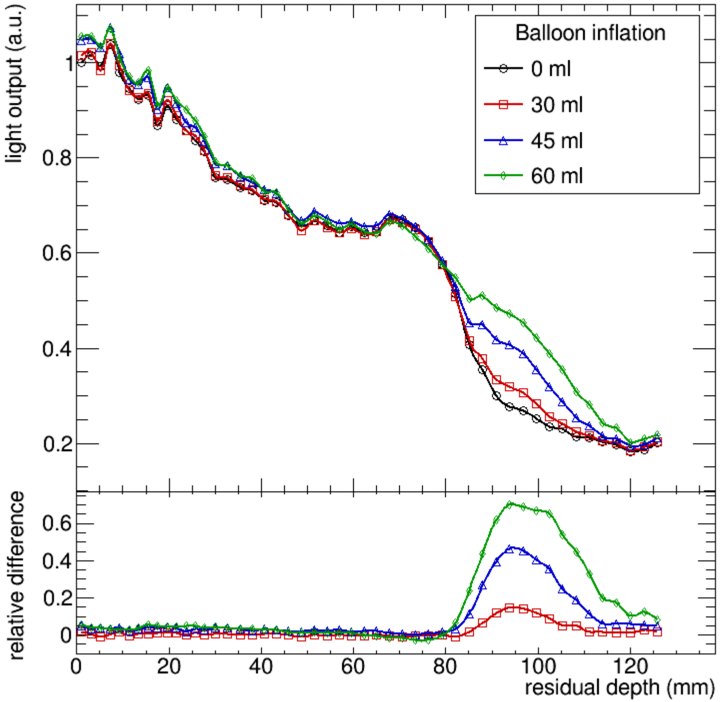


Pelvis phantom 2: results

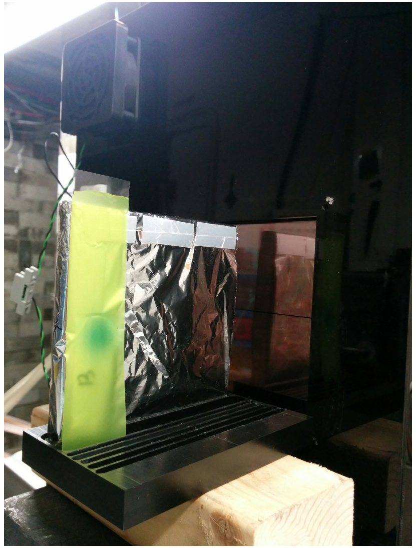
Beams eye view





Experimental Runs

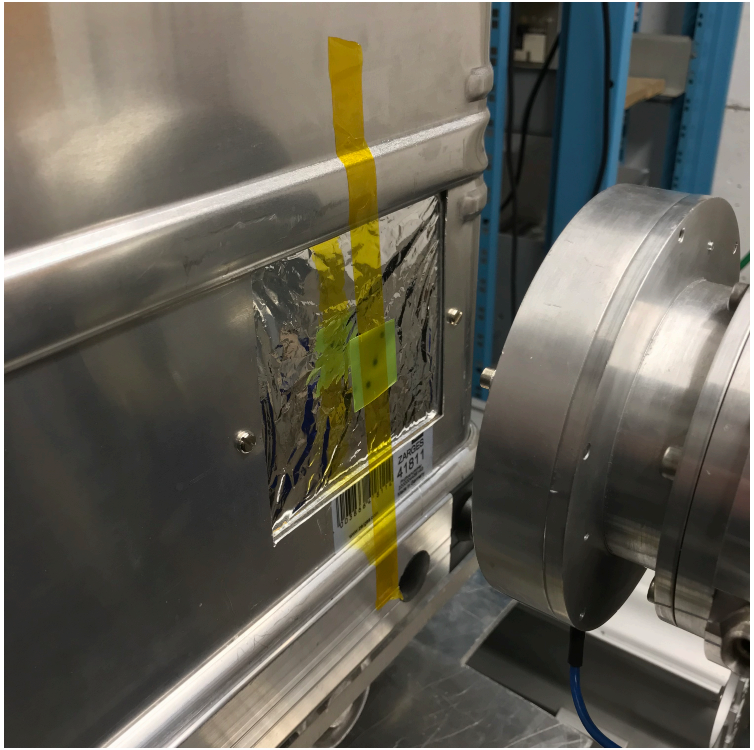
2016	2017	2018	2019
	Birmingham	Birmingham MedAustron Heidelberg Clatterbridge	Heidelberg



Sep. 2017

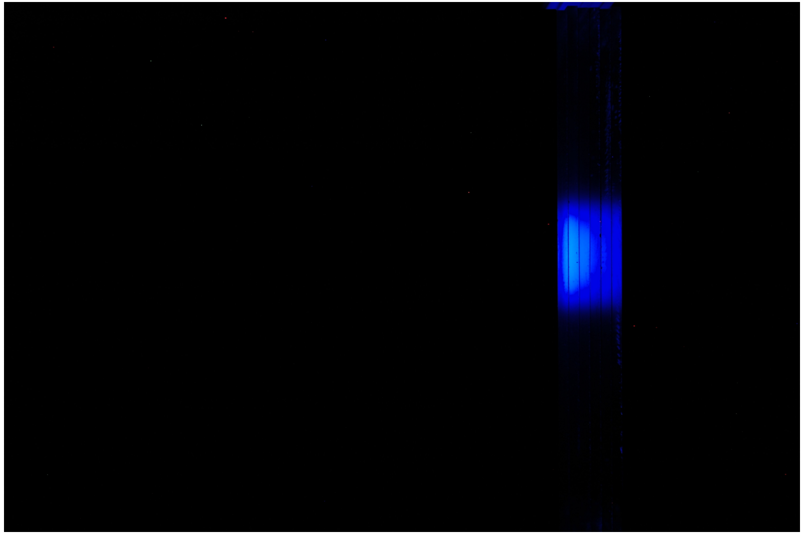
Beam tests of 10 mm, 4 mm and 3 mm scintillator sheets with PRaVDA CMOS pixel sensors (PRIAPUS) at the Birmingham Cyclotron (28 MeV beam)

First Bragg Peak!



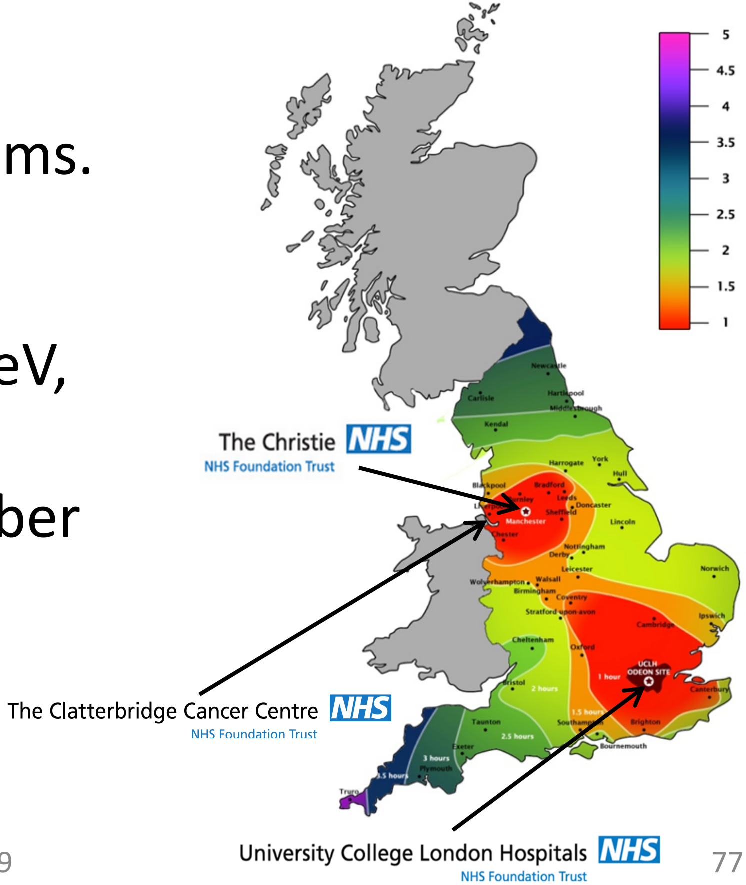
March 2018

Beam test at the Birmingham Cyclotron (36 MeV).
A Bragg Peak measurement was carried out to confirm the exact beam energy



NHS England PBT Centres

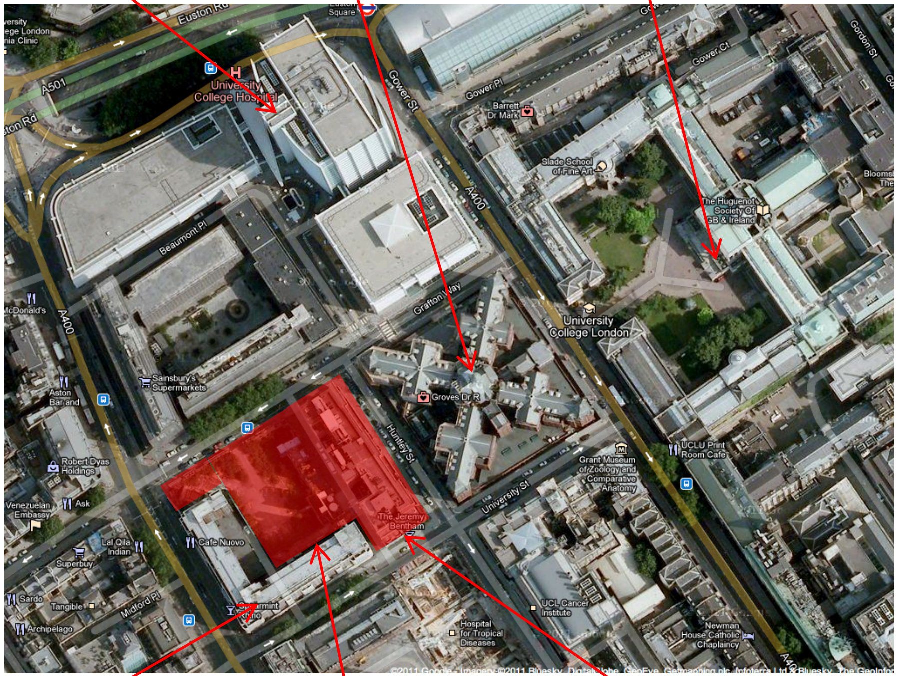
- Two new national centres:
  - UCLH (London): 4 treatment rooms.
  - The Christie (Manchester): 3 treatment rooms.
  - Pencil beam scanning 70-245 MeV, 360° rotating gantries
- The Christie started treating December 2018; UCLH will start in 2020.
- More private centres in Wales, the Northeast and Reading



UCLH PBT: July 2019

https://www.uclh.nhs.uk/aboutus/NewDev/NCF/Pages/Blogandupdates.aspx

UCLH　Cruciform Building　UCL



Paramount Court

New proton therapy site

Jeremy Bentham (Deceased)

UCLH PBT