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An Introduction to Proton Therapy

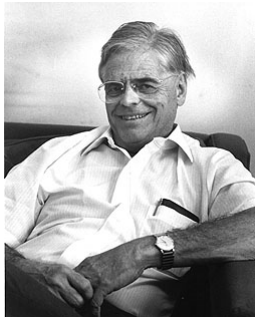
MPHY0038

Callum Gillies – Proton therapy physicist, UCLH
callumgillies@nhs.net

Outline

- Background and history
- Proton Physics
- Key uncertainties in proton treatment planning
  1. Uncertainties in proton range calculation
  2. Set-up uncertainties and anatomy changes over the course of RT
  3. Organ motion and the ‘Interplay effect’
  4. Complex in-homogeneities within the proton beam
  5. Proton Radiobiology
- Robust Proton Planning:
  - Current state
  - Looking to the future
- Clinical applications of proton therapy
- Proton therapy in the UK

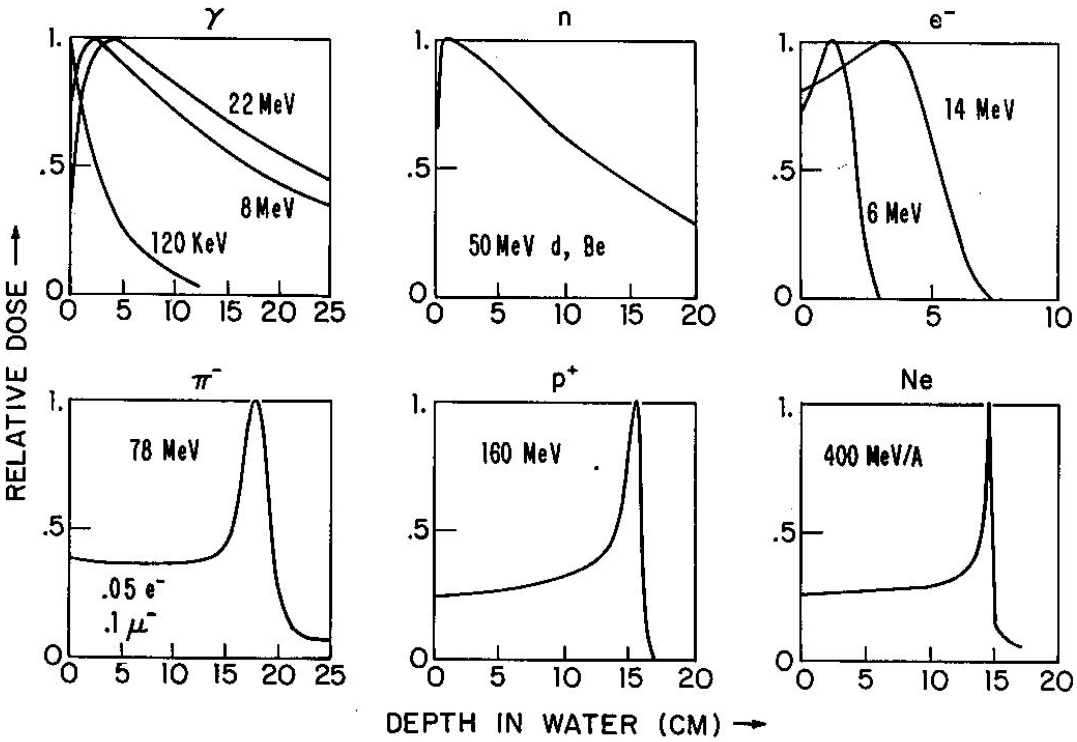
A Brief History



- 1946: Therapeutic use of proton beams first proposed by Robert Wilson: *Radiological use of fast protons. Radiology. 1946;*
- 1954: First patient treated at the UC Lawrence Berkeley Laboratory (LBL)
- 1957: Proton radiosurgical techniques for brain tumors developed at the Gustaf-Werner Institute, Uppsala, Sweden
- 1961: Radiosurgery of small intercranial targets at the Harvard Cyclotron Laboratory
- 70s – 80s: Physics facilities worldwide – notably, the Paul Scherrer Institute (PSI) in Switzerland
- 1989: The world's first hospital-based low-energy ocular proton beam therapy facility opened at Clatterbridge Cencer Centre, UK
- 1990: The world's first hospital-based high-energy proton beam therapy facility opened at Loma Linda University Medical Center, California
- 2000s - : Rapid growth in number of proton facilities internationally

Proton Physics

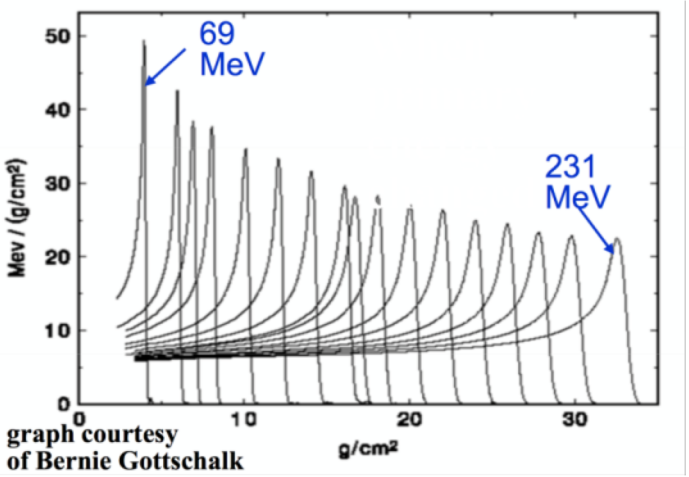
Why Protons?

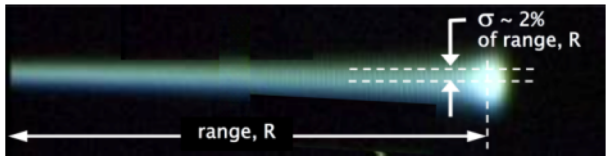


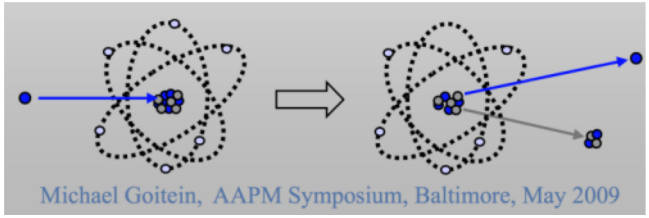
- **Neutral particles** fall **exponentially** (after the dose builds up at the entrance) as particles are lost to various interactions.
- **Charged particles** are not lost, but slow down by myriad collisions with atomic electrons. A slower particle loses more energy per cm because it spends more time interacting with the electrons, producing the **Bragg Peak** of dose.

Proton Interactions with Matter

- Stopping
  - The beam range depends on the initial energy of the protons. When protons pass through matter they slow down and stop due to Coulomb interactions with atomic electrons. The 'Blethe-Bloch' equation describes this process.
- Multiple Coulomb scattering
  - When protons pass through a slab of material they suffer millions of collisions with atomic nuclei. The statistical result is a small multiple scattering angle
- Nuclear interactions
  - About 20% of 160 MeV protons stopping in water have a non-elastic nuclear reaction where the primary protons, neutrons and nuclear fragments appear.





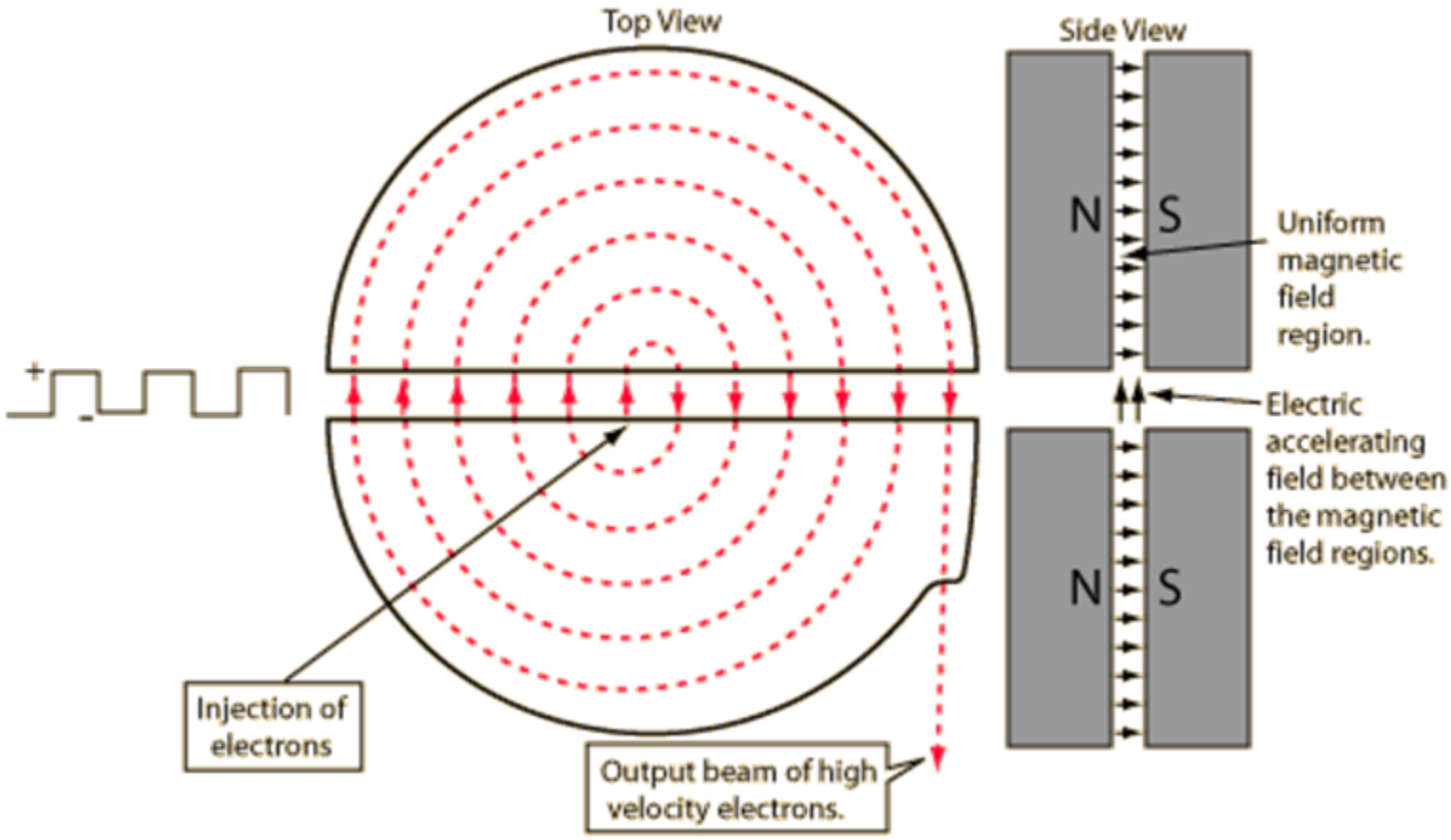


Getting a clinically useful beam

The Cyclotron

- A proton is injected at the centre of the cyclotron
- It is accelerated across a fixed gap
- It path is curved by a strong magnetic field
- The proton is accelerated back across the same gap
- The proton is curved back round with a larger radius than before (due to the increased momentum)
- After this has happened many times the proton is ejected at a maximum energy
- To deliver lower energies…
- Use a degrader
- This reduces the efficiency and higher currents are required.

The Cyclotron



The Cyclotron

- The magnetic field applies a force on the particle causing it to curve

$$\frac{mv^2}{r} = Bqv$$

- m = particle mass
- v = velocity
- r = path radius
- B = Magnetic field strength
- q = particle charge

- Rearranging gives the angular velocity

$$\frac{v}{r} = \frac{Bq}{m} = \omega$$

- Angular velocity is important for the alternating frequency in the acceleration gap

- Time for one rotation = Distance/Speed

$$T = 2\pi r \div \omega r = \frac{2\pi m}{Bq}$$

- Time is independent of radius
- A square wave with angular frequency $\omega_{cyclotron} = {}^{Bq}/_{m}$ is applied between two sides of the magnetic poles.

Pop Quiz

- A beam of 3.5 GeV Carbon ions is required for a radiotherapy treatment
- The final radius of the cyclotron is 4m
- Atomic number of Carbon is 6
- Proton charge is 1.6×10^{-19}C
- Carbon ion rest mass = 1.99×10^{-23}kg
- 1eV = 1.602×10^{-19}J

- Calculate the field strength required

Answer!

- The Carbon ion has an Energy of 3.5×10^9 eV
- It's kinetic energy so…

$$3.5\times10^{9}\times1.602\times10^{-19} = \frac{1}{2}mv^2$$

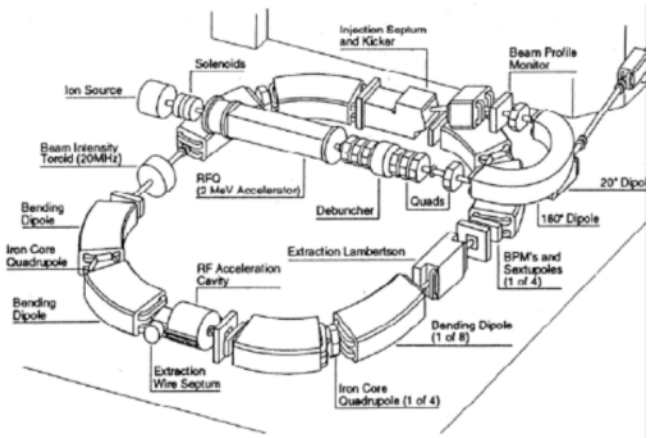
- We know that m is $1.99 * 10^{-23}$
- Solving for v gives 7,506,780.85

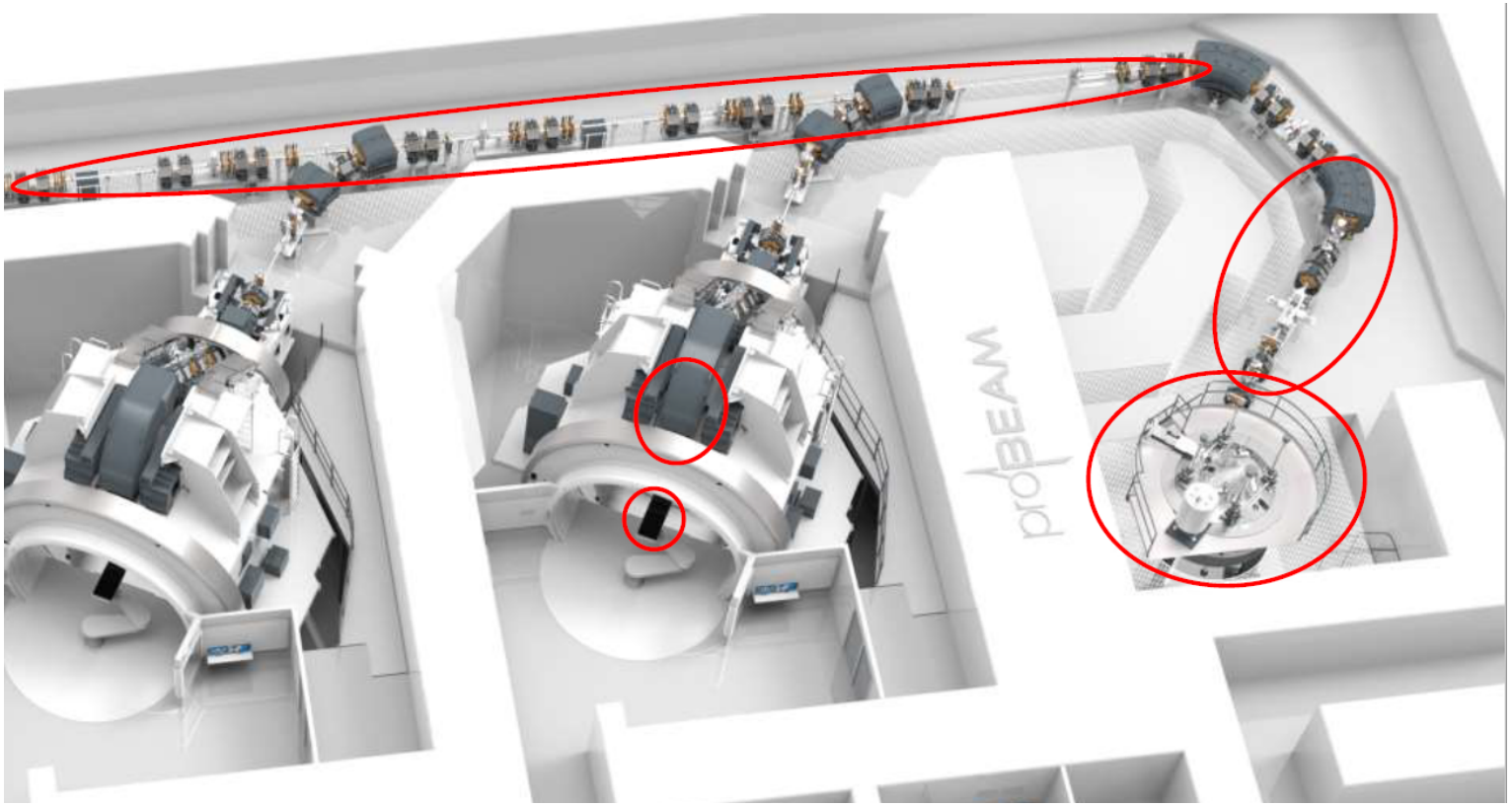
$$\frac{mv^2}{r} = Bqv \;\; \therefore B = \frac{mv}{qr}$$

- Putting in values (not forgetting q=6 x proton charge) is…
- $(1.99 * 10^{-23} \times 7506780.85) / (6 \times 1.6 * 10^{-19} \times 4)$
- 38.85 Tesla (No clinical magnets are this strong!)

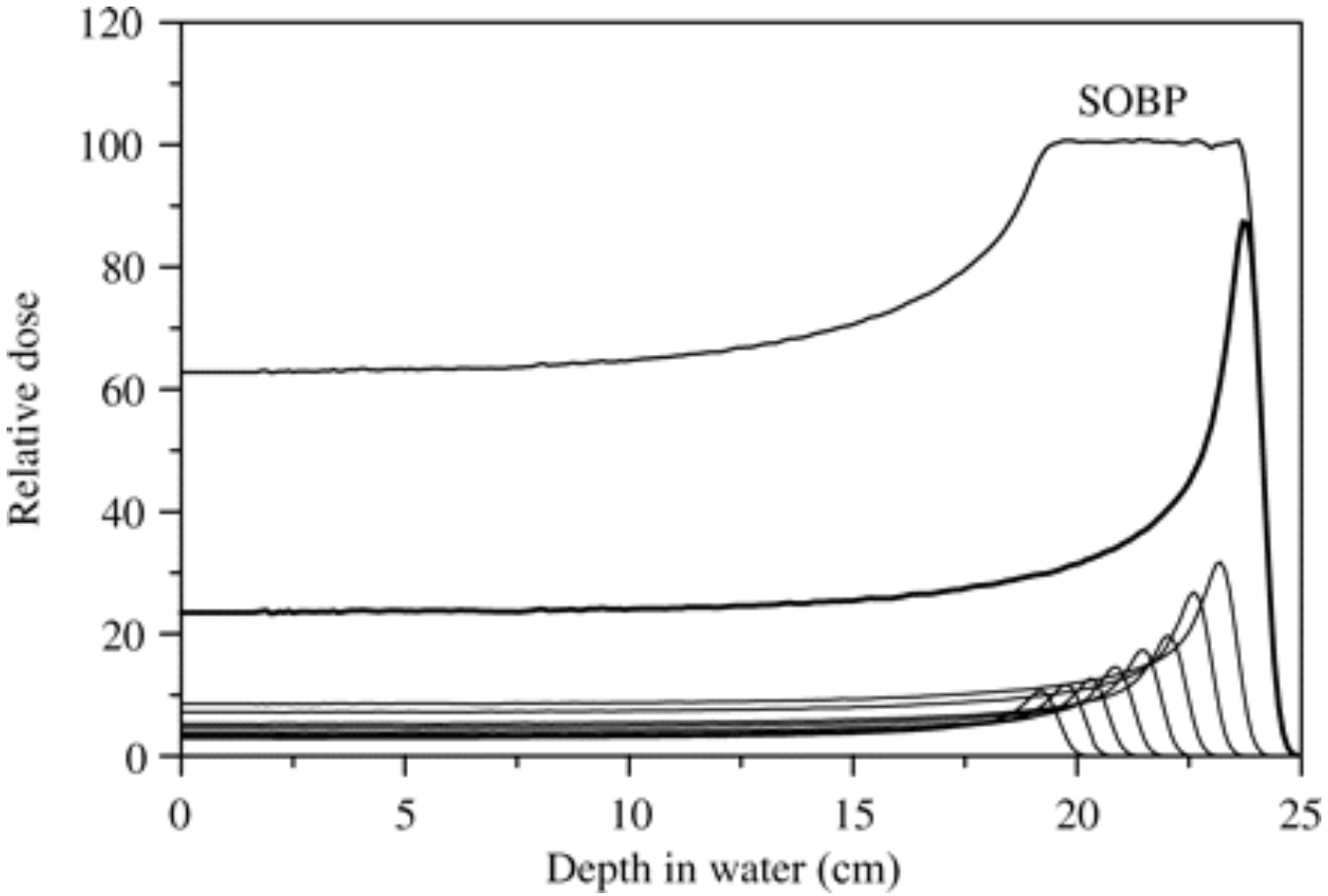
Synchrotron

- Particles are accelerated in a fixed, closed loop
- Magnetic fields synchronised with increasing speed of the particle
- Also has to account for relativistic mass of particles
- Can spill off energy without degrading the beam
- However – changing energy is too slow so requires some modulation
- Synchrotrons are also much larger (6-8m) with the requirement of an injection beam

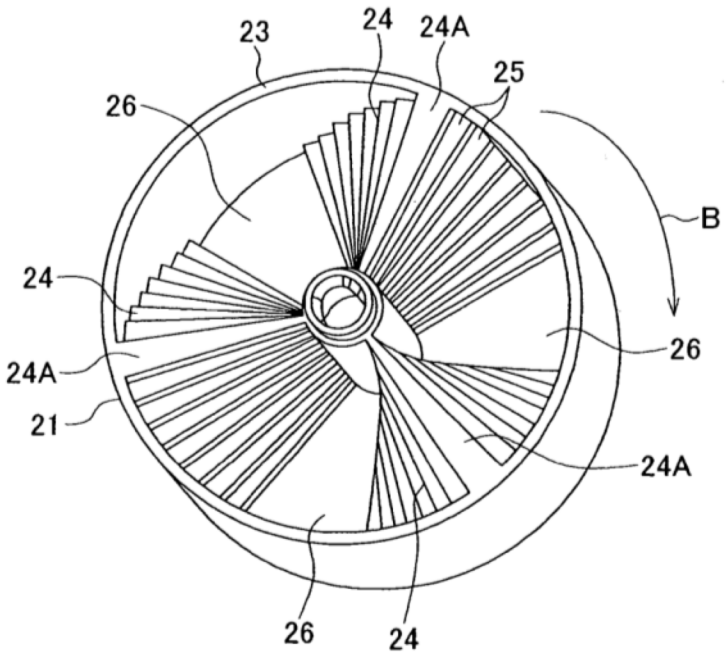



proBEAM

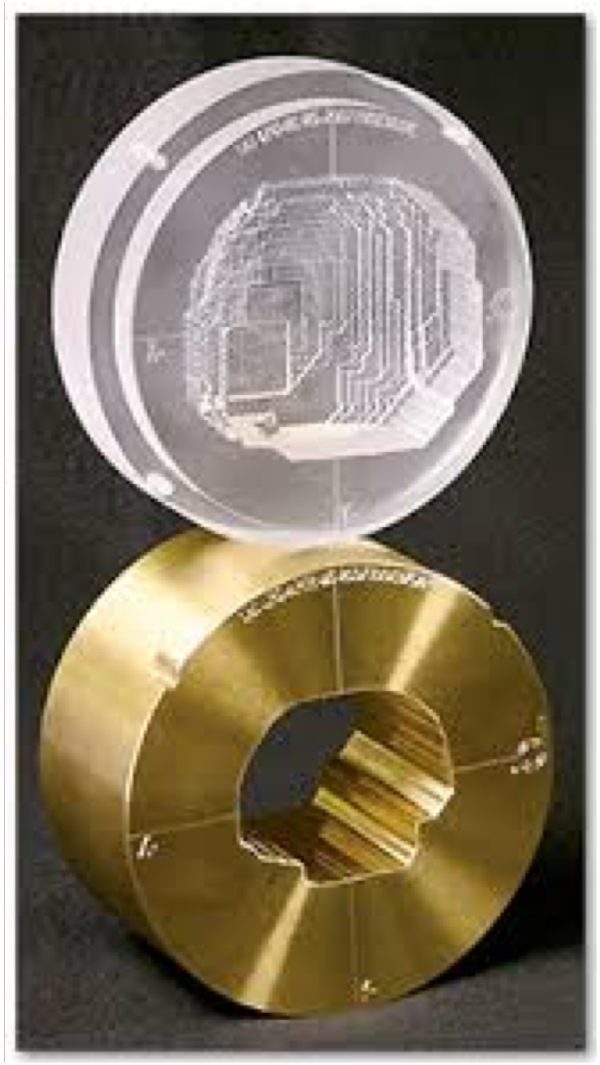
Spread Out Bragg Peak (SOBP)



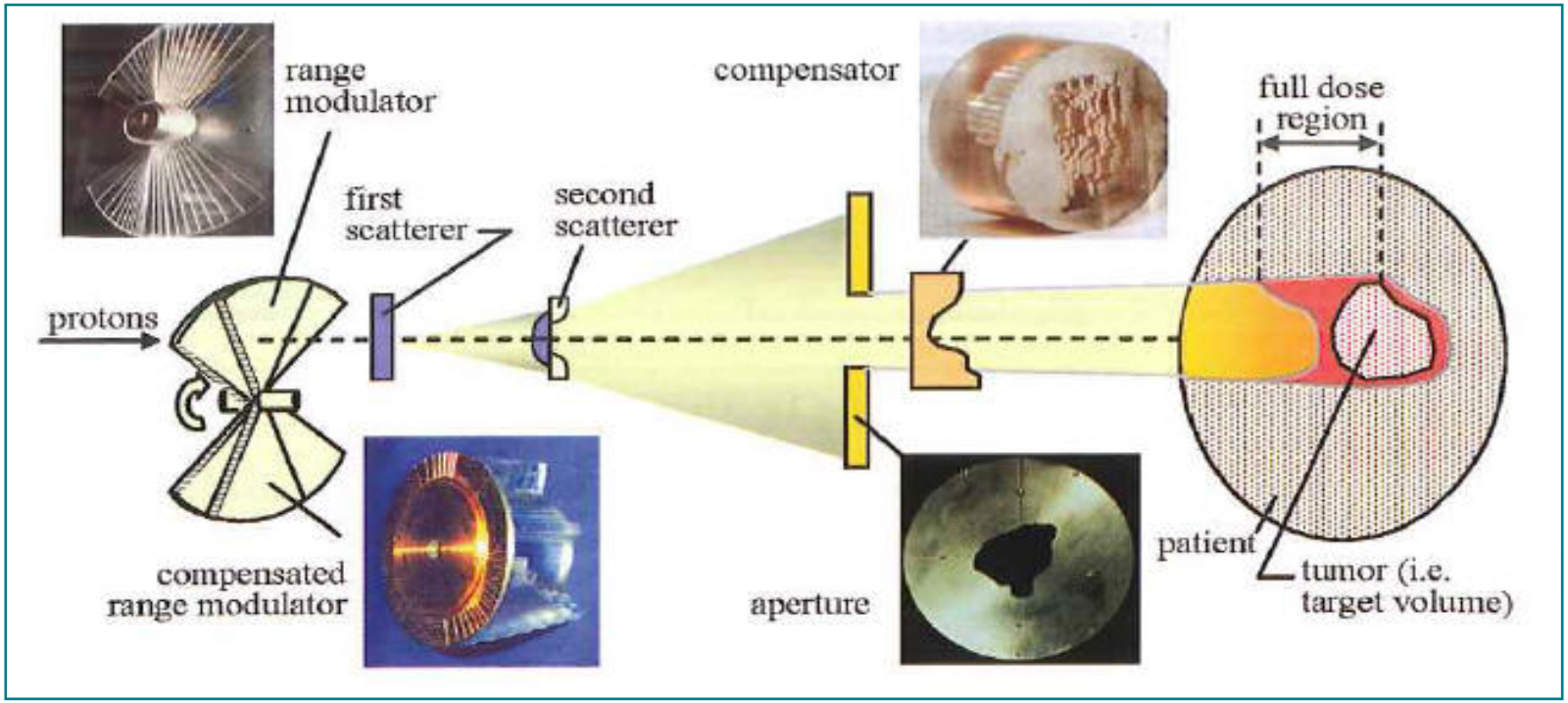
Getting a clinically useful beam



Passive Scattering



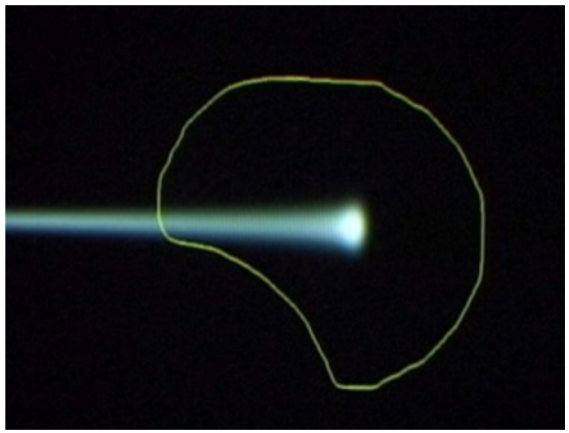
Passive Scattering… Eurgh



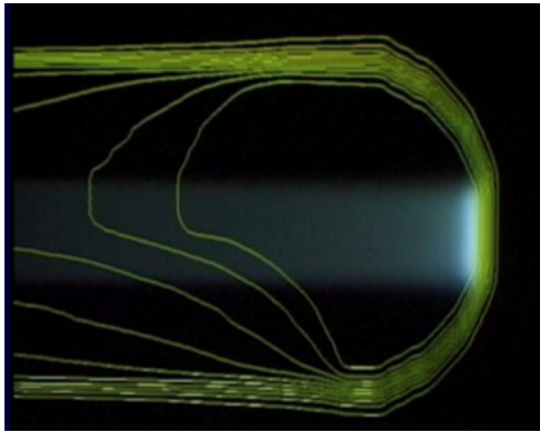
Pencil Beam Scanning (PBS)

- **Protons have charge…**

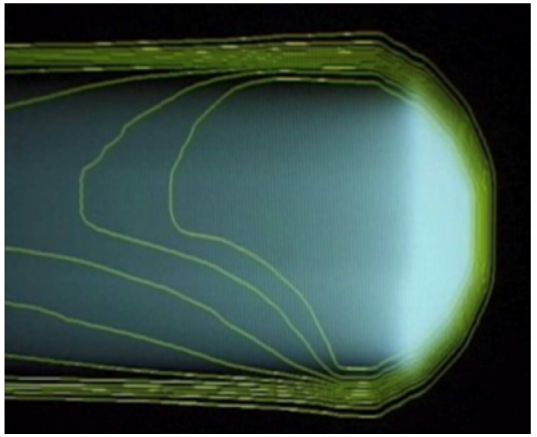
  …they can be focused and deflected (scanned) magnetically



A proton pencil beam



A “layer” is irradiated by scanning a pencil beam in *x* and *y*



Several (*z*) layers irradiated using beams of different energies

Pencil Beam Scanning

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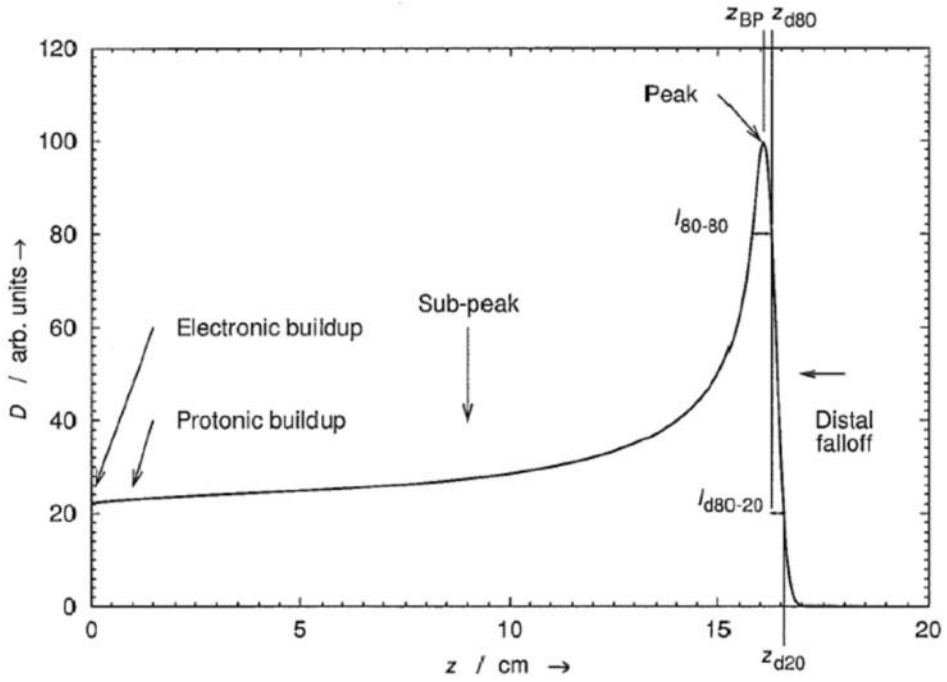
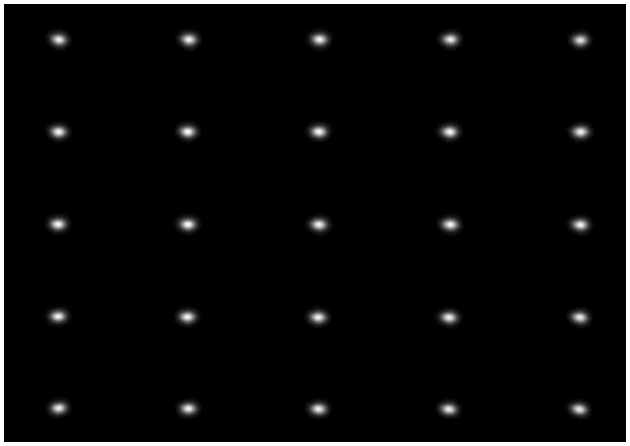
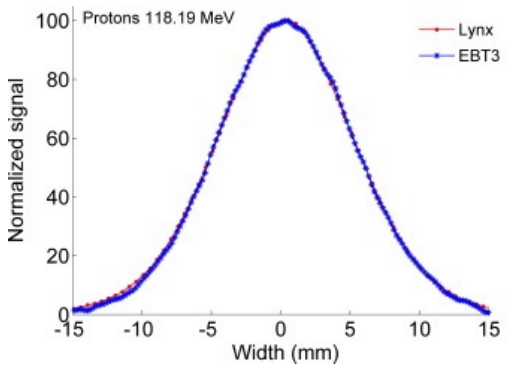
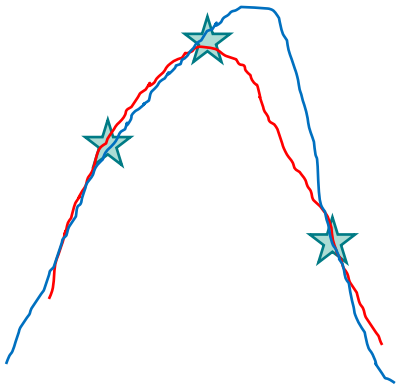


- Range
- Peak width
- Peak to plateau region
- Spot Size (depth, region?)
- Spot Position
- Steepness?
- Fall off?
- Entrance dose?







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Pro Beam Delivery Nozzle

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Pro Beam Delivery Nozzle

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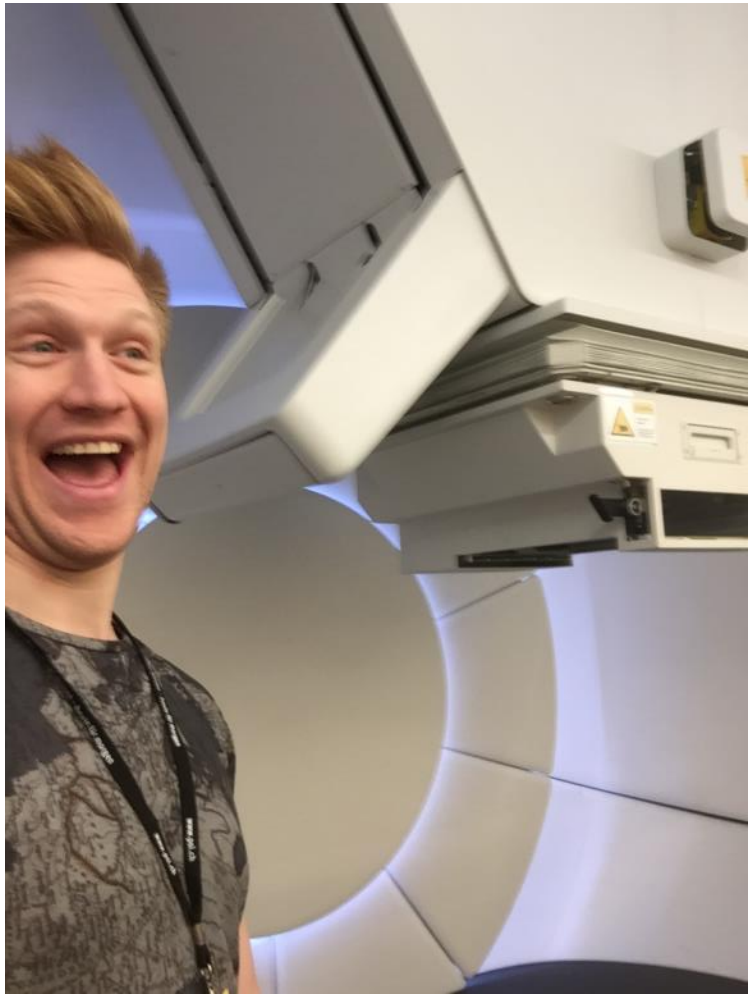

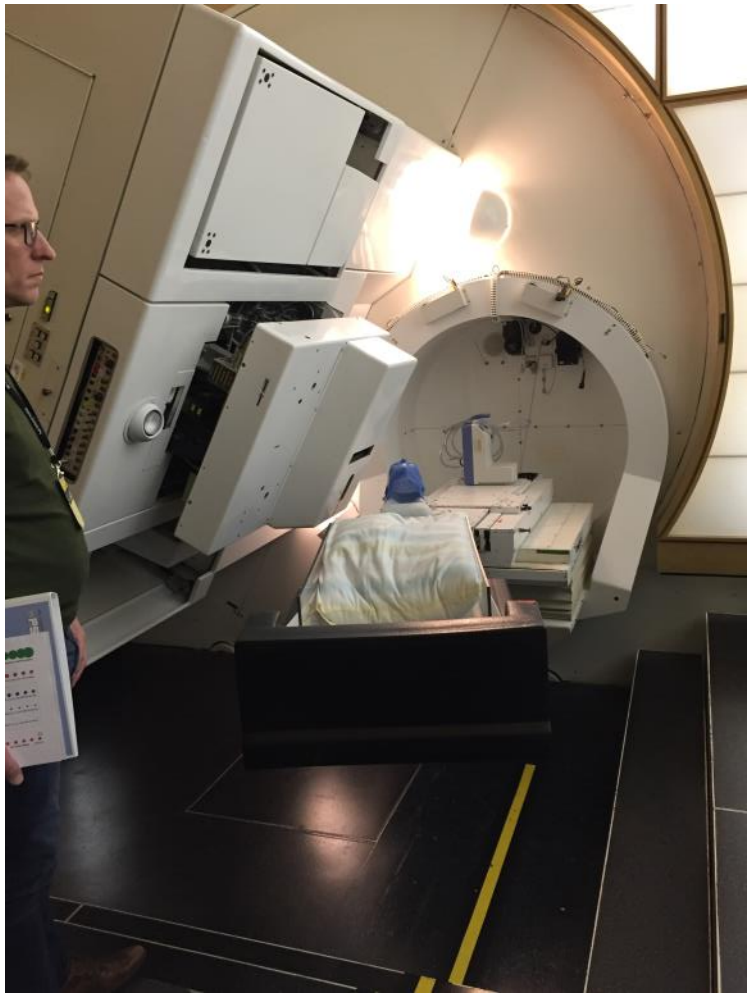

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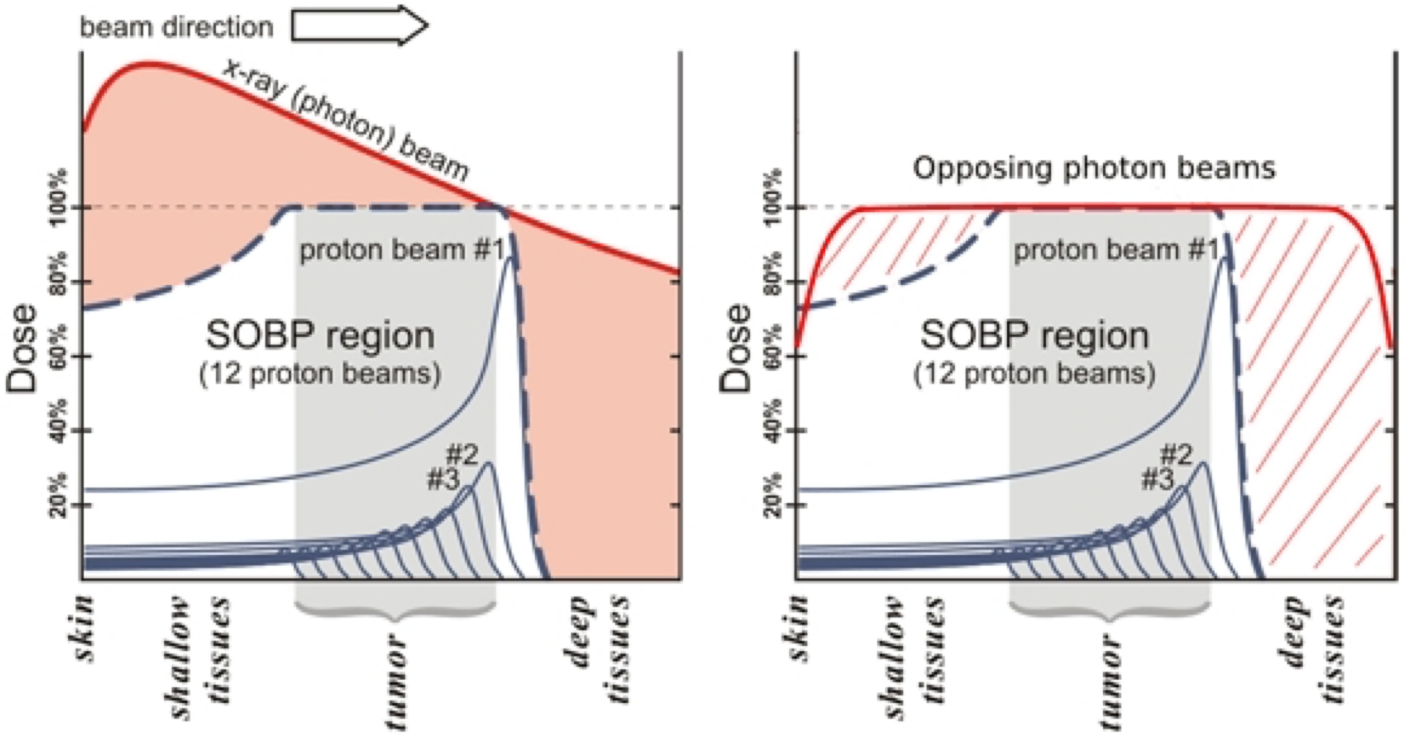
Some Characteristics

Pencil Beam Scanning

Basic Characteristics for Scanning Technique

FEATURE	SCANNING
energy range at isocenter	Typically 70-245 MeV
average dose rate	2 Gy / l / min
maximum field size at isocenter	30 x 40 cm
beam accuracy at isocenter (radius)	≤ 1 mm
nominal spot size (one sigma value)	5.4 – 4 mm (+/- 15%)
layer switching time	< 0.9 s
IMPT capable	yes

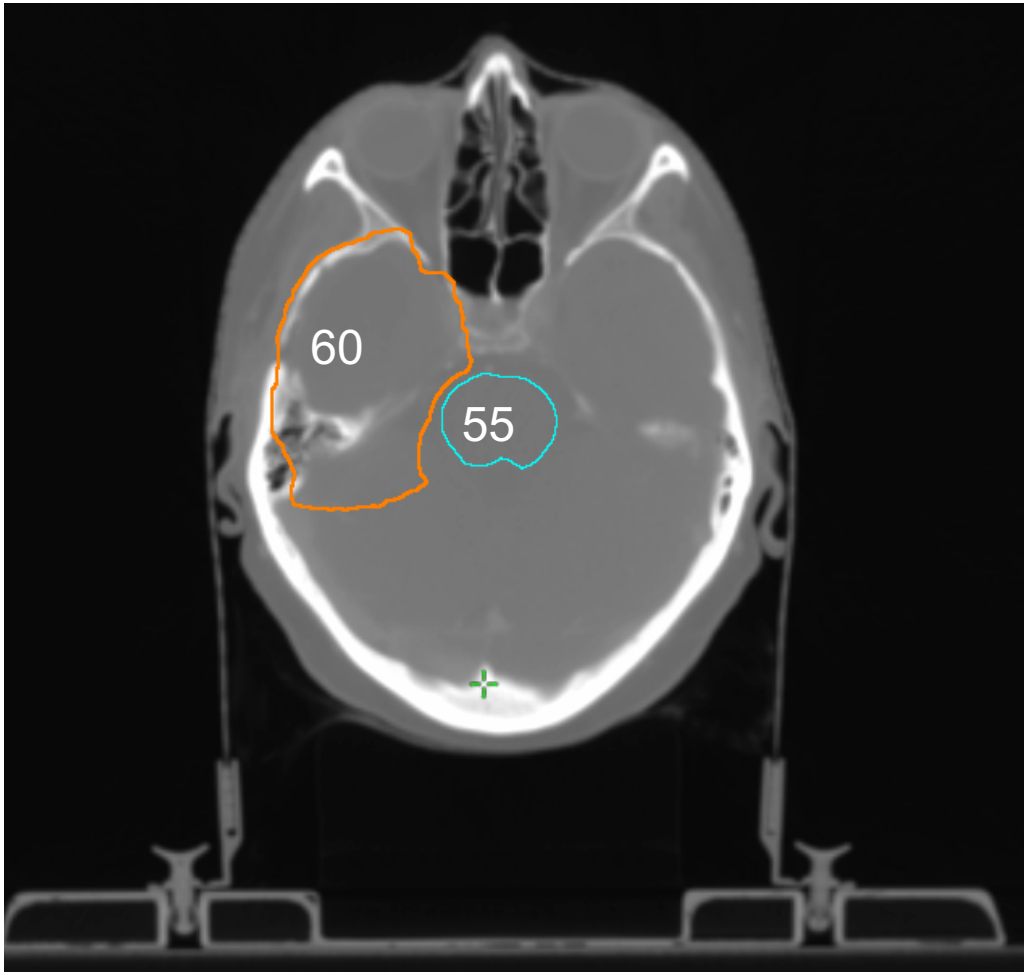
Depth Doses – the inherent advantage



Spread Out Bragg Peak (SOBP)

Uncertainties in Proton Treatment Planning

What's the problem?

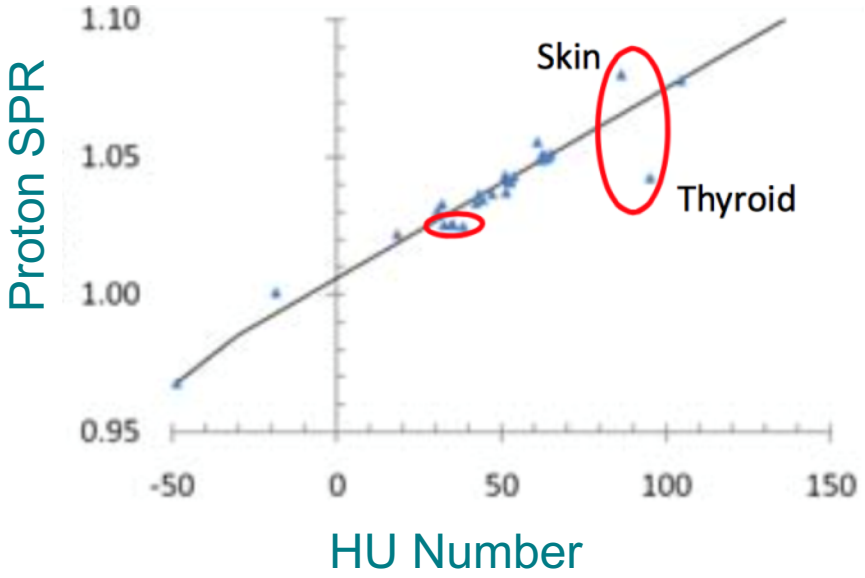


1. Hounsfield Unit (HU) to Stopping Power Ratio (SPR) Conversion

i. Proton dose calculations use patient CT data (currently)

ii. Each HU is assigned a proton SPR using a calibration curve. This curve is established by imaging materials of known elemental composition

iii. The assigned SPRs are used by the Treatment Planning System (TPS) for proton range and dose calculations



Uncertainties in the calibration translate into uncertainties on the calculated proton range and dose distributions.

For real human tissues there is a degeneracy problem:

$HU(\rho_1 Z_1) = HU(\rho_2 Z_2)$

$SPR(\rho_1 Z_1) \neq SPR(\rho_2 Z_2)$

Further, within patients HU deviate from their calibrated values e.g. according to patient size (beam hardening)

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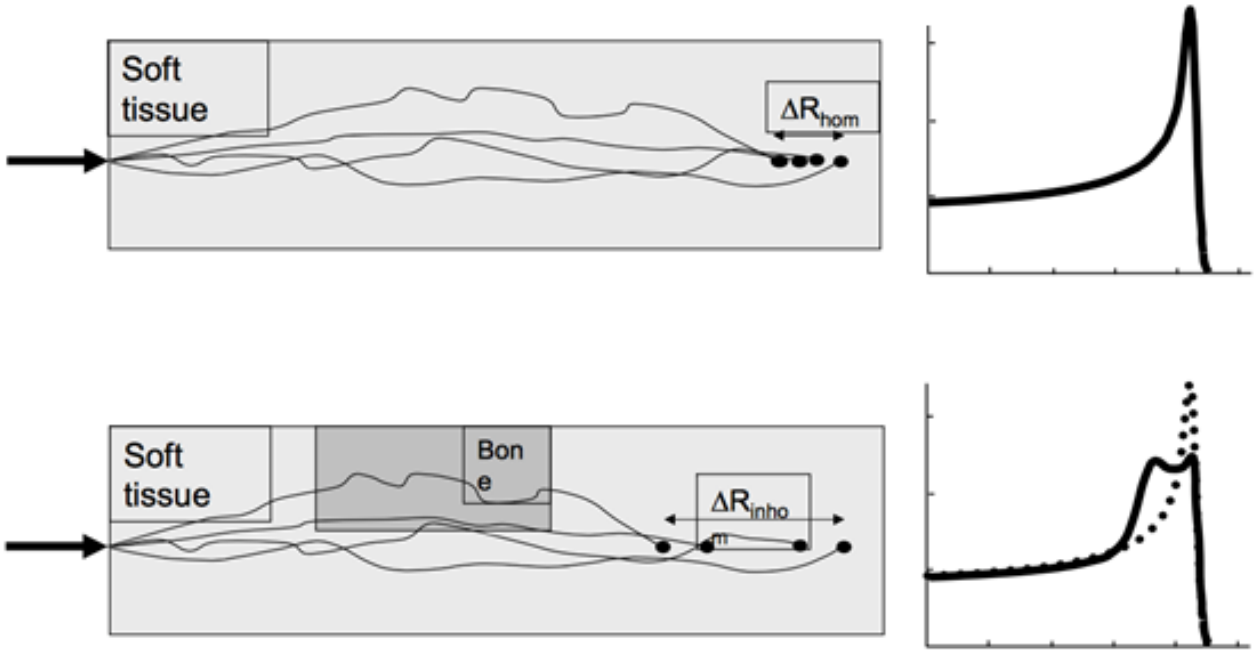
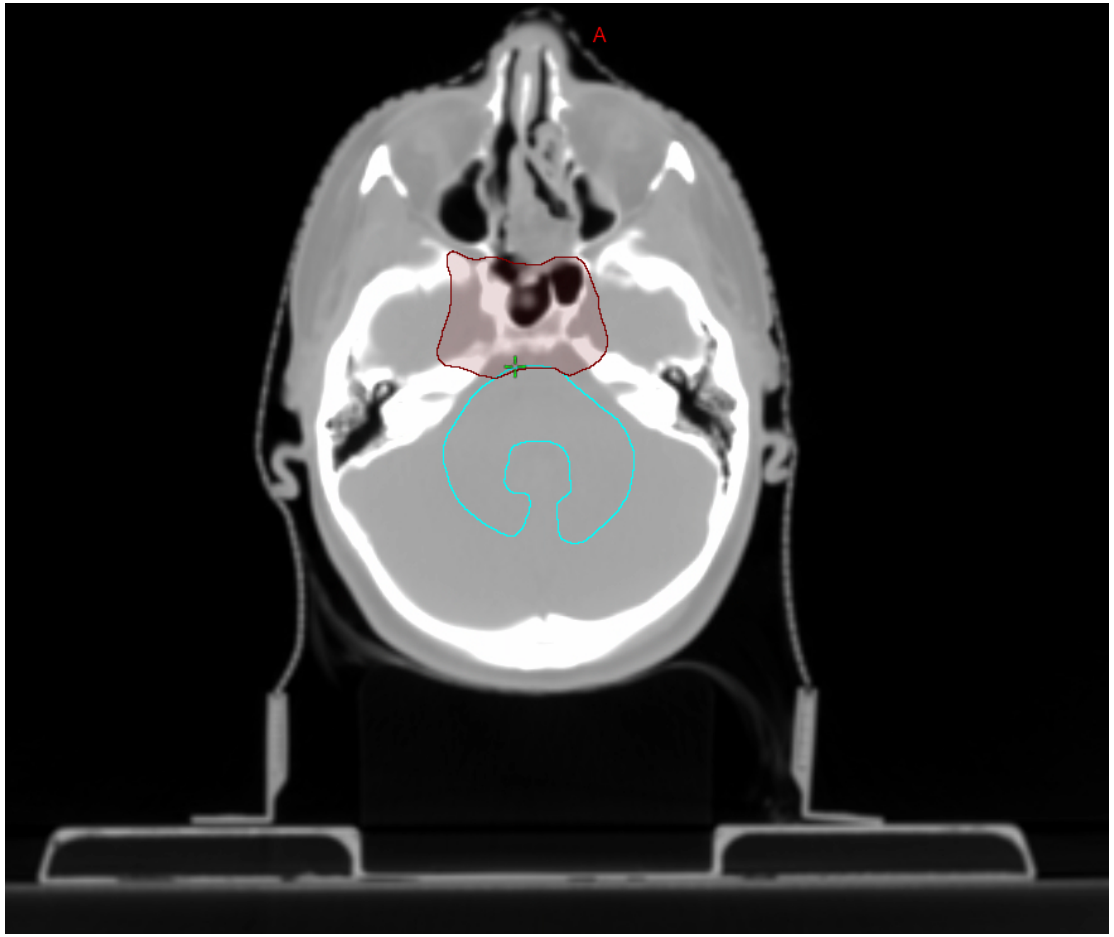
2. Set-up uncertainties and anatomy changes over the course of RT

Bony structures moving in and out of the beam alter the range of the Bragg peak. The target volume and surrounding structures must be in their planned positions.

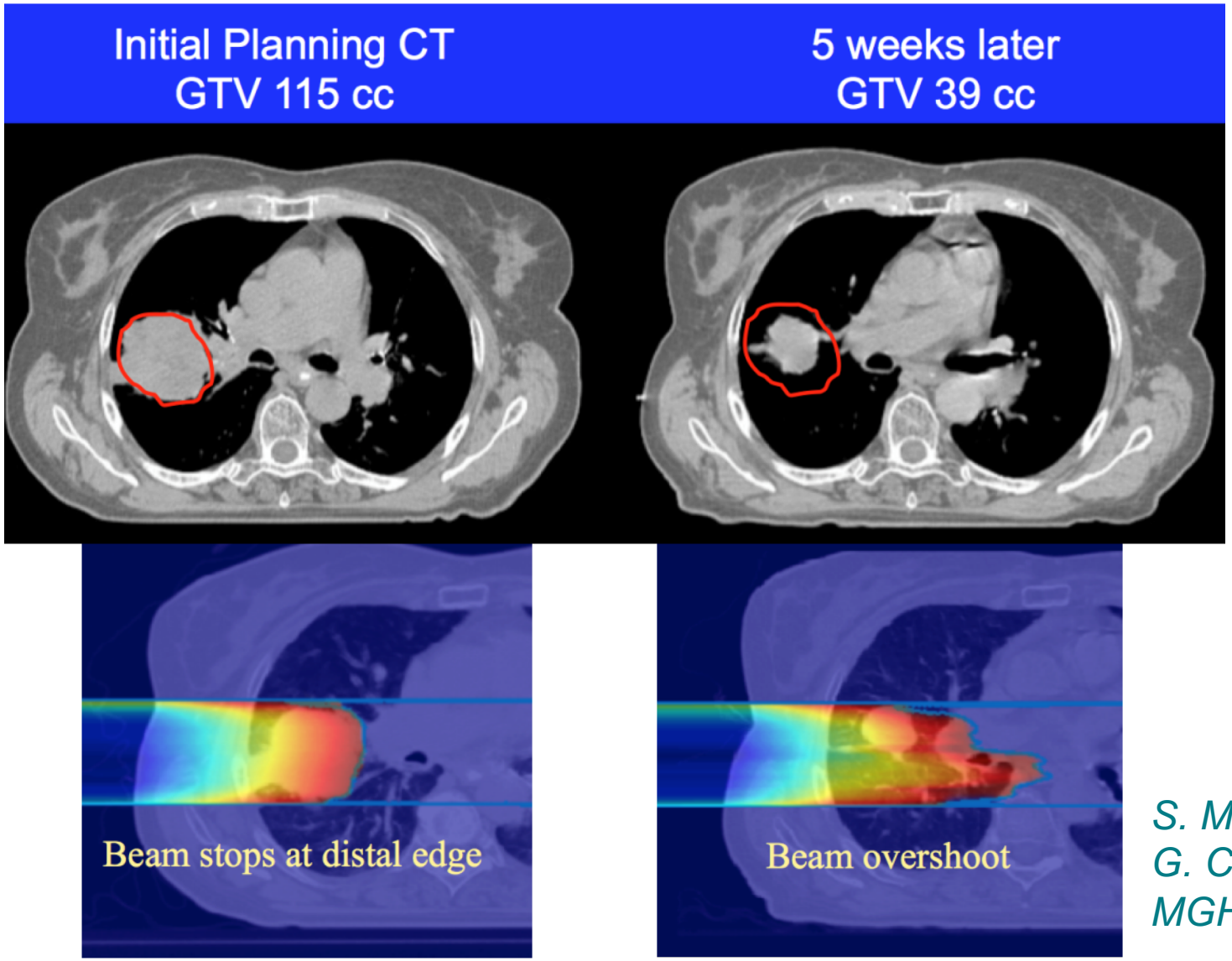


Lomax (AAPM SS 2003)

Any problems here?



2. Set-up uncertainties and anatomy changes over the course of RT



S. Mori, G. Chen, MGH

2. Set-up uncertainties and anatomy changes over the course of RT

- Protons are much more sensitive to density changes
- This imparts more importance on anatomical monitoring
- Perhaps necessitates increased imaging.

There are many more issues that can arise

- Weight loss
- Weight gain
- Bowel gas
- Rectal/Bladder filling
- Sinus filling
- Oedema
- Tumour response
- Even hair in the beam path.

3. Organ motion and the PBS interplay effect

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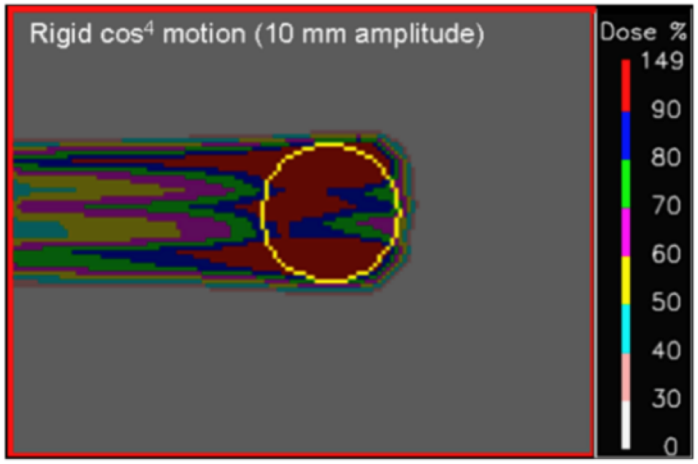
- For moving targets, the interplay effect describes heterogeneous dose coverage that stems from non-instantaneous beam delivery
- Whilst changing energy layers the patient may enter a different phase of their breathing cycle
- This is mitigated by increasing scanner speed, layer repainting and the averaging over many fractions.

Nominal dose distribution for a static object



Dose distribution where the time structure of beam delivery is taken into account and a 10 mm peak-to-peak motion of the target is assumed

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4. Complex inhomogeneity's within the proton beam

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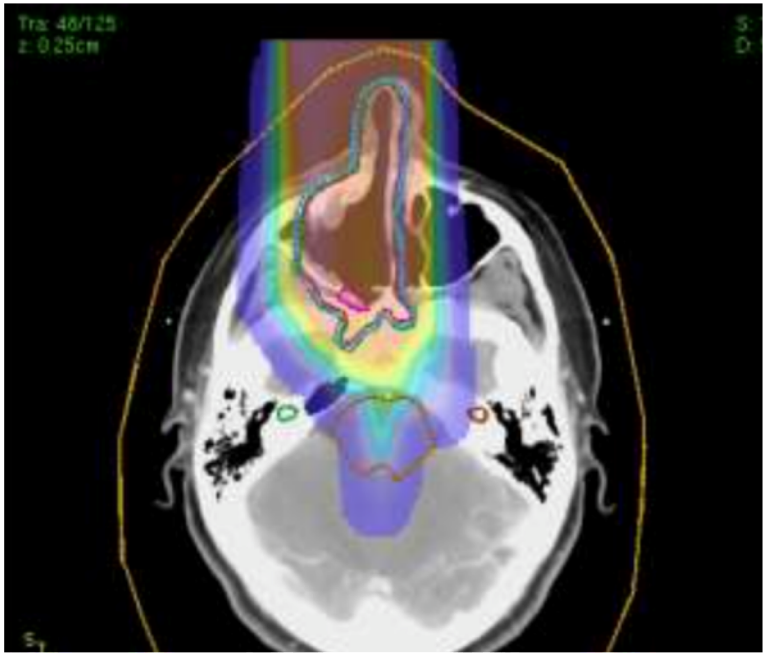
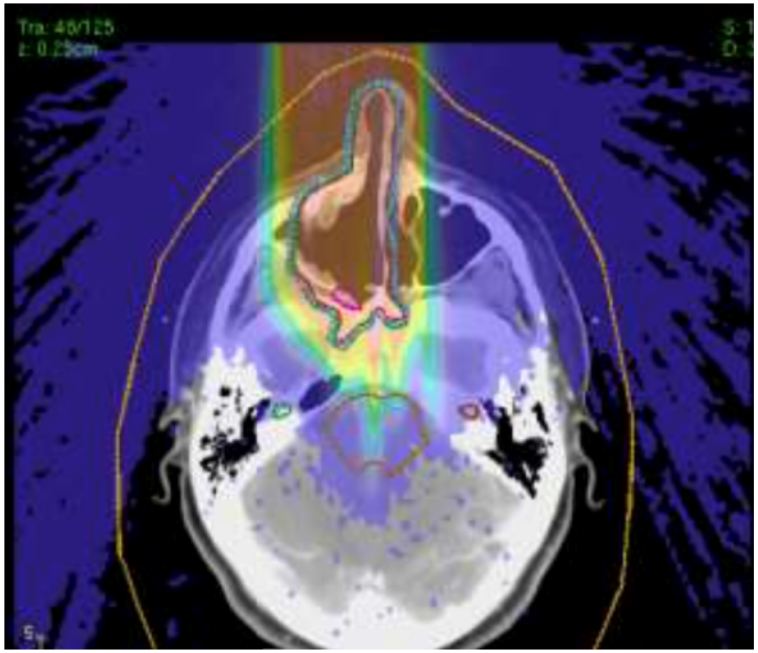
- Pencil Beam algorithms (as typically employed by proton treatment planning systems) cannot accurately model proton transport through complex inhomogeneities
- There is a strong need for “Monte Carlo” treatment planning***

Head and neck example



Pencil beam algorithm



Monte Carlo dose calculation

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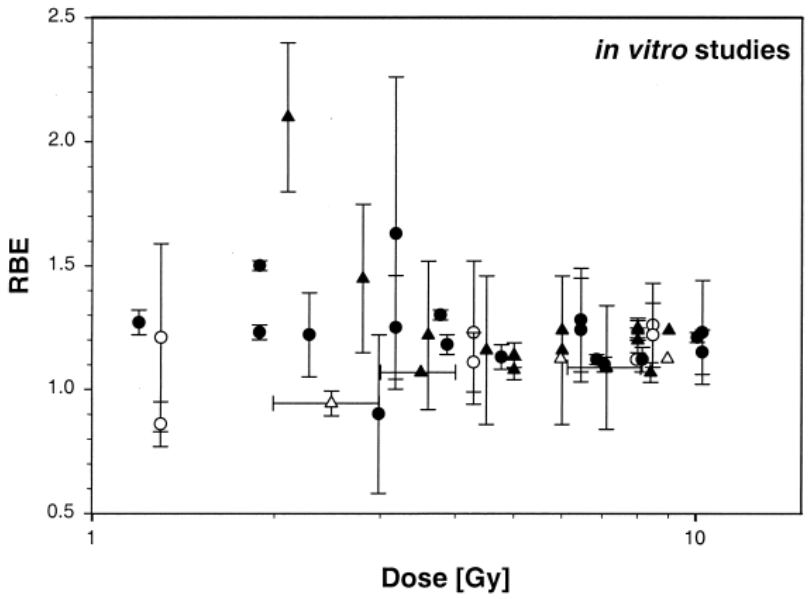
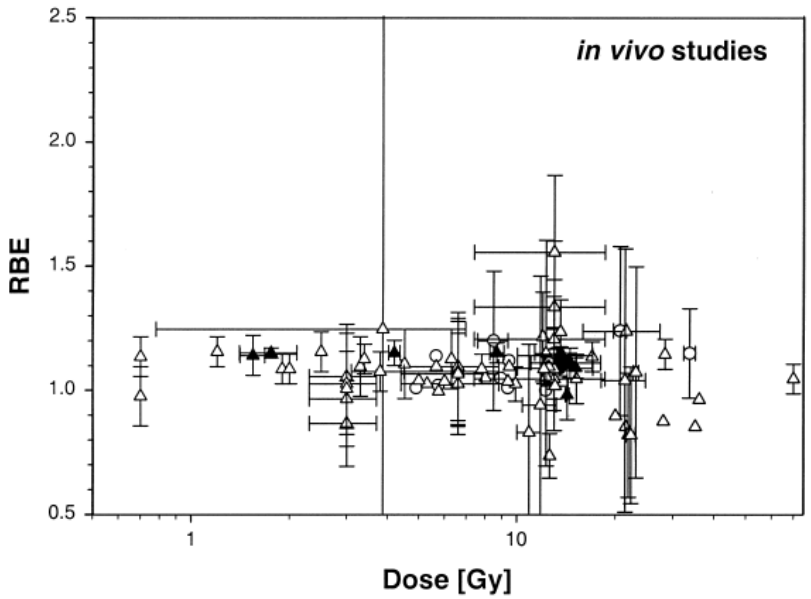
5. Proton Radiobiology

- How do Oncologists prescribe proton therapy dose?
- They use the same prescription as for photons divided by 1.1



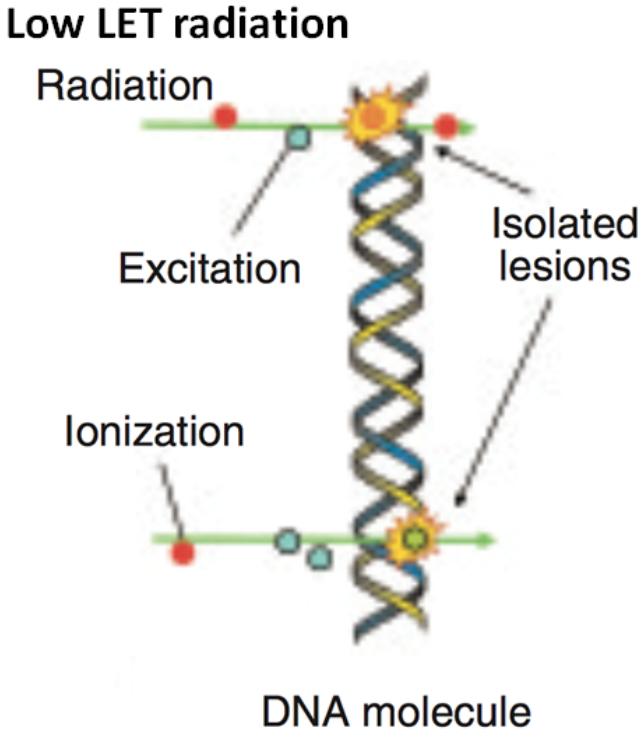


- This isn't quite sufficient but is our current best estimate
- Much more work needs to be done
- Some encouraging progress is being made in LET optimisation

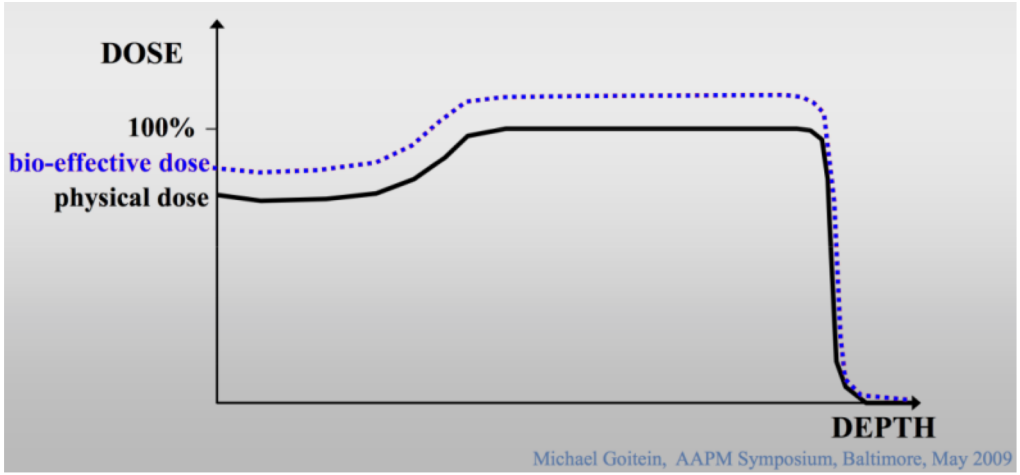
Paganetti 2002, RBE for PBT

5. Proton Radiobiology

- A proton's rate of energy loss or "Linear Energy Transfer" (LET) increases as its velocity … decreases
- Within a proton SOBP the average proton LET is <2 keV/μm, at the distal edge it can exceed 8 keV/μm
- Increased LET is known to correspond with increased radiation damage

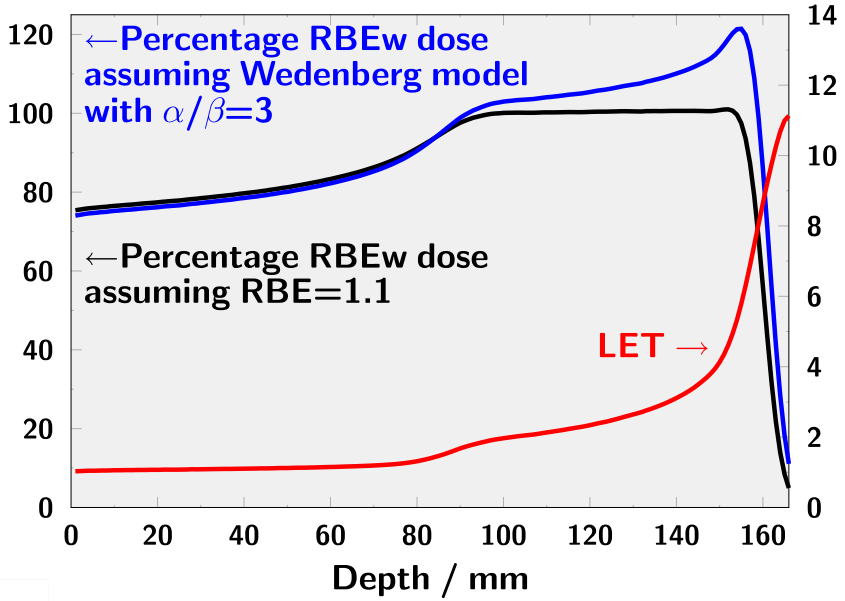


5. Proton Radiobiology



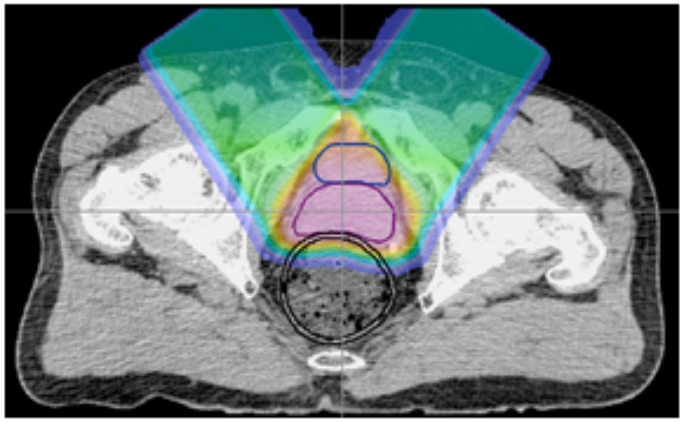
- Currently, an RBE of 1.1 is assumed along the entire beam path

- From in-vitro cell experiments, we expect proton RBE to rise across the SOBP, rising rapidly at the end, extending the "biological range" by ~1-2mm

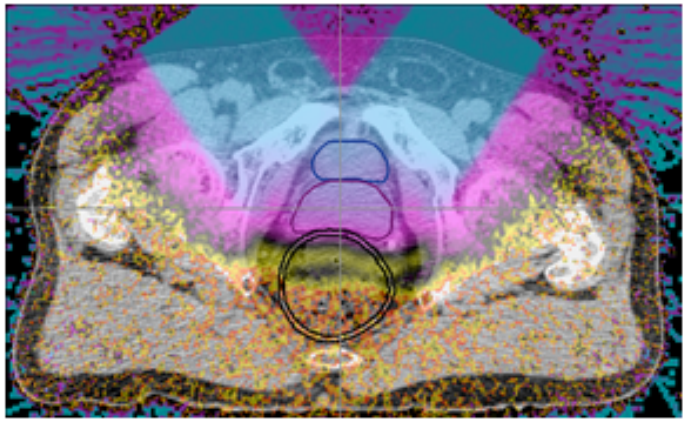


5. Proton Radiobiology

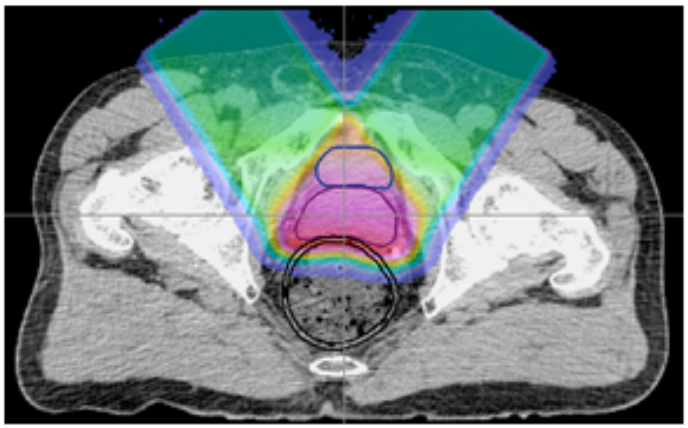
- Monte Carlo simulations can provide both dose maps and LET maps, which can be used for radiobiological modelling of variable proton RBE



Dose assuming an RBE of 1.1



LET

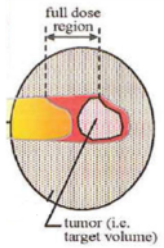


Modelled "variable RBE-weighted" dose

- However, radiobiological models based on *in-vitro* data are difficult to verify *in-vivo*
- Our clinical experience does not (yet) indicate that assuming a fixed RBE of 1.1 for proton therapy is detrimental

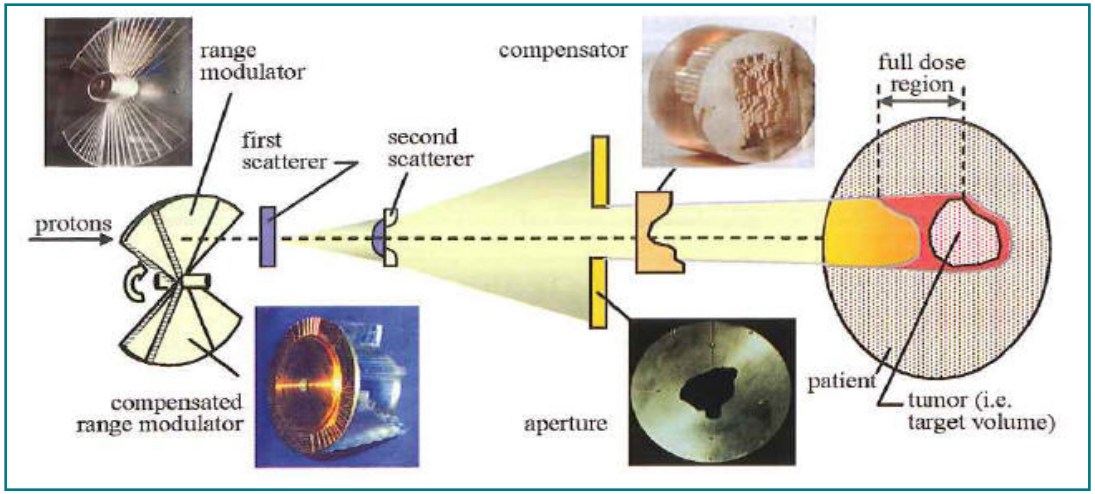
Robust Proton Planning: Current status

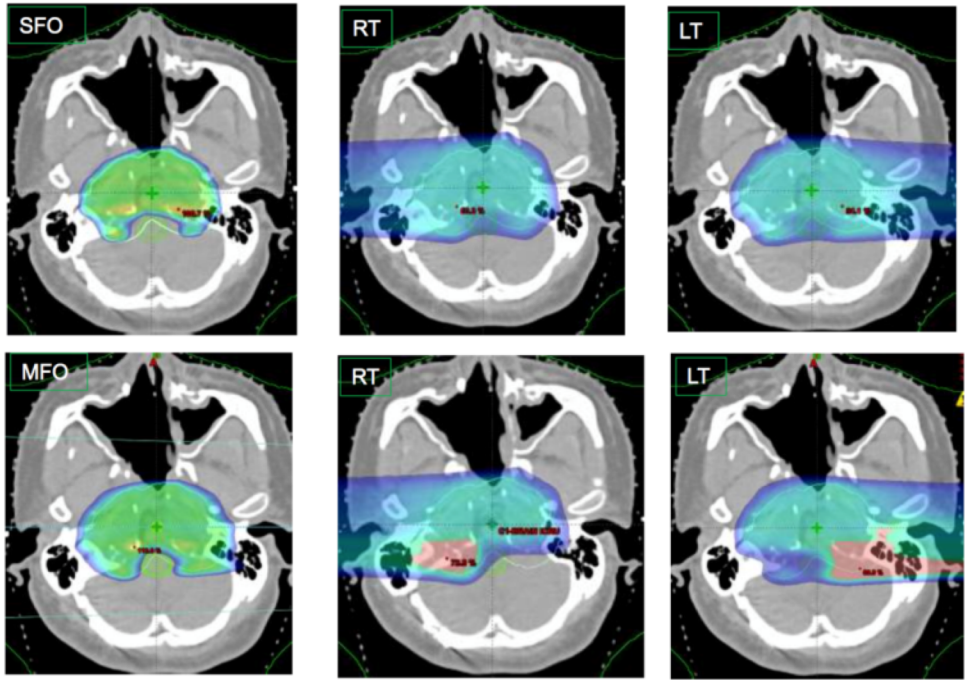
Robust Proton Planning



- Passive Scattering – Most robust, least conformal
  - Cannot conform to proximal edge
  - Rapid Layer switching
- Single-Field Uniform Dose – less robust, more conformal
  - Conforms to proximal edge
  - Spot scanning technique (slower)
  - No splitting of the volume
- Multi-Field Optimisation – Least Robust, most conformal
  - Similar speed to SFUD
  - Ability to modulate dose within the target

Robust Planning





Robust Planning

- Sites to treat – (CNS vs. Lungs)
- Increase emphasis on patient positioning (imaging)
- Using multiple beam angles
- ***Appropriate selection of beam angles***

All of these considerations make the plan more robust!

How can we further improve robustness?

1. Selecting the right patients
2. Improving SPR's
3. Robust Optimisation
4. In-Vivo Range verification

1. Selecting the right patients

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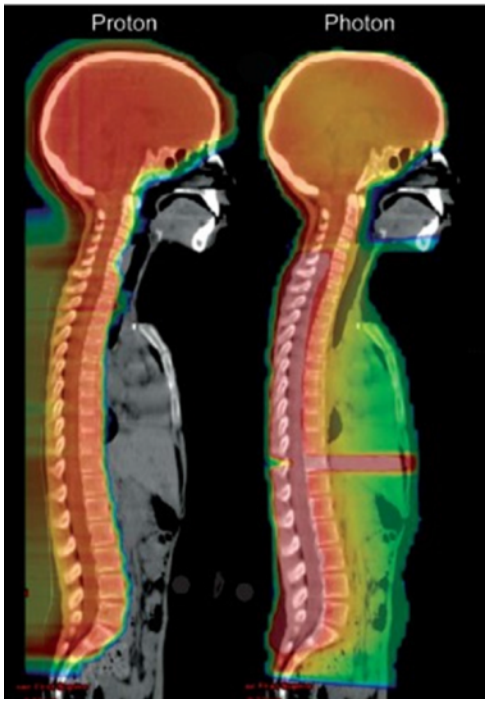
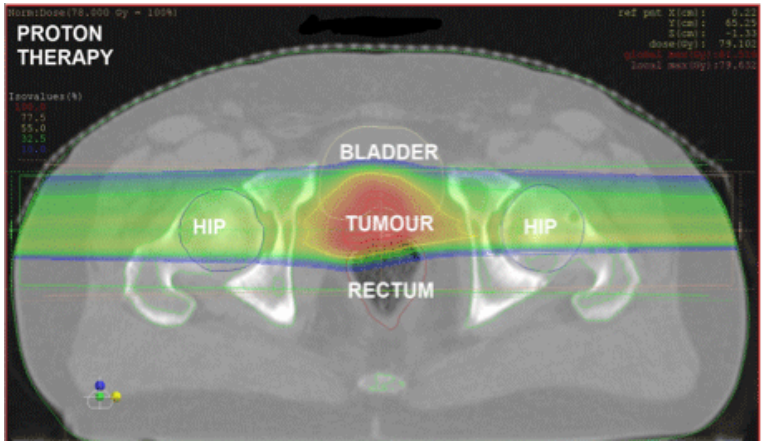
- Proton therapy will be a limited resource in the UK for the next few years at least.
  - Normal tissue complication probability (NTCP) can be applied to both photon and proton plans to select those patients likely to derive the greatest benefit from proton therapy
  - Machine learning approaches can be applied to predict achievable organ at risk dose levels (for photons and protons), ultimately using just the geometric arrangement of the target volume in relation to the Organ's at Risk (OAR's) as input





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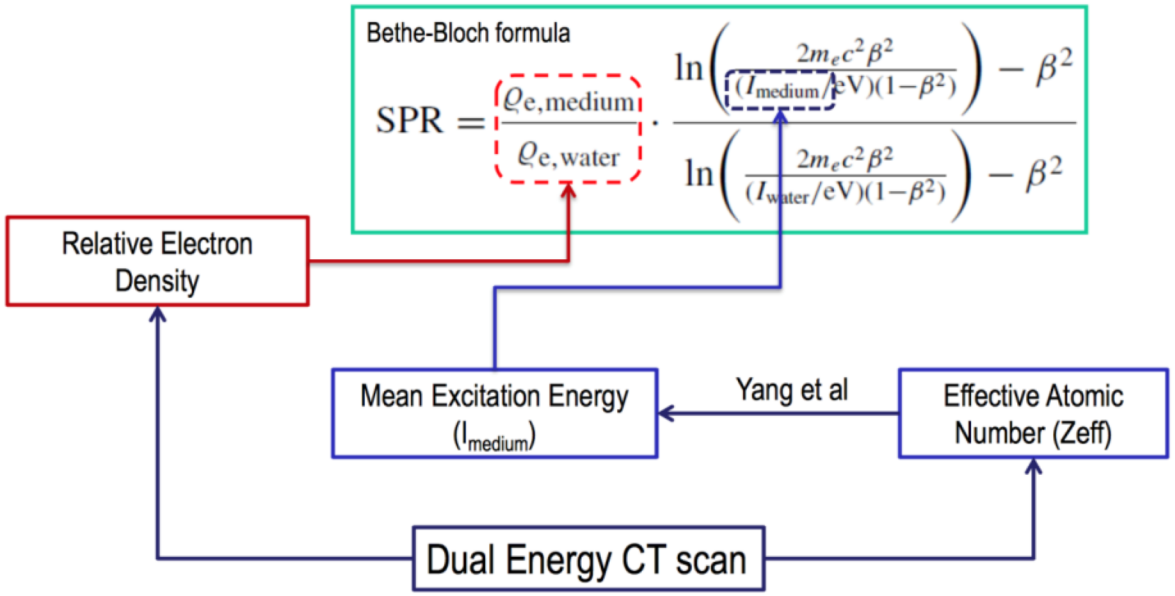
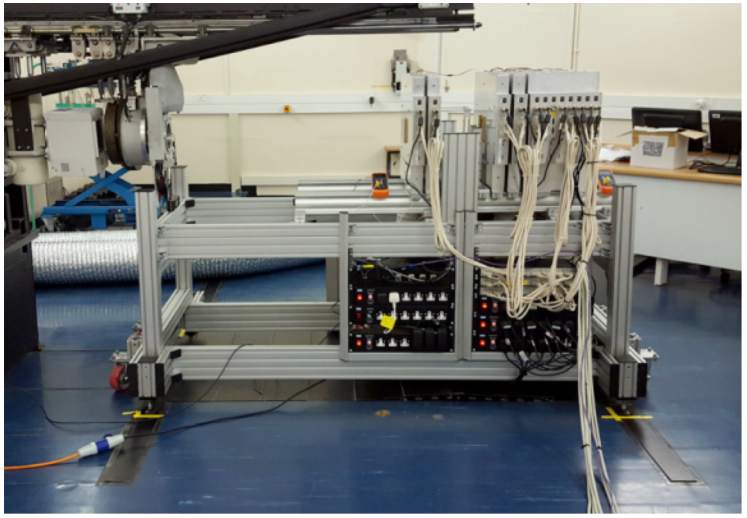
2. Improved proton Stopping Power Ratio (SPR) calculation

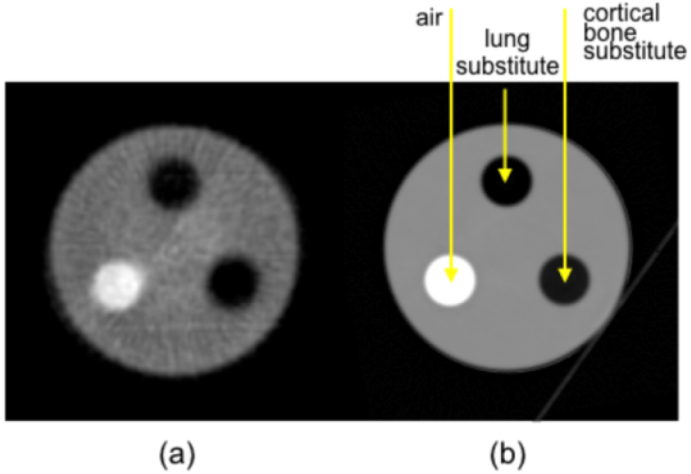


- **Dual Energy X-Ray CT**
  - We have two unknowns in proton SPR calculation: relative electron density and Zeff. Via dual energy CT we have two measurements.
  - At diagnostic photon CT energies, the Compton effect is proportional to relative electron density and the photo-electric effect is proportional to Zeff. The cross-sections for both vary with photon energy.
  - N.B. Dose burden (ALARA): typically the imaging dose is split over the two energies leading into a imaging dose-neutral approach for most applications.

2. Improved proton Stopping Power Ratio (SPR) calculation

- **Proton CT**
  - A low-intensity beam of high-energy protons is sent through the patient
  - The entrance and exit positions, directions and energies are measured for each proton
  - This enables determination of linear integrals of proton stopping power and reconstruction of a patient's volumetric distribution of SPR
  - Low dose, but no "clinical" system yet exists
  - Detectors are complex: a significant volume of material is required to stop a proton beam of 50 MeV, let alone higher proton energies





First relative scattering power proton CT (a); compared to x-ray CT (b), for a test phantom.

3. Robust Optimisation

- The nominal case is calculated
- Certain user defined perturbations are applied e.g. 3mm shift in each direction with 3.5% range error
- The optimisation parameters are then applied to each of these situations

- Anyone see any problems with this?

3. Robust Optimisation, including Proton LET

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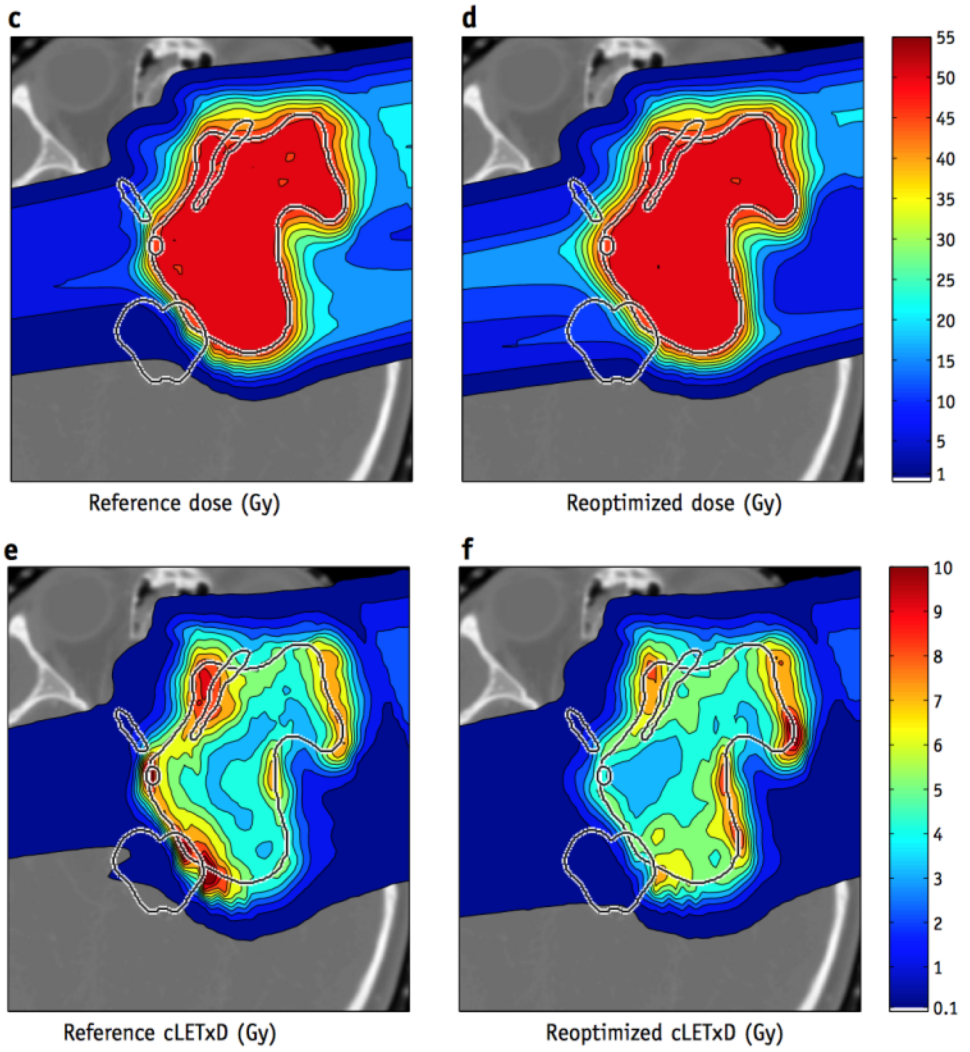
- Proton planning is inherently degenerate (many methods for one solution) which allows for some sophisticated optimisation
- LET could be introduced to the optimisation



Jan Unkelbach

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4. In-Vivo range verification (IVRV)

- Pre-Treatment (using a low intensity test beam): Testing to see if it will hit where you think
  - Direct dose measurement:
    Using an implanted dosimeter
  - Proton Acoustics:
    If pulsed, sound waves can be caused by the thermal effects of the radiation beam
  - Prompt γ-ray detection:
    Proton-nuclear interactions produce γ-rays that can be detected on the couch. The current issue is in the practicalities of the detector γ-ray

4. In-Vivo range verification (IVRV)

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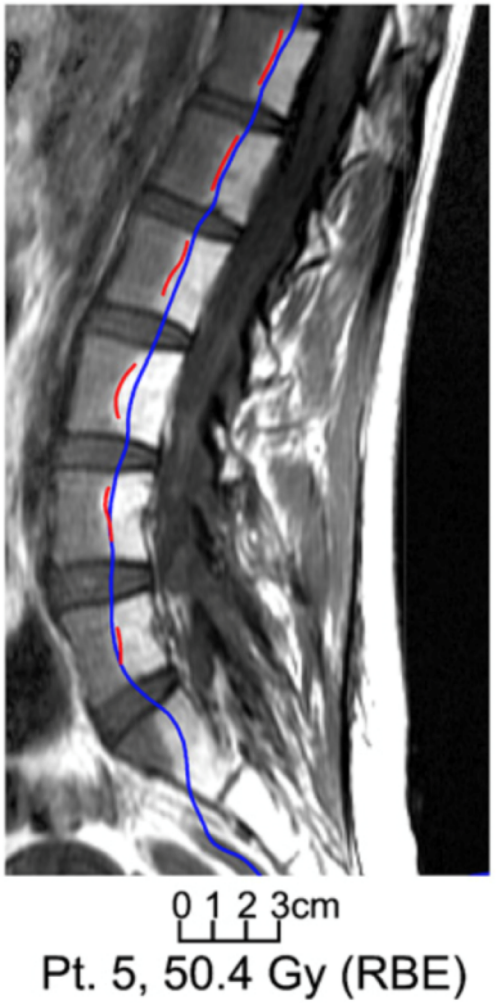
- Post Treatment: Testing to see if you hit where you thought
  - Positron Emission Tomography (PET):
    A number of the products of proton therapy are positron emitters (11C and 15O) but time is an issue here
  - Magnetic Resonance Imaging (MRI):
    Quite delayed feeback, but some work was performed by Paganetti to investigate the anatomical changes months after treatment to try and further explain the biological effect of proton therapy.



T1-weighted MRI changes within the lumbar spine post-proton therapy. The extent of the changes (red) aligned well with the planned proton range (blue)
Gensheimer (2010

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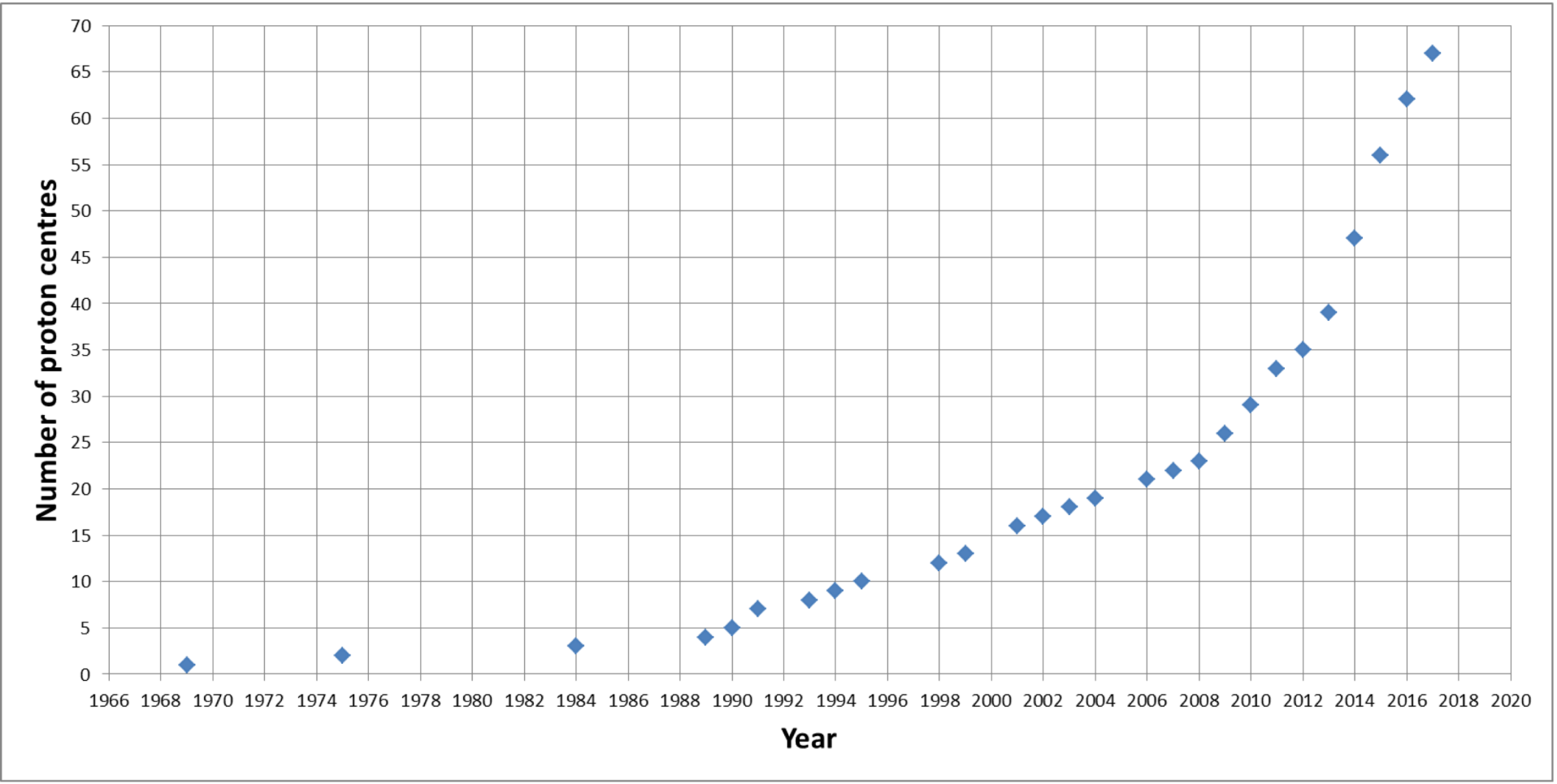
Clinical Application of proton therapy

How many proton centres?



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Clinical Investigation

Establishing Evidence-Based Indications for Proton Therapy: An Overview of Current Clinical Trials

Mark V. Mishra MD *, Sameer Aggarwal MD †, Soren M. Bentzen PhD, DMSc ‡, Nancy Knight PhD *, Minesh P. Mehta MD §, William F. Regine MD, FACR, FACRO *

Show more

https://doi.org/10.1016/j.ijrobp.2016.10.045

Results

A total of 122 active PBT clinical trials were identified, with target enrollment of >42,000 patients worldwide. Ninety-six trials (79%), with a median planned sample size of 68, were classified as interventional studies. Observational studies accounted for 21% of trials but 71% (n=29,852) of planned patient enrollment. The most common PBT clinical trials focus on gastrointestinal tract tumors (21%, n=26), tumors of the central nervous system (15%, n=18), and prostate cancer (12%, n=15). Five active studies (lung, esophagus, head and neck, prostate, breast) will randomize patients between protons and photons, and 3 will randomize patients between protons and carbon ion therapy.

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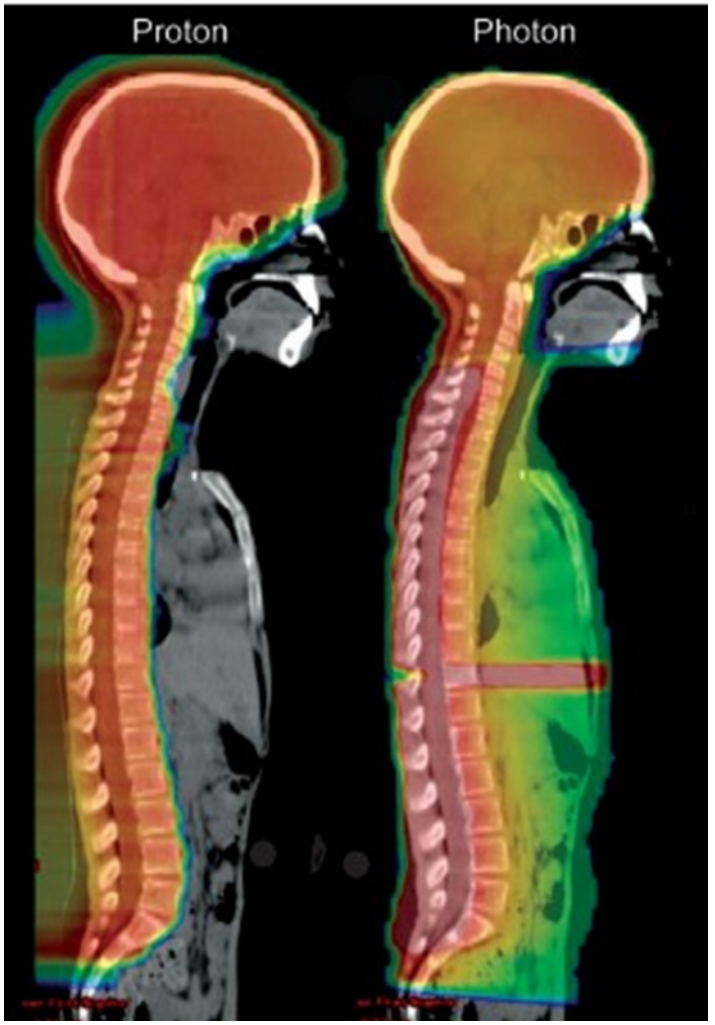
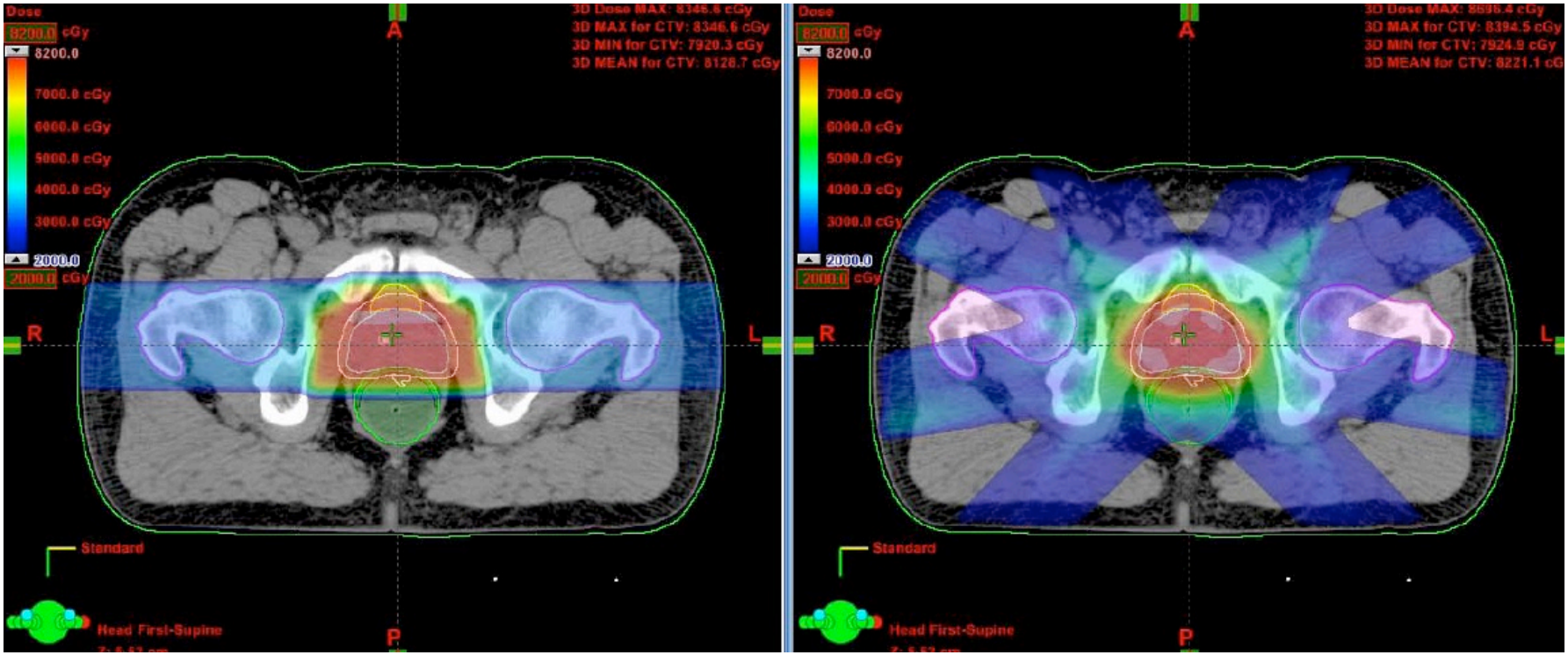
Medulloblastoma

Protons or Photons?



Prostate



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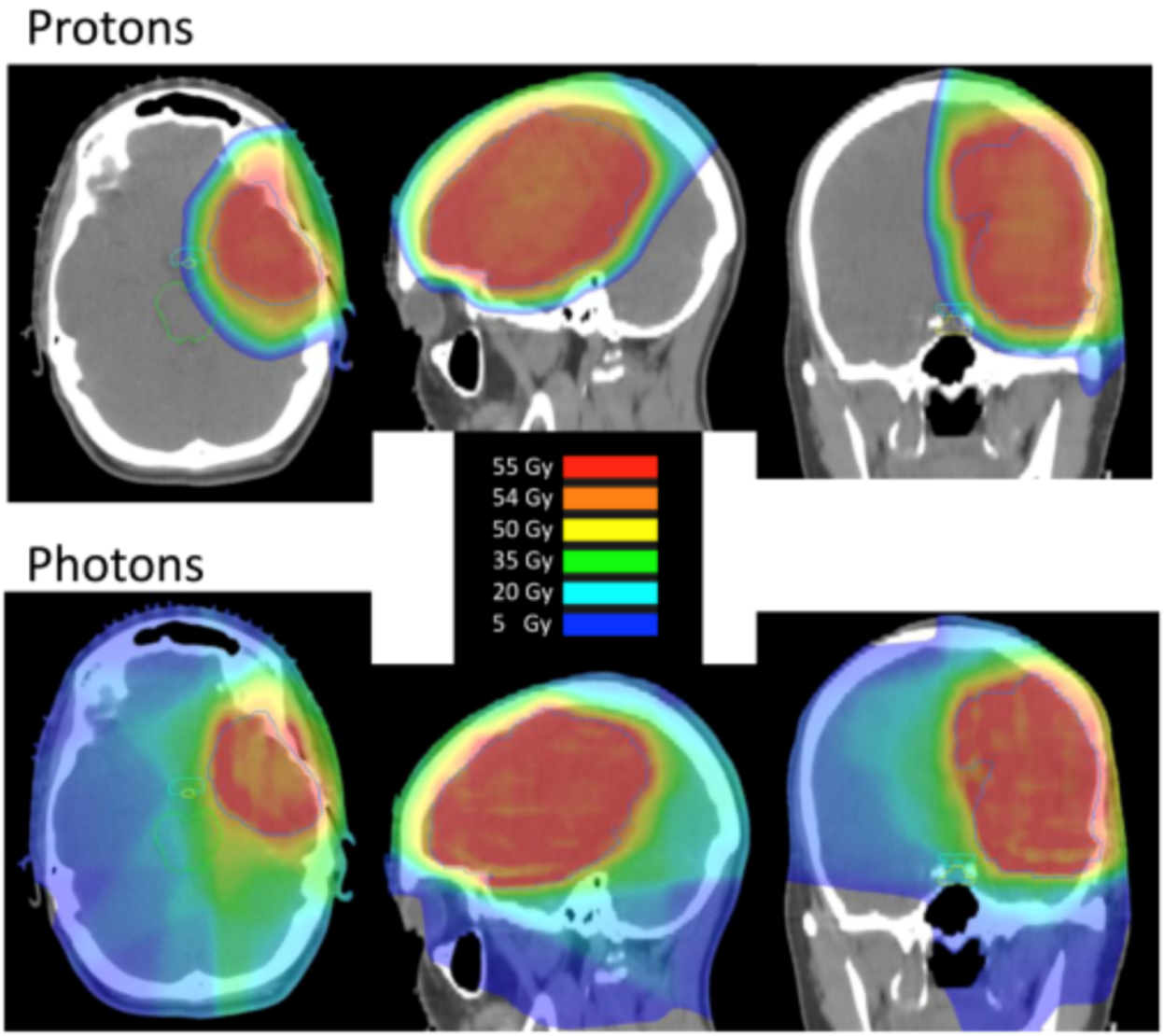
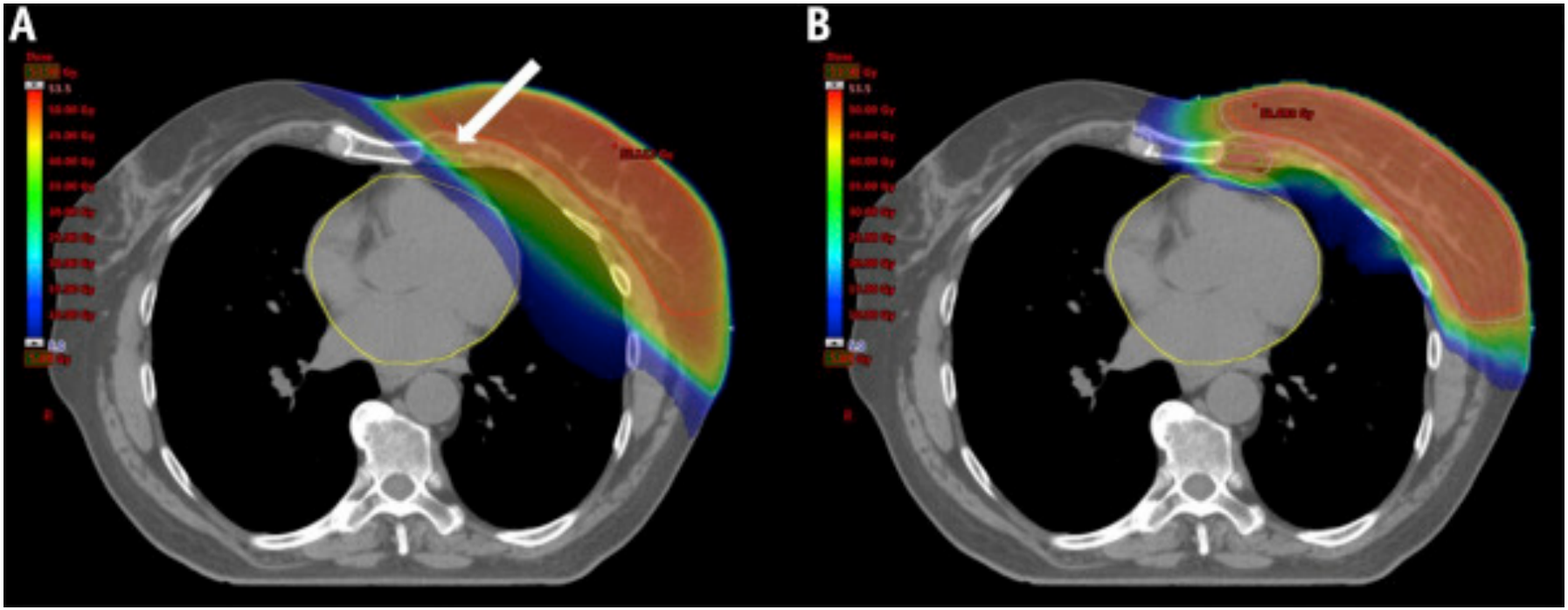
Brain



Breast



Sarcoma (Limbs)

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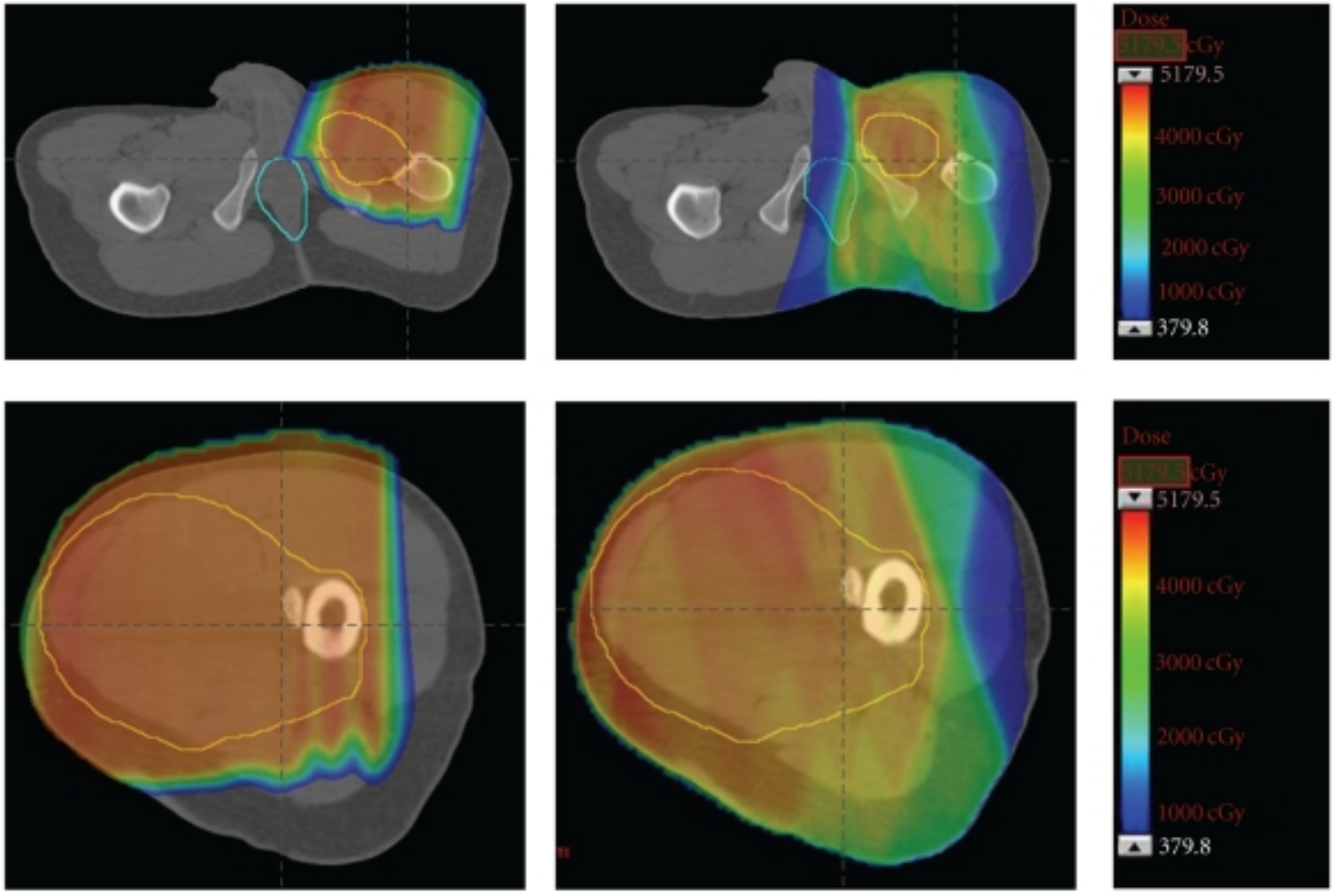

(a) (b)

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Proton Therapy in the UK

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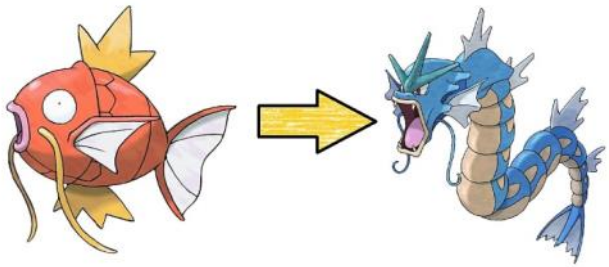
UCLH Indications list

Total is ≈ 1500

This list is constantly evolving



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Paediatric	Chordoma / chondrosarcoma	15
Paediatric	Rhabdomyosarcoma orbit	5
Paediatric	Rhabdomyosarcoma Parameningeal and H&N	15
Paediatric	Rhabdomyosarcoma pelvis	10
Paediatric	Osteosarcoma	3
Paediatric	Ewings	9
Paediatric	PPNET (extra-osseous Ewing's)	5
Paediatric	Ependymoma	25
Paediatric	Glioma - low grade	5
Paediatric	Glioma - optic pathway	12
Paediatric	Cranipharyngioma	15
Paediatric	Medulloblastoma (PNET)	70
Paediatric	Hodgkins	5
Paediatric	Retinoblastoma	5
Paediatric	Meningioma	3
Paediatric	Intracranial germinoma	10
Paediatric	Nasopharynx (H&N)	15
Paediatric	Difficult cases	5
Paediatric	Very young age (extra cases)	20
Adult	Choroidal melanoma	100
Adult	Ocular / orbital	25
Adult	Chordoma base of skull	60
Adult	Chondrosarcoma base of skull	30
Adult	Para-spinal / Spinal sarcoma (inc chordoma)	180
Adult	Meningioma	100
Adult	Acoustic neuroma	100
Adult	Craniospinal NOS (pineal)	10
Adult	H&N and paranasal sinuses	300
Adult	PNET (medullo/intracranial)	30
Adult	Difficult cases (e.g. young adult, previous radiotherapy treatment, abnormal anatomy)	300
Adult	General Sarcoma	??

Proton therapy at Clatterbridge Centre for Oncology

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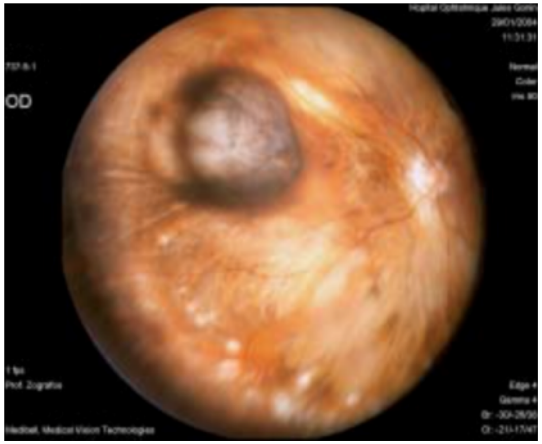
- The world's first hospital-based low-energy ocular proton beam therapy opened at Clatterbridge in 1989
- 60MeV protons: ocular treatments only (maximum range is <5cm)
- Extremely high success rates – local control >95%



Ocular melanoma
G. Goitein

Clatterbridge proton set-up

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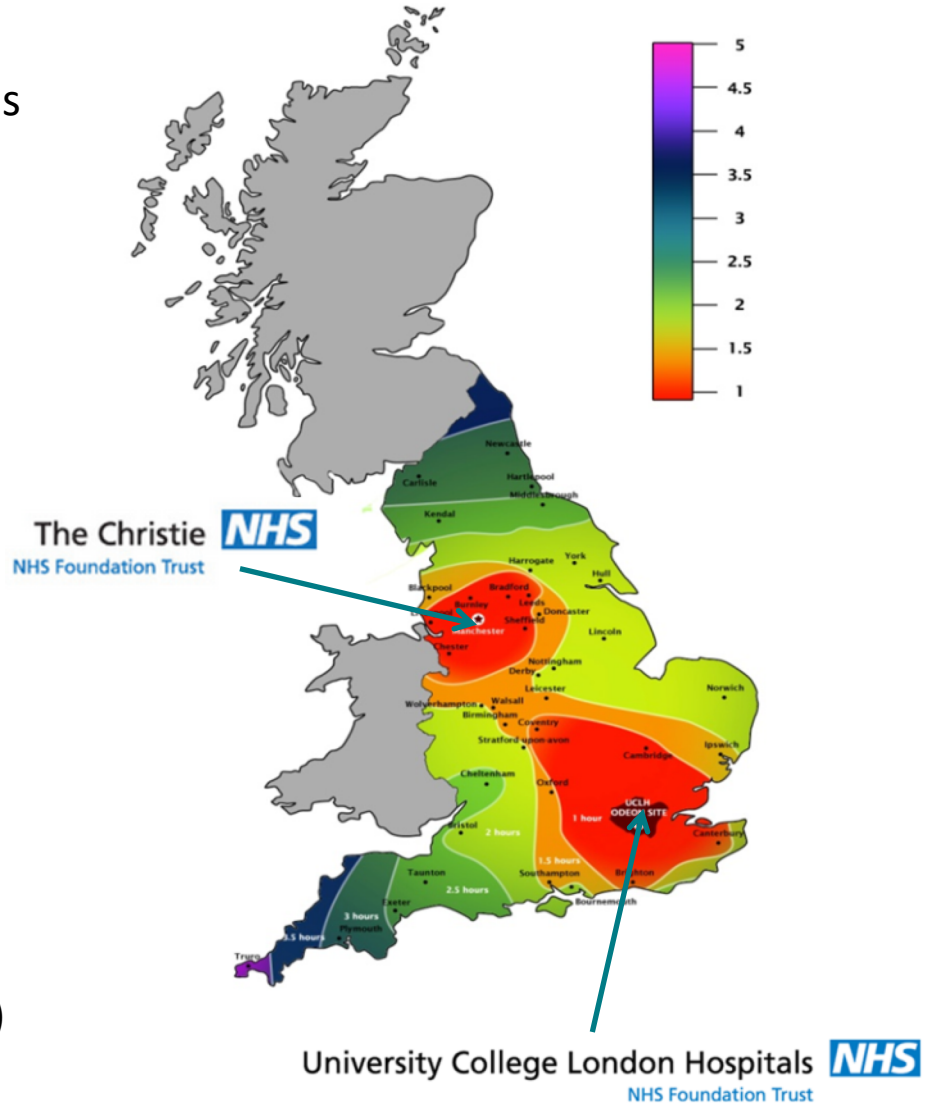
National Proton Beam Therapy Service in England

University College London Hospitals NHS Foundation Trust

- National service on two sites
  - Manchester – 3 treatment rooms
  - London – 4 treatment rooms
- Pencil beam scanning only
- Full 360º rotating gantries
- Additional research capacity

CATEGORIES	1500
Paediatric	278
TYA	185
Adult Core	314
Devolved Administrations	147
Total	924
Remaining Capacity	576

- First patients:
  - Manchester – 2018
  - London - 2020 (Originally 2016)



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Our build Progress

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- December 2015
- https://www.youtube.com/watch?v=aBio2ttQiQY

- June 2017
- https://www.youtube.com/watch?v=_XMJQc1qi2w

- July 2017
- https://www.youtube.com/watch?v=PcWH_bh84Oc&t=26s

- September 2018
- https://www.youtube.com/watch?v=4CA4pYs_rTk

- Cyclotron Delivery
- https://www.youtube.com/watch?v=XQ9VPRdumjE&t=2s

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Recommended Link

- https://www.youtube.com/watch?v=vgbPQfzySTQ

Thank you for listening

Any Questions?!

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Thanks to Tracy Underwood, Richard Amos, Jem Hebden, Gary Royle, Derek D'Souza, Andy Poynter and Google for most of lecture content!