Opportunities and Challenges arising from Laser-driven particle therapy

Seminar, Cosener`s House, STFC, Abingdon UK

Bleddyn Jones MD

University of Oxford

1. Gray Institute for Radiation Oncology & Biology
2. 21 Century School Particle Therapy Cancer Research Institute, Oxford Physics.

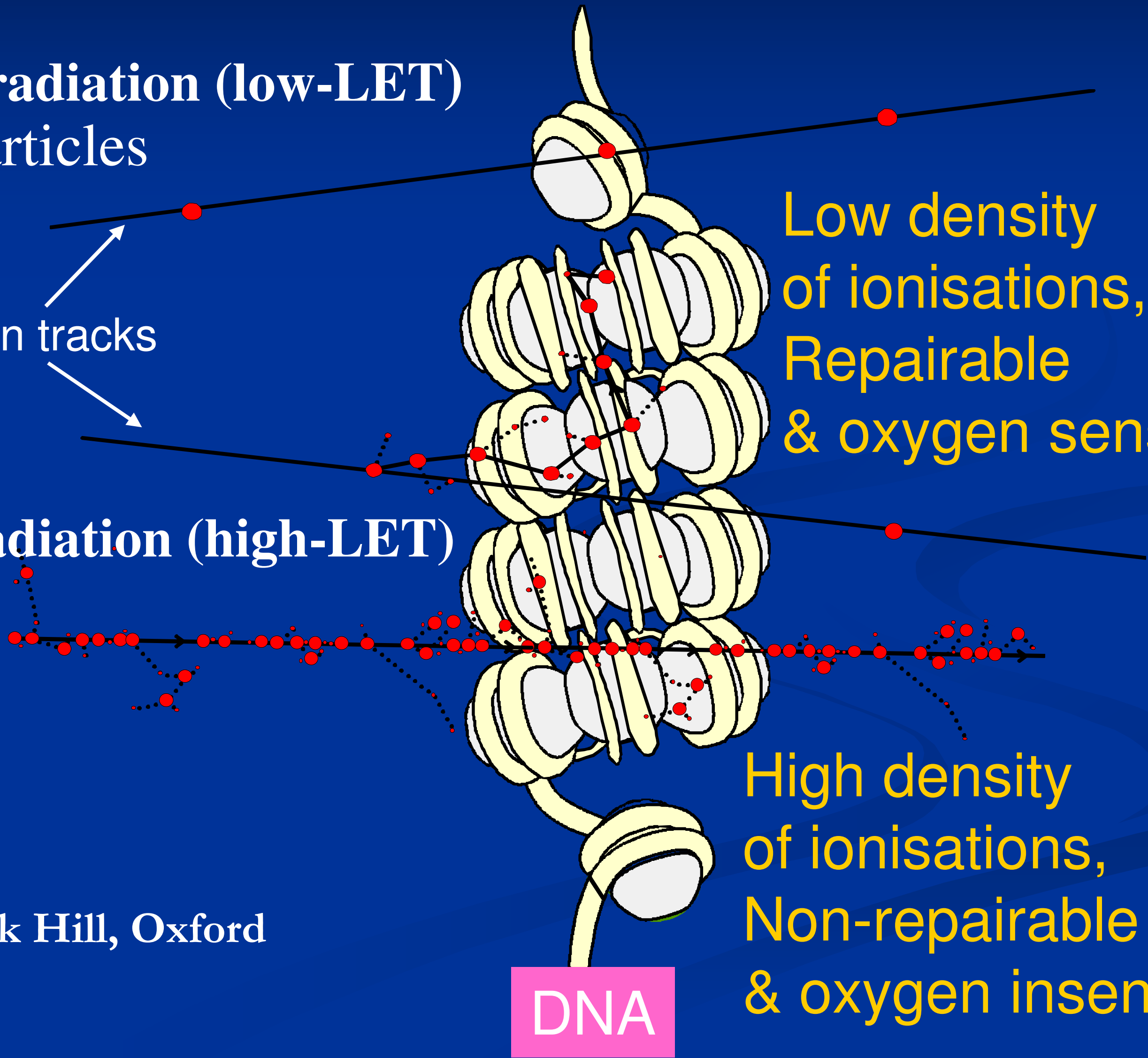
Medical Research Council

CANCER RESEARCH UK

Ionising Radiation and DNA

Sparsely ionising radiation (low-LET)
e.g. γ-rays, β-particles

electron tracks



Low density
of ionisations,
Repairable
& oxygen sensitive

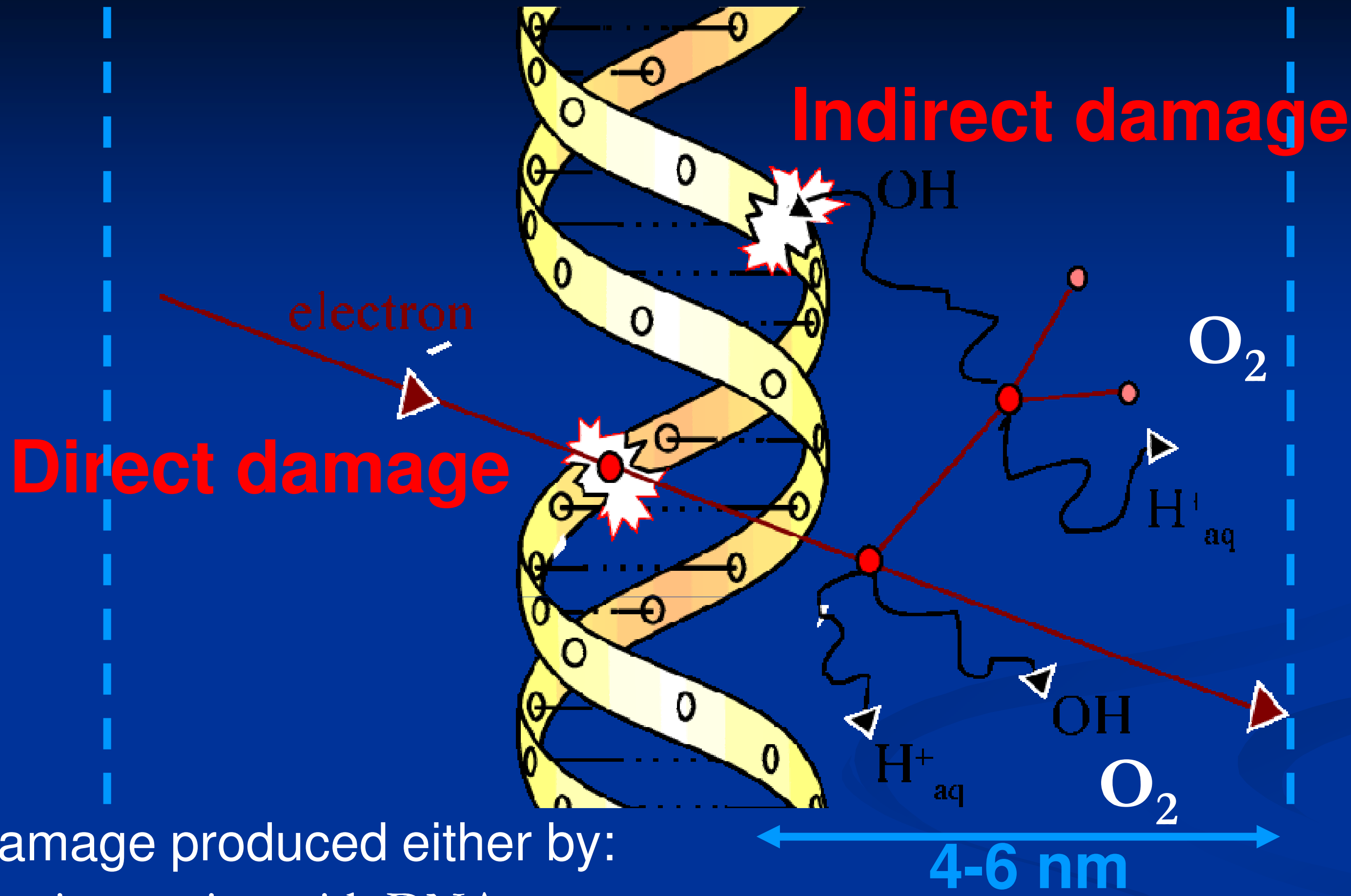
Densely ionising radiation (high-LET)

e.g. α-particles
$C6^{+}$ ions

High density
of ionisations,
Non-repairable
& oxygen insensitive

Courtesy of Dr Mark Hill, Oxford

Radiation Interactions with DNA



DNA damage produced either by:

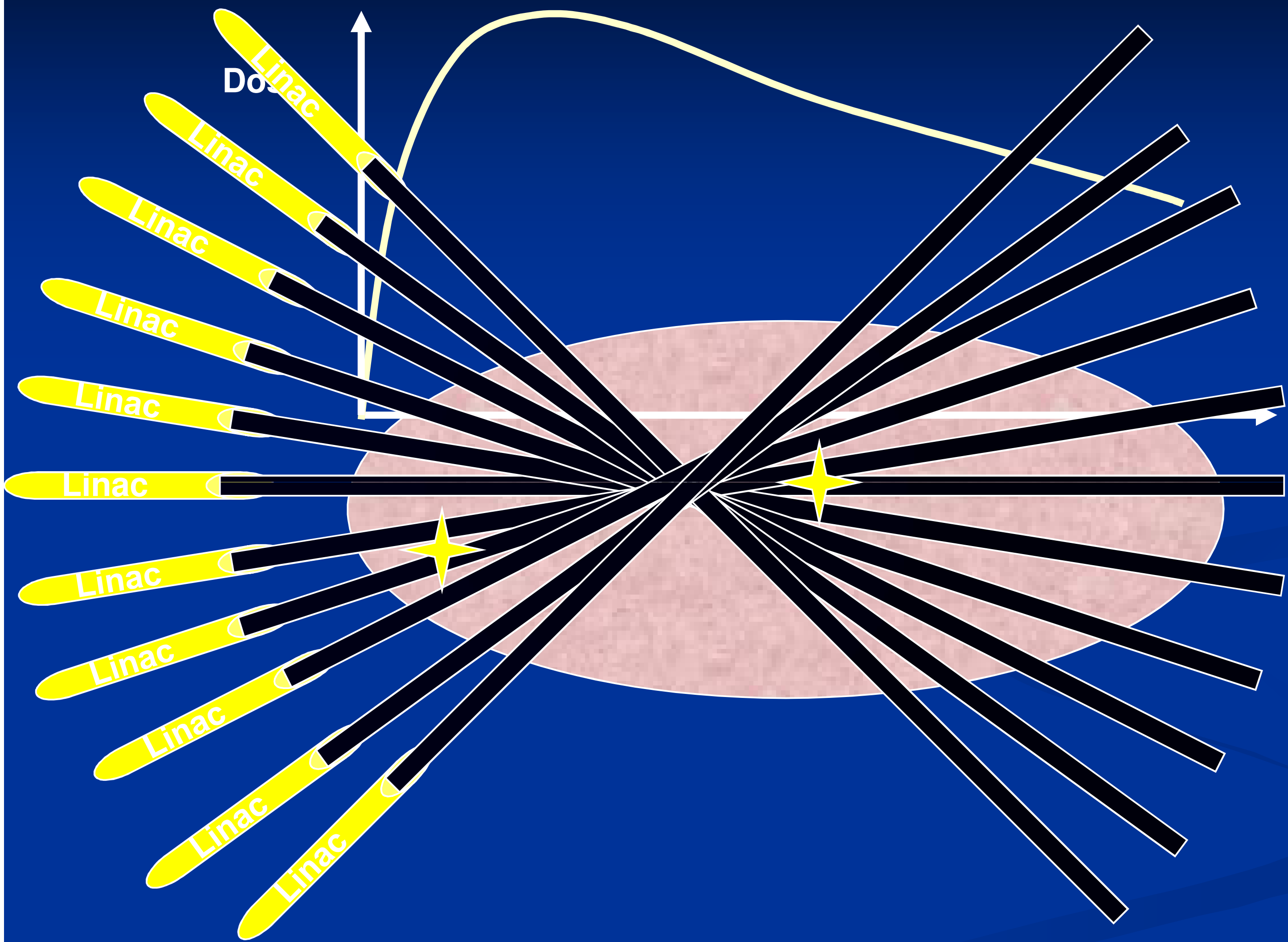
- Direct interaction with DNA
- Indirectly through reaction with free radicals, mainly hydroxyl radicals (OH•) produced in surrounding water. Scavengable
  - *contributes ~70% for x-rays*
  - *diffusion distance v. small (~4 – 6 nm) therefore track structure maintained*

Time courses of radiation effects in biology

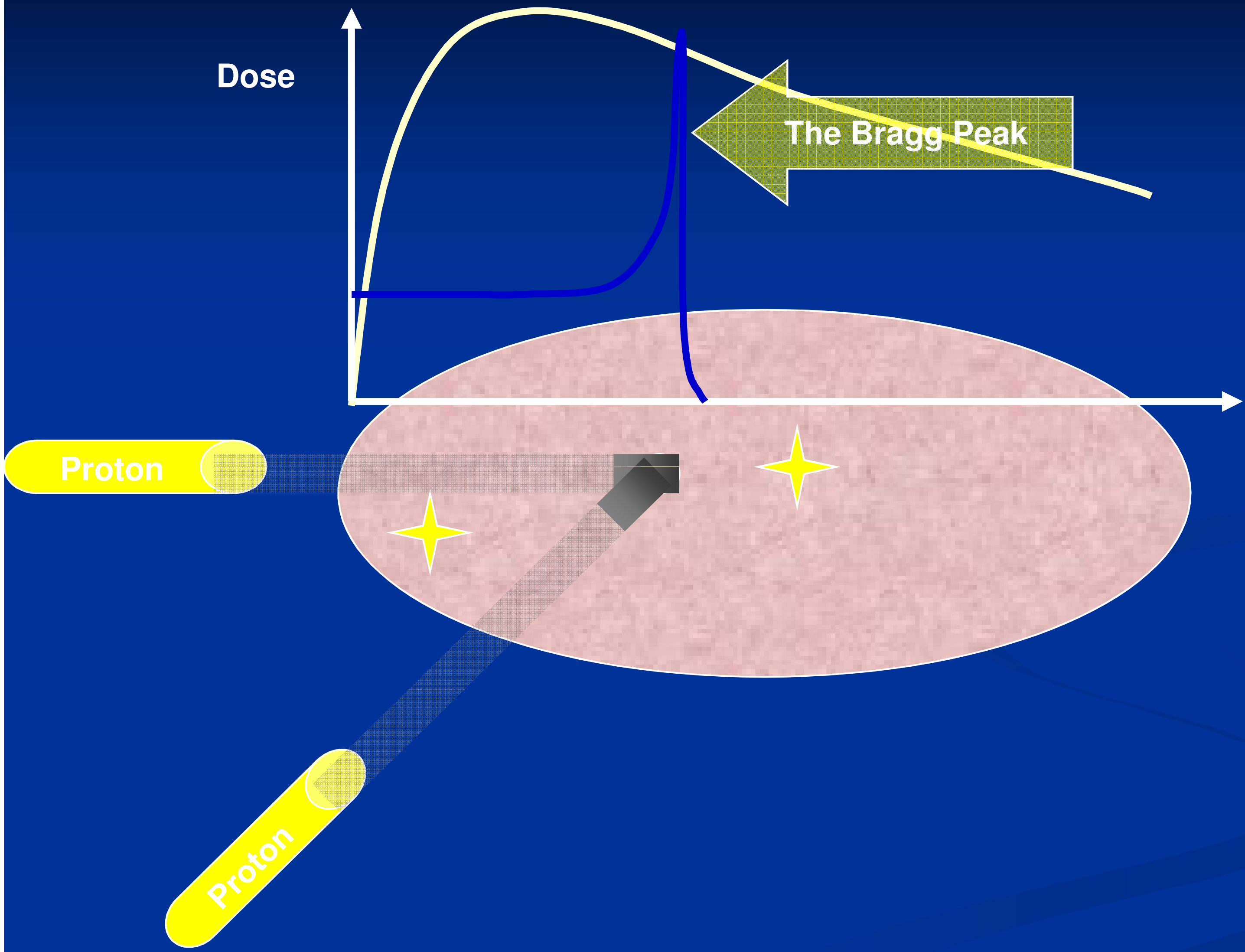
- Fento-seconds…..Nano-seconds : radiolysis of water and ionisation of DNA. Radical Scavengers.
- Micro-seconds: additional oxygen fixation
- Minutes to hours: damage recognition and enzymatic repair processes
- Days – weeks: cellular repopulation, gross re-oxygenation of tumours.
- Years…vascular damage, carcinogenesis.

Which form of technology would you like used to treat your cancer?

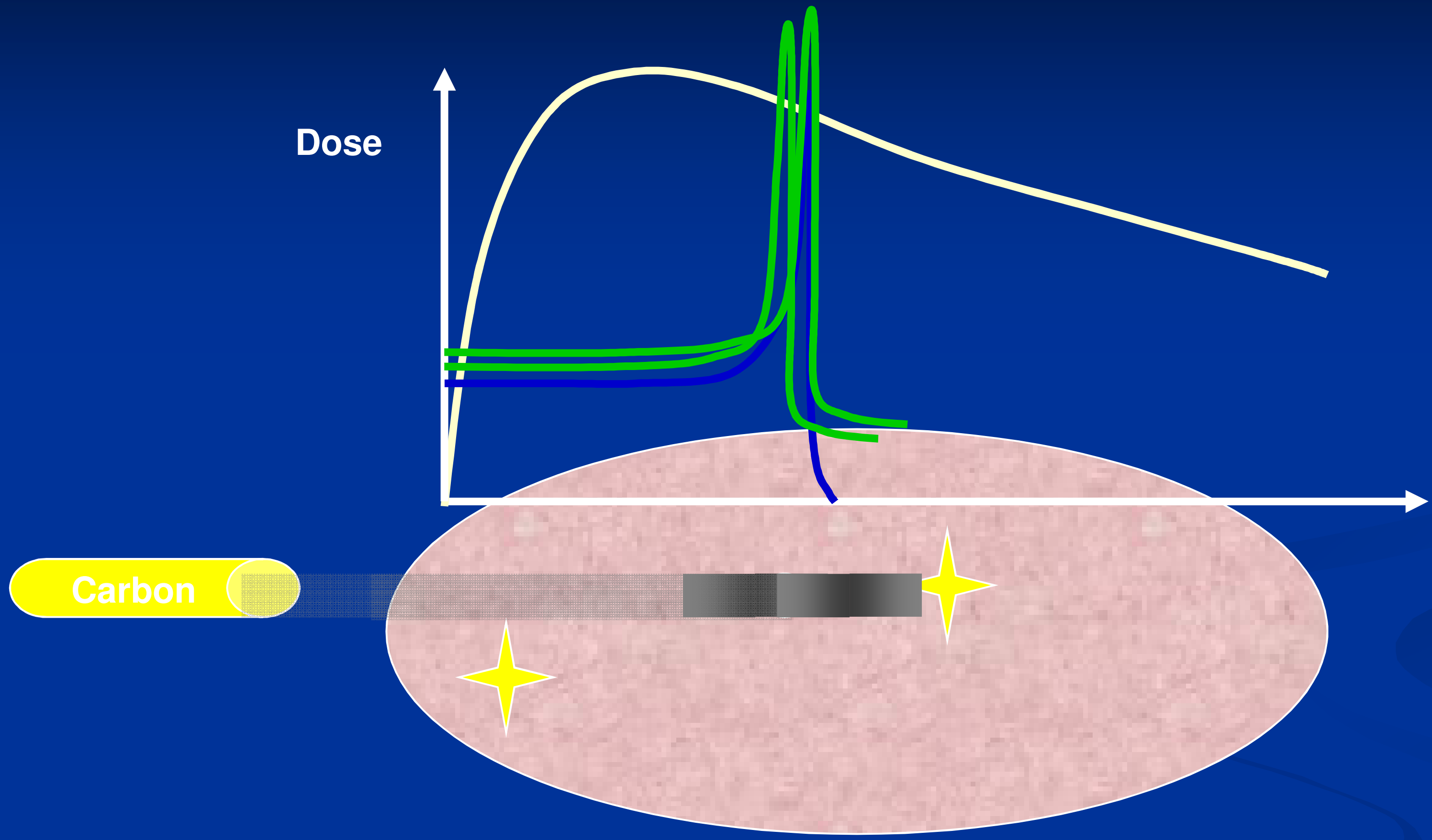
Curing Cancer with X-rays



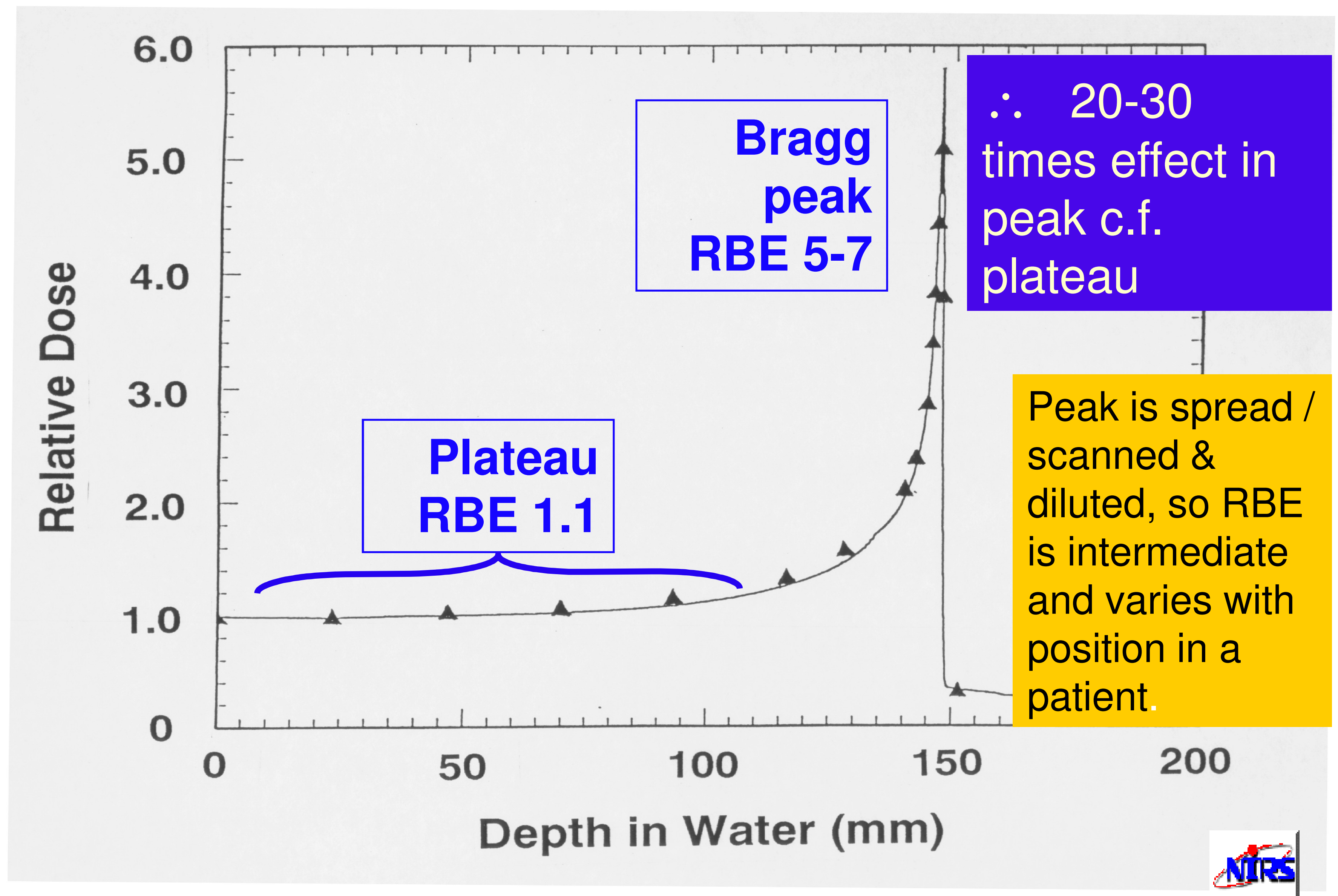
Can we do better?



Can we do even better?



Carbon Ion Beam Profile

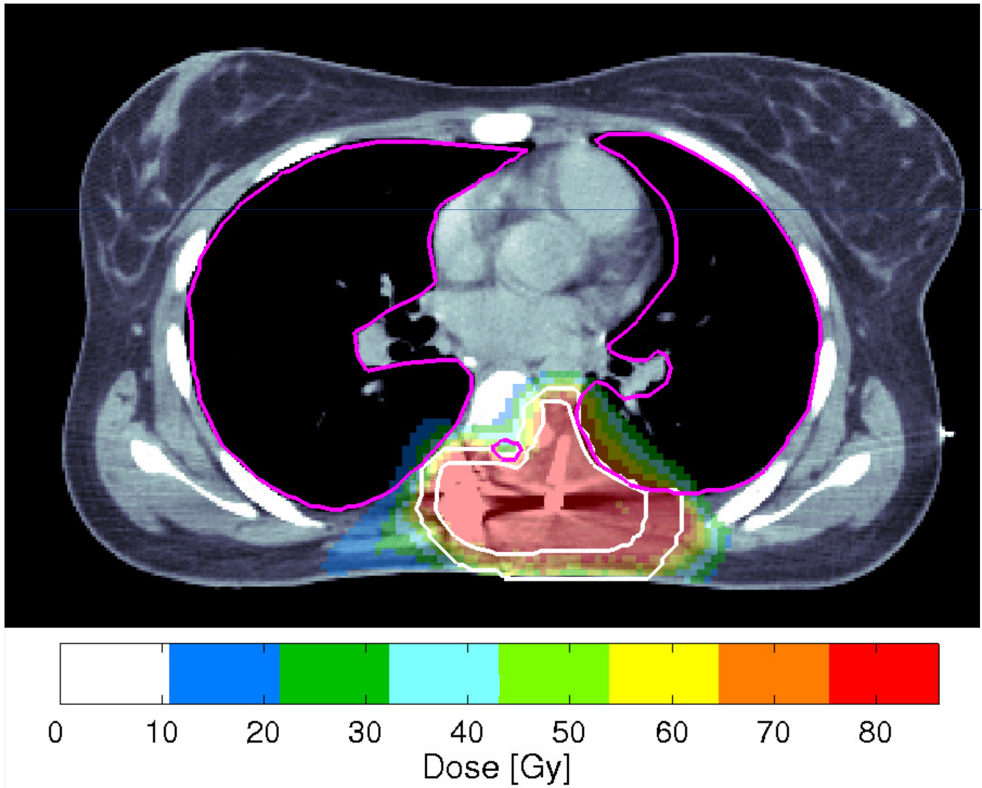


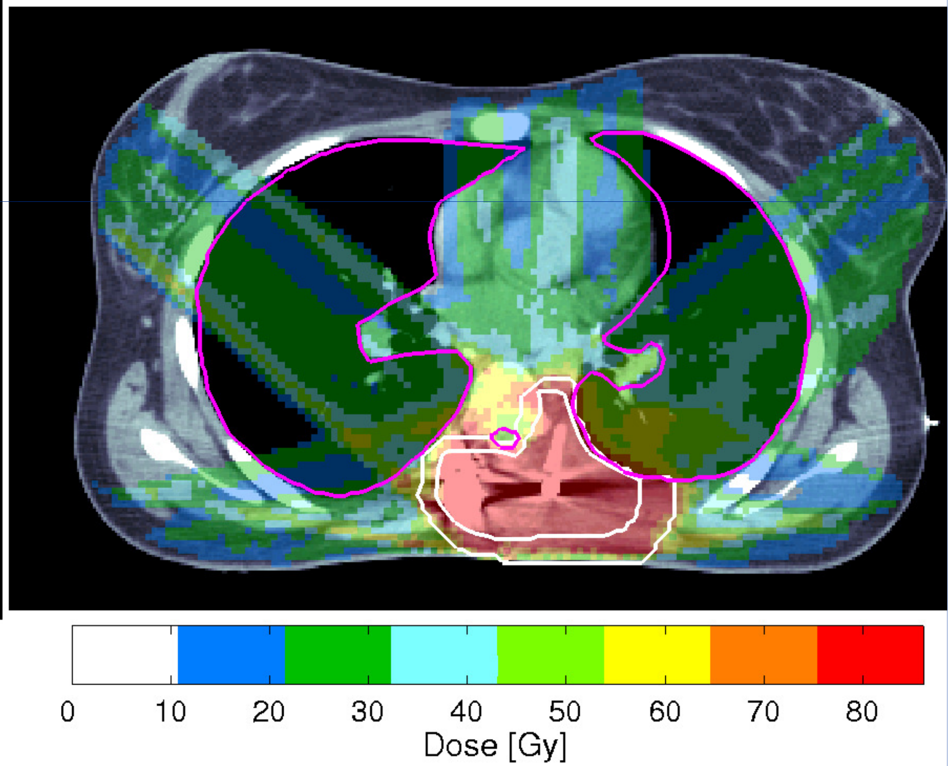
∴ 20-30 times effect in peak c.f. plateau

Peak is spread / scanned & diluted, so RBE is intermediate and varies with position in a patient.

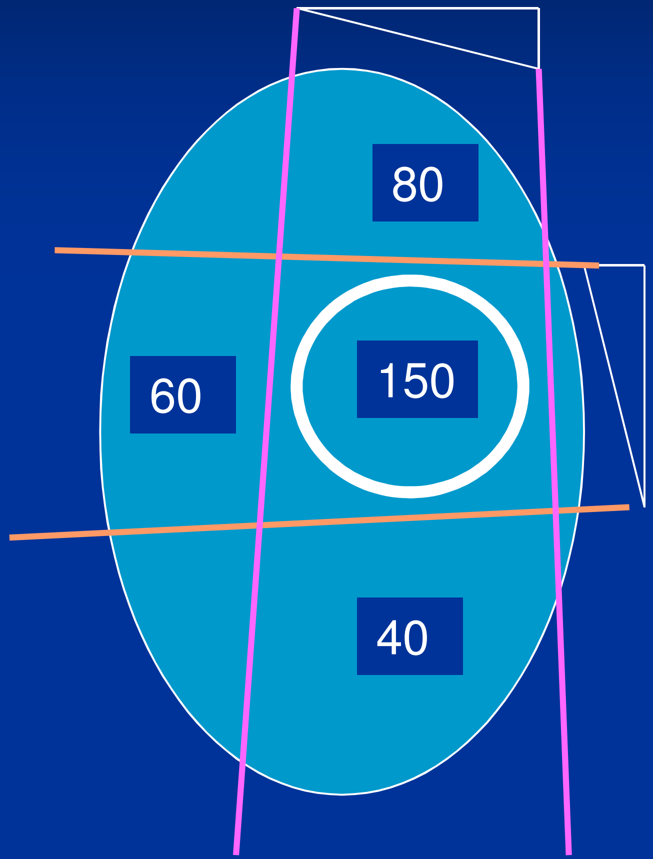
Spinal cancer

IMPT **IMXT**

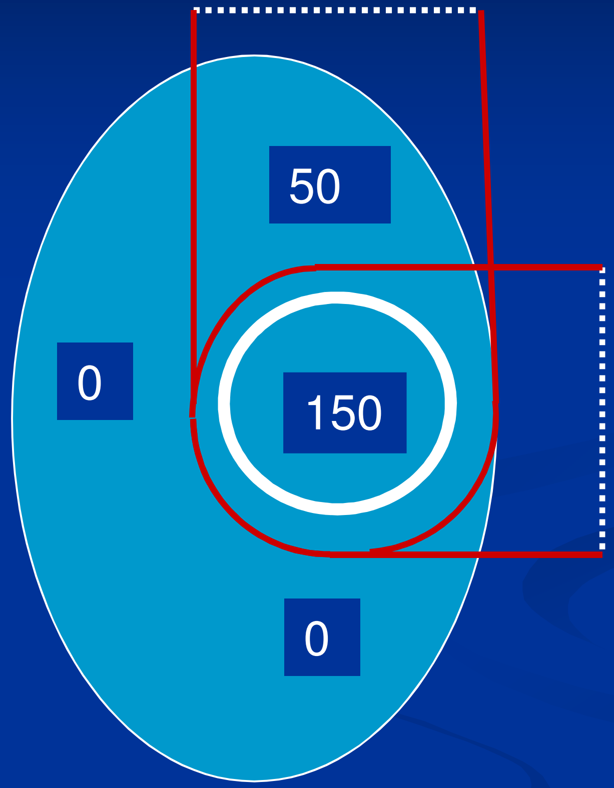




X-Rays or

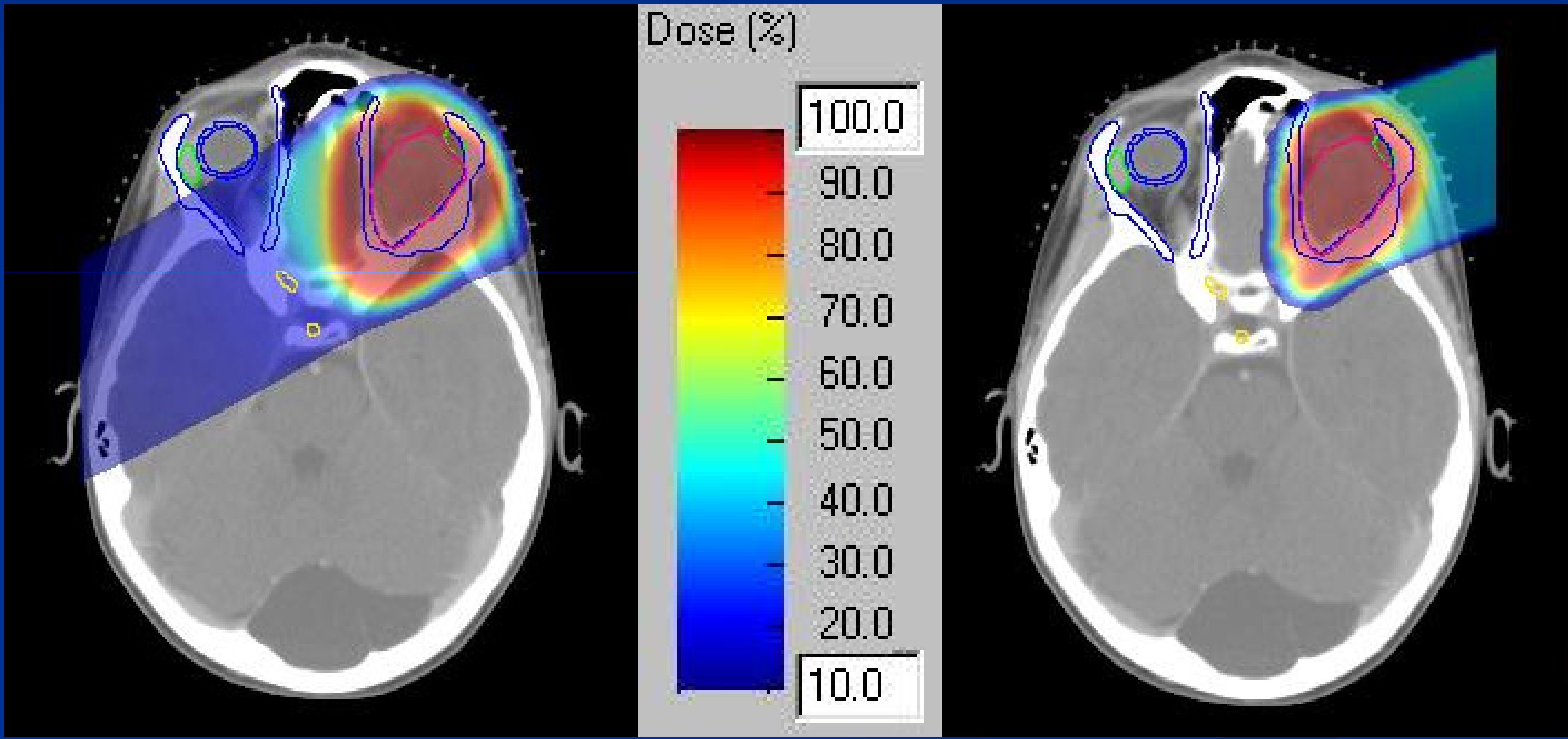


Protons/Ions



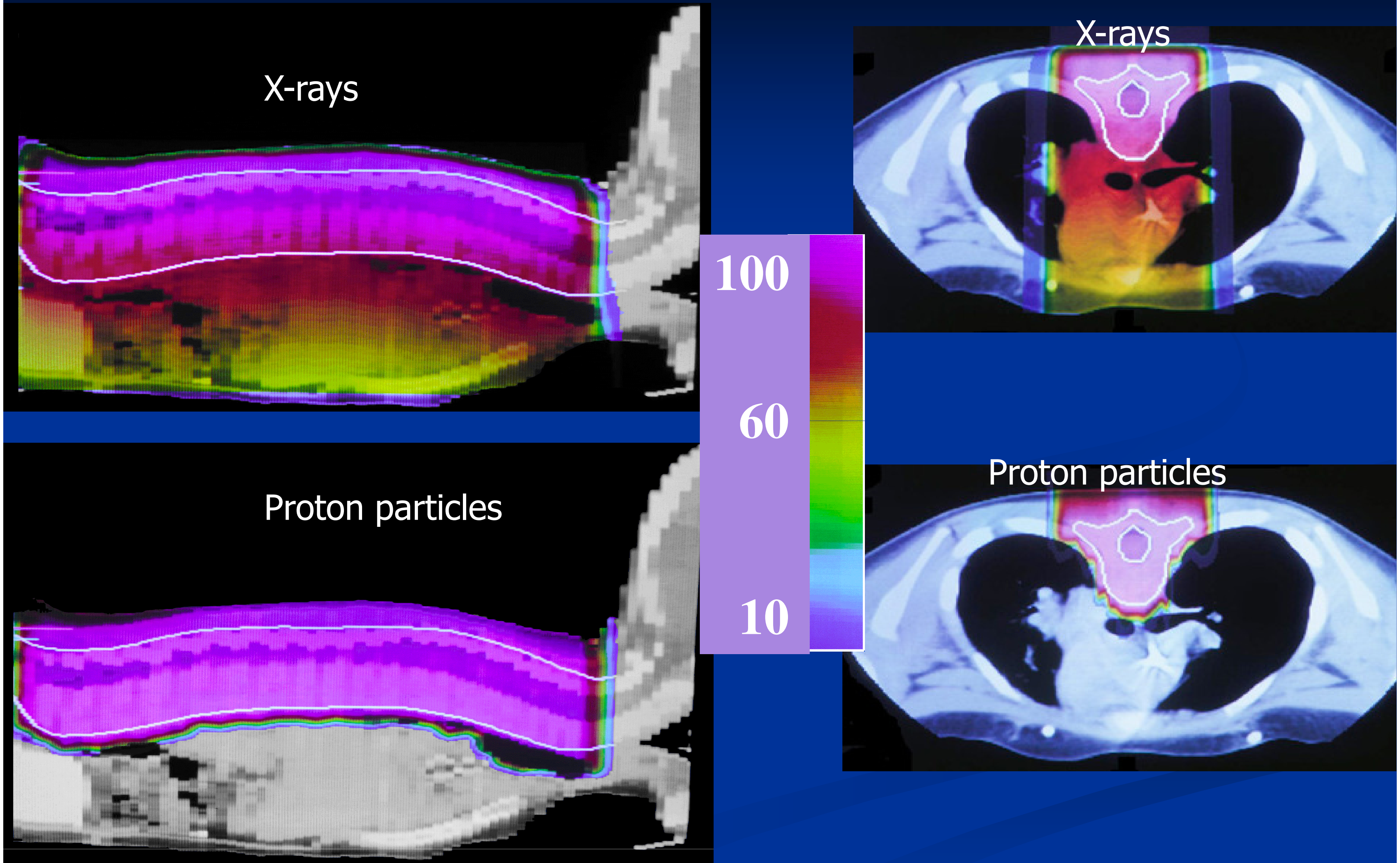
Orbital Rhabdomyosarcoma

X-Rays **Protons**

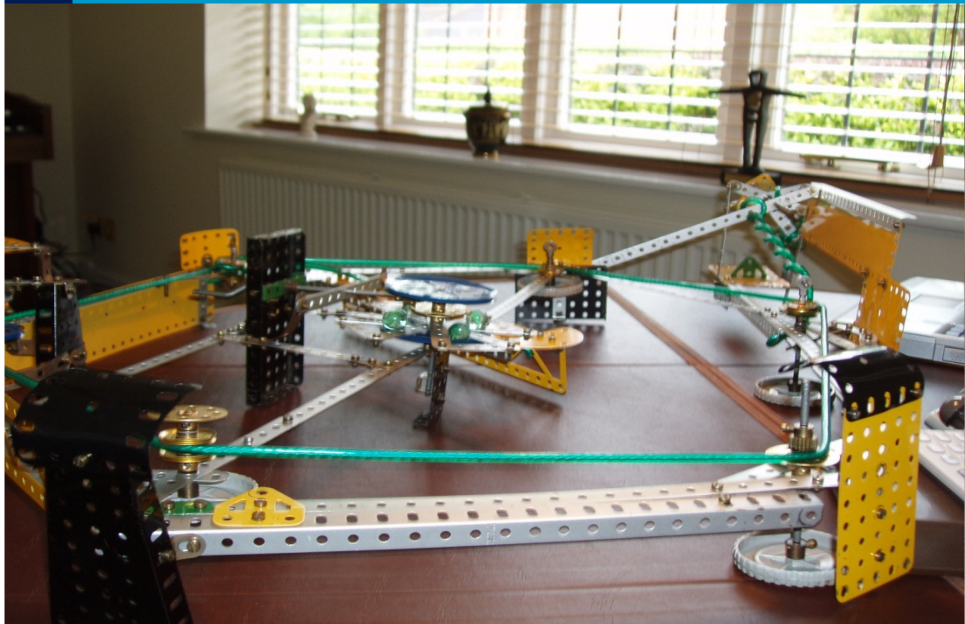


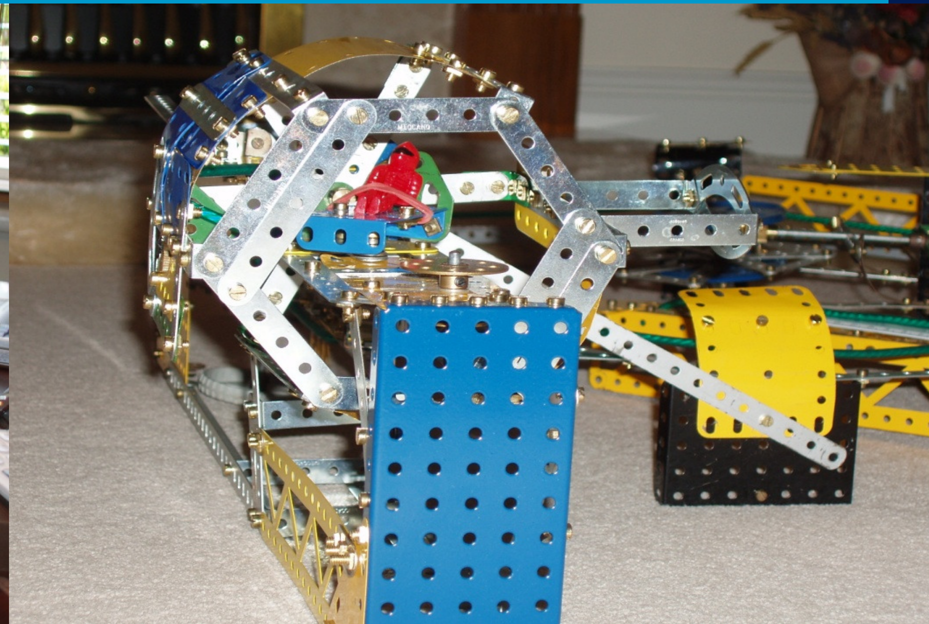
Courtesy T. Yock, N. Tarbell, J. Adams

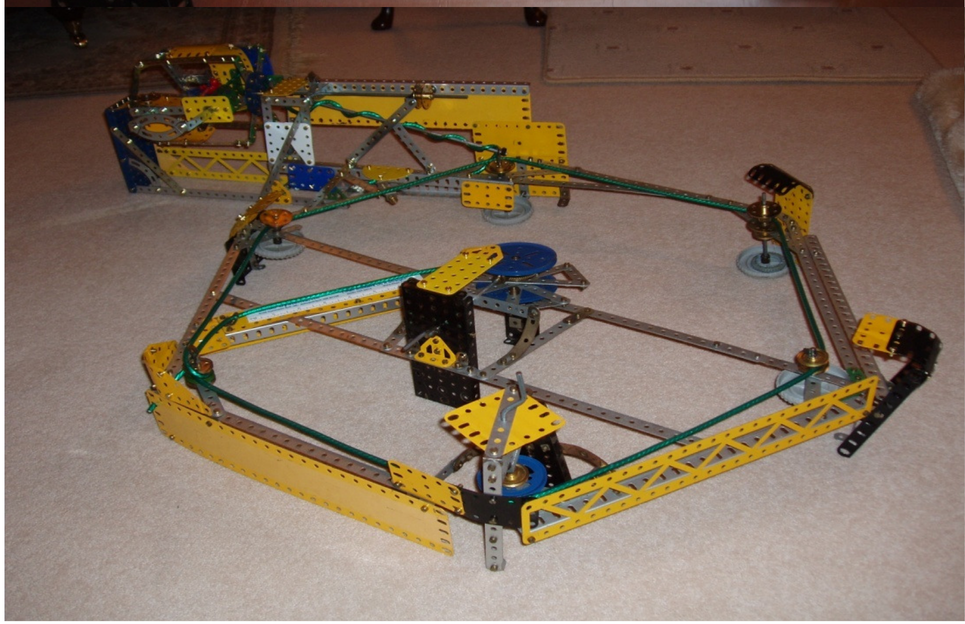
Medulloblastoma in a child

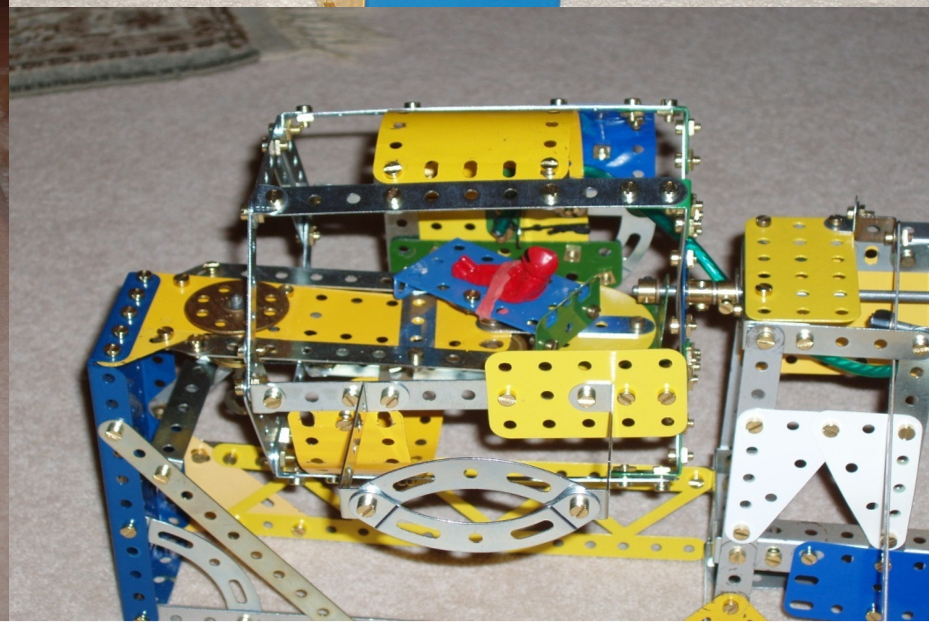


The only carbon ion model in UK (funded by NHS doctor working during his holiday)

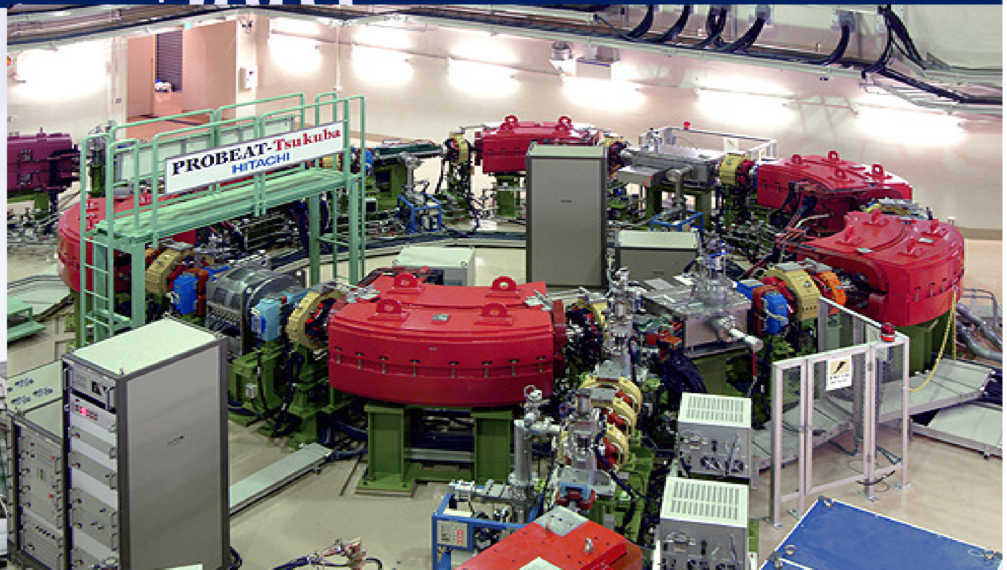


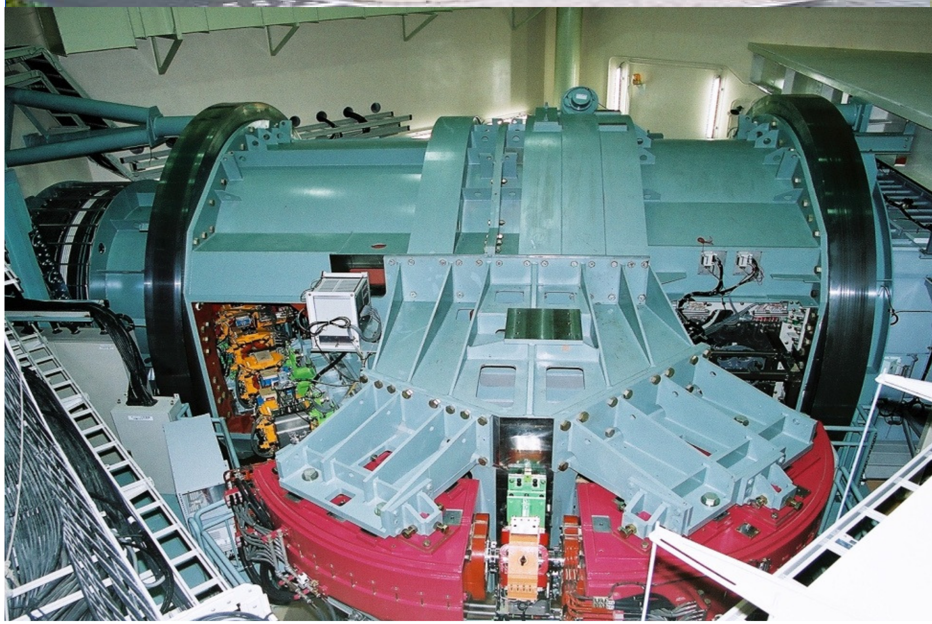






Japan: Tsukuba University Proton Medical Research Center, 2001

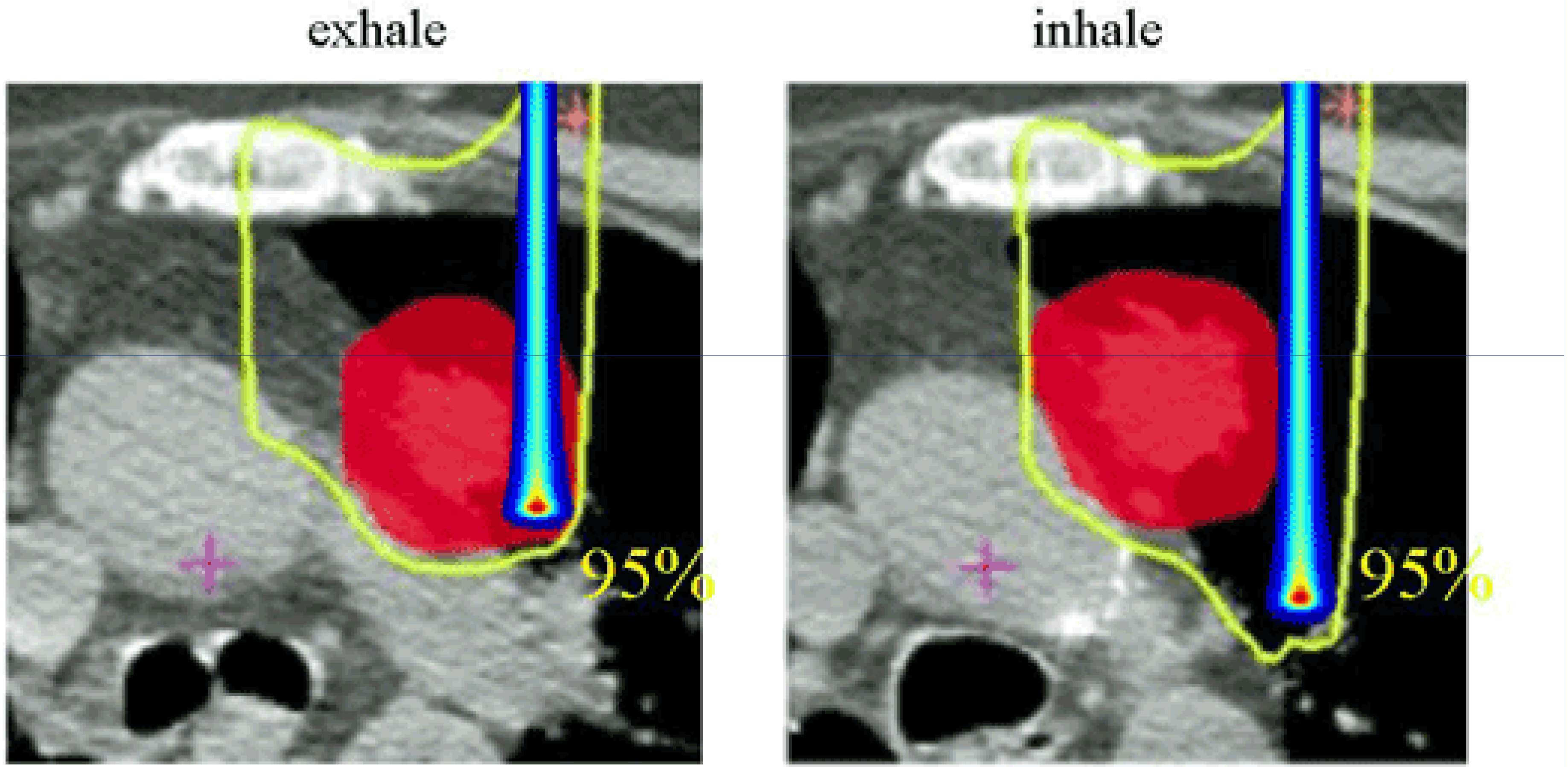




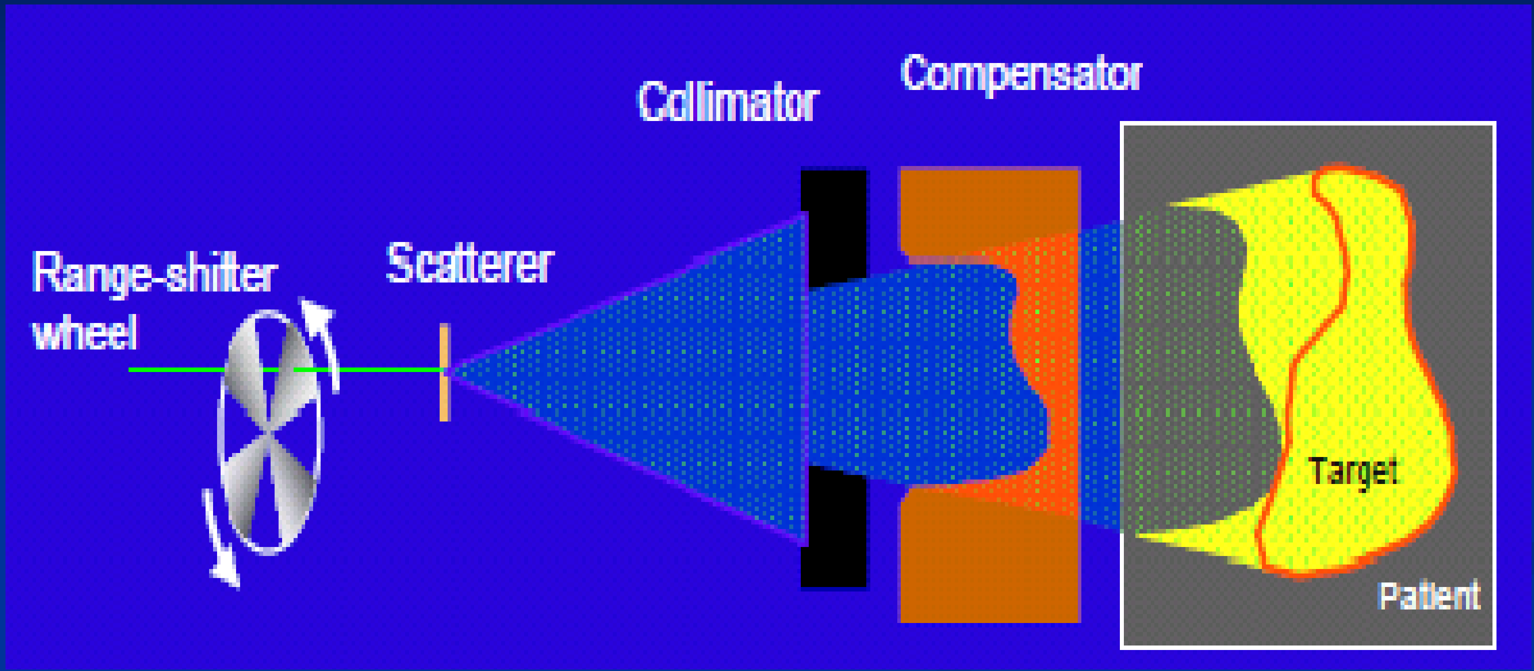
What advantageous features can lasers offer?

- Different particles based on composition of target……there may be unique indications for different ions in different anatomical locations…..e.g. Helium has 'sharpest' beam with least side scatter and nuclear fragmentation products.
- ? Mixed modality fields.
- As injectors to synchrotron/cyclotrons….rapid changes in ion source can be achieved [needs high rep. rate]
- Choosing target geometry to match tumour topology.

Issues 2: Range effects of breathing, 4D CT



Engelsman et al., IJROBP 64(5):1589-1595, 2006



T.Lomax, PSI, Switzerland.

Spot scanning

• parallel proton pencil beams

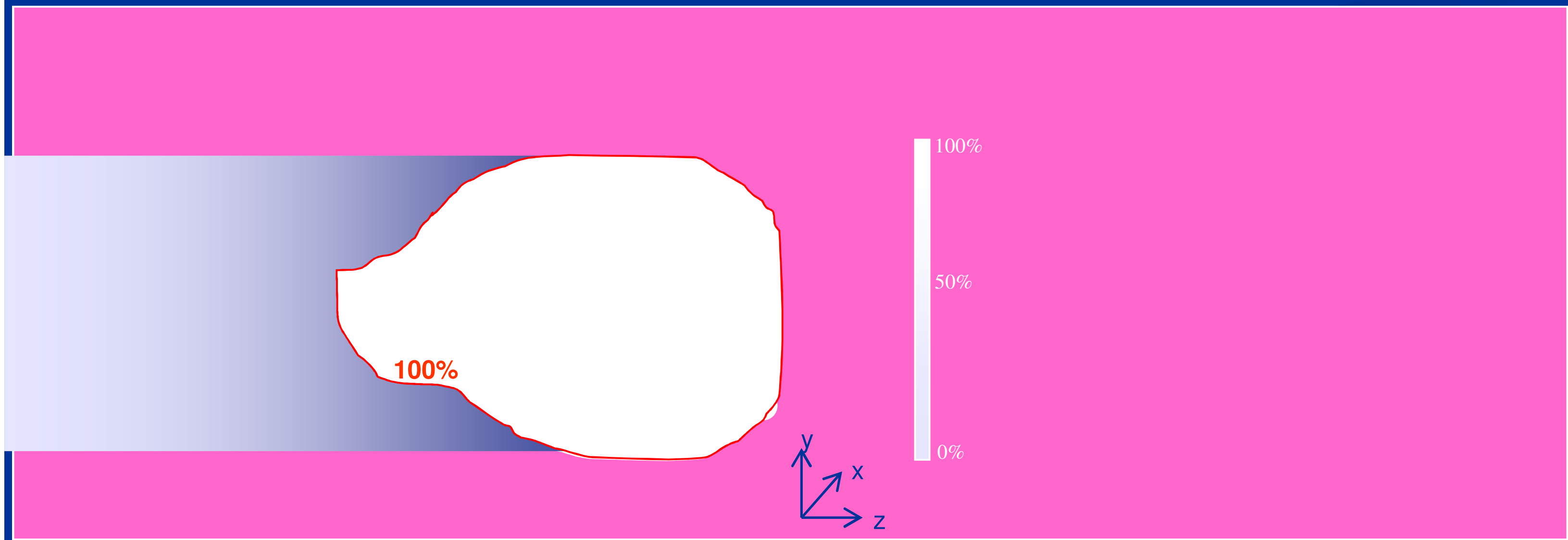
•position and dose of each spot chosen by computer in TPS

•sweeper magnets used to scan target volume in transverse plane (steps of 4mm)

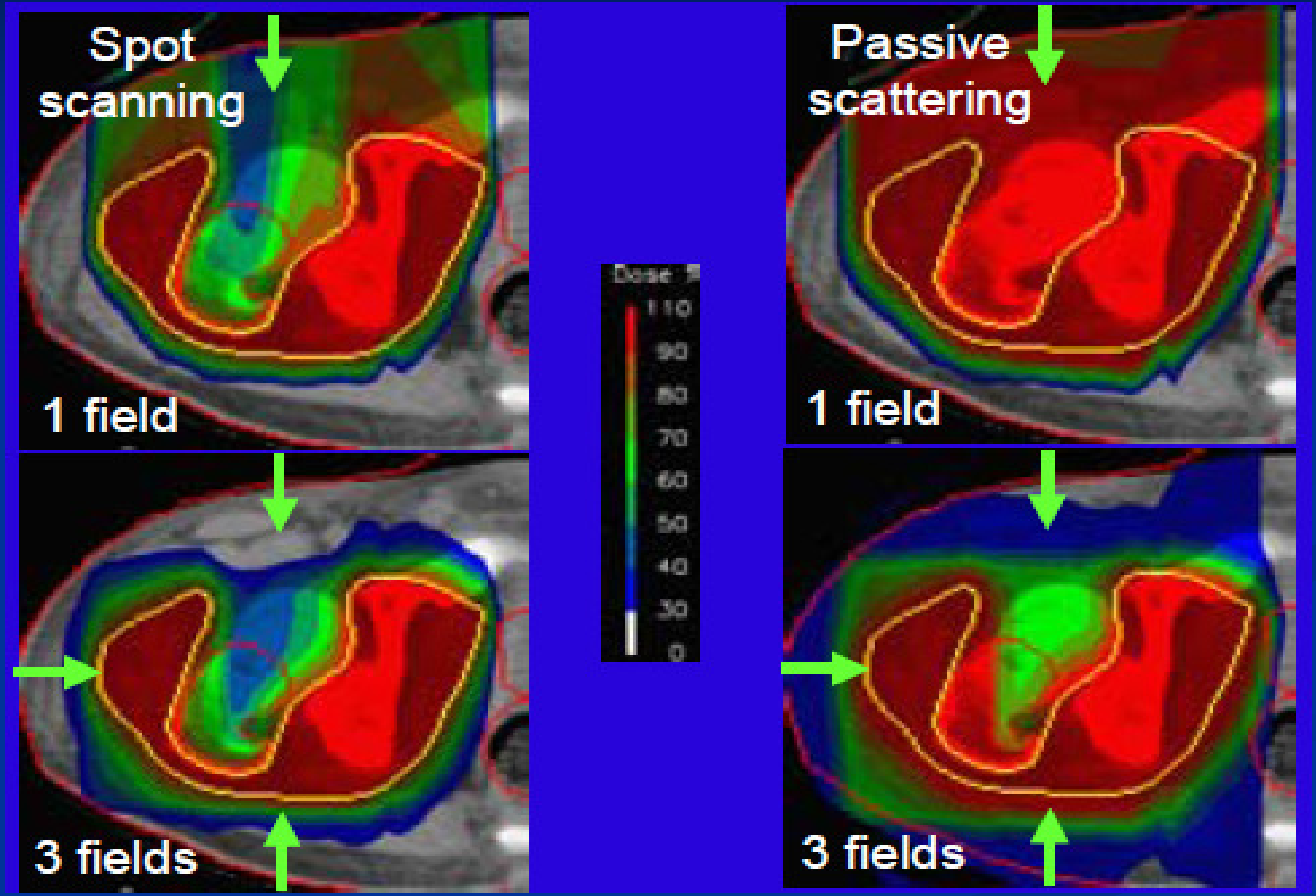
•scanning depth controlled by changing beam energies.

• 1 litre target volume typically 10,000 spots in < 5min….more advanced technology aims to make this faster

•Reduced proximal dose than with broader scattered beams

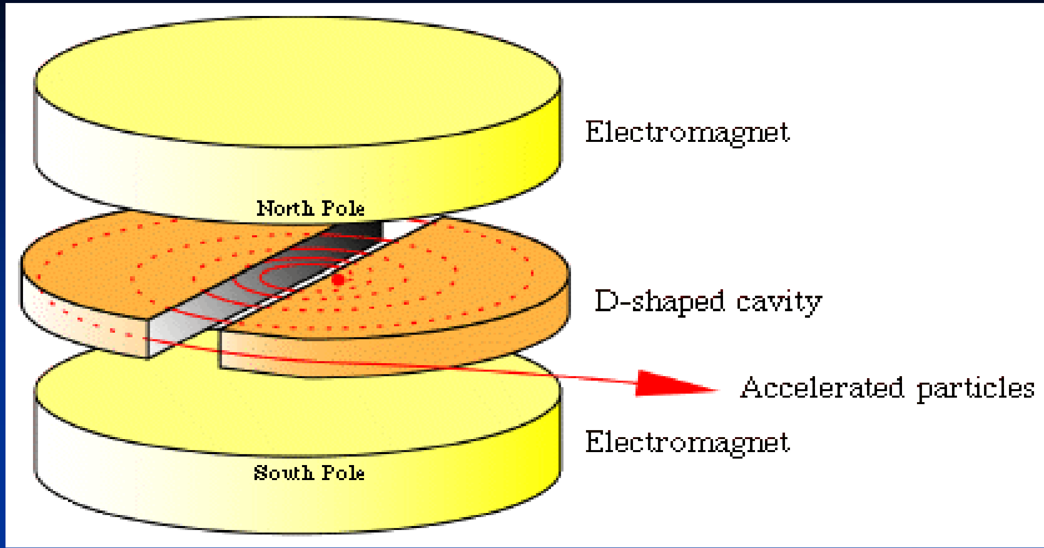


comparisons



Lomax et al PSI, Switzerland

The Cyclotron



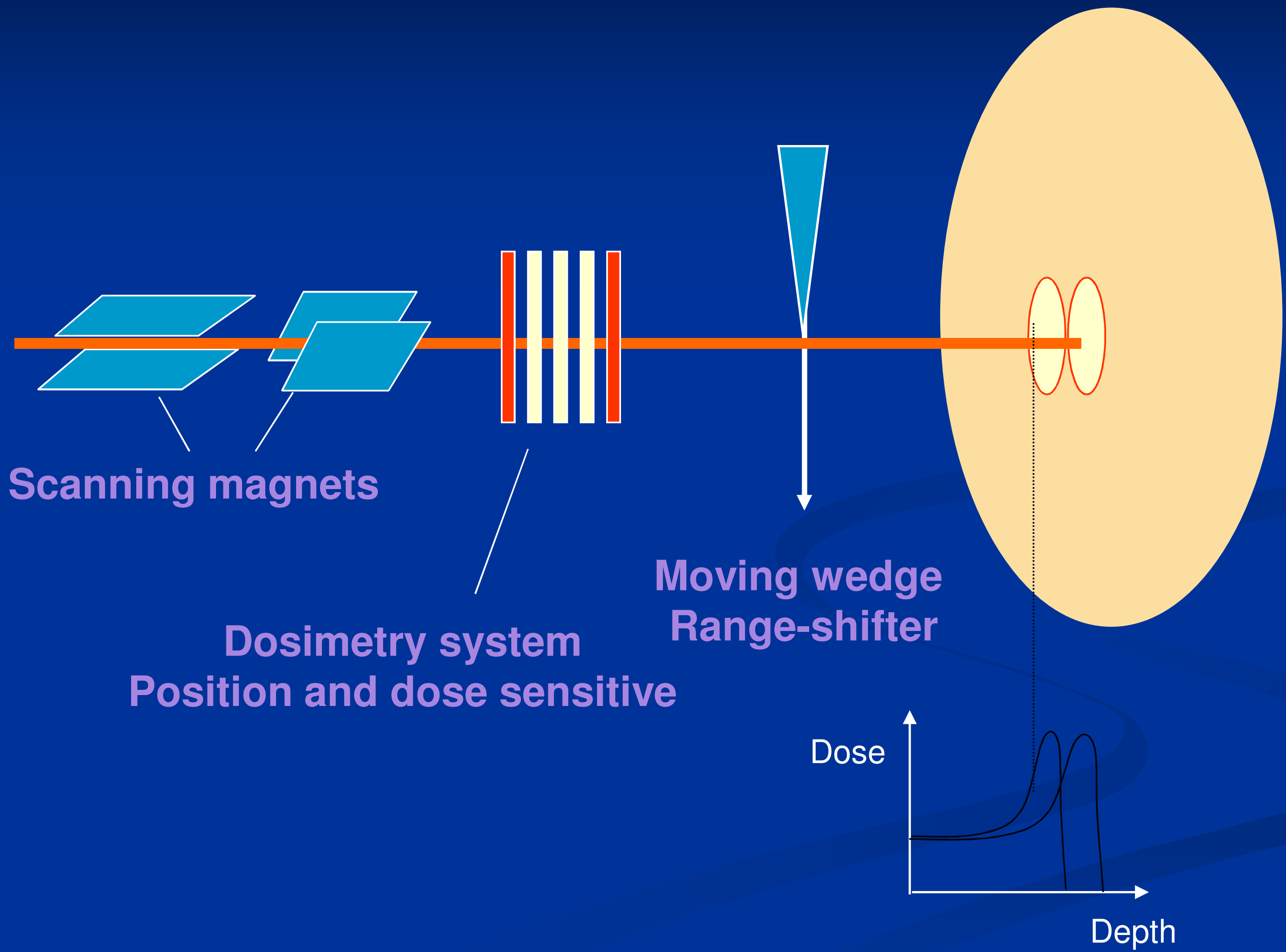
•2 D-shaped cavities between two electromagnets. Particle injected into one D shaped cavity of opposite voltage, & accelerates due to e/m field.

•Particle enters other D, polarity changes, to maintain acceleration

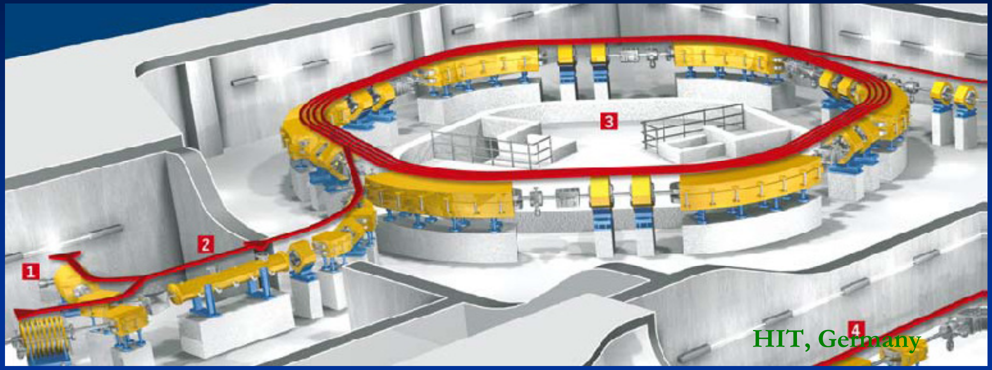
•The combined magnetic fields steers them in gradually increasing spiral since the faster the charged particle, the less it is influenced by magnetic field & extracted at maximum energy.

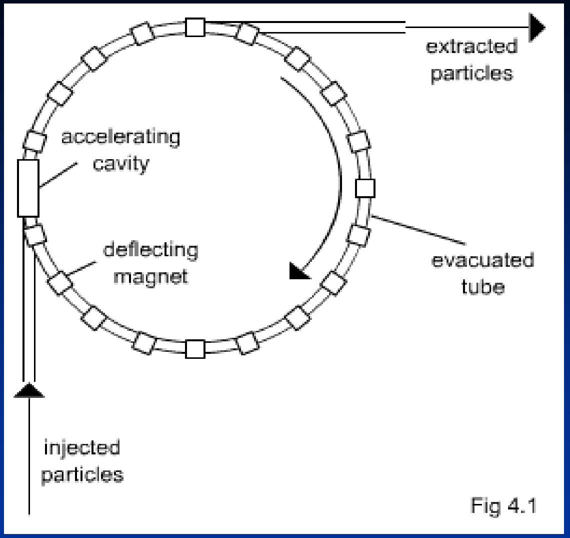
•For clinical use, reduction of energy for tissue Bragg peak ranges appropriate for a particular patient……metal degraders of different thicknesses inserted dynamically into beam….source of secondary radiation and kept out of treatment room.

Spot-scanning beam-line schematic



The Synchrotron





•Particle accelerated in a ring, of consecutive magnets and radiofrequency systems

•Magnetic field gradually increased to match particle speed (energy) to keep constant circular trajectory or radius

•Particles can be extracted with any desired energy, unlike Cyclotron

•But number of particles per second accelerated (the beam current) is less, which means longer treatment times.

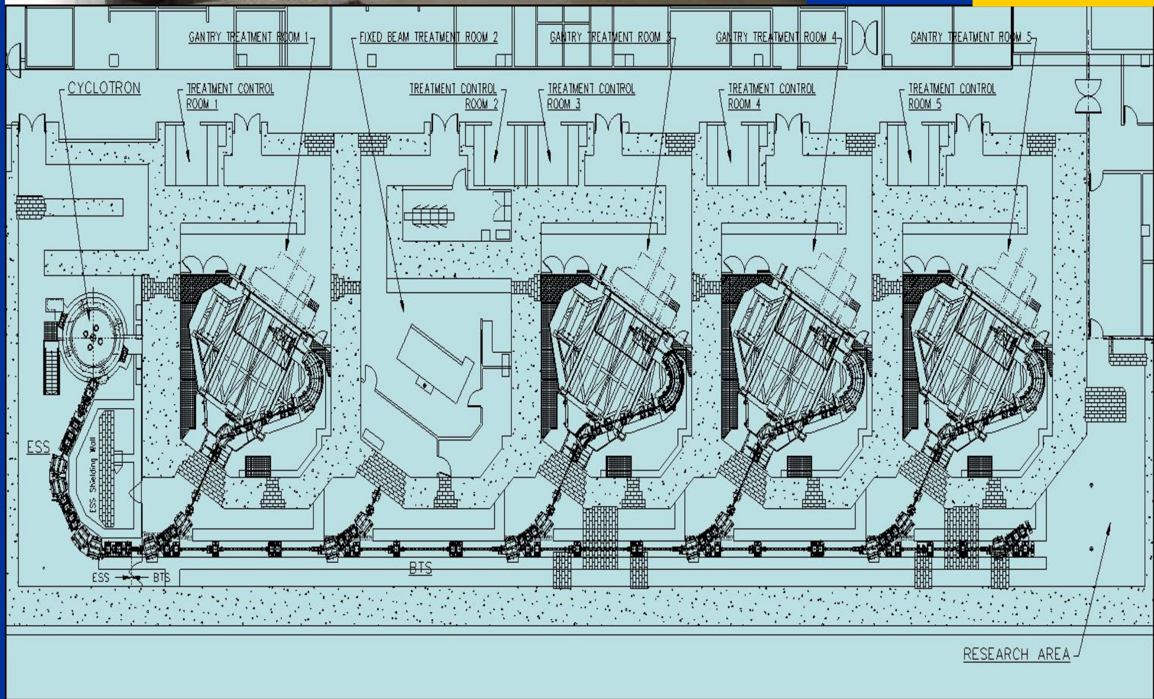
Cyclotron…with 240 MV protons

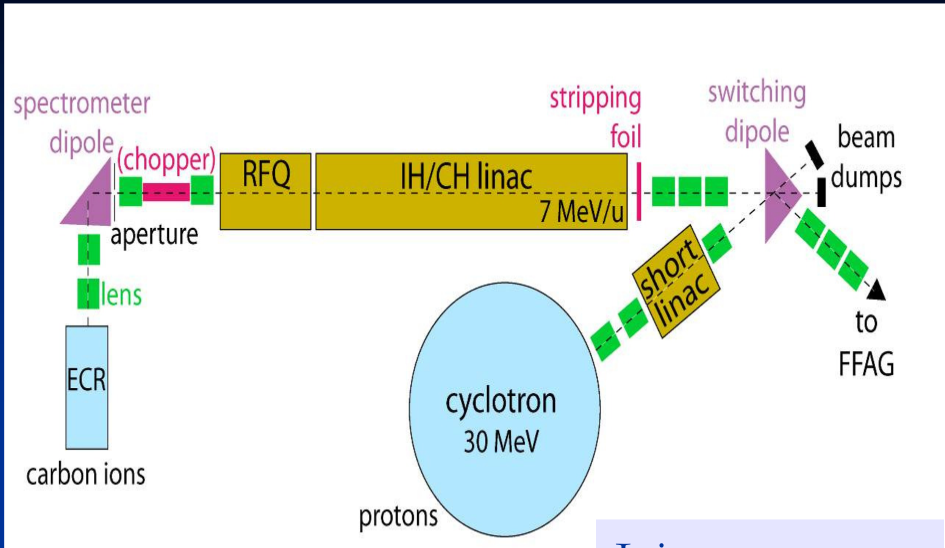
Cyclotron Cost around £10 Million

Needs beam lines to several rooms at about £5-10M per room

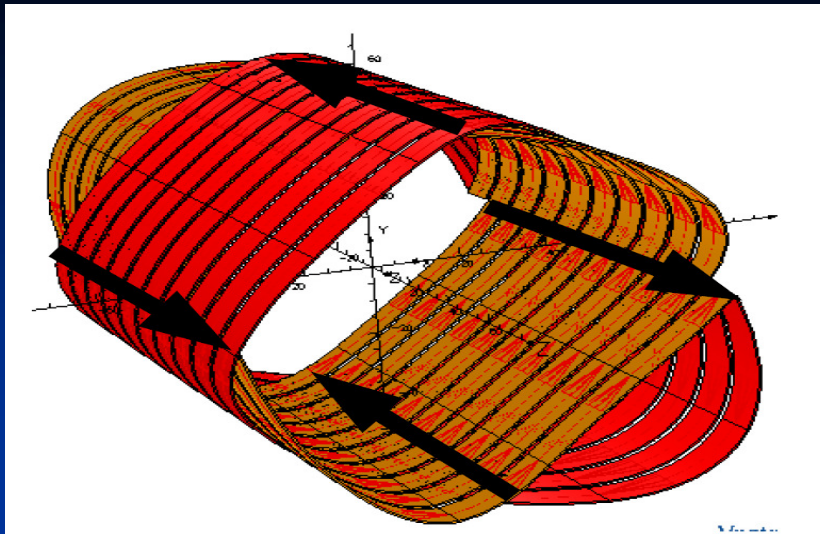
+ Shielding, computer systems etc.

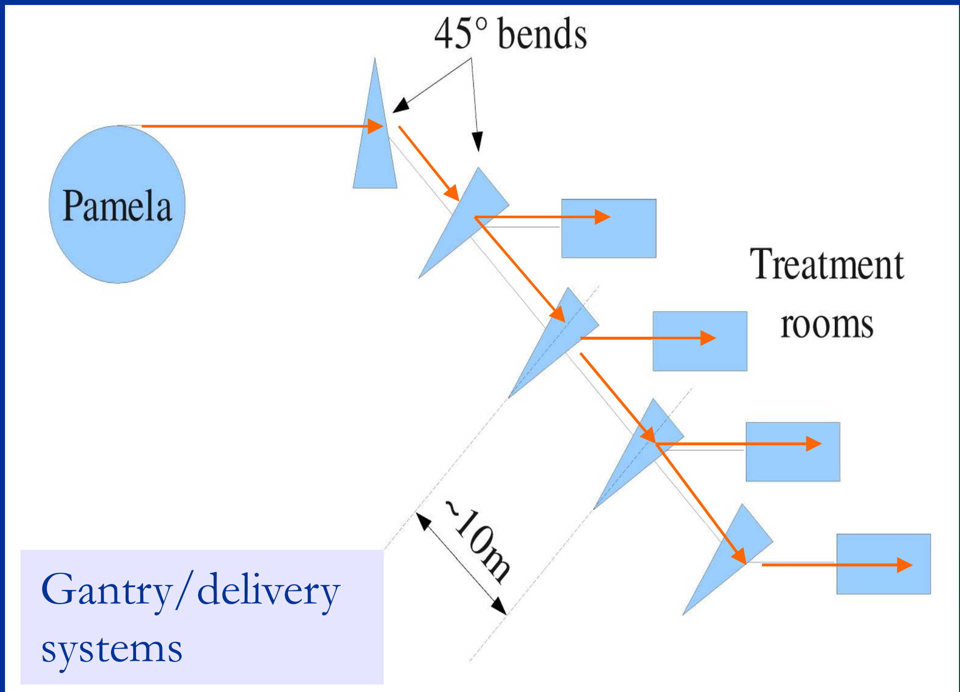
University of Pensylvania, Philadelphia



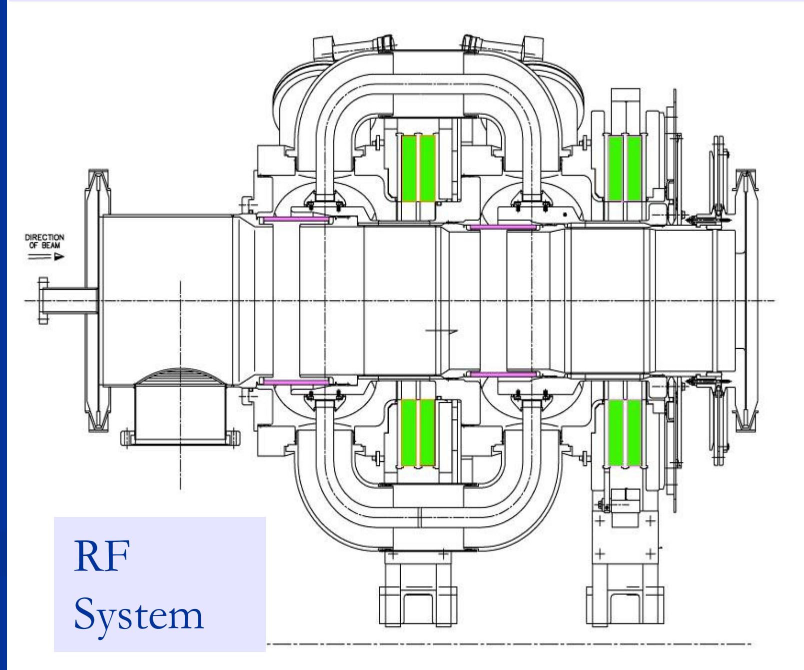


Injector systems


Double-helix coil - smart way of creating a cosine-theta magnet



Gantry/delivery systems



RF System

What advantageous features can lasers offer?

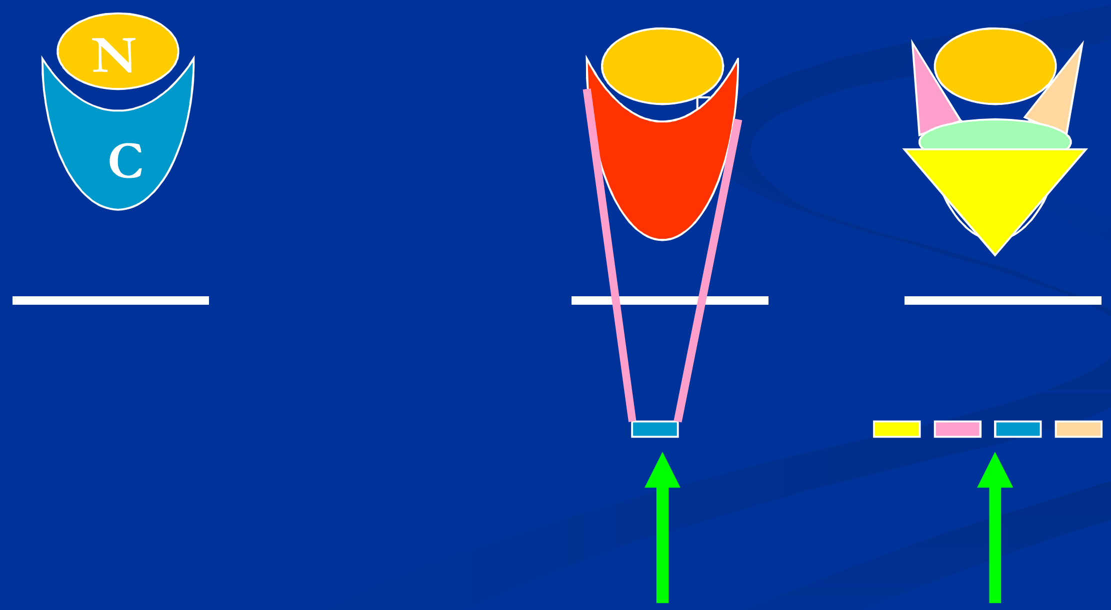
- Gantry size and weight extremely smaller
- Vast reduction in radiation shielded space.
- Mixed fields…..proton, carbon etc, also some γ rays for verification of beam set up using conventional portal digital imaging and reconstructions.
- Efficiency of production….less need to use energy degradation (as in cyclotron beams)
- High Dose rates, faster treatments

Difficulties to overcome

- Final beam collimation…filters, magnets, collimators.
- Precision of energy spectrum, particle ranges and reproducibility
- Need to narrow minimum spot size to 4x4x4 mm, but retain option of using a much larger spot
- How often can spot scanning of tumour be repeated…..ten repeats of scanned beam suggested for mobile tumours…..to cover large target, could be 1000 total spotting episodes
- Combinations of broader beams and spots would provide faster treatments….. inaccuracies would be at tumour periphery more than around its centre.
- Dose limits in a single treatment session…..Japanese 44 Gy Eq…..=44/3=14.67 Gy.

Consideration of

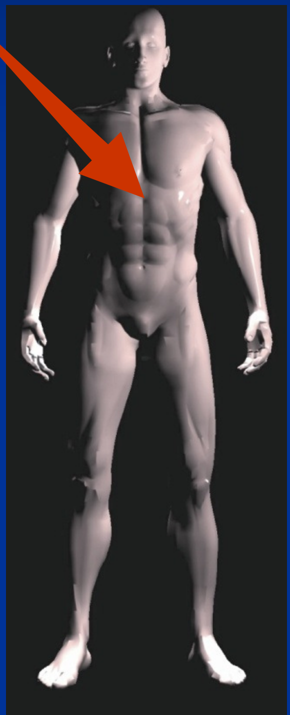
- Dose rate (and so dose duration)
- Ion species (relative biological effects and ballistic properties).
- Patient throughput (per day)
- Dose painting …new features or individual spheres?

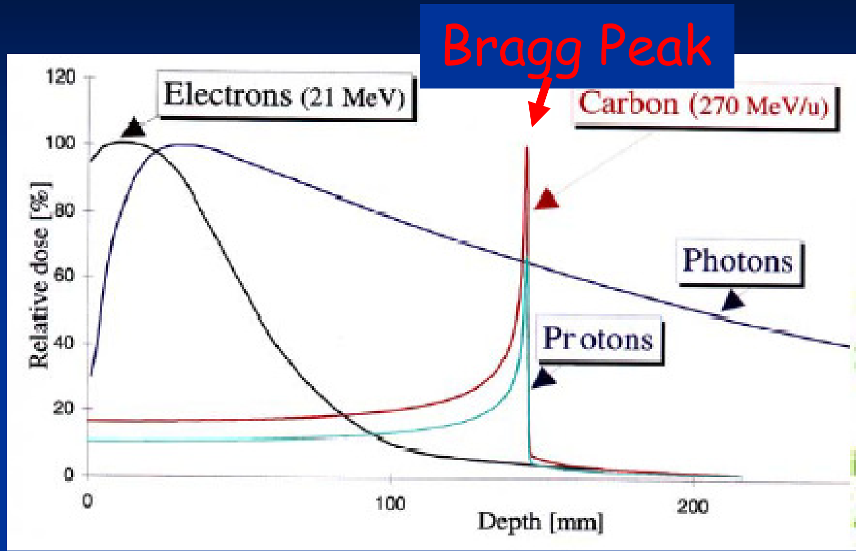


Tissue/human scale

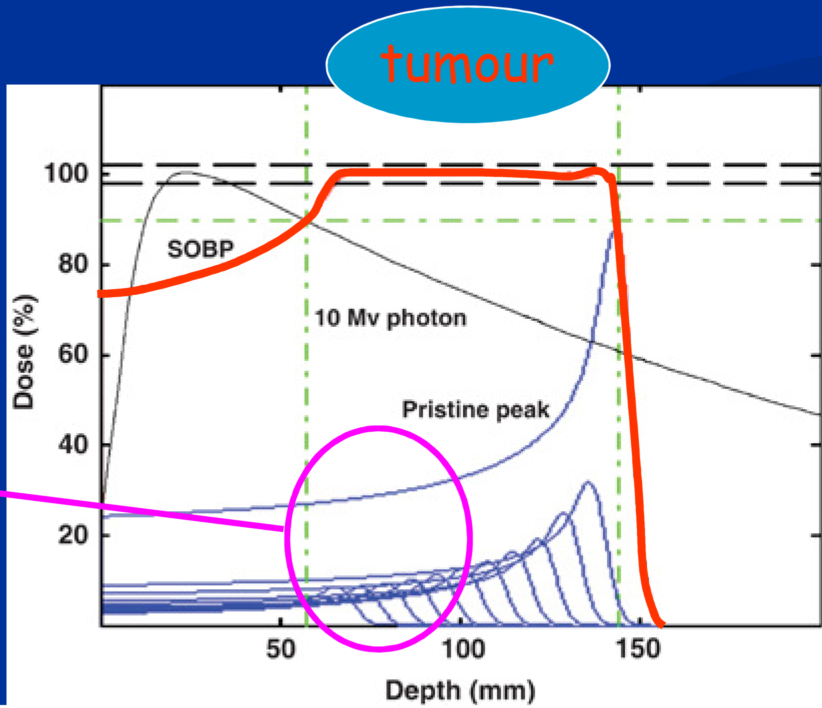
Energy depositions of high-LET charged particles very different to low-LET radiation

Medical exposure





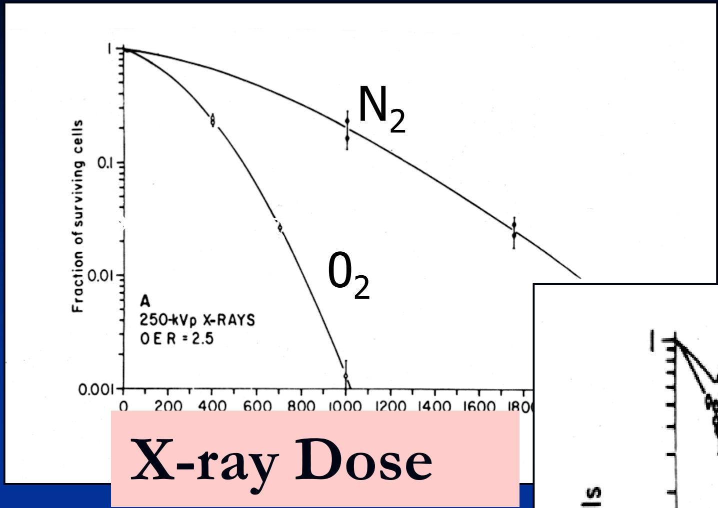
Protons and other ions: dose increases progressively with distance to a maximum at the Bragg Peak then decreases abruptly.

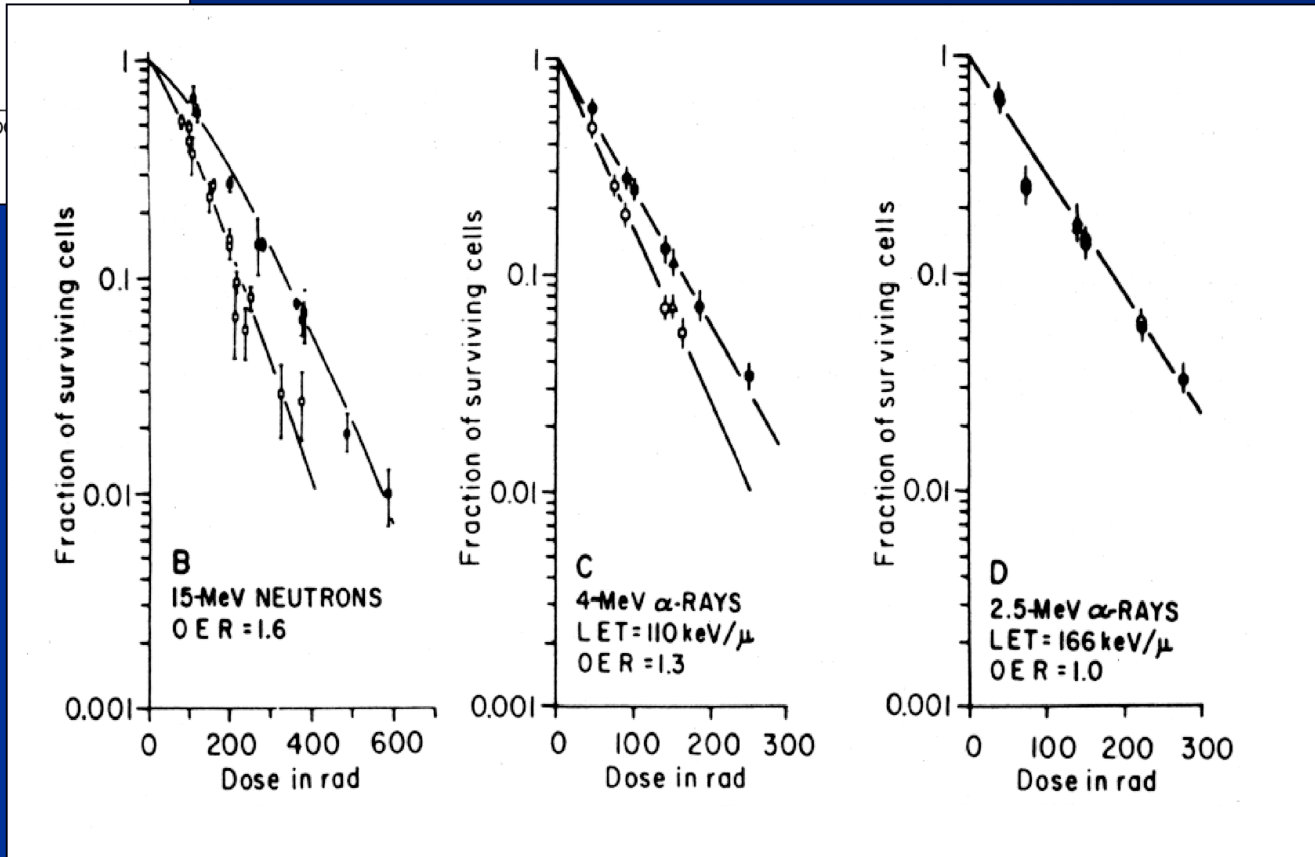


Mixed LET irradiations

Varying the energy is used to spread out the Bragg peak to encompass the tumour

High LET radiations and hypoxic cells

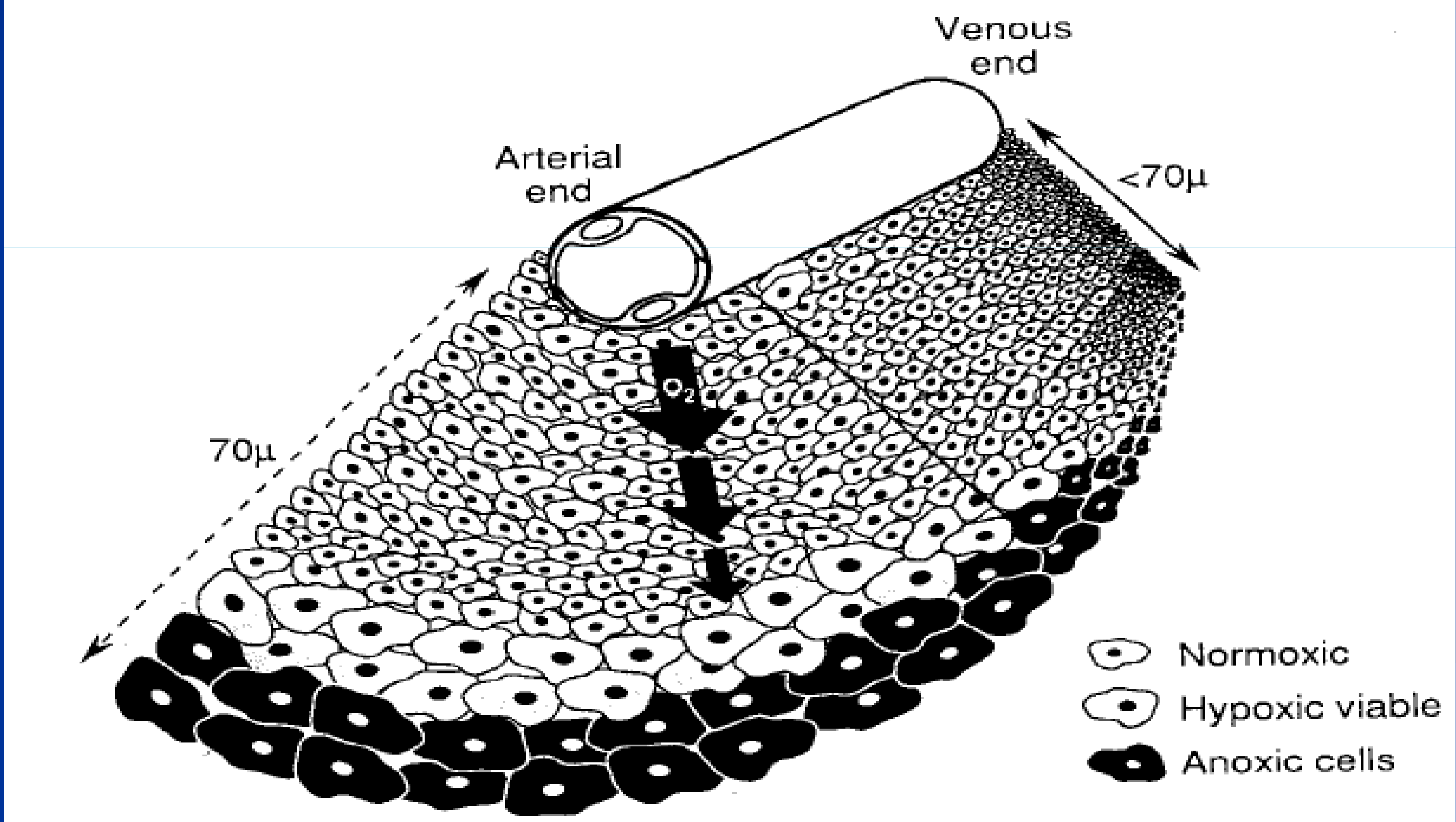




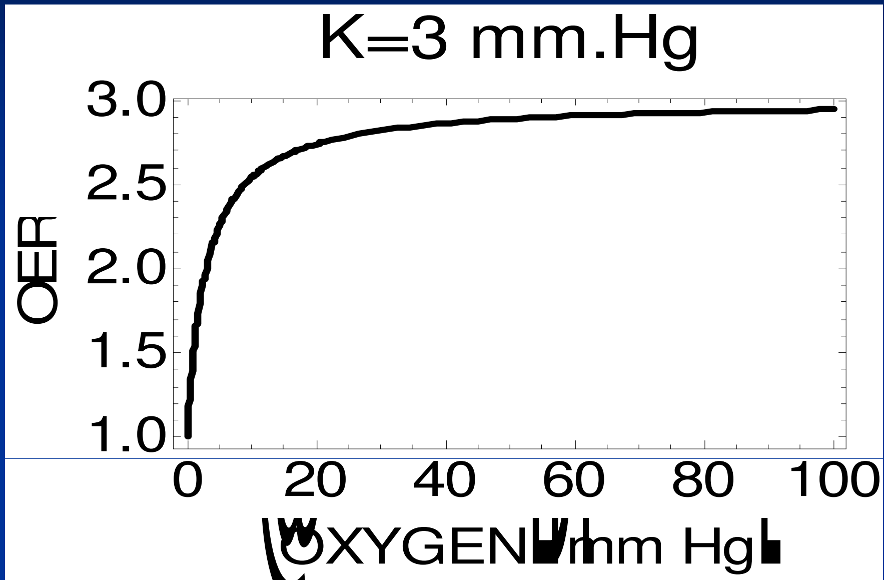
Human renal cells T1, ● hypoxia, ❍ normoxia;

from Broerse & Barendsen, IJRB, 13:559, 1967

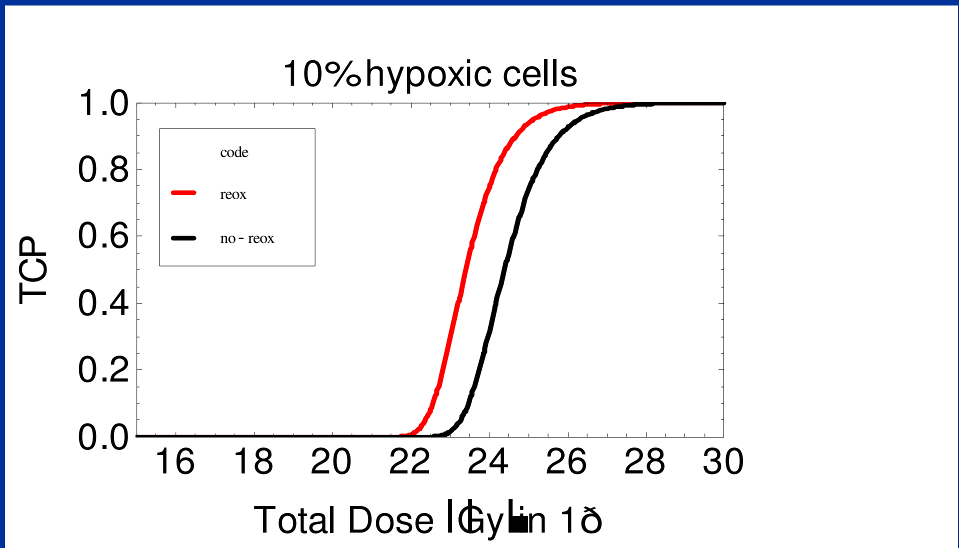
Diffusion of O_2 from a capillary: data shows maximum diffusion distance of ~70μm in mice, longer distances in humans probably due to lower metabolic rate & oxygen extraction. Note 3-D aspect to diffusion distance along a blood vessel



Oxygen deletion in rapid spot scanning?

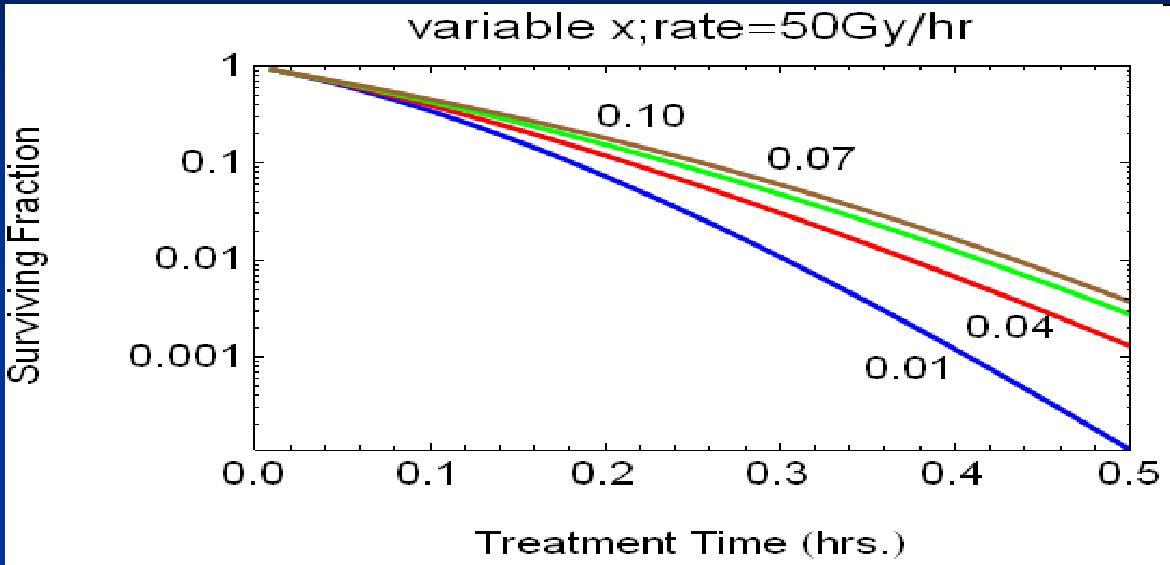


$$OER = \frac{r_{MAX} \cdot p0_2 + K}{p0_2 + K}$$



Very high dose rates: if ionic reactions deplete oxygen, need time for re-diffusion between successive spots to same region of tumour

What if : very high dose rate depletes local oxygen faster than its replacement by diffusion?

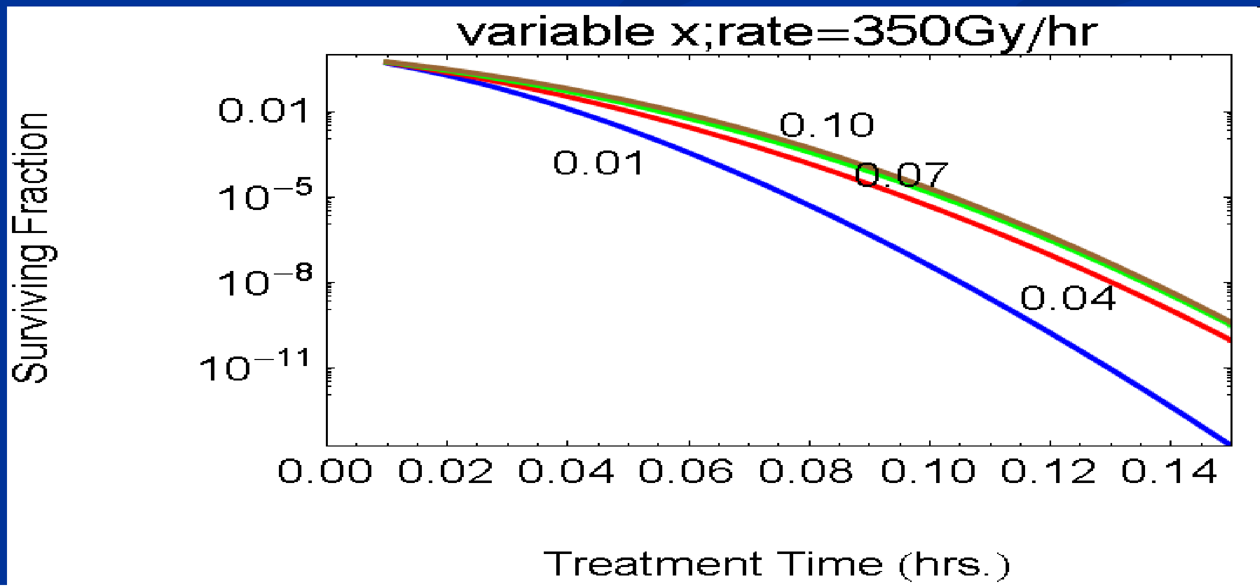


Assumption:

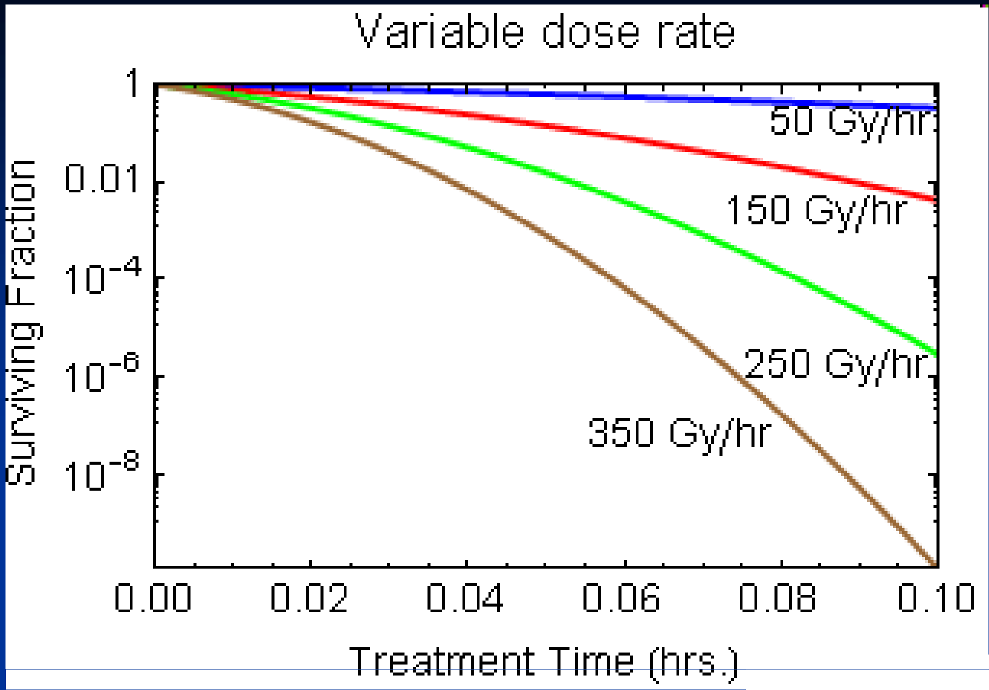
Oxygen depletion related to Exp[- x. dose]

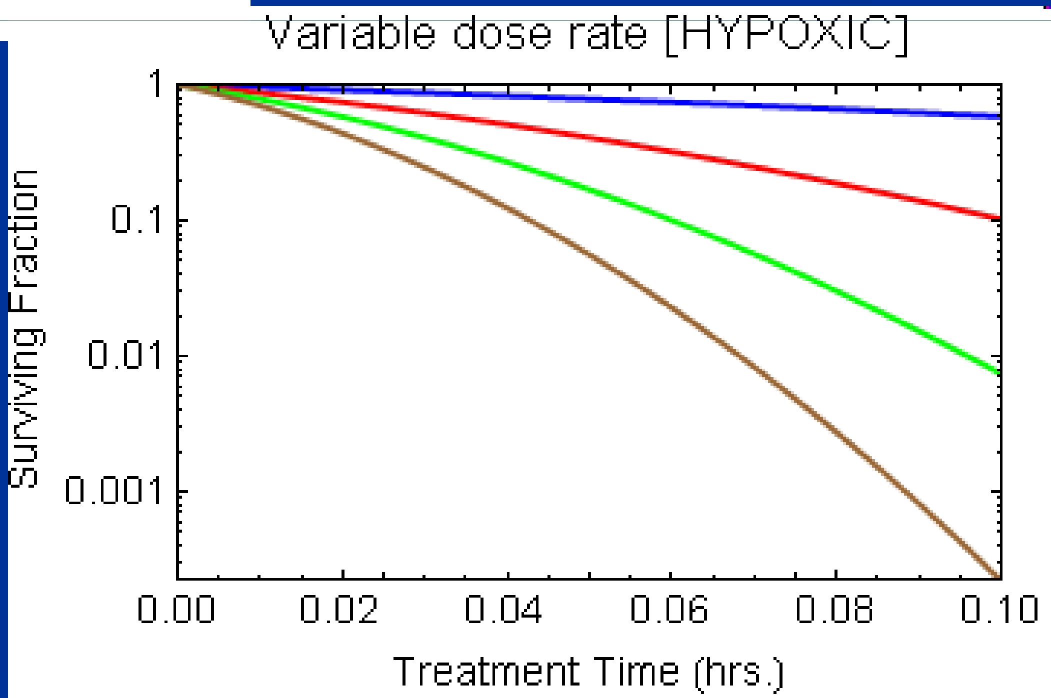
where

dose =rate×time

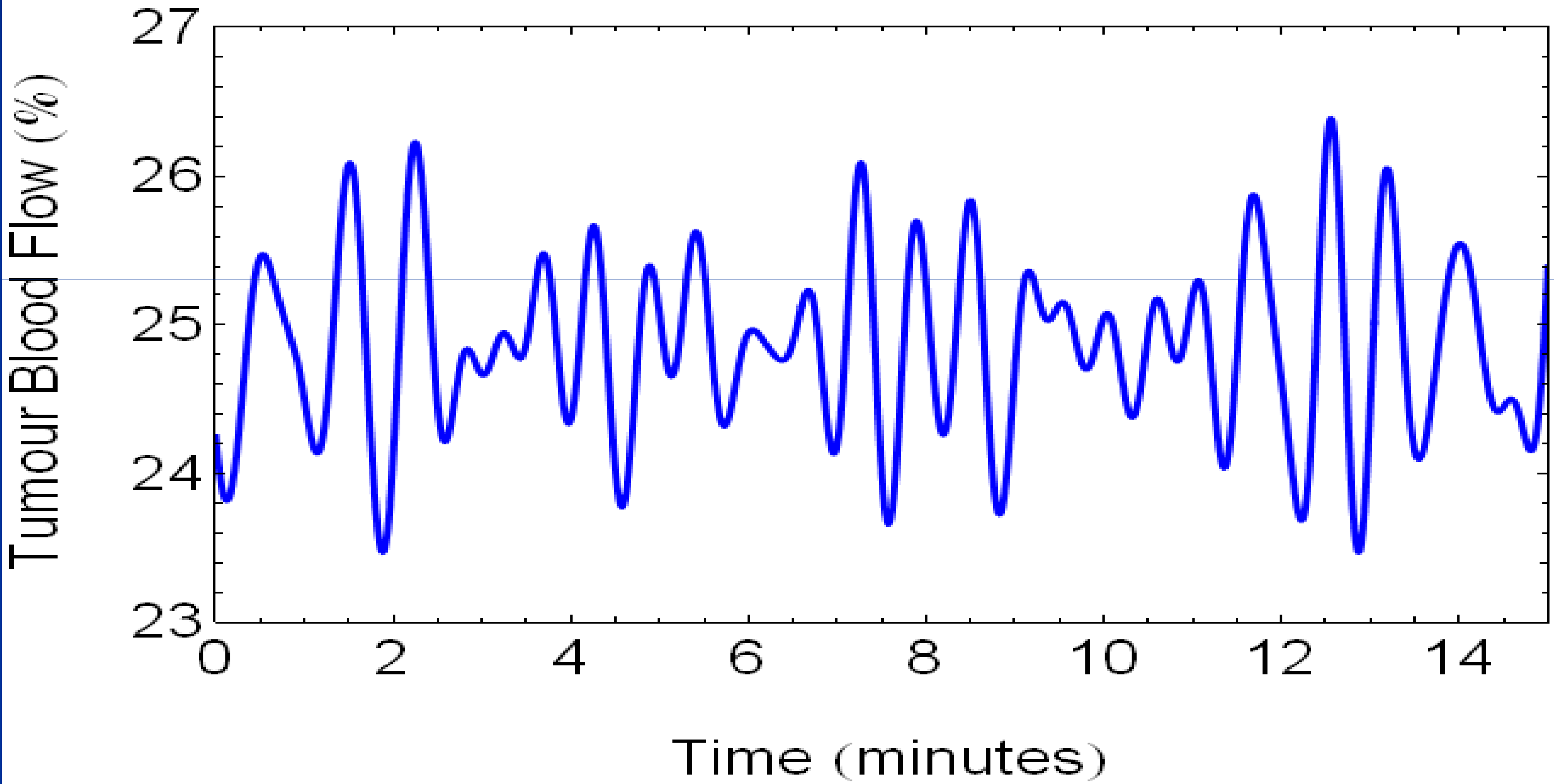


Interaction of dose rate and hypoxia

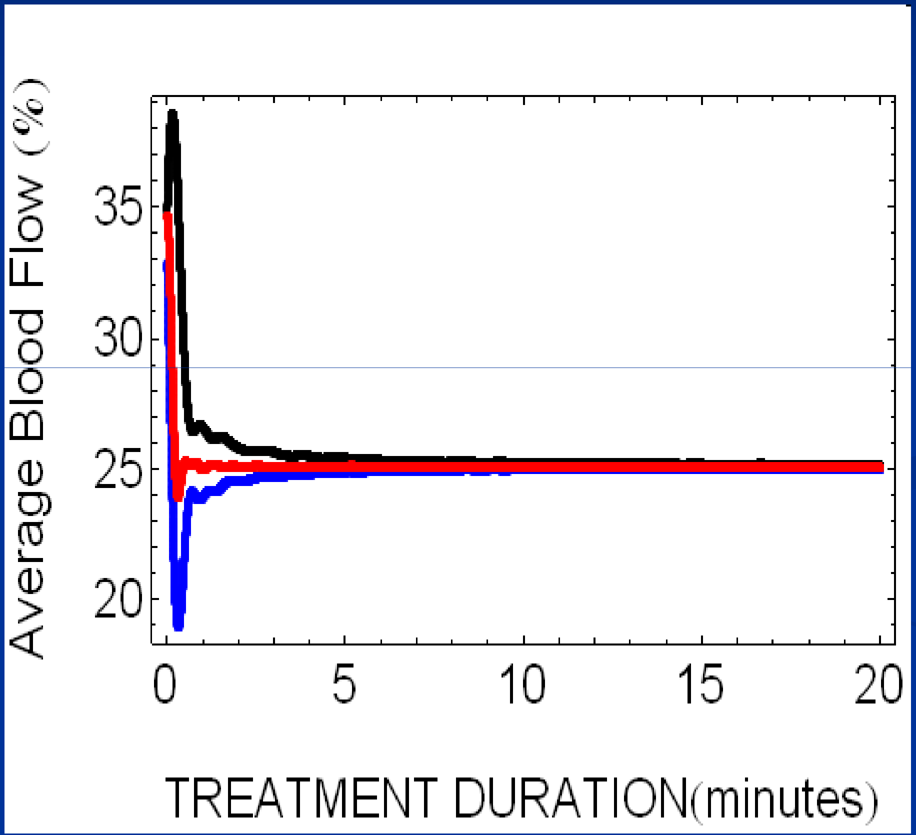




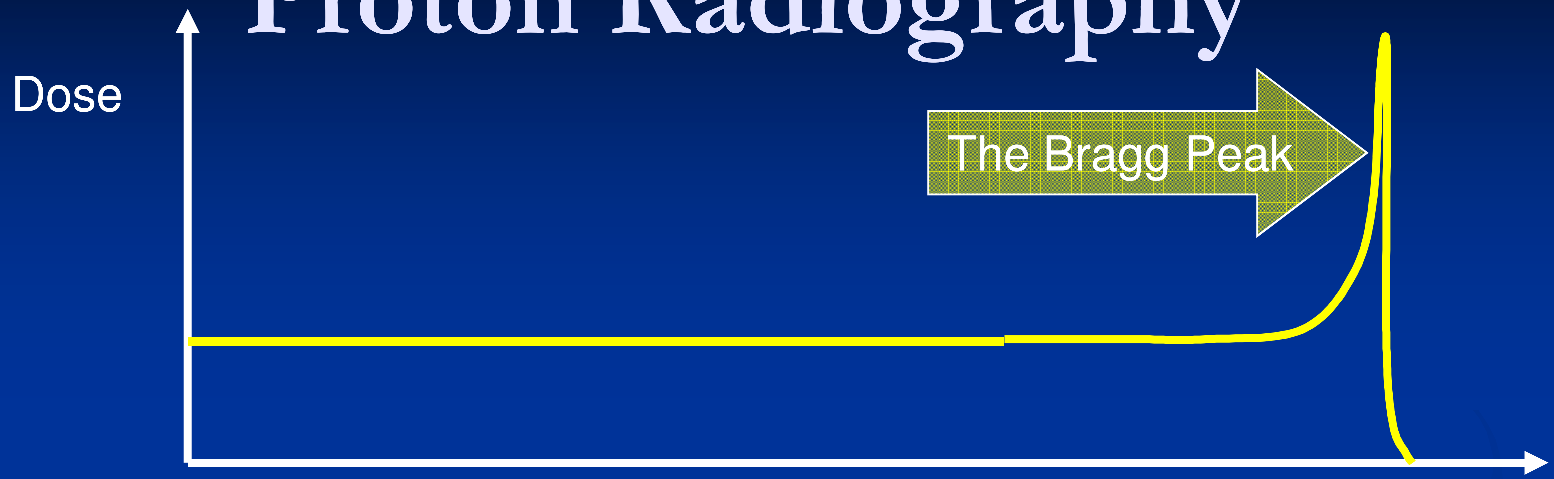
Simulated tumour blood flow fluctuations



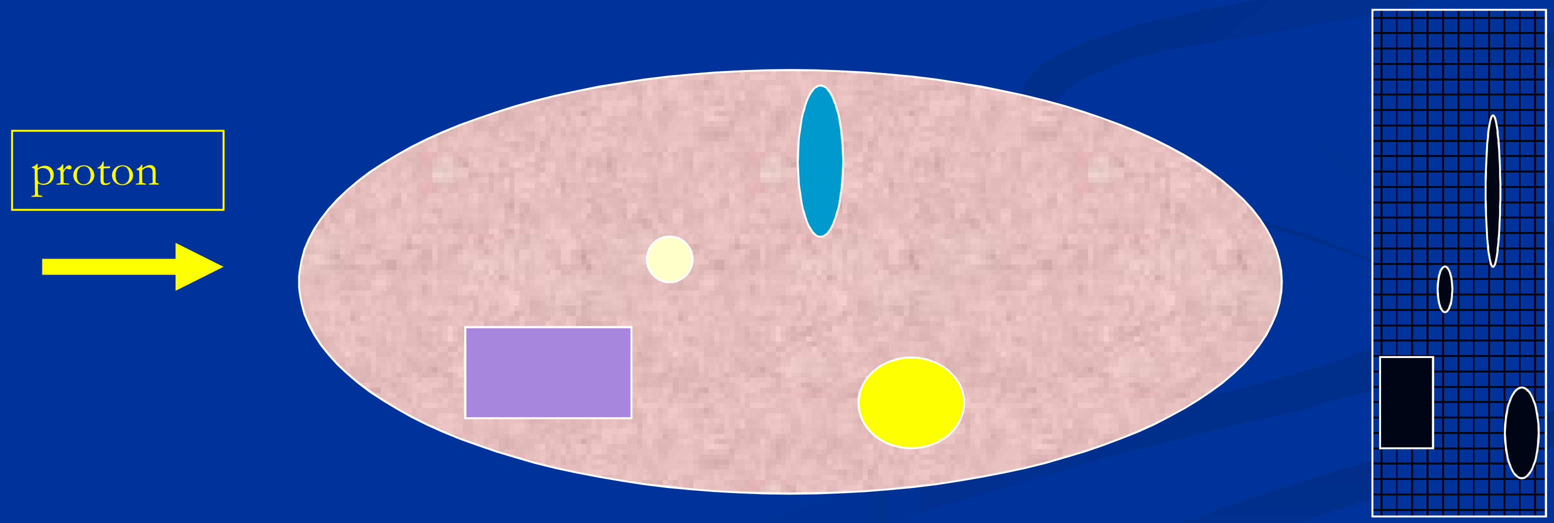
What if treatment is too short?



Proton Radiography



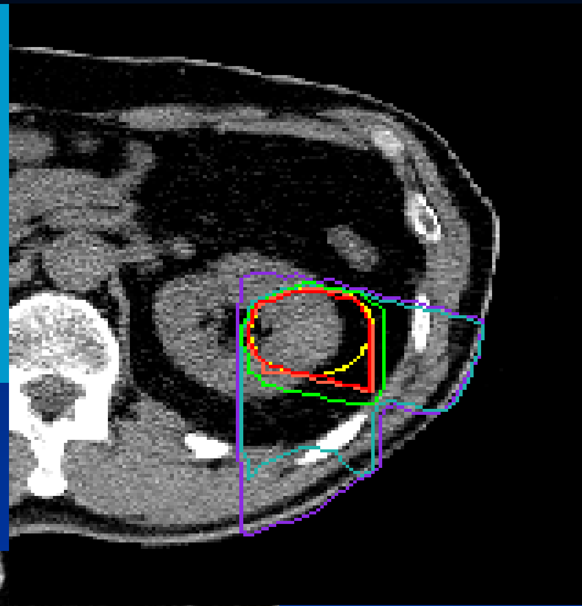
Parallel beam, reduced scatter

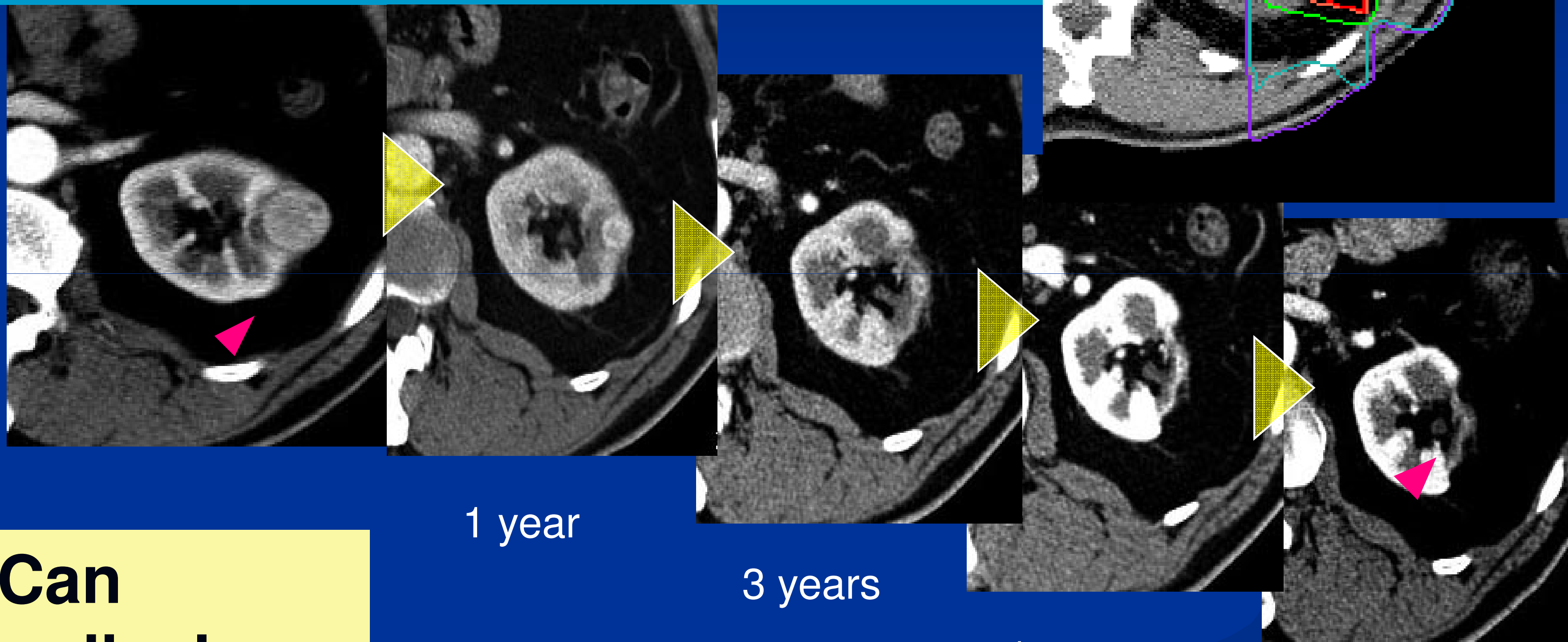


European ion beam centres

- Heidelberg, Vienna, Marburg, Pavia, Kiel, Lyon + Caen
- Some are going ahead without carbon ion gantries…but will have proton gantry rooms (cheaper)
- For some indications there will be little difference when looking at dose distributions only

Kidney Cancer : Stage I, TIa N0 M0 National Institute of Radiological Sciences, Chiba, Japan carbon ions, 80GyE / 16fr. /4wks





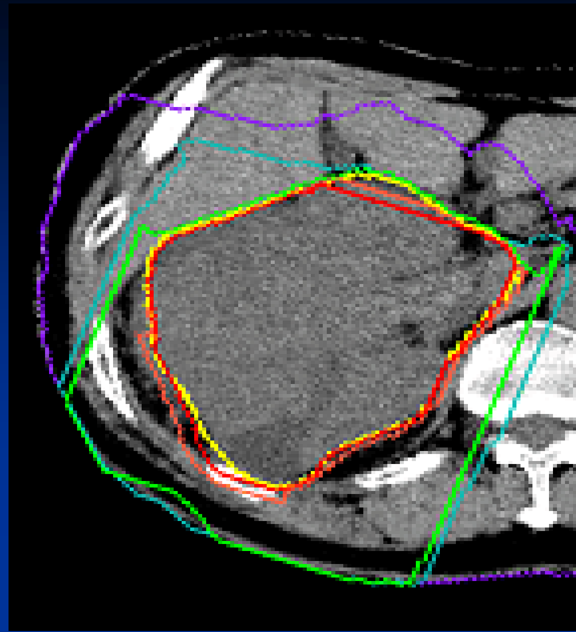
Can radical surgery be avoided?

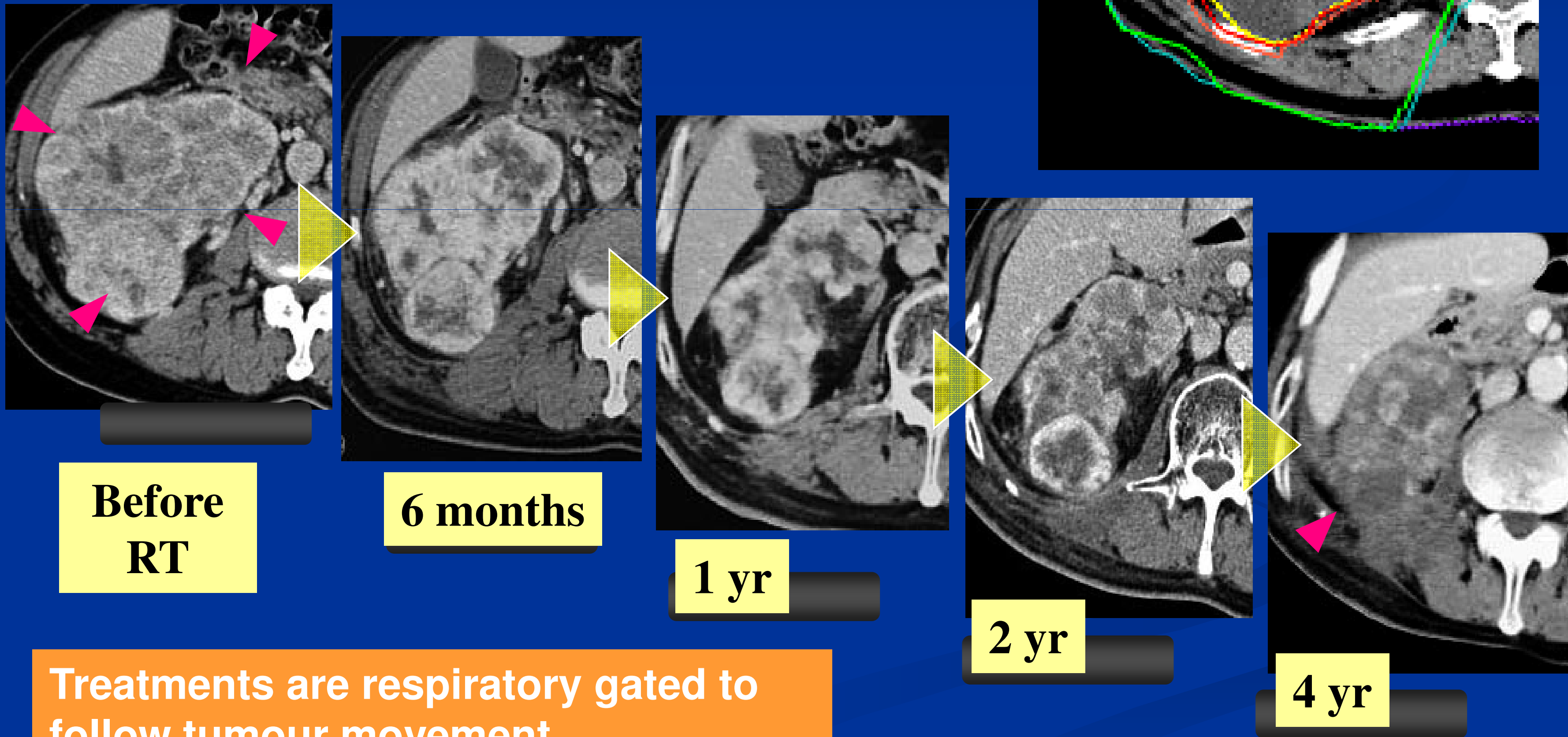
Better cancer screening might create extra need to use physics solutions

Case 6

Stage IV: T4 N0 M0

72GyE / 16fr. /4wks



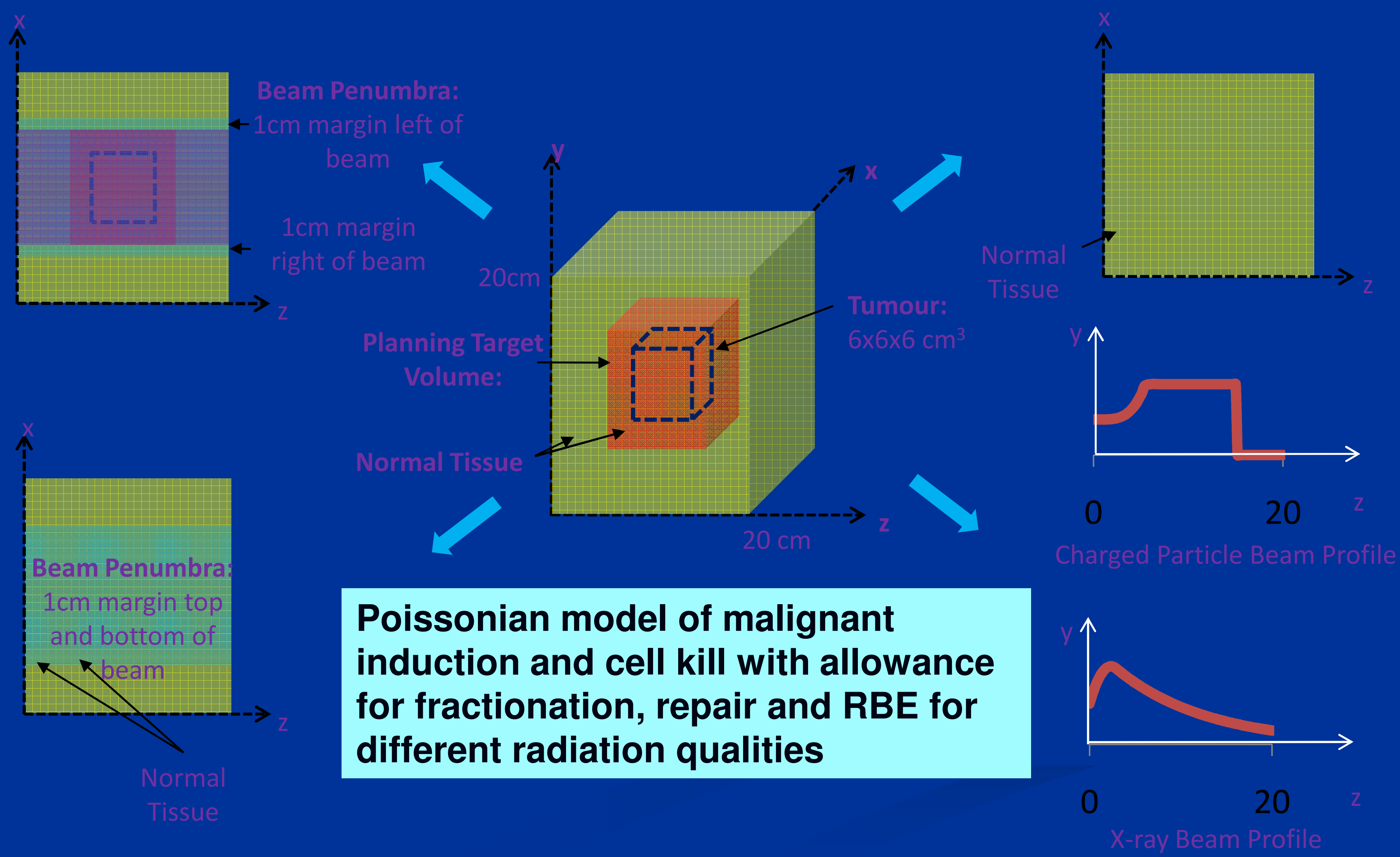


Treatments are respiratory gated to follow tumour movement

Gantries

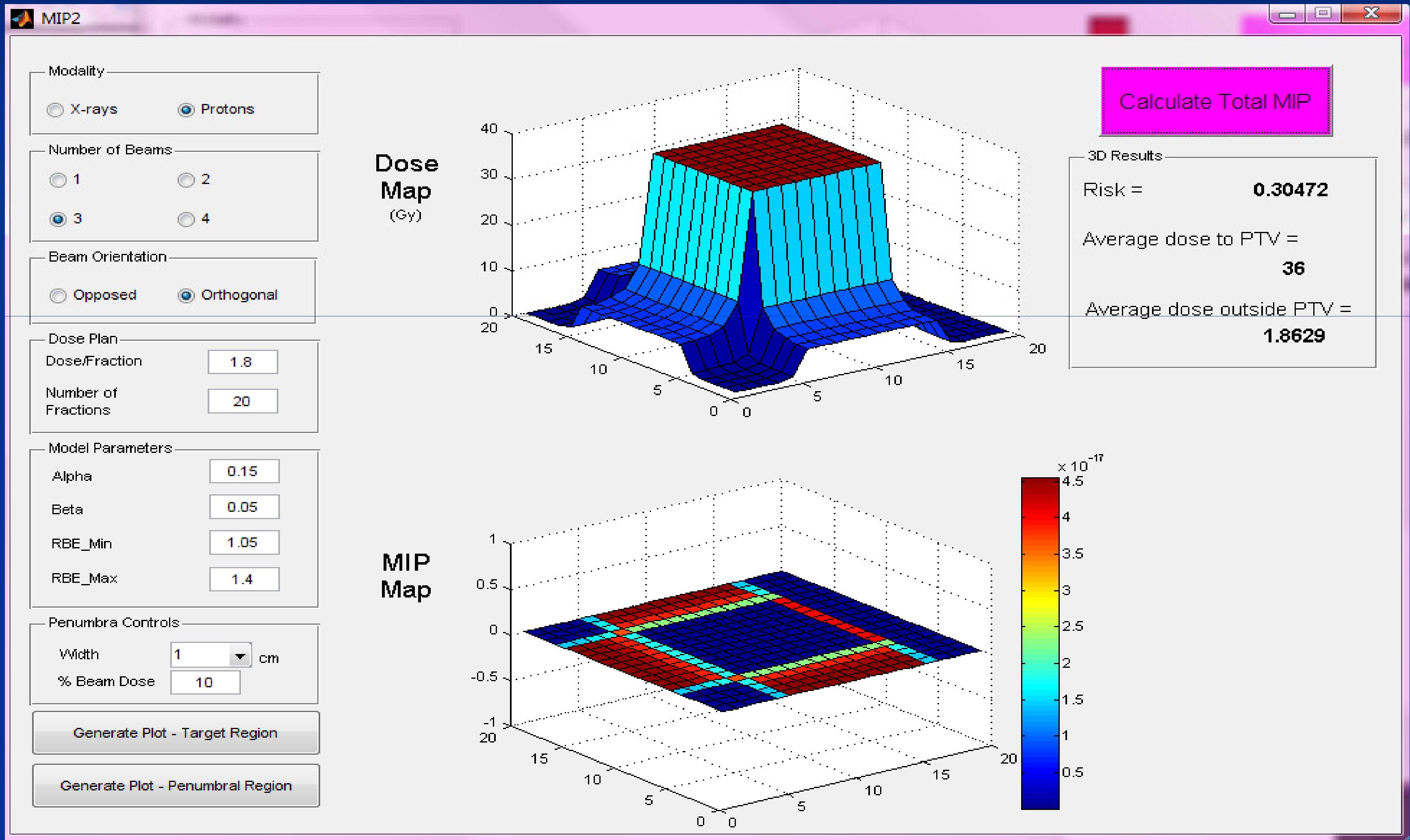
- ? Better malignant induction probabilities (MIP) in treatment planning.
- Because high LET particles are more carcinogenic per cell, so minimise beam tissue-traversion distances to reduce numbers of cells at risk.

3D Geometry

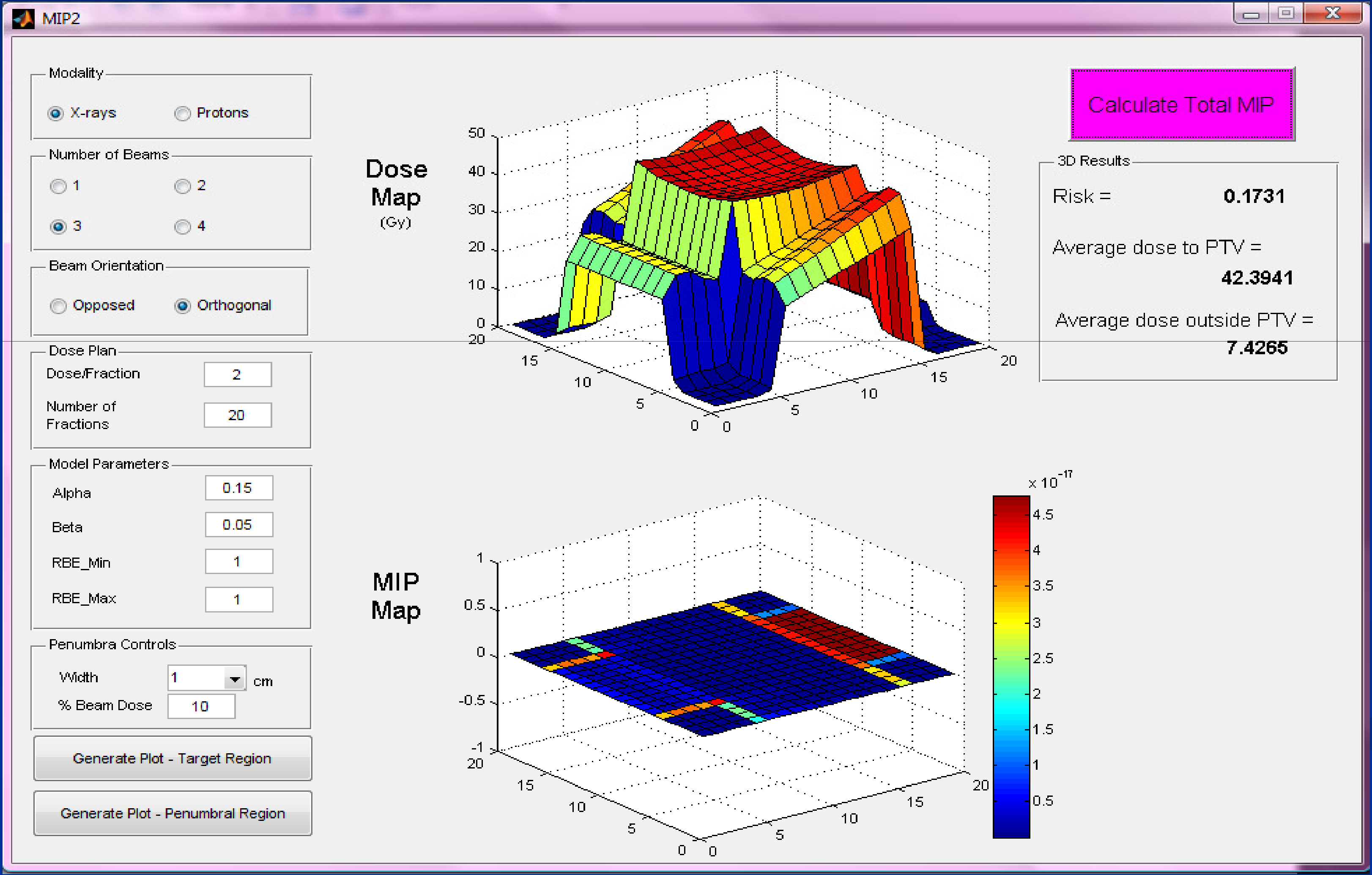


Poissonian model of malignant induction and cell kill with allowance for fractionation, repair and RBE for different radiation qualities

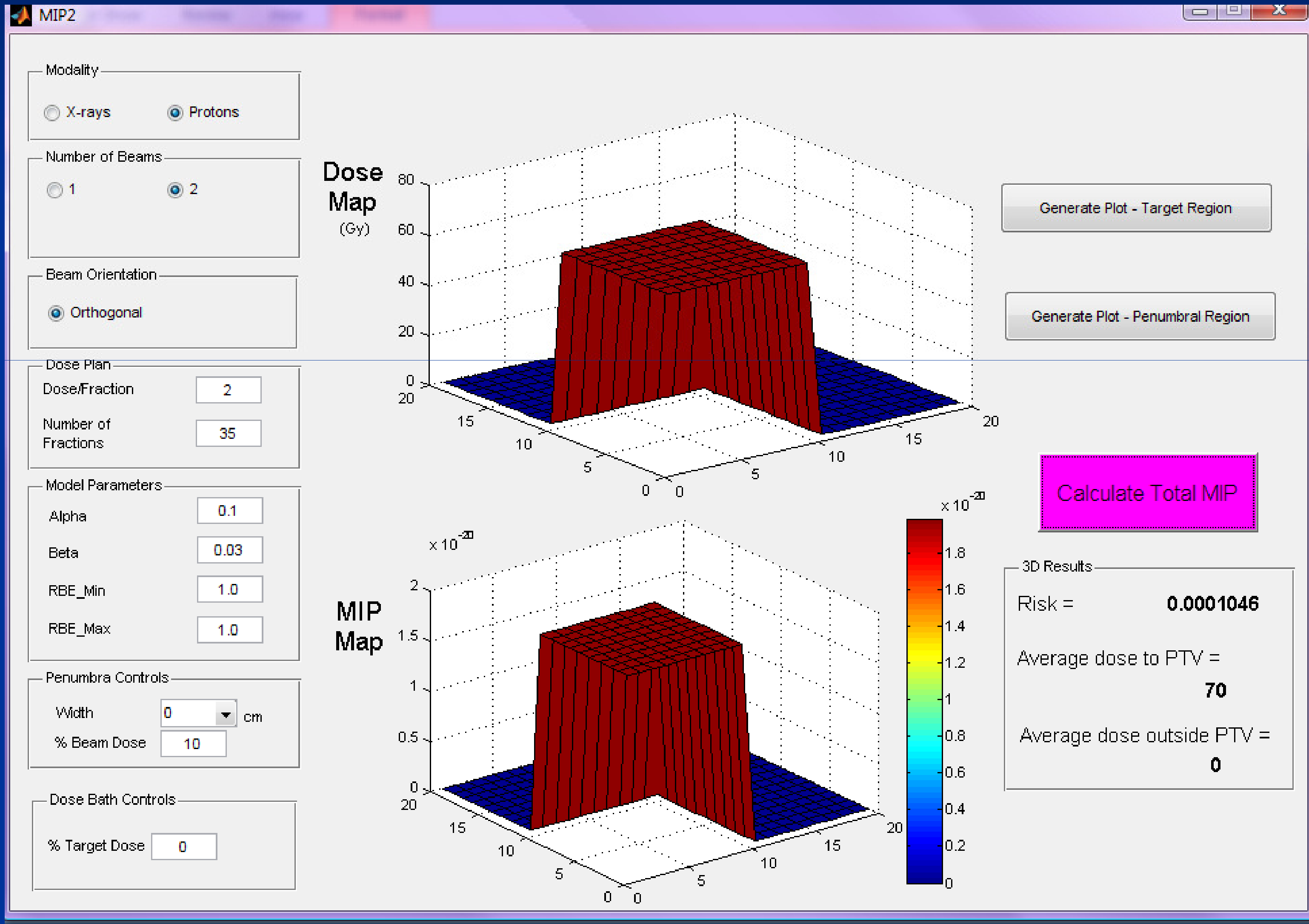
MIP mapping tool: graphical user interface - Protons



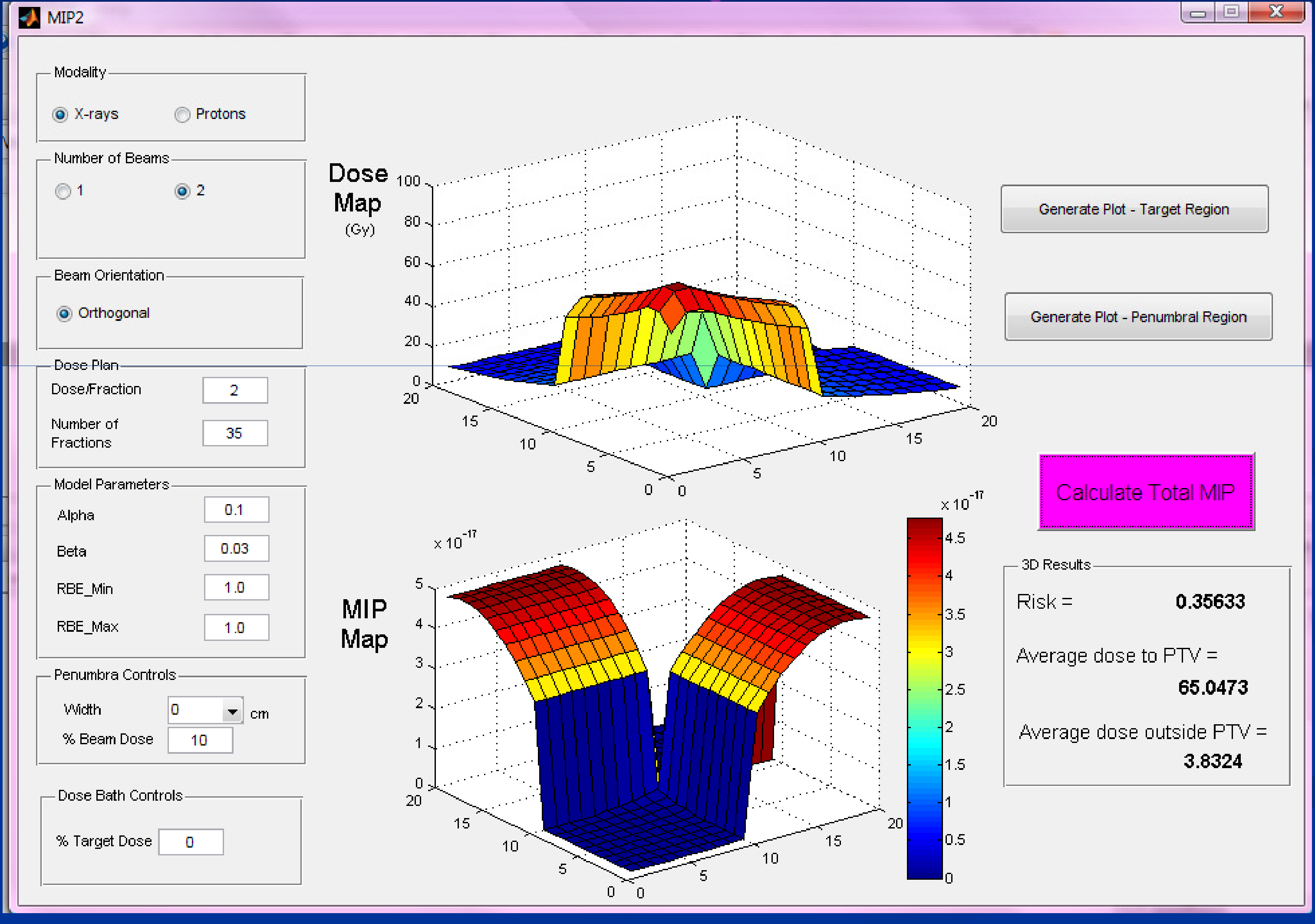
MIP mapping tool: graphical user interface – X-rays

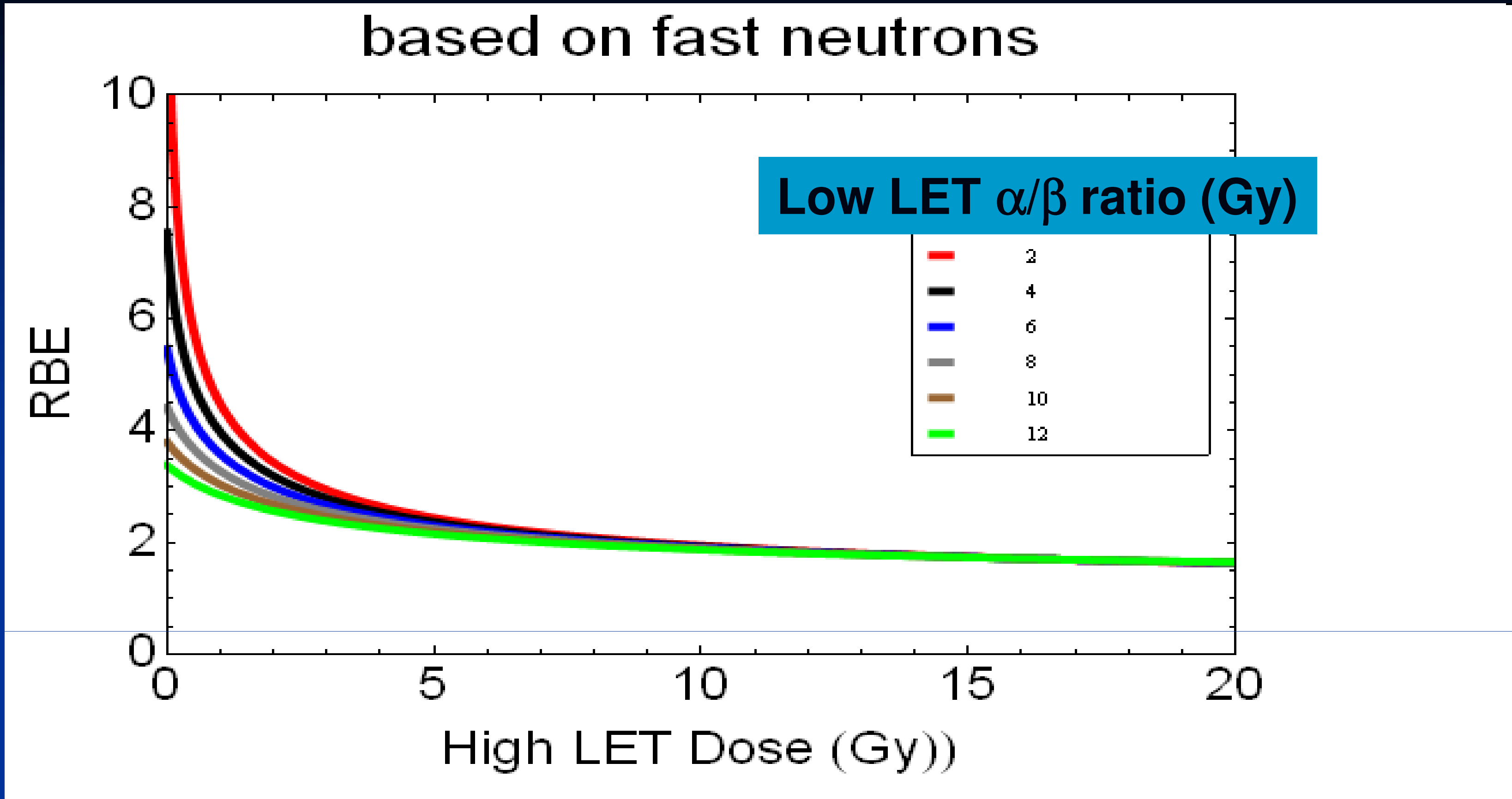


Moving the PTV to the corner – Protons



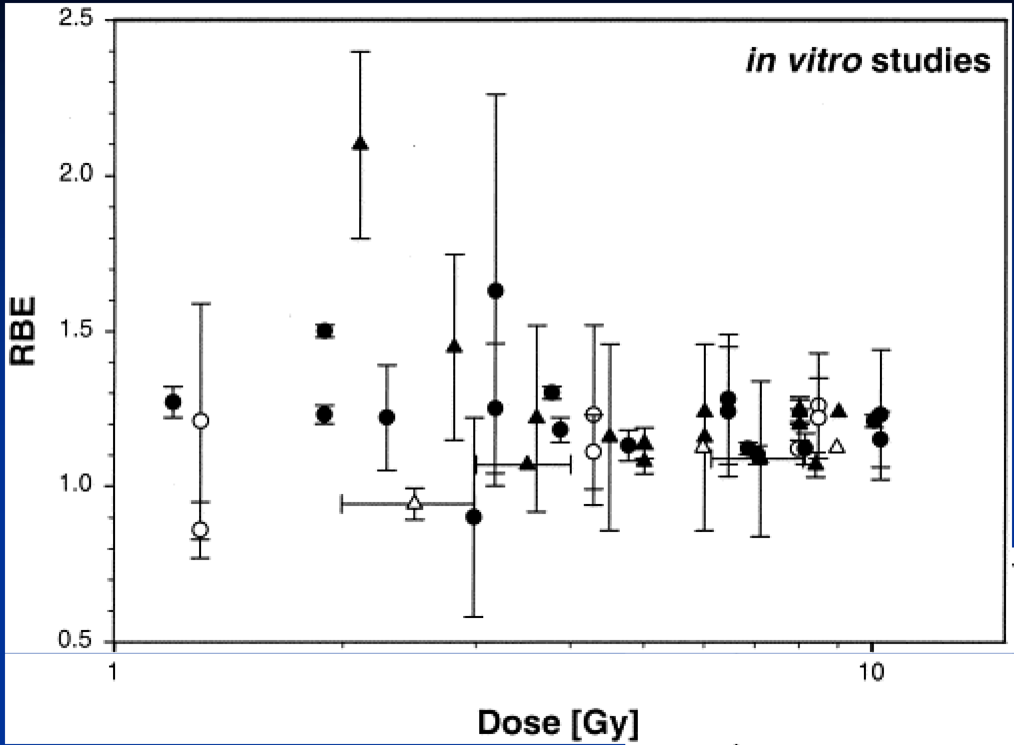
Moving the PTV to the corner – X-rays





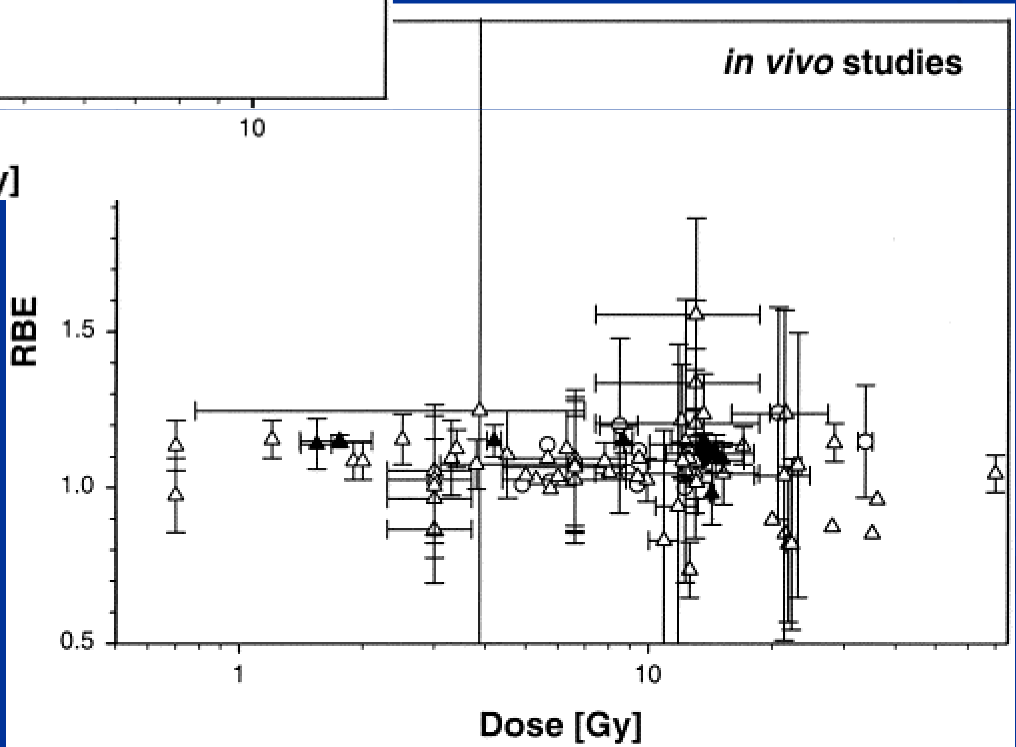
RBE variation mainly found at low dose per fraction, with greater range in late-reacting tissues (low α/β ratio).

Note: most high-LET assays done using low α/β ratio endpoints (respond like brown and green lines).



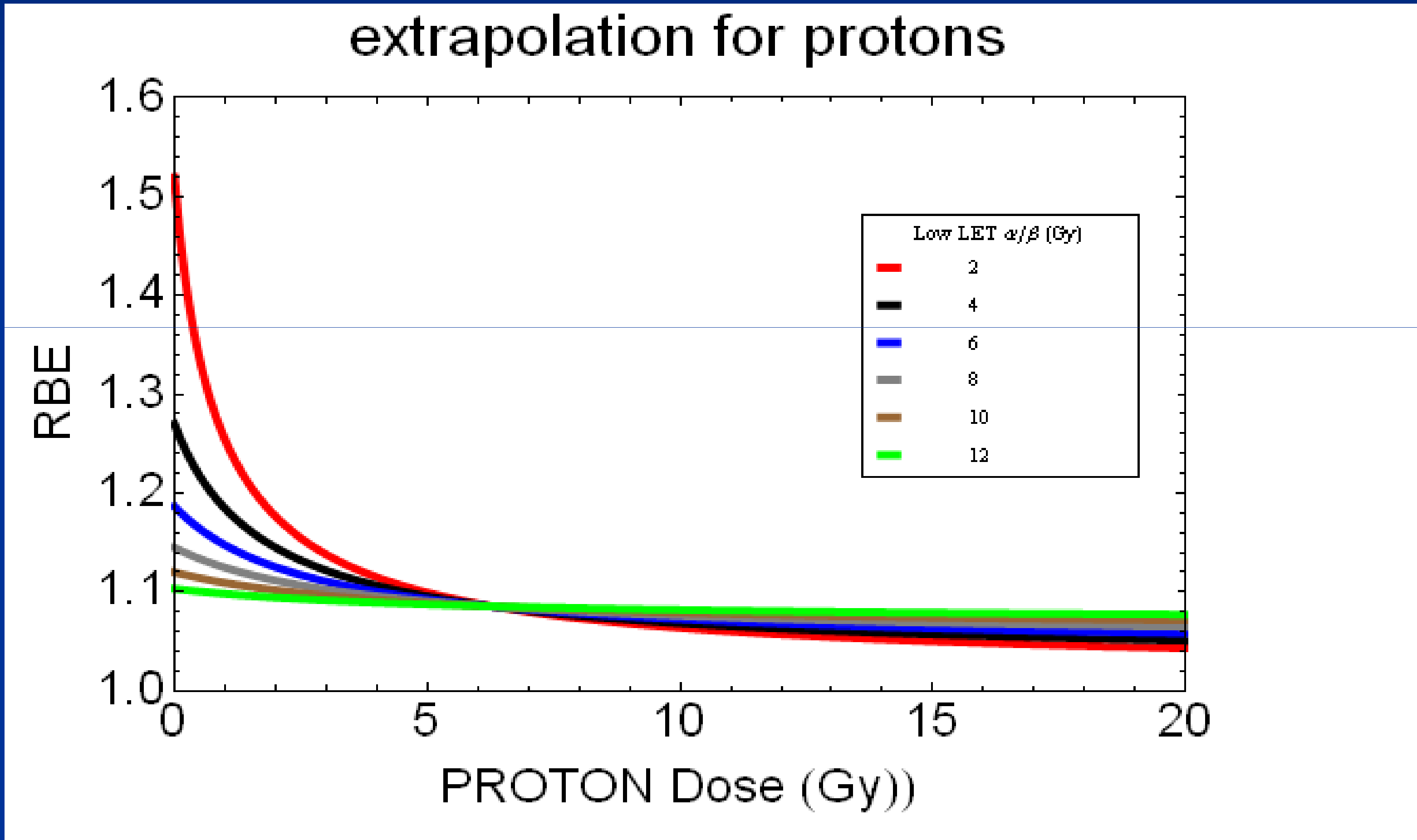
Boston review of proton RBE studies: Paganetti et al IJROBP 2002

In vitro shows trend to higher RBE at low dose



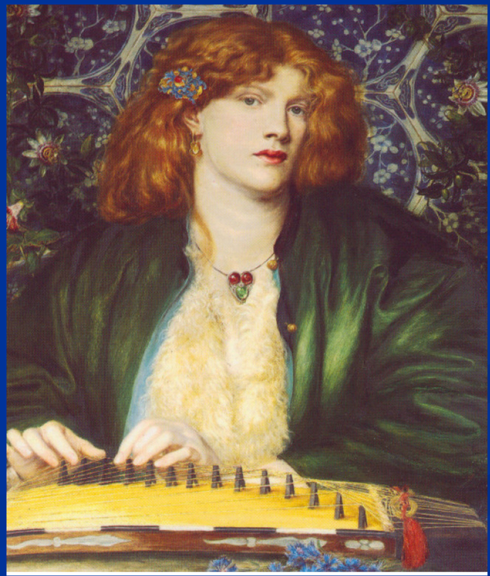
In vivo and *in vitro* results are consistent with high α/β ratio endpoints

Current hypothesis…scaled down for protons… USA results compatible with green & brown curves; there is a danger that CNS RBE may be 1.2-1.3 at 1 Gy per fraction



Expected and achievable benefits

- Reduced fear
- Reduced side effects
- Improved patient experience
- Better quality of life
- More cost effective



Problems that remain to be solved:-

- RBE is uncertain…differences between tissues
- Bragg peak Range uncertainties
- Particles less ‘forgiving’ for mobile cancers *cf* x-rays
- Physician might use smaller and ‘inadequate’ PTV
- Malignant induction may ↑ due to ↑ RBE & <u>lower doses</u> in normal tissues if many particle beams used.
- Skin dose higher (cosmesis) for superficial cancers
- Optimal fractionation?
- Which particle is best for what and where?

Large Research Portfolio

- Cancer Surgery, Imaging, Pathology
- Patient Selection
- Adjuvant therapies…standard + novel
- Academic + Medical physics
- Radiotherapy & Radiography
- Radiation Biology
- Outcomes & Health Economics
- Industry

Summary

- Lasers can offer new solutions to radiation cancer therapy

Several areas to develop:-

- Reproducibility of accurate dose deposition.
- Shapes, dimensions of dose deposition
- 360 degrees access, tilting of target, gantry housing.
- Dose rates, re-painting