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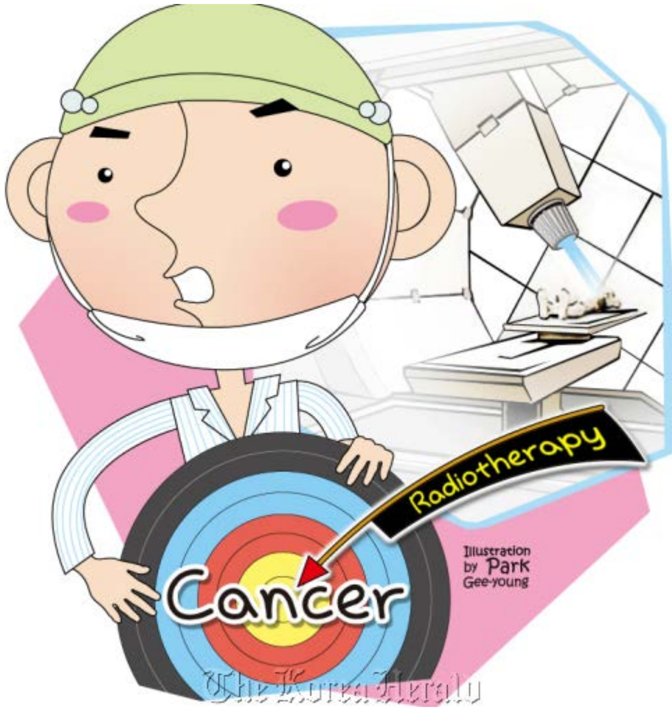
Medical Therapy (Synchrotron Radiotherapy)

Jayde Livingstone – IMBL Scientist

What is radiotherapy?

- Radiotherapy uses radiation, such as x-rays, γ-rays, electrons, protons and other charged particles to treat a disease or medical condition
- Radiotherapy is most commonly used for the treatment of cancer
- About half of all cancer patients will receive some form of radiotherapy during their treatment

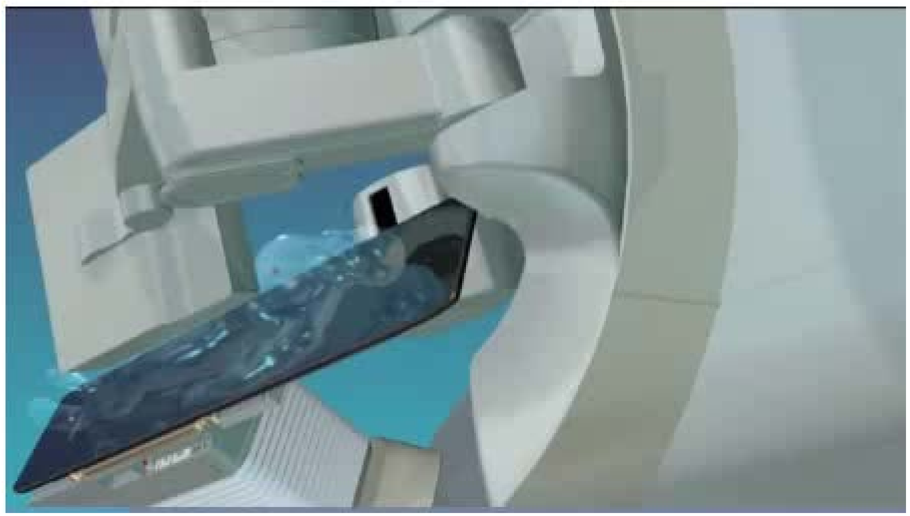


How is the treatment delivered?

- External beam photon radiotherapy is most common
- Radiotherapy is delivered using a medical linac (linear accelerator)
- Electrons are accelerated into a metal target, creating Bremsstrahlung radiation


www.varian.com

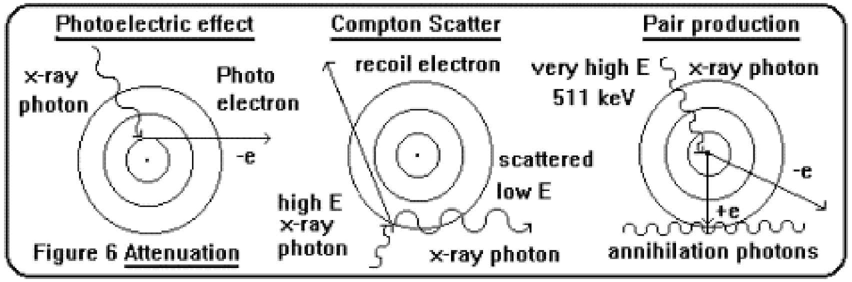
How is the treatment delivered?



www.varian.com

What happens to radiation in the body?

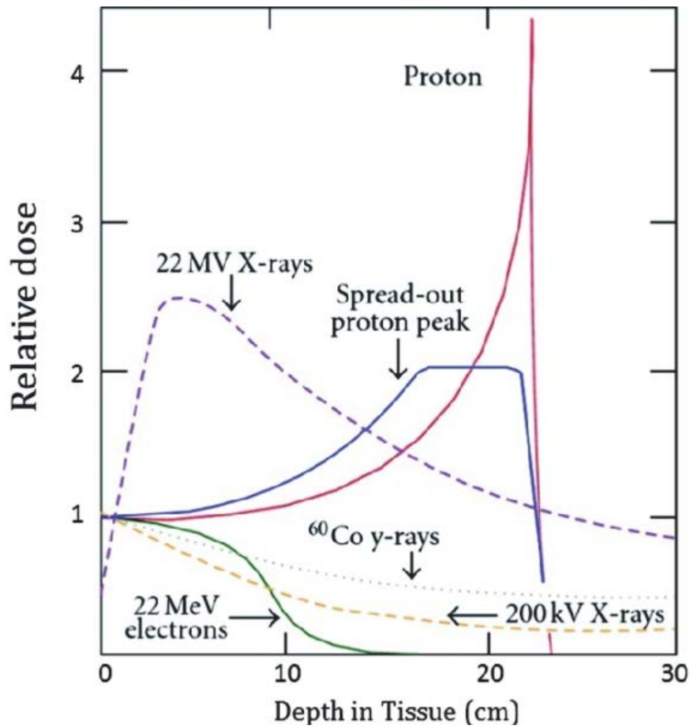
- Radiation loses energy as it travels through matter
- Eg., for photons, the main interactions which result in a transfer of energy to matter are:
  - Photoelectric effect
  - Compton scattering
  - Pair production
- Radiation dose is the amount of energy absorbed per unit mass of matter



http://img.chem.ucl.ac.uk

$$Dose\ (Gray) = \frac{Absorbed\ energy\ (J)}{Mass\ (kg)}$$

Where is the energy deposited?

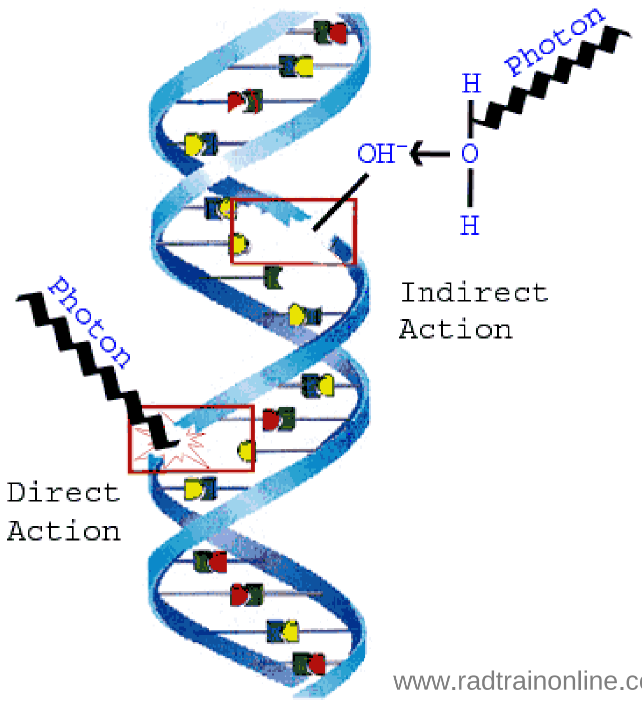


Arjomandy, *J. Proton Therapy*, **1**(1), 2015

- Photons and charged particles have very different dose distributions
- Photons deposit dose everywhere, especially at/near the surface

How does radiotherapy work?

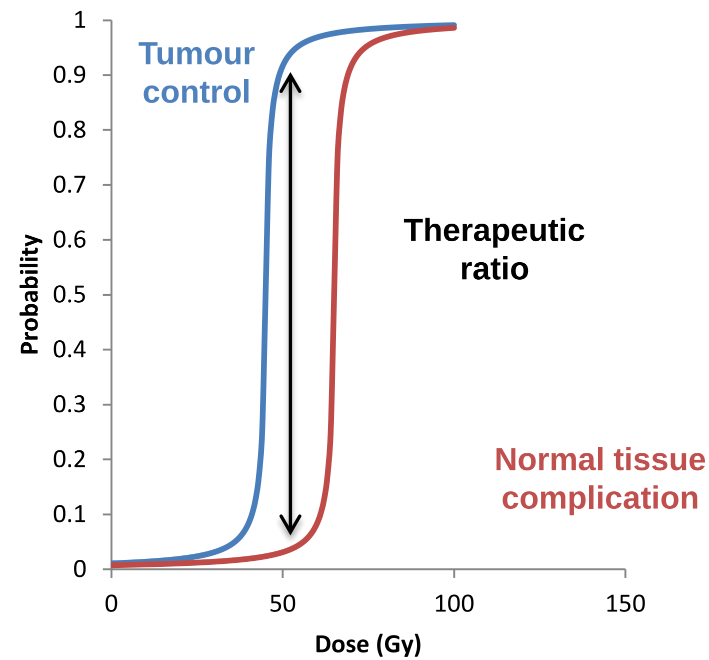
- Ionising radiation causes damage to cells via DNA strand breaks due to:
  - Direct action
  - Indirect action – the hydroxyl radical (OH•) produced by ionisation of water molecules
- Unfortunately radiation doesn't discriminate between healthy and diseased cells!



www.radtrainonline.com

The goal of radiotherapy

- The goal of radiotherapy is of course to kill cancer cells…
- But not at the expense of healthy cells!
- The dose to healthy tissue must remain below a threshold for normal tissue complications



How do we minimise dose to healthy cells?

- Conform the shape of the radiation field to the target
  - Mask (lead or other heavy metal), multi leaf collimators
- Tune the depth of penetration
  - Bolus, compensators, wedges

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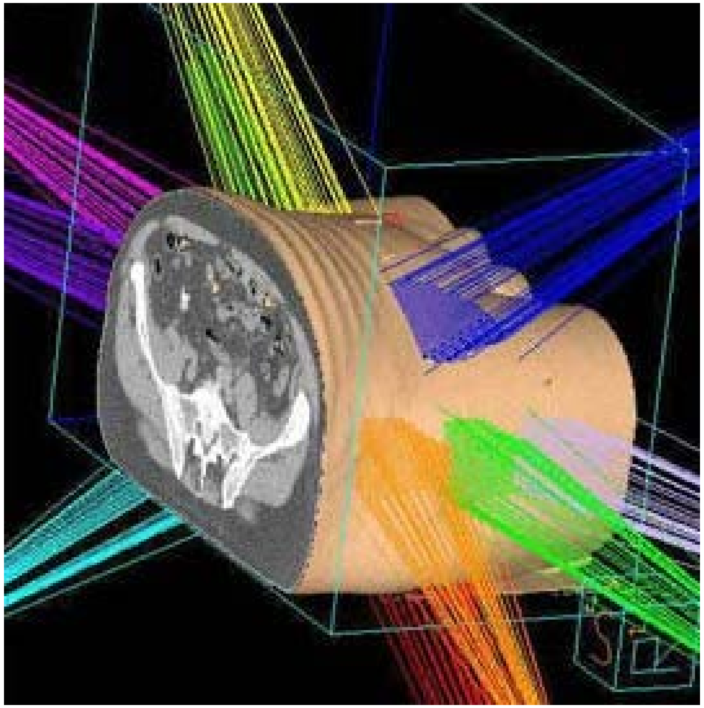

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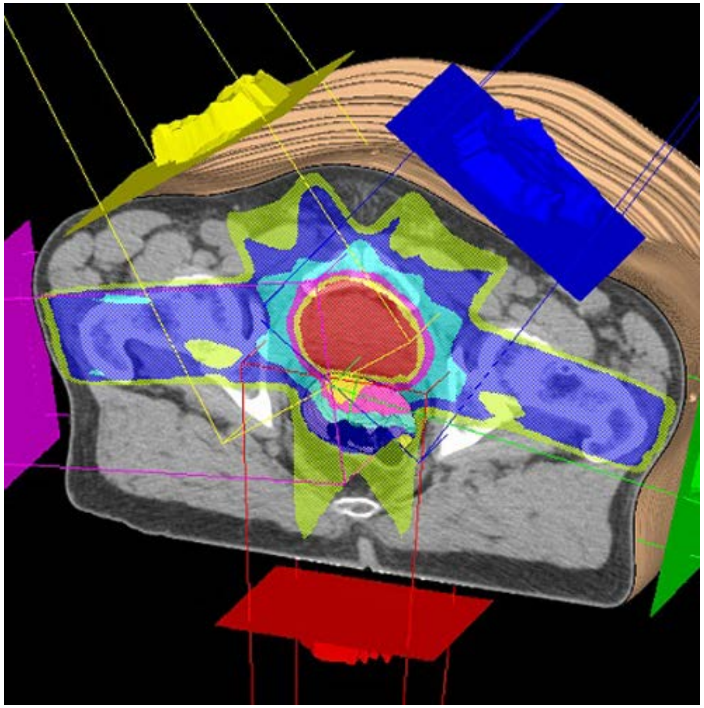

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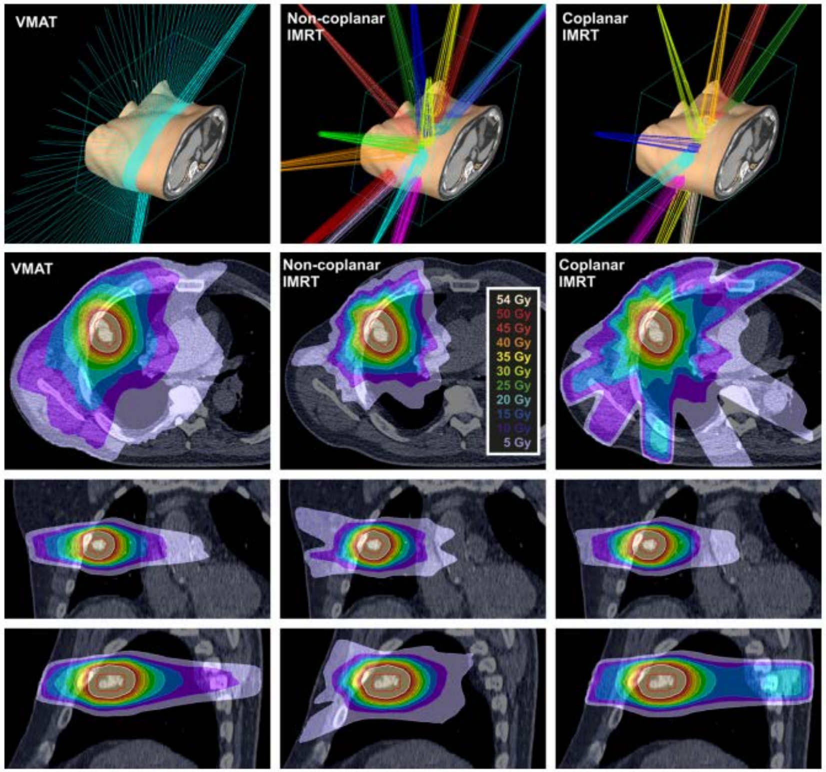

Holt *et al.*, *Int. J. Radiation Oncology Biol. Phys.*, **81**(5), pp. 1560-1567, 2011

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http://osl.uk.com

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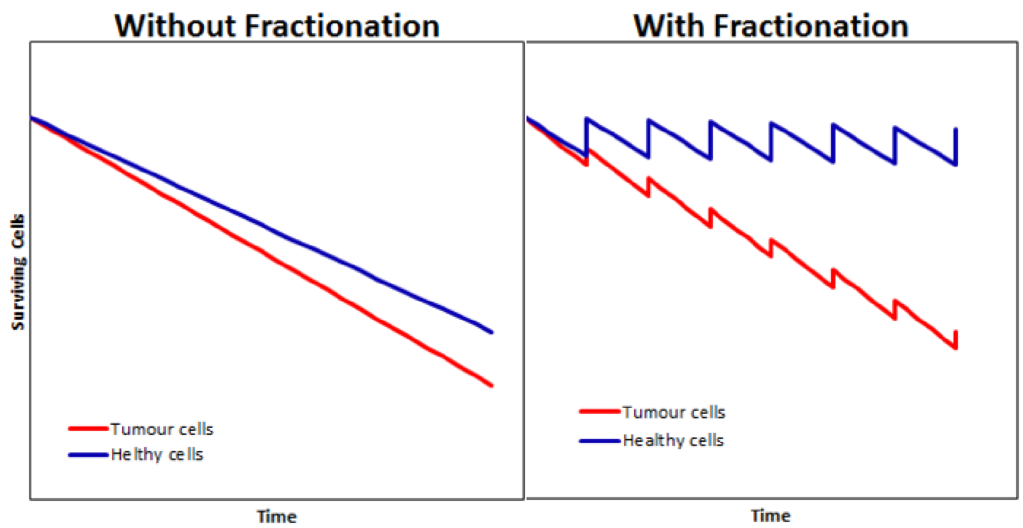
- Patient immobilisation
- Fractionation of the dose
  - Temporal or spatial

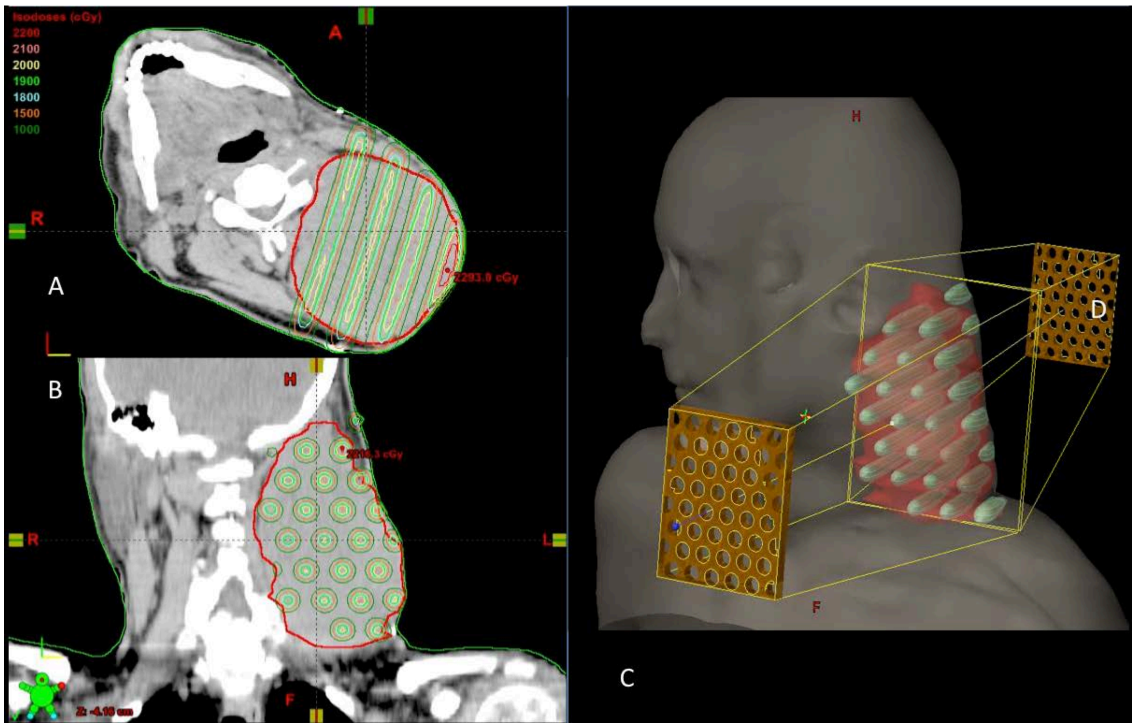
Temporal fractionation: radiobiology

- Temporal fractionation: dividing the treatment into many small doses given daily over a number of weeks
- This increases the therapeutic ratio by:
  - Increasing tumour cell kill
  - Allowing normal cells to repair sublethal damage



http://www.radicalradiationremedy.com

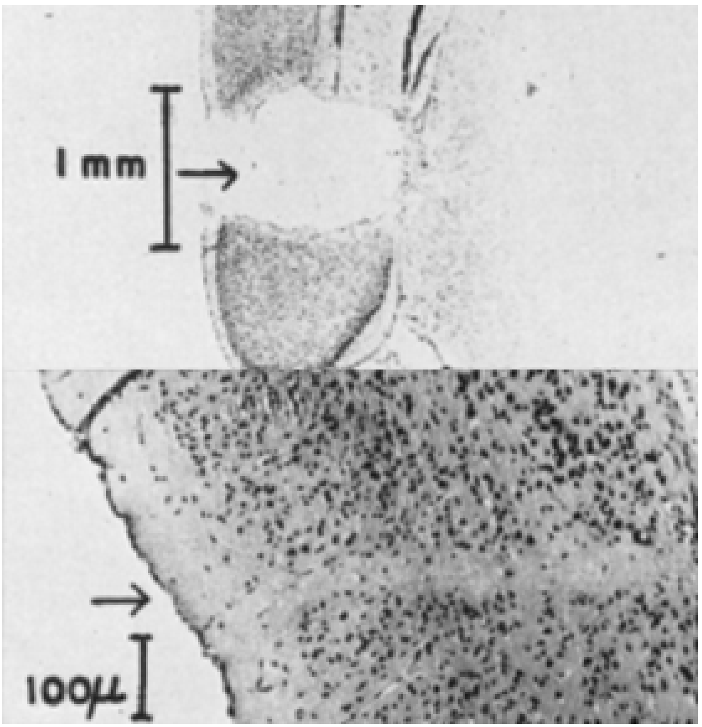
Spatial fractionation: GRID radiotherapy



Mohiuddin *et al.*, *Cureus*, **7**(12), e417

- Uses lead (or other high Z) to collimate beam into smaller beams (~cm)
- Commenced in 1950's
- Demonstration of the **dose-volume effect**

Minimising the beam size = Maximising the dose volume effect



Curtis, H. J., *Radiat. Res., Suppl. 7.*, 1967

- Microbeam tissue sparing effect was observed at Brookhaven National Laboratory in 1960s
- Microbeams (25 µm) of 22 MeV deuterons used to simulate effects of galactic heavy charged particles
- Dose tolerance of mouse normal brain tissue much higher for microbeam than for beam 1 mm wide

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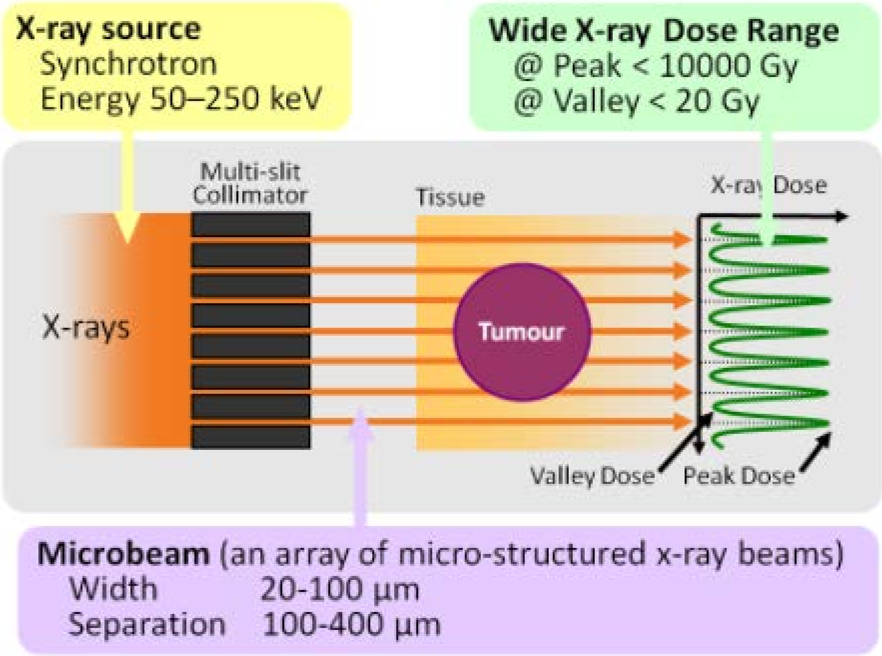
Microbeam radiation therapy (MRT)

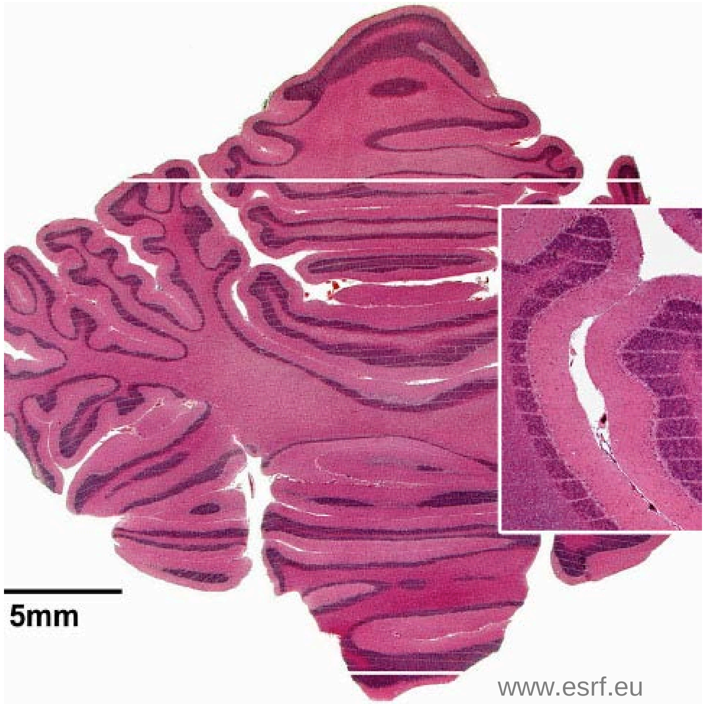
- Third generation synchrotron sources appeared in the 1980's
- MRT research began in the 1990's
- The synchrotron beam is collimated in microbeams using tungsten collimator
- High dose rates (orders of magnitude higher than conventional RT) required to avoid effects from organ movement



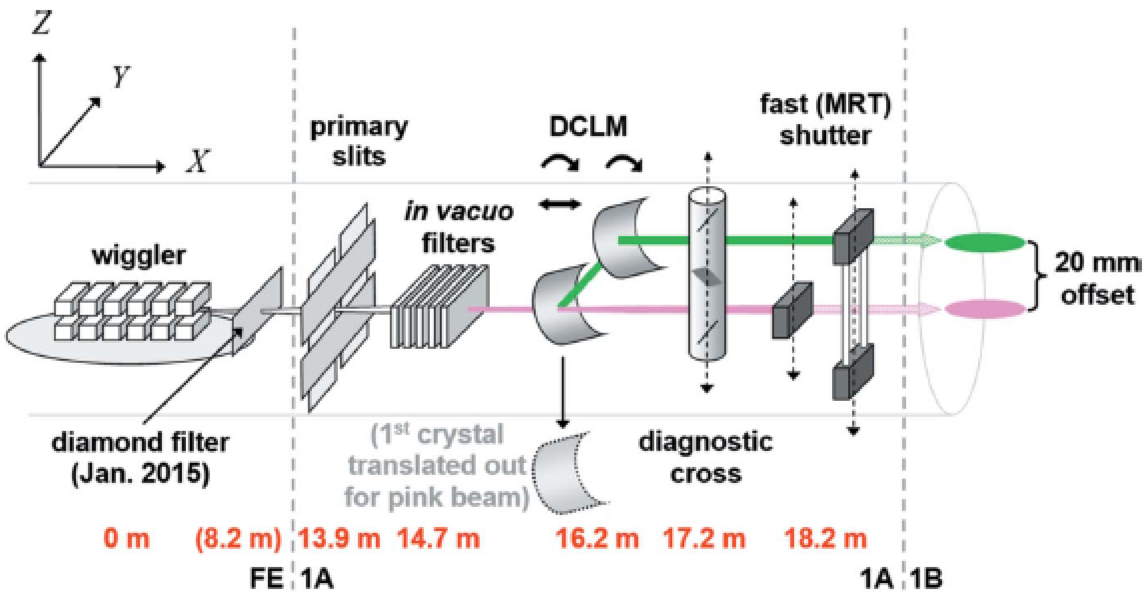
http://mswebs.naist.jp

Microbeam radiation therapy (MRT)

- High dose in beams and very low dose in between
- Currently in preclinical trial stage: mostly small rodents but also pigs
- Results demonstrate tumour control, but also remarkable normal tissue sparing
- Some normal tissues tolerate doses at least an order of magnitude higher than conventional radiotherapy
- There are two synchrotrons with preclinical MRT programs: ESRF and Australian Synchrotron



How is MRT delivered?



Stevenson, *et al.*, *J. Synchrotron Rad.*, **24.**, 2017.

- MRT uses pink beam (filtered white/polychromatic beam) with average energy of 100 keV

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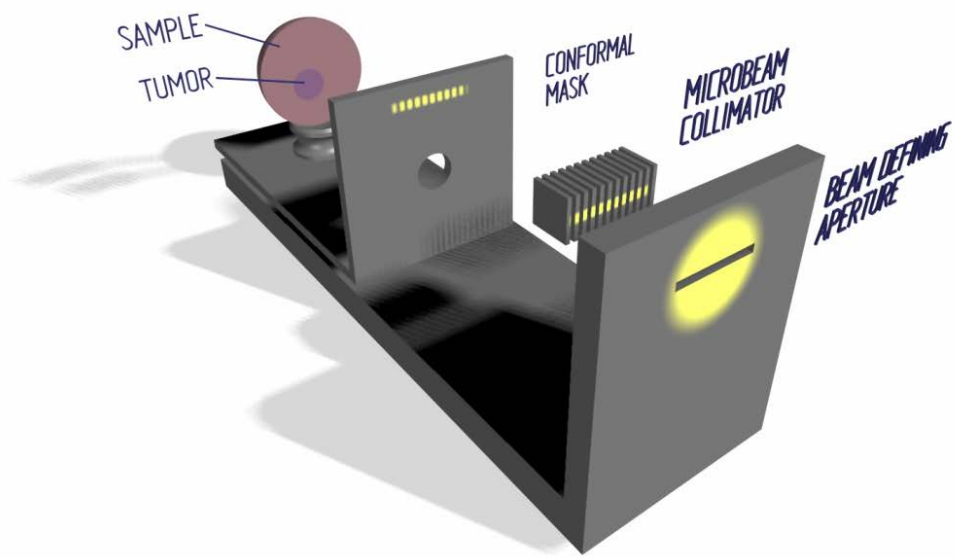
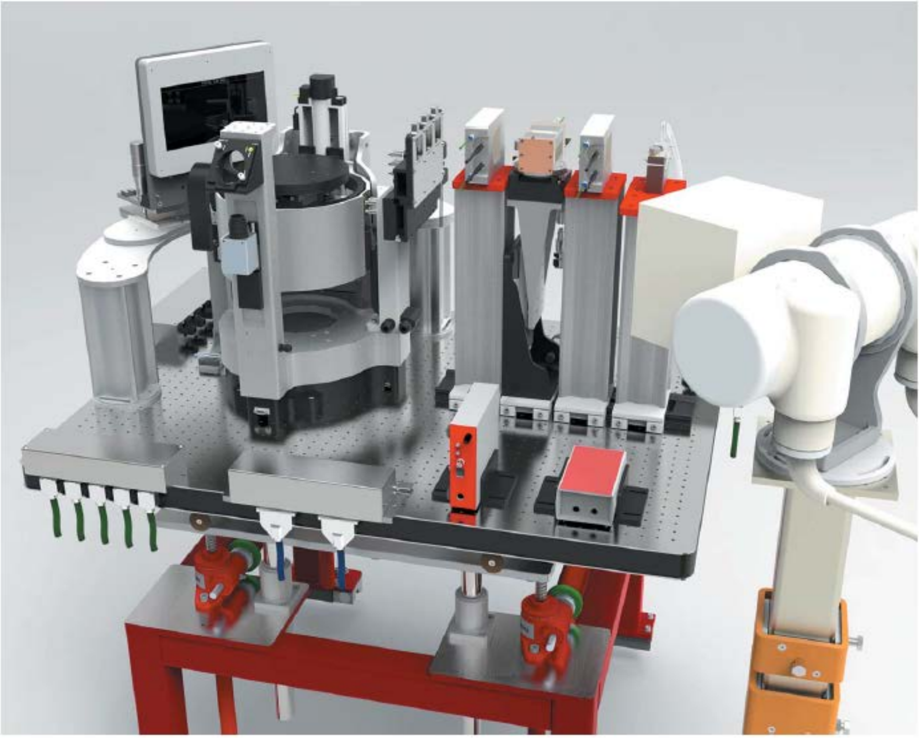


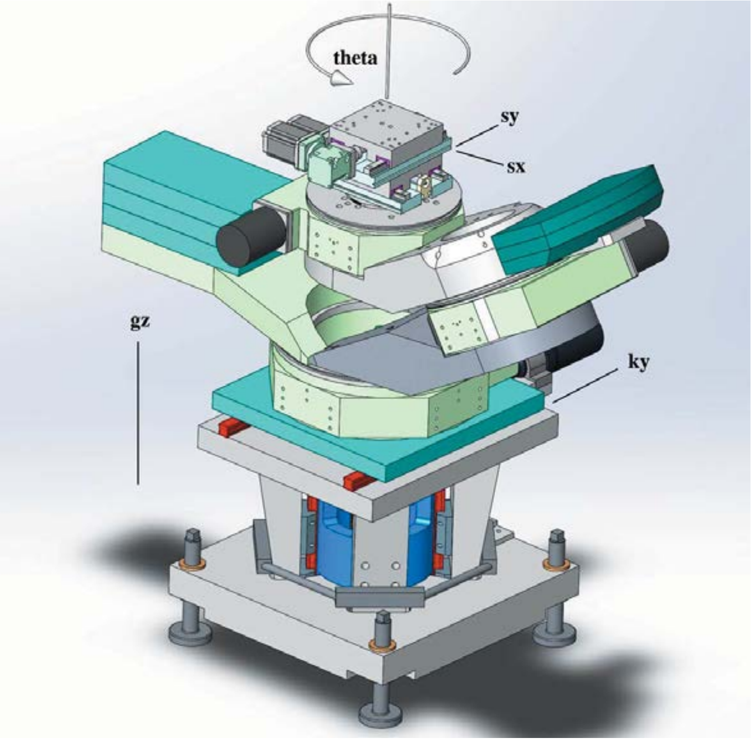
How is MRT delivered?

IMBL – Australian Synchrotron



Livingstone, *et al.*, *J. Synchrotron Rad.*, **24.**, 2017.

ID17 – ESRF



Nemoz, *et al.*, *J. Synchrotron Rad.*, **23**, 2016.

How is MRT delivered?

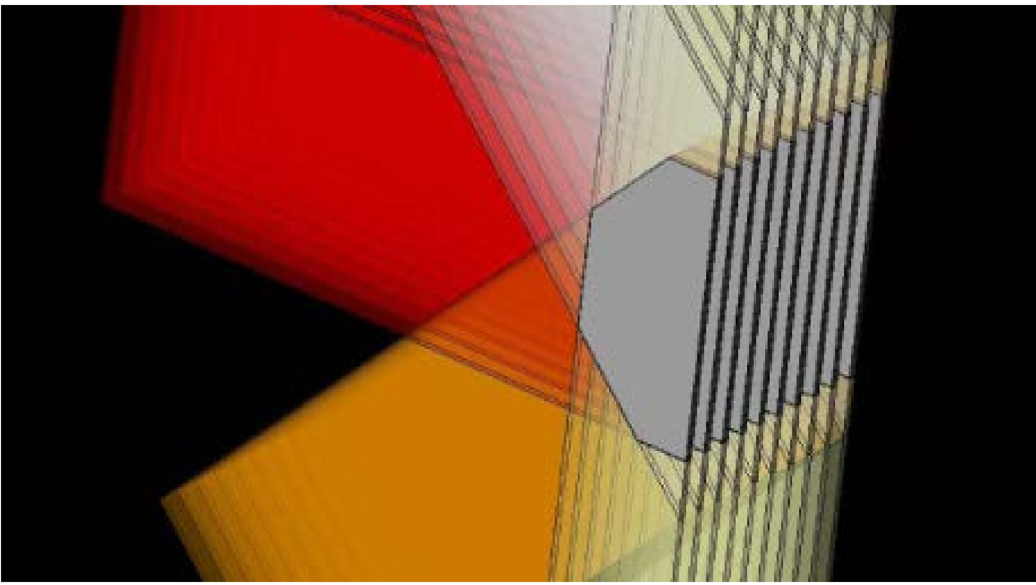
IMBL – Australian Synchrotron

- Designed/built in-house specifically for experimental or preclinical MRT:
  - Dosimetry measurements, cell studies, small animals (mice/rats)
- Designed for ease of use and reproducibility
- Includes kV x-ray tube and imaging detector for positioning
- Limitations due to small range and few degrees of freedom

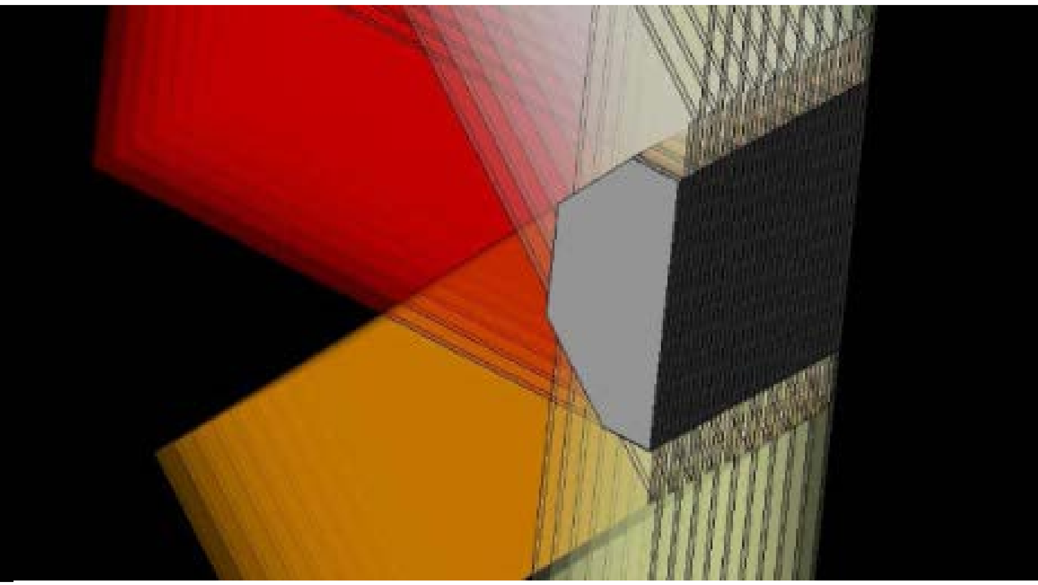
ID17 – ESRF

- Off the shelf solution (goniometer) with all degrees of freedom
- Has been tested on animals up to size of minipig (~20 kg)
- Flexible system
- Synchrotron beam used for image guided positioning

Increasing the differential effect: multiple beams



(a) Normal cross-fired MRT

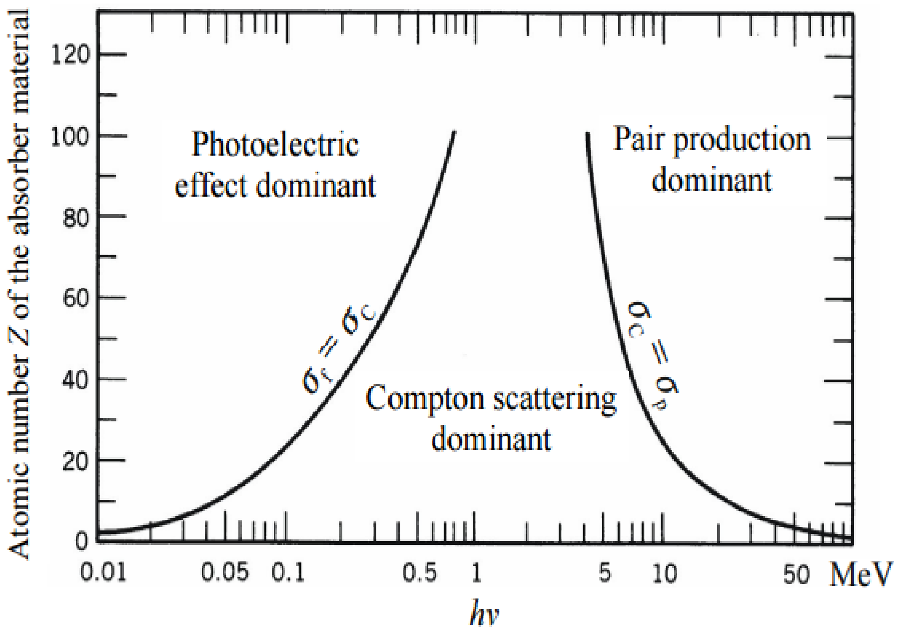


(b) Interlaced MRT

Serduc, *et al.*, *PLOS ONE*, **5**(2), e9028.

Increasing the differential effect: Physical dose enhancement in radiotherapy

- High Z radiosensitisers are explored as a method of increasing the local physical dose absorbed in a tumour
- The local dose enhancement is partially due to increase in photoelectric effect, whose probability increases with Z
- kV x-ray sources, such us synchrotron sources, are of particular interest as probability of photoelectric interaction increases quickly with decreasing energy

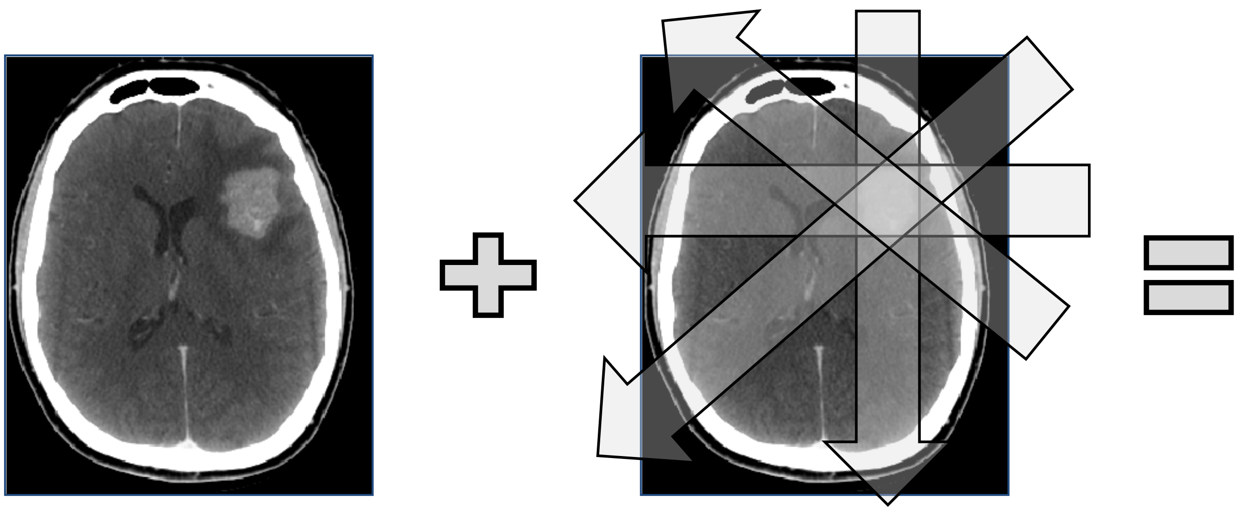


$$\sigma \propto \frac{Z^{4-5}}{E^3}$$

Australian Synchrotron

Stereotactic synchrotron radiotherapy (SSRT)

- Utilises iodine-based contrast agent with monochromatic beams (80 keV)
- Preferential uptake of contrast agent in tumour and enhanced photoelectric effect result in local dose enhancement in tumour volume
- Clinical trials ongoing at ESRF since 2012 (14 patients)



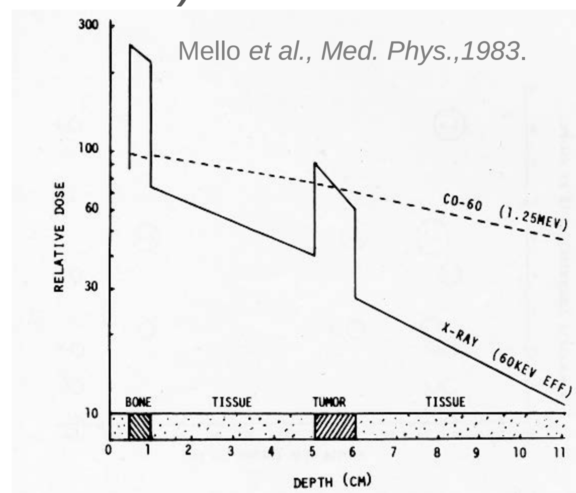
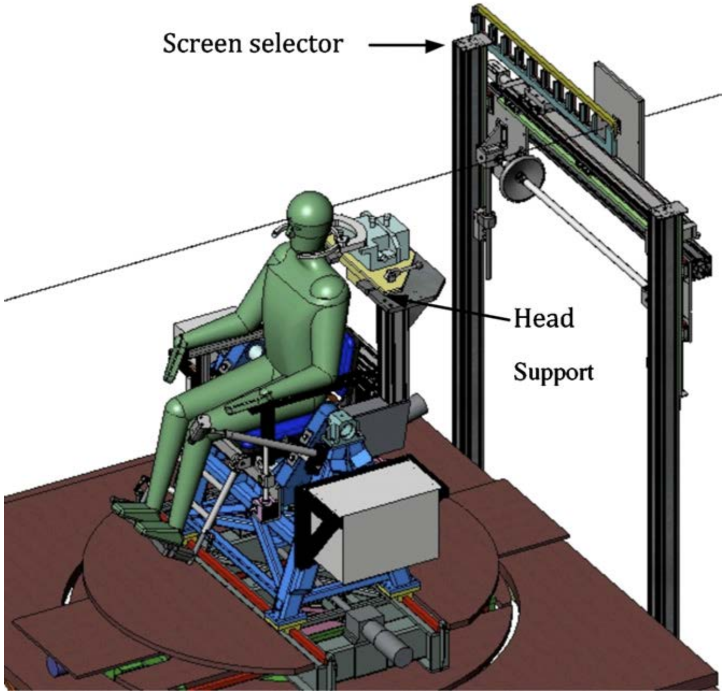


FIG. 2. Depth dose distribution (calculated).

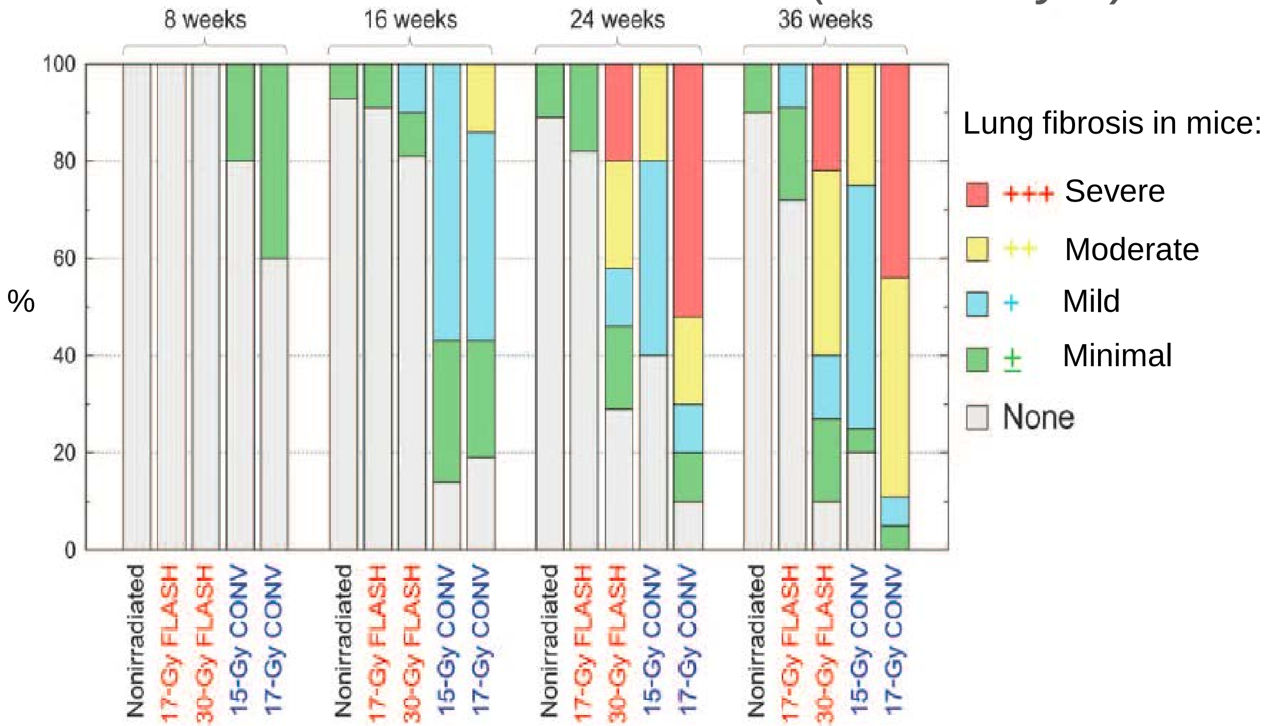
How is SSRT delivered?

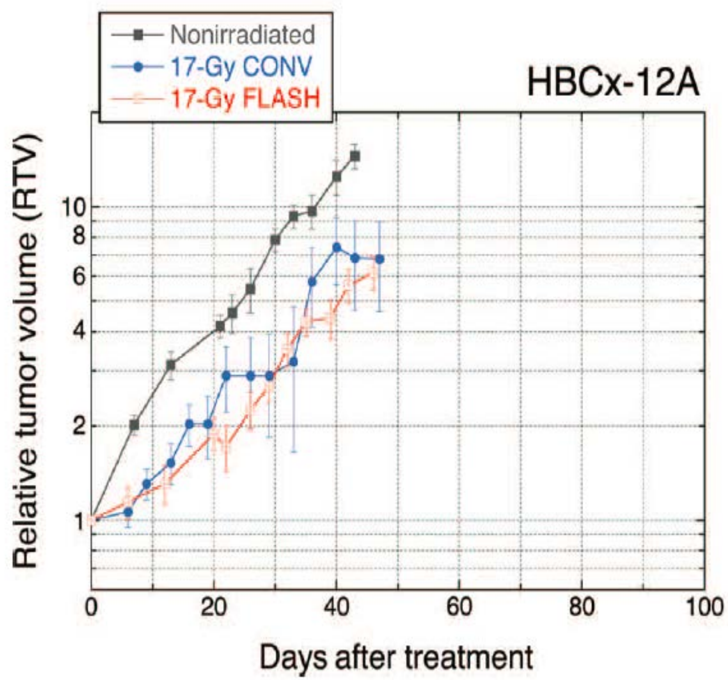
- SSRT treatment is delivered using up to 10 beams
- Fields are shaped using cerrobend (alloy of lead and other heavy metals) masks specific to each patient
- SSRT treatment replaces one fraction in conventional treatment (2 other fractions given at hospital)



FLASH radiotherapy

- Favaudon et al. (2014) demonstrated that for equivalent doses, ultrahigh dose rate (≥40 Gy/s, FLASH) irradiation results in less damage to healthy tissues with same tumour control compared to a conventional dose rate (≤0.03 Gy/s)





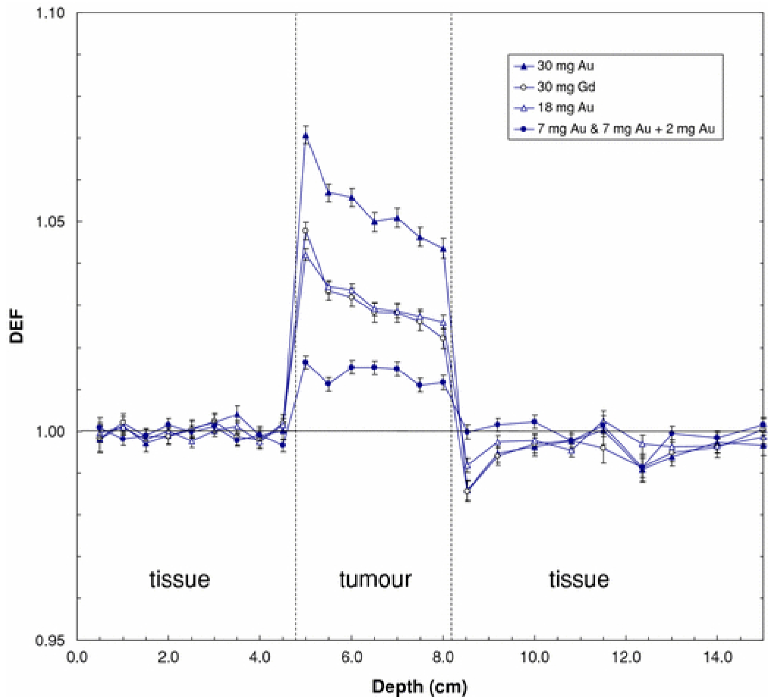
Favaudon *et al.*, *Sci. Transl. Med.*, **6**, 245ra93, 2014

FLASH radiotherapy

- The dose rate at synchrotron biomedical beamlines (like IMBL) is hundreds to thousands of Gy/s!
- The FLASH effect could be pushed to the extreme with such dose rates
- There is research on this, but no results in the literature yet

Combining techniques for maximising the differential effect

- MRT already combines FLASH effect (high dose rate) with spatial fractionation
  - Optimisation of dose rate and beam geometry
- Some researchers have started combining spatial fractionation with dose enhancers (contrast medium or nanoparticles)
  - Calculations have shown that dose enhancers increase and homogenise dose in the tumour whilst maintaining spatial fractionation outside tumour



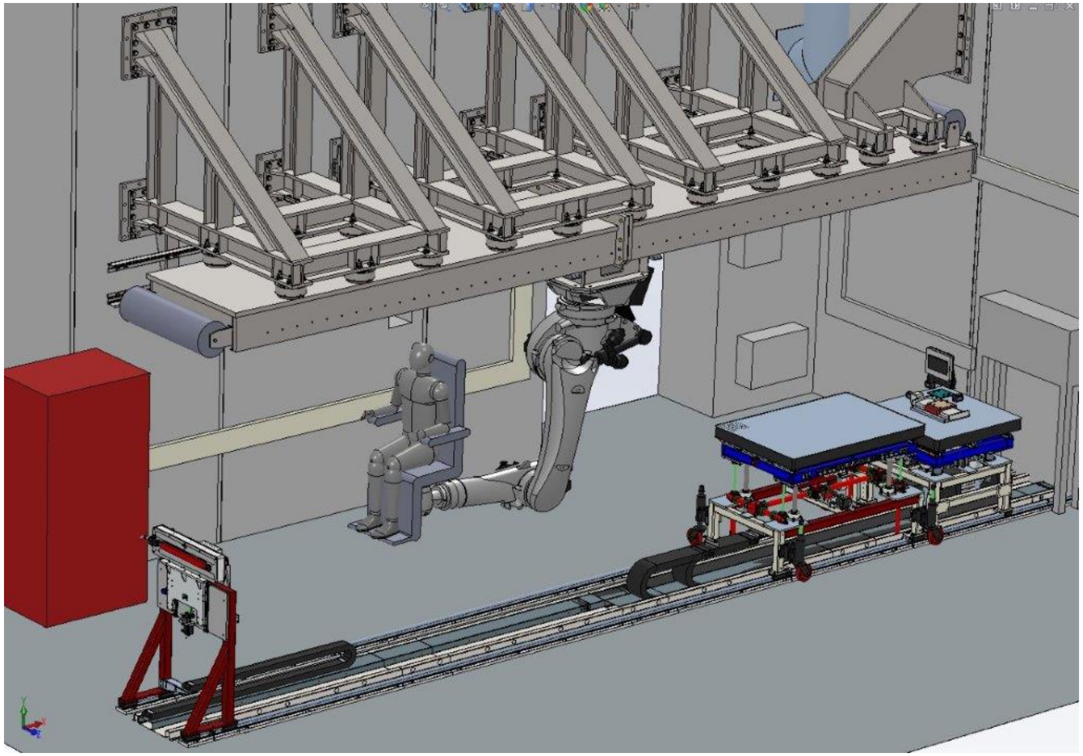
Cho, *Phys. Med. Biol.*, **50**(15), 2005

Synchrotron radiotherapy for the treatment of diseases other than cancer

- MRT has been investigated for treatment of epilepsy resistant to antiepileptic drugs
- Antiepileptic effects were demonstrated in mice with a lasting suppression of seizures after treatment
- Low tissular and functional side-effects observed
- Other models of epilepsy in rodents which are close to epilepsy in humans will be studied

Towards synchrotron radiotherapy clinical trials at IMBL

- There are plans to treat humans at IMBL in future
- We first need to demonstrate safety in long term veterinary studies
- The patient could be positioned in the beam using a robotic chair like the one in 3B (for imaging)



Australian Synchrotron

Summary

- Synchrotrons are explored for radiotherapy applications
- Their unique characteristics offer advantages for increasing the therapeutic ratio via spatial fractionation, high dose rates and dose enhancement
- Patients have been treated using SSRT at the ESRF
- We hope to be the first synchrotron to treat humans with MRT!

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