Medical Student Training in Oncology

Oncology R&I

- Cancer in the News
- Session 1
- Raj Jena

Learning objectives

- Understand how modern radiotherapy plays a part in the treatment of a complex clinical scenario
- Review some fundamentals of radiotherapy
- Consider issues around radiotherapy relating to recent press coverage

Our patient…

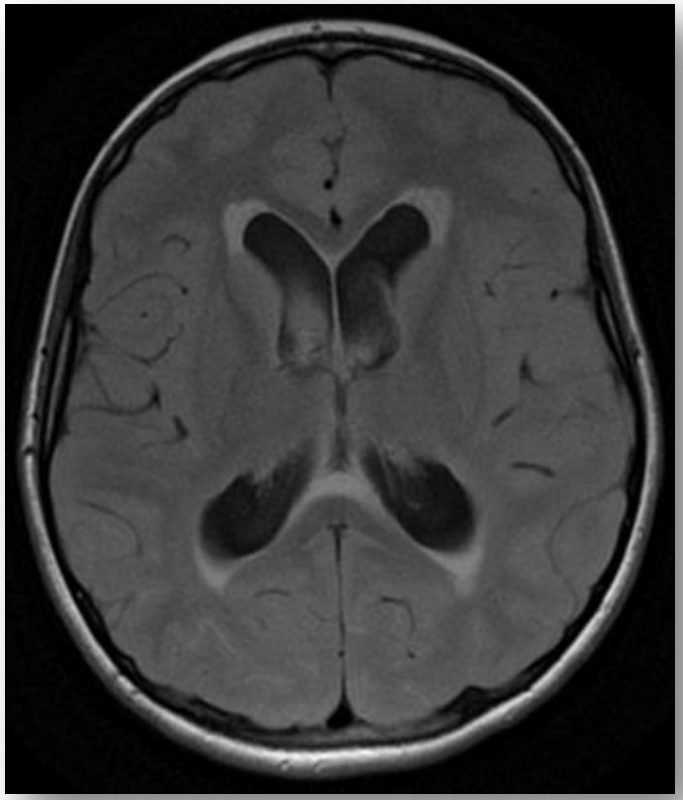
- SJ 12 year old boy
- Mad keen on football, Norwich City fan
- Normal developmental history
- Banged his head on goal post 4 months ago

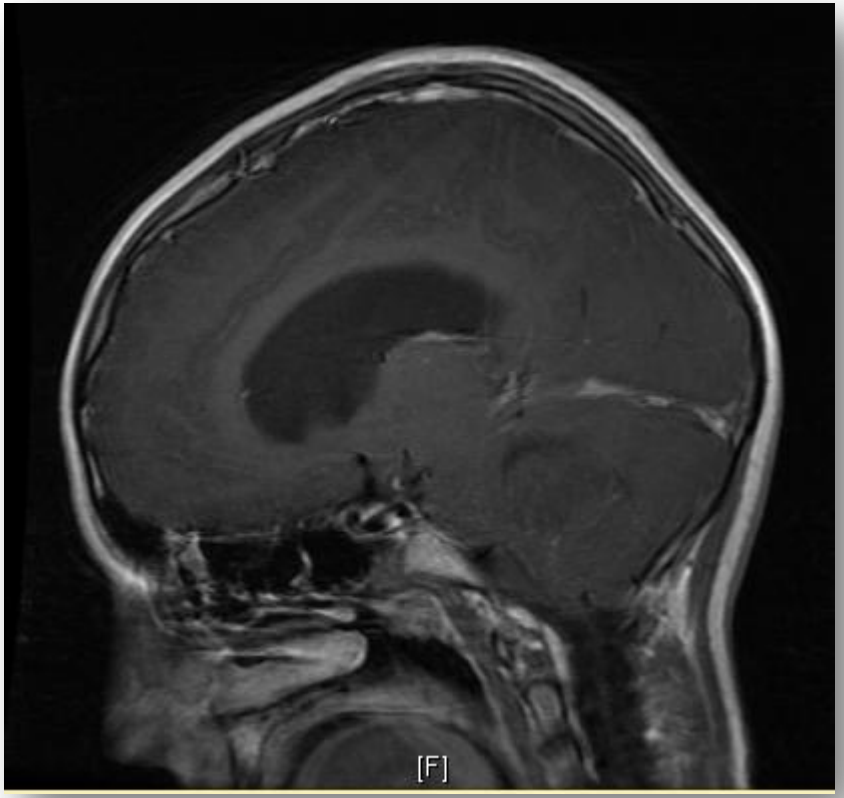
- 8 week hx unwell, lethargic, sports refusal
- 4 week hx headache, worse in the morning
- 2 week hx vomiting in the morning

- Seen by Paediatrics in A&E. Found this…

- What do you do next?

MRI Scan shows

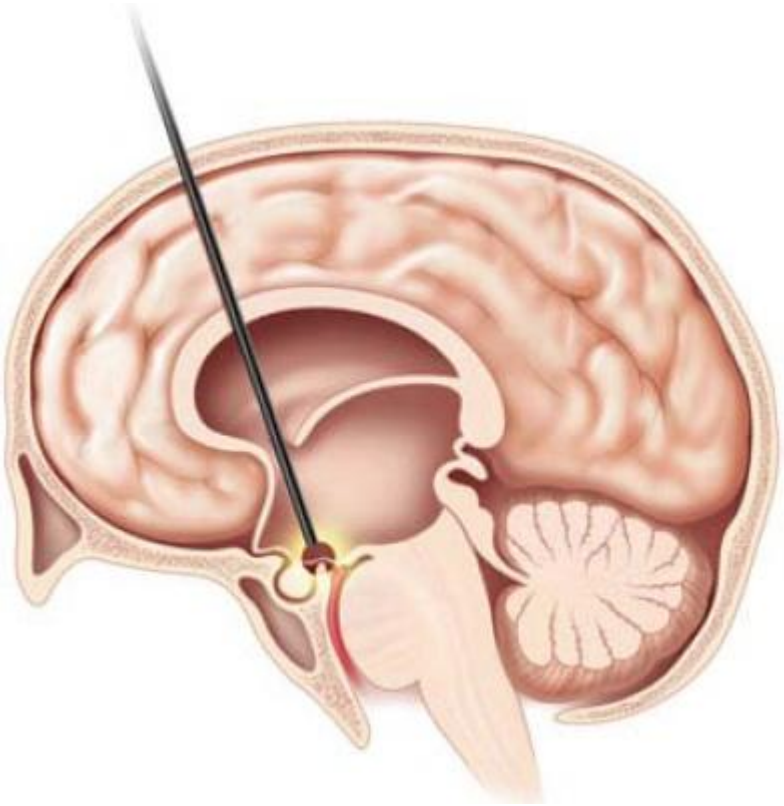




- What is on the differential?

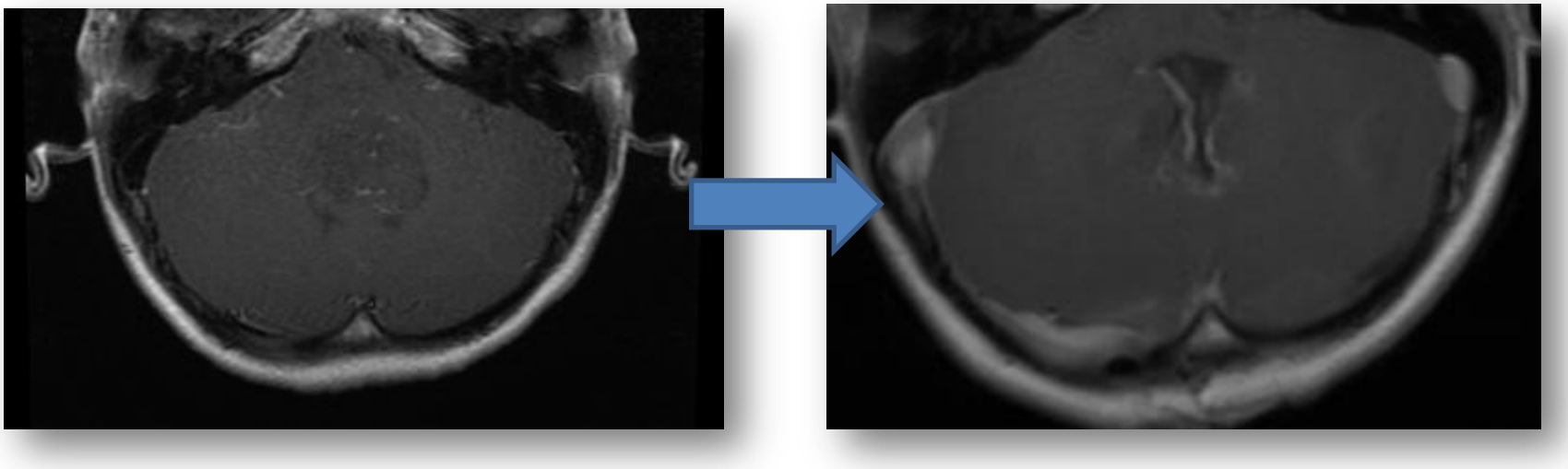
Endoscopic third ventriculostomy

- Small burr hole
- Insert endoscope into lateral ventricle
- Punch hole in anterior floor of 3rd venticle into **basal** and **prepontine** cisterns
- Allow CSF to escape and relieve pressure
- Can also take biopsies via endoscope



Resection of tumour

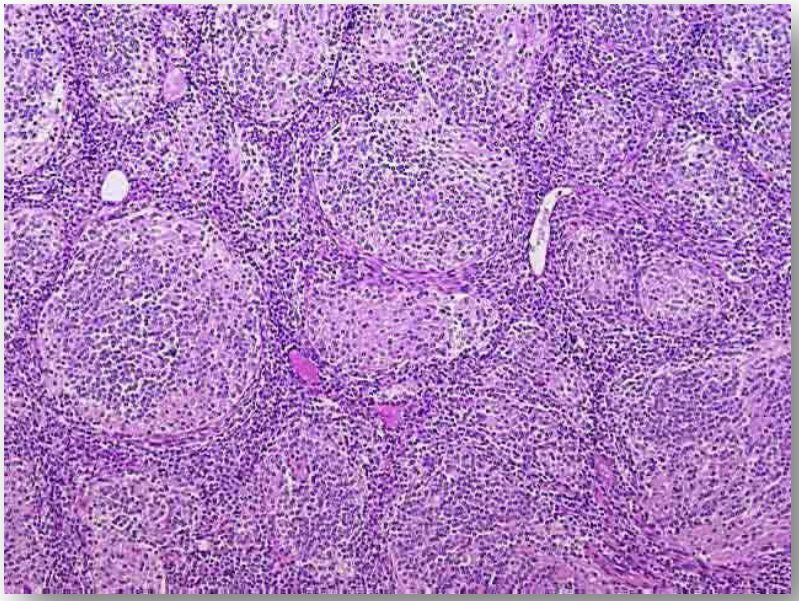
- Access via posterior fossa craniectomy



- What neurological signs might you expect?

Histology

- Small round blue cell tumor composed of sheets of undifferentiated cells with minimal cytoplasm, hyperchromatic and anaplastic nuclei, often elongated and carrot-shaped
- Frequent mitotic figures

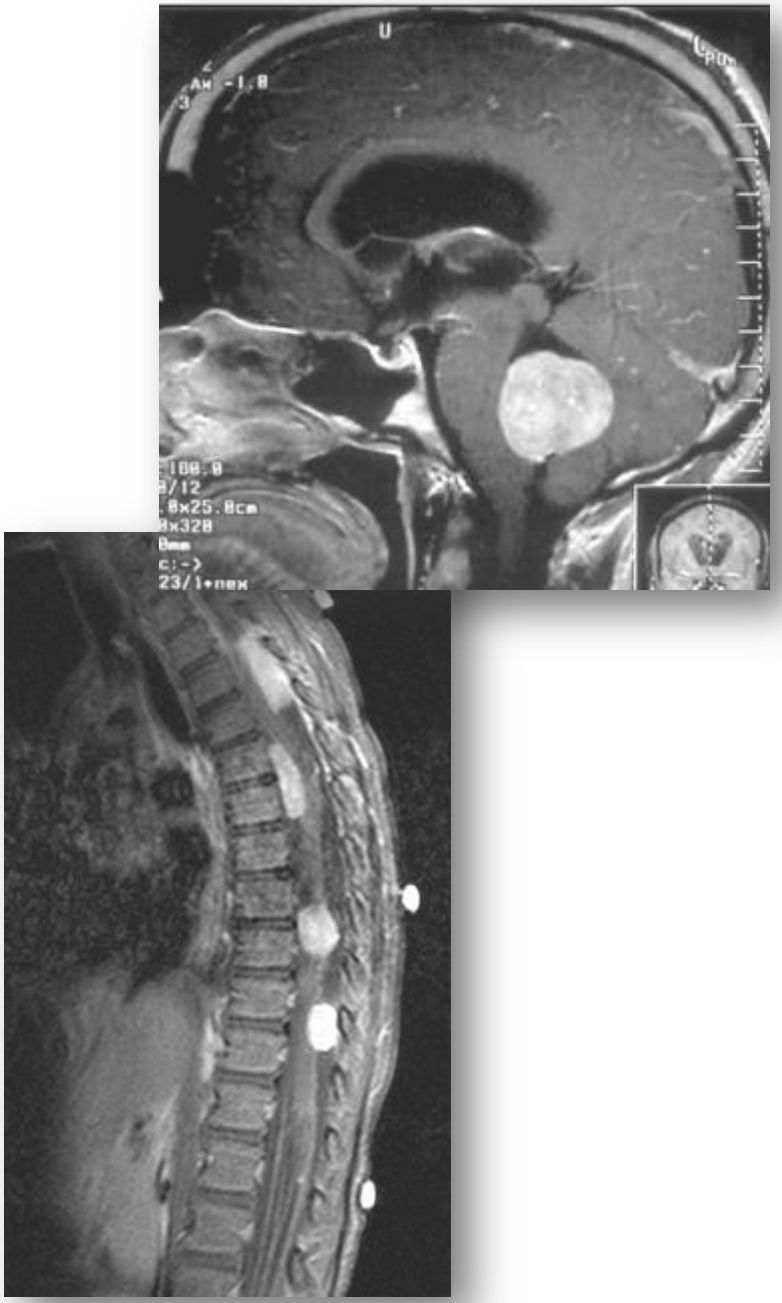


- **Can you guess what it is yet?**

Medulloblastoma

- Primitive neuroectodermal tumour
- Most common in cerebellum or roof of 4th ventricle
- Occurs in kids usually age 5-10 and young adults
- Curable

- **Can spread via CSF throughout neuraxis**
- **Rarely can metastasise outside neuraxis**

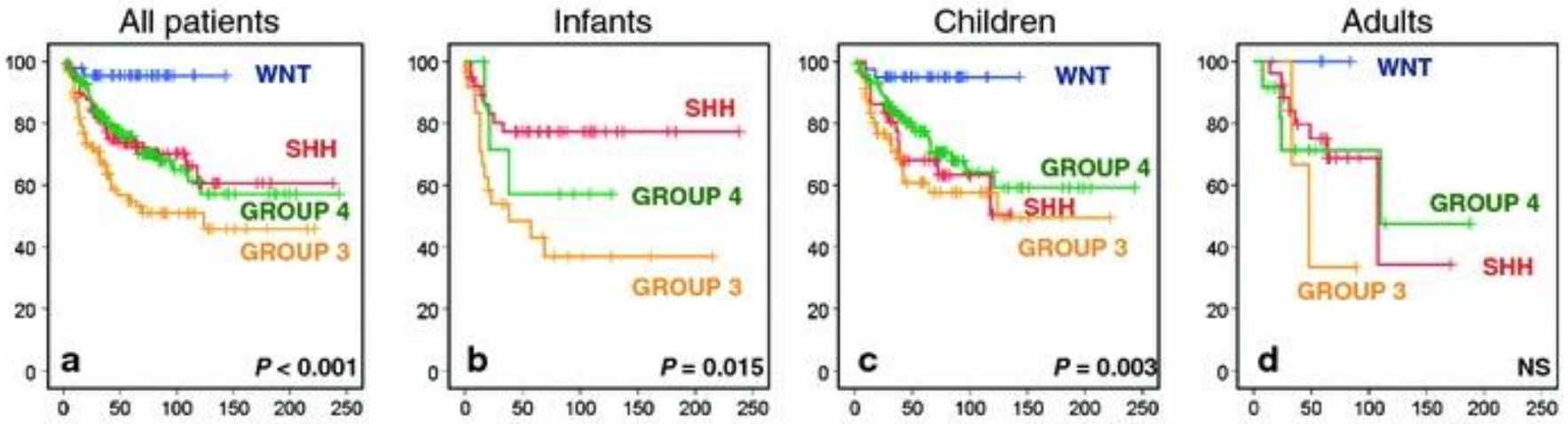


Medulloblastoma : genetic hallmarks

- Resolved using next generation exome sequencing with 20 year sample collection

- 4 subtypes
  - WNT (Cell fate, proliferation, migration)
  - SHH (embryonic development)
  - Group 3 (NPR3)
  - Group 4 (KCNA1)
  - WNT & SHH have potential druggable targets

Prof Collins is an international expert in this field



CCLG guidelines

- **Standard Risk (3+)**
- Reduced dose Craniospinal RT
- Concomitant Vincristine chemo 2w
- Maintenance therapy vincristine / lomustine / cisplatin

- **High Risk [anaplasia, mets, residual disease] (3+)**
- Induction chemo + stem cell harvest
- Craniospinal RT
- Good response get adjuvant chemo Vincristine / lomustine x 6
- Poor response get high dose chemo & stem cell transplant

Treatment issues

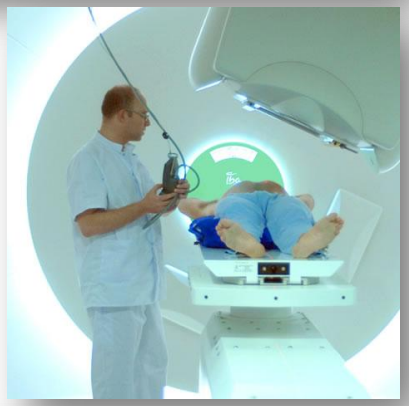
- Staging MRI scan clear, disease confined to post fossa
- Co-factoring : no other issues

- CCLG Standard risk medulloblastoma
- **Curative** treatment

- **Need to consider**
  - Daily GA for CSRT
  - Acute and late of effects of CSRT
  - Hearing loss
  - Posterior fossa / cerebellar mutism syndrome

Radiation therapy

X-rays and particle beams



Timeline of radiation therapy

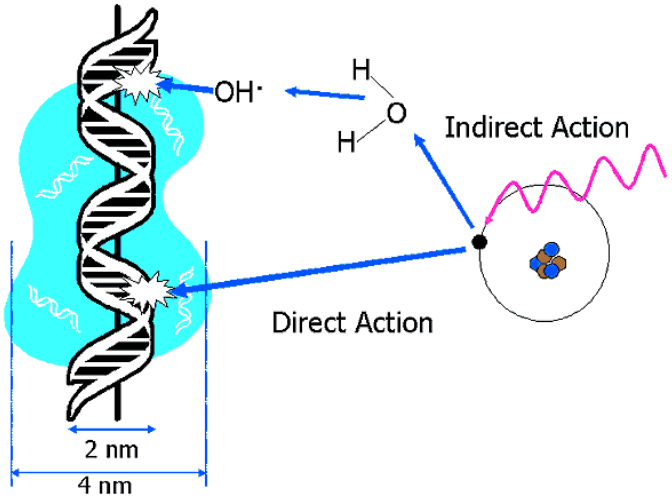
A story of early adoption of new technologies and thinking

- Nov 1895 – discovery of x-rays by Rontgen
- Jan 1896 – first therapeutic use of x-rays for skin lesions from breast cancer (50kv)
- 1904 – first textbook of radiotherapy
- 1913 – first orthovoltage x-ray unit developed by Coolidge to treat deeper tumours (180-200kv)
- 1929 – invention of van der Graaf generator. Cockcroft and Walton develop linear accelerator (1Mv)
- 1930's – x-ray therapy delivered in physics labs
- 1950 – first Cobalt machine for external beam radiotherapy (1.3Mv)
- 1952 – first particle therapy treatment, Robert Wilson
- 1950 – First writeup of 3-dimensional RT in Japan
- 1958 – first clinical linear accelerators (4-6Mev)

- 1984 – first 3D conformal radiotherapy
- 1998 – IMRT first conceived (andres Brahme)
- 1992 – first IMRT treatment
- 2001 – Stanford Cyberknife commisioned for robotic radiosurgery
- 2002 – First Tomotherapy IMRT/IGRT unit developed

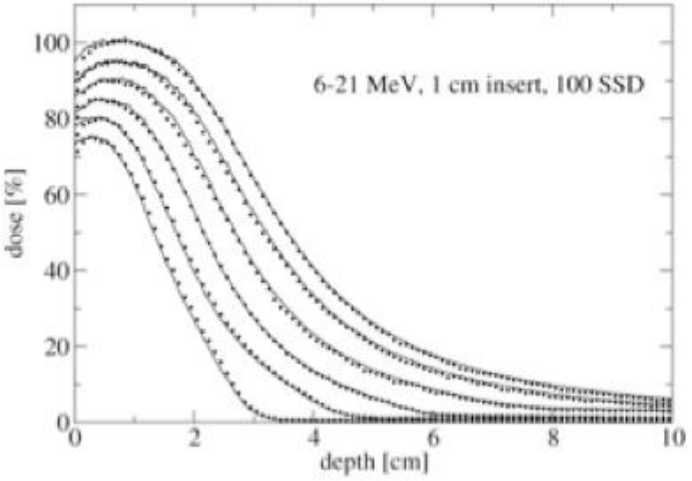
Physical basis for radiotherapy

- High energy x-rays interact with matter to produce high energy electrons
  - Direct effect – direct interaction of electron with DNA to produce DSBs and SSBs
  - Indirect effect – electron interacts with a water molecule close to DNA. The water molecule is split into reactive H· and OH · radicals and these induce double and single stranded breaks



- Without matter to interact with, an x-ray won't deposit dose. This is the **build-up effect**

- Higher energy x-rays pass further through the body before interacting with tissue, hence depositing dose deeper into tissues



Radiotherapy nomenclature

- **Teletherapy**
- **Brachytherapy**

- **X-ray**
- **Gamma ray**

- **Stereotactic radiotherapy**

- **Fractionated radiotherapy**
- **Radiosurgery**

- **Clonogen**

Radiotherapy nomenclature

- **Teletherapy** : radiotherapy delivered where the radiation source is distant from the patient. May also be known as external beam radiotherapy
- **Brachytherapy** : radiotherapy delivered using a radiation source placed inside or on the surface of the patient

- **X-ray** : ionising electromagnetic radiation generated using electricity
- **Gamma ray** : ionising radiation derived from a naturally occuring or man-made radiactive material

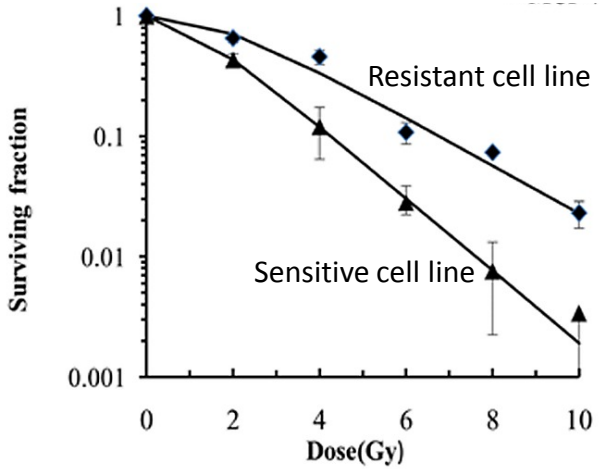
- **Stereotactic radiotherapy** : radiation delivered with high precision to a target within the brain or body, usually achieved by immobilising the patient in some form of frame or rigid fixation device

- **Fractionated radiotherapy** : radiotherapy treatment broken up into a number of doses over several days
- **Radiosurgery** : a single intense dose of radiotherapy, designed to ablate all tissue within the target.

- **Clonogen** : a cancer cell capable of mitotic proliferation

Classical radiation biology

- Radiation biology is a subject in its own right, but some brief principles from radiation biology are helpful at this stage
- Radiation dose response : tumours exhibit a characteristic pattern of response to radiotherapy, illustrated in the clonogenic survival curve



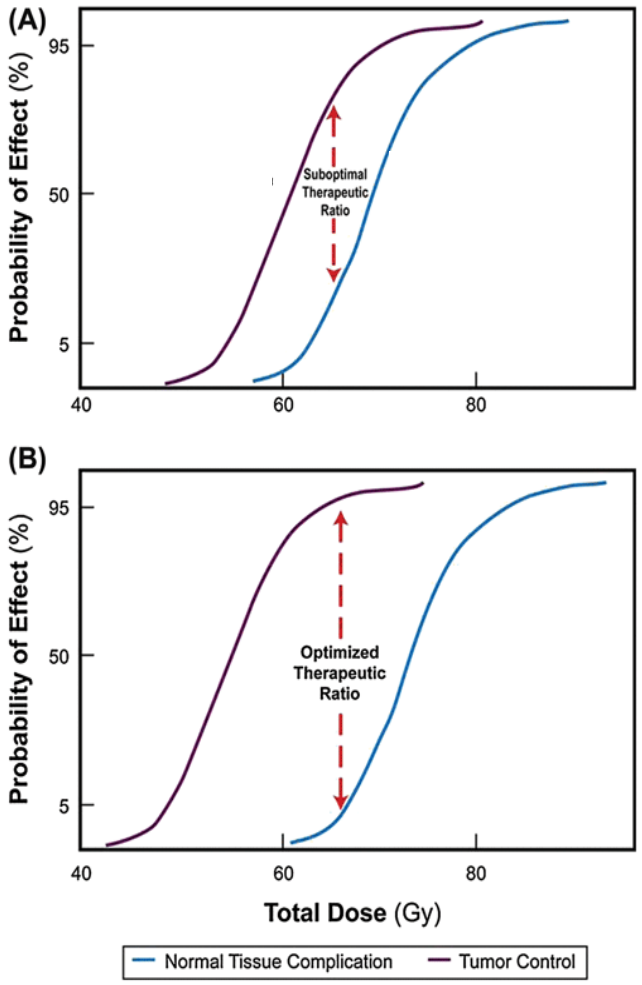
- Here we see two different cell lines irradiated to different doses, and the fraction of surviving cells after each dose is plotted. Note the log scale for surviving fraction
- Note that for doses above 10gy for the sensitive cell line, we won't see much more cell kill effect, as nearly all tumour cells are destroyed at this dose

- We try to deliver a dose of radiation that will kill all tumour clones in the target. In theory if we don't kill all the clones, the tumour could regrow from a single clone
- In practice we describe a *probability* of tumour control according to the estimated number of remaining clonogens, using Poisson statistics

RT Dose & therapeutic index

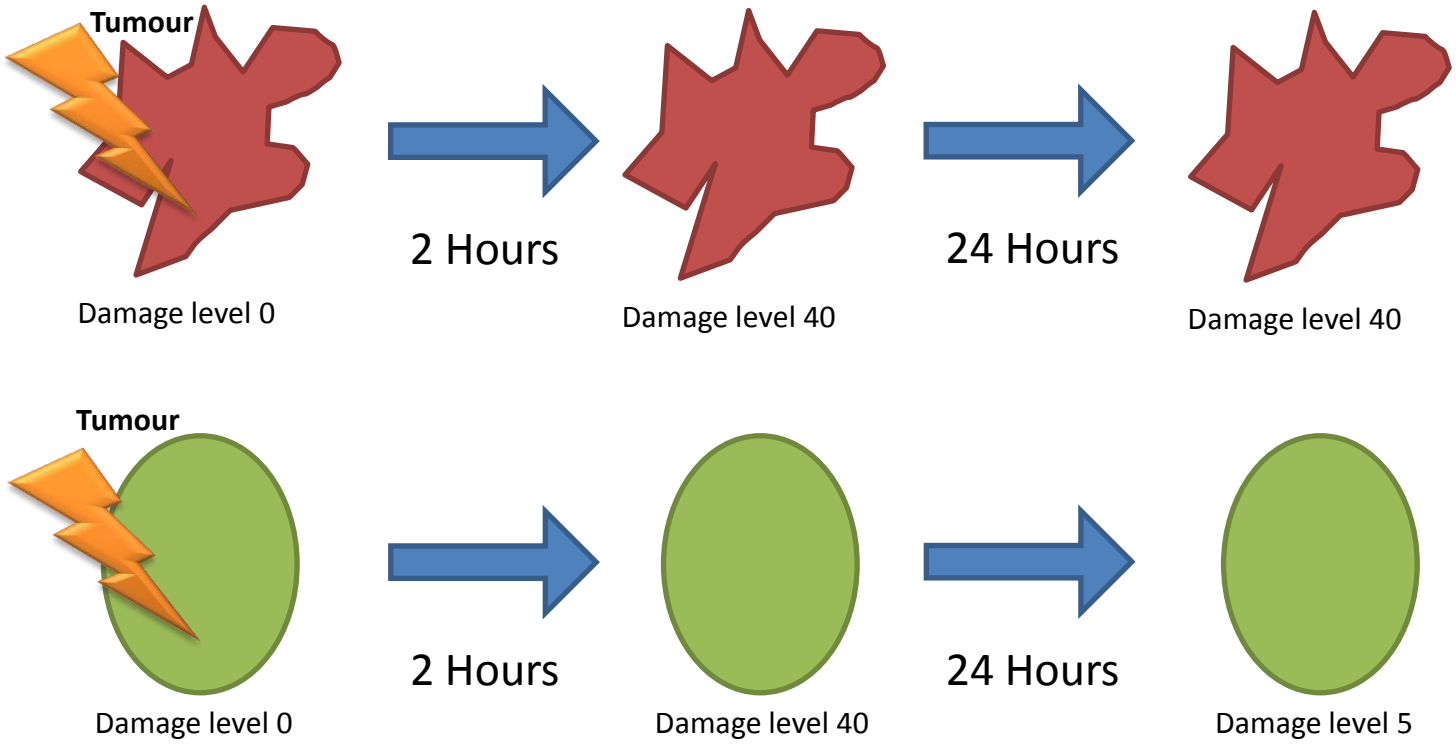
- The problem with patients is that they don't have square tumours with straight edges. So to irradiate a tumour in full, we have to treat some health normal tissue, which also has a similar response to radiation
- We have to balance the probability of curing the patient's tumour, against the probability of causing significant injury to the normal tissues

- **The central tenet of modern radiotherapy** is to try and separate these two curves as much as possible in the following ways
  - *Conform* dose to the tumour and away from normal tissues (Radiotherapy Physics)
  - Break up the treatment into fractions to allow normal tissue to repair (Radiation biology)
  - Enhance tumour kill, or protect health cells, by combining drugs with RT (Cell biology)



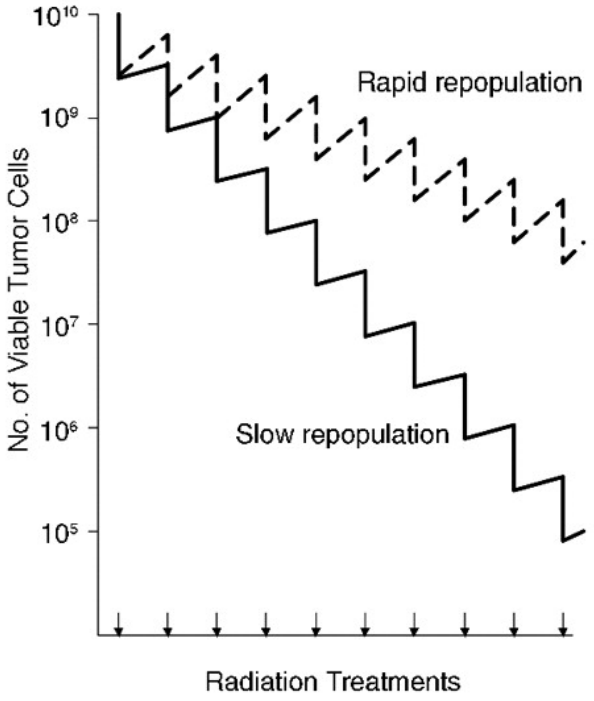
RT Time and fractionation

- Defective DNA repair is a hallmark of cancer
- Normal tissue cells (should) have normal DNA repair. The repair half time in most acute reacting normal tissues is 8 hours
- *Let's do an experiment – irradiate 2 cells and measure DNA damage level over 24 hours*



RT Time and fractionation

- Scale this up to lots and lots of daily treatments, and we see the following effect in the tumour cells, depending on the speed with which they regrow (repopulate) between treatments



- In contrast, normal tissues won't regrow much at all , but they will repair most of the DNA damage between treatments
- *This is why most radiotherapy is given as a 6-7 week course of radiotherapy treatment fractions*

Time, Dose and Fractions in the clinic

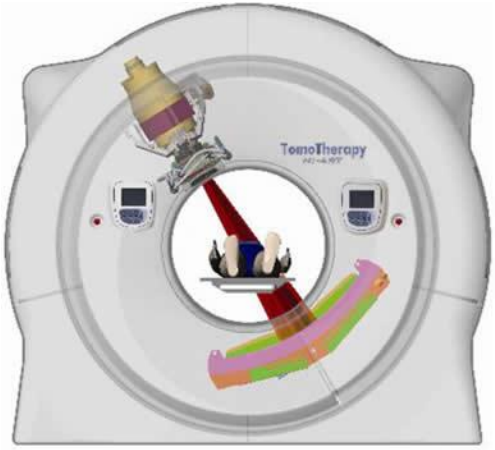
- We make use of time, dose and fractionation all the time in the clinic
- Ablative radiosurgery delivers a single, highly focussed radiation dose to the target. The cell kill is very high. We minimise damage to normal tissue by keeping the high dose out of normal tissues

- Patients with advanced cancer and a short life expectancy may not live long enough to express normal tissue toxicity. We use big doses and small numbers of fractions to give rapid palliation of symptoms

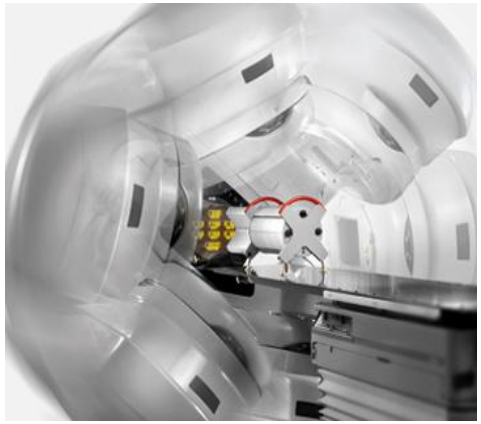
- Some rapidly growing tumours demonstrate high sensitivity to radiation but repopulate quickly between treatments. We sometimes use large numbers of treatment fractions over a short time, treating more than once per day, to over come this (hyperfractionated RT)
- Some slow growing tumours e.g. prostate cancer have a higher sensitivity to fraction size rather than the total dose, so we deliver curative treatment in a smaller number of fractions (hypofractionated radiotherapy)

Pushing the envelope with x-rays

- You may hear about a range of treatment machines which all deliver highly conformal radiotherapy in essentially the same way – by breaking the radiation beam up into lots of tiny beamlets which can be turned on or off individually, and rotating the x-ray beam around the patient. Where the beams converge, the radiation dose will accumulate



The **TomoTherapy** unit has geometry like that of a traditional CT scanner. The radiation beam can rotate fully round the patient as they move through the machine



VMAT or volumetric modulated arc therapy, uses a traditional linear accelerator gantry rotating round the patient.

Cyberknife uses a compact linear accelerator mounted on the end of a 5 axis robotic arm. It can move and arcround the patient with a high number of degrees of freedom

Defining targets for RT : some terms

- We make use of diagnostic imaging (CT, MRI, PET) and clinical examination (EUA, palpation) when planning RT
- We use a standardised nomenclature when describing targets for radiation therapy

- Gross Tumour Volume (GTV)

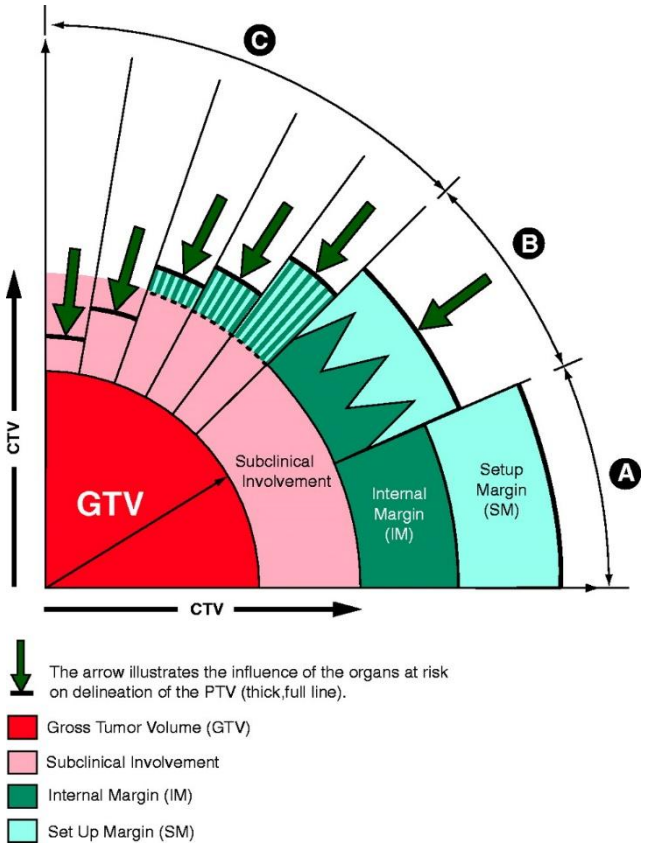
- Clinical Target Volume (CTV)

- Planning Target Volume (PTV)

Defining targets for RT : some terms

- We make use of diagnostic imaging (CT, MRI, PET) and clinical examination (EUA, palpation) when planning RT
- We use a standardised nomenclature when describing targets for radiation therapy

- Gross Tumour Volume (GTV) : This is the visible or palpable tumour that can be assessed at the time of planning treatment. For ad adjuvant treatment, there will be no GTV
- Clinical Target Volume (CTV) : This represents an area around the gross tumour which is at risk of microscopic spread of tumour. It may include contiguous tissues or draining lymph nodes
- Planning Target Volume (PTV) : This represents a margin round the CTV to allow for movement of the tumour or the patient during a course of RT



Defining targets for SJ

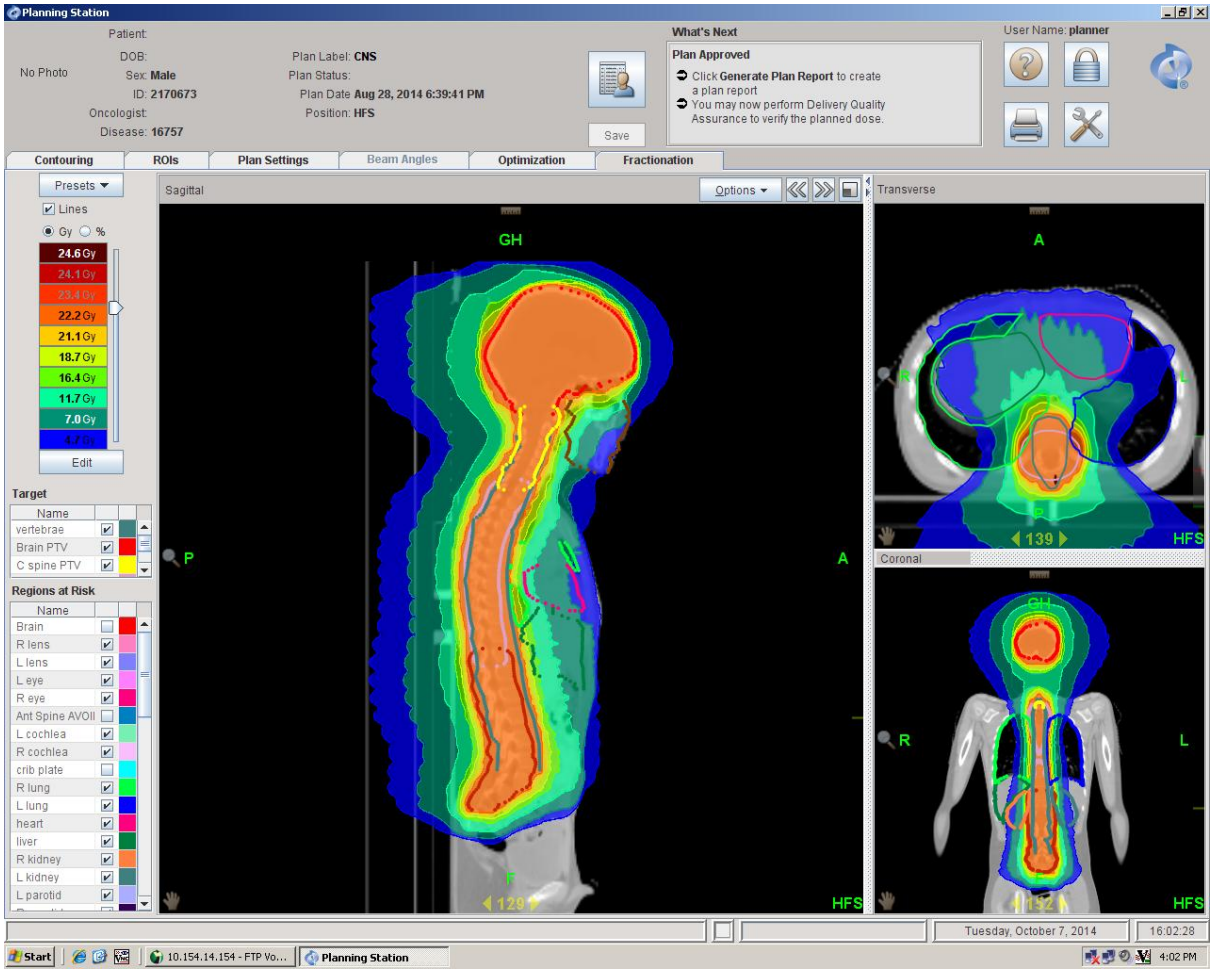
- Gross Tumour Volume (GTV) : There isn't any!

- Clinical Target Volume (CTV) : The entire neuraxis, taking special care for nooks and crannies where the CSF goes
  - Cribriform plate
  - Thecal sac
  - Nerve roots at skull base
  - Optic nerves
  - The entire bony vertebrae (why?)

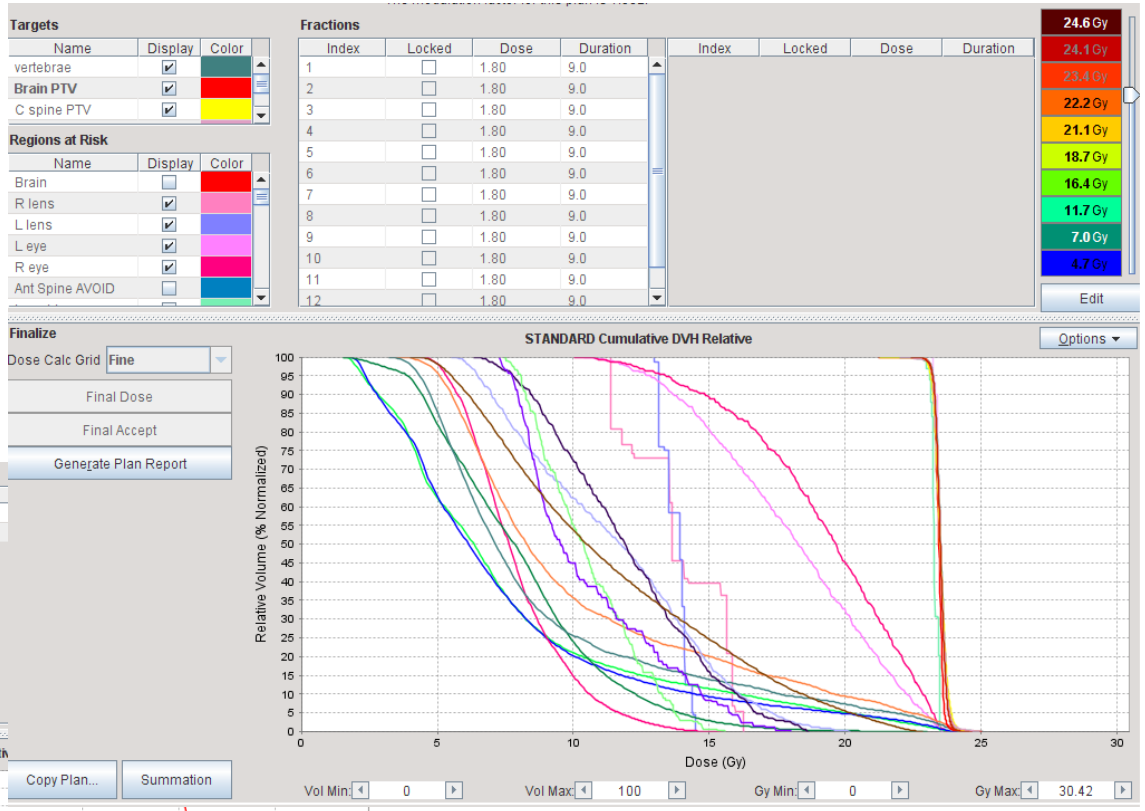
- Planning Target Volume (PTV) : Margin for wriggling patient

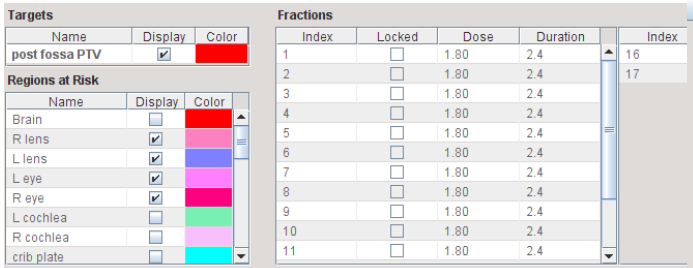
Tomo and CSRT

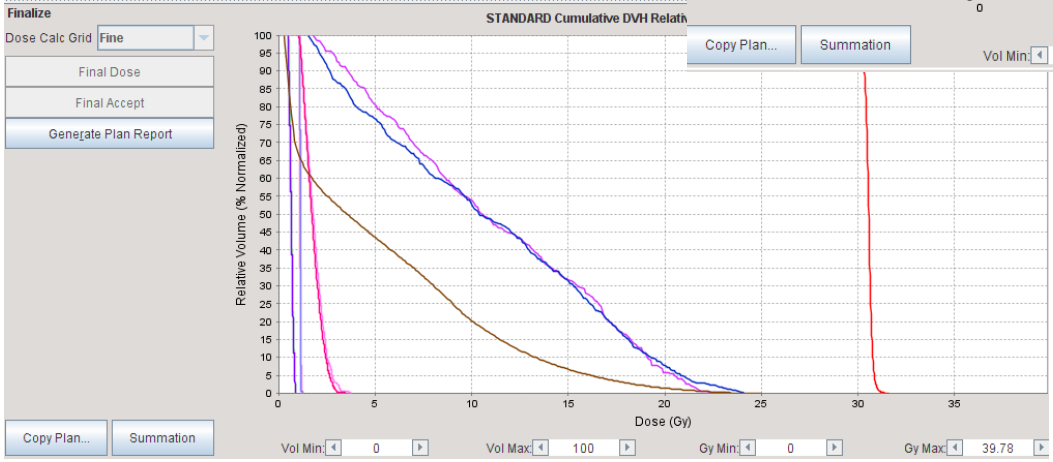
- An elegant solution
  - Patient length not an issue – they move through the machine
  - Image the patient during treatment (keep PTV small)



Tomo and CSRT





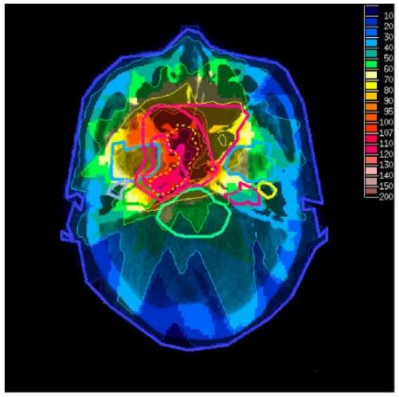


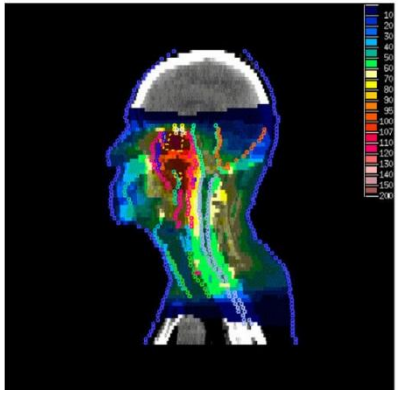
Monitoring during treatment

- Full blood count
- Nutrition status
- Balance

Limitations of x-ray radiotherapy

- As we use more and more beamlets of radiation to target the tumour, we can 'paint' dose with higher spatial precision
- The cost of this is smearing more low dose radiation through the patient

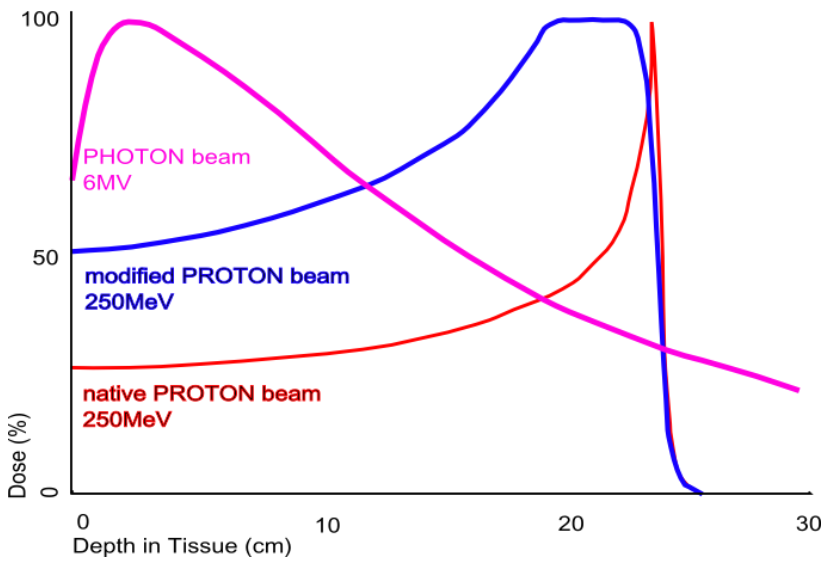




- This IMRT plan shows treatment for a nasopharyngeal carcinoma. The tumour (yellow dashed line) is covered beautifully by the high dose (red) and dose has been sculpted off the R medial temporal lobe (light blue)
- Look further out from the target and you see that most of the head is receiving a low dose 'bath' of around 10-20% of the prescription dose
- Low doses may be important in late effects of radiotherapy, especially in our young lad

Proton beam therapy

- Particle beams (e.g. proton beams) deposit energy in the patient in a very different way
- As particles interact with matter in the patient, they slow down, and their velocity drops, the energy they release per unit volume increases
- Eventually they stop and release all their rest mass energy in a big heap. This is known as the Bragg peak (hypothesized by Bragg at Trinity College, Cambridge)
- The depth in the body at which this Bragg peak occurs can be tuned by changing the energy of the proton beam
- In 1952 Robert Wilson first realized that these properties would be ideal for therapy, as there is no exit dose as observed with x-rays that continue through the patient



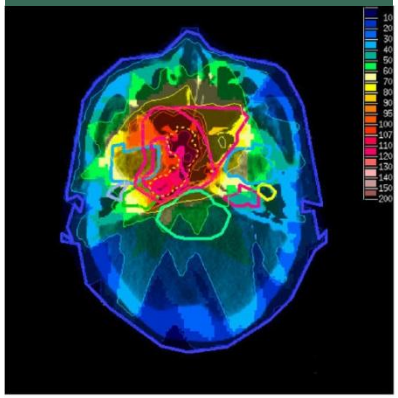
Proton beam therapy in the UK

- We currently only have a low energy proton therapy unit in Clatterbridge for treating eye tumours
- Two clinical facilities are being developed in UCL and Manchester for 2018
- An x-ray based linac unit costs about £1.2-4M
- A proton therapy facility costs around £40-£100M
- We have a mature system in place for treating NHS patients in Switzerland and the USA

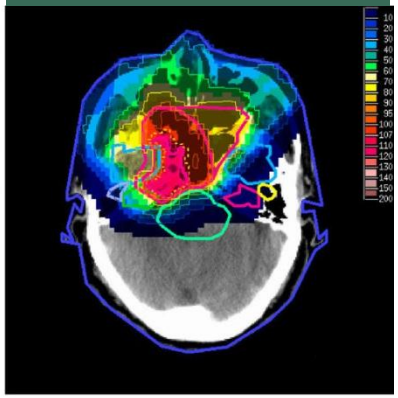
Protons vs Photons : Round 1

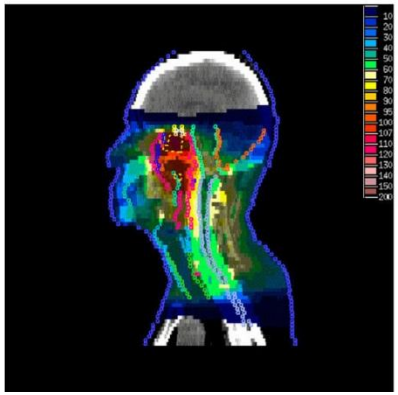
- Let's revisit that nasopharynx cancer case, and compare photon treatment with proton treatment. The proton plan uses two lateral beams coming from either side of the patient

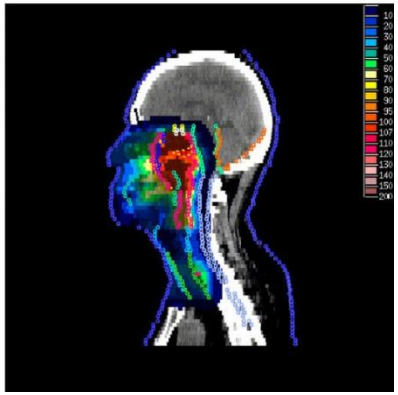
Best X-ray plan (IMRT)



Proton beam plan



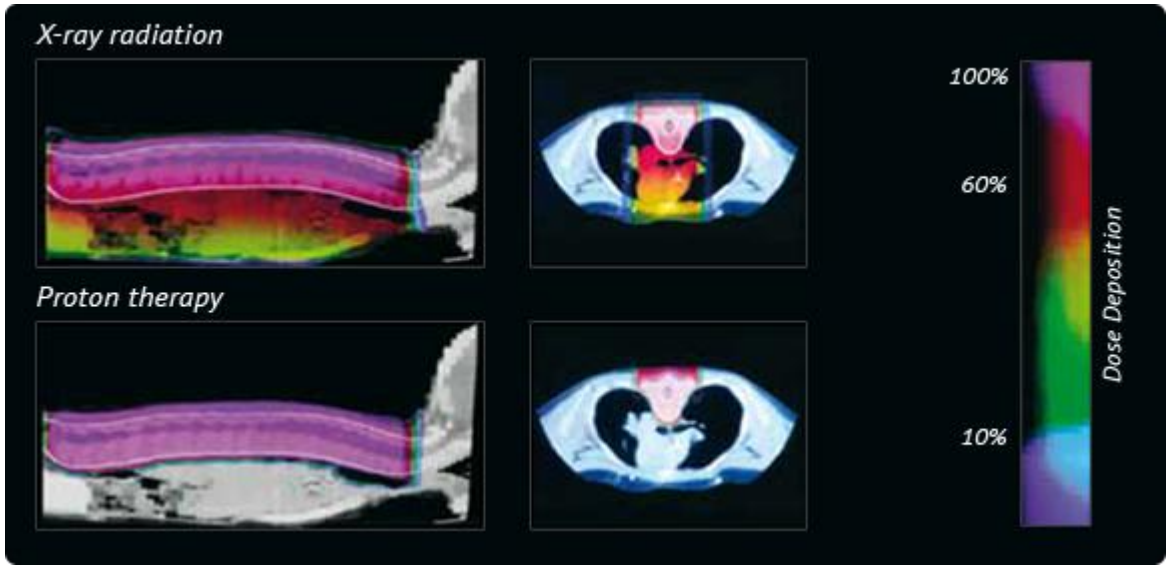




- Dose conformity to the tumour is quite similar in both plans, but there is much less low dose bath with the proton plan. The cerebellum and posterior tissues of the neck receive essentially no dose

Protons vs Photons : Round 1

- For craniospinal treatment, look at the dose deposition pattern below and think which one you would choose?



- The lack of exit dose to the central structures of the body make proton beam therapy very attractive for children. There will be less effects on tissue growth and less risk of second malignancy
- But there are other factors to consider…

Protons vs Photons

*Factors in the Ashya King story that the press **never** mentions*

- Medulloblastoma is curable with x-ray treatment, and follow-up on x-ray based treatment goes back for decades.
- Timely proton beam therapy does not enhance cure rate, though may have reduced late effects
- Post-operative treatment for medulloblastoma in kids is complex. They need RT, and chemo, post-operative care and rehabilitation.
- Prompt starting of CSRT is vital to maintain tumour control. Setting up PBT treatment (even in the same country) takes time.
- Tumour cure probability drops by around **2% per day** after 28 days.
- For these reasons of **holistic care**, children in the UK are not routinely sent overseas for PBT

Protons vs Photons : Round 2

- Modern x-ray based therapy is delivered using image guidance. The fact that an x-ray exits the patient means that we can visualise the path of the beam, and verify it has hit the target as planned
- The TomoTherapy unit is an elegant solution for image guided radiotherapy. It uses the x-ray beam in a similar manner to a CT scanner to build daily 3D images of the patient anatomy, which can be used to verify the position of the patient

Protons vs Photons : Round 2

- It is not possible to do this using proton beam therapy, as the beam does not exit the patient
- Current Proton IGRT solutions involve moving the patient and couch out of the treatment unit and into a CT scanner, manually or with a robot. Clearly this is not as good as imaging the patient in situ
- Sophisticated electronics are being developed to try and detect positron emissions from the Bragg Peak – these are still in early development
- 1Gy x-rays ≠ 1Gy protons. The biological effects of protons are quite complex and not fully characterized, especially for different types of normal tissues.

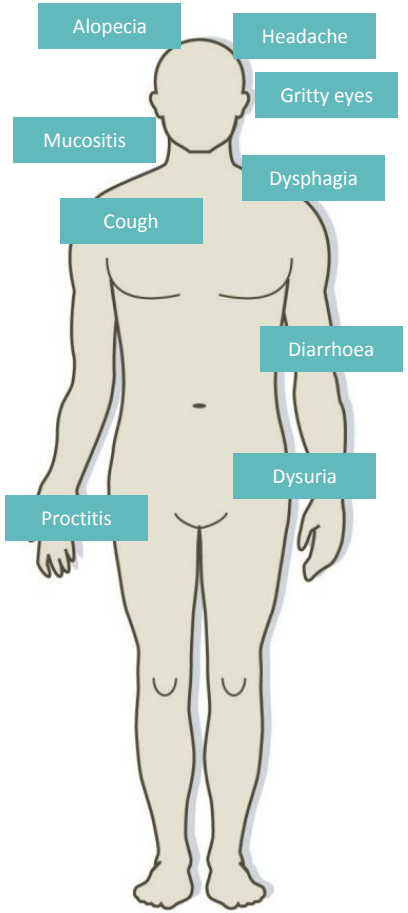
Who would lap Silverstone circuit the quickest?

David Coulthard driving a Mercedes race car blindfolded…

…or groovy granny driving her estate with her eyes wide open!!!

CSRT is used with care…

- RT will cause acute side effects during treatment, depending on anatomical site being treated
- Side effects are dependent on dose and volume of normal tissues being treated. Risk of side effects can be estimated from radiotherapy treatment plan.
- Side effects need to be anticipated, and managed during treatment
- Most acute side effects will settles around 4-6 weeks after a course of radical RT
- Trend towards keeping RT doses as low as possible. Not used at all in under 3's.

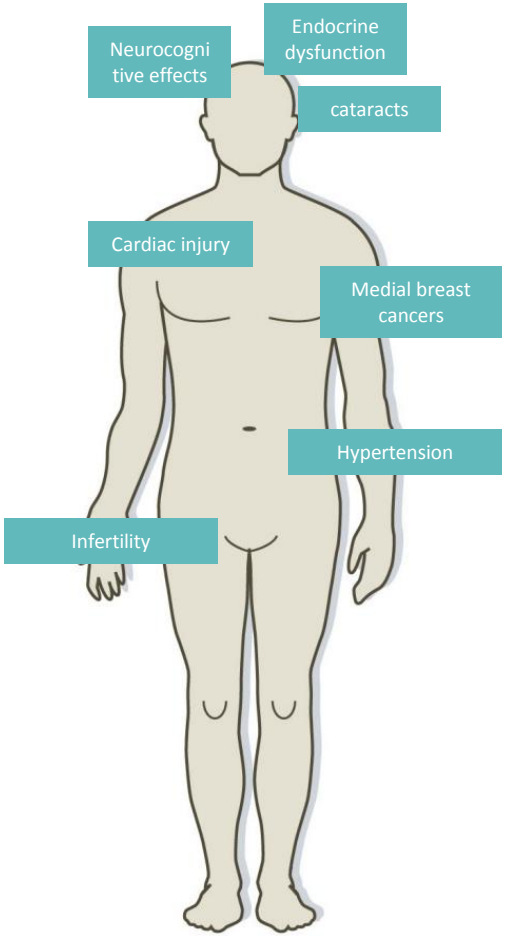


Late effects of CSRT

- Patients must be advised of risks of late effects of RT
- Actuarial risk – patient must survive to express risk of late effect

- Managing late effects needs a multidisciplinary approach, with specialist input

- Second malignancy risk – roughly 1-2% per decade of life for most common treatments



Summary

- Medulloblastoma is an aggressive yet curable brain tumour which can spread through the neuraxis
- Post-operative treatment requires cranio-spinal irradiation
- Late effects of radiation therapy relate to the exit of dose through the body
- Proton beam therapy may be a useful treatment for children
- The principles of RT relate to temporal and spatial effects of radiation dose