Radiotherapy and Chemoradiotherapy

Dr Angus Ades

Health New Zealand
Te Whatu Ora

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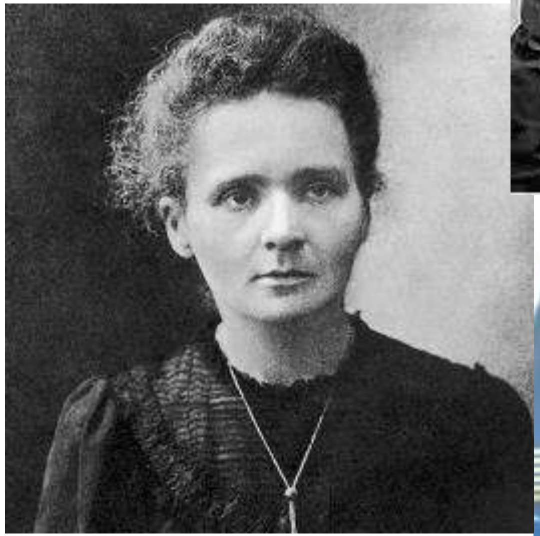
- Scientific basis of radiotherapy
- Types of radiotherapy
- Clinical uses of radiotherapy
- Chemoradiotherapy
- Process of radiotherapy

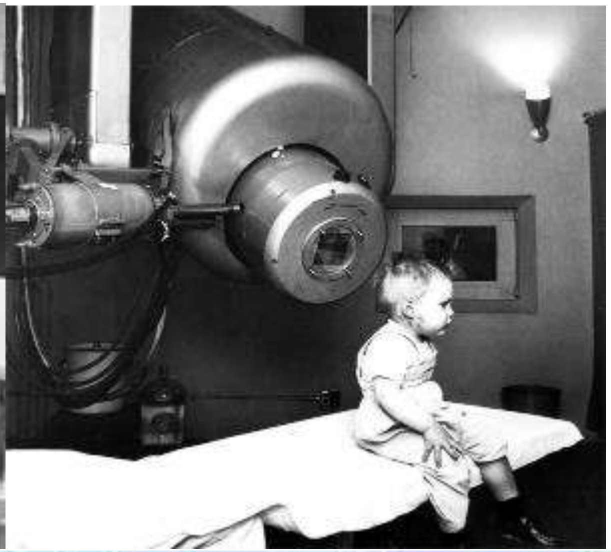
History: Discovery and Quackery

- 1895 – Discovery of X-rays by Wilhelm Roentgen (Won Nobel prize in Physics 1901)
- 1896 – Becquerel and Marie/Pierre Curie describe radioactive decay/natural sources of radiation.
- 1896 – Use of X-rays for treatment of breast cancer (Emil Grubbe).
- 1901 –> 1930 – use of radium and X-rays to treat a variety of malignancies and cutaneous disease. Radioactive substances incorporated into a variety of commercial products.



History: Early Treatments

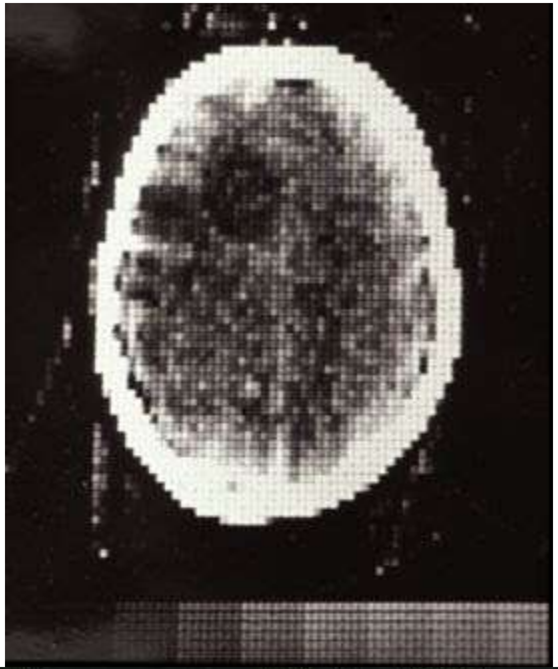
- 1941 – Use of radioactive iodine to treat thyroid ca/hyperthyroidism.
- 1951 – Development of Cobolt-60 teletherapy.
- 1956 – First linear accelerator used for radiotherapy treatment.
- 1968 – Development of Gamma Knife radiosurgery



History: Imaging Improvements

- 1971 – Development of CT

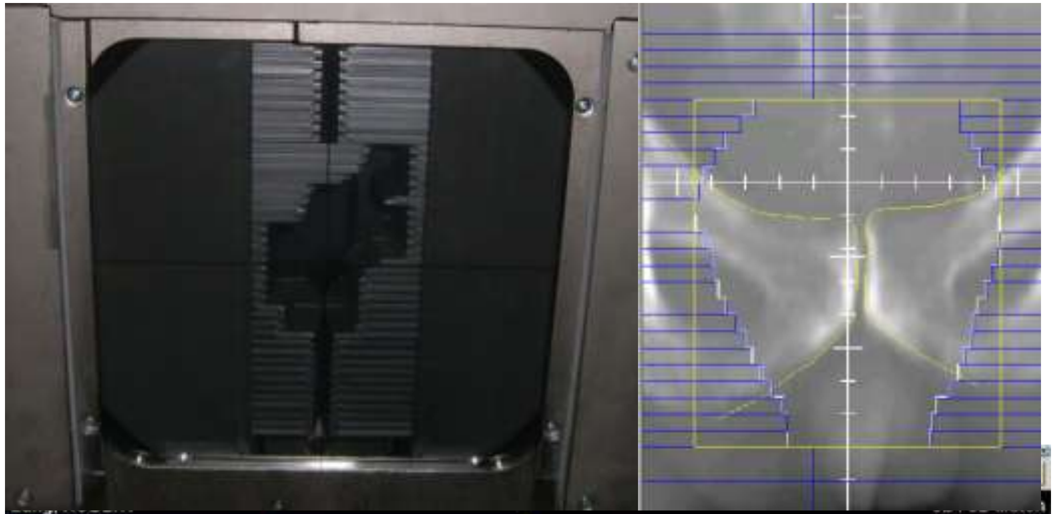
- 1977 – First use of MRI



History: Increasing Sophistication

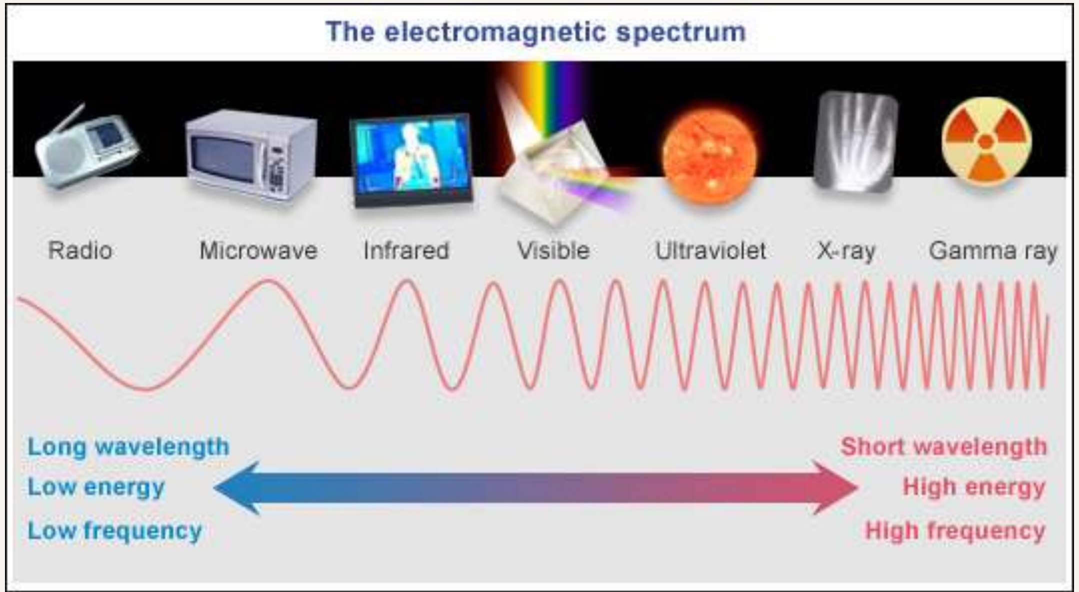
- 1980’s – Development of multi-leaf collimators and Intensity Modulated Radiation Treatment.

- 2000’s – Image guided radiotherapy and widespread adoption of Intensity Modulated Radiation Treatment.



Physical basis of radiotherapy

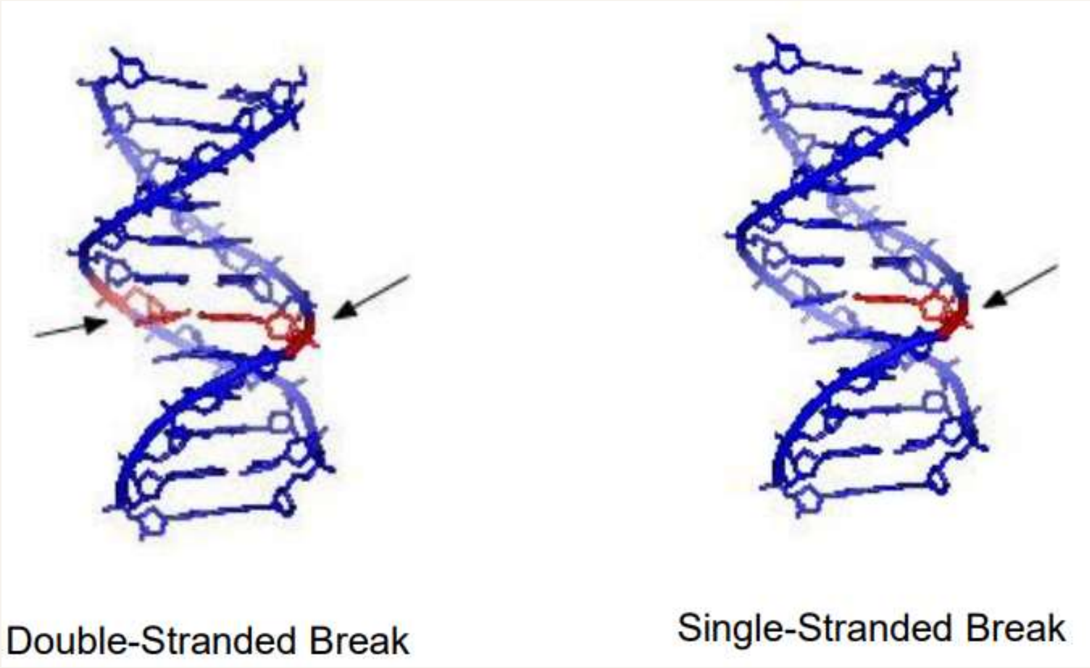
- Photons
  - X-rays
    - Generated by a linear accelerator when accelerated electrons hit a tungsten target
  - Gamma Rays
    - Emitted from a nucleus of a radioactive atom
      - Cobalt treatment machine
      - Radioisotopes used in brachytherapy
- Particles
  - Electrons
  - Protons
  - Neutrons



The radiation behind radios, visible light and nuclear blasts is all exactly the same thing, just with different amounts of energy.

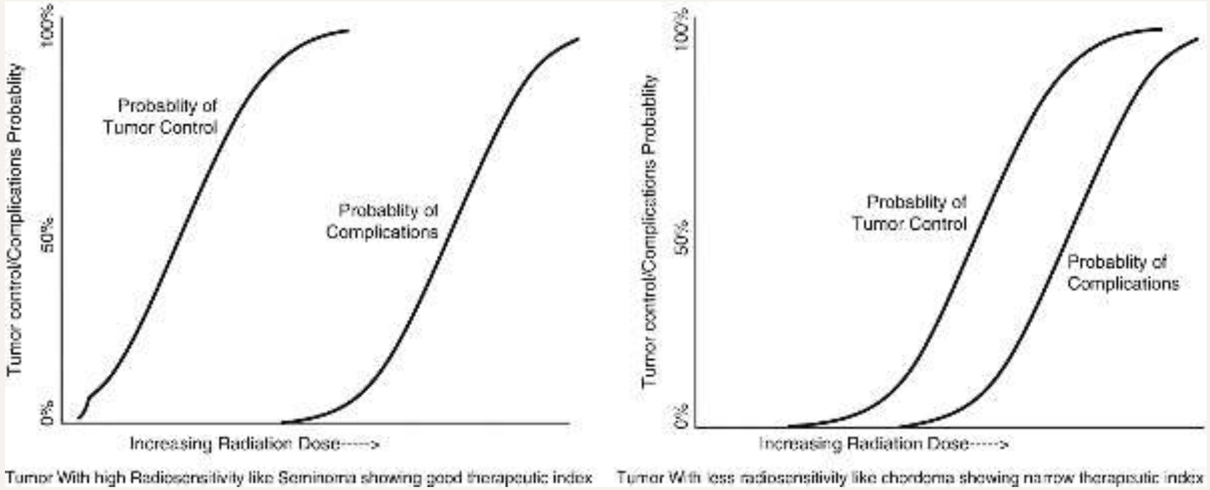
Biological basis of radiotherapy

- Radiation therapy works by directly or indirectly damaging the DNA of cells.
- Double stranded breaks and single strand breaks prevent mitosis and require repair.
- If repair is not possible then apoptotic or necrotic cell death occurs.



Biological basis of radiotherapy

- Cancer cells have a generally impaired ability to repair DNA damage which leads to cell death or inability to replicate.
- A therapeutic benefit is derived from preferentially damaging tumour cells.
- All tissues have a tolerance level, or maximum dose, beyond which irreparable damage may occur



Biological basis of radiotherapy

- Fractionation, or dividing the total dose into small daily fractions over several weeks, takes advantage of differential repair abilities of normal and malignant tissues
- Fractionation spares normal tissue through repair and repopulation while increasing damage to tumour cells through redistribution and reoxygenation -> The 4 ‘R’s’ of radiobiology

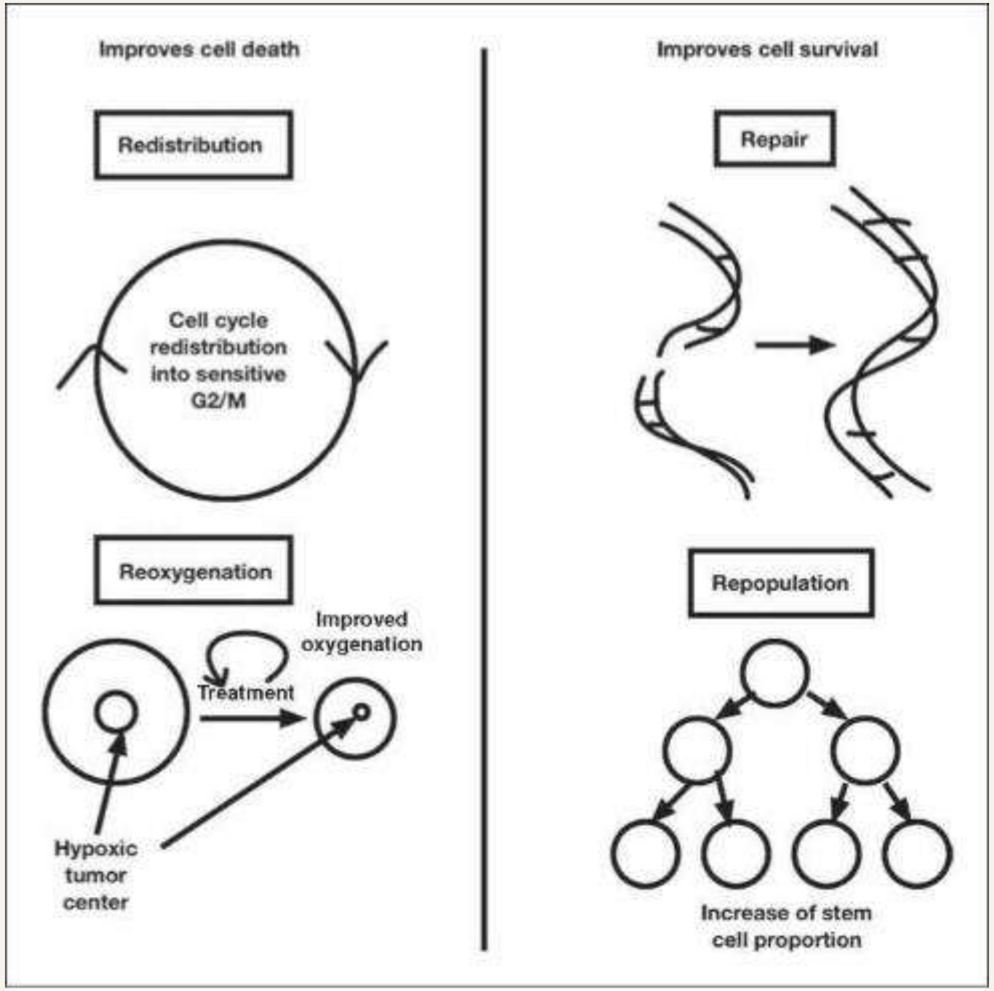
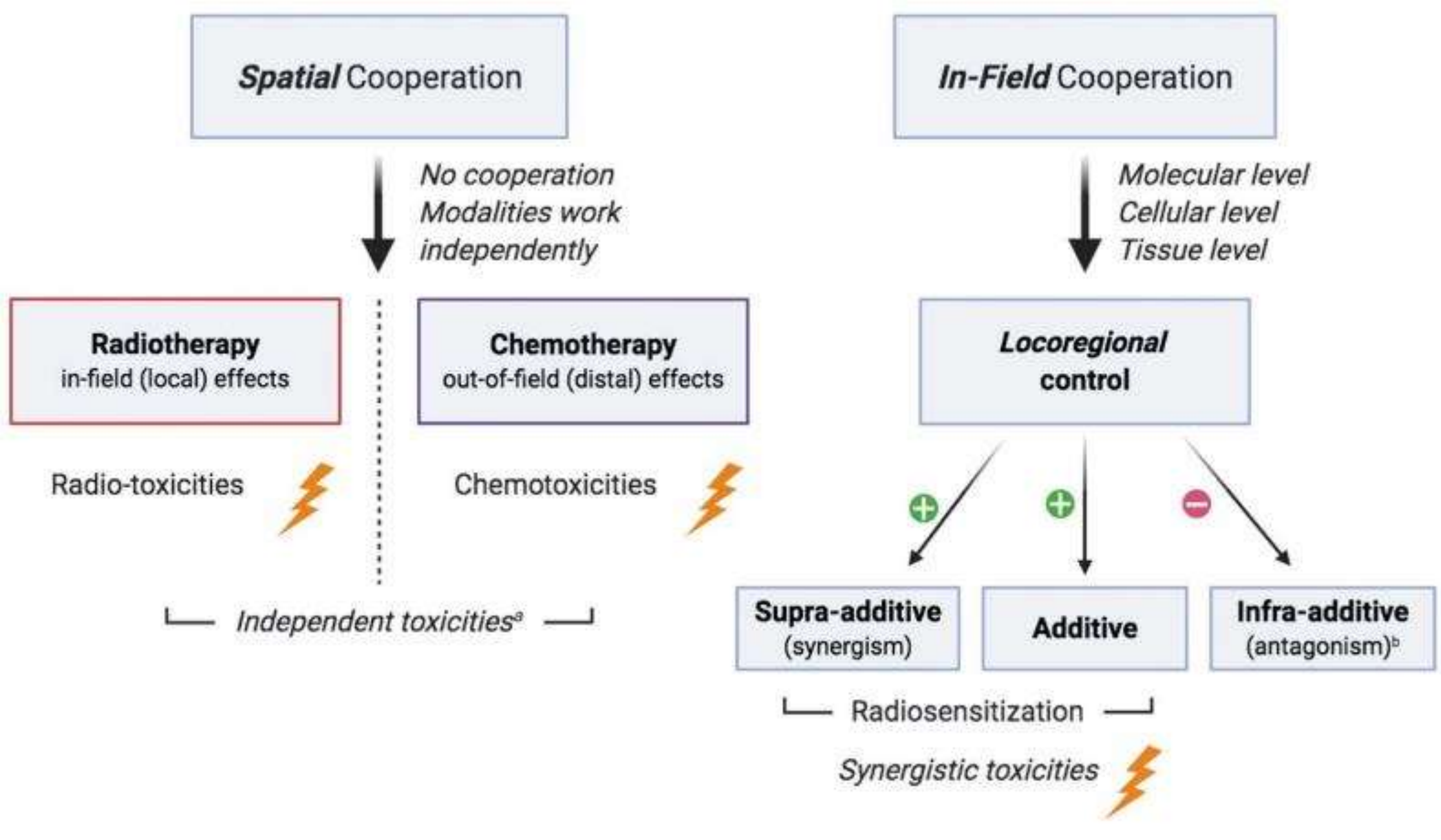


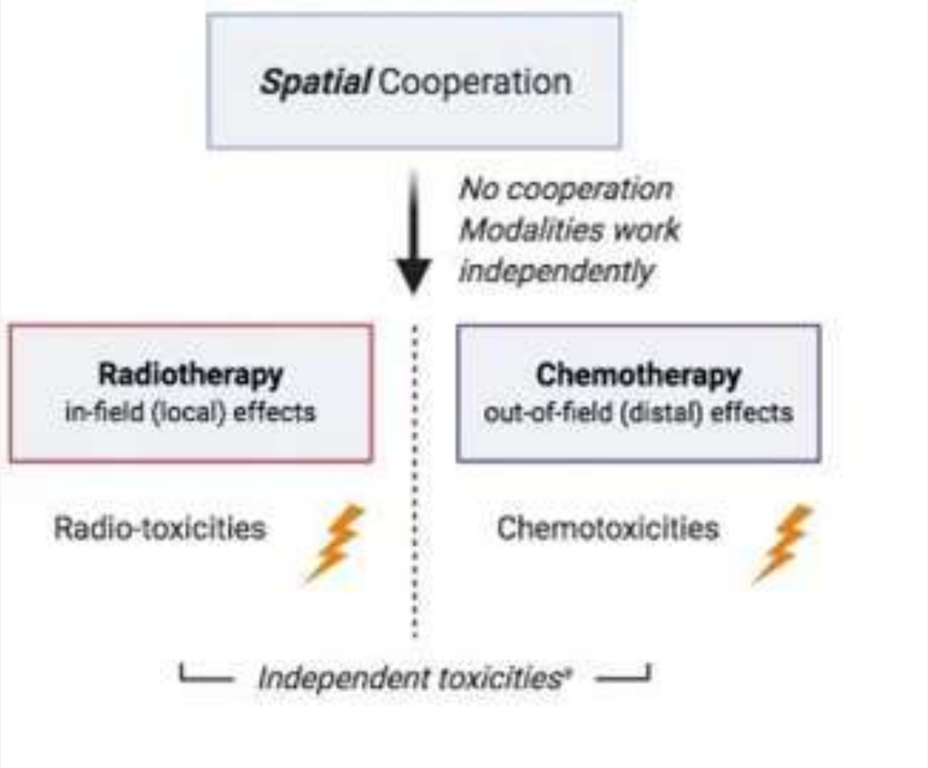
FIGURE 3.7 Four Rs of radiobiology

Chemoradiotherapy



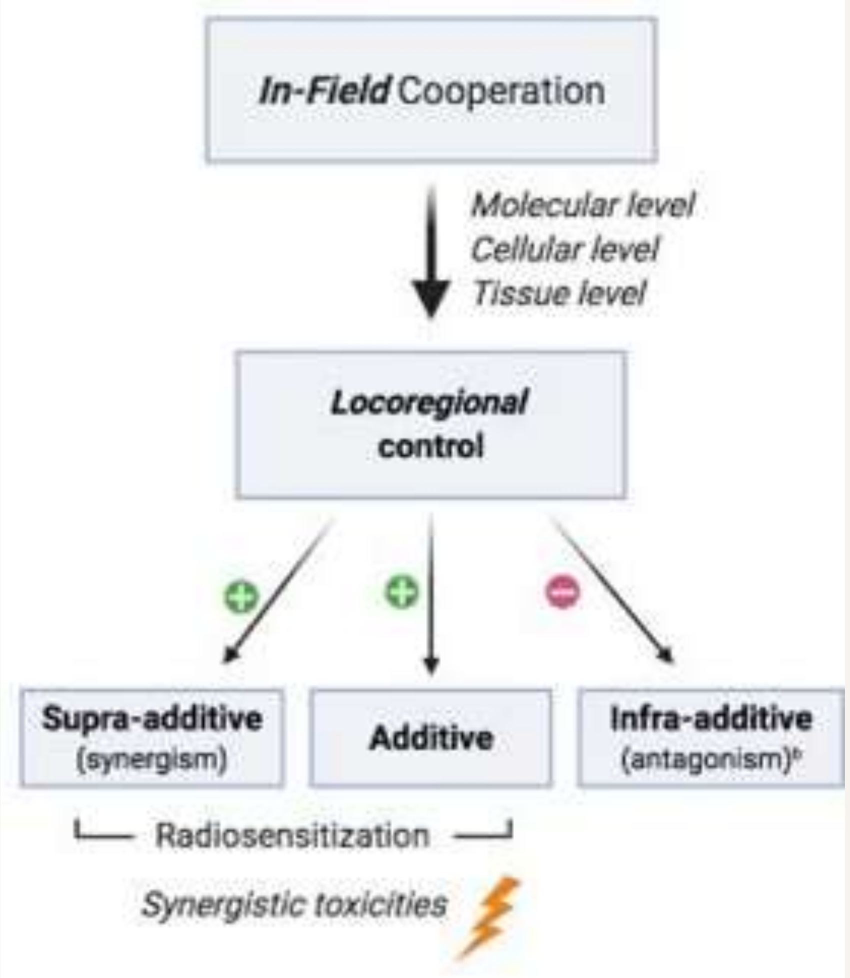
Chemoradiotherapy

- Spatial Cooperation
  - Radiotherapy = local treatment.
  - Chemotherapy = global treatment.
  - Radiotherapy can sterilise gross primary and nodal disease.
  - Chemotherapy can address microscopic metastatic disease.
  - Ideally radiotherapy and chemotherapy will have independent/non overlapping side effects/toxicity.



Chemoradiotherapy

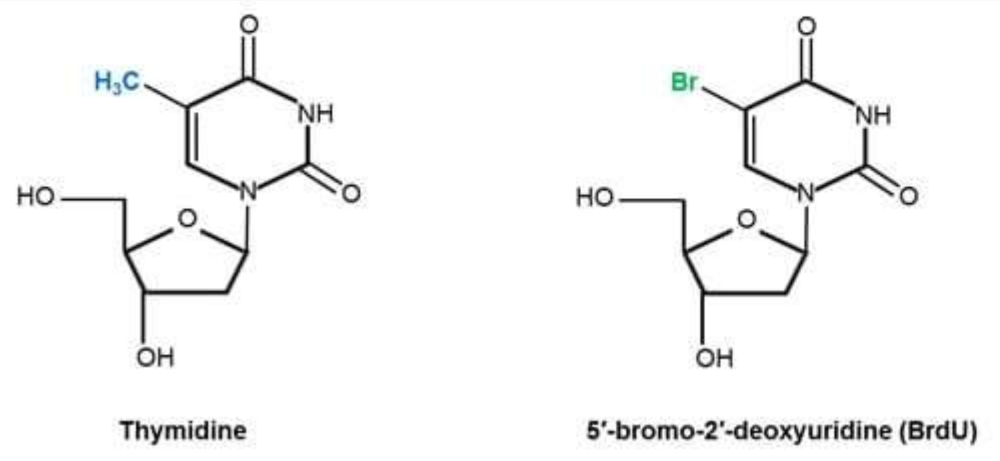
- In field cooperation
  - ‘Additive’ or ‘supra-additive’ effect.
- Radiation Sensitisation
  1. Direct radiation damage enhancement by drug incorporation into DNA/direct damage to DNA
  2. Cellular repair inhibition
  3. Radiosensitive phase cell accumulation or radioresistant phase cell elimination
  4. Hypoxic cell elimination
  5. Inhibition of accelerated cancer cell repopulation



Chemoradiotherapy

Direct radiation damage enhancement by drug incorporation into DNA

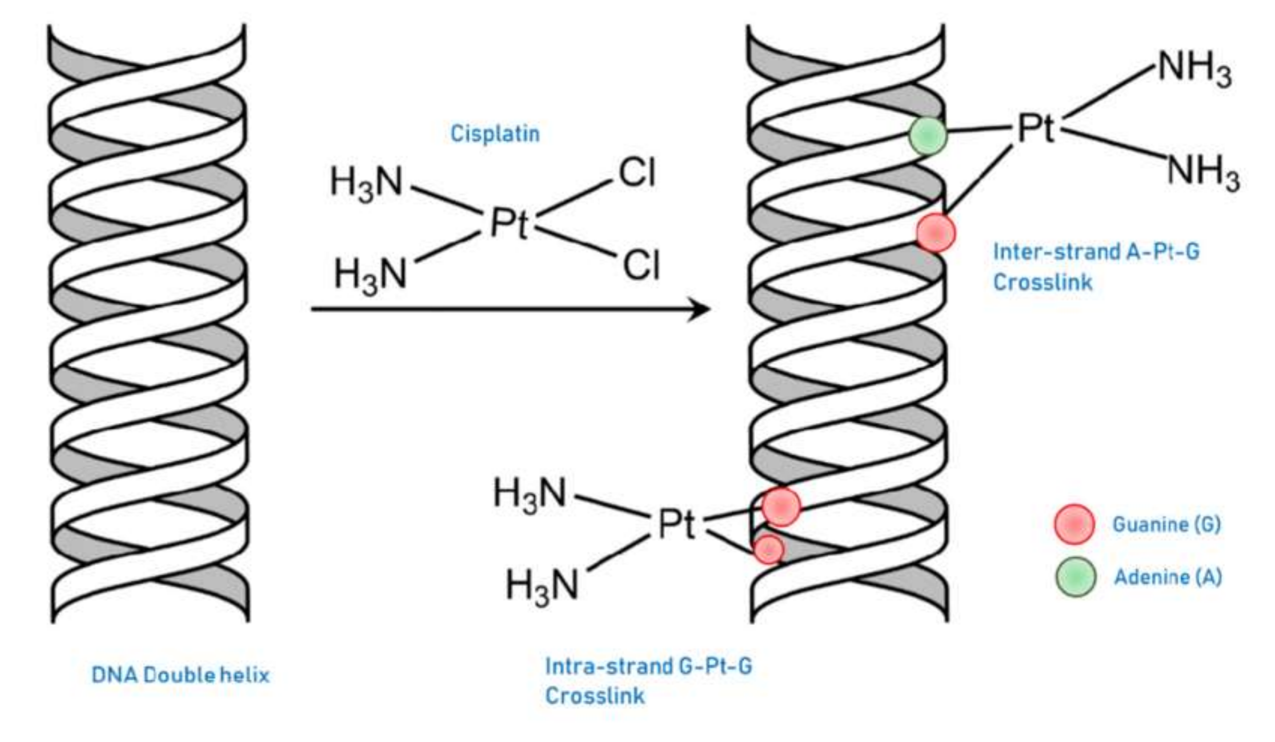
- Halogenated pyrimidines [5-bromodeoxyuridine (BUdR) and 5-iododeoxyuridine (IUdR)]
- Similar to DNA precursor thymidine (halogen substituted for methyl group)
- Weakens the DNA chain – susceptible to RT induced DNA damage



Chemoradiotherapy

Direct damage to DNA

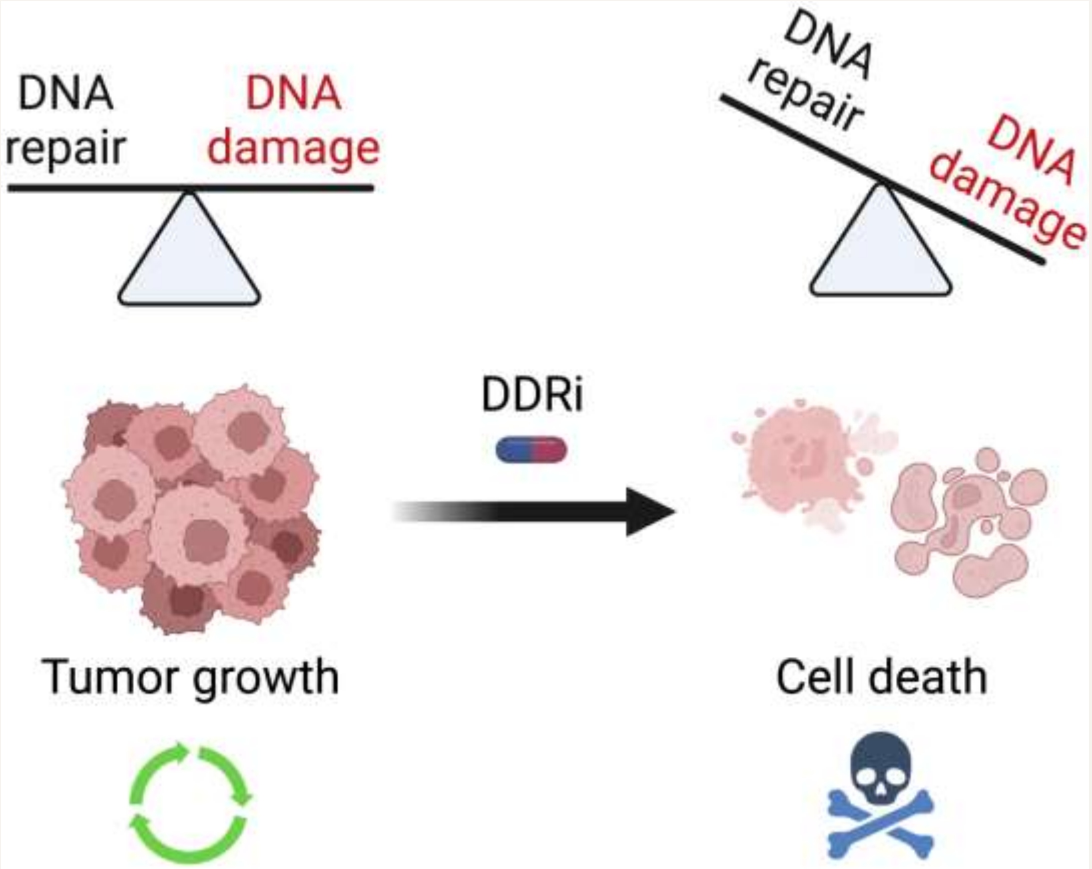
- Cisplatin
- 5FU
- Damage by these agent + SS DNA breaks from RT = double strand break -> unrepairable.



Chemoradiotherapy

Cellular repair inhibition

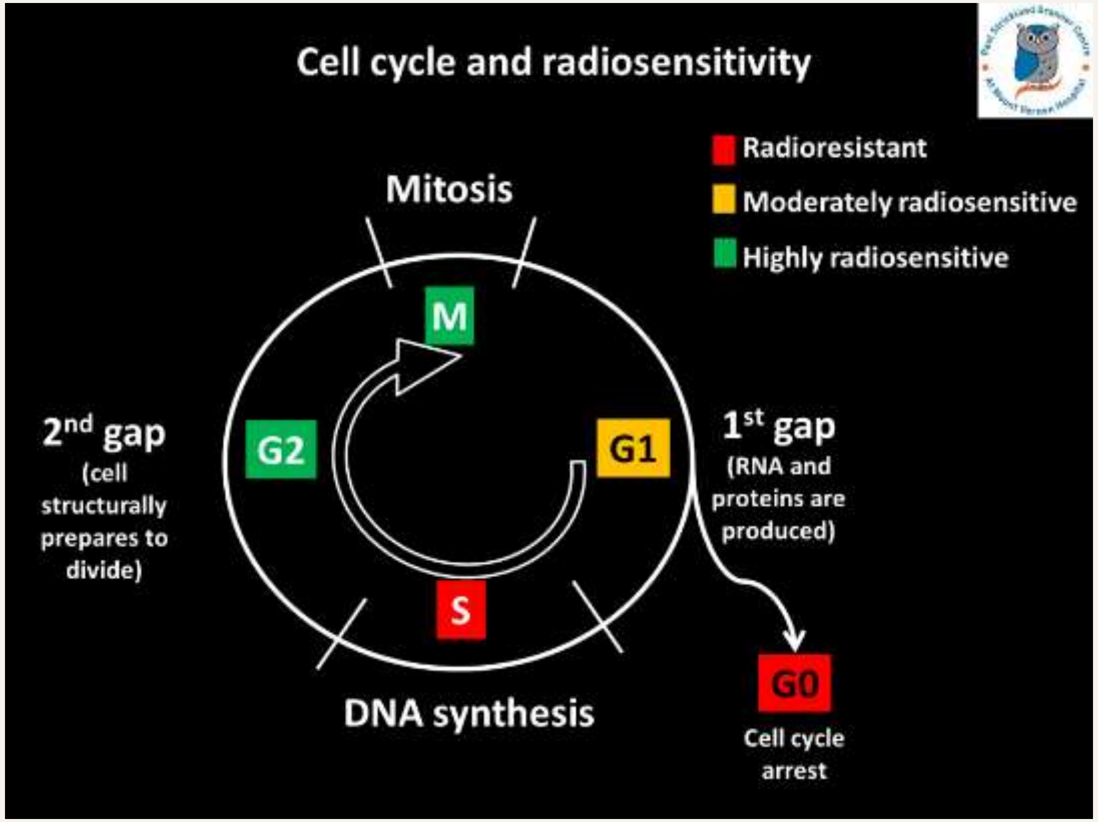
- 5-FU, Gemcitabine, fludarabine, methotrexate, etoposide, hydroxyurea
- If DNA unable to be repaired then causes cell death or subsequent RT can cause cell death.
- More effective in fractionated radiotherapy.



Chemoradiotherapy

Radiosensitive phase cell accumulation or radioresistant phase cell elimination

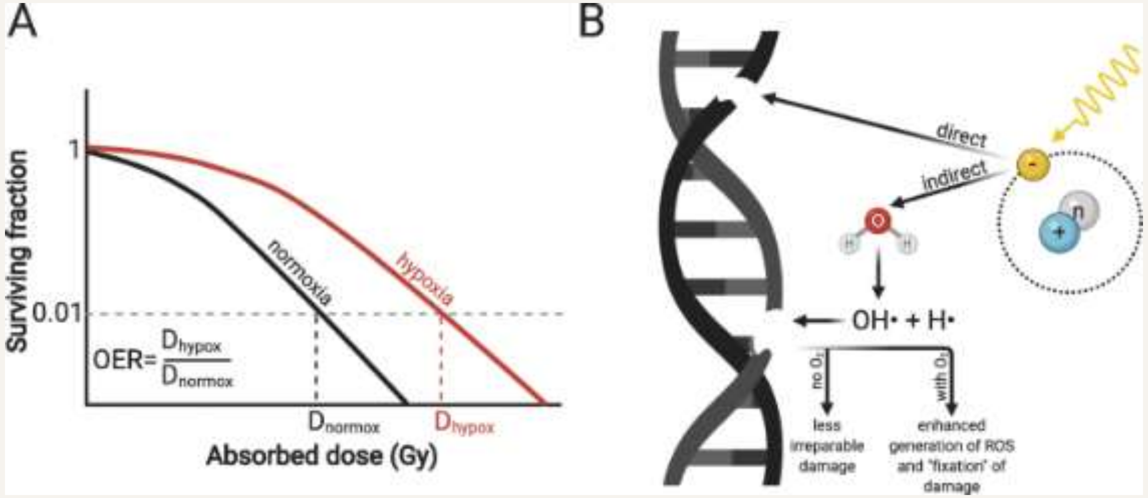
- Taxanes, gemcitabine, fludarabine, etoposide, methotrexate, hydroxyurea
- Sensitive periods in cell cycle for RT induced DNA damage.
- If tumour cells could be synchronised then improved cell kill.
- Good pre-clinical data but unclear if this is replicated in vivo.



Chemoradiotherapy

Hypoxic cell elimination

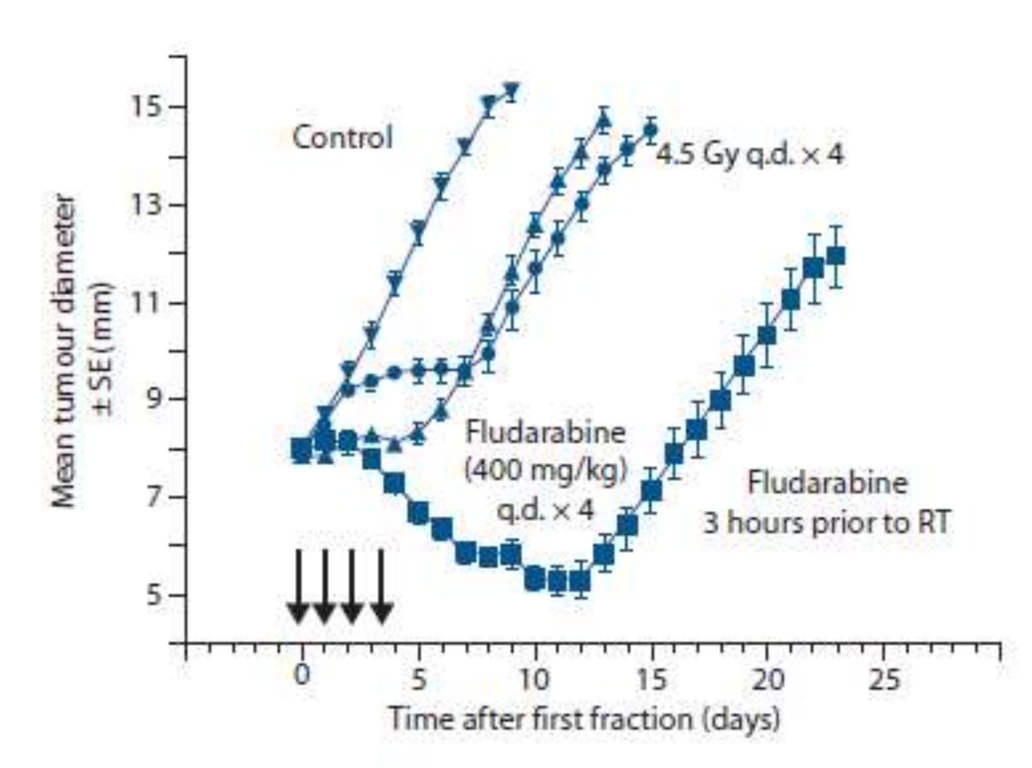
- Indirect DNA damage via oxygen free radicals.
    - Hypoxic cells = radioresistant.
- Chemotherapy -> reduction in tumour bulk therefore improved oxygenation.
- Drugs targeting hypoxic cells (tirapazemine) -> kills tumour cells RT can't.
- Drugs mimicking oxygen (misonidazole).



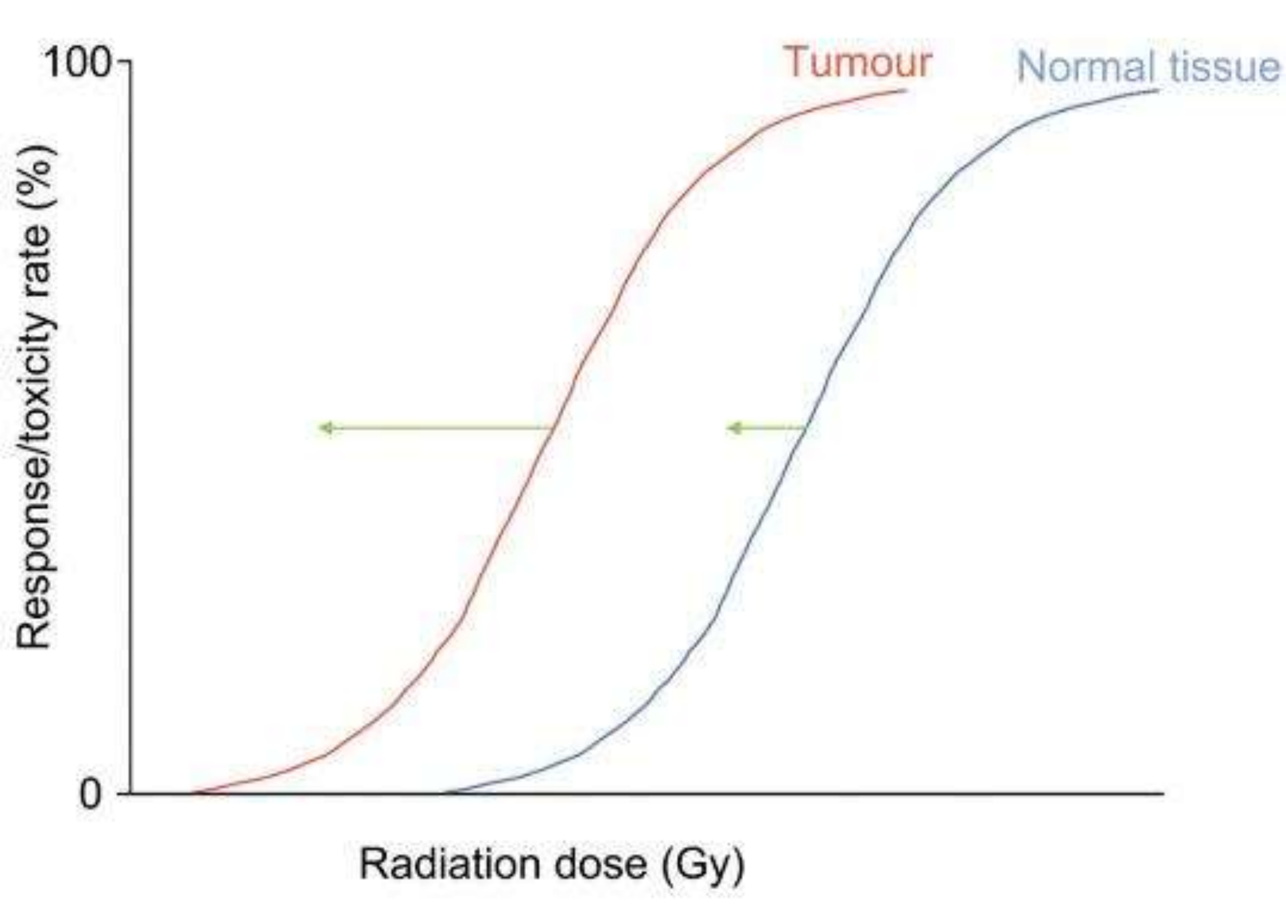
Chemoradiotherapy

Inhibition of accelerated cancer cell repopulation

- Tumours excess cell proliferation compared to cell loss.
- Limited by nutirents, oxygen etc.
- Killing a fraction of tumour cells allows remaining cells to rapidly divide -> *accelerated repopulation.*
- Cytostatic or cytotoxic chemo reduces this therefore improves tumour control.



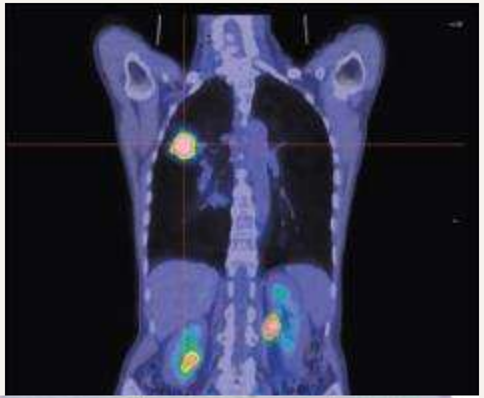
Chemoradiotherapy



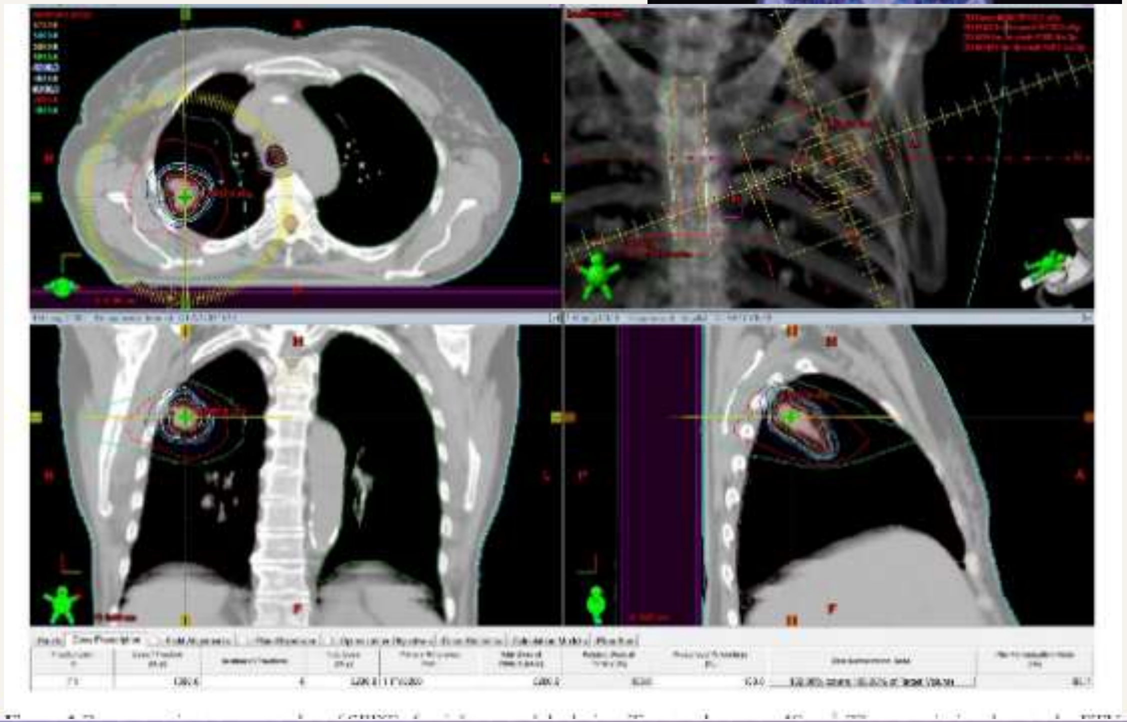
Types of Radiotherapy

- External Beam Radiotherapy
- Photons
  - X-rays from a linear accelerator
  - Most common form of radiotherapy
  - Conventional vs stereotactic treatment.
- Electrons
  - Linear accelerator
- Heavy Charged Particles
  - Protons
  - Carbon ions
- Non External Beam Radiotherapy
  - Brachytherapy
  - Theranostics

Clinical uses of Radiotherapy

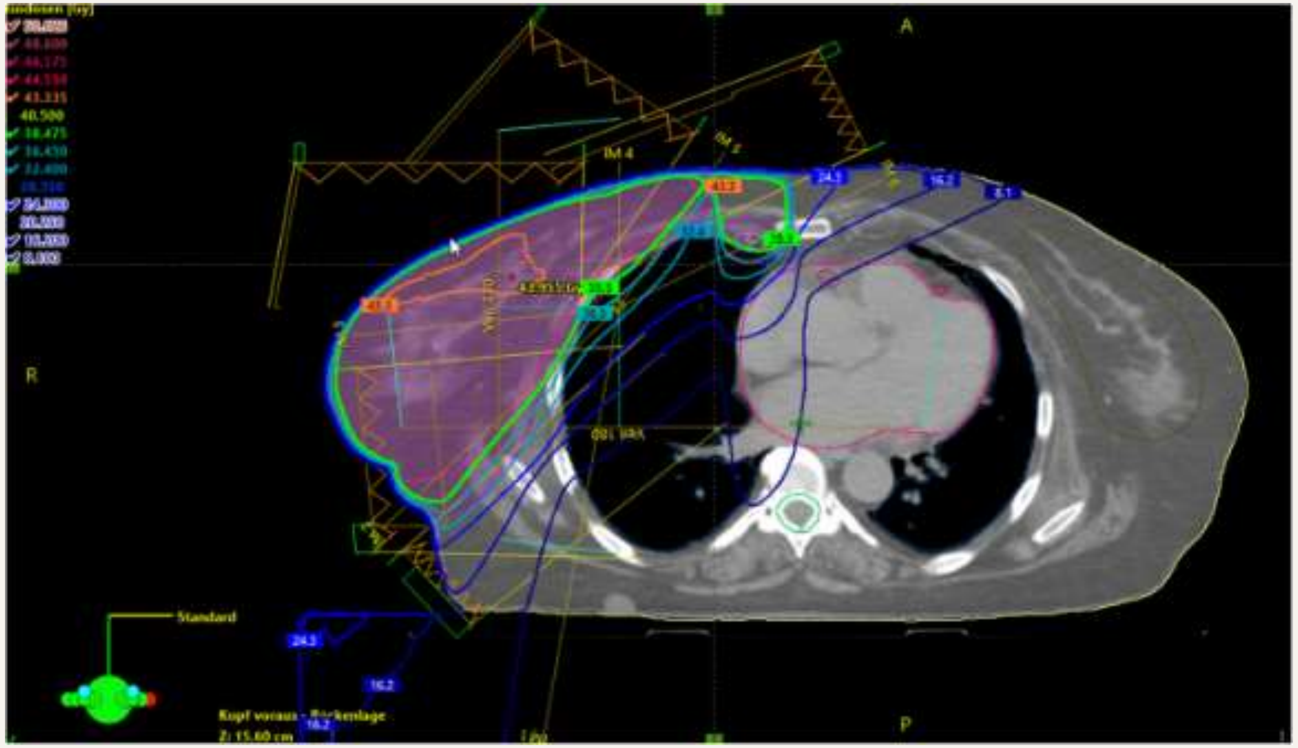


- Definitive
  - Alone
    - E.g. Prostate, Lung, Head/Neck, CNS, lymphoma, skin.
  - Chemoradiotherapy
    - Lung, Gynae, Head/Neck, CNS



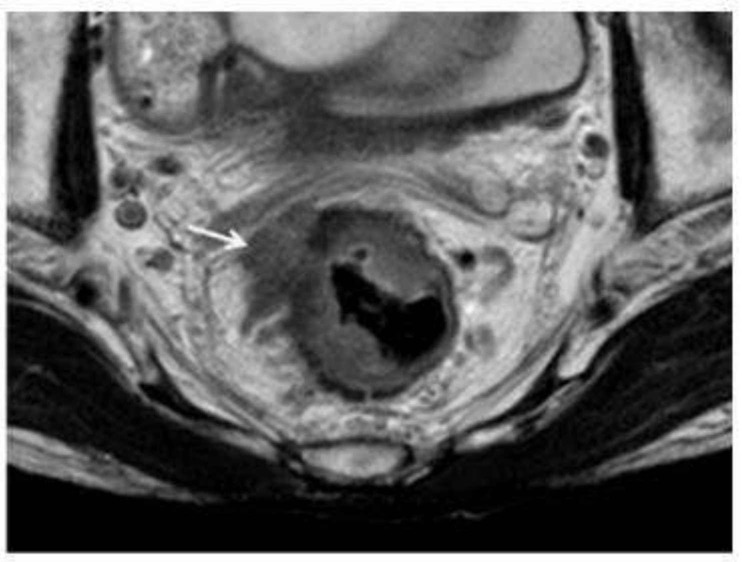
Clinical uses of Radiotherapy

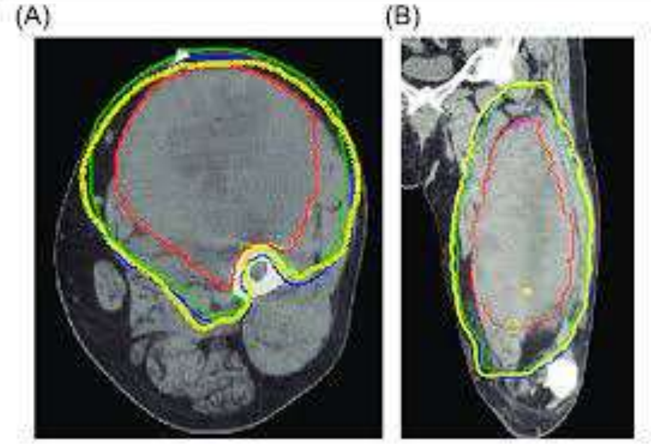
- Adjuvant
- E.g. Skin, Breast, Head/Neck, Gynae, CNS.



Clinical uses of Radiotherapy

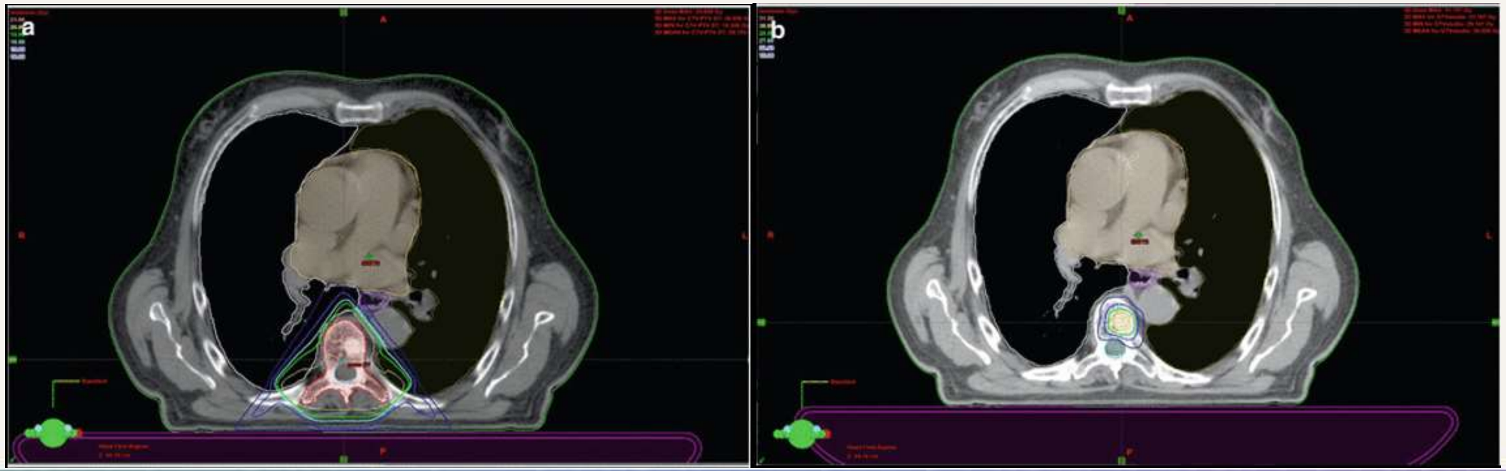
- Neoadjuvant
- E.g. Sarcoma, Rectal.

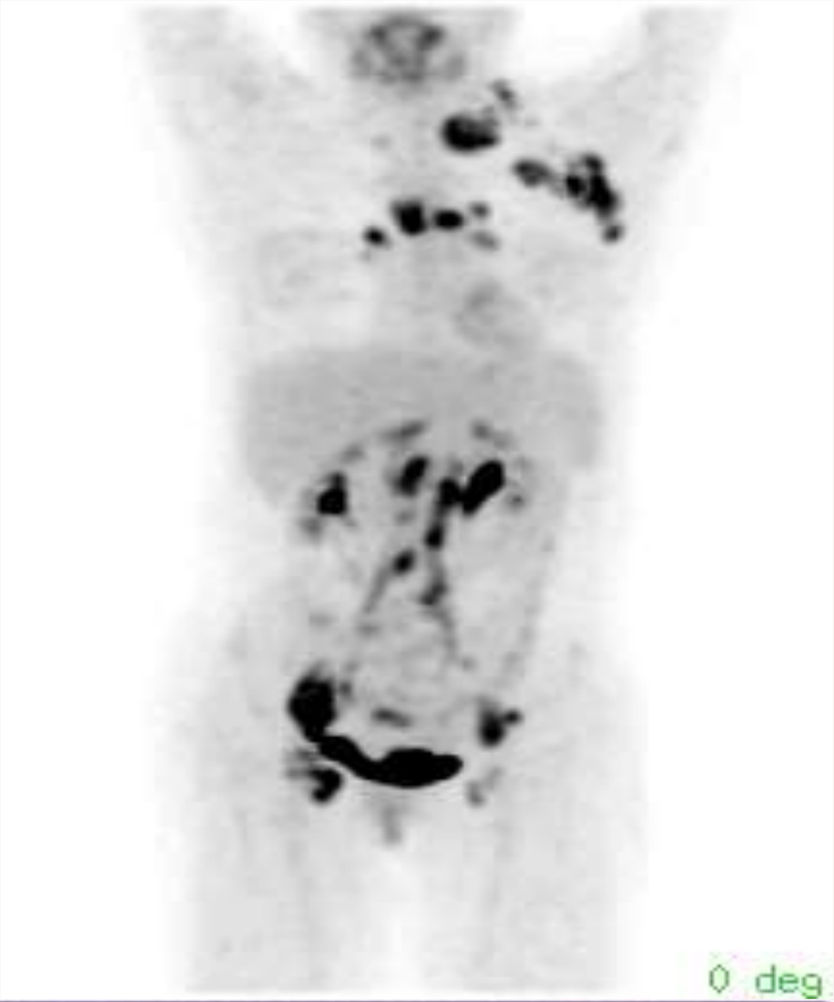




Clinical uses of Radiotherapy

- Palliative
- For symptom management: pain, swelling, bleeding.





Clinical uses of Radiotherapy

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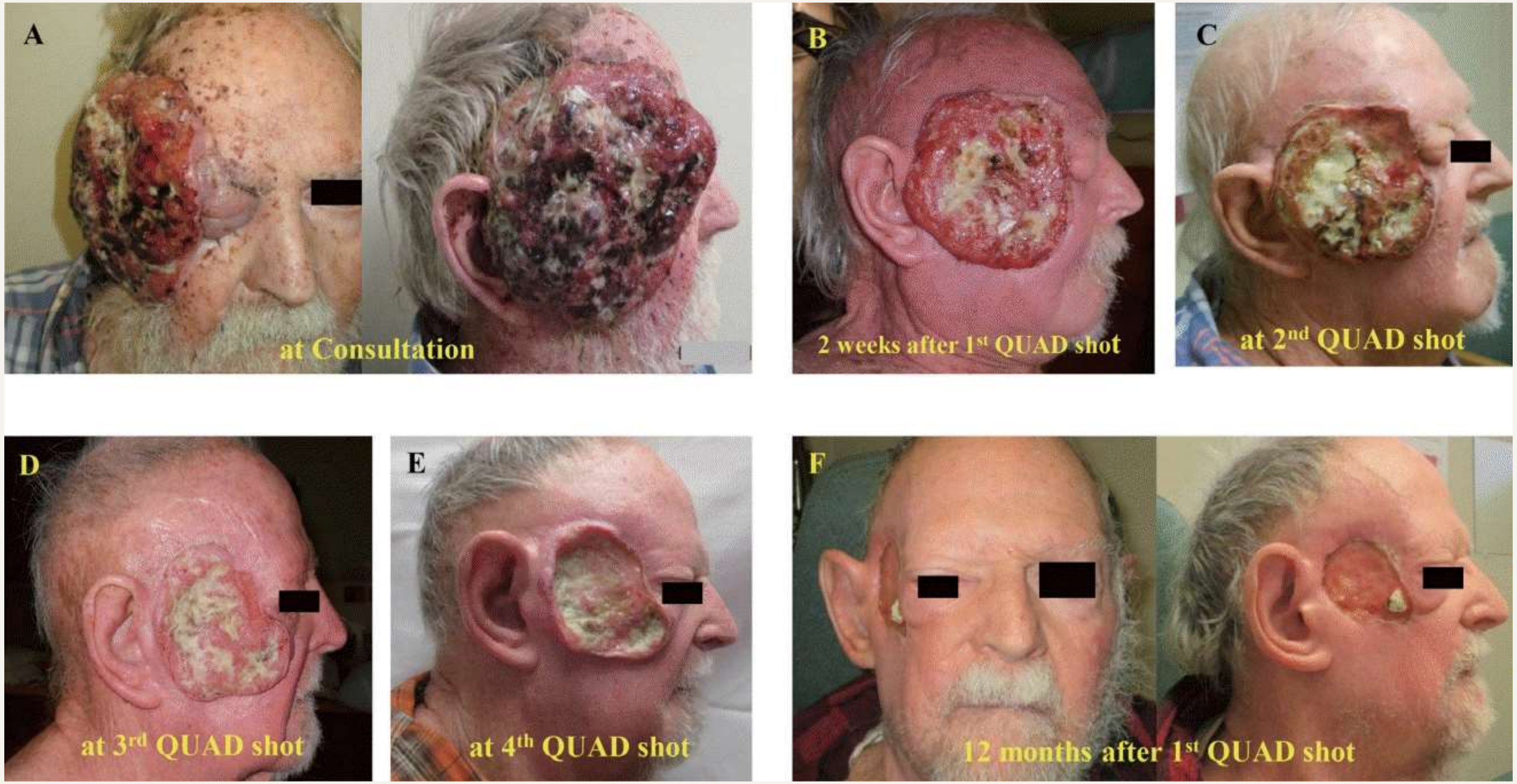
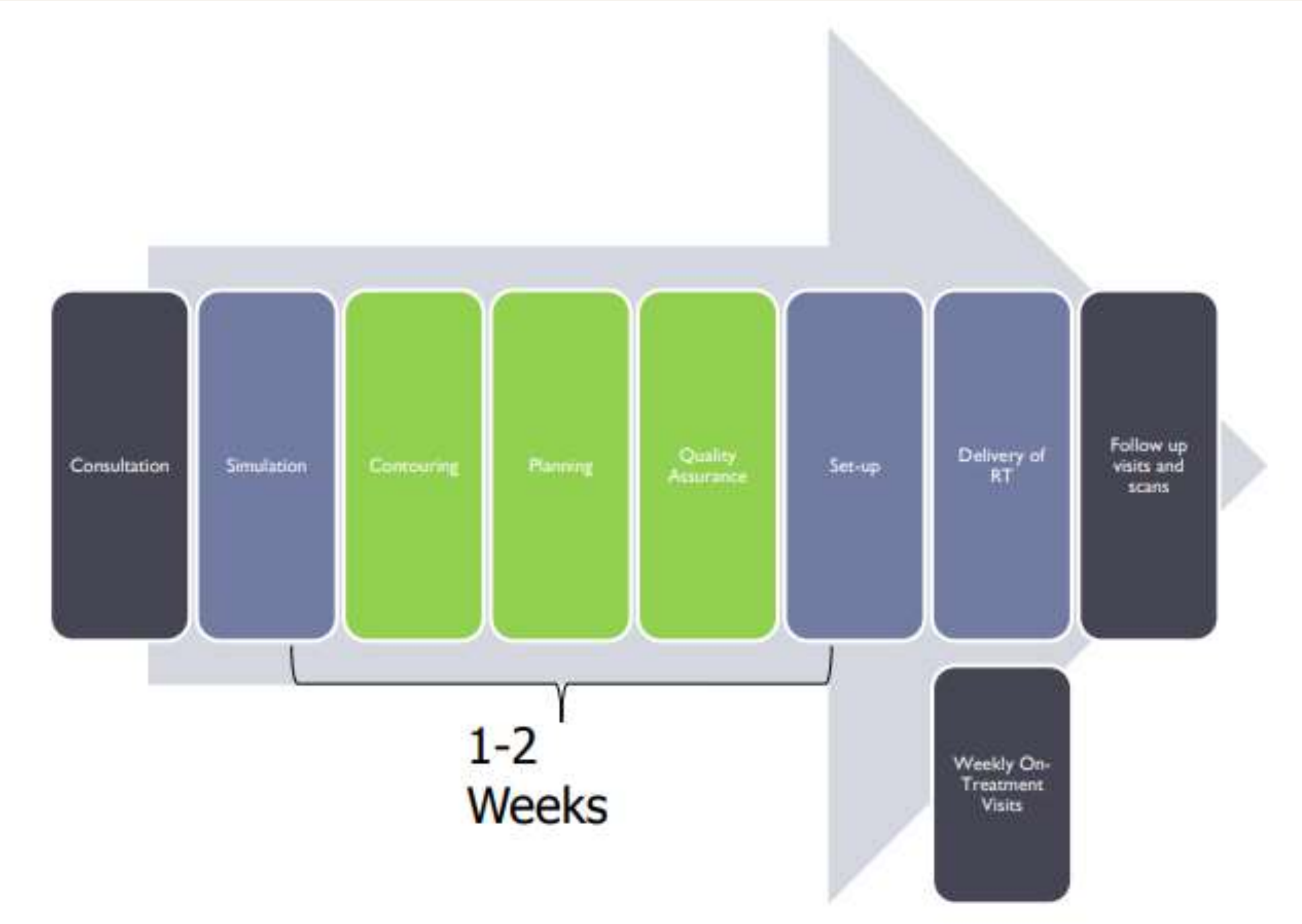


The process of radiotherapy



The process of radiotherapy: Initial Consultation

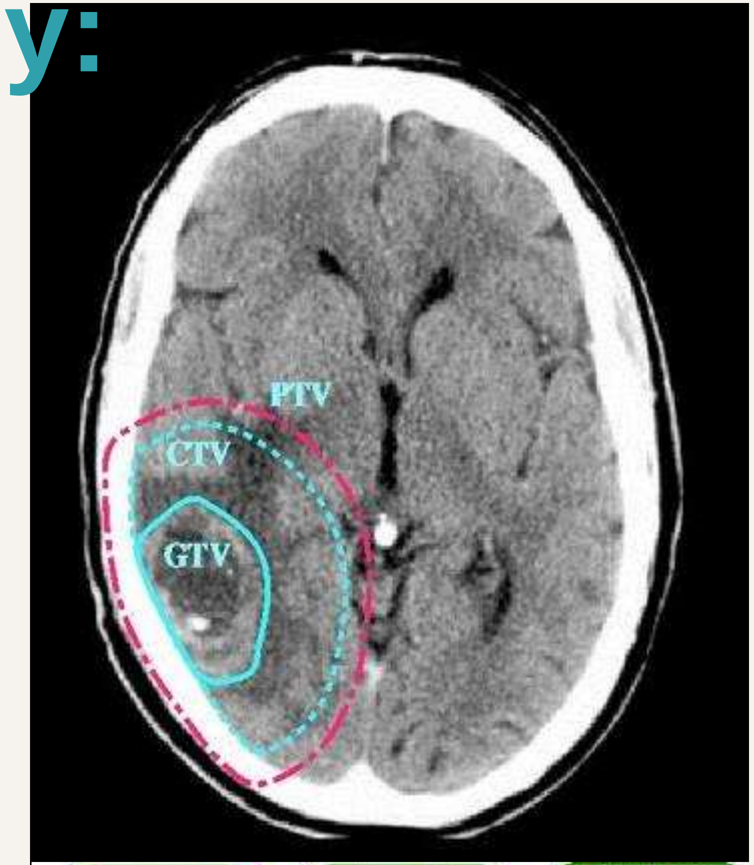
- History
- Examination
- Review of:
  - Imaging
  - Operative reports
  - Histology/pathology
- Assess suitability for radiotherapy
- Informed consent
- Book for radiation treatment
- Referrals to other medical specialities allied health/nursing staff

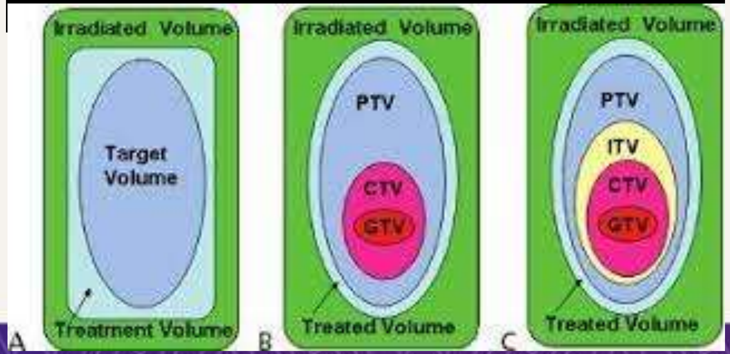
The process of radiotherapy: Simulation

- Patient is set up in treatment position on a dedicated CT scanner
  - Immobilization devices may be created to assure patient comfort and daily reproducibility
  - Reference marks or “tattoos” may be placed on patient
- CT simulation images are often fused with PET or MRI scans for treatment planning

The process of radiotherapy: Contouring

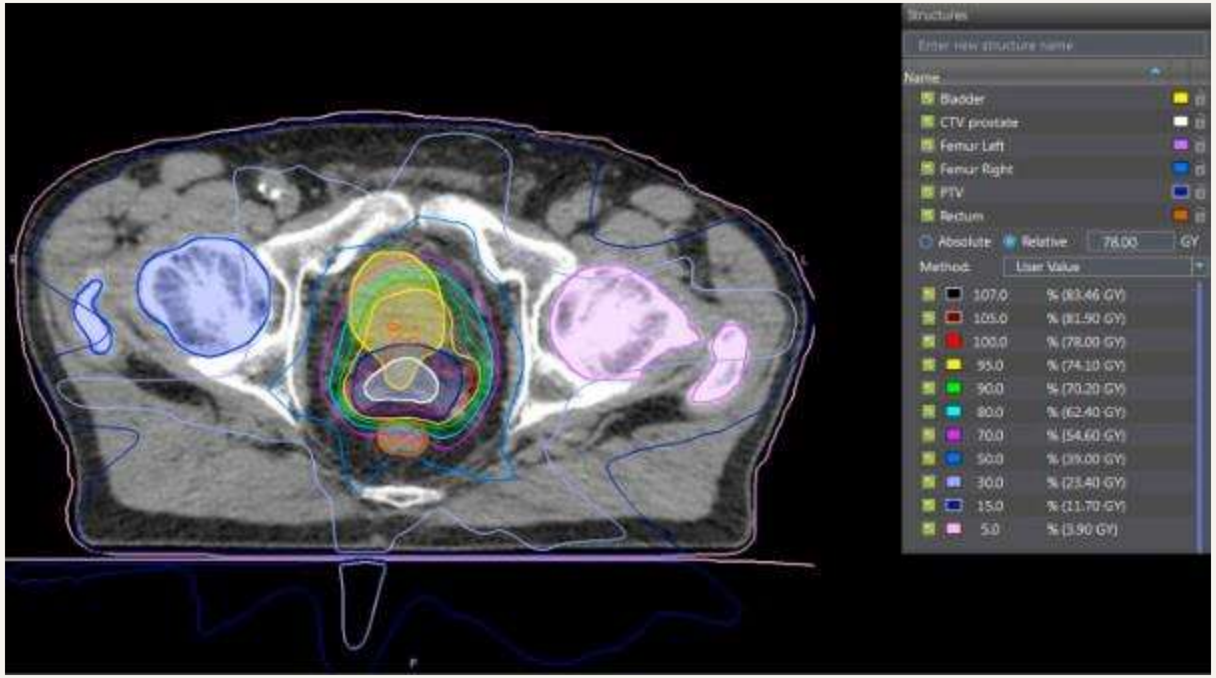
- Gross disease is defined (Gross Tumour volume – GTV)
- Margin around GTV to encompass microscopic disease spread (Clinical Target Volume – CTV)
- Isotropic margin added to CTV to allow for uncertainty in set up or treatment delivery (Planning Target Volume – PTV)
- Define healthy organs – Organs at Risk (OARs)





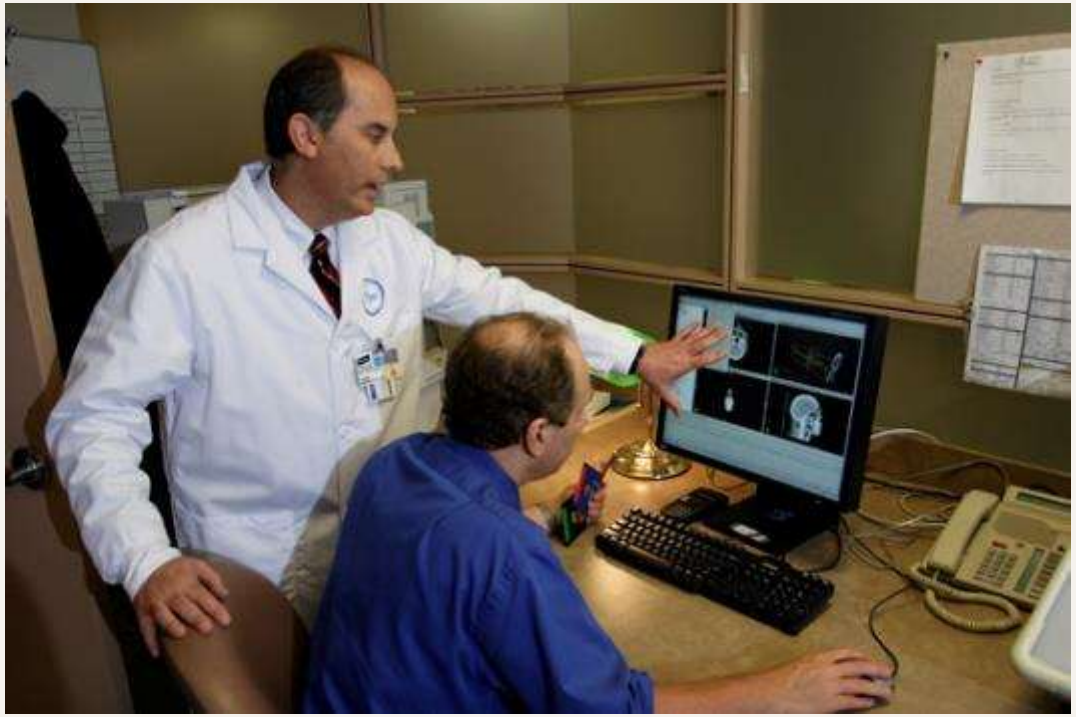
The process of radiotherapy: Planning

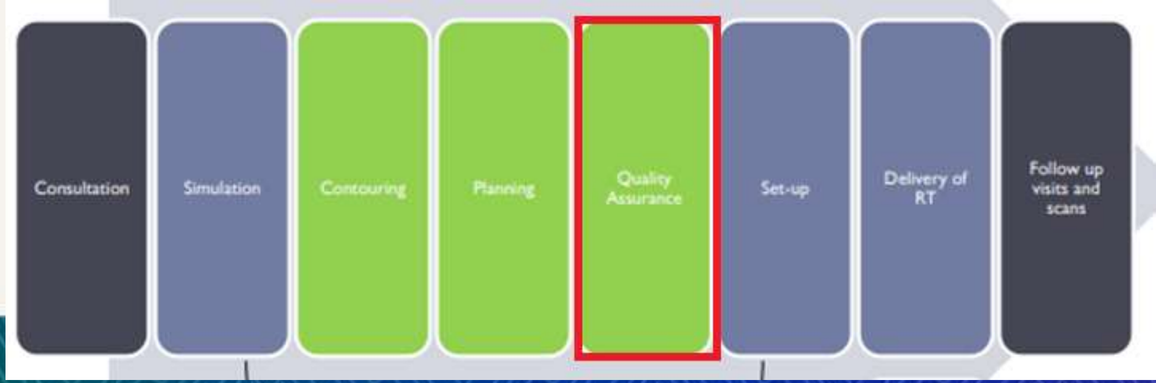
- Sophisticated software is used to carefully derive an appropriate treatment plan
  - Computerized algorithms enable the treatment plan to spare as much healthy tissue as possible while ensuring adequate dose to the PTV
- Medical physicist checks the chart and dose calculations
- Radiation oncologist reviews and approves final plan
  - Is the target being covered adequately?
  - Is the amount of radiation given to normal tissues acceptable?
  - Potential side effects of each particular treatment – short and long term



The process of radiotherapy: Quality Assurance

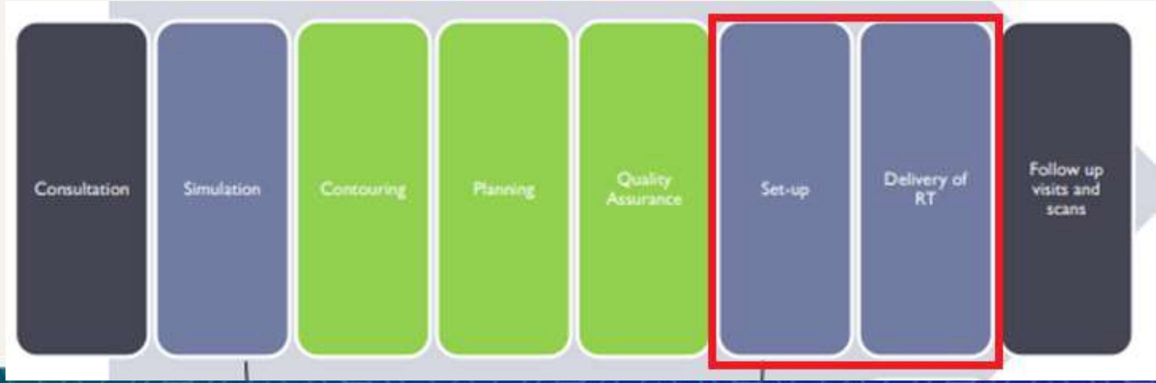
- Each radiation therapy treatment plan goes through many safety checks
- The medical physicist checks the calibration of the linear accelerator on a regular basis to assure the correct dose is being delivered
- The radiation oncologist and medical physicist go through a rigorous multi-step QA process to be sure the plan can be safely delivered
- QA checks are done by the radiation therapist daily to ensure that each patient is receiving the treatment that was prescribed for them





The process of radiotherapy: Set Up/Delivery

- Patients are positioned in the same way as at planning.
- Detailed instructions are followed regarding each individual patients set ups.
- Objective markers such as tattoos are used to ensure position is correct.
- X-rays or cone beam CT is used to match tumour, bony anatomy or implanted fiducials to ensure treatment is accurate.



The process of radiotherapy: Follow up

- On treatment review weekly.
- Post treatment: frequency varies with treatment aim and site.
- History, examination, imaging to ensure no evidence of recurrence, symptoms or late effects.
- Typically follow up ends at 5 years.

Questions