Cambridge Oncology

Module 3 – Radiotherapy in Practice

Learning objectives

- Learn the basic principles of how radiotherapy works
- Understand the different types of radiotherapy treatments available
- Learn about the process of radiotherapy treatment preparation and delivery
- Recognise possible short term and long term side effects of radiotherapy

Introduction

You may now have much experience of radiotherapy but here are some things to consider

- Radiotherapy is an important anti-cancer therapy, and is used in the treatment of 40% of patients who are cured of cancer (compared to 2% for chemotherapy). 50% of cancer patients will need radiotherapy at some point in their cancer journey
- Modern radiotherapy makes extensive use of imaging, computing, and engineering to direct radiation to the tumour target with high precision
- Radiotherapy is an extremely cost effective cancer treatment. A course of radiotherapy costs about £2500, compared to £5500 for a surgical procedure and £13500 for a course of chemotherapy

A brief glossary

Teletherapy / External Beam radiotherapy – This means the radiation source is outside and at some distance from the patient

Brachytherapy - this means the radiation source is inside or on the surface of the patient

Radionuclide therapy – a radioactive isotope is injected or ingested by the patient

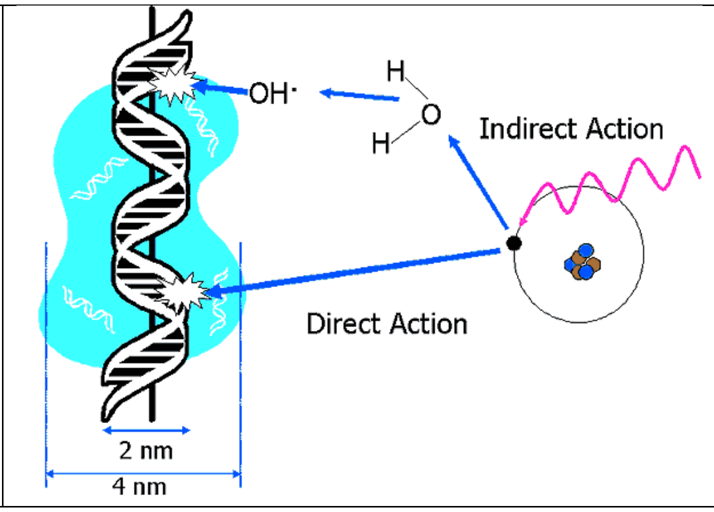
X-ray – electrically generated ionising radiation. We use high energy x-rays for most of our radiotherapy treatments

Gamma ray – naturally occurring ionizing radiation from decay of radioactive isotopes. We use radioactive sources in brachytherapy and implants which emit gamma rays. Physically speaking there is no difference between a gamma ray and an x-ray of the same energy.

X-ray energy – we express x-ray energies as the voltage of the accelerating field used to generate the x-rays. This is typically kilovolts to megavolts.

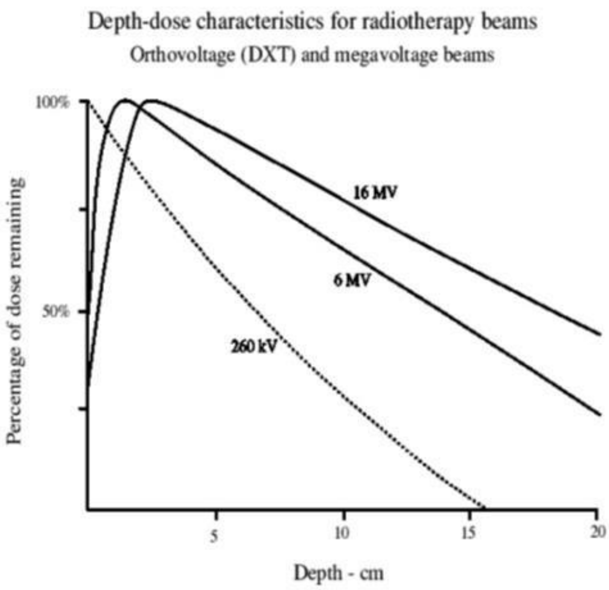
How does radiotherapy work?

Radiotherapy works by damaging DNA. High energy x-rays interact with matter and produce high energy electrons. It is these electrons that damage DNA in one of two ways

The direct effect		**The indirect effect**
Electrons hit the DNA backbone and induce single strand breaks and double strand breaks.		Electrons interact with a water molecule close to the DNA backbone. The water molecule is split into reactive H· and OH · radicals and these induce double and single stranded breaks

We are mainly interested in double stranded DNA breaks as these cause the most difficulty to the cell. Healthy cells have functional DNA repair mechanisms and will either repair DNA damage or recognize the genotoxic injury and undergo apoptosis. Tumour cells have dysregulated DNA repair and replication pathways and will therefore undergo mitotic cell death in response to radiotherapy.

So without matter to interact with, an x-ray won't deposit radiation dose (a bit like that philosophical question about a tree in a forest falling down when no-one is around – does it bother to make a sound). This sounds a bit esoteric but is actually really useful in the **build-up effect**.



This graph shows the amount of energy deposited by an x-ray as it passes through tissue, and its relationship with its energy. The key thing to notice here is that the higher energy x-rays don't deposit their maximum energy at the skin, instead they deposit maximum energy at some depth into the patient. This is because the x-rays have so much energy they don't really start interacting with tissue until they are further in to the body. This means that we can give a higher dose to a deep seated tumour than to the skin on the surface of the patient. When radiotherapy first started being used, the x-rays were of such low energy that most of the radiation dose went into the skin causing radiation burns.

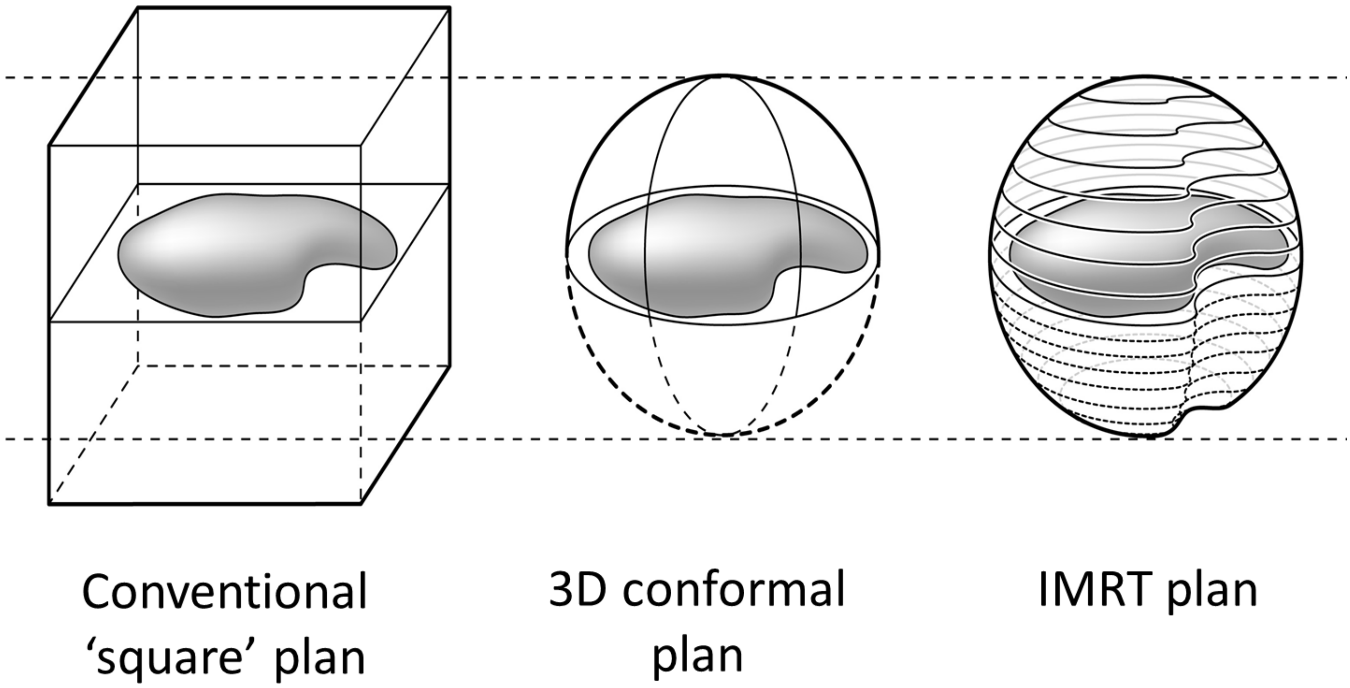
Radiation dose is measured in Gray. It is the SI unit of absorbed radiation dose and is equivalent to 1 joule of energy per kilogram of tissue. It's about the amount of thermal energy in a cup of coffee. Normally we aim to deliver about 60Gy of radiation for a curative treatment.

Modern radiotherapy tries to deliver as high a dose as possible to the tumour, whilst minimizing the dose to healthy surrounding tissues. There are several ways we can achieve this goal:

- Shape the radiation dose as tightly as possible to the shape of the tumour
- Break up the treatment into smaller daily treatments (fractions) to allow health normal tissues to repair between treatments
- Enhance tumour cell kill by combining drug therapy with radiation therapy (chemo-radiotherapy)

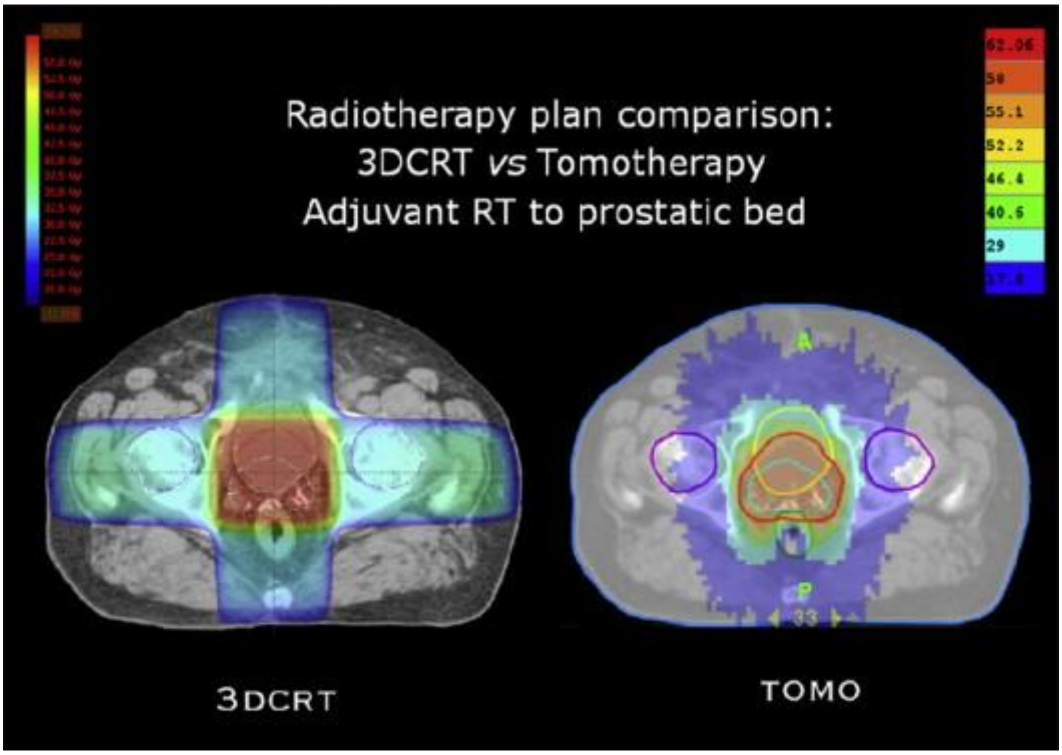
Conformal radiotherapy. Shaping the radiation to the target.

Radiotherapy technology has advanced considerably in the last 10-15 years, allowing us to shape radiation dose with greater accuracy. Modern radiotherapy typically uses multiple beams which treat the target from different directions. The dose in the entry path and exit path of the beam is low, compared to the dose in the area of overlap of the beams.



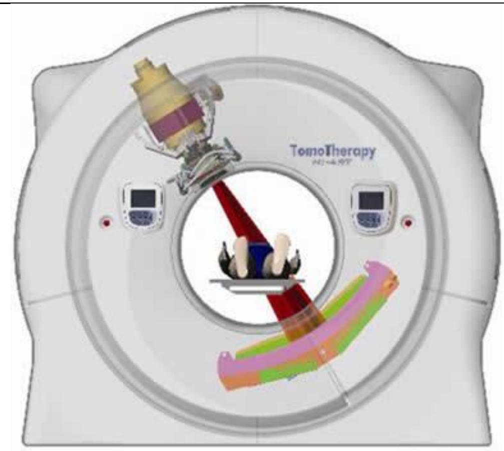
3D conformal radiotherapy means that the radiation beams are shaped to match the profile of the tumour. This is achieved by a device called a multileaf collimator. It moves leaves of lead into the beam go give it the correct shape and shield healthy tissues around the tumour target as much as possible. This is easier said than done – for a 6 million electron volt machine, the leaves of lead have to be 10cm think, and fit together perfectly to that only a minimal amount of radiation leaks out in between the leaves.

Intensity modulated radiotherapy is the next step in conformal radiotherapy. There the machine moves the MLC leaves during treatment to build a very complex distribution of dose. Often the machine will rotate around the patient as the beam shape is being changed. It's *much* easier to visualise with a movie than in words, so check this excellent youtube video showing an animation of a rotational IMRT system.



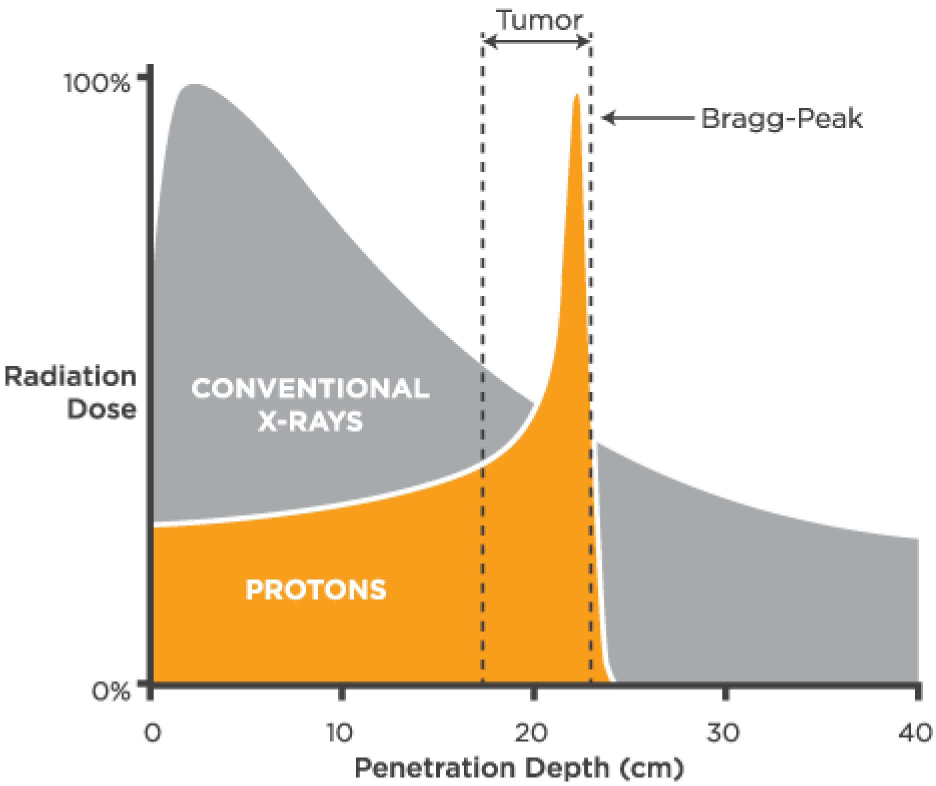
If you look at this dose distribution, you can see the difference that can be achieved between 3D conformal radiotherapy and rotational IMRT (tomotherapy) plans. The red line is the tumour target (in this case the prostate gland), and you can see in the colour wash the dose distribution, with high dose in red and low dose in blue. Note how the high dose is shaped to match the shape of the target with the IMRT plan.

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

There is a cost to using these types of highly conformal radiotherapy. You can't beat the laws of physics and for each little beamlet there will be an entry dose and an exit dose as the x-ray beam passes through the patient. As a result IMRT tends to smear low dose through a larger volume of the patient. This may be particularly relevant in children, where the **low dose bath** increases the risk of growth effects and of second tumour formation.

As an aside, it's worth remembering that low dose radiation is more mutagenic than high dose radiation. High dose radiation will either kill cells, or induce repair mechanisms that fix DNA damage. Low dose radiation may induce low level DNA damage that is not detected and repaired, leading to subsequent mutation.

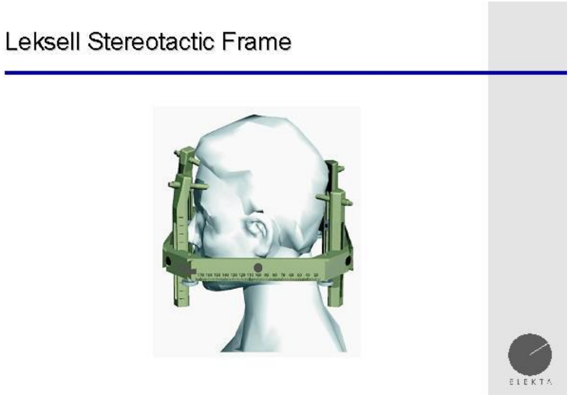


Proton beam therapy is a novel form of radiation therapy that uses particle beams instead of x-rays. The advantage of a particle beam is that the particle can be tuned to stop at a certain distance in the patient. As a result, instead of having a low exit dose, like x-rays, proton beam therapy can achieve no exit dose. Proton beam therapy will start in the UK in 2018, and is likely to focus on children's tumours in the first instance.

Fractionation – breaking radiotherapy up into multiple daily treatments

By breaking treatment up into small daily treatments, we see a cell killing effect in the tumour cells (cell loss), 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. The half-life for mammalian DNA repair mechanisms is about 8 hours, and a 24 hour break between treatments allows 3 half-lives worth of repair to occur. This is why most radiotherapy is given as a 6-7 week course of daily radiotherapy treatment fractions. *Of course tumours don't grow at weekends so we don't need to treat them on a Saturday or Sunday!*

Sometimes we use the fractionation effect in reverse. We deliver a single large dose of radiotherapy to completely ablate everything within the treatment volume. This is known as radiosurgery. In order to achieve this, we have to ensure that we deliver minimal dose to the surrounding tissues. In the brain, we often do this by immobilising the patient using a stereotactic frame, similar to that used for neurosurgery.



Thus the treatment is often known as stereotactic radiosurgery or SRS. Note that although most SRS is undertaken for intracranial lesions such as brain metastases, vestibular schwannoma and arterio-venous malformations, stereotactic radiosurgery can be undertaken in the body too, particularly lung, liver and bone lesions.

Chemo-radiation – enhancing tumour cell kill

In some situations, we combine low dose chemotherapy with radiotherapy to enhance cell kill. When chemotherapy is given in this way it is said to be a radiosensitiser. The results can be quite dramatic. Chemo-radiation in stage 3 cervix cancer yields dramatic improvements in survival:

Metaanalysis	Trials	Patients	Increase	HR	p value
2001 (2005)	24	4921	10% (7 to 13%)	0.69 (0.61 to 0.77)	<0.00001
2002	8	1065		0.74 (0.64 to 0.86)	0.00006
2008	13	3104	6%	0.81 (0.71 to 0.91)	0.0006

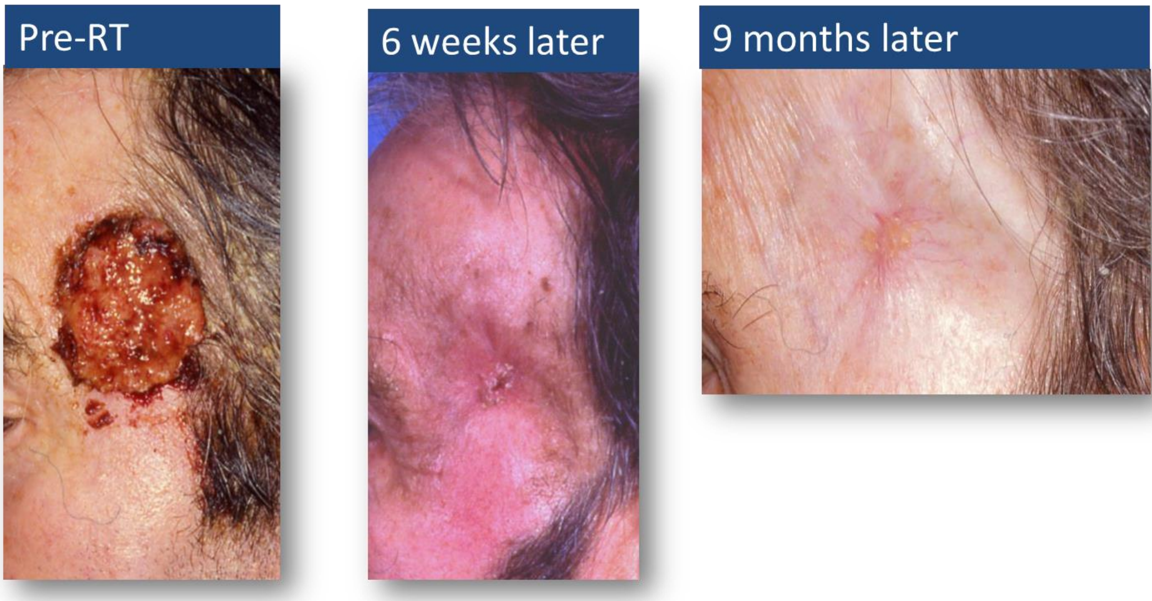
However, chemoradiation also has an increased effect on healthy tissues. Patients in these cohorts had an increased risk of complications such as vesico-vaginal fistula, rectal ulceration and pelvic fractures.

Clinical contexts for radiation therapy

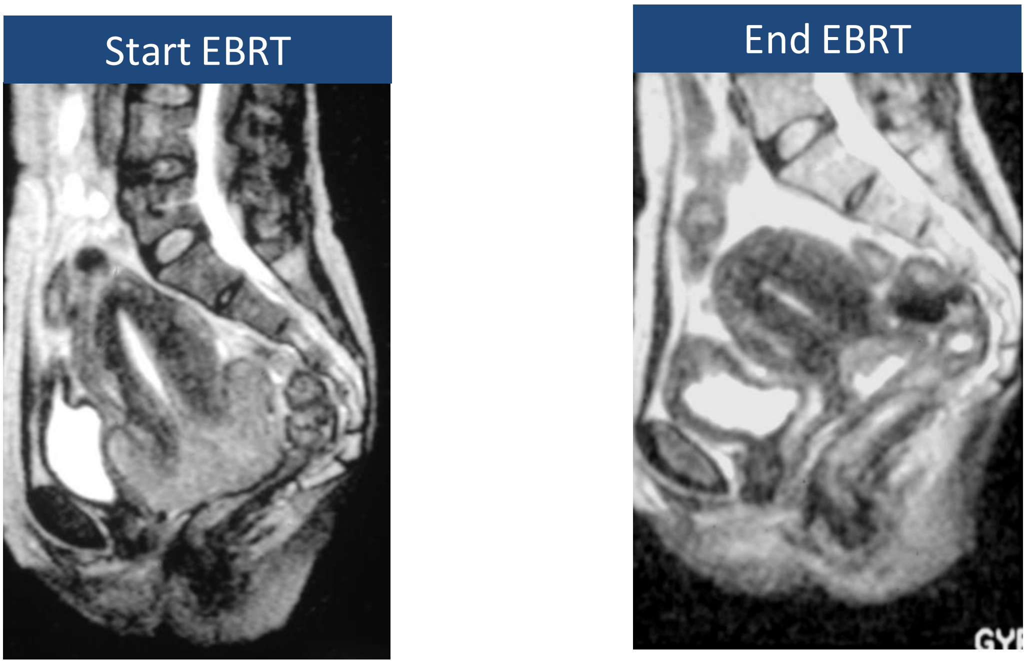
There are a number of ways in which we can use radiotherapy as an anti-cancer treatment

- **Primary curative treatment**. This is where radiotherapy is used in place of surgery as the main modality for cancer cure. Often it is the case that surgery would involve removal of the organ bearing the cancer, resulting in significant loss of function for the patient. Radiotherapy allows curative treatment to be delivered without removing the organ, and is often therefore an organ preserving treatment. Good examples of this are larynx cancer, which would involved removal of the larynx if treated surgically, and anal cancer, which would involve a large AP resection and stoma if treated surgically. Some examples of primary therapy include
    - Skin cancers
    - Cervix cancer
    - Head & neck tumours
    - Lung cancer
    - Anal cancer
    - Lymphoma
    - Prostate cancer

  The results can be very impressive. This is an example of a nasty squamous cell carcinoma on the temple, that would have needed extensive resection and grafting. After treatment the skin is thing and there is telangiectasia visible but a good cosmetic result has been achieved.



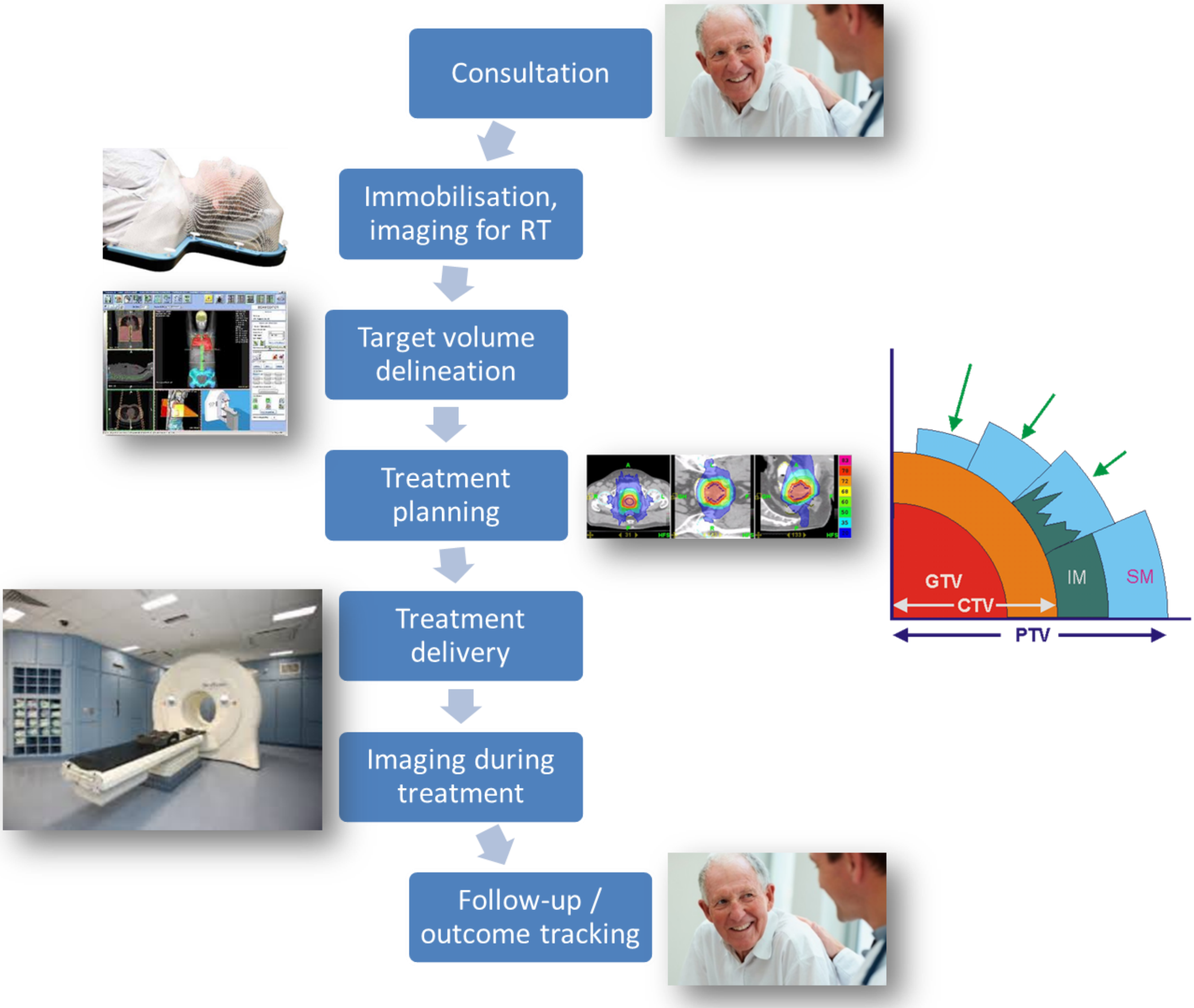
This is a patient with a bulky cervical cancer, treated with radiotherapy. Fast growing squamous cancer can often respond rapidly to radiotherapy.



- **Adjuvant radiotherapy.** This is treatment given after surgical resection to control any microscopic disease that may have been left behind, either in the site of the tumour or adjacent lymph nodes. Radiotherapy is given to improve local control, and it has been well demonstrated that improved local control of early stage cancer leads to improved survival. This represents a large volume of what we do in radiotherapy and example include:
    - Breast cancer
    - Rectal cancer
    - Endomterial sarcoma
    - Brain tumours
    - Sarcoma
- **Palliative radiotherapy.** This is treatment given to patients with advanced disease to improve symptoms or maintain function. As patients liver longer alongside metastatic disease we are giving more palliative radiotherapy. It is useful for localised symptoms such as bone pain, nerve compression pain, and low volume bleeding from a tumour surface (radiotherapy won't work if the bleeding is coming from a large vessel).

Clinical pathway for radiation therapy

All patients receiving radiotherapy treatment follow a pathway for preparation of their radiotherapy, shown in the diagram below:



The key things we want to achieve during radiotherapy are

- Inform the patient what to expect. They are likely to tolerate treatment and maintain a stable treatment position if they know exactly what is happening.
- Find a way to minimize motion of the target area during radiotherapy. This can be done by ensuring the patient if in a comfortable, stable and reproducible position each time they come for radiotherapy.
- Calculate a radiotherapy plan that delivers maximal dose to the tumour, and minimal dose to surrounding healthy tissues.
- Use imaging techniques on the treatment machine to ensure that we are treating what we are supposed to be treating.
- Monitor the patient during therapy for side effects of treatment.

You'll see more about what happens to a patient on the radiotherapy tour. One of the cool things we do to keep patients in the right position is to make thermoplastic shells. These are made of a special plastic sheeting which is flexible when warmed in a water bath to 40 degrees, and then set at room temperature. Again it is much easier to watch than explain, so here is a short video of Sarah Knight, one of our radiographers, making a thermoplastic shell for brain radiotherapy.

Side effects of radiotherapy

As they say on Star Trek, you can't change the laws of physics, and thus if we are treating a tumour within the body with radiation, there has to be some exposure of adjacent structures to radiation, which will cause unwanted side effects. We think of side effects as acute effects which occur during therapy and last for a few weeks afterwards, and late side effects, which can come on years to decades after radiotherapy.

- **Acute toxicity** starts about 2 weeks after the beginning of radiotherapy, and tends to affect the fastest proliferating tissues, causing dermatitis, stomatitis and enteritis. This is what causes the nausea and vomiting after acute radiation exposure. Hair loss can also occur in the area where the radiation fields hit the skin, typically 2-3 weeks after the start of radiotherapy. Radiotherapy also causes fatigue, no matter which part of the body is being treated, presumably as part of the response to radiation injury.
- **Late toxicity** is typically caused by vascular injury to normal tissues after radiotherapy. Radiation effectively causes a small vessel obliterative endarteritis, and fibrosis occurs in response to the ischaemia and cytokine release associated with this.

These images show late effects of radiotherapy. On the left is a poor cosmetic outcome from radiotherapy to the left breast. You can see evidence of breast shrinkage as a result of fibrosis, and extensive skin telangiectasia in the radiation fields. The fibrosis can also be painful. On the right you can see evidence of small vessel damage in the rectum following pelvic radiotherapy.

- **Growth and risk of second malignancy**. When we use radiotherapy in children we worry about the effect of radiation on growth. Radiation to the epiphyses of long bones will result in premature fusion and loss of stature. Asymmetric radiation to the spine will result in scoliosis. Radiation itself can also cause malignancy, and the risk of this varies depending on the volume and type of normal tissue being treated. A good rule of thumb is that for most curative treatments the risk of second malignancy is approximately 3% per decade of life after radiotherapy for children and 1% per decade of life for adults.

Conclusion

Radiotherapy is essentially a spatially targeted anti-cancer therapy which induces DNA damage in cells. The damage is lethal to tumour cells, but can be repaired or recognized in healthy tissues.

Radiotherapy is a tool for achieving local tumour control. It can be used in place of surgery, or as an adjunct to surgery.

New technologies in radiation therapy allow increased precision of the delivery of radiation dose, and image-guided radiotherapy uses a range of imaging technique to ensure we deliver treatment to the target.

Nonetheless, radiotherapy has important acute and long term side effects and has to be used with caution.

For more details, come to the tour of the radiotherapy department which is usually on the second Monday of your attachment, or take a look at **extension resource E2 – a virtual tour of the radiotherapy pathway**.