Principles of radiotherapy

Introduction

As a junior doctor, you will encounter patients who are receiving, or have received, cancer treatment. Radiotherapy is one of the fastest developing and furthest reaching modalities. A good understanding of how it works, how it is administered and its side effects will enhance the competence of any junior doctor.

Molecular basis of radiotherapy

Ionizing radiation has sufficient energy to distract electrons away from atoms, generating ions (Huddart, 2004). It can be delivered in the form of ionizing particles (which have mass) or photons. Conventional external beam radiotherapy uses photons: electromagnetic waves with short wavelength and high energy (Fowler, 1992). Photons may be gamma rays from a radioactive decay source, or X-rays (more widely used). X-rays produced from a generator, used in imaging, are kilovoltage and do not have high enough energy, so a linear accelerator (which produces megavoltage X-rays) is used (Camphausen and Lawrence, 2008).

Photons cause indirect injury to cells through the formation of free radicals and peroxides, which subsequently damage DNA (Carrie and Dunne-Daly, 1999) (*Figure 1*). Direct damage results when energy transfer from highly charged particles breaks DNA itself, and is critical in newer particle therapy techniques.

Double-stranded DNA breaks often lead to cell death or defective DNA (which causes cells to divide slower and die earlier). Malignant cells are more likely to be damaged than their healthy counterparts, as they are more frequently in mitosis and less able to repair damage.

Solid tumours can outgrow their blood supply and become hypoxic. This actually lessens the effectiveness of conventional radiotherapy, as oxygen is needed to produce the free radicals that cause the damage. Oxygen is therefore a potent radiosensitizer. This is why it is important to detect and treat anaemia in patients undergoing radiotherapy.

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Indications for radiotherapy

There are three broad scenarios in which radiotherapy is administered:

Radical radiotherapy

Given with curative intent in diseases that are responsive to radiation, including cervical, prostate, thyroid and brain malignancies. Within this it may be given as:

- Definitive therapy (the principle component of treatment)
- Neoadjuvant therapy (to shrink a tumour before surgery)
- Adjuvant therapy (after surgery to target any microscopic local spread or local lymph nodes) (Delaney et al, 2005).

Emergency radiotherapy

Given to rapidly shrink a tumour mass that is pressing on a vital structure, for example in spinal cord compression or superior vena cava obstruction.

Palliative radiotherapy

Given with the aim of attenuating symptoms, not to improve prognosis. These can include pain from compression of local structures, pain from bone metastases, neurological symptoms from raised intracranial pressure, and dyspnoea and haemoptysis from bronchial tumours (Ashby, 1991).

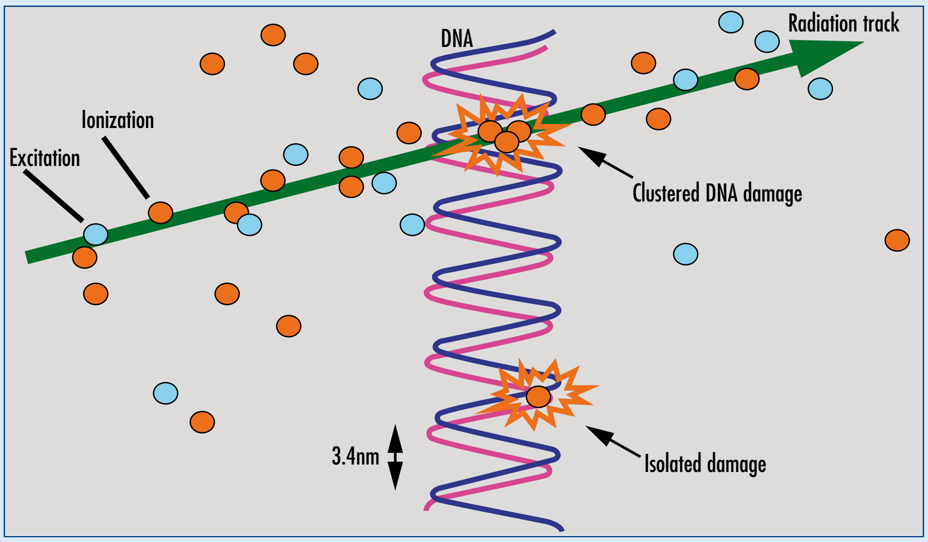
Fractionation

The unit of measurement of radiation is the Gray (Gy). One gray is the absorption of one joule of ionizing radiation by one kilogram of matter. The total amount of Gy given for a tumour varies (up to 80 Gy may be given for solid tumours in radical radiotherapy). The total dose is given in a series of fractions spread out over time, which increases treatment efficacy. Doing so allows normal tissue to repair, while malignant tissue has less capacity to do so. It also provides an opportunity to irradiate tumour cells that were resistant during the previous fraction, either because they were in a radio-resistant phase of the cell cycle or because they were hypoxic at the time but have now had a chance to reoxygenate.

The typical fractionation in radical radiotherapy is 1.8–2 Gy per day (lower in children), 5 days a week. An alternative regimen is CHART (continuous hyperfractionated accelerated radiation therapy), which involves 2–3 smaller fractions a day, and may be given 7 days a week.

When dealing with inpatients, palliative radiotherapy is more frequently encountered. The principles behind this are slightly different: larger doses can be given per fraction, as concerns about long-term

Figure 1. Mechanisms of DNA damage from ionizing radiation.



damage to surrounding tissues are not as relevant, and the aim is to provide maximal relief of tumour-related symptoms. In addition, time is more precious for these patients and durations of treatment should ideally be shorter. Regimens are therefore often hypofractionated, given in larger doses across fewer fractions.

Mechanisms of delivery

External beam radiotherapy

This is the most frequently used form of delivery, involving an external radiation source directed at the body. Conventional (two-dimensional) external beam radiotherapy used beams directed at the body from several angles, using metal blocks to shape the field (*Figure 2*). Three-dimensional conformal radiotherapy is now available, which uses images from computed tomography, magnetic resonance imaging and positron emission tomography scans to increase accuracy. Delivery involves a multileaf collimeter (*Figure 3*), which consists of groups of many small thin (5 mm) metal plates that can be moved independently to block part of the radiation field (Corvo et al, 1997), allowing specific and accurate shaping of the multiple beams. However, three-dimensional conformal radiotherapy has limitations: immobilization is still only accurate to 3 mm, the whole tumour gets a homogenous dose of radiotherapy, and it is not precise enough to spare delicate structures adjacent to or touching the target (Podgorsak et al, 1999).

Intensity modulated radiation therapy represents a further advance, with each beam split into smaller 'beamlets' of individual intensity that can be modulated (Freeman, 2008). These beams can consequently conform to the exact shape of the tumour (Ezzell et al, 2003), although this method is considerably more time and labour intensive (International RadioSurgery Association, 2010).

Figure 2. Linear accelerator used to deliver external beam radiotherapy.

Figure 3. A multileaf collimeter.

Brachytherapy

In this mode of delivery, the radiation source is internal, placed either inside the malignant tissue itself (as in prostate brachytherapy) (*Figure 4*) or adjacent to the tumour. This may be in a lumen (as with gastrointestinal or respiratory malignancy), cavity (cervical or endometrial malignancy) or on the body surface (skin malignancy) (Porter and Forman, 1993).

The cancers most commonly treated with brachytherapy are prostate and gynaecological cancers. The advantage is that radiation is delivered directly to the tumour, lessening exposure to surrounding normal tissues (Radiological Society of North America, 2011a). The radiation source effectively moves with the body, minimizing error caused by small internal movements such as respiratory, bladder and bowel motion. Brachytherapy can be administered as an outpatient, making the process less disruptive for patients. The patient may be admitted for 1 or 2 days to have the therapy placed. An example is in prostate cancer, where the patient needs to be admitted and monitored until haematuria settles. The insertion itself can be uncomfortable (Williamson, 2006).

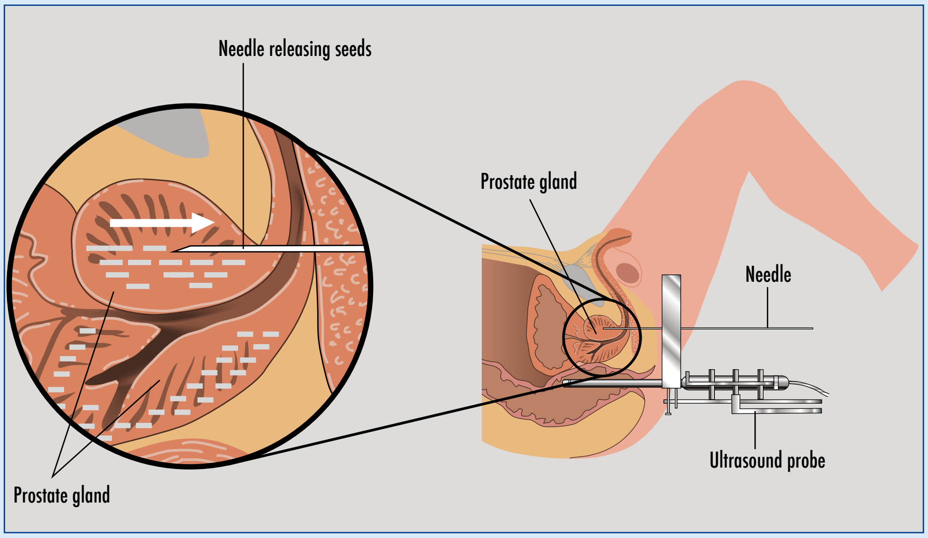
Superficial radiotherapy

In skin malignancies, radiotherapy is used which is of high energy but poorly penetrative, minimizing injury to deep tissues. This can be achieved with superficial kilovoltage X-rays. Electron beams are also used, which have a much sharper decline in dose after the maximum dose is deposited, again resulting in less exposure to deeper tissues.

Radionucleotide therapy

On oncology wards patients may be encountered who have been electively admitted for radionucleotide (or radioisotope) therapy. This targets an organ or system by affecting only those parts that take up or interact with the element. The most common use is of iodine-131 in thyroid cancer. Radionucleotide therapy is also used in the treatment of neuroendocrine tumours (using hormone-bound radioisotopes), neuroblastomas, craniopharyngiomas and in the embolization of hepatocellular carcinomas and liver metastases. In some cases, after the procedure

Figure 4. How radioactive pellets are placed in the prostate gland.



the patient remains isolated in a lead-lined room, for between 1 and 5 days, depending on the dose given, to prevent radiation exposure to other patients and staff. The room is decontaminated after the patient is discharged. This can be a difficult time for the patient as he/she is completely isolated and can only communicate with nurses and relatives through a door or glass screen. After discharge the patient will need further advice regarding minimizing exposure to family and the public until the radioactive dose has sufficiently diminished (Royal College of Radiologists, 2000).

Recent advances

The field of radiotherapy is continually advancing and tumours in difficult places can now be treated without damaging vital nearby structures. This is particularly exciting in CNS oncology.

Stereotactic radiotherapy

The term 'stereotactic' refers to exact targeting of a tissue in three-dimensional space. In the context of radiotherapy it is applied when treating areas where precise positioning is crucial (Levin and Zieve, 2012). Stereotactic radiotherapy uses the same principles as normal radiotherapy, but involves more fixed immobilization of the target, using a frame or facemask to hold the head in place, and infrared positioners (Cancernet.co.uk, 2011). Many beams are delivered which converge on the target. The increased precision allows a very high dose to be given to the tumour without increasing exposure of surrounding tissues.

Stereotactic radiosurgery is a form of stereotactic radiotherapy and extremely precise, with stringent immobilization of the head and a marker system to identify coordinates using three-dimensional imaging. Advantages of such techniques are that they provide an alternative to invasive surgery in difficult-to-reach locations, while still giving definitive treatment in a single sitting (Breneman et al, 2010).

Two forms of stereotactic radiosurgery are the gamma knife and cyber knife. The gamma knife (*Figure 5*) uses gamma ray radiation from a cobalt-60 source (Radiological Society of North America, 2011b), a fixed large metal helmet, and delivery of 201 separate beams (Lunsford et al, 1989). It is highly accurate and enables a large dose to be given in one sitting. It is used to treat small lesions (often less than 3 mm) such as metastases, meningiomas and acoustic neuromas (Alexander et al, 1995).

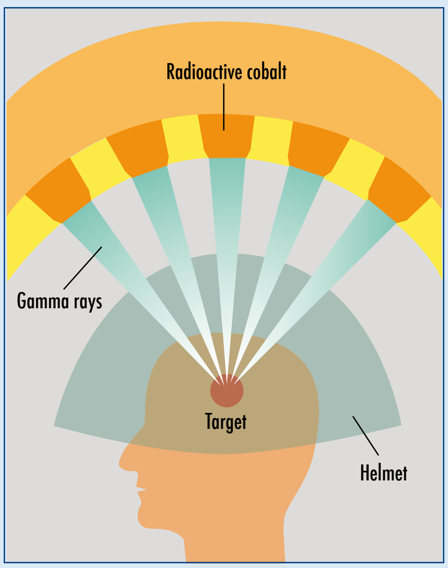
The cyber knife uses X-rays from a linear accelerator, and an immobilization system which is exactly relocatable, allowing it to be used across several sessions. Delivery is via a single beam delivered in multiple arcs from different directions around the target, enabled by a robotic arm that can move the beam in any direction (Adler et al, 1997). It uses a tracking mechanism to constantly monitor the position of the target, and can thus correct for any movement or shift during delivery. This mode can be used on children (as it does not require fixation). Methods are now also being developed to allow stereotactic body radiotherapy, meaning that such levels of precision can be applied to treatment of many other malignancies.

Proton therapy

In this developing field, ionizing radiation is created by firing particles of high energy (and relatively high mass) at targets, using a particle accelerator (Levin et al, 2005). This causes direct damage to the DNA via linear energy transfer. This process is not affected by tumour hypoxia as it does not rely on formation of free radicals (Levy et al, 2009).

Owing to the larger particle mass, there is much less side scatter than with gamma or X-ray beams; the beam does not broaden but remains focused on the target, which inevitably means less radiation to the surrounding healthy tissues. The high energy from the particles drops to zero once they have reached their maximum range, meaning no exposure of normal tissues behind the tumour (Hug et al, 1999). This offers increased scope for treatment of tumours very close to vital structures, and also benefits children who need radiotherapy (as there is no surrounding low dose radiation 'bath', thought to increase risk of secondary malignancy in the long term). There are currently two proton therapy facilities being built in the UK, in London (UCLH) and Manchester (Christie Hospital), and these are likely to be in use by 2017.

Figure 5. How a gamma knife works.



Conclusions

Radiotherapy is one of the major modalities used to treat cancer, along with surgery, chemotherapy and targeted agents. Traditional radiotherapy uses photons to impart ionizing radiation, which damages DNA. Malignant cells are more susceptible to damage from ionizing radiation than normal cells, although when cells become hypoxic radiotherapy is less effective.

In radiosensitive tumours, radiotherapy can be used as definitive treatment, neoadjuvantly or adjuvantly, all with curative intent. It is also a very effective palliative treatment, particularly for pain or compression of local structures. It is used in an emergency to shrink an obstructing tumour, but the therapeutic effects can take days to weeks to manifest, so medical management may be used in the interim. Important aspects of a radiotherapy treatment course include the total dose given, the number of fractions, the period of time the course is given over and the dose per fraction.

The mechanisms of delivering radiotherapy have become more sophisticated over the last three decades and are evolving all the time. External beam radiotherapy is the most common method of delivery and accuracy of treatment is improved by intensity modulated radiation therapy. The goal of any radiotherapy treatment is to give the maximum dose to the tumour while sparing the surrounding normal tissues to limit acute and long-term toxicity. BJHM

Conflict of interest: none.

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KEY POINTS

- Radiotherapy is used in the radical and palliative treatment of malignancies. The vast majority of radiotherapy is given in the outpatient setting.
- Radiation is measured in grays, and the total amount given to a tumour is split into fractions given over a set time period to allow maximum impact on the malignant tissue and repair of normal tissues.
- External beam radiotherapy is delivered via three-dimensional conformal radiotherapy or intensity modulated radiotherapy via many small beamlets, allowing greater conformation to the shape of the target.
- Methods of internal delivery include brachytherapy and radionuclide therapy.
- New developments such as stereotactic radiotherapy give high levels of precision, allowing larger doses to the tumour and more successful results. These methods are now being used in CNS tumours.
- Another recent advancement is that of proton therapy, which relies less on the tumour having adequate oxygen supply and again gives very minimal dosage to surrounding critical structures.