Radiotherapy

What is radiotherapy?

Radiotherapy is a key component of both radical (curative) and palliative treatment for cancer. Radiotherapy forms part of the management of 40% of patients cured of their disease. Most patients are treated using a high-energy beam of X-rays delivered to a precise area, using a linear accelerator. Radiotherapy can be given either as external radiotherapy from outside the body or from within the body, as internal radiotherapy. External beam radiotherapy (EBRT) is the most common form of radiotherapy used.[1]

The dose of radiation is defined as the irradiation absorbed by each kilogram of tissue expressed as Grays (Gy) - 1 Gy = 1 J/kg of tissue. The dose is usually given in a number of daily fractions with the total dose determined by tumour sensitivity and normal tissue tolerance.

Cells start to recover within six hours of radiation. Therefore, if fractions are too close together then normal tissues would suffer excessive toxicity; however, too far apart and sublethal damage to cancerous tissue could be repaired.

Treatment is planned by a multidisciplinary team on the basis of a combination of physical findings, diagnostic imaging information, anatomy, pathology and natural history of the tumour involved.

The efficacy of radiotherapy in treating malignant cells varies widely between different malignancies. Radiation therapy should not be administered during any trimester of pregnancy.[2]

Uses of radiotherapy[2]

In the curative setting, radical radiotherapy can be offered as the sole treatment. It can also be used with surgery, being given before (neoadjuvant) or after resection (adjuvant).[1]

- When used alone in the early stages of certain cancers, radiotherapy can be curative - eg, Hodgkin's disease, non-Hodgkin's lymphoma, carcinoma of the larynx, prostate or cervix, and some tumours of the central nervous system - eg, medulloblastoma.
- Compared with surgery, radiation often offers improved or equivalent tumour control with less morbidity. Radiation and surgery treatments require individual patient assessment and discussion of the patient's condition and preferences.
- Patients medically unfit for surgery - eg, cardiovascular, respiratory or other chronic diseases.
- Anatomically unresectable cancers.
- Close proximity to critical structures - eg, blood vessels, central nervous system, peripheral nerves.
- Pre-operative - eg, to shrink the tumour, facilitating subsequent surgical resection.
- Postoperative - eg, to decrease the risk of local or regional tumour recurrence.
- Palliative radiotherapy can often be used to reduce or eliminate pain from bone metastases, palliate brain metastases, spinal cord compression, compressive symptoms from visceral metastases (eg, airway or gastrointestinal obstruction) and uncontrolled bleeding - eg, haemoptysis or haematuria.[1]

How radiotherapy works[1]

- X-rays deliver energy through waves called photons, which are produced by accelerating a stream of electrons and colliding them with a metal target. High-energy photons produce secondary electrons in human tissue. The electrons cause DNA damage which, if not repaired, is fatal at cell division.

- EBRT is administered using a linear accelerator. EBRT usually uses high-energy X-rays, which penetrate deep into body tissue while relatively sparing the skin. EBRT can also be used to treat skin tumours.
- Proton beams can also be used for EBRT; the dose builds up to a peak and then falls off steeply with no dose beyond their specific range.
- EBRT is normally delivered over multiple sessions (called fractions). This exploits the differences in repair and repopulation between tumour cells and normal cells.
- Single fraction treatment is often used for palliative radiotherapy. Low doses of radiotherapy can provide tumour control for a short time (months) with minimal side-effects.

Planning radiotherapy

- Most EBRT is planned using CT imaging to locate the tumour and provide information on the patient's shape and tissue density. Correlation with diagnostic imaging is essential.
- The best diagnostic imaging for many tumours is MRI. For some sites (eg, the brain), computerised image fusion is used with the planning CT scan to improve the accuracy of tumour localisation.
- Positron emission tomography-CT can help radiotherapy planning for lung cancers and lymphomas.
- Modern techniques can align treatment more closely to the tumour (three-dimensional conformal radiotherapy). This allows sparing of more healthy tissue and less toxicity.

Treatments and reviews

- Each treatment session, or fraction, takes about 10-20 minutes, including time spent ensuring the patient is correctly positioned on the treatment couch.
- Patients receiving multiple fractions are usually reviewed at least weekly by a doctor, to help manage treatment-related side-effects.

Radiotherapy modalities [2]

External beam radiation therapy

- Three-dimensional conformal radiation therapy: CT or MRI is used to target tumours while minimising radiation exposure of healthy tissues.
- Four-dimensional radiation therapy: computer-assisted tracking or gating of CT images of moving targets, for tumours that are susceptible to movement - eg, lung, liver, pancreas or breast.
- Stereotactic radiosurgery (eg, gamma knife): multiple radiation beams converge on the tumour, delivering high-dose radiation to the tumour but little to surrounding tissues.
- Stereotactic body radiation therapy (eg, CyberKnife®): high-dose radiation delivered using robotic guidance.

Internal radiation therapy

- Temporary brachytherapy implant: a radiation source is placed within or near the tumour target and is later removed.
- Permanent brachytherapy implant: a low-dose rate (ie long half-life) radiation source is placed within or near the tumour target.
- Systemic radiation therapy: systemically administered radioisotopes target tumour cells.
- Radioactive I_{131} can be taken orally to treat thyrotoxicosis and thyroid cancers.

Intensity-modulated radiotherapy (IMRT) [1]

- IMRT can create steep dose gradients, which increases sparing of normal tissues. IMRT uses multiple beams with a non-uniform dose across the field.
- IMRT is particularly useful for head and neck cancers because of the high number of important normal tissue structures within close proximity to the tumour.

- Studies have found a reduction in side-effects - eg, reduction in dry mouth following treatment for cancers of the oropharynx, and reduced rectal toxicity in patients treated for prostate cancer.
- For the treatment of breast cancer, improved dose distributions in patients with larger breasts decrease the risk of breast pain and improve long-term cosmesis.
- Sparing of normal tissue means that higher and potentially more effective doses could be used without the risk of increased toxicity.
- Despite normal tissue being spared higher doses, a greater volume of tissue receives a lower dose. As a result, it has been suggested that IMRT may increase the risk of a second cancer.
- Provision of IMRT is variable but access is increasing rapidly in the UK.

Image-guided radiotherapy (IGRT) [1]

- IGRT uses imaging just before the delivery of radiotherapy. This allows positional correction if required. IGRT uses CT imaging or implanting radio-opaque seeds, which allows the target to be identified using treatment X-rays.
- IGRT enables accurate treatment of the tumour and potentially allows smaller safety margins to be used in order to spare healthy tissue.
- Image guidance is essential for IMRT because steep dose gradients carry a risk of the target being given too low a dose and normal tissue being overdosed. Most machines that deliver IMRT also have IGRT capabilities to allow imaging and treatment in a single session.
- Lung cancers move with respiration. Four-dimensional CT can be used to obtain a series of CT scans at different phases of the respiratory cycle. The information can allow delivery of treatment at specific phases of the respiratory cycle.
- The provision of IGRT is increasing in the UK.

Stereotactic radiotherapy (SRT) [1]

- SRT involves very accurate treatment and has been used to treat brain tumours for many years.

- SRT has recently been used to treat small discrete lesions in a limited number of higher-dose fractions.
- Stereotactic radiosurgery refers to SRT delivered in just one session.
- Stereotactic ablative radiotherapy (SABR) allows precise irradiation of extracranial lesions and is increasingly used for sites including the lung, prostate, liver and pancreas.[3]
- The CyberKnife®:
    - Is a frameless robotic system consisting of a linear accelerator mounted on a robotic arm.
    - It can deliver treatment very accurately and uses real-time image guidance to track the tumour.
    - Most tumours therefore require implantation of metal markers, which can lead to complications - eg, pneumothorax when treating lung cancers.
    - Newer software can track some peripheral tumours without markers.
- Clinical outcomes for SABR are promising, especially when used for inoperable lung cancers.
- Accurate delineation of the tumour is essential. Lesions with unclear margins are not suitable.
- SABR is particularly appropriate for smaller lesions. Small metastatic lesions can be treated with high doses of SABR, which may achieve a long disease-free interval.
- SRT and SABR are currently mainly available only at specialist cancer centres within the UK.

Proton beam therapy[1]

- Proton beam therapy uses protons rather than photons to deliver the radiation dose. The use of protons allows the dose to be deposited up to, but not beyond, a specific depth within tissue.
- When compared with photons, this limited range allows improved target coverage, with reduced doses to the normal tissue beyond.

- This is expected to reduce the risks of late effects, including second cancers and cardiovascular risk, which are particularly relevant when treating children and young adults.
- Current indications in adults include spinal tumours and tumours at the base of the skull. In the USA this treatment is widely used for prostate cancer.
- Although results of proton beam therapy can be excellent, there is currently no evidence from randomised trials that protons improve outcomes compared with photons when given at the same dose.
- In the UK, patients suitable for proton beam therapy can now be referred abroad under the NHS Proton Overseas Programme. However, it is hoped that there will soon be two proton therapy units in the UK for children and adults with specific indications.

Complications of radiotherapy [1] [4]

The risk of death directly caused by radiotherapy errors is estimated at two per million courses in the UK. Detailed checks and procedures are in place to ensure that the right patient receives the right treatment.

The likelihood of certain side-effects is largely dictated by the dose fractionation schedule, the site treated and any pre-existing comorbidities. Apart from fatigue, toxicity depends on the anatomical location of the radiotherapy fields. Toxicity can be divided into early and late:

- Early toxicity: generally reversible but must be managed appropriately to avoid unnecessary gaps in treatment. Begins about two weeks into treatment but symptoms tend to peak at two to four weeks after completion of treatment.
- Late toxicity: occurs at least six months after treatment and may present after many years. Late effects are often irreversible.

Rapidly proliferating tissues - eg, skin, mucosa and bone marrow - are most sensitive to the toxic effects of radiotherapy.

Most recent advances in radiation oncology have involved making the radiation beam better conform to the shape of the tumour to reduce the volume of normal tissue within the radiation beam and the dose to normal tissues. Radioprotectors are compounds that protect against radiation injury when given prior to radiation exposure. Radioprotectors can potentially improve the outcomes of radiotherapy for cancer treatment by allowing higher doses of radiation and/or reduced damage to normal tissues. Examples of radioprotectors include amifostine, palifermin and superoxide dismutase.[5]

Acute complications

- Acute effects are defined as occurring during the treatment and within 2-3 weeks after its completion.
- Acute effects can be distressing but tend to resolve.
- General fatigue is the most common acute adverse effect:[1]
    - Fatigue occurs in about 80% of patients receiving radiotherapy.
    - It tends to peak in the second week and improves about four weeks after completing treatment.
    - Fatigue persists in a chronic form in about 30% of patients.
    - Patients should remain as active as possible and exercise programmes may help.
- Distress, anxiety, and depression
    - Studies have shown an increase in distress, anxiety, and depression in patients undergoing radiotherapy.
    - Although these problems tend to decrease when radiotherapy has been completed, a significant number of patients still manifest psychological effects after treatment.

- Skin:
    - Erythema, dry and moist desquamation, skin tanning (starts in hair follicles), hair loss and sweat/sebaceous gland dysfunction.
    - The use of high-energy radiographs has vastly reduced the severity of skin reactions to radiotherapy.
    - When a need for skin irradiation exists - eg, skin involvement by tumour or skin as the target for basal cell cancers - the technique is altered to produce a brisk skin reaction.
    - Where the skin is denuded (moist desquamation), it must be kept scrupulously clean to avoid superinfection.
    - Skin heals from the outer margins inwards by about three weeks.
    - Hair loss occurs in the treatment field but is usually temporary, regrowing within a few weeks of ceasing treatment.
    - Chemotherapeutic agents can enhance skin sensitivity.
    - Topical aloe vera gel has been claimed as a useful prophylactic agent for skin burns in radiotherapy, particularly at high doses. [6] [7] However, some randomised trials have not demonstrated a significant effect. [8]
    - Aqueous cream can be used to soothe the symptoms of dry desquamation. [8]
- Gastrointestinal tract:
    - Loss of taste, salivary dysfunction, oral mucositis, diarrhoea, nausea and vomiting. After radiotherapy 50-80% of patients may experience nausea and vomiting. [9]
    - Severe, painful mucositis may be complicated by yeast or bacterial superinfection and antimicrobials should be considered.

- Bone marrow:
    - Patients may develop cytopenias.
    - In whole body irradiation, white cell count falls with immune suppression.
    - When bone marrow reactions are severe enough, repeat treatments may need to be delayed to allow normal tissues to repair.
- Lungs:
    - Irradiation of the lung can cause pneumonitis with fevers, cough, dyspnoea and pulmonary infiltrates that may require steroids. [10]

Long-term complications

Long-term complications are specific to tissues involved and usually occur if normal tissue tolerance is exceeded. Careful dosimetry and planning are needed to avoid this - eg, >45 Gy to the spinal cord causes myelitis and >20 Gy to the kidney can cause renal impairment.

- Neck: high dose can lead to fibrosis and decreased movement with a woody texture, especially after surgery.
- Jaw muscles: fibrosis impairing mastication. Postoperative jaw exercises may reduce this complication.
- Lymphatic system: lymphoedema, intermittent erysipelas.
- Infertility.
- Wounds: delayed healing.
- Skin:
    - Telangiectases can occur as a late complication.
    - Ulceration over bone with exposure and possible osteoradionecrosis is fortunately rare and requires a long-term approach that may involve antibiotics, hyperbaric oxygen and surgery.

- Salivary function:
    - Loss of salivary flow with xerostomia is a common complication after head/neck irradiation and particularly likely if the parotids have been irradiated.
    - Pilocarpine may help to increase salivary flow. Artificial saliva or frequent sipping of water may be useful.
    - Intravenous amifostine given during treatment has been shown to reduce the severity and duration of radiotherapy-related xerostomia without effects on survival.[11]
    - Close attention should be paid to oral hygiene during head and neck radiotherapy to reduce the risk of oral disease.
    - Oral and gingival tissue may undergo atrophy and telangiectases as a late complication.
- Central nervous system:
    - Spinal cord irradiation may cause transverse myelitis and Lhermitte's symptom (electric shock-like sensation in upper limbs on neck flexion).
    - Full transverse myelitis with Brown-Séquard syndrome is fortunately rare and a complication that should be carefully avoided at all costs.
- Increased risks of cardiovascular events and stroke. The risk varies greatly according to dose and tumour site.[1]
- Endocrine: hypothyroidism occurs in almost 50% of patients after radiotherapy for head and neck cancer.[1]
- Eye: cataracts, dry eye syndrome, retinitis.
- Ears: otitis or sensorineural hearing loss.

Second cancers[1]

- The risk of second cancers after radiotherapy increases over the decades after treatment and depends on the treated volume and dose.

- The risk is particularly relevant for younger patients with a good prognosis. Patients with stage I seminoma have a relapse rate of 4% but an excess second cancer risk of 6% at 25 years after radiotherapy. Therefore, radiotherapy is now rarely used for these patients.
- For early treatment of breast cancer, the risks are lower. This slight increase in second cancers is insignificant in most cases when compared with the risk of recurrence and death from the primary lesion.
- A UK-based cohort study in young patients who received supradiaphragmatic radiotherapy for Hodgkin's disease found that the risk of breast cancer was similar to that of women with BRCA mutations, especially women who were treated under the age of 20 years.
- A USA follow-up study of 650,000 cancer patients found that, overall, a relatively small proportion of second cancers is related to radiotherapy in adults, suggesting that most second cancers are due to other factors.[12]

Further reading

- Schaue D, McBride WH; Opportunities and challenges of radiotherapy for treating cancer. Nat Rev Clin Oncol. 2015 Sep;12(9):527-40. doi: 10.1038/nrclinonc.2015.120. Epub 2015 Jun 30.
- Hughes JR, Parsons JL; FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy. Int J Mol Sci. 2020 Sep 5;21(18):6492. doi: 10.3390/ijms21186492.
- Jarosz-Biej M, Smolarczyk R, Cichon T, et al; Tumor Microenvironment as A "Game Changer" in Cancer Radiotherapy. Int J Mol Sci. 2019 Jun 29;20(13):3212. doi: 10.3390/ijms20133212.

References

1. Ahmad SS, Duke S, Jena R, et al; Advances in radiotherapy. BMJ. 2012 Dec 4;345:e7765. doi: 10.1136/bmj.e7765.
2. Gerber DE, Chan TA; Recent advances in radiation therapy. Am Fam Physician. 2008 Dec 1;78(11):1254-62.

3. Sapkaroski D, Osborne C, Knight KA; A review of stereotactic body radiotherapy - is volumetric modulated arc therapy the answer? J Med Radiat Sci. 2015 Jun;62(2):142-51. doi: 10.1002/jmrs.108. Epub 2015 May 25.
4. Dilalla V, Chaput G, Williams T, et al; Radiotherapy side effects: integrating a survivorship clinical lens to better serve patients. Curr Oncol. 2020 Apr;27(2):107-112. doi: 10.3747/co.27.6233. Epub 2020 May 1.
5. Rosen EM, Day R, Singh VK; New approaches to radiation protection. Front Oncol. 2015 Jan 20;4:381. doi: 10.3389/fonc.2014.00381. eCollection 2014.
6. Olsen DL, Raub W Jr, Bradley C, et al; The effect of aloe vera gel/mild soap versus mild soap alone in preventing skin reactions in patients undergoing radiation therapy. Oncol Nurs Forum. 2001 Apr;28(3):543-7.
7. Maddocks-Jennings W, Wilkinson JM, Shillington D; Novel approaches to radiotherapy-induced skin reactions: a literature review. Complement Ther Clin Pract. 2005 Nov;11(4):224-31.
8. Heggie S, Bryant GP, Tripcony L, et al; A Phase III study on the efficacy of topical aloe vera gel on irradiated breast tissue. Cancer Nurs. 2002 Dec;25(6):442-51.
9. Feyer P, Jahn F, Jordan K; Prophylactic Management of Radiation-Induced Nausea and Vomiting. Biomed Res Int. 2015;2015:893013. doi: 10.1155/2015/893013. Epub 2015 Sep 3.
10. Jenkins P, D'Amico K, Benstead K, et al; Radiation pneumonitis following treatment of non-small-cell lung cancer with continuous hyperfractionated accelerated radiotherapy (CHART). Int J Radiat Oncol Biol Phys. 2003 Jun 1;56(2):360-6.
11. Wasserman TH, Brizel DM, Henke M, et al; Influence of intravenous amifostine on xerostomia, tumor control, and survival after radiotherapy for head-and- neck cancer: 2-year follow-up of a prospective, randomized, phase III trial. Int J Radiat Oncol Biol Phys. 2005 Nov 15;63(4):985-90.
12. de Gonzalez AB, Curtis RE, Kry SF, et al; Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol. 2011 Apr;12(4):353-60.

Authored by:	Peer Reviewed by: Dr Pippa Vincent, MRCGP	
Originally Published: 20/11/2023	Next review date: 24/07/2023	Document ID: doc_2695

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