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Radiotherapy: technical aspects

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Abstract

Radiotherapy is an important cancer treatment: in patients who are cured of cancer, radiotherapy contributes to cure in around 40% of cases. Radiotherapy also has an important role in improving symptoms in individuals with incurable cancer. Whereas palliative radiotherapy is typically given over 1–10 treatments, radical treatments can extend over 4–8 weeks. Radiation is often delivered externally by machines called linear accelerators. It can also be delivered using brachytherapy, where radioactive implants are placed in or close to a tumour, or systemic isotopes, which are swallowed or injected and then locate and destroy cancer cells. Modern imaging, computing and delivery systems have led to dramatic improvements in external-beam radiotherapy. Treatment aims to accurately and precisely deliver high radiation doses to tumour tissue and minimize doses received by surrounding normal tissues. Image-guided radiotherapy increases accuracy by evaluating tumour motion and position during treatment. Stereotactic radiotherapy delivers very high radiation doses very accurately in a small number of treatments and can be used for intra- and extracranial lesions. New developments, including magnetic resonance imaging-based treatment systems and adaptive planning, aim to further improve treatment accuracy and precision, with the ultimate aim of increasing cure and reducing toxicity.

Keywords

Arc therapy; brachytherapy; external-beam radiotherapy; image-guided radiotherapy; intensity-modulated radiotherapy; linear accelerator; molecular radiotherapy; stereotactic radiotherapy

Key points

- Radiotherapy is second only to surgery in its curative contribution in adult cancer patients
- Technical advances in radiotherapy aim to achieve increased cure and reduced toxicity
- Image-guided radiotherapy (IGRT) allows compensation for tumour movement and the potential to reduce the conventional margins placed around tumours, reducing the amount of high-dose irradiation of normal tissue
- Stereotactic ablative body radiotherapy offers high-quality dose distributions in a small number of accurate high-dose treatments
- Magnetic resonance imaging (MRI)-only planning and MRI-linac will lead to improved target and normal tissue discrimination, as will enhanced IGRT for inter-fraction and intra-fraction motion monitoring.

Introduction

Radiotherapy has been in use for ~~over~~over –100 years and remains second only to surgery in its curative contribution to adult cancer treatment. The aim is to deliver a lethal dose of ionizing radiation to tumour tissue; this damages the DNA, leading to cell death, particularly when cells attempt mitosis. Excessive normal tissue damage must be avoided. The differential effect of radiotherapy on normal and malignant tissues results from several factors (see *Practical and Clinical Applications of Radiation Therapy* on pages xx–xx of this issue for further reading):

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- For a given radiotherapy dose, more damage ~~may~~may be inflicted on tumour than normal cells.

•Cell and tissue kinetics usually favour recovery and repopulation of damaged normal tissue rather than tumour.
•Use of fractionated radiotherapy (giving the total dose in small daily amounts) further improves the therapeutic ratio.
The impact of radiotherapy on a tumour depends on its radiosensitivity, capacity to repair, oxygen levels and repopulation rate (the increase in tumour growth rate observed once treatment begins).

External-beam radiotherapy (EBRT), brachytherapy (radioactive implants placed within or close to a tumour) and systemic isotopes or 'molecular radiotherapy' (swallowed or injected isotopes that travel in the circulation and locate and destroy cancer cells) deliver the prescribed dose to a defined volume containing the tumour and regions of potential spread, while minimizing the dose to surrounding normal tissues. Radiotherapy is used for palliative and radical (curative) treatment. This article concentrates on advances in radical EBRT.

Types of therapy

Radiotherapy is usually given as X-rays, γ-rays or electrons; protons are used only in very specific circumstances (see below). The radiotherapy dose is prescribed in Grays (Gy), which reflects the amount of energy deposited in the tissues. The total dose is divided into fractions, typically one fraction being delivered each day. Radical EBRT for epithelial tumours delivers 50–78 Gy over 3–8 weeks in daily fractions of 1.6–2.5 Gy. Lymphomas and seminomas are relatively radiosensitive and can be treated with lower doses of 20–40 Gy over 10–20 fractions. Palliative radiotherapy typically delivers lower doses over 1–10 treatments.

External-beam radiotherapy

EBRT is usually delivered with linear accelerators (linacs; Figure 1), which generate high energy X-rays (photons), at energies of 4–25 MV, that can target deep-seated tumours. Treatment can be modified, particularly by altering the direction and shape of beams to avoid normal tissues. Linacs can also generate electrons. As these penetrate only a short distance before the dose rapidly falls off, they are particularly useful for skin cancers and lesions close to the skin.

Protons are a form of particle radiotherapy. Clinical use of protons is relatively new, is extremely complicated and expensive, and has a relatively low evidence base; it is therefore currently not widely available. Protons deposit their energy at a specific distance from the surface of the patient, and treatments are designed so the dose 'stops' immediately beyond a tumour. As a result, less 'exit' dose is delivered to normal tissues beyond the radiotherapy target compared with photon radiotherapy. Protons therefore result in highly conformal radiotherapy; i.e. the high-dose region closely matches the shape of the radiotherapy target, avoiding critical structures and reducing the likelihood of radiotherapy-induced second primary cancers later in life. In the UK, potentially curable tumours close to the brain and spinal cord, particularly in children, are considered a priority for proton therapy. One UK National Health Service proton centre opened in 2018 and a second is scheduled to open in 2020. The opening of UK proton centres will mean suitable patients no longer need to travel abroad for treatment and will provide an opportunity for research to identify additional suitable indications.

Radiotherapy process

This comprises ~~:~~
~~•~~patient immobilization,
~~•~~tumour localization,
treatment plan design, treatment delivery and image guidance.

Immobilization: this is used for all patients to ensure they maintain a constant position during treatment courses. Extra care is needed when highly sensitive structures lie close to the target or very high doses are used. Devices include thermoplastic shells when treating brain or head and neck cancers (Figure 2), vacuum bags for the chest or trunk, and breast boards.

Tumour localization: this is usually performed by computed tomography (CT) scanning using a CT-simulator, with the patient in the same position as they will be in for treatment. Use of lasers, tattoos and immobilization increases the reproducibility of patient positioning for each treatment. After the scan, the tumour and normal structures are outlined on each CT slice using relevant diagnostic information (e.g. magnetic resonance imaging (MRI), positron emission tomography-CT). Margins are added to the contoured tumour to account for microscopic spread, potential movement and patient set-up inaccuracies.

Radical treatment plan design: this creates a personalized plan aiming to deliver the required dose of radiotherapy to the target (tumour plus necessary margins) and minimizing the dose to surrounding normal tissues. Using advanced computer software, the orientation, intensity and shape of radiotherapy beams are manipulated until the optimal dose distribution is achieved based on one of the following delivery techniques.

3D conformal radiotherapy **(3D-CRT)**, which became generally available in the late 1990s, employs 2–4 radiotherapy beams (or fields) angled around the patient (Figure 3). Each beam can be shaped by multileaf collimators (MLCs) – leaves of tungsten in the linac head that can be positioned to block specific areas of each beam, allowing the treatment field to conform more to the shape of the target, and facilitating normal tissue shielding. The advent of 3D-CRT allowed safe radiation dose escalation (e.g. in prostate cancer).

Intensity-modulated radiotherapy **(IMRT)**, which became generally available in the mid-2000s, involves positioning multiple beams (often 5–9) around the patient. Instead of staying in one position, the MLCs move across each beam during treatment. This varies the photon intensity (or fluence) of each beam. Highly conformal dose distributions are achieved even when targets have complex shapes, and dose distributions can be designed to avoid critical structures (Figure 4).[1] When first introduced this was particularly valuable in head and neck radiotherapy, sparing the parotid glands, often permanently damaged in 3D-CRT, and thus reducing the risk of long-term xerostomia. Critical structures such as the optic nerves and spinal cord, frequently close to tumours, can more easily be avoided. There is a reduction in treatment toxicity with IMRT although as yet no definite randomized evidence of improved overall survival. IMRT can be delivered by standard linacs, but planning the radiotherapy is more labour-intensive than with 3D-CRT.

Arc therapy is a form of IMRT in which instead of radiotherapy being delivered from multiple static beam positions, the gantry rotates around the patient with the radiation beam continuously switched on and the MLCs continually moving.[2] Improved dose distributions can be achieved compared with 3D-CRT and IMRT. There are two main types of arc therapy:

•**tomotherapy** uses a narrow radiation fan beam and delivers radiation slice by slice, analogous to performing a CT scan. MLCs move in and out of the beam to modulate its shape. The patient is moved through the tomotherapy machine while the beam rotates around them, similar to a spiral CT

•**volumetric-modulated arc therapy (VMAT)**, which became generally available around 2010, is delivered by a conventional linac, the whole tumour being treated in one or more full or partial rotations. Changes in dose rate, MLC position and speed of gantry rotation are employed to optimize the treatment. Treatment times are faster than with conventional IMRT.

Radiotherapy can also be delivered using a CyberKnife®, a robotic radiosurgery system with a small linac mounted on a robotic arm, allowing a high degree of flexibility in beam directions for treatment. Multiple small, very precise beams are delivered. It also has the ability to track tumour motion. CyberKnife® is not widely available in the UK, and treatment times are slower than with conventional linacs.

Image-guided radiotherapy (IGRT): tumour position can vary between treatment fractions; for example rectal and bladder filling affect prostate position. IGRT is carried out before a fraction of radiotherapy to ensure that treatment fields are in the correct position in relation to both patient and tumour.[3] Modern linacs have integral imaging devices that can create digital X-ray images (portal images) or simple CT scans (cone beam CT (CBCT); see Figure 1), which are matched to reference images used in the planning process; discrepancies in patient position can be corrected. In some cancers (e.g. prostate), radio-opaque fiducial markers can be inserted into the tumour and visualized on portal images or CBCT to aid positioning. Advanced IGRT offers such improved treatment accuracy that the margins placed around tumours to allow for motion can be reduced, limiting the amount of normal tissue receiving high radiation doses.

Respiratory motion management: if there is concern that a tumour could move considerably with respiration (e.g. lung and upper abdominal tumours), motion management strategies can be employed. *Four-dimensional CT scanning* can be used to create a series of planning scans, each with the tumour positioned in a different phase of the respiratory cycle. The tumour is outlined on each scan and a composite target volume created that encompasses all the varying tumour locations. *Respiratory gating* can be used where the beam is switched on only during a particular breathing phase. One method is to use a fiducial marker, positioned on the chest wall, that moves with the respiration. . *Abdominal compression* uses a plate pressed over the abdomen to reduce diaphragmatic motion and therefore limit movement with respiration. In *breath-hold techniques* respiratory motion is eliminated by the patient holding their breath, and the beam is only turned on during the breath-hold.

Dose and fractionation: conventionally, radical treatments are delivered using 1.6–2.5 Gy once-daily fractions. Large trials have investigated treatments using shorter treatments (acceleration), multiple doses of <1.5 Gy/day (hyperfractionation), single doses of >2.5 Gy/day (hypofractionation) or higher total doses using additional fractions (dose escalation). Acceleration improves local control but not overall survival in head and neck cancer. Hyperfractionation improves local control and overall survival in head and neck and non-small cell lung cancer.

The opposite can apply to breast and prostate cancer as their radiobiological behaviour is different from most other tumours. Large trials have demonstrated that hypofractionated regimens (2.7–3.0 Gy per fraction) offer disease control equivalent to conventional fractionation in breast and prostate cancer, without increased toxicity. This is more convenient for patients and more cost-effective.

Combined systemic therapy and radiotherapy: combined chemotherapy and radiotherapy is more effective than radiotherapy alone in anal, lung, head and neck, and cervical cancer, especially when used concurrently. Combination therapy comes at the expense of increased acute and possibly late toxicity. Cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor, can be used concurrently with radiotherapy in patients undergoing radical treatment for head and neck cancer; it is often reserved for patients with good performance status in whom standard chemotherapy is contraindicated.

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The efficacy of radiotherapy is impaired by hypoxia. Nicotinamide, in conjunction with high oxygen concentrations, can be used as a radiosensitizer for bladder radiotherapy.

Recent technical developments

Stereotactic ablative body radiotherapy (SABR): this is the very accurate delivery of a small number of very high-dose fractions (e.g. 54 Gy in three fractions, considered an ablative dose) to an extracranial tumour, with a very small margin.[4] This is theoretically beneficial in improving cell kill. Initial work in peripheral non-small cell lung cancer suggests outcomes similar to surgery and superior to conventional 3D-CRT. Because of the small margins around the tumour and the very high doses employed, high-quality IGRT and immobilization is essential. More recently, SABR has been adopted for other sites (e.g. prostate, liver, spine), including for treatment of primary tumours and very limited metastatic disease. Local control generally appears excellent and toxicity acceptable, although definitive proof of an overall survival benefit compared with more established treatments is awaited for several tumour sites. SABR can be delivered using standard linac (e.g. using IMRT or VMAT) or specialist delivery systems (e.g. TomoTherapy®, CyberKnife®).

Stereotactic treatments have been used successfully for many years for small intra-cranial lesions, termed *stereotactic radiosurgery*, often using dedicated delivery systems including the Gamma Knife®. About 200 small radiation beams are delivered from multiple angles to precisely and accurately target small intracranial lesions.

Intra-fraction motion monitoring: this is IGRT that evaluates target position *during* each radiotherapy fraction. If fiducial markers are implanted within the tumour, the CyberKnife®, for example, can monitor intra-fraction motion via two in-room stereoscopically mounted imagers and compensate for changes in position (i.e. tracking). For prostate tumours, electromagnetic transponders can be implanted in the prostate, their position monitored and intra-fraction motion tracked. It is also possible to perform CBCT during arc radiotherapy; if excess motion is detected, the beam is paused to allow correction of problems.

Adaptive radiotherapy: this involves altering plans to take account of changes in the target or normal tissues during a course of radiotherapy. For example, patients can experience weight loss during a 7–8-week course of treatment, or a large tumour can shrink. The original radiotherapy plan may therefore no longer 'fit' as well as it should, putting normal structures at risk of excess radiation doses, or target tissues at risk of lower coverage by high-dose radiation. Re-planning adapts to up-to-date anatomy and mitigates such risks.

Magnetic resonance-only planning: tumours are currently usually contoured on CT planning scans, and CT images are necessary for calculating the radiotherapy plan. MRI provides enhanced soft tissue information and is often referred to when delineating tumour on the CT image. MRI images are sometimes formally matched with the planning CT (image co-registration) to further aid contouring of tumour and normal tissue. This is, however, imperfect, introducing uncertainties into the planning process. If contouring and planning could be performed directly on MRI, omitting CT, target delineation would improve and uncertainties reduce. MRI-only planning is now possible for some prostate cancers. Here, tumour localization is performed using an MRI simulator rather than a CT simulator for localization. There is interest in MRI-only planning for several other tumour sites.

MR-linac and MRI-cobalt systems – used in conjunction with MR-only planning, these have provided a recent and exciting development in EBRT.[5] MRI scanning for localization replaces the conventional planning CT scan, with contouring and planning performed directly on MRI as above. In addition, an MRI imager replaces the CBCT to improve inter-fraction IGRT. MRI images are also used to monitor for intra-fraction motion. Based on each day's pre-treatment MR images, EBRT can be rapidly re-planned (while the patient remains on the treatment couch) to create a plan specific to the patient's anatomy on that day (adaptive radiotherapy).

Figure 1.
Lin~~ear accelerator (lin~~ac~~)~~ with cone-~~-~~beam CT equipment at right angles to the treatment head. Figure from Elekta with permission.

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Figure 2. Radiotherapy immobilization mask.

Figure 3. Computer systems help design radiotherapy treatments in which multiple beams are angled around the patient, each beam being shaped to match to the target.

Figure 4. 3D conformal (left) and IMRT (right) radiotherapy plans for a patient undergoing radiotherapy to the prostate and lymph nodes in the pelvis. With IMRT it can be seen that the very-high-dose region (orange colour wash) is more closely shaped to the shape of the prostate target (outlined in yellow), and the high-dose region (turquoise colour wash) more closely matched to the shape of the lymph node target (outlined in blue). In addition, less high and intermediate doses (turquoise and light blue colour washes) are delivered to the rectum (outlined in dark red) and peripheral tissues.

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

QUESTION 1

A 7-year-old boy presented with symptoms and signs of a medulloblastoma, which was confirmed on investigation. Proton therapy was considered to provide a potential cure.

What is the main advantage of the use of protons rather than X-rays or electrons in these circumstances?

A A reduced dose to normal tissues
B A shorter overall course of treatment
C Fewer fractions of radiotherapy needed
D Needs simpler equipment
E Protons penetrate only a short distance

Correct answer: A. Compared to photon radiotherapy (i.e. x-rays), protons have the advantage of a reduced 'exit' dose, i.e. less dose is delivered to the normal tissues beyond the radiotherapy target. Electrons do not penetrate deeply in the body and are therefore only suitable for superficial tumours.

QUESTION 2

An 84 year old ~~gentle~~man presented with a basal cell carcinoma on the tip of his nose measuring 1.0 x 0.8cm in maximum diameter and approximately 6mm deep.

Which radiotherapy modality would be most appropriate to treat him?

A. Intensity-modulated radiotherapy (IMRT)
B. Volumetric-modulated arc therapy (VMAT)
C. Tomotherapy
D. Electrons
E. Protons

Correct answer: D. Electrons are suitable for the treatment of superficial tumours as electrons only deliver dose relatively superficially. IMRT, VMAT and tomotherapy (A, B, C) deliver photons which are more suited to target deep-seated tumours. Protons (E) are also suitable for deep seated tumours.

QUESTION 3

An 86 year old ~~gentle~~man wa~~i~~s found to have ~~diagnosed with~~ a 3cm non-small cell lung cancer in the~~his~~ periphery of the ~~al~~ left upper lobe. There wa~~i~~s no evidence of nodal or metastatic spread. H~~e i~~s performance status was 2 and he had~~s~~ a history of angina, atrial fibrillation (on warfarin) and a previous myocardial infarction. He wa~~i~~s medically unsuitable for surgery and was~~and is~~ therefore referred for radiotherapy.

What is the optimal management? ~~You explain to him:~~

A. Conventionally fractionated 3D conformal radiotherapy (3D-CRT) ~~over four weeks is likely to give him the best chance of local control~~
B. Proton radiotherapy ~~is in his best interests as this will deliver less dose to the normal lung tissue~~
C. Best supportive care ~~is the only appropriate option for him given his poor performance status~~
D. Conventionally fractionated Intensity-modulated radiotherapy (IMRT) ~~over six weeks will target his tumour more accurately than 3D-CRT over four weeks~~
E. Stereotactic ablative body radiotherapy (SABR) ~~is likely to give him superior local control compared to more conventionally fractionated radiotherapy~~

Correct answer: E. SABR radiotherapy has been shown to result in excellent local control for small peripheral lung cancers. Local control appears comparable with surgery and superior to conventionally fractionated radical radiotherapy. Proton beam therapy is not established for the treatment of lung

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cancer. Patients with poor performance status can be considered for SABR. While conventionally fractionated 3D-CRT or IMRT can be used for the treatment of small lung cancers, local control appears superior with SABR. Proton therapy is not well established for the treatment of lung cancer. Best supportive care is an option for patients with poor performance status but SABR offers a better change of local control and is suitable for this patient group.