Principles of cancer treatment by radiotherapy

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Abstract

Radiotherapy plays an integral role in the management of more than 50% of cancer cases and 40% of patients cured of their cancer have radiotherapy as a part of their management. For some patients, it can be used definitively in place of surgery, offering the advantage of organ preservation. It is sometimes used before surgery to improve resection rates or after surgery to reduce recurrence rates. Outcomes may be improved if radiotherapy is combined with systemic therapies such as chemotherapy. The process of delivering radiotherapy is multi-level, involving clinical oncologists, medical physicists and therapeutic radiographers. Each step takes advantage of new technology that allows more accurate definition of the tumour and delivery of radiation, with the aim of improving treatment outcomes and reducing normal tissue toxicity. There have been significant advances in defining the target and delivering the radiation in the last few years, discussed further in this article.

Keywords Adjuvant; cancer; radiation; treatment

Introduction

Radiotherapy is an effective and commonly used treatment modality in cancer management. In England, 125,000 patients each year are treated with external beam radiotherapy (EBRT)[1] and it is estimated that 52% of patients with cancer receive radiotherapy at some point during their illness.[2]

The primary intent can be radical (curative) or palliative (symptom control). Forty per cent of all patients cured of their cancer have radiotherapy as a part of their therapy, either on its own or in combination with surgery or chemotherapy.[1] Radiation therapy can be delivered in three main ways – EBRT (photons/electrons/protons), implanted radioisotopes (brachytherapy) and injected radioisotopes. These are detailed in Table 1. Radiotherapy is usually used as a local or locoregional therapy.

Tumour types have inherently different radiation sensitivities that determine whether radiotherapy has a role in the treatment and also the dose required. Radiosensitive types include seminoma and lymphoma; moderately radiosensitive tumours are breast, lung and squamous cell carcinomas; poorly radiosensitive cancers include osteosarcoma and melanoma.

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Clinical indications for radiotherapy

Radiotherapy plays a variety of roles of in both the radical and palliative treatment of cancer.

Definitive radiotherapy

Radiotherapy may be used as the definitive cancer treatment modality in certain tumour sites. This includes head and neck, anal, prostate, bladder, oesophagus and cervical cancers, where radiotherapy offers the significant advantage of organ preservation over surgical intervention. Radiotherapy may also be an alternative radical treatment for patients unsuitable for surgery because of significant co-morbidities, inoperable disease or proximity of the cancer to critical structures. One example includes early peripheral lung cancers, historically treated with surgery, which may be treated with stereotactic ablative radiotherapy (SABR) as curative alternative, particularly in those with co-morbidities unsuitable for surgery.

Commonly, radiotherapy is given concurrently with a systemic agent to enhance tumour control. Examples include the use of cytotoxic chemotherapy such as cisplatin for cervical cancer and biological agents, including cetuximab, for head and neck cancers.[3] Both agents act as radio sensitizers and enhance the tumourcidal effect of radiotherapy. Hormone therapy such as antiandrogens for prostate cancer is also given with radiotherapy in the definitive setting; it is usually started 3 months prior to radiotherapy to allow time for the prostate to reduce in volume, reducing side effects as well as improving tumour control.

Neoadjuvant radiotherapy

Radiotherapy given prior to definitive surgery is termed 'neoadjuvant' radiotherapy. This approach is used in selected rectal cancer cases to reduce the risk of local recurrence. Given concurrently with chemotherapy, complete pathological response rates (i.e. no residual tumour) of 15–27% have been demonstrated in histopathological specimens.[4]

Adjuvant radiotherapy

Radiotherapy may be given after definitive surgery (adjuvant radiotherapy). An example includes patients with early breast cancer, who may be offered adjuvant radiotherapy to the whole affected breast after breast-conserving surgery, as an alternative to mastectomy. Whole breast radiotherapy in this setting reduces the rate at which the disease recurs by half at 10 years and reduces the breast cancer death rate by approximately a sixth at 15 years.[5]

Salvage radiotherapy

Radiotherapy may be given for local or locoregional relapse after radical surgery. Patients with prostate cancer following radical prostatectomy undergo prostate-specific antigen (PSA) monitoring to detect early relapse. Patients with rising PSA levels (biochemical relapse) often have very low volume disease localized to the surgical bed, that can be treated by radical radiotherapy, thus maximizing the chance of long term control or potential cure.

Palliative radiotherapy

Radiotherapy is effective in the palliative setting for symptom control. It relieves pain from bony metastases in at least 60% of

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Types of radiation treatment used

Type of radiation	Indication
Photons	Able to penetrate deep into the body while sparing the skin. Commonest modality used for most deep-seated tumour types e.g. rectal cancer.
Electrons	Provide a high dose to a few centimetres depth from the skin surface with little dose beyond. Therefore, used for superficial treatment e.g. skin cancers.
Protons	Deposit energy with extreme precision, therefore limiting unwanted dose. Currently used for paediatric cancers, skull base cancers and some spinal tumours.
Brachytherapy	Radioactive sealed sources temporarily or permanently inserted into the tumour e.g. cervical and prostate cancer.
Injected radiotherapy	Radio-iodine for thyroid cancer and strontium-89 for bone metastases.

Table 1

patients[6] and may be used to palliate symptoms from spinal cord compression, brain metastases and uncontrolled bleeding.

Types of radiotherapy

Radiation therapy can be delivered in three main ways – external beam radiotherapy (EBRT) (photons/electrons/protons), implanted radioisotopes (brachytherapy) and injected radioisotopes. These are detailed in Table 1.

The most common type of radiotherapy used is photons. These are high-energy X-rays (6–18 megavolts) targeted to a specific area of the body for treatment. Photons are produced by accelerating electrons colliding with a metal target. They are delivered via a linear accelerator (LINAC) housed in a thick-walled bunker for radiation protection. The dose of radiation is defined as the energy absorbed per unit mass and is expressed in Grays (Gy) (1 Gy = 1 J/Kg). Radical radiotherapy is usually delivered in multiple treatments (fractions) on a daily basis over 3–7 weeks depending on the dose prescribed. Fractionating treatment optimizes the balance between the tumourcidal effect of radiation and the adverse effects on normal tissue. However, the benefit of long fractionation schedules may diminish as improved radiotherapy techniques reduce the volumes of normal tissues being irradiated. Longer schedules also give more opportunity for cancer growth during treatment and are more inconvenient and time-consuming for patients. The optimal fractionation schedule is likely to vary between cancer types but shorter schedules providing effective doses have become standard of care for breast and prostate following results of very large randomized clinical trials e.g. START and CHHiP.[7,8]

How does radiotherapy work?

Radiotherapy can be considered simply as 'targeted DNA damage'. Radiation absorption in tissues can cause ionization and excitation of atoms through electron displacement. These damaged atoms and molecules react with cellular components, consequently breaking chemical bonds to form highly reactive 'free radicals', which in turn may cause cellular insult, particularly DNA damage. This leads to activation of the sophisticated DNA damage recognition and repair (DDR) pathways and most DNA damage is repaired if these pathways are functional; if not, cell death inevitably occurs, usually when the cells try to pass through mitosis. Radiation also has an effect on tumour vasculature and the immune system, with emerging evidence that radiation-induced cell death is 'immunogenic'. These mechanisms of action may explain why certain systemic agents enhance the radiotherapy effect and there is huge interest in combining novel immune checkpoint inhibitors and DDR pathways inhibitors with radiotherapy.

Normal tissue effects may be *acute* due to direct cell death (e.g. mucosal surface), or *late* due to indirect effects on vasculature or stem cell component, thereby impacting future repair mechanisms. Radiation itself may be carcinogenic, with the potential risk of inducing second malignancies, particularly in the young.

The radiotherapy process

The process of radiotherapy is complex and involves an understanding of medical physics, radiobiology, radiation safety, dosimetry, radiation treatment planning, simulation and interaction of radiation with other treatment modalities. It consists of three distinct steps:

- immobilization, imaging and target volume definition
- treatment planning
- treatment delivery and set up verification.

Immobilization, imaging and target volume definition

The first step in the radiotherapy process is a 'planning CT scan', which is used to define the area to be treated. Patients are scanned in the treatment 'set up' position. Treatment positioning commands patient comfort and reproducibility for optimal delivery and is tailored to each tumour site, e.g. supine and arms up for thoracic cancers. To ensure accurate delivery of radiotherapy is maintained for each fraction delivered, patients require appropriate immobilization. This includes the use of thermoplastic shells for head and neck and brain tumours.

Three volumes are usually delineated: the gross tumour volume (GTV) consists of the actual tumour that is then extended with a margin to encapsulate microscopic spread to create the clinical target volume (CTV).[9] The CTV often also includes nodal areas at risk. A further margin is added to the CTV to allow for potential daily variation in tumour position, which can be from patient positioning or from internal organ motion. This is known as the planning target volume (PTV) and ensures that the CTV is always treated.

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