Demystifying Radiotherapy – clinical application and scientific principles

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Abstract

Radiotherapy is a treatment modality which utilises ionising radiation to treat or manage a condition, either benign or malignant, in order to cure a person of a condition, to palliate a person's symptom or as a prophylactic treatment. This article aims to introduce the field of radiotherapy, its role in medicine, the processes involved, the sciences that underpin it, the common side-effects encountered and simple measures to improve the therapeutic ratio of radiotherapy. It is our hope that this article gives a good introduction and understanding to this less-known sphere of medicine.

Introduction

Radiotherapy is a treatment modality which utilises ionising radiation to treat or manage a condition, either benign or malignant, in order to cure a person of a condition, to palliate a person's symptom or as a prophylactic treatment.[1]

Clinical role of radiotherapy

In general, radiotherapy is utilised for the following reasons:

1. Primary definitive treatment for a malignancy

For example, in prostate adenocarcinoma, radical radiotherapy is one of several treatment options and in terms of treatment outcomes, it is equivalent to radical prostatectomy.[2] This is a favourable treatment modality especially for medically inoperable patients.[2] Another example is stereotactic radiotherapy for early stage non-small cell lung cancer as shown in Figure 1(d). The local control rate is equivalent to surgical resection.[3]

2. To reduce the risk of local or regional recurrence after primary surgery

To illustrate this, adjuvant radiotherapy (see Figure 1(c)) is given post wide local excision of breast carcinoma and this treatment is now the standard of care for breast carcinoma.[4] A meta-analysis of randomised control trials has shown that adjuvant radiotherapy reduces local recurrence by 50% compared to wide local excision alone.[4]

3. To down-stage a tumour and increase the chance of complete resection

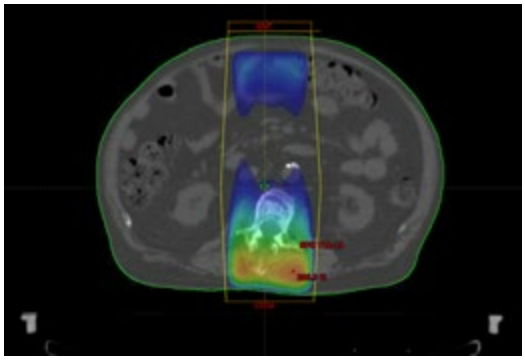
Neoadjuvant long-course concurrent radiotherapy with chemotherapy or neoadjuvant short-course radiotherapy (see Figure 1(b)) for rectal cancer is a good example for this. It is now considered standard treatment for rectal cancer as it has been shown to improve local control and the probability of a complete resection by down-staging the tumour.[5,6]

4. For symptom palliation

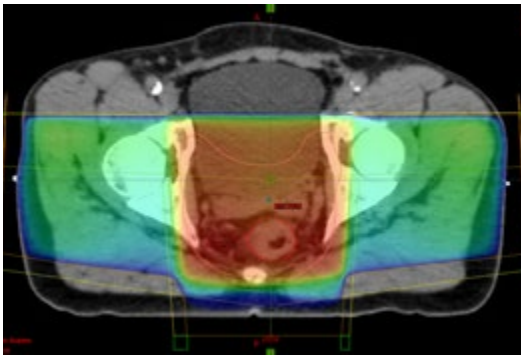
Bone pain secondary to metastases can be difficult to manage with analgesia alone and in these cases, palliative radiotherapy (see Figure 1(a) is shown to be effective in alleviating pain in up to 60% of patients.[7] Palliative radiotherapy is also used to shrink lung or mediastinal lesions to relieve airway obstruction, superior vena cava obstruction or spinal cord compression.[8,9,10]

5. For treatment of benign condition

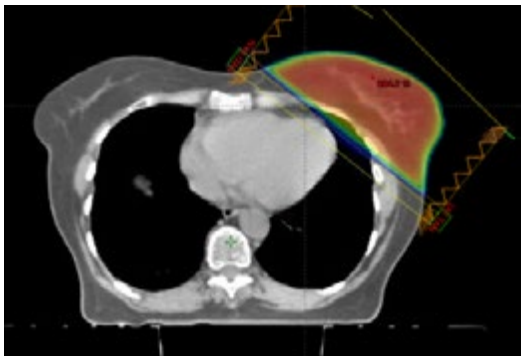
An example would be treatment of Dupuytren's contracture and it has been to shown in WHO Level 2 evidence studies to be effective in preventing or delaying disease progression, reducing the need for surgical intervention and relieving patient symptoms in early stage contracture.[11,12,13]



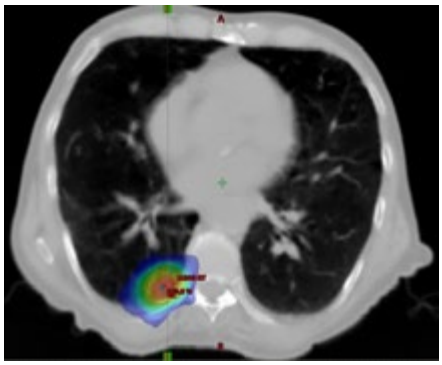
A. The blue region is 50% isodose region and the red region is 100% isodose with the colours in between reflecting isodoses between 50% and 100%. The 100% dose in this plan is 8Gy.



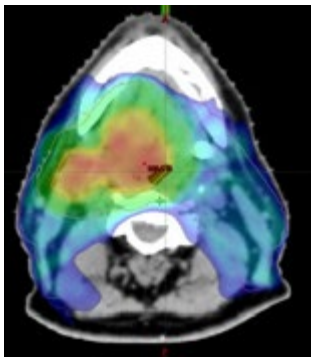
B. The blue region is 50% isodose region and the red region is 100% isodose with the colours in between reflecting isodoses between 50% and 100%. The 100% dose in this plan is 50.4Gy.



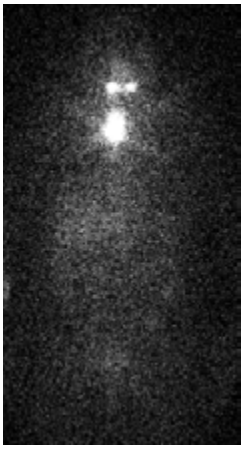
C. The blue region is 50% isodose region and the red region is 100% isodose with the colours in between reflecting isodoses between 50% and 100%. The 100% dose in this plan is 40Gy.



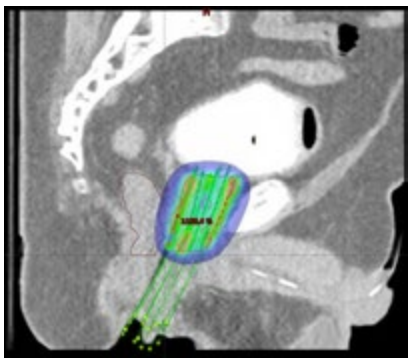
D. The blue region is 50% isodose region and the red region is 125% isodose with the colours in between reflecting isodoses between 50% and 125%. The 100% dose in this plan is 48Gy. Note the high dose within the gross tumour and rapid dose fall-off.



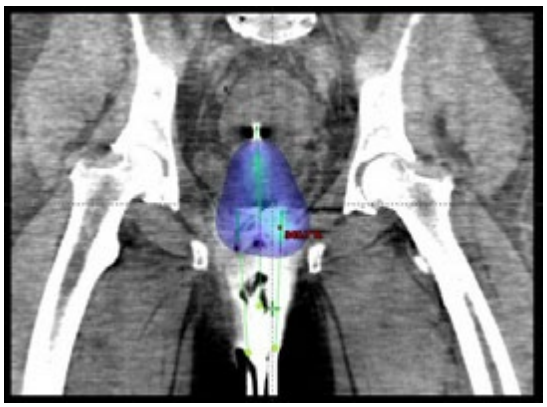
E. The blue region is 75% isodose region and the red region is 100% isodose with the colours in between reflecting isodoses between 50% and 100%. The 100% dose in this plan is 66Gy. Note the high dose region are concentrated at the gross tumour and the low dose region covers the intermediate risk area as well the elective draining lymphatics of level 2 and level 1b.



F. Increased uptake by the thyroid remnants and mediastinal nodes in a patient with mediastinal thyroid carcinoma metastases.



G. The blue region is 50% isodose region and the red region is about 1000% isodose with the colours in between reflecting isodoses between 50% and 1000%. The 100% dose in this plan is 13.5Gy. Note the rapid dose fall off beyond the prostate.



H. The blue region is 50% isodose region and the red region is 350% isodose with the colours in between reflecting isodoses between 50% and 350%. The 100% dose in this plan is 7Gy. Note the rapid dose fall off beyond the cervix and uterus.

Figure 1. a) Simple parallel-opposed pair field arrangement for spine bony metastasis, b) 3D conformal radiotherapy for neoadjuvant rectal cancer, c) Whole breast radiotherapy using tangential field, d) Stereotactic ablative radiotherapy for early stage lung cancer, e) Volumetric Modulation Arc Therapy for base of tongue SCC with large level 2 lymphadenopathy, f) Post Iodine-131 swallow scan, g) Prostate Brachytherapy, h) Cervical brachytherapy.

Patient's journey – sequence of events

When a patient is referred to radiation oncology, they are seen by a Radiation Oncologist. Radiation oncologists are medical doctors who specialise in using radiation to manage oncological conditions as well as other benign conditions. They form part of the core team of medical oncologists, subspecialty surgeons, pathologists, radiologists and subspecialty physicians, in oncology multidisciplinary meetings where patients newly diagnosed with cancer are discussed. Their role is:

- To assess and select which patients will benefit from radiotherapy
- To determine and delineate the treatment volume that needs radiotherapy in order to achieve the intent of the treatment
- To determine and delineate the critical structures to minimise dose to these
- To prescribing the radiotherapy course (dose, fractionation and treatment technique)
- To manage the side-effects that arises from the treatment course

There are a few procedures carried out prior to treatment delivery to the patient. This is illustrated below:

Consultation ⟶ Simulation ⟶ Contouring ⟶ Planning ⟶ Quality Assurance ⟷ Delivery

After consultation, a patient undergoes simulation, where the intended treatment is simulated to plan how it will be delivered and to ensure it is physically possible. During this procedure, the patient is positioned on the bed of a CT scanner and the set-up is documented in great detail. This is so that the patient can be set up in exactly the same way during treatment delivery.

The next step is contouring which involves delineating the 3D treatment volumes on the CT images acquired. The first step is to delineate the gross target volume (GTV) on the acquired CT images slice by slice. The GTV is the tumour that is visible on CT or clinically. To account for microscopic disease, a margin is added to the GTV while respecting natural boundaries. This new volume is called the clinical target volume (CTV). Depending on the treatment intent and the cancer biology of the condition at hand, the CTV may also include delineating the draining lymph nodes as well as neural pathways if there is perineural involvement. To account for set-up uncertainty and organ motion, another margin is added to the CTV. This volume is called the Planning Target Volume (PTV). Once contouring is completed, a radiation therapist will start the planning process and its aim is to generate a treatment plan that can deliver the intended dose as prescribed and conform to the PTV while protecting and minimising dose to surrounding organs at risk. In order to achieve this, the radiation therapist adjusts various variables such as positioning of treatment fields, weighting of the fields and beam modifiers. The treatment plan will then be reviewed by a radiation oncologist to ensure the treatment volume receives the prescribed dose and the doses to the organs at risk are within tolerance or acceptable limits. If these are met, the radiation oncologist then approves the treatment plan. This process may vary from a single day to two weeks depending on the complexity of the case.

Complex treatment plans will also undergo quality assurance by a medical physicist who ensures that the treatment plan is accurate in the delivery of the intended dose.

The patient will start his or her treatment course at an appointed time once a treatment plan has been approved and treatment slots are available. The treatment delivery session involve setting up the patient exactly the same way as they were positioned during planning CT followed by administration of radiation using the approved treatment plan. The same procedure is repeated for further fractions of radiotherapy.

During the treatment course, patients will be reviewed by a radiation oncologist to monitor and manage any side-effects. Once the treatment course is completed, the patient is usually followed up after a few weeks to ensure any acute side-effects that they experienced have resolved or are improving.

Deciphering radiation prescriptions

Radiation doses are normally prescribed in X Gray (Gy) delivered in Y fractions (#) over Z number of days. A fraction is an individual dose given usually once daily. A typical palliative prescription is 20 Gy in 5 fractions over 5 days. This translates to delivery of 4 Gy of radiation once a day for 5 days.

The Gray – Putting it into perspective

$$H_T = W_R D$$

W_R is the radiation weighting factor for radiation type R.

X-rays and electrons $W_R = 1$, Protons $W_R = 5$.

$$E = \sum W_T H_T$$

W_T is the tissue weighting factor.

Example: $W_T = 0.01$ for skin, $W_T = 0.12$ for bone marrow, $W_T = 0.04$ for oesophagus.

Figure 2. Equivalent (HT) and Effective dose (E)

One Gray of radiation (D) is a measure of 1 Joule of radiative energy being absorbed per kilogram of tissue. The concept of the equivalent dose (H_T) applies a weighting factor (W_R) to the absorbed dose to account for the different biological effect of each type of radiation, e.g. photons, electrons, protons. The equivalent dose for 1 Gray (Gy) of photons or electrons to an organ is 1 Sievert (Sv). The concept of effective dose (E) is used to further take into account the varying degree of sensitivity to radiation of human tissues. The total body effective dose is the sum of all equivalent doses to all organs multiplied by their individual radiosensitivity (W_T).[14] On average worldwide, all humans receive approximately 3 mSv in effective dose per annum from their environment.[15] This means that a whole body dose of 1Gy of radiation with a radiation weighting factor of $W_R = 1$ (e.g. x-rays, electrons) is effectively similar to exposing oneself to background radiation over 330 years.

Table 1. The average effective dose received from a selection of common medical procedures[16]

MEDICAL PROCEDURE	Average effective dose (mSv)
Chest radiograph (x-ray)	0.1
Abdominal radiograph (x-ray)	1.2
Abdominal Computed Tomography (CT) Scan	10
Cardiac angiogram	5-15

For a whole body dose of 1Gy of radiation where $W_R = 1$, this is equivalent to radiation exposure from 10000 chest x-rays, 833 abdominal x-rays, 100 abdominal CT scans or 66 cardiac angiograms. For this reason, radiotherapy should only be used when the benefit clearly outweighs any harm it may cause.

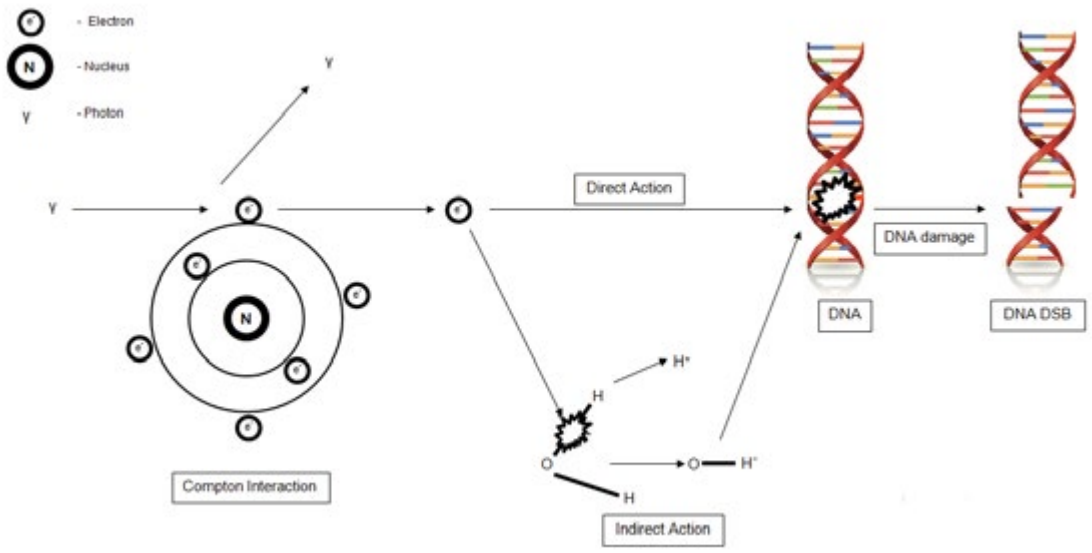


Figure 3. Atomic to molecular to biochemical reaction

Radiobiology - how does it work?

Radiation interacts with tissues in several ways, depending on the type of radiation. Photons interact with matter and cause the release of electrons via ionisation of atoms. These electrons will undergo many interactions in tissues, depositing an amount of radiation dose at each interaction location.[17] The Compton interaction is the main method of interaction of photons with material and is illustrated in Figure 3 below.[17] The electrons ejected are a result of ionisation, where an atom is given enough energy by the incoming photon to release an electron from its orbit around the nucleus. The mechanism of electrons interacting with tissue is either direct or indirect.[17,18] This may involve either direct damage of deoxyribonucleic acid (DNA) or indirect damage of DNA via free radicals when they interact with water.[17,18] The predominant route of DNA damage is via the indirect route.[18] Although they also interact with other structures such as organelles and proteins, the effect is negligible due to the multitude of these structures.[17,19] DNA, on the other hand, is limited in quantity and owing to the complexity of its protein structure, repairing any DNA damage is a complex process.[17,19]

The ionising radiation itself does not differentiate between normal and abnormal cells.[17] The selectivity occurs by the fact that abnormal cells have an impaired DNA repair mechanism, which has led them to transform in the first place, whereas the normal cells have an intact DNA repair mechanism.[17]

Depending on the extent of DNA damage, the cell with the damaged DNA may or may not repair itself.[17] If repair does not occur, the cells with the damaged DNA will undergo mitotic death when they attempt to divide.[17] Normal cells have better organized DNA repair processes so the likelihood of abnormal cells dying at the next mitosis is significantly higher.[17]

As the abnormal cells undergo mitotic catastrophe, the number of abnormal cells decreases as does the proliferation rate by virtue of reducing numbers of actively dividing abnormal cells.[17,18] These eventually result in a smaller tumour volume which translates to symptom alleviation.[17,18] If a high enough dose of radiation is delivered, it could potentially eliminate all the abnormal cells in the volume.[17,18] This is the goal for patients treated with curative intent. The result of the treatment may only be evident a few days, weeks or even months after treatment depending on how fast the cells divide.[17,18]

Why are the doses fractionated?

The therapeutic ratio is the balance achieved between the toxic and therapeutic effects of a treatment.[17,18] The best possible therapeutic ratio is achieved when we have minimised side effects whilst maximising the benefit of a treatment.[17,18] This is especially important when using radiation as a therapy, due to the harmful effect it may have on any tissue it interacts with.[17,18] The healthy tissues irradiated by the therapy beams would suffer severe side-effects if most prescriptions were delivered in one treatment session.[17,18]

The prescription doses are thus fractionated to allow for repair of normal tissue cells in-between fractions.[17,18] Cancer cells generally repair more poorly and at a slower rate than normal tissues, meaning the gaps in-between treatment are not undoing the radiation damage caused.[17,18] Fractionation also improves efficacy of therapeutic effects by:

- Allowing tumour cells to redistribute among cell-cycle phases, of which some are more sensitive to radiation damage[17,18]
- Enabling the reoxygenation of a tumour's hypoxic areas, where cells are more resistant to radiation damage[7,18]

Further details on the radiobiological mechanism behind these are beyond the scope of this paper.

Radiotherapy techniques – how is radiation delivered?

Radiotherapy can be delivered as internal or external radiotherapy. External radiotherapy, or external beam radiotherapy, is the commonest method of delivering radiation.[20] This is delivered from outside the body using a linear accelerator which produces a radiation beam which conforms to the target volume while aiming to spare any surrounding normal tissues.[20] A variety of techniques are available for the method of dose delivery, such as 3D conformal radiotherapy, intensity modulated radiation therapy (IMRT) and stereotactic radiotherapy.[20] Each has its own advantages and is utilised depending on the case at hand. An alternative to a linear accelerator is the traditional Cobalt-60 machine, which holds a Cobalt-60 source instead of producing therapy beams.[20] These machines are nowadays more common in developing countries due to their lower capital and installation cost, cheaper maintenance and servicing cost and lesser dependence on reliable electrical power.[20] However, the main disadvantage likes in the difficulty of disposing the radioactive source once it has passed its optimal clinical use and the need to replace it approximately every 5 years.[20]

Internal radiotherapy encompasses any radiation therapy where the source of the radiation is placed inside the patient. This includes sealed and unsealed source therapy, as well as the use of kV radiation sources placed inside body cavities. Brachytherapy is a radiotherapy modality where radiation is delivered using sealed radioactive sources which are surgically inserted into a cavity (see Figure 1 (g)) or interstitially (see Figure

Figure 4. Electromagnetic spectrum

1(h)).[21] The radiation delivered is short-range and hence, localised to where the source is placed.[20] Another example of internal radiotherapy is treatments such as the Papillon contact radiotherapy where low energy x-rays can be produced from a very small x-ray tube placed inside a cavity inside the patient.[20] This is used for small rectal cancers, skin lesions or intraoperatively during breast cancer lumpectomy.[20]

Unsealed source therapy delivers a radioactive source to within the patients' body either intravenously or orally.[22] Depending on the nature of the source, it is taken up by a particular organ and the radiation is delivered locally to that organ.[22] One example is radioactive Iodine-131 (see Figure 1 (f)) which is preferentially absorbed from the blood stream into thyroid tissues and thyroid carcinoma metastases, hence is used to treat thyroid malignancy.[22]

What exactly is ionising radiation?

Ionising radiations consists of photons or atomic particles that have enough energy to ionise matter at an atomic level via various atomic interactions and an example, as mentioned earlier is, the Compton interaction.[23]

Many types of ionising radiation are used medically, mainly: electrons, protons, x-rays, gamma-rays and ultraviolet rays. Radiotherapy applications require radiation types of specific characteristics for them to be useful as a therapy. Modern radiotherapy utilises electrons, protons, x-rays and γ-rays. X-rays and γ-rays are both particles which carry electromagnetic (light) energy, commonly referred to as photons but drastically differing in the amounts of energy they carry.[24] As illustrated in the electromagnetic spectrum in Figure 4, gamma-ray photons are particles in a higher energy range than x-rays.[24] The energy of a photon determines how it will interact with tissue, mainly to what depth it will deposit its energy, or dose.[24] For example, photons of 80 kilovolts (kV) can be used to treat superficial lesions, whereas high energy 20 Megavolts (MV) photons can deliver dose to deep-seated tumours.

The electrons and protons on the other hand are not part of the electromagnetic spectrum.[25] These are atomic particles.[25] The main difference between these particles is their mass; protons are much heavier than electrons.[25] This determines how many interactions they will have with tissue molecules before they deposit the energy they carry.[25] The lighter the particle, the higher the number of interactions and the more spread-out the dose deposition.[25] The main advantage of protons is the fact that they are so heavy that they travel through tissue until near the end of their range and deposit most of their energy within a well-defined region of tissue.[25]

Selection of the type of radiation and energy used in a particular case is dependent on the location and size of the treatment target, the surrounding healthy organs at risk from radiation damage and the availability of the radiation.[26,27] To illustrate, electron therapy is mostly used for superficial lesions as it delivers a high surface dose and has a steep drop off in dose deposition at depths beyond the target tissue whereas megavoltage photons are mainly used for deep seated lesions as electrons cannot reach these depths without also delivering high doses of radiation to the healthy tissues shallower than the target.[26,27]

This dose change with depth can be illustrated by the concept of the percentage depth-dose curves shown in Figure 5. This is the percentage of the maximum dose deposited in tissue at depth in tissue.

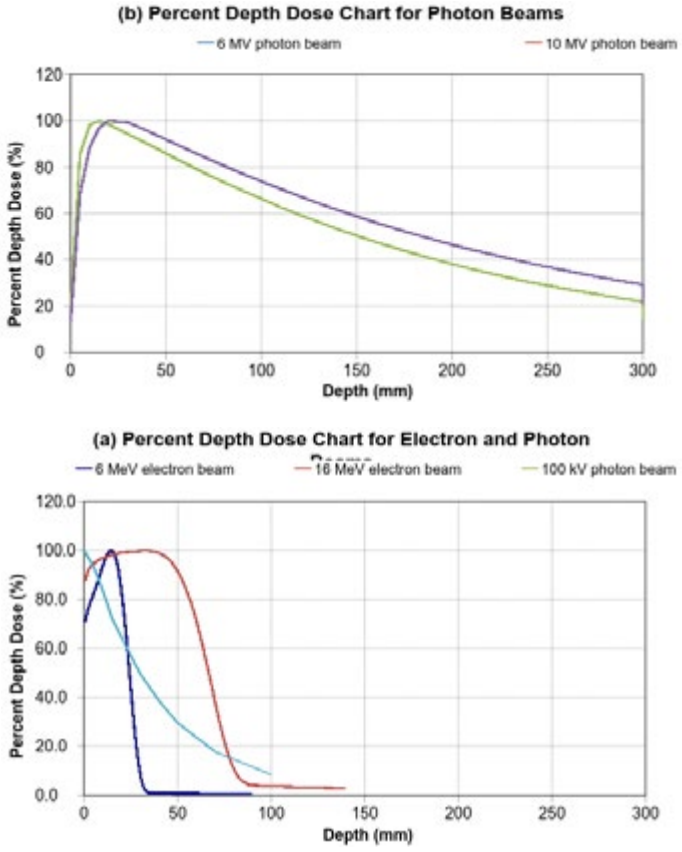


Figure 5. (a) Percentage depth dose of 6MeV electrons, 16MeV electrons, and 100kV photons (b) 6MV photons and 10MV photons.

Common side effects of radiotherapy

Generally, the side effects of radiation therapy can be categorised into systemic and local side effects. Systemic side-effects are mainly fatigue and nausea.

With local side-effects, only the cells within the treatment field are affected and they can be divided into early and late side effects. For example, the patient treated as shown in figure 1(e) will likely experience acute side effects such as radiation mucositis, radiation dermatitis, xerostomia, ageusia, nausea and odynophagia. His late side effects may include chronic radiation-induced skin changes, permanent xerostomia, low risk of radiation osteonecrosis and a very low risk of a secondary malignancy.

Whereas, the patient treated as shown in figure 1(b) will likely experience acute side effects which may include lower urinary tract symptoms such as dysuria, frequency and urgency, and gastrointestinal symptoms such as nausea and diarrhoea. With late side effects, this may include increased urinary frequency secondary to bladder shrinkage, change in bowel habits, rectal radiation-induced telangiectasia, impotence and a very small risk of secondary malignancy.

The risk of severe side-effects are kept as low as possible by ensuring the dose to the normal organs is kept as low as possible and below the safe limit. The acute side effects are usually controlled with medications so that few patients need hospitalization.

Simple measures to improve therapeutic ratio in the wards or clinics

- Treat anaemia (Haemoglobin < 100) especially with radical course

Increased haemoglobin translates to increased oxygen transportation and better oxygenation.[28,29] This in effect improves the efficacy of radiotherapy.[28,29]

- Cessation of smoking

Advise patient to stop smoking during treatment which may improve their blood oxygenation and improve the efficacy of radiotherapy.[30,31,32]

- Simple measures to prevent exacerbation of toxicity such as radiation dermatitis or radiation mucositis

Advise patient to minimise direct heat and trauma to irradiated area such as for radiation dermatitis, to avoid direct sun-light exposure, to keep skin cool and minimise skin friction by avoiding tight clothing and to apply moisturiser regularly to prevent dry skin.

Conclusion

This article aims to introduce the field of radiotherapy; its role in medicine, the processes involved, the sciences that underpin it, the common side-effects encountered and simple measures to improve the therapeutic ratio of radiotherapy. It is our hope that this article gives a good introduction and understanding to this less-known sphere of medicine.

The following websites are useful for further information on radiotherapy:
https://www.arpansa.gov.au/understanding-radiation/radiation-sources/more-radiation-sources/ionising-radiation-and-health
https://www.fda.gov/radiation-emittingproductsradiationemittingproductsandprocedures/medicalimaging/medicalx-rays/ucm115329
https://www.targetingcancer.com.au

Conflict of Interest: None

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