2 Basics Principles of Radiation Oncology

Subhash Gupta, K. P. Haresh, and Bharti Devnani

2.1 Introduction

Treatment of cancer requires multidisciplinary team approach. Radiotherapy (RT) is an integral part of the comprehensive cancer care and is required in around 60–70% patients diagnosed with cancer at some point of the time in the course of disease. Sir Wilhelm Conrad Roentgen discovered X-rays in 1895 and since then it is being therapeutically used to treat cancer [1]. This chapter aims to give insight in basic principles of Radiation Oncology for the surgeons.

There are two types ionizing radiation—

- Photons including x-rays and gamma rays.
- Particulate radiation which includes electrons, protons, α-particles, neutrons, negative π-mesons, and heavy charged ions.

2.2 Mechanism of Action

DNA is the principal target of radiation damage. Double-strand breaks are most important biological lesions produced in chromosomes by radiation resulting in cell kill [2]. There are two types of mechanism of cell kill by radiation—

- Direct action—This form of radiation causes direct ionization or excitation of atoms of the target. Radiation impacts the DNA directly in this type of cell kill that is why it is also known as "direct hit." It is the dominant process with high linear energy transfer (LET) particles which are neutrons and alpha particles.
- Indirect action—This is the common method of damage by radiation where radiation interacts with the non-critical target atoms usually water and forms the free radicals. These free radicals then attack the DNA. This free radical mediated injury is known as indirect action of the radiation. The most radiosensitive phase of cell cycle is G2-M phase while S phase is the most radio-resistant phase.

The principle form of photon interaction for therapeutic radiation is by Compton effect. It occurs due to interaction of the photon with the outer shell electrons which are loosely bound to the atom.

2.3 Radiobiology of Radiation Treatment

Radiotherapy is delivered in the fractionated approach; it means the total dose is divided in to a number of daily doses which are generally delivered 5 days a week. Conventional fractionation of radiotherapy is delivered to a dose of

S. Gupta (✉) · K. P. Haresh · B. Devnani
Department of Radiation Oncology, All India Institute of Medical Sciences, New Delhi, India

© Springer Nature Singapore Pte Ltd. 2021
M. D. Ray (ed.), *Multidisciplinary Approach to Surgical Oncology Patients*,
https://doi.org/10.1007/978-981-15-7699-7_2

1.8–2.0 Gy per fraction, from Monday to Friday. There are early reacting tissues including skin, mucosa while some tissues are late reacting like spinal cord, kidney, etc. The aim of fractionation is to maximize the tumor control probability at the same time minimizing the normal tissue complication probability to optimize the therapeutic ratio.

The biological basis of this fractionation is based on "four Rs" [2] of radiobiology as follows-

- *Repair* of sub-lethal damage—There are 3 types of damage by radiation, namely sublethal damage, potentially lethal damage, and lethal damage. Under normal circumstances, the sublethal damage is repaired in 2–6 hours unless other sublethal damage is being incorporated. This time interval between the two fractions of radiotherapy allows the normal early reacting tissue to repair of sub lethal damage repair.
- *Reassortment*—Cells are in different phases of cell cycle and asynchronous at the start of the radiation. G2-M phase is the most radiosensitive phase of the cell cycle while S2 is the most radio-resistant phase. When radiation is given, cells in sensitive phase (G2-M) get killed and the time gap between the two fractions allows the surviving fraction of cells to progress through cell cycle and synchronize to the more radiosensitive phase.
- *Repopulation*—Once the treatment is started, the tumor cells multiply at a faster pace which is known as accelerated repopulation. This is maximum at 4 weeks from starting the radiotherapy. It is prominent for rapidly proliferating tumors of head and neck cancers and lung cancer. The clinical significance of this phenomenon is that treatment breaks in radiation therapy adversely affects the outcome.
- *Reoxygenation*—The remaining viable cells after a fraction of radiotherapy is hypoxic and fractionation restores the proportion of oxygenated cells by allowing time for re-oxygenation. Hypoxia is an adverse feature which leads to radio resistance and poor tumor control. Re-oxygenation between the two fractionations helps in overcoming the negative effect of hypoxia in a multi fractionated treatment.
- *Importance of Oxygen*—Presence of oxygen is very crucial in manifesting biological effects of ionizing radiation [3]. A damage produced by radiation can be repaired by Sulfhydryl (-SH) groups under anoxic conditions. Oxygen fixes this damage produced by free radical and makes it permanent (lethal) damage. Hypoxic conditions increase the metastatic potential of tumor cells and oxygen enhances the radio sensitivity of the cells. Clinical studies have shown benefit in terms of local control in advanced cases of carcinoma cervix and head neck cancer, when the tumor is well oxygenated.

2.4 Altered Fractionation Schedules [4]

2.4.1 Hyperfractionation

Hyperfractionated schedules deliver a RT dose of 1.15–1.5 Gy per fraction twice daily. The intent is to achieve better tumor control with decreased late effects. This fractionation is commonly used to combat the problem of accelerated repopulation especially in head and neck and lung cancers.

2.4.2 Hypofractionation

Hypofractionated RT is utilized for the treatment of breast and prostate cancers where the tumor is slow growing. The dose per fraction is higher than 2 Gy per fraction and radiation is completed is shorter interval of time. The fractionation schedules are designed as per the alpha:beta ratio of the normal tissue and tumor. The fractionation is commonly used in prostate and breast cancer and in palliative irradiation.

2.4.3 Accelerated Radiation Therapy

In this form of treatment, total dose of radiation is given over a shorter period of time compared to standard radiation therapy. Acceleration and hyperfractionation can be combined, especially in head neck cancers and small cell carcinomas of lung. Accelerated treatment reduces the regrowth of the tumor between sessions, resulting in improved local control. The issue in using such a fractionation lies in the logistics issues as the patient needs to be treated twice a day which causes a problem in high volume centers. Hence, even though it appears to be an appealing modality of dose fractionation, it has not found to have many takers.

2.5 Types of Radiotherapy

Radiotherapy has been conventionally divided into two types [1].

2.5.1 Teletherapy

(Tele-Far) It is also known as External beam radiotherapy and is the most common form of radiotherapy. Tele- When the source of origin of radiation is away from the tumor and radiation is delivered from a distance. Cobalt machines and linear accelerators are being used to deliver the teletherapy by use of photons and electrons.

2.5.2 Brachytherapy

(Brachy- Near) Modality of radiation therapy where radioactive material is placed in or around the tumor [5]. A radioactive source like Ir-192 or Co-60 is the source for gamma radiation in this treatment. This is a type of sealed source radiation therapy (Fig. 2.1).

Brachytherapy is divided into following types based on the location of the implant.

a. Intra-cavitary Brachytherapy—This technique is mostly used for cancers of the uterine cervix and vagina.
b. Interstitial Brachytherapy—This treatment utilizes placement of interstitial needles into the tumor tissue. This method is used in treatment of gynecological, breast, head neck, prostate, penile carcinoma, and sarcomas.

Fig. 2.1 Remote after loading High dose rate Brachytherapy

c. Intraluminal Brachytherapy—The radioactive source is placed into hollow lumen like esophagus, trachea or bile duct. It is especially useful as a boost in esophageal malignancies or as a modality for palliation.
d. Surface (Mold) Brachytherapy—It is used to treat superficial tumors by placing sources on the skin surface. This method is used in treatment of skin malignancies like that of nose, pinna, cheek, scalp and intraoral lesions at hard palate.
e. Intravascular Brachytherapy—The use of this form of brachytherapy is decreasing where sources are placed into vascular lumens.
f. Plaque Brachytherapy: Use of radioisotopes, e.g. Ruthenium has been employed in treatment of ocular tumors like Choroid Melanoma and Retinoblastoma.

Depending on the dose delivered, brachytherapy can be divided into [5] -

- Low dose rate (LDR) brachytherapy—Dose delivered is less than 2 Gy per hour.
- Medium dose rate (MDR) brachytherapy—Dose delivered is 2–12 Gy per hour.
- High dose rate (HDR) brachytherapy—Dose delivered is more than 12 Gy per hour. HDR brachytherapy is most commonly utilized these days.

2.5.3 Unsealed Source Radiation Therapy

Selective Internal Radiation Therapy (SIRT)
This treatment is also known as trans arterial radioembolization (TARE) and used for treating unresectable liver tumors. The procedure involves injecting the Yttrium-90 microspheres into the hepatic artery. SIRT is efficacious in treatment of hepatocellular carcinoma and liver metastasis [6]. An average radiation dose achieved is around 200Gy.

Radionucleotide Therapy (RNT)
Radionucleotide is injected or ingested into the body systemically and based on the material's property concentrated in an organ or site. I-131 for thyroid cancers, Ra-223, Sr-89, Sm-153 for bone metastasis, and Lu-177 for neuroendocrine tumors are some of the example where RNT is used.

2.5.4 Intra-Operative Radiotherapy (IORT)

Intra-operative radiation therapy (IORT) is a technique where radiation is delivered during a surgical procedure directly to the tumor bed. The advantage being precise delivery of a large dose of radiation to the surgical bed with relative sparing of surrounding critical tissues. This is especially helpful in recurrent and residual tumors where dose escalation and reradiation is feasible by IORT which is otherwise difficult with EXRT [7]. The role of IORT has been proven in various malignancies including retroperitoneal sarcomas, pediatric tumors, and recurrent rectal and gynecological cancers. IORT can be delivered using intra-operative electron radiation therapy (IOERT), high dose rate brachytherapy (HDR-IORT), or electronic brachytherapy/low-kilovoltage x-rays (KV-IORT). The advent of mobile linear accelerators and self-shielding devices has further increased the utilization of this technology.

2.6 Intent of Radiotherapy

2.6.1 Definitive/Radical Radiotherapy

Radiotherapy is used as a radical treatment modality with or without concurrent chemotherapy based on the stage of the disease with curative intent. Radiotherapy as a single modality is used in treatment of early stages of head and neck cancers, cervix cancer, while for advanced cases concurrent chemotherapy, e.g. Cisplatin based chemotherapy is used as radiosensitizer. In laryngeal cancers and bladder cancer it helps in organ preservation. The doses range from 60 to 70 Gy by conventional fractionation over 7 weeks. Cervix cancers are being treated by external beam radiotherapy followed by brachytherapy to a total dose of 80–90 Gy for radical treatment [8].

2.6.2 Adjuvant Radiotherapy

When radiotherapy is given postsurgery to eliminate the subclinical risk of micro-metastasis. The suitable time to start adjuvant radiotherapy is between 4 and 6 weeks postsurgery. Intra-operative details and postoperative histopathology is very important for a radiation Oncologist. Post-operative radiation decreases the risk of recurrence and even overall survival benefit in many cancers. It is used in breast cancer, oral cavity, advanced laryngeal cancers, sarcomas, endometrium, and cervical cancers.

2.6.3 Neoadjuvant Radiotherapy

In this approach radiotherapy is given prior to definitive treatment with aim to downsize the tumor with better surgical outcome. It is being practiced in rectal cancers, locally advanced esophageal cancers, advanced head and neck and breast carcinomas to make surgery feasible.

2.6.4 Extra-corporeal irradiation

Extra-corporeal radiotherapy is used in the management of malignant bone tumors. It helps in limb salvage as a biological reconstruction option in bone tumors, e.g. Ewing's sarcoma and Osteosarcoma. After en-bloc removal of the tumor bearing bone segment, it is irradiated to a dose of 50 Gy in a single fraction and re-implanted back in the body.

2.6.5 Palliative Radiotherapy

Palliative radiotherapy is given for tumor growth restrain and control the symptoms of pain, bleeding, obstruction or compression. It plays an important role in management of metastatic disease. It is given as hypo fractionated approach, most commonly used fractionations are 8 Gy in single fraction, 20Gy/5 fractions or 30 Gy/10 fractions. Some examples of Radiation Oncological emergencies where radiation is used namely- [9].

(a) Superior vena cava obstruction.
(b) Spinal cord compression.
(c) Brain metastasis.
(d) To control tumor bleed.
(e) Obstructive dysphagia from locally advanced esophageal cancer.

2.7 Radiotherapy Volumes Definition

The International Commission on Radiation Units and Measurements (ICRU) Report 50, 62 and 83 [10] has recommended definitions of treatment volumes as-

- The gross tumor volume (GTV) denotes demonstrable tumor. It includes primary tumor GTV-T and grossly involved lymph nodes that is GTV-N. GTV is identified by clinical examination and should be supported by the relevant radiological examinations.
- The clinical target volume (CTV) comprises of the GTV and subclinical disease harbinger of micro-metastasis. This is determined by the radiation oncologist based on the evidence on the patterns of spread and existing contouring guidelines.
- The planning target volume (PTV) is an envelope, which includes the CTV and a margin to encompass for geometric uncertainties. It takes into account the inter and intrafraction motion errors.
- Organs at risk are the non-target normal tissue whose radiation sensitivity influences the treatment planning and dose prescription significantly.

2.8 External Beam Radiotherapy Techniques (Table 2.1) [1, 8, 9]

2.8.1 Conventional 2D Technique

It is the primitive technique to deliver radiation which is largely replaced by CT based planning. Field borders are determined by bony landmarks and orthogonal X-rays of the patient. Beam arrangements are limited and square or rectangular fields are commonly used. It is helpful in palliative treatments due to simplicity of the planning methods.

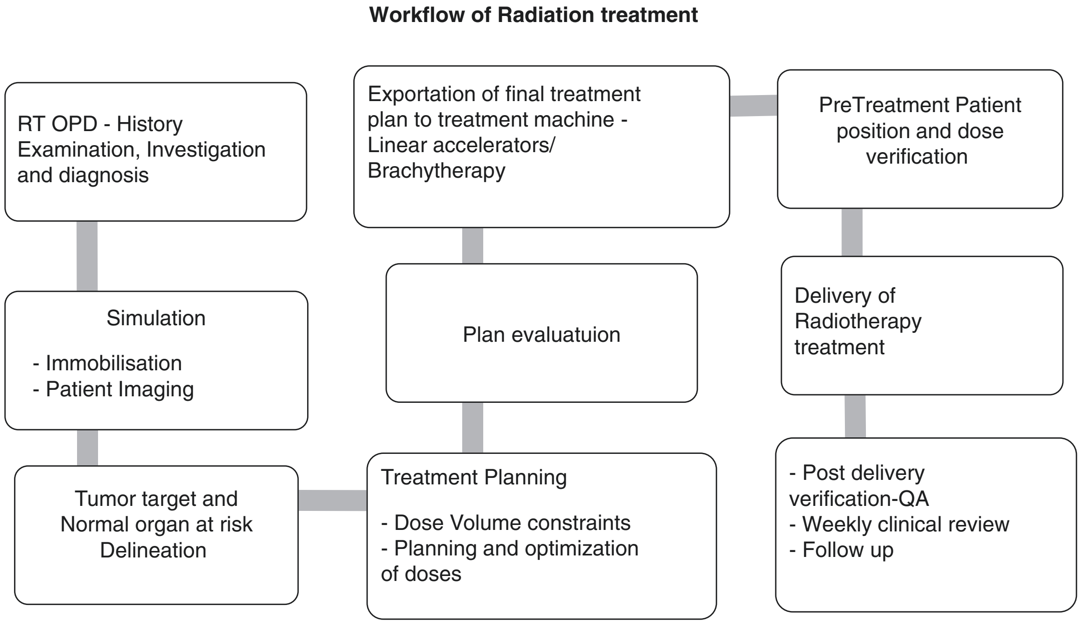
2.8.2 Conformal Radiotherapy

3D Conformal RT (3D-CRT) technique shapes the beams based on 3D reconstructions of the tumor size and shape and the location of nearby normal tissues.

Intensity-modulated radiation therapy (IMRT) changes the intensity of each small beamlet to obtain even more conformal dose distribution and avoidance of normal tissue damage.

Image-guided radiation therapy (*IGRT*) is a method of radiation therapy that incorporates

Table 2.1 Workflow of Radiation treatment



imaging techniques during each treatment session. *IGRT* is used to treat tumors in areas in close proximity to the critical structures and prone for the movement. This technique is required in lung and liver cancer where due to the respiratory motions, there are more chances of intrafraction motion. IGRT helps in precisely delivering the radiation in case of prostate cancer and minimizing the toxicity to the bladder and rectum which are situated are prone for receiving high doses due to variation in filling each day.

2.8.3 Stereotactic Radio Surgery (SRS) and Stereotactic Body Radiotherapy (SBRT)

In stereotactic radiotherapy, ablative doses of radiation are delivered to tumor in a single or few fractions. The technique is based on precise delivery of high dose of radiation to target with minimal injury to the surrounding normal tissues by highly conformal methods. SRS refers to a single-fraction delivery of a high dose to an intracranial target whereas SBRT is hypofractionated treatment applied to extracranial targets.

2.8.4 Hadron Therapy (Particle Therapy) [1, 8, 9]

Proton, Neutron, and Carbon ions are heavy particles which constitute part of Hadron therapy. Proton beam therapy is the most commonly used amongst them. Protons are the positively charged particle which slowly deposit the energy in the tissue up to a certain distance and then deposit their maximal energy also known as 'Bragg peak' with no or minimal exit dose. This helps in sparing the tissues beyond the target. This feature is helpful in reducing the late toxicities especially in childhood cancers like medulloblastoma, ependymoma [11]. Although it is used in almost every site the therapeutic benefit is more pronounced in Choroidal melanomas, Skull base tumors, reirradiation cases and in the tumors which are considered inherently radio-resistant.

2.9 External Beam Radiotherapy Machines [1, 8, 9]

2.9.1 Cobalt-60 Unit

This is a teletherapy machine which utilizes a radioactive source, cobalt-60. The advantage of Co-60 unit is that a simple infrastructure and less power is required, also the maintenance is more cost effective in comparison to Linacs. It is not suitable for deep seated tumors and is associated with more skin toxicities.

2.9.2 Linear Accelerator (Linac)

A linear accelerator is a device that uses high radio frequency electro-magnetic waves to accelerate charged particle such as electrons to high energies through linear tube called the accelerator wave guide. Patient is treated on a movable couch and beam comes out of the gantry which can be rotated around the patient. The principle of linear accelerator was invented by Rolf Wideroe in 1930 and the first patient was treated in 1956 at Stanford University in the USA. Current generation of Linacs have all the advantages of dual photon energy, electron energies, multileaf collimators for beam shaping with improved beam characteristics and image guidance tools in a compact design (Fig. 2.2).

Fig. 2.2 Linear accelerator with advanced technology

2.9.3 Machines to Deliver SRS and SBRT

- *Gamma Knife:* It is a stereotactic radiosurgery unit introduced by Leksell, a Swedish surgeon in 1951 in collaboration with Borje Larrson, a radiation biologist. It has a high precision to deliver high doses of radiation to intra-cranial tumors and used for treatment of Meningiomas, acoustic neuromas and pituitary tumors and brain metastasis [12]. Gamma knife radiotherapy is also useful in benign vascular and functional conditions including arteriovenous malformation, and Trigeminal neuralgia. Historically the unit houses 201 $_{60}$Co sources arranged in a hemispheric array. In the latest system which is named as 'Perfexion' uses 192 $_{60}$Co sources. The gamma knife is not a real knife, instead the highly conformal gamma rays from Cobalt-60 destroy the tumor as a cutting knife.

  Linear accelerator (LINAC): LINAC based systems are also used to deliver stereotactic treatment. The advantages of these systems include more patient comfort because of frameless set up and large lesions can be treated using Fractionated stereotactic Radiotherapy (FSRT). Commonly used systems for this kind of therapy includes CyberKnife, NovalisTx, and Brian Lab. The CyberKnife System has a robotic arm with six degrees of freedom and a real time tumor tracking system. Cyberknife can be used for both for SRS and SBRT in comparison to Gamma knife which can be used only for intra cranial lesions [13].

2.10 Reirradiation

Improved treatment techniques have resulted in a longer survival of the patients. Many patients developed local recurrence or second primary in the irradiated field in the course of their natural history. For years, Reirradiation was an enigma due to risk of normal tissue toxicities and risk of decline in quality of life of the patients. Now there is enough evidence to show that with it is a safe modality if chosen judiciously in carefully selected patient groups. Conformal radiotherapy treatment techniques should be used to minimize the toxicities. Patient and treatment related factors like time elapsed since the first radiation, toxicities from the previous doses and patient's general condition should be considered with maximum care and accuracy [14].

2.11 Common Toxicities of Radiation Treatment

Radiotherapy side effect can be divided into early or late side effects depending upon the time of occurrence.

- Early side effects occur during or within 3 months of radiotherapy. Commonly encountered toxicities are erythema of skin, mucositis, and fatigue depending on the site of radiation. Skin and mucosa are early reacting tissues while spinal cord, kidney, bladder, and lungs are some of the example of late reacting tissue.
- Late effects usually occur post 6 months of radiation for example subcutaneous fibrosis of skin, dryness of mouth, radiation proctitis, and cystitis.

With more conformal radiotherapy techniques both acute and late toxicities are decreasing making radiotherapy a more patient friendly cancer treatment modality.

References

1. Khan FM. The physics of radiation therapy. Baltimore: Williams and Wilkins; 1984.
2. Hall EJ, Giaccia AJ. Radiobiology for the radiologist. Philadelphia: Wolters Kluwer Health/Lippincott Williams and Wilkins; 2012.
3. Hall EJ, Brown JM, Cavanagh J. Radiosensitivity and the oxygen effect measured at different phases of the mitotic cycle using synchronously dividing cells of the root meristem of Vicia faba. Radiat Res. 1968;35:622–34.
4. Mitchell JB, Bedford JS, Bailey SM. Dose-rate effects on the cell cycle and survival of S3 HeLa and V79 cells. Radiat Res. 1979;79:520–36.
5. Gerbaulet A. The GEC ESTRO handbook of brachytherapy. Brussel: European Society for therapeutic Radiology and Oncology; 2002.
6. Sundram FX, Buscombe JR. Selective internal radiation therapy for liver tumours. Clin Med (Lond). 2017 Oct;17(5):449–53.
7. Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. J Clin Oncol. 2007;25(8):971–7.
8. Gunderson LL, Tepper JE, Bogart JA. Clinical Radiation Oncology. Philadelphia: Elsevier; 2016.
9. Halperin EC, Brady LW, Wazer DE, Perez CA. Perez and Brady's principles and practice of radiation oncology (Seventh edition.). Philadelphia: Wolters Kluwer Health/Lippincott Williams and Wilkins; 2018.
10. The ICRU Report 83. Prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT). J Inter Commi on Radiation Units and Measurements. 2010;10(1).
11. Hu M, Jiang L, Cui X, Zhang J, Yu J. Proton beam therapy for cancer in the era of precision medicine. J Hematol Oncol. 2018;11(1).
12. Flannery T, Poots J. Gamma Knife Radiosurgery for Meningioma. Prog Neurol Surg. 2019;34:91–9. https://doi.org/10.1159/000493054. Epub 2019 May 16. PMID: 31096250.
13. Mitrasinovic S, Zhang M, Appelboom G, Sussman E, Moore JM, Hancock SL, et al. Milestones in stereotactic radiosurgery for the central nervous system. J Clin Neurosci. 2019;59:12–9.
14. Nieder C, Langendijk J. Re-Irradiation. New Frontiers: Springer; 2017.