Principles of Radiation Oncology: A Beams Eye View for a Surgeon

A. S. Kirthi Koushik · K. Harish · H. U. Avinash

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Abstract Knowledge about the radiation medicine as a whole has gained importance in the recent past due to better understanding of not only the physical and biological principles but also advancements in the technology and better understanding of oncological principles. This review will try to address some of these aspects that are considered relevant to a surgeon dealing with oncology cases. With recent advancements we are able to achieve a better therapeutic ratio, that is more dose to the tumour and lesser dose to the normal tissues. This review will help the surgeon in understanding the basics and also be aware of the recent advances in radiotherapy.

Keywords Radiation oncology · Oncologic surgeon

History

Radiation Oncology as a branch has evolved in the last century especially in the last two decades by leaps and bounds. The discovery of X-rays and radiation by scientists Roentgen and Becquerel in the late 1800 A.D. initiated a new frontier in medical science. Then the Nobel prize winning

work of Madam Curie on radioactive elements got things in order for application of radiation for clinical use. The first radiobiological experiment was actually an accident as Becquerel left 200 mg of Radium in his vest pocket for 6 h and noted ulceration of skin which healed after a few weeks. Then the field of radiobiology just took off and the greats like Casarett, Bergonie and Tribondeau demonstrated different facets like radiosensitivity and fractionation. Meanwhile the advancements in the technological front in terms of newer radiation production and delivery systems and diagnostic tools ensured greater success of therapeutic radiation [1].

Basic Physics

Radiation is the energy carried by waves or stream of particles and is broadly a term for the emission, propagation and absorption of energy. This includes high energy electromagnetic radiation such as X-rays, gamma rays and particulate radiation such as electrons, protons and neutrons. It produces ions in the cells of the tissues it passes through as it dislodges the electrons from atoms hence known as *ionising radiation*. This in turn produces biological effects by breakage of chemical bonds leading to the formation of highly reactive free radicals, which react with and damage bio molecules such as DNA. X-rays, gamma rays and electrons are the most widely used forms of ionizing radiation in the clinical setting. The unit of absorbed radiation dose is the Gray (Gy) ($1 \text{ Gy} = 1 \text{ joule per kilogram (J/KG)}$). Formerly ‘rad’ was used as unit of absorbed radiation, it is equal to 10^{-2} Gy (1 cGy). The total dose of radiation is divided into several smaller doses called as ‘fractions’ that are given over a span of several weeks. This is done to achieve a better therapeutic ratio (Fig. 1). For most of the cases the treatment is delivered

A. S. Kirthi Koushik · H. U. Avinash
Department of Radiation Oncology, M.S.Ramaiah Medical
College and Hospital, Bangalore, India

K. Harish
Department of Surgical Oncology, M.S.Ramaiah Medical College
and Hospital, Bangalore, India

A. S. Kirthi Koushik (✉)
Department of Radiation Oncology, M.S.Ramaiah Medical
College, Bengalooru, NO: 187, A.G.B IIInd Stage,
Mahalaxmipuram,
Bengalooru 560086, India
e-mail: kirthi.koushik@gmail.com

Fig. 1 Holthusen's curve depicting the therapeutic ratio. As the therapeutic ratio increases, the probability of complications during treatment for a given dose of radiation decreases

once a day except for some where different fractionation is practiced.

Types of Fractionation:

- A. Conventional fractionation is when 1.8–2.2 Gy per fraction are given daily over 5–6 weeks, 5 days in a week, till total prescribed dose is achieved.
- B. Altered Fractionation:
 - Hyper-fractionation is when daily dose is divided into 2 sessions without changing the length of the treatment.
 - Accelerated fractionation is when total dose is given over a shorter period of time by giving the same dose more frequently (more than once a day) [1].
 - Hypo-fractionation is when dose per fraction is more than conventional (Table 1).

The method of delivering radiation can be classified as

1. External beam radiation (Teletherapy).

This involves delivery of radiation from a unit located external to the body. The most commonly used external beam units are: cobalt and linear accelerators. Since the last century this branch has evolved to be a fruitful congruence of surgical as well as medical and radiation principles. This involves multidisciplinary team of clinicians, physicists, dosimetrists, technicians,

specialist nurses and IT specialists. A wide variety of technical equipment and machinery is required and includes linear accelerators, simulators, treatment planning systems and portal imaging systems, CT / MRI scanners linked to planning systems, computer networks and software upgrades. All these have resulted in achieving the most basic principle which is maximum dose to tumor and minimum dose to normal structures. Steps involved in the external beam radiotherapy treatment are compared and summarized below (Table 2).

Lately PET scan is being used for radiotherapy planning. PET is an acronym for Positron Emission Tomography. It is a functional imaging wherein specific radioactive isotopes are tagged to the metabolisable substances (Eg. F18 is tagged to deoxy-glucose in FDG PET). The tumor tissue having high metabolic rate will accumulate these substances in a high concentration. The sensitivity and specificity of PET increases further when the images are coregistered along with CT scan. Now the use of PET CT is gold standard in Radiotherapy planning for ca Lung. The negative predictive value of PET CT in identifying the nodal metastasis approaches 100 % [1, 2]. (Table 3)

Depending on the technology used from Conventional to Intensity Modulated Radiotherapy the distribution varies with the end result of achieving better dose delivery to tumors and less dose to the surrounding normal structures as depicted (Fig. 2) [1].

Its worth mentioning about particle beam therapies in today's practice. Use of charged and uncharged particles accelerated to gain high energy is used in the treatment. The major advantage of particle beam therapy is the characteristic depth dose distribution and high biological effect. It has a phenomenon of Bragg peak, which means dissipation of almost all energy at a particular depth, the dose of radiation distal and proximal to this bragg peak is negligible. Hence this gives most conformal form of radiation therapy with maximum sparing of normal tissues. The examples of Particles are – Proton beam, Carbon Ions and fast neutrons. Since its highly conformal and accurate, its application is in those sites where the tumor is located in close proximity to the critical structures Eg., Skull base tumors and Pediatric Brain tumors. Since it has a high biological effect, it is used in relatively radioresistant

Table 1 Altered fractionation schemes in radiotherapy

Fractionation	Dose/fraction	Indication
HYPOFRACTIONATION	2.3–5 Gy	Ca. Breast
HYPERFRACTIONATION	1.2 – 1.5 Gy	Head & Neck Squamous cell cancers, Non Small cell lung cancer
ART (Accelerated Radiotherapy)	1.4–1.5 Gy	Head & Neck Squamous cell cancers, Non Small cell lung cancer

All tumors are treated with conventional fractionation. Altered fractionation is used only in select situations in the tumors mentioned

Table 2 Steps involved in delivery of external beam radiotherapy in various techniques

Steps	Conventional	3DCRT	IMRT/IGRT	SRS/SRT
INFORMED CONSENT	+	+	+	+
PREPLANNING	+	+	VERY RIGOUROUS	VERY INTENSE
IMMOBILISATION	+	+	+	A MUST
SIMULATION (CT/FLUORO)	XRAY / FLUORO	CT SCAN	CT SCAN/FUSION	FUSION A NECESSITY
CONTOURING (TARGET DELINEATION)	NOT REQUIRED	REQUIRED	REQUIRED	REQUIRED
PLANNING (INVERSE/FORWARD)	CLINICAL	FORWARD	INVERSE	FORWARD/ INVERSE
QA	+	++	+++	++++
EXECUTION	EASY AND SIMPLE	COMPLEX	COMPLICATED AND TIME CONSUMING	VERY COMPLEX
VERIFICATION	+/-	++	+++	++++
SITES	VOCAL CORDS	HEAD AND NECK	CA NASOPHARYNX	AVM/
	PALLIATIVE	PELVIS	CA PROSTATE	TGN/
		BRAIN	CA POST CRICOID	CHORDOMAS/
			PARANASAL SINUS	OLIGOMETES

3DCRT three dimensional conformal radiation therapy, IMRT intensity modulated radiation therapy, IGRT image guided radiation therapy, SRS stereotactic radiosurgery, SRT stereotactic radiotherapy

tumors such as chondrosarcomas. Major disadvantage of these therapies is the huge area involved in installation of accelerators called cyclotrons & synchrotrons, high costs and radiation safety issues [1, 2].

2. Brachytherapy

Brachytherapy means short distance therapy. This involves placement of radioactive sources within tissues/tumors (interstitial therapy) or body cavities (intracavitary therapy) or close proximity to tissues (mould therapy). The advantage of brachytherapy is delivery of high dose to a small area and rapid dose fall-off.

The first clinical use of radioisotope for treatment of cancer was Radium by Dr Danlos in 1901 and first brachytherapy application in malignancy was for a basal cell carcinoma in St Petersburg in 1903. From then onwards brachytherapy which is a combination of surgical skills and radiotherapy principles evolved tremendously. Brachytherapy can be classified (Fig. 3) based on

- Application - preloaded or afterloading (less exposure). Preloaded means the applicators will be loaded with the radioisotope like Radium and will be directly inserted to the desired site by the clinician thereby getting exposed whereas after loading the applicators are placed in situ then the radioisotope is loaded by following a simple principle of 'ALARA' (As Low As Reasonably Achievable).
- Delivery- Low Dose Rate (LDR) or High Dose Rate (shorter treatment time).
- Planning: CT/MRI based or X-ray based (better delineation).
- Source: Iridium (most common), Cesium and Cobalt are commonly employed [1].

There are certain special brachytherapy applicators which need to be placed in the surgical bed per-operatively and the radiation treatment is given in early post operative period. Eg. Use of Mammosite, x-soft and

Table 3 Various brachytherapy sources which are commonly used in radiotherapy practice

Radioisotope	Half life	Indication
RADIUM-226	1600Years	Historical importance – Brachytherapy for Cervix
COBALT-60	5.26Years	Intracavitary, Interstitial & Intraluminal brachytherapy
CAESIUM-137	30 Years	Low dose rate Intracavitary Brachytherapy in Cervix
IRIDIUM-192	73.8Days	Intracavitary, Interstitial & Intraluminal brachytherapy
IODINE - 125	59.4Days	Permanent Implants in Ca. Prostate
STRONTIUM-89	50.5Days	Widespread painful bone Metastasis
PHOSPHOROUS –32	14.3Days	Widespread painful bone Metastasis
GOLD-198	2.7Days	Permanent Implants in Ca. Prostate
YTTRIUM - 90	64 h	Microspheres in Hepatocellular Carcinoma

Fig. 2 Teletherapy techniques
a. Conventional Plan, b.
3DCRT Plan, c. IMRT Plan.
‘Yellow’ colour depicts the
prescription isodose which is
sparing the Critical organs like
spinal cord (Blue) as the
technology increases

interstitial catheter implantation in carcinoma breast post lumpectomy. Mammosite is a simple single balloon catheter (similar to Foleys catheter), which is introduced into the lumpectomy site either at the time of lumpectomy or percutaneously after the procedure. The balloon is inflated later to abut the lumpectomy cavity and the radioactive source is placed in the central lumen of the catheter to irradiate the surgical bed. Mammosite is popular for its simplicity. However close proximity of the cavity to the skin and irregular cavities are contraindications [1, 2].

3. Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) means delivery of radiation at the time of the surgery. The concept evolved in view of surgical bed being the site of highest risk for recurrence in most of the malignancies. The major advantage is – Delivery of high doses to the surgical bed under direct visualization and shielding the normal tissues by mechanically retracting them apart or shielding them. By virtue of these, a high therapeutic ratio will be achieved. Various modalities have been used in IORT namely, Electrons, high energy photons and orthovoltage x rays.

Fig. 3 Classification of Brachytherapy

IORT has been tested in malignancies of stomach, pancreas, retroperitoneal and extremity soft tissue sarcomas, early stage carcinoma breast. Largest body of evidence is in use of orthovoltage x-rays (TARGIT – Targeted intraoperative Radiotherapy) in treatment of lumpectomy cavity in early stage carcinoma breast. TARGIT is shown to be non inferior to the existing standard of care (Whole breast radiotherapy and lumpectomy cavity boost) [2, 3].

Basic Radiobiology

Radiation acts on a dividing cell. Each cell goes through 5 phases of cell cycle and it is important to know that radiation is most effective on G₂M phase of cell cycle. The S phase of the cell cycle is considered the most radio resistant (Fig. 4). DNA damage is the basis for radiation induced cell death which can be either single strand or double strand breaks. This can occur either by direct damage (DNA damage directly by ionization) or by indirect damage (production of free radicals) [1, 2].

Fig. 4 Phases of Celle cycle and its relation with radiation sensitivity

Basis of Fractionation

It is important to know the 4Rs in radiotherapy which forms the basis of fractionation in radiotherapy

Repair All tissues repair including tumor cells but the rate of repair is faster for normal structures which are the basis for fractionation. (i.e. healing of normal tissues are given ample time)

Repopulation It's the general law that when a injury happens there will be compensatory mechanisms to fill the damaged part which happens in tumor too and since radiation acts on the dividing cell fractionated radiation helps in better cell kill.(i.e. as dead cells get replaced by tumor cells)

Reoxygenation Radiation acts by both direct and indirect effect, and the indirect effect is through free radical formation and fixing of radicals requires oxygen hence radiation effect is better in the presence of oxygen. This will be utilized by fractionating the dose as the hypoxic component will be replaced by euoxic cells by rearrangement.

Redistribution All cells will be in different phases of cell cycle. Hence when a particular cell dies there will be redistribution of the remaining cells in to G₂M phase and this is utilized by fractionating radiotherapy.

The aim is to try to target cells which are replicating and which are well oxygenated. By giving a gap between two fractions, the normal tissue cells repair whereas the tumor cells cannot. The other advantage of giving a gap is that cells which are initially in the radioresistant phase move to the sensitive phase which then become susceptible during subsequent fractions. The minimum gap between two fractions should be 6 h. The other ways of modifying the effect of radiation in order to increase the therapeutic ratio and protect normal tissues:

- **Radiosensitisers:** are Chemical or Pharmacologic agents that increase the lethal effects of radiation by various mechanisms if administered in conjunction with it. Eg: Cisplatin in cervical cancers and Temozolamide in Glioblastoma Multiforme.
- **Radioprotectors:** are the substances which reduce the biological effects of Radiation. Eg: Amifostine in prevention of Xerostomia in head and Neck radiation [1, 2, 4, 5].

Clinical Applications of Radiotherapy

Radical Treatment

When radiation is given with the intent of getting a high local tumor control resulting in higher chances of cure it is known

as radical treatment. In the process of delivering tumoricidal dose a reasonable rate of normal tissue toxicity is accepted. Radical radiotherapy may be given as a single modality (eg: ca. vocal cord) or along with chemotherapy (eg: ca.cervix). It has been shown that an absolute survival benefit of 12 % by concurrent chemo radiation is seen in a recent metaanalysis in carcinoma cervix [5]. In order to improve the therapeutic ratio many modifications are made both in terms of technological advancements and with modifiers.

Radical radiotherapy involves complex planning and a protracted fractionated course of treatment. Most radical treatments are given over 4–6 weeks, in 1.8 – 2.20 Gy fractions to a total dose of 55 – 74 Gy. Most of the treatment practices are based on well conducted randomized trials. Concurrent chemo radiotherapy requires scheduling of chemotherapy during the course of radiotherapy. Toxicity is often a significant problem and patients should be monitored closely throughout treatment [1, 5].

Adjuvant Treatment

Adjuvant literally means “in addition to” and is one of the commonest settings following surgery or chemotherapy [1, 6]. The main aim is to eradicate loco-regional residual microscopic disease. In view of tackling the microscopic disease the dose employed is slightly lesser i.e. between 45 and 60 Gy in conventional fractionation. Planning for adjuvant treatment can sometimes be very complex and tolerance also will be an issue due to vascular compromise. Based on evidence the radiotherapy treatment should start after 2–3 weeks following surgery giving just enough time for fibroblastic proliferation and healing of surgical wound. Delaying treatment beyond 8 weeks is not of much value, since the tumor cells repopulate and the effectiveness of radiation treatment will be compromised. Hence it's advisable to deal with cancer as a multidisciplinary team from day of diagnosis. The following cancers may require adjuvant radiotherapy following surgery: breast cancer, sarcomas, endometrial cancer, and head and neck cancer. In Breast cancer Post Operative Radiation showed reduction in the risk of recurrence with an odds ratio of 0.69(95 % CI, 0.58–0.83; $P=0.00004$) and mortality reduction with an odds ratio of 0.83(95 % CI, 0.74–0.94; $P=0.004$) [6].

Neoadjuvant Treatment

Neoadjuvant means prior to the primary modality of treatment. The main indications being to downstage the disease and organ preservation & relative hypothesis is to tackle the microscopic disease and assessment of response to treatment [1]. Surgery should be performed after a gap of 4–5 weeks for maximum benefit in terms of response and also minimum toxicity as shown by the Lyon R90-01 a randomized trial [7].

Examples include the treatment of locally advanced rectal cancer and advanced head and neck cancer [1, 7].

The advantages and the disadvantages of the adjuvant and the neoadjuvant radiotherapy have been summarized in Table 4.

Palliative Treatment

Pallios means “to relieve” and Radiotherapy has a crucial role in the palliative setting and is effective for a variety of symptoms:

1. Pain - especially pain from bone metastases, but also visceral pain.
2. Bleeding – haematuria, haemoptysis, PR bleeding, bleeding/fungating ulcers
3. Tumour obstruction of a hollow viscera e.g. bronchus, oesophagus, rectum.
4. Superior vena cava obstruction (SVCO)
5. Spinal cord compression
6. Symptoms from brain metastases and leptomeningeal disease

Palliative treatment follows a simple principle of “KIS (keep it simple)” and the intent is never to cure or prolong life but to give a good quality of life. Palliation is usually achieved with hypofractionated course of radiation but with lesser than radical doses. Patient set up and radiotherapy techniques are often very simple. Treatment may be given as a single fraction (e.g. 8–10 Gy) or as a short fractionated course (eg: 20 Gy in 5 fractions, 30 Gy in 10 fractions) [1, 2].

Prophylactic Treatment

The indications for prophylactic treatment are [1, 2]:

1. Prophylactic Cranial Irradiation: in ALL in remission and also in SCLC lung.
2. Ovarian Ablation.

Miscellaneous

1. Extracorporeal irradiation: where diseased bone is removed and after irradiation placed back hence customization will not be a issue.
2. Cyberknife : Cyber knife is a robotic radiosurgery device. Here a miniature linear accelerator mounted on a robotic arm which has six degrees of movement is used for treatment. Unlike gamma knife, cyberknife can be used for whole body stereotactic radiotherapy without rigid immobilization. The image guidance and synchrony technologies helps in accurate delivery of radiation to proposed target under a millimeter accuracy. However the long treatment time and the cost are major disadvantages. Since Cyberknife is a form of stereotactic radiotherapy, the indications are same as for any other stereotactic radiotherapy or radiosurgery [1, 2].
3. Blood irradiation: in cases of transfusion in transplantation cases.
4. Benign conditions: AVM, Keloids, Trigeminal Neuralgia, Aggressive Fibromatosis and Pituitary Adenomas to name a few.

Toxicity of Radiotherapy

Like any branch of medicine, radiotherapy also has its share of side effects or accompaniments. These accompaniments actually dictate the dose that can be safely delivered. The severity and time course of the reactions depends on the total dose of radiation, the fraction size, overall treatment time, tissue type, the volume of tissue irradiated and the clinical state of the patient [8]. The achievable tumor control is dependent on the tolerance of surrounding normal structures and the resultant therapeutic ratio. Radiation effects on normal tissues can broadly be divided into early/acute,

Table 4 The advantages and disadvantages of adjuvant and neoadjuvant radiotherapy

Adjuvant treatment	Neo-adjuvant treatment
Advantages	
1 Complete HPE report available	1 in vivo response can be evaluated
2 Microscopic disease only so dose required will be low	2 Facilitates surgery by downstaging the disease and the plane of resection
3 No hypoxic or anoxic component hence radiation effect is better	3 Anatomy preserved so better vascularity and target delineation
	4 Better tolerance of treatment
	5 Organ preservation
Disadvantages	
1 Compromised vascularity	1 Staging and HPE report can be an issue
2 Anatomy distorted so target delineation is a problem	2 Extent of resection is an issue
3 Post op changes result in increased complications	3 Delay in primary modality of treatment
4 Post op complications can delay adjuvant treatment	4 Acute toxicity and wound healing can be a problem
5 Compliance can be an issue	

subacute and late accompaniments. The word accompaniments is used in place of reactions as its natural to have a reaction like giving a scar post surgery is not a adverse event it's a part of surgery. These accompaniments can be called as reaction if not managed properly.

Early/Acute

These occur during, immediately after or within a few weeks of the end of treatment (within 90 days). Acute effects are due to depletion of stem cells and therefore the tissues most affected tend to be the rapidly proliferating tissues such as skin, mucosal tissue and haemopoietic tissue. Acute reactions are usually self-limiting and normally settle within a few weeks of treatment completion. Mucositis is the commonest accompaniment but they subside on their own [1, 8].

Subacute (Early Delayed)

These reactions occur between 1 and 6 months after completion of radiotherapy and are usually self-limiting over a period of a few weeks or months. Examples include:

- Radiation pneumonitis. Often responds well to a course of oral steroids but in today's era of technology this is not seen very often as the lung dose is kept in mind while planning treatment (Fig. 5).
- Lhermitte's sign. This is an electric shock-like pain that shoots down the spine and represents a reversible type of demyelination injury following spinal cord irradiation but is of historical importance alone in the present day technology where spinal cord can be protected by techniques like IMRT and 3DCRT.

Fig. 5 Use of image guided Treatment planning which allows the identification of lungs in the Beams eye view and selectively sparing it

- Somnolence syndrome. Occurs following brain irradiation and manifests as a transient period of severe exhaustion, lethargy and anorexia lasting typically for a few weeks. The concept of whole brain has changed and presently partial brain irradiation is practiced which doesn't cause this syndrome

Late

These effects develop over months or many years following irradiation and are usually progressive. The late effects of radiation are usually the dose limiting factor and tend to affect slowly proliferating tissues such as nervous tissue, lung, kidney, liver and heart [1, 8].

Proctitis (Fig. 6) and Cystitis can be good examples in pelvic radiotherapy. Pituitary or thyroid irradiation may cause endocrine dysfunction. Late effects are dose related and the risk is greater with high radiation doses, large fraction sizes and larger treatment volumes. Damage to stromal tissue (vasculature and connective tissue) and reduced proliferative capacity of stem cells are thought to be the main mechanisms for the late effects of radiotherapy. Carcinogenesis as also a late complication following radiotherapy is quoted in many textbooks but mostly with irradiation to young children. With the availability of newer chemotherapy drugs which are effective the use of radiation is very limited and the incidence has come to <1 % at the end of 20 years.

Summary

Radiation is an effective tool to treat cancer patients and in some cases cure the patient also. The most basic principle is to deliver maximum dose to tumor with minimum dose to surrounding normal structures thus achieving a higher cure rate with acceptable morbidity. Different doses are required for different

Fig. 6 Radiation proctitis: showing the telangiectasias in the background of pale mucosa

malignancies and the setting at which delivered. Recent advancements have helped to achieve a higher therapeutic ratio in the form of concurrent chemotherapy or newer techniques like IMRT or radiosensitisers and even altered fractionation schemes. It's most important to know that effort is on to eradicate misconceptions associated with radiation treatment and its toxicity and eventually make everyone realize that radiation is an integral part of the team in the fight against cancer.

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