Practical Radiation Oncology

Supriya Mallick
Goura K. Rath
Rony Benson
Editors

Springer

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Foreword

The editors of *Practical Radiation Oncology* need to be commended for compiling a succinct and informative handbook. The text integrates the technical and clinical aspects of radiation oncology. Optimal utilization of radiation as a cancer therapy requires a clear understanding of the range of issues, and this book focuses on the basic physics and technical aspects and provides information vividly to the clinician involved in radiation therapy planning, particularly those who are in training and new to practice. The book has been divided into six parts, covering areas such as instruments, brachytherapy, plan evaluation, clinical cases and clinical trials.

It is necessary to understand the specific physical and unique clinical applications of equipment used in radiation oncology. In the first part of the book, the practical aspects of various machines used are elaborated along with the quality assurance, personal monitoring, etc. All of these are important to understand the effective and appropriate use of radiation as a treatment modality. This leads to better clinical practice and greater confidence in recommending radiation treatment with appropriate techniques in a safe and equally effective manner.

Brachytherapy is an important modality of treatment, especially in several gynaecological malignancies, and it is an integral part of radiation oncology. The 'Practical Brachytherapy' part integrates different aspect of brachytherapy, their basics and site-specific applications. Case selection, procedure, planning and plan evaluation are discussed. The practical tips provided in this part will be very useful to the students.

The recent practice of radiation oncology has been revolutionised by technological advances in radiation delivery and imaging systems. The growing impact of imaging in radiotherapy planning has provided new insights into morphological and functional status. There is no doubt that imaging constitutes an extremely important step in radiation therapy management. Finer aspects of plan evaluation including 3D conformal radiotherapy, IMRT and tomotherapy have been discussed. Planning images and clinical examples have also been added so as to bring further clarity into the planning aspects.

The developments in cancer therapy are increasingly arising from studies in basic science, and understanding of radiobiology plays a significant role. The 'Practical Radiobiology' part has been presented in a concise and interesting way. This will serve as a comprehensive guide in radiobiology related to radiation oncology.

The exit examination for students appears as an insurmountable problem for them; this book is conceived and written for medical students preparing for their examination. Thirteen most relevant cases have been discussed in each chapter from an exit examination point of view and will be a useful guide for quick revision. Additionally, this will be an excellent quick reference for all physicians.

The last part of the book deals with relevant topics in clinical trials, translational research and radiation toxicity mitigation and treatment in modern practice of radiation therapy.

The individual chapters in this book are well written and superbly illustrated. I congratulate the authors for their successful efforts, as the authors have gleaned information to make easy reading. Careful attention is given to the concepts that are crucial in understanding modern techniques. The information in this book is presented in a logical and straightforward manner, thus offering an enjoyable learning experience.

It is a great honour and a privilege for me to write a foreword for this book. I am confident that many clinicians would significantly benefit from the information provided by the authors. The data indicate that radiation therapy continues to be an important modality in the treatment of malignant and a large number of benign conditions.

March 24, 2019

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Preface

Practical Radiation Oncology is long due for the radiation oncology community. The radiation oncology field has witnessed a paradigm shift in the last decade and has become a highly sophisticated tech-rich branch of medical science. It had become increasingly difficult to keep pace with the fast technical evolution and to know details of technical integrity of modern radiation oncology equipment. Radiation physics and radiobiology have also evolved to complement our knowledge. Most importantly, clinical application is now very much evidence based and versatile. All these necessitate a book to compile all the necessary information at our fingertips, particularly for those who are in training and those who have entered the arena of practice. We realized these aspects and embarked on writing this book, which deals with practical aspects in practising radiotherapy. We designed the book in six parts, *viz*. *Practical Physics and Instruments, Practical Brachytherapy, Practical Planning Aspects and Plan Evaluation, Practical Radiobiology, Clinical Cases and Other Relevant Topics*. In this book, we have tried to include all the relevant information for day-to-day practice. Being a practically oriented book, we have added only relevant information regarding the history of radiation oncology so as not to overburden the reader. The chapters in the 'Practical Planning Aspects and Plan Evaluation' part deal with practical aspects of how to evaluate a plan systematically with clinical examples, so that the reader understands each concept better. The chapters on clinical cases have been added keeping in mind those preparing for examinations as to how to approach a case including investigations and differentials. Practical planning aspects have also been added to each chapter including images wherever possible. These chapters have been prepared mainly for the resident in training preparing for the exit examination.

The journey started way back in 2016, and it took nearly 2 years to come to a meaningful end. We realized that this is not the end; rather this is the beginning of a new journey. We were very careful to deliver correct information to the best of our knowledge. We have also kept in mind that the book should benefit the students who are pursuing a career in radiation oncology. The presentation has been made very simple so that the reader is not lost in the crowd of information. At the same time, we believe that for practicing radiation oncologists the book may serve as a ready source of information.

We have faced few hurdles as it is expected in any good work. However, we are delighted and feel proud that the guidance of Prof. Rath helped us immensely to overcome all these hurdles. The book would not have been

possible without his profound interest. First of all, we express our gratitude to All India Institute of Medical Sciences, New Delhi, as it gave us the platform to think for such a book. We are overwhelmed by the response we received from all the authors across the globe, who wholeheartedly participated in making this goal achievable in a timely manner. In particular, we express our deep sense of gratitude to Dr. Nikhil Joshi, Dr. Aruna Turaka and Dr. Kiran Turaka.

This book has been prepared to the best of our knowledge but there may be mistakes and shortcomings. But we invite all the reader to come up with constructive criticism so that we can rectify such weaknesses and make this book an all-time reference.

Delhi, India — Supriya Mallick
New Delhi, India — Goura K. Rath
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Contents

Part II Practical Brachytherapy

Part III Practical Planning Aspects and Plan Evaluation

Part IV Practical Radiobiology

Part V Clinical Cases

Part VI Other Relevant Topics

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Part I

Practical Physics and Instrument

Interaction of Radiation with Matter

1

Ashish Binjola

The basics of physical aspects of radiation oncology, radiodiagnosis, and nuclear medicine lie in how various types of radiation interact with matter. In radiation oncology, megavoltage X- and gamma rays and high energy electrons are used for the treatment of the malignant disease (sometimes benign as well). For the simulation and verification of the treatment, use of kilovoltage X-rays (CT and conventional simulators, cone beam CT, etc.) is a routine practice. More exotic heavy ion therapies, with proton (i.e., hydrogen nucleus), carbon ion, and other heavier charged particles, are capable of providing treatment plans with higher conformality of the dose to the target volume and better normal tissue sparing. Tumor biological information in the form of PET-CT functional imaging augment for better delineation of target volumes in many sites/types of malignancies (e.g., involved-site radiation therapy).

This chapter introduces the basic physics of radiation interactions with the matter briefly along with its practical aspects in radiation oncology.

1.1 Basic Physics Concepts to Understand Basic Interactions

Atomic Structure An atom is a basic structure from which all matter is composed, in the same way as a brick is a basic structure from which a wall is built. Atom is derived from the Greek word Atomos means "indivisible" as it was thought to be anciently, but today we know that it has substructure.

The atom is composed of: positively charged (+) protons and electrically neutral neutrons inside the nucleus and negatively charged (−) electrons orbiting around the nucleus. The nucleus determines the identity of the element as well as its atomic mass. The nucleus constitutes almost 99.9% of an atom's mass but size of the nucleus is very small (nuclear radius is approximately 10^{-15} m) compared to the size of the whole atom (the size of an atom is approximately 10^{-10} m), so most of the atom is empty space with electrons in fixed shells, revolving around the nucleus.

Each element has a unique atomic number (number of protons inside the nucleus). Proton number never changes for any given element. For example, the Carbon atom has an atomic number of six indicating that carbon always has six protons.

Neutrons are the other constituent particles of the nucleus of an atom. Unlike protons and

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electrons, neutrons do not possess any charge (electrically neutral)

$$\text{Atomic mass no } A = Z + N$$

Z- Atomic Number (number of protons inside the nucleus); *N*- Number of neutrons inside the nucleus.

Electrons are negatively charged particles that surround the nucleus in "orbits" or "shells." These electrons revolve around the nucleus in well-defined orbits like planets revolving around the sun.

Basic properties of atomic particles are summarized in Table 1.1.

Neutrons and protons are together called the nucleons and they are made up of particles known as quarks. There are six known quarks which are the constituent particles of hadron (protons, neutrons, etc.) particles. These quarks are held inside the hadron particle by exchange particles gluons. The atomic structure of an atom is shown in Fig. 1.1.

Classification of Radiation Radiation can be classified into ionizing (having energy more than that is required to ionize an atom) and non-ionizing. Visible light, radio waves (used for telecommunications), microwaves are some examples of non-ionizing radiations.

Ionizing radiation can further be classified as:

1. Directly Ionizing Radiation: Energetic charged particles are the directly ionizing radiation as it ionizes matter when it interacts with atoms by ionization and excitation. Protons, alpha particles, and electrons are examples of directly ionizing radiation.
2. Indirectly Ionizing Radiation: Electromagnetic radiation (X-rays, gamma rays, and high energy spectrum of UV rays) and neutrons are examples of indirectly ionizing radiation.

Table 1.1 Basic properties of atomic particles

Atomic constituent particle	Charge	Rest mass	Energy equivalence of rest mass	Location
Electron	-1.6×10^{-19} coulomb	9.1×10^{-31} kg	0.511 MeV/C^2	Orbiting around the nucleus
Proton	$+1.6 \times 10^{-19}$ coulomb	1.673×10^{-27} kg	938.28 MeV/C^2	Inside the nucleus
Neutron	Electrically neutral	1.675×10^{-27} kg	939.57 MeV/C^2	Inside the nucleus

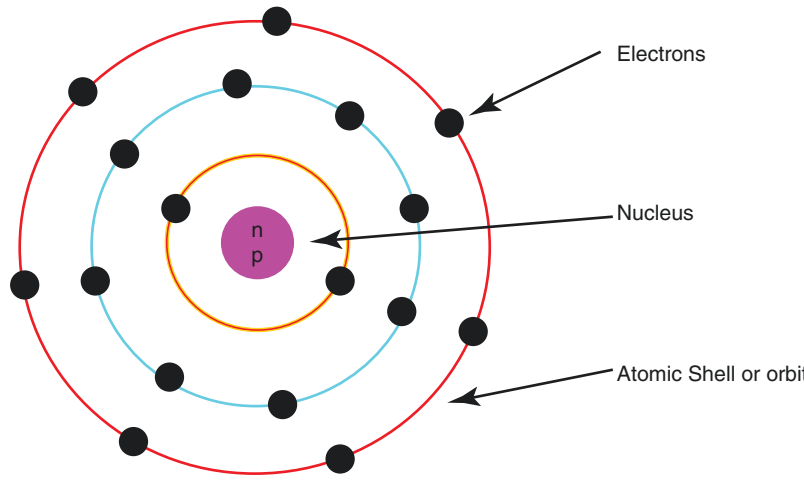

Fig. 1.1 Atomic structure: In an atom, electrons revolve around the nucleus

1.1.1 Electromagnetic Radiation

Electromagnetic radiation is the form of energy, which can traverse in the vacuum with the speed $c \approx 3 \times 10^8$ m/s, in which electric and magnetic field vectors are orthogonal to each other as well as to the direction of propagation. Speed of electromagnetic radiation in the medium is lesser than its speed in vacuum and depends on the refractive index of the medium. Figure 1.2 shows graphical representation of electromagnetic radiation waveform.

1.1.2 Interaction of Charged Particles with Matter

Excitation Charged particles directly interact with the atomic electron and transfer energy that is less than the binding energy of the electron. The electron goes to the higher energy state and while returning to the ground state it emits energy in the form of electromagnetic radiation.

Ionization When charged particle transfers energy more than the binding energy of the orbital electron, it ejects the electron from the atom making it positively charged, while the ejected electron is negatively charged. This creation of ion pair is called ionization. Maximum energy transfer happens during a head-on collision.

If the ejected electrons have sufficient energies for further ionization, it is known as delta rays.

Specific Ionization Specific Ionization is defined as the number of ion pairs produced per unit path length by the charged particles. Specific ionization increases with the square of the charge of the particle and decreases with the square of the particle velocity. It is represented by lp/mm. alpha particles have higher specific ionization compared to the electrons. Higher specific ionization eventually leads to higher absorbed dose in the medium.

When highly energetic heavy charged particles traverse the matter, specific ionization and hence dose deposition in the medium increases to the maximum as the particles slow down at the end of their track. This phenomenon is responsible for the Bragg peak of heavy charged particles. Doses to either side of the Bragg peak is quite lower compared to dose at or very near to the Bragg peak.

When electrons pass through the matter due to their lightweight, undergo multiple scattering,

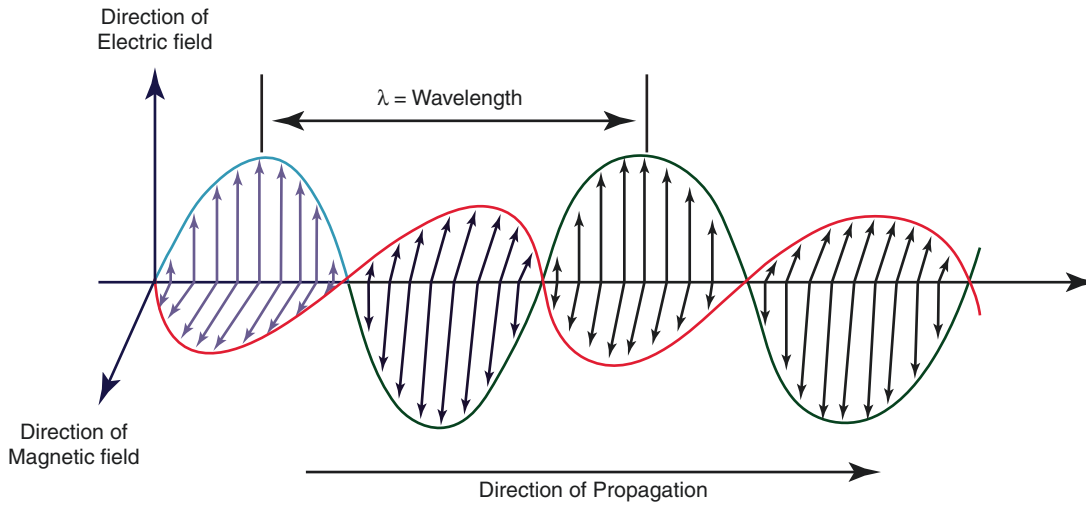

Fig. 1.2 Representation of electromagnetic radiation waveform

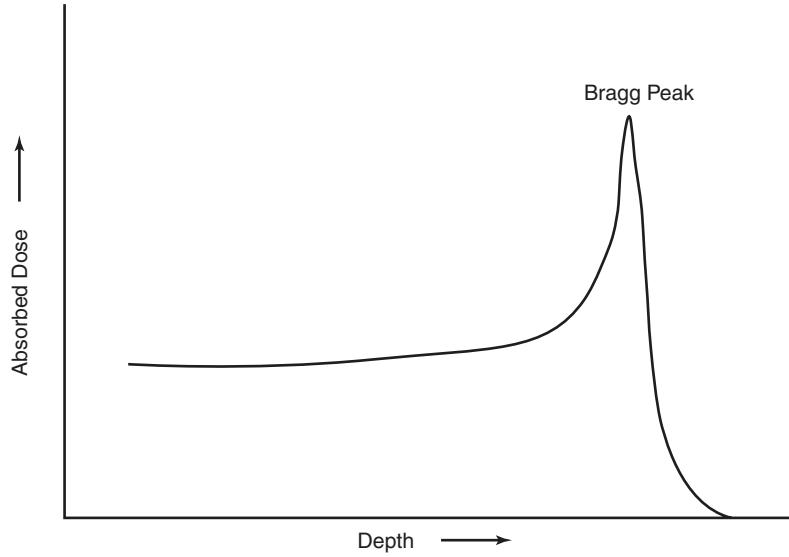

Fig. 1.3 Absorbed dose vs. depth for heavy charged particles

and move in tortuous path, that is why electrons do not exhibit Bragg peak (Fig. 1.3).

Stopping Power Stopping power is the property of the matter in which a beam of charged particles traverses. When charged particles interact with matter, their energy loss mainly depends on properties of the particle (mass, energy, etc.) as well as the absorber. For a particle beam, the rate of energy loss per unit path length in an absorbing medium is called the linear stopping power (−dE/dl, usually expressed in units MeV/cm).

Dividing linear stopping power by the density ρ of the absorber results in the mass stopping power *S*. (Expressed in units of MeV · cm^2 · g^{-1}).

In the viewpoint of a charged particle interacting with matter, we can classify stopping power into two types:

1. Radiative stopping power and
2. Collision stopping power

Linear Energy Transfer (LET) It is the energy absorbed in the medium per unit path length of the particle. LET is expressed in keV/μm. The concept of LET is important as biological effects depend on the rate of energy absorption in the medium.

Alpha particles are comparatively heavier in mass and emitted with the same energy by the nuclei of a particular isotope (e.g., 4.05 MeV for Th-232). Alpha particles lose energy in tissue very rapidly (within few micrometers). Specific ionization and LET are very high for alpha particles. On the other hand, electrons are approximately 1/7300 times lighter than alpha particle (and 1/1840 times lighter than the proton) with unit "–"ve charge, therefore electrons are scattered more easily and have a tortuous path in the matter. Electrons can traverse into the tissue more than alpha particles, with lower specific ionization and linear energy transfer and come to rest after traversing the medium a distance known as range which depends on electrons energy and the density of tissue (range of 10 MeV electrons from the Linac is approx. 5.0 cm in soft tissue and lesser in bone).

1.1.3 Radiative Interaction of Charged Particles

When a highly energetic charged particle passes close to the nucleus of an atom, it undergoes deflection and loses part of its energy in the form of electromagnetic radiation known as Bremsstrahlung radiation (breaking radiation).

Bremsstrahlung interaction increases with the square of atomic number (Z^2) of the medium and decreases with increase in the square of mass (m^2) of the particle. As it is strongly dependent on the mass of the particle, heavier charged particles produce lesser amount of bremsstrahlung X-rays when compared with lighter particles. That is why electrons are the most efficient and widely used for generating X-rays.

1.2 Interaction of Electromagnetic Radiation

Electromagnetic radiation has neither charge nor mass and it ionizes the matter indirectly after producing secondary electrons. Electromagnetic radiation undergoes following types of interactions with matter:

1. Rayleigh scattering
2. Photoelectric absorption
3. Compton scattering
4. Pair production
5. Pair annihilation
6. Photodisintegration

The probability of these interactions depends mainly upon the energy of the radiation and the atomic number of the matter.

1.2.1 Rayleigh Scattering

It is also known as classical or coherent scattering. In this type of interaction X- or γ ray photon is absorbed by an atom following which it goes to higher energy state and ejects out the photon with the same energy in a slightly different direction, as it comes to its ground state. As there is no loss of photon energy taking place, it is also called inelastic scattering. The probability of Rayleigh scattering (Fig. 1.4) at low KV diagnostic energy range is less than 5% (e.g., mammography). This kind of interaction is more probable with high Z material compared to low Z materials

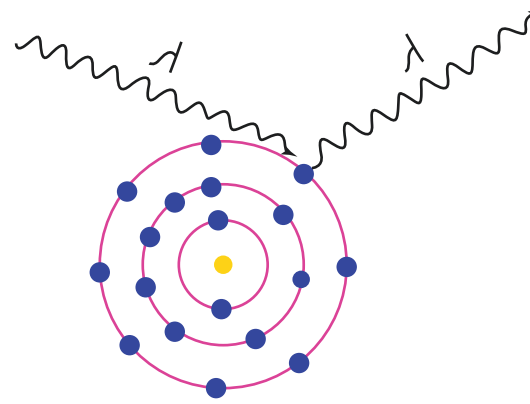

Fig. 1.4 Rayleigh scattering: no change in the energy of scattered photon

and decreases with the photon energy. Scattered photons do not carry any information and only degrade the image quality if detected. So, Rayleigh scattering is highly undesirable interaction.

1.2.2 Photoelectric Absorption

When the X- or gamma-ray photon interacts with a bound electron of an atom, all the energy of the photon is *transferred to the atomic electron, the electron is ejected from its shell* and the *photon is completely absorbed.*

The vacancy thus created by the ejection of the electron is immediately *filled by outer shell electron and in this process, the energy difference between the two shells is emitted as characteristic X-rays (X-ray energies are characteristics of the atom). If the characteristic X-rays interact with other atomic electron and electron is getting ejected by the absorption of the X-ray, this electron is called Auger electron.*

The probability of photoelectric absorption decreases *with the increase of photon energy (approximately* $\propto \frac{1}{E^3}$) but increases *as the atomic number of the medium increases (approximately* $\propto Z^3$). The probability of photoelectric absorption is the maximum *when the photon energy is only slightly more than the B.E. of inner shell electron, known as the k edge.*

A photon of energy $h\nu$ will release an electron with kinetic energy $E_e = h\nu - B.E.$, where B.E. is the binding energy of the electron.

Photoelectric absorption is the key interaction at low diagnostic energies (Fig. 1.5). Differential absorption of X-rays in different body tissues is the important principle for the formation of diagnostic images; however, at MV energies of radiotherapy, this interaction is negligible (Fig. 1.6).

Compton Scattering In Compton scattering (inelastic scattering), a part of the energy of the incident photon is transferred to a free electron. Free electron means, its binding energy is very less compared to the energy of the incident photon. Photon transfers only a part of its energy to the electron and gets scattered at an angle with reduced energy. Before coming to rest, the Compton electron deposits its energy in the medium. Compton scattering is independent of atomic number (Z) and depends on the electron density of the medium. The probability of this interaction decreases with increase in energy (E) of the incident photon but it is the predominant mode of interaction in water equivalent material for high energy photons (30 KeV to 24 MeV).

$$\Delta\lambda = \lambda' - \lambda = \frac{h}{mc}(1 - \cos\varnothing),$$

1.2.3 Pair Production and Pair Annihilation

Pair production and pair annihilation are examples of mass and energy equivalence.

When a photon having energy more than 1.022 MeV interacts with the nuclear field, it gets completely disappeared and there is a particle (electron) and its antiparticle (positron) known as electron–positron pair. An antiparticle is same as its particle in mass and other properties but it has opposite charge.

Threshold *photon energy required for the pair production is 1.022 MeV.* Excess energy is shared as kinetic energies between the electron and the positron.

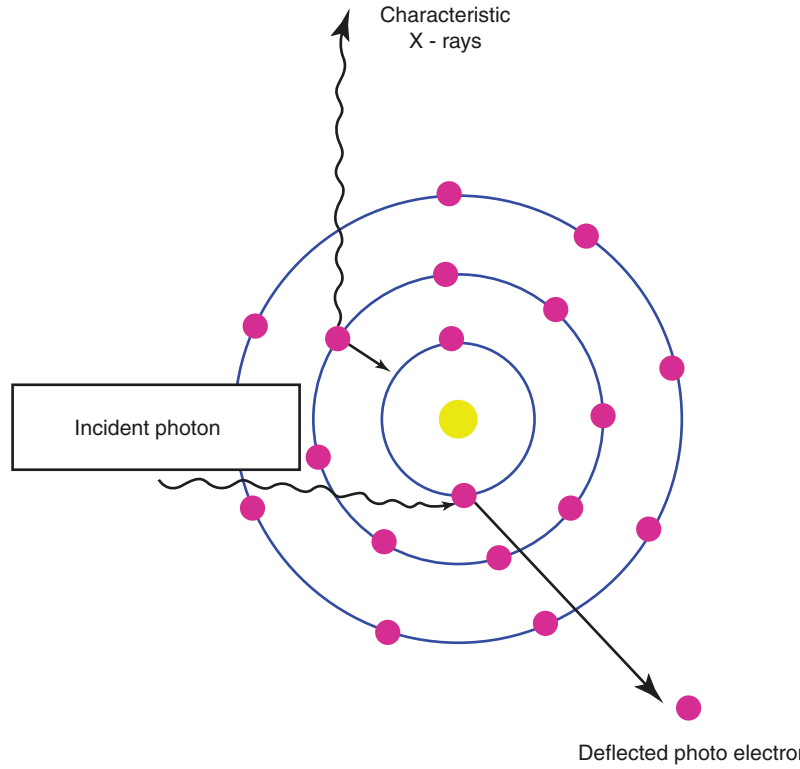

Fig. 1.5 Photoelectric absorption

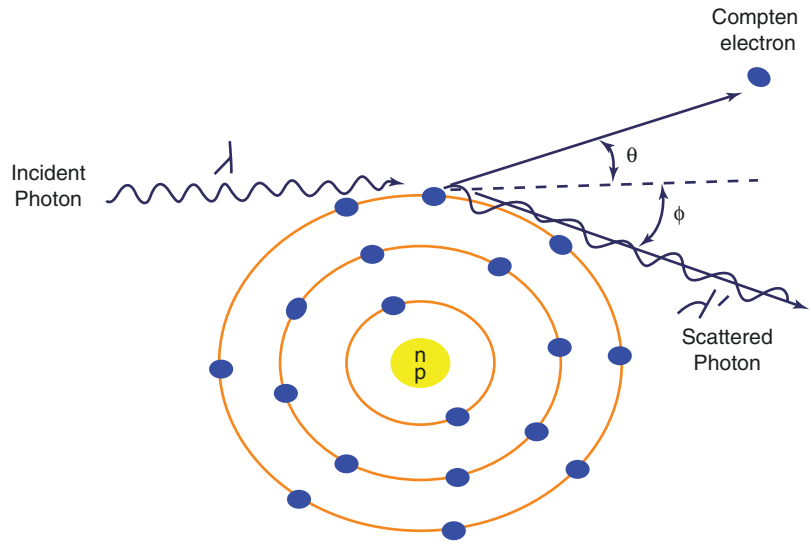

Fig. 1.6 Compton scattering

Positron continuously loses its energy in the medium and *encounters an electron & the two particles annihilate to produce two photons in flight, each of energy 0.511 MeV in opposite direction (for the conservation of momentum)*. This interaction is known as the pair annihilation. The pair annihilation process is the principle behind the positron emission tomography (PET).

The probability of pair production *increases with increasing photon energy beyond the threshold (1.022 MeV) and also with the square of atomic number (Z^2) of the atom. There is no pair production in the diagnostic energy range, in megavoltage radiotherapy, pair production accounts for 6–20% approximately* (Fig. 1.7).

1.2.4 Photodisintegration

In this interaction, a very high energy photon (energy greater than 10 MV) interacts with the nucleus of an atom in such a way that it is completely absorbed by the nucleus. Nucleus goes into the excited state and there is ejection of one or more particles (neutron, alpha particle, etc.).

The probability of photodisintegration increases with photon energy and it is more probable with high Z materials.

When we treat patients using 10 MV, 15 MV, or higher energies, there is neutron production inside the Linac room because of photodisintegration as some high energy photons when interacting with Linac head causes photodisintegration.

1.2.5 Linear Attenuation Coefficient and Mass Attenuation Coefficient

When gamma radiation traverses through matter it undergoes all the described interactions with different probabilities which depend on the energy of the photons as well as on other properties (atomic number, density, electron density, etc.) of the matter.

When the radiation traverses through the matter, its intensity reduces as it passes through the matter. For a point source of monoenergetic radiation, when it passes through an absorber it undergoes exponential attenuation.

$$I = I_0\, e^{-\mu x}$$

where I_0—incident intensity of the radiation; I—intensity transmitted after passing through the absorber; X—the thickness of the absorbing material; and μ—linear attenuation coefficient.

If x is expressed in cm, μ is expressed in per cm (cm^{-1}) and is called linear attenuation coefficient. The quantity μ/ρ is called mass attenuation

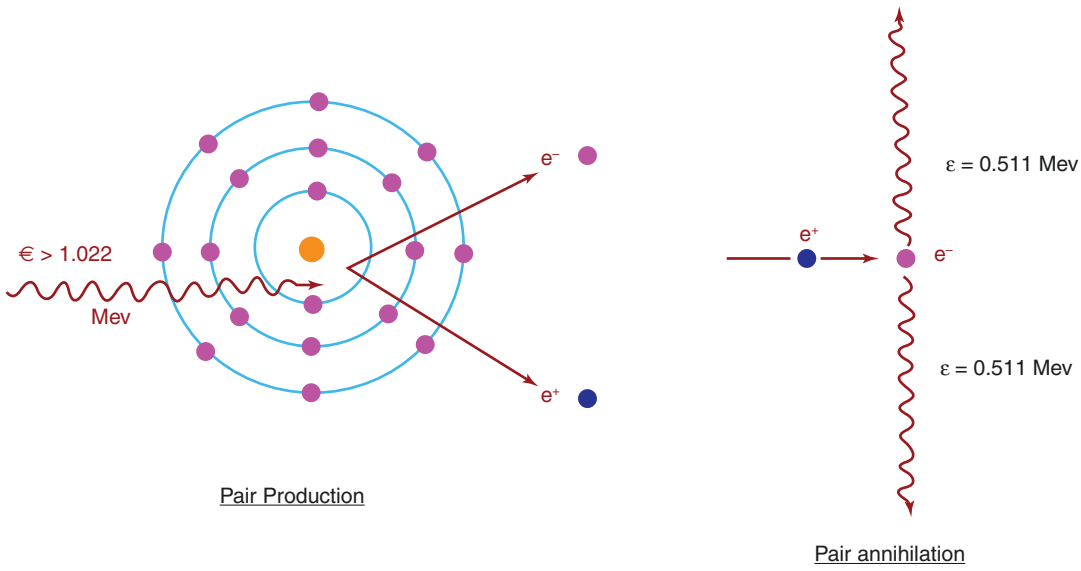

Fig. 1.7 Pair production and pair annihilation

coefficient; where ρ is the density of the medium, it is expressed in cm^2/g.

Half Value Layer (HVL) and Tenth Value Layer (TVL) The term half value layer (HVL) defined as the thickness of an absorber required to attenuate the intensity of the beam to half its original value. HVL we can express using given formula

$$HVL = \ln 2 / \mu \text{ or } 0.693 / \mu$$

TVL is the thickness of material that attenuate X-ray beam by 90% and transmits only one tenth of incident intensity.

$$TVL = \ln 10 / \mu \text{ or } 2.305 / \mu$$

One TVL is approximately equal to the 3.33 HVL of attenuating material. For designing a shielding block, approximately 5 HVL is required.

1.3 Interaction of Neurons with the Matter

Interaction of neutrons: Neutrons are electrically neutral and indirectly ionizing particles. Neutrons are unaffected by coulombic fields. Neutrons undergo interaction with nuclei of the atoms. Important interactions are:

1. Elastic collision
2. Inelastic collision
3. Radiative capture
4. Neutron capture (producing other particles)
5. Nuclear fission

Elastic Collision In this type of interaction total kinetic energy of the neutron and the target nucleus remains the same before and after the collision. Some of the energy of the neutron is given to the nucleus. As per the conservation of energy and momentum principles, the maximum energy transfer will occur for the nucleus of an approximately equal weight of the particle. That is why hydrogenous materials are effective absorbers for neutrons.

Inelastic Collision When a high energy neutron interacts with a heavy nucleus, the neutron is absorbed by the target nucleus and an excited compound nucleus is formed. Neutron is re-emitted with less energy as the nucleus de-excites to ground state by emitting gamma rays. e.g., $X(n, n\gamma)Y$.

Radiative Capture Neutron is captured by the target nucleus and forms a compound nucleus which is in the excited state, and then the target nucleus decays to the ground state by emission of gamma radiation. E.g., Production of ^{60}Co in nuclear reactor ^{59}Co (n, γ) ^{60}Co. Radiative capture is more probable with low energy neutrons.

Neutron Capture Neutron is captured by target nucleus and forms a compound nucleus which is in an excited state due to the capture of a neutron, and then the compound nucleus emits charged particle like proton or alpha particles and comes to the normal state. This kind of interaction is more probable at very high energy of neutrons.

Nuclear Fission In this process, the absorption of the neutron causes a heavy fissionable nucleus to split into two lighter nuclei. Many fission products (radioisotopes ^{99}Mo, ^{131}I, ^{32}P, etc.) are very useful in medicine for diagnosis and therapy. Fission reaction, e.g.,

$$_{92}\mathrm{U}^{235} +_{0} \mathrm{n}^{1} \rightarrow 3_{0}\mathrm{n}^{1} +_{36} \mathrm{Kr}^{92} +_{56} \mathrm{Ba}^{141} + \text{energy}$$

2 Practical Aspects of QA in LINAC and Brachytherapy

Seema Sharma

2.1 Introduction

Radiotherapy treatment involves many steps from immobilization of the patient, imaging, planning, treatment, and daily verification. Quality assurance at all the steps is required to ensure that what has been planned and prescribed, being delivered to the patient. Lack of proper quality assurance can lead to tumor under dosing as well as excess dose to normal tissues.

Medical physicist is primarily responsible for physical and technical aspects of the quality assurance. However, close coordination among physicist, technologist, and oncologist is necessary to ensure the quality treatment to the patient.

Quality assurance (QA) starts from preparing specification for the radiotherapy equipment to be ordered. Once equipment has been purchased, acceptance test is performed to determine the baseline standard. Radiation equipment should undergo extensive baseline checks after any major repair to ensure the compliance with the purchase specifications. Initial calibration and commissioning of the equipment is the next major step and is often time consuming. After commissioning of the equipment, periodic quality assurance steps must be done as recommended by national or international protocol. In addition to doing quality assurance steps, documentation and maintaining log book is essential for each radiation therapy equipment.

Proper quality assurance at every step involving in radiotherapy can minimize the uncertainties in overall treatment delivery; thereby ensure that patient gets what is planned. QA reduces the probability of accidents and errors and helps in optimizing tumor control and limits normal tissue toxicity. Any discrepancy found during routine QA should be investigated and corrected.

2.2 Linear Accelerator Quality Assurance

2.2.1 Acceptance of Linear Accelerator

Acceptance testing has to be done once the LINAC installation is over; vendor has to perform the entire test as per the requirement of the technical specification agreed at the time of purchase. Usually vendor performs the tests as per the company's acceptance format, after that any additional test or requirements as per purchase order specification has to be completed. Institution physicist has to accept the LINAC technically (as per specification) before commissioning.

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Usual tests performed for acceptance testing are radiation survey, jaw symmetry, coincidence of light beam with X-ray beam, mechanical isocenter stability with rotation of collimator and gantry, stability of radiation isocenter with respect to gantry and couch rotation, multileaf collimator (MLC) quality assurance, X-ray beam flatness, symmetry and percentage depth dose (PDD), accuracy of optical distance indicator, table top sagging, field size indicator, etc.

2.2.2 Commissioning of Linear Accelerator

After acceptance test, more data has to be acquired before clinical use of LINAC, the process is known as commissioning. Commissioning is the responsibility of the physicist; physicist will measure all the beam data (required for beam modeling) and fed in to the treatment planning system as per the protocol. After measurement and before using the LINAC for patient treatment, physicist has to validate the commissioned LINAC along with its TPS using AAPM (American Association of Physicist in Medicine) TG (Task Group)-119 end-to-end test. End-to-end test validation is necessary because if there is any problem at any step in commissioning that will be detected during end-to-end test and that will ensure that all the systems are configured with each other properly.

AAPM TG-106 gives the extensive guidelines for commissioning of medical linear accelerators. Various tests are described in TG106, some major tests are tabulated in Table 2.1 [1].

Table 2.1 Major tests for commissioning a medical accelerator

Data	Description
Calibration	Dose per monitor unit calibration of all modalities and energies according to current protocol
Depth dose	Central axis depth dose distribution for all modalities and energies, sufficient number of field sizes to allow interpolation of data
Profiles	Transverse, longitudinal, and diagonal dose profiles for all modalities and energies at d_{max} for electrons and selected depths for photons (e.g., d_{max}, 5, 10, and 20 cm); all cones for electrons and selected field sizes for photons (e.g., 5 × 5, 10 × 10, and 40 × 40 cm^2)
Isodose distribution	Isodose curves for all modalities and energies, all cones for electrons and selected field sizes for photons (e.g., 5 × 5, 10 × 10, 40 × 40 cm^2), all wedge filters for selected field sizes (e.g., 5 × 5, 10 × 10 cm^2, maximum)
Output factors	*Sc*, and *Sp* factors as a function of field size for all photon energies: output factors for all electron energies, cones, and standard inserts; tray transmission factors and wedge transmission factors
Off-axis ratios	A table of off-axis ratios for all photon energies as a function of distance from central axis; these data may be obtained from dose profiles for a 5 × 40-cm field at selected depths (e.g., d_{max}, 5, 10, 20 cm)
Inverse square law	Verification of inverse square law for all photon energies, virtual source position for all electron energies, and effective SSD for all electron energies and cones
Tissue–phantom ratios	Direct measurement of TPRs/TMRs for all photon energies and selected field sizes (e.g., 5 × 5, 10 × 10, 40 × 40 cm) and depths (5, 10, 30 cm) for verification of values calculated from percent depth doses
Surface and build-up dose	For all photon energies and selected field sizes (5 × 5, 10 × 10, 30 × 30, and 40 × 40 cm^2), percent surface dose for all electron energies for a 10 × 10-cm cone
Treatment planning system	Beam data input, generation, and verification of central axis percent depth dose and TPR/TMR tables; sample isodose curves (e.g., 5 × 5, 10 × 10, maximum) for unwedged, wedged, asymmetric, and blocked fields; sample isodose curves for multiple field plans using rectangular and elliptical contours; electron beam depth dose data; isodose curves for all cones and sample isodose curves on rectangular and circular contours
Special dosimetry	Data for special techniques such as total body irradiation, total skin irradiation, stereotactic radiosurgery, intraoperative electron therapy, etc.

SSD source to surface distance, *TMR* tissue–maximum ratio, *TPR* tissue–phantom ratio

2.2.3 Periodic Quality Assurance of Linear Accelerator

Periodic quality assurance programme is essential to maintain the radiation machines within its acceptable performance standards. Various reports/publications are available on quality assurance of linear accelerator (LINAC) and numerous protocols are also available for specialized procedures and equipments, i.e., (1) AAPM TG-24, Physical aspect of quality assurance in radiotherapy (1984), (2) World Health Organization quality assurance in radiotherapy (1988), (3) AAPM TG-40, Comprehensive QA for radiation oncology (1994), (4) IAEA, Setting up a radiotherapy program (2008), (5) AAPM TG-142, Quality assurance of medical accelerators (2009), (6) AAPM, Guidance document on delivery, treatment planning, and clinical implementation of IMRT, (7) AAPM TG-25 and AAPM TG-20, Recommendations for clinical electron beam dosimetry, (8) AAPM TG-42, Stereotactic radiosurgery, (9) AAPM TG101, Stereotactic body radiation therapy, (10) AAPM TG-135, Quality assurance for robotic surgery, (11) AAPM TG-148, Quality assurance for helical tomotherapy, etc.

AAPM TG-142 is most widely used protocol to check the LINAC performance. TG-142 report suggests various types of the tests (i.e., mechanical, radiation, safety) and the frequency of the tests with their respective tolerances [2].

Some of the tests recommended by AAPM TG-142 are tabulated below (Tables 2.2, 2.3, and 2.4):

2.3 Brachytherapy Quality Assurance

Remote afterloading brachytherapy is very sophisticated and standard practice. Remote afterloading machine minimizes the exposure to the personal handling the procedure. Remote afterloading machines are available based on different dose rates, i.e., low dose rate (LDR), high dose rate (HDR).

2.3.1 Acceptance of Brachytherapy (Remote Afterloading)

Objective of performing the acceptance testing is to ensure that the brachytherapy equipment fulfils the purchase order specification. The acceptance testing of the remote afterloading machine can be categorized in four parts as per Glasgow et al.: (1) operational testing, (2) radiation safety check, (3) testing of source calibration and transport, and (4) testing of treatment planning software [3].

Some recommended tests by Glasgow et al. are tabulated below (Table 2.5):

2.3.2 Periodic Quality Assurance of Brachytherapy (Remote Afterloading)

Quality assurance procedures have to be established for the remote afterloader unit and its ancillary accessories, for the process of clinical

Table 2.2 AAPM TG-142 daily QA

Category	Procedure	Non-IMRT	IMRT	SRS/SBRT
Dosimetry	X-ray output constancy (all energies)	3%	3%	3%
Dosimetry	Electron output constancy *(weekly test)*	3%	3%	3%
Mechanical	Laser localization	2 mm	1.5 mm	1 mm
Mechanical	Distance indicator (ODI) at isocenter	2 mm	2 mm	1 mm
Mechanical	Collimator size indicator	2 mm	2 mm	1 mm
Safety	Door interlock	Functional	Functional	Functional
Safety	Door closing safety	Functional	Functional	Functional
Safety	Audiovisual monitors	Functional	Functional	Functional
Safety	Stereotactic area monitor	NA	NA	Functional
Safety	Radiation area monitor	Functional	Functional	Functional
Safety	Beam on indicator	Functional	Functional	Functional

Table 2.3 AAPM TG-142 monthly QA

Category	Procedure	Non-IMRT	IMRT	SRS/SBRT
Dosimetry	X-ray output constancy	2%	2%	2%
Dosimetry	Electron output constancy	2%	2%	2%
Dosimetry	Backup monitor chamber constancy	2%	2%	2%
Dosimetry	Typical dose rate constancy	NA	2%	2%
Dosimetry	Photon beam profile constancy	1%	1%	1%
Dosimetry	Electron beam profile constancy	1%	1%	1%
Dosimetry	Electron beam energy constancy	2%/2 mm	2%/2 mm	2%/2 mm
Mechanical	Light/radiation field coincidence	2 mm/1% an a side	2 mm/1% an a side	2 mm/1% an a side
Mechanical	Light/radiation field coincidence	1 mm/1% an a side	1 mm/1% an a side	1 mm/1% an a side
Mechanical	Distance check device for lasers compared with front pointer	1 mm	1 mm	1 mm
Mechanical	Gantry/collimator angels indicator	1.0°	1.0°	1.0°
Mechanical	Accessory trays	2 mm	2 mm	2 mm
Mechanical	Jaw position indicators (symmetric)	2 mm	2 mm	2 mm
Mechanical	Jaw position indicators (asymmetric)	1 mm	1 mm	1 mm
Mechanical	Cross-hair centering (walkout)	1 mm	1 mm	1 mm
Mechanical	Treatment couch position indicators	2 mm/1.0°	2 mm/1.0°	1 mm/0.5°
Mechanical	Wedge placement accuracy	2 mm	2 mm	2 mm
Mechanical	Compensator placement accuracy	1 mm	1 mm	1 mm
Mechanical	Latching of wedges/blocking tray	Functional	Functional	Functional
Mechanical	Localization lasers	2 mm	1 mm	1 mm
Safety	Laser guard interlock	Functional	Functional	Functional

use of the equipment, e.g., proper execution of a planned treatment.

Quality assurance tests are designed to confirm that the system (remote afterloading unit, facility, applicators, sources, etc.) performs within the tolerances established during the acceptance tests (AAPM TG-41) [4]. In some cases quality assurance test procedure is identical to the acceptance test procedure; on the other hand, less rigorous quality assurance tests are performed. Various protocols and guidelines are available for periodic quality assurance. AAPM Report-13, Physical Aspects of Quality Assurance in Radiation Therapy recommends quality assurance procedures for both conventional and remote afterloaders in brachytherapy. AAPM Task Group 40 has a draft document (1992) on comprehensive quality assurance procedures that includes a chapter on quality assurance for conventional manual brachytherapy and remote afterloaders. ESTRO Booklet-8: a practical guide to quality control to brachytherapy equipment gives the extensive procedures of quality checks and their frequencies.

Some of the periodic tests recommended by ESTRO (European Society for Therapeutic Radiology and Oncology) Booklet-8 are tabulated below [5] (Table 2.6):

The daily quality check should be executed on a routine basis before treating the first patient of the day. Starting the treatment may implicitly assume that daily tests were performed and that the results were satisfactory, according to a department's quality assurance protocol. User departments may develop special daily check forms to record and sign for the execution of these tests on satisfactory completion.

Brachytherapy software (treatment planning system) testing includes verification of dose distribution around the single and multiple sources and matches the software generated dose distribution with published tables. One should also verify the decay correction applied by the soft-

Table 2.4 AAPM TG-142 annual QA

Category	Procedure	Non-IMRT	IMRT	SRS/SBRT
Dosimetry	X-ray and electron flatness change from baseline	1%	1%	1%
Dosimetry	X-ray and electron symmetry change from baseline	1%	1%	1%
Dosimetry	SRS arc rotation mode; MU setting vs delivered	NA	NA	1.0MU or 2%
Dosimetry	SRS arc rotation mode; gantry arc setting vs delivered	NA	NA	1.0 degree or 2%
Dosimetry	X-ray/electron output calibration (TG-51)	1%	1%	1%
Dosimetry	Spot check of field size dependent output factors	2% for $<4 \times 4$ cm^2 1% for $\geq 4 \times 4$ cm^2	2% for $<4 \times 4$ cm^2 1% for $\geq 4 \times 4$ cm^2	2% for $<4 \times 4$ cm^2 1% for $\geq 4 \times 4$ cm^2
Dosimetry	Output factors for electron applicators	2%	2%	2%
Dosimetry	X-ray beam quality (PDD_{10} or TMR^{20}_{10})	1%	1%	1%
Dosimetry	Electron beam quality (R_{50})	1 mm	1 mm	1 mm
Dosimetry	Physical wedge transmission factor	2%	2%	2%
Dosimetry	X-ray MU linearity (output constancy)	2% ≥ 5MU	5% (2-4MU), 2% ≥ 5MU	5% (2-4MU), 2% ≥ 5MU
Dosimetry	Electron MU linearity (output constancy)	2% ≥ 5MU	2% ≥ 5MU	2% ≥ 5MU
Dosimetry	X-ray output constancy vs dose rate	2%	2%	2%
Dosimetry	X-ray output constancy vs gantry angle	1%	1%	1%
Dosimetry	Electron output constancy vs gantry angle	1%	1%	1%
Dosimetry	Electron and X-ray off-axis factor constancy vs gantry angle	1%	1%	1%
Dosimetry	Arc mode (expected MU, degrees)	1%	1%	1%
Dosimetry	TBI/TSET mode	Functional	Functional	Functional
Dosimetry	PDD or TMR and OAF constancy	1% (TBI) or 1 mm PDD shift (TSET)	1% (TBI) or 1 mm PDD shift (TSET)	1% (TBI) or 1 mm PDD shift (TSET)
Dosimetry	TBI/TSET output calibration	2%	2%	2%
Dosimetry	TBI/TSET accessories	2%	2%	2%
Mechanical	Collimator rotation isocenter	1 mm	1 mm	1 mm
Mechanical	Gantry rotation isocenter	1 mm	1 mm	1 mm
Mechanical	Couch rotation isocenter	1 mm	1 mm	1 mm
Mechanical	Electron applicator interlocks	Functional	Functional	Functional
Mechanical	Coincidence of radiation and mechanical isocenter	2 mm	2 mm	1 mm
Mechanical	Table top sag	2 mm	2 mm	2 mm
Mechanical	Table angle	1°	1°	1°
Mechanical	Table travel maximum range	2 mm	2 mm	2 mm
Mechanical	Stereotactic accessories, locks, etc.	NA	NA	Functional
Safety	Follow manufacturer's test procedures	Functional	Functional	Functional

Table 2.5 Acceptance testing of remote afterloading brachytherapy

Functional performance	
Console functions	Main power, battery power, source on/off, door open/close, etc.
Source control	Source dwell time and source retraction at the end of preset time, unplanned interruption, or emergency shutoff
Battery voltage	Adequacy of battery voltage under load conditions and functional performance under battery power
Timer	Timer accuracy and end-time effects
Decay correction	Accuracy of computer-calculated decay corrections
Multichannel indexer	Proper source sequencing and channel selection
Backup systems	Proper functioning during simulated power failures or air pressure losses (for pneumatically driven devices)
Radiation detectors	Proper functioning as specified
Facility check and survey	
Door interlocks	Source retracts when the door is opened; the unit does not start until the door is closed and the interlock is reset
Radiation warning lights	Proper functioning to indicate radiation on/off condition
Patient viewing and communication	Proper functioning of closed-circuit TV and the intercommunication system
Radiation survey	Exposure rates outside the radiation facility should meet the nuclear regulatory commission regulations and the leakage radiation rates around the unit should be acceptable
Source calibration and transport	
Check of source specifications	Leak testing, calibration, transport to the applicators, autoradiograph of simulated source positions, and isodose distribution to determine dose anisotropy

Table 2.6 Periodic test recommended by ESTRO for quality assurance for brachytherapy machines

	Minimum requirements	
Description	Test frequency	Action level
Safety systems		
Warning lights	Daily/3 month	–
Room monitor	Daily/3 month	–
Communication equipment	Daily/3 month	–
Emergency stop	3 month	–
Treatment interrupt	3 month	–
Door interlock	3 month	–
Power loss	3 month	–
Applicator and catheter attachment	6 month	–
Obstructed catheter	3 month	–
Integrity of transfer tubes and applicator	3 month	–
Timer termination	Daily	–
Contamination test	Annual	–
Leaking radiation	Annual	–
Emergency equipment (forceps, emergency safe, survey meter)	Daily/3 month	–
Practising emergency situations	Annual	–
Hand crank functioning	Annual	–
Hand-held monitor	3 month/annual	
Physical parameters		
Source calibration	Source exchange	>5%
Source position	Daily/3 month	>2 mm
Length of treatment tubes	Annual	>1 mm
Irradiation timer	Annual	> 1%
Date, time, and source strength in treatment unit	Daily	–
Transit time effect	Annual	–

ware with respect to standard decay table of the source.

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Radiation Dosimetry

3

Seema Sharma

3.1 Radiation Dosimeter

Radiation dosimeter is a device that measures directly or indirectly exposure, kerma, absorbed dose or equivalent dose, or related quantities of ionizing radiation. The dosimetry system consists of dosimeter and its reader.

The radiation dosimeter must have at least one physical property that is a function of the measured dosimetric quantity and can be used for radiation dosimetry with proper calibration.

Ideal dosimeters are characterized by good accuracy, precision, linearity. Ideal dosimeters should not have dose and dose rate dependence, directional dependence, energy response dependence, and it should have high spatial resolution. An ideal dosimeter that satisfies all the above characteristics does not exist. The refore type of radiation dosimeter that must be used, varies with measuring requirements of the measuring situation [1].

Different types of radiation measuring instruments consider different physical events that can be utilized to make measurements. Different physical events that are commonly applied in radiotherapy dosimetric equipments are summarized below [2] (Fig. 3.1).

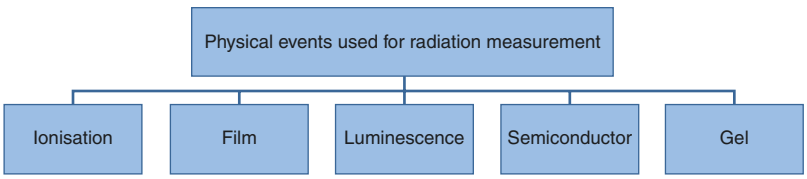

Fig. 3.1 Physical events used for radiation measurement

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S. Mallick et al. (eds.), *Practical Radiation Oncology*,
https://doi.org/10.1007/978-981-15-0073-2_3

3.2 Ionization

3.2.1 Free Air Ionization Chamber [3]

Free air ionization chamber is the primary standard for measuring exposure for superficial and orthovoltage (X-rays up to 300 Kv) (Fig. 3.2).

Free air ionization chamber cannot be used for high energy photon, due to difficulty in maintaining the electronic equilibrium in the collecting volume. Therefore it can be used for superficial and orthovoltage.

Free air ionization chamber is delicate and bulky, therefore cannot be used for routine measurements. They can be used in standardizing laboratories for calibration of chambers used for low energy.

3.2.2 Thimble Chamber

The wall of thimble chamber is like a sewing thimble; therefore it is called as thimble chamber (Fig. 3.3).

By compressing the air required for electronic equilibrium its dimensions can be reduced. Air volume required for electronic equilibrium can be replaced by small air cavity with solid air equivalent wall.

The wall of the thimble chamber should be air equivalent, i.e., graphite (carbon), Bakelite, plastic with inside coating of graphite, or conducting mixture of graphite and Bakelite. Exact air equivalent material (atomic number same as air) is not possible thus difference in atomic number is accounted in its calibration factor.

The volume of air contained in air cavity is the sensitive volume of chamber. The thimble cavity contains air and air can pass on through a small hole in the side of the chamber. For the measurement with thimble chamber the temperature and pressure of the air inside the cavity should be same as the surrounding to maintain the equilibrium.

Thimble chamber is a secondary dosimeter and has to be calibrated against the free air ion chamber or standard cavity chamber.

3.2.3 Farmer Chamber

The original Farmer chamber was developed by FT Farmer in 1955 (Figs. 3.4 and 3.5).

Framer chambers are the most commonly used ion chambers, for the calibration of radiation therapy beams. Farmer type chamber is also known as cylindrical or thimble ionization chamber.

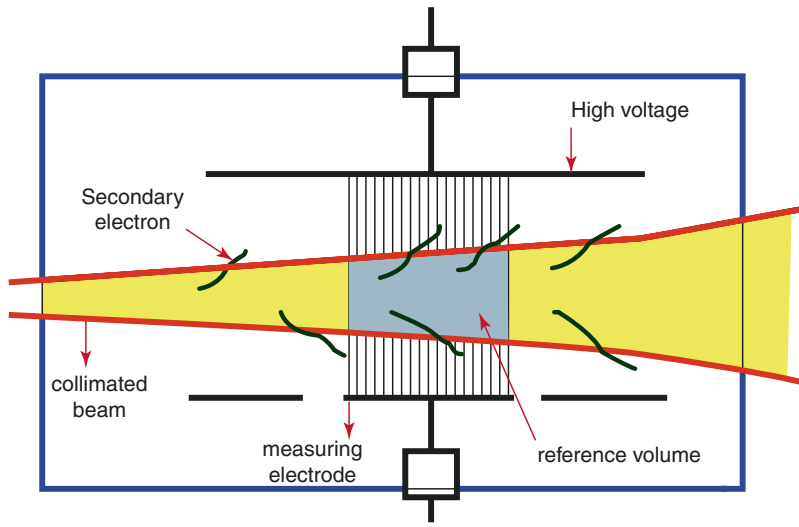

Fig. 3.2 Showing the schematic diagram of free air ion chamber

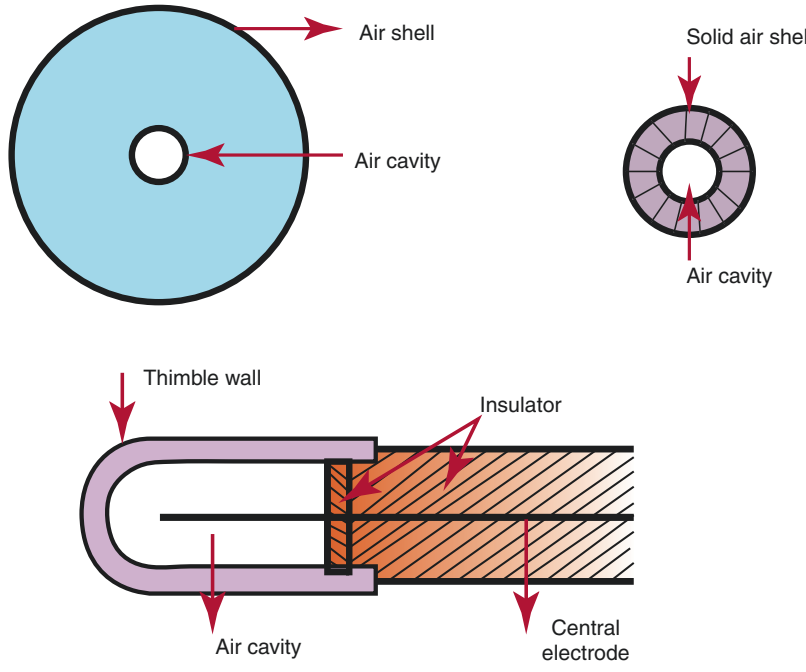

Fig. 3.3 Showing the schematic diagram of thimble chamber

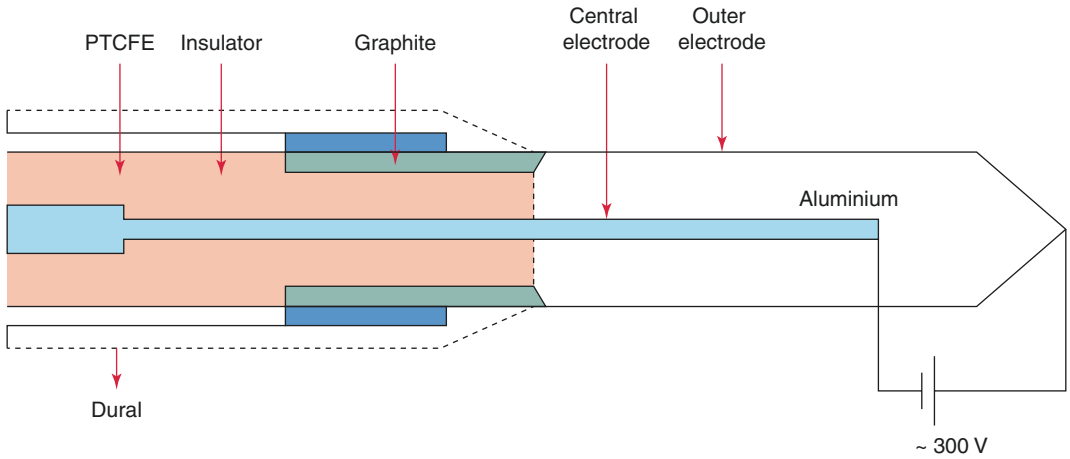

Fig. 3.4 Showing the schematic diagram of Farmer chamber

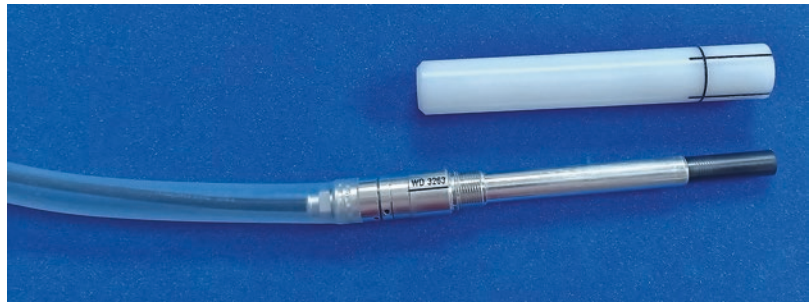

Fig. 3.5 Farmer chamber

An ionization chamber consists of a gas filled cavity with a central collecting electrode surrounded by a conductive outer wall. A high quality insulator separates the wall and collecting electrode to reduce the leakage current when polarizing voltage is applied to the chamber. To further reduce the chamber leakage the chamber also contains a guard electrode.

So many commercially available Farmer chambers are available, they are similar in overall design but differ in composition of the wall material and central electrode.

The cavity of the chamber is vented to outside. The measurement with open air ionization chamber requires temperature and pressure correction to account for the change in the mass of the air in the chamber volume, which changes with surrounding temperature and pressure. Farmer type chamber has 0.6 cc nominal cavity volume.

3.2.4 Parallel Plate Ionization Chamber

Parallel plate chambers have two electrodes in the shape of flat plates parallel to each other. The air gap between two electrodes constitutes the sensitive volume.

There are two kinds of parallel plate chambers: (A) the extrapolation chamber with variable volume, (B) the parallel plate chamber with fixed volume.

1. Extrapolation chamber:
   (a) Extrapolation chamber was designed by Failla in 1937. Extrapolation chamber is used for measuring surface dose or build-up dose in a phantom (Fig. 3.6).
   (b) The beam enters through a thin foil window that is carbon coated from inside to form the upper electrode.
   (c) The lower or the collecting electrode is a small coin shaped region surrounded by a guard ring and is connected to an electrometer.
   (d) The electrode spacing can be varied accurately by a micrometer screw.
   (e) By measuring the ionization per unit volume as a function of electrode spacing, one can estimate the incident dose by extrapolating the ionization curve to zero electrode spacing.
2. Parallel plate (plane-parallel) chamber:
   Parallel plate chamber is similar to extrapolation chambers except that they have a fixed electrode spacing (1–2 mm).
   (a) Parallel plate chamber has two plane walls, one serving as entry window (polarizing electrode) and the other as back wall acting as collecting electrode (Fig. 3.7).
   (b) Usually the window is foil or 0.01–0.03 mm thick Mylar, polystyrene, which allow measurement practically at the surface of the phantom. Collecting electrode consists of a block of conducting plastic or non-conducting material with graphite coating.

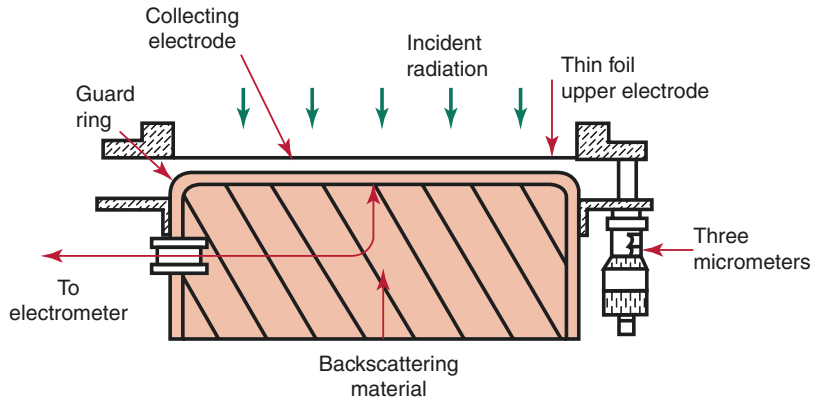

Fig. 3.6 Showing the schematic diagram of extrapolation chamber

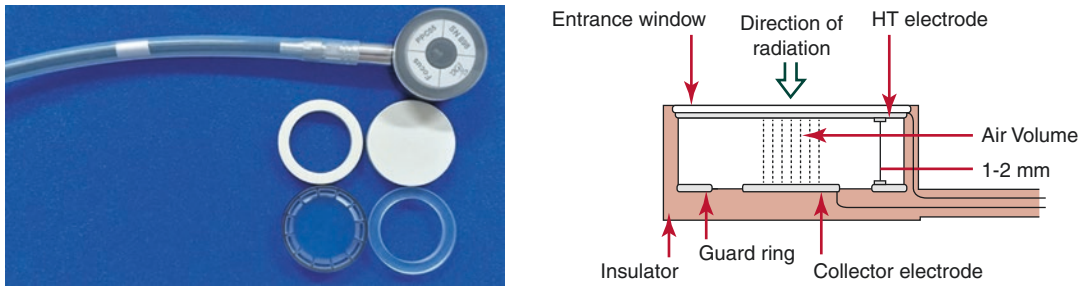

Fig. 3.7 Showing the schematic diagram of parallel plate chamber

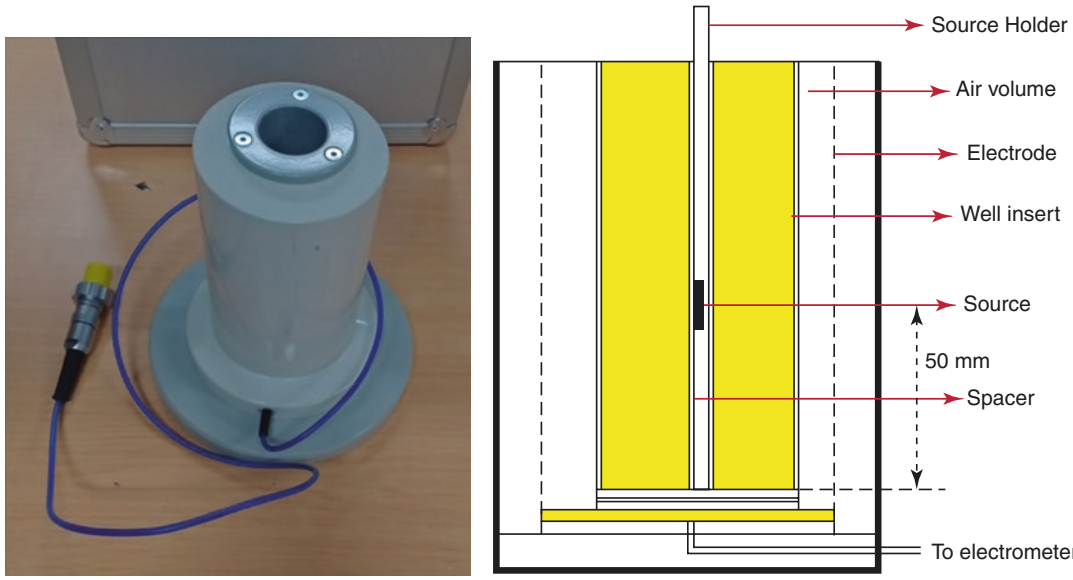

Fig. 3.8 Showing the schematic diagram of well type chamber

(c) It also contains guard ring system. The width of the guard ring is sufficiently large to prevent electrons scattered by the side and back walls of the chamber from affecting the ionization in the ion collecting volume.

3.2.5 Well Type Chamber

Sources used in brachytherapy are low air kerma rate sources that require chambers of sufficient volume (about 245 cc) for adequate sensitivity. This much active volume is large enough to generate sufficient ionization current which can be measured with electrometer (Fig. 3.8).

Well type chambers are re-entrant chambers ideally suited for calibration and standardization of brachytherapy sources. Re-entrant ion chamber is filled with air and communicate to the outside air through a vent hole. Usually calibrated in terms of reference air kerma rate.

3.3 Film

3.3.1 Radiographic Film

Radiographic X-ray film (unexposed) consists of, thin plastic film coated both sides with a radiation sensitive emulsion (silver bromide, AgBr grains suspended in gelatin).

On the exposure (ionization of AgBr grains take place), loosely bound electrons are freed,

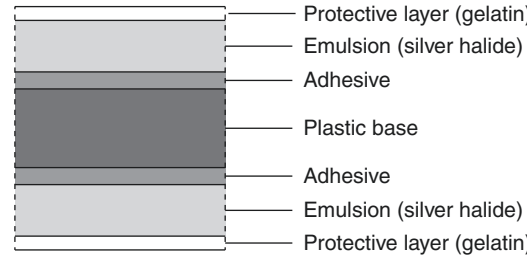

Fig. 3.9 Showing the cross section of radiographic film

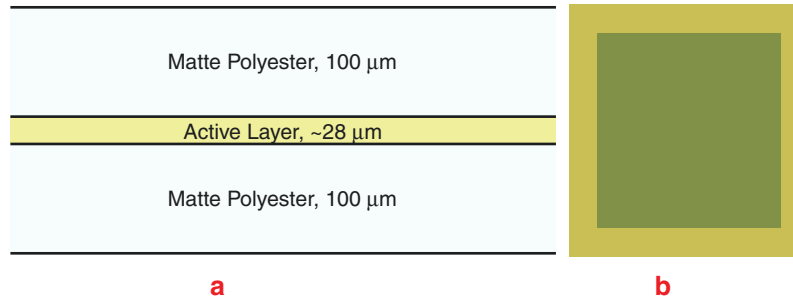

Fig. 3.10 (**a**) Showing the cross section of radiochromic film (**b**) exposed radiochromic film

these electrons aggregate around impurities and form negative charge. This negative charge attracts Ag+ion leaving behind neutral metallic silver and forms the latent image in the film. Latent image becomes visible (film blackening) after film processing (Fig. 3.9).

Film gives excellent 2D spatial resolution, but useful dose range of film is limited.

Response of the film depends on so many factors, which are difficult to control, i.e., consistent film processing, dark room facility.

Film blackening (light transmission) can be measured in terms of optical density (OD) with densitometers. Optical density is converted to absorbed dose via calibration.

Hunter and Driffield (H&D) curve is used to relate the exposure or dose to optical density.

3.3.2 Radiochromic Film [4]

Radiochromic film consists of polyester (Mylar) base which is nearly a tissue equivalent composition.

Radiochromic film contains a special dye that is polymerized upon exposure to radiation. As the active layer polymerizes, it becomes partially opaque in proportion to the incident dose (Fig. 3.10).

The polymer absorbs lights and transmission of light through the film can be measured with suitable densitometer.

Radiochromic film is self-developing; therefore requires no processing or developing. No need of dark room and cassettes.

Radiochromic film has very high spatial resolution and dose rate independence.

Radiochromic film does not require processing but complete polymerization reaction takes time approximately 24 h, therefore it results in delay between irradiation and readout.

3.3.3 Luminescence

Some materials upon absorption of radiation retain part of absorbed energy in metastable states. This energy is subsequently released in the form of ultraviolet, visible, or infrared light, the phenomenon is called luminescence.

Two types of luminescence, (i) fluorescence and (ii) phosphorescence, are known, which depend on the time delay between stimulation

and emission of light. Fluorescence occurs with time delay of 10^{-8} s, phosphorescence occurs with time delay of more than 10^{-8} s or with the suitable excitation with heat or light (Fig. 3.11).

Incident ionizing radiation creates the electron hole pair in the crystal structure. The liberated electron is moved (promoted) to the conduction and migrates to the electron trap. At the same time hole migrates (along the valence band) to a hole trap.

Energy in the form of heat for TLD or light for OSLD is given to electron and hole to escape from their traps. Finally electron hole pair combines at the luminescent center and releases (emits) light.

If the exciting agent is heat, the phenomenon is called the thermoluminescence and the dosimeter is called the thermoluminescent dosimeter (TLD).

If the exciting agent is light, the phenomenon is known as optically stimulated luminescence (OSL) and the dosimeter is called as optically stimulated luminescent dosimeter (OSLD).

3.3.4 Thermoluminescent Dosimeter (TLD)

Many TLD materials are available, the widely used TLD materials are LiF:Mg, Cu, P, LiF:Mg, Ti, $CaSO_4$:Dy, etc. The elements mentioned after the TLD are the dopants or impurities. The dopants are used to create the metastable states or traps.

TLDs are available at various shapes and sizes such as powder, chip, rods, disc, and ribbon

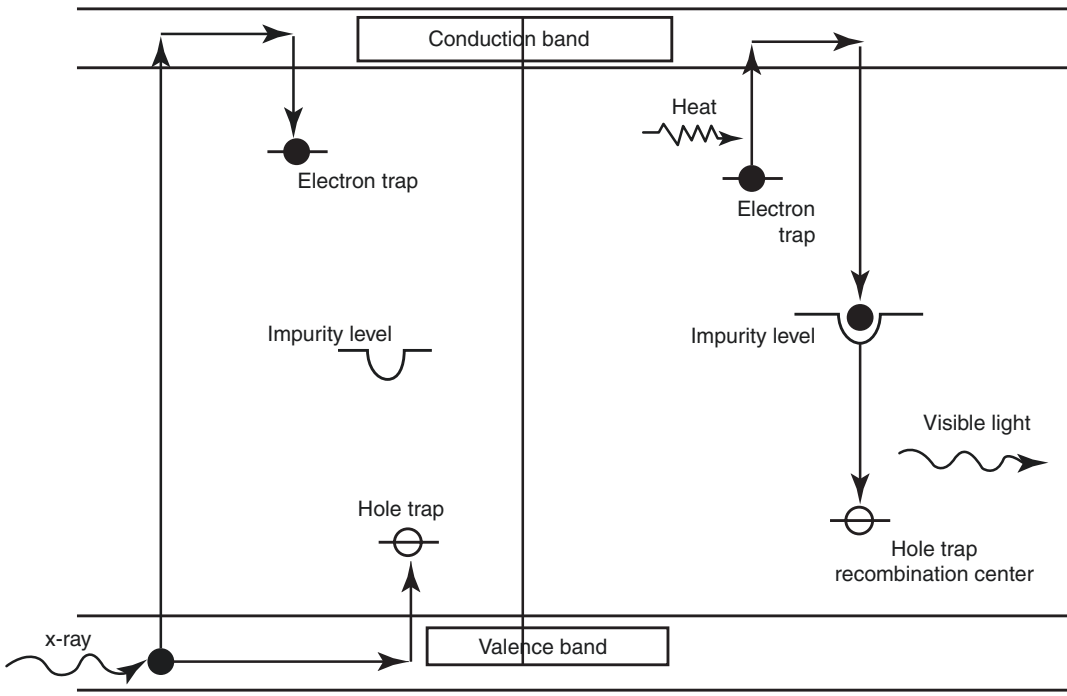

Fig. 3.11 Showing the schematic diagram of luminescence

depending upon their dosimetric requirement (Fig. 3.12).

When TLD is heated, because traps differ in depth, probability of escaping from trap is proportional to temperature. This gives rise to distinct glow peaks (Fig. 3.13).

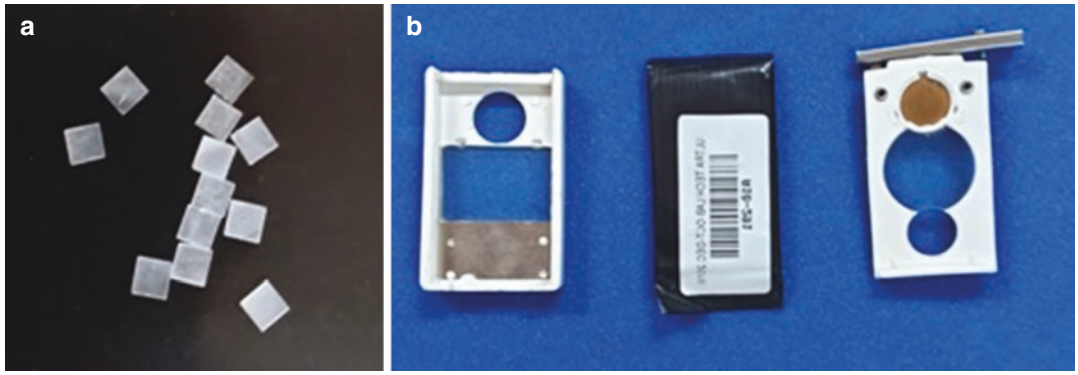

Fig. 3.12 (**a**) TLD chip (**b**) TLD badge for personal monitoring

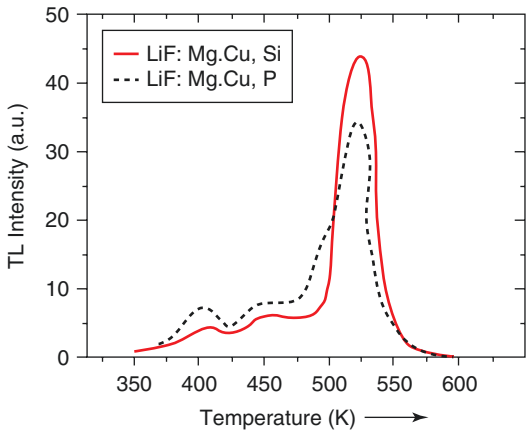

Fig. 3.13 Showing the glow curve

Heating (up to certain temperature) a TLD gives a glow curve, which is a graph of intensity as a function of temperature.

For reuse of TLD annealing has to be done, by which traps are emptied. For annealing process TLD has to be heated at 400 °C (approximately) for 1 h.

3.3.5 Optically Stimulated Luminescent Dosimeter (OSLD)

Al_2O_3:C is sensitive OSLD and used for personal dosimetry. Light emission is achieved by stimulating crystal with light of constant intensity such as LASER, LEDs, lamps, etc.

Emission wavelength is characteristic of OSL material, and the rate of luminescence is proportional to stimulating LASER light intensity.

The OSL reader integrates the photons over the period of stimulation. The stimulating light must be prevented from being interpreted as signal. OSLD reading is fast (1 s).

Before reusing OSLD, bleaching treatment with light from a halogen lamp, fluorescent lamp, or green LED has to be performed. This empties most trap centers and prepares OSLD for reuse.

Deep traps are not emptied in this process may be supplemented with thermal annealing.

3.4 Semiconductor

3.4.1 Diode Detector

Diode dosimeter is comprised of p-n junction diode, which is a junction of P-type and N-type semiconductor. N-type semiconductors are electron donors, P-type semiconductors are electron acceptors. Some known impurities (called dopent) are added to the semiconductors to make P-type of N-type diodes (Fig. 3.14).

When radiation incident upon the sensitive volume or depletion layer of the diode it liberates ions (either electron or holes). Electrons or holes will start to move in sensitive volume due to strong electric field and induce current. This current can be measured by electrometer and further can be calibrated for absorbed dose.

3.4.2 MOSFET Detector

MOSFET (Metal Oxide Semiconductor Field Effect Transistor) consists of three leads, drain, source, and gate.

P-channel MOSFET, source, and drain are composed of P-type semiconductor and gate is composed of N-type semiconductor. In P-channel MOSFET, holes flow between drain and source. Whereas N-channel MOSFET, source, and drain are composed of N-type semiconductor and gate is composed of P-type semiconductor. In N-channel MOSFET, electrons flow between drain and source. Only P-channel MOSFET is used in radiation measurement.

The voltage necessary to initiate current flow between source and drain is known as threshold voltage. When MOSFET device is exposed to radiation, electron hole pairs are generated. The difference in voltage shift before and after the exposure can be measured and can be correlated with the dose.

Unlike TLD/OSLD, the traps cannot be emptied (annealing), therefore MOSFET can be used for permanent dose record (Fig. 3.15).

3.5 Gel Dosimeter

Gel dosimeters are composed of radiation sensitive chemical, when exposed to ionizing radiation they undergo fundamental changes in their property, which is proportional to the absorbed dose. Gel dosimeters are 3D dosimeters and can be molded in any shape and size (Fig. 3.16).

Gel dosimeters are mainly two types: (1) Fricke gel and (2) Polymer gel.

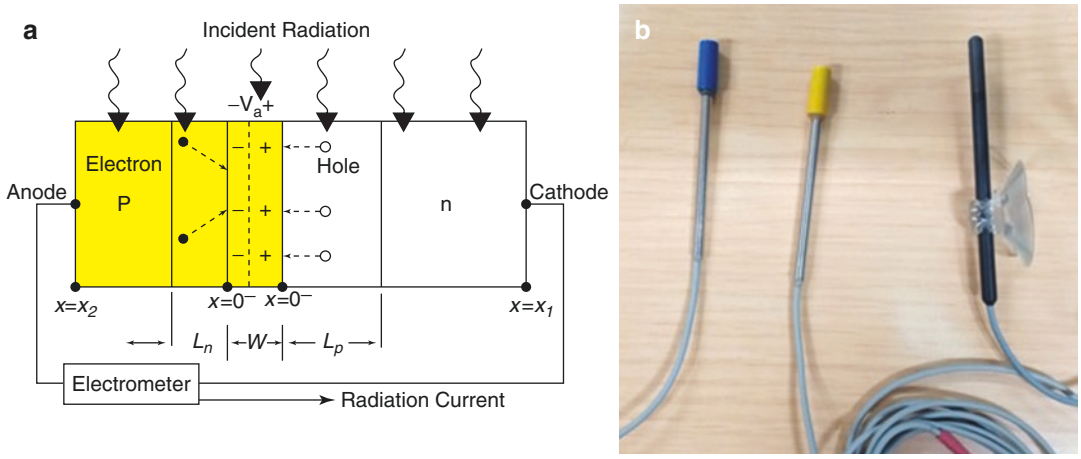

Fig. 3.14 (**a**) Showing the workflow of diode. (**b**) Commercially available diodes

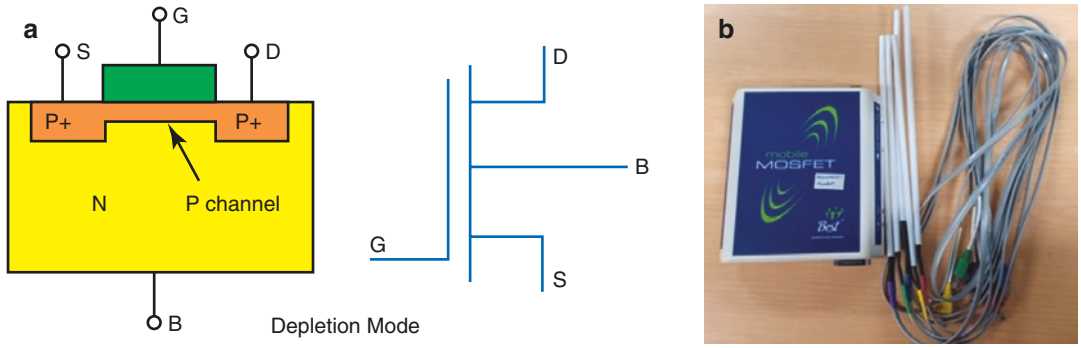

Fig. 3.15 (**a**) Showing the P-type MOSFET. (**b**) Commercially available MOSFET

Fig. 3.16 Showing the gel dosimeter [image taken (with permission) from, Natanasabapathi G, et al. (2015) verifying dynamic planning in gamma knife radiosurgery using gel dosimetry. IFMBE Proceedings 2015, vol51. springer, Cham]

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4 Radiation Protection Practical Aspects

Ashish Binjola

4.1 Introduction

Ionizing radiation has a number of applications that make our life better. In the field of medicine, ionizing radiation is used in the diagnosis of disease as well as for the treatment. In the petroleum industry radioisotopes are used for imaging oil and gas pipelines defects to avoid oil or gas leakage known as nondestructive analysis. Well logging, using radioactive sources is useful in determining whether a drilled well has certain minerals, petroleum, gas, or other valuable substances. In the field of agriculture, radiation helps to produce high yield seeds for better productivity as well as for preserving the food items for a longer duration (food irradiation can delay sprouting and avoid pests in certain crops). Radiation is used for sterilization of healthcare items and equipment, can help to make polymers (radiation polymerization), and have numerous research applications as well in different fields of science, etc. But, on the flip side radiation can pose serious health hazards, if not used in a planned and proper manner as advised by national and international regulators and advisory bodies providing regulations and guidelines for correct use of radiation.

Natural background radiation and the sources of man-made radiation: we are continuously exposed to low level of natural radiation which is known as background radiation. The source of background radiation is radioactive elements present in rocks (terrestrial radiation), cosmic radiation from the space (the level of cosmic radiation increases with altitude), etc., K40 and C12 which are the radioisotopes present inside our body also add to our background radiation.

Medical exposure, exposure due to consumer items, occupational exposure, etc., which may add to our radiation dose, are the sources of man-made radiation.

4.2 Important Organizations Pertaining to Radiation Safety

(a) International Commission on Radiological Protection (ICRP), Ottawa, Canada.
(b) International Atomic Energy Agency (IAEA), Vienna, Austria
(c) National Council on Radiation Protection and Measurements, Washington, DC, USA
(d) The International Labour Organization (ILO), Geneva, Switzerland
(e) International Commission on Radiation Units and Measurements, USA
(f) World Health Organization (WHO), Geneva, Switzerland

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4.3 Basic Quantities and Units in Radiation Safety

Radioactivity Radioactivity is defined as spontaneous emission of radiation from the nucleus of an unstable atom, and in this process, the unstable atom disintegrates into comparatively stable atom (either a different atom or the same atom in lower energy state). The number of disintegration the radioactive substance undergoes per unit time is known as activity (A) of the radioactive substance.

The SI unit of activity is Bq (1 disintegration per second) and the special unit is Ci ($1\ \text{Ci} = 3.7 \times 10^{10}$ Bq).

Exposure The quantity exposure (X) is defined as the quotient of the absolute value of total charge of the ions of either sign produced by the radiation (dQ) in the air by the mass of the air (dm), when all the charges produced in the air are completely stopped in air, i.e., the state of electronic equilibrium exists.

$$X = \frac{\mathrm{dQ}}{\mathrm{dm}}$$

The quantity exposure is defined only for X- and gamma rays and it is only a measure of ionization of air.

The exposure is measured in R (Roentgen).

$$1R = 2.58 \times 10^{-4}\ \text{Coulomb / kg}$$

Radiation Absorbed Dose The quantity absorbed dose, D, is defined as the quotient of $\mathrm{d}\bar{\mathrm{E}} / \mathrm{dm}$, where $\mathrm{d}\,\bar{\mathrm{E}}$ is the mean energy imparted to matter of mass dm by the ionizing radiation.

$$D = \frac{\mathrm{d}\bar{\mathrm{E}}}{\mathrm{dm}}$$

The SI unit of the absorbed dose is joule/Kg. The special name of the unit of absorbed dose is Gy.

$$1\,\text{Gy} = 1\,\text{Joule / Kg}$$

Another special unit of equivalent dose is rad (radiation absorbed dose).

$$1\,\text{rad} = 1\,\text{cGy}$$

Equivalent Dose The equivalent dose (H) is a quantity which is actually derived from the quantity absorbed dose, but it also takes care of the type of radiation as well as its energy for the difference of biological effects (harm to the body tissues). For example, a high energy alpha particle or proton beam will have more harm compared to photon beam due to its higher LET/specific ionization. Equivalent dose is defined as:

$$H = D \times W_R$$

where W_R is known as the radiation weighting factor. W_R takes care of differences in biological effectiveness of different types of ionizing radiation.

The unit of equivalent dose is Joule/Kg and its special name is Sievert (Sv). Another special unit of equivalent dose is rem (radiation equivalent man).

$$1\,\text{rem} = 1\,\text{cSv}$$

Table 4.1 represents the recommended values of W_R by ICRP 103

Effective Dose Effective dose (E) is another very important quantity for radiation protection. Different tissues in the human body have a different probability for stochastic effects of radiation. Effective dose incorporates tissue weighting factor for differences in biological effectiveness of

Table 4.1 Radiation weighting factor for different types of radiation

Recommended values of radiation weighting factor by ICRP 103 [1]	
Radiation type	W_R
X-rays, gamma rays photons, electrons, and muons	1
Protons and charged pi ions	2
Alpha particles, fission fragments, and heavy ions	20
Neutrons	A continuous function of neutron energy, maximum value 20 at 1 MeV

Table 4.2 Tissue weighting factor for various tissues

Recommended values of tissue weighting factor by ICRP 103 [1]	
Tissue	W_T
Bone marrow, breast, colon, lung, stomach	0.12 for each
Gonads	0.08
Bladder, liver, tissue, thyroid	0.04 for each
Bone surface, brain, salivary gland, skin	0.01 for each
Remainder tissues	0.12

different tissues for ionizing radiation. Effective dose (E), for a given tissue, is defined as

$$E = H \times W_T$$

As per ICRP 103 different values of tissue weighting factors are given as follows (Table 4.2):

The effective dose has the same unit as the equivalent dose.

For radiation safety purposes, as a rule of thumb, we may take (only for X- and gamma rays):

$$1\,\mathbf{R} = 1\,\mathbf{rad} = 1\,\mathbf{rem}$$

Or

$$1\,\mathbf{R} = 0.01\,\mathbf{Gy} = 0.01\,\mathbf{Sv}$$

Or

$$1\,\mathbf{mR} = 10\,\mu\mathbf{Gy} = 10\,..\mathbf{Sv}$$

Radiation Effects Ionizing radiation is known to have deleterious effects on human health. These effects can be classified as (1) Deterministic effects or tissue reactions having a threshold limit of the dose after which these effects are certain to occur and severity of effect increases with dose, e.g., radiation-induced cataracts, fibrosis of lungs, skin erythema, radiation-induced nausea, temporary or permanent sterility, etc. (2) Stochastic effects having no threshold limit and the probability of effect increases with dose, e.g., radiation-induced carcinogenesis and hereditary effects.

Radiation Protection In any sort of radiation applications, the goal of radiation protection is to avoid deterministic effects completely and to minimize the probability of stochastic effects below the acceptable limit. There are three basic principles of radiation protection which helps to attain our goal of radiation safety:

1. *Justification of practice*: No practice causing radiation exposure shall be adopted unless its introduction produces a net positive benefit.
2. *The principle of optimization*: All exposures should be kept as low as reasonably achievable (ALARA) taking into account social and economic factors. In radiation applications, doses can be minimized (as low as reasonably achievable) by adopting the principle of time, distance, and shielding explained as:
   (a) *Time*: The radiation dose to an individual is directly proportional to the time spent in the radiation field. Hence by reducing the time spent in the radiation field, one can reduce the radiation dose. Previous practice with dummy sources (dry run) can reduce time spent while handling actual radiation sources, thereby reducing radiation dose.
   (b) *Distance*: Ionizing radiation follows inverse square law; it means that doubling the distance will reduce the dose to one fourth. Use of long forceps for handling the radioactive sources may reduce the dose drastically. We should never touch the radioactive source, as it may deliver a very high dose because of very less distance.
   (c) *Shielding*: Shielding attenuates the radiation beam intensity and so reduces the dose. Shielding of radiation installations/sources is optimized to reduce the doses to the personnel and public below the prescribed limit by the regulator.
      (i) *Shielding for alpha particles*: Alpha particles are positively charged helium nuclei and can be stopped relatively easily. High energy alpha particles have very limited penetration of few mm in tissues. 1.0–2.0 cm of the plastic sheet will be adequate to shield against the beam of high energy alpha particles.

(ii) *Shielding for beta particles*: Beta particles are negatively or positively charged particles (electrons or positrons) emitted from the nucleus of a radioactive atom. Beta particles have a larger depth of penetration compared to alpha particles; high energy electrons from the Linac also have the same properties.

(iii) Sources emitting beta particles can be shielded effectively using a double layer shielding container. The inner layer of the container is made up of low atomic number material to absorb the beta particles with minimum production of Bremsstrahlung X-rays. Outer layer is made up of high atomic number material to attenuate the X-rays produced by electron interactions as well as associated gamma rays followed by emission of a beta particle.

(iv) For patient treatment, high energy electrons in a Linac can be shielded (partly) using lead cutout over the distal end of electron applicator

$$\{\text{Lead Thickness}(\text{mm}) = \frac{1}{2} \times \text{Energy of electron}(\text{MeV}) + 1\}.$$

Concrete shielding used to shield X-ray photons in Linac bunker can provide adequate protection for personnel and public.

(v) *Shielding for X- /gamma rays*: X-rays and gamma rays follow exponential attenuation and it cannot be completely blocked. However, by using proper shielding, we can bring the radiation level around the source well below the safe limits. Lead, steel, tungsten alloy, steel, etc. can effectively attenuate the X or gamma-ray beam. Concrete can be used as an effective shielding material for radiotherapy installations.

(vi) *Shielding for neutrons*: Neutrons are electrically neutral particles and can be shielded using hydrogenous material, e.g., polythene slabs. Concrete is also an effective shielding material for neutron shielding for high energy Linac installation. Borated polythene doors can be used at the entrance of the Linac installation to absorb high energy neutrons, if required.

(d) *Dose limits*: Dose to individuals shall not exceed recommended limits stipulated by ICRP and National regulatory body.

Table 4.3 Dose limit as per International Commission of Radiation Protection

Type of limit	Occupational	Trainee	Public
Stochastic effects: effective dose limits (whole body)	20 mSv per year, averaged over a defined period of 5 years, with no single year exceeding 50 mSv	6 mSv in a year averaged over 5 years	1 mSv in a year
Annual equivalent dose in (parts of the body)			
The lens of the eye	20 mSv per year, averaged over a defined period of 5 years, with no single year exceeding 50 mSv	50 mSv in a year	15 mSv in a year
Skin	500 mSv in a year	150 mSv in a year	50 mSv in a year
Hands and feet	500 mSv in a year	150 mSv in a year	50 mSv in a year

Effective dose limits for the pregnant radiation worker: The dose to the surface of the abdomen is 2 mSv for the entire gestation period and the dose limit to the fetus is 1 mSv

Dose limits for radiation workers and members of the public are provided in the International Commission of Radiation Protection (ICRP) 60 and 103 reports (Table 4.3). Later in the year 2011, ICRP has modified limit for the lens of the eye to 20 mSv per year (ICRP 118) from 150 mSv per year from its previous recommendations [1–3].

4.4 Transport of Radioactive Material

We shall take serious precautions in the transportation of radioactive material. Transport of radioactive materials should never harm person, property, and environment from the effects of radiation during the transport of radioactive material. Personnel involved in the transport of radioactive materials shall have the personnel radiation monitors to monitor their doses and their radiation doses shall be kept within dose limits prescribed by the national regulatory authority. Total number of personnel involved and exposure to them shall be kept as low as reasonably achievable. If there is an emergency situation, a written emergency action plan shall be ready and implemented to protect person, property, and environment. People who are involved in transport shall be well trained for handling radioactive material and to handle an emergency situation.

The protection can be achieved by:

1. Containment of radioactive content.
2. Control of external radiation levels.
3. Prevention of the criticality.
4. Prevention of damage caused by heat

Classification of packages is based upon shielding integrity of the packaging and the quantity of radioactive material and also on whether the material is fissile or not, total activity contained in the package, specific activity of the material, etc.

Every package should meet general packaging requirements of robustness (drop test, water immersion test, stake test, fire test, etc.) depending on the package type as well as specific additional requirements for fissile material. The package should be properly marked and labeled. United Nations number and proper shipment name should be written. Trem (Transport Emergency) card and placards should also be added along with transport index (TI). Apart from this, consignor's declaration should also be provided.

Types of radioactive packages for the purpose of transport can be broadly classified as:

1. Excepted packages
2. Industrial packages
3. Fissile packages
4. Type A (Fig. 4.1)
5. Type B
6. Type C package

In the radiation oncology department, mainly two isotopes are used for the radiotherapy:

1. Co-60 radioisotopes for teletherapy and
2. Ir-192 or Co – 60 sources for brachytherapy. These sources shall be transported only after obtaining the required permission from the regulatory authority. Brachytherapy sources (approximately up to 10 Ci) can be transported in type "A" package. In the transport of

Fig. 4.1 The packaging of radioactive material for transport, the type "A" package

teletherapy source, there is an involvement of higher activity (up to 12,000 Ci) and shall be transported in Type "B" package.

(a) The radioactive material comes under UN class 7 of dangerous goods.

(b) *Transport index (TI)*: The transport index is defined as the maximum level of radiation in mrem/h at 1 m from the surface of the package.

4.5 Equipment Required for Radiation Safety

Radiation protection instruments are essential in ensuring and evaluating the radiation dose which is being received by the individual. These instruments can be either installed and fixed or, portable and handheld.

1. *Installed equipment*: Installed equipment is important in ensuring the general radiation hazard in a particular area of interest; this includes area radiation monitor, airborne particulate monitors, personnel exit monitor, etc.
   (a) *Area radiation monitor*: Area radiation monitor will measure usually gamma rays which have a significant radiation level beyond a threshold. Use of gamma zone monitors is a regulatory requirement for telecobalt and brachytherapy installations (Fig. 4.2). It can avoid unintentional and accidental exposure. Gamma zone monitors are GM based or solid state detector based.
   (b) *Airborne contamination monitor*: This monitor measures the concentration of radiation particle which is ingested or deposited in the lung. They give an alarm in presence of airborne contamination. This monitor is often connected to an integrated safety system in a manner that personnel are prevented from entering the area when airborne contamination is more than the safe limit.
   (c) *Personnel exit monitor (PEM)*: Personnel exit monitors are used to monitor workers in a contaminated controlled area. This monitor can sense the level of exposure or contamination in the surface of the worker's body or the clothing they generally measure alpha beta or gamma contamination. The PEM can be in the form of a hand monitor, cloth frisk probe, or whole body monitor.
2. *Survey meters*: These instruments are compact and handheld. Survey meters are useful to survey a particular area or to check an object or person in detail for the presence of radiation (Figs. 4.3 and 4.4). Survey meter generally measures the dose rate of beta and gamma rays in mR/h or mSv/h Survey meters can be gas based or solid state detector based. In radiotherapy for linear accelerator, being a source of pulsed X-rays, ion

Fig. 4.2 Area gamma monitor installed for brachytherapy installation

Fig. 4.3 Neutron survey meter

Fig. 4.4 Pressurized ion chamber based survey meter

chamber based survey meters are generally used. For better sensitivity, air is pressurized in some ion chambers based survey meters. For gamma rays sources (telecobalt and brachytherapy) GM based survey meters can also be used. For high energy linear accelerators having energies above 10 MV, neutron survey meter is also a useful instrument for measuring neutron dose rate. Neutron survey meters are generally He^3 or BF_3 based gas detectors.

4.6 Radioactive Waste Disposal

In radiotherapy only shielded sources are used, but in nuclear medicine, open sources (liquid sources, as well as gaseous sources which may arise from volatile liquid sources) might be used. Disused sources as well as anything (gloves, syringes, vials, patient secretions, etc.) which contains radioactive contamination should be termed as radioactive waste and should be managed as per the regulations provided by the competent regulatory authority.

Safe management of radioactive waste is important to ensure safety to the people and the environment. If radioactive waste is not managed properly it may harm living beings.

4.6.1 Management of Radioactive Waste

1. *Delay and decay*: This technique is used for short-lived radioisotopes; the reason is to decrease the risk when released to the environment. Short-lived radioisotopes having half-life less than one month can be disposed after approximately delay of 10 half-lives, till then waste is stored in a properly shielded and ventilated room. After 10 half-lives, its activity is being assessed and if its activity is below the prescribed limit, it can be disposed as low activity radioactive waste.
2. *Dilute and disperse*: This technique is used for waste with very less activity (less than 50 KBq), which is diluted and then released to the environment which will not be harmful anymore.
3. *Concentrate and contain*: This technique is used for high activity and long half-life radioactive waste, which should be kept safely in isolation away from the reach of normal public below the ground (burial). E.g., Disused teletherapy source.

4.6.2 Radioactive Waste on the Basis of the Physical Form

1. Liquid waste
2. Solid waste
3. Gaseous waste

Liquid and gaseous wastes can be classified on the basis of the content of radioactivity while solid waste can be classified on the basis of dose rate on the package surface. Liquid waste of category III and IV need to be shielded properly, and category V required shielding and cooling during handling storage treatment and disposal.

1. *Liquid waste*: liquid wastes are contaminated water and effluent waste arising from the chemical processing and decontamination solutions, solvents, blood or body fluids,

discharged liquid and radiopharmaceutical, wound and oral discharge, urine, etc.
2. *Solid waste*: solid waste is formed from tissue paper, plastics, contaminated materials, protective wears, equipment, and materials used on radioactive material.
3. *Gaseous waste*: Management of gaseous is very important because once it is released in air nobody can control it. It may pose the following three kinds of hazards:
   (a) Direct irradiation hazard
   (b) Ingestion hazard
   (c) Inhalation hazard

4.6.3 Quality Assurance and Radiation Safety in Radiotherapy

> Quality Assurance is concerned with all those procedures that ensure consistency of the medical prescription and the safe fulfillment of that prescription as regards dose to the target volume, together with minimal dose to normal tissue, minimal exposure of personnel, and adequate patient monitoring aimed at determining the end result of treatment.—WHO (1998)

In radiation therapy linear accelerators, which are the sources of megavoltage electrons and X-rays, are the most commonly used teletherapy equipment. Radioactive sources Ir -192 and Co-60 are most common for high dose rate brachytherapy. Apart from that, radiotherapy simulator, CT simulator, and cone beam CT are the KV X-ray sources.

- Any equipment used for the diagnosis or treatment of patients should be type approved by the national regulator.
- Equipment shall be installed in the properly designed shielded bunker/room duly approved by the national regulatory body.
- Radiation installations shall be surveyed with the help of a calibrated ion chamber/GM counter. If the Linac is having high energy photons and electrons (greater than 10 MV), it should also be surveyed for neutrons using a calibrated neutron survey meter. Installation should be surveyed from time to time to assess the safety of the areas around the installations.
- All the equipment and sources used in radiotherapy shall conform to the applicable standards of the International Electrotechnical Commission (IEC) and International Standard Organization (ISO) and shall be type approved by the national regulator.
- Acceptance testing of all radiation generating equipment shall be performed as per the guidelines of international bodies (ISO, IEC, IAEA, etc.) along with guidelines of the national regulatory body.
- Radiotherapy equipment must be properly commissioned and QA must be done for equipment including all major and minor accessories.
- Equipment can be used for patient treatment only after obtaining the due license from the national regulatory body.
- All the sources and equipment shall be used for the intended purpose only according to the terms and condition of license by the regulator.
- Quality assurance of all the equipment should be done in stipulated frequency as per the national and international guidelines.
- Proper radiation symbol and warnings should be pasted outside the treatment room and entry to the controlled area shall be restricted.
- The symbol for radiation hazard and X-ray hazard is shown in Figs. 4.5 and 4.6
- Adequate staffing should be done and radiation safety training should be provided by the Radiological Safety Officer to all concerned, time to time.

Fig. 4.5 The symbol for radiation hazard

Fig. 4.6 The symbol for X-ray hazard

- All the radiation professional and workers must be provided personnel with radiation monitors to record their doses.
- Radiation emergency plan shall be clearly written and pasted on the machine console and time to time mock drill of emergency plan should be performed.
- Any accident involving radiation, loss of radioactive source, mis-administration of radiation dose, overexposure to the patient, public or personnel, etc. shall be reported to the regulatory body.
- Records and documentation of all the safety procedures, QA, personnel doses, etc. should be properly maintained.

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Beam Modifying Devices

5

Supriya Mallick and Goura K. Rath

Beam modifying devices are devices which when kept in path of beam produces a desirable modification in the special distribution of the beam.

Types of beam modification are as follows:

- *Shielding*: To eliminate radiation dose to selected part of the treatment area
- *Compensation*: A compensator attenuates the beam based on the irregular contour of the patient
- *Wedge filtration*: Used to produce a desired spacial tilt in isodose curves
- *Flattening*: Where the spatial distribution of the natural beam is made uniform in a LINAC by reducing the central exposure rate relative to the periphery

Types of beam modification devices are as follows:

- Field blocking and shaping devices: Shielding blocks, Custom blocks, Jaws, Multileaf collimators.
  - Compensators
  - Beam spoilers
  - Wedge filters
  - Beam flattening filters
  - Bolus
  - Breast cone
  - Penumbra trimmers

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5.1 Shielding

The aims of the shielding in radiation treatment are as follows:

1. Protecting critical organs by shielding them
2. Avoiding irradiation of surrounding normal tissue
3. Helps in better matching of adjacent fields

The characteristics of the ideal shielding material are as follows:

1. High atomic number
2. High-density material
3. Easily available and inexpensive

The choice material for shielding depends on the type of radiation beam being used.

5.1.1 Gamma and X-Ray Shielding

- High-density materials—more effective for blocking or reducing the intensity of radiation
- Lead (due to its high atomic number) is particularly well suited for shielding of gamma rays and X-rays
- Practically thickness of lead between *4.5–5 half-value layers* results in 5% or less of primary beam transmission (Table 5.1)

- The relationship holds true, only for *monoenergetic* X-ray beams

5.1.2 Neutron Shielding

- Materials composed of low atomic number elements are preferable for shielding neutrons as they have a higher probability of forming cross-sections (through elastic scattering), to interact with the neutrons.
- Hydrogen and hydrogen-based materials are usually used. Thus compounds with a high concentration of hydrogen atoms (such as water) form efficient neutron barrier. Another advantage is that it is relatively inexpensive.
- However, low-density materials can emit gamma rays when blocking neutrons, thus high energy material may be added to block gamma rays. So neutron shielding is most effective when a combination of both high and low atomic number elements is used.

The number of *HVL (n)* required is given by the following expression:

5.2 Custom Blocks [1]

- Used to block of the part of the field and is customly made using Lipowitz metal or Cerrobend (Fig. 5.1)
- Also called: Wood's metal, Bendalloy, Pewtalloy, and MCP
- Contents: 50% bismuth, 26.7% lead, 13.3% tin, and 10% cadmium by weight
- The melting point is 70 °C (158 °F)—main advantage of Cerrobend, can be easily cast into any shape
- Density *9.4 g/cm*^{3} at 20 °C
- *1.21 times* thicker blocks are necessary if made of Cerrobend when compared to lead to get the same attenuation
- Usual thickness is *7.5 cm*
- Shielding blocks types:
  - When central area is blocked it is called positive blocks.
  - When periphery of field is blocked it is called negative blocks.
  - Divergent block—when the edge of the block follows divergence of beam. It helps in reducing transmission penumbrae.
- Blocks are kept at a distance of 20 cm from skin in telecobalt machine, while in kilovoltage radiation lead blocks are placed directly

Table 5.1 Lead thickness required for shielding for different beam energies

Beam energy	Required lead thickness (cm)
4 MV	6.0
6 MV	6.5
10 MV	7.0
Co^{60}(1.25 MeV)	5.0

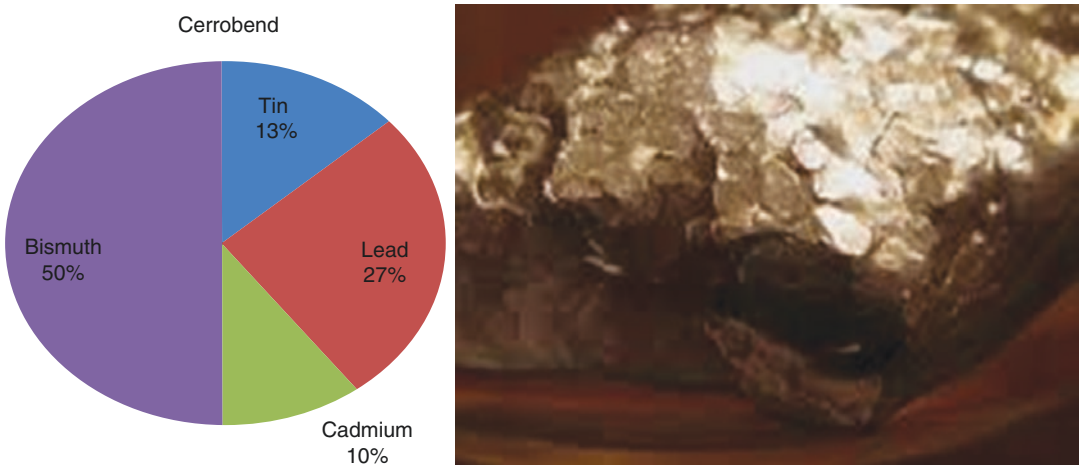


Fig. 5.1 Cerrobend composition and structure

over the patient. This is because secondary radiation is major part in low voltage radiation and benefit of shielding will be lost if distance between shield and patient is larger. Table 5.2 summarizes various materials that can be used for making blocks.

5.3 Independent Jaws

- Used to block of the part of the field without changing the position of the isocenter.
- Thickness is made usually of 10 HVL
- Can be used for beam splitting where the beam is blocked off at the central axis to avoid the divergence.
- Disadvantage: Use of independent jaws can result in the shift of the isodose curves which may alter the dose distribution.

5.4 Multileaf Collimator

Multileaf collimators consist of paired collimating leaves(usually *40* pairs of leaves) having a width of *1 cm* or less (projected at the isocenter) [2]. It is usually constructed with a tongue and groove design to allow easy and fast interleaf movement, while reducing radiation transmission via the leaves. One of the disadvantages of this design is underdosing (10–25%)in the region of the tongue (Fig. 5.2).

- Usually is made of a tungsten alloy.
- Thickness in the range of 7.5–8 cm
- Usual speed—2.5 cm per second

Primary X-ray transmission:

- Transmission via leaves—less than *2%*.
- Interleaf transmission—less than *3%*.
- Transmission via jaws—less than *1%*
- Transmission via Cerrobend blocks—less than *3.5%*

MLCs can also be used as dynamic wedges and electronic compensators in conformal planning

Disadvantages:

- MLCs have jagged boundary, hence matching of various fields may create underdosing and overdosing
- Island blocking is not possible with MLCs alone
- MLCs have a larger physical penumbra than blocks and thus blocks are better for shielding of critical structures, near the field

5.4.1 Types

- Single focus leaves MLC—rounded at end
- Double focus leaves MLC—leaf and leaf size match with beam
- The main aim of both designs is to reduce penumbrae

MLCs with leaf widths between about 2 and 5 mm are called mini MLCS, while micro MLCs have leaf width below about 2 mm.

5.5 Compensators

Compensator is a beam modifying device which is used to compensate for tissue inhomogenicity, so that the skin surface contours are evened out, while retaining the skin-sparing advantage.

Table 5.2 Composition of various materials that can be used for making blocks

Alloy	Melting point	Bismuth (%)	Lead (%)	Tin (%)	Indium (%)	Cadmium (%)
Rose's metal	98 °C (208 °F)	50	25	25	–	–
Cerrosafe	74 °C (165 °F)	42.5	37.7	11.3	–	8.5
Wood's metal	70 °C (158 °F)	50	26.7	13.3	–	10
Field's metal	62 °C (144 °F)	32.5	–	16.5	51	–
Cerrolow 136	58 °C (136 °F)	49	18	12	21	–

5.5.1 Types

The compensators may be two-dimensional or three-dimensional:

- In 2D compensators (Fig. 5.3), thickness varies, along a one dimension only. It can be made of lead, lucite, or aluminum.
- Three-dimensional compensators (Fig. 5.4) measure tissue deficits in *both* transverse and longitudinal cross-sections.

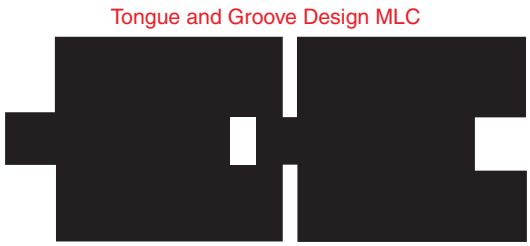


Fig. 5.2 Tongue and groove design of multileaf collimator

Systems used for design of 3D compensators:

1. Moiré camera—consists of a specially designed camera mounted on simulator which

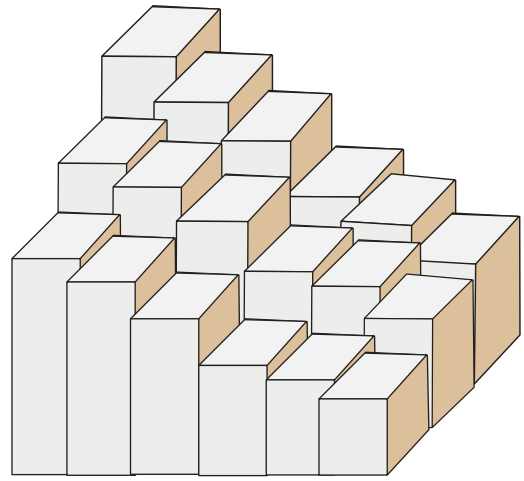
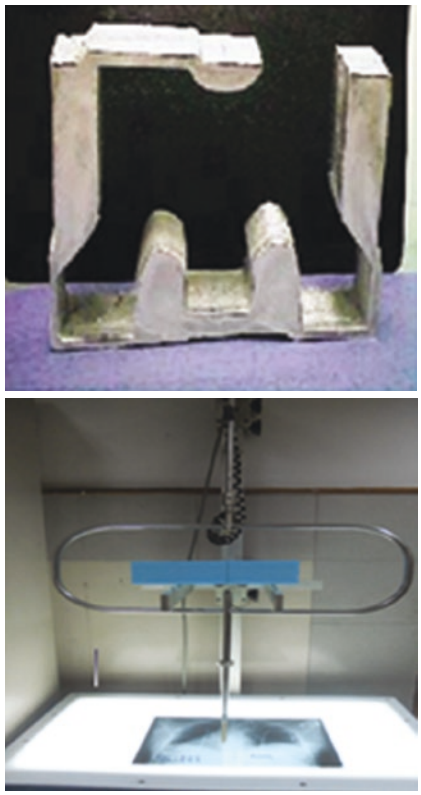


Fig. 5.3 Showing 2D compensator



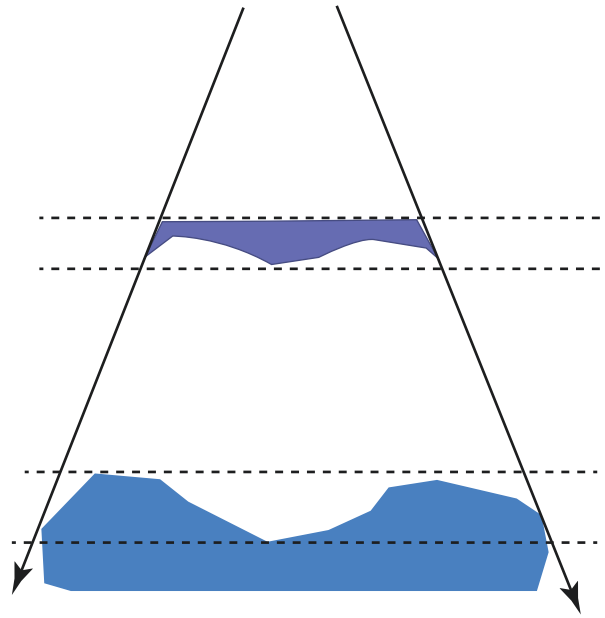


Fig. 5.4 Making of a 3D compensator

makes a topographical map of the patients surface which is used to produce 3D compensators
2. Magnetic digitizers—consist of a magnetic sensor in a handheld stylus which scans the patient body which is used to make 3D compensators
3. Computed tomography based images can also be used to make 3D compensators using compensator designing systems

Electronic compensators: MLCs are used to produce effect similar to a compensator in a LINAC.

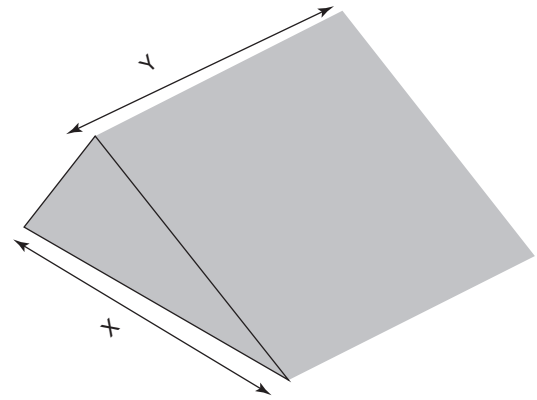


Fig. 5.5 Schematic representation of wedge

5.6 Wedge Filters

Wedge filter is a beam modifying device, which when placed in the path of the beam produces a progressive decrease in intensity *across* the beam, which results in tilting the isodose curves in the desired direction.

- *Material*: Wedge filters can be made of lead, brass, tungsten, and steel
- Usually kept at a distance of about *15 cm* from the patient skin

Types of wedge systems:

– Individualized wedge—Used in cobalt machines
– Universal wedge
– Dynamic wedges
– Enhanced dynamic wedge
– Virtual wedges

- The width (W) of the wedge is fixed and is the important dimension (Fig. 5.5)
- It is possible to use the same wedge in fields with lesser lengths or breadths
- The commonly available wedge systems for telecobalt machine are:
  – 6 W (× 15)
  – 8 W (× 15)
  – 10 W (× 15).

Fig. 5.6 Wedges used for telecobalt and LINACS

- Figure 5.6 shows wedges used for telecobalt and LINACS
- Usual wedge angles are 15°, 30°, 45°, 60°
- Wedge transmission factor (WTF) = Dose with the wedge divided by dose without the wedge and is measured along the central axis of the beam
- Wedge isodose angle (θ in Fig. 5.7) is the complement of the angle through which the isodose curve is tilted with respect to the central axis of the beam
- Hinge angle is the angle between central axis of 2 beams. The wedge angle chosen depends on the "hinge angle"(φ) (Fig. 5.7).
- The two factors on that help in choosing wedge angle are:
  – The hinge angle.
  – The wedge separation.

Motorized wedges are 60° wedges mounted in the treatment head and are moved into the field for part of the time to create the wedge beam profile desired

Dynamic Enhanced Wedge Creates desired wedge beam profile effects by moving jaws in and out of the field

Pseudo Wedge Also called poor man wedge

- Pseudo wedge is created by opening of small field in large field
- E.g., Small field gives 1/2rd dose while larger delivers the rest 1/2 of the dose
- Used in olden days when asymmetrical jaws opening was not possible and no planning TPS were available.

Virtual Wedge

- In virtual wedge dosimetry is produced by movement of collimators using a treatment planning system

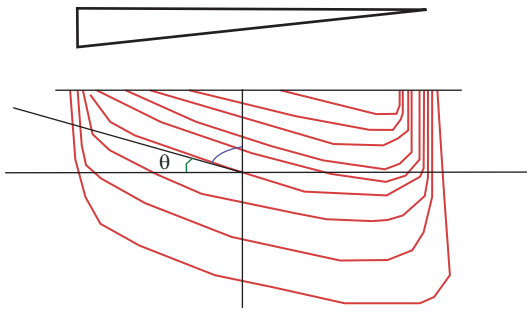


Fig. 5.7 Schematic representation of wedge angle and hinge angle

- The main advantage is that wedge factor is not needed when virtual wedge is used

5.7 Bolus

- Bolus is a tissue equivalent material used to reduce the depth of the maximum dose (D_{max}) or to bring up the surface dose
- Also known as "build-up bolus."
- Use of bolus:
  - In megavoltage radiation bolus—bring up the buildup zone (reduce the skin-sparing effect) in treating superficial lesions.
  - It can act as a compensator for missing tissue or irregular surface.
- Commonly used materials are: (Fig. 5.8)
  - Cotton soaked with water(water acts as bolus)
  - Paraffin wax
  - Mix- D
  - Lincolnshire bolus: made up of 83 percent sugar and 13 percent magnesium carbonate
  - Spiers bolus: made up of 60 percent rice flour and 40 percent calcium carbonate
- Properties of an ideal bolus:
  - Ideal bolus must have similar electron density to the tissue
  - Must be pliable to conform to surface to make it uniform
  - Ideal bolus must have similar absorption and scattering properties as that of tissue
  - Specific gravity must be around 1.02–1.03

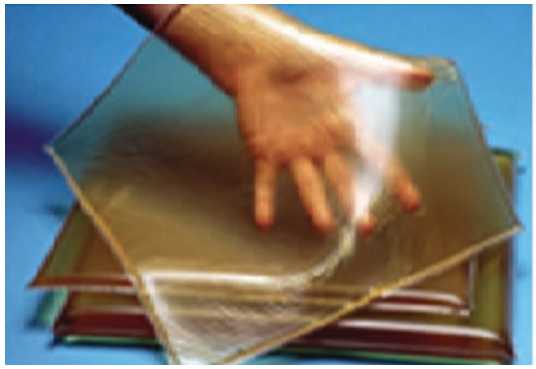


Fig. 5.8 Common bolus used in radiotherapy

- The thickness of the bolus varies according to the energy of the radiation.
  - CO-60: 2–3 mm
  - 6 MV Photons: 7–8 mm
  - 10 MV Photons: 12–14 mm
  - 25 MV Photons: 18–20 mm

5.7.1 Uses of Bolus

1. Increase skin dose
2. Even out the surface
3. If deep structures need to be spared to bring up isodose

5.8 Breast Cone

A beam directing device used in tangential field's therapy in breast cancer radiotherapy.

Advantages:

- Directs beam to the central axis of the area of interest
- Helps position, the patient and ensure correct position at SSD
- Provides compensation for tissue inhomogeneity
- Provides effective shielding of lungs below breast tissue

5.9 Penumbra Trimmers

The penumbra is the region of steep dose rate decrease (between the points at which the 20% and 80% isodose curves) at the edge of radiation beam

Types

- Geometrical penumbra; due to the size of the source with larger geometrical penumbra for larger source size
- Transmission penumbra; occurs due to the beam emerging from the edges of blocks or collimators

Penumbra width of a beam depends on the following factors:

- Diameter of the source—Penumbra width increases as source diameter increases
- Source to skin distance—Penumbra width increases as source to skin distance increases
- Depth
- Source to diaphragm distance—inversely related

Penumbra trimmers are made of heavy metal and placed in the path of the beam so as to attenuate the beam in the penumbra region there by reducing penumbra.

Other measures to reduce penumbra

- Increase the source to diaphragm distance, which leads to a reduction in geometric penumbra
- Placing secondary blocks close to the patient (e.g., 15–20 cm)

5.10 Flattening Filters

Used in linear accelerators—reduces the central exposure rate relative to that of the edge of the beam.

Thus it is shaped as a cone with the thickest part is in the center.

Materials used to make flattening filters: copper or brass.

5.11 Beam Modifying Devices for Electron Beams

- A primary collimator is provided close to source—defines the maximum field size.
- Electron cone— used to provide collimation for the electron beam.
- A secondary collimator, near the patient defines the treatment field.
- Lead cutouts—used for electron field shaping.

- Lead cutouts—placed directly on the skin.
- A tissue equivalent material (wax/dental acrylic) is coated over the lead shield to protect against backscatter electrons.
- Examples of areas where coating with wax or dental acrylic is required are the buccal mucosa and eye lids.

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6 Simulators

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6.1 2D Simulators

Conventional two dimensional X-ray simulator is used to image the tumor in two dimensions for determination of the field borders, location and to define the target. Milliampere (mA) and kilo voltage (kV) can be modulated to impact the noise and attenuation of the tissue. Skin markers play an important role in the reproducibility of treatment, ensuring accurate targeting and proper dose applied to tissue. The target is defined in relation to anatomic landmarks; the extent of fields is driven by knowledge of anatomy and by disease pathways. Physical examination, palpation, and physical measurements of the patient are important in 2D planning. Dose distribution information limited to single plane of major significance in order to cover the target. Energy selection is defined by the AP and lateral separation of the patient. Typically if the AP separation >16 cm better to use four fields rather than two fields (http://www.myradiotherapy.com/general/ct_planning/Simulators/radiotherapy_simulators).

6.2 3D Simulators

6.2.1 CT Simulators (https://www.healthcare.siemens.com/magnetic-resonance-imaging/magnetom-world/hot-topics/mri-in-radiation-therapy/articles-and-case-studies)

In 3D CT simulator, a dedicated CT is used for radiotherapy treatment simulation. CT scanner acquires volumetric CT-scan and the CT-simulation software provides virtual representation of the geometric capabilities of a treatment machine. The components of a CT simulator include X-ray tube, large bore CT scanner with an opening of up to 85 cm, detectors systems, collimators and attenuator, flat patients couch, laser. The main difference between a diagnostic CT machine and a radiation CT simulator is the wide bore and flat couch to ensure reproducibility between the imaging position and treatment position. Patient positioning and immobilization forms the cornerstone for accurate beam delivery. During the CT simulation radiopaque markers are kept on the skin adjacent to the region of interest and it forms the patient isocenter and this is used to define the tumor isocenter during treatment planning. 3D radiation therapy simulation allows graphic display of the 3D anatomy of tumor and normal tissues. The CT images provide excellent soft tissue contrast which helps in

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Fig. 6.1 Shows a radiotherapy CT simulator that has a wide bore of 85 cm with a flat couch which is similar to the treatment couch

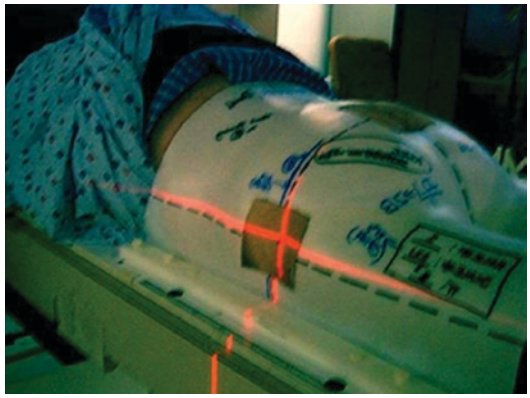

Fig. 6.2 Shows a patient of carcinoma rectum being imaged with a thermoplastic immobilization device

better tumor localization in comparison to conventional simulator. Electron density information from CT images is used in the calculation of dose inhomogeneity. Figure 6.1 shows a CT simulator, and Fig. 6.2 shows a patient with carcinoma rectum being simulated.

6.2.2 MRI Simulators

MRI simulators has superior soft tissue contrast compared to CT, functional imaging are additive tools for MR simulation (Fig. 6.3). The basic requirements include patient set-up, identical

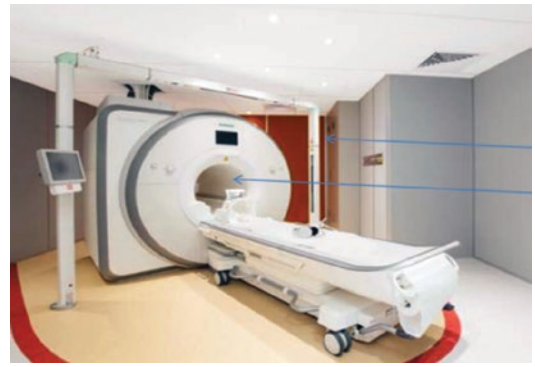

Fig. 6.3 MRI simulator

patient positioning to CT simulation and treatment, flat bed couch with the necessary radiofrequency coil, MRI compatible immobilization devices, placement of RF coils must not alter patient position. MRI simulators are being increasingly used for brachytherapy procedures in gynecological malignancies, adaptive replanning in head and neck malignancies (https://www.healthcare.siemens.com/magnetic-resonance-imaging/magnetom-world/hot-topics/mri-in-radiation-therapy/articles-and-case-studies).

6.2.3 PET-CT Simulators

PET is done after CT imaging in the same patient position. About 6–7 bed positions are planned in the 3-D acquisition mode for scanning the entire patient with 5–7-min acquisition at each bed position. The PET-CT can scan a maximum length of 145 cm for one patient [1]. The field of view of PET scan is 58.5 cm. It has a spatial resolution of 5 mm, and the sections are post processed to a thickness of 2.4 mm. The PET/CT scanners allow for functional/metabolic evaluation of the tumors.

Reference

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Telecobalt

7

Rony Benson and Supriya Mallick

7.1 History

- Began to be used from 1950s [medical linear accelerator was developed in the 1970s].
- The first patient—1951, at Victoria Hospital in London.
- First cobalt-60 teletherapy unit in India—Cancer Institute, Adyar in 1956.

7.2 Isotope [1]

- Naturally occurring cobalt is a hard, bluish-gray, easily breakable metal with 27 protons, 32 neutrons, and 27 electrons.
- Nonradioactive cobalt—imparts blue color to glass and ceramics.
- The isotope Co-60 was discovered at California Berkeley University in 1930.
- Co-60 is now produced commercially in nuclear reactors [by bombarding Co-59 with neutrons].
- Decay of Co-60 starts with a b-decay, followed by two gamma emissions with energies of 1.17321 and 1.33247 MV (Fig. 7.1).
- Half-life (1/2 *t*, i.e., the time required for the activity of the source to half) of Co-60 is 5.27 years. For practical purposes it is considered harmless and inactive after 10 half lives. Thus, Co-60 should be stored safely for approximately 53 years.
- The source is cylindrical in shape and has diameter of 2 cm.
- The source activity is generally between 5,000 and 15,000 Curie.
- A source with an activity of less than 3000 Ci is replaced with a new one; this is necessary after 5–7 years of use.
- Source is in form of disc-stacked one over another and doubly encapsulated.
- Capsule prevents leakage and absorbs beta rays.
- The source-isocenter distance (SAD) is 80–100 cm.
- Rotational movement of the gantry is motorized and controlled in two directions continuously; its rotation speed can be adjusted. The gantry can rotate by 360°.
- BRIT—Board for Radiation Isotope Technology—[Mumbai]—provides sources for Co-60, Ir-192.

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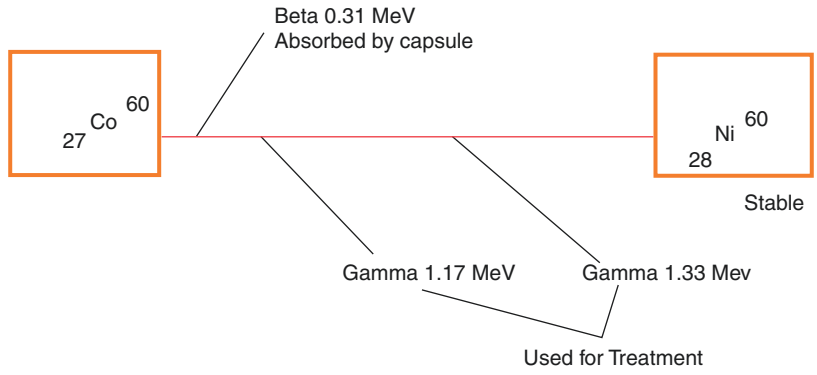

Fig. 7.1 Decay of Cobalt-60

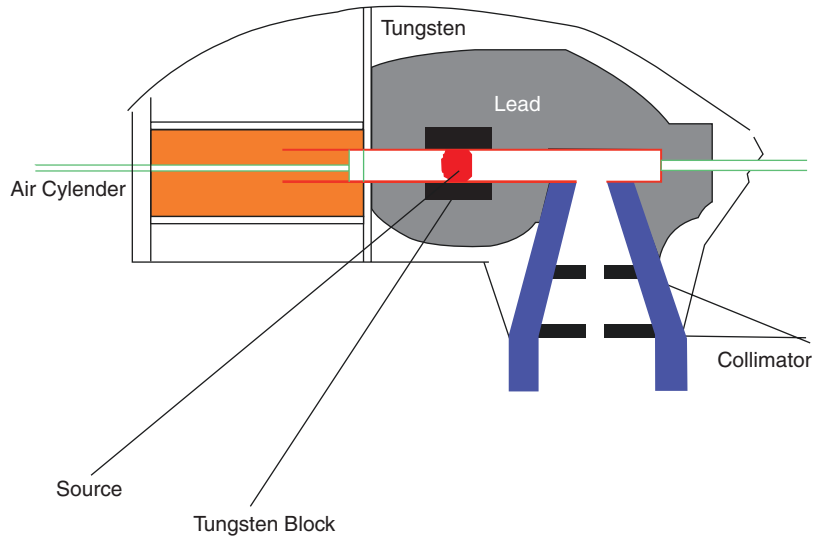

Fig. 7.2 Treatment head of telecobalt machine

7.3 Machine Details

The cobalt source (*orange*) is situated in a drawer and surrounded by lead. When the device is in the resting position, the source is protected by layers of enriched uranium. The source is then pushed by a pneumatic system to the treatment position. Figure 7.2 shows schematic representation of treatment head of telecobalt machine

- Activity = 9,000–12,000 curie.
- Primary barrier—130 cm of concrete.
- Secondary barrier—65–70 cm of concrete.

7.4 Source Stuck

Steps to follow in case of accidental source stuck

- Turn the gantry to opposite direction and ask the patient to come out (if patient can move).
- Go in with T-rod.
- Get out of the patient first.
- The head has the source indicator rod attached with the source drawer and moves with the source that indicates beam is ON.
- The external T-rod (Fig. 7.3) should be fitted with this indicator rod to push the source to the OFF position.

Fig. 7.3 T-rod with colors indicating source position

- Insert T-rod to yellow zone indicated on it [T-rod—red—danger, yellow—safe].
- If source does not go inside, lock the room and inform Radiation Safety Officer, hospital director, licensee, and then inform AERB.

7.5 Miscellaneous Points [2]

- Indian Cobalt Machines—Bhabhatron and Bhabhatron-II.
- Advantages over LINAC—less expensive, less service cost, less QA.
- Disadvantages—has large part as penumbrae, MLC and asymmetric jaw not available in most of machines, does not produce electron. Figure 7.4 compares telecobalt with LINAC.

		Telecobalt	LINAC
Cost		Less Expensive	More Expensive
Electricity			Requires higher electrical energy requirements
Energy		1.25 MeV Gamma	X ray 4-21 MV Multiple energies availbale
Field	Max	35*35 cm	40*40 cm
	MIN	5*5 cm	0.5*0.5 cm
Penumbra		1.5 cm	Less 6 mv=7 mm
Source size		Cylinder of diameter 2 cm, height 3 cm	Virtual -3-5 mm[focal spot]
PPD at 10 cm		55%	6 mv-67%
Shields		5HVL= Lead 5.5 cm	4 mv-6 cm Lead 6 mv-6.5 cm Lead
Barrier		Primary-130 cm Secondary-70 cm	Prim barrier 250-300 cm depending on energy
Max dose rate		Fixed reduces with time	Variable, higher dose rate available for SBRT in HDR mode
Wedges		Individualized wedges	Universal wedges
Collimator transmission		3%	0.5%
Maintenence cost		Less	More
Radiation hazard		Always on	Only when machine is on
Electrons		Only Gamma rays available for treatment	Availability of electrons
Source change		Need for source change after 5-8 years	No need to change source But life span low

Fig. 7.4 Comparison of telecobalt and linear accelerator

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8 Gamma Knife

Renu Madan

Gamma Knife radiosurgery is also known as stereotactic radiosurgery (SRS). It is a form of radiation used to treat brain disorders. In contrast to its name, the procedure does not involve any surgical intervention. It is a type of radiation delivery where multiple ionizing beams are focused and make them to collide at one point. Each radiation beam is consisted of low radiation dose to spare normal tissues, whereas higher dose is delivered to kill the tumor cells. Currently, it is a worldwide accepted method to treat variety of intracranial tumors, vascular and functional brain disorder.

History Concept of SRS was first given by a neurosurgeon, Lars Leksell in 1951. It was in 1951 in Stockholm, Sweden, when first patient was treated by SRS. Initially X-rays were used however later they were replaced by radioactive cobalt. This was defined as Gamma Knife stereotactic radiosurgery (GKS). First Gamma Knife machine in USA was used in the University of Pittsburgh in 1987 [1]. In Asia, First Gamma Knife center was opened in Japan in 1990 in the University of Tokyo Hospital [2] and ASAN Medical Center (Seoul, South Korea) [3].

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8.1 Indication of Gamma Knife Surgery

8.1.1 Single-Fraction GK SRS

1. Tumor size: 3–4 cm
2. Distance from optic nerve at-least 2 mm
3. Maximum lesions that can be treated in single session: 30

8.1.2 Multiple Fraction GK SRS (Extend System)

1. Tumor size >4 cm
2. Tumor too close to optic apparatus

8.2 Evaluation of Gamma Knife/ Various Models

There have been multiple developments in the design and technique of the Gamma Knife machine.

Four important models have been described: model U or A (Introduced in 1967), model C (Introduced in 1999), Perfexion (Introduced in 2006), and Gamma Knife Icon (Developed in 2016). The first model (U/A) had 201 cobalt 60 sources, arranged in hemispheric configuration. There were issues with loading and re-loading of the sources in this model. To overcome this, models B, C, and 4C were designed in which

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sources were arranged in circular configuration. Automatic positioning system (APS) was developed with the model C which was replaced by patient positioning system (PPS) in the newest model Perfexion (Elekta Instruments AB, Stockholm, Sweden).

Availability of computer based robotic device for GKS has significantly improved the safety and clinical implementation of SRS. The APS is a robotic computer controlled device in model C and 4C (Elekta instrument AB) which was used for automatic change of the patient head position when it is fixed in the stereotactic frame. Whereas in PPS, entire couch moves with the patient head that provides more comfort to the patient. It gives extremely high precision of 0.1 mm in any co-ordination direction. Use of this system has resulted in high selectivity and conformity indices leading to delivery of more homogenous dose to the target area and avoiding excessive dose to normal brain parenchyma [4].

Model C was designed in 1999 and first installed in 2003 in the University of Pittsburgh. This model had advanced techniques consisting of automatic positioning system (APS) and robotic engineering that obviated the need of manually adjusting the co-ordinates in a multiple isocenter plan. Subsequently this spares time on each patient and also increases accuracy [5]. An updated version of model 4C was introduced in 2005 and was first installed in the University of Pittsburgh. It provides better radiation protection for patients and staffs, as sources are always in the off position during patient shifting from one to another position, transition into new stereotactic co-ordinates, or during emergency interruption.

8.3 Leksell Gamma Knife (LGK) Perfexion

This relatively newer model of LGK has similar radiation dose profile as per the previous units. However the additional properties are:

1. Better dosimetry
2. Deep intracranial access
3. Better radiation protection
4. Fully automated treatment system
5. More comfortable to patient

Instead of 201 cobalt-60 sources in earlier, Perfexion has 192 cobalt-60 sources that are arranged in a cylindrical arrangement (in contrast to previous hemispheric arrangement). These sources are arranged in five concentric rings and source to focus distance for each ring ranges from 377 to 433 mm. In contrast to the primary and secondary collimators in the earlier models, there is only single integrated and permanent tungsten collimator array ring (120 mm). It has opening of three different diameters of the collimator (4, 8, and 16 mm) which are divided into eight sectors. These sectors move independently around the edge of the device [6]. Each sector consists of 24 sources and 72 collimators (24 for 4, 8, and 16 mm each). By servo-controlled motor system, these can be moved independently in five positions:

1. Home position with standby system
2. 4 mm collimator position
3. 8 mm collimator position
4. 16 mm collimator position, and
5. Sector off position, i.e., blocking all the beams

During the treatment these collimators can be used or blocked individually. A single isocenter can also be generated by use of different sized collimator (composite or hybrid shot). This method increases conformity and selectivity and is more effective when tumor is located near critical structures. This can also be used to treat larger tumors and are otherwise out of the tumor size criteria [6]. Larger tumor (three times as compared to previous models) can be treated on LKG Perfexion. Additional advantage is modification of the dose distribution by blocking some collimators also known as dynamic shaping. If critical organs are delineated as named as “risk volume,” the system automatically blocks the beam passing through it [7]. Automatic off and on of beam during transition of co-ordinates from one isocenter to other also reduces the treatment time [8]. Thus multiple tumors, i.e., brain metastasis,

can be treated and reapplication of the stereotactic frame can be avoided. More advanced technology with Perfexion can also be used to treat previously non-accessible tumors, i.e., skull base tumors, maxillofacial tumors, and tumors of cervical spine.

Perfexion couch has mechanical accuracy of <0.05 mm. APS in model C has been replaced by patient positioning system (PPS) in Perfexion. Entire couch moves according to the stereotactic co-ordinates (in contrast to only head in previous models) providing more comfort to the patient. Fully automated system reduces the work-load on staff and decreases human errors.

8.4 Technique

The first and foremost part of the treatment planning with Gamma Knife is placement of stereotactic frame. Pre-operative images should be reviewed in advance to decide for the optimal frame place strategy. After frame placement, patient is enclosed in PPS by an adapter (attached to the standard stereotactic Leksell G frame with three clips). Here, patient can be attached in three different gamma angles of 70°, 90°, or 110° that reflect neck flexion or extension. The gamma angle is the only parameter that requires manual set up.

Frame adaptor is used to attach the frame on the table. Every attempt has to be made to avoid the collision of the frame base plate and patient head with the collimator helmet. Position of patient head with respect to the treatment plan is checked by frame cap. Position of the frame can be changed on the base ring using the ear bars. Fiducials should be placed on the frame prior to sending the patient to MRI unit.

Neuro-imaging Protocol Imaging is one of the most important parts of Gamma Knife treatment planning. Contrast-enhanced magnetic resonance imaging (CEMRI) is the current standard of care. MRI is considered as a standard modality for radiosurgery as it provides excellent resolution and allows ideal 3D localization of the soft tissue or the targets. However as multiple complex nuclear reactions are involved in MRI, this modality also is a source of errors which may result in distortion artifacts and affect image quality and accuracy. Thus, MRI alone for radiosurgical treatment planning should be used with caution. Although resolution is poor with CT, it is less prone for the localization errors. It also has the potential of better visualization of bony structures, it can be used to correct the distortion artifact created by MRI. The automated algorithm of the Leksell GammaPlan allows easy co-registration of MRI and CT. The fused images can provide better information as compared to the individual modality. Thus, routine acquisition of CT scans and use of fused images is a more practical option even if the tumor is well identified on MRI.

1.5 T MRI is a valid option due to easy availability as compared to 3T MRI. The standard MRI imaging protocol used for SRS treatment planning of brain tumors consists of conventional spin-echo (SE) or turbo spin-echo (TSE) T1- and T2-weighted sequences, post contrast T1-weighted SE or TSE, and T1-weighted sequences with magnetization transfer contrast. The use of contrast media is recommended [9]. Contrast-enhanced perfusion weighted imaging (PWI), dynamic contrast-enhanced MRI (DCE-MRI), MR spectroscopy (MRS), diffusion-weighted imaging (DWI), and diffusion tensor imaging (DTI) are also used sometimes. Incorporation of functional MRI techniques into the routine morphological imaging protocols may identify the extent and biologically the most aggressive parts of the target [10].

Bi-plane angiograms are used along with MRI to see AV malformations.

Target Delineation For target delineation, 1–1.5 mm slices are constructed. It is an important step to make a conformal plan. Delineation can be done using the LGPâ software (manual or semiautomatic mode). Although experienced personnel can create conformal dose plan without delineating the target, delineation of target and critical structures allows for a better assessment of the plan and various parameters

such as dose volume histograms for tumor and critical structures along with selectivity and conformity indexes can be calculated.

Treatment Planning Several options are available for a conformal plan on Gamma Knife. In model C, treatment planning can be done using robotic automatic patient positioning system (APS mode), manual positioning (trunnion mode), or mixed treatment (some isocenters in APS mode and some in trunnion mode). Most of the users prefer shots and directly place them over the target. However, inverse dose planning algorithm (WizardÒ) can also be used to create a plan which can be later optimized manually.

The best change in treatment planning with Perfexion is the generation of single isocenter by use of multiple different sized collimators. Multiple small collimators lead to better conformal planning.

In this, a newer version of Leksell GammaPlan PFX (LGP PFX) with Linux operating system is used. There are three approaches in treatment planning:

1. Use of classic combination of 4, 8, and 16 mm collimators (shots)
2. Composite combination of 4, 8, and 16 mm
3. Sectors block to protect volume at risk-dynamic shaping.

Typically multiple shots are used to treat the tumor. This is more helpful in case of irregular tumor to increase the conformity. However irregular and large tumors are at increased risk of developing postradiation complications because the normal tissue may get the higher dose [11]. In these cases, the prescribed dose can be decreased to reduce the risk of complication. However, optimal target coverage should also be kept in the mind.

In forward treatment planning, a single radiation shot delivers the maximum dose to the target, i.e., large portion of higher isodose lines a small target area, leading to uniform high-dose radiation to the target and a steep dose gradient and sharp fall-off of the dose outside the target. Thus in case where multiple shots have to be used for the treatment of large or irregular shaped tumor, one should always attempt to generate multiple shots that mimics the dose distribution of a single shot.

The disadvantage of using multiple shots is an overlapping of the isodose curves on the target. This phenomenon is known as “normalization effects” between the shots also known as hot spot.

In GKS single or multiple isocenters of various beam diameter can be used for the desired coverage of the target. Total numbers of isocenters depend on the size, shape, and location of the target. Each isocenter has three stereotactic co-ordinates (X, Y, Z Cartesian co-ordinates) that correspond to its location in the 3D space which is defined by rigidly fixed stereotactic frame.

Once the APS treatment plan is generated, it can be directly transferred from the planning computer to control computer. Combination of isocenters of same beam diameter (run) is then selected that matches the collimator helmet on the gamma unit. Patient’s head frame is fixed into the APS which is moved to dock the position. The precision of the docking position is checked. This is followed by the clearance checks for all planned isocenters in which the pins, posts, frame, or patient’s head should be less than 12 mm away from the inner surface of the collimator helmet. The clearance check is done by moving the patient to the desired positions under APS manual control and also by visual check of collision with the collimator helmet. Once these tests are done, position checks are made to see the positions of isocenters that use the same helmet. This is done by moving the patient’s head to these positions using APS manual control. It should be make sure that patient is comfortable in all head position. After all the mandatory tests, radiotherapy is given to the patient.

The APS moves the patient to all planned positions, one by one, until the isocenters using that size collimator helmet are completed. Set up of patient and co-ordinates of different iso-centres is done on the control computer.

LGK Perfexion is a fully automatic machine. All aspects of the procedure are set automatically, i.e., setting of the stereotactic co-ordinates and different sector positions that define size of the collimator to be used, adequate exposure time, and blockade of the beam to spare normal tissue. All the treatment data is then exported to the treatment console. The only thing which has to be adjusted manually is the positioning of the head in the docking device and couch adjustment for the patient comfort. Around 95% of the SRS with Perfexion can be administered in a single run. During SRS patient can be communicated by an audio-visual system, and the treatment can be interrupted at any time in case of emergency.

8.5 Quality Assurance

Daily quality assurance is necessary to check the proper functioning of the system according to nuclear regulatory commission (NRC) guidelines. These guidelines include testing of radiation monitors, camera and console, door interlock, emergency interruption of the treatment button, emergency removal of the patient, functioning of helmet hoist to change the collimator helmet, and checking of APS and PPS. A test run simulating the treatment is performed to check the functioning of APS and PPS.

8.6 Common Indications, Target Doses, and Dose to Critical Structures

1. Acoustic neuroma (vestibular schwannoma): There are two options for the treatment: microsurgery and radiosurgery. Generally, surgical resection is recommended. However, there has been increase in the number of patients undergoing SRS for acoustic neuroma. The main objective of GKS in VS is growth control and at the same time preserving neurological functions, especially useful in those cases where the tumor is in close vicinity of cranial nerves. Large number of published reports have reported a tumor control rate of >95% [12]. As compared to surgery, GKS has a high rate of preservation of facial nerve function and hearing [13]. Typically, a radiosurgery dose of 12–13 Gy at the 50% isodose line leads to adequate tumor growth control and at this dose, temporary or permanent treatment related dysfunction of the VII cranial nerve can be avoided in 99% of cases. The radiation dose in SRS to the cochlea should not exceed 4 Gy.
2. Sellar tumors: Pituitary adenomas (PA) and craniopharyngiomas (CPH) are the most common tumors in the sellar-suprasellar region. Combined, they represent around 15% of all intracranial tumors. PA arise from the anterior pituitary gland, while CPH arise from epithelial cells of Rathke's pouch.

   Microsurgery is the gold standard for the treatment. Surgical removal has various advantages including histopathological confirmation, immediate decompression of the optic apparatus, and rapid reduction of the excessive hormonal secretion. However, 3–4% of the patients develop severe morbidity after surgery (visual loss, ophthalmoplegia, stroke) and less severe complications can be seen in 5–20% [14] Overall recurrence rate after microsurgery ranges between 8% and 57% (for both PA and CPH) [14]. Medical treatment with dopamine agonists and somatostatin analogue can also be used; however, in a meta-analysis of 35 studies, hormonal normalization was reported in 55% to 90% while the tumor regression rate was from 20% to 80% [14]. Studies have shown that SRS is the ideal treatment of PA if microsurgery and/or medical treatment does not control tumor growth or if there is any contraindication to these modalities. Good control of PA has been reported after SRS, however results vary for endocrinopathies. Overall, GH and ACTH over secretion are better controlled as compared to prolactin [15].

   For hormone secreting PA mean recommended dose is 25 Gy while lower doses are effective for nonsecreting PA (mean recommended dose is 15 Gy). For CPHs, the mean recommended dose is 9–12 Gy.

Recommended maximum dose to brain stem should not exceed 12 Gy.

Maximum tolerated dose for optic apparatus is 8 Gy but in some cases, a dose of 10 Gy is also accepted with a low risk of complications. However, volume receiving >10 Gy should not exceed 9 mm^3

3. Meningioma: The recommended dose for non-benign meningiomas ranges from 14 to 20 Gy. For smaller tumors a dose of 18–20 Gy can be given. For tumors with a volume of ~10 cm^3, 15–16 Gy, and for larger tumors, SRS dose is generally limited up to 14 Gy.
4. Brain metastasis: The marginal dose of 20–22 Gy at 50% isodose is used for the treatment of brain metastasis and for trigeminal neuralgia, a dose of 85–90 Gy is associated with adequate pain relief.

8.7 Complications

The complications after radiation arise due to exposure of normal tissue to radiation. Several treatment parameters may affect the severity of complications, i.e., dose, dose volume, dose rate, and tissue radiosensitivity. Thus all attempts should be made to minimize the radiation dose to critical structures. Gamma Knife surgery is generally a safe procedure. Few patients can experience fatigue, headache, or nausea.

Gamma Knife Icon Icon is the advanced version and the next generation of the Leksell technology. It is an upgradation of LGK Perfexion and was introduced in 2016 (Elekta AB, Stockholm, Sweden). The most important benefit of icon is that patients can be treated without head frame. A custom face mask is used in contrast to the more rigid head frame. The technique and procedures of radiation are similar as the previous model [16]. Additionally it has a gantry with an X-ray tube and image detector, thus CBCT imaging and intrafraction motion management are possible.

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Linear Accelerator

9

Supriya Mallick and Rony Benson

9.1 What Is a Linear Accelerator?

A linear accelerator is a machine for radiotherapy treatment which uses high radio-frequency (RF) electromagnetic waves to accelerate electrons to high energies in a linear path, using an accelerator waveguide. The resonating cavity frequency of the medical LINACS is about 3 billion Hertz (cycles/s). The current medical LINAC has evolved from DC voltage accelerators and RF accelerators.

9.2 Generation of LINACS

- Low energy photons: 4–8 MV
- Medium energy photons (10–15 MV) and electrons
- High energy photons (18–25 MV) and electrons
- High energy photons and electrons: with electronic portal imaging device; multileaf collimator
- High energy photons and electrons: with intensity modulation

9.3 Components of LINAC

The major components of a linear accelerator (Fig. 9.1).

1. Drive stand
2. Gantry
3. Modulator cabinet
4. Treatment table
5. Control console

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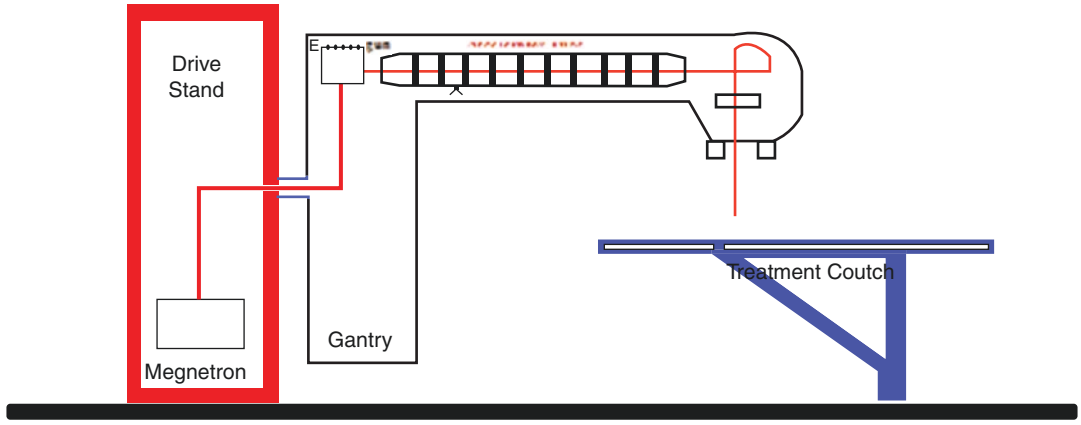

Fig. 9.1 Major components of LINAC

9.4 Drive Stand

Drive stand is the large rectangular cabinet that is firmly secured to the floor of the room. The gantry rotates on horizontal axis in the drive stand.

Major components located in the drive stand:

1. Klystron or magnetron
2. RF waveguide
3. Circulator (connects Klystron to RF waveguide)
4. Cooling water system

Microwaves are used to accelerate electrons to the desired kinetic energy. Magnetron acts as a source of high power microwaves required for electron acceleration, while a klystron is a microwave amplifier.

9.4.1 Klystron

- It is a specialized linear-beam vacuum tube
- Klystron is not a source microwaves but it is an amplifier of microwaves
- Used in >6 MeV
- Costlier than magnetrons

9.4.2 Magnetron

- Provides microwaves—to accelerate the electrons
- Lesser average power and gain
- Usually uses 2 MW peak power
- Cheaper, preferred for lower electron energies, 4–6 MeV LINACS
- For higher energies the Klystron is a better choice

9.4.3 Water Cooling System

- Located in the drive stand
- Provides thermal stability to the system
- Helps in maintaining a constant temperature so that the components in the drive stand and gantry function properly

9.5 Gantry

- Gantry direct the X-ray (photons) or electron beams to the patient
- It rotates 360° around the isocenter

There are three main components of the gantry (Fig. 9.2):

1. Electron gun
2. Accelerator guide
3. Treatment head

Electron Gun Electrons are produced by electron guns (Fig. 9.3) by thermionic emission. It

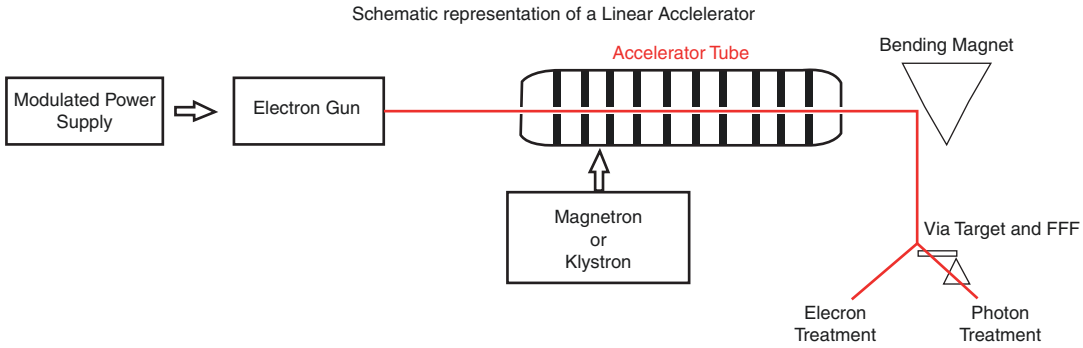

Fig. 9.2 Schematic representation of a gantry of linear accelerator

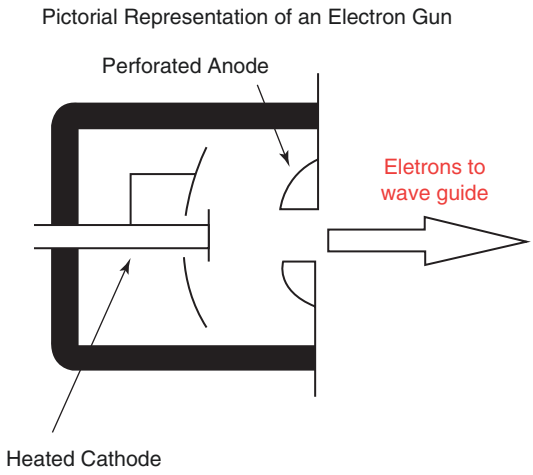

Fig. 9.3 Pictorial representation of an electron gun

consists of a heated filament cathode and a perforated grounded anode.

9.5.1 Accelerator Guide

- It is called the accelerator waveguide. It is mounted horizontally in the gantry for high energy single or dual energy machines with klystrons and vertically for low energy machines with magnetrons
- Waveguides are evacuated or gas filled structures and are used in the transmission of microwaves
- Its structure includes series of discs placed at equal distances with circular holes in the center
- Microwave is produced by klystron or magnetron and transported to the accelerator structure

9.5.2 Treatment Head

- Contains beam directing, modifying, and monitoring devices
- For photon therapy, they consist of the bending magnet, target, primary collimator, beam flattening filter, ion chambers, secondary collimators, and one or more slots for trays, wedges, blocks, and compensators

Bending Magnet Changes the direction of the electron beam, downwards toward the patient

- Bends the electron beam towards the target for X-ray production or toward the scattering foil for electron treatments
- Produces different beam paths for different energies
- Needed for energies greater than 6 MeV
- There are two common bending magnet configurations, 90° bending and 270° bending (achromatic bending)

X-Ray Target The collision of the electrons with the high density transmission target creates the X-rays (photons), forming a forward peaking shaped X-ray beam in the direction of the patient's tumor.

- The target for X-ray production is positioned at the focus of the bending magnet so that X-rays can be produced efficiently
- Majority of electron energy [94%] goes into heat
- Each photon energy has its own unique target—flattening filter combination

Beam Flattening Filter It is a conical shaped metal absorber that absorbs more forward peaking photons than the ones in the periphery. It shapes X-rays in their cross-sectional shape

- It is required to create a flattened beam with uniformity and symmetry
- Material made to make beam flattening filter—tungsten, steel, lead, uranium, and aluminum
- Dual energy photon LINACS—requires two flattening filters for the low and the higher photon energies

9.5.3 Scattering Foils

- The electron beam needs to be broadened and made uniform for clinical use
- There is a different scattering foil for each electron beam energy produced
- Made out of aluminum or copper

Collimators There are primary collimators as well as secondary collimators (jaw):

- The primary collimator defines a maximum field size. The primary collimator provides a circular field. The secondary collimator further shapes the field [usually into a square field [usually 40 × 40 cm]]
- The radiation beams are collimated by adjusting the upper and lower collimator jaws
- Jaws—made of high Z number, like tungsten or lead
- The jaws can define a field of up to 40 cm by 40 cm for X-ray beams
- Transmission via jaws—<2% of the open beam

9.5.4 Monitor Ionization Chambers

- Ionization chambers monitor dose, dose rate, and symmetry of the field
- The radiation that leaves the X-ray target or the electron scattering foils passes through the dual monitor ionization chambers
- This ionization current is proportional to the X-ray of electron beam intensity

9.5.5 Multileaf Collimators (MLCs)

- They are heavy metal field-shaping devices with independent moving mechanisms used to create a custom like block to spare normal tissue and direct the radiation dose to the tumor
- The MLCs became a key element in the treatment delivery of X-ray beams with IMRT (Intensity Modulated Radiation Therapy)
- Micro-MLCs—projects 1.5–6 mm leaf widths at isocenter

9.6 Modulator Cabinet

The modulator cabinet is located inside the treatment room and is one of the noisiest part of the LINAC.

Contains three subcomponents:

1. Fan control
2. Primary power distribution system
3. Auxiliary power distribution system

9.6.1 Newer and LINAC Modifications

1. MRI LINAC (Table 9.1)
   - LINAC is placed with MRI magnets to improve delineation of target during treatment to reduce interfraction error and allow dose escalation

Table 9.1 Types of MRI Linear Accelerators

Equipment	Elekta unity	ViewRay MRIdian
Photon energy	6 MV	6 MV
MRI	1.5 Tesla	0.35 Tesla

- Important for GI tumors to plan adaptive radiotherapy
- Accurate target delineation (typically GTV or tumor bed) [1]
- High risk volume can be better defined by functional imaging
- Figure 9.4 shows image of ViewRay MRIdian

2. LINAC with FFF beam
   - Advantage—FFF X-rays is to provide much higher dose rates for IMRT treatments
   - Dose rates provided are 1400–2400 MU/min
   - Commercially available for treatment
     - Varian True BEAM—1400 MU/min for 6 MV X-rays and 2400 MU/minutes for 10 MV
     - Elekta—Versa HD
   - Especially helpful for SBRT or SRS treatments
   - Significantly reduces treatment time
   - Maximum advantage is when treating small field sizes
3. CyberKnife
   - Uses X band LINAC in a robotic arm—uses higher microwave frequency to reduce the weight of LINAC
   - Pencil beams of radiation for treatment
   - Uses orthogonal kV X-ray for image guidance
   - Major advantage of the CyberKnife is its coupling to the imaging systems which continuously monitor organ movement and feed this back to the robot [2]
   - Typically, three radiation beams are delivered and then delivery pauses and a pair of images is acquired—based on these images, a corrected position is transmitted to the robot, which adapts beam pointing to compensate for any patient movement
   - Generations of CyberKnife

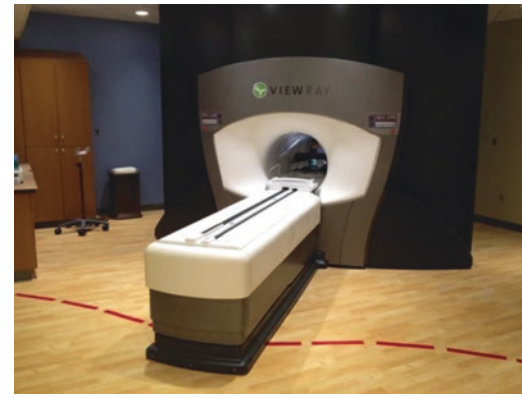

Fig. 9.4 Image of ViewRay MRIdian

1. 1st generation
   - 12 interchangeable circular collimators
   - SSD of 80 cm
   - Collimators provide a beam diameter from 5 to 60 mm
2. Second generation
   - 800 mu/min Linear accelerator
   - Monte Carlo algorithm for dose calculation
   - Iris variable aperture collimator
   - RoboCouch

Disadvantages are as follows:

- No posterior (below couch) possible
- Prolonged treatment planning time
- Requires significant quality assurance prior to treatment
- Electrons not available for treatment unlike other LINACS

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Helical Tomotherapy

10

Supriya Mallick and Rony Benson

Tomotherapy involves delivery of radiotherapy using a fan beam where the target is treated slice by slice. It can be of serial or helical type of tomotherapy.

Serial tomotherapy was the first form of tomotherapy clinical use where a normal linear accelerator was modified to deliver tomotherapy. The multivane intensity modulating collimator (MIMiC) was retrofit into an accelerator and the radiation beam was collimated to a narrow fan beam defining a trans-axial slice. The MIMiC consists of 2 × 20 finger attenuators that can be driven into and out of the field.

The serial tomotherapy was one of the earliest forms of intensity modulated radiotherapy even before MLC based intensity modulated radiotherapy.

Components of serial tomotherapy are as follows:

- Treatment planning system was peacock
- Patient-fixation device—talon
- Ultrasound based target localization—bat

One of the disadvantages of the serial tomotherapy was the uncertainty with junctions between fields as the couch is moved for treatment of a large volume. This led to the development of the helical tomotherapy where the machine moves in a helical manner, thereby avoiding junctions.

10.1 Helical Tomotherapy

In this type of tomotherapy the linac head and gantry rotate like a helical diagnostic CT scanner while the patient moves into the machine. The main advantage of this type of tomotherapy is the problem of junctions is minimized because of the continuous helical motion of the beam (Fig. 10.1). Another advantage of helical tomotherapy is the megavoltage imaging available with helical tomotherapy [1].

Another advantage is reduced room shielding requirements due to presence of primary beam stopper I the gantry head. Figure 10.2 shows structure of a tomotherapy machine.

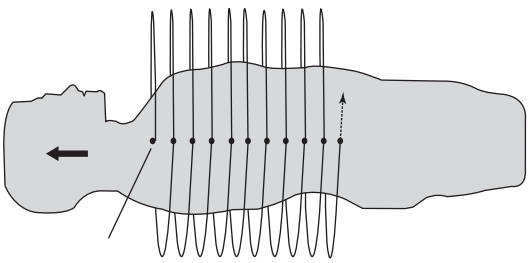

Fig. 10.1 Continuous helical motion of the beam in tomotherapy

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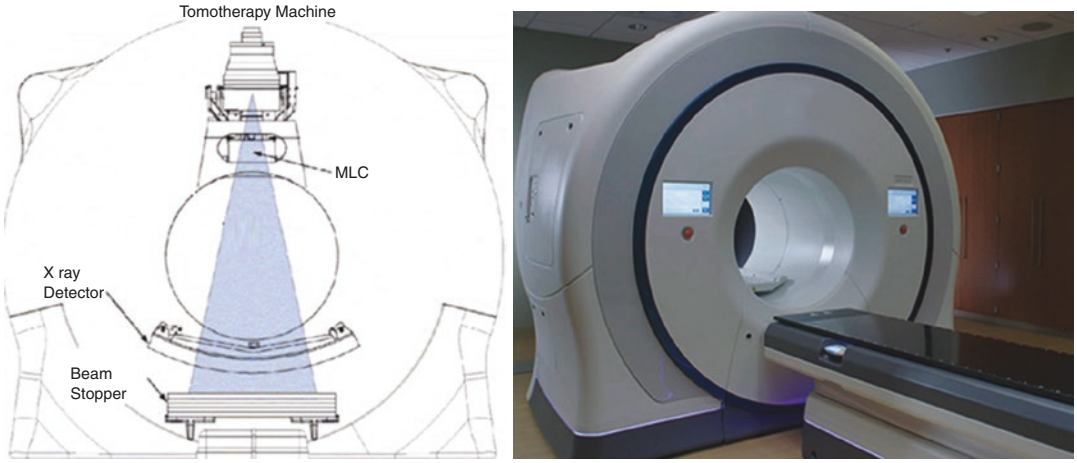

Fig. 10.2 Tomotherapy machine

10.2 Main Properties of Helical Tomotherapy [2]

- Energy 6 MV X-ray for treatment
- Has beam stopper that shields the beam after passing through the patient, hence less room shielding is required—precludes need for a primary barrier
- The ring gantry also contains a detector system that is mounted opposite to the accelerator and is used to collect data for MVCT acquisition
- MVCT imaging performed by 3.5 MeV beam
- Primary collimation produces 0–5 cm slice width
- Binary MLC—64 leaves
- The leaves are made from 95% tungsten and are 10 cm thick
- Interleaf transmission—0.5%
- 85 cm gantry aperture
- No flattening filter (high dose rate)—output rate 10 Gy/min
- Maximum field width 40 cm
- Maximum field length 160 cm
- 1–6 rotations per minute
- There is less scatter contamination
- During treatment full rotation is divided into 51 projections
- Table 10.1 compares tomotherapy to linear accelerator

Table 10.1 Comparison of tomotherapy vs. linear accelerator

Tomotherapy	Conventional linear accelerator
Single photon energy	Dual or triple energy photons
Electrons not available for treatment	Electron treatment possible
Imaging is MV	Imaging with KV CBCT—better quality
Couch, collimator rotation not possible	Couch, collimator rotation possible
Non coplanar treatments not possible	Non coplanar treatments possible

10.3 Clinical Uses

1. Craniospinal irradiation—No junctions and better dose distribution
2. Total marrow or total lymphatic irradiation—due to the length of the field unique advantage of single field technique
3. Breast cancer—improved homogeneity of breast dose and lesser dose to lung when compared to 3D conformal radiotherapy
4. Head and neck radiotherapy—better conformal treatment and allows for adaptive RT [3]

10.4 Disadvantages

1. Increase in the integral dose to normal tissues
2. Higher penumbra in the craniocaudal direction
3. Unavailability of non-coplanar beam arrangements
4. Extra dose (up to 0.6–2 cGy) due to MV-CT
5. Electron treatment not possible
6. Treatment time usually higher than VMAT

The widespread availability of volumetric modulated arc therapy (VMAT) which can be done in a conventional linear accelerator can produce similar dose distribution to tomotherapy, which has reduced the enthusiasm on tomotherapy. But in treatments like craniospinal irradiation, tomotherapy may score better.

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11 Electrons

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- Electron is a subatomic particle with negative charge of 1.602×10^{-19}.
- Discovered by J.J Thompson in 1897.
- Rest energy is 0.511 MeV.
- Mass is 1/1836 that of proton.
- Stable with mean lifetime of 6.6×10^{28} years.
- Radiation dosimetry: electron beam with energies between 1 and 50 MeV—ICRU 21(1972), ICRU 35(1984).
- Prescribing, recording, and reporting electron beam therapy—ICRU 71 in June 2004 (Fig. 11.1).

11.1 Sources

- Van de Graff generators (1930s).
- Betatron (1940s)
- Microton
- Linear accelerator (1960s) provides electron energies ranging from 4 to 25 MeV.

11.2 Interaction with Matter

Electrons while traveling through a medium interact with atoms (nuclei and electrons) of the absorbing medium by Coulomb's force of interaction (Tables 11.1 and 11.2).

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- Through these interactions electron continuously loses its kinetic energy, which is known as continuous slowing down approximation.
- Kinetic energy loss is described by mass stopping power (S/r) and scattering described by scattering power (T/ρ).

Depth dose curve (Fig. 11.2):

- *Most probable energy* (Ep): Most probable energy is the kinetic energy (K.E.) possessed by most of the incident electrons at phantom surface.
- *Mean energy* (E0): It is the mean energy of incident electron at the surface of patient. Mean energy is slightly less than Ep.
- *Range*: Range is the depth at which the electron loses all its kinetic energy in the absorbing medium.
- The *therapeutic range* is the depth of an isodose curve which covers the treatment volume. Usually depth of 90% isodose curve of electron beam is taken as the therapeutic range, rarely 80% isodose curve is selected.
- *Practical range (Rp)*: Point of intersection of the extrapolated line of bremsstrahlung tail and the tangential line through the dose falloff.
- *Maximum range (R_{max})*: Depth at which extrapolation of the tail of the central axis depth dose curve meets the bremsstrahlung

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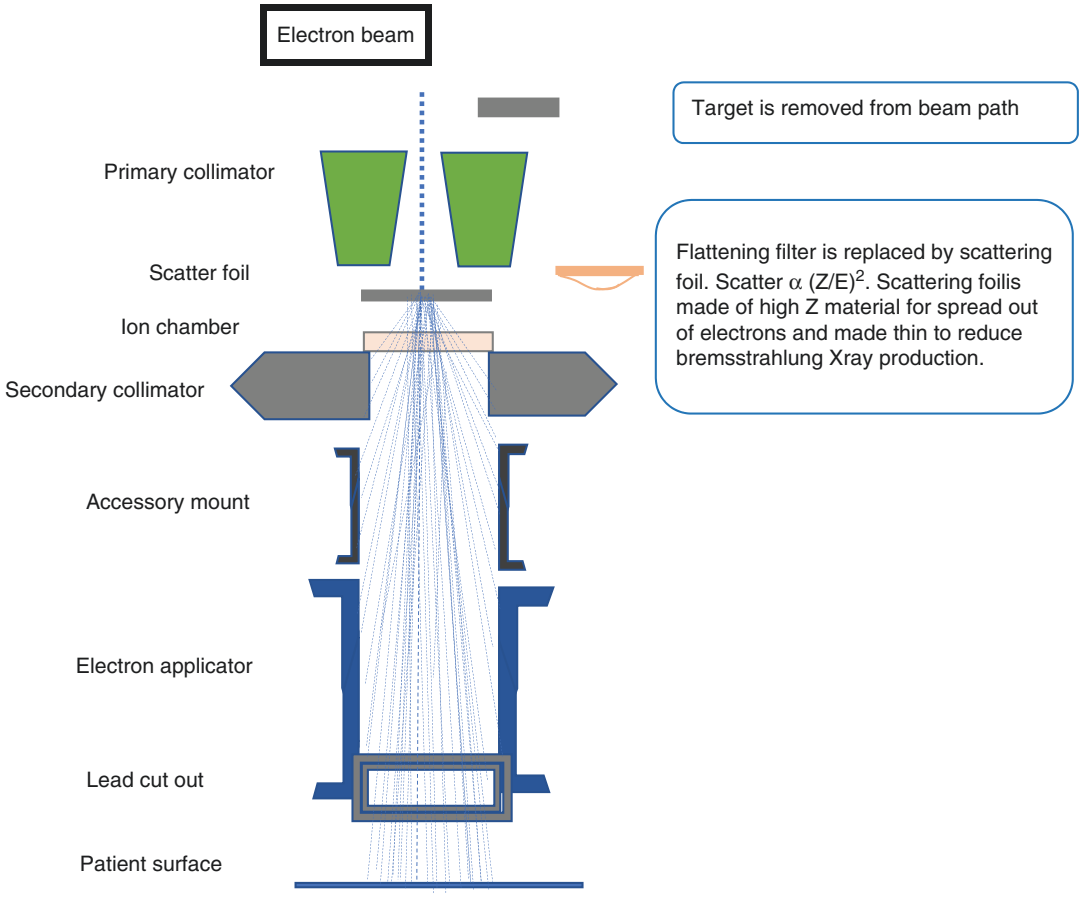

Fig. 11.1 A schematic representation of treatment head for electron beam

Table 11.1 Elastic collision of electrons

Elastic collision of electrons (no loss of kinetic energy)	With nucleus	Nuclear scattering	• Causes change in direction of incident electron (deflection and redistribution) • Scattering α (Z^2/K.E^2) • That is why high Z materials are used for making scattering foils
	With atomic electrons of absorbing medium	Electron–electron scattering	

background. It is the maximum penetration depth of electrons in absorbing medium.

- *R q*: Depth at which maximum dose level intersects with the tangents through the steepest curve of the electron depth dose curve.
- *R 90, R 80, R 50*: Depth at which the PDDs beyond the depth of maximum attains values of 90%, 80%, and 50% isodose, respectively.
- Z_{max}: Depth of maximum dose.
- *Dose build-up region* is the depth region between the phantom surface and the depth of maximum dose.

Depth dose distribution formulae for electrons:

- Depth of 90% isodose curve, R90 = E/3.2 cm.
- Depth of 80% isodose curve, R80 = E/2.8 cm.
- Depth of 50% isodose curve, R50 = E/2.33 cm.
- Practical range Rp = E/2 cm.
- Mean energy (E0) = 2.33 × R50.

Table 11.2 Inelastic collision of electrons

Inelastic collision of electrons (loss of kinetic energy)	• With atomic electrons of absorbing medium	Causes ionization and excitation (collision loss)	• Ionization and excitation occur in low atomic number material like water, tissue • Collision loss depends on electron density of the medium • α K.E. • Rate of energy loss is greater for low atomic number material (loss bound electron, higher electrons per gram) • The rate of energy loss is 2 MeV/cm
	Two types of collision process • Hard collision—the kinetic energy acquired by the ejected electron is large enough to cause further ionization • These electrons are known as secondary electrons or delta rays (contribute to dose build up) • Soft collision—ejected orbital electrons gain insufficient energy to ionize its own matter		
	• With nuclei	Produce bremsstrahlung X-ray (radiation loss)	• X-ray production is more for high Z material and higher energy electron • Radiation loss (bremsstrahlung) is proportional to energy and square of atomic number (α Z^2, K.E.) • Therefore X-ray production is more for higher energy electrons and with higher atomic number
	• Bremsstrahlung production 6–10 MeV → 0.5–1% 12–15 MeV → 1–2% 16–20 MeV → 2–5%		

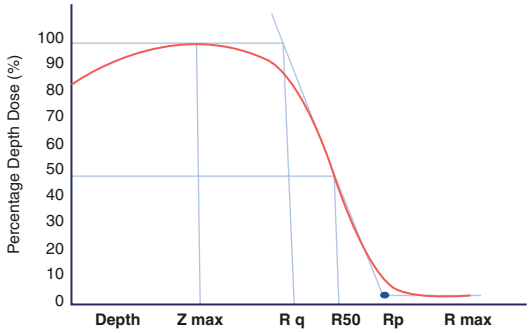

Fig. 11.2 Depth dose curve for electrons

Table 11.3 Surface dose and R90 of different electron energies

Energy (MeV)	R90 (cm)	Surface dose (%)
6	1.7	81
8	2.4	83
10	3.1	86
12	3.7	90
15	4.7	92
18	5.5	96

The electron energy is selected so that
R90 is more than the maximum depth of PTV
Rp is less than the minimum depth of critical structures

- Most probable energy Ep0 = 0.22 + 1.98Rp + 0.0025Rp2.
- Energy at depth Z (Ez) = E0 (1 − z/Rp).

11.3 Features of Electron Beam

- High surface dose, varying from 75% to 95%.
- Surface dose increases with increase in electron energy.
- There is no skin sparing effect.
- Lower energy scatters more and through larger angles, resulting in more rapid build-up region, but narrower depth.
- Dose build-up region is broader with higher energies.
- PDD increases as energy increases.
- There is rapid dose falloff beyond the maximum dose (Z_{max}).
- Electron beam energy selected should cover the target volume completely within 90% isodose curve.
- Mean deposition of energy in tissue is 2 MeV/cm.
- Bolus is used to achieve adequate surface dose of 90–100%.
- Table 11.3 shows surface dose and R90 of different electron energies.

11.4 Isodose Curves

- As the electron beam enters a medium scattering occurs and the beam expands rapidly below the surface.
- In the central region the isodose curves are flat and closely spaced.
- For low-energy beams all the isodose curve bulges out.
- For higher energies only the lower isodose curves bulge out, the higher isodose curves show lateral constriction, which becomes worse with decreasing field size
- 2E (in MeV) mm constriction for 90% isodose on each side for the higher energy electrons.

11.5 Effect on Field Size

- Lateral scatter equilibrium (LSE) exists when the electron fluence scattered away from an area is replaced by electrons scattering into that area.
- Minimum field radius for LSE (Req) is $Req \approx 0.88\sqrt{E_P}$, where E_p is the most probable energy.
- Minimum field size for a square to have LSE is E/2.
- When the field is reduced below that required for lateral scatter equilibrium, (Radius < Req).
  - D_{max} and R90 shifts to surface.
  - Surface dose increases.
  - PDD decreases.
  - Rp remains same.
- Thus, the depth dose distribution for small fields is field size dependent, while for large fields it is independent of field size.

11.6 Beam Obliquity

- Ideally, electron beam should be incident perpendicular to skin surface.
- As the beam obliquity increases,
  - D_{max} shifts towards surface.
  - Increased surface dose.
  - Reduces therapeutic range.
  - Penumbra decreases for surface close to source and vice versa.
- The effect becomes significant when the incident angle is 45 degrees or more.
- Bolus can be used to smoothen and reduce the obliquity.

11.7 Bolus

- Flatten out an irregular surface and reduce dose inhomogeneity.
- To increase the surface dose (to increase dose to skin or scar).
- Sparing of distal critical structures.
- Commonly used materials are paraffin wax, polystyrene, acrylic (PMMA), Super Stuff, Super flab, and Super-flex.

11.8 Air Gap

It is the separation between the end of the applicator cone end and the patient surface. The standard air gap is 5 cm. As the gap increases dose to the patient will decrease.

11.9 Field Matching

- Electron–Photon, when an electron field is matched with the photon field, hot spot will develop on the side of the photon field due to scattering of electrons from electron field.
- Electron–Electron, when two electron fields are matched there will be areas of hot spot due to bulging isodose curves and areas of cold spot depending on the field separation. At the region of junction there is non-homogenous dose distribution. Matching is even complex when the surface is irregular.

11.10 Field Shaping

- Electron applicators/cones help to hold the lead cutouts close to the patient surface and to collimate the beam.
- Electron applicators can be closed or open, with square or rectangular shape.

- Field shaping is done with lead cutouts of variable shape.
- For an irregularly shaped field, the radius in any direction must be greater than or equal to Req for the establishment of LSE.
- Internal shielding with lead or tungsten, to protect the normal structures at risk which are in close proximity to the target volume.
- Used in the treatment of lip, buccal mucosa, earlobe, and eyelid lesions with electrons.
- But the electron backscatter from the lead shield enhances the dose (at interface) to the tissue in contact with the shield.
- This dose due to electron backscatter can range from 30 to 70%.
- To reduce the effect of electron backscatter, lead shield is coated with suitable material of low-atomic number like wax.
- High density material, tungsten is also used for making eye shields. The acrylic/enamel coated tungsten can shield electron up to 9 MeV.
- The thickness of lead for shielding (mm) is given by E(MeV)/2.
- The density of Cerrobend is 20% less compared to lead. Therefore, thickness of Cerrobend is 20% greater than that of lead.
- Another 1 mm is added as safety margin.

$$\text{Thickness of lead} = \text{E} / 2\left(\text{MeV}\right) + 1\,\text{mm}$$

$$\text{Thickness of Cerrobend} = 1.2 \times \text{thickness of lead.}$$

11.11 Case Scenario 1 (Fig. 11.3)

For example, to treat a target volume of 3 cm depth, electron energy of 10 MeV is used. For calculating lead thickness for internal shielding, the energy reaching at shield tumor interface is calculated first. In this case it is 4 MeV (10 − (2 × 3)), 2 MeV is lost for each centimeter. For protecting the organ at risk, the lead thickness required for internal shielding is obtained by (4 MeV/2) + 1 mm = 3 mm. To reduce the backscatter electrons into the normal structure the lead is coated with low atomic material such as wax.

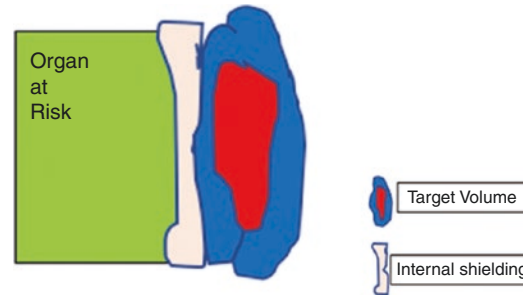

Fig. 11.3 Clinical example for electron planning

11.12 Extended SSD

- Reduction in output.
- Larger penumbra. (Minimized by placing collimation on the skin surface).
- Minimal change in PDD.

11.13 Heterogeneity Corrections

Dose distribution varies significantly in presence of tissue inhomogeneity such as lung or bone. The simplest correction for a tissue inhomogeneity involves the scaling of the inhomogeneity thickness by its electron density relative to that of water and the determination of the coefficient of equivalent thickness (CET).

The coefficient of equivalent thickness (CET) of a material is given by its electron density relative to the electron density of water (Table 11.4).

- In lung—1 cm thickness of lung is equivalent to 0.25 cm of tissue. Dose penetration in lung is 3–4 times that of unit density tissue. Beam that penetrates 1 cm in water would penetrate 4-cm depth in lung having a density of 0.25 g/cm^3.
- In bone—There will be cold spots beneath bone and hot spots lateral to bone.
- In air—Electron penetrates to deeper tissue and produces hot spot beneath the air cavity. There will be areas of hot and cold spots, at junction which produces dose inhomogeneity up to 20%.

Table 11.4 Coefficient of equivalent thickness of various tissues

Organ	Density (g/cm^3)	CET
Lung	0.25	0.25
Solid bone	1.6	1.6
Spongy bone	1.1	1.1
Air	0.0013	

11.14 Common Clinical Uses

- Posterior neck electron boost for nodes in head and neck malignancies.
- Post-mastectomy chest wall irradiation.
- Boost to the lumpectomy cavity in Ca breast.
- Skin malignancies.
- Superficial sarcomas.
- IMN irradiation.

11.15 Special Technique with Electron Beam

1. Total skin electron therapy.
2. Intraoperative electron beam therapy.
3. Total scalp irradiation.
4. Craniospinal irradiation.
5. Total limb irradiation.
6. Electron arc therapy.

Proton Therapy

12

Supriya Mallick

Researchers from the Lawrence-Berkeley National Laboratory were the first to use proton for clinical use in the 1950s. The first hospital based proton treatments started in 1990 and over the last 3 decades there has been a rapid explosion in the number of centers providing proton treatment.

Protons are positively charged subatomic particle with mass 1800 that of electron. Proton therapy is a type of ionized, particle therapy. Figure 12.1 shows type of radiation.

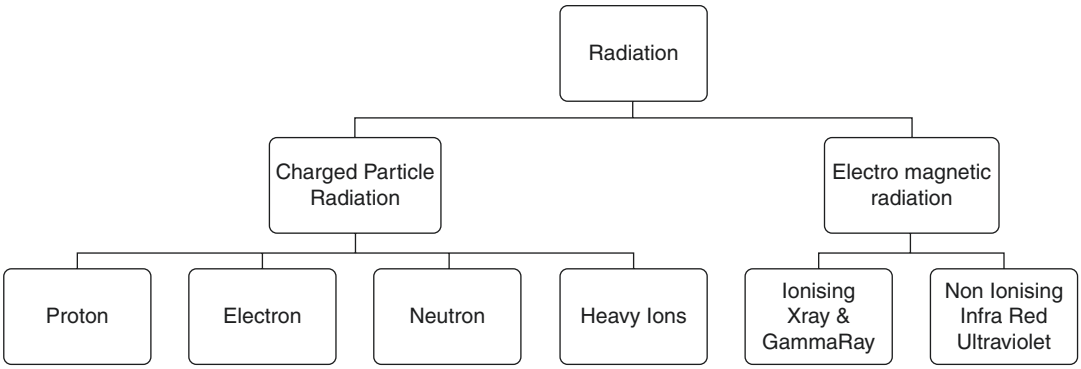

Fig. 12.1 Types of radiation

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12.1 Interaction of Protons

Protons interact with both electrons nuclei by

- Inelastic collisions.
- Elastic scattering.

12.2 Unit of Dose

- Dose delivered with protons are prescribed as Cobalt Gray Equivalents (CGE).

12.3 Advantage of Proton Over Photon

Conventional photon energy after incidence in the skin surface starts interaction and after a small build-up region deposits its maximum energy (D max). Thereafter energy deposition decreases exponentially with increasing depth in tissue. In that way photon energy has a skin sparing effect but it has a significant exit dose, and a high integral dose.

12.3.1 Proton Dose Distribution

- Depends on linear energy transfer (LET).
- Linear energy transfer is energy deposited per unit path length.
- Rate of energy loss of proton is proportional to the square of the particle charge and inversely proportional to the square of its velocity.
- Energy loss maximum particle—when velocity approaches zero (near the end of its range)—Bragg peak (Fig. 12.2).
- Rapid distal dose fall-off after Bragg peak occurs.
- Bragg peak of a mono-energetic proton beam is too narrow—Difficult to use clinically.
- Superimposition of Bragg peaks of different energies—wider depth coverage = spread-out Bragg peak (SOBP) [1] (Fig. 12.3).
- Lateral penumbra of proton beam at higher depth is slightly more than that of photon beam (few mm).

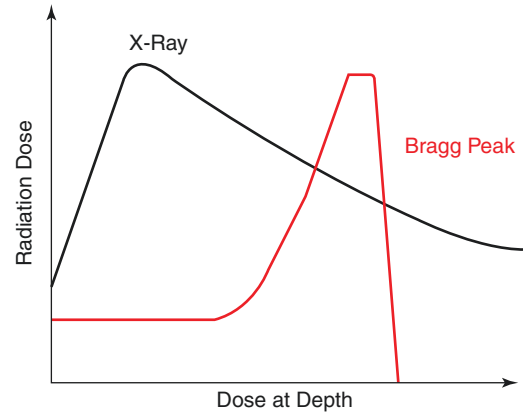

Fig. 12.2 Comparison of X-ray versus proton

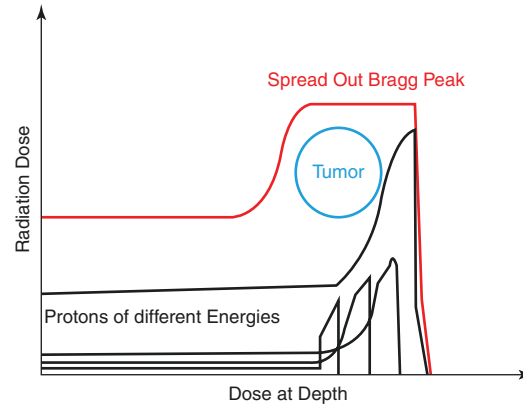

Fig. 12.3 Spread-out Bragg peak

12.3.1.1 Spreading of Braggs Peak

There are two methods for spreading the Bragg's peak, namely active modulation and passive modulation

- Active modulation—In active modulation the beam deflected by 2 magnetic dipoles to vary the energy of the beam. Although the treatment planning is more complex it allows for better tailored dose distribution.
- Passive modulation—In passive modulation fixed energy is attenuated by range shifters of variable thickness (Collimators & compensators). Treatment planning is simpler than active modulation but the treatment plan is sensitive to movements of the target.

Relative biological effectiveness (RBE): Dose of reference radiation is divided by dose of proton to achieve similar biological effect. A RBE value of 1.1 is applied to all proton beam treatments irrespective of other factors. The RBE may be higher at the Bragg peak due to higher LET at the end of range of the proton with some researchers quoting a RBE as high as 1.3 [2].

There is a steady increase of LET throughout the SOBP which is significant at the end of the SOBP. This results in an extension of the bio-effective range of the beam of a few mm and merits its consideration in treatment planning. This is more important for single field plans or close to a critical structure.

12.3.2 Parts of Proton Therapy System

1. Particle accelerator.
   (a) Cyclotron
      (i) Isochronous cyclotron
      (ii) Synchrocyclotron
   (b) Synchrotron
2. Beam line
3. Gantry
4. Delivery Systems
   (a) Passive scanning
   (b) Active scanning
   (c) IMPT

Protons are produced from hydrogen gas by electrolysis of deionized water or from commercially available hydrogen gas.

1. Particle accelerator
   (a) Cyclotron—A cyclotron consists of two D shaped hollow metal electrodes inside a vacuum chamber known as Dees (Fig. 12.4) which leads to a cylindrical space within them where the particles move. When static magnetic field B is applied perpendicular to the electrode plane and particles are injected in the center of the cylindrical space between the Dees, the particles path bends in a circle due to Lorentz force. A radio frequency alternating voltage is also applied between the Dees as a result of which each time the particles cross the gap from one Dee electrode to the other particles get accelerated. Due to this increasing speed the particles move in circle with increasing radius in each rotation outward from the center of the Dees. Upon reaching the periphery a small voltage on a metal plate deflects the beam and directs it to hit a target located at the exit point.

   Advantage of cyclotron over Van de Graaff generator:
   (i) In Van de Graaff generator particles are accelerated by voltage and the particles' energy is equal to the accelerating voltage.
   (ii) In cyclotron particles encounter the accelerating voltage and leads to very high output energy.

   (b) Synchrocyclotron
   In synchrocyclotron frequency of the driving radio frequency electric field is varied to compensate for relativistic effects as the particles' velocity begins to approach the speed of light.

   (c) Isochronous cyclotron
   In the isochronous cyclotron, magnetic field increases with radius, rather than with time. It requires azimuthal variations in the field strength to produce a strong focusing effect and to keep it in the spiral trajectory.

   (d) Synchrotrons
   In synchrotrons both the magnitude of the magnetic field and the RF frequency are varied to maintain a synchronous particle at a constant orbit radius. The beam aperture is small and the magnetic field does not cover the entire area of the particle orbit reducing the cost of the machine. Various particle accelerators are summarized in Table 12.1.
2. Beamline
   (a) The beam exiting from the accelerator has a clinically effective range of 70-250 MeV.
   (b) The beam is directed by a di-pole magnet and shaped with the help of a quadrupole magnet.

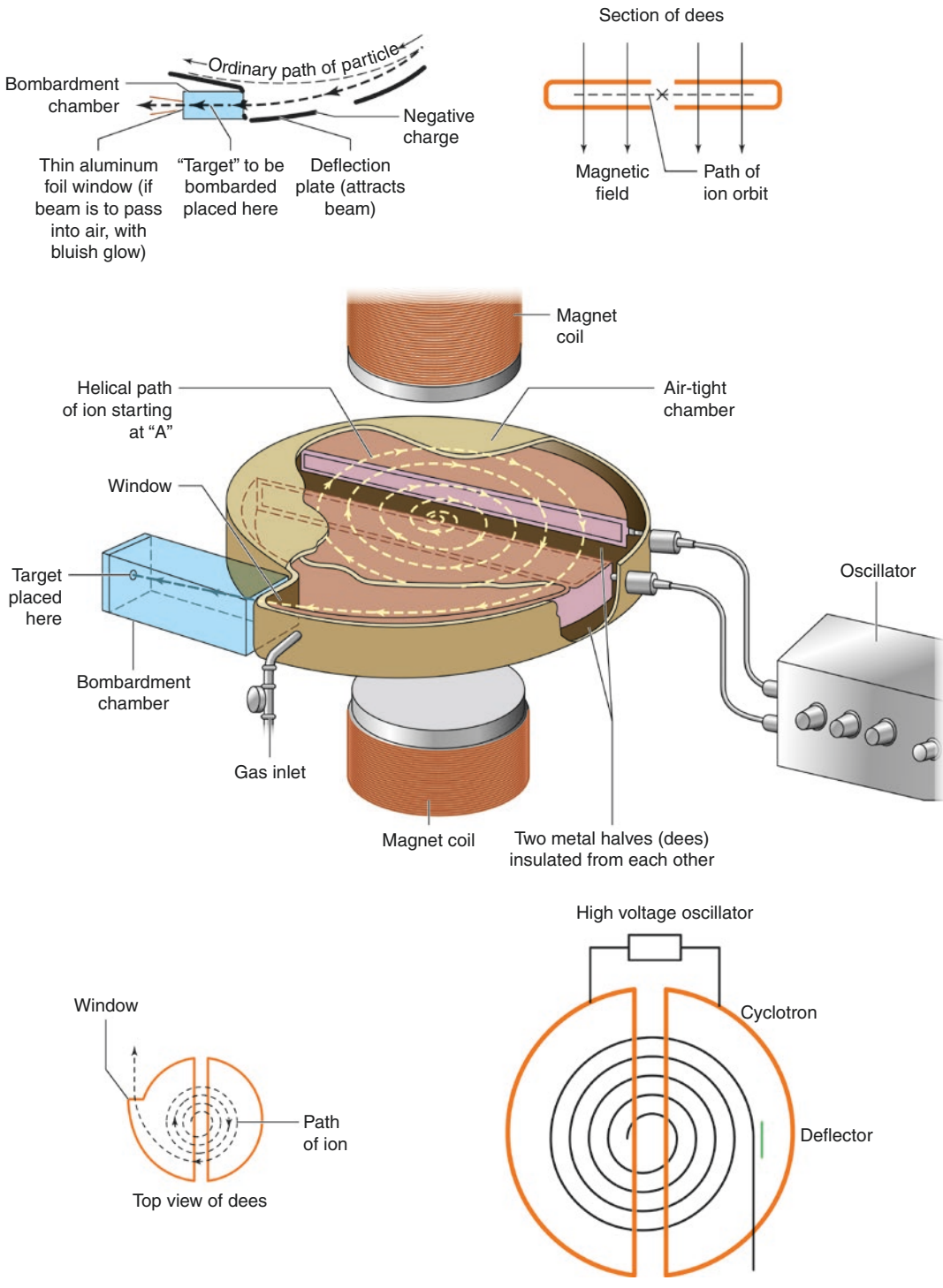

Fig. 12.4 Schematic representation of a cyclotron

Table 12.1 Accelerator technology comparisons

Type	Synchrotron (rapid cycle)	Synchrotron (slow cycle)	Cyclotron
Energy level selection	Continuous	Continuous	Fixed
Size (diameter) (m)	10	6	4
Average power (beam on) (kW)	200	370	300
Emittance (RMS unnorm.) (μm)	0.2	1–3	10
Repetition rate (Hz)	60	0.5	Continuous
Duty factor (beam-on time)	Pulses	20%	Continuous

Fig. 12.5 Parts of a proton treatment system

(c) As proton beam with variable energy may be required to form the SOBP, the beam passes through a wedge shaped graphite filter known as beam degrader.

3. The proton beam produces significant neutron production near the degrader.
4. Gantry: The gantry is a large structure to enable protons with therapeutic energies bent. In addition it accommodates different beam monitoring and beam shaping devices (Fig. 12.5). In the treatment nozzles ionization chambers may consist of parallel electrode planes divided into horizontal and vertical strips for quantification of the lateral uniformity of the radiation field. The nozzle has snout, which allows attachment of compensator and aperture as required.
5. Delivery Systems
   (a) Passive scattering.
   In case of small fields a single lead scattering foil is applied to broaden the beam. But single scattering is not adequate for larger field sizes and may require double-scattering.
   (b) Scanning: Scanning is done in x–y axis perpendicular to the beam.
      (i) Discrete spot scanning: In this beam is delivered to a static position and once delivered it is moved to the next spot.

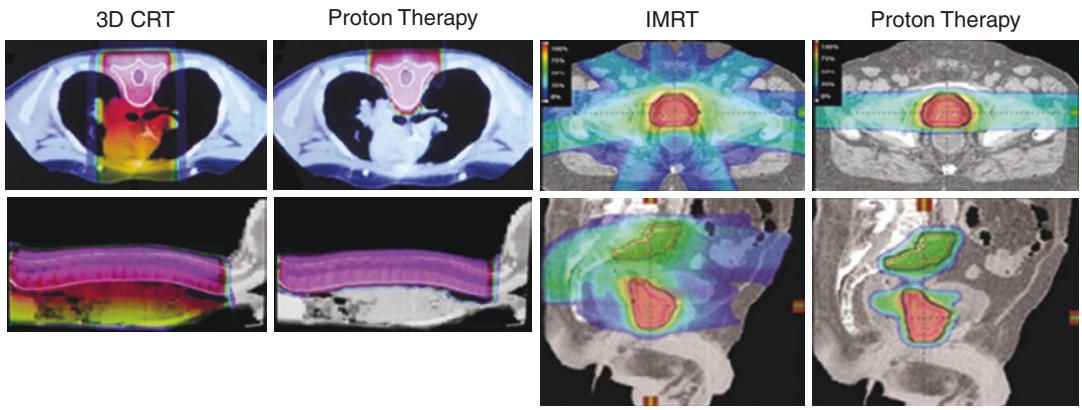

Fig. 12.6 Comparison of IMRT vs proton treatment for craniospinal irradiation and prostate

(ii) Raster scanning: It is similar to spot scanning but the beam is not switched off during transition from point to point.
(iii) Wobble scanning.
(iv) Dynamic scanning: beam is scanned continuously across the target volume.

12.3.2.1 Planning

- Broad based: With the introduction of pencil beam models broad beam models are being replaced gradually.
- IMPT: IMPT has the following advantages:
  - Improved dose conformality and steeper dose gradients,
  - Further reduction of integral dose,
  - Less sensitivity to range uncertainties and other sources of uncertainty.

12.3.2.2 Indications

- Standard Indications [3]
  - Pediatric tumor
  - Skull base tumor
  - Ophthalmic tumor
  - Carcinoma prostate
  - Brain tumor
  - Craniospinal irradiation
- Evolving evidence
  - Lung cancer
  - Breast cancer
  - GI cancer

Figure 12.6 shows IMRT vs Proton treatment for Craniospinal irradiation and Prostate cancer.

12.3.2.3 Advantages

1. Exit dose less—reduces toxicity
2. In pediatric tumor—reduces chances of second malignancy
3. Skull base/ophthalmic tumor in proximity to critical areas—treatment with required dose
4. In prostate and other malignancy—dose escalation is possible, this may result in better outcome

12.3.2.4 Disadvantages

1. For large depths the penumbra for proton beams is wider than photons

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Radiation Facility Development

13

Ritesh Kumar and Divya Khosla

International Agency for Research on Cancer has estimated that there were 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 [1]. There is a gradual increase in cancer burden worldwide [2]. Radiotherapy is an integral component of multimodal cancer treatment and approximately 50–60% of people who develop cancer will require radiotherapy at some point [3]. Therefore, for an effective management strategy for cancer, radiation facility is essential and should be within reach of patients [4]. Establishment of radiation facility is expensive, and different newer machines are required in a tertiary care center to deliver the state-of-the-art treatment to the patients. A radiation oncologist needs to be in the forefront for creation of an effective radiation facility. This chapter will concentrate on the basics on creation of a radiation facility.

13.1 Location

The location of the department is according to the radiation protection guidelines for the design of structural shielding for radiation installations (NCRP Reports 49 and 51). Radiation facility is best located where it adjoins the earth on several sides and has no departments below, thus the basement or ground floor would be the most suitable location. It should have mandatory thick walls and ceilings for radiation protection and required access for the placement or removal of equipment. It should be near to the outpatient department and transport facilities as most of the patients are outpatients.

13.2 Radiotherapy Equipment

The radiotherapy equipment required in a tertiary care institute comprises of teletherapy units and brachytherapy units. Teletherapy machines deliver radiation from a distance, i.e., radiation sources are at a distance of 80–100 cm from the patient. Brachytherapy machines deliver radiation from a short distance, i.e., radiation sources are placed inside or near the tumor [5].

13.3 Teletherapy Units

1. Telecobalt

   Telecobalt was earlier one of the most widely used machines for the teletherapy treatment. It uses Cobalt-60 radioisotope which emits high energy gamma rays that are used for the treatment. It is a simple and relatively cheap machine. The radioactive source has to be replaced every 5–10 years.

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2. Linear Accelerator

   Linear accelerator (LA) electrically generates high energy X-rays for the treatment. It is now the most widely used machine worldwide for the teletherapy treatment. With improvement in technology, various modifications have been incorporated in a LA to deliver high-tech radiation modality in form of
   (a) 3DCRT (Three Dimensional Conformal Radiation Therapy)
   (b) IMRT (Intensity Modulated Radiation Therapy)
   (c) VMAT (Volumetric Modulated Arc Therapy)
   (d) IGRT (Image Guided Radiation Therapy)
   (e) SBRT (Stereotactic Body Radiotherapy)
3. Gamma Knife

   This is a high precision radiotherapy machine for treating small intracranial tumors. It delivers very high dose of radiation to a small area in brain with a high degree of accuracy while effective sparing of critical normal structures. It uses Co-60 as radiation source. This technique is known as stereotactic radiosurgery (SRS).
4. Simulator

   A simulator is a machine which simulates the teletherapy machine and is used for radiation treatment planning. Various types of simulators are required as per the treatment plan, i.e.,
   (a) Conventional simulator—2-dimensional treatment planning
   (b) CT-simulator—3-dimensional treatment planning (3DCRT/IMRT)
   (c) 4D-simulator—Respiratory gating is possible (IGRT)

13.4 Brachytherapy Units

1. Sources

   Radioisotopes are required to deliver the brachytherapy treatment. The most common and widely used radioisotope for brachytherapy is Iridium-192 (Ir-192). Other radioisotopes used are Cesium-137, Iodine-125, Palladium-103, and Gold-198 [6].
2. Equipment

   The machine stores the radioisotope in safe position and the isotope is moved near the tumor as per the required dose and treatment planning. Thus, a very high dose to the tumor is delivered in a short time with sparing of normal tissues.
   (a) LDR (low dose rate) equipment
   Delivers radiation at low dose rate (0.2 to 2 Gy per hour)
   Radium-225 is used as radioisotope
   Requires inpatient admission. Cannot be done on outpatient basis.
   (b) HDR (high dose rate) equipment
   Delivers radiation at high dose rate (>12 Gy per hour)
   Iridium-197 is used as radioisotope
   Can be done on outpatient basis
3. Operation theater

   Brachytherapy facilities require anesthesia in most of the cases. Thus, operation theater facilities are required. A dedicated brachytherapy suit operation theater is preferred.

13.5 Personnel Requirements

The organizational team consists of radiation oncologists, medical physicists, radiation technologists, nurses, counsellor, and a dietitian [7].

1. Radiation oncologist

   The head of the radiotherapy department is a radiation oncologist. Radiation oncologist is a doctor who is trained in the use of radiotherapy and is responsible for prescribing and supervising radiation treatment.
2. Medical physicists

   A radiation expert—who helps to plan the treatment with the oncologist. Together they will decide the best way of giving the prescribed amount of radiation. The physicist is also responsible for making sure the radiotherapy equipment is used accurately. He monitors the technical issues and radiation safety issues.
3. Technologists

   Operate the machine and deliver the prescribed radiation dose to the patient. They are trained in giving radiotherapy and in patient care. They help patients cope with any problems during the treatment, can give

information, support, and counselling. They work closely with radiation oncologist and a physicist to plan and execute radiation treatment.

4. Mould room assistant

   A technical staff who prepares accessory devices which are used in patient treatment and radiation beam modification.

5. Nurses

   Nurses look after patient's general needs such as dressings and medicines. The nurses also give information and advice about the treatment, as well as practical support.

6. Dietitian

   A dietitian advices regarding dietary management during radiotherapy, problems of eating and drinking during the radiotherapy treatment (for example—difficulty in swallowing or a dry mouth).

7. Speech and language therapists

   A speech and language therapist helps the patients receiving radiation to neck region regarding the voice changes and recovery after radiotherapy.

8. Social worker

   Social worker gives advice about any non-medical problems including practical and financial help. Social workers can also provide or arrange counselling and emotional support for the patient and family.

9. Palliative care team

   Gives extra help and support to people with symptoms or side effects of treatment that are causing problems. Palliative care is specially important for terminally ill patients.

13.6 Requirements and Guidelines for Procurement of Radiation Equipment [7]

1. Clearance of the radiation therapy unit by the national regulatory board
2. Approval of room layout plan of radiation therapy installation
3. Appointment of radiation therapy staff
4. Nomination and approval of radiological safety officer
5. Procurement of Personnel Monitoring Devices for monitoring of radiation dose
6. Measuring and monitoring instruments
7. Authorization to procure radiation sources
8. Road transport approval
9. Receipt of sources
10. Installation of the unit
11. Loading of the source/switching on radiation in case of radiation generating equipment
12. Quality assurance/acceptance test
13. Commissioning approval for patient treatment
14. Periodic performance/quality assurance test
15. Annual status report

13.7 Radiation Protection

A radiation protection program is defined as the sum of all methods, plans, and procedures used to protect the health and environment of personnel from exposure to sources of ionizing radiation. The principle of ALARA (as low as reasonably achievable) is followed. The authority of the Radiation Safety Program is delegated to the Director, Radiation Safety Officer (RSO), and ultimately to the Radiation Safety Committee.

Monitoring in radiation protection is essentially required to assess compliance with established dose limits. Personnel monitoring, area monitoring, and environmental monitoring need to be performed to ensure radiation safety [8].

1. Personnel monitoring

   Personnel monitoring is performed by making external and internal dose measurements. Thermoluminescent dosimeters (TLD), film badges, fast neutron monitors, and direct reading dosimeters are used for external dose measurement on personnel.

2. Area monitoring

   Area monitoring includes measurement of radiation dose rates, airborne activities, and surface contamination. Monitoring devices like ionization chamber, proportional counter, Geiger Muller tube, and scintillation detector are used.

3. Environmental monitoring

   Environmental monitoring is used to detect any significant increase of radiation dose above background.

13.8 Disposal of Radiation Waste

Improper disposal of radioactive waste presents potential hazards to the general public. The program director and the RSO are responsible for the proper storage and disposal of radioactive waste. Radioactive waste should be stored properly in closed containers and should be labeled with a "Caution Radioactive Material" sticker. The standard operating procedures for disposal of radioactive sources are mentioned below [8].

1. The licensee/authorized user initiates necessary regulatory procedures with the help of RSO.
2. The RSO helps the licensee in filling up the relevant regulatory forms and coordinate with the AERB for obtaining necessary approval for the safe disposal of radioactive sources.
3. The permission to transport the radioactive waste is also obtained from AERB.
4. The decayed/disused radioactive sources are sent to the original supplier of the source.
5. Under no conditions, the radioactive waste is treated as ordinary waste or abandoned/disposed off in public.

13.9 Conclusions

Radiotherapy facilities form an important part of comprehensive cancer care in a tertiary care institute. It requires a team approach including radiation oncologists, medical physicists, radiation technologists, mould room assistants, and other support staff. Radiation machines have high technological requirements, and radiation safety issues are the most important aspect which cannot be overlooked.

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Intraoperative Radiotherapy

14

Supriya Mallick and Goura K. Rath

Intraoperative radiotherapy (IORT) enables delivery of radiation directly to the operated tumor bed in the operation theater, thereby reduces the requirement of extra anesthesia and completes entire adjuvant treatment or the boost phase of the adjuvant radiation.

14.1 Types

1. Intraoperative HDR brachytherapy:
   (a) Hamburg applicator
   (b) Freiberg applicator
2. Mobile intraoperative electron accelerator:
   (a) Mobetron- ELIOT
   (b) LIAC

   A summary of mobile intraoperative electron accelerator is shown in Fig. 14.1.
3. Mobile X-ray based equipment (Fig. 14.2):
   (a) Intrabeam (Zeiss)—Intrabeam comes with XS4 miniaturized linear accelerator with an inbuilt internal radiation monitor for real time dose monitoring
   (b) Papillon (Ariane)
   (c) Xoft (iCAD)

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Equipment	Mobetron	LIAC-HWL
	Self-shielded electron-beam linear accelerator (LINAC) machine, Integrated Shielding	Self-shielded electron-beam linear accelerator (LINAC) machine
Energy	6 MeV, 9 MeV, 12 MeV	4, 6, 8, 10, 12 MeV:
Dose Rate	10 Gy/Min	10 Gy/Min
Indication		
Applicators	Range of field sizes from 3 to 10 cm in . 5 cm increments. Bevel angles: 0°, 15°, 30°, 45° Precise Soft Docking Alignment	PMMA applicator, Bevel angles: 0°, 15°, 30°, 45° Hard Docking Alignment
Stray radiation		0.2 μsV/Gy at 3 m
Image		

Fig. 14.1 Mobile intraoperative electron accelerators

Equipment	Intrabeam	Papillon	Xoft
Energy (kV)	50	50	40, 50, 60
Current (mA)	0.04	0.1, 0.5	0.3
Indication	Breast, Skin, Brain, GI	Breast, Rectum, Skin	Breast, Skin, Gynecology
Image			

Fig. 14.2 Mobile X-ray based intraoperative brachytherapy machines

14.2 Comparison of Intraop Electron vs. Intraop HDR Brachytherapy

Intraop electrons are costlier but less time consuming than intraop HDR brachytherapy. Other differences are described in Table 14.1.

Table 14.1 Comparison of intraop electron vs. intraop HDR brachytherapy

Intraop electron	Intraop HDR brachytherapy
Costlier	Cheaper
Treatment time 2–4 min	Treatment time 4–30 min
Total procedure time less 30 min	More time 60–120 min
Only in accessible locations	Any area

14.3 Applicators

The common applicators and peculiarities of applicators are summarized in Fig. 14.3.

14.4 Clinical Uses

Patient selection is very important for successful implantation for intraoperative radiotherapy protocols. Generally patients selected are those in whom surgery alone is unlikely to achieve good local control and close margins are anticipated and EBRT alone may not give adequate doses for tumor control.

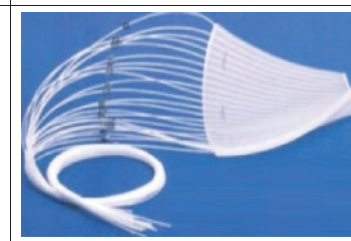
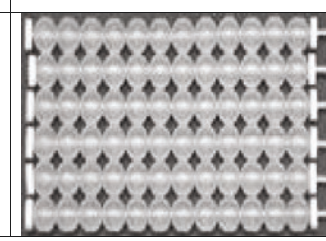
Applicator	Commend	Image
Flat Applicator	Surgically exposed surfaces	
Surface Applicator	Tumors on the surface of the body	
Needle Applicator		
Hams Applicator	Silicone rubber 8mm in thickness Catheters spaced 1cm apart Flexible	
Frieberg Applicator	Large and curved anatomies Easy to match treatment area Reproducible dosimetry	

Fig. 14.3 Common applicators used for intraoperative radiotherapy

Table 14.2 Important trials on intraoperative radiotherapy

Trial	Comparison	Dose	Inclusion Criteria	Result
ELIOT trial, Phase III (n = 1305)	EBRT vs. IOERT	21 Gy	Age ≥48 and <75 Unifocal breast carcinoma ≤2.5 cm	Local recurrence (LR) rate 4.4%
TARGIT-A Phase III, (n = 3451)	EBRT vs. IORT	20 Gy	Age ≥45-years Breast cancer T1–T2 ≤ 3.5 cm, N0–1	5 year LR: 1.3% vs. 3.3% 2.5% non-inferiority margin not achieved
TARGIT-B	IORT boost with EBRT boost	20 Gy	EBC with high risk of local recurrence	NA
TARGIT-E Phase II (n = 265)	IORT	20 Gy	Age ≥7 years Unifocal breast cancer, cT1c N0 M0, IDC, No LVSI	Ongoing

Another potential advantage of IORT is the higher biologic effectiveness of a single dose of IORT. The main dose limiting structure especially in sarcomas of extremity, pelvis, or retroperitoneum is peripheral nerve.

Indications—stomach, pancreas, retroperitoneal and pelvic sarcomas pelvic, breast [1–3]. Important trials on intraoperative radiotherapy are summarized in Table 14.2.

14.5 IORT Dose

- Boost 10 to 20 Gy, depending on the amount of tumor remaining after maximal resection
- Breast IORT: 20–21 Gy.

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Part II

Practical Brachytherapy

Evolution of Brachytherapy

15

V. R. Anjali

	• Wilhelm Conrad Roentgen is a German physicist • Discovered X-ray in 1895 • First Nobel Prize for Physics in 1901 • Radioactive element Roentgenium 111 is named after him
	• Marie Curie and Pierre Curie • In 1898, extracted radium from pitchblende ore • Coined term radioactivity • Pierre Curie—Nobel Prize for Physics (1903) • Marie Curie received Nobel Prize for Physics (1903) and Chemistry (1911) • Discovered radioactive element polonium

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15.1 Dosimetric Systems in Intracavitary Brachytherapy

1. Stockholm system
2. Paris system
3. Manchester system

15.1.1 Stockholm System

- Introduced in 1910 by Gosta Forssell et al. in Radiumhemmet.
- Fractionated course of radiation in 2–3 applications over 3 weeks.
- Each treatment lasting for 20–30 h separated by 1 week.
- Flexible intrauterine rubber tubes with 30–90 mg of radium.
- Vaginal applicators/boxes (silver/gold) contained 60–80 mg of radium.
- Uterine and vaginal applicators are not fixed to each other, held in approximation by gauze packing.
- No fixed geometry was present.
- Used unequal loading pattern in uterine and vaginal applicators.
- Total dose of 6500–7100 mg Ra was prescribed, and 4500 mg Ra was from vaginal applicator, dose rate of 110R/h.

15.1.2 Paris System

- Developed in 1919 by Regaud, Lacassagne et al. at Institute of Radium, Paris.
- Single application.
- Treatment time of 120 h (5–8 days).
- Intrauterine tubes with three radioactive sources with source strength of ratio 1:1:0.5(13.33, 13.33, 6.66 mg).
- Vaginal applicators as two cork colpostats connected to each other by metallic spring.
- Not a fixed geometry.
- Total dose of 7200 mg–8000 mg h Ra.
- Contribution from intrauterine and vaginal applicators were equally divided ~ 3600–4000 mg h Ra from each.

15.1.3 Manchester System

- Described by Todd and Meredith in 1938 at Holt Radium Institute.
- Fractionated dose in two applications.
- Each treatment duration of 72 h (total 144 hours) with 4–7 days gap between each treatment.
- Intrauterine tube
  - Thin intrauterine rubber tubes are used—two standard lengths of 4 cm and 6 cm and one nonstandard length of 3.5 cm.
- Vaginal ovoids
  - The ovoids are fixed and held apart by spacer at distance of 1 cm. In narrow vagina ovoids are held in position by washers.
  - Largest ovoid is placed to obtain maximum lateral throw off.
- Defined 1 unit as 2.5 mg of radium filtered by 1 mm Pt, and all loadings in the intrauterine tube and ovoids were made in terms of integral multiples of this unit.
- Tables 15.1 and 15.2 describe loading pattern for intrauterine tubes and ovoids

15.1.3.1 Defined

- Paracervical triangle—The loose areolar fascia between the broad ligament is the parametrial fascia and the firm supporting tissue surrounding cervix is paracervical fascia. Paracervical triangle is roughly pyramidal in shape, with its base resting on the lateral fornix and the apex curving round with the anteverted uterus. Dose to this region gives tolerance dose for normal tissue.

Table 15.1 Loading pattern for intrauterine tubes, from fundus to cervix

IU Tubes	Length	Units	Total radium (mg)
Long	6	6-4-4	35
Medium	4	6-4	25
Short	2	8	20

Table 15.2 Loading pattern for ovoids

Ovoids	Diameter (cm)	units	Total radium
Large	3	9	2.5 × 9 = 22.5 mg
Medium	2.5	8	2.5 × 8 = 20 mg
Small	2	7	2.5 × 7 = 17.5 mg

Table 15.3 Summary of Stockholm, Paris, and Manchester system for brachytherapy

Dosimetric system	Stockholm system	Paris system	Manchester system
Year	1910	1912	1930
Number of fractions	Fractionated	Single application	Fractionated
Treatment duration	2–3 fraction, each treatment period 20–30 h, separated by 1 week Treatment over 1 month	Treatment over 120 h in 5–8 days	In 2 fractions, 1 week apart Each treatment over 72 h Total treatment of 144 h
Intra uterine tubes	Rubber with 30–90 mg of radium	Rubber tubes	Rubber tubes
Intravaginal	Vaginal boxes with 60–80 mg of radium.	Cork/vaginal Colpostats	Ovoids
Loading pattern	Unequal	Equal	Unequal
Geometry	Not fixed	Not fixed	Not fixed
Total dose	6500–7100 mg-h 4500 by vaginal boxes	7000–8000 mg-h Over 5 days	7500R at point A
Dose rate	110R/h	45R/h	53R/h

- Point A is 2 cm lateral to the central canal of the uterus and 2 cm from the mucous membrane of the lateral fornix in the axis of the uterus. It reflects the dose to the paracervical triangle.
- Point B is 5 cm from the mid-line and on the same level as Point A. It gives the dose received by obturator nodes.
- Aim is to deliver an exposure of 8000 R at 55.5 R/h to Point A and 3000R to Point B.
- Table 15.3 summarizes Stockholm, Paris, and Manchester system for brachytherapy

15.2 The Fletcher Technique

- Developed by Fletcher et al. at MD Anderson Hospital in 1940.
- Combined dosimetry from Paris and Manchester system.
- Tandem and ovoids were designed for the use of *preloaded* radium source.
- Used high density metal (tungsten alloy) shields to reduce the dose in antero-posterior direction, without compromising dose to the paracervical region.
- The rectal and bladder shields were present in ovoids.

15.3 Modified Fletcher Techniques

15.3.1 Fletcher Suit Modification

- In the 1960s Suit et al. modified the Fletcher applicator for using *afterloading* technique with standard *radium* tubes to reduce the radiation exposure.
- The afterloading ovoids are of the same diameter as the Fletcher ovoids, but are 1 mm longer.

15.3.2 Fletcher Suit Delclos (FSD) Modification

- In the 1970s Delclos developed mini ovoids with diameter of 1.6 cm and flat medial surface, for using in narrow or distorted vagina.
- No shields were used for mini ovoids.
- Smaller diameter and no shielding resulted in high vaginal surface dose.
- It was compatible with remote afterloading technique.

15.3.3 Fletcher Green Modification

- Green et al. modified the Fletcher applicator with afterloading ovoids, less bulky, round handles, and a simpler radium holder mechanism.

For the Fletcher family of colpostats due to shielding of ovoids, the radiation dose in the anterior posterior direction is reduced by 15–25%. But after considering the dose from the uterine tandem the net reduction in dose intensity is ~10–15%

15.4 Henschke Applicator

- In 1960, Henschke developed a flexible applicator system to permit *manual afterloading*.
- Radioactive sources of cobalt 60, iridium 192, cesium 137, or radium were used.

15.5 Tandem and Ring Technique

- Intrauterine tandem of varying angle and length, and ring of different diameter.
- Vaginal ring is perpendicular to the tandem and lies in the fornix.
- E.g.: Vienna ring applicator (Fig. 15.1)

15.6 Tandem and Cylinder Technique

- Narrow vagina.
- To treat varying length of vagina.
- Intrauterine tandem of varying length.
- Vaginal cylinders of varying diameter from 2 to 4 cm are available.
- Superficial lesion <5 mm in vagina.
- Figure 15.2 shows tandem and cylinder applicator

15.7 Tandem and Mold Technique

- Creteil method
  - One intrauterine source and two vaginal sources. Alginate impression/acrylic mould of vagina is taken.
  - Uses ^{192}Ir wires.
  - The maximum dose prescribed is 60 Gy.
- Institut Gustave Roussy method
  - Intrauterine source of varying length covers at least lower two third of the uterus.
  - Two vaginal sources, parallel to each other.
  - A dose of 60 Gy is prescribed to this reference isodose.

15.8 Dosimetric System for Interstitial Brachytherapy

1. Paterson–parker system/Manchester system
2. Quimby system
3. Paris system

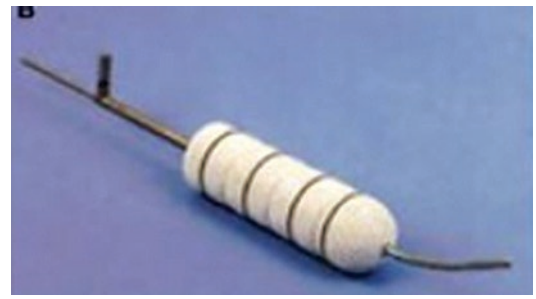


Fig. 15.2 Tandem and cylinder applicator

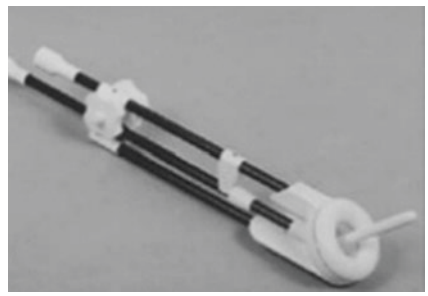
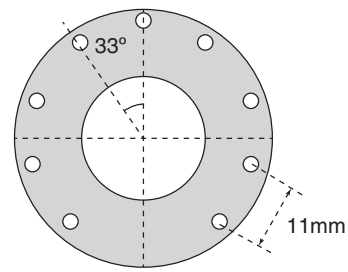


Fig. 15.1 Vienna ring applicator



15.8.1 Manchester System*Paterson–Parker System*

- The Manchester system was developed by Ralston Paterson (radiation oncologist) and Herbert M Parker (physicist) at Holt Radium Institute, Manchester in the 1930s.
- Non-uniform distribution of activity to yield uniform distribution of dose.

15.8.1.1 Distribution Rules for Planar Implantation

- Needles to be arranged in parallel to each other in a row.
- Spacing between the needles should not be more than1cm.
- Deliver a uniform dose of ±10% from the prescribed or stated dose throughout the volume to be treated.
- Active ends are crossed by crossing needles at right angles to the implant and placed not more than 1 cm from active ends.
- If ends are uncrossed effective area of dose uniformity is reduced. The area is reduced by 10% for each uncrossed end for planar implant.
- If multiple planes are used, the separate planes should be arranged as for single planes, parallel to each other, and if they differ in area, then the average area is used to determine the mg-hrs and the activity is proportioned to each plane. Figure 15.3 summarizes the types of implants.
  - The rules for the Manchester system are established for geometrical volumes of tissues: either slabs of uniform thickness of rectangular area or cylinders and spheres.
  - The given target volume is included in such a volume for the implantation.
  - Sources are distributed based on the size of the target area, with more source strength concentrated in the periphery for compensating for the dose fall-off, thereby improving dose uniformity.
  - Ratio of amount of radium in periphery and center depends on the area of implant (Table 15.4).
  - Correction factors are used for plane separations larger than 1 cm in order to achieve dose homogeneity of ±10% than the prescribed dose (Table 15.5).
- Mid plane dose for thick target volumes can be as much as 20–30% lower than the prescribed dose.

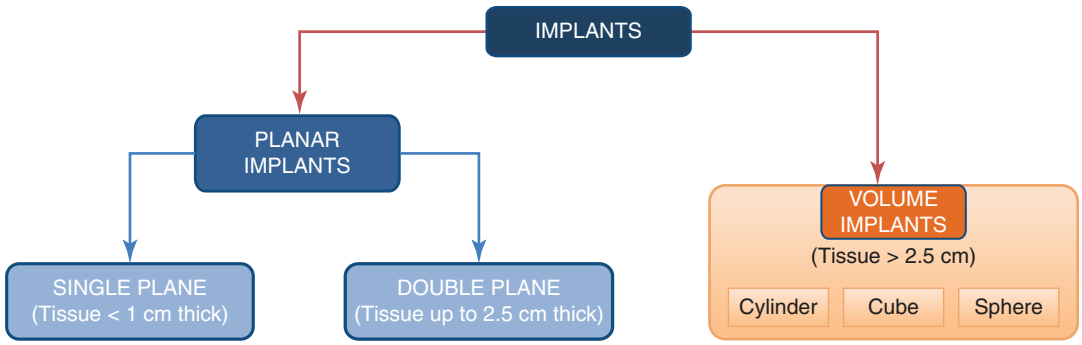


Fig. 15.3 Types of implants

Table 15.4 Table showing area, fraction used in periphery, and activity at center

Area (cm^2)	Fraction used in periphery	Activity at center
<25	2/3	1/3
25–100	½	½
>100	1/3	2/3

Table 15.5 Table showing correction factor for various separation

Separation (cm^2)	Correction factor
1.5	1.25
2.0	1.4
2.5	1.5

15.8.1.2 Volume Implant

- Tumor containing tissue is encompassed in simple geometric form such as cylinder, sphere, or cube.
- Sources are placed as evenly as possible not more than 1.0 to 1.5 cm apart.
- Volume is considered with 75% activity at surface and 125% activity at the core (Table 15.6).
- Activity divided into eight parts and distributed depending on the shape of the volume (Table 15.7).
- For volume implant, 7.5% is reduced from volume for each uncrossed end.
- Volume implants have different sets of rules and tables.
- Table reading is correct, where all dimensions are equal or the longest side or diameter is less than 1.5 times the shortest.
- When ratio exceeds the limit, correction for elongation is required (Table 15.8)

Table 15.6 Table showing activity at core, ends and outer parts

Outer part/rind/belt	50% activity
Core	25% activity
Ends	12.5% activity on each end.

Table 15.7 Table showing activity divided depending on the shape of the volume

Sphere	Cylinder	Cube
Belt—6 part Core—2 part	Belt—4 part Core—2 part Ends—2 part	Belt—6 part Core—2 part

Table 15.8 Elongation factor and elongation correction

Elongation factor	Elongation correction (%)
1.5	3
2.0	6
2.5	10
3	15

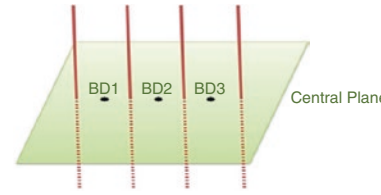
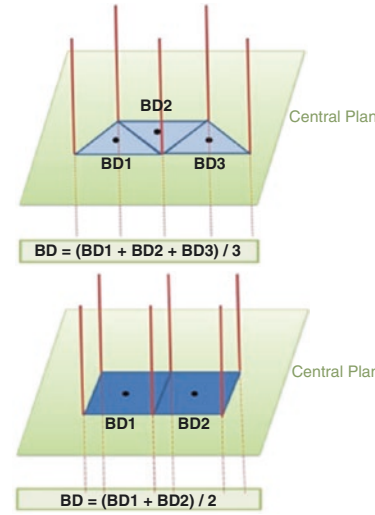
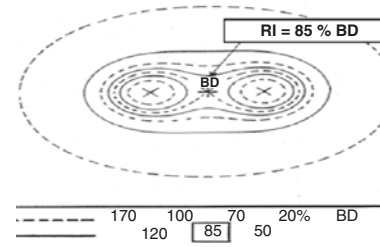
15.8.2 Quimby System

- The Quimby system was developed by Edith Quimby et al. at New York Memorial Hospital in the 1930s.
- Uniform distribution of sources of equal linear activity, resulting in non-uniform dose distribution.
- Usually, the dose in the center of the treatment volume is higher than the dose near the periphery.
- Central dose is typically 25–30% higher than the prescribed dose.
- Distance between sources is 1–1.5 cm.

15.8.3 Paris System

- Developed by Pierquin and Dutreix in the 1960s in Paris for flexible 192Ir wire.
- The active sources should be linear and parallel to each other.
- Sources should be equidistant from each other spacing between adjacent sources is not less than 8 mm or more than 15 mm.
- The linear activity must be uniform and identical for all sources.
- The plane on which the midpoints of the sources lie, the central plane, should be perpendicular to the axis of each source.
- Used for single and double plane implants and not for other types of volume implant.
- The active sources should be 20 to 30 percent longer than the target volume at both ends, to compensate for the uncrossed ends.
- The basic concepts of Paris system are summarized in Table 15.9.

Table 15.9 The basic concepts of Paris system

Central plane: • Plane at which the midpoint of sources lies, and it is at the right angle to the long axis of the sources • Dose is specified within the target volume, in the central plane	
Basal dose rate (BD): • Basal dose rate is the minimum dose rate between a pair or group of sources • It is the arithmetic mean of the minimum dose rates between the sources within the implant along the central plane	
Reference dose rate (RD): • Defined as 85% of the basal dose rate • Dose is prescribed to the reference isodose line • RI = 0.85 × BD	

16 Basics of Brachytherapy and Common Radio Nucleotides

V. R. Anjali

16.1 Basics of Brachytherapy

Brachytherapy is a method by which radiation treatment is delivered with the help of sealed radionuclide which is kept close to the target tissue. The factors which contribute to the therapeutic effect of treatment include specific activity, range, photon energy, and half-life of radionuclide (Table 16.1).

16.2 Common Radionuclides

Radioactivity is the property of substances to undergo spontaneous disintegration, with emission of particle (alpha, beta, and neutrons) or radiation or both due to instability of the nucleus. Antonie Henry Becquerel discovered radioactivity in 1896 and won Nobel Prize for Physics in 1903.

Activity is defined as the number of disintegrations per unit time. SI unit of radioactivity is Becquerel (Bq). Old unit is Curie, defined as activity of 1 gram of radium 226, which is 3.7×10^{10} disintegrations per second.

$$1\,\text{Becquerel} = 2.7 \times 10 - 11\,\text{Ci}.$$

$$1\,\text{Curie}\,(\text{Ci}) = 3.7 \times 1010\,\text{Bq}.$$

An element with same atomic number (number of protons are same) but with different mass numbers (number of neutrons are different) is known as isotope. If the isotopes of an element have the property of radioactivity and undergo radioactive decay, then it is called radioisotope/radionuclide. Radionuclide decays in one or more step, with series of decay products. The final stable atom produced in the decay chain will not be radioactive.

For elements with atomic number greater than 82, the interaction between the attractive force (nuclear binding energy) and the repulsive force (between protons) becomes large enough to overcome the attractive force and undergoes radioactive decay.

16.2.1 Types of Radioactive Decay

16.2.1.1 Alpha Decay

- Radioactive element disintegrates by emission of alpha particle.
- Atomic number is reduced by two and mass number by 4.
- E.g. 88 RA226 → 86 Rn222 + 2 He4 + 4.87 MeV.

Beta decay—Decays by emission of negatron or positron from the nucleus.

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Table 16.1 Brachytherapy treatment types depending on dose rate

	Dose Rate	Sources	Radiobiology	Advantage	Disadvantage
High dose rate (HDR)	>12 Gy/h	^{192}Ir, ^{60}Co	• Better cell kill at higher dose rate • Short treatment time doesn't allow repair of sublethal damage • At higher dose rate, detrimental effect on normal tissue is negotiated by (1) Fractionation (2) Adequate separation between source and normal tissue	• Allows dose optimization by changing dwell position and dwell time • Short duration of treatment- less patient discomfort, helps maintain applicator in position • Outpatient procedure • Can treat large number of patients	• Poor therapeutic ratio • Source gets stuck high dose of radiation exposure to patient and staffs • High shielding required • Due to short time available and complex procedure, error prone • Multiple treatment fractions are required • High cost and more human resources required
Medium dose rate (MDR)	2–12 Gy/h	^{137}Cs	• Results have shown inferior results • Not used in routine practice		
Low dose rate (LDR)	LDR 0.4–2 Gy/h	^{226}Ra, ^{137}Cs	• Sufficient time for repair of sublethal damage • Tumour cells are preferentially killed compared to normal tissue • Overall treatment time is shorter, prevents accelerated repopulation • Reassortment of tumour cells into radiosensitive G2M phase during treatment • Acute hypoxia gets corrected during treatment and oxygen enhancement ratio is lower for LDR than for HDR	• Superior radiobiological effect • Predictable clinical effects • Minimum intersession variability in dose distribution • Practised since long time	Prolonged treatment time and bed rest LDR sources is less manufactured Radiation exposure to staff
	Ultra LDR 0.01–0.3 Gy/h	^{125}I, ^{103}Pd			
Pulse dose rate (PDR)	One pulse per hour One pulse of ~70 c Gy × 39–40 pulses, to a dose of 28–30 Gy	^{192}I	• Radiobiological advantage similar to LDR	• Radiobiological advantages of LDR • Better dose distribution by optimization • Minimal radiation exposure for patient • Radiation free interval for patient • Compensation for source decay by widening the hourly pulses, keeping the overall treatment time and average dose rate fixed	• More expensive than LDR, maintenance difficult • Less utility in high volume centre • Caution while dose conversion from LDR to PDR

16.2.1.2 Negatron Emission

- Beta minus decay.
- High neutron to proton ratio in nucleus.
- Neutron changes to proton by emitting negative electron and antineutrino.
- Atomic number increases by one.
- E.g. 15P32 → 16 S 32 + e^- + γ + antineutrino.

16.2.1.3 Positron Emission

- Beta plus decay.
- High proton to neutron ratio in nucleus.
- Proton changes to neutron by emission of positron and neutrino.
- Atomic number decreases by one.
- E.g. 11Na22 → 10 Ne 22 + e^+ + γ + neutrino.

16.2.1.4 Gamma Decay

- Usually after electron capture or beta decay, the daughter nuclei in excited state will emit excess energy as gamma rays instantaneously and attain stable state.
- E. g.: 27 Co 60 → 28Ni 60 + β + γ (1.33 MeV, 1.25 MeV).

16.2.1.5 Isomeric Transition

- After undergoing radioactive decay by parent atom, the daughter nucleus remains excited for reasonable time. The excited state of daughter nucleus is called metastable state. Later they emit energy and attain stable state. The final product formed will have same atomic number and mass number as that of metastable isomer but with different energy level.
- E.g. 99Mo (67 h) → 99m Tc (6 h) + −1β0 → 99Tc + γ.

16.2.1.6 Electron Capture

- Unstable nuclei with high proton to neutron ratio, and atom does not have sufficient energy for positron decay, it captures orbital electron into nucleus and convert proton to neutron to gain stability. Usually K-shell electrons are captured known as K capture.
- Vacancy created in K shell is filled by outer orbital electron, with release of characteristic/fluorescent X ray (internal photo electric effect) or Auger electrons. For higher atomic numbers, fluorescent yield will be predominant.
- E.g. ^{125}I.

16.2.1.7 Internal Conversion

- When the nucleus is in unstable state, losses its energy by emission of gamma energy. This excess nuclear energy is transferred to orbital electron, which acquires energy and gets ejected from the shell (internal photoelectric effect). The vacancy is filled by outer orbital electron with production of characteristic photon or auger electron.

Radionuclide is classified according to the radiation emitted.

- Pure beta emitter—H-3, P-32, Sr-90, Y-90, Ru-106.
- Pure gamma emitter—Cr-51, Fe-55, Co-57, Tc-99m, I-125.
- Gamma and beta emitters—Na-24, Co-60, I-129, I-131, Xe-133, Au-198.
- Positron emitter—F 18.
- Alpha and gamma emitter—Ra-226, Rn-222, Am 241.
- Neutron emitter—Cf 252 (Fig. 16.1).

16.3 Sealed Radionuclide

16.3.1 Radium 226 (Ra 226)

- Discovered by Marie Curie in 1898.
- Isolated from pitchblende ore.
- Decays by alpha decay to Radon 222 and finally to stable lead.
- Half-life—1622 years.
- Gamma energy—0.83 MeV (0.184–2.45 MeV).
- Maximum energy of beta rays—3.26 MeV.
- HVL—14 mm of lead.
- Available as cell, tubes, needles.
- Used in interstitial, intracavitary, and mould brachytherapy.

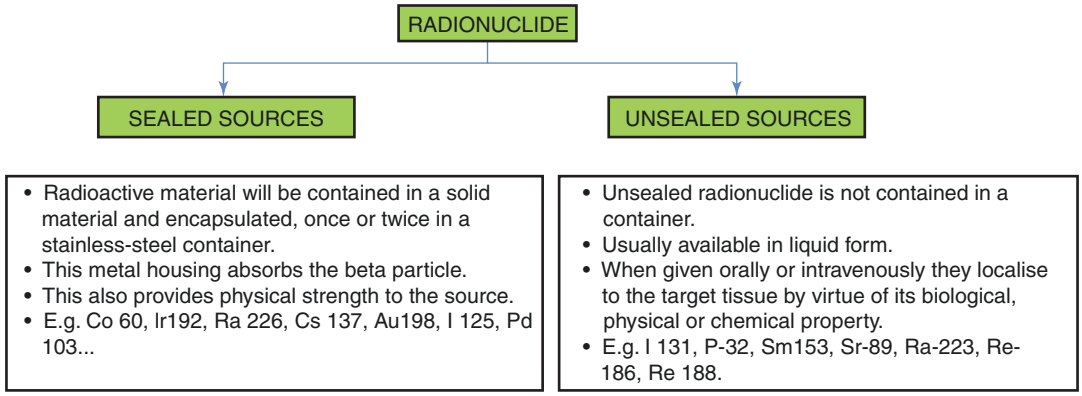

Fig. 16.1 Types of radio nucleotides

16.3.2 Cobalt 60

- Naturally occurring as stable Co-59.
- Cobalt-60 is produced by the neutron activation of stable cobalt (Co 59).
- Decay scheme: 6027Co → 6028Ni + −1 0e + y.
- Half-life–5.26 years.
- Gamma energy—1.173 MeV and 1.333 MeV (average—1.25 MeV).
- Beta energy = 0.318 MeV
- HVL—10 mm of lead.
- Available as pellets, needles, slug.
- Used in intracavitary brachytherapy, teletherapy, plaque brachytherapy.

16.3.3 Iridium 192

- Naturally occurring as 77 Ir 192 and 77 Ir193.
- Iridium 192 produced by neutron activation in nuclear reactor.
- Decays by beta emission (95%) to platinum 192 and by electron capture (5%) to osmium 192.
- Half-life 73.83 days.
- Gamma energy—0.380 MeV (0.136–1.06 MeV).
- Beta particle energy −0.670 MeV.
- HVL −4.5 mm of lead.
- Available as seeds, wires, hairpin, ribbon, slugs, miniature source.
- Used in intracavitary, interstitial, and intravascular brachytherapy.

16.3.4 Cesium 137 (Cs 137)

- Naturally occurring as stable 55Cesium 133.
- Produced by nuclear fission of Uranium-235.
- Decay scheme: 55137 Cs → 13756Ba + 0-1e + γ
- Half-life—30.22 years.
- Monoenergetic gamma ray emitter—0.662 MeV.
- Beta energy—0.51 MeV.
- HVL—5.5 mm of lead.
- Available as tubes, needles, pellets, miniature source.
- Used in intracavitary brachytherapy.
- Radioactive Cesium chloride is hygroscopic and highly dispersible.

16.3.5 Gold (Au 198)

- Naturally seen as stable gold197.
- Gold 198 is produced by irradiation of thermal neutrons Au197.
- 79Au197 + 0n1 → 70Au198 + γ
- Gold decays to form stable mercury by emission of beta and gamma particle.
- Half-life—2.7 days.
- Gamma energy—0.412 MeV.
- Beta energy maximum of 0.960 MeV.
- HVL 2.5 mm of lead.
- Available as gold grains encapsulated in platinum capsule.
- Permanent brachytherapy implant.

16.3.6 Iodine 125 (I 125)

- Produced from Xenon 124and its isotope by neutron capture.
- Decays by electron capture to 125Telleurium.
- $125I + e^- \rightarrow 125Te + \gamma$
- T1/2 = 59.4 days (60 days).
- Emits gamma rays with average energy of 28 keV (27–31 keV).
- Half-value layer: 0.025 mm Pb.
- Available as seeds.
- Used for permanent interstitial and plaque brachytherapy.

16.3.7 Palladium (Pd 103)

- Produced by neutron bombardment of Palladium 102.
- Decays by electron capture to Ruthenium-103.
- $103Pd + e^- \rightarrow 103Rh + \gamma$
- Half-life is 17 days.
- Average gamma energy—21 KeV (20–23 KeV).
- Half-value layer—0.004 mm of lead.
- Available as pellets, seeds.
- Used in permanent interstitial brachytherapy.

16.3.8 Strontium 90 (Sr 90)

- Produced by thermal fission of uranium 235.
- Pure beta emitter which decays to yttrium90 and Y-90 m.
- Yttrium 90 decays by emitting beta rays (2.27 MeV) to stable zirconium90.
- Beta energy—546 keV.
- Half-life—28.2 years.
- Half-value layer: 0.14 mm lead.
- Used in plaque and intravascular brachytherapy (Table 16.2).

16.4 Unsealed Radionuclide

16.4.1 Iodine 131 (I 131)

- Produced from nuclear fission of uranium atom.
- Decays by beta minus decay to xenon.
- Half-life—8 days.
- Emits gamma rays of 364 keV.
- Emits beta rays of 600 keV (250–800 keV).
- HVL—3 mm lead.
- Iodine 131 is taken up by differentiated follicular thyroid tissue and concentrates it 6.6 times more than other body tissue.

16.4.2 Phosphorus 32 (P 32)

- Produced by irradiating Sulphur 32 with fast neutrons.
- $S\ 32 + n \rightarrow P\ 32 + p$.
- Decays by beta decay to S-32.
- Pure beta emitter.
- Maximum energy—1.71 MeV.

Table 16.2 Summary of commonly used sealed radio nucleotides

Element	Half-life	Energy (MeV)	Exposure rate constant ($mCi^{-1}\ h^{-1}$)
Radium (Ra226)	1626 years	0.83	8.25
Cesium (Cs137)	30 years	0.662	3.28
Iridium (Ir 192)	73.8 day	0.38	4.69
Cobalt (Co60)	5.26 years	1.25	13.07
Iodine (I 125)	60 days	0.028	1.45
Palladium (Pd 103)	17 days	0.021	1.48
Gold (Au 198)	2.7 days	0.412	2.35
Strontium (Sr 90)	28.9 years	0.546 (β)	–
Americium (Am 241)	432 years	5.48 (α) 0.060 (γ)	0.12
Californium (Cf 252)	2.65 days	2.4 (n)	–
Cesium (Cs 131)	9.69 days	0.030	0.64

- Average energy—0.70 MeV.
- Half-life: 14.3 days.
- Aqueous form used in treatment of CML, polycythaemia vera.
- Colloidal form in malignant pleural and pericardial effusion.
- Intraperitoneally used in ovarian cancer.
- Shielding is done with low density material like plexiglass, acrylic, Lucite, wood.
- High density material results in bremsstrahlung production.
- White vinegar can be an effective decontamination solvent for this nuclide in most forms.

16.4.3 Radium 223 (Ra 223)

- Produced artificially by irradiating radium 226 with neutron.
- Radium 223 is prepared from radium 226 by "milking" it from actinium 227.

$$\mathrm{Ra}\,226 + \mathrm{on}^{1} \rightarrow \mathrm{Ra}\,227 \xrightarrow[42\,\mathrm{min}]{} \mathrm{Ac}\,227 \xrightarrow[21.8\,\mathrm{years}]{} \mathrm{Th}\,227 \xrightarrow[18.7\,\mathrm{days}]{} \mathrm{Ra}\,223$$

- Half-life—11.43 days.
- Emits alpha particle (95.3%) energy of 5–7.5 MeV.
- Beta particle (3.6%) energy of 0.45 MeV.
- Gamma particle (1.1%) energy of 0.01–1.27 MeV.
- Range of alpha particle<100 micrometre.
- Approved by FDA in May 2013 for castration-resistant prostate cancer with symptomatic bone metastasis with no visceral metastasis.
- Phase III trial ALSYMPCA showed overall survival in patients with CRPC with symptomatic bony metastasis.
- Dose is 50 kBq per kg body weight, at 4 weeks interval for 6 cycles.
- When given intravenously Radium 223 di chloride mimics calcium and forms complexes with hydroxyapatite and target bone metastasis.
- Side effects: thrombocytopenia, diarrhoea, vomiting, nausea, bone fracture, pancytopenia, neutropenia (Table 16.3).

Table 16.3 Summary of commonly used unsealed radio nucleotides

Unsealed radionuclide	Half-life	Energy		
		α	β	γ
Iodine (I 131)	8 days	–	190 keV	346 keV
Phosphorus (P 32)	14.3 days	–		–
Strontium (Sr 89)	50.5 days	–	0.583 MeV	–
Samarium (Sm-153)	46.3 hours	–	0.23 MeV	103 keV
Radium (Ra-223)	11.4 days	6 MeV	330 keV	270 keV
Rhenium (re-188)	17 hours	–	2.1 MeV	155 keV

Brachytherapy in Carcinoma Cervix

17

Prashanth Giridhar and Goura K. Rath

The chapter is divided in the following headings:

1. Applicators in gynaecological brachytherapy
2. Intracavitary brachytherapy (carcinoma cervix)
   (a) Patient selection and indications
   (b) Procedure
   (c) Contouring for MR brachytherapy
3. Interstitial brachytherapy (carcinoma cervix)
   (a) Patient selection and indications
   (b) Procedure
4. Ultrasound in gynaecological brachytherapy
5. Evolving role of Doppler in gynaecologic brachytherapy

17.1 Applicators for Cervix Interstitial Brachytherapy

Venezia Applicator (Fig. 17.1):

- Recently launched by Elekta
- Applicator can be used for intracavitary, interstitial and intravaginal brachytherapy in cervical cancers
- Adds a unique insertion tool to place needles at exact depths allowing better preplanning

17.1.1 MUPIT (Fig. 17.2)

- Can be used for cervix, vulva, urethra, prostate and rectal interstitial brachytherapy. It is therefore called universal template
- The angled needles can cover up to 7 cm of parametrium
- The inner table is sutured to perineum with stay sutures

17.1.2 Applicators in Cervix Intracavitary Brachytherapy

Modified Fletcher-Suit applicator (Fig. 17.3):

- Commonly used ICRT applicator
- Ovoid of various sizes available to fit properly in vagina
- The flange has adjustable lock to be placed for different intrauterine lengths
- Only CT compatible

MR compatible intracavitary applicator (Fig. 17.4a):

- MR compatible applicator is thicker in size and therefore difficult for placement in stenosis of cervical OS (requires more dilatation) and vagina
- Can be used in CT based reconstruction as well

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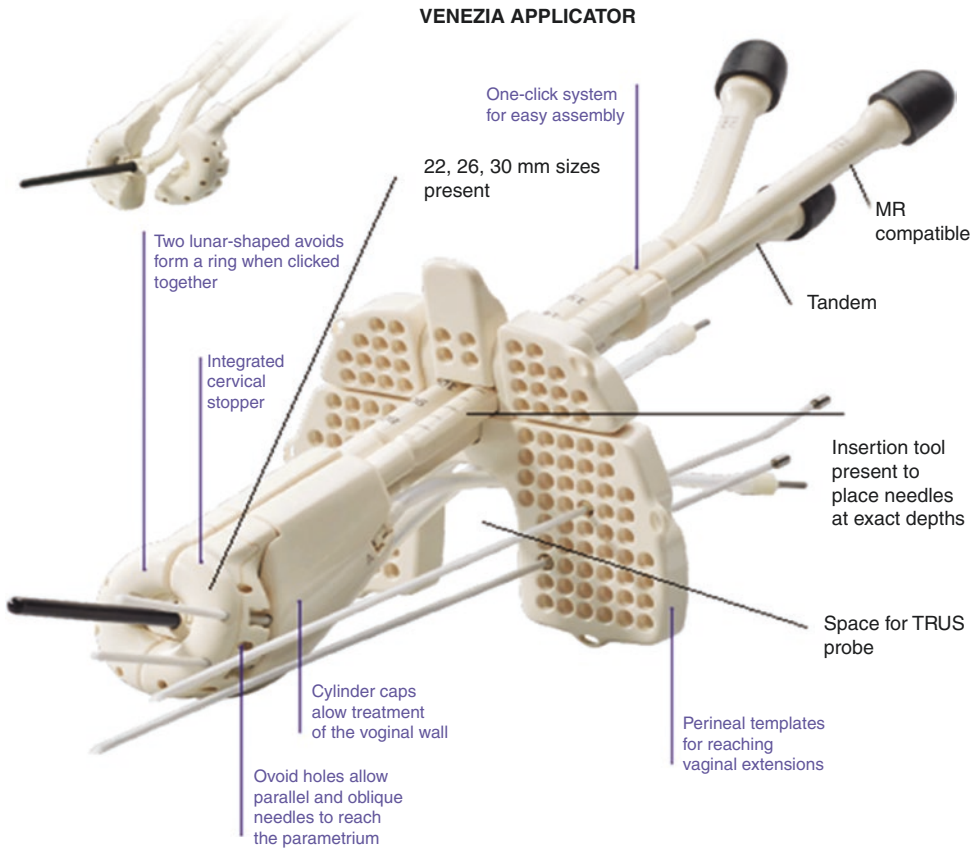


Fig. 17.1 Venezia applicator for cervix interstitial brachytherapy

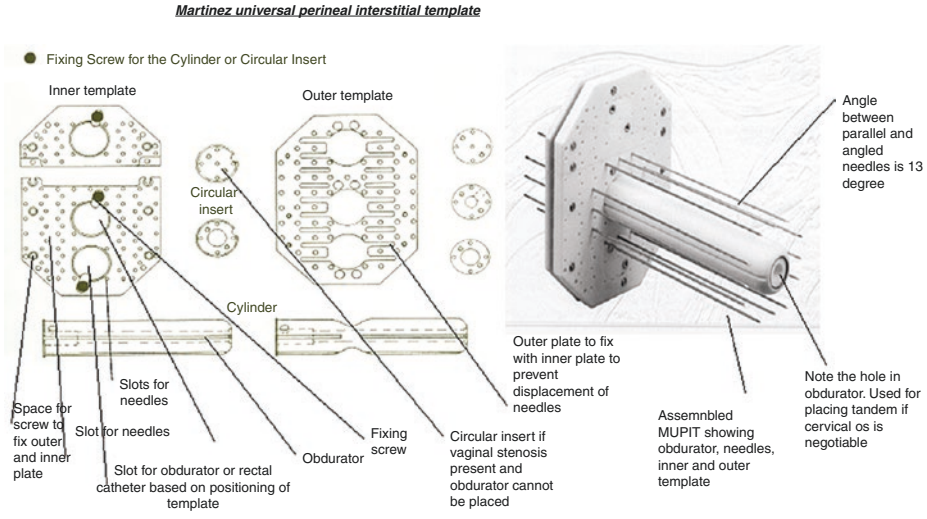


Fig. 17.2 MUPIT applicator for cervix interstitial brachytherapy

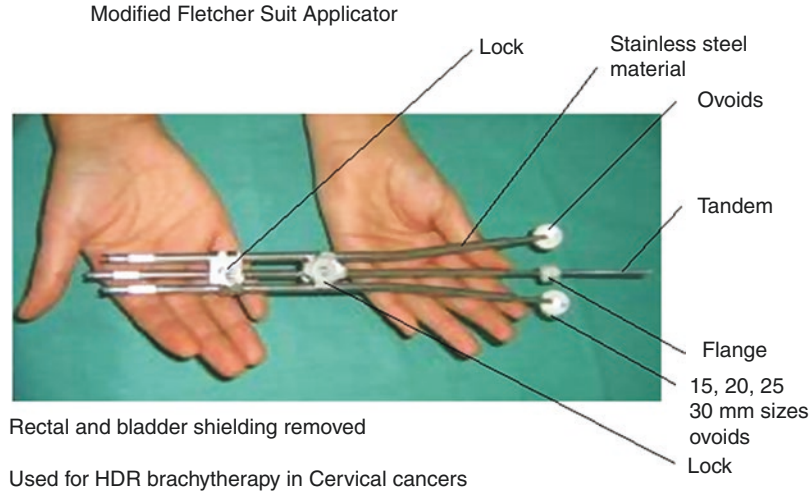


Fig. 17.3 Modified Fletcher-Suit applicator

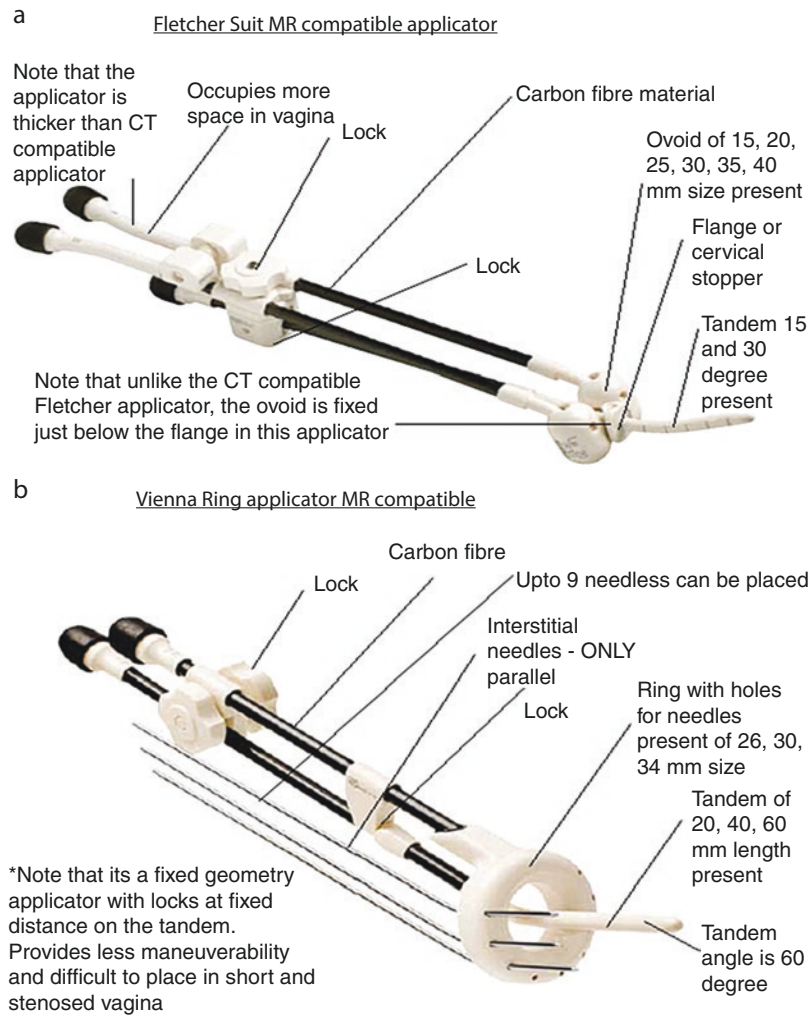


Fig. 17.4 (**a**) MR compatible intracavitary applicator, (**b**) Vienna ring applicator

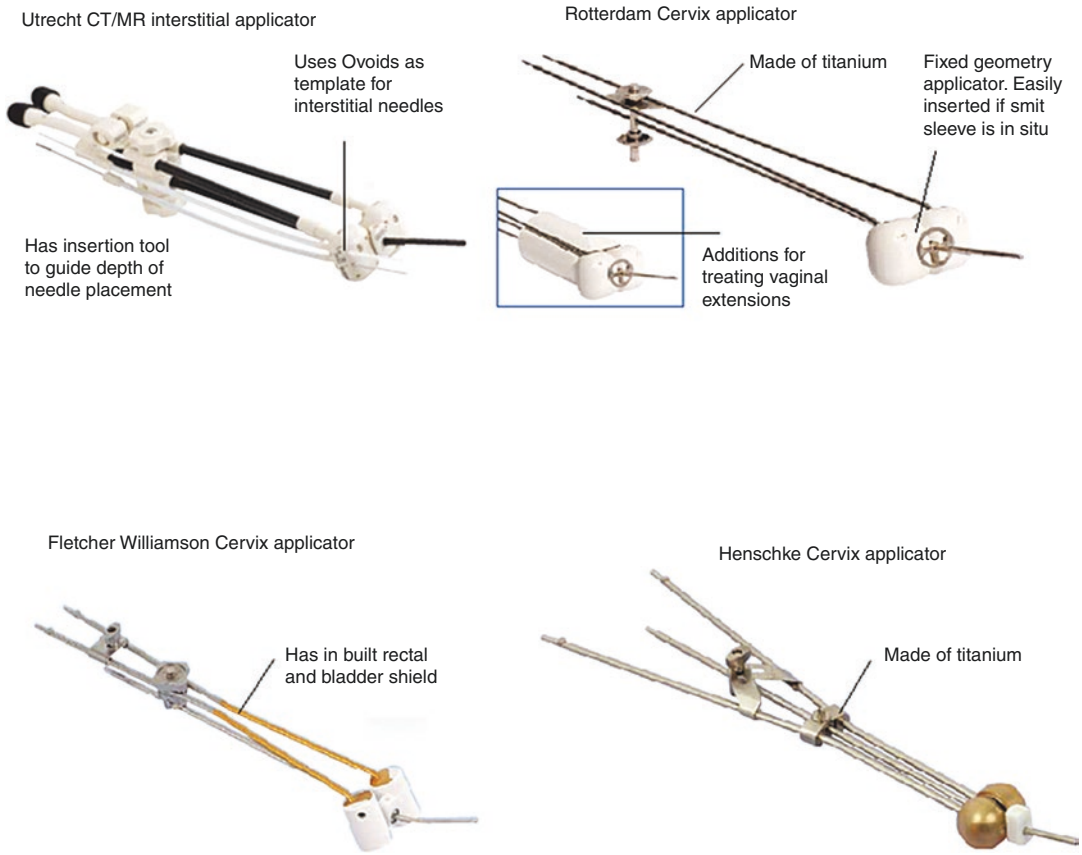


Fig. 17.5 Applicators used for intracavitary brachytherapy in carcinoma cervix

Vienna ring applicator (Fig. 17.4b):

- It has 2 locks placed at fixed distances making placement difficult in short vagina
- The angle of the ring is also fixed
- Only parallel needles can be placed and so the lateral throw into parametrium is less

Other applicators are shown in Fig. 17.5.

17.2 Intracavitary Brachytherapy (ICRT) in Cervix

Patient Selection All patients undergoing external beam radiotherapy for carcinoma cervix should be evaluated for intracavitary brachytherapy. *Examination of supraclavicular fossa, inguinal region and per speculum/vaginum needs to be done to ascertain extent of disease.* Patients may be taken for applicator placement under mild sedation and analgesia or under spinal anaesthesia. We personally prefer using spinal anaesthesia due to three reasons:

1. Pelvic muscle relaxation leading to better manoeuvrability and easier placement of applicators
2. Good analgesia during applicator placement and treatment leading to more patient compliance for subsequent sessions
3. Minimal voluntary movement of lower limbs decreases risk of displacement of applicators

Spinal anaesthesia has the following risks (specific to carcinoma cervix patients):

1. Prolonged immobilization may lead to higher risk of deep vein thrombosis (cancer being thrombophilic)

2. Full analgesia may make it difficult to detect vaginal tears and uterine perforations early during the procedure

17.2.1 Tumour Specific Criteria for Patient Selection of ICRT

1. No vaginal stenosis
2. Os negotiable
3. Tumour size <4 cm (i.e. 2 cm on either side of os) at time of ICRT
4. No or minimal parametria extension at the time of ICRT
5. No involvement of lower vagina
6. No adjacent organ involvement

17.2.2 Patient Specific Criteria for Patient Selection of ICRT

1. Normal hemogram and prothrombin time
2. Patient can be placed in lithotomy position or at least with lower limb abducted and externally rotated >30 degrees

17.2.3 Procedure

1. Patient placed in lithotomy position after anaesthesia/analgesia
2. Cleaning of perineum done
3. Two-way Foley catheter placed in bladder and 7 mL of diluted (2 mL contrast and 5 mL water) contrast placed in bulb
4. Draping of perineum done
5. Transrectal ultrasound (TRUS) used (Fig. 17.1) to identify a. Uterine position—Retroverted versus anteverted; b. Presence or absence of pyometra; c. Approximate length of uterus
6. Uterine sound placed through os to confirm the length of uterus
7. Hegar dilator used to dilate cervical os for placement of tandem
8. Tandem of appropriate length placed such that it reaches the uterine fundus
9. TRUS used to confirm placement within uterus
10. Ovoids or ring of largest possible size placed in vagina at the level of flange
11. The applicator locks are placed
12. Initial posterior packing behind the ovoids or ring to decrease rectal dose followed by anterior packing to decrease bladder dose done

17.2.4 Contouring for MR Guided Brachytherapy

1. *Pre-RT* MR imaging is ideal for imaging of the primary cervical disease. Evaluation of the vagina can be optimized by inserting vaginal contrast, such as gel.
2. Information on clinical examination is also helpful in addition to MRI
3. A pelvic surface improves resolution of the MR imaging.
4. Ideal time for MR imaging for BT contouring is while the BT applicators are in situ.
5. GEC-ESTRO recommends MRI imaging for BT in 3 T2WI planes [fat saturation is not required]—axial, coronal and sagittal
6. Advantage of T2 images—even with treatment tumour shows intermediate to high signal intensity
7. Enlarging pelvic lymph nodes could be a sign of disease. Some of the lymph nodes after EBRT undergo cystic necrosis and may have the appearance with multiple cysts [similar to ovary].

17.3 Interstitial Brachytherapy (Carcinoma Cervix)

17.3.1 Patient Selection and Indications

1. Vaginal stenosis present
2. Os not negotiable
3. Tumour size >4 cm (i.e. >2 cm on either side of os) at the time of brachytherapy
4. Parametria extension at the time of brachytherapy
5. Involvement of lower vagina present
6. Adjacent organ involvement present at baseline
7. Normal hemogram and prothrombin time

8. Patient can be placed in lithotomy position or at least with lower limb abducted and externally rotated >30°

17.3.2 Pre-procedure Checklist

1. Physical examination to check vaginal stenosis, adjacent organ involvement and extent of parametria involvement and rule out progressive disease
2. Pre-brachytherapy imaging check (ideally MRI) to look at the extent of disease and rule out progressive disease
3. Pre-brachytherapy TRUS to check the depth of needle placement required during procedure and organ involvement (if any)

17.3.3 Procedure (MUPIT Applicator)

1. Patient placed in lithotomy position after *combined spinal epidural anaesthesia*
2. Cleaning of perineum done
3. *Three-way* Foley catheter placed in bladder and bulb inflated
4. Draping of perineum done
5. Transrectal ultrasound (TRUS) used (Fig. 17.2) to identify (a) Adjacent organ involvement; (b) Parametria extent; (c) Doppler if available can be used to identify major vessels in the area of implant to reduce risk of bleeding
6. If there is no vaginal stenosis, the length of vagina is measured with obdurator. The inner template of MUPIT is then fixed with obdurator
7. If cervical os is negotiable, place tandem with TRUS guidance
8. The obdurator is placed in vagina with tandem within it and inner plate is sutured to perineal skin
9. With guidance of pre-BT MRI images and TRUS, interstitial needles are placed at required depths
10. Initially the anterior (periurethral needle) is placed due to two reasons: (a) Reduce chance of acoustic shadow hampering further needle placement; (b) Save the Foley bulb from getting ruptured
11. The parametria (lateral) needles are placed next
12. Finally, the posterior needles (perirectal) are placed and position confirmed with TRUS and clinical P/R
13. Stoppers are placed over all needles now to prevent inward displacement of needles
14. Outer plate is placed and screws are placed
15. Stoppers are placed again on needles to prevent outward displacement of needles
16. Check is made for haematuria or fresh bleed P/R
17. Patient shifted to recovery room

17.3.4 Special Scenario

1. *If os not negotiable:* Tandem not placed and dose coverage achieved with interstitial needles
2. *If complete vaginal stenosis:* Obdurator not placed. Inner plate closed with circular insert as shown in figure
3. *If adjacent organ involvement:* Needles are placed in bladder or rectum to achieve adequate dose. Patients to be monitored for bleeding which is usually self-limiting or settles with conservative measures

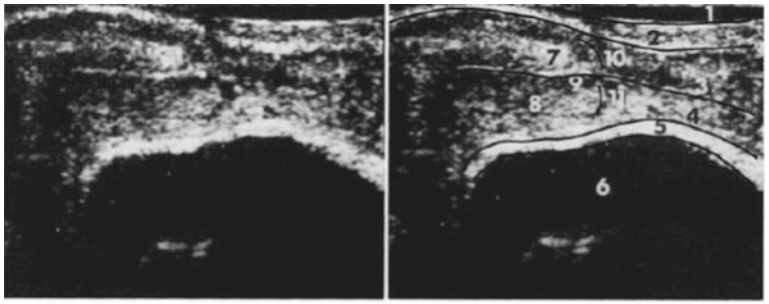
17.4 Ultrasound in Gynaecological Brachytherapy

Transrectal ultrasound is routinely used in prostate brachytherapy but less commonly used in cervix brachytherapy. This section will deal in brief with advantages of TRUS, interpretation of TRUS images to understand the extent of disease and evolving role of Doppler in cervical cancer.

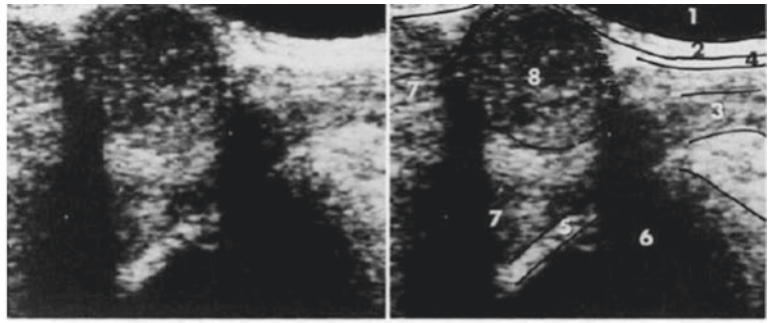
Advantages of TRUS guidance in cervix brachytherapy:

1. Accessibility in the operating room is high
2. Real-time image guidance during insertion is possible
3. Catheter and target visualization is high

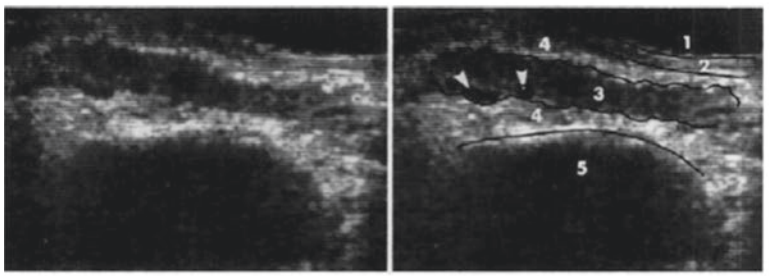
Figure 17.6 shows sagittal views of TRUS for defining the extent of disease. Once the extent of disease is defined, interstitial implant can be done following the steps explained earlier.



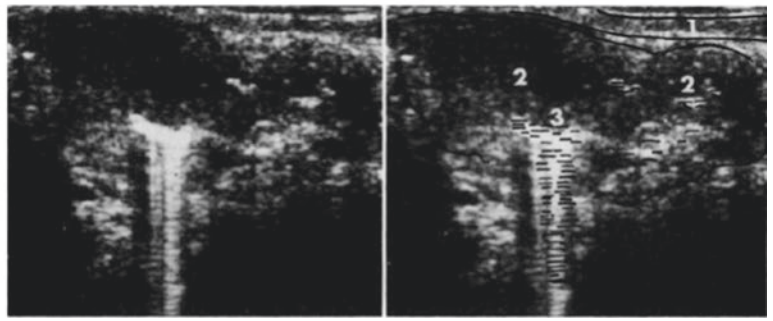
Sagittal san (0°) of normal anatomy. 1 = rectum, 2 = anterior wall of the rectum, 3 = posterior wall of the vagina, 4 = anterior wall of the vagina, 5 = posterior wall of the bladder, 6 = bladder, 7 = posterior lip of the cervix, 8 = anterior lip of the cervix, 9 = cervical canal, 10 = posterior fornix, 11 = anterior fornix.



Sagittal san (0°) of stage IB cervical carcinoma. 1 = rectum, 2 = anterior wall of the rectum, 3 = vagina, 4 = rectovaginal space, 5 = posterior wall of the bladder, 6 = bladder, 7 = cervix, 8 = nodular hypoechoic neoplasm that is distinct from the normal cervical stroma.



Lateral san (45°) of normal anatomy.1 = rectum,2 = anterior wall of the rectum, 3 = parametrium,4 = areolar connective tissue, 5 = bladder, arrowheads = parametrial vascular structures.



Lateral san (60°) of stage IIB cervical carcinoma.1 = anterior lateral wall of the rectum, 2 = neoplastic involvement of the distal parametrium,3 = areas of gaseous necrosis

*Paulo innocenti et al; Staging of Cervical cancer: Reliability of Transrectal ultrasound (TRUS) published in Radiology 1992

Fig. 17.6 Imaging features of TRUS in cervical cancer: (*A pictorial depiction*∗). The images shown below depict sagittal views of TRUS for defining the extent of disease. Cervical cancer usually is not distinguishable from normal cervical stroma and is hypo or isoechoic. The images shown depict normal structures as well as early and locally advanced cervical cancer [1]

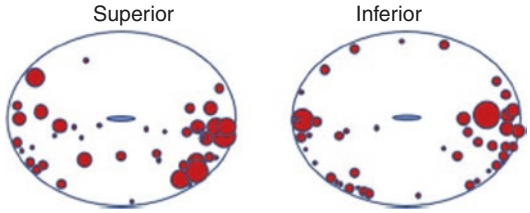
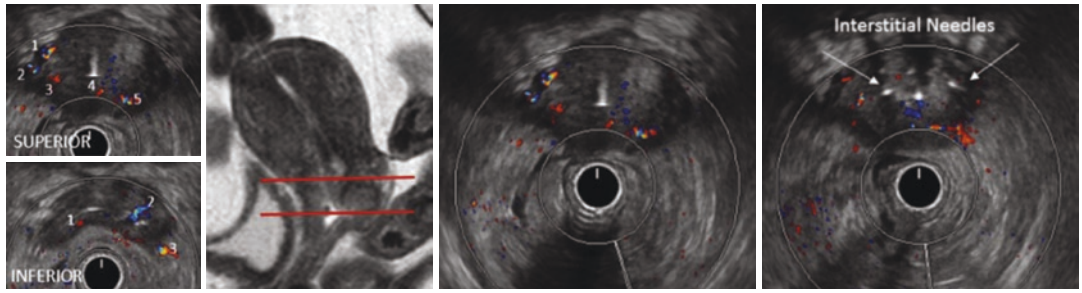


Fig. 17.7 Vessel size and distribution on Doppler USG



Courtesy *Rajni Sethi et al; Real time DOPPLER ultrasound to identify vessels and guide needle placement for gynaecologic interstitial brachytherapy; Brachytherapy 2018

Fig. 17.8 The use of real-time Doppler ultrasound to identify vessels to guide needle placement in interstitial brachytherapy

17.5 Emerging Role of Doppler in Cervix Brachytherapy [2]

- Bleeding although rare is a potential fatal complication of interstitial brachytherapy
- The addition of Doppler to the TRUS allows identification of vessels as the needle is being inserted and thus reduces the risk of bleeding
- Newer TRUS probes have Doppler capability and are thus useful
- Puncture of cervical vessels can cause intravaginal bleed and puncture of paracervical vessels may lead to fatal intraperitoneal haemorrhage.
- Figure 17.7 shows vessel size and distribution on Doppler USG3
- Figure 17.8 shows use of real-time Doppler ultrasound to identify vessels during interstitial brachytherapy.

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Brachytherapy in Head and Neck Cancers

18

Supriya Mallick and Goura K. Rath

Brachytherapy in head and neck cancer can be used as definitive modality alone or as boost in patients with larger tumors. Brachytherapy can also be used as salvage modality especially in localized recurrence. Brachytherapy may also be used in setting of re-irradiation due to the conformal distribution in sites like nasopharynx.

Exophytic lesions do better than infiltrative type of lesions with brachytherapy. A potential advantage of brachytherapy over EBRT alone is better organ preservation due to higher biologically equivalent dose that can be delivered [1]. One of the potential limitations for its use as a sole modality is inability to treat nodes, so radical radiotherapy alone must be used only in patients with a low chance of nodal spread. Another potential demerit is the invasive nature of the procedure, pain associated, and the need for anesthesia during procedure. The key to success to head and neck brachytherapy protocol is proper patient selection.

18.1 Indications [2]

The indications for brachytherapy in head and neck cancers and outcomes are summarized in Table 18.1.

18.2 Pre-brachytherapy Evaluation

1. Local imaging: MRI provides better soft tissue delineation and hence should be preferred to estimate the extension (particularly important for oral tongue), CECT of face with puffed cheek maneuver in important for carcinoma buccal mucosa.
2. Mouth opening: Patient should have at least three finger wide mouth opening to allow better visualization and provide access to the site of interest.
3. Dental prophylaxis: As patients will require self retaining retractor patients should be evaluated for any loose teeth and an extraction of such teeth should be performed at least 7 days prior to the procedure. Proper management of dental hygiene should be done.
4. Patients with short neck, intervertebral disc prolapsed, or vertebral column disorder should be carefully selected as it may become difficult for the procedure.
5. A nasal intubation is always preferred as it gives better visualization.
6. A pre-procedure tracheostomy may be required for patients with primary in base or posterior tongue.
7. In patients with tumors of the posterior part of the oral cavity and oropharynx, an examination under general anesthesia is necessary. This should be done in combination with

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Table 18.1 Indications for head and neck brachytherapy and outcomes

Site		HDR dose	Patient selection	Result
Oral cavity	Radical	40–44-4 Gy in 4 Gy per #	T1/early T2 N0 lesions Avoid in lesions of tip of tongue/<5 mm from mandible	80–90% local control
	Boost	16–20 Gy in 4 Gy per #	When node positive disease has shrunk/ when upfront brachytherapy is possible	
Oropharynx	Boost	16–20 Gy in 4 Gy per #	Technically challenging T1/early T2 N0 lesions Contraindicated when tumor extends to retromolar trigone, the nasopharynx, the larynx, the hypopharynx	90% local control for T1/2 lesions
Nasopharynx	Salvage	60 GY LDR	Residual disease/ relapse must be 1. Tumor <1 cm thick 2. Not infiltrating bone/ITF 3. Not extending to nasal cavity/oropharynx	82% local control for T1/2 lesion when Brachy used in boost
	Boost	12–18 Gy in three fractions		

panendoscopy to rule out synchronous second primary tumors.

8. In patients with primary in lip, oral tongue, floor of mouth, and buccal mucosa a 3–5 mm thick lead spacer should be used to reduce the dose to the mandible and prevent necrosis. However, this lead may produce secondary electron and induce more mucositis. Therefore, it should be coated with plastic or latex.

18.3 Absolute Contraindication

1. Large locally advanced tumor.
2. Moderate to extensive sub-mucosal fibrosis as it reduces mouth opening.

18.4 Relative Contraindication

1. Short neck: as it becomes difficult to position the patient with neck hyperextended.
2. Deviated nasal septum/nasal synechiae/ pathology that interferes with nasal intubation.

18.5 During the Procedure

1. Head ring should be used to stabilize the head.
2. For buccal mucosa a later position is preferred and in oral tongue, floor of mouth, base of tongue a hyperextended neck should be considered.
3. Nasal intubation is preferred.
4. A laryngeal gauge should be placed to avoid aspiration of blood or water.
5. Self retaining retractor should be placed in opposite angle of mouth.
6. A stay suture may be considered for carcinoma oral tongue.
7. A Ryles tube should be placed before completion of the procedure.
8. Catheters should be placed at least in two planes; catheters should be parallel and equidistant; and ideally spaced at 1–1.5 cm from each plane and each catheter. Figure 18.1 shows brachytherapy catheter placement for a patient with carcinoma of the buccal mucosa.

18.6 Target Definition

1. The GTV should be delineated carefully. It should incorporate the visible tumor and any palpable induration. The prior radiological inputs must be considered for GTV delineation.
2. The CTV should incorporate the entire GTV with an isotropic expansion of 5–10 mm.
3. In "Perfect" implant the CTV should be considered as the PTV.
4. The skin should not be considered in the target volume and attention should be paid during source loading.

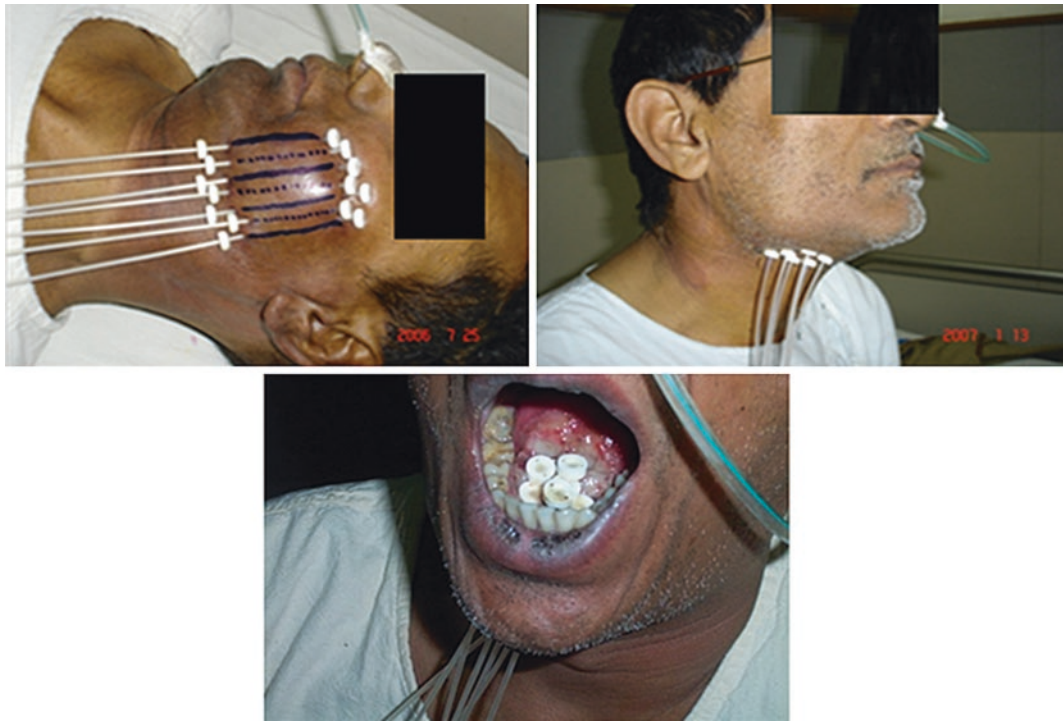

Fig. 18.1 Brachytherapy catheter placement for buccal mucosa, floor of mouth, and oral tongue

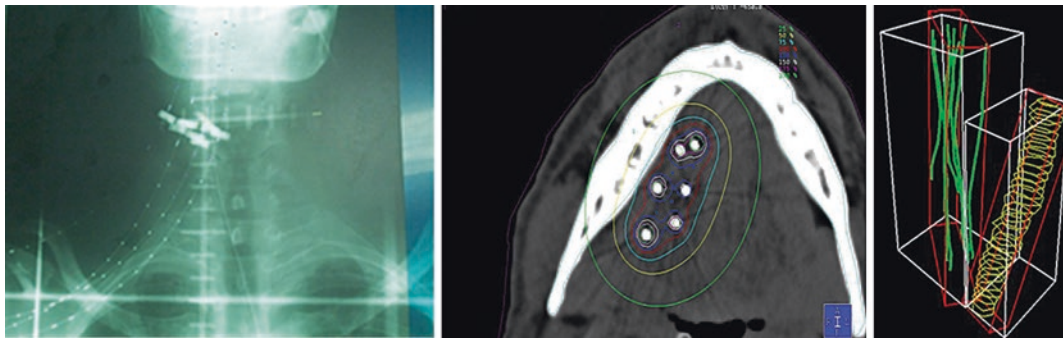

Fig. 18.2 2D X-ray based and CT based planning in patients with head and neck brachytherapy

18.7 Dose and Plan Evaluation

1. According to GEC-ESTRO doses between 3 and 4 Gy per fraction should be used.
2. Radiation should be delivered twice a day, the interval between fractions should be as long as possible, with a minimum of 6 h.
3. In definitive setting a HDR dose of 40–44Gy @ 4 Gy per fraction, twice daily at least 6 h apart may be used.
4. It is advisable to start the treatment on Monday avoid gap in the weekend.
5. As boost the dose may be 16–20 Gy @ 4 Gy per fraction. Whenever, brachytherapy is being used as boost it should follow EBRT.
6. The entire PTV should be well covered by 100% isodose line.
7. Volume receiving 200% of prescription dose should not exceed 15–18% of the target volume.
8. According to ABS the total duration (EBRT + Brachytherapy) should not exceed 8 weeks. Figure 18.2 shows 2D X-ray and CT based planning for head and neck brachytherapy.

18.8 Catheter Removal

1. Catheter removal should be done with great care as there are chances of bleeding and aspiration.
2. It should be done in operating room with adequate preparedness for sudden bleeding and airway management.
3. At least two persons should be available.
4. In case of bleeding bimanual pressure for 5–10 min should be sufficient, otherwise figure of eight suturing may be required.
5. The end of the catheter should be secured with tooth forceps first as the catheter head may plunge in the edema. The catheters should be cut from the distal end. Care should be taken to minimize the travel of the catheter through the tissue to reduce infection.

Source of Images The image was taken from a patient treated by authors as per hospital protocol and consent was taken.

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1. Quon H, Harrison LB. Brachytherapy in the treatment of head and neck cancer. Oncology (Williston Park). 2002;16(10):1379–96.
2. Kovács G, Martinez-Monge R, Budrukkar A, Guinot JL, Johansson B, Strnad V, et al. GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update: improvement by cross sectional imaging based treatment planning and stepping source technology. Radiother Oncol. 2017;122(2):248–54.

Prostate Brachytherapy

19

Prashanth Giridhar and Aruna Turaka

19.1 Patient Evaluation

1. Pre-treatment AUA/IPSS scores and baseline colonoscopy
2. Pre-treatment sexual evaluation—SHIM score
3. History of prior pelvic radiation/previous urologic surgery—brachytherapy to be done only more than 3 months of TURP/TUIP and urethral dose constraint should be kept less than 110% of prescribed dose
4. History of rectal surgery can lead to difficulty in TRUS evaluation and also recurrent rectal cancer to be ruled out
5. History of inflammatory bowel disease—brachytherapy should be done in carefully selected asymptomatic patient who is not on active treatment for last 6 months or more
6. Patients evaluation for bony pelvic defects and ability to position in lithotomy position
7. The ESTRO/EAU/EORTC with recommendations on patient selection for LDR brachytherapy are shown in Table 19.1
8. Neoadjuvant androgen deprivation therapy (ADT) may be used in patients with large prostate prior to brachytherapy to reduce its volume.

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19.2 Absolute Contraindications

1. Presence of rectal fistula
2. Anesthetic contraindications
3. Contraindications to LDR brachytherapy are summarized in Table 19.2.

19.3 Pre-procedure Patient Preparation

1. Anesthetic check-up and clearance obtained before procedure
2. Rectal preparation—Proper bowel preparation is critical and patient must take polyethylene glycol 48 h and 24 h prior to the procedure. Additional laxatives and enema may be given if needed before the procedure.

19.4 LDR Brachytherapy

19.4.1 Equipment Required for LDR Brachytherapy

1. A transrectal ultrasound (TRUS) probe (high resolution between 5 and 12 Mhz) with dedicated prostate brachytherapy software. The TRUS should have sagittal and transaxial visualization
2. Stepping unit support system containing a cradle to hold the ultrasound probe and allow three-dimensional movement and can

Table 19.1 ESTRO/EAU/EORTC recommendations for indications on LDR brachytherapy [2]

	Recommended (do well)	Optional (fair)	Investigational (poor outcome)
PSA (ng/mL)	<10	10–20	>20
Gleason score	5–6	7	8–10
Stage	T1c-T2a	T2b-T2c	T3
IPSS	0–8	9–19	>20
Prostate volume (g)	<40	40–60	>60
Q_{max} (ml/s)	>15	15–10	<10
Residual volume (cm^3)			>200
TURP			+

Table 19.2 Contraindications to LDR brachytherapy, as recommended by ABS and ESTRO/EAU/EORTC

ABS guidelines [1]		
Absolute	Relative	ESTRO/EAU/EORTC guidelines [2]
• Limited life expectancy • Unacceptable operative risks • Distant metastases • Absence of rectum, precluding the use of TRUS • Large TURP defects • Ataxia telangiectasia	• High IPSS >20 • History of prior pelvic radiotherapy • TURP defects • Large median lobes • Prostate gland >60 cm^3 at implantation • Inflammatory bowel disease	• Life expectancy less than 5 years • Metastatic disease • Recent TURP with persisting large defect • Bleeding disorder • Prostate gland >50cm^3 at implantation

be mounted on the operating table or on the ground
3. Perineal template—matched to the grid displayed on the ultrasound image and fixed onto the stepping system
4. Implantation needles-18 Gauge around 20 cm long
5. Locking/ stabilization needles—optional
6. 3 way Foley catheter and aerated gel (lubricating gel mixed with air)—to visualize the urethra on TRUS.

19.4.2 Techniques for Needle Implantation

1. Preloaded needle technique: done on a preplan, but can be based on intra-operative planning also
2. Free seed technique: uses a Mick applicator or similar device to load the seeds into the prostate.

19.4.3 Procedure of LDR Brachytherapy

19.4.3.1 Step 1: Volume Delineation

TRUS is performed and volumes defined. Figure 19.1 shows intra-operative TRUS image of the prostate

Tumor Volume Definition

- *GTV* (Gross tumor volume) is contoured on the pre-implantation TRUS image in and correlated with pre-treatment MRI imaging. Figure 19.2 shows the advantage of MRI over CT for delineation of prostate
- *CTV* (Clinical target volume) includes entire prostate gland with a margin expanded with constraints to the anterior rectal wall and bladder neck:
- T1-2 CTV = visible prostate contour +0.3 cm margin
- T3 CTV = visible prostate contour + visible extracapsular extension +0.3 cm margin

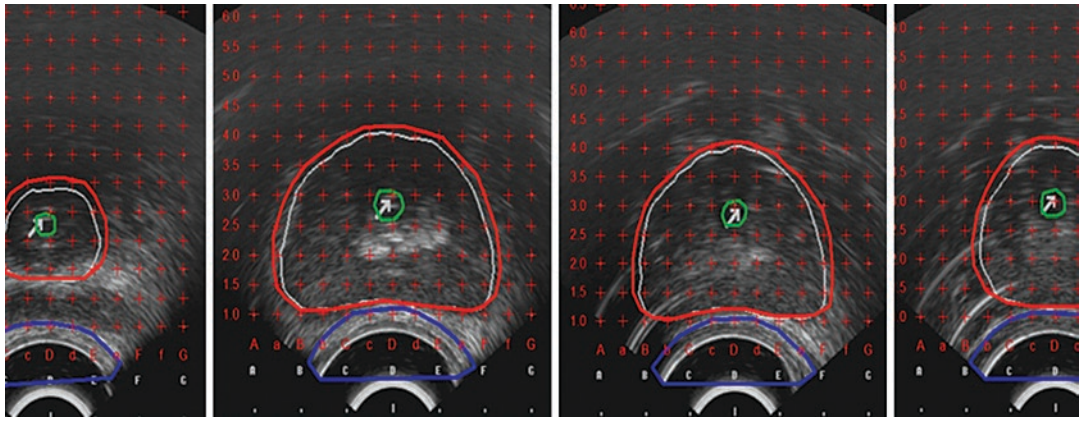

Fig. 19.1 Intra-operative transrectal ultrasound guided volume study from base to the apex of prostate

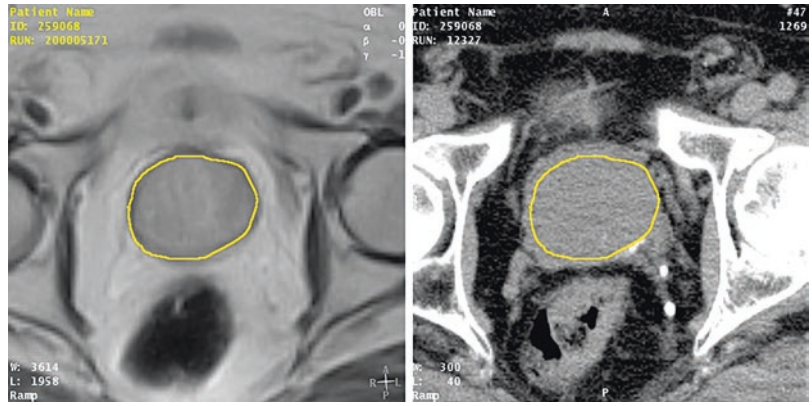

Fig. 19.2 Pre-implant volume study with an MRI and the difference in the prostate contours between MRI and CT scans

Table 19.3 Recommended doses for brachytherapy based on the NCCN-risk groups

	Low-risk group	Intermediate-risk group	High-risk group	Recurrence
LDR brachytherapy alone			EBRT + brachytherapy	
^{125}I	145 Gy	145 Gy	110–115 Gy	145 Gy
^{103}Pd	125 Gy	125 Gy	90–100 Gy	125 Gy
^{131}Cs	115 Gy	115 Gy	85 Gy	115 Gy

- *PTV* = CTV
- *Organs at risk (OAR)* defined includes prostatic *urethra* and *rectum* (contour the outer and inner walls)
- The prescription doses and various radioisotopes used for brachytherapy are mentioned in Tables 19.3 and 19.4.

19.4.3.2 Step 2: Pre-plan Generation

- The pre-plan dose parameters can be based on recommendations by international guidelines
- ABS guidelines recommend limiting 1 cc of the rectum to 100% of the prescription dose (RV 100 < 1 cc) [1]
- Post-implant D90 is generally lower than the pre-plan hence it is important to aim for a higher pre-plan D90
- An intra-operative plan generated for LDR Brachytherapy is shown in Fig. 19.3
- ESTRO/EAU/EORTC guidelines for pre-plan generation are summarized in Table 19.5.

Table 19.4 Various isotopes used for permanent prostate brachytherapy

Radionuclide	Half-life (days)	Avg. energy (keV)	Typical monotherapy seed strength	
			(mCi)	(U)
Iodine-125	59.4	28.4	0.3–0.6	0.4–0.8
Palladium-103	17.0	20.7	1.1–2.2	1.4–2.8
Cesium-131 [5]	9.7	30.4	2.5–3.9	1.6–2.5

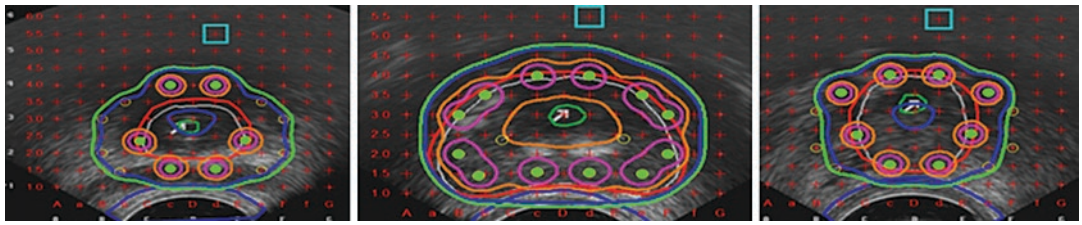

Fig. 19.3 Intra-operative plan, day 0 (base to the apex)

Table 19.5 Dose parameters pre-plan recommendations by ESTRO/EAU/EORTC

GTV	GTV >150%
CTV	V100 ≥95% D90 >100% V150 ≤ 50%
Rectum	Primary: D2cc < 145 Gy Secondary: D0.1cc (D_{max}) < 200Gy
Prostatic urethra	Primary: D10 < 150% Secondary: D30 < 130%

19.4.3.3 Step 3: LDR Brachytherapy Implant Procedure

1. Patient position—dorsal lithotomy position
2. Perineal template is mounted onto the stepping unit. Concordance with the template grid displayed on the ultrasound image must be ensured
3. Locking or fixation needles—can be inserted initially to fix the prostate gland
4. The needle loading report from the pre-plan that indicates for each needle: (a) the x and y coordinates, (b) the number of seeds, and (c) retraction of needle tip from base plane (z coordinate)
5. Needle types
   - Needles—usually fixed number of 2–5 seeds
   - Needles with special loadings (no seeds in the middle portion)—used adjacent to the urethra to keep the urethral dose low
6. Needle insertion
   - Start insertion from the anterior row—minimize TRUS interference
   - Needle is guided by TRUS transverse imaging
   - Needle rotation (tip of the bevel "flashes" up and down)-ensures placement of needle at the correct depth
7. Seed placement—2 methods, the preloaded technique and the after loading technique
   - Preloaded technique—seeds are placed into the needle beforehand
   - After loading technique—the needles are positioned in the prostate first, and then seeds are inserted into the needle
   - The seeds are advanced into the intended position along the needle using the stylet
   - Then the seeds are deposited carefully by holding the stylet stationary and carefully withdrawing the needle over the stylet (done carefully as if the needle is pulled out too swiftly, the seeds may slip inferiorly)
8. Good coverage of the prostate is ensured by a fluoroscopic image and ultrasound scan from base to apex of the prostate
9. The seed number has to be counted and accounted in the fluoroscopic images before leaving the operating room

10. Survey the operating area—using Geiger–Muller counter or scintillation detector for misplaced seeds
11. Cystoscopy—if clinical suspicion of loose seeds in the bladder.

19.4.3.4 Step 4: Post-Implant Dosimetry

Post-implant dosimetry (CT based) must be performed within 60 days of the implant (ABS)

- For palladium-103, 16 ± 4 days
- For iodine-125, 30 ± 7 days.

Figure 19.4 shows week 3 post-implant dosimetry.

Dosimetry reporting in LDR prostate brachytherapy is summarized in Table 19.6.

ESTRO recommendations for post-implant dosimetry evaluation [2]:

1. Two prostate CTV should be reported:
   - CTV-P = CTV for prostate (on post-implant imaging)
   - CTV-PM = CTV for prostate +0.3 cm 3-D uniform margin
2. Prostatic urethra—urinary catheter or aerated gel helps in defining prostatic urethra
3. Rectum—outer and inner walls are contoured on MRI and outer rectal wall if only CT

19.4.4 Post-Implantation Care

- Perineal bruising—conservative management and perineal ice packs may be helpful
- Prophylactic antibiotics are recommended for 1 week after implant
- Obstructive and irritative urinary—alpha-blockers can improve urinary morbidity [3]
- Prophylactic anti-inflammatory drugs useful to improve dysuria
- Loose seeds passing via the urethra

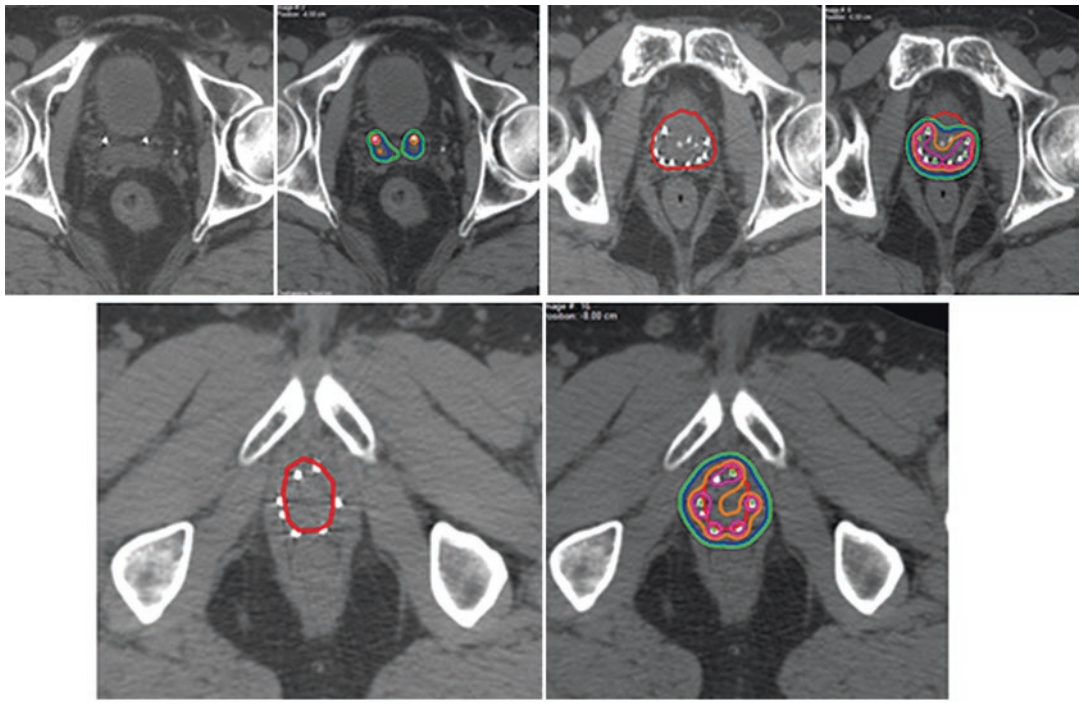

Fig. 19.4 Week 3 post-implant dosimetry (base to the apex)

Table 19.6 Published recommendations from ABS [1, 3] and ESTRO/EAU/EORTC [2, 6] on post-implant dosimetry reporting in LDR prostate brachytherapy

	ABS	ESTRO/EAU/EORTC	
		Primary parameters *Mandatory*	Secondary parameters *May be reported*
Prostate CTV	$D_{100,}$ D_{90}, D_{80} V_{200}, V_{150}, V_{100}, V_{90}, V_{80}	D_{90} V_{100} V_{150}	V_{200} D_{100} • Natural dose rate • Homogeneity index • Conformal index
OAR: Rectum	RV_{100}	D_{2cc}	$D_{0.1cc}$ V_{100}
OAR: Urethra	UV_{150} UV_5 UV_{30}	D_{10}	$D_{0.1cc}$ D_{30} D_5
Other reporting recommendations	• Total volume of prostate • Number of days between implantation and post-implant imaging study	• Volume implanted • Number of seeds • Number of needles used • Total activity implanted • Prescribed dose	

OAR organs at risk, *D90* Dose covering 90% of the prostate volume; *V100* Volume that has received 100% of the prescribed dose, *UV* urethral volume, *RV* rectal volume
ESTRO recommends that volume (V) parameters should always be expressed in absolute values (cc)

  - Urine needs to be passed via a sieve while admitted in hospital
  - If seeds are found in the lavatory, it can be flushed away
- Condom use is generally recommended during sexual intercourse (likelihood of ejaculation of a seed is very low)
- Children and pregnant women should avoid close contact (less than 1 m) for at least one half-life depending on the radionuclide used
- The patient should be given written information on the details of implanted sources, strength, date of implantation, and contact numbers
- Cremation not recommended for 2 years post-implantation (Risk of contamination and release radioactive material).

Further information regarding radiation safety for permanent prostate implants can be found in more detail in the ICRP 98 document [4].

19.5 High Dose Rate (HDR) Prostate Brachytherapy

1. Anesthesia—Combined spinal epidural anesthesia preferred
2. Position—lithotomy position, both lower limbs are abducted, externally rotated, and flexed as much as possible (reduce pubic arch interference)
3. Position and fix the prostate template with transrectal ultrasound probe onto the stepper device
4. Cleaning and draping of the perineal area and thighs done
5. Three-way Foley's catheter is inserted and bulb inflated with 10–15 mL water (bulb must not to be pulled till bladder neck to avoid iatrogenic puncture during needle insertion)
6. The scrotum and penile shaft is strapped on to the abdomen to avoid interference during the procedure
7. Check transrectal ultrasound (TRUS) is done to assess prostate volume and extent. Rectal wash with saline done if artifacts appear on TRUS due to minimal rectal content
8. Stabilization needles/fixation needles are inserted (mid-gland peri-urethrally) to stabilize prostate gland
9. The next step is to image the entire prostate gland with urethra, bladder, and anterior wall of rectum at a rate of 5 mm to 1 cm/s on TRUS. Axial images are obtained and stored

Table 19.7 Dose fractionation used in HDR brachytherapy (commonly used)

Type of treatment	Dose per fraction (Gy)	Number of fractions
HDR monotherapy	9.5–10.5	3–4
HDR boost	9.5–10.5	2

Table 19.8 OAR constraints in HDR brachytherapy (commonly used)

Organs at risk	Constraint parameter	Value
Urethra	V100 V125 V150	<90% prescription <1 cc 0 cc
Bladder	V75	<1 cc (*Soft constraint*)
Rectum	V75 V80	<1 cc <0.5 cc

10. The next step is target delineation on SWIFT Oncentra treatment planning system
11. Organs at risk (OAR) defined include prostatic urethra and rectum
12. A pre-plan is generated and modified as needed for the best target coverage and least organs at risk dose. Position of catheters (HDR) that needs to be inserted on the template are defined on the pre-plan
13. Needle insertion done as per the pre-plan. The prostate stabilization needles keep the prostate stable during the procedure
14. The needles are reconstructed on images and plan re-generated similar to the pre-plan with optimization as needed
15. Dose fractionation is summarized in Table 19.7 and OAR constraints are summarized in Table 19.8
16. Catheters are connected to HDR machine and all staff leave the OT (brachytherapy room) and treatment is done
17. After the dose is delivered, the catheters and prostate hook are removed
18. Perineum pressure is applied for 5–10 min to decrease bleeding and minimize post-procedure pain
19. Mild hematuria is common and is managed conservatively and usually settles down within 24 h post-procedure
20. Once the patient is stabilized patient shifted to recovery room.

19.6 Follow-up

1. Follow-up at an interval of every 6–12 months is considered suitable, digital rectal examinations (DRE) and PSA at regular intervals are recommended
2. Phoenix definition is recommended by ABS for defining failure (beware of PSA bounce)
3. Prostate biopsy result may be difficult to interpret within 30 months of brachytherapy.

Consent for Images Images have been taken from patients treated by authors as per institutional guidelines and consents have been taken.

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Brachytherapy in Breast Cancer

20

Ritesh Kumar and Divya Khosla

20.1 Introduction

Radiotherapy forms an integral component in the management of breast cancer in both early and locally advanced cases. After breast-conserving surgery (BCS), adjuvant external whole breast irradiation (WBI) with an additional local boost is an integral part of breast conservation [1]. Brachytherapy (BT) has a role as a sole modality for adjuvant radiotherapy (APBI) or as a technique for boost [2]. In this chapter, we will focus on the role of BT in breast cancer treatment and discuss different techniques, and provide an overview of outcomes and future trends.

20.2 Role of Brachytherapy in Local Boost Therapy

- Adjuvant breast irradiation aims to reduce the risk of local recurrence after BCS and potentially increase the overall survival [1].
- Patterns of failure studies showed that highest risk of recurrence after BCS is in the peritumoral tissue immediately surrounding the primary tumor bed [3]. This was the rationale for dose escalation to the tumor bed after WBI.
- Randomized studies have shown that the local boost therapy reduced 5-year local recurrence rates from 7.3–13.3% to 3.6–6.3% [4, 5]. The EORTC 22881-10882 trial was the landmark study that showed significant benefit for local boost after WBI in terms of local control rates, however, without overall survival benefit [6]. 20-year follow-up of the trial showed reduction in ipsilateral breast tumor recurrence (IBTR) from 16.4% to 12% with the addition of boost. The benefit was highest for patients with younger age, close margins, extensive intraductal component (EIC), and triple negative tumors. Interstitial BT is one of the oldest and widely used techniques of boost application and has been used by several institutions participating in the EORTC 22881-10882 trial.
- Photons, electrons, and intraoperative radiotherapy (IORT) are also other methods for delivering boost dose [7, 8].
- Until now, no significant difference could be identified in terms of local control and side effects like fibrosis between BT and other modalities. All the modalities show excellent or good cosmetic outcome; however, prospective large randomized comparisons between the modalities are not available.
- The treatment volumes with BT are always lower as compared to EBRT, thus giving BT an advantage over external beam techniques.

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- There has been a significant reduction in radiation dose to OAR such as lung, ribs, skin, and heart with HDR BT as compared to external beam radiotherapy as seen in some studies [7].

20.3 Role of Brachytherapy in Accelerated Partial Breast Irradiation

- Majority of the local recurrences (69–90%) arises in the very close vicinity of the initial tumor area after BCS followed by WBI [9]. BT provides an excellent technique to give a high radiation to the tumor bed with a rapid dose falloff around the target volume.
- The linear quadratic radiobiological model formed the basis of the accelerated fractionation scheduling in partial breast irradiation. Based on the concept of radiobiological equivalence, shortening a treatment course requires decreasing the total dose, and the reduction in treated volume permits an increase in the dose per fraction to achieve the same clinical outcome as with a longer treatment course.
- The techniques for APBI are summarized in Fig. 20.1.
- The initial APBI trials used BT in form of multicatheter interstitial brachytherapy (MIB) where multiple interstitial catheters delivered radiation to the lumpectomy cavity [10]. The earliest trials using MIB for APBI were started in the late 1980s by Guy's Hospital using LDR MIB for monotherapy in 27 patients, followed by the Ontario trial with 39 patients [11]. Both studies included patients with unfavorable risk factors like positive resection margins, large tumors, and node positive disease, resulting in high ipsilateral in-breast recurrence rates (37% and 16.2%).
- The higher rates of local recurrence in these trials led to further trials using strict selection criteria for APBI like young age, tumor size, node-negative disease, negative resection margins [12]. The GEC-ESTRO guidelines for APBI are summarized in Table 20.1.
- The development of image-based catheter implantation, implant reconstruction resulted in a marked improvement in tumor dose coverage.
- The landmark GEC-ESTRO Breast Cancer Working Group study which included 1184 early breast cancer patients from multiple centers in Europe showed 5-year local control, disease-free survival, and overall survival were similar for MIB APBI and external WBI [13].
- The standard HDR BT dose for APBI is 34 Gy in 10 fractions in 5 days (two fractions per day, 6 h apart).
- APBI using MIB is one of the options for local treatment of ipsilateral breast tumor recurrence (IBTR) after a second course of BCS with promising results on local control [14]. But as of now, radical mastectomy is still regarded as the gold standard treatment for IBTR.

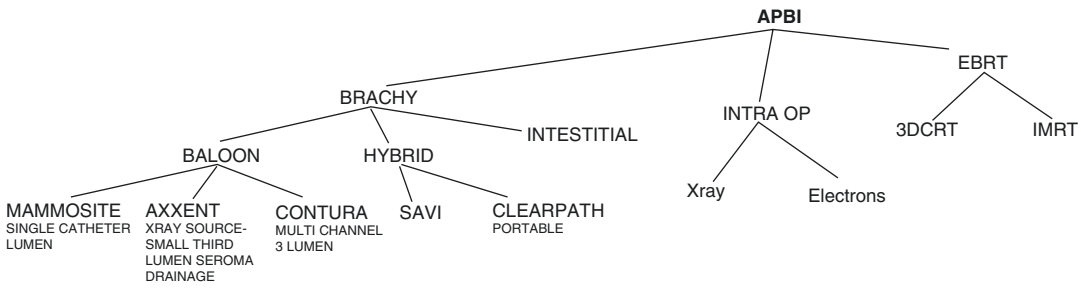

Fig. 20.1 Techniques for APBI

Table 20.1 GEC ESTRO guidelines for patient selection for APBI

	Good	Intermediate	High risk
Age (years)	>50	40–50	<40
Tumor size	<3 cm		>3 cm
Nodal status (ALND/SLNB)	N0		N2
Histology-IDC	Unifocal	Multifocal <2 cm	Multifocal >2 cm
			Multicentric
DCIS	–	Allowed	
ILC	–	Allowed	
LCIS	Yes		
LVSI/EIC/NACT	Absent		Present
ER/PR	Any		
Grade	Any		
Surgical margins	Negative >2 mm	Margin <2 mm	Positive margin

20.4 Balloon-Based Brachytherapy Techniques

- The various devices for balloon-based or hybrid brachytherapy applicators are MammoSite® (Hologic, Marlborough, MA, USA), Contura® (Hologic), and Savi® (Cianna Medical, Aliso Viejo, CA, USA) [15].
- The 5-year analysis of treatment efficacy, cosmetic outcome, and toxicity of MammoSite breast BT from the American Society of Breast Surgeons showed excellent results comparable to other forms of APBI [16].
- MammoSite is a single-channel—dosimetric limitation to shape the radiation dose to the target volume and OAR.
- MammoSite—Double lumen catheter with an inflatable balloon at the distal tip. Inflated to a diameter 4–5 cm. May be inserted for treatment at the time of surgery or up to 10 weeks afterwards.
- Multi-luminal hybrid BT devices like Contura and Savi combine the advantage of MammoSite and MIB. These devices provide adequate targeting of the tumor bed and reduced dose to critical structures [16].

20.5 Single Dose IORT

- May use Intraop photons and electrons
- Intraoperative photons (50 kV)—TARGIT trial, a single dose of 20 Gy as compared to standard WBI
- Intraoperative electrons—ELIOT trial, a single dose of 21 Gy, similar local control and survival compared to standard WBI [17]

20.6 Conclusion

Radiotherapy plays an important role in breast-conserving treatment, and EBRT is the most widely used modality. However, BT can deliver radiation doses to the target volume in a highly conformal way, thereby minimizing exposure of normal surrounding structures and OAR. The use of modern imaging technologies like CT, or even ultrasound and MRI, together with highly sophisticated treatment planning software, has further improved the accuracy of individualized treatment planning.

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Brachytherapy in Soft Tissue Sarcoma

21

Prashanth Giridhar and Susovan Banerjee

21.1 Indications for Brachy-Monotherapy

All three criteria must be met for monotherapy

1. High grade sarcoma (FNCLCC grading)
2. Negative margins (>1 cm)
3. <10 cm size
   - FNCLCC grading of sarcoma is summarised in Fig. 21.1

21.2 Indications of Combined Brachytherapy and External Beam Radiotherapy

1. Low grade sarcoma >5 cm size
2. >10 cm size
3. Positive or close margins not amenable to re-resection

The doses and special considerations as defined by American Brachytherapy Society are summarised below in Figs. 21.2 and 21.3

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21.3 Procedure of Interstitial Brachytherapy (Perioperative)

1. Brachytherapy catheter insertion is done at the time of surgery
2. After gross tumour is resected out by surgeon, clips are placed in tumour bed
3. The tumour bed and areas at risk of residuum and microscopic disease are delineated
4. The planned points of entry and exit are marked with ink on skin close to incision site
5. Insertion of catheter started usually at perpendicular direction to incision
6. Insertion is done parallel to incision if tumour bed follows curvature of extremity
7. Initially, a straight cutting needle is placed inside a hollow metallic stylet and inserted through points of entry and brought out through points of exit (Fig. 21.4)
8. The cutting needle is now removed from stylet
9. The plastic catheters with button on one end are threaded through the hollow metallic stylet
10. The metallic stylet is removed and button placed in the free end
11. The entry and exit point at skin is kept at least 1 cm from incision
12. Catheters are placed parallel to each other and at 1–1.5 cm between each other (Fig. 21.5)

S. Mallick et al. (eds.), *Practical Radiation Oncology*,
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Fig. 21.1 FNCLCC grading of soft tissue sarcoma

Tumour Differentiation

Score 1 Sarcomas closely resembling normal adult mesenchymal tissue (e.g., well differentiated liposarcoma and leiomyosarcoma).

Score 2 Sarcomas for which histological typing is certain (e.g., myxoid liposarcoma & conventional leiomyosarcoma)

Score 3 Embryonal and undifferential sarcomas, Pleomorphic sarcomas, synovial sarcomas, osteosarcomas, PNET)

Mitotic Count

Score 1 0–9 mitoses per 10 HFP*
Score 2 10–19 mitoses per 10 HFP*
Score 3 ≥20 mitoses per 10 HFP*

Tumor Necrosis, determined on histologic sections

Score 0: No tumor necrosis
Score 1: Less than or equal to 50% tumor necrosis
Score 2: More than 50% tumor necrosis

Histological grade

Grade 1 Total score 2,3
Grade 2 Total score 4,5
Grade 3 Total score 6,7,8

13. If gross residual disease is present, double plane implant may be needed
14. The distance between planes should also be 1–1.5 cm
15. The wound is closed by surgeons after drain placement
16. Negative pressure wound therapy is encouraged
17. Flagging and numbering of catheters in order is done.

21.4 Special Considerations during and after Procedure[1]

1. Avoid penetrating blood vessels during catheter insertion
2. Avoid direct contact of catheter with bone and nerve
3. The buttons should not be placed too tight with skin (to allow expansion due to seroma formation)
4. Sterile precautions should be taken during removal of catheter after treatment.

21.5 Intra-operative Radiotherapy (IORT) Retroperitoneal Soft Tissue Sarcoma (Important Points)

1. Radiotherapy dose is delivered during surgery
2. Dose limiting structures like the bowel and nerves are displaced from tumour bed and shielded
3. Pre-operative EBRT to a dose of 50–55 Gy in conventional fractionation delivered
4. Maximal resection is done 4–6 weeks after EBRT
5. Criteria for IORT:
   (a) Surgery likely to be incomplete
   (b) Absence of distant metastases
   (c) Displacement of dose limiting structures possible
6. IORT can be delivered with HDR brachytherapy, electrons or kV X-rays. The specific differences are discussed elsewhere

[1]For further reading regarding procedure, readers may review ABS guidelines by A O Naghavi et al.

Recommended BT prescription dose and constraints for primary STS

BT type	Modality	EBRT (Gy)	BT (Gy)	BT duration (d)	Dosing
LDR/PDR	BT		45–50	4–6	0.45–0.5 Gy/h
	BT + EBRT	45–50	15–25	2–4	0.45–0.5 Gy/h
HDR	BT		30–50	4–7	2–4 Gy bid
	BT + EBRT	45–50	12–20	2–3	2–4 Gy bid
IORT	IORT + EBRT	45–50	10–20	Intraoperative	1 fraction
Volume	Constraints	Common	Ideal		
CTV	V_{100}	≥90%	≥95%		
	V_{150}	≤50%	≤40%		
	D_{90}	≥90%[a]	≥100%[a]		
	DHI	≥0.6	≥0.8		
OAR	Constraints	IORT (Gy)	Postoperative BT (Gy)	SBRT end point (adapted OAR)	Comments
Skin	$D_{0,1cc}$	20	40	Ulceration	≤2/3 the prescribed dose
	D_{2cc}	18	37	(Skin)	
Nerve	$D_{0,1cc}$	16	32	Neuropathy	Full dose if involved
	D_{2cc}	14	30	(Cauda equina/sacral plexus)	(Max BT ~50 Gy)
Vascular	$D_{0,1cc}$	20	53	Aneurysm	Full dose if involved
	D_{2cc}	18	47	(Great vessels	
Bone	$D_{0,1cc}$	20	43	Fracture	Caution with periosteal stripping
	D_{1cc}	18	35	(Ribs)	avoid acral bone BT
Stomach/Duodenum	$D_{0,1cc}$	12	32	Ulceration/fistula	IORT <15 Gy, avoid postoperative
	D_{1cc}	11	18	(stomach/duodenum)	BT in upper abdomen

BT = brachytherapy; CTV = clinical tumor volume; DHI = dose homogeneity index; EBRT = external beam radiation therapy; HDR = high-dose rate; LDR = low-dose rate; OAR = organ at risk; PDR = pulsed dose radiation; SBRT = stereotactic body radiation therapy.

Fig. 21.2 American Brachytherapy Society guidelines for doses in soft tissue sarcoma

Considerations when treating with brachytherapy

Specific situation	Preferred treatment	Treatment considerations	To minimize toxicity
Extremity/trunk			
Low grade: Superficial. <5 cm, and wide margin (≥1 cm)	Surgery alone	Limb-sparing surgery	• Nomograms available to assess risk (consider RT if >10% 5-y risk)
High grade: <10 cm and negative margin	BT alone	30–50 Gy	• Avoid acral lesions (esp. phalangeal) • <10 catheters • ≤ 1-cm dose depth • ≤4.5 Gy/fraction • <9,000 eGy to nerve • >5 d postop
Low grade: deep, >5 cm, or negative margins (<1 cm) High grade: >10 cm negative margin	BT + EBRT	BT + EBRT >60 Gy	• Lower extremity; $TV_{150} \leq 27$ mL • BT > 5 d postop • Chemo > 10 d after BT
All grades: close/positive margin	BT + EBRT	BT + EBRT ≥65 Gy	• Delineation of margin required • Re-resection if possible • Flap closure • Staged reconstruction with NPWT
Recurrent (not previously radiated)	BT + EBRT	BT + EBRT ≥65 Gy	
Re-irradiation	BT alone	30–50 Gy	• Limit radiation to wound closure • Fresh vascularized tissue closure • Staged reconstruction with NPWT • Cumulative dose <111 Gy • Re-irradiation dose <60 Gy
Special considerations			
Retroperitoneum	BT + EBRT	BT + EBRT ≥60 Gy	• Avoid postop BT to upper abdomen • IORT <15 Gy • Tissue expander • IMRT ± integrated boost
Head and Neck	BT + EBRT	IORT>15 Gy	• ≤4 Gy/fraction bid (postop BT) • <5 catheters • TV_{150} <13 cc • Mandible/vascular D_{10} < 4 Gy
Pediatrics	BT alone	Consider adding IMRT/protons for extensive disease	• Avoid in children age ≤6 y • HDR-IORT <12 Gy • Maximal safe resection (HNC) • Incorporate iodine-125 • Cover residual disease (vulva/vaginal)

BT = brachytherapy; EBRT = external beam radiation therapy; HDR = high-dose rate; IORT = intraoperative radiation therapy; NPWT = negative pressure wound treatment; postop = postoperative.

Important considerations:

- **Avoid acral lesions**
- **Keep dose < 4.5 Gy per fraction**
- **Brachytherapy treatment to start > 5 days after surgery**
- **Strongly consider wound management with negative pressure wound therapy**

Fig. 21.3 American Brachytherapy Society special considerations in soft tissue sarcoma

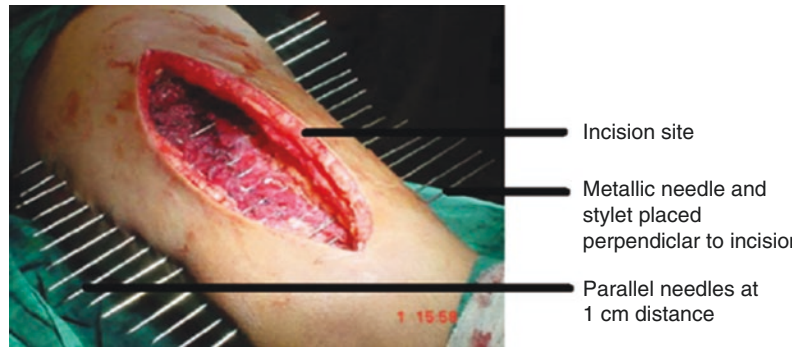

Fig. 21.4 Catheter implantation for brachytherapy soft tissue sarcoma

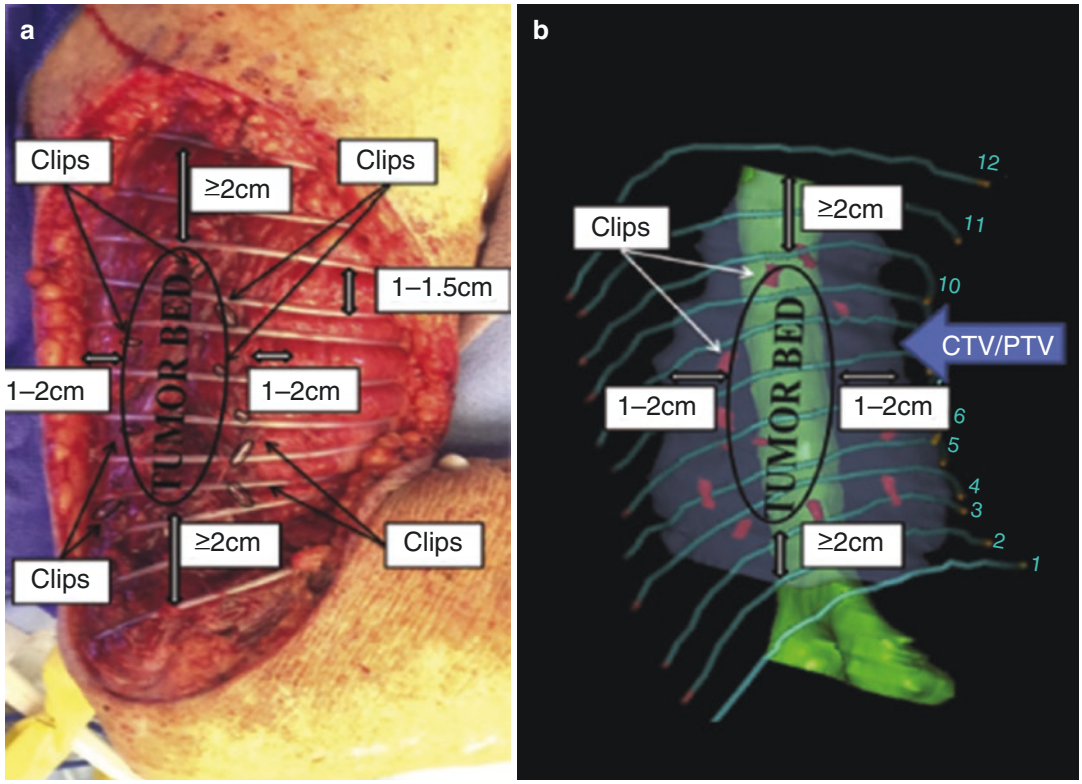

Fig. 21.5 Brachytherapy planning for soft tissue sarcoma shows tumour bed with clips, placement of plastic catheters (**a**) and CTV (**b**) (courtesy: Naghavi et al.)

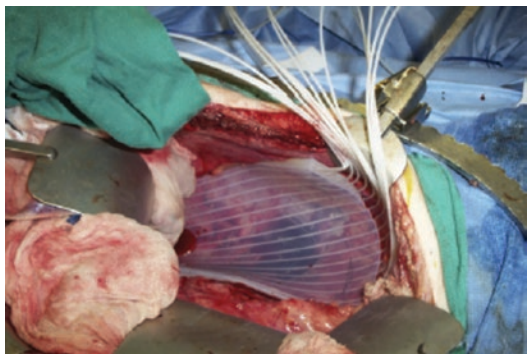

Fig. 21.6 HAM applicator (courtesy: Larrier et al.), catheters placed at 1 cm distances, placed directly on tumour bed after displacing OARs

7. For HDR brachytherapy, *HAM (Harrison Anderson Mick) applicator* is used (Fig. 21.6)
8. IORT doses:
   (a) R0 resection: 10–12 Gy
   (b) R1 resection (Positive margins): 12.5–15 Gy
   (c) Gross residual disease: 15–20 Gy
9. The organs at risk dose limits are provided in Fig. 21.2. Other applicator used primarily for skin brachytherapy also being used in IORT is the Freiburg applicator.

Surface Mould Brachytherapy

22

Rony Benson, Supriya Mallick, and Goura K. Rath

Mould brachytherapy includes delivery of radiotherapy by mould designed to provide a constant and reproducible frame for source positioning.

Moulds are made to fit to the external patient surface and the catheters must remain in the exact position during each radiation fraction.

Surface mould brachytherapy can be delivered by two techniques

- Custom made implants–custom made to fit to the external patient surface—more useful for irregular surfaces [1]
- Predesigned applicators like H.A.M and Freiburg.

A customized mould can be made from

- Acrylic resin
- Wax
- Thermoplastic material.

Indications

- Skin cancer
- Selected cases of T1-T2N0 M0 hard palate, soft palate

Steps

- Step 1—Patient selection—Only patients with superficial tumors with depth less than 5 mm and where mould can be applied are suitable candidates [2]. This is the first and most important step in successful implementation of mould brachytherapy protocols. Patients with tumor depth more than 1 cm may require interstitial implants.
- Step 2—Perpetration of mould and fixing of catheters. The catheters should be parallel to each other and at a distance of 1 cm (Fig. 22.1)
  - In order to avoid large dose gradient over the skin, the catheters must be placed at least 5 mm from skin
  - In order to ensure proper dose delivery on borders of target, catheters must be placed to cover the whole target with margin
- Step 3—Planning CT (0.5–1 cm thick cuts) and contouring of the volumes and planning (Fig. 22.2)
- Step 4—Plan evaluation—Coverage and homogeneity
  - D90
  - VPTV[90–150] = Volume of PTV receiving 90–150% of prescribed dose
  - Conformal index (CI)
  - Homogeneity index (HI)
- Step 5—Treatment delivery (Fig. 22.3)—Ensure proper fitting of the mould during each fraction. It is very important that the

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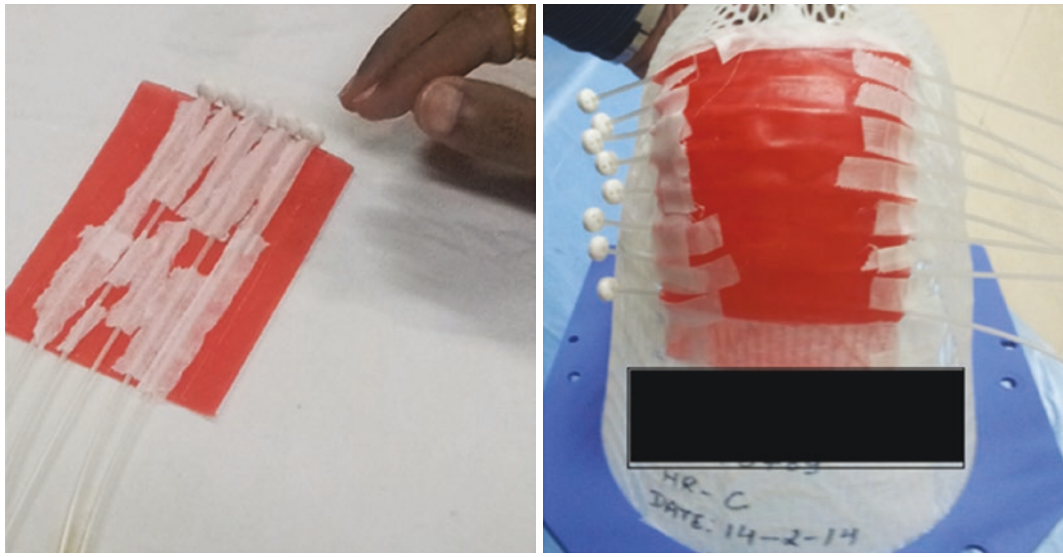

Fig. 22.1 Making a surface mould implant

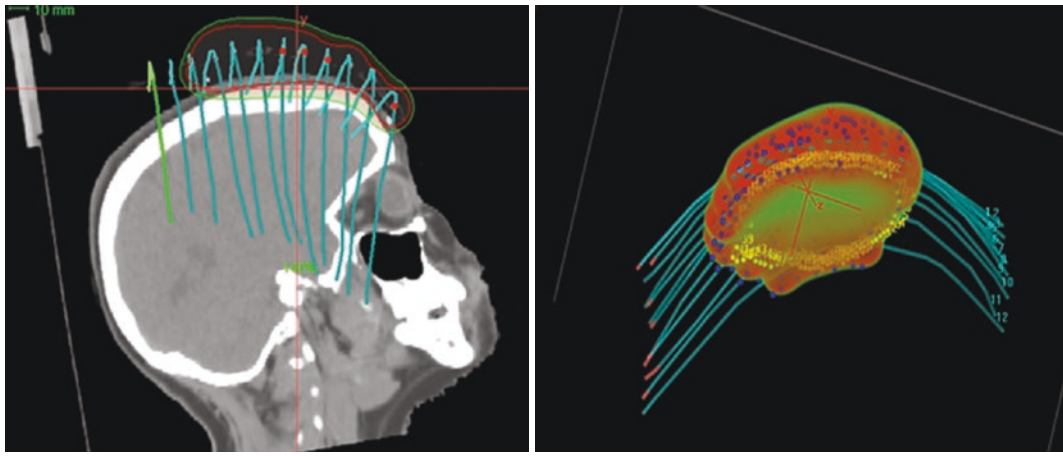

Fig. 22.2 Radiotherapy planning for surface mould implant

mould is in same position as planning and there is no misplacement of catheters.

Advantage

- Mould can be used for flat surfaces and irregular shapes (e.g., earlobe or nose, a potential advantage over electrons and also for electronic brachytherapy)
- It is a reasonable alternative to surface electronic brachytherapy
- Cheap and easy to perform with available brachytherapy machine
- With the availability of 3D-planning highly conformal radiotherapy can be delivered.

Dose Fractionation

- The usual dose as in other skin brachytherapy which delivers a dose 60 Gy LDR equivalent
- The fraction size depends on the volume irradiated.

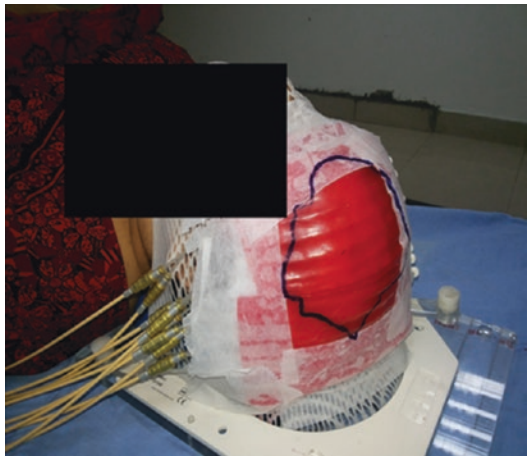

Fig. 22.3 Radiotherapy plan execution for surface mould implant

Source of Images The image was taken from a patient treated by authors as per hospital protocol and consent was taken.

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Part III

Practical Planning Aspects and Plan Evaluation

23 Plan Evaluation in 3D Conformal Radiotherapy

Subhas Pandit

The goal of radiotherapy treatment is to deliver adequate dose to tumor while limiting dose to surrounding normal structure to reduce side-effects. Plan evaluation is a critical decision-making step in radiotherapy planning process to ensure that the treatment plan meets this goal.

23.1 What Is Radiotherapy Treatment Plan?

In 3D-conformal radiotherapy, treatment plan is a computer generated instruction set which includes information on beam arrangement, geometry, energy, 3D image set with localization coordinates, and dose prescription information. This instruction set is generated in computer system called treatment planning system (TPS).

23.2 How to Evaluate a Plan?

After completion of planning and dose calculation by the physicist, radiation oncologist evaluates the plan. Plan is selected for treatment if its dose distribution fulfills the medical prescription; otherwise it again goes in iterative process of re-planning and re-evaluation.

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To select plan whose dose distribution fulfills the clinical requirement is a difficult task, as it involves analysis of large amount of qualitative and quantitative data. Oncologists generally utilize 3D display of dose distribution, dose statistics, and dose–volume histogram to answer these two questions [1].

1. Is this plan good for treating a patient?
2. Which plan is better? Plan A or Plan B?

Treatment plan evaluation and approval are key responsibilities of treating oncologist. It should be done in an orderly and systematic manner similar to checklist approach in surgery. Any error identified at this stage can be corrected before actual delivery of radiation.

23.3 Methods of Displaying Dose

Before the use of computers in radiotherapy, planning was a manual process. External contour of patient was generated using a wire and was drawn in a paper. Isodose chart of individual radiation fields was traced over the contour. Resultant dose distribution was calculated, normalized and isodose lines were drawn joining points with equal dose. These isodose lines were usually drawn in a single mid-transverse plane and evaluated.

Advances in CT simulation and computer TPS in 1990s made this method of plan evaluation

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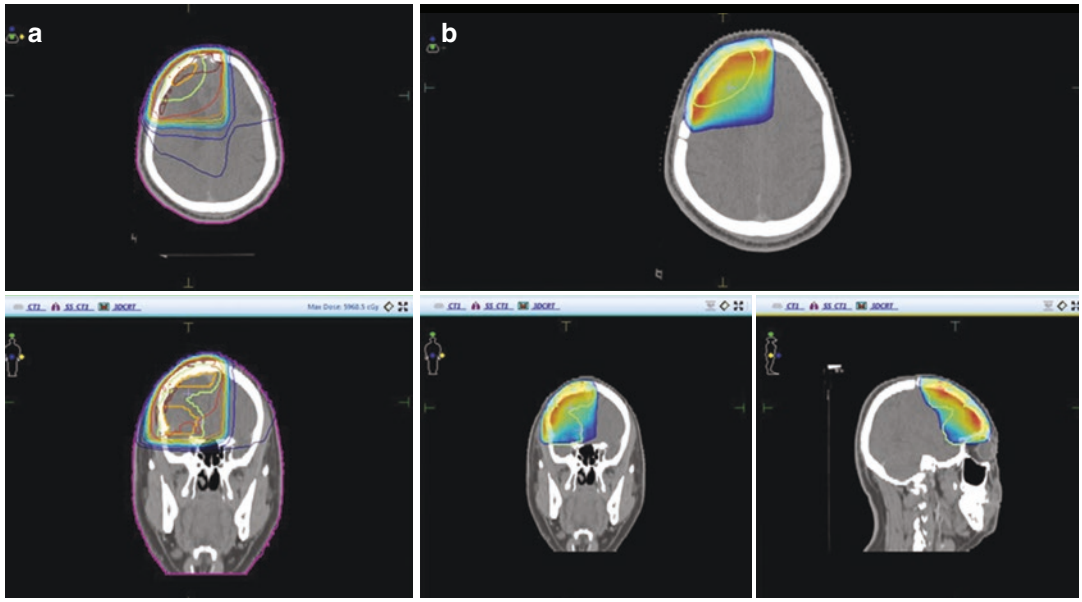

Fig. 23.1 (**a**) Dose distribution displayed with isodose line in transverse and coronal plane. (**b**) Same distribution shown in color wash in transverse, coronal, and sagittal section

inadequate. Evaluation of 3D conformal plan required 3D visualization of radiation plan. New methods of observing and evaluating the plans in TPS monitor were developed.

Now isodose lines could be drawn in all the transverse sections, superimposed over planning CT images. Moreover, they could be drawn in sagittal and coronal planes too (Fig. 23.1).

Dose color wash is another tool commonly used to visualize dose distribution. Calculated dose in each voxel is color-coded and superimposed over planning CT image. Color temperature is scaled to a certain dose range which can be visually reviewed over grayscale image. This color wash can be scrolled in transverse as well as coronal and sagittal planes. By simultaneously changing display plane in transverse, coronal, and sagittal planes, impression of dose distribution in 3D is created.

23.4 Dose–Volume Histogram

Dose–volume histogram (DVH) is a frequently used tool in plan evaluation at it allows rapid visual inspection of dose range and uniformity. DVH is a graphical representation of frequency distribution of dose in a defined structure. DVH condenses large amount of 3D dose distribution data into a simple 2D curve [2, 3].

In DVH, dose is in horizontal axis and volume in vertical axis. Both dose and volume can be in relative or absolute scale. So there can be four possible combinations in axis which should be noted carefully. DVH can be plotted in differential form or cumulative form. Cumulative DVH is more commonly used in clinics for plan evaluation. Figure 23.2 shows differential and cumulative dose–volume histogram.

DVH has certain limitations. As there is loss of spatial information, it cannot tell about location of overdose or under dose in plan. DVH is calculated only from contoured structure. So if a structure is not delineated, then its DVH cannot be analyzed. If these are hotspots outside contoured volume, it can be missed in DVH. Figure 23.3 shows a clinical example to use a DVH.

23.5 Dose Indices

These are scalar quantity which can be deduced from DVH. Also known as dose statistics, they provide quantitative information on dose received by target or OAR and are valuable in plan evaluation.

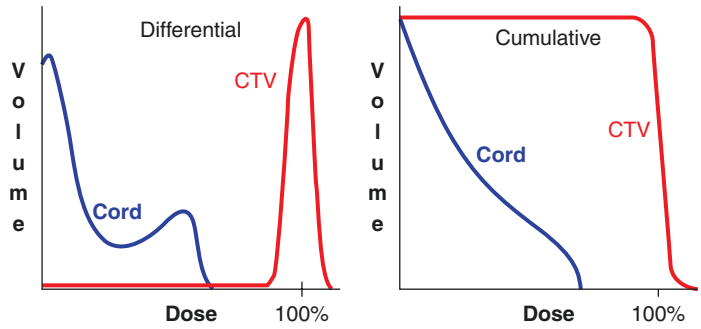

Fig. 23.2 Differential and cumulative dose–volume histogram. Source: David S. Chang. (2014). Basic Radiotherapy Physics and Biology. Springer

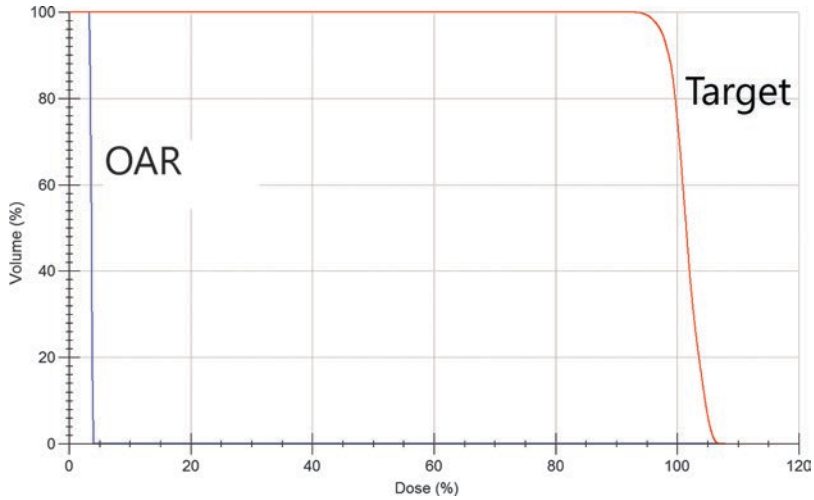

Fig. 23.3 DVH of Target and OAR. Ideally target DVH should be flat up to 100% dose and a sharp falloff thereafter. For OAR, DVH should fall to 0% dose as early as possible

Some commonly used physical dose indices are:

- Minimum dose to the volume
- Maximum dose to the volume
- Mean dose to the volume.

When reporting these indices, point dose can be spurious. So minimum volume of 3 mm × 3 mm × 3 mm (= 0.03 cc) is usually defined as a point.

Dose–Volume Parameters:

- Vd: Volume of structure that receives more than or equal to dose D
- Dv: Dose that a volume V of a structure reaches or exceeds

Both V and D can be absolute or relative, so they need to be interpreted according to their use. For example, V20 in lung means 20Gy dose.

Some radiobiologically based indices in use are:

- Tumor control probability (TCP)
- Normal tissue complication probability (NTCP)
- Probability of uncomplicated tumor control (P+)
- Equivalent uniform dose (EUD)

23.6 Steps of Plan Evaluation

23.6.1 Field Arrangement

First step in plan evaluation is to look for beam selection. In 3D conformal radiotherapy planning physicist chooses the beam angle and aperture. Responsibility of oncologist is to look at each field and see that arrangement is sensible. Beam angles are more important when number of

beams is limited. Beam entry and exit should generally avoid critical normal structures. There should not be excessive normal tissue in beam path. For example in brain tumors, vertex field is commonly used (Fig. 23.4). It should be ensured that they are not exiting to neck/chest. Non-coplanar beam has relatively complex beam path and needs careful overview.

Beam can be evaluated in both room-eye-view (REV) to look for field arrangement and individual beam's eye view (BEV) to look for MCL shaping and relation to OARs [4]. Numbers of field and beam geometry are important in scoring plan. For example, non-coplanar and multi-field plan are more time consuming to deliver. So they are generally avoided in palliative plans.

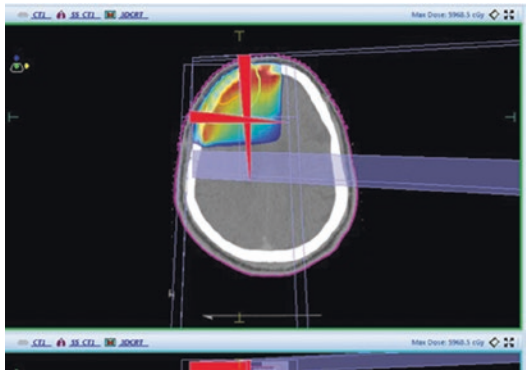

Fig. 23.4 Anterior-lateral beam arrangement with wedge pair in a case of brain tumor

23.6.2 Dose to Target

Next step in plan evaluation is to look for coverage and homogeneity of dose within target. Target coverage can be deduced from cumulative DVH. Planner can aim for different PTV coverage based on specific protocol or departments practice. Common PTV coverage prescriptions in use are

- 95% of prescription dose to cover 95% of PTV (95/95)
- 100% of prescription dose to cover 95% of PTV (100/95).

It is advisable not to cover 100% PTV with prescription dose as forcing dose to cover all of PTV can create unacceptable hot regions. Plan should be normalized such that at least 95% of PTV is covered by prescription dose. It ensures that no part of PTV is under-dosed by more than 5%.

According to ICRU 50, entire PTV should be covered by 95–107% of prescription dose.

Then DVH of all targets including CTVs and GTV is analyzed. DVH of multiple plans can be displayed in single graph for rapid comparison. As DVH does not give spatial information, it should always be analyzed together with 3D dose distribution. A clinical example to use DVH to compare two plans is shown in Fig. 23.5.

Next step is qualitative evaluation by visual inspection of 3D dose distribution. Isodose contour and color wash superimposed over structure

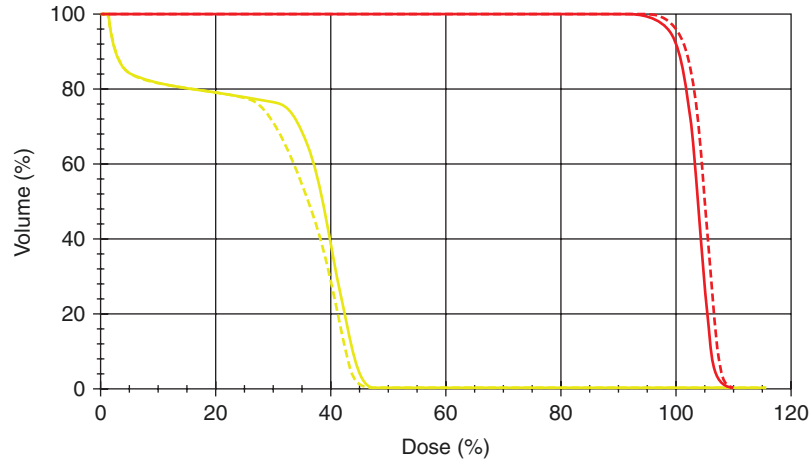

Fig. 23.5 Comparison of two plans using DVH of both loaded in a same graph

contour in CT images are used. Prescription isodose should cover the PTV. Color wash is usually set from 95% to 107% of dose and visual inspection of each transverse section is done. Inadequate coverage, dose inhomogeneity, and excessive spills outside PTV can be identified. Color wash can be independently windowed to look for specific feature in plan. For example, it can be set in higher dose level to see for distribution of hotspot. Likewise, lower dose level is set to look for spills.

While evaluating hot and cold spots, volume, magnitude, and location are to be assessed.

- By definition, cold spot is inside PTV while hotspot may be inside or outside PTV,
- Cold spot should be <1% of PTV, preferably located in periphery of PTV and not inside CTV,
- Hotspot should be less than 15–20% of PTV and <15% above prescription dose. Hotspots should be inside CTV and preferably inside GTV.

Figure 23.6 shows plan evaluation displaying color wash in transverse.

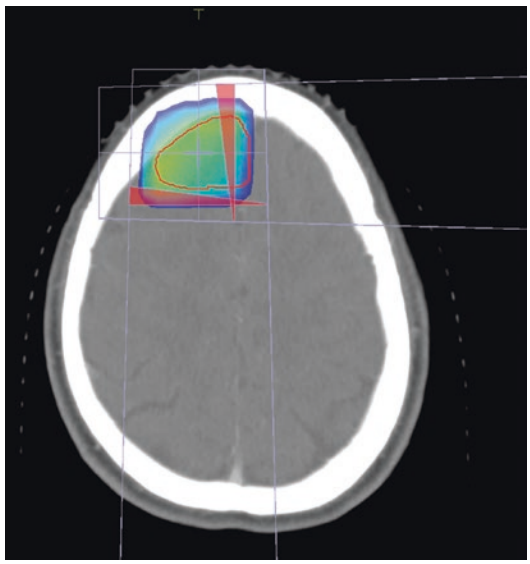

Fig. 23.6 Plan evaluation displaying color wash in transverse, coronal, and sagittal sections along with DVH and BEV window

23.6.3 Dose to Organs at Risk [5–7]

Individual organs at risk are assessed in dose distribution as well as DVH and dose statistics. Good practice is to look for one OAR at a time. Some OAR like optic structure, spinal cord is more critical than others like parotids or oral cavity. Guidelines like QUANTEC are helpful to ensure that OAR dosages are within the limits. It should be ensured that there are no hotspots in OAR.

Serial Organs Maximum dose is crucial. In some crucial organs like spinal cord, toxicity can be devastating in form of radiation myelitis. Therefore, conventional 5/5 (5% probability of complication in 5 years) is unacceptable. So, stringent limit like 0.2% probability with conventional dose of 50 Gy is selected as dose limit.

Parallel Organs Mean dose and dose–volume parameter are more important. For example in lung cancer, volume of lung receiving 20 Gy or more (V20) corresponds with radiation pneumonitis and is limited below 35%. Similarly to reduce xerostomia, mean dose of parotid gland is limited to <26 Gy.

23.6.4 Dose to Remaining Volume

In radiotherapy practice, only tumor target and critical normal structures are contoured. Critical structures are those whose tolerance can alter radiotherapy plan. So much of irradiated volume is not contoured hence not seen in DVH. However, it is good practice to evaluate dose in these "remaining volume at risk" (RVR) to avoid unwanted dose deposition.

Important points:

- Always evaluate plan in absolute dose.
- DVH is helpful for plan evaluation. But should not be relied solely to approve plan.
- DVH should always be evaluated with dose-display and dose statistics.

- Simple plan scores over complex plan. For similar dose distribution, plans having fewer and simpler beam arrangement are chosen over complex plan. This is especially true in palliative cases.

Head and Neck
- Beam should not enter directly through eye.
- There should not be direct vertex beam exiting into body.
- If possible, avoid bilateral beams for the tumors located away from midline.
- If possible, avoid beams entering through shoulder region while treating tumors extending inferiorly.
- OAR should not get more than 105% of prescribed dose (spine, brainstem).

Thorax
- Evaluate V20 in lung cases. Low dose spills are important in lung.
- Try to avoid contralateral lung from field.
- There should be adequate skin flash (2 cm) in breast cases.
- To reduce lung dose mean lung distance of beam should be minimum (<2.5 cm).
- If SCF is present in breast case, there should not be any overlap or gap between the fields.

Pelvis
- More than 105% of prescribed dose should not be in bowel region.
- Femoral heads should be shielded without compromising PTV.
- High energy beam (10–15 MV) is preferred.

Pediatrics
- Treatment may require general anesthesia. Shorter treatment time is preferred.
- Whole of vertebra should be irradiated if some part comes in treatment field, to avoid growth deformity.
- Dose to gonads should be considered and minimized.

Source of Images The image was taken from a patient treated by authors as per hospital protocol and consent was taken.

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Plan Evaluation in IMRT and VMAT

24

Sandeep Muzumder and M. G. John Sebastian

24.1 Introduction

Radiation therapy for treatment of malignant disease results in damage of both tumor and normal cells. Better therapeutic ratio is achieved with increasing dose to target with lesser dose to organ at risk (OAR). Radiation therapy has evolved over time from manual planning to conformal therapy. The multi-leaf collimators have replaced the use of wedges and compensators, and hence simplified radiation delivery by better conforming the tumors. The improved imaging, especially (computed tomography) CT scan, and better treatment planning system have paved way for intensity-modulated radiation therapy (IMRT). IMRT is a form of 3DCRT where TPS determines non-uniform fluence to attain customized dose distribution, where dose is sculpted to target while sparing proximal OARs. IMRT is carried out by delivery of multiple beamlets of non-uniform fluence. The calculation of fluence is done by high performance computers using algorithms taking an iterative approach, called inverse planning. The inverse planning starts with desired result and works backwards to achieve best possible beam shape and fluence pattern. IMRT has become the de facto external beam radiation therapy (EBRT) delivery method for many tumors, especially in head and neck cancer (HNC). Though IMRT has revolutionized the way of EBRT delivery, it is prudent to realize that IMRT process does not guarantee an optimal solution in all cases. ICRU report 83 gives a detailed introduction to IMRT and new reporting guidelines [1]. The numerous ways of implementing IMRT are enumerated in Table 24.1. All

Table 24.1 Types of IMRT

Static gantry	Gantry delivering from a small number of fixed angles
Segmental MLC (step-and-shoot)	MLC static during beam delivery
Dynamic MLC (sliding window)	MLC moves at different rates during beam delivery
Dynamic gantry	Gantry moves in one or more rotating arcs during beam delivery
Cone-beam (IMAT/VMAT)	Leaves move while the gantry is rotating
Fan-beam (tomotherapy)	Binary leaves modulate a fan beam
Serial tomotherapy	Gantry rotates around the patient with the couch fixed. The couch moves in a stepwise fashion after each rotation
Helical tomotherapy	Gantry and couch move synchronously
Robotic radiotherapy	Multiple non-coplanar pencil beams delivered by a LINAC mounted on a robotic arm

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implementation strategies differ in terms of delivery mechanism of non-uniform fluence. The LINAC and MLC based system are more versatile and acceptable. IMRT can be delivered with rotational therapy using intensity modulated arc therapy (IMAT) or tomotherapy. The combination of dynamic MLC and arc therapy in LINAC is called IMAT. The volumetric modulated arc therapy (VMAT) is synonymous with IMAT. In VMAT, in addition to IMAT, there is a simultaneous change in dose rate, gantry speed, and collimator system. Different vendors have given specific proprietary names like RapidArc (Varian), VMAT (Elekta), and SmartArc (Philips), adding to the confusion of nomenclature. As there is no direct comparison in clinical setting, the superiority of one technique over another cannot be ascertained.

The advantage of IMRT lies in superior conformality compared with 3DCRT. It can produce concave-shaped dose distribution, especially useful in sparing spinal cord in HNC which is not possible in 3DCRT without compromising target. Multiple simultaneous therapy can be delivered at the same time to same region, in particular simultaneous integrated boost (SIB). SIB may offer added radiobiologic advantage. With sharp dose fall-off at PTV edges, IMRT achieves excellent normal organ sparing. With all these advantages, various risks and uncertainties are associated with IMRT, like the uncertainty of target delineation and dose calculations. Whether patient actually receives the planned dose distribution is questionable. The geographical misses due to steep dose fall-off at PTV margins, data remains scarce. What is the significance of large volumes receiving less doses, remains unknown? The fate of normal tissues in high risk PTV receiving higher doses in SIB? Only longer follow-up will answer these questions. Also, a learning curve exists in IMRT practice for HNC, and experience of treating oncologist reduces the chance of failure. The RTOG 0022 study reported higher failure in oropharyngeal cancer patients with major IMRT protocol violations [2]. High-volume providers have decreased all-cause mortality, aspiration pneumonia, and better OS compared with low-volume providers of IMRT for HNC. The key finding of this population-based study was the impact of experience of IMRT provider. For every additional 5 patients per year, the risk of mortality decreased by 21% [3].

24.2 Plan Evaluation

Evaluating a radiation plan is an essential task for the radiation oncologist (RO), which has become more complex due to IMRT. Multiple factors must be evaluated before approval of final IMRT plan. Various checklists are available for evaluating a radiation plan like SPIDERplan [4] and CB-CHOP (https://appliedradiationoncology.com/articles/cb-chop-a-simple-acronym-for-evaluating-a-radiation-treatment-plan). This chapter describes the practical approach to IMRT treatment planning and evaluation from a radiation oncologist's perspective.

24.2.1 Patient Selection

The radiation oncology department at our hospital decides the suitability for IMRT on evidence-based literature and dosimetric superiority over IMRT. This mostly includes cancer of head and neck, prostate, cervix with para-aortic node, and post-operative irradiation in stomach and pancreas. For other patients for whom IMRT may be beneficial, it is discussed on a case-by-case basis.

24.2.2 Patient Immobilization/ Positioning and Simulation

An accurate and precise patient positioning is more important, as IMRT is less forgiving compared with 3DCRT due to sharp dose fall-off. Custom-made thermoplastic cast is made for head-and-neck cancer. Vacuum bag or positioning devices are used for abdominal or pelvic IMRT. A point to remember is that reproducibility may not be achieved by using immobilization devices. In a study at our institute, no-immobili-

zation technique with leg separator was the most reproducible technique with the smallest PTV margins in pelvic irradiation compared with whole body vacuum bag cushion and six point Aquaplast pelvic cast [5]. A radiation therapy planning (RTP) CT scan is done through the region of interest at 2.5 mm thickness for IMRT planning.

24.2.3 Contouring

The contouring is the most important aspect of IMRT planning and evaluation process. An appropriate window level and window width must be selected for specified contouring. A GTV might have to be contoured in two different window settings, like a chest wall-based lung lesion. In this case, GTV must be contoured both in lung and soft-tissue window setting. Special care must be taken during fusion. Many a times, the fused MRI or PET-CT is done at different positions compared with planning RT scan. A RO must remember that planning and dose distribution is done on RT planning scan. MRI or PET may show tumor better, but CT scan has better spatial resolution. Also, the planning process and evaluation is done on RTP CT scan. Hence, the principle to be used is "MRI/PET finds it and RTP CT scan defines it." The contours should not be jagged especially target. The skin contours should be smoothed in the area of IMRT planning. Also, checking for unintended/accidental contour and auto-contour should be carried out by the treating RO. Any expansion of margins for CTV or PTV should be reviewed for accuracy. For example, a GTV or CTV may have been modified without appropriate re-expansion of the corresponding PTV. ICRU Report 83 strongly recommends that the margins not be compromised when delineating the PTV or PRV, even in those situations in which these volumes might encroach on an OAR or CTV because systematic uncertainties have more impact on the accuracy of absorbed dose delivered to the patient than do random uncertainties. A PTV may have to be trimmed under skin, for plan evaluation unless skin is involved by tumor. Tissues outside the delineated volume, i.e., target volume and OARs, should be named the remaining volume at risk (RVR). To avoid high doses to unsuspected areas, RVR should receive a dose constraint. Before plan evaluation, the radiation oncologist should recheck the contours of target and organ at risk (OAR) once again before starting the actual evaluation process. It is more important when contouring is done by others. An OAR may have been omitted unintentionally and may have to be contoured, as dose spills in that OAR or it is in path of a non-coplanar beam.

24.2.4 Objectives: Target Dose and OAR Dose Constraints

The objectives must be assigned to the planning physicist before starting IMRT plan in TPS. The common language used for these are the "D and V" notations. These notations designate doses and volumes of target and OARs. D designates the minimum absorbed dose received by percentage volume of the target or OARs. For example, 99% of PTV volume will receive at least 70 Gy and will be represented as: D99 PTV = 70 Gy. Likewise, V designates the volume that receives a specified dose. For example, 20% of lung receiving 30 Gy will be written as: V20 lung = 30 Gy. These V and D notations are not to be confused during prescription or evaluation. The next step is to identify the priority of these constraints. Here, RO should take a pragmatic approach and know the limitation of IMRT based on experience or literature. For simplicity and better understanding, the author recommends either priority 1 or priority 2 for the OARs. The dose received by priority 1 OARs like spinal cord and brainstem is more important than target coverage. Whereas, coverage of target becomes more important than priority 2 OARs like salivary gland and pharyngeal constrictors. The dose trade-off among multiple OARs must be communicated directly with the planning physicist to achieve the objectives. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) dose constraints are most commonly used for IMRT planning [6].

24.2.5 Beam Arrangements

The IMRT planning process is relatively insensitive to beam direction, unlike 3DCRT. But, conformality increases with increase in number of beams. For IMRT plans, one should specify the number of fields or arcs and points of entry. A typical IMRT in HNC has seven to nine fields in equally spaced angles. Two fields are never opposed in fixed-field IMRT plan. When placing non-coplanar field to enhance conformality, the OARs in the path must be accounted for. The numbers of fields might be increased, if desired target coverage or OAR constraints are not achieved. Increasing number of fields or arcs will increase the treatment time. With longer treatment time, organ motion and patient immobilization especially in palliative setting becomes an issue.

24.2.6 Qualitative Assay: Spatial Dose Distribution

The result of treatment plan is a prediction of distribution of dose deposited within patient seen on RTP CT scan. The various methods of dose display are: isodose lines, color wash, isodose surface dose or isodose, and color wash combinations. The plan should be evaluated slice by slice viewing structure and isodose. The prescription isodose should cover its corresponding target. Any inadequate coverage or excessive dose spillage outside the PTV should be identified. Any unmarked OARs in area of dose spillage must be contoured. The display of dose distribution on RTP CT scan slice by slice is relation to target and OARs is the most direct and informative method of assessing a plan. All other methods of assessing dose distribution, namely quantitative assay, are surrogate to this and involve a loss of information to some extent.

24.2.7 Quantitative Assay: Dose-Volume Histogram

Dose distribution is graphically displayed using a dose-volume histogram (DVH). In DVH, the X-axis displays dose in relative (%) or absolute (Gy) and Y-axis displays relative (%) or absolute (in cc) volume of target or OARs. Often coverage is considered adequate when at least 95% of the PTV is treated to the prescription dose or 95% of prescription dose covers more than 99% of target. Though variations are acceptable depending on the treating RO on a case-by-case basis, the treating RO may compromise between PTV coverage and OAR constraints to avoid unacceptable toxicity. The DVH must be used with caution. As spatial information is lost, DVH is only a secondary check. The appropriateness of target and OAR coverage cannot be assessed by DVH. The DVH could report 100% coverage of the PTV by the prescription dose, but the PTV could be delineated incorrectly. There may be an excessive dose spillage in OARs, which can be seen only in graphical dose distribution and not through a DVH.

24.2.8 Quantitative Assay: Heterogeneity Versus Homogeneity

In principle, IMRT can deliver more homogenous plan, compared with 3DCRT due to non-uniform fluence. Ironically, heterogeneity is the rule in practice due to the tight constraints of proximal OARs. Heterogeneity refers to the variability in dose distribution throughout target. It includes examining the minimum PTV dose (cold spot) and the maximum body dose (hot spots), whether it is inside or outside PTV. In IMRT plan, acceptable cold spot is 95% and hotspot is 110% of prescribed dose. This approach is more pragmatic in present volumetric IMRT planning compared with point based 3DCRT planning. After determining the quantitative values of the cold and hot spots, it is critical to review their locations within the treatment plan. Ideally, the hotspot should be inside PTV, and limiting hotspots near OARs during IMRT planning. A hot spot within the GTV may be more acceptable, as opposed to it being in a critical OAR. Similarly, a cold spot at the edges of the PTV is preferred to it being within the GTV. Presently, the ICRU report 83 on IMRT recommends evaluating and record D2 and

D98. Among multiple IMRT plans, a more homogenous one should be approved, provided acceptable target coverage and OAR dose constraints are achieved. Homogeneity or heterogeneity index can be calculated, to compare competing IMRT plans.

24.2.9 OARs Dose Constraints Evaluation

After evaluating target coverage, next objective is to verify dose received by OARs. First to check the objective assigned to planning physicist and identifying the priorities. Certain OARs, especially serial organs have critical dose threshold beyond which unacceptable toxicity may occur. These OARs are given priority 1 and their dose constraints cannot be violated. Sometimes, under-dosing the PTV and reducing the prescription dose are the only option to achieve dose constraints to priority 1 OARs. For example, dose constraint of optic chiasm is more important to prevent blindness than target coverage. Dose constraints to priority 2 OARs are less important than target coverage. For example, a dose constraint to parotid is less important to prevent xerostomia than target coverage. Both, spatial dose distribution and DVH should be reviewed for OAR dose evaluation. In situation of PTV and OAR overlap, priority of OAR should be considered. Sometimes, PTV may be under covered or cropped to protect OARs but ensuring adequate GTV coverage. The dose constraints of OARs can be found in literature. The most commonly used dose constraints are from QUANTEC, RTOG protocol, or recent randomized controlled trials. When dose per fraction is changed, it is important to change appropriate value with biologically effective dose (BED) for OAR constraints.

24.2.10 Prescription

The final step is to confirm dose prescription, i.e., to verify total prescribed dose, dose per fraction, and fractionation schedule. The prescribed dose might have to reduce if dose constraint to priority 1 structure is not achieved. For example, to prescription dose to target by few grays to achieve optic chiasm dose constraints. Also, the beam energy, number, and angle of beam should be noted. The image guidance protocol should be specified for each IMRT plan. It is based on the site of irradiation, PTV margin, and set-up error. In general, daily cone-beam CT is required in IMRT of carcinoma prostate, where daily organ motion is substantial due to rectal filling. In HNC IMRT, where custom-made Aquaplast cast give rise to minimal set-up error, weekly imaging is adequate. But, PTV margin of less than 3 mm may necessitate daily CBCT even in HNC IMRT.

24.3 Conclusion

This chapter provides a stepwise pragmatic approach for evaluating an IMRT plan. Since IMRT plan approval is a critical step, a checklist should be formulated in every department doing IMRT to reduce errors. A systematic approach will give rise to a common language for various ROs, physicists and residents for consistency and easy implementation of IMRT in clinics. The contouring and plan evaluation should be verified by a second RO. All IMRT cases should be discussed in clinical chart review. If required, a RO should never hesitate to replan for better coverage and organ sparing. But RO should know the limitations of IMRT and should not delay start of treatment unnecessarily. Since the responsibility for final approval of plan lies with the radiation oncologist, it is important to have an objective approach of IMRT evaluation. The success of IMRT largely depends on imaging. ICRU report 83 states IMRT increase the need for accurate target delineation. This largely depends on training and experience. The follow-up of patient receiving IMRT is required to document failure and toxicity pattern. Correlating with patient data will bring about further refinement of IMRT process.

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Plan Evaluation for TomoTherapy

25

Shikha Goyal and Susovan Banerjee

25.1 Introduction

Tomotherapy is a term used for the teletherapy equipment as well as for a specific technique of intensity modulated radiation therapy (IMRT) planning and delivery whereby the relative relationships between the gantry, multileaf collimator (MLC), and couch are more dynamic than in a conventional linear accelerator (LINAC). It has a rotating CT-gantry-like platform and a non-stationary couch that continually moves translationally inwards through the bore; the system uses a narrow pencil beam (6 megavolts, MV) for treatment delivery in a helical manner over 360° around the couch enabling slice-by-slice treatment delivery. This arrangement introduces some unique possibilities as well as limitations into the system. It was one of the first devices with the capability of in-built image guidance system and uses the same LINAC head for MV imaging for verification. Since its first conceptualization in the early 1990s by Mackie and Reckwerdt at University of Wisconsin, Madison to its most modern form, the Radixact system by Accuray, there have been several hardware, design and software improvements, making the system more robust, with clinical patient treatments ongoing since 1994 [1–3].

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The treatment is essentially MV image guided IMRT with volume-based planning and non-isocentric helical delivery. The largest field size that can be opened is 5 cm × 40 cm, and the smallest 1 cm × 0.625 cm while owing to the helical nature of delivery, a continuous translational length of 135 cm can be treated without interruption. Interruptions, however, are possible to enable imaging for verification at any level during the entire length of treatment. The dose distribution within the target volumes is characteristically homogenous compared to other IMRT systems, although owing to the rotational/helical nature of treatment delivery, the low dose spread is considerably higher and needs particular attention.

25.2 Ideal Candidates for Tomotherapy

Tomotherapy is capable of treating almost all sites and all tumors that need teletherapy with photons. Owing to the characteristic of 135 cm length treatment capability, the system finds its largest application in long field junction less treatments such as whole spine or craniospinal irradiation, total body or total marrow irradiation, long paraaortic chain, and pelvic fields such as extended field radiation for cervical carcinoma. It is more efficient than conventional LINACs in treating complex volumes such as carcinoma anal canal with large pelvic and inguinal nodes, whole

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brain radiotherapy with simultaneous boost to gross metastases, whole scalp radiotherapy with brain sparing, stereotactic body radiation therapy, and stereotactic radiosurgery, etc., with better sparing of intervening normal tissues, and potentially lesser acute toxicity [4–7]. Figures 25.1 and 25.2 illustrate some common applications of Tomotherapy.

A specific module for delivering paired field IMRT was developed keeping in mind the requirement of tangential beam arrangement for breast cancer. This module is called TomoDirect or Topotherapy and uses a pair of opposed beams (or many sets of pairs with differing angulation) [8]. Unlike parallel-opposed beams in conventional or three dimensional conformal radiotherapy, these beams are modulated across their path and are again delivered in a slice-by-slice fashion (the gantry beam position remains fixed while the couch translates horizontally towards the bore). This can also be used to deliver parallel-opposed beam

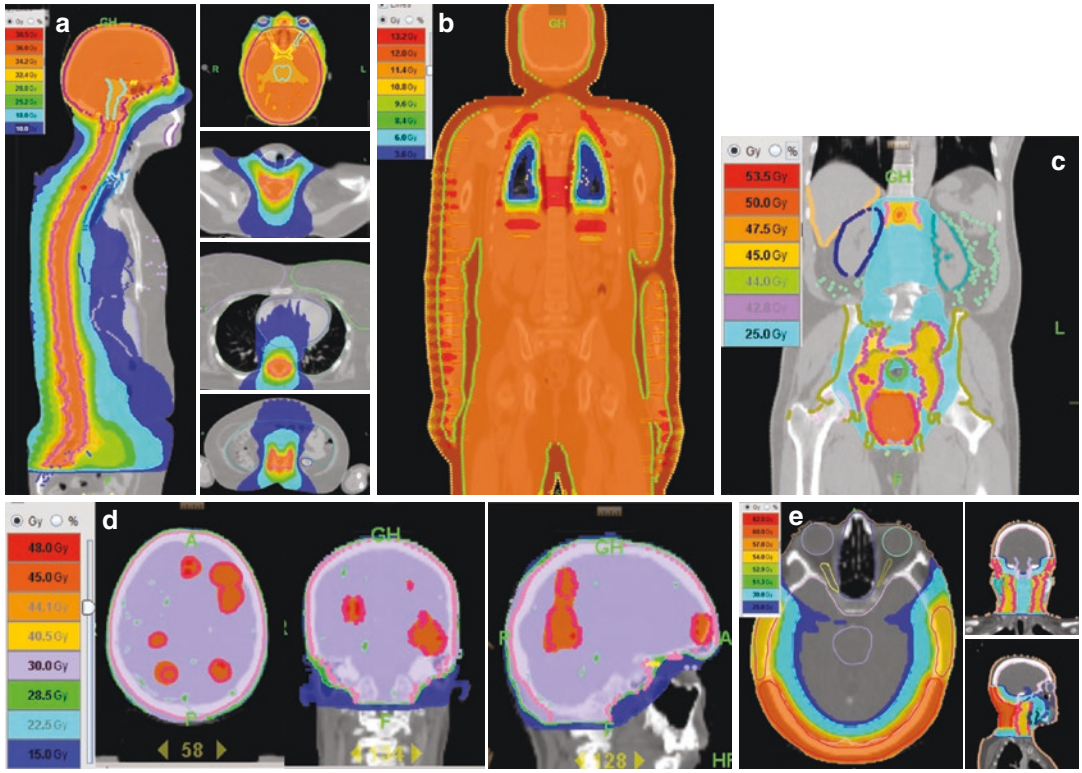


Fig. 25.1 Plan images showing the various special applications of tomotherapy. (**a**) Adult medulloblastoma planned for craniospinal radiation (36 gray, Gy in 20 fractions). Dose profiles are displayed in sagittal and various axial sections. The outermost blue isofill represents 10 Gy. (**b**) Relapsed acute leukemia planned for total body irradiation (12 Gy in 6 fractions, twice daily) as conditioning regime prior to stem cell transplant. The lungs received a mean dose of 8 Gy. The blue isofill represents 3 Gy. (**c**) A case of carcinoma prostate with pelvic and paraaortic nodes and oligometastatic disease involving D10 vertebra was planned for radiation following excellent response to androgen deprivation therapy. A dose of 66 Gy in 33 fractions was planned for prostate and 45 Gy in 25 fractions to pelvic and paraaortic nodal chain as well as D10 vertebral body in a single plan. (**d**) Adnexal carcinoma scalp, postop. Involved area of scalp with margin was treated to a dose of 60 Gy and bilateral neck node levels II–IV treated to 54 Gy, both over 30 fractions. Cranial sparing could be achieved despite the complex volume. The innermost blue isofill represents 25 Gy. Mean cochlear dose was 21 Gy. (**e**) Carcinoma breast with multiple brain metastases. Whole brain RT of 30 Gy and simultaneous boost to gross metastases of 45 Gy over 15 fractions each was planned. A mean eye dose of 12 Gy and lens dose of 3 Gy was achieved

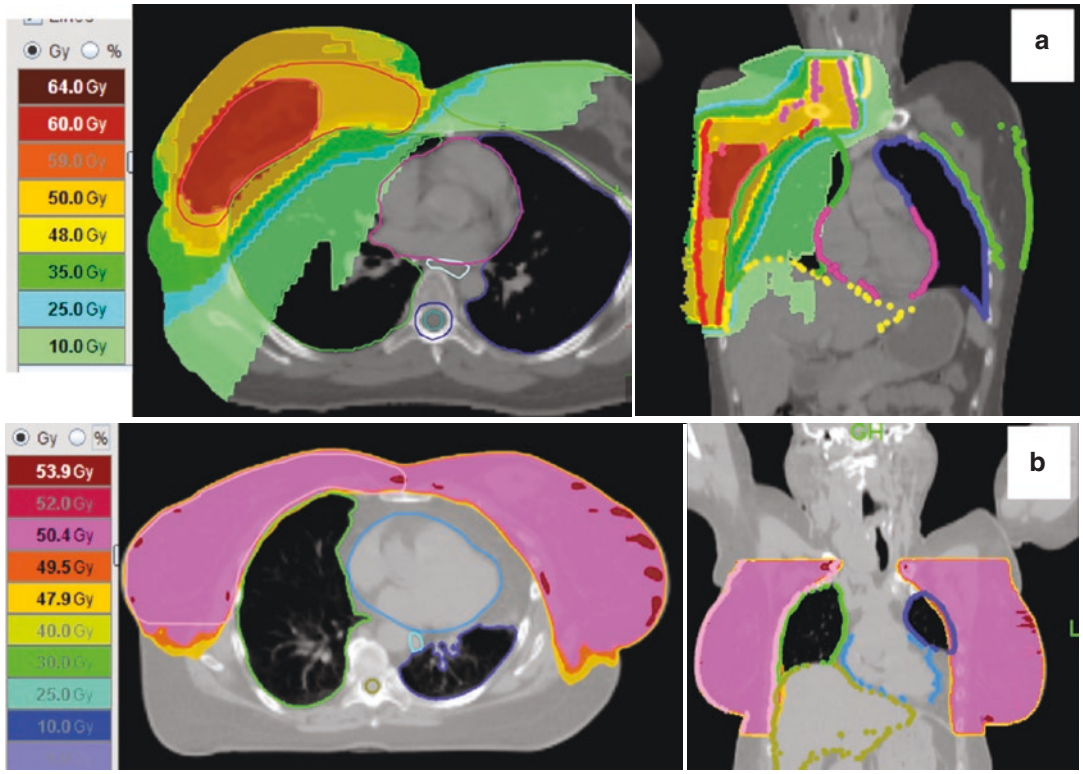


Fig. 25.2 (**a**) Right sided carcinoma breast T2N1M0, post breast conservation surgery (BCS), planned for breast and supraclavicular radiation (50 Gy) and simultaneous boost (60 Gy) in 25 fractions. Note the 10 Gy dose splash into ipsilateral lung, liver and contralateral breast. (**b**) Bilateral breast cancer (right T1N0M0, left TisN0M0, post BCS, planned for bilateral breast irradiation 50.4 Gy in 28 fractions. Note the dose homogeneity within target in both plans. Both cases were planned with helical tomotherapy

arrangements as required for palliative treatments, limb sarcomas, etc. This reduces the overall integral dose since the beam is open for only a part of the gantry rotation, and also considerably reduces the treatment time compared to helical delivery.

25.3 Non-Ideal Conditions

Patients with small superficial tumors that need irradiation to <1 cm depth, peripherally located lesions such as lateral abdominal wall mass in a large diameter patient, any tumor needing focal electron therapy or total skin electron therapy, or concerns with large integral doses or low dose spillage are not suitable for Tomotherapy. Additionally, there is no integrated motion management in Tomotherapy, hence it is less efficient than gating or deep inspiration breath hold in normal tissue sparing in tumors located in lower thorax or upper abdomen. The system is not equipped for delivering simple 3DCRT treatments. Since there are no cones and the smallest field size is still considerable, very small volume treatments such as radiosurgery for trigeminal neuralgia or for very tiny lesions may not be deliverable without significant spread-out dose.

Some salient points about the machine that influence the planning process [9, 10]:

1. The LINAC energy is fixed at 6 MV without flattening filter, irrespective of depth.
2. Mode of treatment delivery is helical with 360° gantry rotation with delivery at 51 beam angles 7° apart from each other, which means

that the couch with be in the beam path for a considerable period of treatment delivery and hence attenuation due to the same has to be accounted for in the planning process.

3. Image guidance is integrated in the form of a fan beam MVCT beam (called CTrue) with 3 MV energy. No treatment fraction can be initiated before imaging. Imaging is 3-dimensional, in treatment position and using treatment source. The image quality may be less than for kilovoltage CT (KVCT) but suffices for most treatments. High atomic number materials such as dental implants, hip prosthesis, etc., can be imaged without artifacts unlike KVCT.
4. The gantry bore is 85 cm and source to axis distance (SAD) is also 85 cm.
5. There is one set of independent jaws (15 cm thickness) and the jaw width for various treatments can be 1 cm, 2.5 cm, or 5 cm (smaller widths for more complex or smaller field treatments such as stereotactic body radiation therapy (SBRT). The jaws can be in static mode or dynamic mode depending on the kind of modulation needed (lesser scatter superior and inferior to target with dynamic mode). Pneumatically driven binary MLCs (32 pairs) are used for further beam shaping and the beam that finally emanates is a modulated fan beam. MLC leaf projects to 6.25 mm along transverse axis at isocenter.
6. Beam modifying devices such as wedges and external shields cannot be used. There is limited benefit of bolus due to rotational beam.
7. Couch movement is constant throughout treatment for a given plan, with direction towards the bore during treatment. Hence treatments that involve below hip irradiation may need simulation in feet first position. Also, the couch is capable of lateral movement of up to 2.5 cm on either side and only rotational shifts in roll can be corrected besides translational shifts at the time of verification imaging.

25.4 Preparation and Simulation Process

The mould room process should account for the fact that treatment would be carried out with a closed gantry system with a maximum bore of 85 cm, and only accessories that would fit into that dimension should be used. The positioning and immobilization devices should give a stable and reproducible set up due to inability to correct rotational shifts in pitch or yaw. Indexed positioning devices, whenever feasible, would minimize the possibility of rotational errors considerably. Use of bolus, or any additional devices whose positioning cannot be guaranteed on a daily basis, should be limited. The side-to-side dimensions of the entire set up should be limited to 70 cm or less. The target needs to be as close to the center of the bore (center of the 85 cm ring) as feasible to ensure homogenous dose without thread effect. For this purpose, the mould room process may require off-center positioning of a carcinoma breast case where the target (breast) is relatively lateralized and peripheral. Patient is simulated in the treatment delivery position. Simulation should ensure that in the region of the target, the entire circumference of the body as well as all accessories (circumferential extent of vacuum cushion or cast, manifold cushions, etc.) are included the CT scan acquired, since contribution from attenuation due to beams passing across the entire circumference has to be accounted for. This may require the use of a larger field of view (FOV) than usual, but efforts should be made to limit the FOV to minimum required; too large an FOV will degrade the image quality. The height of the couch should be such that the entire couch width is included in the scan. Usually a 10 cm clearance from the FOV edge ensures this. Multiple LASER alignments apart from fiducials should be marked on the body to ensure correct position reproducibility at treatment.

Slice thickness should be uniform throughout, and is generally 2–3 mm. The planning CT should be extended cranially and caudally beyond the target for accurate dose calculations. This extent may vary from at least 3.5 cm on either side for gantry width 1 cm and 8.5 cm for gantry width 5 cm. As a rule of thumb, scans are extended for 10 cm in either direction. The rest of the immobilization and simulation process (fiducials, contrast administration, bowel/bladder protocols) are similar to that used for other LINACs.

The Tomotherapy planning system (TomoPlan) accepts only raw CT DICOM data. Any third party treatment planning system that manipulates CT images before transfer should not be used. The existing planning system is not suited for extensive contouring nor does it accept any additional image sets (MRI, PET, prior CT) for fusion with the planning CT dataset. It is used only for minor corrections. For the purpose of delineation, any other contouring workstation can be used and contoured images along with structure sets can be transferred to planning system.

25.5 Contouring Tips

Target volumes and organs at risk (OARs) are case-specific and are no different from non-Tomotherapy situations.

Skin or patient body is not required for optimization by the system but when delineated, it helps in limiting/defining other structure dimensions and for quantification and control of dose spill during planning by displaying Global dose maximum outside target. It represents all normal tissue not included in any other contoured volume.

Contours should be smooth and all efforts should be made to avoid any erroneous or stray volumes. PTV should be limited inside the body contour by at least 1 voxel (2–5 mm depending on site) since the optimizer tries to push dose into every target voxel. Consistency in contour across various slices should be ensured with no sudden jumps in shape or size from one slice to the other.

Since treatment is delivered rotationally, many dose-limiting help structures are needed besides OARs to reduce dose spillage. When there are paired OARs in the field (e.g., lungs as OAR for breast cancer), drawing them separately helps control dose to each of them better than a single large volume. Also sub-segmentation (dividing ipsilateral lung into segments that lie closer to the breast and farther from it) also helps refine and define the dose fall-off. All empty regions (posterior neck in head-and-neck radiation, soft tissue between multiple targets in the same vicinity, e.g., prostate and pelvic nodes in prostate cancer, right and left neck PTV in head-and neck-cancer) should be delineated as dose-limiting volumes (DLV). DLV should ideally be separated by 1–1.5 cm from planning target volume (PTV) to ensure optimum PTV coverage. Ring structures drawn around the PTV at 1–2 cm margin may help control dose spill beyond that limit. Partial rings around PTV (e.g., different rings towards skin and towards viscera) may help alter the rate of dose fall-off by giving different constraints. Some of these DLVs may be used to block the beam projection in that direction (complete or directional) in the planning system. For instance, periphery of opposite lung may be drawn as blocking structure for a carcinoma breast case to limit dose to opposite lung and breast. Figure 25.3 illustrates some common contouring scenarios where DLVs are required.

If use of bolus is being considered (although due to helical delivery, impact is expected to be lower), it should be prepared and included at the time of simulation to study its true impact. An additional image set without bolus should also be taken to assess the degree of benefit, if at all.

Rotational treatment delivery minimizes the skin sparing effect. Targets too close to the skin may lead to high skin doses, especially with respiratory motion, and adequate precautions should be taken to avoid this. If the PTV contour extends to skin or outside it, the optimizer will try hard to push dose into that voxel increasing fluence in air, and results in unacceptable hot spots even if they are not displayed on the plan image.

When drawing multiple targets (cranial and spinal in CSI, multiple brain metastases, postoperative cervix bed and pelvic nodes, breast and supraclavicular nodes), control of OAR dose and optimization within targets is better if they are drawn and optimized as separate targets rather than a single volume even if same dose is being prescribed.

25.6 Planning and Plan Evaluation

All planning images are down-sampled to 256 × 256 in planning workstation. After importing CT images and radiation therapy structure set into planning system and contour correction as required, the CT couch is identified and removed

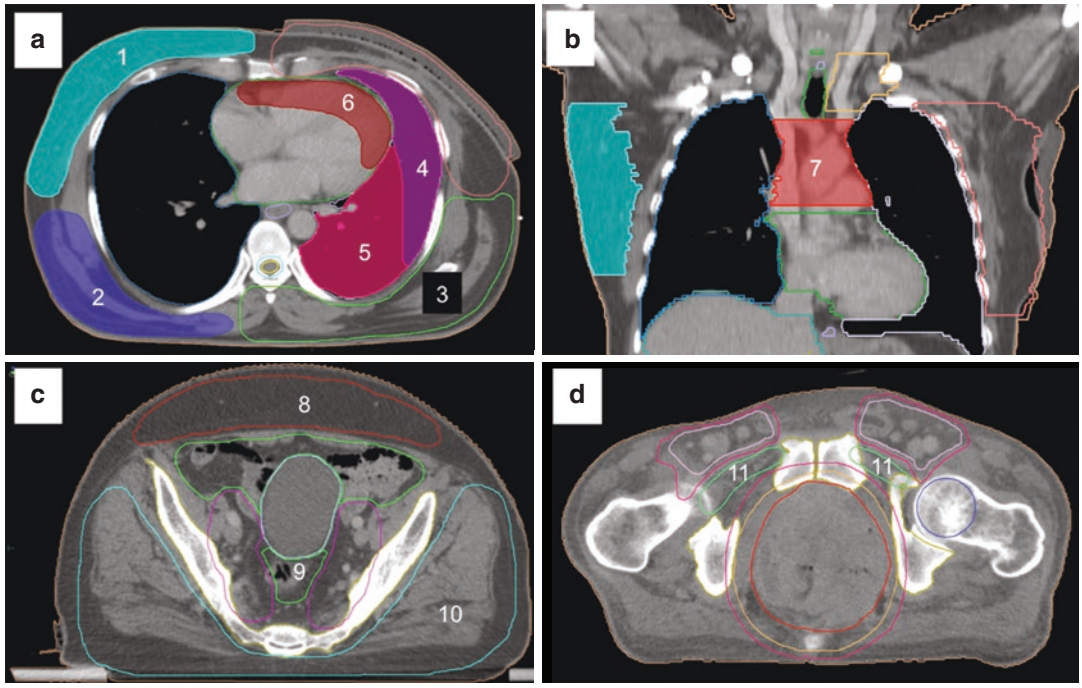


Fig. 25.3 Radiotherapy planning images showing the various dose limiting volumes (DLVs) needed for planning a case for tomotherapy. (**a**) A case of carcinoma breast for chest wall and supraclavicular radiation with bolus over chest wall. Contralateral breast (1) can serve as DLV. Opposite side lateral chest wall (2) serves as directional block to reduce dose spill to right lung. Rest of left chest wall (3) is another DLV to reduce spillage from high dose volume in left chest wall target. Left lung is divided into lateral (4) and medial (5) segments and differential constraints may be given to each for dose optimization. (**b**) High dose spill to anterior heart (6) and be prevented by delineating it separately as DLV. Another coronal section of the same patient shows a superior DLV above the heart (7) to reduce dose spillage into mediastinum. (**c**) A case of carcinoma prostate with anterior abdominal wall (8) as DLV, a loop of bowel (9) between the right and left pelvic nodal target volumes that needs optimized to reduce dose spillage from both targets. (**d**) A case of carcinoma anal canal with prostatic involvement with target volumes including primary site as well and pelvic and inguinal nodes. The targets are separated by unnamed tissue (11) which needs to be delineated as DLV to prevent dose bridges

from the CT scan image, and in its place, the Tomotherapy couch is virtually inserted. This step helps account for the treatment couch attenuation irrespective of the kind of CT scanner used.

The contoured structures have to be separated into targets and OARs. If there are multiple overlapping structures, the overlapping priority is defined for the optimizer. The optimizer always gives a higher weightage to the target. Also, among different overlapping volumes, the structure with the higher overlap priority (lower numeric digit) gets more weightage (overlap priority 1 > 2). For instance, consider a head-and-neck cancer case (carcinoma right tonsil T2N1M0) where there are two targets (PTV54 which includes bilateral neck node stations II–IV, and right tonsillar region with margins, PTV70 which includes the gross tonsillar lesion with 1 cm margin and gross right level II node with 1 cm margin). The right parotid is partially overlapping PTV54. Also assume that a part of mandible is within PTV54 and we wish to give it a serial dose constraint (Dmax < 53 Gy). The other OARs for head and neck may also have a partial overlap with PTV54. The targets are defined as overlap priority of 1 for PTV70, and 2 for PTV54. In this manner, the optimization for PTV54 happens only for the volume outside PTV70. If PTV54 were given priority of 1, the optimizer would not consider the other two targets since they are completely hidden within PTV54. Now,

for the OARs, the part of the right parotid overlapping with PTV54 would not be considered for dose optimization. Also, the maximum dose constraint for the mandible overlapping with PTV70 cannot be met because it being an OAR has lesser priority than the PTV. For achieving these objectives, the PTV may further be divided into non-overlapping and overlapping parts (PTV54 outside parotid, PTV54-parotid overlap, PTV54-mandible) and they may separately be optimized with differing objectives (Fig. 25.4). The cumulative dose volume profile of the entire volume can also be seen on the dose volume histogram (DVH). It is possible to select certain volumes only for dose display and not "use" them for optimization, e.g., right cochlea for a left parotid malignancy treatment, or spinal cord for an early breast cancer treatment. Figure 25.5 details the various planning steps for a case of bilateral breast carcinoma treated with helical tomotherapy

Tomotherapy room has a set of green and red LASERs. The red LASER intersection correspond to the machine or bore isocenter, and the green LASER is 70 cm outwards horizontally, which is called the virtual isocenter. On simulation, the center of the CT scan defaults to the green LASER. After the images are imported into Tomoplan, the red LASER as identified by the planning system should be matched to the fiducial marks. Red LASER (i.e., fiducial slice) can offset ~18 cm from green LASER (i.e., slice that is midway between the superiormost and inferiormost sections). This forms the planned position.

Subsequently treatment delivery mode (Helical or Direct), plan mode (IMRT or 3DCRT), field width (1, 2.5 or 5 cm), jaw mode (fixed or dynamic), pitch, and image value to density table (IVDT) are selected. The 3DCRT mode is not true 3DCRT but represents planning in the static gantry mode, which is most commonly used for lateralized breast treatments simulating tangential fields (effect akin to forward planned IMRT). If 3DCRT is selected, beam angles have to be predefined. Usually a single pair of beams is used but some plans may benefit with 2 or 3 pairs as well, with dose spill much lesser than helical tomotherapy despite use of multiple beam pairs.

For the bilateral breast carcinoma plan shown in Fig. 25.4, helical mode with 2.5 cm jaw width and dynamic delivery was selected. Target goals and OAR constraints were specified in the optimization window. The detailed planning process is given in image description.

After the dose—volume parameters for a given target are achieved (say at least 95% of target volume received the prescription dose), look for both

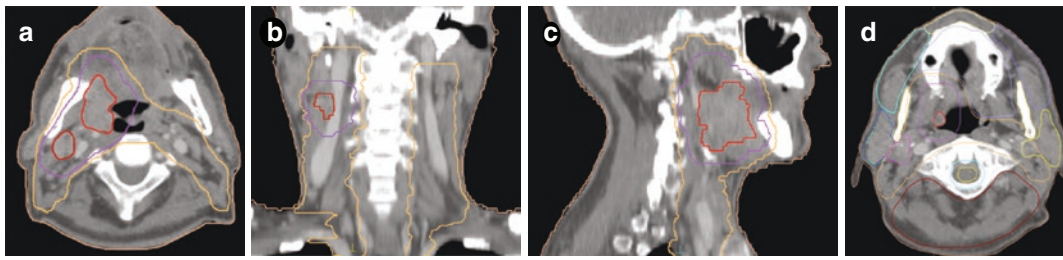


Fig. 25.4 Carcinoma right tonsil T2N1M0, planned for radical radiation (**a**–**c**, axial, coronal and sagittal sections). GTV primary (red) and GTV node (dark red) are delineated. PTV70 (purple) is 1 cm expansion around GTV. PTV54 (orange) is another 5 mm expansion around PTV70 and also includes bilateral neck node levels II–IV. The overlap priority given to PTV70 is 1 and PTV54 is 2. During optimization, the part of PTV54 overlapping with PTV70 is not optimized for 54 Gy since it has lesser priority than PTV70. (**d**) Right parotid partially overlaps with PTV54.Since it is an OAR, it has lesser priority than the target. During optimization, only the part outside PTV54 is optimized for parotid constraint. To prevent hot spots within the overlap region without underdosing target, multiple volumes are generated: PTV54 minus parotid, PTV54-parotid overlap (magenta) and parotid outside PTV (dark blue) and the first two are optimized as separate targets. Similarly volume of mandible overlapping with PTV54 can also be delineated separately and optimized to reduce hot spots. Posterior neck, oral cavity, lips, buccal pad of fat are all delineated as dose limiting volumes (DLVs) to prevent low dose spill

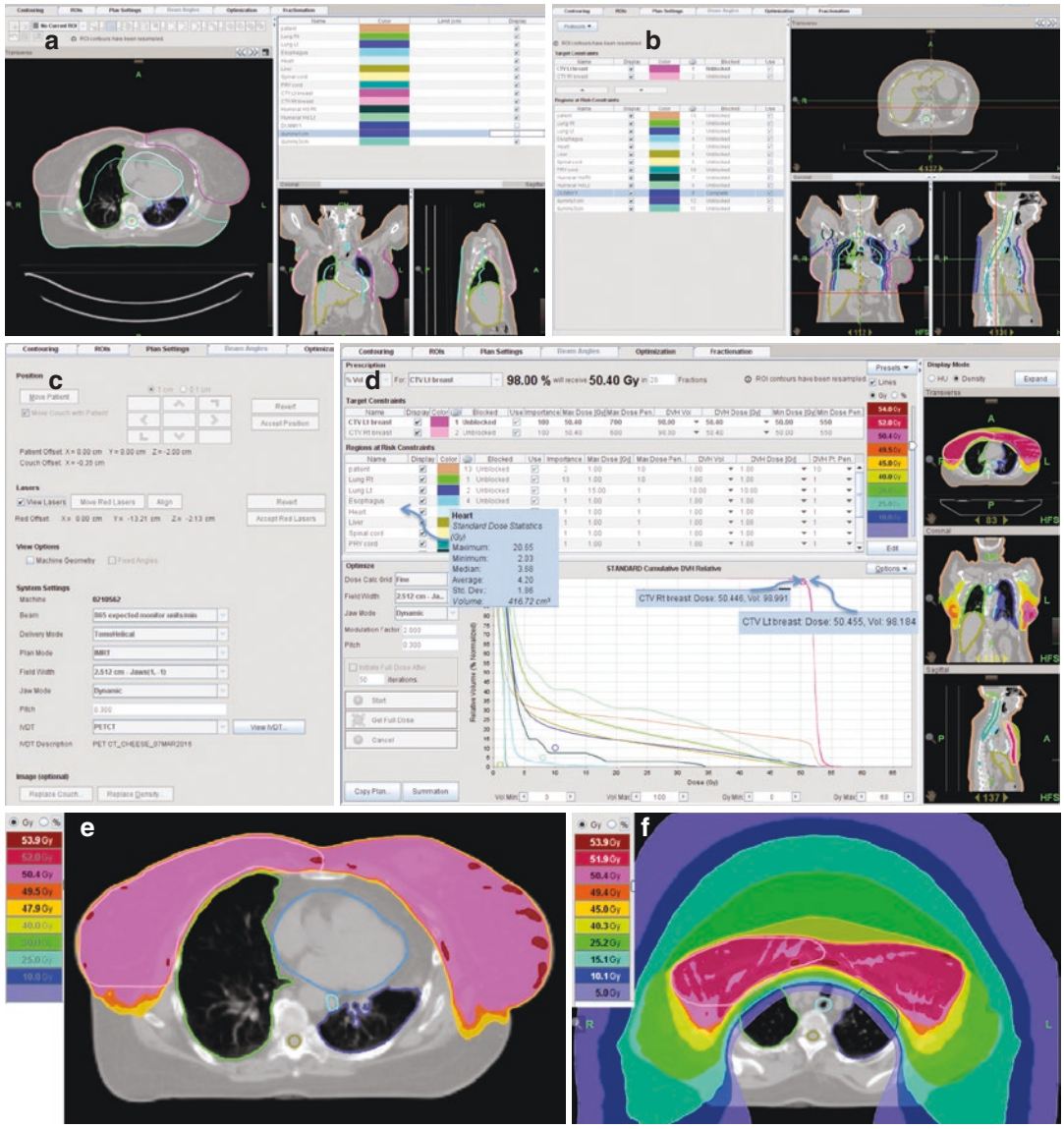
Fig. 25.5 (**a**) Bilateral breast cancer CT and RT structure sets imported into Tomoplan. Additional contouring of DLVs can be performed at this step in "Contouring" tab if not done already. Note the FOV is large enough and the couch height optimal to include the entire width of CT couch in axial image. (**b**) Note the axial section where CT couch has been replaced by tomotherapy couch. In the ROIs tab, the contoured structures are segregated into targets and regions at risk. (**c**) In the plan settings tab, the red LASER is brought to align with the fiducial markings. Various plan parameters (helical delivery, IMRT, field width, jaw mode etc.) are specified at this step. Since this plan was taken for helical delivery, the beam settings tab (needed for TomoDirect) is not highlighted. (**d**) The optimization tab requires inputs for all target and OAR dose requirements, Total dose, dose per fraction, percent volume coverage requirement by prescription isodose have to be specified. Overlap priorities have already been defined earlier but have to be checked here. OAR constraints can be given in terms of maximum and volume dose constraints. Up to 3 volume constraints can be given for an OAR. "Importance" and "Penalty" for targets and OARs are specified in order of importance. The dose volume histogram at the bottom shows real time dose optimization over several iterations. The colored circles specify the prescribed goals and the solid lines represent the dose for a given volume at that stage of the plan. Both absolute and percentage volume parameters can be assessed. Dose distribution across all 3 planes can be viewed. The various dose levels can be customized as per case and planner/evaluator preference. Ideally, doses at 100%, 105–107% and above, 95%, 90%, 50%, 20% of prescription dose are visualized in all planes as well as on the DVH to evaluate the dose distribution. The target goals are achieved first and then the constraints for specific OARs may be made more stringent to achieve lower doses. For example, if V20 for lungs is achieved at 20% and V5 at 45%, the optimizer may be made to work for achieving V20 of 18% and V5 of 40%, further optimizing till the target coverage starts to reduce. The hot spot region of each target and OAR seen as tail on extreme right is to be especially evaluated and identified in axial slices. Scrolling over DVH will give the respective dose level for a given volume and vice versa. (**e**) The final dose distributing shows a highly conformal plan and doses of 107% and above are scattered and amount to less than 2% of total target volume. There are no regions of high dose bands or strips. (**f**) When reviewed for low dose regions up to 5 Gy and doses higher than 107% prescription, the true heterogeneity and integral dose may be apparent. Optimization is continued till a satisfactory plan is achieved. A final check on all low dose distributions away from the target should finally be made before iteration at fine resolution and final acceptance of plan

hot and cold spots and their respective magnitude, volume, and location. The optimizer goals with importance and penalty may be changed to fine-tune till satisfactory distribution is achieved. A cold spot may be acceptable if it is <1% of PTV volume, receives dose of at least 95% of prescribed, and is located in the periphery of PTV (never within clinical target volume, CTV) where it is unlikely to compromise disease control. A hot spot volume should ideally be less than 15% of PTV, located within CTV (preferably within GTV) but never at the periphery of PTV at interface with OAR, and magnitude ideally less than 115% of prescription dose, with less than 15% of its volume receiving more than 110% prescription dose. Check for any high dose volumes (more than prescription dose) outside PTV and try to eliminate or at least reduce them. Whenever hot spots are observed at periphery in a tomotherapy plan, review the dose constraints for adjacent OAR and try to relax them for reducing the hot spots and then tighten those constraints gradually till satisfactory distribution emerges.

After a satisfactory plan is achieved and fine resolution optimization achieves final doses, it is reviewed by clinical and physicist and approved if acceptable. A patient specific delivery quality assurance of all plans is recommended before treatment delivery and a variation of up to 3% is acceptable. After approval, the given plan is available for delivery at the treatment station.

25.7 Summary

The Tomotherapy planning process is fairly user-friendly but involves a lot of effort and foresight to identify possible areas of dose spill or low dose spread and then mark these with dose limiting volumes. It is especially well suited for large and complex volumes though not applicable across all teletherapy indications. Proper case selection ensures optimal clinical outcomes. The principles of plan evaluation remain the same as all other modalities with a few equipment-specific tweaks.



Source of image Images have been taken from patients treated by author and consent has been taken.

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26 Plan Evaluation in LINAC Based SRS and SABR

Prashanth Giridhar

26.1 Salient Points

1. In SRT/SRS, the definitions of GTV, CTV, and PTV have been largely ignored
2. Traditionally, prescription has been done to a particular isodose
3. Plan evaluation traditionally included isodose coverage instead of dose volume histogram
4. *ICRU 91 recommends use of dose volume parameters*
5. Absorbed dose at a point is not meaningful in SRS due to heterogeneity within target volume

26.2 Reporting of SRS Plan Should Include the Following as per ICRU 91 [1]

1. Brief clinical history
2. Relevant clinical examination
3. Location of lesion to be targeted with radiotherapy
4. Diagnostic technique used for identification of lesion
5. Histological diagnosis
6. Prior treatment
7. Performance status
8. Treatment intent (Curative vs palliative)
9. Patient simulation (Immobilization devices, simulation protocols, etc.)
10. Description of target volumes (GTV, CTV, PTV) and organs at risk
11. Planning aims and dose volume constraints
12. Dose reporting to target and organs at risk

26.3 Dose Reporting [2, 3]

The following metrics are to be included in dose reporting of SRS.

26.3.1 Metrics for Target Coverage

1. PTV median absorbed dose (D50%)
   Note: If CTV is defined, CTV median absorbed dose is to be reported. In peripheral lung lesions, where the dose distribution is strongly affected by tissue density, a dose to target (GTV or CTV) that does not include uninvolved lung parenchyma should be reported
2. SRS PTV D-near max
   Note: For PTV > 2 cc, report D2%. For PTV < 2 cc, report D35mm^3
3. SRS PTV D-near min
   Note: For PTV > 2 cc, report D98%. For PTV < 2 cc, report PTV D (v – 35 mm^3)

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26.3.2 Metrics to Report for Doses to Organs at Risk

1. Vd
   Note: Volume of tissue receiving a clinically relevant dose
2. Dmean
3. Dmedian
4. SRT D near max (D2% or D35mm^3)

26.4 Indices in SRS Plan Evaluation

26.4.1 Conformity Index

There are different conformity indices described. The most common one used is the Paddick conformity index. It is given by the formula:

$$\text{Paddick Conformity Index} = \frac{TV_{PIV}^2}{TV \times PIV}$$

TV_{PIV} Target volume within the prescription isodose volume; TV Target volume; PIV Prescription isodose volume

26.4.2 Gradient Index

$$GI = \frac{PIV_{half}}{PIV}$$

PIV_{half}: Prescription isodose volume at half the prescription isodose; PIV: Prescription isodose volume

26.4.3 Homogeneity Index

Due to huge differences in the dose within the PTV in stereotactic treatments, a consensus has not yet been reached in defining homogeneity index for SRS/SABR plans. It is advised to note the D2% and D98% for high and low dose, respectively.

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Part IV

Practical Radiobiology

27 Clinical Significance of Cell Survival Curves

Prashanth Giridhar and Goura K. Rath

27.1 Introduction

Cell cycle in a dividing cell consists of two phases—the mitotic (M) phase where the cell actually divides and the S (synthetic) phase where the DNA is replicated. These are separated by two gaps, the G1 and G2 phases. The time between two successive divisions is called the cell cycle time. Of these different phases, the G2M phase is the most radiosensitive while the S phase is the least radiosensitive. Cell death of non-proliferating cells is defined as the loss of specific function and for cells capable of many divisions it is defined as the loss of reproductive integrity.

Cell death induced by radiation at conventional fractionation is primarily by creation of double strand breaks. Explaining how radiation interacts with DNA leading to cell death is beyond the scope of this chapter. At higher dose per fraction other processes like endothelial damage and immune system stimulation play a role.

27.2 Cell Survival Curves

Cell survival curve is used to describe the relationship between the surviving fraction of cells to radiation and the absorbed dose. The surviving fraction is usually represented in a logarithmic scale in the cell survival curves. The shape of cell survival curves also depends on the type of radiation used. Neutrons and carbon ions which are densely ionising show an exponential curve while X-rays and gamma rays show an initial slope followed by a shoulder which again becomes straight (Fig. 27.1).

Experimental studies on cell lines and clinical data have helped us in deriving a meaningful cell survival curve. Performing studies on cell lines and collecting data from clinical studies is often cumbersome and time taking.

Mathematical models with a strong biological basis have helped us in understanding and explaining this curve. These will help in improving therapeutic ratio by creating dose fractionation schedules with equivalent or higher biological effective doses. This chapter mainly focuses on models explaining the cell survival curve of X-rays (Llow LET).

27.3 Mathematical Models

Older empirical models were derived from past clinical data and could go disastrously wrong if used outside the dose fractionation they were derived from. These include the cumulative radiation effect model (CRE), nominal standard dose model (NSD), time dose fractionation model (TDF) and tumour significant dose model (TSD).

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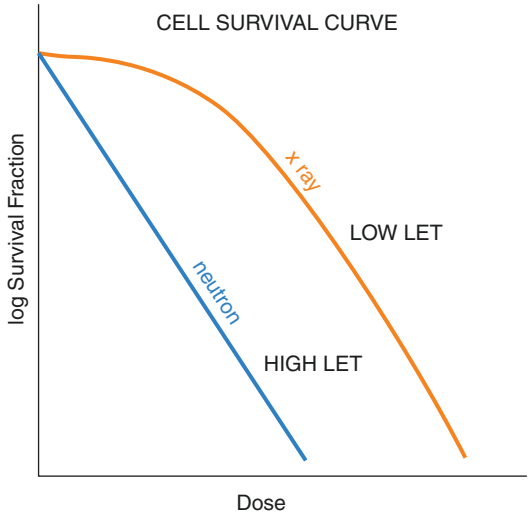

Fig. 27.1 Representative image of cell survival curve. Note that the cell survival curve of neutrons is a straight line while that for X-rays the survival curve has an initial slope followed by a shoulder and then becomes a straight line

The failure of these models led to creation of the linear quadratic model (LQ).

27.4 The Linear Quadratic Model

The LQ model is a mechanistic, biologically based model. It has sufficiently few parameters to be practical. It is reasonably well validated experimentally and theoretically. The model makes a few assumptions to work well. The assumptions include:

1. Cell killing is primarily a result of DNA damage (double strand breaks)
2. For multifractionated treatment, the fractions are well separated in time
3. Irradiation time for EBRT is short and with a constant dose rate

The *LQ model considers two types of radiation damage*:

- The first type of damage, responsible for *the linear component*, is assumed to result from a single event. This damage is *lethal* for the cell. The probability to produce such a damage is *proportional to dose*. This is called the *alpha* component.
- The second type of damage, responsible for the *quadratic component*, is by itself not lethal for the cell. This is called *sublethal damage*. Only combination of two such lesions can yield a lethal event for the cell. *The probability to produce a single sublethal damage is again proportional to dose.* The probability to produce two of such lesions is proportional to the square of dose. This constitutes the *beta* component.

The survival at a given radiation dose is due to a combination of alpha and beta killing and can be represented by the following formula:

$$S(D) = e^{-\alpha D - \beta D^2}$$

S: Surviving fraction at dose D; D: Dose

The above formula works well for single fraction treatments. When the treatment is fractionated and protracted, a time factor has to be included in the formula to account for *dose rate* and also *the rate of damage repair* during this time. This modification called the generalised time factor (G) was provided by Lea and Catcheside.

$$S = \exp\left[-\left(\alpha D + G\beta D^2\right)\right].$$

G: Generalised time factor

27.4.1 The Alpha by Beta Ratio and Its Implication in Radiation Oncology

The radiation dose at which the alpha killing (lethal) is equal to beta killing (combinations of sublethal killing leading to lethal killing) is called the *alpha by beta ratio*. Its unit is *Gray*. Cells with poor repair capability (e.g. tumours) tend to develop more lethal damage than cells with good repair capability (e.g.: Late responding normal tissue). This leads to a higher alpha/beta ratio for tumours with a straighter cell survival curve than late responding tissue

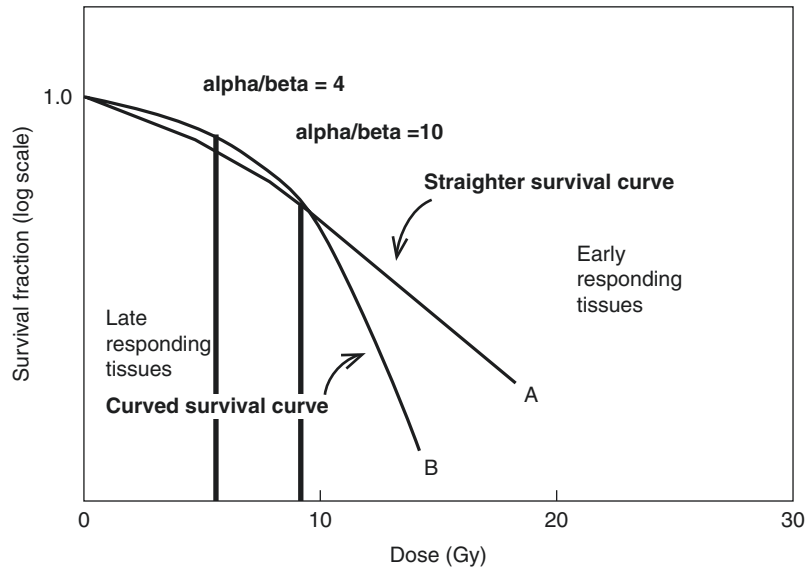

Fig. 27.2 Difference in cell survival curve between early (tumour) and late responding tissue as explained by LQ model

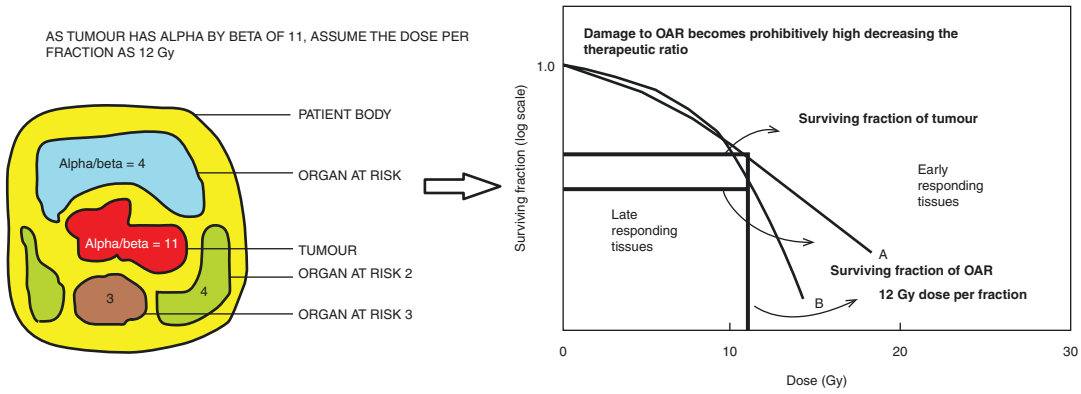

Fig. 27.3 Effect of different tissues with different alpha/beta ratios as explained on cell survival curves

(Fig. 27.2). This difference in cell survival curves provides rationale for fractionated radiation therapy treatment.

The alpha by beta ratio for most tumours is 10 or higher with prostate and breast cancers being the exceptions (<3). The alpha by beta ratio is the dose at which the survival curve bends and killing tends towards exponential. Therefore, adopting a dose per fraction more than the alpha by beta ratio will kill more cells than when dose per fraction is less than the alpha by beta ratio for the same given total dose. This seems practically feasible only in tumours with a low alpha by beta ratio as normal late responding tissue around the tumour with a lower alpha by beta ratio tends to get damaged more. This phenomenon is pictorially depicted in Fig. 27.3 for better understanding. Alpha/beta ratio of different tissues is summarised in Fig. 27.4.

The classical LQ model described above has the following limitations:

1. It does not include the effect of redistribution and reoxygenation in a protracted treatment course
2. The cell survival curve predicted by the LQ model is continuously bending but in reality, the cell survival curve becomes linear at higher doses

Early-Responding Tissues	α/β	Late-Responding Tissues	α/β^b
Jejunal mucosa	13	Spinal cord (110, 166, 245, 284, 285, 322)	1.6–5
Colonic mucosa	7	Kidney (44, 127, 291, 305)	0.5–5
Skin epithelium	10	Lung (90, 211, 214, 275, 289, 295)	1.6–4.5
Spermatogenic cells	13	Liver (91)	1.4–3.5
Bone marrow	9	Human skin (32, 211, 279, 280)	1.6–4.5
Melanocytes (302)	6.5	Cartilage and submucosa (171, 329)	1.0–4.9
Tumors			
Mouse fibrosarcoma metastases (173)	10	Dermis (106)	2.5 ± 1.0
Human tumors (169, 171, 195, 258)	6–25	Bladder (252, 265)	5.0–10.0
Experimental tumors (306)	10–35	Bone (212)	1.8–2.5

Fig. 27.4 Alpha/beta ratio of different tissues

3. Robust clinical data is missing for LQ model validity at high dose per fraction (>10 Gy)

The solutions to the above limitations are explained in brief in the next section.

27.5 The LQR Model

The LQR model is an extension of LQ model to account for redistribution and reoxygenation. It regards both the processes by a single term called re-sensitisation. This model adds two parameters to the LQ formalism—re-sensitisation magnitude and re-sensitisation time. It assumes that the re-sensitisation is monotonic i.e. it always increases the radiosensitivity of tissues. Explaining the LQR model in detail is beyond the scope of this chapter and readers are requested to refer to the original article by Brenner et al. on LQR model [1].

27.6 Models for High Dose per Fraction

The LQ model fails at high dose fractionation and due to continuously bending curve predicted by it, the model overestimates the killing at higher doses. The following models have been proposed to circumvent problems in the era of SRS and SBRT:

1. Universal survival curve
2. LQL model

27.7 Universal Survival Curve (USC) Model

The USC model combines the LQ model and multitarget model. The multitarget model states that multiple targets are hit for cell killing after radiation. As there is no clear biological basis for the above statement at low doses (DNA is the target), the multitarget model was not universally accepted. But at higher doses, with endothelium and immune cells also becoming targets for tumour cell kill, the multitarget model started getting importance. The USC model uses the LQ model for survival prediction at low dose per fractions and the multitarget model for higher dose per fraction. By combining the two models, the curve predicted at higher doses is straighter and more in line of experimental data. The model introduced two terms i.e. surviving fraction equivalent dose (*SFED*) and standard effective dose (*SED*). Explaining the USC model in detail is beyond the scope of this chapter and readers are requested to refer to the original article by Park et al on USC model [2].

As all processes involved in cell killing at higher doses have not been completely elucidated, it is difficult to decide on the most suitable model to be used in doses used in SBRT and SRS.

27.8 Conclusion

Understanding the cell survival curve and the basics of *mathematical models* predicting cell survival is of utmost importance for radiation oncologists. This chapter provides only insights into various mathematical models without venturing into formulae and technical terms. We encourage the readers to go through the original articles of LQ, LQR and USC models.

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6Rs of Radiation Oncology

28

Renu Madan and Divya Khosla

Radiotherapy is an integral part of cancer treatment in most of the solid malignancies. The basic principle is to deliver maximum dose to the target while sparing normal tissues as much as possible. Total dose, dose per fraction, overall treatment time, time interval between fractions, intrinsic radiosensitivity, and dose rate are the important factors affecting therapeutic ratio. 4Rs of Radiotherapy is a well established term and was initially described almost 50 years back for better understanding of time dose and fractionation in radiotherapy. These 4Rs are repair of sublethal damage in normal tissues, reoxygenation of the tumor cells, redistribution of the tumor cells in more radiosensitive phase, and repopulation of tumor and normal cells. Dividing a dose into several fractions will spare normal tissue due to repair of sublethal damage and repopulation of the cells if time between the two fractionation is sufficiently long. At the same time tumor damage will be higher due to reoxygenation and reassortant or redistribution of the cells in more radiosensitive phase (G2/M). Later on the concept of 4Rs was changed to 6Rs. Radiosensitivity and remote (bystander effect), are the 5th and 6th R respectively. These 6Rs are the basis of time dose and fractionation in radiotherapy.

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The 6Rs are described below:

1. Repair or recovery of sublethal damage: Cell kill by ionization radiation happens because of the DNA double strand breaks (DSB). Ionization radiation causes two types of DNA damage, non-repairable or lethal and repairable or non-lethal. Most of the radiation induced DNA damage is sublethal and gets repaired at lower doses. But at higher doses multiple sublethal damages can convert into lethal damage. High dose will lead to increased tumor cell kill as well as increased normal tissue toxicity. It is believed that tumor cells have slower recovery as compared to normal cells. Thus when a gap is given between the two doses of radiation, normal cells recover fast as compared to tumor cells. However excessive prolongation may repair tumor cells as well.
2. Redistribution: Radiation sensitivity of various cells depends on the cell cycle phase. Cells in mitosis (M) or G2 phase are most radiosensitive while least radiosensitive in G1/S phase (DNA synthetic phase) [1]. When a single large dose of radiation is given, the surviving cells are most likely to be in a radioresistant phase thus the immediate second dose may not be effective. The next fraction after a gap may allow the surviving cells to shift to more radiosensitive G2/M phase which may lead to increased cell killing [2].

S. Mallick et al. (eds.), *Practical Radiation Oncology*,
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3. Reoxygenation: Effect of radiotherapy is more profound in the presence of oxygen. In hypoxic conditions, the chemical changes in the target get repaired while presence of oxygen leads to irreparable and permanent damage [3]. Percentage of hypoxic cells in a tumor ranges from 10 to 15% and generally it is the central part of the tumor which is hypoxic. Acute hypoxia can be because of blockage of a blood vessel while chronic hypoxia can be because of the limited diffusion of oxygen in the tissues. Any given tumor is a mixture of oxic and hypoxic cells. Acute hypoxia is not permanent as the blood vessels open and close intermittently. Thus when 1st dose of radiation is given, the oxygenated cells will be killed. But as hypoxia is not permanent, when next dose of radiation is given, hypoxic cells may get reoxygenation and thus can be killed [4].
4. Repopulation: It is described as cell division in normal and tumor cells after a certain time of radiation. Rapidly dividing tissues such as skin, mucosa, and bone marrow are likely to experience more acute toxicity which happens as a result of balance between the cell killing and cell regeneration [5]. Thus delay in the radiation treatment is actually better than the treatment interruption due to any reason because of the accelerated repopulation.

   Mitotic catastrophe: Tumor repopulation during radiotherapy is considered as an undesired phenomenon. However it can sometimes lead the cells to be more radiosensitive as more cells enter into mitosis with unrepaired DNA [2].
5. Radiosensitivity: intrinsic radiosensitivity is a feature of tumor which is why few tumors respond very well to the radiation while few do not respond at all. Concept of intrinsic radiosensitivity arises from genetically instability of the tumor cells [6]. Activation of EGFR (epidermal growth factor receptor), p53 and Ki 67 protein signalling cascade is the important pathways relevant to intrinsic radiosensitivity.
6. Remote bystander effect: This occurs when non-irradiated cells, situated in the close vicinity of the irradiated cells undergo similar cellular changes as irradiated cells. Earlier it was thought the radiation exposure leads to target cell killing. However remote bystander effect contradicts this thought and cells that are actually not exposed to radiation also show sign of radiation damage [7]. This happens when radiation hit cell sends damage signals to non-target cells by gap junction. This effect has been seen in both normal and tumor cells which may also have some clinical implication.

These Rs are very important in determining time dose and fractionation of radiotherapy. In any given situation there must be an optimal combination of

(a) Total dose
(b) Dose per fraction
(c) Time interval between fractions
(d) Overall treatment time
(e) Intrinsic radiosensitivity
(f) Dose rate à brachytherapy

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29 Radiosensitizers and Radioprotectors

Renu Madan

29.1 Introduction

Radiation therapy is commonly used in most of the solid malignancies in neoadjuvant, adjuvant, definitive, or palliative setting. It damages tumor cells by either direct action (direct DNA damage) or by indirect action (DNA damage by means of free radicals). The goal of radiation therapy is to widen therapeutic ratio by delivering maximum dose to the tumor while at the same time avoiding excessive radiation dose to normal tissues to reduce the side effects. Despite the availability of advanced radiotherapy techniques, normal tissue irradiation always happens.

Although most of the cancer, i.e. head and neck, cervix, prostate, and lymphoma show good response to radiation, there are many cancers which show intrinsic radioresistance, i.e., sarcoma, melanoma, etc. Radioresistance due to hypoxia is also a major issue. Therapeutic ratio can be widened by using agents that selectively sensitize the tumor cells to radiation while protecting the normal tissues from radiation. Radioprotectors are the compounds that are used to decrease the damage to normal tissue caused by radiation. Radiosensitizers are the products that are used to enhance radiation damage to tumor cells [1]. These agents are collectively known as radiation modifiers.

29.2 Radiosensitizers

Radiosensitizers enhance the tumor cell killing without having any altered response of radiation on normal tissue. Radiation dose can be reduced depending on the extent of sensitization. Thus therapeutic ratio is widened with similar tumor control and reduced normal tissue toxicity.

The mechanism of action is mentioned below [2]:

1. Direct enhancement of radiosensitivity of tumor cells
2. Independently cause DNA damage or inhibit DNA double strand break repair
3. Disruption of cell survival pathways
4. Target vasculature of tumor cells
5. Improve oxygenation or selectively act on hypoxic cells
6. Direct cytotoxic action, thus reduce the number of tumor cells required to be killed by radiation
7. Redistribution of the cells in more radiosensitive phase

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29.3 Various Radiosensitizing Agents Are Described Below

Hyperbaric Oxygen Therapy (HOBT) As we know hypoxic cells are radioresistant, numerous trials have been conducted to manipulate hypoxic environment of tumor cells but most of them are inconclusive. Increased oxygen tension in tumor cells just before radiotherapy may lead to increased production of free radicals resulting in cellular damage. However it is cumbersome to put the patient in high pressure oxygen tank before each fraction of radiotherapy. Use of HOBT was started almost 50 years back in a clinical trial by Churchill–Davidson and Foster et al. [3]. Subsequent trials showed improvement in cervical and head and neck cancer patients using HOBT. In a meta-analysis of 32 trials using HOBT in head and neck cancer, improved local control did not turn into improved survival [4].

Carbogen Other strategy to improve oxygen tension in tumor cells is breathing carbogen which is a mixture of 95% oxygen and 5% carbon dioxide at atmospheric pressure. It does not produce vasoconstriction as with 100% oxygen. It is a simple procedure as compared with HOBT [5]. Carbogen is believed to overcome chronic hypoxia and is generally used in combination with Nicotinamide that overcomes acute hypoxia. Nicotinamide is an inhibitor of Poly ADP Ribose polymerase I which repairs single strand DNA break. However results are disappointing in clinical practice.

Metronidazole and Its Analogs Metronidazole and its analogues such as misonidazole, etanidazole, and nimorazole have been shown to increase radiosensitivity of hypoxic tumor cells [6]. These agents are selectively activated in hypoxic environment and act as oxygen and stabilize DNA so that it does not get repaired. Misonidazole deplete sulfhydryl groups in cells and thus inhibiting glycolysis and the repair of radiation-induced damage. Use of misonidazole may lead to CNS side effects. Etanidazole crosses the blood–brain barrier in limited extent and thus CNS side effects are lesser.

Nimorazole also has a better safety profile and thus high dose can be used. Nimorazole has shown to improve 5 year loco-regional control in head and neck cancer as compared to placebo [7].

Tirapazamine Tirapazamine is an agent which is selectively cytotoxic to hypoxic cells. Under hypoxic conditions it reduces to highly reactive product leading to DNA damage. It has been studied in lung and head and neck cancer. Side effects can be nausea, muscle cramps, and hematological toxicities [8]. Mitomycin-C also has selective cytotoxicity to hypoxic cells. It is a bioreductive alkylating agent and has been studied in pancreatic and head and neck cancer.

Hyperthermia Chronically hypoxic cells with a low intracellular Ph and cells in S-phase of cell cycle are considered as radio resistant and are more susceptible to thermal killing. Following are the mechanism of cell killing by hyperthermia [9]:

1. Hyperthermia increases the fluidity of membranes
2. Inhibits the metabolism
3. Inhibition of DNA, RNA, and protein
4. Inhibition of DNA repair
5. Inhibition of repair of sublethal and potentially lethal cellular damage.

Chemotherapeutic Agents Radiosensitization by chemotherapeutic agents is because of various mechanisms. Cisplatin, carboplatin, taxanes, and 5FU are commonest radiosensitizers used with radiotherapy in cervix, head and neck, esophageal and lung cancer. Nedaplatin, approved in Japan, is also radiosensitizer but less nephrotoxic as compared to cisplatin. Cisplatin produces single strand breaks by creating inter- and intrastrand DNA adducts. These single strand breaks are converted to lethal double strand breaks by radiation. Concurrent chemoradiotherapy has shown to be more effective in cervix, head and neck, esophageal and lung cancer as compared to radiotherapy alone. Due to the synergistic action of cisplatin and radiotherapy, a lower dose of each can be used which would be otherwise insufficient to

cause cell death if administered alone. The synergistic effect of cisplatin and radiotherapy is due to below mentioned mechanisms:

1. Increased binding of toxic platinum intermediates in the presence of radiation-induced free radicals
2. Radiation-induced increased cisplatin uptake
3. Cell cycle disruption
4. Inhibition of repair of radiation-induced DNA damage.

5 Fluoro-Uracil (5FU) 5FU is one of the most common drugs used for colorectal cancer treatment and breast cancer. It is an anti-metabolite agent. It also causes radio-sensitization by impairing double strand break repair during the S phase and by acting as free radical scavenger. However, as it is particularly toxic to dividing cells, clinical use is limited by its severe side effects on normal cells. For locally advanced rectal cancer, preoperative 5FU or capecitabine is now considered as the standard of care because of the decreased local recurrence rate and improved survival with addition of 5FU.

Taxanes (Paclitaxel and Docetaxel) Taxanes are microtubule stabilizers and act as radiosensitizer by arresting the cells in G2-M phase.

Topoisomerase Inhibitors: Irinotecan It is a camptothecin derivative that has its cytotoxic effect by targeting topoisomerase I. In addition to having direct cytotoxic effect, these agents have excellent radiosensitization property that may lead to increased cell killing by radiation. Combination of topoisomerase inhibitors and radiation is a new promising approach.

Gemcitabine Gemcitabine is effective as a single agent in variety of solid tumors. The mechanism of radiosensitization by gemcitabine is not clear [10]. However preliminary studies have shown that the radiosensitization with gemcitabine is not because of increase in the radiation-induced DNA double strand breaks. It is said that probably gemcitabine induced radiosensitization is due to apoptosis of the cells undergoing radiotherapy, but the exact mechanism of action is under investigation.

Thymidine analogs The thymidine analogs bromodeoxyuridine and iododeoxyuridine have been used as radiosensitizers in a battery of cancers including head and neck cancers, malignant gliomas, brain metastases, soft tissue sarcomas, intrahepatic cancers, and cervical cancers. These agents produce radiosensitization by incorporating themselves in DNA that increases the DNA susceptibility to single strand breaks from radiation-produced free radicals. However, the adverse effects such as myelosuppression and toxicity in the irradiated area are a concern.

Hydroxyurea It causes cytotoxicity by inhibiting ribonucleotide reductase, an enzyme responsible for the transformation of ribonucleotides to deoxyribonucleotides. It is often used to treat hematologic malignancies and myeloproliferative disorder [11]. Its use as a radiosensitizer is investigated since 1960s in patients with head and neck cancer, malignant glioma, and cervical cancer. Since it has no cytotoxicity for these tumors, any positive result is assumed to be because of radiosensitization.

Membrane Active Agent Cell membrane is also a critical target for cell killing. Drugs such as local anesthetic (procaine and lidocaine hydrochloride) and tranquilizers (chlorpromazine) interact with cell membranes and alter their structural and functional organization. These drugs have been observed to increase the radiosensitivity in Escherichia coli under hypoxic conditions. These drugs have been observed to enhance radiosensitivity of hypoxic mouse lymphoma cells while radioprotection of these cells was seen under euoxic conditions.

Sulfhydryl Group Suppressor Intracellular compounds containing sulfhydryl (thiol) groups are known to have radioprotective properties. Thus depletion of these compounds may increase the radiosensitivity. Glutathione is the major intracellular sulfhydryl compound. N-Ethylmaleimide, diamide, and diethylmaleate

deplete the glutathione level and thus increase radiosensitivity. Decrease in the glutathione content also inhibits the repair of single strand DNA breaks under aerobic conditions [12].

PARP inhibitors are also believed to increase radiosensitization by targeting DNA damage, endothelium, and tumor vasculature in pre-clinical studies. However, implementation of these results in actual clinical scenario is not known yet.

29.4 Radioprotectors

Other than sensitizing the tumor cells to radiation, protection of normal tissues from radiation injury is also an approach to widened therapeutic ratio. Radiation protectors protect normal tissue from deleterious effect of radiation, making a potential for radiation escalation and thus improvement in therapeutic ratio. Both acute and late toxicities can be reduced as these agents limit the initial extent of tissue damage.

Radiation exposure to normal tissue is an inevitable event which may lead to a battery of side effects ranging from mild symptoms to life threatening complications. Radiation related toxicity depends on many factors such as dose, volume fractionation, overall treatment time, and intrinsic radiosensitivity. Although advanced radiation techniques such as Intensity Modulated Radiotherapy (IMRT), image-guided radiotherapy, and proton radiotherapy have been shown to reduce these toxicities, intrinsic radiosensitivity of the cells is a component which cannot be taken care with these technologies. This is why radioprotectors are important.

Radioprotector agents should have the following characteristics:

1. It should not protect tumor cells
2. It should have minimal toxicity
3. Easy administration.

Mechanism of Action of Radioprotectors Majority of these agents prevent DNA damage by scavenging free radicals. Radioprotectors should have the capacity of entering the nucleus of the cell and to reside near the DNA because free radicals have very short life and range [2].

Although many agents have been identified as radiation protectors in preclinical stages, only Amifostine and Nitroxides have been found to be useful. In clinical setting only, Amifostine is the FDA approved agent; however, tumor protection is a controversial issue with this. Antioxidants also have shown to have some radioprotector properties [13].

Amifostine (WR-2721) It is the most widely used radioprotector as it has been shown to concentrate less in tumor tissue as compared to normal tissue probably due to tumor acidosis and lower expression of alkaline phosphatase in tumor cells. It is known to induce hypoxia in the tumor cells and causes DNA condensation [14]. It is an inactive drug and converts to active thiol by dephosphorylation by alkaline phosphatase in normal endothelium. In the dephosphorylated state, it enters into the cells and scavenges free radicals responsible for tissue injury. Studies have shown that it significantly reduces moderate to severe xerostomia in head and neck patients who receive postoperative radiotherapy. Other than xerostomia, it also protects lungs, bone marrow, heart, intestines, and kidneys and provides protection in cisplatin induced nephrotoxicity, ototoxicity, and neuropathy and cyclophosphamide induced hematologic toxicity. However 2008 ASCO guidelines state that due to concern of tumor protection, the routine use of amifostine in these settings is not recommended. Side effects of amifostine can be hypotension, nausea, vomiting, dizziness, sneezing, hot-flashes, hypocalcemia, and mild somnolence.

Antioxidants as Radioprotectors As side effects of radiotherapy imitate oxidative damage, antioxidants (Vitamin A, C, E, glutathione, lipoic acid) are believed to protect the normal cells against radiation [15]. *Nitroxide* also has unique antioxidant properties and is another promising agent for future use as radiation protectors. However as with amifostine, there is a risk of tumor protection due to non-selective free radical scavenging. The use of antioxidant vitamins during the course of radiotherapy was associated with poor tumor control in head and neck cancers.

Superoxide dismutase (SOD) is an antioxidant enzyme which is present in human cells. Ionizing radiation leads to formation of highly reactive superoxide radicals that has a potential of cellular damage. SOD acts as an antioxidant and catalyzes the conversion of superoxide to oxygen and hydrogen peroxide. Animal models have been used for gene therapy to increase SOD expression in tissue expected to receive radiation [16].

Melatonin is also an antioxidant and increases the expression of antioxidant enzymes i.e. SOD and glutathione peroxidase.

Alpha-Tocopherol/Vitamin E (Vit E) VE containing gargles before radiotherapy and 8–12 h after radiotherapy has been shown to reduce the incidence of oral mucositis in patients who received radiotherapy for oral cavity and oropharyngeal cancers.

Radiation Mitigators These are the agents that function after initial exposure to radiation and thus limit late radiation injury such as fibrosis. Pentoxifylline and vitamin E are the examples which have been used to treat cutaneous fibrosis after breast radiotherapy.

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30 Altered Fractionation Radiotherapy

Supriya Mallick and Goura K. Rath

Radiation therapy is an important component in the multimodality treatment of various tumors. The evolution of concept of fractionation was one of the major landmarks which helped in the safe delivery of radiation. The concept of fractionation was developed by Thor Stenbeck who used small doses of radiation each day to cure skin cancer and later by Coutard who showed that protracted fractionation schedule results in better tumor control as well as reduced skin and mucosal toxicity. With better understanding of 4 Rs of radiobiology, radiobiology behind different fractionation schedule was known. In conventional fractionation radiation therapy each fraction consists of 1.8–2.0 Gy and is delivered once daily for 5 days a week. The treatment is usually delivered over a period of 6–7 weeks. Hyper-fractionation, accelerated fractionation, hypo-fractionation, or a combination or hybrid fractionation are the common altered fractionation schedules used clinically [1]. A comparison of various fractionation schedules is summarized in Table 30.1.

30.1 Hyper-Fractionation

- In hyper-fractionation, radiation is delivered in smaller dose per fraction [1.2–1.5 Gy/#] with two or three fractions delivered every day with a gap of 6 h between fractions. Radiobiologically it uses the better ability of normal cells to repair injury than tumor cells
- More helpful for tumors with higher α/β ratio than that for the dose-limiting, late-responding normal tissue
- Hyper-fractionation also helps in increased tumor kill by cell-cycle redistribution
- In addition reduction of the fraction size from 2.0 Gy to 1.1–1.2 Gy permits a dose escalation to 7–17%
- Head and neck cancers have shown the maximum clinical benefit with hyper-fractionation-survival benefit of 8% at 5 years in the MARCH meta-analysis [2]
- Major limitation-logistic reasons in implementing the twice daily schedule
- Summary of few trials which evaluated hyper fractionation in head and neck malignancies is summarized in Table 30.2

30.2 Accelerated Fractionation

Radiobiological basis: accelerated repopulation is one of the major hurdles for improving tumor control. Accelerated repopulation occurs after a

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Table 30.1 Comparison of various fractionation schedules

	Radiobiological basis	Overall treatment time	Dose per #	Total dose	Acute toxicity	Late toxicity
Hyper fractionation	Normal tissues have better repair mechanism than tumor Also re-oxygenation, redistribution	Usually Same	1.2–1.5 Gy/#	Increased by 7–17%	Increased	Decreased
Accelerated fractionation	To prevent accelerated repopulation	Decreased	1.8–2 Gy/#	Same or decreased	Increased	Same/ increased
Hypo-fractionation	Useful in tumors with low alfa/beta	Decreased	>2.2 Gy/#	Decreased	Same	Increased

Table 30.2 Summary of few trials comparing conventional vs. hyper fractionation in head and neck malignancies

	Nature of trial	Number of patients	Outcome	Toxicity
RTOG 9003	Randomized trial	1076	Survival benefit with hyper-fractionation with a HR 0.81, $P = 0.05$	No increase in late toxicity with hyper-fractionation
MARCH meta-analysis	Meta-analysis	6515	8% absolute survival benefit at 5 years with hyper-fractionated radiotherapy schedule	–

Table 30.3 Summary of selected trials in head and neck on accelerated fractionation

	Nature of trial	Number of patients	Outcome	Toxicity
MARCH meta-analysis	Meta-analysis	6515	Absolute survival benefit at 5 years • Accelerated radiotherapy [ART] without total dose reduction—2% • ART with dose reduction—1.7%	–
DAHANCA 6&7	Randomized controlled trial [RCT]	1485	Disease-specific survival—73 vs 66% favoring accelerated arm Overall survival same	Higher acute radiation in the accelerated radiotherapy [53 vs 33%] Late toxicity—similar
IAEA-ACC study	RCT	458	5 year overall survival 35% vs 28% favoring accelerated arm	Higher acute radiation in the accelerated radiotherapy Late toxicity—similar
ARTSCAN study	RCT	750	No significant benefit in overall survival or locoregional control between accelerated and conventional schedules	Higher acute radiation in the accelerated radiotherapy

lag of 4 weeks and during this phase the resistant tumor clonogens start accelerated repopulation. An incremental dose of 0.6 Gy/day is required to counter the accelerated repopulation to achieve good tumor control. In accelerated fractionation schedule an attempt to complete radiotherapy before the onset of accelerated repopulation is tried.

The various accelerated fraction schedules used clinically are

- Pure accelerated fractionation regimens—pure accelerated regimens aim to reduce the overall treatment time without changes in the fraction size or total dose. Commonly used strategy includes treating 6 days in a week. It has shown maximum benefit in head and neck cancers. Increased acute toxicity is however a major concern. Some of the trails that evaluated accelerated fractionation and its results are summarized in Table 30.3.

- Hybrid accelerated fractionation schedules alter the fraction size, total radiation dose, and time distribution in addition to reducing the overall treatment time. The commonly used hybrid accelerated fractionation schedules are
  - Type A—overall treatment time is much shortened with a reduction in the total dose. The prototype for type A is continuous hyper fractionated accelerated radiotherapy (CHART)
  - Type B—duration of treatment is more modestly shortened, but the total dose is kept in the same range. Makes use of twice daily fractionation. E.g. EORTC 22851 trial. Split-course accelerated radiotherapy was previously used but is inferior due to the gap and must not be practiced
  - Type C—duration of treatment is more modestly shortened than type B. Total dose is kept same. Makes use of concomitant boost approach. One of the most widely used approach. Logistically easier with intensity modulated radiotherapy.

Continuous, hyper-fractionated, accelerated radiotherapy [CHART]: Pioneered by Mount Vernon Hospital in UK, the CHART schedule delivers a dose of 54 Gy in 36 fractions (1.5 Gy per fraction thrice daily at 6 h intervals) over 12 days. The schedule aims to improve tumor control by reducing the overall treatment time and reduce late effects by using lower dose per fraction. The trial schedule showed very good local control and tolerable acute toxicity [occurred after completion of treatment], but logistic issues and increased spinal cord toxicity are of concern.

30.3 Hypo-Fractionation

- Hypo-fractionated schedule of fractionation uses a higher dose per fraction and is best suited for tumors with low alfa/beta like breast and prostate cancer [3]. Tumors with low α/β ratio have shown better local control to hypo-fractionated radiation.
- The rationale behind hypo-fractionation in palliative setting is delivery of higher biologically equivalent doses at shorter treatment duration, but at the risk of higher late normal tissue toxicity
- The dose per fraction and fractions varies with the tumor treated and schedule.
- Trials on melanoma, carcinoma prostate, and whole breast radiation—established hypo-fractionated schedule as a standard in these tumors
- With development of modern radiation delivery technique this approach has been extended to laryngeal lung cancers and glioblastoma, showing promising results
- It is also used in the palliative setting where long term toxicity is of lesser concern.
- This reduces the number of fractions [e.g., in breast from 25 to 15] and is of economical benefit also. This approach is also suited in areas where there is high burden of patients on machines especially in developed countries.
- Summary of important trails that evaluated role of hypo-fractionation is summarized in Table 30.4.

Table 30.4 Summary of trials using hypo-fractionation

Subsite	Author/year	Nature of trial	Number of patients	Fraction size	Local control	Toxicity
Larynx	Sung et al./2013	Phase III randomized trial—T1–2 glottic cancer	156	2.2 Gy per fraction	5-year local progression-free survival was 77.8%—conventional fractionation arm 88.5%—hypo-fractionation arm	No difference in toxicity compared to conventional arm
Breast	START A trial	Phase III—early breast cancer	2236	3.2 Gy or 3.0 Gy per fraction	Similar local control	Similar late adverse effect
	START B trial	Phase III—early breast cancer	1105	2.67 Gy per fraction	Similar local control to 50 Gy/25fractions	Similar late adverse effect
Prostate	HYPRO trial	Phase III—intermediate-risk to high-risk prostate cancer	820	3.4 Gy per fraction	Not superior to conventional radiotherapy with respect to 5-year relapse-free survival	Similar acute genitourinary and gastrointestinal toxicity

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Therapeutic Index and Its Clinical Significance

31

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- The main purpose of delivering radiotherapy is to cure the disease with no or minimal normal tissue complications. An ideal radiotherapy plan should have a 100% chance of curing the disease while there is 0% chance of normal tissue complications which never occur. But in reality normal tissues undergo significant dammage by the dose required to control the tumor; while the tumor may not receive an adequate dose if the 100% normal tissue protection is planned.
- When we plot a graph of probability of tumor control in Y axis against radiation dose in X axis what we get is the tumor control probability (TCP). Similarly when probability of normal tissue complications in Y axis is plotted against radiation dose in X axis we get the normal tissue complication probability (NTCP) [1]. TCP and NTCP curves are sigmoid in shape. The therapeutic index (TI) defines how the TCP relates to NTCP for different doses of radiation (Fig. 31.1).
- TI = NTCP/TCP
- Usually radiosensitive tumors like seminoma have a wide therapeutic index, while those with radioresistant tumors have a narrow therapeutic index (Fig. 31.2).
- The therapeutic index for a particular tumor may also depend on the location of tumor, e.g., a soft tissue sarcoma of the extremity may have a good therapeutic index, while a retroperitoneal sarcoma located near to kidneys will have a very unfavorable therapeutic index.
- Dose volume histograms created in conformal radiotherapy plans and TCP and will help clinicians during treatment planning.
- An ideal radiotherapy plan where there is 100% chance of tumor control and 0% chance of normal tissue toxicity never really exists in real world scenario. Achieving an optimal balance between TCP and NTCP is a basic aim of any radiotherapy plan. This can be achieved

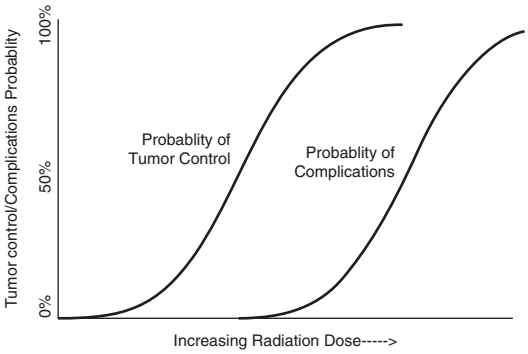

Fig. 31.1 Diagram showing concept of therapeutic index

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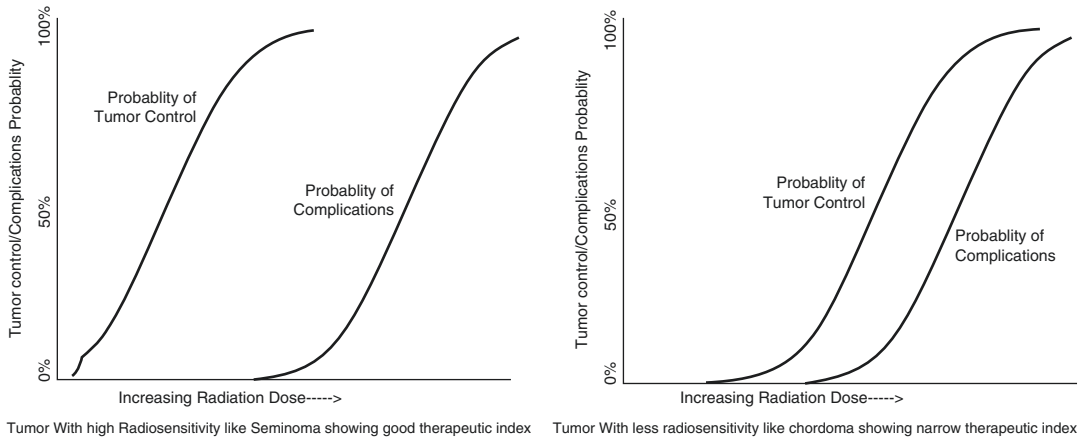

Fig. 31.2 Therapeutic index for radiosensitive and radioresistant tumors

by altering the radiation fractionation or radiation sensitizers or radiation protectors.

31.1 Modifying Therapeutic Index for Clinical Advantage

Modifying therapeutic index is the main advantage of adding chemotherapy or radiation sensitizers or radio protectors.

1. Hyperfractionation—In hyperfractionation small dose per fraction with two or three fraction delivered per day is used to achieve a higher biologically effective dose to the tumor. Using the lower dose per fraction also reduces the chances of long term normal tissue complications (shifting the NTCP to right), thereby improving the therapeutic index.
2. The therapeutic index is improved by reducing the size of the target volume and the margins by using image guidance in radiotherapy planning [2].
3. Concurrent Chemotherapy—The use of concurrent chemotherapy acts as a radiosensitizer and thereby shifts the TCP to left, thus improving therapeutic ratio. The nonoverlapping toxicity with concurrent chemotherapy (some overlapping toxicity exists like mucositis with concurrent cisplatin) does not greatly alter the NTCP.
4. Radiation Sensitizers—The use of radiosensitizers helps in optimizing therapeutic index by overcoming hypoxia. This can be achieved either by use of agents like nimorazole which is a hypoxic cell sensitizer or by administration of agents that are preferentially cytotoxic to hypoxic tumor cells (e.g., hyperthermia). This leads to shifting of TCP curves to the left, thereby improving therapeutic index.
5. Radio Protectors—The radio protectors (e.g., Amifostine) mainly act by neutralizing free radicals generated by ionizing radiations in the normal tissue, thereby reducing normal tissue complication rates [3]. Thus this leads to shifting of NTCP curves to the right, thereby improving therapeutic index.
6. Extracorporeal radiotherapy where tumor tissue is removed and the bone is irradiated outside the body may be one of the radiotherapy plans where we may archive something near to an ideal therapeutic index.

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Part V

Clinical Cases

Carcinoma Cervix

32

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32.1 History Taking

- Bleeding PV
- Discharge P/V (foul smelling)—necrotic growth
- Swelling in the groin
- Back pain—involvement of uterosacral ligament, vertebral mets
- Pain in the abdomen—PA-LN mets, hydroureteronephrosis
- Urinary symptoms—bladder infiltration
- Bleeding PR—rectal infiltration

32.2 Other Relevant History

- History of other STDs
- Multiple sexual partners—HPV
- Early first intercourse, high parity
- Smoking

32.3 Examination

- Start with inspection of external genitalia—labia majora and minora, mons
- Per speculum
  - Vagina
  - Urethral mass
  - Mass/ulcer if seen—explain in detail (size, margins, location, discharge/bleeding)
- P/V—empty bladder in lithotomy position, do a bidigital and bimanual palpation
  - Uterus-anteverted/retroverted—important during ICRT application
  - Cervical growth—in detail
  - Vagina
  - Fornices
- P/R—bimanual
  - Anal tone, rectal mucosa
  - Parametrium—thickening, nodularity, lateral extent, and fixity to lateral pelvic wall
- Examination of inguinal area—LN
- Abdominal examination—rarely hepatomegaly or PA-LN
- Respiratory, CVS and CNS examination
- Do a breast examination also

32.4 Differential Diagnosis

- Ca cervix
- Ca endometrium
- Cervical polyp—mass with bleeding

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- TB—especially when patient presents with discharge
- PID—especially when patient presents with discharge

32.5 Work-Up

- Complete blood counts, RFT, LFT
- Examination under anaesthesia and punch biopsy
- CECT abdomen and pelvis (or MRI pelvis) from stage IB
- HIV testing if at risk
- Cystoscopy and sigmoidoscopy—from stage IB2

32.6 Staging: FIGO—Clinical Staging FIGO 2018

IA—microscopic d/s disease limited to cervix <5 mm stromal invasion

- A1—<3 mm stromal invasion
- A2—≥3 to 5 mm stromal invasion

IB—disease limited to cervix with deepest invasion ≥5 mm

- B1—>5 mm stromal invasion and less than <2 cm size
- B2—≥2 cm and <4 cm in greatest dimension
- B3—≥4 cm

IIA—extension to upper 2/3 of vagina (IIA1 < 4 cm, IIA2 ≥ 4 cm)

IIB—extension to parametrium but not to pelvic wall

IIIA—extension to lower 1/3 of vagina

IIIB—extension to pelvic wall/hydronephrosis/nonfunctional kidney

IIIC—pelvis (C1) or paraaortic LN (C2)

IVA—bowel/bladder involvement

IVB—metastatic disease

32.7 Nodal Involvement with Stage

Incidence of pelvic and paraaortic nodes with clinical stage is summarised in Fig. 32.1.

Risk of Lymph node involvement as per stage

STAGE	PELVIC LN	PARA A-LN
1A1	0.5	0
1A2	5	<1
1B	15	2.2
IIA	25	11
IIB	30	20
III	45	20
IV	55	40

Fig. 32.1 Incidence of nodal involvement with stage

32.8 Prevention and Screening

- Pap smear is done for only patients with normal appearing cervix, those with visible lesion should be biopsied
- Screening should begin approximately 3 years after a woman begins to have sexual intercourse, but no later than 21 years old by 3 yearly pap smear
- >30 years—cytology + HPV testing may be done every 5 years
- >65 years—screening not required
- Pap smear not very good for screening adenocarcinoma
- Liquid-based cytology—more sensitive, and allows a faster turnaround time
- To be effective, vaccination needs to be given in adolescence (age recommended is 9–26 years, 3 doses)
- Bivalent vaccine—against HPV 16 and 18—PATRICIA trial
- Quadrivalent—activity against HPV 6, 11, 16, and 18–90% efficacy—FUTURE-I, FUTURE-II trials
- Nine-valent—in addition covers HPV 31, 33, 45, 52, and 58
- Vaccination does not obviate the need for screening as there are other virus types that cause cervical cancer

32.9 Treatment Outline

- CA in situ/IA-Conisation/LEEP/trachelectomy (1A2)/SH
- 1A1—brachy alone is also an option
- 1A2—RH is general recommendation (LN dissection is usually recommended)
- IB-IIA—surgery preferred (adjuvant RT/

CTRT as per indicated)
- 1B2, IIA2—CTRT may be preferred over surgery [1]
- IIB-IVA—CTRT
- IV—Pall RT±chemo
- Adjuvant RT (Sedlis criteria)—>4 cm, deep cervical stromal invasion, only simple hysterectomy, LVSI, closemargin-3 mm (to the middle or one-third depth)-PFS benefit [2]
- Adjuvant CTRT-LN, parametrium, margin positivity—overall survival benefit
- Concurrent cisplatin from 1B2 treated radically [3]

32.10 Surgery

- In surgically treated patients—premenopausal patients may preserve ovaries. Postmenopausal patients should also have a BSO
- LN dissection is usually recommended from 1A2 onwards
- More preferred over RT if multiple uterine fibroids are present
- Table 32.1 summarises various treatment options in carcinoma cervix

Table 32.1 Treatment options in carcinoma cervix

Surgery in early carcinoma cervix	RT in early carcinoma cervix
Surgery is preferred for young women as radical hysterectomy and pelvic lymphadenectomy Advantages of possible ovarian conservation and preservation of sexual function Shortening and fibrosis of the vagina can be limited if the woman is sexually active Pelvic relapses can be successfully cured by radiotherapy Surgery allows the status of the lymph nodes, the most dependent variable associated with survival, to be assessed accurately	Easier to deliver for patients who are obese/elderly or have severe illness—major C/I to the surgical approach Avoids the risks of anaesthesia and the laparotomy scar Iatrogenic mortality is rare Complications after radiotherapy arise later than after surgery, although radiotherapy-related complications are often permanent
	Radiotherapy-induced menopause Vaginal stenosis Late complication of radiation-induced carcinogenesis Other—cystitis and proctitis

32.11 Radiotherapy

32.11.1 EBRT Planning

2D Planning—4 field technique borders (Fig. 32.2)

- Superior border—between L4 and L5 vertebrae
- Inferior border—2 cm below the lower extent of the clinical tumour or the inferior edge of obturator foramina
- Lateral borders—1.5–2 cm outside the bony pelvic side wall
- Posterior border—lower border of S2 vertebra
- Anterior border—through the symphysis pubis

Lateral beams are usually used to spare the rectum with decreased weighting of the posterior beam. Doses of 80–90 Gy for the bladder and 70–75 Gy for the rectum and sigmoid colon are generally accepted. A comparison of 2D vs 3D planning is summarised in Fig. 32.3.

32.11.2 Conformal Radiotherapy

- MRI fusion preferable to aid in delineation, GTV as per MRI and clinical examination findings
- Bladder and rectal protocol to be adhered to
- CTV-T includes the primary GTV-T with potential microscopic spread to cervix, uterus, parametrial tissues, upper vagina, and broad and proximal utero-sacral ligaments
- CTV-N includes obturator, internal, external, and common iliac and upper presacral nodes
- CTV to PTV margin of 10–20 mm

Figure 32.4 shows conformal radiotherapy plan for carcinoma cervix.

The radiation doses for carcinoma cervix are summarised in Table 32.2.

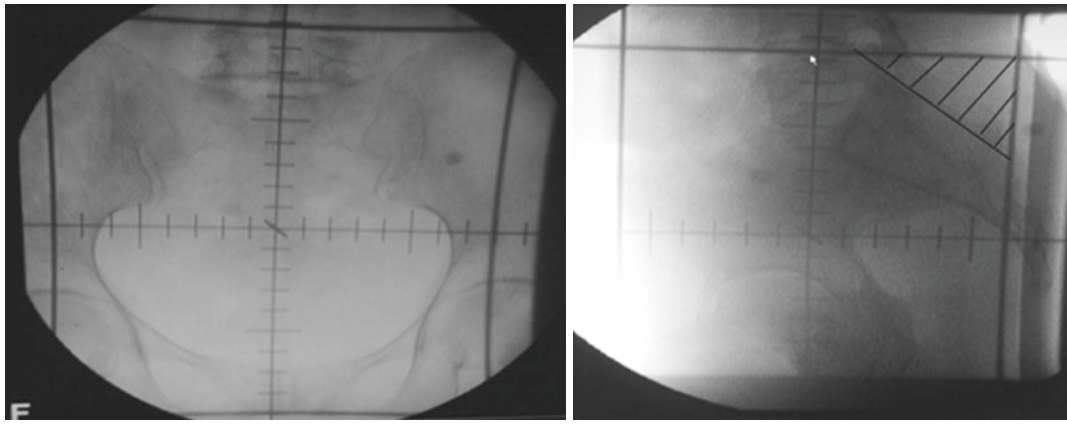

Fig. 32.2 2D planning in carcinoma cervix

2 FIELD	4 FIELD
Less time required for planning more skin reaction Can treat lower presacral lymph nodes/utero sacral Useful when lower part of vagina involved May have hour glass contraction	Less skin & subcutaneous reaction More homogenous dose distribution (especially in large separation) Lateral most part of parametrium also gets effective dose If beam weightage is adjusted the dose to bladder and rectum can be decreased Under dose to uterosacral ligaments

Fig. 32.3 Comparison of 2 field and 4 field technique in carcinoma cervix

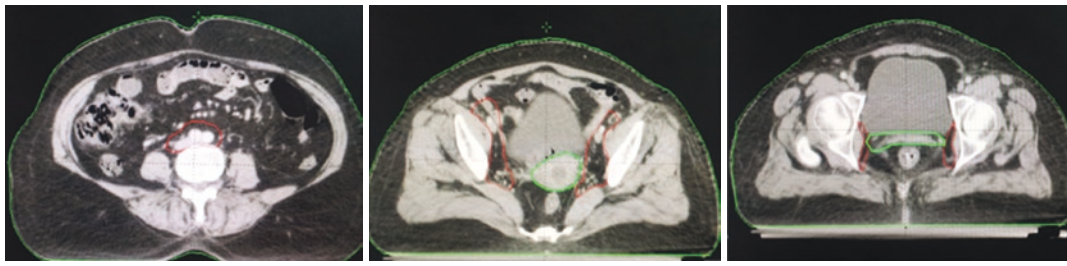

Fig. 32.4 Contouring CTV for conformal planning in carcinoma cervix

32.11.3 Brachytherapy (More Details in Brachytherapy Cervix Chapter)

- The dose is prescribed to Manchester point A, defined as 2 cm above the lateral vaginal fornices and 2 cm lateral to the central uterine tube.
- The ICRU bladder point is the posterior surface of the bladder balloon, and the rectal point is 5 mm behind the posterior vaginal wall at the level of the lower end of the intrauterine source.
- Doses of >87 Gy to the HR CTV have been associated with improved local control.
- If image-guided HRCTV includes cervix and any residual disease or T2 grey areas in MRI.
- Doses for 2 mL of tissue volume (D2cc) for the OAR are calculated at 2 Gy per fraction.

Table 32.2 Radiation options and doses in carcinoma cervix

Radiotherapy dose		
CIN/IA1	Stage IB2 and IIA	Stage IIB or above
Brachy alone	EBRT 45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks followed by	EBRT 50.4 Gy in 28 daily fractions of 1.8 Gy given in 5.5 weeks followed by
	The dose is prescribed to the 100% isodose using 6–10 MV photons	
LDR equivalent 65–75 Gy HDR—7∗5/7∗6 (35–42 Gy)	Intracavitary brachytherapy 14 Gy in 2 fractions given in 5–8 days to point A	Intracavitary brachytherapy 21 Gy in 3 fractions over 5–8 days to point A
	EBRT boost to central tumour when brachytherapy not feasible (OR if perforation) 15 Gy in 8 daily fractions/20 Gy in 11 daily fractions	
Adjuvant		
45 Gy in 25 daily fractions of 1.8 Gy given in 5 weeks 50.4 Gy in 28 daily fractions of 1.8 Gy in 51/2 weeks if macroscopic residual disease Followed by HDR—6–8 Gy at 0.5 cm from surface of applicator in 2 fractions		

Iso-equivalent doses of 80–90 Gy for the bladder and 70–75 Gy for the rectum and sigmoid colon are generally accepted.

- Overall treatment time should not exceed 56 days including brachytherapy (ideally < 49 days).
- Ideal brachytherapy application
  - Tandem—1/3 of the way between S1 and S2 and the symphysis pubis.
  - The tandem-midway between the bladder and S1–S2.
  - Marker seeds should be placed in the cervix.
  - Tandem should bisect the ovoids.
  - The bladder and rectum should be packed away from the implant.
  - The ovoids should fill the vaginal fornices—largest ovoid size to be used.
  - The ovoids should be separated by 0.5–1.0 cm, admitting the flange on the tandem.
  - The axis of the tandem should be central between the ovoids.
- Packing is done with 40% iodinated contrast to identify on radiographs.
- HDR to LDR conversion factor—0.56–0.6.

32.11.4 Palliative RT

- 20 Gy in 5 fractions or 30 Gy in 10 Fractions

32.11.5 Chemotherapy

- Concurrent weekly cisplatin 40 mg/m^2 is given for both high risk early stage disease and locally advanced tumours unless patient is medically unfit.
- Concurrent cisplatin around 10% survival advantage compared to radiation alone—greater benefit in patients in earlier stages (IB2 and IIB).
- Concurrent carboplatin or non-platinum chemoradiation regimens are options for patients who may not tolerate cisplatin-containing schedules.
- Radio-equivalence of adding cisplatin = 10 Gy.
- Pall chemo—Final analysis from the GOG-0240 trial found that bevacizumab in combination with cisplatin paclitaxel is associated with a significantly improved overall survival (16.6 months versus 13.3 months) versus chemotherapy alone and is the standard palliative chemotherapy regimen.
- Platinum paclitaxel or single agent platinum or paclitaxel may be also used as clinical scenario or financial aspects permit.

32.11.6 Follow-Up

- Every 3 monthly ∗2 years, then 6 monthly ∗5 years, then annually
- Annual Pap smear
- Imaging not routinely recommended
- Dilation to prevent stenosis started 2–4 weeks after radiotherapy

32.11.7 Survival Stage Wise

- IA: 95–100%
- IB1: 85–90%
- IB2: 60–70%
- IIA: 75%
- IIB: 60–65%
- IIIA: 25–50%
- IIIB: 25–50%
- IVA: 15–30%
- IVB: <10%

32.11.8 Recurrence

- Recurrence postsurgery—RT
- Recurrence post-RT—surgery/can try reirradiation if >1 year

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Case Carcinoma Breast

33

Rony Benson, Supriya Mallick, and Goura K. Rath

33.1 History Taking

- Breast—lump [fibroadenoma common < 35 years]
- Discharge/bleeding
  - Blood—carcinoma, duct papilloma
  - Pus—abscess
  - Milk—galactocele
- Skin/nipple changes—recent retraction of nipple
- Cyclical pain in fibroadenosis [more aggravated by cyclic changes in hormones]
- Loss of weight
- Swelling in the axilla
- Symptoms of metastasis—liver, lung, bone, brain
- Gynecological symptoms—bleeding [endometrial cancer]—common age and common risk factors

33.2 Other Relevant History

- Diabetes/hypertension—diabetes is associated with liver, pancreas, endometrium, colon and rectum, breast, bladder cancer
- Age of menarche, no of children [more in nulliparous]
- Breast feeding and duration
- OCP use—increases risk of breast, cervix cancers, but reduces the risk of ovarian, endometrial, colon cancers
- Hormone replacement therapy (HRT) use—combined HRT use is more risky than estrogen only HRT. Risk increases with duration of HRT
- Smoking—higher risk of breast cancer in younger, premenopausal women
- Family history of breast/gynecological cancers—draw a pedigree chart
- A comparison of BRCA 1 and 2 is summarized in Table 33.1

33.3 Examination

- Obesity—BMI increased risk of breast cancer

Examination of breast—patient must be stripped to waist

Inspection Always compare with normal side [arms by side/arms elevated [lump more visible as well as axilla]/bending forward]

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Table 33.1 Comparison of BRCA 1 and 2

	BRCA 1	BRCA 2
Gene	17q21	13q
Incidence	2% of breast cancers	1%
Risk breast cancer	40–85% lifetime risk of breast	25–65% lifetime risk of breast cancer
Risk ovarian	25–65% lifetime risk of ovarian cancer	10–15% lifetime risk of ovarian
Type of cancer	ER-, PR-, and HER2-negative, often with a basal-like phenotype	ER+ Can occur in males BRCA2 tumors typically express ER and PR and tend to be of higher grade with less tubule formation

1. Compare the 2 sides first—any swelling/skin changes
2. Nipple
   - Position [nipple will be pulled towards lump in carcinoma while in fibro adenoma it will be pushed away], measure length of level of nipple from clavicle and midline
   - Look for retraction of nipple [recent or not pulled towards tumor]
   - Look for erosion—Paget's
   - Discharge [blood—carcinoma/papilloma, black—duct papilloma, milky—galactocele, purulent]
3. Areola—cracks/eczema/ulcers— [involved in Paget's]
4. Breast—position, size and shape, puckering, swelling
5. Skin over breast
   - Color[red]/Peau d'orange
   - Enlarged veins—phyllodes tumor
   - Retraction-blockage of sub-cuticular lymphatics
   - Puckering
   - Nodules
   - Ulcer
6. Arm and thorax—for nodules, edema [axillary lymphatic obliteration], thrombosis in veins
7. Axilla, SCF—for nodes

Palpation

Sitting position—arms by side/arms in hip/supine

Palpate the normal breast first—with palmar surface of fingers

Each quadrant must be palpated systematically, then nipple and axillary tail

1. Local rise of temperature/tenderness—compare with opposite side
2. Mass site [quadrant/site as in clock], size, surface, margin [first with flat hand then between fingers]
3. Consistency
4. Fixity to skin—any tethering/dimpling on moving skin [dimpling is due to involvement of Cooper's ligament]
5. Fixity to pectoralis major—place arm over hip firmly [first check with normal position and then look for restricted mobility by placing arm over hip firmly]. Must look for mobility in plane parallel and perpendicular to muscle
6. Fixity to serratus anterior—check tumors of the outer lower quadrant [by pushing against the wall and checking mobility in vertical and transverse position]
7. Fixity to chest wall
8. Palpation of nipple—periphery to nipple and then behind nipple to look for any tumors deep to nipple and any discharge
9. Palpation of axilla
   - Pectoral group—using right hand of the examiner for left side axilla of the patient
   - Central and apical
   - Brachial group—using left hand for left side
   - Subscapular—along post axillary fold, from behind
10. Infraclavicular, supraclavicular fossa and neck for any nodes

Examination of the abdomen

- Hepatomegaly, free fluid

Examination of the respiratory system

- Pleural effusion/consolidation

Examination of the skeletal system—for bony tenderness

Examination of CNS—headache, diplopia, seizure

PV Examination

- Krukenberg deposits
- Uterine/ovary—malignancies

33.4 Differential Diagnosis for Carcinoma Breast

- Phyllodes tumor—Large tumor, dilated veins, less LN
- Fibro adenosis—30–40 years, painful, bilateral lesion with pain showing cyclical variation with menstrual cycles
- Fibro adenoma [breast mouse]—30–40 years as mobile, rubbery, round movable swelling
- Fat necrosis—associated trauma, ecchymosis over the skin
- Abscess—non-lactating breast, fever, rapid onset of symptoms
- Mastitis—in lactating breast, occurs within 3 m of delivery
- Duct papilloma—no mass with bloody discharge

33.5 Work Up

- Complete blood count, Renal function test and Liver Function test
- Biopsy—Trucut biopsy preferred over FNAC as it can differentiate DCIS from carcinoma and in assessing ER/PR/Her2 status [triple assessment includes a complete history, triple assessment is performed including: physical examination, radiological investigation, and needle biopsy]
- FNAC of suspicious axillary LN
- B/L mammogram with USG—look for multifocality, look for contralateral breast cancer
- MRI if axillary lymphadenopathy with unknown primary malignancy, in patients with breast implant and for assessment post neoadjuvant chemotherapy.
- T1 and T2 primary breast tumors <2% incidence of metastatic disease, so routine staging of asymptomatic patients for metastases is not indicated in T1 and T2 cancers
- CECT chest abdomen pelvis and bone scan in T3/N1 [in nearly stage disease done if altered LFT, high ALP or if symptomatic]
- PET may be done instead of CECT chest-abdomen-pelvis and bone scan

33.6 Staging

- The AJCC staging and stage grouping are tabulated in Tables 33.2 and 33.3

Table 33.2 AJCC 2017 staging for carcinoma breast

T1: tumor ≤2.0 cm in greatest dimension • T1mi—<1 mm • T1a: tumor >0.1 cm–≤0.5 cm • T1b: tumor >0.5 cm–≤1.0 cm • T1c: tumor >1.0 cm–≤2.0 cm T2: tumor >2.0 cm–≤5.0 cm T3: tumor >5.0 cm T4a: extension to chest wall, not including pectoralis muscle T4b: edema (including Peau D'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast T4c: both T4a and T4b T4d: inflammatory carcinoma	*Clinical N* N1: Mobile ipsilateral axillary LN N2a: I/L axillary lymph nodes fixed/matted N2b: ipsilateral internal mammary nodes in the absence of axillary lymph node N3a: I/L infraclavicular N3b: ipsilateral internal mammary lymph node(s) and axillary lymph node(s) N3c: metastasis in ipsilateral SCF *Pathological N* pN1a: 1–3 axillary lymph nodes pN2A: metastasis in 4–9 axillary lymph nodes pN3A: metastasis in ≥10 axillary lymph nodes

Table 33.3 AJCC stage grouping for carcinoma breast

AJCC stage		Group	
I	I	Early Breast Cancer	T1
II	IIA		T2/N1
	IIB		T2+N1/T3
III	IIIA	LABC	T3+N1/N2
	IIIB		T4
	IIIC		N3
IV	IV	Metastatic	M

33.7 Screening

- US preventive services task force recommends screening for women aged 50–74 with biennial screening mammography
- American Cancer Society recommends yearly mammograms for women aged 50–54 years and biennial screening mammography for women aged >55 years

Prevention approaches [1]:

1. Risk assessment most commonly is done by GAIL method (limitation: overestimation of risk in non-Caucasian women).
2. In GAIL criteria the following criteria is considered "menarche, age at first live birth, patient's current age, number of first-degree relatives with IBC, race/ethnicity, number of prior breast biopsies, and the results of these biopsies".
3. Eligible patients: any woman more than 35 years with a GAIL model prediction risk for breast cancer of at least 1.66% at 5 years
4. Agents: In premenopausal—tamoxifen 20 mg for 5 years; and post-menopausal—either raloxifene or exemestane can be used.
5. It reduces only chances of hormone sensitive breast cancer.
6. Other different agents are being evaluated for reducing the risk of hormone non-sensitive breast cancer (viz., fenretinide, metformin, statins, tibolone, etc.).
7. For BRCA mutated women, bilateral mastectomy and salpingo-oophorectomy is advised.

33.8 Treatment Outline

Early Breast Cancer [EBC]

- Breast conservation surgery (BCS)/modified radical mastectomy (MRM) + sentinel lymph node biopsy (SLNB) [in node negative] followed by adjuvant radiotherapy (RT) ± chemotherapy ± hormone therapy ± anti-Her2neu therapy
  - Adjuvant chemotherapy risk predictors—adjuvant online, PREDICT
  - Adjuvant chemotherapy genomic scoring—oncotype-DX (18 gene signature), prosigna, endopredict, mammaprint (70 gene signature)

Locally Advanced Breast Cancer [LABC]

- NACT ± anti Her2neu therapy followed by surgery [BCS/MRM] followed by RT ± hormone therapy ± anti Her2neu therapy
- MRM followed by RT ± chemotherapy ± hormone therapy ± anti Her2neu therapy

Metastatic Breast Cancer [MBC]

- In oligometastatic disease treatment should follow the protocol of LABC
- Remaining patients: Options are
  - Surgery: toilet mastectomy
  - Radiation: palliation for bone, brain metastasis
  - Systemic therapy:

    ER positive and Her2/neu negative and not in visceral crisis hormonal therapy should be considered standard

    ER positive and Her2/neu positive and not in visceral crisis hormonal therapy with anti-her2/neu therapy should be considered standard

    ER negative and Her2/neu positive and not in visceral crisis chemotherapy with anti-her2/neu therapy should be considered standard

    ER negative and Her2/neu negative OR patient in visceral crisis chemotherapy should be considered standard

33.9 Surgery

- Breast conservation surgery should be offered to all eligible patients
- Absolute contra indications for BCS are multifocal breast cancer, previous irradiation of the breast, persistent positive tissue margins after surgery, and other contraindication for radiotherapy
- SLNBx should be done in all early stage breast cancer patients with negative LN. Done by injecting blue dye and a radioactive colloid tracer around the tumor (peritumoral), into the dermis (subdermal) or under the nipple (subareolar)
- In SLNB if 1–2 nodes are positive further ALND may be omitted but patients must receive whole breast radiation by tangential field
- SLNB in node positive patients after NACT is being evaluated. In such cases prior assessment with axillary USG and placement of clip is recommended
- Disease-free margins of at least 1 mm are acceptable

33.10 Radiotherapy

- All patients of BCS should receive adjuvant radiation
- A boost dose of 10–16 Gy resulted in a greater reduction of local failure in patients younger than 50 years
- Boost irradiation leads to a 50% risk reduction in patients with age <50 years, grade 3 tumor, and vascular invasion [2]
- Adjuvant chest wall RT is recommended for patients with T3–T4, ≥4 positive lymph nodes, and excision margin <1 mm
- Patients with 1–3 positive lymph nodes may also benefit from chest wall RT and SCF RT especially in patients with grade 3, T2 disease or presence of LVE
- Adjuvant radiotherapy—reduces the incidence of locoregional recurrence from 30% to 10% at 20 years and breast cancer deaths by 5% at 20 years
- Radiotherapy Dose
  - Conventional fractionation: 50 Gy/25 fractions followed by a boost of 10–16 Gy
  - Hypofractionation: 40 Gy/15 fractions (boost is not mandatory) [START A, START B, Canadian trial] [3]
  - Extreme hypofractionation:
    Once in a week dose: 28 Gy in 5 fractions or 30 Gy in 5 fractions [UK FAST trial]
    Continuous in a week dose: 26 Gy in 5 fractions or 27 Gy in 5 fractions [UK FAST FORWARD trial]
- Indication of adjuvant RT after NACT: No randomized evidence
  - Patients with Stage III B/Stage IIIC disease (>5 cm tumor and cN+), or residual disease after NACT (<pCR)
- Omission of Rt in elderly: PRIME II and CALGB trial reported significantly higher local recurrence after omission of RT even in the most favorable patients (Age 70 years, Stage I (T1N0M0), ER+)
- RT in TNBC: No randomized data
  - Radiotherapy significantly lower risk of locoregional recurrence irrespective of the type of surgery
  - Radiotherapy not consistently associated with OS
  - Benefits may be obtained in women with late-stage disease and younger patients
- Internal mammary radiation: IMN radiation along with chest wall and SCF was found to impart disease free survival benefit. However, the true benefit from IMN radiation could not be assessed in these trials. Risk of cardiac side effects also may increase. Hence only in patients with disease in inner quadrant should be considered eligible.

33.11 EBRT 2D Planning

- Most commonly the patient is treated supine with a breast board
- Prone position may be helpful in patients with pendulous breasts
- Use of respiratory motion management is further beneficial

Table 33.4 Field borders for 2D planning in carcinoma breast

Field borders			
	Chest wall/ whole breast	SCF	SCF and axilla
Medial	Midline	1 cm meaxial to midline	1 cm meaxial to midline
Lateral	Mid axillary line	Outer border of 1st rib or medial most surgical clip	Lateral border of humeral head
Superior	Suprasternal notch	C7/T1, covering SCF fossa	C7/T1, covering SCF fossa
Inferior	1–2 cm, below breast tissue	Superior border of chest wall field	Superior border of chest wall field

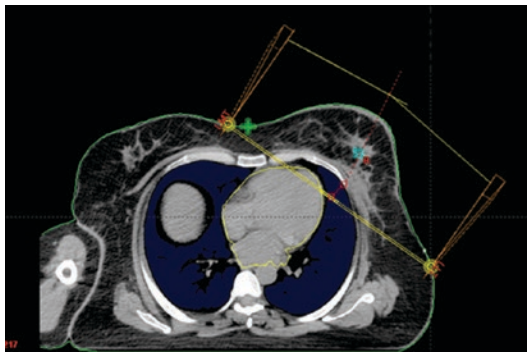

Fig. 33.1 2D planning for carcinoma breast

- The anterior border of the field in free air should be at least 1.5 cm from the skin surface
- Field borders for 2D planning are summarized in Table 33.4
- Figure 33.1 shows 2D planning for carcinoma breast

33.12 Conformal Radiotherapy

- The CTV post BCS is the glandular breast tissue. The PTV is the CTV with a 1 cm margin, usually allowing 5 mm skin-sparing.
- The CTV post mastectomy includes the skin flaps, but not the muscle or the rib cage. Bolus may be used in patients with inflammatory tumors, positive skin margins (Fig. 33.2)

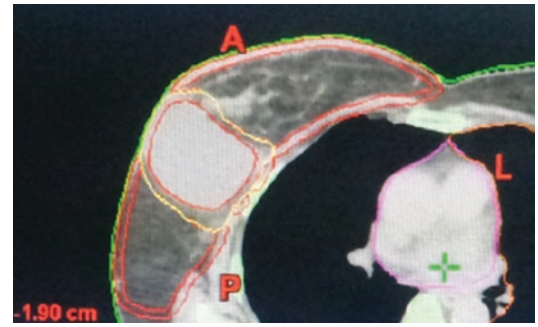

Fig. 33.2 Contouring CTV for conformal planning in carcinoma breast

- CTV for SCF includes SCF and level 3 axillary lymph nodes
- CTV for axillary lymph node includes levels 1–3 of the axilla and the medial SCF nodes
- Simple, forward-planned, field-in-field IMRT is the preferred conformal treatment technique for whole breast radiotherapy and it reduces the late toxicity and improves cosmetic outcome following adjuvant RT

33.13 Organ at Risk (OAR)

- 2-D planning-central lung distance [CLD] should be less than 2 cm and maximum heart distance (MHD) must be kept to less than 1 cm
- For 3-D Planning—ipsilateral lung V30% should be kept ≤17% and V25% of the heart kept ≤5% and V5% of the heart kept ≤30%

33.14 Brachytherapy

- Maybe used as boost or as sole treatment in form of APBI
- Further details are given in chapter on breast brachytherapy

33.15 Palliative RT

- For bleeding or pain—36 Gy in 6 fractions of 6 Gy once or twice weekly/20 Gy in 5 fractions

- For bone metastasis—8 Gy single fraction for painful bone metastasis; however, 30 Gy in 10 fractions may be advised for patients with limited bone metastasis and hormone sensitive tumor

33.16 Neoadjuvant/Adjuvant Chemotherapy

- Sequential anthracyclines and taxanes is one of the most preferred agents [e.g., ACT → T]
- Trastuzumab if indicated may be added with taxanes and continued for 1 year

33.17 Palliative Chemotherapy

- Sequential single agents preferred over combination
- Patients whose tumors are ER positive may be considered for palliative chemotherapy in patients with endocrine resistance/visceral crisis
- An anthracycline/taxane may be used in first line[if it has not been used in the adjuvant setting]
- Taxane may be used in second line if anthracycline used in first line and vice versa
- Capecitabine or vinorelbine may be used in third line
- Chemotherapeutic agents like capecitabine, vinorelbine, and paclitaxel can be continued as long as there is a response/unacceptable toxicity

33.18 Adjuvant Hormone Therapy

- All hormone sensitive patients should receive either tamoxifen for 5 years (premenopausal) or aromatase inhibitor (AI) for 5 years (post-menopausal)
- Before starting AI patients should be advised for DEXA scan and accordingly may be advised for bisphosphonate and oral calcium supplement.
- Extending adjuvant tamoxifen up to 10 years might be beneficial for selected patients with high risk of disease recurrence (Grade II IDC, node positive tumor)
- In premenopausal ovarian function suppression with exemestane is also an option

33.19 Palliative Hormone Therapy

- Palliative first line—in patients without visceral crisis [visceral crisis is defined as severe organ dysfunction with signs and symptoms, laboratory studies, and rapid progression of disease]
  - Post-menopausal—CDK inhibitor plus AI/fulvestrant
  - Premenopausal—ovarian function suppression and AI plus CDK inhibitor/Tamoxifen
- Primary endocrine resistance is relapsed while on the first 2 years of adjuvant endocrine therapy or progression within first 6 months of first line endocrine therapy
- Secondary endocrine resistance is relapsed after the first 2 years to within 12 months of completing adjuvant endocrine therapy, or progression within after 6 months of first line endocrine therapy
- Options in second line—AI if first line tamoxifen, exemestane, fulvestrant, exemestane plus everolimus

33.20 Anti-Her2u Treatment [in Her2 U 3+/FISH Positive]

- The main toxicity of trastuzumab is cardiac toxicity. Patients should have left ventricular function assessed before starting trastuzumab and every 3 months during treatment
- Adjuvant preferred agent—Trastuzumab plus chemotherapy [1 year is preferred]
- Neoadjuvant preferred agent—trastuzumab ± pertuzumab plus chemotherapy
- Metastatic Setting
  - First line—trastuzumab + pertuzumab + taxane
  - Second Line—TDM-1
  - Third Line—lapatinib + capecitabine

  - In case of progression on trastuzumab, the combination of trastuzumab + lapatinib is also a reasonable treatment option in the course of the disease

33.21 Zoledronic Acid

- Zoledronic acid inhibits osteoclasts activity and has been shown to reduce skeletal-related events
- Bisphosphonates may be helpful to reduce loss of bone mineral density in patients with endocrine therapy for early breast cancer

33.22 Follow Up

- Every 3–6 months for first 2 years, then every 6 months till 5 years and then annually thereafter
- In each visit clinical examination should be done
- Mammogram should be advised every year

33.23 DCIS

- The aim is of surgery is to achieve a margin status of at least 1 mm
- Adjuvant radiotherapy following BCS reduces local recurrence across all subgroups of women with DCIS. Radiotherapy has no effect on survival in DCIS
- Adjuvant hormone therapy is advocated in DCIS
- For treatment of LCIS, observation alone is the preferred
- The pleomorphic variant of LCIS and LCIS with comedo necrosis—treated as DCIS

33.24 Inflammatory Breast Cancer

- Patients should receive neoadjuvant chemotherapy followed by mastectomy and ALND plus adjuvant RT with or without adjuvant hormone, with or without adjuvant trastuzumab
- Immediate reconstruction is generally not recommended

33.25 Male Breast Cancer

- Lobular carcinoma does not occur in males
- Generally are ER+/PR+/Her2/neu negative
- Usually present in advanced stages due to anatomical reason
- Adjuvant and metastatic therapy guidelines are similar to female patients
- Tamoxifen is the preferred option for adjuvant endocrine therapy

33.26 Survival Stagewise

- 5 year survival rates
  - Stage I: 98–100%
  - Stage II: 90–93%
  - Stage III: 65–75%
  - Stage IV: 20–40%
- Nottingham prognostic index (NI) is calculated as follows: NI = (0.2 × size) + lymph node stage + grade
  - For lymph node stage, score 1 (if N0), score 2 (if 1–3 LNs are positive), score 3 (if 4 or more LNs are positive).
  - For grading, score 1 (for grade 1), score 2 (for grade 2), and score 3 (for grade 3)

33.27 Recurrence

- Chest wall recurrence—in patients with chest wall recurrence due to the high risk of concomitant distant metastases, patients should undergo full restaging, including assessment of chest, abdomen, and bone. Chemotherapy after first local or regional recurrence improves long-term outcomes primarily in ER negative disease. ET in this setting improves long-term outcomes for ER positive disease.
- In metastatic recurrence—a biopsy should be advised from the lesion
  - Change in ER and HER2 receptor status between the primary and metastatic site 10–13% and 3%
  - 8–10% show loss of ER expression and 2–3% with a gain in ER
  - HER2 gain occur slightly more frequently than HER2 loss (2–3% compared to 0–1%)

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Oral Cavity Carcinoma

34

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Oral cavity carcinoma is a very common malignancy inflicting more commonly tobacco users.

34.1 Risk Factors [1]

- Smoking
- Smokeless tobacco
- Alcohol
- Betel nut chewing
- Premalignant lesions (leukoplakia 5% risk of developing cancer, erythroplakia 50% risk)
- Older age

34.2 Sub-Sites

- Oral tongue—risk of bilateral nodal spread high. Risk of skip metastases present
- Mucosal lip—risk of nodal spread very low (3–8%)
- Buccal mucosa
- Alveolar ridge
- Retro molar trigone
- Floor of moth—risk of bilateral nodal spread high
- Hard palate

34.3 History Taking

- Ulcer/growth in oral cavity
- Pain at local site/radiation to ear/head
- Bleeding from lesion
- Masses in neck
- Tongue movement restriction—extrinsic muscle involvement
- Regurgitation of food into nose—fistula on palate
- Loss of sensation over mental area—inferior alveolar nerve in mandible involvement
- Difficulty in opening mouth—if long standing, sub-mucous fibrosis. If acute, pterygoid muscle involvement
- Ask history of smokeless tobacco use
- If young patients, sexual history
- If lip lesion, sun exposure

34.4 Examination

34.4.1 Local/Locoregional Examination: Check for

- Halitosis—anaerobic infection, necrotic growth
- Trismus and grade of trismus
- Describe ulcer/growth—location, type, size, extensions, feel on touch, bleeding
- Skin involvement/fistula
- Bone involvement
- If hard palate lesion. Check for fistula

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- Systematic neck nodal examination
- Indirect laryngoscopy—to identify extension to base of tongue/synchronous lesions in larynx/hypopharynx
- Always note leukoplakia/erythroplakia
- Chest examination—to identify intercurrent illness—COPD/emphysema

34.4.2 Differential Diagnosis

1. Malignancy
2. Tuberculosis
3. Syphilitic ulcer

34.4.3 Workup

1. Complete blood count
2. Liver and renal function tests
3. CEMRI face and neck (salient points detailed later)
4. If MRI not feasible, CECT face and neck
5. Chest X-ray—PA view

34.5 CEMRI Face and Neck of Oral Cavity (Important Points for a Radiation Oncologist)

1. >1.5 T scan to be advised/preferred
2. Imaging to be done with *puffed cheek*—To separate out mucosal surfaces
3. The sequences needed—(**a**) Axial, sagittal, coronal T1 weighted images. (**b**) T2 weighted FSE with fat saturation. (**c**) Axial, sagittal, coronal post gadolinium T1 weighted images with fat saturation
4. Differentiate myocutaneous flap from recurrence—*flap has striations* interposed with *bright fat* on T1 imaging while *recurrence is homogenous* intermediate signal intensity lesion without striations
5. Normal post radiotherapy changes:
   (a) Thickened skin
   (b) Reticular subcutaneous fat
   (c) Brightly enhancing pharyngeal mucosa
   (d) Bulky epiglottis
   (e) Retropharyngeal/Carotid sheath oedema
   (f) Brightly enhancing parotid gland followed by atrophy

34.6 Staging

AJCC 2017 staging of oral cavity cancers is summarised in Table 34.1

34.6.1 Treatment Overview [2, 3]

Treatment overview is summarised in Table 34.2

34.6.2 Brachytherapy Alone

Brachytherapy alone is an acceptable treatment in T1 and early T2 lesions with low risk of lymph nodal spread (Eg: lip) with the following criteria being met:

1. Patient preference
2. Tumour in area of functional importance (commissure)
3. Tumour in area of cosmetic importance
4. Medical contraindications to surgery
5. If previously irradiated and small recurrence

Doses[1]: HDR: 6 Gy per fraction, 2 fractions per day till a total dose of 48 Gy
5 Gy per fraction, 2 fractions per day till a total dose of 45 Gy

Further details of brachytherapy are discussed in brachytherapy chapter.

34.7 Combined External Beam Radiotherapy (EBRT) and Brachytherapy

Combined EBRT and brachytherapy is an acceptable mode of treatment in:

[1]As per GEC ESTRO ACROP guidelines 2017.

Table 34.1 AJCC 2017 staging of oral cavity cancers

T stage		N stage	
Tis	Carcinoma in situ	N1	1 ipsilateral LN, ≤3 cm without ENE
T1	Tumor ≤2 cm, ≤5 mm depth of invasion (DOI)	N2a	**1 ipsilateral/contralateral LN ≤3 cm with ENE**, 1 ipsilateral LN >3 cm ≤6 cm without ENE
T2	Tumor ≤2 cm, DOI >5 mm and ≤10 mm or tumor >2 cm but ≤4 cm, and ≤10 mm DOI	N2b	>1 ipsilateral LN ≤6 cm without ENE
T3	Tumor >4 cm or any tumor >10 mm DOI	N2c	>1 ipsilateral/contralateral LN ≤6 cm without ENE
		N3a	1+ LN >6 cm without ENE
T4a	Moderately advanced local disease: (lip) tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose); (oral cavity) tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face); **note that superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4**	N3b	1 ipsilateral LN, >3 cm with ENE, 1+ ipsilateral/contralateral LN with ENE
		M stage	
T4b	Very advanced local disease; tumor invades **masticator space, pterygoid plates**, or skull base and/or encases the internal carotid artery	M1	Metastatic disease

Summative Stage

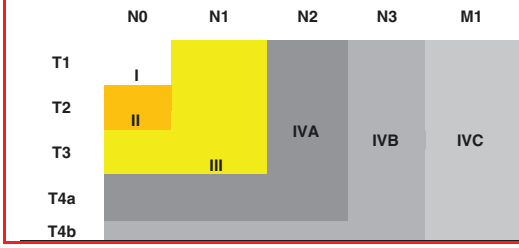

Table 34.2 Treatment overview for oral cavity cancers

Surgery	
T1-2, N0	Resection of primary + ipsilateral neck dissection
T3N0, T1-4 N+	Resection of primary + bilateral neck dissection
Definitive radiation	
T1-T2N0 Unresectable T4 lesions (high ITF above Mandibular notch, tongue lesion with base involvement)	Consider brachytherapy (in lip lesions) Consider definitive chemoradiation (brachytherapy as part increases local control)
Adjuvant radiation	
Positive margins	Adjuvant chemoRT (cisplatin category I) if cannot re-resect
ECE	Adjuvant chemoRT
Other risk factors[a]	RT

[a]pT3/T4, N2/N3, PNI, level IV/V, LVSI, DOI 4 mm or more for tongue, DOI 6 mm or more for floor of mouth

1. T1/T2 tumours with substantial risk of lymph node spread (e.g. tongue) but patient unfit for surgery
2. Locally advanced T3/T4 N+ tumours unsuitable for surgery due to poor functional outcome

Doses (see footnote 1): HDR: 6 Gy per fraction, 2 fractions per day till a total dose of 21 Gy
3 Gy per fraction, 2 fractions per day till a total dose of 18 Gy

34.7.1 External Beam Radiation Therapy

- *Timing*: Should be started within 4–6 weeks of surgery
- Dose:
  - High risk (close/positive margins/ECE)—63–66 Gy in 30–33 fractions
  - High risk (tumour bed)—60 Gy in 30 fractions

  - Intermediate risk (operative bed)—54–60 Gy in 30 fractions
  - Low risk—54 Gy in 30 fractions
- Target: Tumour bed, operative bed, draining lymphatics (levels I–IV, level V if node positive). Consider unilateral treatment for well lateralized retro molar trigone, buccal mucosa and alveolar ridge without nodal disease (Table 34.3).
- Techniques: VMAT, IMRT with half beam block and matched AP low neck field, IMPT. 2D plan for a carcinoma tongue and a conformal plan for carcinoma buccal mucosa are shown in Figs. 34.1 and 34.2.

Table 34.3 Site specific nodal volumes to be included in radiotherapy

Sub site	Stage	Nodes in addition to involved nodes to be treated
Well lateralised Buccal mucosa, alveolus	T1/2, N0-N2a	Ipsilateral I, II, III
	T3/4 Node > N2a	Ipsilateral I–IV Consider contralateral-III;
		Include level V if level II or IV involved
Oral tongue, floor of mouth	T1/T2 N0	Bilateral I–IV IV optional for FOM
	T3/4 N+	Bilateral I–V

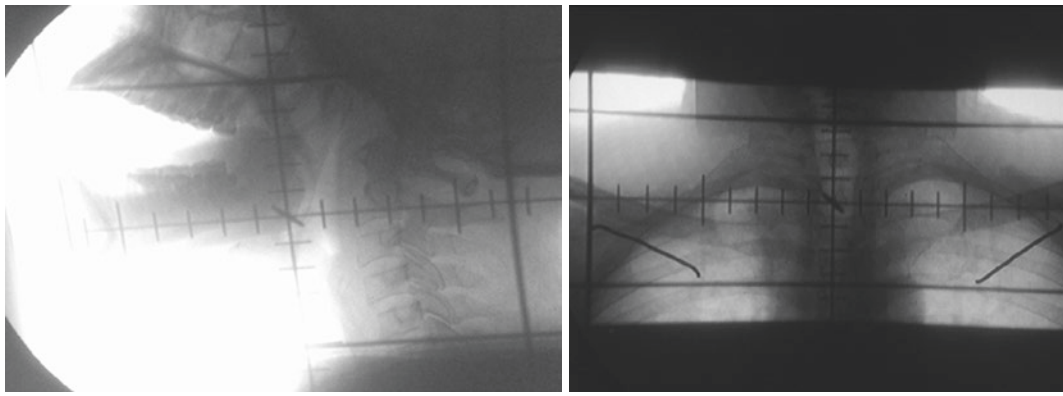

Fig. 34.1 2D planning for post operative radiotherapy for oral tongue, with tongue bite using 2 lateral fields and a single anterior beam

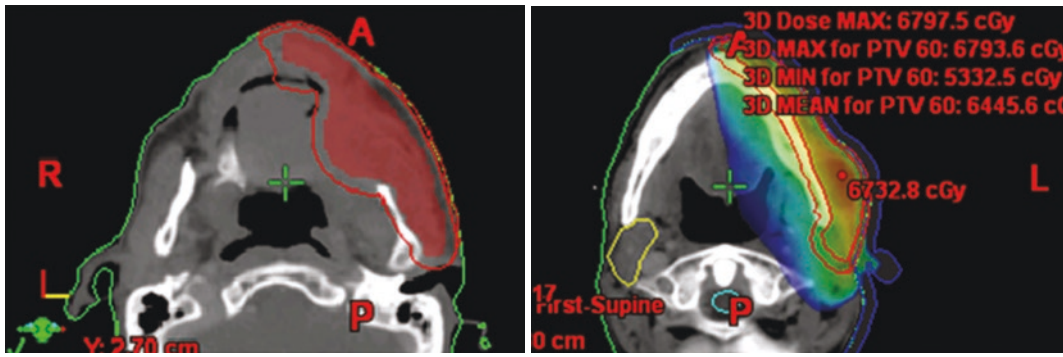

Fig. 34.2 Conformal plan for post op radiotherapy for buccal mucosa cancers

- Simulation: Supine, consider mouth opening tongue forward (oral tongue), tongue lateralizing (buccal/alveolar/retromolar trigone) or ramp (FOM) dental stent, Aquaplast mask. Wire scar. 3 mm bolus 2 cm around scar.

34.7.2 Follow-Up

- History/physical exam: Every 3 months for 1 year → every 4 months for 2nd year → every 6 months for 3rd year → yearly to 5 years (CT Face and neck at 6 months and every 6 months for 2 years)
- Assess compliance with fluoride application, neck/lymphedema exercises

34.8 Important Trials

34.8.1 Adjuvant ChemoRT vs. RT: EORTC 22931/RTOG 95-01

- *RTOG 95-01*—416 patients with primary in the oral cavity, oropharynx, larynx, hypopharynx with high risk features (2 or more positive lymph nodes, or extracapsular extension, or margin positivity) were included. Adjuvant RT alone vs RT with concurrent cisplatin (100 mg/m^2) was compared. Radiotherapy dose was 60 Gy/30# plus optional boost to 66 Gy [4].
- *EORTC 22931*—Trial included 334 patients with primary in oral cavity, oropharynx, hypopharynx or larynx. T3-4 stage patients negative margins or T1-2 N2-3 or T1-2 N0-1 with high risk features (extracapsular extension, margin positivity, PNI or LVI); or oral cavity/oropharynx with LN+ at levels IV or V were included. Adjuvant RT alone vs. RT + concurrent cisplatin (100 mg/m^2) was compared in this randomised trial. RT dose 54 Gy/27# with a boost to 66 Gy for high risk areas [5].
- Combined analysis showed patients with extracapsular extension or margin positivity had a significant overall survival benefit with the addition of concurrent cisplatin [6].

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Oropharynx Cancer

35

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35.1 History Taking

- Neck swelling
- Otalgia
- Dysphagia
- Odynophagia
- Oral tongue fixation
- Trismus
- Oropharyngeal bleeding
- Voice change ("hot potato voice" with tongue base cancer)
- Weight loss, fevers, or night sweats
- Dyspnea.

35.2 Other Relevant History

- h/o tonsillectomy, thyroid surgery, or other head and neck surgeries
- h/o medical co-morbidities (including renal dysfunction or hearing loss)
- Social support
- h/o smoking (pack years)
- h/o alcohol intake
- h/o smokeless tobacco, drug abuse
- h/o high risk sexual behavior, total lifetime sexual partners
- h/o immunodeficiency
- h/o previous radiation/chemotherapy.

35.3 Examination

- General nutritional status, performance status

Inspection

1. Inspect the entire oral cavity and oropharynx with special attention to the tongue
2. Assess tongue for bulk, fasciculations and tongue deviation on protrusion. Inability to protrude the tongue may indicate deep musculature involvement
3. Assess bilateral anterior and posterior tonsillar pillars, soft palate, and uvula
4. Assess extent of tonsil primaries (size, involvement of tongue base, soft palate, and distance from midline)
5. Assess for trismus which may indicate pterygoid muscle involvement.

Palpation

1. Palpate the glossotonsillar sulcus and tongue base for firmness/mass
2. Palpate the oral tongue for submucosal involvement
3. Palpate the soft palate (difficult due to gag reflex—use local anesthetic)

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4. Palpate bilateral necks one at a time starting with the normal side if applicable from cranial to caudal extent including the parotid, submental, and submandibular nodal areas

35.3.1 Flexible Endoscopy in the Office

Performed in the sitting position with neck in neutral position; 2% lidocaine is sprayed in the nares and oral cavity. Adequate time is allowed for anesthesia to take effect. The flexible endoscope lubricated with lidocaine gel is advanced through the nares. Serial inspection of the following structures is performed—the opening of the Eustachian tubes, torus tubarius, fossa of Rosenmuller, nasal aspect of the soft palate, tongue base, and vallecula (patient is asked to protrude the tongue and mandible). The glossotonsillar sulcus is also inspected. The supraglottic/glottic/hypopharyngeal structures are also inspected (aryepiglottic folds, piriform sinuses, post-cricoid space, false vocal cords, ventricles, true vocal cords, and subglottis). Tongue base and vallecula masses are often submucosal.

35.3.2 Examination of the CNS

- Particular attention must be given to the examination of cranial nerves depending upon the extent of disease.

35.3.3 Systemic Examination

- Relevant systemic examination should be done in addition to general ear, nose, and throat examination.

35.4 Differential Diagnosis for Oropharyngeal Cancer

- Oropharyngeal carcinoma (HPV positive or negative)
- Lymphoma
- Minor salivary gland tumor
- Sarcoma
- Tonsillitis
- Tongue base/vallecula cyst
- AV malformation

35.5 Work-Up

- CBC, RFT, LFT
- Core biopsy/punch biopsy of the primary lesion during examination under anesthesia (with p16 IHC)
- Core biopsy of an enlarged lymph node (with p16 IHC)
- Contrast enhanced CT neck
- Contrast enhanced MRI of the neck (in select situations)
- Whole body PET CT
- Comprehensive dental evaluation (extractions must be completed 14–21 days before radiation)
- Comprehensive audiometry
- Speech and swallow evaluation
- Smoking cessation counselling [1].

35.6 Staging

AJCC 2017 staging for HPV related and HPV negative oropharyngeal cancer is summarized in Tables 35.1 and 35.2.

35.7 Treatment Outline

Treatment for oropharynx cancer does not differ by HPV status. While treatment de-intensification approaches are being explored for low risk HPV+ oropharyngeal tumors, these approaches are currently investigational and are discouraged outside of a clinical trial.

Early oropharynx cancer (AJCC 7th edition: T1-2, N0-1)

- Unimodality treatment is favored with either radiation or surgery alone

Table 35.1 AJCC 8th ed., 2017 oropharynx-HPV related

Clinical and pathologic staging: AJCC 8th ed., 2017 oropharynx (HPV related) [14]							
T0	No primary identified	NX	Regional lymph nodes cannot be assessed	I	cT0-T2 pT0-T2	cN0-N1 pN0-1	M0
T1	≤2 cm in greatest dimension	cN1	One or more ipsilateral lymph nodes, none >6 cm	II	cT0-T2 cT3 pT0-T2 pT3-T4	cN2 cN0-N2 pN2 pN0-N1	M0
T2	>2 but not >4 cm in greatest dimension	cN2	Contralateral or bilateral lymph nodes, none >6 cm	III	cT0-T4 cT4 pT3-T4	cN3 cN0-3 pN2	M0
T3	>4 cm in greatest dimension or extension to the lingual surface of the epiglottis	cN3	Lymph node(s) >6 cm	IV	Any T	Any N	M1
T4	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or beyond[a]	pN1	≤4 lymph nodes involved				
		pN2	>4 lymph nodes involved				
		M1	Distant metastasis				

[a]Mucosal extension to lingual surface of the epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx

Table 35.2 AJCC 8th ed., 2017 Oropharynx-p16 negative

Clinical staging: AJCC 8th ed., 2017 oropharynx (p16 negative) [14]							
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed				
Tis	Carcinoma in situ	N0	No regional lymph node metastasis				
T1	≤2 cm in greatest dimension	N1	Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(−)	0	Tis	N0	M0
T2	>2 but not >4 cm in greatest dimension	N2a	Metastasis in a single ipsilateral lymph node >3 cm but not >6 cm in greatest dimension and ENE(−)	I	T1	N0	M0
T3	>4 cm in greatest dimension or extension to the lingual surface of the epiglottis[a]	N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(−)	II	T2	N0	M0
		N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(−)				
T4a	Tumor invades the larynx, deep/ extrinsic musculature of the tongue, medial pterygoid, hard palate, or mandible	N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(−)	III	T3	N0	M0
					T1-3	N1	M0
T4b	Tumor invades the lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, or encases carotid artery	N3b	Clinically overt ENE(+)	IVA	T4a	N0-1	M0
					T1-4a	N2	M0
				IVB	T4b	Any	M0
					Any	N3	M0
		M1	Distant metastasis	IVC	Any	Any	M1

[a]Mucosal extension to lingual surface of the epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx

Locally advanced oropharynx cancer (AJCC 7th edition: T3-4, N0-N3 or T1-2, N2a-N3)

- Bimodality treatment is favored with either concurrent chemoradiation or surgery followed by adjuvant radiation
- Appropriate case selection should avoid trimodality treatment but this might be necessary for selected cases (chemoradiation followed by salvage neck dissection for high nodal burden or surgery followed by radiation with concurrent chemotherapy for ECE or positive margins)

Recurrent non-metastatic disease amenable to curative therapy

- Surgical salvage followed by aggressive adjuvant re-irradiation with or without chemotherapy

Incurable oropharynx cancer (metastatic or non-metastatic) not amenable to curative therapy

- Cisplatin-based palliative chemotherapy
- Palliative immunotherapy
- Palliative radiation (conventional, Quad Shot, or stereo tactic body radiotherapy for select cases)
- Palliative surgery in select cases.

35.8 Surgery

- Early stage oropharyngeal cancers amenable to transoral resection are treated with this approach along with an ipsilateral modified radical neck dissection
- Ideal cases include well lateralized, well-defined primaries with minimal nodal burden (without clinical ECE, <N2b nodal disease AJCC 7th edition), in medically fit patients with adequate mouth opening
- Tonsil primaries should ideally be away from the carotid artery (a medialized carotid is not favored); the node and primary should preferably be separated
- Well-selected cases may be treated with surgery followed by adjuvant radiation in order to avoid chemotherapy
- Patients who would require a more extensive surgery are favored to be treated with definitive chemoradiation. Surgery (combined with free flap reconstruction) is typically reserved for salvage in this setting.

35.9 Radiotherapy and Chemotherapy

- T1-2, N0-N1 (AJCC 7th edition) oropharyngeal cancers can be treated with definitive radiation alone (70 Gy in 35 fx or 66 Gy in 30 fractions to gross disease) [2]
  - Dose to the elective neck is typically 56 Gy in 35 fractions or 54–60 Gy in 30 fractions, respectively
- More advanced cases are treated with either definitive chemoradiation or surgery followed by adjuvant radiation or chemoradiation
- Definitive radiation is usually 70 Gy in 35 fractions with concurrent high dose cisplatin chemotherapy (100 mg/m^2) [3]
  - Dose to the elective neck is typically 56 Gy in 35 fractions delivered simultaneously
- Cisplatin ineligible patients are treated with concurrent cetuximab (400 mg/m^2 loading dose followed by 250 mg/m^2 weekly) [4, 5]
- Chemotherapy/Cetuximab ineligible patients may be treated with altered fractionated radiation (70 Gy in 35 fractions over 6 weeks or hyperfractionation 81.6 Gy in 68 fractions at 1.2 Gy twice a day 6 h apart) [6, 7].

35.10 EBRT IMRT Planning

- IMRT is strongly recommended for all cases
- In general, GTV = all disease noted on exam and radiology (include flexible endoscopy exam; image fusion with available imaging is highly recommended)
- CTV high dose = GTV + 5 mm margins (shaved off air, bone and other uninvolved structures) (Fig. 35.1)
- CTV low dose = GTV + 10 mm margins (shaved off air, bone and uninvolved structures and includes structures based on the "T" stage) [8]

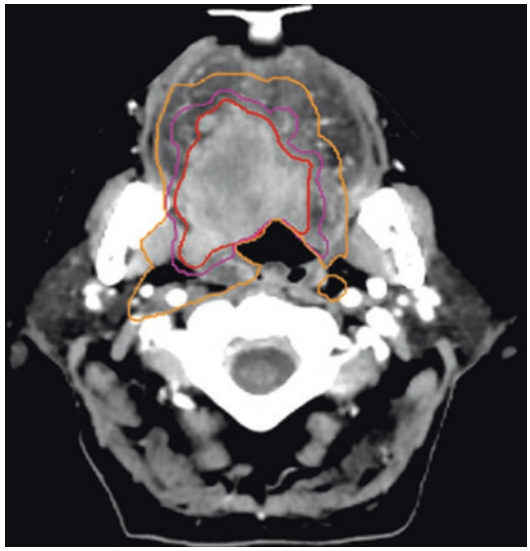

Fig. 35.1 GTV (red), high dose CTV (purple), and low dose CTV (gold) in a patient with carcinoma of the right tongue base

- CTV low dose will also include relevant nodal contours (retropharyngeal nodes and levels II–IV bilaterally for most cases)
- The contralateral elective neck may be omitted in cases where the contralateral neck is node negative and the primary is located in the tonsil, "T" stage T1-2, well lateralized (>1 cm from midline), and with <1 cm superficial involvement of the soft palate or base of tongue with limited nodal burden (N0-N2a disease per AJCC 7th edition; N2b disease is discretionary) [9]
- Contralateral retropharyngeal nodes may be omitted for the node negative contralateral neck with a well-lateralized ipsilateral primary
- Level IB may be omitted if only one level in the neck is positive and the "T" stage is T1-2
- Level V may be omitted if only one level in the neck is positive and the involved node is anterior to the internal jugular vein and carotid artery
- PTVs = CTV + 3 mm margin when using daily image guidance with cone beam CT.

35.11 OAR

- It is highly recommended that the following set of OARs is delineated for each case (brainstem, brainstem PRV3mm, cochlea, spinal cord, spinal cord PRV 5 mm, parotids, submandibular glands, lips, oral cavity, mandible, oropharynx, supraglottis, larynx or glottic-supraglottis, esophagus, trachea, and brachial plexus)
- Additional structures like eyes, lens, optic nerves, chiasm, and temporal lobes may be added for individual cases
- It is recommended that doses to each of the OARs be reduced as much as possible without compromising PTV coverage—guidance for dose constraints may be found in current RTOG protocols (e.g., RTOG 1016) [5].

35.12 Re-Irradiation and SBRT

- Select cases may be amenable to re-irradiation after salvage surgery or SBRT—this discussion is outside the scope of this chapter.

35.13 Palliative RT

- Standard palliative fractionation schemes include 8 Gy in 1 fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions, or Quad Shot approach (14 Gy in 4 fractions; 2 fractions a day 6 h apart over 2 days repeated q 4 weeks up to 3 times)

35.14 Follow-Up

- First follow-up: PET CT [10] is recommended with a contrast enhanced CT neck at 3 months after definitive treatment while CT neck and chest with contrast are recommended at 3 months after adjuvant radiation/adjuvant chemoradiation along with a detailed history and physical exam

- Further follow-up is scheduled every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter
- Further imaging of the neck is directed by symptoms or post-treatment imaging; low dose CT chest is recommend for former/current smokers [11]
- Regular dental follow-up, smoking cessation, speech and swallowing physiotherapy, and enrolment into a survivorship clinic are recommended
- Thyroid stimulating hormone every 6–12 months if the neck is irradiated.

35.15 Oncologic Outcomes

- The survival and locoregional control for HPV related oropharyngeal cancer is better than HPV unrelated oropharyngeal cancer (stage for stage)
- 3-year overall survival rates per the risk stratification (included HPV related and unrelated oropharynx cancer) by Ang et al. [12]: (a) low risk, 93% (b) intermediate risk, 70.8%, and (c) high risk, 46.2%
- 3-year locoregional and distant control, respectively, per risk stratification (HPV related oropharyngeal cancer) by O'Sullivan et al. [13]: (a) low risk, 95% and 93% (b) high risk, 82% and 76%
- 3-year locoregional and distant control, respectively, per risk stratification (HPV unrelated oropharyngeal cancer) by O'Sullivan et al. [13]: (a) low risk, 76% and 93% (b) high risk, 62% and 72%
- Oropharynx overall survival and progression free survival calculator by NRG Oncology https://www.nrgoncology.org/Nomograms/Oropharynx-Cancer-Overall-Survival-Calculator

Source of Images The image was taken from a patient treated by authors as per hospital protocol and consent was taken.

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Laryngeal Cancer

36

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36.1 History Taking

- Hoarseness—usually the first sign of glottic cancer, glottic tumor becomes symptomatic earlier than supraglottic, so detected in earlier stage
- Throat pain, dysphagia, odynophagia
- Neck nodes
- Symptoms of airway obstruction—Stridor, dyspnea in advanced stage
- Referred otalgia is sign of advanced disease (involvement of CN X)
- Tobacco use (smoking, chewing), bidi, marijuana use
- History of alcohol use.

36.2 Other Relevant History

- History of respiratory illness
- Past history of radiation exposure
- Medical comorbidity (including renal dysfunction, hearing loss).

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36.3 Examination

36.3.1 Physical Exam

Complete head and neck exam.

36.3.2 Palpation for Cervical Nodes

- Localized pain/tenderness or bulge over ala of cartilage suggests thyroid cartilage invasion
- Disappearance of laryngeal crepitus suggests postcricoid involvement.

36.3.3 Indirect Laryngoscopy

Direct laryngoscopy (examination under anesthesia): Evaluate tumor extent, look for second primary, biopsy and feasibility of conservation larynx surgery.

36.3.4 Fiber-Optic Flexible Endoscopy

For early laryngeal lesions, narrow band imaging endoscopy may also be used to better assess the mucosal infiltration if available [1]

Speech pathology review—For assessment as well as post-treatment planning.

S. Mallick et al. (eds.), *Practical Radiation Oncology*,
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36.4 Investigations

- CBC, RFT (For cisplatin), CCT, audiology evaluation
- Biopsy
- USG neck to evaluate cervical lymphadenopathy
- CT scan is gold standard. Extent of disease, pre-epiglottic and paraglottic involvement, extra-laryngeal spread, thyroid cartilage involvement, assessment of lymphadenopathy is done.
- MRI imaging is complimentary. It is preferred for evaluation of soft tissue extent but susceptible to motion
- Chest X-ray—to look for pulmonary pathology as well as metastasis.
- PET-CT may be used for metastatic workup in advanced cancers, or in patients having high-suspicion of distant metastasis.

36.5 Staging

36.5.1 T Staging Supraglottis

- T1: Tumor limited to 1 subsite of supraglottis with normal vocal cord mobility
- T2: Tumor invades more than 1 adjacent subsite of supraglottis or glottis or region outside the supraglottis without fixation of the larynx
- T3: Tumor limited to larynx with vocal cord fixation and/or invading the postcricoid area, pre-epiglottic tissues, paraglottic space, and/or invasion of inner thyroid cartilage
- T4a: Tumor invades through the thyroid cartilage, and/or invades the trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus
- T4b: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

36.5.2 T Staging Glottis

- T1: Tumor limited to the vocal cord, with normal mobility
- T1a: Tumor limited to 1 vocal cord
- T1b: Tumor involves both vocal cords
- T2: Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
- T3: Tumor limited to the larynx with vocal cord fixation and/or invades paraglottic space, and/or invasion of inner thyroid cartilage
- T4a: same as supraglottis
- T4b: same as supraglottis.

N, M stage and stage grouping as in oral cavity tumors (Chap. 35).

36.6 Treatment Outline

Apart from cure, preservation of laryngeal function is an important aim of treatment. Laryngeal functions are airway protection, phonation, and respiration.

36.7 Early Glottic Cancer

- T1/T2 glottic cancer can be treated by RT, transoral laser surgery, or conservation laryngeal surgery.
- Although there is insufficient evidence regarding superiority of one modality over other it is generally agreed that RT gives best voice quality.
- Patient who fails after radiotherapy can be salvaged with surgical modality and vice versa.
- Radiotherapy failure can be salvaged with partial laryngectomy in suitable patients. Total laryngectomy can be a salvage option after RT or conservation laryngectomy.

36.8 T3 Laryngeal Cancer

- Treatment of T3 laryngeal cancer is somewhat controversial; they can be generally divided into two groups.
- Favorable group have small volume unilateral disease, have good airway, and have reliable follow-up. These patients are candidate for

larynx preservation and are offered concurrent chemoradiotherapy with surgery as salvage.
- Unfavorable patients fare better with upfront total laryngectomy. Most of these patients require postoperative radiotherapy.
- Indications of postoperative radiotherapy are close or positive margins, significant subglottic extension (1 cm or more), cartilage invasion, perineural invasion, extension of the primary tumor into the soft tissues of the neck, multiple positive neck nodes.
- Patients having extracapsular extension of lymph node or positive margin benefit from postoperative chemo-radiation.

36.9 Advanced Laryngeal Cancer (T4)

- T4 patients are offered upfront total laryngectomy + B/L selective node dissection (level 2.3.4), usually followed by postoperative RT.
- Definitive RT for those who refuse total laryngectomy or medically unfit patients.
- Even if disease is controlled, patient may have dysfunctional larynx and will require tracheostomy and feeding tube.

36.10 Supraglottis Stage I and II (T1/T2)

- Supraglottis has rich-lymphatic supply and risk of nodal spread is much higher than glottic tumor. Management decision therefore includes management of neck as well.
- Radical radiotherapy is preferred modality.
- Transoral laser microsurgery and supraglottic partial laryngectomy are other treatment options.

36.11 T3 Supraglottis Tumors

- If laryngeal function is intact—organ conservation approach with concurrent chemoradiotherapy is preferred.
- Patients unfit for concurrent chemoradiotherapy can be treated with concurrent cetuximab-radiotherapy or altered fractionation radiotherapy.
- Surgical option is supraglottic laryngectomy with selective neck dissection.
- If laryngeal function is compromised—Near-total or total laryngectomy with selective neck dissection and adjuvant (chemo)-radiotherapy.

36.12 Supraglottis T4 Tumor

- Near-total or total laryngectomy with selective neck dissection and adjuvant (chemo)-radiotherapy is preferred.
- Definitive RT for those who refuse total laryngectomy or medically unfit patients.

Upfront neck dissection followed by definitive chemo-radiotherapy for small primary tumor with large neck node has been attempted but lacks high-quality evidence [2].

36.13 Radiotherapy Technique

T1 glottis tumor is traditionally treated with limited opposed lateral fields should consist of a 5 × 5 cm square extending to the bottom of the hyoid bone or the top of the thyroid notch superiorly, the bottom of the cricoid inferiorly, the anterior edge of the vertebral bodies posteriorly, and 1 cm flash anteriorly. For T2 field was extended accordingly. Carotid sparing technique using IMRT is being explored in these tumors which may translate to reduced incidence of carotid artery stenosis.

For all other stages 3D CRT or IMRT is recommended.

36.13.1 CT Simulation

- Supine with flat table top, use thermoplastic mask for immobilization
- Neutral head position and CT thickness of 2–3 mm is recommended

- Scanned from above base of skull to below sternoclavicular joint
- IV contrast should be used.(May be omitted in T1 glottic cancer)
- Co-registration with MRI is not much helpful in this site.

36.13.2 Target Delineation in 3D Conformal/IMRT [3]

Following terminology is used as recommended by consensus guideline for delineation of primary tumor.

- GTV-P: delineated from clinical and imaging assessment.
- CTV-P1: High risk CTV, correspond to GTV-P plus a 5 mm margin and prescribed to highest dose.
- CTV-P2: Intermediate risk CTV, correspond to GTV-P plus a 10 mm margin and prescribed to intermediate/prophylactic dose.
- CTVs are modified excluding air cavities and considering anatomical barrier like bone, cartilage, or fascia.

36.13.3 Glottic Tumor Target Volumes

- In superficial glottis cancer (T1 or early T2), only one CTV can be drawn with 5 mm isotropic expansion of GTV.
- T1 tumor: CTV typically includes para glottis space, anterior commissure in anterior cord tumor, anterior part of contralateral cord for tumor extending to anterior commissure, vocal process of the arytenoid cartilage for tumor extending to the posterior vocal cord, excludes thyroid cartilage and air cavity.
- T2 tumor: CTV-P2 typically includes cranial part of subglottis, the ipsilateral ventricle, and the caudal part of the supra-glottic mucosa in addition to the abovementioned structures.
- T3 tumor CTV-P2 usually includes part of cricoid cartilage caudally, the pre-epiglottic space anteriorly, and the medial wall of the piriform sinus postero-laterally. Excludes extra-laryngeal tissue, oropharynx, and posterior pharyngeal wall.
- T4 tumor CTV-P2 includes part of the thyroid cartilage in relation to the GTV-T, part of the cricoid cartilage caudally, and the pre-epiglottic space, anteriorly; extends outside of the thyroid cartilage, but it does not go beyond the strap muscles (sterno-thyroid or thyro-hyoid muscles). Includes part of the thyroid gland. Excludes hyoid and vertebral body, however vertebral body included if prevertebral space involvement (T4b).

36.14 Supraglottic Tumor: Target Volumes

- T1/T2: CTV-P2 typically includes pre-epiglottic space and para-glottic space, glottis in tumor of ventricle, vallecula in tumor of AEF/suprahyoid epiglottis. Excludes thyroid cartilage and air cavity of laryngo-pharynx and in arytenoid tumors—posterior pharyngeal wall
- T3 tumors: CTV P2 typically includes post-cricoid area in addition to the above structures
- T4 tumor: CTV P2 includes thyroid cartilage but is limited by strap muscle and part of thyroid gland.

Subglottic tumor: They are rare as constitute only ~5% of laryngeal tumors. However, principle of contouring primary tumor is similar to other laryngeal tumors.

36.14.1 Nodal Target Volume [4]

- CTV 70 involved nodes are included in this volume and in selected cases nodes adjacent to the tumor
- Elective nodes in T1/2 N0 glottis—None
- Elective T1/2 supraglottis—Bilateral level II, III
- Elective T3-4NO glottis/supraglottis—Bilateral level II, III, and IV.

36.14.2 Dose/Fractionation

- Glottis: 63 Gy in 28 fractions or 65.25 Gy in 29 fractions for T1N0 and T2N0 tumors, respectively [5]. Alternatively, 66 Gy in 33 fractions or 70 Gy in 35 fractions, respectively.
- For T3/T4: 70 Gy in 35 fractions
- Postoperative: 60 Gy in 30 fractions
- High risk post-operative: 66 Gy in 33 fractions.

36.15 Chemotherapy

- Preferred regimen for organ conservation is concurrent radiotherapy with cisplatin 100 mg/m^2 every 3 weekly as demonstrated by RTOG 9111 study [6].
- Induction chemotherapy has been employed in larynx preservation protocol [7]. However, their role is still controversial as none of trials have shown survival gain compared to concurrent RT + CT. When induction regimen is used 3 drug combination is recommended [8].
- RT + Cetuximab has survival benefit compared to RT alone and is recommended for patients who cannot tolerate chemotherapy [9].

36.16 Follow-Up

- Follow-up is scheduled every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter.
- Further imaging of the neck is directed by symptoms or post-treatment imaging; low dose CT chest is recommended for former/current smokers.
- Regular dental follow-up, smoking cessation, speech and swallowing physiotherapy and nutritional rehabilitation, screening for depression, and enrolment into a survivorship clinic are recommended.
- CXR annually. Thyroid stimulating hormone every 6–12 months if the neck is irradiated.

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Parotid Tumour

37

V. R. Anjali

37.1 History Taking

- Swelling in front/below the ear
- Rapidly enlarging swelling (malignant)
- Pain (involvement of deep structures)
- Cranial nerve involvement (CN VII, V2, V3, IX, X, XI, XII)
- Skin changes (cutaneous and mucosal surface)
- Neck swellings
- Trismus (pterygoid plate involvement).
- Fixity to surrounding structures
- Ear symptoms
- Fever/bilateral swelling.

37.2 Other Relevant History

- History of exposure to ionising radiation, ultraviolet exposure (dose response effect)
- Previous surgery for parotid
- Occupational exposure to hair dye, silica, nickel
- Smoking associated with Warthin's tumour.

37.3 Examination

37.3.1 General Examination

- Performance status
- Built and nourishment
- Pallor, icterus, clubbing, cyanosis, lymphadenopathy, pedal oedema
- Vitals—pulse rate, blood pressure, temperature, respiratory rate.

37.3.2 Local Examination

37.3.2.1 Inspection

- Facial asymmetry
- Swelling
- Erythema/skin changes
- Mouth opening.
- Facial nerve palsy
- External auditory canal.

37.3.2.2 Palpation

- Size, location, margins with respect to bony landmark, consistency, fixity, skin over the swelling
- Movement of jaw
- Facial nerve examination
- Examination of neck nodes: size, number, nodal level, laterality, consistency, fixity, margins, skin over the swelling.

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37.3.3 Examination of Other Systems

- Central nervous system: Higher mental function, *cranial nerve examination*, sensory system, motor system, skull and spine examination.
- Respiratory system
- Gastrointestinal system
- Cardiovascular system.

37.4 Differential Diagnosis

- Malignant tumour of parotid
- Benign lesions of parotid (pleomorphic adenoma, Warthin's tumour)
- Parotitis/calculi
- Tuberculosis
- Autoimmune disease
- Lymphoma.

37.5 Work-Up

Baseline investigation	Complete blood counts
	Liver function test (LFT)
	Renal function test (RFT)
	Serum electrolyte
	Chest X-ray
FNAC	High sensitivity (87–96%) and specificity (90–97%)

Open biopsy/excision biopsy is contraindicated in view of tumour seeding and facial nerve injury.

Investigations to know local disease extent are summarised in Table 37.1.

37.6 Pathology

Common histological subtypes of salivary gland tumours are summarised in Table 37.2 and histological grades are summarised in Table 37.3.

37.7 Staging-AJCC 08

AJCC 2017 staging for salivary gland tumours is summarised in Table 37.4.

Lymph nodal spread: intra-parotid, peri-parotid, pre-auricular, submandibular upper and mid jugular nodes, apex of the posterior triangle (level V) nodes, and occasionally to retropharyngeal nodes. Table 37.5 summarises the risk of lymph node risk as per histological subtype.

37.8 Treatment

Surgery—Well planned and carefully executed.

Table 37.1 Radiological investigations to know locoregional disease extend

Ultrasonography face and neck	High sensitivity—95–100% Malignancy suspected • Heterogenic internal echo pattern • Irregular border • Increased vascular flow Guided biopsy Assess nodes Cost effective	Not useful if deep lobe is involved or if para pharyngeal extension is present or in locally advanced disease Less accurate in distinction of benign/low grade and high grade neoplasm
Contrast enhanced computed tomography head and neck	Local extend of disease Nodal status Cortical bone erosion	
Magnetic resonant imaging head and neck	Investigation of choice in malignant lesions • Delineate soft tissue • Peri-neural spread • Bone marrow invasion • Recurrent lesion	
PET CT		Mild-moderate physiological uptake in salivary glands Low sensitivity

Table 37.2 Common histological subtypes of salivary gland tumours

Histology	Mucoepidermoid	Adenoid cystic	Acinic cell	Carcinoma ex pleomorphic adenoma	Squamous cell carcinoma
Incidence	Most common 30–35%	2nd most common 15–20%	8–14%	10% over a period of 15 years	Rare
Most common Site	Parotid	Minor salivary gland	Parotid	Parotid	Parotid
Features	Lymph nodal spread common	High perineural spread, late recurrence, MC site of metastasis-lung	Low grade	Aggressive	Most aggressive
Overall survival	Low grade—80–90% OS High grade—40–50% OS	OS-90%	OS-97%	OS-50%	OS-40%
Prognosis	Low grade—good prognosis	Variable prognosis depending on histologic subtype	Best prognosis	Poor prognosis	Worst prognosis

Table 37.3 Histological grades of salivary gland tumours

	Malignant	
Benign	Low grade	High grade
• Pleomorphic adenoma • Warthin's tumour • Oncocytoma	• Low grade mucoepidermoid • Low grade adenocarcinoma • Acinic cell carcinoma • Basal cell adenocarcinoma • Sebaceous carcinoma	• High grade mucoepidermoid carcinoma • Adenoid cystic carcinoma • Mucinous adenocarcinoma • Squamous cell carcinoma • Undifferentiated carcinoma • Carcinoma ex pleomorphic adenoma • Salivary duct carcinoma

Table 37.4 AJCC staging salivary gland tumours 2017

T1—≤2 cm, without extra parenchymal extension	N—as in other head and neck cancers	
T2—>2 cm ≤ 4 cm, without extra parenchymal extension	M—as in other head and neck cancers	
T3—>4 cm, with or without extra parenchymal extension	STAGE I	T1 N0 M0
T4a—moderately advanced disease (involvement of skin, mandible, ear canal, facial nerve)	STAGE II	T2 N0 M0
	STAGE III	T3/N1 M0
T4b—very advanced disease (involvement of skull base, pterygoid plate, carotid artery encasement)	STAGE IV A	T4a/ N2 M0
	STAGE IV B	T4b/ N3
	STAGE IV C	Any T, any N, M1

Table 37.5 Lymph node involvement risk according to histological subtype

Lymph node involvement risk and histology		
High risk	Intermediate risk	Low risk
Squamous cell carcinoma Undifferentiated carcinoma Salivary duct carcinoma	Mucoepidermoid carcinoma	Acinic cell carcinoma Adenoid cystic carcinoma Carcinoma ex pleomorphic adenoma

37.8.1 Early Stage

- Small primary (<4 cm)
- Low grade

- Superficial tumour
- Confined to superficial lobe.

EARLY STAGE: Superficial parotidectomy with adequate margins and preservation of facial nerve

37.8.2 Locally Advanced

- Tumour >4 cm
- High grade tumours
- T3/T4 disease
- Deep lobe involved
- If skin, muscle, bone, involved
- Adenoid cystic carcinoma requires exploration of nerve towards and through skull base foramina to achieve tumour clearance
- If pre-operatively facial nerve function is normal and not infiltrated by the tumour try to preserve facial nerve
- If facial nerve injury has occurred, microsurgical nerve repair is considered
- Gross tumour encasement/infiltration of facial nerve/facial nerve palsy-nerve is sacrificed and nerve grafting is done (sural nerve).

37.9 Neck Dissection

LOCALLY ADVANCED: Total Parotidectomy + LN dissection

- Low grade/superficial tumours—Observation only. Prophylactic neck dissection is not done
- High grade/locally advanced disease, clinically/radiologically node negative—SOHND
- High grade/locally advanced disease, clinically/radiologically node positive—MRND
- Neck dissection provides details on extra capsular spread which is a poor prognostic factor.

37.10 Complication of Surgery

- Facial nerve palsy-temporary/permanent
- Frey's syndrome (gustatory sweating)
- Numbness over the ear (greater auricular nerve)
- Hematoma
- Infection
- Flap necrosis
- Parotid fistula.

37.11 Radiotherapy

37.11.1 Indications

Indications for radiotherapy for parotid tumours are summarised in Table 37.6.

Adjuvant radiotherapy is planned 4–6 weeks after surgery.

37.11.1.1 Pre-treatment Assessment

- Clinical examination
- Dental evaluation
- Audiology
- Thyroid function test (neck is addressed)
- Written consent.

37.11.1.2 During Radiotherapy

- Weekly review
- Assessment of acute toxicities and management.

Table 37.6 Indications for radiotherapy

Adjuvant radiotherapy	• High grade histology • R1/R2 resection • Lymph node positive/ECE • Nerve involvement/perineural invasion • Recurrent tumour • Tumour spillage • T3/T4 tumour
Pleomorphic adenoma	• Positive or close margin, revision surgery not possible • Recurrent tumour
Radical	• Medically inoperable • Unresectable primary
Palliative radiotherapy	• Pain • Bleeding, fungating mass • Poor general condition

37.12 EBRT Planning

37.12.1 Patient Positioning and Immobilisation

- Patient supine, neck extended, hands by side
- *OR* Right/left lateral position (depending on tumour laterality) and customised head rest in lateral position, neck extended
- Wire the scar site
- Immobilisation with thermoplastic head and neck mask.

37.12.2 Target Volume

- For disease confined to superficial lobe of parotid, early stage, low grade—Post-op tumour bed
- For locally advanced disease, high grade, recurrent disease—Post op tumour bed + Neck Nodal region
  - If nodes are surgically not addressed in clinically N0 neck—Prophylactic/elective RT to ipsilateral neck nodal levels VII b, 1b, II, III, IV
  - If multiple nodes positive/multiple nodal levels/ECE—Nodal irradiation from level Ib to level V and VII b
- If adenoid cystic carcinoma, facial nerve is traced up to stylomastoid foramen.

Conventional 2D/Simulator-based planning beam arrangement

- Superior—zygomatic arch
- Inferior—lower border of hyoid/cover scar
- Anterior—anterior border of clenched masseter/anterior to upper second molar
- Posterior—mastoid process.

37.13 Special Consideration in 2D Planning

- Neck extended—to avoid exit dose to opposite eye.
- Half beam block technique also helps in avoiding exit dose to contralateral eye.
- For electron field 1 cm extra margin is given from photon field in all direction to account for constriction of higher isodose, and cover PTV adequately.
- Bolus is used if skin is involved, close superficial margin, capsule rupture, and tumour spillage.
- Photon beam provides a more homogeneous distribution but can increase dose to the contralateral parotid gland.
- Tissue heterogeneity (air cavity, external auditory canal, bones) has to be taken into consideration.

37.14 3D Conformal/IMRT Planning

CT Simulation From vertex to carina at 3 mm slice thickness with intravenous contrast. Target volume delineation guidelines is summarised in Table 37.7.

Table 37.7 Target volume delineation guidelines

Definitive RT	Adjuvant RT	Pleomorphic adenoma
• GTV 65—Gross primary disease and gross nodal disease • CTV 65—GTV 65 + 5 mm margin • CTV 60—CTV 65 + 5 mm and nodal regions harbouring gross nodes • CTV 54—Elective nodal regions	• CTV 60—Post-operative tumour bed+ high risk nodal region • CTV 54—Low risk nodal volume • GTV 65—Macroscopic residual disease (if R2 resection) • CTV 65—GTV 66 + 5 mm margin + microscopic residual disease	• GTV 60–66 Gy if gross residual disease (definitive) • CTV 50–55 Gy microscopic residual disease (post-op) • No elective nodal irradiation

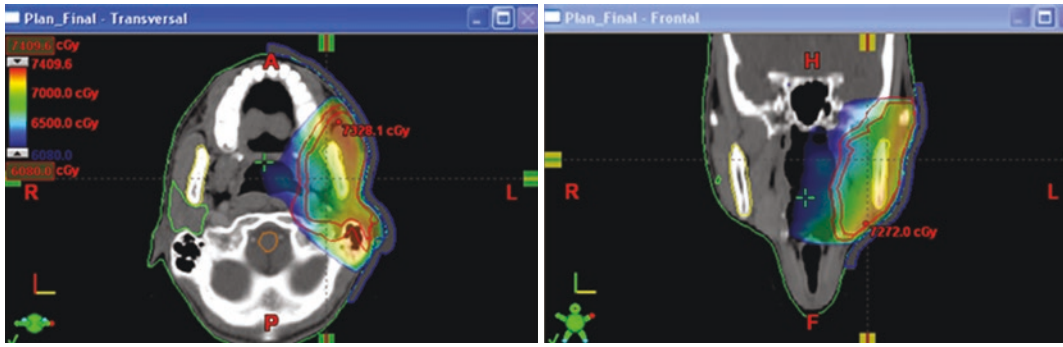

Fig. 37.1 3D conformal planning in patient with carcinoma parotid

Contralateral neck is not treated electively. A conformal plan for carcinoma parotid is shown in Fig. 37.1.

37.15 Beam Arrangements

1. Ipsilateral anterior and posterior oblique wedged fields with photon.
2. Ipsilateral anterior and posterior oblique wedged fields and direct on field with photon.
3. Ipsilateral direct on field with photon electron combination.
4. Ipsilateral anterior and posterior oblique wedged fields with photon and direct on field electrons.

37.16 Energy

- Photon—^{60}Co, 4 to 6 MV
- Electron 12–16 MeV electrons
- Photon electron weightage is 1:4 (20% from photon and 80% from electron).

37.17 Organ at Risk and Dose Constraints

Relevant OARs for salivary gland tumours are summarised in Table 37.8.

Table 37.8 Relevant OARs for salivary gland tumours

Brainstem	D_{max} < 54 Gy, 1 cc < 60 Gy
Spinal cord	D_{max} < 45 Gy, 0.03 cc < 48 Gy
Mandible	D_{max} < 70 Gy, 1 cc < 75 Gy
Oral cavity	D_{mean} < 40 Gy
Contralateral parotid	D_{mean} < 26 Gy V 30 < 50%
Cochlea	D_{mean} < 45Gy, V55 < 5%
Submandibular gland	D_{mean} < 45Gy

37.18 Neutron Therapy for Salivary Gland Tumours

- Neutrons are densely ionizing particulate radiation, with RBE >3.
- Less affected by hypoxia.
- Differential effect on various tissue.

37.18.1 Indications

- Unresectable gross disease
- Macroscopic gross residual disease
- Positive margin
- Recurrent disease.

RTOG-MRC trial is the only phase III RCT comparing neutron versus photon treatment for unresectable salivary gland tumours.

10-year follow-up data showed:

- Improved locoregional disease control for neutrons (56% vs. 17%, $p = 0.009$)
- No improvement in overall survival
- Increased late grade 3 and 4 toxicity in neutron treatment arm (impaired taste, temporal lobe necrosis, mucositis, pain, fibrosis).

37.19 Toxicity

Common acute and chronic radiation toxicity in salivary gland tumours are summarised in Table 37.9.

Table 37.9 Common acute and chronic radiation toxicity in salivary gland tumours

Acute	Late
Skin changes	Subcutaneous fibrosis
Mucositis	Xerostomia
Fatigue	Hearing loss
Dry mouth/thickened saliva	Hypothyroidism
Dysgeusia	Osteoradionecrosis
Otitis media	Second malignancy
Hearing loss/ear ache	

37.20 Follow-Up

First follow-up at 6–8 weeks after radiation treatment.

Every 3–4 monthly for first 2–3 years with physical examination.

Every 6 monthly for next 2–3 years with physical examination.

Then annually thereafter.

Source of Image Image has been taken from patient treated by author and consent has been taken.

Extremity Soft Tissue Sarcoma

38

Supriya Mallick and Goura K. Rath

Soft-tissue sarcomas are relatively uncommon cancers accounting for less than 1% of all new cancer cases. It includes a wide variety of histological subtypes with variable chemosensitivity and radiosensitivity

38.1 Risk Factors

Only few environmental risk factors have been associated with the development of soft tissue sarcoma:

- Chlorophenols in wood preservatives and phenoxy herbicides
- Vinyl chloride increased risk of angiosarcoma
- Human herpes virus 8 has been implicated in the development of Kaposi's sarcoma

38.2 History Taking

- Swelling
- Pain
- Change in color
- Any history of trauma

38.3 Examination

- Start with examination of the swelling
- Site, number
- Size
- Shape—spherical, oval, irregular
- Surface and skin over swelling—color, punctum, inflammation, scars over swelling—recurrence, dilated veins
- Borders/edge—well defined and regular
- Consistency—soft, cystic, firm, hard
- Pulsations
- Palpation—tender/local rise of temperature—first to do in palpation
- Fixity—skin and deeper structures—pinch skin over swelling, move in direction and perpendicular to fibers
- Location—contraction of muscle
  - Superficial remains mobile and become prominent
  - Muscular—becomes immobile and fixed
  - Deep to muscle it becomes less palpable—look at draining LN
- Distal pressure effects in limb swelling
  - Distal wasting of muscles, movements and power of distal muscles, sensations—for nerve compression
  - Distal pulsations—for arterial occlusion
  - Distal effects including edema—pressure effects and dilated veins—for venous occlusion

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- Examination of lymph nodal region adjacent to the swelling
  - Particularly in: RMS, angiosarcoma, clear cell sarcoma
- Abdominal examination—rarely hepatomegaly or PA LN
- Respiratory—lung metastasis is common
- CVS and CNS examination

38.4 Differential Diagnosis

- Benign soft tissue mass
- Metastasis
- Organized hematoma

38.5 Workup

- Complete blood counts, RFT, LFT
- Biopsy: Direction should be parallel to the tumor, planned in such a way that the biopsy pathway and the scar can be safely removed by definitive surgery
- FNAC: Advised in few cases
- MRI—local part, preferred except in retroperitoneal and thoracic tumors where CT may be sufficient
- CECT Chest
- CT scan abdomen/pelvis—in patients with myxoid/round cell liposarcoma and leiomyosarcoma

38.6 Staging: FIGO—Clinical Staging

The factors that are taken into account for the TNM staging of soft tissue sarcomas are tumor size, nodal status, grade (differentiation score), and metastasis.

The AJCC 08 TNM staging for extremity soft tissue sarcoma is summarized in Table 38.1.

Three-tier system is commonly used for grading. The FNCLCC (French) system is the preferred grading system (Table 38.2).

Table 38.1 AJCC08 TNM staging for extremity soft tissue sarcoma

T staging	N staging	Stage grouping
T1—Size less than or equal to 5 cm T2—Size greater than 5 cm < 10 cm T3—5–10 cm size T4—Size more than 15 cm	N0—No N1—Yes *M staging* M0—None M1—Yes	• IA—T1 N0 M0 G1 • IB—T2-4 N0 M0 G1 • II—T1N0 M0 G2-3 • IIIA—T2 N0 M0 G2-3 • IIIB—T3-4 N0 M0 G2-3 • IV—N1/M1

Table 38.2 French Federation of Cancer Centers Sarcoma Group grading

Tumor differentiation	Mitotic count	Tumor necrosis	Grade
1 point: resembles normal adult mesenchymal tissue 2 points: histologic typing is certain 3 points: synovial sarcoma, osteosarcoma, Ewing's sarcoma, etc.	1 point: 0–9 mitoses 2 points: 10–19 mitoses 3 points: 20 or more mitoses	0 points: no necrosis 1 point: <50% necrosis 2 points: >50% necrosis	Grade 1: Total 2–3 points Grade 2: 4–5 points Grade 3: 6–8 points

38.6.1 Patterns of Spread

- Distant metastases—most common pattern of spread
  - 10% have distant metastasis at presentation
  - Lung is the most common site (70–80%) of spread of extremity sarcomas
  - 80% of distant metastasis appear within 2 years
- Lymph nodes—Less common than distant metastasis
  - Only 5% of the patients with sarcomas have positive lymph nodes at presentation
  - Increased risk of lymph node metastasis occurs in synovial sarcoma (14%), clear cell sarcoma (28%), angiosarcoma (23%), rhabdomyosarcoma (15%), and epithelioid sarcoma (20%) (SCARE)

Risk of Distant Metastasis *Depends on Grade*, tumor size, depth, and neurovascular bone involvement are independent predictors of metastasis.

38.6.2 Prognostic Factors

38.6.2.1 Increased Risk for Local Recurrence

- Age >50
- Recurrent disease
- Positive surgical margins
- Fibro sarcoma (including desmoid)
- Malignant peripheral nerve tumors

38.6.2.2 Increased Risk of Distant Metastasis

- Size >5 cm
- High grade
- Deep location
- Recurrent disease
- Leiomyosarcoma

38.6.3 Treatment Overview

Surgery Historically amputation was the treatment of choice for extremity, then full compartment resection. At present en-bloc resection with 2 cm margin considered standard. Resection of skin and bone rarely required.

38.6.3.1 Approaches

1. Amputation vs. limb-sparing surgery + post-op chemo-RT
   - *National Cancer Institute* randomized 43 patients with high-grade soft tissue sarcomas of the extremities, without distant metastasis to either amputation vs. limb-sparing surgery + post-op chemo-RT [1]
   - *Radiation dose*: 45–50 Gy followed by a boost to 60–70 Gy
   - All patients received post-op chemotherapy
   - Outcome: Local failure limb-sparing 15% vs. amputation 0% ($p = 0.06$)
   - 5-year DFS 71% vs. 78% (NS)
   - 5-year OS 83% vs. 88% (NS)
2. Surgery + post-op EBRT vs. surgery alone
   - *National Cancer Institute* randomized patients with extremity to either limb-sparing surgery followed by adjuvant radiation of 63 Gy with concurrent chemotherapy or chemotherapy alone [2]
     - High grade: local recurrence chemo-RT 0% vs. chemo 19%
     - 10-year OS 75% vs. 74% (NS)
     - Low grade tumors: local recurrence RT 4% vs. observation 33% (SS)
     - It reflected that adjuvant RT is highly effective in preventing local recurrence
3. Preoperative radiotherapy

   Trials on pre-operative radiotherapy are summarized in Table 38.3
4. Preoperative RT vs. adjuvant RT

   O'Sullivan et al. from NCI Canada performed a randomized trial comparing pre-op RT vs. post-op RT which included 190 patients. Primary endpoint was a major wound complication. The pre-op RT group received 50 Gy in 25 fractions with an option of additional 16–20 Gy post-op boost. The post-op RT arm received a dose of 66–70 Gy. Initial radiotherapy field included 5 cm proximal/distal margin followed by the boost which included 2 cm proximal/distal margin. Longitudinal strip of skin was untreated for at

Table 38.3 Trials on pre-operative radiotherapy

Trial	Number	Inclusion criteria	Arms	outcome
RTOG 95–14 [3]	64	Large (≥8 cm), high grade (G2-3) expected R0 resection	Neoadjuvant sequential chemo-RT	3-year LRF 18% 3-year DFS 57% Toxicity-high
DeLaney et al. [4]	48	Large (≥8 cm), high grade (G2-3)	Neoadjuvant sequential chemo-RT	5-year LC 92% DFS 75% OS 44%

least half the course to avoid lymphedema. Acute wound complications worsened after pre-op RT but long-term extremity function worsened after adjuvant RT [5].

Al-Absi et al. performed a meta-analysis of 5 studies with 1098 patients and found that local recurrence was better in pre-op group (HR 0.6, SS). Survival pre-op group was 76% vs. 67% in the post-op RT cohort [6].

38.7 Radiotherapy Planning for Soft Tissue Sarcoma

38.7.1 Indications for RT

- RT for all tumors >5 cm and deep
- High grade even if ≤5 cm and deep
- If the surgical margin was less than 10 mm

38.7.2 PORT Dose

- 66–70 Gy in 2 Gy per fraction depending on margin status

38.7.3 Volumes

- 2 Phase plan
  - Phase 1 CTV for limbs—operative bed plus 5 cm longitudinal and 2 cm radial margin and includes the scar and biopsy sites
  - Phase 2 CTV has only a 2 cm longitudinal margin
  - A 2D plan for extremity soft tissue sarcoma is shown in Fig. 38.1
  - Spare a strip of skin to avoid long-term lymphedema

Target volume according to VORTEX trial: 2 cm cranio-caudal margin to GTV and minimum margin of 2 cm axially forms the CTV 1 cm margin for PTV, treatment in single phase (no Boost)

VORTEX trial was aimed to look into the feasibility of reducing volume of tissue irradiated

Control arm (C): 50 Gy in 25 fractions to CTV1 (GTV + 5 cm cranio-caudally and 2 cm axially) followed by 16 Gy in 8 fractions to CTV2 (GTV + 2 cm cranio-caudally and axially) or the Experimental arm (R): 66 Gy in 33 fractions to CTV2 alone. Two hundred sixteen patients were randomized. The initial results show 5-year local recurrence free survival (LRFS) rates were 86% vs. 84%. 5-year overall survival was 72% vs. 67%.

Brachytherapy for Soft Tissue Sarcoma
Described in brachytherapy chapter.

38.8 Chemotherapy

38.8.1 Adjuvant

- The definite role of adjuvant chemotherapy is not proven beyond doubt—Maybe considered for high-risk patients—high-grade tumors, deep, >5 cm tumor, after discussing with patients potential toxicity and benefits
- Ifosfamide and adriamycin chemotherapy

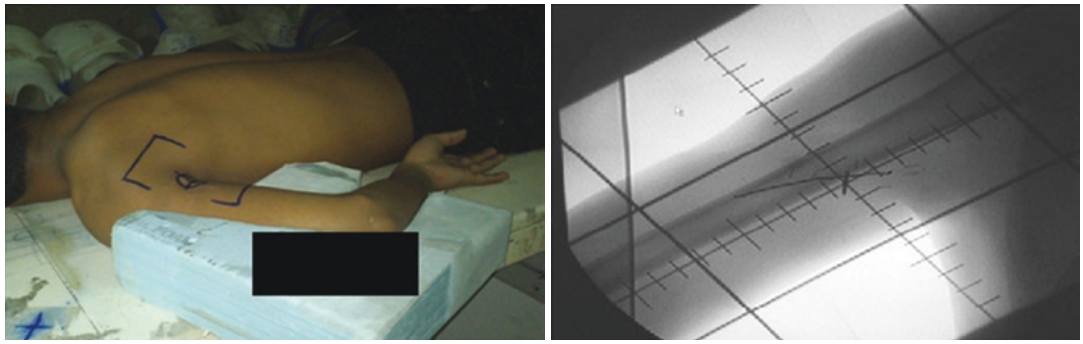

Fig. 38.1 2D planning in a patient with limb sarcoma

38.8.2 Metastatic

- Maybe useful in metastatic setting—histology driven chemotherapy
- Relatively chemoresistant
- If limited lung metastasis—may be considered for resection
- Single agent anthracyclines are preferred first line agent
- Only agent proved beneficial in combination with anthracycline-olaratumab (blocks PDGF-AA and PDGF-BB from binding PDGFRα) has OS benefit
- Other agents
  - Myxoid/round cell liposarcoma—trabectedin
  - Undifferentiated pleomorphic sarcomas—gemcitabine and docetaxel
  - Pazopanib—advanced *non*-adipocytic STS
  - Sunitinib—alveolar soft-part sarcomas and solitary fibrous tumor
  - Angio sarcoma—taxanes may be beneficial
  - Eribulin—liposarcoma

38.9 Follow-Up

- History and physical examination with X-ray or CT chest every 3–6 months in first 2–3 years
- Then every 6 months till 5 years and then annually

Source of Image Image have been taken from patient treated by author and consent have been taken.

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39 Orbital Tumors and Retinoblastoma

Kiran Turaka and Aruna Turaka

39.1 Introduction

Retinoblastoma (RB) is the most common primary intraocular tumor in children. RB is more common in children in underdeveloped countries and associated with higher mortality. The mortality in developed countries is lower due to early diagnosis and latest treatment techniques. RB develops from cells that have cancer-predisposing variants in both copies of *RB1* gene: the first one may be inherited and second one somatic (double hit hypothesis). It can be unilateral or bilateral and in unilateral cases can be unifocal or multifocal. The median age of diagnosis of bilateral retinoblastoma is 15 months compared to 24 months for unilateral cases. Bilateral and multifocal disease are more likely to be inherited RB. Hereditary RB is inherited in an autosomal dominant pattern and is also at a higher risk for non-ocular tumors [1–5]. Patients with retinoblastoma, in addition to complete ocular examination, also need a systemic work-up to rule out intracranial lesions. Early diagnosis and treatment of RB is important in order to retain useful vision, reduce morbidity, prevent metastasis, and increase survival. A multidisciplinary team of ophthalmologist, pediatric oncologist, radiation oncologist and pathologist is important in management of these patients to optimize outcomes.

Treatment options for retinoblastoma include local treatment like cryotherapy, laser photocoagulation [transpupillary thermal therapy (TTT])], and plaque brachytherapy [1–5]. Chemotherapy (intravenous, periocular, intravitreal, intra-arterial), external beam radiotherapy, and proton beam irradiation also have a role in the management of RB. Usually a judicious combination of these modalities is needed to optimize outcomes. Each of these treatments is associated with unique side effects. External beam radiotherapy (EBRT) and plaque brachytherapy are associated with radiation induced complications and second malignancies. The side effects of systemic intravenous chemotherapy (IVC) include acute toxicity which includes hematological toxicity, nephrotoxicity, ototoxicity, and long-term toxicities mainly blood dyscrasias and infertility. Second malignant neoplasms (SMN) are known to occur after treatment with systemic chemotherapy and EBRT especially in hereditary RB than sporadic RB cases. Pinealoblastoma can also occur in patients with RB (hereditary RB) and MRI of the brain may be needed.

Figure 39.1 summarizes common intraocular tumors among children and adults.

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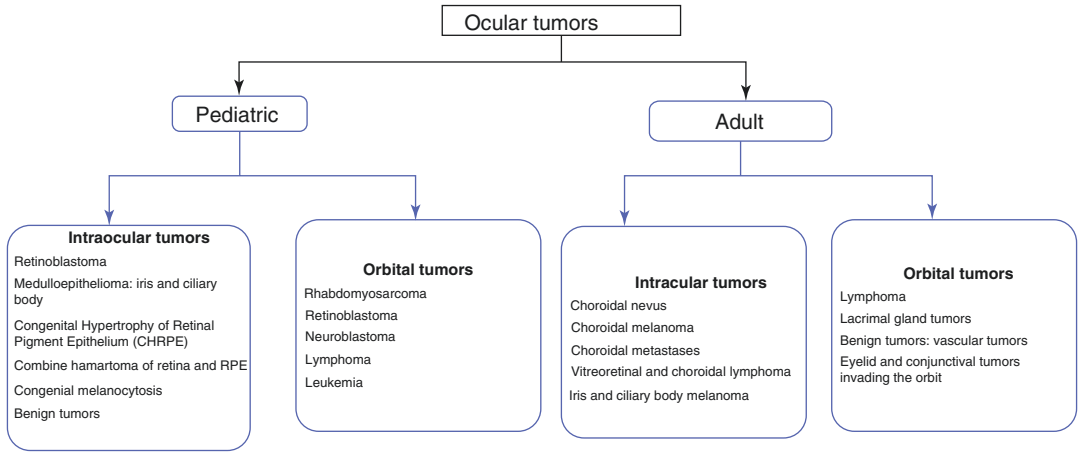

Fig. 39.1 Common intraocular tumors among children and adults

Choroidal melanoma is the most common intraocular lesion among adults. It can present as a small nevus and later grow to a melanoma involving the entire eyes. Choroidal melanoma is also associated with systemic metastasis (most commonly liver) and can occur years after treatment is also one of the life threatening intraocular tumors like RB [4, 6]. All patients need complete ocular examination including best corrected visual acuity (VA), slit-lamp examination, binocular indirect ophthalmoscopy, fundus photography, fundus autofluorescence (AF), fundus fluorescein angiography (FFA), indocyanine green angiography (ICG-A), optical coherence tomography (OCT), A and B scan ultrasonography (USG), computerized tomography (CT) of the chest, magnetic resonance image (MRI) of the abdomen, and liver function tests. Fundus autofluorescence (AF) can detect changes in the RPE and has advantage of being non-invasive. Hyperautofluorescence on AF is indicative of lipofuscin deposits in RPE cells, and hypoautofluoresce, whereas continuous pattern on AF suggests normal function of RPE cells overlying the tumor. AF is ideal to identify overlying tumor features and its margins.

Heidelberg-Spectralis or Spectral-Domain OCT is useful for identifying the level of the tumor, thickened choroid, presence of SRF, retinal folds, and retinal thickening. Fundus fluorescein angiography (FFA) offers very little features to distinguish between choroidal melanoma, choroidal metastasis, and hemangioma. ICG-A has a unique advantage in that it shows clear visualization of the tumor through retina unlike FFA.

Ultrasonogram (USG) is one of the most useful diagnostic tools especially in patients with amelanotic choroidal melanoma (very difficult to distinguish from choroidal metastasis). Tumor vascularity, solidity, and choroidal excavation can be evaluated on USG, although there may be some overlapping features for choroidal metastasis and melanoma. Choroidal melanoma can be plateau, dome or mushroom shaped lesions ± RD on B scan USG. Fine needle aspiration biopsy (FNAB) can be done through transvitreal route with a 27 G needle and has an accuracy of 90-98% in lesions of > 2 mm in thickness and is a highly accurate diagnostic test to confirm the histology of both anterior and posterior segment tumors of the eye. FNAB has been shown to have a very high yield of up to 99% with few complications.

Computerized tomography (CT) scan of the chest is helpful in detecting the metastatic lung tumors. MRI of the abdomen is helpful in diagnosis and follow-up of metastatic lesions in the liver. Positron emission tomography (PET) scan, a newer evolving imaging modality is useful to evaluate for distant metastases and to assess the tumor response to treatment.

The goal of treatment of intraocular tumors is to restore or stabilize the vision, improve quality of life, and improve survival. Various treatment options include observation, chemotherapy (intravitreal anti-VEGF or systemic chemotherapy), immunotherapy, radiotherapy (external

beam (EBRT), plaque brachytherapy and proton beam therapy (PBT)), laser therapy (transpupillary thermotherapy (TTT), photodynamic therapy (PDT)), hormone therapy, and surgery (enucleation) [4, 6]. Treatment decision for choroidal melanoma depends on the tumor size, depth, extent, number of tumors, location and laterality of tumors, visual acuity of status of the affected eye, presence of other distant metastasis, age, and performance status of the patient.

Plaque brachytherapy is useful for selective lesions of the choroid (melanoma, metastasis, and hemangioma) and provides rapid and effective tumor control. Common radioisotopes used for plaque brachytherapy includes Iodine (I-125), Ruthenium (Ru106), and Palladium-103 [4]. Plaque brachytherapy is usually delivered as inpatient technique over a period of 3–7 days unlike EBRT (takes 3–4 weeks). Plaque brachytherapy can deliver radiation dose up to 60–70 Gy to the apex of the tumor. Unlike EBRT plaque brachytherapy delivers very little dose to neighboring structures in the eye and orbit [6]. Common complications after plaque brachytherapy of choroidal melanoma include radiation papillopathy, retinopathy and maculopathy, retinal vascular occlusions, vitreous hemorrhage, chorioretinal atrophy, dry eyes, cataract, and secondary glaucoma.

Genetic profiling via FNAB can be useful in prognosticating patients with choroidal melanoma. Loss-of-function of the *BAP1* gene or expression of a cancer-testis antigen PRAME (preferentially expressed antigen in melanoma) is associated with the higher metastatic risk. Gain-of-function of *SF3B1* and *EIF1AX* genes is associated with better prognosis. High-risk patients can be identified for clinical trials and may be treated by targeted therapy for metastatic disease.

39.1.1 History (Fig. 39.2)

- Age—most important in diagnosis
- Pediatric—retinoblastoma, RMS
- Adult—lymphomas, melanoma, metastasis
- Presenting symptoms
- White reflex/squint—in retinoblastoma
- Floaters—vitreous involvement
- Proptosis—unilateral or bilateral
- Pain
- Loss of vision/visual field loss—melanoma
- Headache and vomiting—intracranial extension
- B symptoms—lymphoma
- Phthisis bulbi—common in neglected RB
- History of known malignancy—possibly metastasis

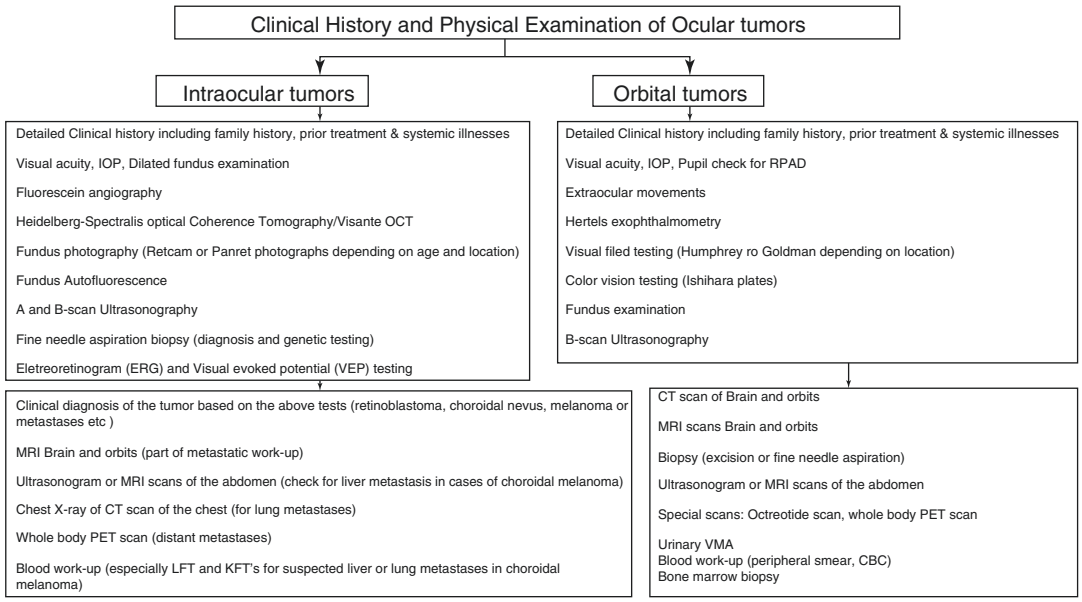

Fig. 39.2 Clinical history and physical examination of intraocular and orbital tumors

- History of treatment for malignancy—possible second malignant neoplasm like sarcomas
- Family history—important in retinoblastoma.

39.1.2 Clinical Examination (Fig. 39.2)

- Eye—external and dilated fundus examination
- Check visual acuity
- Check intraocular pressure (IOP)
- Gonioscopy (iris and ciliary body nevus/melanoma, medulloepitheliomas)
- Look for LN—parotid area and neck.

39.1.3 Investigations (Fig. 39.2)

- Fundus photograph—color and red free (Retcam for RB, Panret for ciliary body melanoma)
- Fundus autofluorescence photographs
- Optical coherence tomography (OCT)
- USG of the globe and the orbit (A and B scans)
- CT scan orbit—presence of calcifications—RB
- MRI of the brain and orbits—more helpful than CT helps in optic nerve and intracranial involvement
- Lumbar puncture/bone marrow involvement in selected cases (primary vitreoretinal or uveal lymphoma)
- Chest X-ray—to rule lung lesions (in case of choroidal metastases for primary lung lesions or choroidal melanoma with distant metastases to the lung)
- USG abdomen—in choroidal melanoma to rule out liver metastasis
- CT scan of the chest and MRI scan of the abdomen as part of metastatic work-up
- Blood work-up (liver function tests, kidney function tests as part of choroidal melanoma metastatic work-up)
- Whole body PET scan (to check for distant metastasis and treatment follow-up).

39.2 Clinical Cases of Retinoblastoma and Choroidal Melanoma Treated by Plaque Brachytherapy and External Beam Radiation and Its Complications

39.2.1 Case 1: Retinoblastoma Treated Successfully by Iodine-125 Plaque Brachytherapy

A 6-month-old male child presented with leukocoria in both eyes (noticed by the parents). He was a full-term born boy with no perinatal illnesses. There was a family history of retinoblastoma (RB) with father being treated in the past for RB by chemotherapy and radiation therapy (RT). On examination, visual acuity was not fixing or following the light with both eyes. There was alternating esotropia (ET). On examination under anesthesia, anterior segment was unremarkable in both eyes. Dilated fundus examination revealed a creamy white tumor of 1.5 mm in basal diameter and 1 mm in thickness, located in the midperipheral retina [ICRB (International Classification of Retinoblastoma) Group A, Reese-Ellsworth (RE) Group Ia] retinoblastoma in the right eye. There was a 9.5 mm basal diameter and 3.9 mm thickness white tumor located at the optic disc, ICRB Group C, RE Group IIa, in the left eye (Fig. 39.3a). There were no subretinal or vitreous seeds in either eye. Magnetic resonance imaging (MRI scan) of the brain was unremarkable with no intracranial lesions. Intraocular pressure was 15 mmHg in the right eye and 18 mmHg in the left eye. Patient was treated with 6 cycles of systemic intravenous chemotherapy with vincristine, etoposide, and carboplatin [chemoreduction (CRD)]. Additional treatment was done by consolidated cryotherapy to the local intraocular retinoblastoma in both eyes which regressed the RB (Fig. 39.3b). After 5 months of chemotherapy, the right eye was

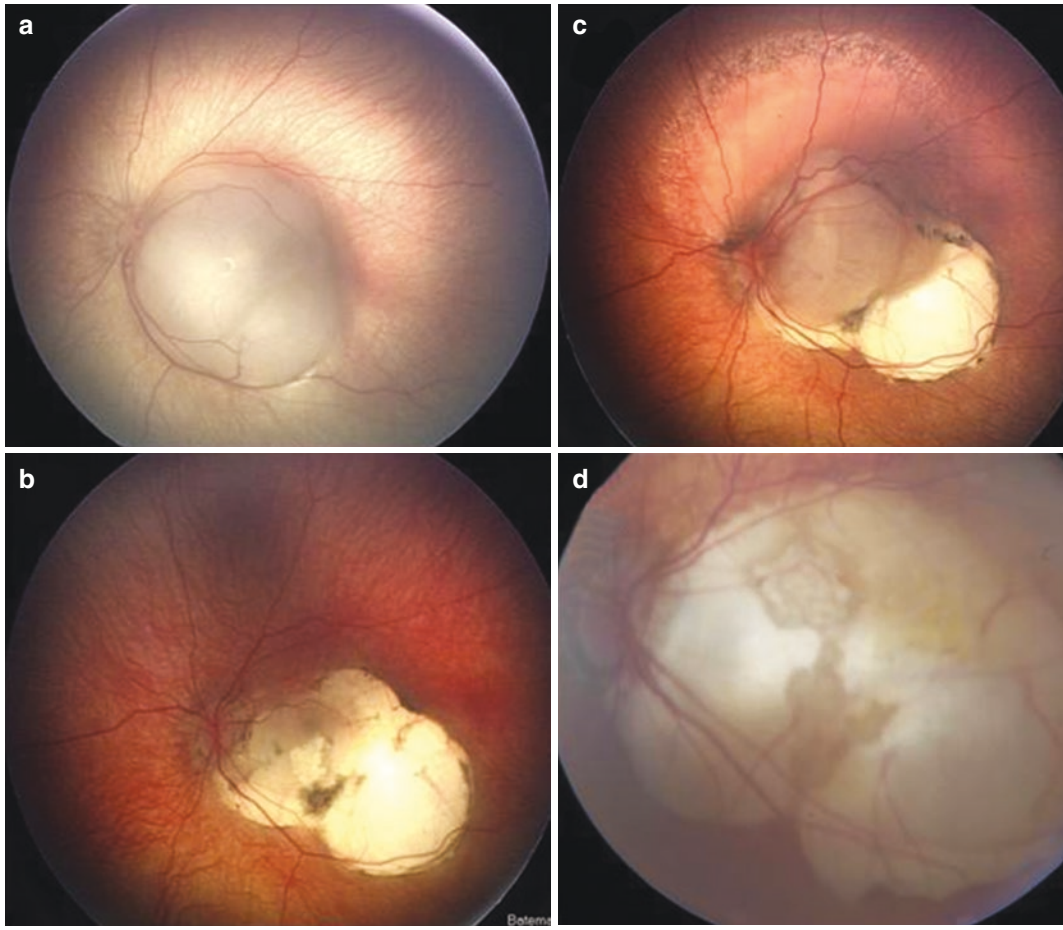

Fig. 39.3 Fundus photograph of the left eye (**a**) showing ICRB Group C retinoblastoma located at the optic nerve that regressed (**b**) completely after treatment with 6 cycles of CRD. Ten months following chemoreduction, recurrent RB tumor seen at the optic nerve (**c**), that was further treated by I-125 plaque radiotherapy (40 Gy). At 5-year follow-up, no signs of recurrence or radiation complications (**d**) noted with complete regression of RB

quiet with completely regressed retinoblastoma, whereas in the left eye there was a recurrence of the tumor that was treated by transpupillary thermotherapy. At 10 months of follow-up, right eye was stable with no tumor recurrence or subretinal or vitreous seed recurrence. However, in the left eye there was a new tumor noted superior to the initial retinoblastoma measuring 8 mm in basal diameter and 3.5 mm in thickness (Fig. 39.3c) with no recurrence of subretinal or vitreous seeds (ICRB Group C). The new retinoblastoma tumor in the left eye was treated with plaque brachytherapy (Iodine-125 (^{125}I), 40 Gy over 3–5 days). After 5 years of follow-up, the patient was alive with no systemic metastases and no local intraocular recurrence of RB in either eye. Visual acuity was 20/60 in right eye and hand motion in the left eye. There were no radiation related complications or tumor recurrence noted in the left eye (Fig. 39.3d).

39.2.2 Case 2: Retinoblastoma Treated by Iodine-125 Plaque Brachytherapy and EBRT

A 4-month African-American male was referred when leukocoria was noted by pediatrician in both eyes. On examination, there was a large white tumor at the optic nerve measuring 10 mm

in basal dimension and 6 mm in thickness with surrounding subretinal seeds, subretinal fluid, and vitreous seeds (RE-Group Vb, ICRB Group C) in the right eye. There was 14 mm basal diameter creamy white tumor near the optic nerve with a thickness of 9 mm in the left eye (RE-Group VIb, ICRB Group D) with multiple subretinal seeds, vitreous seeds, and retinal detachment (Fig. 39.4a). MRI scan of the brain revealed a pinealoblastoma. He was diagnosed with trilateral retinoblastoma and treated by chemoreduction with 6 cycles of vincristine, etoposide, and carboplatin. Patient was followed up every month by examination under anesthesia and after 2 months of follow-up, there was subretinal seed recurrence that was treated by cryotherapy in both eyes (Fig.39.4b). At 3 months of follow-up, a new tumor was seen measuring 2 × 2 mm tumor located in the midperipheral retina with few subretinal seeds but no vitreous seed recurrence in the right eye. This new RB in the right eye was treated by plaque radiotherapy (^{125}I plaque brachytherapy, 40 Gy over 4 days). However, in the left eye along with tumor recurrence, there were multiple vitreous seed recurrence and a new tumor measuring 4 × 3 mm in the mid peripheral retina were noted (Fig. 39.4c). The new RB and the recurrent tumors in the left eye were treated by external beam radiotherapy (EBRT, 40 Gy, 10 fractions). After 1 year of treatment, there was no recurrence of retinoblastoma in either eye (Fig. 39.4d) with stable pinealoblastoma, but after two and half years of treatment he died with multiple systemic metastases.

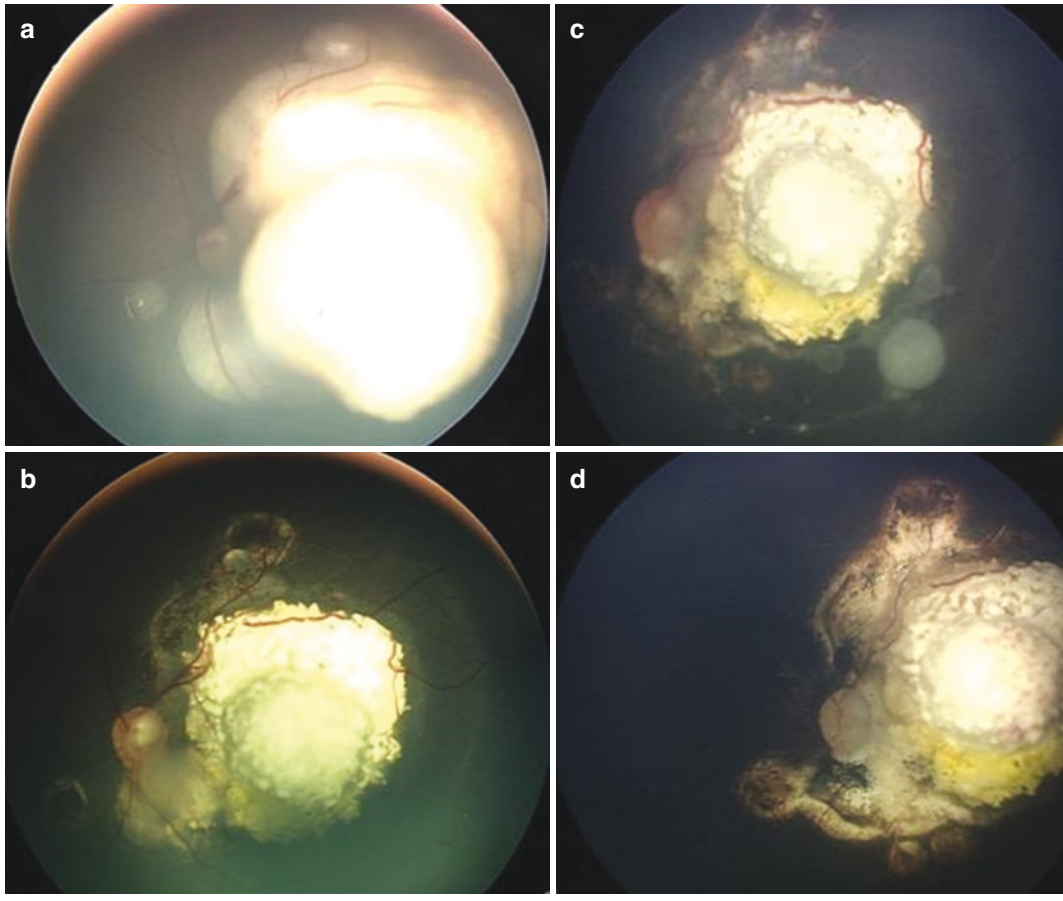

Fig. 39.4 Fundus photograph of the left eye (**a**) showing ICRB Group D retinoblastoma that was treated with 6 cycles of CRD. Regressed RB after treatment (**b**), but there was a tumor recurrence at 3 months of follow-up (**c**), that was treated by EBRT (4000 cGy), and at 1 years of follow-up after EBRT, there is no recurrence of the RB tumor (**d**) in the left eye

39.2.3 Case 3: Choroidal Melanoma Treated Successfully by Iodine-125 Plaque Brachytherapy

A 50-year-old male was referred with a diagnosis of pigmented spot in the right eye. Visual acuity was 20/20 in each eye. Intraocular pressure was 15 mmHg in both eyes. Slit lamp biomicroscopic examination was unremarkable in the right eye and there was a small pigmented lesion on the iris of the left eye. Dilated fundus examination revealed a pigmented choroidal lesion measuring 8 × 6 × 3 mm (Fig. 39.5a, b) with overlying orange pigment and additional subretinal fluid. Patient was diagnosed with choroidal melanoma and was treated with Iodine-125 plaque radiotherapy. After 4 months of treatment, visual acuity in the right eye was 20/25 and 20/20 in the left eye and intraocular pressure was 19 mmHg in both eyes. The choroidal melanoma in the right eye has regressed to 1.7 mm (Fig. 39.5c, d) with no radiation related side effects. Systemic work-up by liver function tests, ultrasound abdomen, and chest X-rays revealed no evidence of metastasis.

39.2.4 Case 4: Second Malignant Neoplasms as a Complication of EBRT After Treatment of Retinoblastoma

An 8-month-old child presented with bilateral leukocoria to the pediatric ophthalmology department. Upon examination under anesthesia, there were large creamy white tumors in both eyes

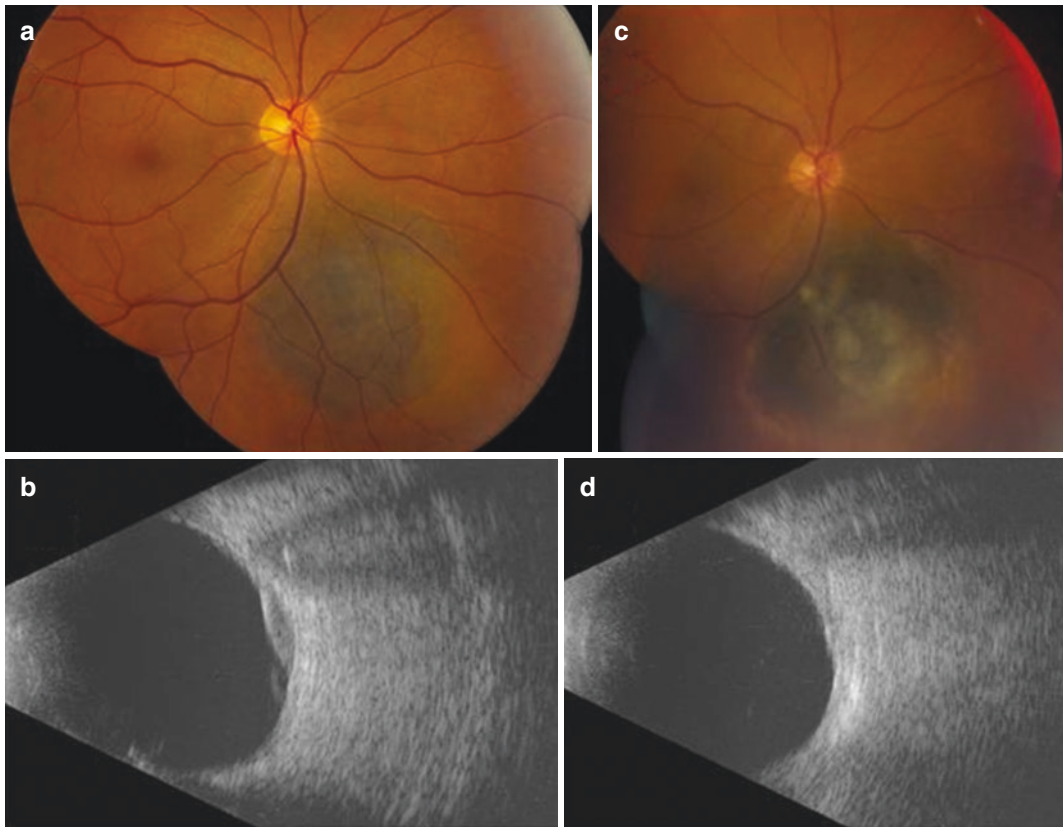

Fig. 39.5 Color fundus photograph of the right eye showing a pigmented melanoma inferior to the optic nerve measuring 8 × 6 mm in basal diameter (**a**) with a thickness of 3 mm on B-scan ultrasonogram (**b**). After 4 months of plaque radiotherapy, the choroidal melanoma (**c**) regressed to 1.7 mm in thickness (**d**)

(measuring more than 15 mm in basal dimension and 10 mm in thickness) with multiple subretinal and vitreous seeds. He was diagnosed with ICRB Group E RB in the right eye (Fig. 39.6a) and Group D RB in the left eye. He was treated with 6 cycles of vincristine, etoposide, and carboplatin (VEC). Enucleation of the right eye was performed due to advanced RB, whereas tumor consolidation therapy with cryotherapy was done for the left eye RB followed by EBRT (44 Gy). After 3 years of treatment, left eye was stable with no recurrence of RB, whereas in the right socket, there was a small non-pigmented lesion. Computerized tomography (CT) scan of the orbits revealed an inferotemporal orbital mass on the right side (Fig. 39.6b). Biopsy from the lesion showed epithelioid cells that stained positive with Melan A, vimentin, and S100 proteins suggestive of invasive malignant melanoma. He was treated by right orbitotomy and further chemotherapy. At seven years of follow-up, the right socket was free of tumor, whereas in the left temporal area there was a mass. Further studies by MRI scanning revealed a large mass in the temporal fossa on the left side (Fig. 39.6c). Biopsy revealed rhabdomyosarcoma (RMS) that was treated by excision,

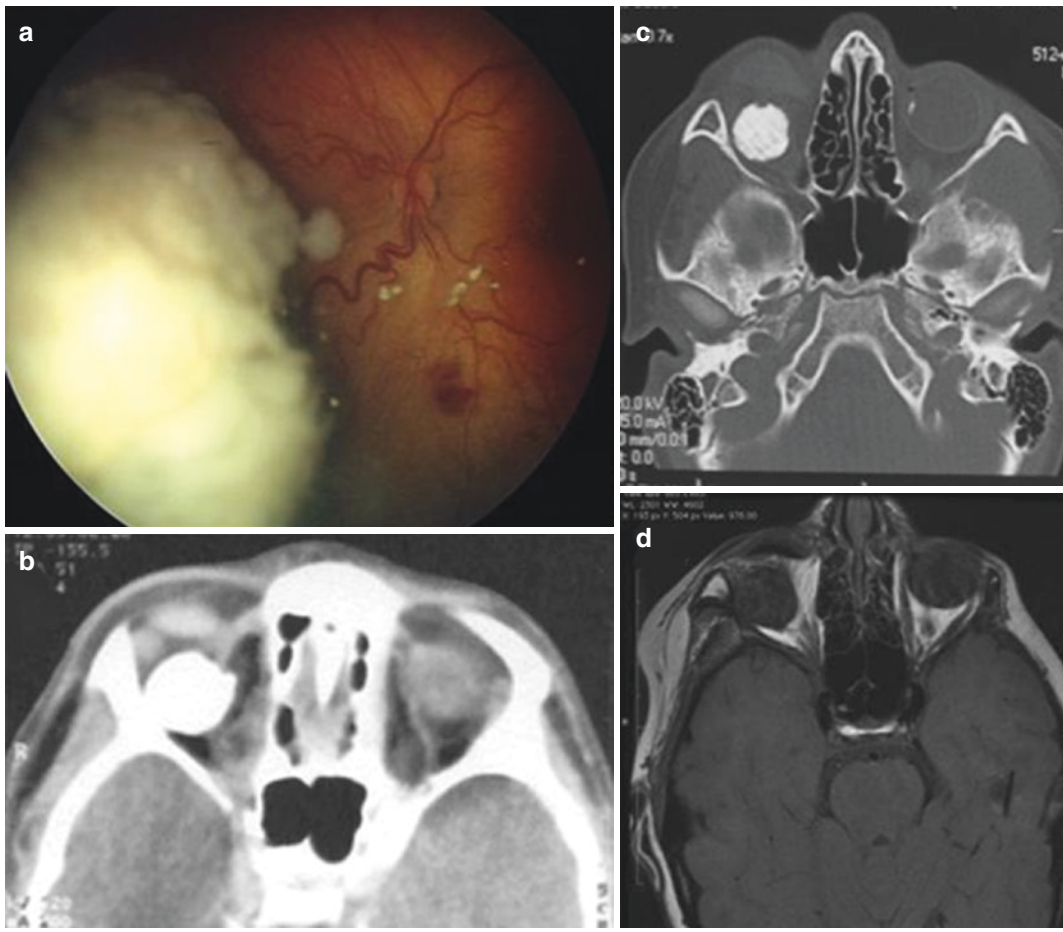

Fig. 39.6 Retcam fundus photograph showing Group E retinoblastoma in the right eye (**a**) treated by enucleation and CRD plus EBRT to the left eye for Group D RB. After 3 years of follow-up, there was an amelanotic lesion with well-defined margins on the CT scan in the inferotemporal right orbit (**b**), and was treated by excision (malignant melanoma). At 7 years of follow-up, no tumor recurrence in the right orbit, but there was a homogeneous lesion in the left temporal fossa (**c**) which was treated by excision (rhabdomyosarcoma), further chemotherapy and EBRT and at 9 years of follow-up no tumor recurrence seen on either side (**d**)

6 more cycles of chemotherapy, and additional EBRT (50 Gy). MRI scan of the orbits and brain after 9 years of initial treatment, he was alive and active with no tumor recurrence in right socket or left temporal fossa (Fig. 39.6d) and there was no evidence of systemic metastases.

Consent of the patients has been taken for presenting the case scenarios. The patients were not a part of trial and was treated as per standard protocol of the hospital.

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Carcinoma Rectum

40

Bhanu Prasad Venkatesulu

40.1 History Taking

- Bleeding PR
- Discharge PR-mucoid, sometimes mixed with blood
- Alteration in bowel habits—constipation, constipation alternating with diarrhea, change in caliber of stools, feeling of incomplete evacuation of stools (low rectal cancer)
- Rectal tenesmus—sensation of needing to pass stool, accompanied by pain, cramping, and straining
- Incontinence—sphincter involvement
- Anemia—in case of occult bleeding
- Back pain—advanced stages with nerve involvement
- Colicky abdominal pain—partial obstruction
- Weight loss.

40.2 Other Relevant History

- Non-vegetarian diet with consumption of processed red meat
- Obesity, smoking, alcoholism
- Inflammatory bowel disease—ulcerative colitis, Crohn's disease
- Family history of rectal cancer—inherited conditions like HNPCC-Lynch syndrome, FAP-Familial adenomatous polyposis, Peutz–Jeghers syndrome, MYH-associated polyposis
- History of adenomatous polyps
- H/o radiation to pelvis.

40.3 Examination

- Per rectal examination—Sims position (left lateral position)—Start with inspection of perianal region—Perianal tags, fissure, fistula. Palpation—Massage the external sphincter and slowly do PR comment on sphincter tone, nature of growth-proliferative or ulcer proliferative, how circumferential, extent of the tumor from anal verge, able to get above the tumor or not, describe in terms of clockwise position, perirectal, pararectal mobility, blood and fecal soiling of gloves
- Examination of inguinal area—LN
- Abdominal examination—rarely hepatomegaly or para-aortic lymph node
- Respiratory, CVS, supraclavicular lymph node.

40.4 Differential Diagnosis

- Ca Rectum
- Hemorrhoids
- Rectal polyp

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40.5 Work-Up

- Complete blood counts, RFT, LFT,S.CEA
- Colonoscopy with biopsy—to rule out other synchronous lesions
- MRI pelvis with CT of chest and abdomen(or CECT chest, abdomen, and pelvis)
- Endorectal ultrasound in lower rectal cancer (non-stenotic lesions).

40.6 Staging and Survival Stage Wise

- Table 40.1 summarizes AJCC staging of rectal cancers and survival.

40.7 Staging: AJCC 8th Edition 2017—Points to Remember [1]

- Minimum of 12 lymph nodes needed for adequate nodal staging
- N1c—indicates tumor deposits that lack associated lymph node tissue, vascular or neural structures and is found within the lymphatic drainage area of the primary carcinoma
- N1c even in the absence of nodal metastases is stage III.

40.8 Treatment Outline

Treatment outline in rectal cancer is summarized in Table 40.2.

40.9 Treatment Scheme

50.4 Gy in 28 daily fractions of 1.8 Gy in 51/2 weeks with concurrent Capecitabine or 25 Gy in 5 fractions over 5 days if short course followed by surgery in 4–6 weeks followed by adjuvant chemotherapy.

Table 40.1 Stage-wise survival in rectal cancer

Rectal cancer staging	5-year survival (%)
Stage 1 T1-2N0M0	90
Stage 2A T3N0M0 2B T4N0M0	60–85
Stage 3A T1-2N1M0 B T3-4N1M0 C T1-4N2M0	55–60 35–42 25–27
Stage 4 T1-4N0-2M1	5–7

Table 40.2 Treatment outline in rectal cancer

Rectal cancer treatment		
Low risk[a,b]	cT1-2N0 cT3N0-≤5 mm extramural invasion, distance to mesorectal fascia >1 mm	Total mesorectal excision
Intermediate risk	cT1-3N1 cT3N0->5 mm extramural invasion, distance to mesorectal fascia >1 mm	5∗5 Gy preoperative radiotherapy followed by TME
High risk	–any cT+N2 –any cT+ suspicious extramesorectal nodes –cT3 distance to mesorectal fascia ≤1 mm –cT4	Neoadjuvant chemoradiation followed by surgery

[a]Indications for transanal endoscopic microsurgery (TEM)-<3 cm in size,<30% circumference of bowel, mobile, nonfixed, within 8 cm of anal verge, tumor limited to submucosa (T1), N0, no LVSI, no PNI, well to moderately differentiated

[b]In lower rectal cancer, the rectum lacks peritoneum, surgical plane of dissection is difficult and distal resected margin should be at least 2 cm for sphincter preservation. In these scenarios, even in low risk rectal cancer, neoadjuvant therapy followed by surgery is recommended if patient is not suitable for TEM

40.10 Radiotherapy Planning

40.10.1 EBRT Planning

2D Planning—4 Field Technique Borders

- Superior border—between L5 and S1 vertebrae

- Inferior border—3 cm below the lower extent of the clinical tumor or the inferior edge of obturator foramina whichever is the most inferior
- Lateral borders—1.5–2 cm outside the bony pelvic side wall
- Posterior border—1.5 cm behind the anterior bony sacral margin
- Anterior border—posterior margin of the symphysis pubis, anterior margin of the symphysis pubis (if to include external iliac LN).

40.10.2 Conformal Radiotherapy (Fig. 40.1)

- The patient needs to fast for 4 h before CT simulation, empty bladder, and drink 100 mL of water 30 min before CT simulation. Patient is placed in prone position with a belly board to displace the small bowel, placing a rectal marker and using rectal contrast helps to delineate the tumor and placing a radiopaque marker along the perineum helps to block the skin and reduce skin toxicity
- CTVA: internal iliac, pre-sacral, perirectal.
- CTVB: external iliac nodal region
- CTVC: inguinal nodal region

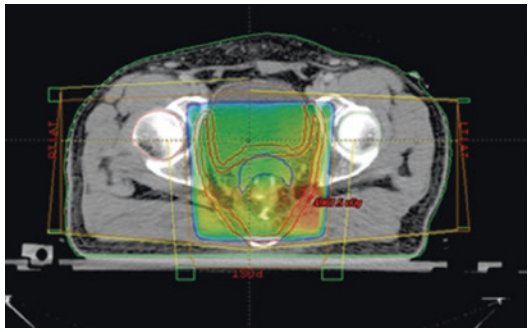

Fig. 40.1 3D conformal radiotherapy plan for rectal cancer

- CTVA would be the only volume to receive elective radiation. Extension into GU structures—add CTVB, extension to the perianal skin—add CTVC
- MRI fusion preferable to aid in delineation, GTV as per MRI and clinical examination findings.

40.10.3 Palliative RT

- 25 Gy in 5 fractions in metastatic cancer patients to prevent bleeding or reduce chances of luminal obstruction.

40.11 Chemotherapy

- Capecitabine—850 mg/m^2 twice daily with radiation with weekends off and with food or within 30 min after eating a meal.

40.12 Follow-Up

- Clinic visit 4–6 weeks after treatment
- Two CT scans of chest, abdomen, and pelvis in the first 3 years and regular blood tests
- Colonoscopy 1 year after surgery and if colonoscopy is normal another in 5 years.

40.13 Recurrence

- Recurrence post-surgery alone—RT
- Recurrence post-RT—Surgery/can try reirradiation if >1 year, reirradiation dose is 39 Gy in 26 fractions twice a day over 13 days.

Source of Image Image has been taken from patient treated by author and consent has been taken.

Reference

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Carcinoma Anal Canal

41

Bhanu Prasad Venkatesulu

41.1 History Taking [1]

- Perianal pain or bleeding
- Incontinence of solid or liquid stool or gas
- Sensation of anal mass or prolapse
- Local wetness and irritation
- Weight loss.

41.2 Other Relevant History

- H/o chronic hemorrhoids
- Perianal skin tags or warts
- Anal fissure, anal fistula
- HPV—anoreceptive intercourse or drip down effect from other HPV infected secretions
- HIV or post-organ transplant-immunosuppression.

41.3 Examination

- Per rectal examination—SIM position (left lateral position)—Start with inspection of perianal region—Perianal tags, fissure, fistula. Palpation—Massage the external sphincter and slowly do PR comment on sphincter tone, nature of growth-proliferative or ulcer proliferative, how circumferential, extent of the tumor from anal verge, able to get above the tumor or not, describe in terms of clockwise position, perirectal, pararectal mobility, blood and fecal soiling of gloves
- Examination of inguinal Area—LN
- Abdominal examination—Rarely hepatomegaly or para-aortic lymph node
- Respiratory, CVS.

41.4 Differential Diagnosis

- Ca rectum
- Hemorrhoids
- Rectal prolapse
- Condyloma.

41.5 Work-Up

- Anoscopy and rigid proctoscopy to determine the size of the primary lesion and the extent of the spread of disease with biopsy
- If inguinal lymph nodes are enlarged, core needle biopsy of LN should be done
- Complete blood counts, RFT, LFT
- CECT chest, abdomen, and pelvis.

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41.6 Staging: AJCC 8th Edition 2017

- T1—tumor size ≤2 cm
- T2—tumor size >2 but less than 5 cm
- T3—tumor size more than 5 cm
- T4—invades adjacent organ, e.g., vagina, urethra, bladder.

Regional lymph nodes: mesorectal, inguinal, superior rectal, external iliac, and internal iliac

- N1a—inguinal, mesorectal, or internal iliac lymph nodes
- N1b—external iliac nodes
- N1c—external iliac nodes + N1a
- M1—presence of distant metastasis.

41.7 Staging and Survival Stage Wise

Stage wise survival in patients with anal cancer is summarized in Table 41.1.

41.8 Treatment Outline [2]

Treatment outline in anal cancer is summarized in Table 41.2.

41.9 Radiotherapy Planning

41.9.1 EBRT Planning (Fig. 41.1)

2D Planning—4 field technique borders

- Superior border—between L5 and S1 vertebrae
- Inferior border—3 cm below the lower extent of the clinical tumor or 3 cm below the anal verge
- Lateral borders—1.5–2 cm outside the bony pelvic side wall

Table 41.1 Stage wise survival in patients with anal cancer

Stage grouping	5 year overall survival (%)	Local control (%)
I—T1 N0	90	13
IIA—T2 N0 IIB—T3 N0	82 74	17 18
IIIA—T1-2 N1 IIIB—T4 N0 IIIC—T3 N1, T4 N1	70 57 57, 42	26 44 44, 60
IV—M1	Median PFS 4 months with median OS 11.5 months	

Table 41.2 Stage wise treatment in patients with anal cancer

T1N0M0[b, c]	CTRT with mitomycin-C and 5-FU	45–50.4 Gy in 28 fractions to the primary
T2 onwards node negative	CTRT with mitomycin-C and 5-FU	54–59.4 Gy to the primary and 45 Gy to the uninvolved nodes
Node positive disease, <3 cm[a]	CTRT with mitomycin-C and 5-FU	54–59.4 Gy to the primary and 50 Gy to the uninvolved nodes
Node positive disease, >3 cm[a]	CTRT with mitomycin-C and 5-FU	54–59.4 Gy to the primary and 54 Gy to the uninvolved nodes

[a]Perirectal, inguinal, internal, external iliac groups of lymph nodes are included in the radiation portal
[b]Local excision is an option for patients with T1 tumors less than 1 cm in size
[c]Elderly T1N0MO can give 5-FU alone with RT

- Posterior border—1.5 cm behind the anterior bony sacral margin
- Anterior border—Anterior margin of the symphysis pubis.
- Inguinal fields: Medial border abuts the lateral border of the pelvic fields
  - Lateral border: vertical tangent along the lateral border of shaft of femur
  - Superior border: horizontal tangent along the head of femur
  - Inferior border: 3 cm below the lower border of obturator foramen.

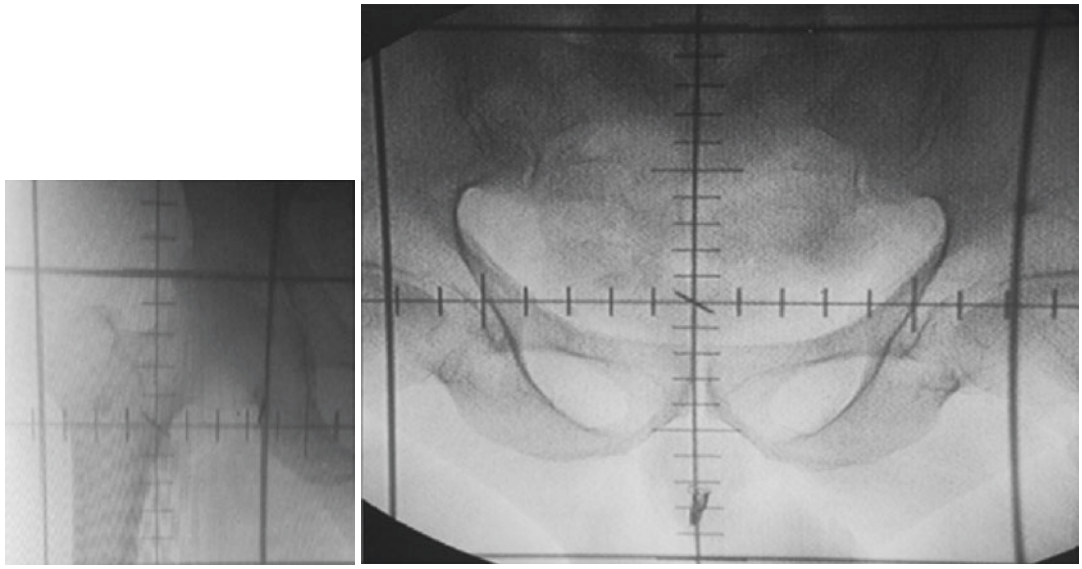

Fig. 41.1 2D planning in patient with anal cancer

41.10 Conformal Radiotherapy

- The "frog legged" supine position avoids radiation dermatitis and allows auto-bolus of the anal region. Custom immobilization devices such as vac-loc cradles may be used to aid in reproducibility with rectal tube and contrast
- CTVA: internal iliac, pre-sacral, perirectal.
- CTVB: external iliac nodal region
- CTVC: inguinal nodal region
- Anal canal contours should have CTVA, CTVB, and CTVC.
- MRI fusion preferable to aid in delineation, GTV as per MRI, and clinical examination findings

Figure 41.2 shows contouring and IMRT plan in patient with anal cancer.

41.11 Palliative RT

- 25 Gy in 5 fractions in metastatic cancer patients to prevent bleeding or reduce chances of luminal obstruction.

41.12 Chemotherapy

Wayne State or Nigro regimen—infusional FU 1000 mg/m^2 on days 1–4 and 29–32 (plus mitomycin 10–15 mg/m^2 on day 1 concurrent with RT).

41.13 Follow-Up

- Patients in complete remission at 8 weeks should be evaluated every 3–6 months for a

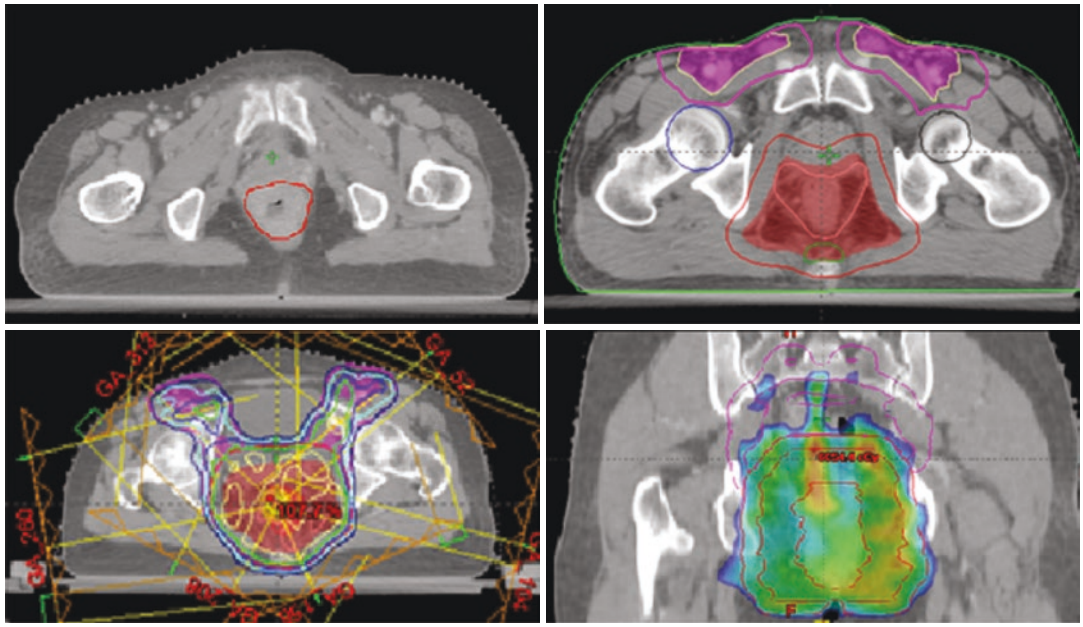

Fig. 41.2 Contouring and IMRT planning in patient with anal cancer

period of 2 years, and 6–12 monthly until 5 years, with clinical examination including DRE and palpation of the inguinal lymph nodes.

- Digital examination at 11, 18, and 26 weeks from the start of the treatment, abdominopelvic CT at week 26, confirm residual or recurrent disease by biopsy.

41.14 Recurrence

- Recurrence—surgery(APR)

Source of image Images have been taken from patients treated by author and consent has been taken.

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Skin Cancer

42

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42.1 History Taking

- Skin lesion—location, onset, duration, progression (especially from previous lesions)
- Bleeding
- Pain
- Tingling, numbness, or other neurologic deficits (typically cranial nerve palsies from head and neck skin cancers)
- Adjacent swelling or associated lesions
- Lymph node swelling in the adjacent lymphatic bed.

42.2 Other Relevant History

- H/o previous skin cancers
- H/o sun exposure
- H/o immunosuppression (organ transplant, low grade lymphomas, HIV, etc.) [1, 2]
- H/o occupational exposure (arsenic)
- H/o field treatment for skin cancer (5-fluorouracil cream, blue light therapy or radiation therapy)
- H/o chronic irritation (chronic ulcer in diabetic patients, chronic osteomyelitis, long standing sinus/fistula, burn ulcer, etc.)
- Relevant medical and surgical co-morbidities.

42.3 Examination

- General nutritional status, performance status

Inspection

1. Inspect the index lesion for size, color, borders (regular/irregular), bleeding, satellite nodules
2. Whole body examination to rule out other lesions.

Palpation

1. Palpate the lesion for tenderness, induration, depth, and fixity to underlying structures
2. Palpate the relevant nodal drainage areas, especially the parotid gland, occipital, suboccipital nodes, and spinal accessory nodes for head and neck skin cancers

42.3.1 Examination of the CNS

- Particular attention must be given to examination of cranial nerves depending upon the extent of disease especially if neurologic symptoms are noted.

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42.3.2 Systemic Examination

- Relevant systemic examination should be done in addition to general ear, nose, and throat examination for head and neck skin cancers
- Complete skin examination for other skin cancers.

42.4 Work-Up

- CBC, RFT, LFT
- Punch biopsy of the primary skin lesion
- Core biopsy of any enlarged lymph node
- Contrast enhanced CT scan of the relevant anatomical site
- Contrast enhanced MRI of the skull base to assess extent of neurotropic head and neck skin cancers
- Whole body PET CT
- Comprehensive dental evaluation for head and neck skin cancers (extractions must be completed 14–21 days before radiation)
- Comprehensive audiometry if cisplatin will be used.

42.5 Staging

AJCC staging cutaneous squamous cell carcinoma of the head and neck is summarized in Table 42.1 and Brigham and Women's Hospital (BWH) staging system for cutaneous squamous cell carcinoma is summarized in Table 42.2.

42.6 Treatment Outline

Early skin cancer (AJCC 8th edition SCC or BCC: T1-2, N0 or BWH SCC: T1-T2a stage)

- Unimodality treatment is favored with either radiation or surgery alone

Locally advanced skin cancer (AJCC 8th edition SCC or BCC: T3-4, node positive, recurrent cases or BWH SCC: T2b-T3)

- Bimodality treatment is favored with surgery followed by adjuvant radiation (with or without chemotherapy) when possible (an exception is AJCC 8th edition T3 BCC which may be treated with surgery alone/radiation alone)
- Unresectable primaries maybe treated with definitive radiation (with or without chemotherapy or cetuximab)
- Indications for adjuvant treatment with radiation or chemoradiation are controversial and being explored in prospective clinical trials
- Locally advanced BCCs—usually treated with surgery, reconstruction, and adjuvant radiation especially when recurrent (select cases may be treated with surgery alone)
- Periorbital BCCs with significant orbital/globe involvement—usually treated with exenteration, reconstruction, and adjuvant radiation especially when recurrent; vismodegib is being explored in the neoadjuvant setting and may be used for patients refusing surgery/radiation
- Unresectable BCCs—usually treated with definitive radiation; vismodegib may be used for patients refusing radiation or for multiple BCCs (basal cell nevus syndrome)

Recurrent non-metastatic disease amenable to curative therapy

- Surgical salvage followed by aggressive adjuvant radiation (or re-irradiation) with or without chemotherapy

Incurable skin cancer (metastatic or non-metastatic) not amenable to curative therapy

- Palliative immunotherapy with cemiplimab [5]
- Palliative radiation (conventional, Quad Shot, or stereotactic body radiotherapy for select cases)
- Palliative surgery in select cases.

Table 42.1 AJCC staging for cutaneous squamous cell carcinoma of the head and neck

Staging: AJCC 8th ed., 2017 cutaneous squamous cell carcinoma of the head and neck [3]					
TX	Primary tumor cannot be assessed	cNX	Regional lymph nodes cannot be assessed	pNX	Regional lymph nodes cannot be assessed
Tis	Carcinoma in situ	cN0	No regional lymph node metastasis	pN0	No regional lymph node metastasis
T1	≤2 cm in greatest dimension	cN1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(–)	pN1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(–)
T2	>2 but not >4 cm in greatest dimension	cN2a	Metastasis in a single ipsilateral node >3 cm but <6 cm in greatest dimension and ENE(–)	pN2a	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(+); Or a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(–)
T3	>4 cm in greatest dimension or minor bone erosion or perineural invasion or deep invasion[a]	cN2b	Metastases in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE(–)	pN2b	Metastases in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE(–)
T4a	Gross cortical bone/ marrow invasion	cN2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)	pN2c	Metastases in bilateral or contralateral lymph node(s), none >6 cm in greatest dimension and ENE(–)
T4b	Skull base invasion and/or skull base foramen involvement	cN3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)	pN3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)
M1	Distant metastasis	cN3b	Metastasis in any node(s) and ENE(+)	pN3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); Or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); Or a single contralateral node of any size and ENE(+)
0	Tis N0 M0				
I	T1 N0 M0				
II	T2 N0 M0				
III	T3 N0 M0				
	T1-3 N1 M0				
IV	T1-3 N2 M0				
	Any T, N3, M0				
	T4, any N, M0				
	Any T, any N, M1				

[a]Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical/radiographic involvement of named nerves without skull base invasion or transgression

Table 42.2 Brigham and Women's Hospital (BWH) staging system for cutaneous squamous cell carcinoma [4]

High-risk factors	T stage	
Tumor diameter ≥2 cm	T1	0 High-risk factors
Poorly differentiated	T2a	1 High-risk factor
Perineural invasion ≥0.1 mm	T2b	2–3 High-risk factors
Tumor invasion beyond fat (bone invasion is automatically T3)	T3	≥4 High-risk factors or bone invasion

42.7 Surgery

- Early stage cancers are usually treated with Mohs micrographic surgery. This is indicated for small, well-defined primary skin cancers in areas of cosmetic importance where a negative complete circumferential and deep margin is desired with maximal preservation of normal tissue. This is usually followed by primary closure or local tissue rearrangement for closure.
- Larger primaries in areas where cosmesis is less important are treated with wide local excision. These primaries may be subjected to slow Mohs margin assessment to ensure a negative margin. This is usually followed by skin grafting or free tissue transfer, especially if adjuvant radiation is indicated.
- Neck dissection is usually reserved for clinically node positive cases; select cases may undergo an elective neck dissection.
- Sentinel lymph node biopsy (SLNB) is being explored where the risk of lymph node spread reaches or exceeds 15–20%. This is especially useful for cases where the draining lymph node bed is less obvious and risk of nodal spread is higher. Caution must be exercised in sites like the head and neck where false negative rates for SLNB may be higher.
- A positive SLNB is usually followed a therapeutic lymph node dissection.

42.8 Radiotherapy

- Early skin cancers may be treated with definitive radiation. This can be accomplished by a variety of techniques including superficial/orthovoltage radiation, electron therapy, brachytherapy (mold brachytherapy or interstitial brachytherapy), or photon therapy
- More advanced cases are treated with surgery followed by adjuvant radiation [6] (with or without chemotherapy or cetuximab)
- Definitive radiation doses and volumes differ by the size, location and vascularity of the tissue surrounding the cancer (see table below)
- Adjuvant radiation doses and volumes are extrapolated from mucosal head and neck cancers (60–66 Gy in 30–33 fractions). Similar doses are utilized for sites outside of the head and neck region, while considering adjacent organ at risk constraints and expected morbidity. Doses and volumes for these sites usually follow generally accepted guidelines for each subsite. ACR appropriateness criteria examples of curative radiotherapy regimens are summarized in Table 42.3.

42.8.1 EBRT Planning

- IMRT is strongly recommended for all head and neck cases in the adjuvant setting
- In general, pre-operative GTV = all disease noted on exam and radiology (image fusion with available imaging is highly recommended)

Table 42.3 ACR appropriateness criteria examples of curative radiotherapy regimens [7]

[a]60–70 Gy in 30–35 fractions
50–55 Gy in 17–20 fractions
40–44 Gy in 10 fractions
40 Gy in 5 fractions (twice weekly)
30 Gy in 3 fractions (once weekly)
20–25 Gy in 1 fraction

[a]Longer fractionation schedules are preferred when target volumes are in proximity to radiosensitive organs at risk

- CTV high dose = post-operative tumor bed including the primary and positive nodes (shaved off air, bone and other uninvolved structures); this will include at least ipsilateral neck nodal levels II through IV. Levels IB, parotid nodes and level V are also considered at risk for skin cancers. For example, levels IB and parotid nodes are included for pre-auricular/face and lateralized anterior scalp cancers; suboccipital nodes, level V nodes are included for post auricular and lateralized posterior scalp cancers, in addition to levels II through IV.
- CTV low dose (optional) = at risk areas other than the CTV high dose (shaved off air, bone and uninvolved structures)
- Particular attention is directed towards coverage of the cranial nerves at the skull base for neurotropic skin cancers [8] (especially cranial nerves V, VII)
- The use of wires, bolus, and setup/pre-operative photographs is highly encouraged at the time of simulation and planning to aid in designing the treatment
- PTVs (head and neck skin cancer) = CTV + 3 mm margin when using daily image guidance with cone beam CT
- Sites other than the head and neck are simulated and treated as above. Particular attention must be paid to set up at simulation. Customized immobilization is recommended when possible. Relevant nodal basin contouring guidelines maybe referenced [9].
  - PTVs (non-head and neck sites) = CTV + 5–7 mm depending upon the site treated. Daily image guidance with cone beam CT is highly recommended.

42.8.2 OAR

- It is highly recommended that the following set of OARs is delineated for each head and neck case (brainstem, brainstem PRV3mm, cochlea, spinal cord, spinal cord PRV 5 mm, parotids, submandibular glands, lips, oral cavity, mandible, OAR pharynx, supraglottis, larynx or glottic–supraglottis, esophagus, trachea, and brachial plexus)
- Additional structures like eyes, lens, optic nerves, chiasm, and temporal lobes may be added for individual cases
- It is recommended that doses to each of the OARs be reduced as much as possible without compromising PTV coverage—guidance for dose constraints may be found in current RTOG protocols (e.g., RTOG 1016)
- Relevant OARs should be delineated for non-head and neck cases. Guidance for dose constraints is extrapolated from protocols used for these sites.

42.9 Palliative RT

- Standard palliative fractionation schemes include 8 Gy in 1 fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions or Quad Shot approach (14 Gy in 4 fractions; 2 fractions a day 6 h apart over 2 days repeated q 4 weeks up to 3 times).

42.10 Follow-Up

- Early skin cancers are followed clinically after surgery or definitive radiation
- Locally advanced head and neck skin cancers—first follow-up: CT neck and chest with contrast are recommended at 3 months after adjuvant radiation/adjuvant chemoradiation along with a detailed history and physical exam
- Locally advanced non-head and neck skin cancers—first follow-up: CT with contrast (site based; chest is usually included)
- Further follow-up is scheduled every 3 months for the first 2 years, every 6 months for the next 3 years and annually thereafter
- Further imaging is directed by symptoms or post-treatment imaging; low dose CT chest is recommended for former/current smokers [10]
- Regular dental follow-up, speech and swallowing physiotherapy, and enrolment into a survivorship clinic are recommended for head and neck skin cancers

- Thyroid stimulating hormone every 6–12 months if the neck is irradiated
- Sun protection and whole body skin checks are recommended every 6–12 months based on the risk of skin cancer.

42.11 Oncologic Outcomes [4]

- 10 year cumulative incidence for local recurrence per BWH staging
  - T1 0.6%
  - T2a 5%
  - T2b 21%
  - T3 67%
- 10 year cumulative incidence for nodal metastasis per BWH staging
  - T1 0.1%
  - T2a 3%
  - T2b 21%
  - T3 67%
- 10 year cumulative incidence for disease specific death per BWH staging
  - T1 0%
  - T2a 1%
  - T2b 10%
  - T3 100%

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Lymphoma

43

Rony Benson, Supriya Mallick, and Goura K. Rath

43.1 History Taking

Patients of lymphoma may present with one or more of the following symptoms:

- Swelling in the neck, axilla or inguinal region.
- Note: Asymptomatic lymph node enlargement is the most common symptom in patients with lymphoma. Spontaneous regression of enlarged lymph nodes may be seen in some patients with low grade lymphoma
- B symptoms—Unexplained weight loss (>10% of total body weight) in past 6 months, unexplained fever >38 °C or drenching night sweats
- Fever (Classic Pel Ebstein)—High fever for 1–2 weeks, followed by an afebrile period of 1–2 weeks, is classically seen in Hodgkin's disease
- Pruritus or pain at sites of nodal disease precipitated by drinking alcohol is also seen in Hodgkin's disease
- Dyspnoea, cough, features of shortness of breath may be seen in patients with large mediastinal mass—seen in Hodgkin's disease, lymphoblastic lymphoma (more with T cell) and primary mediastinal B cell lymphoma
- Advanced high-grade lymphoma may present with high fever, tachycardia, sepsis
- Fatigue and weakness generally indicate advanced stage disease
- Symptoms of extra nodal involvement (testicular swelling, CNS symptoms, etc.) especially in NHL.

43.2 Other Relevant History

- Family history—Nodular sclerosis Hodgkin's lymphoma may have a genetic association.

43.3 Examination

Examine all lymph node areas systematically as follows:

- Preauricular, postauricular, occipital, parotid, neck, axilla, epitrochlear, inguinal and popliteal regions separately on both sides.
- Examine for mass in tonsils, base of tongue or adenoids
- Look for associated hepatosplenomegaly
- Examine for features of superior vena cava obstruction.

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43.4 Differential Diagnosis

- Non-Hodgkin's lymphoma—Non-contiguous lymph nodes in older patients
- Hodgkin's lymphoma—Contiguous lymph nodes of neck and mediastinum with rubbery consistency and possibly Pel Ebstein fever
- Metastatic lymph nodes—Hard lymph nodes which are often matted
- Benign reactive lymph nodes—Especially limited to inguinal or submandibular area (generally <2 cm, soft, mobile non-matted)
- Infections
  1. CMV—Infectious mononucleosis—Tender lymph node, pharyngitis, Heterophile Test+
  2. TB—Non-tender lymph node with fever
  3. HIV—Rash, fever, diarrhoea and loss of weight
  4. Leprosy—Lymph node with nerve enlargement
- Sarcoidosis—Predominantly mediastinal lymph nodes with wheeze and skin involvement.

43.5 Work-Up

- CBC/LFT/KFT/ ESR/LDH
- CECT neck, chest, abdomen and pelvis (OR) PET scan (in HL and high-grade NHL)
- Bone marrow study—can be avoided in selected patients with PET negativity and absence of B symptoms
- Cardiology (Echocardiography—if planned for adriamycin), pulmonary function test (if planned for bleomycin)
- Excision biopsy of the lymph node
- Reproductive counselling (younger patients) and urine pregnancy test (younger female patients).

43.6 Staging: Modified Ann Arbour Staging

Stage I indicates that the disease is located in a single lymph node region

Stage II indicates that the disease is located in two lymph node separate regions, confined to one side of the diaphragm

Stage III indicates that the disease has spread to both sides of the diaphragm

Stage IV indicates diffuse or disseminated involvement of one or more extra lymphatic organs, (liver, bone marrow, or nodular involvement of the lungs)

- B: presence of B symptoms (fever (temperature >38 °C), drenching night sweats, unexplained loss of >10% of body weight within the preceding 6 months) if not A
- S: spread to the spleen
- E: spread to extranodal organ
- X: is used to indicate bulky disease (>10 cm large/ bulky mediastinal disease)
- *Note: The lymphatic system includes lymph nodes, spleen, thymus, Waldeyer ring, appendix, and Peyer's patches.*

43.7 Prognostic Indices

Various prognostic indices useful in lymphoma are summarised in Table 43.1.

43.8 Treatment Outline Hodgkin's Lymphoma

Treatment outline in Hodgkin's lymphoma is summarised in Table 43.2.

43.9 Treatment Outline Non-Hodgkin's Lymphoma

Treatment outline in non-Hodgkin's lymphoma is summarised in Table 43.3.

43.10 Radiotherapy

Involved field radiotherapy (IFRT) [1]

Table 43.1 Prognostic indices in lymphoma

The GHSG unfavourable risk factors (stage I and II Hodgkin's lymphoma)	1. Presence of a large mediastinal mass, measured by means of a chest X-ray; *one third of the transverse diameter of the thorax* 2. Extra-nodal disease 3. High erythrocyte sedimentation rate (ESR) of 50 mm/h if B-symptoms are absent and 30 mm/h if B-symptoms are present 4. Involvement of three or more lymph node *areas*	Presence of one or more factors makes it unfavourable and treatment plan gets modified as mentioned below
International prognostic index for NHL	• Age >60 year • PS 2–4 • Stage 3 or 4 • Elevated LDH • >1 extra nodal site	*Estimated 5 year survival* • Low (score 0/1) 73% • Low intermediate (score 2) 51% • High intermediate (score 3) 43% • High (score 4 or 5) 26%
FLIPI scoring for follicular lymphoma	• >4 involved nodal sites • Elevated LDH • Age ≥60 years • Advanced stage III/IV disease • Haemoglobin <12 g/dL	Score / 5 year OS / 10 year OS 0-1 / 91 / 71 2 / 78 / 51 ≥3 / 53 / 36

Table 43.2 Treatment outline in Hodgkin's lymphoma

NLPHL	I/IIA—IFRT alone 30–36 Gy (IFRT 30 Gy F/B Boost of 6 Gy) If less than CR → chemo (ABVD/CHOP)
	ADVANCED STAGE—Chemo ABVD/ CHOP Rituximab may be added
EARLY FAVOURABLE DISEASE CHL	2 ABVD F/B IFRT (20 Gy/10#/2 weeks)
EARLY UNFAVOURABLE DISEASE CHL	2 ABVD + 2 escalated BEACOPP F/B IFRT (30 Gy/15#/3 weeks)
LATE DISEASE CHL	6 cycles of ABVD IFRT if indicated—residual/ bulky disease

Table 43.3 Treatment outline in Hodgkin's lymphoma

	Stage	Treatment
Indolent lymphoma (follicular lymphoma—grade 1/2 SLL, marginal zone lymphoma)	Stage I-II-contiguous non-bulky (<7.5 cm)	IFRT
	Advanced stage	Chemoimmunotherapy—If indication for treatment Palliation-RT
Aggressive DLBCL FL-grade III	Stage I-II non-bulky (<7.5 cm) and no extra-nodal disease	• Combined modality therapy with abbreviated chemotherapy (4 × CHOP ± R[if CD20+] followed by IFRT) OR • Full chemotherapy alone (6 × CHOP ± R[if CD20+])
	Stage I-II bulky/stage III/ IV	• 6–8 × CHOP ± R[if CD20+] • RT bulky or residual
Very aggressive	Lymphoblastic lymphoma	ALL like protocol, consolidation RT given residual disease/extra nodal sites *PCI is given*
	Burkitt	ALL like protocol No PCI

Table 43.4 Treatment borders of IFRT

	Upper border	Lower border	Medial border	Lower border
Neck[I/L]	1–2 cm above mastoid tip	2 cm below clavicle	Ipsilateral transverse processofvertebraifSCF–Contralateral transverse process of vertebra if SCF+	Include medial two-third of clavicle
Mediastinum	C5/6	5 cm below carina/2 cm below pre-chemo disease	NA	Hilar area +1/1.5 cm OR Post-chemo disease+1/1.5 cm
Axilla	C5/6	Tip of scapula/2 cm below pre-chemo disease	Ipsilateral cervical transverse process	Flash in sin
Para-aortic	T11 upper border	L4 lower border	NA	Edge of transverse process of vertebra
Inguinal	Mid sacroiliac joint	5 cm below lesser trochanter	Medial obturator foramen/2 cm medial to midline	2 cm lateral to greater trochanter

- Encompasses the nodal region and not the individual nodes
- Major involved-field regions
  1. Neck (unilateral)
  2. Mediastinum (including bilateral hilum)
  3. Axilla (including supraclavicular and infraclavicular)
  4. Spleen
  5. Paraaortic
  6. Inguinal (femoral and iliac nodes).
- Initially involved prechemo sites and volume are treated, except for the transverse diameter of mediastinal and PA LN for which the reduced post-chemotherapy volume is treated
- Treatment borders of IFRT are summarised in Table 43.4.

Involved-nodal radiotherapy (INRT) [2, 3]

- Logic for INRT—pattern of relapse in patients treated with chemotherapy alone showed that most recurrences occurred in the initially involved lymph nodal area. Smaller radiation fields should also lead to a decrease in late complications as the amount of irradiated normal tissue is reduced
- INRT design requires accurate pre-chemo or pre-biopsy information PET in the treatment position
- Pre-chemotherapy extent of involved lymph nodes modified within post-chemotherapy anatomical boundaries to form IN-CTV.

Involved Site RT (ISRT)

Table 43.5 Comparison of INRT vs ISRT

INRT	ISRT
CTV = pre chemotherapy extent of involved lymph nodes modified within post-chemotherapy anatomical changes	CTV = pre-chemotherapy extent of involved lymph nodes with an expansion of 1.5 cm in the craniocaudal direction of lymphatic spread
PTV was created by adding an isotropic margin of 1 cm	PTV was created by adding an isotropic margin of 1 cm
Smaller volumes	Higher volumes in supero-inferior direction
Very difficult to implement	More easy to implement

- In most centres, pre-chemotherapy PETCT scans are not carried out in the radiotherapy treatment position with immobilisation devices as required for INRT
- Hence ISRT—A more practical approach
- Pre-chemotherapy extent of disease is expanded cranio-caudally by 1.5 cm in the direction of lymphatic spread to form IS-CTV
- Comparison of INRT vs ISRT is summarised in Table 43.5.

43.11 EBRT Planning

Treatment Position

- Hyperextension for neck nodes
- Axilla-Akimbo position helps shield shoulder, also minimal skin folds in axilla

Arms above head—pulls axillary nodes away from chest, hence helps maximal sparing of lung

Radiotherapy Dose Hodgkin's Lymphoma

- Early favourable—20 Gy/10#/2 weeks
- Early unfavourable/advanced—30 Gy/15#/3 weeks
- Residual disease—May increase dose up to 36 Gy
- NLPHD-Stage I/IIA—IFRT alone 30–36 Gy.

Radiotherapy Dose Non-Hodgkin's Lymphoma

- Indolent lymphoma—24 Gy/12#/2.5 weeks
- Aggressive lymphoma—30 Gy/15#/3 weeks
- Residual disease 36–40 Gy
- Palliative RT
- Indolent—24 Gy/12# or 4 Gy/2# (90% response—explained by the predominant mode of tumour cell death largely mediated by apoptosis)
- Aggressive 30 Gy/10.

Radiotherapy Dose Extra nodal Non-Hodgkin's Lymphoma [4]

- Generally 30 Gy/15# as ISRT, treat the involved site with margins of 2 cm
- Primary CNS lymphoma—WBRT 45 Gy/25#/5 weeks may be reduced to 30–36 Gy if CR in chemotherapy (chemotherapy follows the De Angelis protocol)
- Sino-Nasal NK cell lymphoma—RT higher dose 45–50 Gy (chemotherapy includes SMILE regimen)

43.12 Follow-Up

The patients may be followed up every 3 month for 2 years and then 6 monthly till 5 years and then annually

Physical examination to be done in each visit

Investigations

- CBC each visit
- PET CT at three months to verify complete metabolic response. No routine imaging needed after that
- 2 D Echo after 10 years
- Breast evaluation by breast MRI after 8 years in females if RT to mediastinum
- TSH—annually if RT to neck

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Carcinoma Lung

44

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44.1 History Taking [1, 2]

- Cough
- Dyspnoea
- Wheeze
- Haemoptysis
- Chest pain
- Recurrent laryngeal nerve involvement: Hoarseness of voice
- Phrenic nerve involvement: hiccups, shortness of breath due to unilateral paralysis of diaphragm
- Weight loss.

44.1.1 Other Relevant History

- Smoking
- Family history of lung cancer
- Exposure to asbestos/radon
- Passive smoking.

44.1.2 Superior Vena-Cava Syndrome

- Sensation of fullness in the head and dyspnoea
- Swelling of the face and arms.

44.1.3 Pancoast Syndrome

- Shoulder pain
- Horner's syndrome
- Brachial plexopathy.

44.1.4 Paraneoplastic Syndrome

- Cushing syndrome
- Syndrome of inappropriate antidiuretic hormone secretion
- Hypercalcemia
- Lambert-Eaton myasthenic syndrome
- Hypertrophic osteoarthropathy.

44.2 Examination

- Performance status (ECOG/KPS)
- Build and nourishment
- Pallor, icterus, clubbing, cyanosis, lymphadenopathy, oedema
- PR/BP/RR/temperature
- Respiratory system examination
- Inspection: Upper respiratory tract including nose and oral cavity, shape of the chest, symmetry, position of trachea, apex beat, respiratory movements, respiratory rate, rhythm and type, scars, sinuses, visible pulsations, dilated veins, oedema

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- Palpation: Position of trachea, respiratory movements, vocal fremitus, tenderness of chest wall
- Percussion: Pleural effusion
- Auscultation: Intensity and type of breath sounds, any adventitious sounds, vocal resonance, any miscellaneous sounds
- Cardiovascular system
- Central nervous system: Higher mental functions/cranial nerve examination/sensory system/motor system/any signs of meningeal irritation/skull and spine examination
- Gastrointestinal system: Hepatomegaly/other palpable mass/ascites.

44.3 Differential Diagnosis

- Carcinoma lung
- Tuberculosis
- Bronchopneumonia
- Mediastinal mass: Lymphoma/thymoma/GCT/neurogenic mass
- Sarcoidosis.

44.4 Work-Up

- Blood work-up: CBC, LFT, RFT, Serum sodium, potassium, calcium, magnesium
- Radiological investigations:
- Chest X-ray AP/lateral
- Contrast enhanced CT scan of thorax and abdomen
- PETCT scan
- Tissue diagnosis:
  - Sputum cytology
  - CT guided FNAC/biopsy
  - Bronchoscopy: Cytologic brushings, biopsy
  - Endoscopic ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA)
  - Thoracentesis
  - Mediastinoscopy/mediastinotomy/thoracotomy.

44.5 Staging

T1. Tumour ≤3 cm surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus

- T1a Tumour ≤1 cm
- T1b Tumour >1 cm but ≤2 cm
- T1c Tumour >2 cm but ≤3 cm.

T2. Tumour >3 cm and ≤ 5 cm or tumour and involves main bronchus or visceral pleura or atelectasis or obstructive pneumonitis

- T2a Tumour >3 cm but ≤4 cm
- T2b Tumour >4 cm but ≤5 cm.

T3.

- Tumour >5 cm and ≤ 7 cm
- Separate tumour nodule(s) in the same lobe of lung
- Tumour that invades: chest wall, phrenic nerve, or parietal pericardium.

T4.

- Tumour >7 cm
- Separate tumour nodule(s) in a different ipsilateral lobe
- Invades: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body and carina.

Nodal

- N1—ipsilateral peribronchial or hilar lymph nodes
- N2—ipsilateral mediastinal nodes
- N3—contralateral mediastinal, or supraclavicular lymph node.

Metastasis:

- M1a—Separate tumour nodule(s) in a contralateral lobe; pleural or pericardial nodules or malignant pleural or pericardial effusion

- M1b—Single extra thoracic mets
- M1c—Multiple extra thoracic mets.

The AJCC eighth edition 2017 stage grouping and stage specific survival is summarised in Table 44.1 [3].

44.6 Screening

Low dose CT advised in the following setting, after a discussion of risks and benefits between physician and patient.

- Age 55–74 years
- A history of smoking at least 30 pack years
- Current smoker or has quit smoking foe less than 15 years.

44.7 Treatment Outline

Treatment outline in non-small cell lung cancer and small cell lung cancer is summarised in Tables 44.2 and 44.3.

44.8 Radiotherapy Dose

- NSCLC: 66 Gy in 33 daily fractions of 2 Gy in 6.5 weeks with concurrent chemotherapy.
- SCLC: 45Gy in 30 twice daily fractions along with 4–6 cycles of cisplatin and etoposide 3 weekly. The first cycle of chemotherapy was given before radiotherapy and the second was given concurrently with radiotherapy (etoposide 100 mg/m^2 iv on D 1–3 and cisplatin 25 mg/m^2 iv on D 1–3).

Table 44.1 The AJCC 2017 staging with stage specific survival of lung cancer

Lung cancer staging				c 2 years OS	c 5 years OS	p 2 years OS	p 5 years OS
Occult carcinoma			TxN0M0				
Stage 0			TisN0M0				
Stage 1	IA	1A1	T1mi-1aN0M0	97	92	97	90
		1A2	T1bN0M0	94	83	94	85
		1A3	T1cN0M0	90	77	92	80
	IB		T2aN0M0	87	68		
Stage 2	IIA		T2bN0M0	79	60	82	65
	IIB		T1a-3N1M0, T3N0M0	72	53	76	56
Stage 3	IIIA		T1a-2bN2M0, T4 N0–1 M0	55	36	65	41
	IIIB		T1a-2bN3M0, T3-4N2M0	44	26	47	24
	IIIC		T3-4N3M0	24	13	38	12
Stage 4	IVA		Any T, any N, M1a-M1b	23	10		
	IVB		Any T, any N, M1c	10	0		

Table 44.2 treatment outline in non-small cell lung cancer

Non-Small Cell Lung Cancer [4–7]		
Stage I, II	Surgical exploration with resection and mediastinal lymph node dissection/ sampling	I: Adjuvant RT for positive margins[a] IIA and above: Adjuvant RTCT for positive margins[a] Adjuvant chemotherapy for all N1 Adjuvant CTRT for all N2
Clinically N2-3M0 disease	Definitive CTRT	
Stage IIIA(T4 N0–1)		Resectable: surgery Non resectable: definitive CTRT
Superior sulcus tumour: possibly resectable	NACTRT f/b evaluation	Resectable: surgery Non resectable: continue CTRT

Unresectable disease i/v/o of local extensions can be considered for definitive CTRT if amenable
Medically inoperable cases can be considered for Definitive RT/RTCT
[a]Only if reresection not planned

Table 44.3 treatment outline in small cell lung cancer

Small Cell Lung Cancer [8–12]		
Stage I	Lobectomy + Mediastinal lymph node dissection	N0-N1: Adjuvant CT N2: Adjuvant CTRT
Limited stage	Definitive CTRT	
Extensive stage	Patient tailored treatment	

- *Limited stage*: Confined to ipsilateral hemithorax which can be safely encompassed within a radiation field (included I/L and C/L mediastinal and I/L hilar and supra-clavicular)
- *Extensive stage*: Disease beyond the ipsilateral hemithorax including malignant pleural or pericardial effusion or hematogenous metastasis

(*Veterans Association Lung Study group-1950*)

- *Limited stage*: Stage I to III (any T, any N, M0) that can be safely treated with definitive radiotherapy
- *Extensive stage*: Stage IV (any T, any N, M1a/b) or T3 or T4 with multiple lung lesions that are too extensive to be encompassed in a tolerable radiation plan

(*Based on 2010 TNM; IASLC Review*)

44.9 Radiotherapy Planning Volumes

44.9.1 2D-EBRT Planning

44.9.1.1 Upper Lobe Tumours

- Bilateral supraclavicular field
- Upper mediastinum
- Subcarinal field (two vertebra below carina) or (five to six centimetres below carina)
- Primary tumour +2 cm.

44.9.1.2 Hilar Tumours

- Superior: thoracic inlet
- Inferior: 8–9 cm below carina
- Includes mediastinum
- Primary tumour +2 cm

44.9.1.3 Lower Lobe Tumours

- Superior: thoracic inlet.
- Inferior: up to the diaphragm.
- Includes mediastinum.
- Primary tumour +2 cm.

44.10 Conformal Radiotherapy

- Treatment position: Supine, with arms above head. Immobilisation using chest board and fixed arm position. The patient should be breathing normally.
- Simulation: Patient is asked to be nil per oral for 4 h. A planning CT scan with intravenous contrast is performed in treatment position. Patient should be breathing normally. 2.5 mm slice images are taken from zygoma to lower border of liver. Fuse the PET CT scan images. Whenever possible a 4DCT scan should be done to identify complete tumour movement during respiration.
- Contouring: Gross tumour volume (primary or nodal) is contoured based on PET images.
- A CTV margin of 6 mm for squamous histology and 8 mm for other histology is to be given. PTV margins are being given based on department protocol (Fig. 44.1).

44.10.1 Stereotactic Radiotherapy

In medically inoperable patients with T1, T2 N0 diseases.

44.11 Post-Operative Radiotherapy in Carcinoma Lung [13]

44.11.1 Indications

1. R0 resection with N2 disease.
2. R1 (extracapsular extension in node) and R2 resections when reresection not possible (*any stage*).

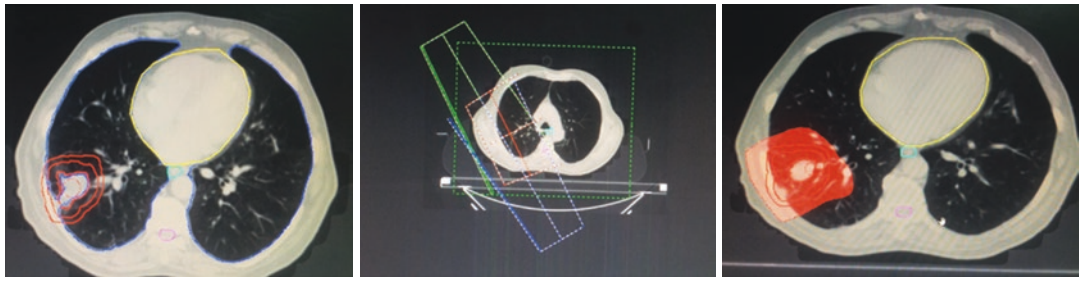

Fig. 44.1 Contouring, beam arrangement, and planning in patient with non-small cell lung cancer

44.11.2 Sequencing with Chemotherapy

1. In N2 disease radiotherapy should be given sequentially after chemotherapy.
2. In R1 and R2 resections radiotherapy can be given either sequentially after chemotherapy or concurrent with chemotherapy.

44.11.3 Dose

1. R0 resection 50–54 Gy in 1.8–2.0 Gy\fraction.
2. R1 resection 54–60 Gy in 1.8–2.0 Gy\fraction.
3. R2 resection 60 Gy in 1.8–2.0 Gy\fraction.

44.12 Palliative Radiotherapy

Dose: 30Gy in 10 fractions in

- Symptomatic advanced disease/poor performance status
- Symptomatic metastatic sites: bone/brain/node.

44.13 Prophylactic Cranial Irradiation [14–16]

- Limited stage SCLC who had a partial/complete response after definitive treatment.
- Extensive stage disease showing good response to chemotherapy.
- Recommended dose is 2500 cGy in 10 fractions.

44.14 Follow-Up

Repeat CT scan/PET CT scan after 2–3 months of treatment completion for response evaluation.

Follow-up every 3–6 months for 2 years, then annually.

44.15 Recurrence

Loco-regional: Salvage surgery or chemoradiation; palliative radiation therapy or chemotherapy.

Distal metastasis: Palliative chemotherapy or radiation therapy.

44.16 Case Report 1: NSCLC

A 58-year-old male presented to the out-patient Department of Pulmonary Medicine with history of fever and dry cough for 3 months duration. He gives history of smoking around 10 cigarettes per day for past 25 years and consuming alcohol of around 90 ml per day for past 30 years.

He was evaluated with a chest X-ray which showed patchy opacity in left upper lobe. A CECT thorax revealed a 2.3 × 2 cm mass in left upper lobe with centrilobular emphysema in both lungs. A PETCT showed a 2 × 1.9 × 1.9 cm metabolically active soft tissue density nodule with speculated margins in the apico-posterior segment of left upper lobe of maximum SUV 11.4 and multiple metabolically active lymph nodes in aortopulmonary window and subcarinal region with maximum SUV: 2.9.

A CT guided biopsy of the lung nodule was done. Histopathological examination was sug-

gestive of infiltrative neoplasm. The neoplastic cells were positive for CK7 and TTF1 and negative for P63 and CK20. Histomorphology and immuno-profile were consistent with a primary pulmonary adenocarcinoma.

A diagnosis of carcinoma left lung cT1N2M0; Stage IIIB was made according to AJCC seventh edition.

Patient was planned for definitive chemoradiation to a dose of 6000 cGy in 30 fractions along with 2 cycles of concurrent 3 weekly pemetrexed and carboplatin (C1—5 days before RT, C2—on 14th day of RT, C3—10 days after completing RT).

Radiotherapy planning was done on GE Lightspeed 4 Slice CT machine and 2.5 mm images were accrued and was transported to MONACO version 5.10.04 contouring station. Organs at risk in the field of irradiation including bilateral lungs, heart, spinal cord and oesophagus were contoured. The planning CT scan images were fused with PET-CT and gross tumour volumes (GTV) were marked. An 8 mm symmetrical margin was given to GTV primary and 5 mm symmetrical margin to GTV nodes. PTV margins were 1 cm cranio-caudal and 7 mm axial. A 3-dimensional conformal radiotherapy plan was generated using XIO treatment planning system.

During treatment he developed Grade 3 esophagitis, Grade 1 skin reaction and Grade 2 pain which were managed conservatively.

A PETCT scan done 1 month after completion of radiotherapy showed a decrease in size of the left upper lobe mass measuring 18 × 13 × 7 mm with max SUV 1.8 and complete metabolic response of the lymph nodes. Patient received two more cycles of adjuvant chemotherapy with pemetrexed and carboplatin. A CECT scan done after treatment showed no mass lesions in bilateral lungs and mediastinum indicating no evidence of disease.

Patient is on regular follow-up. The patient has a disease-free survival of 2 years and 10 months till date.

44.17 Case Report 2: SCLC

A 60-year-old male presented to the out-patient Department of Pulmonary Medicine with history of fever and cough for months duration. He also complaints of loss of weight and loss of appetite over 2 months. He gives history of smoking around 25 beedis per day for past 40 years.

A contrast enhanced CT scan showed an ill-defined right hilar lesion compressing the superior vena cava, right pulmonary artery, right main bronchus and its branches. Another 16 × 11 mm speculated lesion was seen in posterior segment of right upper lobe with no enlarged mediastinal nodes. A video-bronchoscopy showed a growth completely obstructing the bronchi supplying the upper lobe. The endobronchial biopsy of the lesion was suggestive of a small cell lung carcinoma.

Patient was diagnosed as small cell lung carcinoma cT3N0M0 (Stage IIB), limited stage.

Patient was planned for definitive chemo radiation to a dose of 4500 cGy in 30 fractions along with 2 cycles of concurrent 3 weekly cisplatin and etoposide (C1—7 days before RT, C2—on 13th day of RT). He received 2 more cycles of adjuvant chemotherapy with cisplatin and etoposide. He received prophylactic cranial irradiation to a dose of 2400 cGy in 8 fractions after completing adjuvant chemotherapy (Fig. 44.2).

Radiotherapy planning was done on GE Lightspeed 4 Slice CT machine. Images were accrued at 2.5 mm thickness and were transported to MONACO contouring station. Organs at risk in the field of irradiation including bilateral lungs, heart, spinal cord and oesophagus were contoured. Gross tumour was marked as per

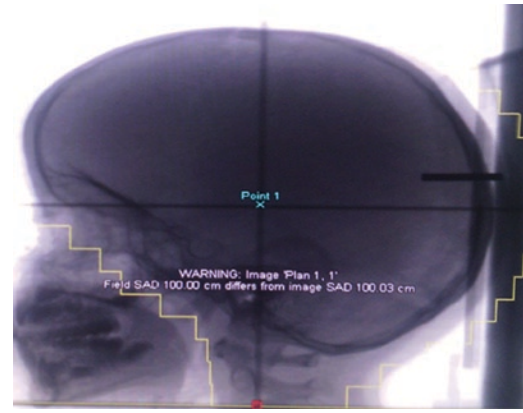

Fig. 44.2 Prophylactic cranial irradiation planning

the CT scan. An 8 mm symmetrical margin was given to GTV primary. PTV margins were 1 cm cranio-caudal and 7 mm axial. A 3-dimensional conformal radiotherapy plan was generated using XIO treatment planning system.

Patient developed Grade 2 esophagitis, Grade 3 neutropenia which were managed conservatively.

Patient is doing well on last follow-up and has a disease-free survival of 4 years and 2 months.

- Consent of the patient 1 and 2 has been taken for presenting the case reports.
- The patients were not a part of trial and were treated as per standard protocol of the hospital.

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Part VI

Other Relevant Topics

Critical Appraisal of a Clinical Trial

45

Bhanu Prasad Venkatesulu

Clinical trials form the backbone of evidence-based medicine. General tendency of a resident is to read the abstract of clinical trial and conclude if the trial is significant or not (https://handbook-5-1.cochrane.org). We have tried to simplify the process on how to evaluate a trial in a clear manner

1. Is the research question of the clinical trial appropriate? Is the population, intervention, comparators, and the endpoints assessed are appropriate?—There is a tendency to assess placebo vs new intervention; especially chemotherapy-based studies which are inappropriate trial design.
2. Read the protocol of the study previously published and confirm if the endpoints and trial design are similar [1].
3. Sample size calculation.
4. The trial design—Superiority trial, non-inferiority trial, or equivalence trial.
5. Look for the following biases in the study.

Table 45.1 lists the checklist for critical appraisal of a clinical trial.

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Table 45.1 Checklist for critical appraisal of a clinical trial

Random sequence generation	How was the randomization process done? For example, central telephonic randomization, table of random numbers, computer random number generator
Allocation concealment	How was the allocation of numbers concealed? For example, radiopaque envelopes, web-based allocation
Blinding/matching	If the outcome is definitive endpoint like overall survival—open label study is acceptable Quality of life studies—preferable that the physician and the patient are blinded to the intervention and the outcomes are reported by the patient
Attrition bias	If any trial has attrition rate more than 10%, then either the intervention is too detrimental or too beneficial that the patients do not follow up
Selective reporting bias	The study's prespecified outcomes are not reported in complete totality. Typically if the intended outcomes is contrary to expectations or makes a trial negative study, the trial authors tend to omit the outcome
Other biases	Funding source Conflict of interest of the trial authors Whether the trial was monitored by independent data monitoring committee

Whether the analysis was intention to treat or per protocol analysis
Whether the cost-effectiveness of the intervention is reported
The universal applicability of the trial
Route of administration of the intervention
Whether the intervention is acceptable to patient's cultural values

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Radiation Toxicity

46

Supriya Mallick, Rony Benson, and Goura K. Rath

Common radiation side effects include:

1. Dermatitis
2. Mucositis
3. Pneumonitis
4. Cystitis
5. Proctitis
6. Cardiac toxicity
7. Hepatic toxicity

Radiation toxicity can be divided into acute and late toxicity (Table 46.1):

- Acute—during or within few weeks after RT, main pathology is inflammation
- Chronic—seen months to years after therapy (>6 months, RTOG uses 3 months), main pathology is vascular

46.1 Temporal Association

Skin changes: The skin changes show a peculiar temporal association (Table 46.2) as well as other toxicity in head and neck also shows temporal association (Table 46.3).

Table 46.1 Comparison of acute and late radiation toxicity

Acute	Chronic
Tissue with high cell turnover rate (mucosal membrane/skin)	Tissues with slow cell turnover
Usually transient	Persistent/ progressive
Dose per fraction not very important	Fraction size matters

Table 46.2 Summary of skin changes following radiotherapy

	Dose (Gy)	Onset
Early transient erythema	2	Hours
Faint erythema	6–10	7–10 days
Definite erythema/hyper pigmentation	12–20	2–3 weeks
Dry desquamation	20–25	3–4 weeks
Moist desquamation	30–40	4 weeks
Ulceration	>40	6 weeks

Table 46.3 Temporal association of other radiation toxicity following head and neck radiotherapy

	Dose (Gy)	Onset
Taste loss	10 Gy	1st week
Mucositis	15–20 Gy	2nd week
Hyposalivation	20–25 Gy	2nd week–3rd week
Radiation caries	55–60	6th week

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46.2 Management of Radiation Toxicity

1. Prevention of radiation toxicity is most important, this can be achieved by
   (a) Patient selection
   (b) Nutrition
   (c) Comorbidity
   (d) Syndromic association
   (e) Good radiation planning, IMRT
2. Treatment approach
   (a) Regular evaluation
   (b) Interruption when required
   (c) If >grade II introduction of management

46.3 Radiation Dermatitis

Radiation dermatitis was one of the common dose limiting side effects in patients receiving radical radiotherapy. The incidence is decreasing with the use of more conformal and higher energy radiation techniques. The incidence is also decreasing with the less frequent use of telecobalt and more availability of linear accelerator.

The main pathophysiology includes damage to the stem cells in the basal layer of the skin, thereby preventing the process of repopulation.

46.3.1 Risk Factors

- Higher incidence with telecobalt than linear accelerators
- Incidence is higher in areas with skin folds like inguinal area even with same dose
- Volume of skin treated, with higher risk with more volume irradiated, due to higher damage to stem cells
- Radiation dose—Dry desquamation starts with 20–25 Gray and moist desquamation occurring at 30–40 Gray
- Chemotherapy use can increase skin toxicity, e.g., cisplatin, 5-fluorouracil
- Smoking and tobacco increase the risk of radiation dermatitis
- There is increase in incidence of radiation skin toxicity as age increases

46.3.2 Grading

- Grade I—Presence of faint erythema/epilation/dry desquamation/decreased sweating
- Grade II—Presence of bright erythema/patchy moist desquamation/moderate edema
- Grade III—Presence of confluent, moist desquamation at areas other than skin folds/presence of pitting edema
- Grade IV—Presence of ulcer, necrosis, or hemorrhage

46.3.3 Prevention of Radiation Dermatitis

1. Avoid shaving and tight clothing
2. Avoid mechanical injuries
3. Avoid smoking
4. Avoidance of hot spots in skin during radiation planning
5. Conformal or intensity modulated radiotherapy to reduce the normal tissue irradiated
6. Reduce sun exposure
7. Only gentle washing of irradiated area with mild soaps

46.3.4 Treatment of Radiation Dermatitis

- Grade I reaction—consider emollients and moisturizers, consider prophylactic steroids
- Sitz bath if irradiation of perianal or pelvic areas
- Diagnose and early treatment of secondary infection
- Analgesics including narcotic analgesics for pain

- Treatment breaks if grade III or higher skin toxicity, and restart treatment once reaction resolves
- Reassurance and psychiatric counseling of the patient if anxious

46.4 Radiation Mucositis

Mucositis is a treatment limiting acute side effect of radiotherapy for head and neck cancer. It has significant impact on treatment and limits the oral intake and causes treatment breaks in patient undergoing radiotherapy for head and neck cancer [1]

- The spectrum of oral mucositis includes oral pain, odynophagia, reduced oral intake, and secondary infections
- Rapidly dividing cells in the mucosa of the oral cavity and oropharynx irradiated are particularly susceptible
- The incidence of radiation mucositis is significantly increased by adding concurrent chemotherapy
- The incidence of grade 3 or higher mucositis is higher in patients receiving altered fractionation radiotherapy (56%) vs conventional radiotherapy (34%)

46.4.1 Risk Factors

1. Age > 65 years
2. Baseline poor oral hygiene
3. Periodontal diseases
4. Reduced saliva production
5. Poor nutritional status
6. Co-morbidities—Diabetes, predisposes to secondary infection

46.4.2 RTOG Grading of Oral Mucositis

- Grade I—Irritation/mild pain not requiring analgesic for pain relief
- Grade II—Patchy mucositis with serosanguinous discharge/moderate pain requiring analgesia
- Grade III—Confluent fibrinous mucositis/severe pain requiring narcotic analgesic for pain control
- Grade IV—Presence of ulceration, necrosis, or hemorrhage

46.4.3 Prevention of Radiation Induced Oral Mucositis

1. Pretreatment oral cavity check-up
2. Maintaining good oral hygiene and use a soft-bristle toothbrush to maintain oral hygiene
3. Avoid hot and spicy food items, smoking, and alcohol during radiotherapy
4. Better radiation planning, e.g., conformal or intensity modulated radiotherapy to reduce the normal tissue irradiated
5. Benzydamine: Incidence of oral mucositis may be reduced by 2.6 times with benzydamine mouthwash. (Chlorhexidine mouth gargles is only recommended for chemotherapy induced oral mucositis)
6. Prophylactic low level laser therapy (LLLT): by diode lasers including red and infrared wavelengths

46.4.4 Treatment of Radiation Induced Oral Mucositis

1. Benzydamine mouth gargles
2. Treatment of secondary infection in patients with oral mucositis
3. Oral mucosa should be sent for bacterial and fungal culture and sensitivity—antimicrobials may be tailored accordingly
4. Treatment interruption may be required in severe OM (Grade III or IV)
5. Feeding—Application of local anesthetics before food. Liquid or semisolid food with high calorie and protein may be very helpful and in severe mucositis. Some patients may also require alternate enteral feeding
6. Pain control; initial weeks may be controlled by topical analgesics including aspirin and lignocaine. Later morphine mouth gargles may be required for controlling oral pain associated with mucositis and may reduce the need for systemic morphine. Doxepin oral

rinses may be also helpful in reducing pain of oral mucositis
7. LLLT with low level He– Ne laser therapy
8. Radiation should be started early as mucositis heals as prolonging overall treatment time decreases local control

46.5 Radiation Pneumonitis

The alveolar epithelium consists of 2 types of cells, type 1 and type 2 pneumocytes. Type 1 covers about 90% of alveolar surface [2]. The most radiosensitive part of the lung is the alveolar-capillary complex.

Radiation induced lung injury occurs in two different phases:

1. Early (<6 months)—radiation pneumonitis
2. Late (>6 months)—radiation induced lung fibrosis

46.5.1 Risk Factors

1. Patient factors: Age more than 65 years, poor pulmonary function (FEV1 and DLCO) prior to radiotherapy
2. Smoking
3. Mid and lower lobe tumors—higher risk due to increased oxygen free radical production
4. RT volumes technique (e.g., active breath holding, breath holding, etc.)
5. Use of concurrent chemotherapy
6. Higher serum TGF B1 associated with development of pneumonitis, similarly elevated levels of IL 1a and IL 6 before, during, and after radiation treatment correlate with the development of radiation pneumonitis

46.5.2 Pathophysiology of Radiation Pneumonitis

Main pathology is the destruction of the type I pneumocytes which starts at 2–4 weeks. The production of cytokines, proteases, and growth factors leads to acute pneumonitis. With continued inflammation, production of reactive oxygen species (ROS) and β-TGF production occurs by the 6th week which subsequently leads to radiation induced lung fibrosis. Endothelial destruction also occurs which leads to neo-vascularization and subsequent radiation induced lung fibrosis.

46.5.3 RTOG clinical grading scale of Radiation Pneumonitis

- Grade 1: Presence of mild dry cough not requiring medications
- Grade 2: Presence of cough requiring narcotic anti-tussives or dyspnea present not at rest
- Grade 3: Severe cough not controlled by drugs/dyspnea present at rest
- Grade 4: Patient requiring continuous oxygen or assisted ventilation to maintain oxygenation

Radiation pneumonitis is a diagnosis of exclusion, by excluding other causes. Patient presents with dry cough, low grade fever, and shortness of breath. History is very important to find the clue about the temporal association between of start of treatment and development of respiratory symptoms.

46.5.4 Investigations

- Throat swab, sputum culture/sensitivity and AFP
- Chest X-ray
- CT chest: Changes usually limited to areas of irradiation/radiation portals

Radiological grading of radiation pneumonitis is given in Table 46.4

Table 46.4 Grading of radiation pneumonitis

Grade	CT Findings
1	Ground glass opacities without fuzziness of the subjacent pulmonary vessels.
2	The findings may vary from ground glass opacities, extending beyond the radiation field, to consolidation
3	Clear focal consolidation ± elements of fibrosis
4	Dense consolidation, cicatrization atelectasis, (traction bronchiectasis), significant pulmonary Volume loss and pleural thickening

46.5.5 The Differentials

- Disease progression: especially in lung primary
- Concomitant infection: high grade fever, productive sputum, and myalgia may be pointers toward an infective pathology
- Tuberculosis also needs to be excluded
- Exacerbation of chronic obstructive pulmonary disease

46.5.6 Management of Radiation Pneumonitis

1. Steroids; oral prednisolone 1 mg/kg (max-60 mg) for a period of 2 weeks usually produces symptomatic benefit. Steroids form the mainstay of treatment of radiation pneumonitis; steroids must be tapered slowly over 6 weeks.
2. Pentoxifylline reduces risk of lung fibrosis. Usually started at 400 mg thrice daily and continued for of 2 weeks in patients with radiation pneumonitis.
3. ACE inhibitors, Enalapril—definite evidence is lacking.
4. Other supportive measures including treatment of concurrent infection as needed.

Management of radiation induced lung fibrosis: The management for established fibrosis is difficult with no standard guidelines. Options include:

1. Supportive management and clearance of airway secretions
2. Anti-inflammatory therapy: Corticosteroids although are the mainstay of management in acute radiation pneumonitis their role in established lung fibrosis is not clear
3. Treatment of concurrent infection

46.6 Radiation Cystitis

Radiation cystitis (RC) involves inflammation of bladder occurring as a complication of pelvic radiotherapy. Radiation cystitis is usually sterile although secondary infections can occur. The clinical spectrum ranges from asymptomatic hematuria to hemorrhagic cystitis (most severe clinical manifestation).

46.6.1 Risk Factors

- The incidence of radiation cystitis is directly proportional to radiation dose and volume of bladder irradiated.
- Newer techniques like intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT) reduce the bladder dose as well as volume of normal bladder irradiated, thereby reducing the risk of RC.
- Concurrent use of chemotherapy like ifosfamide increases risk of RC.
- Age of patient: Some studies have reported increased incidence of cystitis in patients more than 60 years. (1.9%), respectively.

46.6.2 Pathogenesis of Cystitis

Radiation causes single and double stranded DNA breaks leading to both gene repair and apoptosis. Endarteritis also occurs which leads to compromised blood supply and inadequate supply of nutrients to bladder tissue.

46.6.3 Symptoms and Work Up

- Radiation cystitis can occur up to years after radiation and there is no definite time frame.
- Patients typically present with hematuria, dysuria, frequency and hesitancy, and sometimes retention secondary to blood clots obstructing the urethra.
- If the patient presents with hematuria, urinary calculi, tumors, infections need to be excluded.
- Urine routine and cytology along with blood counts is needed.
- Cystoscopy aids in diagnosis and in removing clots. Cystoscopy also helps in treatment like formalin instillation.

Table 46.5 Grading of radiation cystitis

Acute genitourinary toxicity	Chronic genitourinary toxicity
Grade I—increased frequency of urine	Grade I—micro hematuria, mild telangiectasia
Grade II—frequency of urination > 1 h/pain requiring local analgesics	Grade II—increased frequency, generalized telangiectasia, intermittent gross hematuria
Grade III—frequency of urination < 1 h/pain requiring narcotic analgesics	Grade III—severe increased frequency, severe telangiectasia, frequent hematuria
Grade IV—obstruction/ulcer/necrosis, hematuria requiring transfusions	Grade IV—hemorrhagic cystitis, ulcer/fistula, bladder capacity <100 ml

- Imaging—CT and USG may be helpful in selected cases.

Grading: Radiation Therapy Oncology Group for radiation cystitis is summarized in Table 46.5.

46.6.4 Prevention

There is no preventive modality to decrease the incidence of radiation-induced hemorrhagic cystitis except better radiation planning. Maintaining the bladder dose within tolerable limit and minimizing volume irradiated are the key to prevention of radiation cystitis.

- Acceptable tolerance depends on primary tumor irradiated and dose. Common dose limits may be V65 < 50%, V70 < 35%, V75 < 25%, and V80 < 15%
- Steroids, vitamin E, trypsin, and orgotein—Tried but no clinically significantly benefit has been reported

46.6.5 Treatment

Treatment options for hemorrhagic cystitis include continuous bladder irrigation, instillation of alum or formalin, hyperbaric oxygen therapy, embolization, and cystectomy with urinary diversion. These treatment modalities have to be used judiciously for the treatment of radiation cystitis.

- Discontinuation of any anti-coagulant if patient is using.
- Serial hemoglobin monitoring and blood transfusion as needed.
- Saline bladder irrigation: Continuous bladder irrigation and clot removal forms the initial treatment. Urokinase is secreted by kidneys, which can lead to continued bleeding, and continuous bladder irrigation removes urokinase and thus helpful.
- Intravesical formalin instillation has a success rate of up to 90%. The main mechanism is precipitation of cellular proteins of bladder mucosa. Concentrations of 1–10% have been used and a contact period of 3–30 min is usually recommended.
- Alum (1%) irrigation: Acts by protein precipitation leading to vasoconstriction and reduction in edema and inflammation. Bladder irrigation with alum with up to 30 liters has been used. Alum irrigation is more safe and cheaper than formalin. But there are reports of renal impairment with the use of alum.
- Aminocaproic acid acts as a plasminogen activator inhibitor and counteracts the effect of urokinase, thus reduces bleeding.
- Hyperbaric oxygen is highly effective especially in refractory cases. It acts by reducing neovascularization, enhancing granulation tissue formation, and optimizing immune function.
- Nd: YAG laser coagulation results in thermal coagulation of bleeding mucosa. It is highly effective in control bleeding with success rates more than 90%. Rare cases of bladder perforation have been reported.
- Internal iliac artery embolization: Reserved for patients who do not respond to other conservative approaches. Gangrene of the bladder, neurological deficit of lower limbs have been rarely reported.
- In refractory cases urinary diversion and cystectomy remain the only treatment option.

46.7 Radiation Proctitis

Radiation proctitis (RP) is one of the long term complications that occurs following pelvic radiation especially in malignancies like cervix and prostate which requires relatively higher dose for local control. The patient usually presents with blood in stools or altered bowel habits.

46.7.1 Risk factors

Pathophysiology of radiation proctitis is similar to radiation cystitis although threshold level is lower than that for the development of radiation cystitis. Endarteritis is the primary pathology. Incidence of radiation proctitis varies from 2 to 39% in historical series with the incidence reducing with the advent of latest radiation delivery techniques like IMRT. Acute radiation proctitis is defined as development of symptoms within 3 months of treatment completion while chronic occurs more than 3 months.

46.7.2 Symptoms and Work Up

- Symptoms can occur after months or years after radiation.
- Patients typically present with hematochezia.
- Other symptoms include abdominal pain, tenesmus, vomiting, diarrhea.
- Other causes of hematochezia to be ruled out are infection or inflammatory bowel disease.
- Stool routine examination.
- Complete blood count and coagulation parameters.
- Colonoscopy or sigmoidoscopy—presence of friability and telangiectasia is suggestive of RP. Helps in diagnosis and treatment.
- Imaging—CT required in selected conditions.

46.7.3 Grading

- Grade I—Presenting with mild diarrhea or cramping, bowel frequency < 5 times per day, mild bleeding
- Grade II—Presenting with moderate diarrhea and colic, bowel frequency > 5 times per day, excessive rectal mucus or intermittent bleeding
- Grade III—Presenting with obstruction or bleeding that requires surgery
- Grade IV—Presence of necrosis, fistula, or perforation

46.7.4 Prevention

Prevention is the most important aspect in the management of RP. Maintaining the rectal dose within tolerable limit and minimizing volume irradiated are the key. The use of image guidance and IMRT usually helps in maintaining rectal dose within tolerable limit.

Acceptable tolerance limits may be V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 < 15%.

46.7.5 Treatment

Acute form is usually self-limiting and improves on treatment interruption. The supportive measure that may be used includes anti-inflammatory, antidiarrheal, hydration and steroid or 5-aminisalicylic acid enema is required.

Chronic proctitis requires the exclusion of other causes which can present with similar clinical picture like infection or inflammatory bowel disease. Patients with inflammatory bowel disease are also at an increased risk of developing radiation proctitis.

Non-invasive treatment option includes NSAIDs, anti-oxidants, sucralfate, short chain fatty acids, and hyperbaric oxygen.

Invasive treatment consists of ablative procedures like formalin application, endoscopic YAG laser coagulation, or argon plasma coagulation and surgery as a last resort as in patients with RC.

- Formalin instillation—Mechanism of action of formalin instillation is same as in the treatment of radiation cystitis. It is used either as 4 or 10% solution and a contact period of

2–3 min is advocated. Perianal skin needs to be protected to prevent stricture and skin damage that can be caused by contact with formalin. Rare side effects include bleeding, perforation, and fistulas.

- Hyperbaric oxygen (HBO)—HBO is also an effective modality in management of RP, especially in patients not responding to conservative management. Availability is one of the major limitations for its use.
- Laser coagulation—YAG laser coagulation and argon plasma laser coagulation are also one of the options in patients not responding to conservative management. Patients usually require 2–3 sessions. Response rate as high as 75–80% has been reported. The rare but fatal complications include incontinence and rectal ulceration.
- Surgical treatment—Fecal diversion with either colostomy or ileostomy is reserved as a last resort in non-responding patients.

46.8 Radiation Induced Heart Disease

Radiation induced heart disease (RIHD) is one of the late and important but often overlooked complication of radiotherapy for mediastinal lymphoma, breast, lung, and esophageal cancer. RIHD is often aggravated with the addition of chemotherapy especially anthracyclines used for treatment of breast and lymphomas. One of the reasons why RIHD has not been extensively studied is the long latent period for the development of RIHD. RIHD includes a spectrum of cardiovascular complication ranging from subclinical asymptomatic microscopic changes in heart to overt heart failure. The most common cardiac complication to radiotherapy is pericardial (ranging from asymptomatic pericardial effusion to constrictive pericarditis), and conduction abnormalities are the least common.

46.8.1 Pathogenesis

RIHD can be acute or chronic effects on heart. Radiobiologically heart acts both as a parallel and series organ. For example, injury to a small part of myocardium may be asymptomatic and goes unnoticed while injury to a small segment of coronary arteries or the conducting system may be dangerous and life threatening.

Presentation of acute RIHD may range from asymptomatic involvement to acute pericarditis. The acute phase is mediated by tumor necrosis factor (TNF), and interleukins (IL) IL-1, 6, and 8 further leading to neutrophil infiltration. The acute effects are usually self-limiting and respond well to conservative management.

Chronic RIHD is the more important clinically than acute RIHD. The pathogenesis is mediated by inflammatory mediators such as IL-4, IL-13, and TGF-β which lead to changes leading to fibrosis. Pathological examination shows inflammatory cells, fibroblasts, and collagen deposition. Radiation induced fibrosis of the myocardium ultimately leads to decrease in elasticity and distensibility, thus leading to reduction in ejection fraction and cardiac failure. Another mechanism for chronic RIHD is accelerated atherosclerosis in the medium to large coronary arteries leading to infraction like changes. Subendothelial fibrosis leads to vascular injury in small coronary arteries which can lead to ischemia and arrhythmias due to involvement of vascular supply to the conducting tracts or nodes.

Chemotherapy also contributes to development of cardiac disease in cancer patients. Anthracyclines and trastuzumab are also important and may have synergistic effect to radiation in development of heart disease. The development of transtuzumab is more acute than radiation induced heart failure and can occur during treatment.

46.8.2 Diagnosis

Diagnosis of RIHD is often challenging and usually is a diagnosis of exclusion of common causes like ischemic and hypertensive heart disease. A good clinical examination and prompt investigations including ECG, 2D Echo must be done. The knowledge about latent period for development of RIHD is also important (takes 10–15 years) for the diagnosis of RILD.

Prevention: Dose constrains that need to be kept in mind are Mean Dose < 26 Gy. Other constrains that can be kept are V40 < 30%, V30 < 40%, V20 < 50%, and D MAX of 60 Gray.

46.8.3 Management

The tolerance, clinical symptoms management, and prognosis depend on the tissue that is affected by RIHD. The symptoms and signs depend on the tissue involved and there are no specific symptoms specific to identify RIHD. The patient needs to be managed by an expert cardiologist.

Pericardial disease: Pericardial disease is the most common manifestations of RIHD and occurs if a significant proportion of heart (>30%) receives a dose of 50 Gy. The latent period for development of pericarditis is approximately 1 year. Acute pericarditis is rare and develops during or after radiation. Sign and symptoms may include fever, chest pain, and pericardial rub. Acute pericarditis usually resolves by itself and few patients require supportive measures like NSAIDs. Pericardial effusion usually does not require drainage if asymptomatic and drainage is needed if patients present with tamponade.

Myocarditis and cardiomyopathy: Myocarditis risk usually begins to increase after 5 years of radiotherapy and the main pathology is microvascular injury. Most of the patients present with exercise intolerance and reduction in left ventricular ejection fraction (EF). Treatment usually requires ACE inhibitors, angiotensin receptor blocker, aldosterone antagonist, and beta-blockers.

Coronary artery disease: Radiation induced coronary artery disease begins to increase 10 years after radiation and is progressive with time. Even though rare this is one of the most fatal complications following radiation to heart. Exact mechanism is unknown. Management of radiation induced CAD is same as in non-radiation related CAD.

Arrhythmias: Arrhythmias are a rare complication of RIHD. Fibrosis of myocardium may be the primary mechanism for conduction abnormalities following radiotherapy. The management is mainly medical including use of anti-arrhythmic. Clinical features and treatment options are summarized in Table 46.6.

46.9 Radiation-Induced Liver Disease

Radiation-induced liver disease (RILD) is a subacute form of liver injury due to radiation and is of upmost importance in patients planned for radiation therapy for hepatobiliary or upper gastrointestinal malignancies [3]. The better knowledge of tolerance of liver and better investigations to document functional reserve along with modern radiation delivery techniques have greatly reduced the incidence of RILD.

Patho-Physiology Retrograde congestion of the liver is the main pathology that occurs in the development of RILD. These abnormalities of RILD are similar to that for veno-occlusive disease and are predominantly evident around the central vein. The microscopic changes include endothelium swelling, terminal hepatic venule narrowing, sinusoidal congestion, parenchymal atrophy of zone, and proliferation of collagen. Transforming growth factor-beta 1 (TGF-beta 1) may of prime importance in the development of RILD.

Radiobiologically liver parenchyma has parallel architecture in which individual functional units work independently, thus allowing smaller volumes to receive high-dose as long as the mean dose the normal liver is kept within tolerance limit.

46.9.1 Risk Factors

- Radiation Dose: RILD incidence is about 5–10% when the whole of liver is treated to 30–35 Gy. Mean dose of 30 Gy is usually considered as safe tolerance limit to liver. Patients with deranged liver function are more susceptible for development of RILD and a lower threshold for liver tolerance needs to be applied for these patients. With the more availability conformal image guided radiotherapy these constraints are

Table 46.6 Clinical features and treatment options in radiation-induced heart disease

Syndromes	Clinical Features	Investigations	Treatment
Acute pericarditis	Fever, chest pain and pericardial rub	ECG 2D-Echo Investigations to rule out other causes-TB, SLE etc.	• Self-limiting • Bed rest • NSAIDs • Diuretics
Chronic pericarditis and Tamponade	Dyspnea, Low blood pressure and weak pulse Elevated JVP	ECG 2D-Echo Chest X-ray CECT chest Needle Pericardiocentesis	• Loop diuretics • Pericardiocentesis • Pericardiectomy
Cardiomyopathy and CHF	Dyspnea Fatigue and weakness Edema Pulmonary Edema	ECG 2D-Echo Cardiac enzymes	• Loop diuretics • ACE inhibitors • Nitro-glycerine • Vasodilators • Inotropic agents
Coronary artery disease	Chest pain or heaviness Dyspnea Fatigue and weakness	ECG 2D-Echo Angiography Cardiac enzymes	• Anti-platelets • ACE inhibitors, Beta blockers • Dilatation • Stents • Coronary artery bypass graft
Conduction abnormalities	Palpitations Dizziness Shortness of breath Chest discomfort or pain	ECG Holter monitoring 2D-Echo	• Antiarrhythmic drugs • Antiplatelet drugs • Pacemaker placement • Catheter ablation

usually achievable. Dose per fraction is another important factor to the development of RILD and liver is more sensitive to hypofractionated and accelerated radiotherapy than that of conventional schedule.

- Baseline liver status: The baseline liver function is an important factor in development of RILD and background hepatic cirrhosis may be a major risk factor. The Child-Pugh Grading may be helpful in assessing the baseline liver function.
- Chemotherapy and hepatotoxic drugs: Hepatotoxic chemotherapy may be additive to radiotherapy in development of RILD. The treating physician must take into consideration the concurrent use of chemotherapy and other hepatotoxic drugs.
- Other risk factors: Prior transcatheter arterial chemoembolization (TACE), patients with primary hepatobiliary malignancies.

Prevention: There are no effective treatment strategies in the management of RILD, and prevention must be of prime importance. Proper assessment of the patient including functional liver reserve is very important.

- The use of image guidance and respiratory motion management techniques (abdominal compression, shallow breathing, breath holding, gating, and tracking) helps in reducing the PTV margins and thus the target volume.
- Keeping the tolerance limit is also of prime importance.
- Animal studies have shown that the use of amifostine protects hepatocytes from ionizing radiation without compromising tumor cell kill, but good human data is lacking.
- Dose constrains: The mean dose to the liver has to be kept less than 32 Gray and the V30 must be kept <60%.

46.9.2 Clinical Features and Investigations

- Symptoms of RILD occur 2–8 weeks after completion radiotherapy
- Clinical features are like hat of veno-occlusive disease—fatigue and right upper quadrant pain, massive ascites, and hepatomegaly
- Jaundice is unlikely. Cholangitis may be one of the differentials in addition to disease progression in patients presenting with jaundice
- Patients usually present with raised alkaline phosphatase and transaminitis. Alkaline phosphatase usually increases to more than two times the normal level
- Viral markers, serum protein and prothrombin time must also be measured
- Ultrasound of the abdomen—ascites and hepatomegaly
- Magnetic resonance imaging—low signal intensity on T1-weighted images and high signal on the T2
- Cytopathologic evaluation of the ascitic fluid to rule out malignancy
- Liver biopsy—may help confirm diagnosis

46.9.3 Treatment

There are no specific guidelines for the treatment of RILD, and no therapy has shown to modify the natural course of the disease. Treatment is mainly directed at control of symptoms and includes:

- Diuretics for fluid retention
- Paracentesis for ascites
- Correction of coagulopathy
- Anticoagulants and thrombolytics if hepatic vein thrombosis
- Steroids to reduce hepatic congestion

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Cancer in India

47

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The incidence of cancer has been on an increasing trend in India as in the rest of the world. Changes in the lifestyle, food habits and increased life expectancy are the major factors that contribute to the increased incidence [1]. The National Cancer Registry Programme was initiated by Indian Council of Medical Research [ICMR] in 1981 with the aim of collecting data on cancer incidence. The program started with three population based cancer registries at Bangalore, Chennai, Mumbai and three hospital-based cancer registries at Chandigarh, Dibrugarh and Thiruvananthapuram [2]. As of 2018, there are 31 Population Based Cancer Registries and 29 Hospital Based Cancer Registries under National Cancer Registry Programme. The Population Based Cancer Registries [PBCR] represent different geographical regions in India and covers approximately 10% of the Indian population.

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47.1 Worldwide Facts

- 60 lakh deaths per year worldwide—12 percent of all deaths
- Second leading cause of death in the developed countries—25 lakh cases of deaths per year
- Third leading cause of death in the developing countries—38 lakh cases of deaths per year
- Projected WHO estimates about cancer deaths world wide—by the year 2020–100 lakh/year

47.2 Cancer Burden in India

The latest publication on cancer incidence by ICMR was published in May 2016. In males, lung cancer is the leading site in 11 registries and breast cancer is the leading site amongst females in 19 registries. The northeast registries reported high burden of tobacco related sites of cancer while highest burden of childhood cancers was in Delhi urban registry. Estimated incidence of

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various cancers is summarised in Tables 47.1, 47.2 and 47.3 [3].

Population Based Cancer Registries although represent only 10% of the Indian population, give us very useful information on cancer incidence, trend and mortality. The information obtained from these cancer registries is very important in planning and evaluating cancer control programmes and thus helps in reducing cancer burden and mortality in the country.

Table 47.1 Estimated burden in India, PBCR report

New cancer	2016	2020
All sites	14.5	17.3
Breast	1.5	1.9
Lung	1.14	1.4
Cervix	1.0	1.0
Death	7.36	8.8

Table 47.2 Cancer incidence variation in India

Registry	Incidence male	Registry	Incidence female
Aizwal district	270.7	Papumpare district	249
Papumpare district	230.4	Aizwal district	207
East Khasi Hill district	218.3	Kamrup Urban district	174
Mizoram state	211.5	Mizoram state	165.8
Kamrup Urban district	206	Delhi	144.8
Mizoram excl. Aizwal	175	Mizoram excl. Aizwal	136.6
Meghalaya	169.6	Chennai	126.2
Delhi	149.4	Bangalore	125.9
Thiruvananthapuram	132	Thiruvananthapuram	120.4
Nagaland	125.8	Mumbai	118.5
Barshi expanded	40.9	Barshi expanded	52.0

Table 47.3 Sexwise cancer incidence in India

	Male		Female	
Subsite	Registry	Incidence	Registry	Incidence
Tongue	East Khasi Hill district	11.7	Bhopal	3.7
Oesophagus	East Khasi Hill district	71.2		
Stomach	Papumpare district	50.2	Papumpare district	29.2
Gall bladder			Kamrup urban district	17.1
Lung	Aizwal district	37.9	Aizwal district	40.8

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