

II. The practice of radiation oncology

A. Principles of radiation therapy

1. Definition of RT

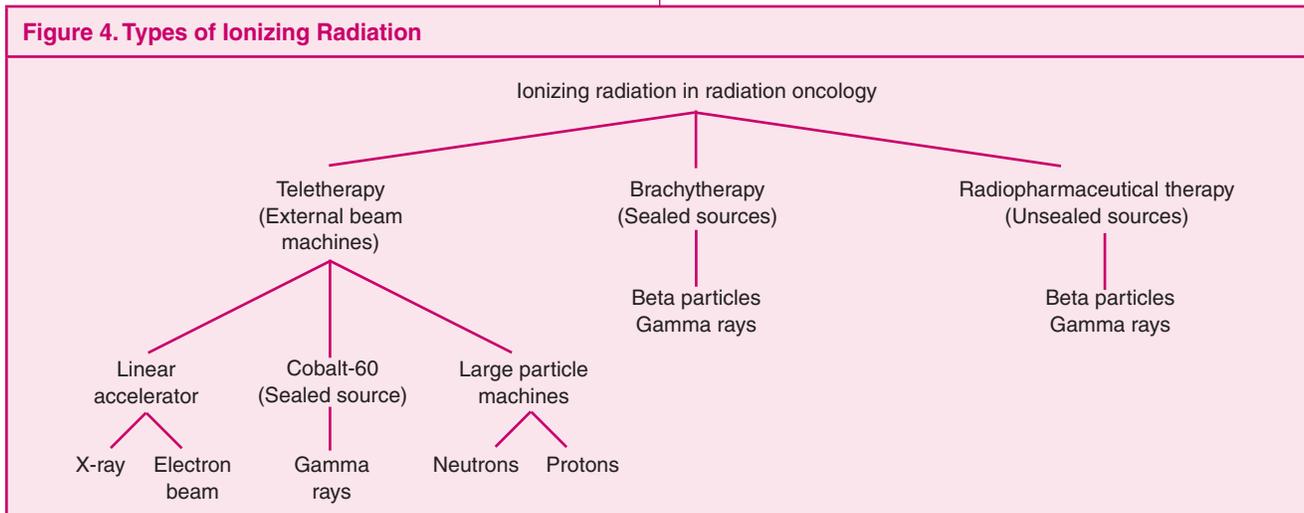
- a) RT is the use of high-energy x-rays or other radiation particles to treat malignant and some benign diseases.
- b) Radiation with sufficient energy to disrupt atomic structures by ejecting orbital electrons is called *ionizing radiation* (Khan, 2003).

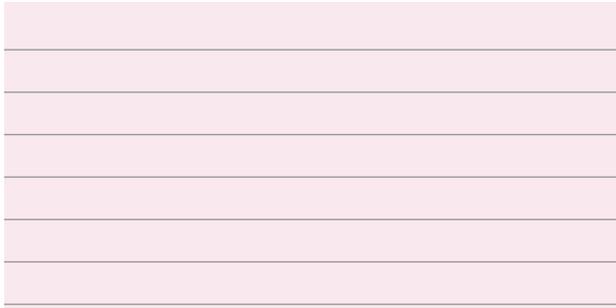
2. Types of ionizing radiation commonly used in treatment (see Figure 4)

- a) Electromagnetic radiation: X-rays and gamma rays have the same characteristics but differ in origin.
 - (1) X-rays: Photons (i.e., “packets” of energy generated from an electrical machine, such as a linear accelerator)
 - (2) Gamma rays: Photons emitted from the nucleus of a radioactive source (e.g., ^{60}Co , ^{137}Cs , ^{192}Ir)
- b) Particulate radiation: Consists of particles, including alpha particles, electrons, protons, and neutrons
 - (1) Alpha particles: Large, positively charged particles with poor penetrating ability; emitted during disintegration (i.e., decay) of some radioactive sources (e.g., radium); have a mass approximately 8,000 times that of an electron
 - (2) Electrons: Small, negatively charged particles accelerated to high energies by an electrical machine
 - (3) Beta particles: Electrons emitted during disintegration of radioactive sources

- (4) Protons: Large, positively charged particles that may be generated by an electrical machine; have a mass approximately 2,000 times that of an electron
 - (5) Neutrons: Large, uncharged particles that may be generated by a large machine (e.g., cyclotron)
- #### 3. Sources of radiation for treatment (see Figure 4) (Van Dyk, 1999)
- a) Megavoltage machines: Treatment machines used for external beam RT (EBRT) or teletherapy (treatment from a distance)
 - (1) Linear accelerator: Machine that generates ionizing radiation from electricity. These machines are commissioned to treat with high-energy (1–50 MeV [megaelectron volts]) x-rays (intermediate to deep penetration and low to moderate skin dose) or (1–50 MeV) electrons (shallow penetration and high skin dose). The depth of treatment varies with energy and type of radiation. Linear accelerators may have multiple energies of both x-rays and electrons so that various depths of treatment may be selected.
 - (2) ^{60}Co machine: Radioactive source (^{60}Co) emission of gamma rays; treatment depth is comparable to a 4 megavolt (MV) x-ray beam (intermediate penetration).
 - (3) Cyclotron: Large, electrically powered machine that produces neutrons (large particles) or protons
 - b) Radionuclides: Radioactive sources that emit radiation in the form of alpha particles, beta particles, gamma rays, or a combination; each radionuclide emits particles

Figure 4. Types of Ionizing Radiation





or rays with energies that are characteristic of that specific radionuclide.

- (1) Brachytherapy (internal radiation): Therapy performed by placing radioactive material in or near the treatment volume. Sources are placed directly into (interstitial) or adjacent to (intracavitary, intraluminal, surface) tumors. Therapy may be administered with solid or liquid radioactive material. Brachytherapy is the therapeutic use of radionuclides that are sealed within metal containers; radioactive particles or rays penetrate the container to treat the disease. Small volumes of normal tissue and cancer can be irradiated to relatively high doses.
 - (a) Temporary: Sealed radioactive sources (e.g., ^{192}Ir , ^{137}Cs) are removed after the prescribed dose is reached in the calculated number of hours.
 - i. High-dose-rate (HDR) treatment: One or several doses are administered and separated by at least six hours. Each dose is administered over a few minutes.
 - ii. Low-dose-rate (LDR) treatment: Continuous LDR treatment is administered over several days in a protected lead-shielded room.
 - (b) Permanent: Sealed radioactive sources are left permanently in the tissue. Sources used for permanent placement (e.g., ^{125}I , ^{198}Au , ^{103}Pd) have relatively short half-lives and weak gamma emissions.
- (2) Radiopharmaceutical therapy: Treatment with unsealed liquid radioactive sources that are ingested, injected, or instilled; each radionuclide has characteristics that determine where it can concentrate in the body. For example,

oral ^{131}I is used to treat thyroid diseases, and IV ^{89}Sr and ^{153}Sm are used to treat multiple bone metastases.

4. Radioactivity

- a) Isotope: The nucleus contains protons and neutrons. The number of protons and neutrons determines which “element.” The number of neutrons determines which “isotope.” An element may have both stable and radioactive isotopes (Khan, 2003).
 - b) Nuclei of radioactive elements have excess energy. Radioactive materials (also called radionuclides or radioactive sources/isotopes) decay and emit radiation in the form of alpha and beta particles and gamma rays until they become stable. *Radioactivity*, or *radioactive decay*, is the spontaneous emission (disintegration) of highly energetic particles or rays from the nucleus of an element. Radioactivity is measured in disintegration per second (DPS).
 - c) *Half-life* is the period of time required for a radioactive substance to lose one-half of its radioactivity through nuclear decay. The spontaneous decay or expulsion of particles and rays from a radionuclide occurs at a characteristic rate for each element.
 - d) A radioactive element radiates energy that is characteristic of that element. Some radioactive sources emit more penetrating radiation than others and therefore require more shielding to absorb the radiation. Fifty percent of the radioactivity from a source is absorbed by one half-value layer (HVL) of a substance, such as lead.
 - e) The characteristics of a radionuclide vary with the specific isotope. Table 2 shows the half-life, energy, and HVL of common elements.
- #### 5. Measurement of radiation (see Figure 5) (Khan, 2003)
- a) Radiation-absorbed dose (rad) is the amount of energy absorbed per unit mass. Radiation previously had been prescribed in rad but is now prescribed in gray (Gy). $1 \text{ Gy} = 100 \text{ centigray (cGy)} = 100 \text{ rad}$.
 - b) Dose equivalent is used in radiation protection. Badge readings have been reported in millirem (mrem). Sievert (Sv) is the international unit for dose equivalent. $100 \text{ rem} = 1 \text{ Sv}$.
 - c) Activity of radioactive sources has been measured in millicuries (mCi) and curies (Ci). Becquerel (Bq) is the international unit. Both units are measured as DPS. $1 \text{ Ci} = 3.7 \times 10^{10} \text{ dps}$. $1 \text{ Bq} = 1 \text{ dps} = 2.7 \times 10^{-11} \text{ Ci}$.

Table 2. Characteristics of Radionuclides

Element	Half-Life	Energy	Half-Value Layer ^a (Lead)
Cesium-137 (¹³⁷ Cs)	30 years	0.66 MeV (gamma)	0.65 cm
Cobalt-60 (⁶⁰ Co)	5.2 years	1.25 MeV (gamma)	1.2 cm
Gold-198 (¹⁹⁸ Au)	2.7 days	0.41 MeV (gamma)	0.33 cm
Iodine-125 (¹²⁵ I)	60.2 days	0.02 MeV (gamma)	0.02 cm
Iodine-131 (¹³¹ I)	8 days	0.36 MeV (gamma)	0.3 cm
Iridium-192 (¹⁹² Ir)	64.2 days	0.13–1.06 MeV (gamma)	0.6 cm
Radium-226 (²²⁶ Ra)	1,620 years	1 MeV (gamma)	1.66 cm
Strontium-89 (⁸⁹ Sr)	50.5 days	1.46 MeV (beta)	1 mm of lead blocks (100% of ⁸⁹ Sr)

^a One half-value layer blocks 50% of the radiation.
 Note. Based on information from Cember, 1996; St. Germain, 1993a, 1993b.

Figure 5. Units of Measurement for Radiation

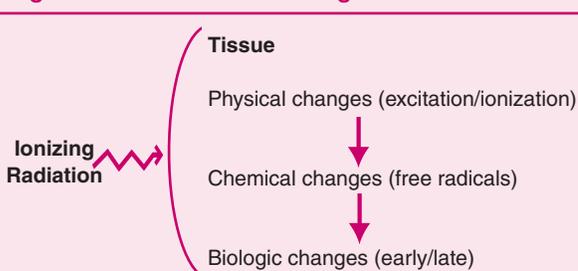
- Absorbed dose (gray [Gy], radiation-absorbed dose [rad]) (therapeutic doses)
1 Gy = 100 rad; 100 centigray (cGy) = 100 rad
- Dose equivalent (sievert [Sv], rem) (radiation protection)
1 Sv = 100 rem
- Activity (becquerel [Bq], curie [Ci]) (activity of radionuclides)
1 Bq = 2.7×10^{-11} Ci = 1 dps; 1 Ci = 3.7×10^{10} dps

B. Radiobiology

1. *Radiobiology* is the study of events that occur after ionizing radiation is absorbed by a living organism. Ionizing radiation can result in breaking of chemical bonds and, eventually, in biologic change (see Figure 6). The nature and severity of effects and the time in which they appear depend on the amount and type of radiation adsorbed and the rate at which it is administered. Early- and late-responding tissues are affected differently by these factors. Interaction of radiation in cells is random and has no selectivity for any structure or site (Hall, 2000).
2. If critical sites are damaged by radiation, the probability of cell death is higher than if a noncritical site is damaged. DNA is considered to be the critical target for radiation damage. Cells can successfully repair much of the damage caused by ionizing radiation (Hall, 2000).
3. Response to ionizing radiation: Damage to DNA may lead to cell alteration or death. All living cells, whether normal or cancerous, are susceptible to the effects of radiation and may

be injured or destroyed by RT. Injury generally is expressed at the time of cell division (reproductive death).

- a) Physical stage: Excitation and ionization of atoms or molecules
- b) Radiochemical stage: Formation of free radicals, which are highly reactive
- c) Biologic stage: Damage to critical target (DNA, which is composed of two strands that form a double helix)
 - (1) Single chromosomal strand breaks: These generally are repaired readily and have little biologic consequence (Rossi, 1996). Misrepair (incorrect repair) may result in mutation.
 - (2) Double chromosomal strand breaks (DSBs): DSBs are believed to be the most important damage produced in chromosomes by radiation and may result in cell death, mutation, or carcinogenesis. DSBs may activate an oncogene or inactivate a tumor suppressor gene (Hall & Cox, 1994).

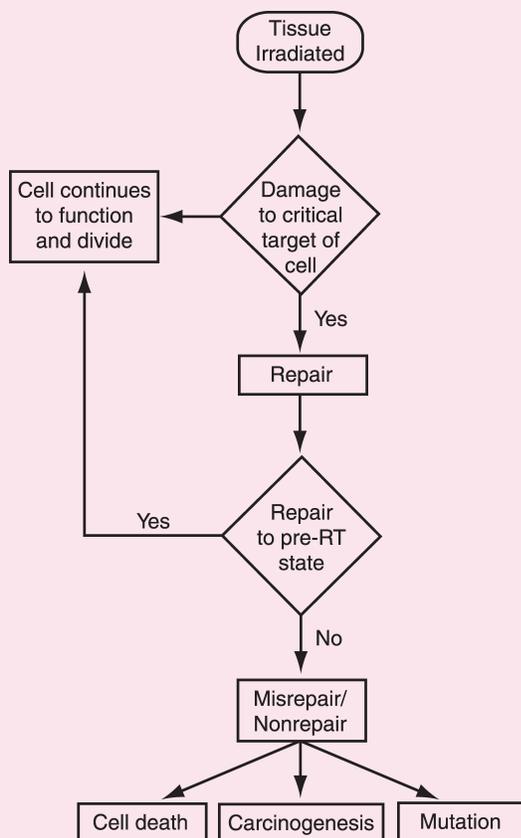
Figure 6. Interaction of Ionizing Radiation in Tissue

Note. Based on information from Fritz-Niggli, 1995.

4. Potential effects on a single cell in an irradiated volume of tissue (see Figure 7)
 - a) No effect or no cell injury occurs in critical target.
 - b) Radiation damage to critical target is repaired; cell continues to function and divide.
 - c) Radiation damage to critical target is misrepaired, and mutation occurs.
 - d) Cell death occurs.
5. Radiation-induced chromosome aberration effects (Bender, 1995; Hall, 1994, 2000; Hall & Cox, 1994)
 - a) Cell death induced by radiation
 - (1) Chromosome damage may cause reproductive failure (death at the time of cell division).
 - (2) Apoptosis (programmed cell death), the process that occurs during normal development of organs and tissues, is enhanced by toxic treatments such as RT (Dewey, Ling, & Meyn, 1995).

- b) Mutation (germ cells): Heritable change in genes expressed in later generations; a large variation in mutation types exists.
 - c) Carcinogenesis (somatic cells): Chromosome aberration that may cause oncogene activation or suppressor gene loss (Hall, 1994)
6. *Radiosensitivity* is the innate sensitivity of cells, tissues, or tumors to radiation. Both normal and cancer cells are affected by radiation. Cells vary in their expressed sensitivity to radiation. Generally, rapidly dividing cells (e.g., mucosa) are most sensitive and are referred to as *radiosensitive*. Nondividing or slowly dividing cells (e.g., muscle cells, neurons) generally are less radiosensitive, or are *radioresistant*. Exceptions include small lymphocytes and salivary gland cells, which are nondividing but very radiosensitive. These may experience an interphase death (death prior to mitosis).
 - a) Manifestations of radiation effects occur at different times for different tissues (Hall & Cox, 1994).
 - (1) Acutely responding tissues demonstrate effects in hours to days and include the bone marrow, ovaries, testes, lymph nodes, salivary glands, small bowel, stomach, colon, oral mucosa, larynx, esophagus, arterioles, skin, bladder, capillaries, and vagina.
 - (2) Subacutely responding tissues demonstrate effects in weeks to several months after RT and include the lungs, liver, kidneys, heart, spinal cord, and brain.
 - (3) Late-responding tissues, including the lymph vessels, thyroid, pituitary gland, breasts, bones, cartilage, pancreas (endocrine), uterus, and bile ducts, rarely show acute effects and demonstrate effects months to years after RT.
 - b) Factors that influence radiation sensitivity (Fritz-Niggli, 1995; Hall & Cox, 1994)
 - (1) Cell cycle phase: Cells in the late G₂ and mitosis (M) phases are more sensitive. Cells in the late synthesis (S) phase are most resistant to radiation.
 - (2) Oxygen: The presence of oxygen enhances radiation damage. When oxygen is not present, chemical damage in DNA may be repaired. Reoxygenation occurs as the tumor shrinks during RT, and previously hypoxic cells become better oxygenated. Hypoxia may contribute to radioresistance.
 - (3) Differentiation: Poorly differentiated tumors generally are more sensitive. Far more radiation is required to destroy the function of a differentiat-

Figure 7. Possible Response of a Cell in Irradiated Volume of Tissue



Note. Based on information from Fritz-Niggli, 1995; Hall & Cox, 1994.

ed cell than to destroy a dividing cell (Hall, 2000). However, poor differentiation of a tumor is associated with a poor disease-free survival rate, perhaps because of a more aggressive natural history (Bentzen, 1993).

- (4) Proliferative capacity: Rapidly dividing cells generally are more sensitive to the effects of radiation. Nondividing or slowly dividing cells usually are less sensitive, or are radioresistant.
- (5) Repair of radiation damage: The greater the repair capability of the normal tissue, the greater the effectiveness of the treatment. DNA damage can be repaired to its original state or misrepaired with errors (mutation). Most repairs are believed to occur within six hours after a treatment.
- (6) Tumor size: Tumor size is a major factor in dose-response outcomes of RT. Larger tumors generally are more difficult to control than small tumors of the same type. Control of large tumor masses may require a radiation dose that would result in unacceptable damage to normal tissue. Often, the tumor bulk indicates a poorly oxygenated mass that is less radiosensitive.
- (7) Fractionation: This is the division of a total prescribed dose into smaller daily doses, or *fractions*. Daily fractions generally are 1.8–2 Gy. Fraction size is the dominant factor in determining late effects on tissue, with large fractions causing an increase in late effects (Hall, 2000). Fractionation varies depending on goal of therapy.
 - (a) Hyperfractionation: Multiple daily fractions (e.g., 1.2 Gy twice a day) are delivered, generally separated by at least six hours to allow for repair of damage to the normal tissues from the first dose before administration of the second dose. The intent is to decrease late effects while achieving equal or improved tumor control and equal or only slightly increased early effects. A **higher total physical dose** is administered.
 - (b) Hypofractionation: The total dose of radiation is divided into large doses, and treatments may be given less than once a day. Also called hypofractionated RT. A lower total physical dose is administered,

but a higher biologically equivalent dose is expected because of the larger fractional doses. Hypofractionation may have high potential for therapeutic gain as well as economic and logistic advantages for some tumors (e.g., RT for prostate cancer has been extensively investigated), but it may lead to increased late effects for surrounding normal tissues.

- (8) Quality of radiation: Energy of various types of radiation is distributed differently in tissues. Heavy particles (e.g., neutrons, alpha particles) ionize densely and quickly; light particles (e.g., electrons) ionize sparsely in tissues.
 - (a) *Linear energy transfer* (LET) is the distribution of energy along the ionization track in irradiated material. High LET radiation is densely ionizing and is less influenced by the presence of oxygen (i.e., more effective on hypoxic cells than low LET radiation) and the cell cycle phase. Less repair occurs with high LET radiation. Low LET radiation is sparsely ionizing.
 - (b) Relative biologic effectiveness of a radiation type is dependent on LET. High LET radiation is more biologically damaging than low LET radiation.
7. Effect of radiation on normal cells versus cancer cells (Hall & Cox, 1994)
 - a) Although both normal cells and cancer cells are affected by radiation and respond similarly to RT, only cancer cells are believed to undergo reoxygenation.
 - b) Malignant tumors differ greatly in radiosensitivity because of innate sensitivity, mitotic activity, hypoxic component, and blood supply.
 - c) Dividing a dose into multiple daily fractions spares normal tissues because of damage repair between fractions and repopulation of cells if overall time is sufficient. Dose fractionation increases damage to cancer cells because of reoxygenation of the tumor and reassortment of cancer cells into more sensitive phases of the cell cycle.
 - d) Side effects are the result of radiation damage to normal cells.
 8. Biomarkers for RT: A *biomarker*, or *biologic marker*, is a substance used as an indicator of a biologic state. It is a characteristic that is objectively measured and evaluated as an in-

indicator of normal biologic processes, pathogenic processes, or radiobiologic responses to RT treatments. Research is being conducted on biomarkers for tumor/tissue response and treatment assessment in predictive radiation oncology (Riesterer, Milas, & Ang, 2007).

C. Dose prescription, treatment planning, and simulation

1. Specification of dose and volume: The method of writing and interpreting a prescription is essential to the success of treatment.

a) The International Commission on Radiation Units and Measurements (ICRU) Report 50 (ICRU, 1993) definition of the treatment volume is separated into three distinct boundaries: (a) visible tumor, (b) a region to account for uncertainties in microscopic tumor spread, and (c) a region to account for positional uncertainties. These boundaries create three volumes (see Figure 8).

- (1) Gross target volume, or GTV: This is the gross extent of the malignant growth as determined by palpation or an imaging study.
- (2) Clinical target volume, or CTV: This is the tissue volume that contains the GTV and/or subclinical microscopic malignant disease.
- (3) Planning target volume, or PTV: This volume is defined by specifying the mar-

gins that must be added around the CTV to compensate for the effects of organ, tumor, and patient movements and inaccuracies in beam and patient setup.

b) ICRU (1993) also defined two other dose volumes.

- (1) Treated volume: This is the volume enclosed by an isodose surface that is selected and specified by the radiation oncologist as being appropriate to achieve the purpose of treatment (e.g., 95% isodose surface).
- (2) Irradiated volume: This is the volume that receives a dose significant in relation to normal tissue tolerance (e.g., 50% isodose surface).

c) *Organs at risk*, or OARs, are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning or prescribed dose (e.g., rectum and bladder for prostate treatment).

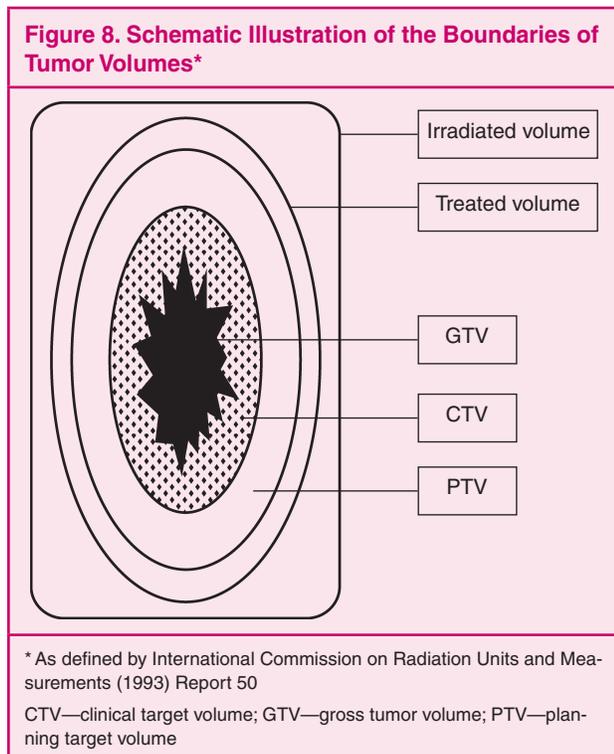
d) ICRU (1993) defined a series of doses including the minimum, maximum, and mean dose for dose reporting purposes. Additionally, an ICRU reference dose is defined at the ICRU reference point. The ICRU reference point is chosen based on the following criteria: it must be clinically relevant, be defined in an unambiguous way, and be located where the dose can be accurately determined (not in a region with steep dose gradients). In general, this point should be in the central part of the PTV.

e) Dose-volume histograms (DVHs) play an essential role in evaluating and reporting three-dimensional RT dose distributions.

- (1) A cumulative DVH plots the fraction of a structure receiving at least a specified dose against the specified dose.
- (2) A differential DVH plots the fraction of a structure receiving a dose within a specified interval against the dose.

2. Treatment planning: RT is a complex procedure that requires comprehensive treatment planning and quality assurance (QA). Treatment planning entails interactions among the radiation physicists, dosimetrists, radiation oncologists, residents (if available on the team), and radiation therapists and the use of a large number of software programs and hardware devices for geometric and dosimetric planning and QA. The following are the steps in the treatment planning process (Fraass et al., 1998; Kutcher et al., 1994).

a) Patient positioning and immobilization to ensure a consistent position during the course of imaging and treatment



- b) Patient data acquisition (computed tomography [CT], magnetic resonance imaging [MRI], positron-emission tomography [PET], manual contouring)
 - c) Data transfer to treatment planning system
 - d) Definition of treatment volumes and OARs
 - e) Treatment design (modality, beam arrangements, modifiers)
 - f) Computation of dose distributions
 - g) Plan evaluation (review of isodose distributions, DVHs, or other physical or biologic dosimetric parameters)
 - h) Computation of monitor units or minutes based on the prescribed dose
 - i) Production of blocks and beam modifiers
 - j) Plan implementation (treatment simulation, data transfer to record and verify system)
 - k) Patient-specific treatment planning QA (review the plan, chart, monitor unit calculation, and port film, and perform additional calculations or measurements to verify the dose)
3. Simulation: This is the process of aiming and defining the radiation beams to meet the goals of the prescribed therapy. It is mainly concerned with geometric aspects of a treatment, such as the orientation of beams, their sizes, the placement of field-shaping blocks, and the placement of marks on the patient to allow for reliable reproduction of treatment geometry from day to day. Unforeseeable problems with a patient setup or treatment technique also can be solved during simulation.
- a) A *treatment simulator* is an apparatus that uses a diagnostic x-ray tube but duplicates a radiation treatment unit in terms of its geometrical, mechanical, and optical properties.
 - b) By radiographic visualization of internal organs, correct positioning of fields and shielding blocks can be obtained in relation to external landmarks (Farmer, Fowler, & Haggith, 1963; Greene, Nelson, & Gibb, 1964; Van Dyk, 1999).
 - c) A *virtual simulator* is a piece of software that performs treatment simulation based on a digital representation of the patient derived from serial CT or other tomographic images (Sherouse, Mosher, Novins, Rosenma, & Chaney, 1987).
4. Three-dimensional conformal RT (3DCRT): The goal of 3DCRT is to conform the spatial distribution of the prescribed radiation dose to the precise three-dimensional configuration of the treatment volume while at the same time minimizing the dose to the surrounding normal tissues (Smith & Purdy, 1991).
- a) A three-dimensional treatment planning system (3DTPS) is needed to plan a radiation treatment based on the three-dimensional treatment volume. A 3DTPS generally is characterized by acquisition of three-dimensional patient data, delineation of treatment portals based on a beam's eye view projection of the PTV, calculation of dose in three-dimensional patient geometry, and display of dosimetric information in volumes.
 - b) 3DCRT is commonly delivered with megavoltage photon and electron beams using multileaf collimators (MLCs) or custom-designed blocks (cutouts) to shape uniform open fields (to match the beam's eye view projection of the PTV) or using wedges or custom-designed compensators to account for the effect of surface irregularities and internal heterogeneities (to achieve uniform dose at a selected treatment depth, usually through the middle of the target volume).
5. Intensity-modulated RT (IMRT): IMRT is an advanced form of 3DCRT in which varying intensities (i.e., weights) of small subdivisions of beams (i.e., beamlets, field segments) are used to custom-design optimal radiation dose distributions (Webb, 2001). Because of the conformal dose distributions and steep dose gradients that can be achieved with IMRT, requirements for patient immobilization, target and structure delineation, treatment planning, beam delivery, and dose verification are more stringent (Boyer et al., 2000; Ma et al., 2000, 2003).
- a) Special treatment planning software is needed to optimize the weights of individual beamlets (or field segments) via inverse planning (Bortfeld, Bürkelbach, Boesecke, & Schlegel, 1990; Brahme, 1988; Webb, 1992) or forward planning (Galvin, Croce, & Bednarz, 2000; Xiao, Galvin, Hossain, & Valicenti, 2000) to achieve superior target coverage and normal tissue sparing based on the specified dose requirements for the treatment volumes and dose constraints on the OARs.
 - b) IMRT fields are commonly delivered using a computer-controlled MLC (Convery & Rosenbloom, 1992; Ma, Boyer, Xing, & Ma, 1998; Spirou & Chui, 1994). However, beam intensity modulation also can be achieved using complex physical compensators.
 - c) IMRT is time- and resource-intensive. Adequate time to perform reviews and quality checks is essential. Therefore, as noted by Moran et al. (2011), "Team members need to acknowledge that initiation of [IMRT] treatment may need to be delayed to allow time for necessary quality assur-

ance checks and subsequent investigations of problems” (p. 195).

6. Image-guided radiation therapy (IGRT): IGRT is an advanced radiation treatment technique that uses imaging technology during treatment to ensure tumor location and beam delivery accuracy (Sharpe, Craig, & Moseley, 2007). The goal of IGRT is to decrease radiation dose to normal tissue and/or improve local control and quality of life by dose escalation or hypofractionation. Traditionally, diagnostic imaging technologies such as CT scans, x-rays, ultrasound, gamma cameras, PET scans, and MRI have been used to determine tumor location and size for treatment planning procedures. However, difficulty arises when trying to ensure accuracy of the beam delivery because many body parts may have moved from the time the original images were taken (e.g., bladder fullness, etc.). IGRT systems allow for frequent two- or three-dimensional imaging to correlate the actual tumor position with the radiation treatment plan to ensure accurate target dose delivery.

D. Purpose of radiation therapy

1. RT is used to treat local or regional disease and, rarely, systemic disease. The aim is to destroy malignant cells in the treated volume of tissue while minimizing damage to normal tissues.
2. RT can be selected for various purposes (Haas & Kuehn, 2001).
 - a) Definitive treatment: RT is prescribed as the primary treatment modality, with or without chemotherapy, for the treatment of cancer. Examples can include cancers of the head and neck, lung, prostate, or bladder or Hodgkin lymphoma.
 - b) Neoadjuvant treatment: RT is prescribed prior to definitive treatment, usually surgery, to improve the chance of successful resection. Examples include esophageal or colon cancers.
 - c) Adjuvant treatment: RT is given after definitive treatment (either surgery or che-

motherapy) to improve local control. Examples may include breast, lung, or high-risk rectal cancers.

- d) Prophylaxis therapy: RT is delivered to asymptomatic, high-risk areas to prevent growth of cancer. Examples are prophylactic cranial irradiation in lung cancer or central nervous system (CNS) cancers to prevent relapse of certain forms of leukemia.
- e) Control: RT is given to limit the growth of cancer cells to extend the symptom-free interval for the patient. Examples may include pancreatic or lung cancers.
- f) Palliation: RT is given to manage symptoms of bleeding, pain, airway obstruction, or neurologic compromise to alleviate life-threatening problems in incurable illness or to improve the patient's quality of life. Examples may include relieving spinal cord compression, opening airways in patients with pneumonia, or relieving pain from bone metastases.

E. Tissue tolerance dose: The radiation dose to which a normal tissue can be irradiated and continue to function (see Table 3)

1. Organs vary in their ability to tolerate radiation injury. Normal tissue tolerance to radiation depends on the ability of the dividing cells to produce enough mature cells to maintain function of the organ. The tolerance dose is the dose of radiation that results in an acceptable probability of a treatment complication (Hall, 2000).
2. The dose prescribed to eradicate a cancer ultimately is dependent on the normal tissue tolerance of the dose.

F. Factors related to radiation-induced injury of normal tissue (Bentzen & Overgaard, 1994)

1. Patient-related factors
 - a) Age
 - (1) In children: Growth-related factors (e.g., growth retardation, endocrine changes)
 - (2) In adults: Limited data available
 - b) Hemoglobin level
 - (1) Low hemoglobin has been found to decrease local control probability in cancers such as squamous cell carcinoma of the head and neck (Fein et al., 1995; Regueiro et al., 1995), carcinoma of the cervix (Werner-Wasik et al., 1995), and transitional carcinoma of the bladder (Cole et al., 1995).
 - (2) Little information is available concerning hemoglobin level related to normal tissue reactions.

Table 3. Minimal and Maximal Tissue Tolerance to Radiation Therapy Dose

Tissue	Dose-Related Injury	Minimal Tolerance Dose TD 5/5 ^a (Gy)	Maximal Tolerance Dose TD 50/5 ^b (Gy)	Amount of Tissue Treated (Field Size or Length)
Bone marrow	Aplasia, pancytopenia	2.5 30	4.5 40	Whole Segmental
Brain	Infarction, necrosis	60	70	Whole
Eye	Blindness			
	Retina	55	70	Whole
	Cornea	50	> 60	Whole
	Lens	5	12	Whole
Fetus	Death	2	4	Whole
Heart	Pericarditis, pancarditis	45 70	55 80	60% 25%
Intestine	Perforation, ulcer, hemorrhage	45 50	55 65	400 cm ² 100 cm ²
Kidney	Acute and chronic nephrosclerosis	15 20	20 25	Whole (strip) Whole
Liver	Acute and chronic hepatitis	25 15	40 20	Whole Whole (strip)
Lung	Acute and chronic pneumonitis	30 15	35 25	100 cm ² Whole
Spinal cord	Infarction, necrosis	45	55	10 cm
Stomach	Perforation, ulcer, hemorrhage	45	55	100 cm ²
Uterus	Necrosis, perforation	> 10	> 200	Whole
Vagina	Ulcer, fistula	90	> 100	Whole

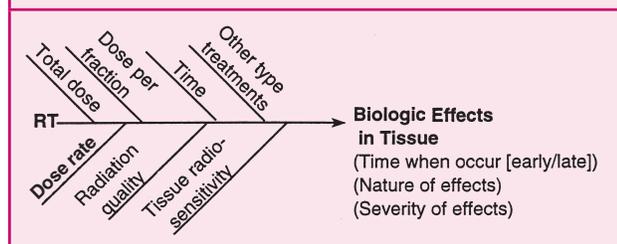
^aTD 5/5 = minimal tolerance dose; the dose, given to a population of patients under a standard set of treatment conditions, that will result in no more than a 5% rate of severe complications within five years after treatment.

^bTD 50/5 = maximal tolerance dose; the dose, given to a population of patients under a standard set of treatment conditions, that will result in a 50% rate of severe complications within five years after treatment.

Note. Based on information from Bentel et al., 1989; Rubin et al., 1975.

- c) Smoking: Can enhance some early and late side effects (Bentzen & Overgaard, 1994)
 - d) Tumor invasion: May interfere with normal tissue reactions
 - e) Infections: May increase normal tissue injury, especially when the immune system is compromised
2. Intrinsic radiosensitivity
- a) Genetic syndromes: Some are associated with increased sensitivity to RT (e.g., ataxia telangiectasia).
 - b) Autoimmune diseases (e.g., systemic lupus erythematosus)
- G. Considerations for radiation therapy
1. Diagnosis and staging: Tumor histology and extent of disease
 2. General condition of the patient and comorbid conditions
 3. Tumor site: Whether normal tissues are included in treatment fields
 4. Combination therapy (e.g., chemotherapy, hyperthermia, immunotherapy, biotherapy): The goal is to improve the therapeutic ratio relative to the use of a single modality of treatment (Hall & Cox, 1994).
 5. Available treatment facilities
- H. Radioresponsiveness of normal tissue (see Figure 9)
1. Expression of normal tissue injury varies greatly from patient to patient.
 2. Response of a tissue or organ primarily depends on the radiosensitivity of the cells and the

Figure 9. Factors Affecting Normal Tissue Radioresponsiveness



kinetics of the population in which the cells are functioning.

3. Treatment characteristics include total dose, dose per fraction or dose rate, and overall treatment time.
4. With combined-modality therapy (e.g., sequential or concomitant chemotherapy), interactions may substantially influence side effects of RT.

I. Side effects

1. Early side effects
 - a) Occur during or immediately after RT
 - b) Depend on total dose, dose per fraction, and overall treatment time (Bentzen, 1993)
 - c) Do not predict for late side effects
2. Late side effects
 - a) Occur months to years after RT and usually are the result of damage to the microcirculation
 - b) Depend highly on dose per fraction. High dose per fraction results in more severe late effects.
 - c) The time from RT to a specific late effect is the *latent period*.
 - d) Late injury expression is time dependent. The severity and percentage of patients expressing the injury increase overtime (Bentzen, 1993).

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