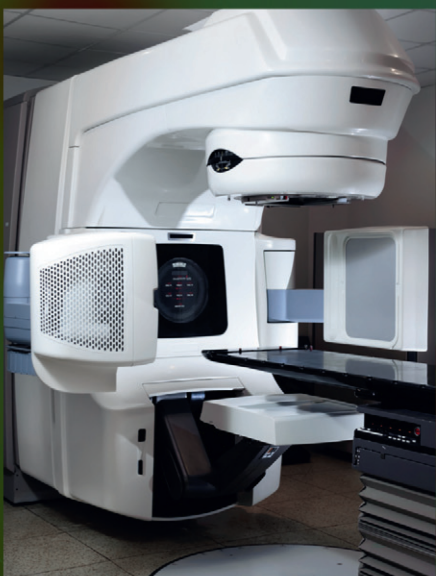
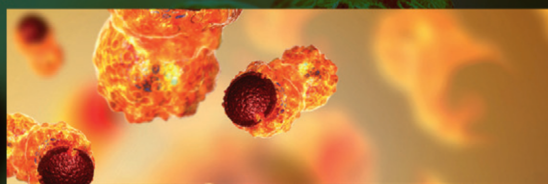
THIRD EDITION

FUNDAMENTALS OF RADIATION ONCOLOGY

PHYSICAL, BIOLOGICAL, AND CLINICAL ASPECTS





Hasan Murshed

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PHYSICAL, BIOLOGICAL, AND CLINICAL ASPECTS

THIRD EDITION

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Dedication

This book is dedicated to my children Ishraq and Ishmam.

*Their faces remind me every day that "may I always act so as to preserve the finest traditions of my calling and may I long experience the joy of healing those who seek my help."**

*—*Hippocratic Oath, Modern version, Louis Lasagna, MD, 1964*

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Foreword—James A. Bonner

Once again, Dr. Murshed has done an excellent job of producing an information-packed textbook that can be used in the day-to-day practice of radiation oncology. This new issue of *Fundamentals of Radiation Oncology* is an important compilation of the new and established literature that affects routine and complex decision-making in our clinics. Since the last edition of *Clinical Fundamentals for Radiation Oncologists*, there have been many new advances in radiation oncology. These advances have occurred in almost every disease site. This wealth of new information is difficult to summarize in a concise manner, but Dr. Murshed and all the contributors have artfully accomplished this goal. This edition is filled with crucial information for the busy practitioner.

Since the publication of the last edition, there have been breakthroughs in stereotactic radiosurgery, proton therapy, and immunotherapy to name just a few innovative areas. This textbook provides detailed information regarding new applications of radiotherapy, while still maintaining a strong backbone of basic principles of radiation oncology, radiobiology, and physics. The textbook creatively organizes and summarizes the major clinical trials, frequently using helpful tables, in each disease site.

It is also important to note that Dr. Murshed has substantially increased the number of contributing authors for this edition of the text. This edition includes contributions from 48 experts in the field. These experts have been able to encapsulate the major advances in a manner that highlights the most significant issues that frequently arise on a daily basis. This is the beauty of this textbook. It is also noteworthy that the contributors represent programs from all over the world and these authors provide a comprehensive perspective to radiation oncology care.

Therefore, Dr. Murshed has done a very thorough job of presenting the basic and detailed issues that are associated with all oncologic disease sites. He has made this information relevant for the daily practice of radiation oncology. Dr. Murshed has always had a strong interest in the educational aspects of our field. This fact was obvious during his residency at The University of Alabama at Birmingham. He has continued this interest over the past 20 years, and this updated version of *Fundamentals of Radiation Oncology* is a great testament to his commitment to our field. I believe that all radiation oncologists will find this textbook a "must have" in their armamentarium.

James A. Bonner, M.D.
Merle M. Salter Professor and Chairman
Department of Radiation Oncology
University of Alabama at Birmingham
Birmingham, Alabama, United States
June, 2018

Foreword—Thomas A. Buchholz

I would like to personally acknowledge and thank Dr. Hasan Murshed for providing our community with an outstanding Third Edition of the *Fundamentals of Radiation Oncology*. This comprehensive textbook includes 26 chapters authored by a variety of thought-leaders. It is unique in including chapter authors from around the world in addition to notable authorities in the United States.

The field of radiation oncology is rapidly changing, and this new edition provides a single source that captures the many conditions seen by radiation oncologists. In addition, it provides much of the foundational science behind the field of radiation oncology. Selected chapters are also dedicated to the importance of technique, including describing the role of newer proton techniques and the important evolving role of stereotactic treatments for intracranial and extracranial disease. Finally, exciting new materials are provided regarding the interactions of radiation oncology and immunotherapy, an area that is likely to significantly increase in importance over the next decade.

One hallmark that has impressed me about this textbook is its comprehensive content and ease of use. The structure and design allow for this book to use for an immediate reference or to address an immediate clinical question. However, it also serves as an outstanding comprehensive study guide for the field of radiation oncology.

I am sure that many will share my very high opinion of this impressive work. More importantly, I am sure that this textbook will help bring forward the many clinical and technical advances in radiation oncology to centers around the world, and in doing so, help raise the standard of care. On behalf of the radiation oncology community and the patients who benefit from their excellent care, I say thank you to Dr. Murshed and the nearly 50 contributing authors.

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La Jolla, California, United States
June, 2018

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Preface

Cancer management, specifically Radiation Oncology, has undergone ground breaking changes over the past several years. The AJCC 8th staging system has been implemented, and new tools for cancer diagnosis, and novel radiation modalities and techniques are now available. Most importantly, new studies and their associated data have led to rapid changes in recommendations for cancer treatment, requiring this third edition of *Fundamentals of Radiation Oncology*.

This new edition continues to provide current, concise, and a readily available source of clinical information for busy practicing radiation oncologists. The book consists of 26 chapters, divided into four parts.

Part I describes the basic science of radiation oncology, with discussions of radiation physics, radiation protection, and radiation biology, as well as molecular biology.

Part II describes techniques and modalities of radiation oncology including brachytherapy, intensity-modulated radiation therapy (IMRT), stereotactic radiotherapy (SRS), stereotactic body radiation therapy (SBRT), and proton therapy. Significant recent advances made in the areas of immunotherapy and combined modality therapy; as such, these chapters have also been added to this new edition.

Part III describes the clinical science of radiation oncology including risk factors, symptoms/signs, and investigations needed for the cancer diagnosis and up-to-date treatment recommendations in accordance with the new AJCC staging system. In addition, radiation treatment techniques, with an emphasis on IMRT, have been expanded to all the chapters. Also included in this version of the book is a chapter on benign diseases. Updated annotated bibliographies of latest landmark studies providing evidence-based rationale for the recommended treatments are presented at the end of each chapter.

Part IV describes palliative radiation treatments to improve the quality of life for cancer patients and the management of side effects from radiation treatment.

This updated edition was made possible through an international collaboration of contributing authors from Australia, Canada, India, Turkey, United Kingdom, and United States. I am immensely indebted to all of the contributing authors; without their assistance, this book would not be. I am especially grateful to Ugur Selek, M.D., who contributed several chapters to this edition. I am also thankful for his continuing friendship over the past 16 years.

In addition, I sincerely thank all of the excellent reviewers of this book for their thoughtful input in updating the clinical chapters. Finally, I wish to thank Tracy Tufaga, Rafael Teixeira and Poulouse Joseph at Elsevier for their commitment to excellence and expert editorial contribution to this book.

May this updated edition provide you, the reader, the best knowledge, excellent skills, and the compassion to "*cure sometimes, treat often, comfort always.*"*

Hasan Murshed, M.D.
June 2018

*Hippocrates Asclepiades (460 BC−370 BC).

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PART I

BASIC SCIENCE OF RADIATION ONCOLOGY

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CHAPTER

1

Radiation Physics, Dosimetry, and Treatment Planning

Wilhelm Roentgen discovered X-rays in 1895 while experimenting with a gas-filled cathode tube; Henri Becquerel discovered radioactivity in 1896 while experimenting with uranium salts. Soon after these discoveries, radiation was used to treat cancer and other diseases. To effectively use radiation, it is important to understand its basic properties, which are addressed in this chapter.

FUNDAMENTAL PHYSICAL QUANTITIES

Mass, energy, charge, and force all have key roles in radiation physics.

Mass

Mass is the amount of matter within any physical object. Mass is measured as weight and the standard international (SI) unit of mass is the kilogram (kg), represented by a lump of platinum–iridium alloy kept in Paris, France. In the much smaller realm of atomic physics, weights are expressed as atomic mass units (amu or u). An amu is equivalent to 1/12th the mass of one atom of carbon (C^{12} isotope).

Einstein's theory of relativity ($E = mc^2$) suggests that mass (m) can be converted into energy (E), as a function of the speed of light squared (c^2). One amu of mass is converted into 931 MeV of energy. The mass of a moving object, its "relativistic mass," is larger than its mass at rest because the kinetic energy associated with its motion adds to the resting mass.

Energy

Energy is the ability of a system to perform work. There are two types of energy—potential energy and kinetic energy. One electron volt (eV) is the energy acquired by an electron when it moves across a potential of 1 V. One million electron volts are designated by MeV.

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Charge

Electric charge is the property of matter that causes it to experience a force in the presence of an electromagnetic field. Charges are positive or negative with an electron being the smallest unit of negative charge (−1) and the proton being the smallest unit of positive charge (+1). The SI unit of charge is the Coulomb (6.25×10^{18} elementary charges).

Force

A force is an interaction that can change the direction or velocity of an object. Coulomb force (electromagnetic force) is the force between two charged bodies. Protons and electrons are held together by the Coulomb force. Gravitational force is the attraction between two masses. It is a very weak force unless the masses are very large, like the earth or the sun. Strong force holds particles together in the atomic nucleus (protons, neutrons, and quarks), is the strongest known fundamental physical force, but only acts over atomic distances. Weak force is the force that is responsible for particle decay processes (beta decay) and is approximately one-millionth of the strong force.

ATOMIC STRUCTURE

The atom consists of three fundamental particles: protons, neutrons, and electrons. The particles are bound together by the abovementioned four fundamental forces.

Atomic Models

In the Rutherford model of the atom, protons and neutrons reside in the center (nucleus), whereas electrons revolve around the nucleus in circular orbits. The Bohr model of the atom introduced four refinements to the Rutherford model.

1. Electrons can only occupy certain discrete orbits while revolving around the nucleus.
2. When electrons are in stationary orbits, they do not emit radiation as predicted by classical physics.
3. Each stationary orbit has a discrete energy associated with it.
4. Radiation is only emitted whenever an electron moves from a higher orbit to a lower orbit, and radiation is absorbed whenever an electron moves from a lower orbit to a higher orbit.

Electron Binding Energy

Because negative electrons are bound to the positive nucleus by the Coulomb force, it requires a certain amount of energy to remove an electron from the atom. This energy is called "ionization energy."

Atomic Shell Filling Rules

Electron shells are labeled from the nucleus outward either by the letters K, L, M, N… or by the numbers 1, 2, 3, 4… (principal quantum numbers, n). The maximum number of electrons allowed in a given atomic shell is given by:

Maximum number of electrons in a given shell $= 2n^2$ where n is the principal quantum number.

Characteristic Radiation

When an electron acquires enough energy from an incident photon to leave an inner orbit of the atom, a vacancy is created in that shell, which is immediately filled by an outer shell electron, emitting the excess energy as a photon. This photon is a "characteristic X-ray."

Auger Electrons

The characteristic X-ray can leave the atom or it can displace an outer shell electron. The displaced electron is called as "Auger electron," and its kinetic energy is equal to the energy of the characteristic X-ray that displaced it minus the energy required to remove the electron from its shell.

Nuclear Binding Energy

The particles contained in the nucleus are bound together by the strong and the weak nuclear forces discussed above. The mass of a nuclide is always less than the mass of the constituent components. This deficiency of mass is called the mass defect. The energy required to separate the nucleus into its constituent particles is called the nuclear binding energy. It can be computed using Einstein's equation.

NUCLEAR STRUCTURE

Atoms are identified by their atomic symbols $^{A}_{Z}X$, where X is the atomic symbol, A is the mass number (number of protons plus neutrons), and Z is the atomic number (number of protons). The number of neutrons (N) in an atom can be determined by the equation $N = A - Z$.

Special types of nuclei are defined as follows:

- **Isotopes:** Isotopes are atoms that have the same number of protons (Z), but a different number of neutrons (A − Z). Examples of two isotopes are $^{12}_{5}C$ and $^{14}_{6}C$.
- **Isobars:** Isobars are atoms with nuclei that have the same number of total particles (A), but a different number of protons (Z) and neutrons (A − Z). Example of isobars are $^{40}_{19}K$ and $^{40}_{20}Ca$.
- **Isotones:** Isotones are nuclides that have the same number of neutrons (A − Z) and a different number of protons (Z). Examples of isotones are $^{14}_{6}C$ and $^{15}_{7}N$.
- **Isomers:** Isomers are atoms with nuclei that have the same number of total particles (A) and the same number of protons (Z), but different levels of energy in the nucleus. Examples of isomers are $^{99}_{43}Tc$ and $^{99m}_{43}Tc$.

RADIOACTIVE DECAY

Radioactivity is the process by which an unstable nucleus is transformed by giving off the excess energy and forming a new stable element. The transformation may involve the emission of electromagnetic radiation or emission of particles, involving mechanisms such as beta decay, alpha decay, or isomeric transitions. Examining the ratio of neutrons to protons in all stable nuclei, the following conclusions can be made (see Fig. 1.1):

If Z is less than or equal to 20, the ratio of neutrons to protons is 1.

If Z is greater than 20, the ratio becomes greater than 1 and increases with Z.

As more protons are added to the nucleus, the effects of the Coulomb force begin to overwhelm the strong nuclear forces, which can make an atom unstable. This unstable nucleus will tend to lose energy by different decay mechanisms, described in the next section, to reach a more stable state.

MODES OF RADIOACTIVE DECAY

Alpha Decay

Radionuclides that have a Z greater than 82 are decayed most frequently by the emission of a helium nucleus, or alpha particle (α). The alpha particle is identical to the nucleus of a helium atom, ${}_{2}^{4}He$.

Beta Decay

By this process, a radioactive nucleus emits either an electron or a positron. There are two types of beta decay: β^- (beta minus or negatron emission) and β^+ (beta plus or positron emission).

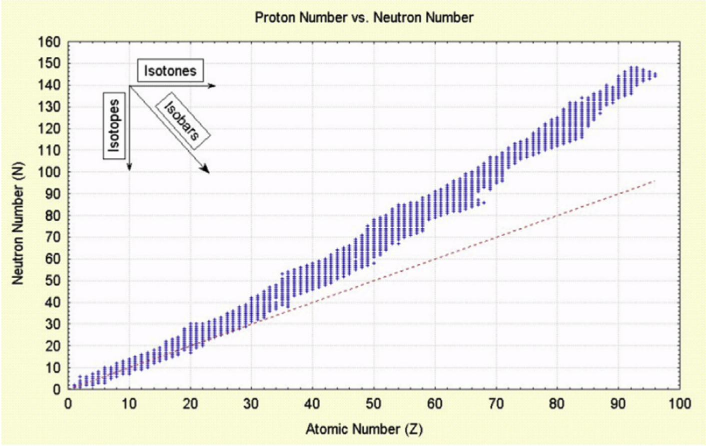

FIGURE 1.1 Neutron versus proton in stable nucleus.