Physics of Nuclear Oncology

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Contents

Abstract

The study of the basic physics used in nuclear oncology involves understanding the way energy associated with radioactive emissions can be best utilized to image, diagnose, stage, treat, and monitor the patient with cancer. In this chapter we will cover the physics involved in these processes.

Keywords

Physics • Radionuclides • Imaging • Therapy

Glossary

AAPM	American Association of Physicists in Medicine
Bq	Becquerel unit
Bremsstrahlung	Braking radiation
DOTA	1,4,7,10-Tetra-azacyclododecane-1,4,7,10-tetraacetic acid
DOTATE	DOTA-octreotate
e	Electron
E	Energy
EC	Electron capture
eV	Electron volt
Gy	Gray unit
h	Planck's constant
HCC	Hepatocellular carcinoma
IC	Internal conversion
ICRP	International Commission on Radiological Protection

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ICRU	International Commission on Radiation Units and Measurements
IT	Isomeric transition
J	Joule
keV	Kilo-electron volt (10^3 eV)
LET	Linear energy transfer
m	Metastable
MeV	Mega-electron volt (10^6 eV)
MIRD	Medical Internal Radiation Dose Committee
n	Neutron
p	Proton
PET	Positron emission tomography
PSMA	Prostate-specific membrane antigen
SI	International System of Units
α	Alpha particle
β	Beta particle
γ	Gamma radiation
λ	Decay constant
λ	Wavelength of a radiation
ν	Neutrino
σ	Atomic cross section
υ	Frequency of a radiation

Structure of the Atom

To describe nuclear processes and the energy associated with radioactive decay, we will make use of a simple conceptual model of the atom. At the turn of the twentieth century, soon after the discovery of natural radioactivity and the first production of X-rays, the British physicist Lord Rutherford proposed a model for the atom similar to that used to describe the orbit of the planets of the solar system about the sun (the "planetary" model, see Fig. 1). The Rutherford model had a central positive core, the nucleus, about which a cloud of electrons circulated. It predicted that most of the space in matter was unoccupied (thus allowing particles and electromagnetic radiation to pass through, as had been observed experimentally). The Rutherford model, however, presented a problem because classical

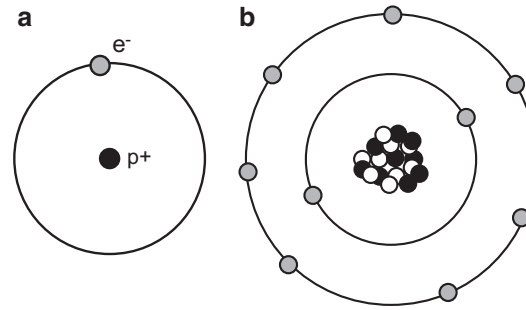

Fig. 1 Examples of the planetary model of the atom are shown for (**a**) hydrogen (^1_1H) and (**b**) fluorine-18 ($^{18}_9F$). Protons are indicated by the *solid circles*, neutrons by the hollow *circles*, and circulating electrons by the *gray circles*

physics predicted that the revolving electrons would emit energy continuously, resulting in a spiraling of the electrons into the nucleus. In 1913, Niels Bohr introduced the constraint that electrons could only orbit at certain discrete radii, or energy levels, and that in turn only a small, finite number of electrons could exist in each energy level. Most of what was required to understand the subatomic behavior of particles was now in place. This is referred to as the Bohr (planetary) model of the atom. Later in 1932, the neutron was proposed by James Chadwick as a large particle roughly equivalent to the mass of a proton, but without any charge, that also existed in the nucleus of the atom.

We shall continue to use this basic model of the atom for much of our discussion. The model breaks down in the realm of quantum mechanics, where Newtonian physics and the laws of motion no longer apply, and particles approach relativistic speeds (i.e., approaching the speed of light). Also, there are times when we must invoke a non-particulate model of the atom where the particles need to be viewed as waves (or, more correctly, *wave functions*). Electrons, for example, can be considered at times to be waves. This helps to explain how an electron can pass through a "forbidden" zone between energy levels and appear in the next level without apparently having passed through the forbidden area, defined as a region of space where there is zero probability of the existence of an electron. It can do so if its wave function

is zero in this region. For a periodic wave with positive and negative components, this occurs when the wave function takes a value of zero. Likewise, electromagnetic radiation can be viewed as particulate at times and as a wave function at other times. The planetary model of the atom is composed of nucleons (protons and neutrons in the nucleus of the atom) and circulating electrons. It is now known that these particles are not the fundamental building blocks of matter but are themselves composed of smaller particles called *quarks*.

Energy and Mass

Energy and Frequency

In 1900 Max Planck made the important observation that the energy (E) of electromagnetic radiation was simply related to the frequency of the radiation (υ) by a single constant (Planck's constant, h):

$$E = h\upsilon$$

Planck's constant has a value of 6.626×10^{-34} $J.s$. This provided support to the notion that electromagnetic radiation behaved like a wave. In addition, experiments indicated that the radiation was only released in discrete "bursts." This was a startling result as it departed from the classical assumption of continuous energy to one in which electromagnetic radiation could only exist in integral multiples of the product of $h\upsilon$. The wave-like radiation was said to be quantized, where each quantum contained an amount of energy that was an integer multiple of $h\upsilon$. The unit of energy in the SI system is the Joule (J); however, a derived unit used frequently in discussions of the energy of electromagnetic and particulate radiation is the electron volt (eV). The electron volt is defined as the energy acquired when a unit charge is moved through a potential difference of one volt. Energy in Joules can be converted to energy in electron volts (eV) by dividing by the conversion factor $1.6 \times 10^{-19}\text{J.eV}^{-1}$. Thus the energy in Joules for visible light photons of, for example, 450 nm would be:

$$E = h\upsilon = \frac{hc}{\lambda} = \frac{6.63 \times 10^{-34} J.s \times 3 \times 10^{8} m.s^{-1}}{450 \times 10^{-9} m} = 4.42 \times 10^{-19} J$$

which can be expressed in units of eV as:

$$E = 4.42 \times 10^{-19} J \equiv \frac{4.42 \times 10^{-19} J}{1.6 \times 10^{-19} J.eV^{-1}} = 2.76\, eV$$

X-rays and gamma rays have energies of thousands to millions of electron volts per photon (keV–MeV).

Energy and Mass

Einstein's special theory of relativity published in 1905 predicted, among other things, that the speed of light was constant for all observers independent of their frame of reference (and therefore that time was no longer constant) and, importantly, that mass and energy were *equivalent*. This means that we can talk about the rest-mass equivalent energy of a particle, which is the energy that would be liberated if all of the mass were to be converted to energy. By rest mass we mean that the particle is considered to be at rest, i.e., it has no kinetic energy. Consider the electron, which has a rest mass of 9.11×10^{-31}kg; we can calculate the amount of energy this mass is equivalent to using Einstein's equation:

$$\begin{aligned} E &= mc^2 \\ &= 9.11 \times 10^{-31} kg \times \left(3 \times 10^{8}\right)^2 m.s^{-1} \\ &= 8.2 \times 10^{-14} J \\ &\equiv 8.2 \times 10^{-14} J / 1.6 \times 10^{-19} J.eV^{-1} \\ &= 511\ keV \end{aligned}$$

The reader may recognize this as the energy of the photons emitted in positron–electron annihilation.

Radioactivity and Radiation

Radiation can be classified into electromagnetic or particulate. Ionizing radiation is radiation that has sufficient energy associated with it to remove electrons from atoms, thus causing ionization. This

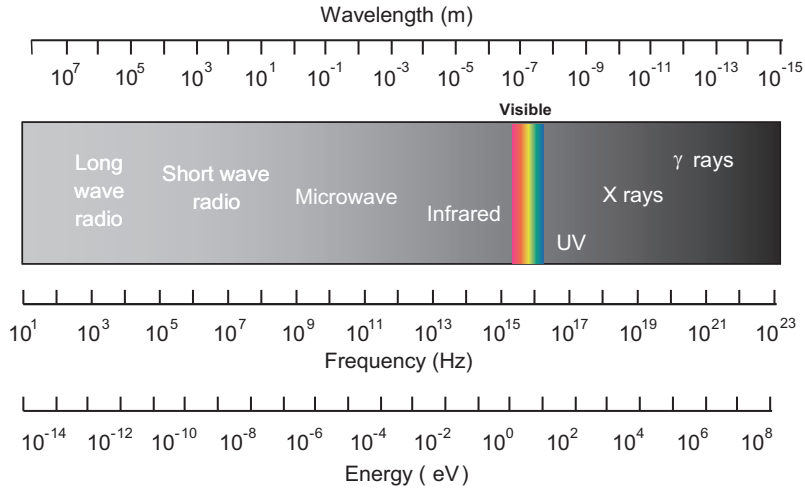

Fig. 2 The electromagnetic spectrum showing energy in units of eV

is restricted to high-energy electromagnetic radiation (X- and γ-radiation) and charged particles (α, β^-, β^+). Examples of non-ionizing electromagnetic radiation include light, radio, and microwaves (see Fig. 2). We will concern ourselves specifically with ionizing radiation as this is of most interest in nuclear medicine and radiological imaging.

Electromagnetic Radiation

Electromagnetic radiation is pure energy. The amount of energy associated with each "bundle," or quantum, of energy is determined by the frequency or wavelength (λ) of the radiation. Human senses are capable of detecting some forms of electromagnetic radiation, for example, thermal radiation, or heat, ($\lambda \approx 10^{-5}$m), and visible light ($\lambda \approx 10^{-7}$m). The energy of the radiation can be absorbed to differing degrees by different materials: light can be stopped (absorbed) by paper, whereas radiation with longer wavelength (e.g., radio waves) or higher energy (γ-rays) can penetrate the same paper.

It had long been known that light acted like a wave, most notably because it caused interference patterns from which the wavelength of the light could be determined. Radiation was thought to emanate from its point of origin like ripples on the surface of a pond after a stone is dropped into it. This concept was not without its difficulties, most notably, the nature of the medium through which the energy was transmitted. This proposed medium was known as the "ether," and many experiments sought to produce evidence of its existence to no avail. Einstein, however, interpreted some experiments performed at the turn of the twentieth century where light shone on a photocathode could induce an electric current (known as the *photoelectric effect*) as showing that light acted as a particle. Einstein proposed that radiant energy was quantized into discrete packets, called photons. Thus, electromagnetic radiation could be viewed as having wave-like and particle-like properties. This view persists to this day and is known as the wave-particle duality. In 1924 Louis Victor, the duc de Broglie, proposed that if wave-particle duality could apply to electromagnetic radiation, it could also apply to matter. It is now known that this is true: electrons, for example, can exhibit particle-like properties such as when they interact like small billiard balls or wave-like properties as when they undergo diffraction. Electrons can pass from one position in space to another, separated by a "forbidden zone" in which they cannot exist, and one way to interpret this is that the electron is a wave that has zero amplitude within the forbidden zone. The electrons could not pass through these forbidden zones if viewed strictly as particles. An important subsequent postulate proposed by Niels Bohr was that de Broglie's principle of wave-particle duality was complementary. He stated that either the wave or the particle view can be taken to

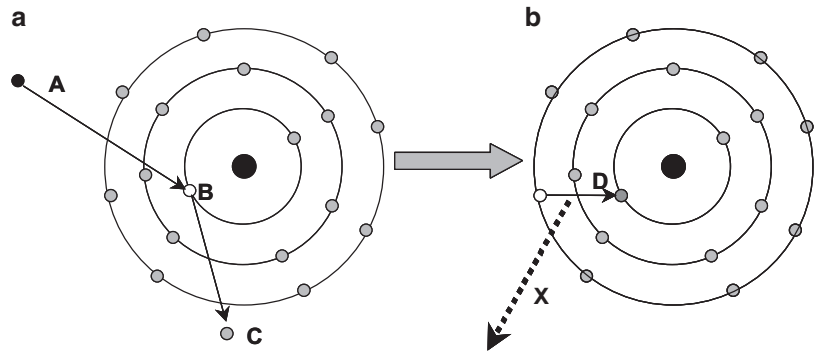

Fig. 3 The production of characteristic X-rays is shown. The electron (*A*) causes a vacancy at *B* with the liberated electron (*C*) leaving the atom. An outer-shell electron (*D*) drops down to fill the vacancy and, in doing so, gives off a discrete amount of radiation as a characteristic X-ray

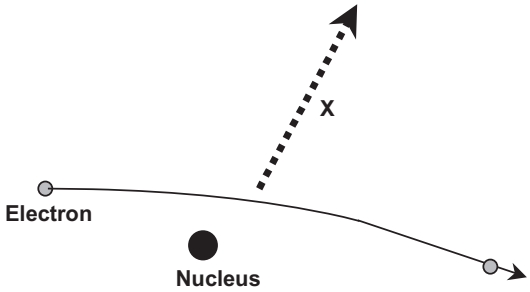

Fig. 4 Continuous radiation emitted by an electron under the influence of the nucleus is known as Bremsstrahlung

explain physical phenomena, but not both at the same time.

Electromagnetic radiation has different properties depending on the wavelength, or energy, of the quanta. Only higher-energy radiation has the ability to ionize atoms, due to the energy required to remove electrons from atoms. Electromagnetic radiation which can cause ionization is restricted to X- and γ-rays, which are discussed in the following sections.

X-Rays

X-rays are electromagnetic radiation produced within an atom, but outside of the nucleus. Characteristic X-rays are produced when orbital electrons drop down to fill vacancies in the atom after an inner-shell electron is displaced, usually by firing electrons at a target in a discharge tube. As the outer-shell electron drops down to the vacancy, it gives off energy and this is known as a characteristic X-ray as the energy of the X-ray is determined by the difference in the binding energies between the electron levels (see Fig. 3).

As any orbital electron can fill the vacancy, the quanta emitted in this process can take a number of energies. The spectrum is characteristic, however, for the target metal and this forms the basis of quantitative X-ray spectroscopy for sample analysis. The spectrum of energies emerging in X-ray emission displays a continuous nature, however, and this is due to a second process for X-ray production known as *Bremsstrahlung* (German: "braking radiation"), as shown in Fig. 4.

Bremsstrahlung radiation is produced after a free electron with kinetic energy is decelerated by the influence of a heavy target nucleus. The electron and the nucleus interact via a Coulomb (electrostatic charge) interaction, the nucleus being positively charged and the electron carrying a single negative charge. The process is illustrated in Fig. 6. The electron loses kinetic energy after its deceleration under the influence of the target nucleus, which is given off as electromagnetic radiation. There will be a continuum of quantized energies possible in this process depending on the energy of the electron, the size of the nucleus, and other physical factors, and this gives the continuous component of the X-ray spectrum.

X-rays generally have energies in the range of $\sim 10^3$–10^5 *eV* and can be used for imaging as well as therapy.

Gamma Radiation (γ)

Gamma rays are electromagnetic radiation emitted from the nucleus after a spontaneous nuclear

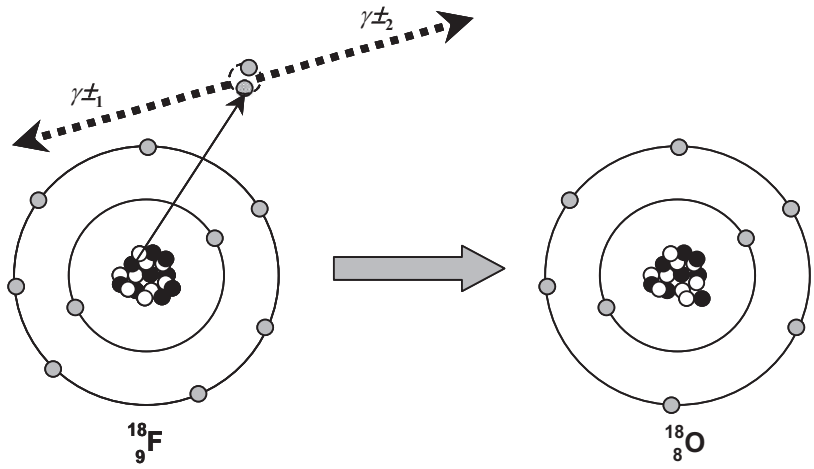

Fig. 5 The radioactive decay of ^{18}F by positron emission is shown. The emitted positron annihilates with an electron in the surrounding environment, and two annihilation photons (γ±) are emitted

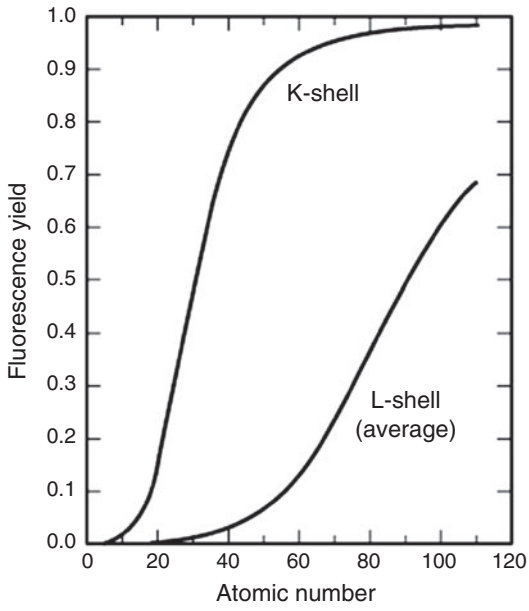

Fig. 6 Fluorescence yield of Auger electrons from the K and L shells is shown as a function of atomic number

decay. This is usually associated with the emission of an alpha or beta particle although there are alternative decay schemes. X- and γ-rays are indistinguishable after they are emitted from the atom and only differ in their site of origin. After the emission of a particle in a radioactive decay, the nucleus can be left in an excited state and this excess energy is given off as a γ-ray.

Gamma ray emission is characteristic, and it is determined by the difference in energy levels between the initial and final states of the energy level transitions within the nucleus.

Annihilation Radiation (γ±)

Annihilation radiation is the energy produced in the form of photons (usually two) by the positron–electron annihilation process. The energy of the radiation is equivalent to the rest mass of the electron and positron. Annihilation radiation, arising from positron–electron annihilation, is produced outside of the nucleus and often outside of the positron-emitting atom. There are two photons produced by each positron decay and annihilation. Each photon has energy of 0.511 MeV, and the photons are given off at close to 180° opposed directions (see Fig. 5). It is this property of collinearity that we exploit in positron emission tomography (PET), allowing us to define the line of sight of the event without the need for physical collimation. The general equation for β^+ decay is:

$$ {}^{A}_{Z}X \rightarrow {}_{Z-1}{}^{A}Y \; + \; \beta^{+} $$

Particulate Radiations

Particle emission from radioactive decay was the first observation of natural radioactivity. Wilhelm Röntgen had produced X-rays in 1896, and a year

later, Henri Becquerel showed that naturally occurring uranium produced radiation spontaneously. While the radiation was thought initially to be similar to Röntgen's X-rays, Lord Rutherford showed that some types of radiation were more penetrating than others. He called the less penetrating radiation alpha (α) rays and the more penetrating ones beta (β) rays. Soon after, it was shown that these radiations could be deflected by a magnetic field, i.e., they carried charge. It was clear that these were not electromagnetic rays and were, in fact, particles.

Alpha Radiation (α)

Alpha particles are emitted from large nuclei, often as part of a radioactive series (e.g., thorium series, radium series). An α-particle consists of two protons and two neutrons and thus is identical to a doubly ionized helium atom. For this reason it is often written as ${}_2^4He^{2+}$. Alpha decay results in a daughter nuclide with an atomic number of 2 less than the parent nuclide and a mass number of 4 less. The equation for α decay is:

$$ {}_Z^AX \rightarrow {}_{Z-2}^{A-4}Y + {}_2^4He^{2+}(\alpha \text{ particle}) + \gamma $$

Over the last several years, researchers have taken an interest in the use of α-particle-emitting radionuclides attached to tumor-specific targeting agents, such as antibodies. The advantage of α-particles for targeted radionuclide therapy is their high energy (5–9 MeV) and short range (50–90 μm) resulting in a high density of local energy deposition close to the decay site. Therefore α-emitters are especially suited to the treatment of disseminated cancers such as leukemias or micrometastatic disease. In addition, the high rate of the energy loss per unit track length, referred to as the linear energy transfer (LET), results in a greater radiobiological effectiveness of cell kill for α-particles relative to β-s and photon (low LET) radiations. Radiation dose estimates to normal tissues for α-particle-emitting radionuclides can be made (if imaging data resulting from concomitant X- or γ-rays emitted have been obtained) using the medical radiation dose committee (MIRD) assumption of total local absorption for non-penetrating radiations. However, the calculated organ and tissue doses need to be accepted with the following caveats: (i) at low doses the stochastic nature of energy deposition must be considered, i.e., an average dose of 0.2 Gy is the consequence of a Poisson distribution of cellular hits in which some cell nuclei receive α-particle hits, while others receive no hits; (ii) the microdistribution of the agent may be non-homogenously distributed with respect to the biological organ or structure, e.g., radium bone-seeking agents may deposit on bone surfaces, leading to high doses at the marrow–bone interface with zero dose to the central marrow regions; and (iii) the selective uptake or accumulation of α-emitters to cells can result in local doses that greatly exceed the average tissue dose.

Although not common, α-particle-emitting radionuclides have begun to be employed in the clinic. Current indications include ^{213}Bi (and ^{225}Ac)-labeled M195 antibody against leukemia, [^{211}At]-anti-tenascin antibody against brain tumors, [^{211}At]-methylene blue for melanoma, and, perhaps most importantly, the recent approval in Europe and the USA of $^{223}RaCl_2$ (Xofigo®) as a therapy for bone metastases in patients with castrate-resistant prostate cancer. Radium, as a calcium analog, localizes in regions of bone remodeling, frequently the sites of metastatic disease. The extremely short range (<80 μm) of the α-emissions mean that the radiation dose is highly locally deposited, killing cancer cells residing at the bone surfaces, yet sparing hematopoietic stem cells, many of which are located deeper within the marrow spaces and beyond the range of the alpha radiation dose.

Beta Radiation (β^-)

Beta decay is any process in which the nuclear charge changes by one. This includes β^-, β^+, and electron capture decays. Beta-minus particles are emitted from nuclei which have an excess of neutrons and are done in an attempt to approach the line of nuclear stability in terms of the relative number of protons and neutrons within the atomic nucleus. A β^- particle consists of an electron ejected from the nucleus after a neutron is converted into a proton. The β^- is ejected so that charge is conserved during this transformation.

Beta-minus decay results in a daughter nuclide with an atomic number of 1 greater than the parent nuclide and a mass number which is unchanged. Beta-minus particles have a continuous range of energies up to a maximum. This appeared at first to be a violation of the conservation of energy. To overcome this problem, in 1931 Wolfgang Pauli proposed that another particle was emitted which he called the neutrino (ν). He suggested that this particle had a very small mass and zero charge. It could carry away the excess momentum to account for the difference between the maximum beta energy and the spectrum of energies that the emitted beta particles displayed. In fact we now refer to the neutrino emitted in beta-minus decay as the antineutrino, indicated by the "¯" over the symbol ν.

The equation for β^- decay is

$$ {}^{A}_{Z}X \rightarrow {}_{Z+1}{}^{A}Y + \beta^- \quad + \overline{\nu} $$

The nucleus of the daughter nuclide is often left in an excited state with excess energy, and therefore this energy is often emitted in the form of a gamma ray after β^- decay.

The following shows an example of a beta-decay scheme for ^{131}I:

$$ {}^{131}_{53}I \rightarrow {}^{131}_{54}Xe + {}_{-1}{}^{0}\beta^- + \gamma + \overline{\nu} $$

The half-life for ^{131}I decay is 8.02 days. The most abundant β^- particle emitted has a maximum energy of 0.606 MeV, and there are many associated γ-rays, the most abundant (branching ratio = 0.81) having an energy of 0.364 MeV.

β^- Dosimetry

The most commonly used radionuclide for nuclear medicine therapies is ^{131}I, which is used for the treatment of a variety of thyroid disorders, benign and malignant, as well as for a several therapeutic radiolabeled antibody therapies such as ^{131}I-tositumomab (Bexxar®) for the treatment of follicular, non-Hodgkin's lymphoma. The pure β^- emitter ^{90}Y has also become routinely used for radioimmunotherapy applications, e.g., ibritumomab tiuxetan (Zevalin®), for the treatment of B-cell non-Hodgkin's lymphoma. The use of ^{90}Y-resin microspheres (SIR-Spheres®) has also become used as a new intra-arterial therapy for the treatment of hepatocellular carcinoma (HCC) and other diseases metastatic to liver. An advantage of ^{90}Y is the extremely low yield of penetrating photon emissions (only Bremsstrahlung radiation) facilitating the handling of large activities and resulting in lower radiation exposures to personal within proximity of the patients. However, the lack of photons for imaging can be a disadvantage when using ^{90}Y radiopharmaceuticals, and therefore to verify safety of delivery, protocols usually incorporate a pre-scan using the ^{111}In-labeled agent. Another β^--emitting radionuclide in increasing clinical use is ^{188}Re. This radionuclide has the advantage that it is produced from a tungsten-188 generator system, making it more readily available for use in developing nations, without access to radionuclide production facilities. ^{188}Re-lipiodol is an alternative to ^{90}Y-microspheres for the treatment of HCC and has the advantage of allowing imaging (using the 155 keV γ – 15% abundance)-based treatment planning. The average β^--emission energy is high at 795 keV, comparable to the 935 keV of ^{90}Y.

The dose versus distance for a point source of beta particles obeys the relationship first described by Loevinger [1], which consists of an inverse square geometric term and a power term to account for absorption. The dose from a point source therefore falls more sharply than the inverse square law. However, for distributed sources as in most medical applications of radiopharmaceuticals employing β^- sources, the dose is assumed to be uniform within most organ structures. The MIRD methodology classifies all β^- particles as non-penetrating radiations that are deposited locally within the source organ, i.e., cross fire between different organs is considered to be negligible. A detailed discussion of the heterogeneity of β^--emitting radiopharmaceuticals and the dosimetric implications is provided in ICRP Report 67 [2].

Positron Decay (β^+) and Electron Capture (EC)

A proton-rich radionuclide has two options for converting a proton into a neutron in an attempt

to reach the line of stability: (i) positron decay and (ii) electron capture. Positron emission from the nucleus is secondary to the conversion of a proton into a neutron as in:

$$ {}_1^1p^+ \rightarrow {}_0^1n + {}_1^0\beta^+\nu $$

with in this case a neutrino being emitted. The positron is the antimatter conjugate of the electron emitted in beta-minus decay.

The general equation for β^+ decay from an atom is

$$ {}_Z^AX \rightarrow {}_{Z-1}^AY + {}_1^0\beta^+ + \nu $$

The atom X is proton rich and achieves stability by converting a proton to a neutron. The positive charge is carried away with the positron. As the daughter nucleus has an atomic number one less than the parent, one of the orbital electrons must be ejected from the atom to balance charge. This is often achieved by a process known as internal conversion, where the nucleus supplies energy to an orbital electron to overcome the binding energy and leave it with residual kinetic energy to leave the atom. As both a positron and an electron are emitted in β^+ decay, the daughter nucleus must be at least two electron masses lighter than the parent.

The β^+ will have an initial energy after emission, which, similar to the case of beta-minus decay, can take a continuum of values up to a maximum. After emission from the nucleus, the β^+ loses kinetic energy by interactions with the surrounding matter.

The competing process, electron capture, occurs when an electron passing in the vicinity of the nucleus is "captured" by the nucleus and combined with a proton to produce a neutron. This has the same effect as positron emission, i.e., that a proton is converted into a neutron. This process, which in many proton-rich radionuclides competes with positron emission, may occur in a significant fraction of nuclear transformations. Many β-emitting tracers involve a competition in which a fraction of the decays occur by each process. For example, ^{18}F decays 96.9% by β^+ emission and 3.1% by electron capture. It is important to note that it is an advantage for β^+ emitters used for PET functional imaging to have shorter half-life to minimize the radiation dose to the patient. However, for applications in which tumor-specific macromolecules such as antibodies that exhibit both slow blood clearance and tumor uptake are employed, long-lived PET radionuclides are mandatory, examples of which are ^{124}I (4.2 days half-life) and ^{89}Zr (3.3 days half-life). These diagnostic PET radionuclides can result in a radiation dose burden to a patient per unit administered activity, which is similar to ^{131}I, the β^- emitter commonly used for therapeutic applications. This places significant restraints on the multiplicative usage of radioimmuno-PET and is a major impetus in the rapid interest in tumor-targeting peptides, whose rapid blood clearance allows the use of short-lived PET radionuclide such as ^{68}Ga; examples include DOTATATE which binds to somatostatin receptors and ^{68}Ga-binding PSMA peptides.

Several of the radionuclides most widely employed in nuclear medicine are those which decay exclusively by electron capture such as ^{67}Ga, ^{123}I, and ^{201}Tl. The equation for electron capture (EC) is

$$ {}_Z^AX + e^- \rightarrow {}_{Z-1}^AY + \nu $$

From the dosimetric perspective, such radionuclides have been preferred because instead of high-energy β^- emissions, they emit very low-energy X-ray and particulate emissions called Auger and Coster–Kronig electrons.

Auger Electrons

Auger electrons are emitted as a consequence of atomic relaxation after the electron captured by the nucleus leaving the atom with an inner-shell atomic electron shell vacancy. Most commonly we learn that any inner shall vacancy is rapidly filled by an electron transition from a higher orbital, thereby resulting in a characteristic X-ray of energy equal to the difference between the binding energies of the two electron shells (E_{b1}–Eb_2). However, this same energy can be instantaneously transferred to an additional

outer-shell orbiting electron of binding energy E_{b3}, which is ejected with energy equal to $(E_{b1}–E_{b2}) – E_{b3}$. Electrons emitted from the atom in this way are referred to as either Auger electrons or Coster–Kronig electrons if the ejected electron emanates from the same orbital as the electron involved in the transition to fill the initial inner-shell vacancy. Electrons are classified by the electron shells involved. For example, an Auger electron could be K–L–M, which would mean that the initial vacancy arose in the K shell was filled by an electron from the L shell resulting in an electron ejected from the M shell (see Fig. 6). Since Auger and Coster–Kronig electrons are the consequence of transitions between electron orbitals, they have discrete energies (unlike β^- particles) which are emitted as an energy spectrum. The energies of Auger and Coster–Kronig electrons range from that just below the characteristic X-ray energies to a few electron volts. The ranges of these electrons are mostly submicron.

The fraction of initial inner-shell vacancies filled by radiative or fluorescent transitions, i.e., with characteristic X-ray emission, relative to the total radiative and non-radiative (Auger) is given by the fluorescent yield. The fluorescent yield decreases with increasing atomic number. This means that radiative transitions for high-Z radionuclides, e.g., ^{201}Tl, the filling of a K-shell vacancy is almost always by radiative transition. However, such transitions are mostly K–L transitions, moving the vacancy to the L shell. Since the fluorescent yield for the L shell is small, these vacancies as well as subsequent to higher shells are mostly non-radiative. A consequence of non-radiative transition is a cascade of inner-shell electron transitions (and Auger electron emission) until all vacancies have reached the outermost atomic shell. Therefore the number of Auger and Coster–Kronig electrons increases with increasing atomic number of the radionuclide.

The total energy emitted during the atomic de-excitation is shared between the Auger and Coster–Kronig electrons and fluorescent X-ray photons emitted. Since the total energy emitted is small, it has often been disregarded in organ and total body dosimetry estimates. In general the dose contribution from Auger and Coster–Kronig electrons is extremely small, hence the appropriate selection of electron capture (and isomeric transition – see later) decaying radionuclides for imaging purposes. However, under specific circumstances, the cascade of soft electrons emitted as a consequence of electron capture decay can produce high-LET-like biological effects. This was first observed in experiments in which the electron capture decaying radionuclide ^{125}I was directly incorporated into the cellular DNA via the thymidine analog [^{125}I]-iododeoxyuridine. However, for decays at other intracellular locations such as in cytosol or membrane bound, the radiation effects were comparable of β^- particles. For a detailed summary of Auger electron dosimetry and their biological effects, the reader is referred to the paper by AAPM Nuclear Medicine task group no. 6 [3].

Auger electron emitters have been used in clinical studies in order to selectively exploit the high-LET effectiveness of these agents when targeted to cancer cells. Such work has included the use of [^{125}I]-thymidine precursors as well as ^{125}I-labeled antibodies. A review of these efforts in Auger targeting therapies can be found by Mariani et al. [4].

Isomeric Transition (IT) and Internal Conversion (IC)

If, subsequent to a nuclear decay, an excited nuclear state exists for a defined period of time (>1 ns), with subsequent release of the excess energy by γ-emission, this is termed an *internal* or *isomeric transition*. We have seen that both α- and β^--emissions are often both associated with spontaneous γ-ray emission. In some cases, however, the nucleus remains in an excited state for an appreciable time, and this is termed an *isomeric* state denoted by the symbol *m* (for "metastable") appended to the mass number (e.g., ^{99m}Tc, ^{113m}In, etc.). As the energy is released via γ-emission, there is no change to the number of nucleons and the only change is the loss of energy. The equation for an isomeric transition is

$$ {}^{Am}_{Z}X \rightarrow {}^{A}_{Z}X + \gamma $$

An alternative to an isomeric transition is a process known as *internal conversion*. In this process, the energy that would have been emitted as a γ-ray is transferred to an orbital electron and the electron is ejected from the atom. The energy of the liberated IC electron is equal to the energy of the corresponding γ-ray minus the binding energy of the electron shell the electron was liberated from. As with electron capture, internal conversion results in the atom being left in a state with an inner-shell vacancy from which a cascade of inner-shell electron transitions ensues yielding both characteristic X-rays and Auger and Coster–Kronig electrons.

The most common radionuclide used in nuclear medicine is ^{99m}Tc that undergoes this type of decay with a half-life of 6.02 h. De-excitation of the metastable state occurs 88.9% through the emission of a 140.5 keV γ-ray and 11.1% through internal conversion. In addition to radionuclides undergoing isomeric transitions, rapid internal conversion may occur subsequent to any β-decay process. For example, ^{123}I decays by electron capture, but a significant percentage (~18%) of the 159 keV γ-rays undergoes internal conversion.

Radioactive Decay

The rate at which nuclei spontaneously undergo radioactive decay is characterized by the parameter called the half-life of the radionuclide. The half-life is the time it takes for half of the unstable nuclei present to decay. It takes the form of an exponential function, where the number of atoms decaying at any particular instant in time is determined by the number of unstable nuclei present and the decay constant (λ) of the nuclide. The rate of decay of unstable nuclei at any instant in time is called the activity of the radionuclide. The activity of the nuclide after a time t is given by

$$A_t = A_0 e^{-\lambda_d t}$$

where A_0 is the amount of activity present initially, A_t is the amount present after a time interval t, and λ_d is the decay constant. The decay constant is found from:

$$\lambda_d = \frac{\log_e(2)}{t_{1/2}}$$

where the units for λ_d are time^{-1}. The SI unit for radioactivity is the Becquerel (Bq). One Becquerel (1Bq) equals one disintegration per second.

Interaction of Radiation with Matter

When high-energy radiation interacts with matter, energy can be transferred to the material. A number of effects may follow, but a common outcome is the ionization or excitation of the atoms in the absorbing material. To facilitate the description of these interaction processes, radiations are commonly divided into particulate and non-particulate or photon radiation. Particulate radiations are then further divided into whether they are charged (electrons, protons, α-particles) or uncharged (neutrons) particles.

Interaction of Particulate Radiation with Matter

The particulate emissions encountered in nuclear medicine applications include electrons (β^- particles) and α-particles. β^- particles are light charged particles and therefore continuously undergo electrostatic interactions with the outer-shell atomic electrons of the medium through which they traverse. Each interaction may result in an elastic or nonelastic scattering, changing the direction of the electron. With inelastic scattering events, sufficient energy may be transferred to the orbiting atomic electrons of the medium to either excite or ionize the atom. It is this energy deposition resulting in ionization to tissue that results in the biologically relevant radiation dose. Such energy transfers along the track of the β^- so that the particle slows down until it has no more energy and reaches the end of its range. A small fraction of the electrons pass through the electron clouds and are deflected by the nucleus. The strong positive charge field of the nucleus causes the electron to undergo a massive angular deflection and

therefore decelerate. This process of rapid deceleration causes the charged electron to lose energy radiatively by X-ray emission. The X-rays released by this mechanism are referred to as Bremsstrahlung which means "braking radiation." In tissue, the dominant means of energy transfer is through collisional losses from electron– electron interactions. However, the yield of Bremsstrahlung increases with increasing β-particle energy (is important for ^{90}Y or ^{32}P but insignificant for ^{3}H) and becomes especially important for high-Z materials such as lead (the Bremsstrahlung yield varies with Z^2). It is for this reason that it is better to contain a high-energy β-source, e.g., ^{90}Y, in a plastic vial behind which is lead, rather than place such sources directly into a lead container. β-Sources would produce a significant Bremsstrahlung fluence from a high-Z container, resulting in a greater radiation exposure than from the defined range resulting from the β-particles themselves.

Charged α-particles lose their energy through the same interaction processes as β^- particles. However, α-particles lose their energy much more quickly. Even an 8 MeV α-particle can travel only ~80 μm in the soft tissue. This is because of the much high stopping power associated with the higher (+2) charge and large mass of the He nucleus. As a consequence α-particles are not a significant radiation protection concern unless radionuclides emitting such particles are directly ingested.

Neutrons are uncharged particles that interact with matter through direct collisions with intranuclear nucleons (protons and neutrons). It is through "knock-on" protons that charged particles are set in motion and atomic ionizations occur. Since neutron (or proton) sources are not used in nuclear medicine applications, they are beyond the scope of this book.

Interaction of Photons with Matter

High-energy photons interact with matter by three main mechanisms, depending on the energy of the electromagnetic radiation. These are (i) the photoelectric effect, (ii) the Compton effect, and (iii) pair production. In addition, there are other mechanisms such as coherent (Rayleigh) scattering, an interaction between a photon and a whole atom which predominates at energies less than 50 keV, triplet production, and photonuclear reactions, where high-energy gamma rays induce decay in the nucleus and which require energies of greater than ~10 MeV. We will focus on the three main mechanisms which dominate in the energies of interest in imaging in nuclear medicine.

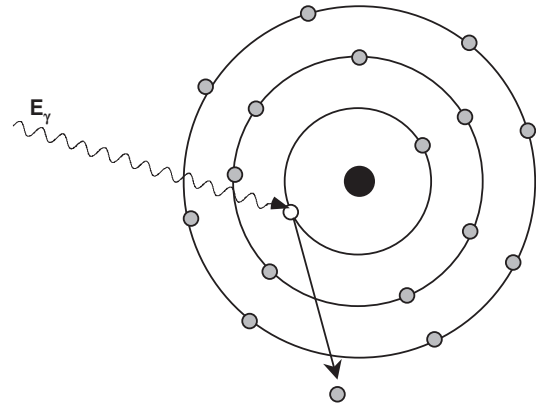

Fig. 7 The photoelectric effect. An incident photon displaces an inner-shell electron, thereby ionizing the atom. X-rays and Auger electrons may be produced after as the vacancy is filled by an outer-shell electron

Photoelectric Effect

The photoelectric effect occupies a special place in the development of the theory of radiation. During the course of experiments which demonstrated that light acted as a wave, Hertz and his student Hallwachs showed that the effect of an electric spark being induced in a circuit due to changes in a nearby circuit could be enhanced if light was shone upon the gap between the two coil ends. They went on to show that a negatively charged sheet of zinc could eject negative charges if light was shone upon the plate. Philipp Lenard demonstrated in 1899 that the light caused the metal to emit electrons. This phenomenon was called the photoelectric effect. These experiments showed that the electric current induced by the ejected electrons was directly proportional to the intensity of the light. The interesting aspect of this phenomenon was that there appeared to be a light intensity

threshold below which no current was produced. This was difficult to explain based on a continuous wave theory of light. It was these observations that led Einstein to propose the quantized theory of the electromagnetic radiation in 1905, for which he received the Nobel Prize.

The photoelectric effect is an interaction of photons with orbital electrons in an atom. This is shown in Fig. 7. The photon transfers all of its energy to the electron. Some of the energy is used to overcome the binding energy of the electron, and the remaining energy is transferred to the electron in the form of kinetic energy. The photoelectric effect usually occurs with an inner-shell electron. As the electron is ejected from the atom (causing ionization of the atom), a more loosely bound outer orbital electron drops down to occupy the vacancy. In doing so it will emit radiation itself due to the differences in the binding energy for the different electron levels. This is a characteristic X-ray. The ejected electron is known as a photoelectron. Alternately, instead of emitting an X-ray, the atom may emit a second electron to remove the energy and this electron is known as an Auger electron. This leaves the atom doubly charged. Characteristic X-rays and Auger electrons are used to identify materials using spectroscopic methods based on the properties of the emitted particles.

The photoelectric effect dominates in human tissue at energies less than approximately 100 keV. It is of particular significance for X-ray imaging and for imaging with low-energy radionuclides. It has little impact at the energy of annihilation radiation (511 keV), but with the development of combined PET/CT systems, where the CT system is used for attenuation direction of the PET data, knowledge of the physics of interaction via the photoelectric effect is extremely important when adjusting the attenuation factors from the X-ray CT to the values appropriate for 511 keV radiation.

Compton Scattering

Compton scattering is the interaction between a photon and a loosely bound orbital electron. The electron is so loosely connected to the atom that it can be considered to be essentially free. This

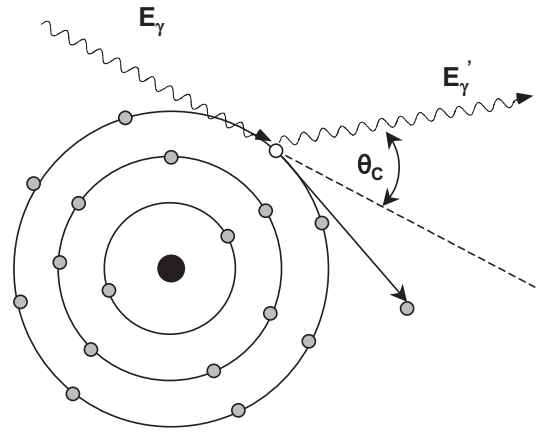

Fig. 8 Compton scattering occurs when a photon interacts with a loosely bound electron in an outer orbital shell. The atom is ionized and the photon undergoes a deflection causing a change in direction through the angle $\boldsymbol{\theta}_C$. This interaction is of most interest as a degrading factor in nuclear medicine imaging and quantification

effect dominates in the human tissue at energies above approximately 100 keV and less than ~2 MeV. The binding potential of the electron to the atom is extremely small compared with the energy of the photon, such that it can be considered to be negligible in the calculation. After the interaction, the photon undergoes a change in direction and the electron is ejected from the atom. The energy loss by the photon is divided between the small binding energy of the energy level and the kinetic energy imparted to the Compton recoil electron. The energy transferred does not depend on the properties of the material or its electron density.

The energy of the photon after the Compton scattering can be calculated from the Compton equation:

$$E'_\gamma = \frac{E_\gamma}{1 + \frac{E_\gamma}{m_0 c^2}(1 - \cos(\theta c))}$$

where E_γ and E'_γ are the incident and resulting gamma ray energies, respectively, m_0c^2 is the rest-mass equivalent energy of the electron, and θ_C is the scattering angle of the photon (see Fig. 8). From the consideration of the Compton equation, it can be seen that the maximum energy

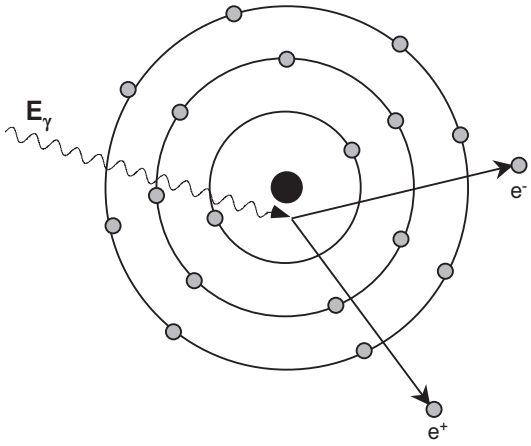

Fig. 9 Pair production occurs when a high-energy photon passes in the vicinity of the strong nuclear force. A positron–electron pair may be spontaneously created

loss occurs when the scattering angle is 180° (cos {180°}) = −1), i.e., the photon is backscattered.

Pair Production

The final main mechanism for photons to interact with matter is by pair production. When photons with energy greater than 1.022 MeV (twice the energy equivalent to the rest mass of an electron) pass in the vicinity of a nucleus, it is possible that they will spontaneously convert into two electrons with opposed signs, to conserve charge. This direct electron pair production in the Coulomb field of a nucleus is the dominant interaction mechanism at high energies. Above the threshold of 1.022 MeV, the probability of pair production increases as energy increases. At 10 MeV, this probability is about 60%. Any energy left over after the production of the electron–positron pair is shared between the particles as kinetic energy, with the positron having slightly higher kinetic energy than the electron as the interaction of the particles with the nucleus causes an acceleration of the positron and a deceleration of the electron.

Pair production was first observed by Anderson using cloud chambers in the upper atmosphere, where high-energy cosmic radiation produced tracks of diverging ionization left by the electron–positron pair.

The process of pair production demonstrates a number of conservation laws. Energy is conserved in the process as any residual energy from the photon left over after the electron pair is produced is carried away by the particles as kinetic energy; charge is conserved as the incoming photon has zero charge and the outgoing positive and negative electrons have equal and opposite charge; and momentum is conserved as the relatively massive nucleus absorbs momentum without appreciably changing its energy balance (see Fig. 9).

At energies above four rest-mass equivalents of the electron, pair production can take place in the vicinity of an electron. In this case it is referred to as "triplet production" as there is a third member of the interaction, the recoiling electron.

Attenuation and Scattering of Photons

In the previous section, we have seen how radiation interacts with matter at an atomic level. In this section we will examine the bulk "macroscopic" aspects of the interaction of radiation with matter, with particular reference to positron emission and detection.

Calculations of photon interactions are given in terms of atomic cross sections (σ) with units of cm^2/atom. An alternative unit, often employed, is to quote the cross section for interaction in barns/

Table 1 Narrow-beam (scatter-free) linear attenuation coefficients for some common materials at 140 keV (the energy of ^{99m}Tc photons) and annihilation radiation (511 keV) (Tabulated from Hubbell [5] and *ICRU Report 44 [6] and [7], [8]). ¶This is the density of non-inflated lung. §Measured experimentally

Material	Density(ρ) [g×cm^{-3}]	μ (140 keV) [cm^{-1}]	μ (511 keV) [cm^{-1}]
Adipose tissue*	0.95	0.142	0.090
Water	1.0	0.150	0.095
Lung*	1.05¶	∼0.04–0.06§	∼0.025–0.04§
Smooth muscle	1.05	0.155	0.101
Perspex (Lucite)	1.19	0.173	0.112
Cortical bone*	1.92	0.284	0.178
Pyrex glass	2.23	0.307	0.194
NaI(Tl)	3.67	2.23	0.34
Bismuth germanate (BGO)	7.13	∼5.5	0.95
Lead	11.35	40.8	1.75

atom (b/atom) where 1 barn = 10^{-24} cm^2. The total atomic cross section is given by the sum of the cross sections for all of the individual processes, i.e.,

$$\sigma_{\text{tot}} = \sigma_{\text{pe}} + \sigma_{\text{incoh}} + \sigma_{\text{coh}} + \sigma_{\text{pair}} + \sigma_{\text{tripl}} + \sigma_{\text{nph}}$$

where the cross sections are for the photoelectric effect (pe), incoherent Compton scattering (incoh), coherent (Rayleigh) scattering (coh), pair production (pair), triplet production (tripl), and nuclear photoabsorption (nph). Values for attenuation coefficient are often given as mass attenuation coefficients (μ/ρ) with units of cm^2.g^{-1}. The reason for this is that this value can be converted into a linear attenuation coefficient (μl) for any material simply by multiplying by the density (ρ) of the material:

$$\mu_l\left(\text{cm}^{-1}\right) = \mu/\rho\left(\text{cm}^2 \cdot \text{g}^{-1}\right)\mu/\rho\left(\text{g} \cdot \text{cm}^{-3}\right)$$

The mass attenuation coefficient is related to the total cross section by

$$\mu/\rho\left(\text{cm}^2 \cdot \text{g}^{-1}\right) = \frac{\sigma_{\text{tot}}}{u(g)A}$$

where $u(g) = 1.661 \times 10^{-24}$g is the atomic mass unit ($1/N_A$ where N_A is Avogadro's number) defined as 1/12th of the mass of an atom of ^{12}C and A is the relative atomic mass of the target element.

Table 2 Radionuclides of interest in nuclear oncology

Radionuclide	Half-life	Principal radiations emitted	Energy of emission (MeV)	Abundance (in same order as emissions)
^{11}C	20.5 min	$\beta^+(\gamma\pm)$	0.39	100%
^{13}N	9.97 min	$\beta^+(\gamma\pm)$	0.49	100%
^{15}O	122.2 s	$\beta^+(\gamma\pm)$	0.74	100%
^{18}F	109.8 min	$\beta^+(\gamma\pm)$	0.24	96.9%
^{32}P	14.2 days	β^-	0.695	100%
^{64}Cu	12.8 h	$\beta^+(\gamma\pm),\beta^-$	0.28 (β^+),0.19 (β^-)	17% (β^+),39% (β^-)
^{67}Cu	61.8 h	β^-,γ	0.116, 0.149, 0.184 (β^-), 0.185 (γ_1), 0.093 (γ_2)	57% (β^+_1), 22% (β^+_2), 20% (β^+_3), 49% (γ_1), 16% (γ_2)
^{67}Ga	78 h	γ	0.093, 0.184, 0.300, 0.394	38%, 24%, 16%, 4%
^{68}Ga	68 min	$\beta^+(\gamma\pm)$	0.74	88%
^{82}Rb	75 s	$\beta^+(\gamma\pm)$	1.4	96%
^{89}Sr	50.5 days	β^-	0.585	100%
^{89}Zr	78.4 h	$\beta^+(\gamma\pm),\gamma$	0.396 (β^+),0.909 (γ_1)	23% (β^+), 99.9% (γ_1)
^{90}Y	64 h	β^-	0.93	100%
^{99m}Tc	361.2 min	γ	0.1405	89%
^{111}In	67.4 h	γ	0.172, 0.247	89%, 94%
^{123}I	13 h	γ	0.159	97%
^{124}I	4.2 day	$\beta^+(\gamma\pm),\gamma$	0.97 (β^+_1), 0.69 (β^+_2) 0.603 (γ_1),1.69 (γ_2)	11% (β^+_1),12% (β^+_2), 62% (γ_1), 10% (γ_2)
^{125}I	60.2 days	γ	0.036	7%
^{131}I	8.04 days	β^-,γ	0.19 (β^-), 0.364 (γ_1), 0.637 (γ_2)	90% (β^-), 83% (γ_1), 7% (γ_2)
^{131}Cs	9.7 days	γ	0.353	100%
^{153}Sm	1.95 days	β^-,γ	0.20 (β^-_1), 0.23 (β^-_2), 0.27 (β^-_3), 0.070 (γ_1), 0.103 (γ_2)	32% (β^-_1), 50% (β^-_2), 18% (β^-_3), 5% (γ_1), 28% (γ_2)
^{166}Ho	26.8 h	β^-	0.70 (β^-_1), 0.65 (β^-_2)	50% (β^-_1), 49% (β^-_2)
^{169}Er	9.4 days	β^-	0.10	100%
^{177}Lu	6.73 days	β^-,γ	0.15 (β^-_1),0.12 (β^-_2)	79% (β^-_1), 9% (β^-_2)

^{186}Re	3.78 days	β^-,γ	1.07 (β^-_1), 0.93 (β^-_2), 0.140 (γ)	74% (β^-_1), 21% (β^-_2), 9% (γ)
^{188}Re	17.0 h	β^-,γ	0.79 (β^-),0.73 (β^-_2)	70% (β^-_1), 26% (β^-_2)
^{198}Au	2.7 days	β^-,γ	0.32 (β^-), 0.40 (γ)	99% (β^-), 96% (γ)
^{201}Tl	73 h	γ,X	0.167 (γ), 0.070 (X_1),0.080 (X_2)	8% (γ), 74% (X_1), 20% (X_2)
^{211}At	7.14 h	α	5.868	42%
^{212}Pb	10.64 h	β^-	0.096 (β^-_1), 0.173 (β^-_2), 0.239 (γ), 0.148 (IC)	82.5% (β^-_1), 12.3% (β^-_2), 43% (γ), 32% (IC)
				^{212}Pb decays to an α-emitting progeny ^{212}Bi
^{212}Bi	1.01 h	α,β^-	6.1 (α), 2.25 (β^-)	34% (α) + 66% (^{212}Po α), 55% (β^-)
				The β^- decay branch to ^{212}Po ($\tau = 0.299$ μs) undergoes further α decay to the ground state ^{208}Pb
^{213}Bi	45.6 min	α	5.5–5.9 (α)	100% (α)
^{223}Ra	11.4 days	α,γ	5.5–5.7 (α), 0.270 (γ)[a]	100% (α), 14% (γ)
				There are four α-emitted from parent to stable daughter
^{225}Ac	10.0 days	α,γ	5.8 (α), 0.218 (γ from ^{221}Fr daughter)	100% (α), 12% (^{221}Fr γ)
			0.440 (γ from ^{213}Bi daughter)	26% (^{213}Bi γ)
				There are four α-emitted from parent to stable daughter

Average energy of β-emission

[a]Radium-223 and its progeny emit numerous γ-rays. Only the most abundant γ-ray emitted by the parent is provided in the table

Photon Attenuation

We have seen that the primary mechanism for photon interaction with matter at energies in the range 0.1–2 MeV is by a Compton interaction. The result of this form of interaction is that the primary photon changes direction (i.e., is "scattered") and loses energy. In addition, the atom where the interaction occurred is ionized.

For a well-collimated source of photons and detector, attenuation takes the form of a mono-exponential function, i.e.,

$$I_x = I_0 e^{-\mu x}$$

where I represents the photon beam intensity; the subscripts "0" and "x" refer, respectively, to the unattenuated beam intensity and the intensity measured through a thickness of material of thickness x; and μ refers to the attenuation coefficient of the material (units: cm^{-1}). Attenuation is a function of the photon energy and the electron density (Z number) of the attenuator. The attenuation coefficient is a measure of the probability that a photon will be attenuated by a unit length of the medium. The situation of a well-collimated source and detector is referred to as narrow-beam condition. The narrow-beam linear attenuation coefficients for some common materials at 140 keV and 511 keV are shown in Table 1.

However, when dealing with in vivo imaging, we do not have a well-collimated source, but rather a source emitting photons in all directions. Under these uncollimated, broad-beam conditions, photons whose original emission direction would have taken them out of the acceptance angle of the detector may be scattered such that they are counted. This is known as a "broad-beam" conditions indicating increased acceptance of scattered photons leading to an overall lower effective attenuation coefficient.

Radionuclides Used in Nuclear Oncology

Nuclear medicine uses radionuclides for both diagnostic studies (including some non-imaging ones) and therapeutic applications. Diagnostic studies include γ-emitting radionuclides produced in nuclear reactors or cyclotrons as well as β^+-emitting radionuclides. Therapeutic radionuclides always emit a particle and may or may not emit a γ-ray which can be used to image the radionuclide distribution and uptake. Table 2 summarizes the main radionuclides of interest in nuclear oncology and their principal emissions and other characteristics. Only the dominant emissions are shown.

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