

Radiobiology

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Introduction

Radiobiology refers to the wide array of cellular effects of electromagnetic radiation to biologic systems. Electromagnetic radiation is radiant energy in motion that demonstrates both wave and particle characteristics. The effects of radiation depend on the type of radiation, quantity, and the biologic system affected and include cell killing, DNA damage, genetic mutation, neoplastic transformation, and cell cycle disturbances among others. Radiobiology as it relates to radiotherapy focuses on radiation that has the ability to cause ionization of atoms. In general, radiation energy above 10 eV is capable of producing ionizations. The most significant effect of radiation is cell killing as a result of the chemical bonds broken due to the ionization of atoms.

Interaction of Radiation with Matter

In superficial radiotherapy (low-voltage X-ray) electrons are accelerated towards a target such as tungsten to yield a resultant beam of photons when treating skin cancer. Radiation methods may be categorized based on kilovoltage. Photons (X-rays) with kinetic energies between 20 and 100 keV are referred to as superficial or soft X-rays, between 200 and 400 keV orthovoltage X-rays, 400–800 keV supervoltage X-rays, and those with kinetic energies above 1,000 keV are called megavoltage

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X-rays [1]. Other methods involve the use of linear accelerators to produce a continuous stream of electrons (electron beam radiotherapy), typically in the range of 6,000–9,000 keV to treat skin cancer, all of which are capable of producing ionizations in matter.

Interaction Types

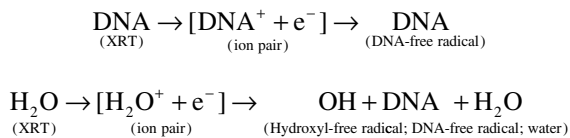
Photon interactions: A photon can penetrate matter without interacting, it can be completely absorbed by depositing its energy, or it can be scattered (deflected) from its original direction and deposit part of its energy as follows:

1. Photon to electron interaction: a photon transfers all its energy to an electron located in one of the atomic shells, usually the outer shell. The electron is ejected from the atom and begins to pass through surrounding matter.
2. Compton interaction: only a portion of the energy is absorbed and a photon is produced with reduced energy. The photon that is produced leaves in a different direction than that of the original photon. This reaction is classified as a scattering process because of this change in direction.
3. Pair production: the photon interacts with the nucleus in such a way that its energy is converted to matter producing a pair of particles, an electron and a positively charged positron. This only occurs with photons with energies in excess of 1.02 MeV.

Electron interactions: Energized electrons transfer energy to surrounding tissues. These electrons are produced by the dislodging of an electron from an atom's outer shell by use of photons or by a direct stream of electrons produced by linear accelerators. Electrons immediately begin to transfer their energy to surrounding material, interacting with other electrons without touching them because they carry an electrical charge. As these energized electrons pass through material they push other electrons away, if the force is sufficient to remove another electron subsequent ionizations result. For example, in air a 50 keV photon undergoing a photon to electron interaction can eject an electron capable of ionizing over 1,000 additional atoms. The major biological effect of photons (X-ray) is due to electron interactions.

Within cells radiation may interact with DNA or water. The damage caused by these interactions is categorized as either direct (DNA is damaged directly) or indirect (cells are damaged indirectly via free radicals). Radiation is more likely to interact with water as it accounts for 70 % or more of the total cell mass [2] and DNA is present only as a tightly folded double strand within the nucleus. Therefore the majority of cell killing with radiation is through the indirect action of free radicals on the cells that are ionized. Direct damage to DNA, when it occurs, more often causes reproductive death; i.e., cells continue to undergo normal metabolic function but are unable to undergo cell division. When the radiation has enough energy it can eject an electron from the orbital shell of the hydrogen atom of water; it causes the water molecule to disassociate into hydrogen and a hydroxyl-free radical and is

therefore ionizing. The highly reactive free radicals formed by radiolysis of water are capable of adding to the direct DNA damage of radiation by migrating to and damaging the DNA indirectly [3, 4].



Ionizing radiation deposits energy as it traverses an absorbing medium; when it does, it may produce interactions that occur along a path. Photons and displaced electrons deposit random and discrete packets of energy referred to as “spurs” (100 eV or less deposited), “blobs” (100–500 eV), or “short tracks” (500–5,000 eV). Discrete is the term used because the energy deposition is discontinuous and a relatively large amount of energy is deposited (on a microscopic scale) in a small volume of tissue. The average amount of energy deposited on a macroscopic scale, however, is minuscule. This is considered an efficient process for producing biologic damage. If the beam of energy used to treat a skin cancer were converted entirely to heat it would raise the temperature of the tissue by less than 0.01 °C [5]. This efficiency is demonstrated by another example, the total amount of energy deposited in a 70-kg human that will result in a 50 % probability of death is only about 70 cal, the same energy absorbed in one sip of hot coffee [4].

Dose/Units

There are several basic measurements that pertain to radiation. Within the realm of radiobiology only the absorbed dose is of primary concern. As stated previously radiation may pass through material totally unaffected, may be partially absorbed resulting in reduced energy, or it may be completely absorbed. The absorbed energy is considered biologically effective. In the past the absorbed dose of radiation was expressed in units called “rad” (radiation absorbed dose). A dose of 1 rad is equal to the absorption of 100 ergs of radiation energy per gram of absorbing material. The modern SI units used today are the gray (Gy). A dose of 1 Gy is equal to the absorption of 1 J of radiation energy per kilogram of absorbing material. For comparison, 1 Gy (100 centigrays) is equal to 100 rads, thus centigrays (cGy) and rads are equivalent.

Linear Energy Transfer

The total absorbed dose is, by itself, insufficient in determining the net biological effectiveness of different forms of radiation. Linear energy transfer (LET) is a measure of the energy transferred to a material as an ionizing particle traverses it, and is

used to quantify the effects of ionizing radiation on biological systems. Different forms of radiation produce a different number of ionizations along a particle's track. In the microdosimetric pattern of energy deposition, the density or spacing of ionization events determines the biological effectiveness of that specific radiation. The closer the ionization events are to one another within a given length the more the energy will be deposited, and hence the more biologically effective per unit dose the type of radiation will be. It is a function of both the charge and mass of the ionizing particle and is measured in $\text{keV}/\mu\text{m}$. Heavier particles such as alpha particles will produce more events per unit length than photons which set in motion electrons with negligible mass. For example, a 250 keV X-ray (photon) has an average LET of $2.0 \text{ keV}/\mu\text{m}$, whereas alpha particle has an LET of $100\text{--}150 \text{ keV}/\mu\text{m}$. It is also important to note that for a given type of radiation, the LET increases with decreasing particle energy and the number of ionizations increases as a particle slows down [6].

Relative Biological Effectiveness

Relative biological effectiveness (RBE) is a number that expresses the relative amount of damage that a fixed amount of ionizing radiation of a given type can inflict on biological tissues. The International Committee on Radiological Protection (ICRP) uses the term "radiation weighting factor" to determine the equivalent biological effectiveness of different radiation types (Table 1) and went on to say "The RBE of one radiation compared with another is the inverse ratio of the absorbed doses producing the same effect." In light of the differences between high LET (alpha particles) and low LET (X-rays), it allows for comparison of two radiation beams of different LETs required to give the same biologic endpoint. Early on it was established that X-rays, gamma rays, and beta radiation were equivalent for all cell types in biologic effect, therefore X-rays (photons) at 250 keV energy were

Table 1 International Committee on Radiological Protection (ICRP) summary of the equivalent biological effectiveness of different radiation types

Radiation	Energy range	Radiation weighting factor/RBE
X-rays, gamma rays, electrons, positrons, muons		1
Neutrons	<10 keV	5
	10–100 keV	10
	100 keV–2 MeV	20
	2–20 MeV	10
	>20 MeV	5
Protons	>2 MeV	2
Alpha particles		20

Adapted with permission from 1990 Recommendations of the International Commission on Radiological Protection [7]

used as the standard and assigned an RBE of 1. This formula is applicable to all subsequent forms of radiation modalities (positrons, neutrons, alpha particles) and allows for useful comparison. Below is the formula for RBE:

$$\text{RBE} = \text{Dose of reference radiation (low LET)} / \text{Dose of test radiation (high LET)}$$

For example, if 40 Gy of X-rays (photons) kills 50 % of tumor cells and it takes 2 Gy of alpha particles to produce the same effect, the RBE would be $40/2=20$ using X-rays as the reference radiation.

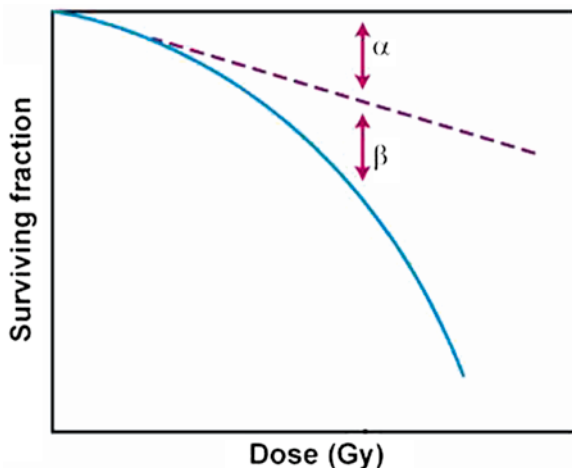
It is expected that research conducted in radiobiology to determine RBE values will state the exact experimental conditions, as it is highly variable and depends on several radiation parameters such as type of radiation, total dose, dose rate, fractionation schedule, and the biologic endpoint being measured. It is also important to note that there is a linear relationship between LET and RBE, with increasing RBE as the LET increases up to a maximum of 100 keV/ μm , beyond this point the RBE begins to fall due to “over-kill effect.” A given radiation type may have several RBEs depending on the biologic endpoint being measured. For example, the RBE for alpha particles whose measured biologic endpoint is tumor death is different from the RBE for the same alpha particles when the measured endpoint is radiodermatitis.

Cell Survival Curves

In radiotherapy for cancer, cell death is the biologic endpoint of greatest interest. Cell death to radiobiologists is somewhat different from the traditional definition of death, referring to a permanent cessation of vital functions. In the radiobiologic sense it refers to the loss of reproductive ability of a cell and is termed “clonogenic” or “reproductive” death. It follows that the cell may remain physically intact and metabolically active for some time after undergoing irradiation, with some cells even undergoing a few additional mitoses before dying in the traditional sense.

Cell survival curves are determined by an in vitro plating method. A known number of tumor cells are plated then irradiated. The numbers of surviving colonies are counted to determine the proportion of cells able to survive that dose of radiation. The fraction of surviving cells is plotted on a logarithmic scale against radiation dose on a linear scale. Initial survival curves were based on a single-hit, “all-or-nothing” inactivation of a single target, followed by survival curves based on target theory (multiple target or multiple hits to the same target). The single-hit, multi-target model has since been invalidated though its parameters are still used for comparative purposes today. In the 1970s the linear-quadratic or “alpha-beta” formula was introduced to reflect what was observed in practice, clinical studies, and mammalian cells at the low dose region of the survival curves and with fractionated doses [8]. The equation proved to fit survival data well and was based on the

Fig. 1 Alpha-beta formula representing the rate of cell kill from the interaction of two sublesions. α =the rate of cell kill by a single-hit process; β =the rate of cell kill by a two-hit mechanism



proposition that a radiation-induced lethal lesion resulted from the interaction of two sublesions or events [9]. Fig. 1 shows α which is the rate of cell kill by a single-hit process and β which is the rate of cell kill by a two-hit mechanism.

Powers of Ten

The goal of radiotherapy is to reduce the number of clonogenic cells. Tumor control is achieved when these cells are killed or inactivated. The probability of local tumor control is derived from Poisson statistics using the equation $P = e^{-n}$, where P is the tumor control probability and n is the average number of surviving clonogenic cells. The “powers of ten” describes the logarithmic relationship of tumor control based on exponential cell killing. The “powers of ten” terminology does not infer the percentage probability of cure relates by a factor of 10 to the number of clonogenic cells left after a course of radiotherapy but rather describes the logarithmic (10^x) numbers of clonogenic cells that must be eradicated to achieve a certain percentage of cure probability. For example, in most tumors if an average of two clonogenic cells exists at the end of radiotherapy the control rate would be 10 % (i.e., 9 out of 10 tumors of the same size and radio sensitivity will recur); at 0.1 clonogenic cells per tumor the control probability increases to 90 % and at 0.01 cells the control would be 99 % [6].

Oxygen Effect

Molecular oxygen is the best known chemical modifier of radiation action. The presence or absence of oxygen within a cell influences the biological effect of ionizing radiation. The larger the cell oxygenation, the larger the biological effect of

radiation. This effect was observed first in the early 1900s whereby decreased radiation skin reactions were noticed when pressure was applied to skin decreasing the blood flow [10]. A simple model of the effect of oxygen holds, in that oxygen is required to create free radicals necessary to damage DNA following irradiation and it is believed that hypoxic cells are 3 times more resistant to radiation damage [4]. Furthermore, irradiation converts previously hypoxic cells to “Oxygenated” cells making them radiosensitive. Conceptually this may explain why anoxic tumor cells or tissues’ locations with naturally lower oxygen levels, such as the lower extremities, have higher recurrence rates as well as longer periods of healing.

Cell Kinetics

Radio sensitivity of a cell depends on its phase within the cell cycle. The two well-defined periods of cell proliferation are M (mitosis) and S (DNA synthesis), with G_1 and G_2 occurring as apparent gaps of inactivity between the mitosis and the synthetic phase. In general, cells are the most sensitive to radiation in the M and G_2 phases and the most resistant in the late S phase. Ionizing radiation can cause perturbations of the cell cycle to influence radio responsiveness of tissues directly and indirectly. In tumors there is an asynchronous population of cells at various points in the cell cycle. Following radiation tumor cells are thought to be set in synchrony, and following redistribution (commencement of the cell cycle), the cell population as a whole becomes sensitized to subsequent doses of radiation [11].

Fractionation

Fractionation is the term used to describe the period of time over which a radiation dose is given (usually 2 weeks or more) rather than as a single dose. Its goal is to achieve an optimal therapeutic ratio, which is the destruction of tumor cells and the recovery and viability of normal tissue. Conclusions based on early research revealed that repair of sublethal damage occurred quickly within 6 hours of radiation, that cells become synchronized following a first dose of radiation, and that the sensitivity of a cell is dependent on the cell cycle phase [12]. Due to cell recovery between fractions, a larger total dose for a given biologic effect is needed than if given as a single dose. Healthy cells recover faster and more completely which allows for preferential killing of tumor cells and survival of healthy cells.

Strandquist [13] was the first to correlate dose with treatment time to produce an equivalent biological isoeffect. He utilized a 250 keV X-ray machine at a standard fractionation of 2 Gy/day at five treatments per week in his research of 280 skin carcinomas. He plotted a logarithm of dose versus log time for skin and connective tissue tolerance with a straight line separating the incidence of skin necrosis from that of recurrences. Later Ellis [14], using the isoeffect data for skin from Strandquist,

attempted to correlate the number of fractions with the dose and total time over which the treatment was delivered. His introduction of the concept of nominal standard dose (NSD) allowed comparison of various treatment schemes or the changing of one scheme to another to gain equivalent biological effect. The formula which will be discussed in more depth in Chap. 9 is $D = \text{NSD} \times T^{0.11} \times N^{0.24}$, where D is the total dose in rads, N is the number of fractions, and T is the overall time in days. Ellis' clinical observation was that fractionation was twice as important as time [15]. Time Dose Fractionation schedules are discussed further in the chapter on superficial radiotherapy treatment planning.

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