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Textbook of Radiological Safety



Kuppusamy Thayalan

2nd Edition

Foreword
Paul Ravindran

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CHAPTER 2

Radiation Biology

INTRODUCTION

Radiation biology deals with the study of the nature of damage caused by ionizing radiation on body tissues. The degree of response of body tissue against radiation exposure depends on various factors such as type of radiation, amount of dose, dose rate, fractionation, nature of exposure (whole body/partial body), cell cycle, presence of radioprotectors or sensitizers, and age of the exposed individual, etc. This chapter gives an overview of radiobiology related to medical exposures of ionizing radiation.

CELL

Cells are divided into two types, namely prokaryotic, e.g., bacteria, and eukaryotic, e.g., animal cell. Human body is a multicellular organism, and the size of each cell is around 10^{-15} μm. Adult human body contains about 10^{14} cells. Cell is a structural and functional unit of every living organism (*Robert Hooke*, 1665). Cells of similar nature constitute a tissue and different tissues form an organ. Many organs constitute a system, namely integumentary, skeletal, muscular, nervous, endocrine, circulatory, lymphatic, respiratory, digestive, urinary and reproductive systems.

Body cells are classified into somatic cells and germ cells. All cells of the body are considered as somatic cells except the cells, which participate in the reproductive process. The cells which are involved in the reproductive process are called germ cells. They are sperm in males and ovum in females. Human body contains 23 pairs of chromosomes. Among these, 22 pairs are called autosomes and one pair is called sex chromosomes. Male has 22 pairs of autosomes and one pair of sex chromosomes, namely X and Y chromosomes. Female has 22 pairs of autosomes and one pair of X chromosomes as sex chromosomes.

Mammalian cell consists of a nucleus, cytoplasm, internal membrane, and outer plasma membrane **(Fig. 2.1)**. Cytoplasm is a viscous liquid occupies about 70% of cell volume and consists various organelles such as mitochondria, rough and smooth endoplasmic reticulum, Golgi complex, lysosome, and ribosome. Each organelle has a specific function of its own. For example, ribosome plays a role in protein synthesis, Golgi complex modifies proteins before use, mitochondria provides the necessary energy for cell function, and lysosomes are the digestive organelle of the cell.

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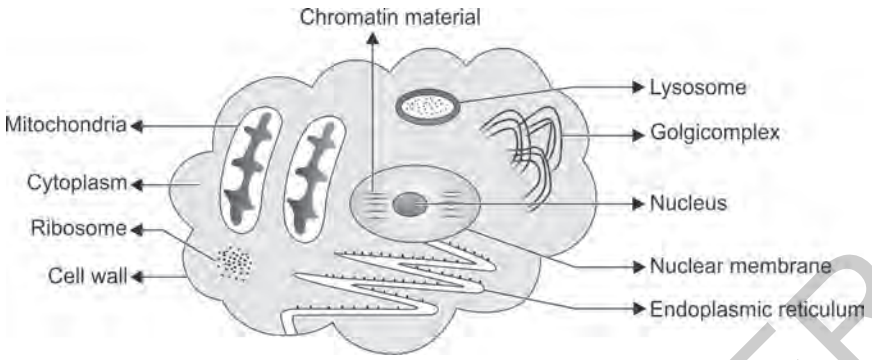


FIG. 2.1: Mammalian cell structure containing, nucleus, cytoplasm, internal membrane, and outer plasma membrane.

Nucleus and Deoxyribonucleic Acid

The nucleus is a control center of the cell, contains deoxyribonucleic acid (DNA), and nucleolus. It has machinery for DNA replication and ribonucleic acid (RNA) transcription and processing. It is enveloped in a double membrane and the outer membrane is fused with endoplasmic reticulum.

Deoxyribonucleic acid is double-stranded form, having helical structure with series of repeating nucleotides arranged in certain sequence. Nucleotide contains a nucleobase [adenine (A), guanine (G), cytosine (C), or thymine (T)], a pentose sugar, and phosphorous. Nucleotide present on one strand is connected to the nucleotide present on the opposite strand by hydrogen bond. Sections of DNA contain information for specific functions called genes. The double-stranded DNA is in the form of helical structure with a width of about 2 nm and is wound around histones, which undergo condensation to form chromatin. It appear as beads-on-a-string with dimension of 11 nm. It is closely packed as series of looped domains wound in a tight helix. Extended form of chromosome has the dimension of 300 nm, whereas the final condensed metaphase chromosome is 1,400 nm. Any damage to DNA molecule such as single-strand break (SSB) is recognized by repair enzymes and repairs perfectly. However, if the damage is severe like double-strand break (DSB), the repair may be a right repair or wrong repair. The wrong repair may lead to cell death or mutation.

Cell Cycle and Death

Cell undergoes cell division to produce two daughter cells. During this process, the cell undergoes various phases such as G1 (gap 1), S (synthesis), G2 (gap 2), and M (mitosis). The G1, S, and G2 are said to be interface of the cycle. During the S phase, the DNA molecule is replicated into two molecules. Cell cycle is regulated by *cyclin-dependent kinase (Cdk)*. The length of each phase varies with the type of cells, mitosis is the shortest phase (hour), and S phase lasts for 6–8 hours. Cell cycle variation is generally due to the differences in the length of G1 phase.

Mitosis is further divided into four phases, namely *prophase, metaphase, anaphase, and telophase*. *Mitotic index* is the ratio of cells in mitosis to the total number of cells in the sample. Cell division process of germ cell is referred as meiosis, and it has two stages, namely meiosis I, and meiosis II.

Cell death may be in three ways, namely—(i) autophagy, (ii) necrosis, and (iii) apoptosis or programmed cell death. Autophagy is the process of self-degradation,

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and necrosis is a death by injury. In apoptosis, body's ability decides the time of cell death.

Tumor Cells

Malignant tumor cells are heterogeneous in population and said to have stem cells. Cancer stem cells are a type of adult or progenitor cell found in most types of cancer. These cells generally represent just 1–3% of all cells in a tumor, but they are the only cells with the ability to regenerate malignant cells and fuel the growth of the cancer. Solid tumors have necrotic central portion surrounded by hypoxic cells that are not proliferating but viable with oxygen. Tumor is not spherical in shape, and its center is 200 μm away from blood supply.

Tumor staging is the estimation of extent of the tumor spread. There are four stages, namely stage 1, stage 2, stage 3, and stage 4. *Union for International Cancer Control* (*UICC*) has suggested TNM staging based on primary tumor (T), nodal spread (N), and distant metastasis (M) status. In addition, American Joint Committee on Cancer (AJCC) staging, and Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging for gynecological cancer are available. Detailed discussion of tumor staging is beyond the scope of this text.

INTERACTION OF RADIATION WITH CELLS

Radiation deposits energy in tissues randomly via excitation, ionization, and thermal heating. Time interval between the radiation exposure and manifestation of effects is divided into four stages, namely (i) physical stage, (ii) physiochemical stage, (iii) chemical stage, and (iv) biological stage. In physical stage, biomolecules, which absorb energy, result in excited and ionized molecules (10^{-13} s). Physiochemical stage involves formation of free radicals and primary lesions in target molecules (10^{-10} s). In chemical stage, primary lesions result in molecular alterations (10^{-6} s). In biological stage, the molecular alteration causes biological effects (seconds-years). Biological effects include lethality, mitotic inhibition, division delay, chromosome aberration, and mutation.

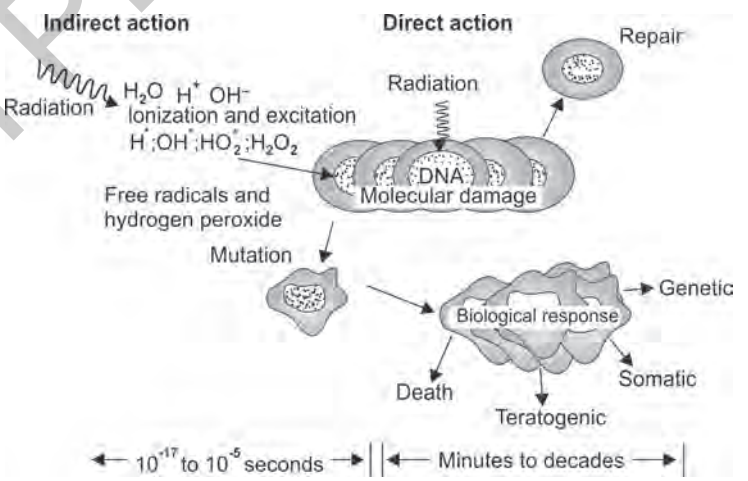


FIG. 2.2: Interaction of radiation in cell: Physical, chemical, and biological response of ionizing radiation by both direct and indirection action.

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Direct and Indirect Action

Radiation causes biologic effects by interacting with the target molecules either directly or indirectly **(Fig. 2.2)**. Direct action is dominant in high-linear energy transfer (LET) radiations. For example, an alpha particle breaks the chemical bonds directly in a DNA molecule. In indirect action, radiation interacts with water molecules in the cell and produces free radicals, a process known as *radiolysis of water*. Free radicals are atoms or molecules or ions with an unpaired electron in the outermost shell. They are highly reactive, interact with biomolecules, and cause damage. Indirect action is a dominant process in low LET radiations. The damaging effect of free radical is enhanced in the presence of oxygen.

Radiolysis of Water

Human body cell is composed of about 80% water. The absorption of radiation by water molecule results in ion pairs (H_2O^+, H_2O^-), which are unstable and form free radicals such as H* (hydrogen), OH* (hydroxyl), and hydrated electron (e^-_{aq}).

$$H_2O + \text{X-ray} \rightarrow H_2O^+ + H_2O^-$$

$$H_2O^+ \rightarrow H^+ + OH^*$$

$$H_2O^- \rightarrow H^* + OH^- \qquad (2.1)$$

CELL SURVIVAL CURVES

If cells are irradiated with ionizing radiation it will result in partial cell death and partial survival of cells. Cells that lose reproductive capacity and fail to divide further are called dead cells. Cells that retain reproductive capacity and able to divide indefinitely are called surviving cells. There is direct relation between number of cells killed and the radiation exposure. Radiation dose and the surviving fraction (SF) of cells can be plotted in a semi-log paper, which is referred as *survival curve*. This curve is useful to understand the radiosensitivity, repair, and recovery ability of the cell. SF is a fraction of cells that survive after radiation exposure:

$$\text{SF} = \frac{\text{Number of colonies counted}}{\text{Number of celles seeded} \times \text{Plating efficiency}} \qquad (2.2)$$

where, plating efficiency (PE) is the percentage of seeded cells that survive to form colonies under control conditions, which is obtained by in vitro study. To express this in mathematical terms, *(i) point heat theory, (ii) target theory, and (iii) linear quadratic (LQ) theory* were proposed. As per point heat theory, absorption of radiation enhances temperature, which is responsible for the inactivation of cells, which was not successful.

Target Theory

Target theory (*Crowther and Lea*) assumes critical targets in cell, which needs to be hit to kill the cells. This theory includes single-target, multitarget, and multihit models. Single target model does not account for dose rate, fractionation, and irradiation environment. Multitarget model assumes more than one target and the

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survival curve appears with shoulder. Cell inactivation needs at least one hit to each target in cell. It fails to explain the experimental results of survival fraction of cells. Multihit theory assumes single target, which needs more than one hit. In general, survival curve exhibits initial linear part, shoulder, and final linear part. D_0 is the dose required to reduce the survival from 1 to 0.37, often referred as D_{37}. The number of targets (n) in the cell is a measure of width of the shoulder. However, there is no shoulder for radiations of high LET. The initial slope of the survival curve is not explained by the above models.

Linear Quadratic Model

Linear quadratic model accounts both single-hit and two-hit events in cell death. Single hit refers to initial part of the survival curve where cell killing is linear. At higher doses, two-hit events are involved, which are quadratic in nature. It believes that cell killing is caused by DSBs, which have both linear and quadratic part in the survival curve **(Fig. 2.3)**. The linear part is due to single ionizing event, quantified by αD, where α is the probability for such events per unit dose. The quadratic part is due to two separate ionizing events quantified by βD^2, where β is the probability of such events per unit dose. The α damage is irreparable, whereas β damage is reparable. The surviving fraction (S) of cells is given by:

$$S = e^{-(\alpha D + \beta D^2)}$$

Or,
$$-\ln S = (\alpha D + \beta D^2) \quad (2.3)$$

The LQ model explains the cell killing in a better way in the low-dose region (0–3 Gy) and clinically much useful. The dose D at which cell killing due to linear and quadratic component is equal is given by:

$$\alpha D = \beta D^2 \text{ or } D = \frac{\alpha}{\beta} \text{ ratio} \quad (2.4)$$

This ratio varies with the type of cells. For early reacting normal tissues and tumor cells, $\frac{\alpha}{\beta}$ ratio is high and for late reacting normal tissue, $\frac{\alpha}{\beta}$ ratio is low. Studying the $\frac{\alpha}{\beta}$ ratio is useful to compare the radiosensitivity of different cell lines as the shape of the survival curve is determined by this ratio. As per this model, the shape of the curve is continuously bending which is not observed experimentally. It is also against the belief that cell killing is an exponential function of dose represented by a straight line in a semi-log plot. Although this model has certain drawbacks mentioned above, it is sufficient to explain the cell killing for doses used in fractionation applied in clinical radiotherapy.

DNA DAMAGE AND ITS REPAIR

Deoxyribonucleic acid (DNA) is the most important target molecule, which undergoes variety of changes such as intramolecular cross-linking, intrastrand cross-linking, degradation, etc., due to radiation. Intramolecular cross-linking refers to the cross-linking that occurs between bases on the same strand of a DNA. Intermolecular cross-linking includes DNA–DNA, and DNA–protein cross-link. In intrastrand cross-linking, two adjacent thymine bases on the same strand of DNA get linked to each

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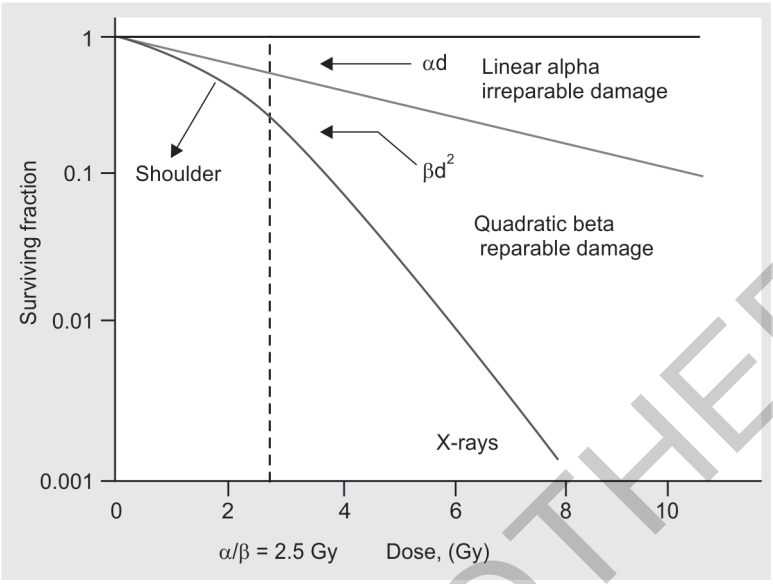


FIG. 2.3: The survival curve and the linear quadratic model for mammalian cells exposed to X-rays. The dose at which the linear and quadratic components are equal is the ratio of alpha/beta.

other by covalent bond. It reduces the distance between two thymine molecules resulting in distortion of the sugar–phosphate backbone.

Deoxyribonucleic acid degradation occurs due to breaks in DNA strand. The break may be either SSB or DSB. If the break is located on one strand, it is referred as SSB. It is easy to repair by taking a template from opposite strand. Oxygen can cause the broken strand becomes per oxidized and prevent it from rejoining. Thus, presence of oxygen potentiates the radiation damage. If two breaks are located on opposite strands, separated by five bases, it is referred as DSB. It is difficult to repair since template from opposite strand is not available for repair. DSB is repaired by homologous recombination (HR) and nonhomologous end joining (NHEJ). If the repair is not proper, it may lead to mutation. This may lead to carcinogenesis through activation of oncogenes, inactivation of tumor suppressor genes, or loss of heterozygosity. A DSB can result in chromosome aberrations. Base damage includes deletion, substitution, and addition to one or both strands of DNA. The loss of change of base is also considered as mutation **(Fig. 2.4)**.

In addition to the above, radiation also causes other damages such as deamination, depurination, oxidation, opening of ring structures, and denaturation. Extent to which the different kinds of molecular lesions affect the cells depends on nature of repair systems present.

The DNA checkpoints monitor the damage at specific points within the cell cycle. It halts the cell cycle to allow time to repair the damage.

Chromosome Aberrations

There are two types of chromosome aberrations namely stable and unstable aberrations. Stable aberration is carried out through number of cell divisions, whereas unstable aberration leads to cell death.

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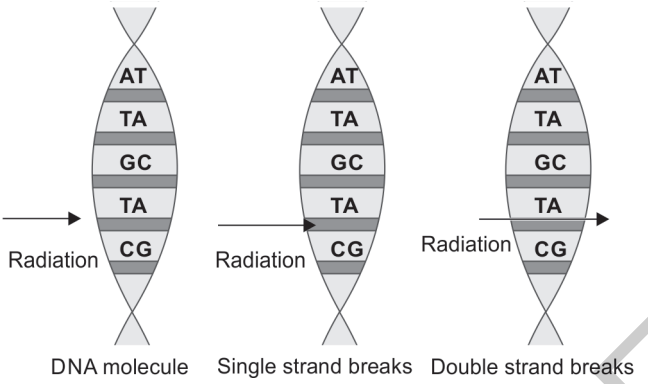


FIG. 2.4: Radiation action on DNA molecule: Single and double strand breaks.

Deoxyribonucleic acid strands break that occurs before S-phase DNA replication gives rise to chromosome aberration. DNA strands break that occurs after the S phase [irradiation of cells in the late interphase (G2)] is called chromatid aberrations. In this, one arm of the sister chromatid is broken.

The unstable chromosome aberrations are: *(i) dicentric, (ii) ring, and (iii) anaphase bridge*. In dicentric, the broken ends of two different chromosomes get united resulting in the formation of dicentric chromosome with two centromeres, hence the name dicentric. In ring aberration, the breaks that occur in both arms of a chromatin get united and appear as ring. Ring and dicentric formation is due to strong force of cohesion between broken ends. In anaphase bridge, the damaged sister chromatids do not separate properly, instead stretch to either pole of the cell. It occurs in late interface and prevents separation of parent into daughter, resulting reproductive death.

Stable chromosome aberrations are: *(i) symmetric translocation and (ii) small interstitial deletion*. In symmetric translocation, break occurs in two different chromosomes at the early interphase (G1) and later broken ends are exchanged and get rejoined. It presents for several years and are passed on to the progeny. This can be easily seen in fluorescent in situ hybridization (FISH) and chromosome painting techniques. In small interstitial deletion, two breaks occur in the same arm of a single chromosome and the sticky ends may rejoin with deletion and loss of DNA. It may lead to malignancy in humans.

The frequency of chromosomal aberrations increases with radiation dose, hence, the magnitude of aberrations is used as an indicator of radiation dose absorbed. Dicentric chromosome aberrations (DCAs) in human lymphocytes are scored and used to estimate radiation dose.

Mutation

Mutation is a change in DNA base sequence that is not recognized by repair enzymes. It has changes in large segment of DNA such as deletion, which encompass more than one gene. There are about 25,000–30,000 genes in human genome, which occupy specific position on the chromosome. The gene has hereditary information, which is coded in the form of specific sequence of bases in DNA. Individual receives two identical genes from his/her parents. In other words, mutation is the change in

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the information that contained in genes. Muted cell may have normal reproductive capacity but have altered information in one of the gene. Gene mutation may be either dominant or recessive. Dominant means that a single copy of the gene, if mutated, is enough to cause the disease. Recessive means both the copies of the gene need to be mutated to cause the disease. *Huntington's* disease is a common example of an autosomal-dominant genetic disorder.

Radiation can cause mutations both in germ cells and somatic cells. Mutations that occur in somatic cell may lead to cancer induction. Mutations that occur in germ cells (sperm or ova) are passed onto the progeny of the host. Germ cell mutation leads to heritable diseases in the offspring known as genetic mutation.

Radiation Damage in Cells

Radiation damage in mammalian cells is divided *into—(i) lethal damage (LD), (ii) potentially LD (PLD), (iii) sublethal damage (SLD), and (iv) nonlethal damage (NLD)*.

The LD is an irreparable damage caused by radiation leads to cell death. Cell fails in reproductive capacity resulting interphase and mitotic death. PLD is lethal under normal conditions, but repair is possible if the postirradiation environment is manipulated. If several hours are allowed between irradiations, cells get repaired. It delays the complex mitosis process and permits DNA damage repair, referred as *rest and recover*. Properly repaired cell continues to function normally, and improper repair leads cell fatality or undergoes mutation.

Sublethal damage is repaired in few hours after irradiation. Repair of SLD is the inherent process by the cell system and supports appearance of shoulder in the survival curve. Repair of SLD is related to radiation quality and dose rate and is seen with low LET radiation. Similarly, repair of SLD is more with low-dose rate compared to high-dose rate radiation. NLD is one in which cell continues to reproduce.

BIODOSIMETRY

In biodosimetry, radiation-absorbed dose is determined by analyzing a biological sample such as blood obtained from the exposed person. It is useful in determining the radiation dose received by a person who is accidentally exposed to high radiation dose (>100 mGy). It helps the exposed individual in assessing the required course of medical management. Various biodosimetric techniques are: *(i) Dicentric Chromosome aberration (DCA) assay, (ii) micronucleus assay, (iii) FISH, (iv) premature chromosome condensation, and (v) γH2AX assay*.

For biological dosimetry purpose, the cell to be assayed should be matured with a long residence time in the body and should be easily obtained from the body. The small lymphocyte present in the blood is highly suitable for this purpose. Generally, the cell is in the stage of cell cycle; hence, it is ideal to collect these cells for biological dosimetry. Though various methods are available, the gold standard for estimation of radiation dose is DCA technique. It is referred as *chromosome aberration analysis (CAA)* and useful in the dose range of 0.1–6 Gy.

Dicentric chromosome aberration assay is based on dicentric scoring in a metaphase spread. This involves many steps with stringent requirements. To perform DCA assay, blood sample is collected within few weeks of whole-body exposure from the exposed individual, and lymphocytes are cultured in growth medium containing antibiotics and phytohemagglutinin (PHA) for 48 hours at 37°C. The PHA is added

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to stimulate cells to divide. At 45 hours, colcemide is added to arrest the cells at metaphase. At 48 hours, the culture is centrifuged, and the cells are suspended in 0.075 M KCl for 10 minutes to provide hypotonic treatment. The cells are then resuspended in fixative (3:1 methanol:acetic acid). Cells are washed again with the above fixative and the slides are prepared and stained with fluorescence and Giemsa. The cells are then scored for chromosomal aberration analysis. Cells having aberrations such as dicentrics and rings are carefully noted. For biological dosimetry purpose, several hundred cells are scored to get the right estimation of dose. The scoring is studied with a standard dose response curve to estimate the radiation dose.

It is important that the laboratory carrying out the biological dosimetry work must construct its own dose-response curve. The dose-response curve is prepared by exposing in vitro blood samples with different radiation doses. The aberration per cell for each dose is scored. Then, a graph is fitted between absorbed dose (Gy) and aberrations per cell in X- and Y-axis, respectively. The frequency of chromosome aberration is a LQ function of dose for low LET radiation.

MODIFICATION OF RADIATION DAMAGE OR CELL SURVIVAL CURVES

Radiation damage or shape of the survival curve can be modified by the following factors: (i) oxygen, (ii) LET, (iii) dose rate, (iv) dose fractionation, (v) cell cycle stage, (vi) radioprotectors, (vii) radiosensitizers, and (viii) hyperthermia. These are the physical and biological factors influencing cell survival often referred as dose-modifying agents.

Oxygen Effect

Oxygen is a radiosensitizer that can be used to increase cell killing. In the absence of oxygen, cells show resistance to cell killing. The ratio of dose required to bring certain level of damage with oxygen (euoxic) to that without oxygen (anoxic) is called *oxygen enhancement ratio (OER). Barendsen et al.* established the dependence of OER on LET for mammalian cells. Oxygen effect is very important for low LET radiations and it ranges from 2.5 to 3. The OER decreases as LET increases and become 1 for alpha and 1.6 for neutron. Hence, oxygen is important only for low LET radiations. Cells are well oxygenated, if the oxygen tension is about 20–40 mm Hg in human body.

It is believed that tumor consists both oxygenated and hypoxic cells. Since capillaries are far away, it limits diffusion of nutrients and oxygen to the cells deep inside the tumor. Hypoxic cells show high degree of resistance to radiation. Fractionation, hyperbaric oxygen, high LET radiation, hypoxic sensitizer, and hyperthermia can be used to overcome hypoxic cell resistance.

Linear Energy Transfer

The LET is the average energy deposited by the ionizing radiation per unit path length of the medium through which it traverses and is given by the unit keV/μm **(Table 2.1)**. More densely ionizing radiation deposits greater energy along their path than sparingly ionizing radiation (Refer Chapter 1, **Table 1.1**). All radiations can produce same type of biologic effects, but the magnitude of the effect per unit dose differs. In other words, different radiations of equal dose do not produce the same level

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of biologic response. To evaluate the effectiveness of different radiations, *relative biological effectiveness (RBE)* is used:

$$\text{RBE} = \frac{\text{Dose of high energy X-rays above 200 kV or } {}^{60}\text{Co or } {}^{137}\text{Cs gamma radiation required to produce certain effect}}{\text{Dose of test radiation required to produce the same effect}} \quad (2.5)$$

Effects include chromosomal mutation, cataract formation and acute lethality, etc.

Relative biological effectiveness increases with LET and reaches maximum at 100 keV/μm and decreases with further increase in LET **(Fig. 2.5)**. Maximum value indicates that the LET required to produce optimum number of ionizations to inactivate the cell and additional energy deposited get wasted. Thus, beyond 100 keV/μm, the RBE decreases with increasing LET due to overkill of cells.

Relative biological effectiveness variation depends not only on LET but also on dose rate, fractionation, temperature, oxygen concentration, pressure, absence of

TABLE 2.1 **The LET of X- and γ-rays and tissue penetration in HVL.**

X- and γ-rays energy (keV)	*LET (keV/μm)*	*HVL (mm) in tissue*	*Source*
80	1.0	38	Diagnostic X-rays
140	1.5	46	^{99m}Tc
364	2.8	65	^{131}I
511	3.5	70	Positron emitters
1,000	5.2	100	^{60}Co

(LET: linear energy transfer)
Courtesy: David J. Dowsett, 2006.

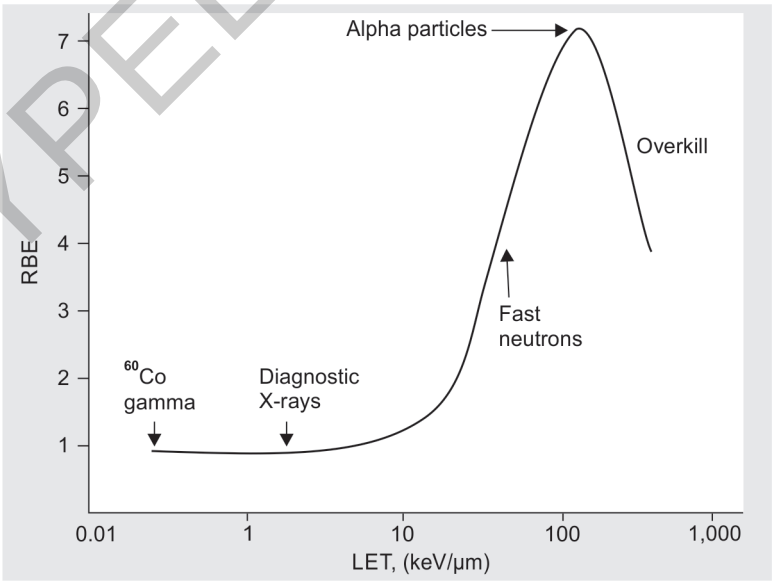


FIG. 2.5: The relation between linear energy transfer and relative biological effectiveness. It is flat initially, then increases with LET and reaches maximum later decreases.

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free radicals, and dose distribution within the irradiated material. The specific ionization of 100 ion pairs per micron in water due to X-rays is taken as unity, which is equivalent to LET of 3.5 keV per micron in water. The RBE values of different radiations are different **(Table 2.2)**.

High LET radiations such as carbon ions, negative pion, proton, neutron, and Cf-252 have higher RBE compared to X-rays. The hypoxic cell resistance is much lower and variation of radiosensitivity with cell cycle also smaller for high LET radiations.

Success of high LET radiations in radiotherapy depends upon the *therapeutic gain factor*. It is defined as the ratio of RBE for tumor cells to that of normal tissue. RBE values have been obtained for many tumors, and normal tissues. It is believed that tumor have higher RBE due to the presence of hypoxic cells. In many tumors, the RBE is between that of skin and the intestine. Hence, application of fast neutron in tumor depends on the type of tumor and the normal tissue associated with it.

Carbon ion radiotherapy (CIRT) is practiced in many centers due its highest LET and high RBE (2.5–5). It has Bragg peak and offers clustered damages in DNA. It provides higher dose distribution to the target while reducing dose to organs at risk (OAR). It is suitable for slow-growing tumors with dose escalation.

Cell Cycle

Cell sensitivity to radiation depends on phases of cell cycle due to variation of cell's repair capacity. Most sensitive cells are those in M and late G2 phase, their survival curve is steeper and has no shoulder. Cells in the late S phase are radioresistant and their survival curve is less steep with broader shoulder. Cells in G1 and early S have intermediate sensitivity. An asynchronous cell population is selectively killed in M phase during irradiation. Cells become synchronous after the dose fraction. Position of cells in the second fraction decides the degree of cell kill. To overcome the radiosensitivity variation of cell cycle, fractionation and high LET are used in radiotherapy.

Law of Bergonie and Tribondeau

The law states that cells are radiosensitive, if they *(i) have high-mitotic rate, (ii) have long mitotic future, and (iii) are undifferentiated (primitive).* Cells with high-mitotic rate (rapidly dividing) are relatively killed with low-radiation dose. They do not have enough time to repair cellular damage. Cells with low-mitotic rate show more radioresistant.

Rapidly dividing cells such as intestinal epithelium, bone marrow cells, and reproductive cells are more radiosensitive. Highly differentiated tissues such

TABLE 2.2 **RBE values for different radiations.**

Particle	***RBE***
X-rays, γ-rays, electrons	1
Thermal neutrons	Vary with energy and endpoint
Protons	2
Heavy particles e.g., alpha	20
(RBE: relative biological effectiveness) *Courtesy*: Kelsey CA, 2014.	

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as muscle and brain are least radiosensitive. Liver has long mitotic future and more sensitive than nerve cells. If a part of liver is cut, cells multiply, and liver is regenerated.

Dose Rate Effect

Survival curves of cells irradiated with low LET radiation at low-dose rate show much lesser steepness compared to that of high-dose rate due to repair of SLD of cells. Variation of effectiveness with dose rate is referred as dose rate effect and found in the range of 1 mGy/min to 1 Gy/min. It is absent at high LET radiation since the damage is less accessible to repair.

In clinical radiotherapy, effective cell killing demands a critical dose rate. In critical dose rate, cells are arrested in mitosis and die while attempting division. Critical dose rate for HeLa cells having cell cycle time of 24 hours is 0.3 Gy/h. Wide range of dose rate is used in radiotherapy, few Gy/min in external radiotherapy and 0.5 Gy/h in brachytherapy. 1–125 seeds use 1.3 Gy/day in seed brachytherapy.

Dose Fractionation

Mammalian cell is characterized by wide shoulder and an exponential region at low doses. Initial shoulder reflects the cell's ability to accumulate some damage before it is killed. The damage below the critical level required for cell killing is called sub lethal dose (SLD). *Elkin and Sutton* had showed the ability of cell to recover from such SLD. A given total dose delivered as single fraction is more effective compared to the same dose delivered in two or more fractions separated by an interval. Following irradiation, cells in M phase are killed and those cells in S phase survive. During the interval between fractions, cell survival increases initially and then decreases and reaches a dip at 6 hours, and again increases. The rise in survival during the first 2 hours is due to repair of SLD. After 2 hours, there is a progression of cells into other phases, which results in a dip in the curve.

Recovery of SLD is possible with dose fractionation techniques. Normal tissue recovers in-between fractions and reduces their damage. Survival curves reappear with shoulder in such fractionation. It is also believed that normal tissue repair is better than tumor cells. Fractionation also helps hypoxic cells to certain extent by redistributing cells in the sensitive phases of the cell cycle. However, its role is limited in high LET radiation. Some tumors have wide shoulder, indicate their ability to accumulate SLD, and perform repairs. It may be reason for failure of radiotherapy in certain cases.

Radioprotector

Chemical compound, which offers protection against radiation, is called radioprotector. It causes vasoconstriction by metabolism and reduces oxygen concentration. Cells become hypoxic and get protected from radiation. Such chemicals include -NH_2 and -SH groups, e.g., cysteine. *Dose reduction factor (DRF)* is the ratio of the dose required to produce certain effect with protector to that required to produce the same effect without protector. The maximum DRF that can be obtained is about 1.7.

Radioprotectors scavenge free radicals produced by indirect action and donate hydrogen atom to restore DNA structure. It blocks the proxy radicals formed in the presence of oxygen. However, they are ineffective under high LET radiation. New

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