# Basic Radiation Oncology

Bearbeitet von
Murat Beyzadeoglu, Gokhan Ozyigit, Cüneyt Ebruli

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# Radiobiology

# 2

Murat Beyzadeoglu, Gokhan Ozyigit, and Cuneyt Ebruli

## 2.1 Cell Biology and Carcinogenesis

Radiobiology, in general terms, is the science that evaluates the effects of radiation in living organisms. In the field of radiation oncology, it is defined as the science that investigates the interactions between ionizing radiation and living systems, and the consequences of these interactions.

### 2.1.1 Cell Structure

Atoms form molecules, molecules make macromolecules, macromolecules build complex organic structures, and then cells – which are the main structural component of tissues, and reflect all features of life – are formed. All cells have generally similar structures. However, they specialize according to the location of the tissue (i.e., according to the functions of that tissue). The basic structures of all organisms are formed from these cells. In humans, there are approximately $10^{14}$ cells [1].

All cells are surrounded by a cell membrane, and they have a liquid-like cytoplasm and organelles within the membrane (Fig. 2.1).

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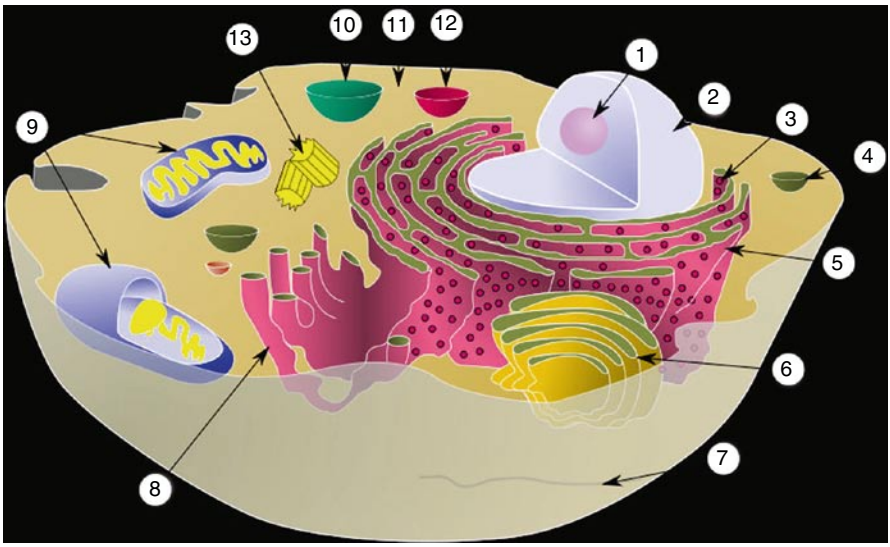



**Fig. 2.1** Schematic illustration of a eukaryotic cell. *1*, Nucleolus; *2*, nucleus; *3*, ribosome; *4*, vesicle; *5*, rough endoplasmic reticulum (ER); *6*, Golgi apparatus; *7*, cytoskeleton; *8*, smooth endoplasmic reticulum; *9*, mitochondria; *10*, vacuole; *11*, cytoplasm; *12*, lysosome; *13*, centrioles within a centrosome

### 2.1.2 Cell Types and Organelles

Cells can be simply divided into two categories: prokaryotic cells and eukaryotic cells [2].

- **Prokaryotic cells.** Bacteria and blue–green algae belong in this group. These cells have no nucleus and are surrounded with a nuclear membrane. In addition, they do not have any membranous organelles, such as mitochondria. DNA – genetic material – is scattered within the cytoplasm. These cells do have ribosomes. The vital functions of this type of cell are performed in the cytoplasm and cellular membrane.
- **Eukaryotic cells.** These cells have membranous organelles, so their nuclear material is not scattered within the cytoplasm, and they have a real nucleus. Eukaryotic cells are more highly developed than prokaryotic cells – the cells of animals, plants, fungi and protists are eukaryotic. These cells have organelles in their cytoplasm. Chromosomes, consisting of DNA and proteins, are located in the cell nucleus. Eukaryotic cells divide by mitosis.

**Cytoplasm.** The cytoplasm is a semifluid matrix that fills the space between the cell membrane and the nucleus. All vital events occur in the cytoplasm in a living organism. It generally forms a homogeneous transparent mass.

**Mitochondria.** These are ellipsoidal or cudgel-shaped organelles of length 2–3 μm and diameter 0.5 μm. They are the energy-generating unit of cells. The citric acid cellular respiration cycle (the Krebs cycle) occurs in this organelle. The energy released by breaking the chemical bonds of organic molecules is transformed into ATP within mitochondria.
**Lysosome.** This is a round organelle surrounded by a membrane, and it contains hydrolytic enzymes. They perform the function of digestion in the cell, clearing away excessive or harmful intracellular structures.
**Golgi apparatus.** The Golgi apparatus or complex consists of a combination of membranous tubes or saccules. It is generally close to the nucleus, and is particularly conspicuous in actively secreting secretory cells. Its main function is believed to be the storage of proteins secreted by the cell. It performs the functions of secretion and packing.
**Endoplasmic reticulum.** The endoplasmic reticulum ensures that nutrition circulates in the cytoplasm and synthesizes lipids and hormones. It is a complex serial channel system located between the cell membrane and the nuclear membrane. If it does not contain ribosomes it is called "smooth endoplasmic reticulum." This secretes steroid hormones in steroid-secreting cells and performs detoxification in others.
**Ribosome.** Ribosomes are located along the channels of the endoplasmic reticulum and are found scattered within the cytoplasm. They perform protein synthesis. They are approximately 150 Å in diameter. Their structures are composed of 65% RNA (ribonucleic acid) and 35% protein. Proteins synthesized by ribosomes are sent to either intracellular or extracellular regions with the aid of the endoplasmic reticulum.

**Cell nucleus.** This has a granular and fibrous structure (Fig. 2.2). Most of the genetic information of the cell is located in the cell nucleus within chromosomes, which are long, linear, folded DNA molecules formed through the collection of many proteins like histones. The genes located in these chromosomes comprise the nuclear genome of the cell. The role of the cell nucleus is to maintain the integrity of these genes and to control cellular functions by arranging gene expression.
**Nuclear membrane.** This is the outer covering of the nucleus. Ribosomes are stuck in the nuclear membrane, and it contains pores.
**Chromatin.** This is the structure that transforms into chromosomes during division and when moving towards poles.
**Nucleolus.** This is the center of the nucleus, and it synthesizes proteins and ribosomes.
**Nuclear matrix.** This fills the space between the chromatin and the nucleus, and contains proteins and ions.

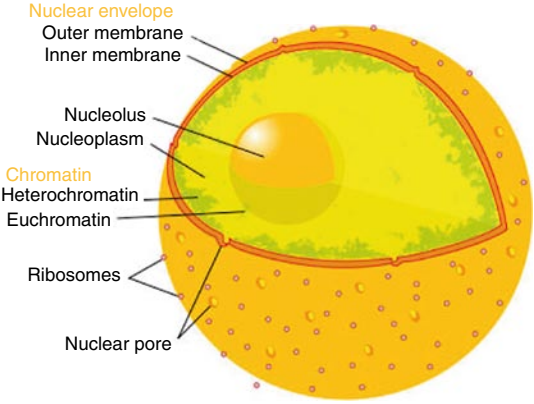



**Fig. 2.2** Eukaryotic cell nucleus

**Chromosome** [3]. The nucleus contains most of the genetic material in the cell (Fig. 2.3). This genetic material actually consists of multiple linear DNA molecules called chromosomes. Chromosomes are found in the form of a complex combination of DNA and proteins termed chromatin during most of the cell cycle, and chromatin forms the chromosomes of one karyotype during division (Fig. 2.4).

A small number of cellular genes are found in mitochondria:

1. Chromatid
2. Centromere
3. Short arm
4. Long arm

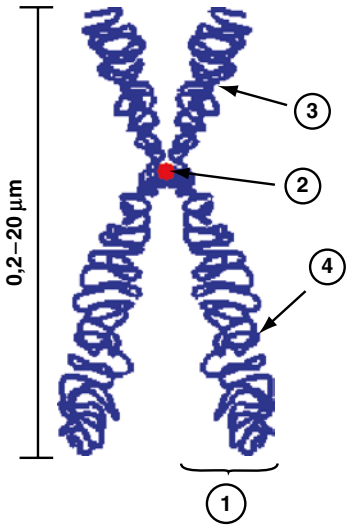



**Fig. 2.3** The structure of a chromosome

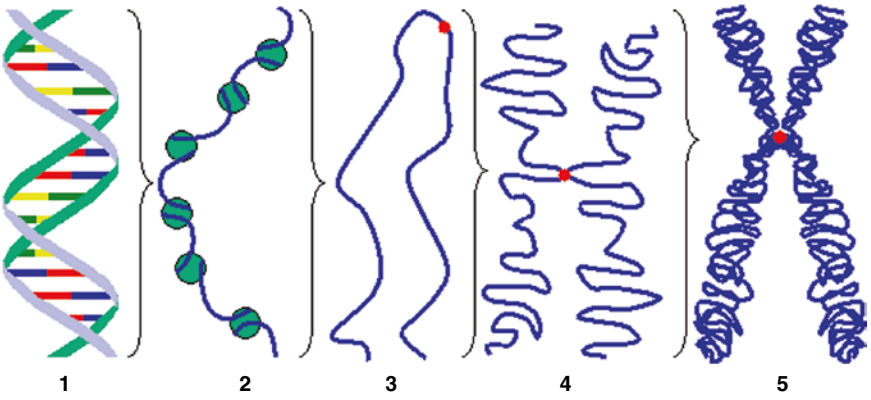



**Fig. 2.4** Relationship between DNA and chromosomes. *1*, DNA; *2*, DNA+protein; *3*, chromatin; *4*, chromatids; *5*, chromosome. DNA molecules combine and make proteins, proteins form chromatins, chromatins mate with each other during division and become chromatids, and chromatids combine and forms chromosomes

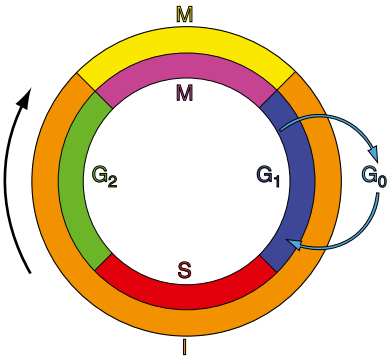
### 2.1.3 Cell Cycle

During its life, a cell generally exhibits a long period or phase (interphase) during which no division occurs, and a division phase (mitosis). This is called the cell cycle [4]. The cell cycle is repeated at each cellular stage, and the length of time corresponding to a cell cycle varies with cell type (Fig. 2.5). The interphase is very long in some cells, and these types of cells never divide during the life period of the organism (an example is a neuron). Generally, cells grow until they reach a certain size, then they divide.

**M: Mitosis**
- Prophase
- Metaphase
- Anaphase
- Telophase

**I: Interphase**
- $G_1$
- $S$
- $G_2$
- $G_0$

**Fig. 2.5** Cell cycle and its stages




**The Stages of Mitosis** [4]

Mitosis is the division of a cell into two cells through the mating of its genome. Mitosis is only observed in eukaryotic cells. Somatic cells are formed via mitosis, whereas germ cells are formed by meiotic division.

1. **Prophase** (Fig. 2.6)
   The nuclear membrane and endoplasmic reticulum disappear.
   The chromosomes shorten and thicken.
   Centrosomes move towards opposite poles.
   The nucleolus disappears.
   Spindle cells form from the poles to the center.
2. **Metaphase** (Fig. 2.7)
   The chromosomes shorten and thicken further.
   Sister chromatids are kept together using centromeres.
   The chromosomes are arranged side-by-side in a row in the equatorial plane.
   The chromosomes hold on to spindle cells with their centromeres.
3. **Anaphase** (Fig. 2.8)
   The contraction and relaxation movements of spindle cells break the centromeres that lock the chromatids together.
   The sister chromatids are separated from each other and are moved to opposite poles.
4. **Telophase** (Fig. 2.9)
   The chromosomes stop moving.
   The chromosomes unwind their helices and become chromatins.
   The nucleolus reappears.
   RNA and protein syntheses start.
   Spindle cells disappear.
   The nuclear membrane forms, and the endoplasmic reticulum takes on a shape again.
   Vital events restart in the cell.
   Cytogenesis occurs, and division finishes.

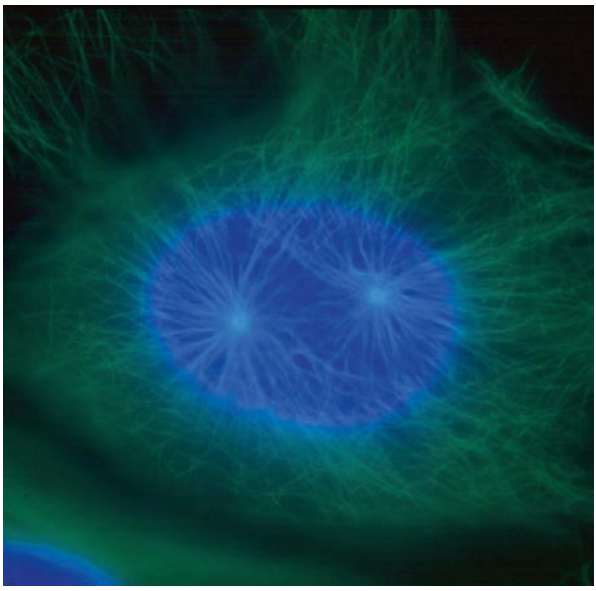


**Fig. 2.6** Prophase

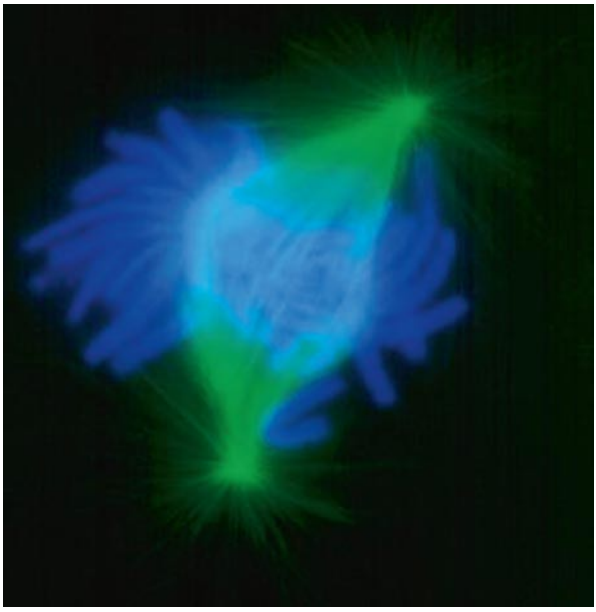


**Fig. 2.7** Metaphase

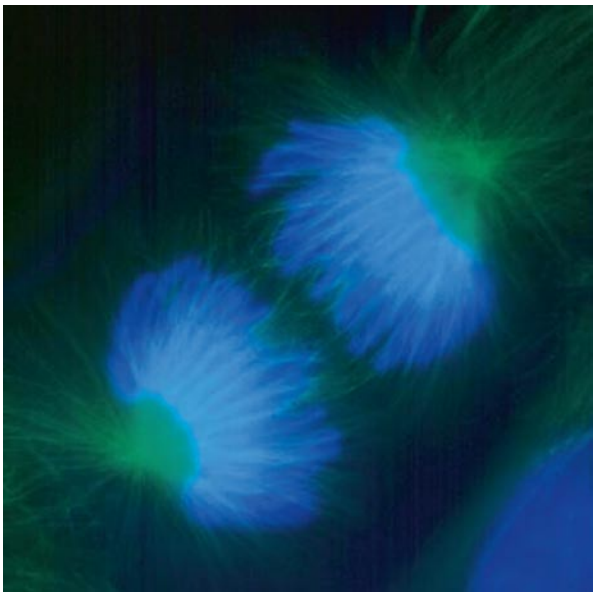


**Fig. 2.8** Anaphase

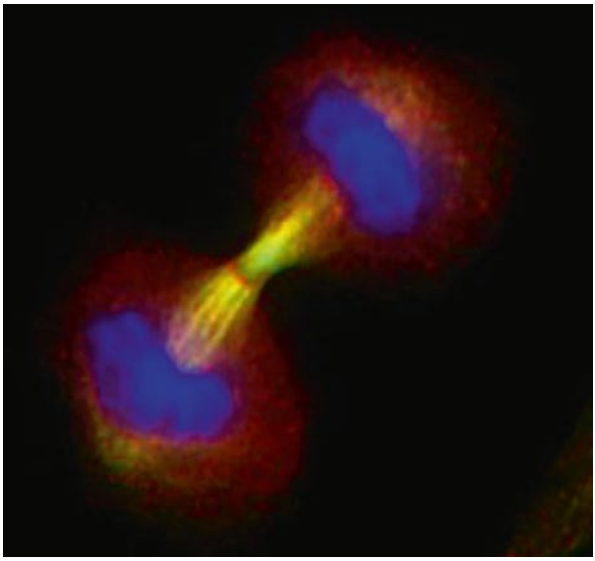


**Fig. 2.9** Telophase

**Interphase and Its Stages** [4, 5]

The interphase is the preparation phase for the redivision of a divided cell. It is the longest phase of the eukaryotic cell cycle. For instance, the interphase of a human skin cell is about 22 h, while the cell cycle of such a cell lasts approximately 24 h. The interphase is divided into three stages.

**$G_1$ → (G: $Gap_1$)**

This occurs just after cytogenesis.

Metabolic events continue intensely.

This is the stage where matter transportation, synthesis, lysis reactions, organelle production, RNA synthesis and tissue functions continue at their highest levels.

It is the longest stage. Dividable cell growth occurs during this stage.

Cells that lose their ability to divide continue with their functions and life activities (e.g., muscle and nerve cells still function at this stage).

**S → (S: Synthesis)**

DNA is duplicated and the number of chromatins doubles (→ replication).

The most intense protein synthesis is performed at this stage.

The order of centromere duplication is observed.

**$G_2$ → (G: $Gap_2$)**

Enzymes related to division are synthesized.

The number of organelles increases.

DNA synthesis finishes, but RNA synthesis continues.

Centrosome synthesis finishes, and these centrosomes start moving towards opposite poles.

**$G_0$ phase**

Cells have a natural mechanism that protects them during difficult developmental conditions. Under these conditions, the cells transiently stop their cellular activities. This phase is called the $G_0$ phase. In the $G_0$ phase, some genes in the DNA are covered with various proteins; i.e., the DNA is programmed.

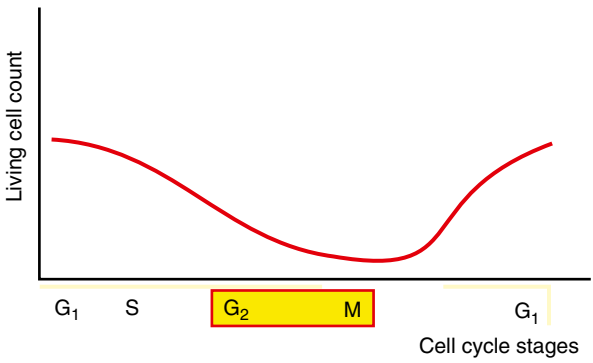



**Fig. 2.10** Relationship between cell cycle stages and living cell count

The most radiosensitive stages during the cell cycle are the early $G_2$ and M stages (Fig. 2.10).

The radiosensitivity of a cell is fourfold greater during the mitotic phase than during the interphase. Radioresistance is high in the S, late $G_1$ and $G_0$ phases. The resistance of the S phase is due to the large amounts of synthesis enzymes present, which have the ability to rapidly repair DNA.

### 2.1.4 Carcinogenesis and the Cell Cycle

Cell proliferation in tissues is a normal function in organisms. Decreasing cell proliferation or increasing the death rate prevents any excessive increase. The replication of cell into two similar cells is prompted by extrinsic biochemical signals, and a series of phases regulated by inner or outer growth factors occur. Some oncogenes and proteins specific to the cell cycle are activated synchronously throughout the cell cycle and are then inactivated.

**Oncogenes.** Genes that are mutated or synthesized in abnormally excessive amounts and easily transform normal cells into cancer cells are termed oncogenes.

The development of cancer at the cellular level is termed *carcinogenesis*. The combination of mutations that affect biological events such as cell survival, growth control and differentiation is the basis for carcinogenesis. Tumor cells gain several phenotypic features during the development of cancer. Those changes cause the rapid and uncontrolled proliferation of tumor cells, as well as their spread to surrounding tissues. In addition, those cells can survive independently in specific microenvironments and have the ability to metastasize.

**Cyclins** [6]. These are specific proteins that activate various phases of the cell cycle. Most cells with proliferative abilities divide as a response to external signals like growth factors, some hormones, and antigen histocompatibility complexes that affect cell surface receptors. These cell surface receptors transmit the received signal to the nucleus and the cell divides. Tyrosine kinases are an important component of cascade reactions, which are initiated by proliferative signals from extracellular growth factors, and propagate to the nucleus. Cyclins combine with specific tyrosine kinases called cyclin-dependent kinases, activating them as well as regulating their effects. Various cyclins are synthesized throughout the different phases of the cell cycle, and their levels either increase or decrease synchronously during each phase of the cell cycle.

Cells with proliferative capacity normally stop at certain checkpoints. The most important of these is the first, which occurs just before DNA synthesis, and the second, which occurs just prior to mitosis. These histologic resting periods probably occur due to the decreased activity of cyclin-dependent kinases and tumor suppressor proteins. Actually, since cells in these phases of the cell cycle synthesize the proteins used in the next phases, they are biochemically active. At these checkpoints, any genetic defects are repaired. In summary, while the cell progresses through the cycle, it stops at two checkpoints and is controlled. Normal cells have mechanisms for detecting errors in the DNA sequence. A group of repair mechanisms replace damaged nucleotides with normal molecules when the DNA is damaged. These mechanisms ensure that the genetic material in each of the two daughter cells is the same as that of the mother cell.

**The first checkpoint of the cell cycle** [7]. This is located in the late $G_1$ phase just prior to the S phase. DNA should be error-free before it exits from $G_1$, and even extracellular signals specific for DNA synthesis and all of the mechanisms should work properly. If any damage is detected, the cells try to either repair the damage or die by apoptosis. The protein p53 plays a prominent role in checking for DNA damage at this checkpoint.
**The second checkpoint of the cell cycle** [7]. This is located just prior to the M phase. Cell cycle inhibitors stop the cell cycle until they are sure that the new daughter cells will have perfect genetic copies of the DNA in the original cell. If DNA replication does not finish entirely and correctly, or all of the proteins, spindle cells and other materials needed for mitosis are not formed completely, the cell cycle stops at this checkpoint until all errors have been corrected. It then enters the M phase.

A small proportion of the normal cell population consists of immortal cells (i.e., they have the capacity for unlimited division). These cells can renew themselves based on signals from other parts of the organism; they also mature and differentiate into new cells that perform the required functions of the organism. However, only a few tissue types can differentiate; most lose their survival abilities, passing into the resting period after aging, and consequently die. Eukaryotes have four populations of cells.

**Eukaryotic Cell Populations** [8]

*Germ cells*. These have the capacity for unlimited proliferation, probably due to meiotic division. Unlike cancer cells, these cells form immortal cell lines through meiotic division.

*Stem cells*. These cells have two functions. The first is proliferation; the second is differentiation and then to carry out the required specific functions of the organism. Unlike cancer cells, these cells can only pass through a limited number of cell cycles.

*Partially differentiated cells*. These have a limited capacity for proliferation, and their daughter cells are fully differentiated with no proliferative ability.

(*continued*)

(continued)

*Fully differentiated cells*. These cells never proliferate.

- Differentiated normal cells, in contrast to immortal cancer cell lines, have a biological timer that counts the number of cell divisions. When a certain number of divisions have occurred, the cell cannot divide any further. For instance, human fibroblast cells divide approximately 50 times in cell lines. After that, they cannot divide, regardless of the nutritive conditions present.

### 2.1.5 Features of Cancer Cells

Cancer is a disorder characterized by the continuous proliferation of cells [9]. This event happens when the increase in the number of excessively proliferating cells is not balanced by normal cell loss. These cells continuously invade and damage the organs of organisms. Although cancer cells die more quickly than the normal cells they derive from, new cell formation occurs so quickly that the cancer cells accumulate. This imbalance arises from both the genetic abnormalities of cancer cells and the inability of the organism to recognize and destroy these cells.

**Unique Features of Cancer Cells** [9, 10]

*Clonal origin*. Most cancer cells originate from just one abnormal cell. However, some cancers arise from more than one malign clone. These clones are formed because of either field damage (tissue cells exposed to more than one carcinogen) or heritable defects in some genes.

*Immortality*. Most normal cells can undergo a limited number of divisions. On the other hand, cancer cells can undergo an unlimited number of divisions and form endless numbers of cells. One of the mechanisms for immortality is associated with telomeres, which are the tips of chromosomes. During normal cell differentiation in, these telomeres shorten. However, the telomeres are renewed by the effect of the enzyme telomerase in cancer cells and stem cells. Telomerase activity normally decreases during cell differentiation. Since the cell loses its capacity for proliferation, fully differentiated cells enter a resting state and consequently die. However, telomerase retains its efficacy in several cancer types, or it is reactivated. Therefore, the telomere length remains constant in these cells and they proliferate indefinitely (they become immortal).

*Genetic instability*. This situation is caused by defects in the DNA repair process and in DNA mismatch recognition, which results in the heterogeneity of cancer cells. Cancer cells form clones that gradually respond less and less to the proliferation control mechanism. The ability of these clones to survive in foreign environments also gradually increases, and they gain the ability to metastasize.

*Loss of contact inhibition*. Normal cells growing in culture medium cannot divide if they do not stick to the bottom layer. Normal cells also lose their ability to divide when they form a layer across the whole surface. They do not divide, even in the presence of all of the required growth factors and other nutritional elements in the Petri dish. Cancer cells, however, divide independently without needing to stick to the bottom layer of the Petri dish. Furthermore, they continue to grow even when they have formed more than one layer in the cell culture.

*Continuous increase in proliferation*. This situation is a characteristic of cancer cells in culture medium. Although cancer cells consume the required nutrition factors, they continue to grow, and they actually end up killing themselves.

*Metastasis*. This feature is not found in benign tumors and normal cells. Metastasis occurs because of the loss of cellular proteins responsible for adherence to the extracellular matrix, intercellular interaction defects, abnormalities in cell adherence to the basal membrane, abnormalities in basal membrane production, or the destruction of basal membrane by enzymes like metalloproteases.

## 2.2 Cellular Effects of Radiation

Ionizing radiation injects energy into a material as it passes through it, like a microscopic bullet, until the radiation is stopped by the material due to absorption [11]. In addition, radiation breaks the molecular bonds of the material in its path, and changes the structure of the material. If the material consists of long molecular chains, the chains that are broken by the radiation form new bonds at random. In other words, radiation cuts long molecules at various positions, like a welding flame, and reconnects them in different ways.

Living cells commonly consist of long protein chains, and some of these molecules can be broken by exposing the cell to radiation. The molecular fragments can then rebond in various ways, resulting in new molecules. These new molecules cannot function like the original molecules, and so they need to be repaired. Otherwise, these defective molecular structures will accumulate in the cell, changing the cell's metabolism; if the defective molecule is DNA, it can result in the formation of a cancer cell. Cells have certain repair mechanisms that they can employ for this type of damage. Cells in developed organisms can even check their molecules one by one, and they prefer to rebuild these molecules at certain intervals rather than repairing any damage. However, the capacity for cell repair is limited, and if this limit is exceeded, the damaged molecules will start to accumulate and affect the vital survival functions of the cell.

There is no such thing as a fully radioresistant cell. Structures that form the cell, such as the nucleus, and particularly chromosomes undergoing division, are more radioresistant than the cell cytoplasm. One of the most prominent effects of radiation at the cellular level is the suppression of cell division. The growth of cells that are exposed to radiation, particularly during cell division (mitosis), is interrupted.

The presence of ionizing radiation increases mutation frequency. Mutation frequency is linearly related to dose (Fig. 2.11). Since low mutation rates occur with low doses, this relation is not linear at low radiation doses. Dose rate (i.e., the amount of radiation received over a specific amount of time) does not affect mutation frequency. In other words, the total number of mutations is the same regardless of the period of exposure to the radiation [12].

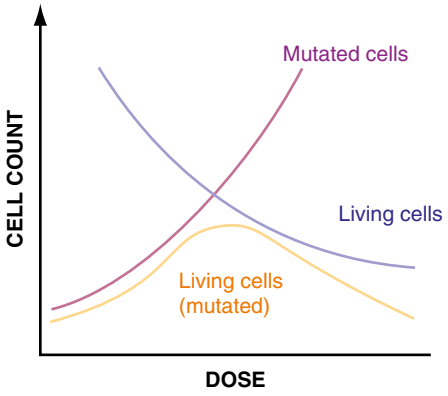



**Fig. 2.11** Relationships between dose and mutated cell, living cell, and mutated living cell counts

Ionizing radiation can cause breaking, sticking, clamping and curling in chromosomes. Broken chromosomes can reorganize, remain the same, or combine with other chromosomes. All of these events result in mutations or in eventual cell death (Fig. 2.12).

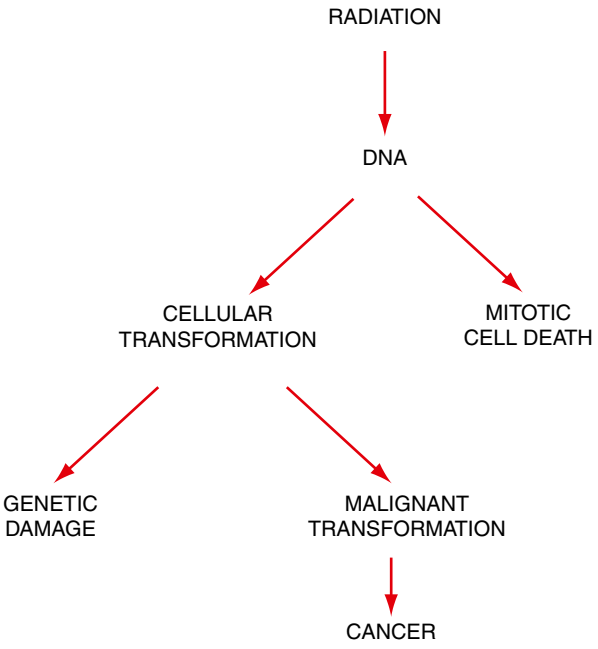



**Fig. 2.12** Radiation and carcinogenesis

Although all molecules can be damaged by radiation, DNA molecules that carry genetic information related to cell division and growth are the most probable targets. Radiation may damage or change a small part of the DNA molecule (e.g., only one gene); it can break one or several locations on the DNA helix. The damage is repaired in most cases, but cell death or transformation is observed in some circumstances, and this may result in malign transformations and cause cancer. Dead cells are normally eliminated by the organism. However, if the number of cell deaths exceeds a certain limit, they will affect the proper functioning of the organism and can kill it.

Radiation can have direct and indirect effects on DNA molecules.

### 2.2.1 The Direct Effect of Radiation at the Molecular Level

Radiation directly affects DNA molecules in the target tissue (Fig. 2.13a) [13]. The direct ionization of atoms in DNA molecules is the result of energy absorption via the photoelectric effect and Compton interactions. If this absorbed energy is sufficient to remove electrons from the molecule, bonds are broken, which can break one DNA strand or both (Fig. 2.13b, c). A single broken strand can usually be repaired by the cell, while two broken strands commonly result in cell death.

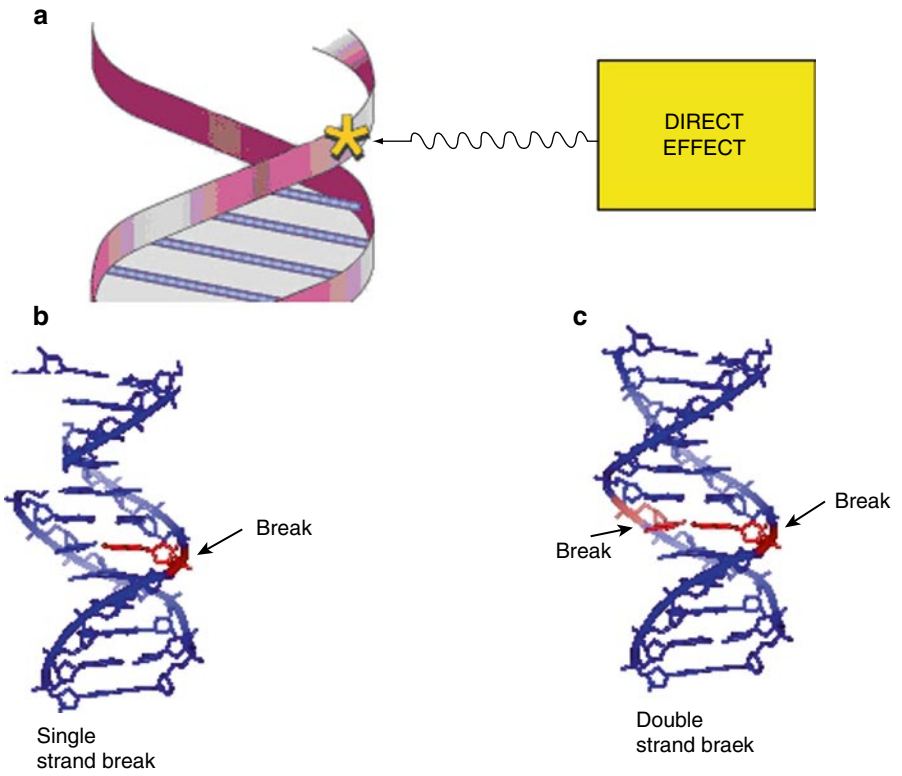



**Fig. 2.13** (**a**) Direct effect of radiation. (**b**) Single-strand DNA break. (**c**) Double-strand DNA break

A dose of 2 Gy of X-rays is equal to an energy of 2 J/kg. Since 1 J/kg is equal to $6.25 \times 10^{18}$ eV/kg [13], 2 Gy is equal to $12.5 \times 10^{18}$ eV/kg. Since the minimum energy required for ionization is 33 eV, the number of ions per kilogram is calculated by dividing $12.5 \times 10^{18}$ eV/kg by 33 eV, which yields $\sim 4 \times 10^{17}$ ions/kg. If we apply two doses to the whole body (we know that there are $9.5 \times 10^{25}$ atoms/kg in the human body), the number of atoms in the whole body ionized by a dose of 2 Gy can be found by dividing the ions/kg by the atoms/kg. The result is nearly $1 \times 10^{-8}$ (one in a hundred million), which means that the direct effect of X-rays in terms of DNA damage in tissue is relatively minor.

The direct effect of radiation is to ionize molecules in its path. While the direct effect of low linear energy transfer (LET) radiation is largely insignificant (e.g., in terms of DNA damage), the direct effect dominates for high-LET radiation [13].

LET → loss of energy per unit tract length.

When normal cell DNA is damaged by radiation provided in the kinds of doses normally used in radiotherapy, the cell cycle is stopped by the protein p53. The DNA is repaired; the cell then re-enters the cell cycle and continues to proliferate. If the DNA cannot be repaired, the cell enters apoptosis – the programmed cell death pathway. At high radiation doses, the molecules utilized by the DNA repair mechanisms are damaged, so repair is not possible, the cell loses its ability to divide, and it subsequently dies.

A quarter to a third of the damage produced in cellular macromolecules by radiation is due to its direct effect. This means that most of the damage is caused by the indirect effect of the radiation. Damage to cellular proteins following irradiation at biologically relevant doses appears to be of relatively minor importance.

### 2.2.2 The Indirect Effect of Radiation at the Molecular Level

The indirect effect of radiation on molecules includes the formation of free radicals by energy transfer from radiation, and the resulting molecular damage caused by the interactions of these free radicals with DNA (Fig. 2.14) [13, 14]. This phenomenon is most probably due to the interaction of radiation with water molecules, since the human body is approximately 70% water. Free radicals are electrically neutral atoms that contain “free” (i.e., unbound) electrons. They are highly electrophilic and reactive.

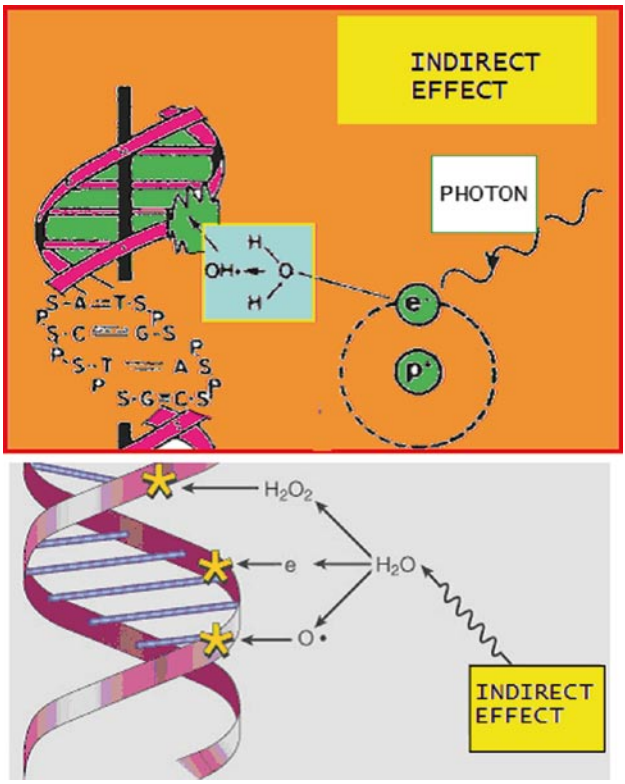



**Fig. 2.14** Indirect effect of radiation (Fig. 1.1 of [65])

Water ($H_2O$) is ionized when exposed to radiation, and as $H_2O \rightarrow H_2O^+ + e^-$, a positively charged water molecule and a free electron are formed [14].

This free electron ($e^-$) interacts with another water molecule in the reaction $e^- + H_2O^+ \rightarrow H_2O^-$, resulting in the formation of a negatively charged water molecule.

These charged water molecules undergo the reactions $H_2O^+ \rightarrow H^+ + OH$ and $H_2O^- \rightarrow H + OH^-$, yielding $H^+$ and $OH^-$ ions. These H and OH free radicals may combine with other free radicals or with other molecules.

If the LET of the radiation is high (particularly in the case of alpha particles), the free $OH^-$ radicals do not recombine with $H^+$ radicals, and so they do not form $H_2O$. They combine with each other in the reactions $OH^- + OH^- \rightarrow H_2O_2$ and $H^+ + H^+ \rightarrow H_2$, forming hydrogen peroxide and hydrogen gas molecules [14].

Simple free radicals (H or OH) have very short lifetimes ($10^{-10}$s), and this time span is too short for them to travel from the cytoplasm to the nucleus, where the DNA is located. Therefore, the H combines with $O_2$ and transforms into a more potent and lethal free radical with a longer lifetime, called hydrogen dioxide ($HO_2$) [14]. Although hydrogen peroxide,

$H_2O_2$, has an even longer lifetime ($10^{-5}$s), it cannot move from one place to another. It oxidizes the surroundings of the cells close to where it is formed, and prevents the nutrition of neighboring tissues or cells. This results in cell death through nutritive deficiency or the isolation of these cells from other tissues.

Free radicals formed by the hydrolysis of water affect DNA. The negative effect of hydrogen peroxide on cell nutrition may be employed as evidence of the indirect effect of radiation.

## 2.3 Factors Modifying the Biological Effects of Ionizing Radiation

The biological effects of ionizing radiation depend on factors such as the characteristics of the radiation (energy, intensity, content) and the target (structure of irradiated tissue; age, gender, general health of the person exposed to the radiation).

### 2.3.1 Characteristics of the Radiation

The potential harm to biological materials caused by their irradiation is directly proportional to the efficacy with which the radiation deposits energy in the material. Proton, neutron and alpha particles lose their energies over much shorter distances than X-rays and gamma rays with the same energy.

**Linear Energy Transfer** (Table 2.1) [15]

The energy transferred to the tissue by ionizing radiation per unit tract length is called the LET.

- The LET is a function of the charge and the velocity of the ionizing radiation.
- The LET increases as the charge on the ionizing radiation increases and its velocity decreases.
- Alpha particles are slow and positively charged. Beta particles, on the other hand, are fast and negatively charged. Therefore, the LET of an alpha particle is higher than that of a beta particle.
- Lethal effects increase as the LET increases.
- The units of the LET are keV/μm.

Since high-LET radiation (particulate radiation) transfers more energy per unit length of material, the probability of causing DNA damage in a short period of time is high. Thus, a

**Table 2.1** LET values for various radiation types [15]

| Radiation | Energy | Relative LET value (keV/μm) |
|---|---|---|
| 250 kV X-ray | 250 kV | 3 |
| 3 MV X-ray | 3 MV | 0.3 |
| Cobalt 60 | 1.17–133 MV | 0.3 |
| Beta 10 kV | 10 kV | 2.3 |
| Beta 1 MV | 1 MV | 0.25 |
| Neutron 2.5 MV | 2.5 MV | 20 |
| Neutron 19 MV | 19 MV | 7 |
| Proton 2 MV | 2 MV | 16 |
| Alpha 5 MV | 5 MV | 100 |

dose of high-LET radiation is more destructive than the same dose of low-LET radiation (electromagnetic radiation).

**Absorbed dose** [16]. The basic quantity of radiation measurement in radiotherapy is the "absorbed dose." This term defines the amount of energy absorbed from a radiation beam per unit mass of absorbent material. The unit of absorbed dose is the Gray (Gy). It changes continuously along the path of the radiation because the radiation slows down. In addition, secondary radiation energies occur due to secondary scattering from the particle's path in tissue. The type and effects of each form of radiation type should be known exactly in order to define the total effect of the radiation.

**Equivalent dose (= dose equivalent)** [16, 17]. Different radiations cause different damages in human tissues. The *absorbed dose* (→ Gy) is not adequate for studies of radiation protection. Thus, the absorbed dose in tissue should be multiplied by the radiation weighting factor for this radiation type. The calculated result is defined as the equivalent dose, measured originally in roentgen equivalent in man units (REMs), but now measured in Sieverts (Sv).

If the mean absorbed radiation dose (Gy) in a tissue or organ is multiplied by the appropriate radiation weighting factor ($W_R$), the equivalent dose ($H_T$) is found.

Sv is a large unit, so doses are frequently expressed in millisieverts (mSv) or microsieverts (μSv) for practical purposes.

Radiation weighting factors ($W_R$) are determined in order to compare the biological effects of different radiation types [18, 19]. These weighting factors are also called radiation quality factors (QF) (Table 2.2).

**Table 2.2** Weighting factors for various radiation types (ICRP 1991)

| Radiation type | Energy interval | Weighting factor = quality |
|---|---|---|
| Photon (gamma and X-rays) | All energy levels | 1 |
| Electron | All energy levels | 1 |
| Neutron | <10 kV | 5 |
| Neutron | 10–100 kV | 10 |
| Neutron | 100 kV–2 MV | 20 |
| Neutron | 2–20 MV | 10 |
| Neutron | >20 MV | 5 |
| Proton | >20 MV | 5 |
| Alpha particles, heavy nuclei | All energy levels | 20 |

**Dose Rate** [20]

This is the dose delivered per unit of time. If a radiation dose that causes irreparable damage when delivered over a short time period is delivered over longer periods, the cell or organism may survive.

## 2.4 Target Tissue Characteristics

Different tissues have different radiosensitivities. Cells that divide frequently (e.g., blood-forming cells in the bone marrow) are frequently affected by radiation more than rarely dividing cells (e.g., connective and fat tissue). Metabolic factors such as the oxygen concentration in the irradiated volume are also important.

The International Commission on Radiological Protection (ICRP) defined a mean reference human in order to estimate the absorbed doses at certain places on the body (Fig. 2.15). In general, the results on radiation absorption obtained in this way can be related to real irradiation. A further simplification was recommended by the ICRP in 1977. The recommended limits on dose equivalence are based on regular irradiation of the whole body. Irradiation of the whole or only part of the body can be expressed as the equivalent whole-body irradiation by taking into account weighting factors for certain organs (Table 2.3) [18, 19].

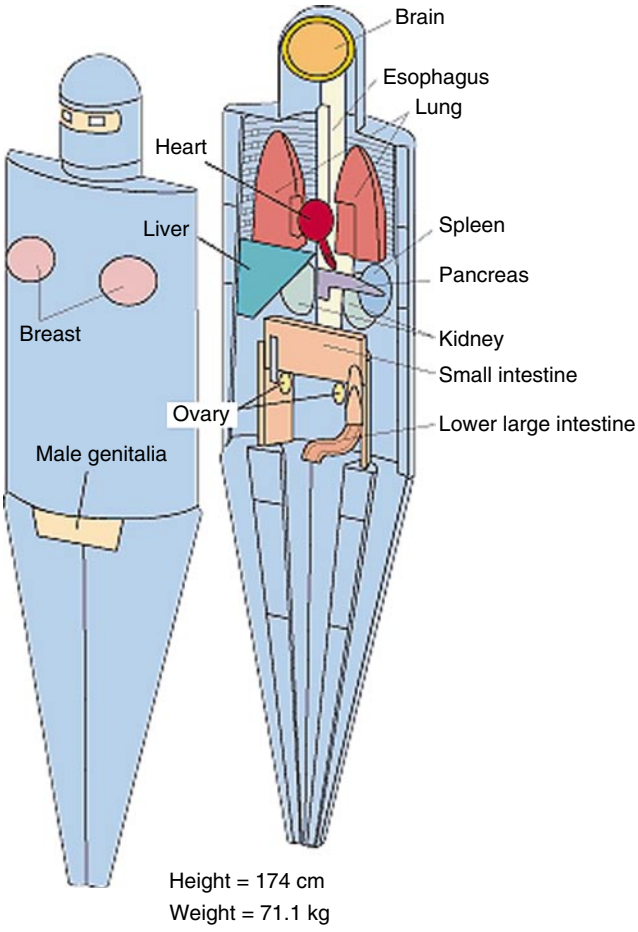



**Fig. 2.15** Reference human according to the ICRP (Fig. 4.21 of [66])

**Table 2.3** Tissue weighting factors

| Tissue | Tissue weighting factor ($W_T$) |
|---|---|
| Gonads | 0.20 |
| Lung, bone marrow, stomach, colon | 0.12 |
| Thyroid, liver, esophagus, breast, bladder | 0.05 |
| Bone surface | 0.01 |
| Skin | 0.01 |
| Other organs | 0.05 |
| Total | 1 |

**Whole Body Dose Equivalent** [17]

$$H_{wb} = \Sigma_T W_T H_T \quad (2.1)$$

$H_T$: dose equivalent for tissue
$W_T$: weighting factor for tissue

**Effective Dose** [17]

This is the dose calculated by multiplying the equivalent dose by the tissue weighting factor ($W_T$) (Fig. 2.16).

- The units of effective dose are sieverts, just like equivalent dose.


**Fig. 2.16** Relationship between exposure and equivalent dose

$$\mathrm{WT} = \frac{\text{Risk at organ or tissue (depending on stochastic effects)}}{\text{Total risk at body (depending on stochastic effects)}} \tag{2.2}$$

**Relative Biological Effect (RBE)** [21, 22]

The RBE is the ratio of the 250 kV X-ray dose that produces a specific biological effect to the test dose of any radiation that produces the same effect. The RBE is related to the LET.

$$\mathrm{RBE} = \frac{\text{The 250 kV X - ray dose required for a specific effect}}{\text{Tested dose of any radiation required for a specific effect}} \tag{2.3}$$

**Overkill Effect**

The decrease in the curve of RBE vs. LET at LET values of above 100 keV/μm has been interpreted as an "overkill effect," where the ionization density within a single cell is greater than the two ionization events needed to inactivate the cell (Fig. 2.17). In other words, any dose beyond that needed to produce the two events per cell is, in effect, wasted. Densely ionizing radiation is inefficient at producing the maximum amount of cell death.

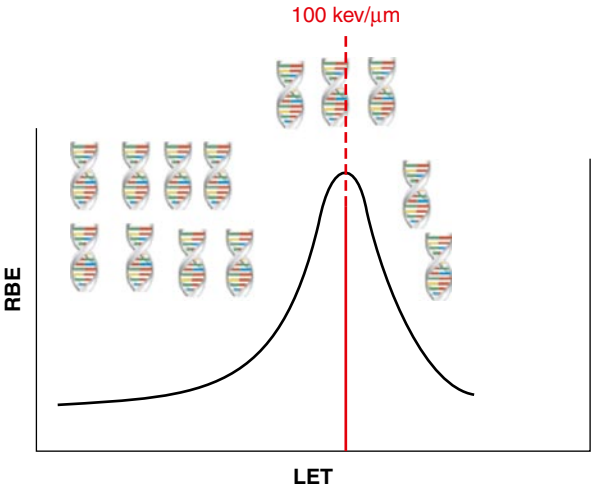



**Fig. 2.17** Overkill effect

The durations of physical, chemical and biological events after radiation has penetrated the cell are shown in Fig. 2.18.

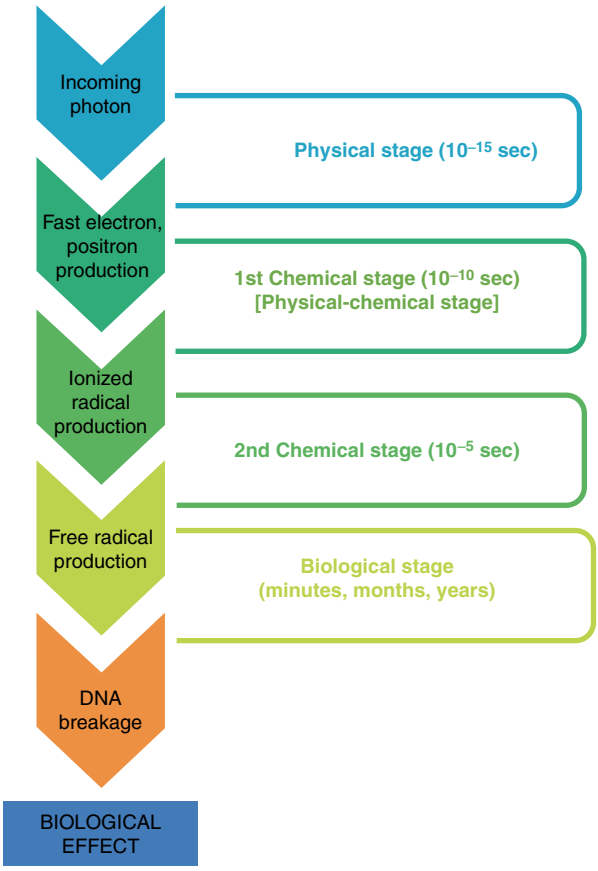



**Fig. 2.18** Durations of physical, chemical and biological stages

## 2.5 Target Theory

The number of DNA or critical target cells "hit" by the radiation depends on random events in target theory, and has no direct relation to the ionizing radiation dose [23]. Therefore, there is no threshold at which the effects of the radiation are observed. Whatever the delivered radiation dose, there is always a chance of it hitting DNA or cells and producing harmful effects. The phenomenon where the effects of the radiation do not depend on dose is known as the "stochastic effect."

Target theory explains the cell damage caused by radiation based on the principles of probability. It assumes that there are certain critical molecules or critical targets within cells that need to be hit or inactivated by the radiation to kill the cell.

**Single target–single hit** [23, 25]:
Here, there is only one target in the cell that is associated with cell death, and a single hit on this target is adequate to inactivate the target.

- This is a valid assumption for viruses and some bacteria.

**Multiple target–single hit** [23, 24]:
Here, there is more than one target per cell, and a single hit of any of these targets is required for cell death.

Not all targets are hit; some of them are killed, while others are damaged by low doses. This type of damage is called sublethal damage (SLD). Cells with SLD may repair themselves during interfractional periods.

This is a valid assumption for mammalian cells.

## 2.6 Cell Survival Curves

The number of cells in cell lines within cell cultures can increase in one of two ways: either arithmetically or exponentially (geometrically).

The number of cells increases linearly (by a constant number) with each generation in an arithmetic increase. In an exponential increase, the number of cells doubles with each generation, and so exponential growth is faster than arithmetic growth (Fig. 2.19).

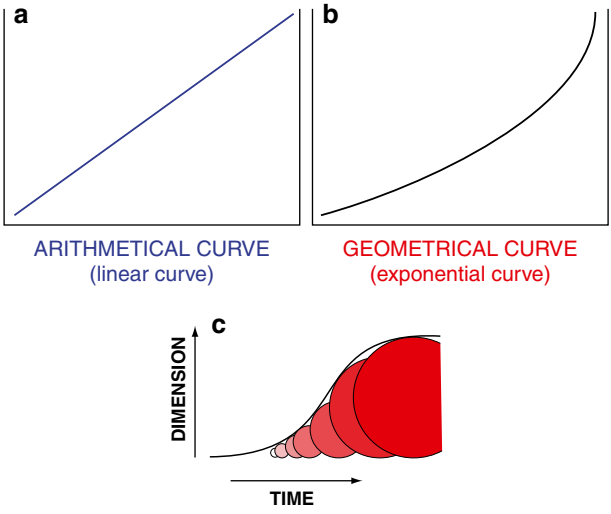



**Fig. 2.19** Survival curves: (**a**) arithmetical; (**b**) geometrical (exponential). (**c**) Exponential increase in cell number

When cell culture lines are exposed to radiation, some of them lose their capacity to divide and cannot form colonies (→ reproductive cell death), some only divide to a small degree and form small colonies, some divide slowly and form colonies over longer periods, some lose their capacity to divide but continue to grow and become giant cells, while still others degenerate and die. The remaining cells are not affected by the radiation, and they represent the surviving fraction (SF) after irradiation of the cell culture (→ SF) [26].

**Surviving Fraction** [26, 27]

The ratio of the number of cells that form colonies to the number of seed cells under normal conditions (i.e., no irradiation) in a cell culture is termed the plating efficiency (PE). The same ratio obtained under irradiated conditions and divided by the PE is called the surviving fraction (SF):

$$\text{Surviving fraction (SF)} = \frac{\text{Colony number}_{\text{rad}}}{\text{Seeded cell number}_{\text{rad}} \cdot \text{PE}} \tag{2.4}$$

- For example, if 100 cells are seeded into an unirradiated culture, and ten colonies are formed, then the PE is 10/100. If there are five colonies after a 450 cGy dose of radiation, the SF is 5/[100 × 10/100] = 1/2. Thus, the SF of 450 cGy is 50%.

If the SF is calculated for various doses, then it can be presented as a cell–dose plot. Combining the points on the plot leads to a cell survival curve.

Curves showing the relation between the radiation dose and SF are termed cell survival curves. If the dose is plotted on the *y*-axis and the SF (as a percentage of the original number of cells in the culture) is plotted on the *x*-axis, a sigmoid curve is obtained (Fig. 2.20a). If the logarithm of the SF is plotted on the *x*-axis, a semilogarithmic curve is obtained (Fig. 2.20b) [27].

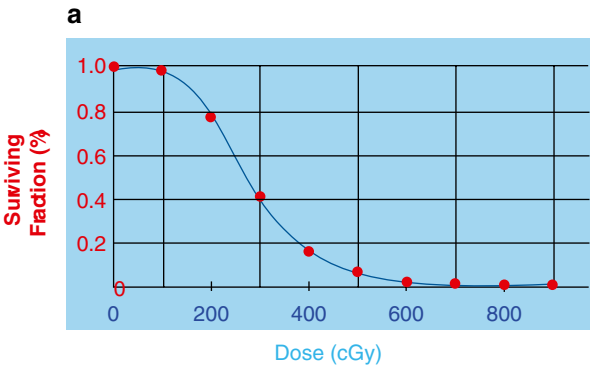
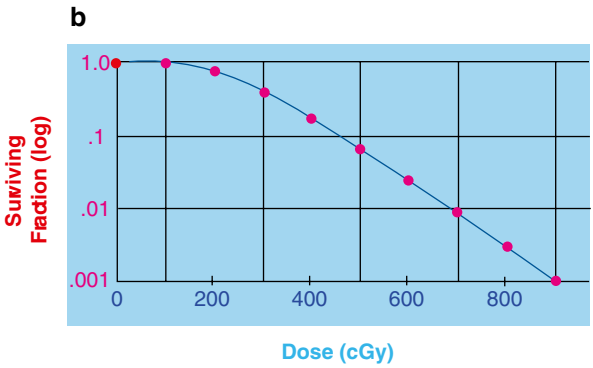



**Fig. 2.20** **(a)** Sigmoid curve; **(b)** semilogarithmic curve

**Fig. 2.20** (continued)




LD50 value can be obtained from a sigmoid survival curve (LD50 is the dose that kills 50% of cells → lethal dose).

Survival curves are radiobiologically defined using semilogarithmic curves, and these curves provide information on some parameters such as the number of cells killed by the radiation and cell radiosensitivity.

### 2.6.1 Exponential Survival Curves

These are the survival curves resulting from the single target–single hit hypothesis of target theory (Fig. 2.21) [16, 26–28]. They show that cell death due to irradiation occurs randomly. At certain doses with one unit increase, both same number of cell deaths and same proportion of cell death occur.

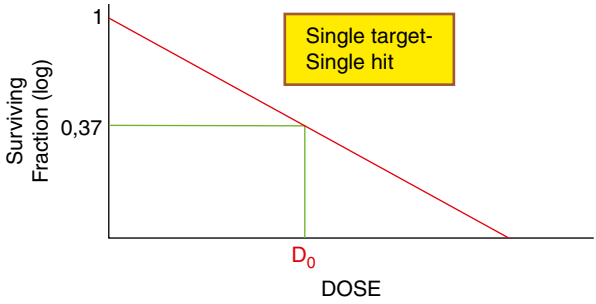



**Fig. 2.21** Single target–single hit hypothesis

After 100 radiation "hits," the probability that one of the hits will be a target → $e^{-1}$ ($e \approx 2.718 \ldots$).

- $e^{-1}$ is approximately 37%. In other words, 63% of the targets will be hit after 100 hits, while 37% of the targets will survive.
- This corresponds to the survival curve observed for viruses and some bacteria.
- Some cells are observed to be very sensitive to radiation (for example, germ cells) also show this behavior.
- It may also be observed at very low dose rates and for high-LET radiation.

$D_0$ = dose that decreases the surviving fraction to 37%.

This is the dose required to induce an average damage per cell.

A $D_0$ dose always kills 63% of the cells in the region in which it is applied, while 37% of the cells will survive.

$1/D_0$ = the slope of the survival curve.

As the value of $D_0$ decreases → $1/D_0$ increases → slope increases → *radiosensitive cell.*
As the value of $D_0$ increases → $1/D_0$ decreases → slope decreases → *radioresistant cell.*

For exponential survival curves, SF is given by

$$SF = e^{-D/D_0} \tag{2.5}$$

This can be used to determine the proportion of the original cells that will survive if a dose $D$ is delivered.

#### 2.6.1.1 Shouldered Survival Curves with Zero Initial Slope

These survival curves are based on the multiple target–single hit hypothesis of target theory [16, 26–28]. They are produced by the hypothesis of requiring multiple targets per cell, and only one of these targets needs to be hit to kill the cell (Fig. 2.22).

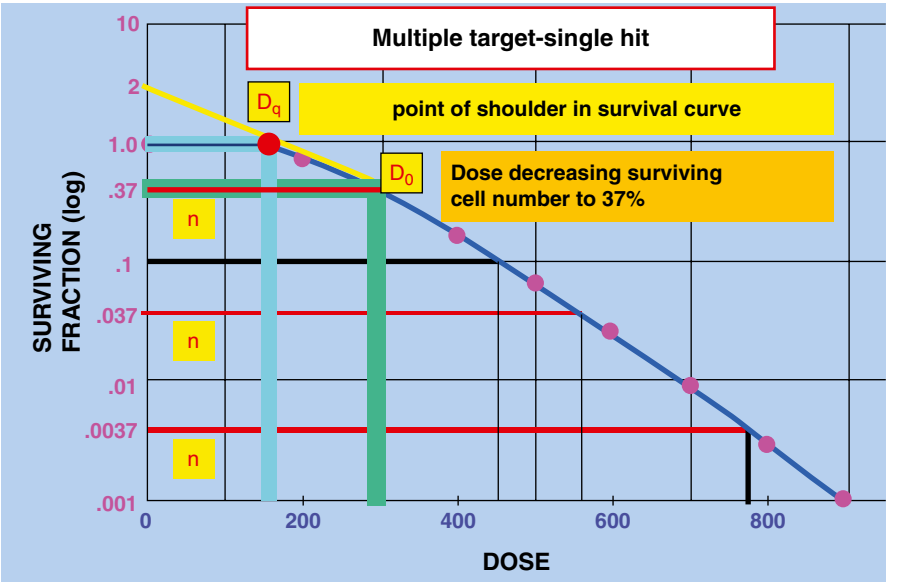



**Fig. 2.22** Multiple target–single hit hypothesis

$D_0$: the dose that yields a surviving fraction of 37%.
$D_q$: half-threshold dose → the region of the survival curve where the shoulder starts (indicates where the cells start to die exponentially) (= quasi-threshold dose).
$n$: extrapolation number (the number of $D_0$ doses that must be given before all of the cells have been killed).

SF for shouldered survival curves with zero initial slope:

$$SF = 1 - \left[1 - e^{-D/D_0}\right]^n \tag{2.6}$$

This gives the proportion of the original cells that survive if a dose $D$ is delivered.

$D_q$ → the width of the shoulder region.

$$D_q = D_o \log_n 2.7 \tag{2.7}$$

If $n$ increases → $D_q$ increases → a wide shouldered curve is observed.
If $n$ decreases → $D_q$ decreases → a narrow shouldered curve is observed.
If $D_q$ is wide and $D_0$ is narrow, the cell is radioresistant.
The $D_0$ and $D_q$ values for the tumor should be smaller than those of normal tissue to achieve clinical success.

### 2.6.1.2 Shouldered Survival Curves with Nonzero Initial Slope

If we carefully examine the shouldered survival curve with an initial slope of zero, the curve is straight when the dose is small [26–28]. This indicates that there is a threshold dose where the radiation starts to exert an effect. However, studies have demonstrated that the radiation has an effect regardless of the radiation dose. The model that takes this observed behavior into account has two components with a nonzero initial slope.

**Components of Shouldered Survival Curves with Nonzero Initial Slope** (Fig. 2.23) [16, 27, 28]

- Component corresponding to the single target–single hit model (blue in the figure)
  This shows lethal damage.
  This shows the cells killed by the direct effect of the radiation.
  This shows the effect of high-LET radiation.
- Component corresponding to the multiple target–single hit model (red in the figure)
  This shows the accumulation of SLD.
  This shows the cells killed by the indirect effect of the radiation.
  This shows the effect of low-LET radiation.

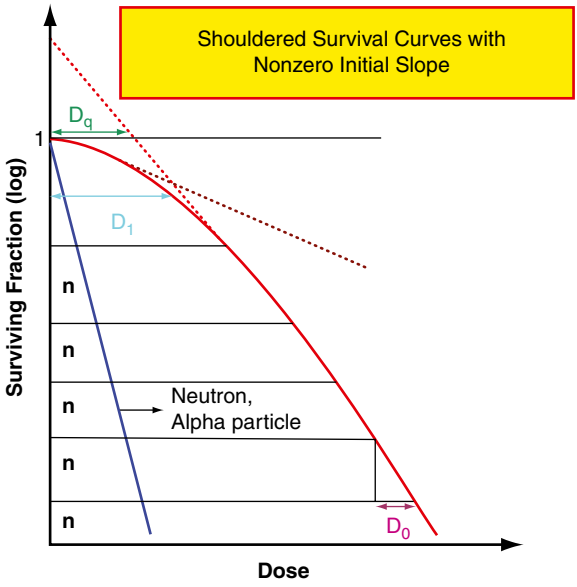



**Fig. 2.23** Shouldered survival curves with nonzero initial slope

$1/D_1$: the slope of the component corresponding to multiple target–single hit (the slope of the initial region).
$D_q$: the dose at which the shoulder starts for the multiple target–single hit component (the quasi-threshold dose).
$1/D_0$: the slope of the terminal region of the multiple target–single hit component.
$n$: extrapolation number.

SF for shouldered survival curves with nonzero initial slope:

$$SF = e^{-D/D_1}\left[1-(1-e^{-D/D_0})^n\right] \tag{2.8}$$

### 2.6.2 Linear–Quadratic Model (LQ Model)

In this model, developed by Douglas and Fowler in 1972, it was assumed that cell death due to ionizing radiation has two components (Fig. 2.24) [29].

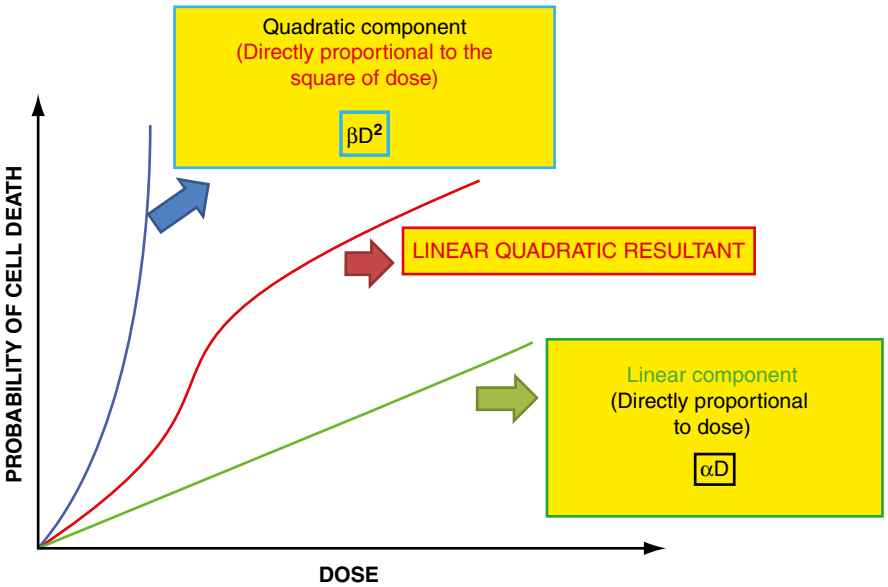



**Fig. 2.24** Components of the linear–quadratic model

*The first component*
Directly proportional to dose → $D$
- Linear component

*The second component*
Directly proportional to the square of the dose → $D^2$
- Quadratic component

If we transform the cell death probability curve into an SF curve, the linear–quadratic model assumes a linear–quadratic relation between fraction dose and fraction number.

If the effect with one radiation hit is *p1*, then

- $p1 = \alpha D.\alpha$ → initial slope of the survival curve (low-dose region)
  $\alpha$ → linear coefficient (Fig. 2.25).
- Corresponds to the cells that cannot repair themselves after one radiation hit.
- Important for high-LET radiation.

  Apoptotic and mitotic death are dominant.

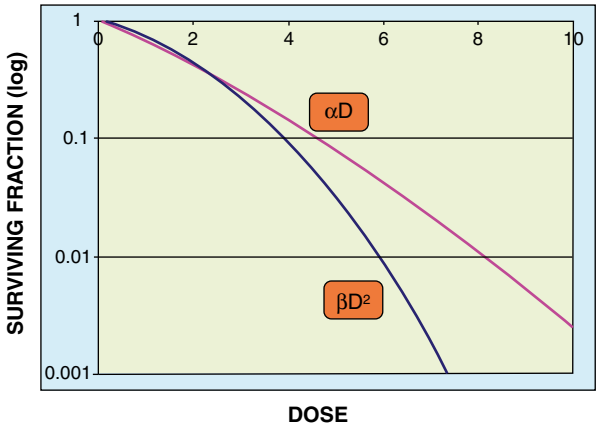



**Fig. 2.25** Relation I between dose and surviving fraction in the LQ model

If the effect of two radiation hits is *p2*, then
- $p2 = \beta D^2$

  $\beta$ → quadratic coefficient.
- Corresponds to cells that stop dividing after more than one radiation hit, but can repair the damage caused by the radiation.
- Important for low-LET radiation.
- Mitotic death is dominant.

$$\text{Total effect } p1 + p2 = \alpha d + \beta d^2 \tag{2.9}$$

$$\text{SF} = e^{-(\alpha d + \beta d^2)} \tag{2.10}$$

α → shows the intrinsic cell radiosensitivity, and it is the natural logarithm ($\log_e$) of the proportion of cells that die or will die due to their inability to repair radiation-induced damage per Gy of ionizing radiation.

β → reflects cell repair mechanisms, and it is the natural logarithm of the proportion of repairable cells due to their ability to repair the radiation-induced damage per Gy of ionizing radiation.

*What is the LQ model used for?*

To formulate equivalent fractionation schemes.

To calculate additional doses after breaks from radiotherapy.

To get information on acute and late responses.

$$E = n\,(\alpha d + \beta d^2) \tag{2.11}$$

$$E = nd\,(\alpha + \beta d) \tag{2.12}$$

$$E/\alpha = nd\left(1 + \frac{d\beta}{\alpha}\right) \tag{2.13}$$

$$E/\alpha = nd\left(1 + \frac{d}{\alpha/\beta}\right) \tag{2.14}$$

$$BED = \frac{E}{\alpha} \tag{2.15}$$

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) \tag{2.16}$$

$$E = nd\left(\alpha + \beta d\right) + \log_e 2\left(T - T_k\right)/T \tag{2.17}$$

$$(\log_e 2 = 0.693)$$

$$BED = E/\alpha = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693}{\alpha T_p}\,(T - T_k) \tag{2.18}$$

$E$ = $\log_e$ of the total cell number, including irreparable cells (α) or partially repairable cells (β)
$n$ = fraction number
$d$ = fraction dose
BED = biological effective dose = extrapolated tolerance dose = response dose.
$T$ = overall treatment time
$T_k$ = kick-off time (repopulation start time)
$T_p$ = potential tumor doubling time

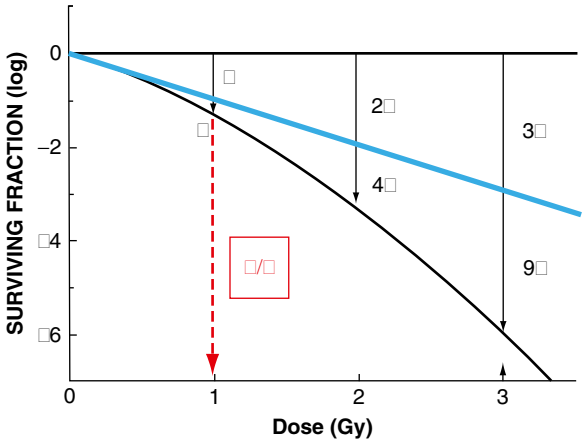



**Fig. 2.26** Relation II between dose and surviving fraction in the LQ model (Fig 1.1, p 9 of [67])

α/β → dose for which the number of acutely responding cell deaths is equal to the number of late-responding cell deaths (the dose for which the linear and quadratic components of cell death are equal) (Fig. 2.26).

Tumor response and acute effects in normal tissues → α/β = 10 Gy.

Late effects in normal tissues → α/β = 3 Gy.

The α/β ratio may differ among tumor types; e.g., it is 1.5 for melanoma and 1.5–3.5 for prostate adenocarcinoma.

- This model does not take into account the effect of treatment time.

### Models Used Before the LQ Model

1. **Strandqvist model** [30, 31]. This was developed by Magnus Strandqvist in 1944. Here, the relationship of skin tolerance to radiation dose for a particular skin cancer treatment time is plotted using a logarithmic curve. The slope of this curve is constant and equal to 0.22. Cohen showed that this slope value was valid for skin cancer, but he was observed that the slope was 0.33 for skin erythema. In summary, this model assumed that the tolerable fraction dose was related to the treatment time $T$ as $T^{0.33}$.
2. **Ellis model** [31, 32]. This was developed by Ellis in 1966. While only the total dose is important in the Strandqvist model, the dependence of the tolerable dose on the number of fractions and the overall treatment time is accounted for in this model. The dose obtained using this model is termed the nominal standard dose (NSD), and so the model is known as the NSD model.

- The NSD is the dose required to cause maximum tumor damage without exceeding the tolerance levels of healthy tissues.

$$D = \mathrm{NSD} \times N^{0.24} \times \mathrm{T}^{0.11} \tag{2.19}$$

$$\text{NSD} = D \times N^{-0.24} \times T^{-011} \quad (2.20)$$

$D$: total dose at skin level
NSD: nominal standard dose
$N$: fraction dose
$T$: overall treatment time

3. **Orton–Ellis model** [31]. This is a modified form of the NSD model. It is also known as the TDF (time–dose factor) model. It can be summarized as:

$$\text{TDF} = d^{1.538} \times X^{-0.169} \times 10^{-3} \quad (2.21)$$

$X$ = treatment time/fraction number
$d$ = fraction number

If a total dose of 66 Gy is given in 30 fractions comprising 2 Gy daily fraction doses for 6 weeks, what are the BED values for acute effects, tumor response, and late effects ($\alpha/\beta = 3$ for late effects, $\alpha/\beta = 10$ for acute effects and tumor response)?

$\text{BED} = nd\,(1 + d/[\alpha/\beta])$.

$\text{BED}_{10} = 2 \times 30 \times (1 + 2/10) = 72$ Gy.

$\text{BED}_{10} = 72$ Gy for acute effects and tumor response.

$\text{BED}_{3} = 2 \times 30 \times (1 + 2/3) = 100$ Gy.

$\text{BED}_{3} = 100$ Gy for late effects.

*The BED formulation is less reliable for fraction doses of more than 3 Gy.*

**In Head and Neck and Lung Cancers**

BED calculation for tumor response:
$T_k = 21$ days and $T_p = 3$ days.
BED calculation for normal tissue:
$T_k = 7$ days and $T_p = 2.5$ days.
In prostate for late effects, $\alpha/\beta = 1.5$ Gy.
In CNS and kidney for late effects, $\alpha/\beta = 2$ Gy.

- Tissues that respond early to irradiation (radiosensitive)
  These die linearly.
  The $\alpha/\beta$ ratio is large.
- Tissues that respond late to radiation (radioresistant)
  These die quadratically.
  The $\alpha/\beta$ ratio is small.
  This hypothesis is valid for both tumor and normal tissues (Fig. 2.27).

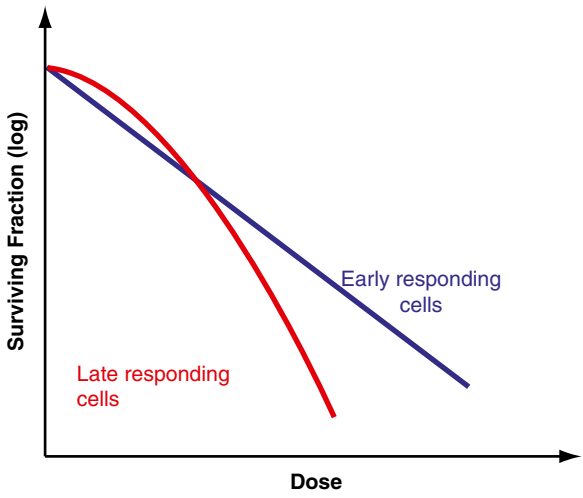



**Fig. 2.27** Relation between SF and radiosensitivity

The BED formula utilizing the LQ model can be employed to compare two different radiotherapy schedules:

$$n_2 d_2 = n_1 d_1 \frac{\alpha/\beta + d_1}{\alpha/\beta + d_2} \tag{2.22}$$

$n_1, d_1 \rightarrow$ fraction dose and number of fractions in the first scheme.
$n_2, d_2 \rightarrow$ fraction dose and number of fractions in the second scheme.

### 2.6.3 Types of Cellular Damage Due to Radiation

1. **Lethal damage** [33, 34]. This is irreversible, irreparable damage, resulting in cell death.
- This usually results from the direct effect of radiation.
- Double strand breakage in DNA (+).
- Particularly observed in high-LET radiation.
2. **SLD** [33, 34]. SLD can be repaired within hours under normal conditions, unless an additional radiation dose is given (inducing further SLD).
- This generally occurs due to the indirect effect of radiation.
- Single strand breakage in DNA (+).
- Observed in low-LET radiation.
3. **Potentially lethal damage** [34]. This is repairable, depending on the changes in the cell environment after exposure to radiation.

- Under normal conditions, this type of damage is lethal to cells undergoing mitosis that are exposed to radiation.
- However, such damage can be repaired in suboptimal environmental conditions after exposure to radiation because the cell gets the signal of that suboptimal conditions that are not suitable for mitosis are present. The cell then prefers to repair this potential damage rather than initiate mitosis.

### 2.6.4 Factors Affecting the Cell Survival Curve

1. **Cell cycle.** Duration of each phase in the human cell cycle: G1 = 1.5–14 h, S = 6–9 h, G2 = 1–5 h, M = 0.5–1 h.
- The responses of cells in different phases to radiation vary (Fig. 2.28).
- The most radiosensitive cell phases are late G2 and M.
- The most radioresistant cell phases are late S and $G_1$.

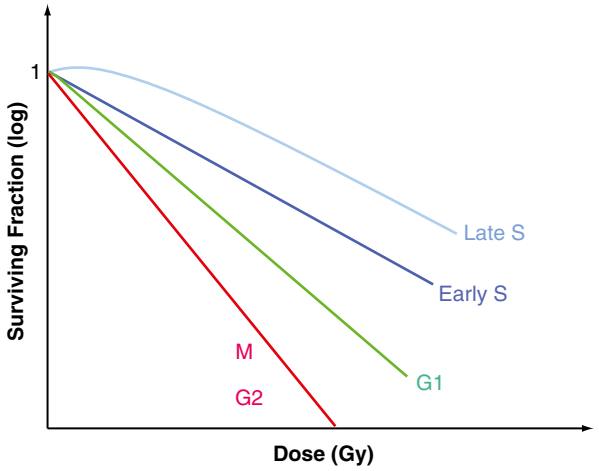



**Fig. 2.28** Cell cycle and SF

2. **LET.** Radiosensitivity increases with high-LET radiation (Fig. 2.29).
- The slope of the survival fraction (SF) curve ($1/D_0$) is large for high-LET radiation.
- The slope of the SF curve ($1/D_0$) is small for low-LET radiation.

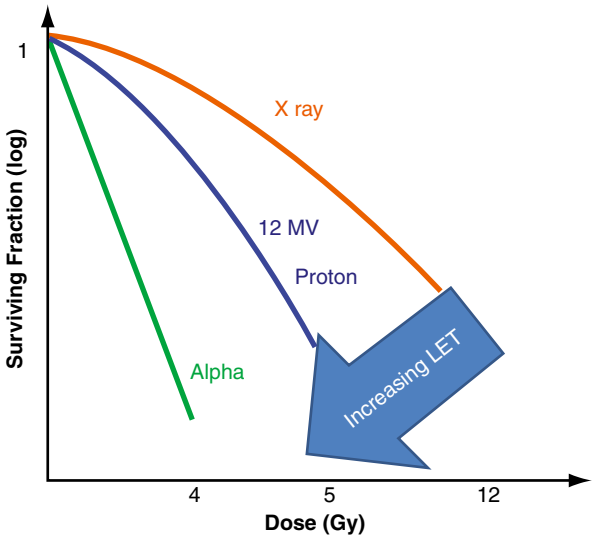



**Fig. 2.29** Linear energy transfer and SF

3. **Repair of sublethal damage (SLDR)** [35]. SLD is usually repaired 2–6 h after the delivery of radiation (Fig. 2.30).

- SLD is not fatal, but the second dose increases radiosensitivity.
- It can be lethal if there is an insufficient repair period between two fractions.
- Repair abilities differ among normal tissues and tumors.
- Inhibition of SLDR is the rationale for the additive effect of chemoradiotherapy.
- SLDR depends on dose rate, and it is evident between dose rates of 0.01–1 Gy/min.

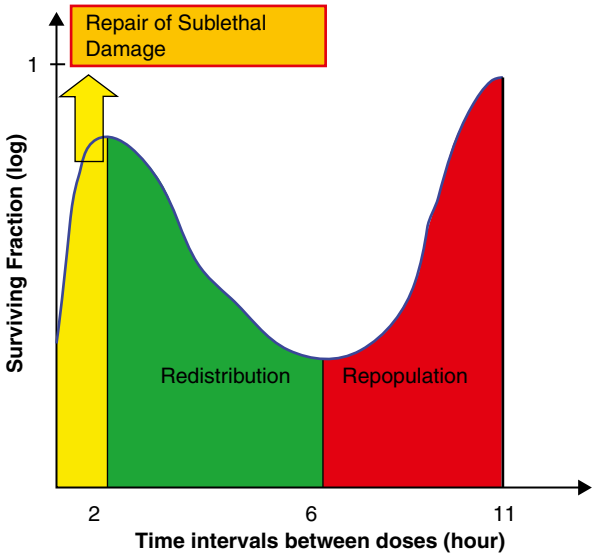



**Fig. 2.30** Repair of sublethal damage and SF

**4. Repair of potentially lethal damage (PLDR)** [36].
Some damage that is lethal during normal growth can be repaired under suboptimal conditions (Fig. 2.31).

- The first human DNA repair gene to be discovered is located in the 18th chromosome.
- Mitomycin C, which selectively affects hypoxic tumor cells, acts through this gene and inhibits PLDR.

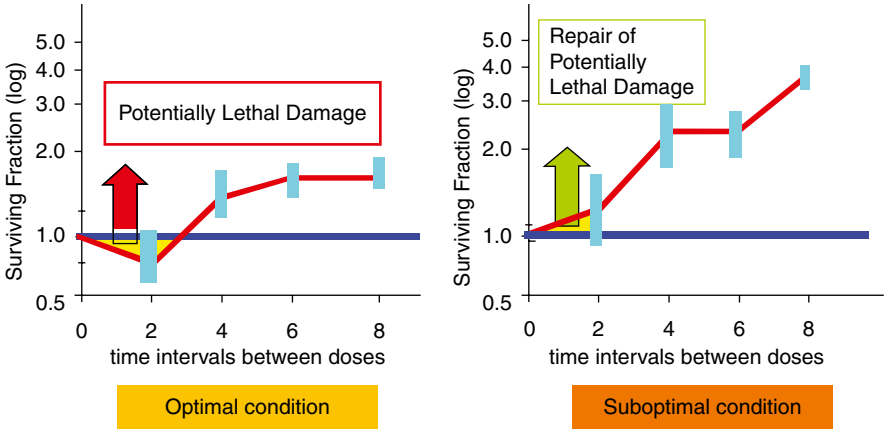



**Fig. 2.31** Repair of potentially lethal damage and SF

**5. Dose rate.** Cell survival is greater for a delivered radiation dose if the dose rate is decreased (Fig. 2.32).

- This is due to the proliferation of undamaged living cells and SLD repair during radiotherapy.
- This effect is very important in brachytherapy applications. The dose rate in external therapy is 100 cGy/min. Low dose rates are used in brachytherapy, and high doses can be given due to normal tissue repair and repopulation.

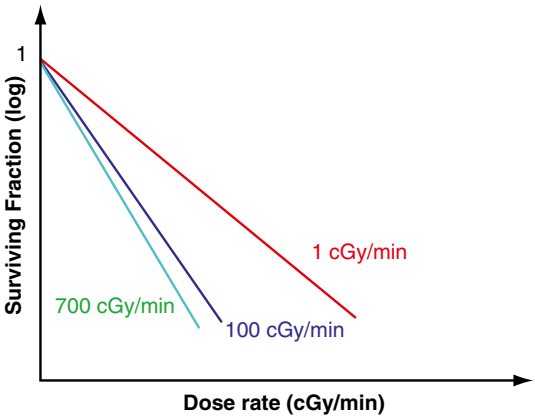



**Fig. 2.32** Dose rate and SF

6. **Oxygenation** [37]. Soluble oxygen in tissues increases the stability and toxicity of free radicals. The increase in the effect of radiation after oxygenation is defined as the oxygen enhancement ratio (OER) (Fig. 2.33).

$$\text{OER} = \frac{\text{Required dose under hypoxic conditions}}{\text{Required dose under oxygenated conditions}} \tag{2.23}$$

The maximum value of the OER is 3. Oxygenation can modify the indirect effect of free radicals. However, the OER plays no role in the direct effect of high-LET radiation; OER is 1 in this case.

Tumors become less hypoxic during fractionated radiation schedules.

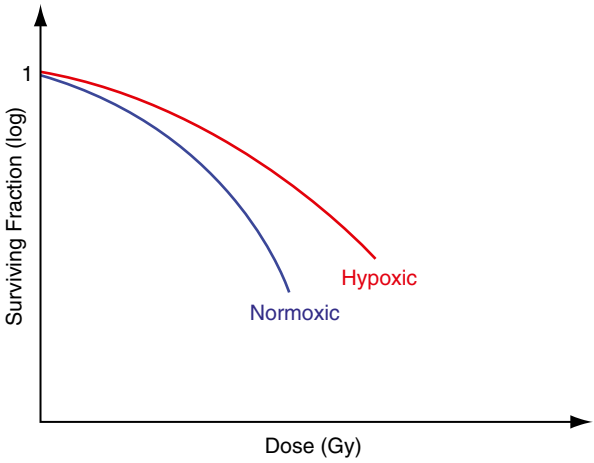



**Fig. 2.33** Oxygenation and SF

7. **Temperature.** Most cells are more sensitive to radiation at high temperatures. However, there are more chromosome aberrations at low temperatures (probably due to the suppression of the DNA repair processat low temperatures).
8. **Chemical agents**

(a) *Radioprotective agents* [38]. Free radical scavengers are radioprotective agents.

- Thiol compounds, sulfhydryl amines like cysteine, cystamine and isothiouronium, dimeric compounds containing excess sulfhydryl (SH) radicals, and antioxidants like vitamins A, C and E can decrease radiation damage.

These compounds protect cells by neutralizing free radicals, producing hypoxic conditions, and forming disulfide bounds in proteins, strengthening protein structure.

Thiols, on the other hand, transiently inhibit DNA synthesis, giving the cell time to repair SLD using repair enzymes. However, they are not used prophylactically as radioprotective agents due to their side effects.

Alcohol, morphine and tranquillizing agents decrease respiration, thus increasing radioresistance.

*Amifostine (WR-2721)*. The results of phase III trials have confirmed the safety and efficacy of amifostine as a radioprotective agent that reduces xerostomia in patients with head and neck cancers who are receiving radiotherapy. It is also a cytoprotectant that prevents cisplatin-induced renal toxicity and neutropenia in patients with ovarian cancer.

(b) *Radiosensitizers* [39]. Oxygen is the leading radiosensitizer. Oxygen mimetic agents with electron affinity (metronidazole, misonidazole, nitroimidazoles, etanidazole (SR-2508)), DNA analogs (actimomycin D, adriamycin, methotrexate, 5-flourouracil), and caffeine can increase the damaging effects of radiation.

## 2.7 Tissue and Organ Response to Radiation

Tissue is defined as a collection of similarly functioning cells that have the same origin and are similar in shape and structure. Tissues form organs. The response of a tissue to radiation is determined by its precursor cells (Table 2.4).

**Table 2.4** Radiosensitivities of various tissues

| | |
|---|---|
| The most sensitive | Lymphocyte<br>Immature hematopoietic cells<br>Intestinal epithelium<br>Spermatogonia<br>Ovarian follicle cells |
| Sensitive | Bladder epithelium<br>Esophagus epithelium<br>Gastric mucosa<br>Epidermal epithelium<br>Optic lens epithelium |
| Moderately sensitive | Endothelium<br>Growing bone and cartilage<br>Fibroblast<br>Glial cells<br>Mammary gland epithelium<br>Lung epithelium<br>Renal epithelium<br>Hepatic epithelium<br>Pancreas epithelium<br>Thyroid epithelium<br>Surrenal gland epithelium |
| Less sensitive | Mature erythrocyte<br>Muscle cell<br>Mature connective tissue<br>Mature bone and cartilage<br>Ganglion cell |

**Bergonie and Tribondeau Law** [40]

The radiosensitivity of a tissue depends on:

- The excess amount of less-differentiated cells in the tissue
- The excess amount of active mitotic cells
- The duration of active proliferation of the cells

According to the Bergonie and Tribondeau law, the effect of radiation on undifferentiated divided cells with high mitotic activity is much greater than the effect of radiation on undivided differentiated cells.

**Michalowski Tissue Sensitivity Classification** [41]

*Hierarchical tissues*. These tissues are divided into two compartments containing differentiated and undifferentiated cell groups, respectively. The cells in these tissues are H-type cells.

- These are cells that can continuously divide, such as stem cells and intestinal epithelial cells.
- They respond acutely to radiation.
- *Flexible tissues*. These are tissues that are not divided into compartments containing different cells. The cells die together during tissue damage, and they are F-type cells.
- These are tissues that consist of cells that divide if necessary, such as liver and thyroid cells.
- They are late-responding tissues.

Many tissues respond to radiation in a manner that can be considered a hybrid of these two tissue types. The response of a tissue to radiation derives from both parenchymal cells and vascular stromal cells. Cells that cannot renew themselves (such as central nervous system (CNS) cells and striated muscle cells) are less sensitive to radiation, and radiation damage is most likely due to the effect on vascular stroma. A radiation dose that kills most of the stem cells in the parenchymal compartment of a tissue activates the repopulation of functional mature cells, and mature cells originating from stem cells play an important role in re-establishing tissue function after irradiation.

*Flexure dose* ($D_f$). This is the dose calculated by multiplying the $\alpha/\beta$ ratio of acutely responding tissue by 0.1 in the LQ model.

It refers to the maximum dose at which F-type tissues are protected.

It is important in hyperfractionation.

$D_f$ is the maximum dose at which late-responding tissues are protected but early-responding tissues die. It is the dose attained just before the death of the first cell.

If $D_f$ is high, late side effects decrease and acute side effects increase. The total dose may increase. If $D_f$ is high, the suitability for hyperfractionation increases.

**Factors Determining Radiation Damage According to Ancel and Vintemberger** [42]

*Biological stress in the cell.*

Biological stress is important in cell division. While radiation damage to rapidly dividing cells is observed early, damage to slowly dividing cells is seen in late.

*Cell status before and after radiation dose.*

This indicates the environmental conditions of the cell → the radiation response of a cell changes in optimal and suboptimal conditions:

- Radiation response increases in optimal conditions.
- Radiation response decreases in suboptimal conditions.

Well-differentiated cells show a reduced capacity to divide compared to undifferentiated ones. This indicates that undifferentiated cells accrue more damage from radiation. For instance, bone marrow cells, intestinal crypt cells, and basal skin cells are undifferentiated cells; these are damaged early and at low doses.

**Rubin and Casarett Tissue Sensitivity Classification** [43]

This classifies tissues according to proliferation kinetics:

*Tissues consisting of vegetative intermitotic cells (VIM).*

These consist of undifferentiated cells.

These cells have a very short cell cycle.

– Examples include stem cells and intestinal stem cells
– These have short lifetimes but can continuously repopulate.
– These are the most radiosensitive tissues.

*Tissues consisting of differentiated intermitotic cells (DIM).*

These consist of cells with a partial proliferative capacity.

Their mitotic activity stops when they become mature.

- An example is spermatogonia

*Multipotential connective tissues (MPC).*

These consist of cells with relatively long lifetimes.

These cells divide at irregular intervals.

- The most prominent example is the fibroblast.

*Tissues consisting of reverting postmitotic cells (RPM).*

These cells do not divide under normal conditions; they only divide if necessary.

These tissues consist of cells with long lifetimes.

- Examples include liver parenchymal cells, pulmonary cells and renal cells.

*Tissues consisting of fixed postmitotic cells (FPM).*

These cells never divide.

These tissues consist of cells with very long lifetimes.

(*continued*)

(continued)

- Examples include CNS cells, muscle cells and erythrocytes.
- These are the most radioresistant tissues.

The radiosensitivities of tissues are variable, except in the cases of VIM and FPM.

The α/β ratio for acute-responding tissues is high (~10).
The α/β ratio for late-responding tissues is low (~3).
The α/β ratio in human tumors varies between 1 and 25.

Tissue and organ radiation tolerance is an important clinical parameter. The tolerance doses of normal tissue and organs surrounding the tumor are very important in radiotherapy planning. The tolerance dose depends on the delivered fraction dose and the irradiated tissue volume.

*TD5/5*: this defines the minimum tolerance dose, which is the dose that yields a complication rate of less than 5% over 5 years.
*TD50/5*: this defines the maximum tolerance dose, which is the dose that yields a complication rate of 50% over 5 years.

Dose-limiting organs are classified into three classes according to their radiation tolerances: I, II and III (Tables 2.5–2.7).

Tolerance doses are determined for 2 Gy daily fraction doses and for 5 days/week.

**Table 2.5** Class I organs: radiation damage is morbid and/or highly fatal [44]

| | Damage | TD 5/5 (Gy) | TD50/5 (Gy) | Irradiated field size or volume |
|---|---|---|---|---|
| Bone marrow | Aplasia, pancytopenia | 25<br>35 | 4.5<br>40 | Total<br>Segmental |
| Liver | Acute and chronic hepatitis | 25<br>15 | 40<br>20 | Total<br>Total thin band |
| Stomach | Perforation, bleeding | 45 | 55 | 100 $cm^2$ |
| Small intestine | Perforation, bleeding | 45<br>50 | 55<br>65 | 400 $cm^2$<br>100 $cm^2$ |
| Brain | Infarction, necrosis | 60<br>70 | 70<br>80 | Total<br>25% |
| Spinal cord | Infarction, necrosis | 45 | 55 | 10 cm |
| Heart | Pericarditis, pancarditis | 45 | 55 | 100 $cm^2$ |
| Lung | Acute and chronic pneumonia | 30<br>15 | 35<br>25 | 60%<br>Total |
| Kidney | Acute and chronic nephrosclerosis | 15<br>20 | 20<br>25 | Total<br>Whole thin band |
| Fetus | Death | 2 | 4 | Total |

**Table 2.6** Class II organs: radiation damage is of low–moderate morbidity, or occasionally fatal [44]

| | Damage | TD5/5 (Gy) | TD50/5 (Gy) | Irradiated field size or volume |
|---|---|---|---|---|
| Oral cavity and pharynx | Mucositis, ulceration | 60 | 75 | 50 $cm^2$ |
| Skin | Acute and chronic dermatitis | 55 | 70 | 100 $cm^2$ |
| Esophagus | Esophagitis, ulceration | 60 | 75 | 75 $cm^2$ |
| Rectum | Ulcer, stricture | 60 | 80 | 100 $cm^2$ |
| Salivary glands | Xerostomia | 50 | 70 | 50 $cm^2$ |
| Bladder | Contracture | 60 | 80 | Total |
| Ureters | Stricture | 75 | 100 | 5–10 cm |
| Testis | Sterilization | 1 | 2 | Total |
| Ovaries | Sterilization | 2–3 | 6–12 | Total |
| Growing cartilage | Growth retardation | 10 | 30 | Total |
| Child bone | Dwarfism | 10 | 30 | 10 $cm^2$ |
| Adult cartilage | Necrosis | 60 | 100 | Total |
| Adult bone | Fracture, sclerosis | 60 | 100 | 10 $cm^2$ |
| Eye | | | | |
| Retina | Retinopathy | 55 | 70 | Total |
| Cornea | Keratopathy | 50 | 60 | Total |
| Lens | Cataract | 5 | 12 | Total/partial |
| Endocrine glands | | | | |
| Thyroid | Hypothyroidism | 45 | 150 | |
| Surrenal | Hypoadrenalism | 60 | 20–30 | Total |
| Hypophysis | Hypopituitarism | 45 | | |
| Peripheral nerves | Neuritis | 60 | 100 | Total |
| Ear | | | | |
| Middle ear | Serous otitis | 50 | 70 | Total |
| Vestibule | Meniere's syndrome | 60 | 70 | |

**Table 2.7** Class III organs: radiation damage is not morbid or is reversibly morbid [44]

| | Damage | TD5/5 (Gy) | TD50/5 (Gy) | Irradiated field size or volume |
|---|---|---|---|---|
| Muscle | Fibrosis | 60 | 80 | Total |
| Lymphatics | Atrophy, sclerosis | 50 | 70 | Total |
| Large artery–vein | Sclerosis | 80 | 100 | 10 $cm^2$ |

(*continued*)

**Table 2.7** (continued)

| | Damage | TD5/5 (Gy) | TD50/5 (Gy) | Irradiated field size or volume |
|---|---|---|---|---|
| Joint cartilage | – | 500 | 500 | |
| Uterus | Perforation, necrosis | 100 | 200 | Total |
| Vagina | Ulcer, fistule | 90 | 100 | Total |
| Breast (adult) | Atrophy, necrosis | 50 | 100 | Total |

**Serial Organs** [45]

The functional subunits (FSUs) of serial organs are structured serially (Fig. 2.34).

- If critical damage due to radiation occurs in any functional subunit, complications are observed in the whole organ.
- Examples include the spinal cord, esophagus, rectum and coronary arteries.

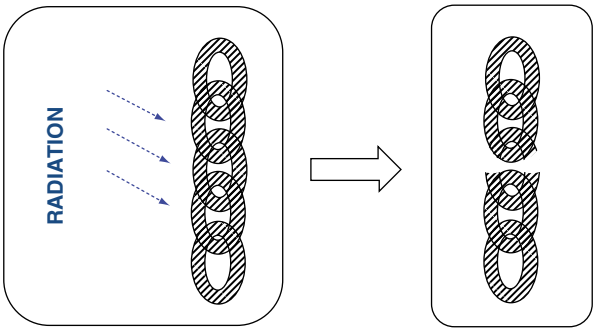



**Fig. 2.34** Response to radiation in serial organs (Fig. 5.7, p 101 of [20])

**Parallel Organs** [45]

Their FSUs are parallel in structure (Fig. 2.35).

- If critical damage due to radiation occurs in any functional subunit, complications are only observed in that subunit, and the organ continues its function.
- Examples include lungs, liver, and myocardium.

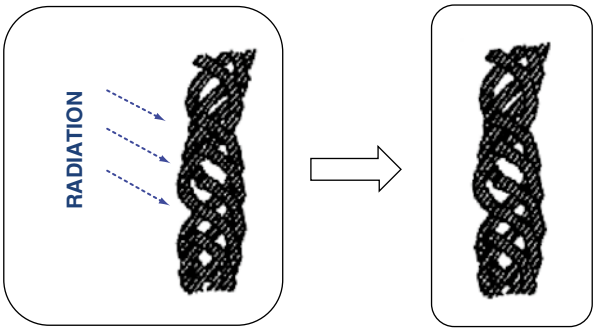



**Fig. 2.35** Response to radiation in parallel organs (Fig. 5.8, p 102 of [20])

## 2.8 Stochastic and Deterministic Effects

The effects of radiation on tissues and organs can be classified into three groups: acute, subacute and chronic [46].

*Acute effects*: changes that occur in the first 6 months.

If the radiation dose is high enough, the organ's parenchymal tolerance is exceeded and organ death occurs. If the dose is low, the organ continues to function fully or partially, even in the presence of parenchymal damage.

*Subacute effects*: changes that occur between 6 and 12 months.

Secondary parenchymal degeneration resulting in decreased resistance to radiation is observed.

*Chronic effects*: changes that occur after 12 months.

Carcinogenesis, genetic mutations and chromosomal aberrations occur.

**Deterministic Effect** [46]

- The acute and subacute effects of radiation are known as deterministic effects (non-stochastic effects) (Fig. 2.36). The intensities of these effects are directly proportional to the dose.

They have a specific threshold dose.

Effects appear at higher doses than the threshold dose.

There is a relationship between dose and individual effects.

Cataract, skin erythema, sterility, radiation myelitis, and fibrosis are all examples of deterministic effects.

For example, if the total body irradiation dose is >5 Gy, bone marrow suppression is observed, but this suppression is not observed for a dose of <5 Gy.

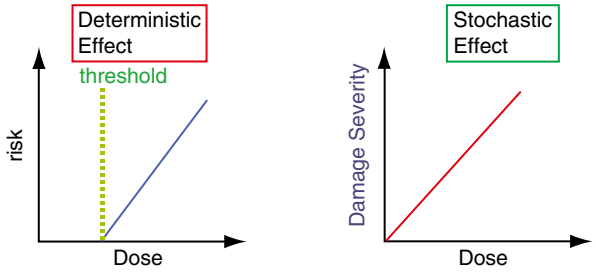



**Fig. 2.36** Deterministic and stochastic effects of radiation

**Stochastic Effects** [46]

- The chronic effects of radiation are known as stochastic effects (Fig. 2.37).

These are statistically measurable effects.
There is no threshold dose for these effects.
There is no relationship between the dose and individual effects.
Carcinogenesis, genetic mutations and chromosome aberrations are all stochastic effects.
*Stochastic incidence* → the incidence of cancer is 250 cases per 1 million for 1 REM radiation.

## 2.9 Tumor Response to Radiation

The aim of radiotherapy is to annihilate the tumor tissue while minimizing damage to the normal surrounding tissues. Thus, the radiosensitivities of the tumor and its surrounding tissues are important considerations when determining the best treatment. It is well known that cells in tumor tissues have chaotic growth patterns and various radiosensitivities. Furthermore, tumor cells exhibit a variety of size, chromosome structures, and cytoplasms. However, this is not true of neighboring normal tissue cells. The principle of *primum non nocere* is always valid in radiotherapy. In light of this principle, several concepts for destroying the tumor while protecting healthy tissues have been developed in the field of radiation oncology.

### 2.9.1 Therapeutic Index

The therapeutic index defines how the tumor control probability (TCP) relates to the normal tissue complication probability (NTCP) for different doses [47]. Normal tissues may get damaged by the dose required to control the tumor; on the other hand, the tumor may not receive an adequate dose if the normal tissues require protection. Achieving the optimal balance between TCP and NTCP is a basic aim of radiotherapy. All new technologies are directed towards this aim.

TCP and NTCP curves are sigmoid in shape. The purpose of treatment is to move the TCP curve to the left and the NTCP curve to the right (Fig. 2.37).

- The therapeutic index (= therapeutic window) increases if the region the between two curves becomes large, and the expected benefit from treatment increases.

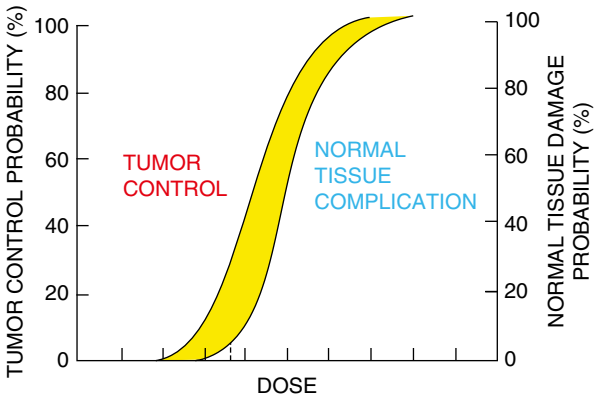



**Fig. 2.37** TCP and NTCP curves

When the fraction dose is increased from 2 to 2.5 Gy, the total dose to control the tumor decreases. Since the maximum tolerable dose is constant, the total dose received by normal tissue increases and the therapeutic window narrows. Therefore, the treatment scheme in the second graphic in Fig. 2.38 is unacceptable compared to that in the first graphic.

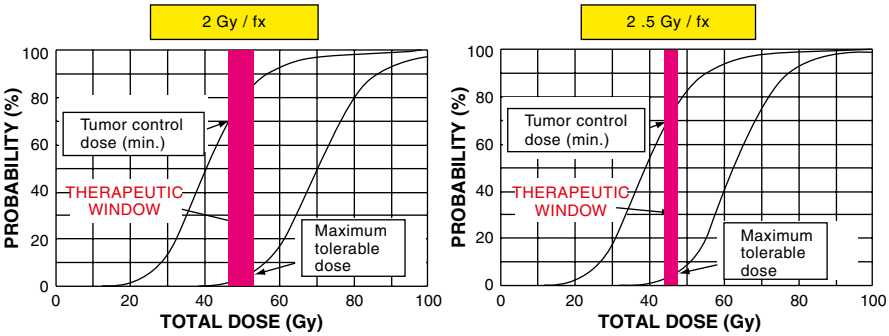



**Fig. 2.38** Relationships between fraction dose, total dose, and therapeutic window

### 2.9.2 Tumor Control Probability (TCP)

The efficacy of radiotherapy treatment is evaluated by the locoregional TCP and the treatment-related NTCP [49].

TCP is directly proportional to the dose and inversely proportional to the number of cells in the tissue (or the volume of the tumor). The total dose required to control the subclinical disease in epithelial cancers is 40–50 Gy, whereas it is 60–70 Gy for clinically observable gross disease. The most important dose-limiting factor is the tolerance of the surrounding tissues to radiation.

*Local tumor control*. This is the destruction of tumor cells, where they are determined. It is also defined as the death of the last clonogenic cancer cell.

Radiation affects tumor cells in a very similar way to normal tissue and organs; its effect is nonspecific.

**Tumoral factors affecting the TCP:**

- Intrinsic radiosensitivity
- Location and size of tumor
- Cellular type of tumor
- Effect of oxygen

**Treatment-related factors affecting the TCP:**

- Dose–time fractionation
- Radiation quality (RBE, LET)
- Dose rate
- Use of radiosensitizers
- Combination of radiotherapy with surgery and/or chemotherapy
- Technique (e.g., small field sizes)
- Treatment modality (e.g., brachytherapy, conformal RT, IMRT, IGRT, targeted RT

The tumor volume decreases if a dose $d_1$ is delivered to a volume $v_1$. If we assume that a second dose $d_2$ is delivered to a new volume $v_2$, the total TCP will be as follows:

$$TCP = TCP(d_1,v_1).TCP\,(d_2,v_2).TCP(d_3,v_3)... = \prod_{i=1}^{n} TCP\,(d_i,v_i) \tag{2.24}$$

$$\mathrm{TCP}\,(D) \approx \mathrm{e}^{N.\mathrm{e}^{-(\alpha d+\beta d^2)}} \tag{2.25}$$

$$\mathrm{TCP} = \mathrm{e}^{-(SF\times N)} \tag{2.26}$$

where SF = surviving fraction and $N$ = clonogenic cell number.

$$P(D) = \frac{1}{1+\left(\frac{D_{50}}{D}\right)^{k}} \tag{2.27}$$

$k$ = slope of dose–response curve
$D$ = total dose
$D_{50}$ = tolerance dose
$P(D)$ = expected probability of cure for the given total dose (%)
$\mathrm{TCD}_{50} = D_{50} = \mathrm{ED}_{50} = \mathrm{TD}_{50}$

- The tissue tolerance dose is equal to the dose that kills 50% of clonogenic cells (Fig. 2.39).

$$(\mathrm{TCD}_{50} = \mathrm{TD}_{50})$$

$$\mathrm{TCD}_{50} = \mathrm{TCP}\,(1 - \mathrm{NTCP}) \qquad (2.28)$$

$$\mathrm{TCD}_{50} = D_{50} = \mathrm{ED}_{50} = \mathrm{TD}_{50}$$

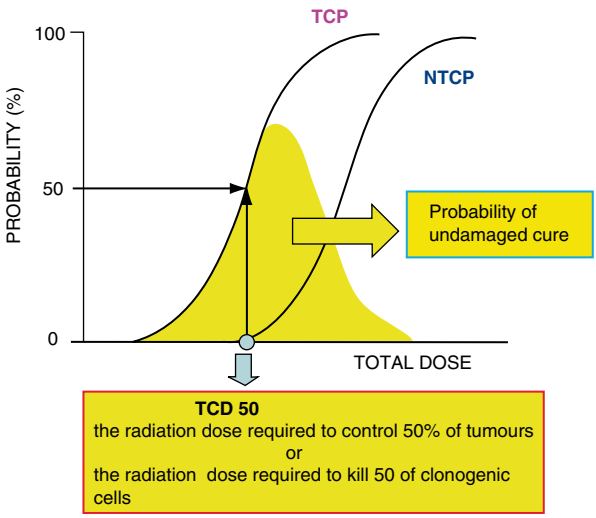



**Fig. 2.39** Relationship between TCP, NTCP, and TCD50

- The dose needs to be increased threefold to increase the TCP from 10 to 90%.

If the TCP and NTCP curves are close to each other → tumor is radioresistant.
If the TCP and NTCP curves are far from each other → tumor is radiosensitive (Fig. 2.40).

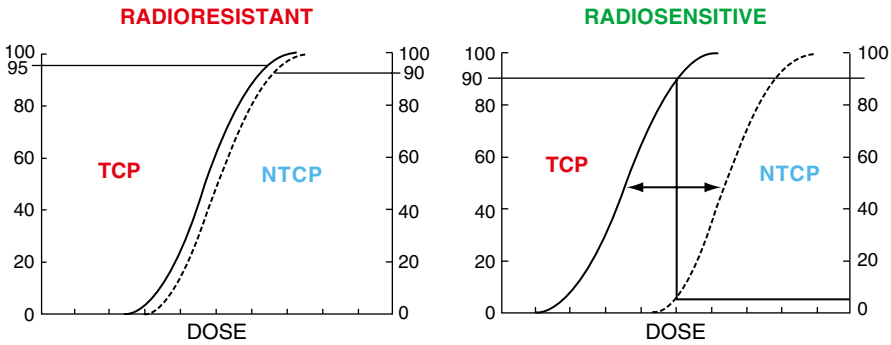



**Fig. 2.40** Relationship between TCP, NTCP, and radiosensitivity

### 2.9.3 Normal Tissue Complication Probability (NTCP)

The TCP is a function of the total dose, fraction dose, irradiated volume including the whole tumor, and treatment reproducibility [49, 50]. The NTCP is a function of the total dose, fraction dose, fraction number and the volume of tissue exposed to the radiation [49, 50].

*The Lyman model* is used in NTCP calculations [51]. This model is highly complex. It is a mathematical model of biological effects based on the use of algebraic definitions.

- The volume of irradiated normal tissue and its radiosensitivity make this model more complex.
- In addition, tissue types (parallel or serial organs) as well as the FSUs of tissues are added to this formulation, making the model even more complex [51].

$$P(D) = \sum_{k=M+1}^{N} \binom{N}{k} \cdot P_{FSU}^{k} \cdot (1 - P_{FSU})^{N-k} \tag{2.29}$$

- However, the most important issue is not the formulation, but the knowledge of TD50, and not to exceed this limit during planning.

$$\mathrm{NTCP} = \frac{1}{1 + \left(\frac{D_{50}}{D}\right)^{k}} \tag{2.30}$$

*Factors affecting NTCP* [51]:
*Factors related to organ tissue*

- Tissue radiosensitivity
- The volume of organ tissue within the radiotherapy portal
- Organ type: serial or parallel

*Factors related to treatment*

- Dose–time fractionation
- Quality of radiation (RBE, LET)
- Dose rate
- Use of radioprotectors
- Combination of RT with surgery and/or chemotherapy
- Technique (e.g., addition of boost field)
- Treatment modality (e.g., brachytherapy, conformal RT, IMRT, IGRT, targeted RT)

TCP and NTCP calculations are mechanistic models. The *critical volume model* was developed by Niemierko in 1997. This model is used empirically for 3D treatment plans that involve calculating the *equivalent uniform dose* (EUD). This model is based on the hypothesis that clonogenic cells that have the same survival curves can be irradiated with same uniform dose. The α/β ratios, clonogenic cell number, dose, number of fractions, type of tissue and type of tumor, as well as the SF2 are fed into this formulation. The EQD2 (equivalent dose at 2 Gy) is derived in addition to the SF2, and this is used to compare different fractionation schemes [52].

- SF2 = surviving fraction after 2 Gy irradiation → as SF2 increases, TCP decreases

$$EQD_2 = D \times \left[ d + \frac{\alpha/\beta}{2} + \alpha/\beta \right] \tag{2.31}$$

where $D$ = total dose and $d$ = fraction dose.

The value of the EUD lies between the minimum dose and the mean dose for tumor control (Fig. 2.41). A decrease in the TCP dose was observed when the EUD was calculated and used.

$D_{min} \leq \text{EUD} \leq D_{mean}$

As the irradiated volume increases, the normal tissue tolerance dose decreases due to the increase in functional subunit number.

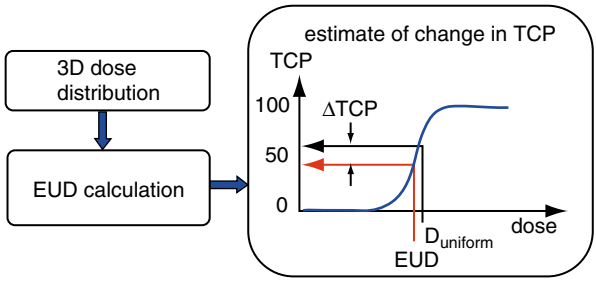



**Fig. 2.41** Relationship between TCP and EUD

The essential parameters of the NTCP are the irradiated tissue volume and the dose delivered (Figs. 2.42 and 2.43).

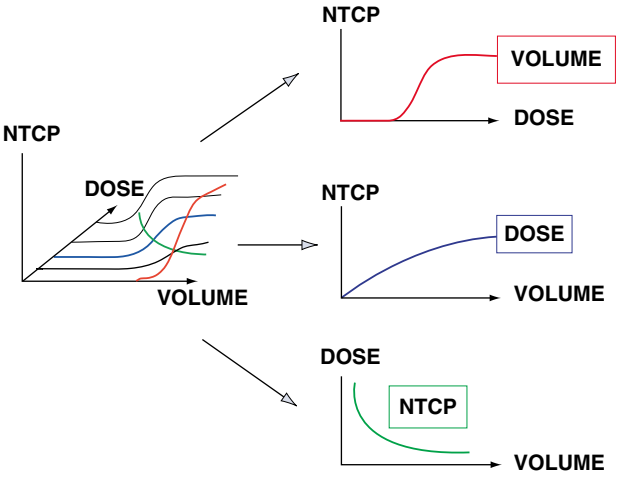



**Fig. 2.42** The essential parameters of NTCP and its relationships (Fig. 5.4, p 97 of [20])

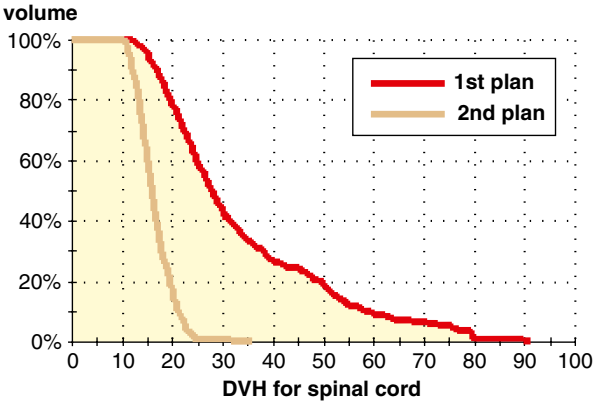



**Fig. 2.43** DVH curves for spinal cord in two different treatment plans (Fig. 5.6, p 100 of [20])

*Major references for NTCP estimation models:*

- Lyman model: Burman C, Kutcher GJ, Emami B, Goitein M (1991) Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 21:123–135.
- Critical volume model: Stavrev P, Stavreva N, Niemierko A, Goitein M (2001) The application of biological models to clinical data. Phys Medica 17(2):71–82.

**The Clinical Importance of TCP and NTCP** [50–52]

- The TCP and NTCP can be used to estimate the treatment success and side effects in particular.
- Dose–volume histograms created by treatment planning systems (particularly 3D-conformal radiotherapy and IMRT) as well as TCP and NTCP mathematical modeling are very useful for graphically demonstrating normal tissue damage ratios within the treated tumor volume, and can be used to guide clinicians during treatment planning (Fig. 2.43).

**Therapeutic Ratio**

TR = normal tissue tolerance dose/tumor control dose.

## 2.10 The Five R's of Radiotherapy

The delivery of radiation in small daily fractions is known as fractionated radiotherapy. Fractionated radiotherapy studies were started after it was realized that single, high-dose radiotherapy is ineffective for tumor control and has serious side effects. Claudius Regaud observed that ram spermatogenesis decreased after fractionated doses, but there were no side effects on the scrotal skin.

Although Regaud started the first fractionation studies, the first radiation oncologist, Grubbe, treated a breast cancer patient (Mrs. Rosa Lee) with radiotherapy for 1 h each day for 18 days in 1896. He found beneficial responses, but did not publish them since he was just a medical student. However, Grubbe published two scientific articles 50 years after his first use of radiotherapy.

Grubbe EH (1946) X-ray treatment; its introduction to medicine. J Am Inst Homeopath 39(12):419–422.

Grubbe EH (1947) The origin and birth of X-ray therapy. Urol Cutaneous Rev 51(5):375–359.

Coutard, a colleague of Regaud, applied fractionated radiotherapy to head and neck cancers in 1934, and obtained successful results [53]. He emphasized the importance of the time–dose concept in radiotherapy (Fig. 2.44).

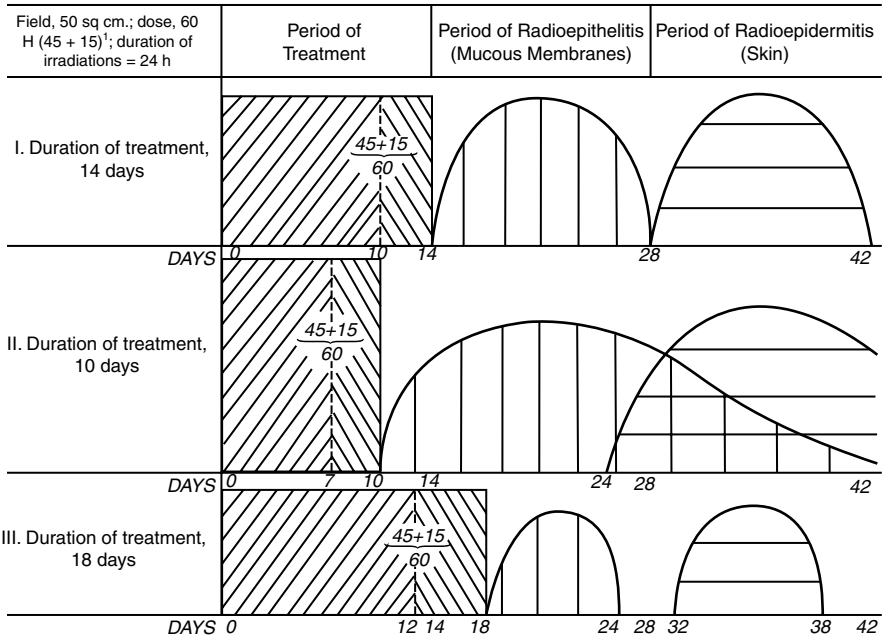



**Fig. 2.44** Relationship between mucosal reaction and time as well as dose (from Coutard)

Coutard observed that skin and mucosal reactions seen during radiotherapy of pharyngeal and laryngeal cancers depend on the dose and the duration of radiotherapy.

Fractioned radiotherapy is founded on five main features:

- Repopulation
- Repair
- Redistribution (= reassortment)
- Reoxygenation
- Radiosensitivity (intrinsic radiosensitivity)

Biological factors that affect the responses of normal and tumor tissues in fractionated radiotherapy were defined as repair, reassortment (redistribution), repopulation and reoxygenation by Withers in 1975. A fifth "R," radiosensitivity, was added to this list by Bernard Fertil in 1981. All of these are important for estimating the responses of normal or tumor tissues to radiotherapy.

### 2.10.1 Repopulation

Both tumor and healthy normal cells continue to proliferate even when they are exposed to radiation [54, 55]. This proliferation is a physiological response of tumor and normal tissues to decreases in cell number.

**The Consequences of Proliferation**

- Increases the number of tumor cells to be destroyed → against treatment
- Increases the number of normal tissue cells following irradiation → in favor of treatment

This repopulation enables tumor cells to partially resist the lethal effects of radiotherapy. The time required for the tumor cell number to double is known as the "tumor doubling time," $T_p$. This doubling time is less than two days for most tumors. This period can also be considered the repopulation time, and it varies during radiotherapy. Repopulation is slow at the beginning of radiotherapy, but it speeds up after the first doses of radiation therapy. This increase in repopulation rate is termed "accelerated repopulation," and the time taken for it to begin is termed the "kick-off time" ($T_k$). This accelerated repopulation becomes even faster if the treatment is interrupted after the tumor doubling time for any reason. Normal tissues also repopulate during radiotherapy; this issue is important for the repair of acute side effects. Therefore, radiotherapy schemes should be arranged so as to allow normal tissues to repopulate.

Resting cells in the $G_0$ phase enter the cell cycle in order to compensate for the cells killed by radiotherapy, and they undergo mitosis → repopulation (Fig. 2.45).

Early-responding tissues repopulate faster than the tumor during interfraction periods.

If the overall treatment time becomes longer than the period required, the tumor enters the accelerated repopulation mode and its response to radiation decreases due to tumoral proliferation.

- Accelerated repopulation begins after 28 days of treatment for head and neck tumors (Fig. 2.46) [55, 56].

Radiotherapy should be completed as soon as possible, within the tolerance limits of acutely responding normal tissues, due to the risk of accelerated repopulation.

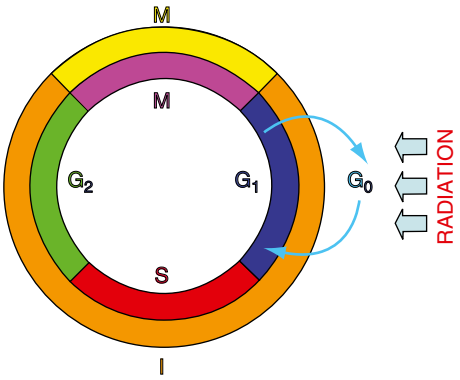



**Fig. 2.45** Cell cycle and repopulation

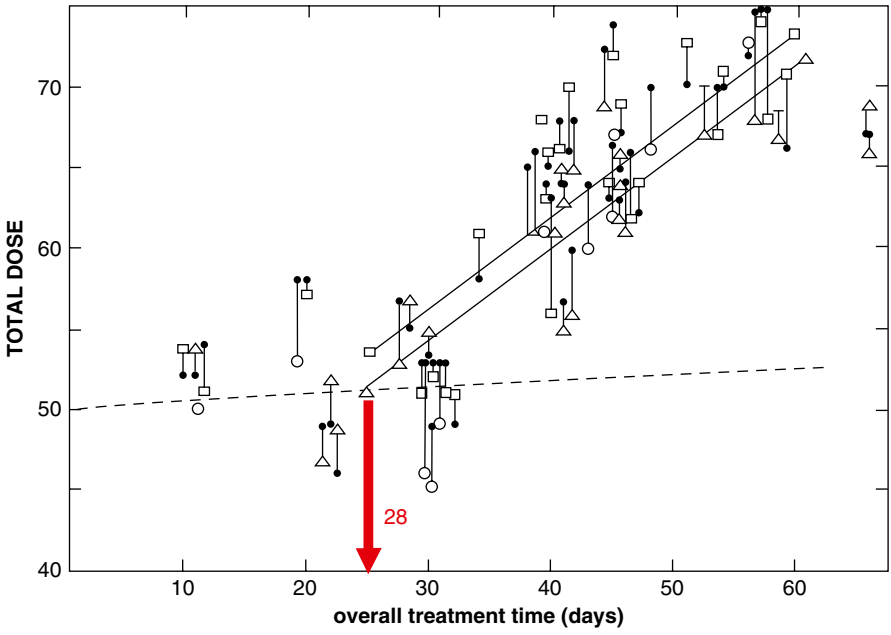



**Fig. 2.46** Accelerated repopulation

### 2.10.2 Repair

Radiotherapy causes lethal damage to tumor cells and SLD in normal tissues. The application of radiotherapy in fractionated doses allows normal tissues time to repair [56, 57].

If an optimal interval is left between fractions (6–12 h), normal tissue cells responding late to radiation have the capacity for faster repair than tumor cells.

According to multiple target–single hit theory, SLD occurs in mammalian cells at low doses, and this damage is repaired during interfraction intervals.

One parameter used in this context is half the time required for cell repair after radiation damage ($t_{1/2}$), and the value of this parameter can be minutes to hours. Therefore, interfraction intervals should be at least 6 h in order to allow normal tissue cells to repair radiation damage.

The repair of SLD in spinal cord is much slower than that in other normal tissues. Thus, the interfraction interval should be at least 8 h in spinal cord irradiation.

Tumor cell SLD repair starts at the initial point of the shoulder ($D_q$) in the survival curve of the LQ model. Fractionating the next dose prevents this sublethal repair, shifting the dose away from the shoulder. Normal tissue cells, on the other hand, start to repair SLD before $D_q$, and so are not affected by the use of fractionation (Fig. 2.47). Repopulation and repair → more important for normal tissues than tumor tissues.

As the protection of normal tissues increases, radioresistance increases.

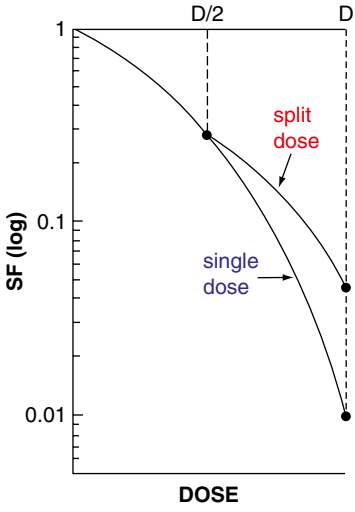



**Fig. 2.47** Fractionated radiotherapy and the cell survival curve

Redistribution and reoxygenation → more important for tumor tissues than normal tissues; as more tumor tissue dies, its radiosensitivity increases.

When the total radiation dose is applied by dividing it into small fractions, and if the interval between two fractions is long enough (>6 h), normal tissues can protect themselves from radiation through SLD repair and repopulation.

### 2.10.3 Redistribution (= Reassortment)

The radiosensitivities of cells vary with the phase of the cell cycle (Fig. 2.48) [55, 58]. The most sensitive phases are M and $G_2$, while the most resistant is the S phase. Cells in resistant phases of the cell cycle may progress into a sensitive phase during the next dose fraction. Therefore, the probability that tumor cells will be exposed to radiation during a sensitive phase increases, and this probability will continue to increase over the course of the treatment, and so the benefit of the radiation will also increase.

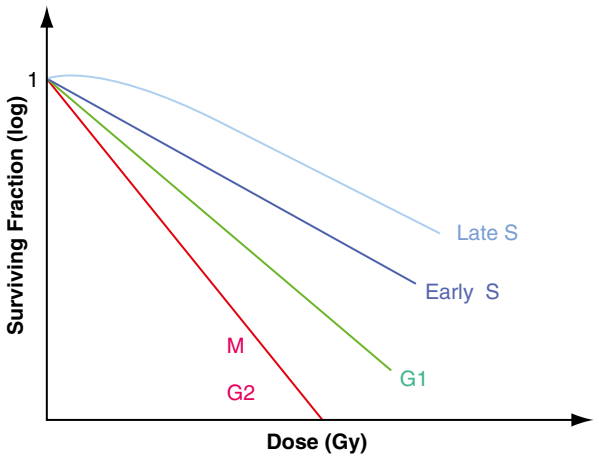



**Fig. 2.48** Phases of the cell cycle and the survival curve

The durations of cell cycle phases: $G_1$ = 1.5–14 h, S = 6–9 h, $G_2$ = 1–5 h, M = 0.5–1 h

- The most sensitive: M and $G_2$
- The most resistant: S

### 2.10.4 Reoxygenation

As the tumor volume increases through the proliferation of tumor cells, the vascularity of the tumor tissue becomes insufficient to meet its requirements, and hypoxic–necrotic regions begin to occur within the tumor tissue [59, 60]. Hypoxic cells are 2–3 times more

resistant to radiation (→ oxygen is required for the indirect effect to occur) (Fig. 2.49). Well-oxygenated cells that are radiosensitive die over the full course of fractionated radiotherapy. Therefore, since the oxygen supply is constant, the hypoxic cells gradually obtain much better vascularity and oxygenation, and their radiosensitivities increase (Fig. 2.50).

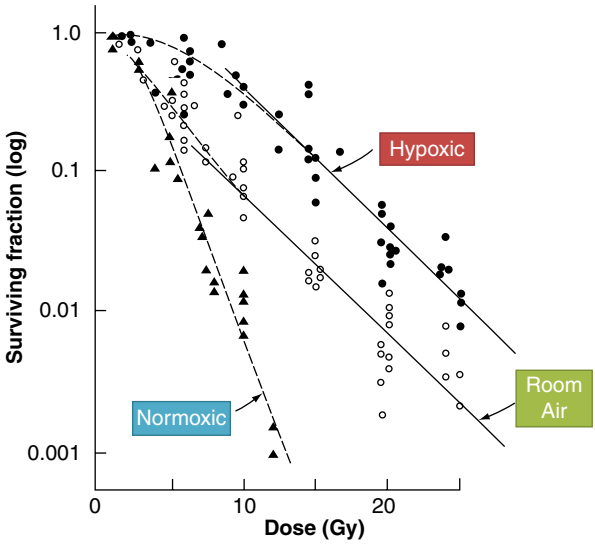



**Fig. 2.49** Oxygenation and the cell survival curve

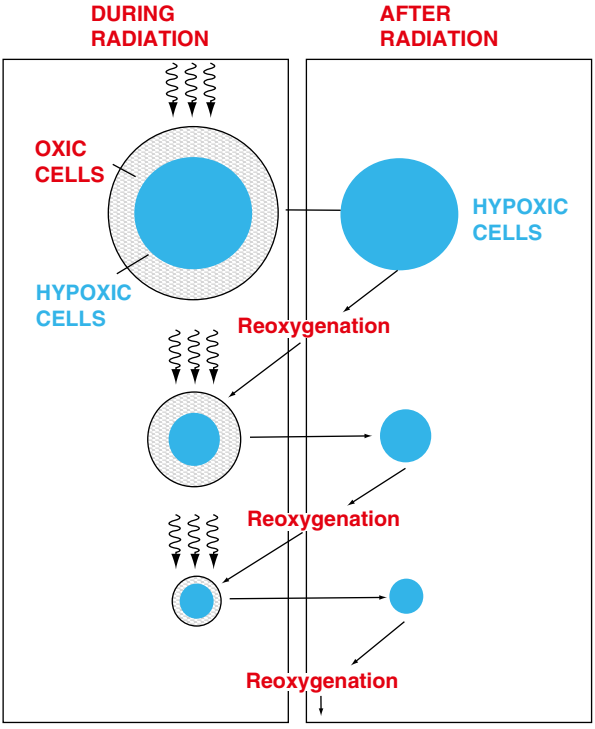



**Fig. 2.50** Fractionated radiotherapy and reoxygenation

Oxygenating a tumor from the hypoxic state

- If hemoglobin is low, a blood transfusion may be given.
- High-pressure oxygen or carbogen may be applied during radiotherapy.
- The patient may be prevented from using hypoxic materials like cigarettes during radiotherapy.
- Hypoxic radiosensitizers may be used (e.g., metronidazole).

If the time interval between fractions is *t* and *T* is the overall treatment time, then for:

| | |
|---|---|
| Reoxygenation | *T* should be minimum |
| Redistribution | *t* should be minimum |
| Repair | *T* should be minimum for normal tissues |
| Repopulation | *T* should be minimum for the tumor |

### 2.10.5 Radiosensitivity (Intrinsic Radiosensitivity)

Radiosensitivity (the fifth R of radiotherapy) is a concept that involves multiple components [52, 60]. Radiosensitivity may be affected by environmental conditions. The term "radiosensitivity" was first defined by Bergonie and Tribendau in 1907; they suggested that radiosensitivity was directly proportional to mitosis and inversely proportional to differentiation. Since radiosensitivity may be affected by external conditions, the term $SF_2$ was introduced by Fertil in 1981.

$SF_2$ = surviving cell fraction after a radiation dose of 2 Gy.
As $SF_2$ increases, radiosensitivity decreases.
$SF_2$ is represented graphically for some tumor cell lines in Fig. 2.51.

- Radiosensitizers are used to decrease $SF_2$.

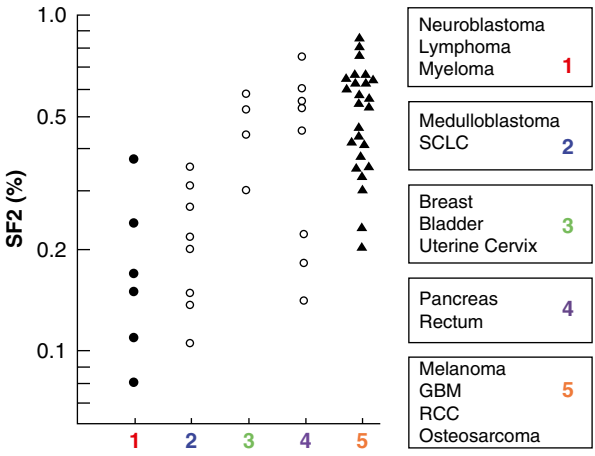



**Fig. 2.51** $SF_2$ in some tumor lines

## 2.11 Fractionation

The five R's of radiotherapy form the basis for fractionation [47, 61, 62]. The total dose cannot be given in just one fraction, since this would produce serious adverse reactions in normal tissues. Therefore, it is necessary to divide the total dose into fractions. Normal cells can protect themselves from the radiation through repair and repopulation during the interfraction periods, whereas tumor cells are sensitized to the radiation through reoxygenation and redistribution.

**Conventional Fractionation**

| | |
|---|---|
| Fraction dose | 1.8–2 Gy |
| Number of fractions per day | 1 |
| Number of fractions per week | 5 |
| Number of fractions per treatment | 25–35 |
| Total dose | 45–70 Gy |

**Hyperfractionation**

| | |
|---|---|
| Fraction dose | 1.1–1.2 Gy |
| Number of fractions per day | >2 |
| Number of fractions per week | 10 |
| Number of fractions per treatment | 60–70 |
| Total dose | 45–70 Gy or >10% |

*Aims of hyperfractionation*

To decrease the fraction dose and increase the total dose

To increase local control

To decrease late effects in normal tissues

*In hyperfractionation*

Acute side effects are similar or slightly increased compared to conventional fractionation.

Late side effects are decreased compared to conventional fractionation.

**Accelerated Fractionation**

| | |
|---|---|
| Fraction dose | 1.1–2 Gy |
| Fraction number/day | >1 |
| Fraction number/week | >5 |
| Fraction number/treatment | 25–35 |
| Total dose | 45–70 Gy or less |

*The aim of accelerated fractionation*

To decrease overall treatment time, to decrease accelerated repopulation

*In accelerated fractionation*

Early side effects are more than conventional fractionation.

Late side effects are same as conventional fractionation.

Treatment may be stopped early or the total dose may be decreased due to the excess amount of early side effects → this may cause a decrease in local control.

**Hypofractionation**

| | |
|---|---|
| Fraction dose | >2 Gy |
| Number of fractions per day | ≤1 |
| Number of fractions per week | ≤5 |
| Number of fractions per treatment | ≤25–35 |
| Total dose | <45–70 Gy |

*The aim of hypofractionation*

Hypofractionation is generally used for palliative purposes in the management of metastatic tumors. Late side effects are undervalued and palliation is provided over a very short time period.

*In hypofractionation*

Early side effects are similar to those associated with conventional fractionation.

Late side effects are increased compared to conventional fractionation.

**Split Course.** This refers to a fractionated treatment regimen that includes a planned interruption in order to decrease acute side effects. It is no better than conventional fractionation with regard to treatment efficacy.

**Concomitant Boost.** Here, two fractions are given daily in the fourth week of radiotherapy in order to prevent accelerated repopulation in head and neck cancers. The boost dose is given to the primary tumor site.

**Hyperfractionation**

Standard regimen:

70 Gy/35 fractions/7 weeks

$BED = D(1 + d/\alpha/\beta)$

$BED_3 = 70\ (1 + 2/3) = 116$ Gy

$BED_{10} = 70\ (1 + 2/10) = 84$ Gy

If we want to give the same total dose using two fractions per day:

$BED_{10} = 84 = X(1 + 1.2/10)$

(*continued*)

(continued)

X = 75 Gy
$BED_3 = 75(1 + 1.2/3) = 105$ Gy
Note that late side effects will increase.
However, 75 Gy/62 fractions = 6 weeks.

**Accelerated Fractionation**

Standard regimen:
70 Gy/35 fractions/7 weeks
$BED = D(1 + d/\alpha/\beta)$
$BED_3 = 70(1 + 2/3) = 116$ Gy
$BED_{10} = 70(1 + 2/10) = 84$ Gy
If we give 70 Gy/45 fractions/5 weeks with 1.6 Gy fractions and 3 fractions per day:
$BED_3 = 70(1 + 1.6/3) = 107$
$BED_{10} = 70(1 + 1.6/10) = 81$ (total treatment time will decrease).

- Early side effects depend on the total dose.
- Late side effects depend on the fraction dose.

## 2.12 Radiation Protection

The ICRP, the International Atomic Energy Agency (IAEA), and similar organizations have published many recommendations relating to protection from ionizing radiation over the last 50 years. Although those recommendations are not enforceable by law, many countries have adopted these recommendations and put them into practice.

In principle, protection from all radiation sources is required. However, no practical measure can be taken to protect ourselves against the normal levels of radiation resulting from natural radiation sources and radioactive fallout due to previous nuclear tests. Nevertheless, we can control whether or how nuclear tests will occur in the future. The use of radiation in medicine is a decision that should be made clinically. In this field, it is not suitable to limit personal doses that are delivered for diagnostic or therapeutic reasons. Thus, collective doses are very high in these circumstances. Medical personnel must carefully follow related laws and ICRP recommendations [63].

On the other hand, the principles of radiation protection should be applied fully to all medical and industrial uses of radiation, as well as by all other users of nonnatural radiation, radiation workers and the normal population.

The essential principles of radiation protection, as published in ICRP report 60 and the IAEA document BSS-115 (*Basic Protection Standards*) are:

- *Justification*. Radiation should never be delivered with no benefit, considering its harmful effects.
- *Optimization*. The dose should be as low as possible, considering personal doses, the number of irradiated persons, economical and social factors, except when medical irradiation is performed for therapeutic purposes. This is known as the ALARA (as low as reasonably achievable) principle [63, 64].
- *Dose limits*. Radiation dose to normal individuals should not exceed the permissible organ and tissue equivalent doses.

**Dose limits for radiation personnel** [63]:

- For the whole body, the effective dose limit for five consecutive years: 100 mSv (i.e., a mean of 20 mSv per year).
- For the whole body, the effective dose limit in any 1 year: 50 mSv.
- For lens, the equivalent dose limit per year: 150 mSv.
- For hands, food and skin, the equivalent dose limit per year: 150 mSv.

**Dose limits for the general public** [63]:

- For the whole body, the effective dose limit for five consecutive years: 25 mSv (i.e., a mean of 5 mSv per year).
- For the whole body, the effective dose limit in any 1 year: 1 mSv.
- For lens, the equivalent dose limit per year: 15 mSv.
- For hands, food, and skin, the equivalent dose limit per year: 50 mSv.
- *Dose limits for 16–18 year old students and trainees (i.e., in those using radiation for educational purposes)* [63]:
- For the whole body, the effective dose limit in any year: 6 mSv.
- For lens, the equivalent dose limit per year: 50 mSv.
- For hands, foot, and skin, the equivalent dose limit per year: 150 mSv.

Note that radiation workers must be at least 18 years old.

The working conditions for radiation personnel who are pregnant should be arranged to ensure that the dose received by the fetus is as low as possible. The fetal dose for the remaining period of pregnancy should not exceed 1 mSv. Lactating personnel should not be allowed to work in places that incur a risk of radiation contamination.

- Patient visitors and volunteers (during diagnosis/treatment): <5 mSv
- Children visiting patients: <1 mSv

**Radiation protection.** Methods of protecting from radiation can be grouped into two classes:

1. **Protection from internal radiation.** Internal contamination occurs via the entry of radioactive materials during respiration, digestion, or through damaged mucosa or skin. The radioactive material will radiate throughout the period when it is in the body. Therefore, precautions should be taken to prevent internal radiation from entering the body through media, foods, clothes, respiration and skin that are already contaminated with radioactive materials. These precautions include the use of special respiration equipment, a full face mask and filters, wearing protective clothes, blocking respiratory entry using towels when such equipment is absent, and banning the consumption of food and water in contaminated regions.
2. **Protection from external radiation.** There are three methods that are used to protect from external radiation:
   (a) *Distance*. As radiation intensity is inversely proportional to the square of the distance from the radiation source (inverse square law), increasing the distance from the source is a good protective measure. For instance; if the dose rate is 100 mSv/h at 1 m, it will be 1 mSv/h at 10 m.
   (b) *Time*. As the amount of radiation delivered is directly proportional to the time spent close to the radiation source, the time spent close to the source should be as short as possible. For instance, if the dose rate is 100 mSv/h, and someone stays in this field for 1 h, they will receive a dose of 100 mSv, but the dose will be 1000 mSv if they stay for 10 h.
   (c) *Shielding*. The most effective method of protecting from external radiation is shielding, and protective barriers with suitable features should be placed between the radiation source and the person in order to decrease the dose received. Shielding can be made from highly protective materials like soil, concrete, steel, and lead.

## 2.13 Pearl Boxes

**Radiation hormesis.** Although the harmful effects of high-dose ionizing radiation are accepted, some preclinical and clinical data show that low-dose radiation actually stimulates some biological functions. The word "hormesis" derives from the Greek word "hormone," which means "stimulate." Radiation hormesis refers to the stimulating effect of ionizing radiation. This concept is generally defined as the physiological benefits gained from exposure to low-LET radiation in the total absorbed dose range of 1–50 cGy.

- In 1996, Yonezawa et al. observed that 30% of 21-ICR rats lived for 30 days after 8 Gy X-ray irradiation, whereas their life spans increased by 70% after a 5 cGy dose.

Adequate time and the optimal medium (adequate nutrition, oxygen) should be provided between each fraction to allow the repair of SLD (→ for normal tissues!).

- SLD is repaired in 0–2 h
- There is a cell cycle phase change every 2–10 h (→ reassortment = redistribution)
- Repopulation starts after 12 h in tumor tissue

**Basic Advantages of Fractionation**

- Protects normal tissues from early side effects.
- Provides reoxygenation in tumor cells.

**Basic Disadvantages of Fractionation**

- Overall treatment time increases.
- Tumor cell proliferation increases during treatment breaks due to increased duration.

Molecular oxygen should be present in the medium during radiotherapy to ensure maximum cell death through the fixation of free radicals. Therefore, hypoxia decreases cellular radiosensitivity. This condition provides the basis for some applications, such as the delivery of oxygen at 3 atm pressure (hyperbaric) to patients during radiotherapy, the use of hypoxic cell sensitizers like nitroimidazole, and the use of high-LET radiation that decreases the inverse effect of hypoxia on tumor cells.

**Bystander Effect**

The bystander effect is where cells that are not exposed to radiation, but which are in close proximity to cells that are, show similar biological effects to the cells exposed directly to radiation.

- This effect is thought to occur due to intercellular communication and cytokines.

**Abscopal Effect**

The occurrence of systemic side effects in the regions that are far away from the irradiated area. Increasing the fraction size over 2 Gy per fraction increases abscobal effect in parallel tissues.

**Avalanche Phenomenon**

The avalanche phenomenon refers to the fact that, when the number of flexible tissue cells has dropped to a certain level (point F in Fig. 2.52) after the cells have been exposed to radiation, the remaining cells die more rapidly. This effect is more prominent at high doses and with additional treatments (chemotherapy, surgery). This dose dependency is due to not only cell turnover but also the entry of other lethally irradiated cells into the cell proliferation mode, and cell death occurs as an avalanche or cascade.

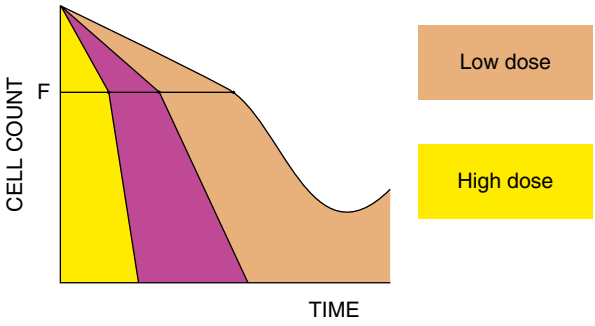



**Fig. 2.52** Avalanche phenomenon

**Radiation Recall Phenomenon.** This is a severe reaction that is observed in particular in the skin of the irradiated area during chemotherapy after the end of external radiotherapy. Skin edema, erythema, rashes and discoloration are seen. The mechanism that causes this is the interaction of basal layers of the irradiated skin with cytotoxic agents secreted from dead cells due to chemotherapy. In general, this effect is observed in patients receiving chemotherapy after a long period of radiation (weeks, months). The chemotherapeutic agents that most often cause this phenomenon are actinomycin, doxorubicin, methotrexate, fluorouracil, hydroxyurea, and paclitaxel.

The half-life of a free radical is longer (microseconds) than that of an ion radical. Free radicals can diffuse and so damage regions outside of the primary radiation pathway. They play an important role in the oxygen effect. They are the basis for the indirect effect of radiation.

Two hundred meV proton radiation and 1.1 MV gamma radiation are examples of low-LET radiation, like 250 kVp X-rays.

The components of cosmic rays are high-LET radiations, like Fe ions and carbon ions, while solar flares are composed largely of energetic protons (which are a low-LET radiation).

Telomeres shorten during each period of mitosis due to the low telomere activity in primary human fibroblasts and most other somatic cells.

- This shortening generally causes a loss of replicative potential and $G_1$ arrest, which is also known as replicative cell aging.
- Primary human fibroblast aging can occur due to various mechanisms, including exposure to ionizing radiation. Some somatic cells may undergo additional divisions before a proliferative block, and this condition is termed a crisis. The crisis includes extensive genetic instability and ends in cell death in most situations.

The quadriradial-type aberrant chromosome number increases in Fanconi aplastic anemia. An increase in this type of chromosome is also observed upon exposure to radiation. A prominent increase is also seen upon the use of chemotherapeutic agents that create crosslinkages, like mitomycin.

SLD repair and the value of the β parameter in the cell survival curve decreases as the dose rate decreases.

If there is no shoulder in the cell survival curve, $n = 1$ and $D_{37} = D_0$.

In high-LET radiations, the extrapolation number ($n$) decreases until it reaches 1 as LET increases.

$D_q$ and $n$ are more predictive regarding the effect of fractionation on survival than $D_0$.

As $n$ increases with dose rate, $D_{10}$, $D_0$, and α/β all decrease.

- $D_{10}$ is the dose that decreases the SF to 10%

- A dose rate of 1–0.1 Gy/min allows cellular repair.
- A dose rate of 0.1–0.01 Gy/min allows redistribution.
- A dose rate of 0.01−0.001 Gy/min allows repopulation.

In cases of ataxia telangiectasia, the α component of the cell survival curve is larger than it is in the normal population.

Inhibiting SLD selectively increases double-hit kill and the β component of the cell survival curve increases.

Skin infections occur due to microvessel damage during and after radiotherapy; infections in oral mucosa arise due to decreased saliva, loss of the antibacterial effect of saliva, and increases in oral acidity.

In cell culture, 90% of cells growing exponentially die after receiving a $D_{10}$ dose. The remaining cells are cells in the S phase, which is the radioresistant phase of the cell cycle.

The differences in intrinsic radiosensitivity among several types of cancer cells are mainly due to variations in the α component. Variations in the β component do not affect radiosensitivity so much.

According to animal experiments, the most sensitive fetal phase to radiation is just after conception and before the implantation of the embryo into the uterus.

Irradiation in the early fetal period, corresponding to weeks 8–15 of human gestation, mostly increases the risk of mental retardation.

The main risks of irradiation during preimplantation, organogenesis and the late fetal period are prenatal death, congenital malformation, growth retardation and carcinogenesis, respectively.

The effects of irradiation during gestation (other than inducing cancer) are deterministic, not stochastic. Since there is a threshold dose for deterministic effects, the severity of such an effect depends on the dose. Since the developing embryo/fetus is particularly radiosensitive, the dose received by the fetus should be minimized. Unfortunately, 36% of the 40 million radiological tests performed per year were performed in fertile women until the 1980s.

The most radiosensitive phase of human gestation regarding neonatal deaths is 2–6 weeks, the phase of organogenesis. Some congenital malformations that can occur at this stage are not compatible with life.

The time required for SLD repair in most tissues ($T_{1/2}$) → 1.5 h.

**Normalized Total Dose ($NTD_{2\,Gy}$)**

This is used to convert a BED to an LQ equivalent dose in 2 Gy fractions. The NTD is very useful for deriving hypofractionated regimens in LQ equivalent doses (stereotactic radiotherapy, hypofractionation in prostate cancer and breast cancer, etc.). $NTD_{2\,Gy}$ is the total dose in 2 Gy fractions that would give the same log cell kill as the schedule being analyzed.

$$RE = 1 + \frac{d}{\alpha/\beta}$$

Here, RE = relative effectiveness, $d$ = fraction dose, and α/β = alpha/beta ratio.
Prostate tumor α/β = 1.5 Gy
RE for 2 Gy fractions: 1 + 2/1.5 = 2.33

Divide $BED_{1.5\ Gy}$ by this RE (2.33) to get $NTD_{2\ Gy}$
For example, 7.30 × 5 fractions = 36.5 Gy
$BED_{1.5\ Gy} = 36.5(1 + 7.3/1.5) = 214.13$
$NTD_{2\ Gy} = 214.13/2.33 = 91.9$ Gy
Reference: Fowler JF (2005) The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. Acta Oncolo 44:265–276.

**Normal Tissue Toxicity After Stereotactic Body Radiation (SBRT)**
*SBRT doses per fraction for serial organs:*
Spinal cord: 8–10 Gy/1 fraction, 5–6 Gy/3 fractions, 4–5 Gy/5 fractions
Trachea and bronchi: 7–9 Gy/5 fractions
Brachial plexus: 8–10 Gy/5 fractions
Esophagus: 6–8 Gy/5 fractions
Chest wall and ribs: 10–15 Gy/3 fractions, 6–8 Gy/5 fractions
Small bowel: 10–12 Gy/1–2 fractions, 6–8 Gy/5 fractions
Note that therapeutic or close to therapeutic doses with 1–3 fractions are not recommended for trachea, bronchi, brachial plexus and esophagus.
*SBRT doses per fraction for parallel organs*:
Lung: 20 Gy/1 fraction, 20 Gy/3 fractions, 8–10 Gy/5 fractions
Liver: 25 Gy/1 fraction, 20 Gy/3 fractions, 8–10 Gy/5 fractions
*SBRT dose–volume limits for parallel organs:*
Lung: 700–1,000 mL of lung not involved with gross disease, $V_{20}$ of 25–30%
Liver: 700–1,000 mL of liver not involved with gross disease, two-thirds of normal liver <30 Gy
Kidney: minimize the region receiving >20 Gy, two-thirds of one kidney <15 Gy (assuming that there is another functional kidney)
Reference: Milano MT et al (2008) Normal tissue toxicity after small field hypofractionated stereotactic body irradiation.

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