Chapter 14

BASIC RADIOBIOLOGY

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14.1. INTRODUCTION

Radiobiology, a branch of science concerned with the action of ionizing radiation on biological tissues and living organisms, is a combination of two disciplines: radiation physics and biology. All living things are made up of protoplasm, which consists of inorganic and organic compounds dissolved or suspended in water. The smallest unit of protoplasm capable of independent existence is the cell.

Cells contain inorganic compounds (water and minerals) as well as organic compounds (proteins, carbohydrates, nucleic acids and lipids). The two main constituents of a cell are the cytoplasm, which supports all metabolic functions within the cell, and the nucleus, which contains the genetic information (DNA).

Human cells are either somatic cells or germ cells.

Cells propagate through division: division of somatic cells is called mitosis, while division of germ cells is called meiosis. When a somatic cell divides, two cells are produced, each carrying a chromosome complement identical to that of the original cell. The new cells themselves may undergo further division, and the process continues.

Somatic cells are classified as:

- Stem cells, which exist to self-perpetuate and produce cells for a differentiated cell population (e.g. stem cells of the haematopoietic system, epidermis and mucosal lining of the intestine);
- Transit cells, which are cells in movement to another population (e.g. a reticulocyte that is differentiating to become an erythrocyte);
- Mature cells, which are fully differentiated and do not exhibit mitotic activity (e.g. muscle cells and nervous tissue).

A group of cells that together perform one or more functions is referred to as tissue. A group of tissues that together perform one or more functions is called an organ. A group of organs that perform one or more functions is a system of organs or an organism.

14.2. CLASSIFICATION OF RADIATIONS IN RADIOBIOLOGY

For use in radiobiology and radiation protection the physical quantity that is useful for defining the quality of an ionizing radiation beam is the linear energy transfer (LET). In contrast to the stopping power, which focuses attention on the energy loss by an energetic charged particle moving through a medium, the LET focuses attention on the linear rate of energy absorption by the absorbing medium as the charged particle traverses the medium.

The ICRU defines the LET as follows:

> "*LET of charged particles in a medium is the quotient dE/dl, where dE is the average energy locally imparted to the medium by a charged particle of specified energy in traversing a distance of dl.*"

In contrast to the stopping power, which has a typical unit of MeV/cm, the unit usually used for the LET is keV/μm. The energy average is obtained by dividing the particle track into equal energy increments and averaging the length of track over which these energy increments are deposited.

Typical LET values for commonly used radiations are:

- 250 kVp X rays: 2 keV/μm.
- Cobalt-60 γ rays: 0.3 keV/μm.
- 3 MeV X rays: 0.3 keV/μm.
- 1 MeV electrons: 0.25 keV/μm.

LET values for other, less commonly used radiations are:

— 14 MeV neutrons: 12 keV/μm.
— Heavy charged particles: 100–200 keV/μm.
— 1 keV electrons: 12.3 keV/μm.
— 10 keV electrons: 2.3 keV/μm.

X rays and γ rays are considered low LET (sparsely ionizing) radiations, while energetic neutrons, protons and heavy charged particles are high LET (densely ionizing) radiations. The demarcation value between low and high LET is at about 10 keV/μm.

14.3. CELL CYCLE AND CELL DEATH

The cell proliferation cycle is defined by two well defined time periods:

- Mitosis (M), where division takes place;
- The period of DNA synthesis (S).

The S and M portions of the cell cycle are separated by two periods (gaps) G_1 and G_2 when, respectively, DNA has not yet been synthesized or has been synthesized but other metabolic processes are taking place.

The time between successive divisions (mitoses) is called the cell cycle time. For mammalian cells growing in culture the S phase is usually in the range of 6–8 h, the M phase less than an hour, G_2 is in the range of 2–4 h and G_1 is 1–8 h, making the total cell cycle of the order of 10–20 h. In contrast, the cell cycle for stem cells in certain tissues is up to about 10 days.

In general, cells are most radiosensitive in the M and G_2 phases, and most resistant in the late S phase.

The cell cycle time of malignant cells is shorter than that of some normal tissue cells, but during regeneration after injury normal cells can proliferate faster.

Cell death of non-proliferating (static) cells is defined as the loss of a specific function, while for stem cells and other cells capable of many divisions it is defined as the loss of reproductive integrity (reproductive death). A surviving cell that maintains its reproductive integrity and proliferates almost indefinitely is said to be clonogenic.

14.4. IRRADIATION OF CELLS

When cells are exposed to ionizing radiation the standard physical effects between radiation and the atoms or molecules of the cells occur first and the possible biological damage to cell functions follows later. The biological effects of radiation result mainly from damage to the DNA, which is the most critical target within the cell; however, there are also other sites in the cell that, when damaged, may lead to cell death. When directly ionizing radiation is absorbed in biological material, the damage to the cell may occur in one of two ways: direct or indirect.

14.4.1. Direct action in cell damage by radiation

In direct action the radiation interacts directly with the critical target in the cell. The atoms of the target itself may be ionized or excited through Coulomb interactions, leading to the chain of physical and chemical events that eventually produce the biological damage. Direct action is the dominant process in the interaction of high LET particles with biological material.

14.4.2. Indirect action in cell damage by radiation

In indirect action the radiation interacts with other molecules and atoms (mainly water, since about 80% of a cell is composed of water) within the cell to produce free radicals, which can, through diffusion in the cell, damage the critical target within the cell. In interactions of radiation with water, short lived yet extremely reactive free radicals such as H_2O^+ (water ion) and OH• (hydroxyl radical) are produced. The free radicals in turn can cause damage to the target within the cell.

The free radicals that break the chemical bonds and produce chemical changes that lead to biological damage are highly reactive molecules because they have an unpaired valence electron.

About two thirds of the biological damage by low LET radiations (sparsely ionizing radiations) such as X rays or electrons is due to indirect action.

Indirect action can be modified by chemical sensitizers or radiation protectors.

The steps involved in producing biological damage by the indirect action of X rays are as follows:

- Step 1: Primary photon interaction (photoelectric effect, Compton effect and pair production) produces a high energy electron.

- Step 2: The high energy electron in moving through tissue produces free radicals in water.
- Step 3: The free radicals may produce changes in DNA from breakage of chemical bonds.
- Step 4: The changes in chemical bonds result in biological effects.

Step (1) is in the realm of physics; step (2) is in chemistry; steps (3) and (4) are in radiobiology.

14.4.3. Fate of irradiated cells

Irradiation of a cell will result in one of the following nine possible outcomes:

- No effect.
- Division delay: The cell is delayed from going through division.
- Apoptosis: The cell dies before it can divide or afterwards by fragmentation into smaller bodies, which are taken up by neighbouring cells.
- Reproductive failure: The cell dies when attempting the first or subsequent mitosis.
- Genomic instability: There is a delayed form of reproductive failure as a result of induced genomic instability.
- Mutation: The cell survives but contains a mutation.
- Transformation: The cell survives but the mutation leads to a transformed phenotype and possibly carcinogenesis.
- Bystander effects: An irradiated cell can send signals to neighbouring unirradiated cells and induce genetic damage in them.
- Adaptive responses: The irradiated cell is stimulated to react and become more resistant to subsequent irradiation.

14.5. TYPE OF RADIATION DAMAGE

14.5.1. Timescale

The timescale involved between the breakage of chemical bonds and the biological effect may be hours to years, depending on the type of damage.

If cell kill is the result, it may happen in hours to days, when the damaged cell attempts to divide (early effects of radiation). This can result in early tissue reactions (deterministic effects) if many cells are killed.

If the damage is oncogenic (cancer induction), then its expression may be delayed for years (late effects of radiation). Ionizing radiation has been proven to cause leukaemia and has been implicated in the development of many other cancers in tissues such as bone, lung, skin, thyroid and breast.

In addition to carcinogenesis (induction of cancer), the late effects of radiation include: delayed tissue reactions (deterministic effects) such as fibrosis and other reactions mediated by vascular deficiencies; life span shortening (due largely to cancer lethalities); genetic damage, where the effects may be expressed in subsequent generations; and potential effects to the foetus.

14.5.2. Classification of radiation damage

Radiation damage to mammalian cells is divided into three categories:

- Lethal damage, which is irreversible, irreparable and leads to cell death;
- Sublethal damage, which can be repaired in hours unless additional sublethal damage is added that eventually leads to lethal damage;
- Potentially lethal damage, which can be manipulated by repair when cells are allowed to remain in a non-dividing state.

14.5.3. Somatic and genetic effects

The effects of radiation on the human population can be classified as either somatic or genetic:

- Somatic effects are harm that exposed individuals suffer during their lifetime, such as radiation induced cancers (carcinogenesis), sterility, opacification of the eye lens and life shortening.
- Genetic or hereditary effects are radiation induced mutations to an individual's genes and DNA that can contribute to the birth of defective descendants.

Carcinogenesis expresses itself as a late somatic effect in the form of acute or chronic myeloid leukaemia or some solid tumours, for example in the skin, bone, lung, thyroid or breast. Human data on carcinogenesis have been collected from the following sources:

— Low level occupational exposure;
— Atomic bomb survivors in Hiroshima and Nagasaki;
— Medical radiation exposure of patients (e.g. during treatment of ankylosing spondylitis, treatment of thyroid abnormalities and radio-

therapy of cancer) and staff (e.g. radiologists in the early part of the last century).

14.5.4. Stochastic and deterministic (non-stochastic) effects

The harmful effects of radiation may be classified into two general categories: stochastic and deterministic (previously called non-stochastic). The National Council on Radiation Protection and Measurements (NCRP) defines these effects as follows:

- A stochastic effect is one in which the probability of occurrence increases with increasing dose but the severity in affected individuals does not depend on the dose (induction of cancer, radiation carcinogenesis and genetic effects). There is no threshold dose for effects that are truly stochastic, because these effects arise in single cells and it is assumed that there is always some small probability of the event occurring even at very small doses.
- A deterministic effect (tissue reaction) is one that increases in severity with increasing dose, usually above a threshold dose, in affected individuals (organ dysfunction, fibrosis, lens opacification, blood changes and decrease in sperm count). These are events caused by damage to populations of cells, hence the presence of a threshold dose.

14.5.5. Acute versus late tissue or organ effects

An organ or tissue expresses response to radiation damage either as an acute effect or as a late (chronic) effect.

Acute effects manifest themselves soon after exposure to radiation and are characterized by inflammation, oedema, denudation of epithelia and haemopoietic tissue, and haemorrhage. Late effects are delayed and are, for example, fibrosis, atrophy, ulceration, stenosis or obstruction of the intestine. Late effects may be generic and caused by absorption of radiation directly in the target tissue, or consequential to acute damage in overlying tissues such as mucosa or the epidermis.

14.5.6. Total body radiation response

The response of an organism to acute total body radiation exposure is influenced by the combined response to radiation of all organs constituting the organism. Depending on the actual total body dose above 1 Gy, the response is described as a specific radiation syndrome:

- 1 Gy < dose < 10 Gy: bone marrow syndrome.
- 10 Gy < dose < 100 Gy: gastrointestinal syndrome.
- Dose > 100 Gy: central nervous system syndrome.

Human data on specific radiation syndromes have been collected from the following sources:

— Accidents in industry and research laboratories;
— Exposure to radioactive fallout from the testing of nuclear weapons or the Chernobyl nuclear power plant accident;
— Exposure of humans to high levels of radiation in Hiroshima and Nagasaki;
— Medical exposure of humans to total body irradiations (TBIs).

14.5.7. Foetal irradiation

Between conception and birth the foetus passes through three basic stages of development:

- Pre-implantation (day 1 to 10);
- Organogenesis (day 11 to 42);
- Growth stage (day 43 to birth).

Radiation is a known teratogen (i.e. it causes birth defects). The effects of radiation on the foetus depend on two factors: the dose and the stage of development at the time of exposure. The principal effects of radiation on a foetus are foetal or neonatal death, malformations, growth retardation, congenital defects and cancer induction.

An abortion to avoid the possibility of radiation induced congenital abnormalities should be considered only when the foetal dose has exceeded 10 cGy.

14.6. CELL SURVIVAL CURVES

A cell survival curve describes the relationship between the surviving fraction of cells (i.e. the fraction of irradiated cells that maintain their reproductive integrity (clonogenic cells)) and the absorbed dose. Cell survival as a function of radiation dose is graphically represented by plotting the surviving fraction on a logarithmic scale on the ordinate against dose on a linear scale on the abscissa.

Cell surviving fractions are determined with in vitro or in vivo techniques. Examples of survival curves for cells irradiated by densely and sparsely ionizing radiation beams are shown in Fig. 14.1.

The type of radiation influences the shape of the cell survival curve. Densely ionizing radiations exhibit a cell survival curve that is almost an exponential function of dose, shown by an almost straight line on the log–linear plot. For sparsely ionizing radiation, however, the curves show an initial slope followed by a shoulder region and then become nearly straight at higher doses. Factors that make cells less radiosensitive are: removal of oxygen to create a hypoxic state, the addition of chemical radical scavengers, the use of low dose rates or multifractionated irradiation, and cells synchronized in the late S phase of the cell cycle.

Several mathematical methods of varying degrees of complexity have been developed to define the shape of cell survival curves, all based on the concept of the random nature of energy deposition by radiation.

The linear quadratic model is now most often used to describe the cell survival curve, assuming that there are two components to cell kill by radiation (Fig. 14.1(b)):

$$S(D) = e^{-\alpha D - \beta D^2} \tag{14.1}$$

where

$S(D)$ is the fraction of cells surviving a dose D;
α is a constant describing the initial slope of the cell survival curve;
β is a smaller constant describing the quadratic component of cell killing.

The ratio α/β gives the dose at which the linear and quadratic components of cell killing are equal (8 Gy in the example shown in Fig. 14.1(b)).

For completeness, the earlier multitarget single hit model described the slope of the survival curve by D_0 (the dose to reduce survival to 37% of its value at any point on the final near exponential portion of the curve) and the extrapolation number n (the point of intersection of the slope on the log survival axis). D_q was the quasi-threshold dose. However, this model (Fig. 14.1(a)) does not have any current biological basis.

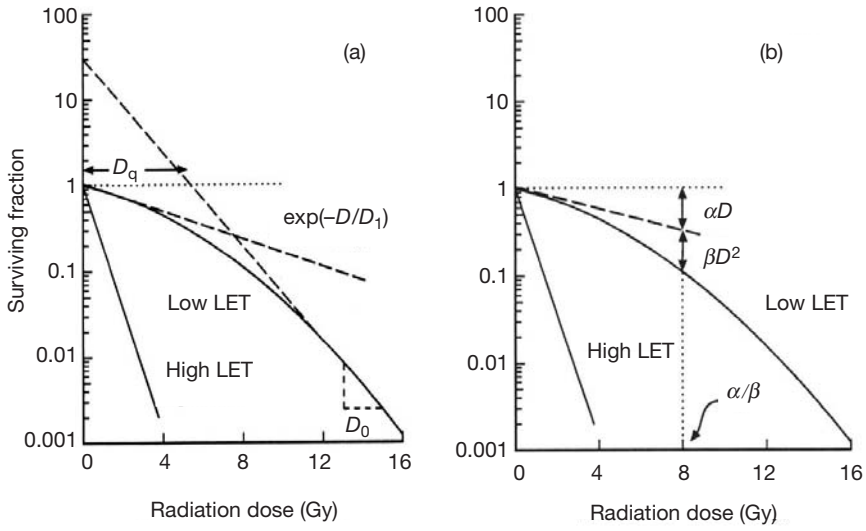

FIG. 14.1. Typical cell survival curves for high LET (densely ionizing) radiation and low LET (sparsely ionizing) radiation. (a) The earlier multitarget single hit model; (b) the current linear quadratic model.

14.7. DOSE RESPONSE CURVES

A plot of a biological effect observed (e.g. tumour induction or tissue response) against the dose given is called a dose response curve. Generally, as dose increases so does the effect.

Three types of dose response relationship are known:

- Linear;
- Linear quadratic;
- Sigmoid.

Dose response curves may or may not have a threshold. A threshold dose is the largest dose for a particular effect studied below which no effect will be observed.

Various dose response curves are shown in Fig. 14.2, with:

— A linear relationship with no threshold;
— A linear relationship with a threshold;
— A linear quadratic relationship with no threshold;

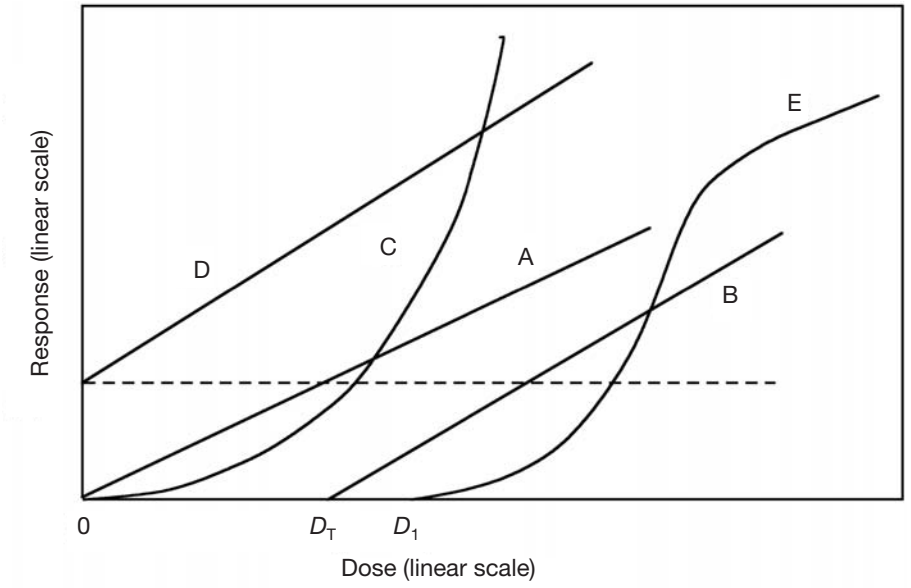

FIG. 14.2. Typical dose response curves for cancer induction (curves A, B, C and D) and for tissue response (curve E). Curve A represents a linear relationship with no threshold; curve B represents a linear relationship with threshold D_T; curve C represents a linear quadratic relationship with no threshold (assumed for stochastic effects, for example carcinogenesis); curve D represents a linear relationship with no threshold (the area below the dashed line represents the natural incidence of the effect, for example carcinogenesis); and curve E represents a sigmoid relationship with threshold D_1, as is common for deterministic effects in tissues, for example tumour control or treatment morbidity. The curves are diagrammatic only and are separated for clarity (in practice the dashed line would be lower).

— A linear relationship (the area below the dashed line indicates the natural incidence of the effect);
— A sigmoid relationship with a threshold.

The response of different tissues or organs to radiation varies markedly, depending primarily on two factors: the inherent sensitivity of the individual cells and the kinetics of the population.

There is a clear distinction in radiation response between tissues that are early responding (skin, mucosa and intestinal epithelium) and those that are late responding (spinal cord), as shown schematically in Fig. 14.3 for the surviving fraction against the dose.

The cell survival curves for late responding tissues are more curved than those for early responding tissues. For early effects the ratio α/β is large and

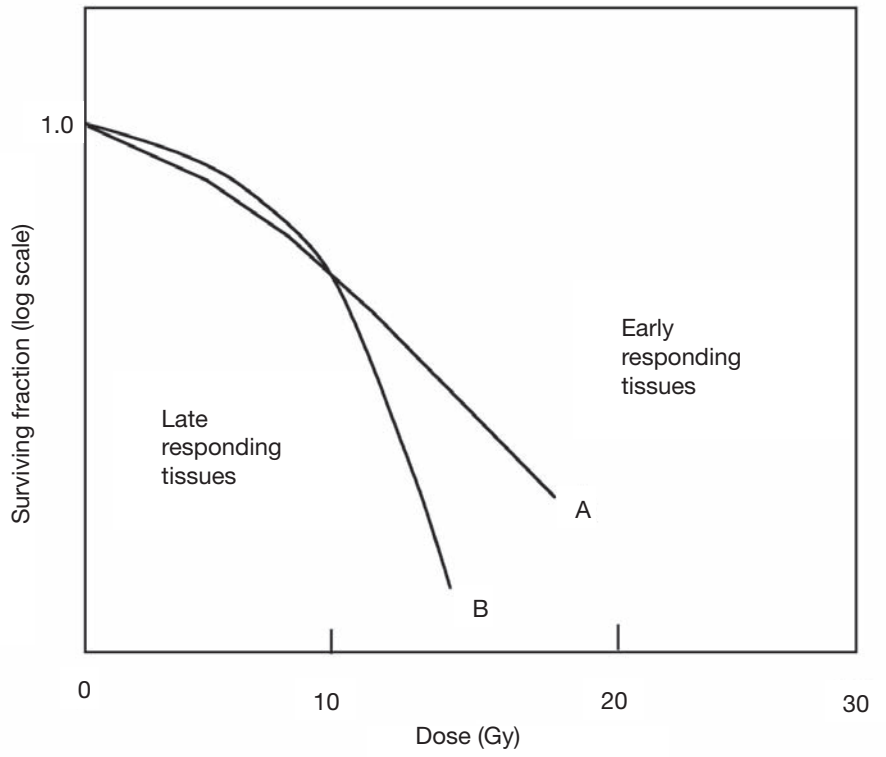

FIG. 14.3. Hypothetical target cell survival curves for (curve A) early responding tissues and (curve B) late responding tissues.

α dominates at low doses. For late effects α/β is small and β has an influence at doses lower than for early responding tissues. The α and β components of mammalian cell killing are equal at approximately $\alpha/\beta = 10$ Gy and $\alpha/\beta = 3$ Gy for early and late effects, respectively.

14.8. MEASUREMENT OF RADIATION DAMAGE IN TISSUE

The effects of radiation on tissue as a function of dose are measured with assays and the measurement results are given in the form of cell survival curves or dose response curves. Three categories of tissue assay are in use:

- Clonogenic assays measure the reproductive integrity of the clonogenic stem cells in tissue, and the measurements result in cell survival curves.

- Functional assays measure functional end points for various tissues and produce dose response curves in which the response is measured on a graded reaction scale or expressed as a proportion of cases in which reactions are greater than a specified level.
- Lethality assays quantify the number of animal deaths after irradiation of the whole animal or of a specific organ with a given dose. The experiments usually result in deduced values of the parameter LD50, where LD stands for 'lethal dose', defined as the dose to animals or to a specific organ of animals that kills 50% of the animals.

14.9. NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

The aim of radiotherapy is to deliver enough radiation to the tumour to destroy it without irradiating normal tissue to a dose that will lead to serious complications (morbidity). As shown in Fig. 14.4, the principle is usually illustrated by plotting two sigmoid curves, one for the tumour control probability (TCP) (curve A) and the other for the normal tissue complication probability (NTCP) (curve B).

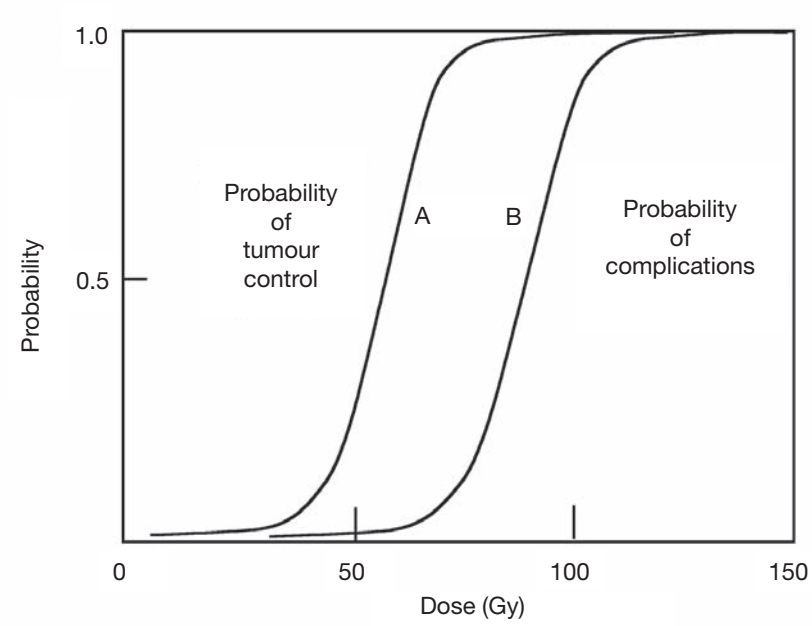

FIG. 14.4. The principle of therapeutic ratio. Curve A represents the TCP, curve B the probability of complications. The total clinical dose is usually delivered in 2 Gy fractions.

The optimum choice of radiation dose delivery technique in the treatment of a given tumour is such that it maximizes the TCP and simultaneously minimizes the NTCP. For a typical good radiotherapy treatment, TCP $\geq$ 0.5 and NTCP $\leq$ 0.05.

The further curve B (NTCP) is to the right of curve A (TCP) in Fig. 14.4, the easier it is to achieve the radiotherapeutic goal, the larger is the therapeutic ratio and the less likely will it be that the treatment causes complications. The therapeutic ratio generally refers to the ratio of the TCP and NTCP at a specified level of response (usually 0.05) for normal tissue.

Figure 14.4 shows an ideal situation; in reality, the TCP curve is often shallower than the NTCP curve, partly because tumours are more heterogeneous than normal tissues. Moreover, the TCP curve for regional control of certain tumours never reaches a value of 1.0, as a result of microscopic or metastatic spread of the disease beyond the primary tumour site. It is imperative that the average doses to normal tissues be kept lower than the doses to tumours in order to minimize treatment complications and optimize treatment outcomes. In modern radiotherapy this is achieved through sophisticated 3-D treatment planning (forward or inverse) and dose delivery (conformal or intensity modulated).

In the early days of radiotherapy it was usually assumed that normal cells were less sensitive to single doses of radiation than tumour cells; however, currently it is accepted that both malignant cells and those normal cells responsible for early reactions exhibit similar values (albeit with individual variations) for D_0 of around 1.3 Gy, with α/β of about 10 Gy.

It is for late reactions in general that the shoulder on the target cell survival curve is effectively greater than it is for target cells in tumours or early reacting tissues, with α/β of about 3 Gy, thus providing a differential that is exploited in hyperfractionation protocols to spare (reduce) late reactions using small dose fractions.

The therapeutic ratio varies with many factors, such as the dose rate and LET of the irradiation, the presence of radiosensitizers or radioprotectors, the design of the treatment plan and the precision of implementation of the treatment plan.

14.10. OXYGEN EFFECT

The presence or absence of molecular oxygen within a cell influences the biological effect of ionizing radiation: the larger the cell oxygenation above anoxia, the larger is the biological effect of ionizing radiation. Especially for low LET radiations, the larger the cell oxygenation above anoxia, the larger the

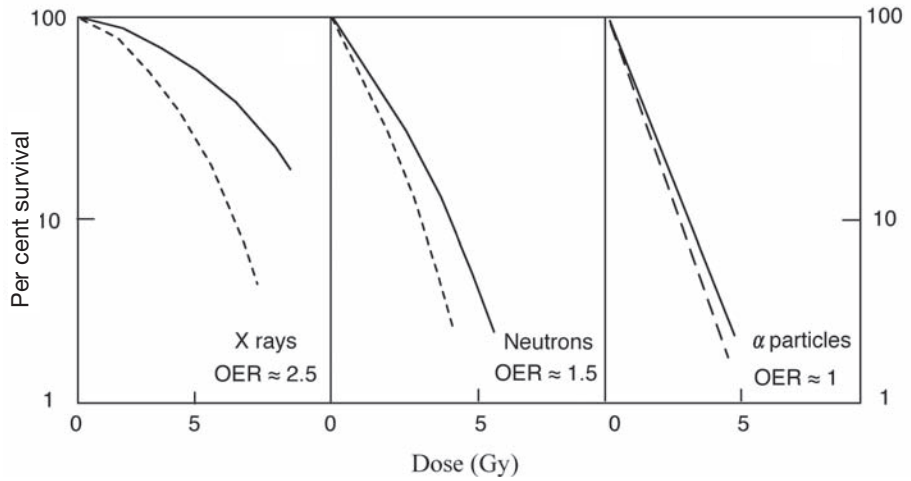

FIG. 14.5. Typical cell surviving fractions for X rays, neutrons and α particles: dashed curves are for well oxygenated cells, solid curves for hypoxic cells.

biological effect until saturation of the effect of oxygen occurs. As shown in Fig. 14.5, the effect is quite dramatic for low LET (sparsely ionizing) radiations, while for high LET (densely ionizing) radiations it is much less pronounced. The ratio of doses without and with oxygen (hypoxic versus well oxygenated cells) to produce the same biological effect is called the oxygen enhancement ratio (OER).

$$\text{OER} = \frac{\text{Dose to produce a given effect without oxygen}}{\text{Dose to produce the same effect with oxygen}} \qquad (14.2)$$

The OER for X rays and electrons is about three at high doses and falls to about two for doses of 1–2 Gy. The OER decreases as the LET increases and approaches OER = 1 at about LET = 150 keV/μm, as shown in Fig. 14.6.

Cells at the periphery of tumour cords growing around blood vessels become chronically hypoxic because of the consumption of most of the oxygen near the blood vessel. The transient closing of blood vessels can also make the whole tumour cord hypoxic for a few minutes at a time. Reoxygenation is the process by which cells that are hypoxic become oxygenated after irradiation, through the killing and removal of oxic radiosensitive cells from the tumour.

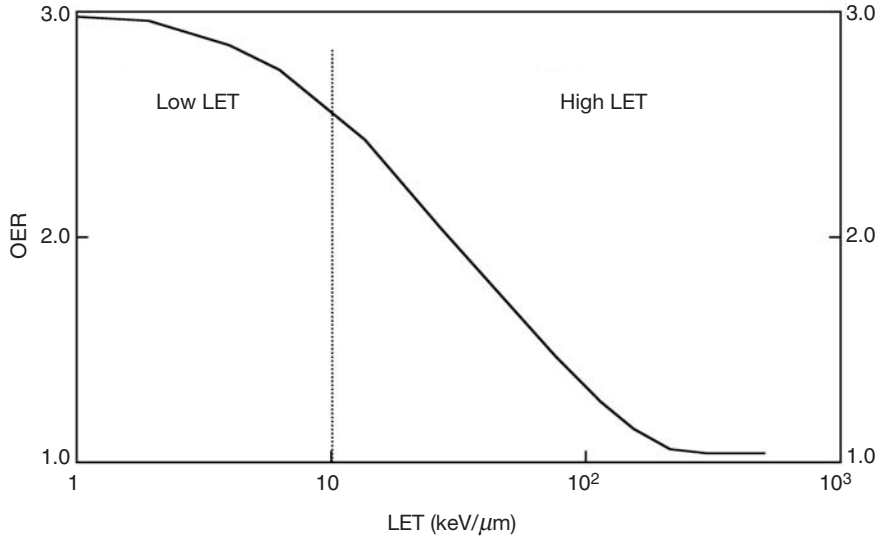

FIG. 14.6. OER plotted against LET. The vertical dashed line separates the low LET region, where LET < 10 keV/μm, from the high LET region, where LET > 10 keV/μm.

14.11. RELATIVE BIOLOGICAL EFFECTIVENESS

As the LET of radiation increases, the ability of the radiation to produce biological damage also increases. The relative biological effectiveness (RBE) compares the dose of test radiation to the dose of standard radiation to produce the same biological effect. The standard radiation has been taken as 250 kVp X rays for historical reasons, but is now recommended to be ^{60}Co γ rays. The RBE is defined by the following ratio:

$$\text{RBE} = \frac{\text{Dose from standard radiation to produce a given biological effect}}{\text{Dose from test radiation to produce the same biological effect}} \tag{14.3}$$

The RBE varies not only with the type of radiation but also with the type of cell or tissue, biologic effect under investigation, dose, dose rate and fractionation. In general, the RBE increases with the LET to reach a maximum RBE of 3–8 (depending on the level of cell kill) at LET ≈ 200 keV/m and then decreases because of energy overkill, as shown in Fig. 14.7.

An increase in the RBE in itself offers no therapeutic advantage unless there is a differential effect making the RBE for normal tissue smaller than that for the tumour, increasing the relative level of tumour cell killing and the therapeutic ratio.

14.12. DOSE RATE AND FRACTIONATION

For the same radiation dose, radiation delivered at a lower dose rate may produce less cell killing than radiation delivered at a higher dose rate, because sublethal damage repair occurs during the protracted exposure. As the dose rate is reduced, the slope of the survival curve becomes shallower and the shoulder tends to disappear, since in the linear quadratic model α does not change significantly; however, $\beta \rightarrow 0$.

The typical dose rates used in radiotherapy are of the order of:

- 1 Gy/min in standard radiotherapy and high dose rate (HDR) brachytherapy;
- 0.1 Gy/min in TBI;
- 0.01 Gy/min in low dose rate (LDR) brachytherapy.

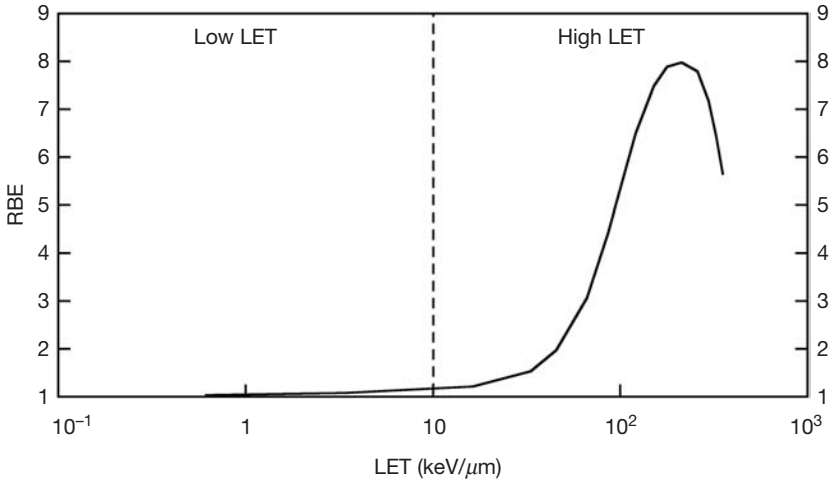

FIG. 14.7. RBE against LET. The vertical dashed line separates the low LET region, where RBE ≈ 1, from the high LET region, where the RBE first rises with the LET, reaches a peak of about 8 for LET ≈ 200 keV/μm, and then drops with a further increase in the LET.

Fractionation of radiation treatment so that it is given over a period of weeks rather than in a single session results in a better therapeutic ratio. However, to achieve the desired level of biological damage the total dose in a fractionated treatment must be much larger than that in a single treatment.

The basis of fractionation is rooted in five primary biological factors called the five Rs of radiotherapy:

— Radiosensitivity. Mammalian cells have different radiosensitivities.
— Repair. Mammalian cells can repair radiation damage. This is a complex process that involves repair of sublethal damage by a variety of repair enzymes and pathways.
— Repopulation. Cells repopulate while receiving fractionated doses of radiation.
— Redistribution. Redistribution in proliferating cell populations throughout the cell cycle phases increases the cell kill from a fractionated treatment relative to a single session treatment.
— Reoxygenation. Reoxygenation of hypoxic cells occurs during a fractionated course of treatment, making them more radiosensitive to subsequent doses of radiation.

Conventional fractionation is explained as follows: division of dose into multiple fractions spares normal tissues through repair of sublethal damage between dose fractions and repopulation of cells. The former is greater for late reacting tissues and the latter for early reacting tissues. Concurrently, fractionation increases tumour damage through reoxygenation and redistribution of tumour cells. A balance is achieved between the response of tumour and early and late reacting normal tissues, so that small doses per fraction spare late reactions preferentially, and a reasonable schedule duration allows regeneration of early reacting tissues and tumour reoxygenation to likely occur.

The current standard fractionation is based on five daily treatments per week and a total treatment time of several weeks. This regimen reflects the practical aspects of dose delivery to a patient, successful outcome of patient treatments and convenience to the staff delivering the treatment.

Other fractionation schemes are being studied with the aim of improving the therapeutic ratio. Some of these are hyperfractionation, accelerated fractionation and CHART:

(i) Hyperfractionation uses more than one fraction per day with a smaller dose per fraction (<1.8 Gy) to reduce long term complications and to allow delivery of higher total tumour dose.

(ii) Accelerated fractionation reduces the overall treatment time, minimizing tumour cell repopulation during the course of treatment.
(iii) CHART (continuous hyperfractionated accelerated radiation therapy) is an experimental programme used with three fractions per day for 12 continuous days.

14.13. RADIOPROTECTORS AND RADIOSENSITIZERS

Various chemical agents may alter cell response to ionizing radiation, either reducing or enhancing the cell response.

Chemical agents that reduce cell response to radiation are called radioprotectors. They generally influence the indirect effects of radiation by scavenging the production of free radicals. The dose modifying factor (DMF) is defined as follows:

$$\text{DMF} = \frac{\text{Dose to produce an effect with radioprotector}}{\text{Dose to produce the same effect without radioprotector}} \quad (14.4)$$

Chemical agents that enhance cell response to radiation are called radiosensitizers and generally promote both the direct and indirect effects of radiation. Examples are halogenated pyrimidines, which intercalate between the DNA strands and inhibit repair, and hypoxic cell radiosensitizers, which act like oxygen.

Another type of radiosensitizer is compounds containing boron, which enhances the effects of thermal neutron radiation therapy. Boron-10 has a high cross-section for reaction with thermal neutrons (kinetic energy of the order of 0.025 eV). When a thermal neutron interacts with ^{10}B an unstable nuclide ^{11}B is formed that undergoes fission and produces α particles delivering a high dose in the immediate vicinity of the compound that contains boron. This boron neutron capture therapy (BNCT) has been investigated since the 1950s; however, successful clinical applications have so far been elusive.

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