Chapter 2: Basic Radiobiology

Slide set of 60 slides based on the chapter authored by R.G. Dale and J. Wondergem of the IAEA publication (ISBN 92-0-107304-6):
Nuclear Medicine Physics: A Handbook for Teachers and Students

Objective:

To familiarize with the possible effects induced by ionizing radiation on living matter.

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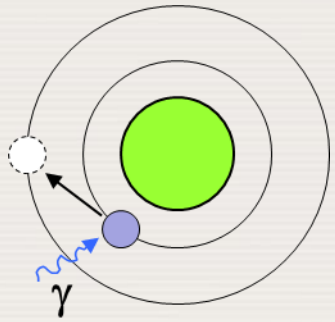
2.1 BASIC RADIOBIOLOGY

2.1 Introduction

- Radiobiology is the qualitative and quantitative study of the **effects of ionizing radiation on living matter**.
- Radiation may induce cells to become **malignant**, alter their **functionality**, or directly induce **cell death**.
- Consideration of the associated radiobiology is:
  - important in **diagnostic** applications of radiation
  - essential in **therapy** applications of radiation.

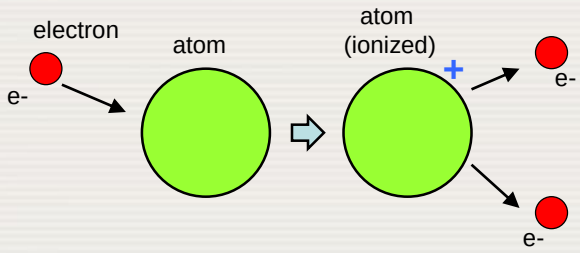
2.2 Radiation effects and timescales

At the **microscopic level**, incident rays or particles may interact with orbital electrons within the cellular atoms and molecules to cause:



- Excitation: raising a bound electron to a higher energy state; the electron does not have sufficient energy to leave the host atom.

- Ionization, the electron receives sufficient energy to be ejected from its orbit and to leave the host atom. Ionizing radiation is able to induce electron ejection process.



The irradiation of cellular material with such radiation gives rise to the production of a flux of energetic secondary particles (electrons).

Energetic and unbound, they are capable of migrating away from the site of production, interact with other atoms and molecules, and give up their **energy to the surrounding medium**.

2.2 Radiation effects and timescales

- This energy absorption process gives rise to **radicals** and **other chemical species** → chemical interactions → cause of **radiation damage**.

- Irrespective of the nature of the primary radiation (particles and/or electro-magnetic waves), **energy is transferred** to matter always via the **secondary electrons** which are produced.

- **Chemical changes** operate over a short timescale (**~10^{-5} s**), but this period is a factor of **~10^{18}** longer than the time taken for the original particle to traverse the cell nucleus. Thus, on the **microscopic scale**, there is a relatively **long period** during which chemical damage is inflicted.

- Initial **ionization events** in the biological material (near-instantaneous at the **microscopic** level) are the precursors to a chain of subsequent events which may lead to the clinical (**macroscopic**) **manifestation** of **radiation damage**.

2.2 Radiation effects and timescales

Expression of **cell death** in individual lethally damaged cells occurs **later**, usually at the point when the cell next attempts to **enter mitosis**.

Gross (macroscopic and clinically observable) radiation effects are a result of the wholesale **functional impairment** that follows from lethal damage being inflicted to large numbers of cells or critical substructures.

The whole process may need **months/ years**

In clinical studies, **deleterious health effects** may be seen **long after** the diagnostic test or treatment

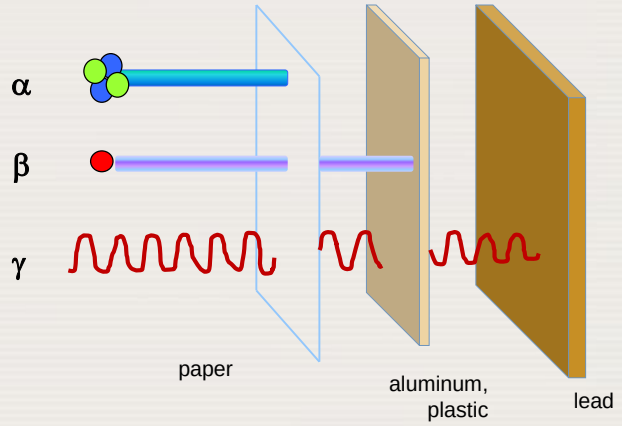
Action	Approximate timescale
Initial ionizing event	10^{-18} s
Transit of secondary electrons	10^{-15} s
Production of ion radicals	10^{-10} s
Production of free radicals	10^{-9} s
Chemical changes	10^{-5} s
Individual cell death	Hours–months
Gross biological effects	Hours–years

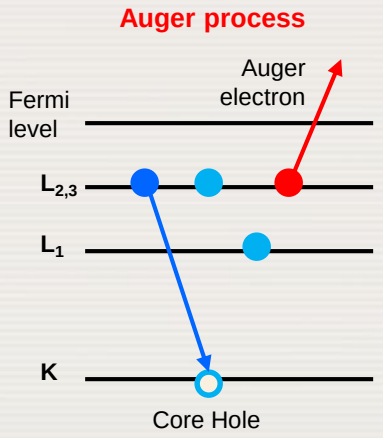
2.3. BIOLOGICAL PROPERTIES OF IONIZING RADIATION

2.3.1. Types of ionizing radiation

In nuclear medicine, **four types of radiation** which play a relevant role in **tumour** and **normal tissue** effects:

- gamma radiation (γ)
- beta radiation (β)
- alpha particles (α)
- Auger electrons (e^-_{Auger})



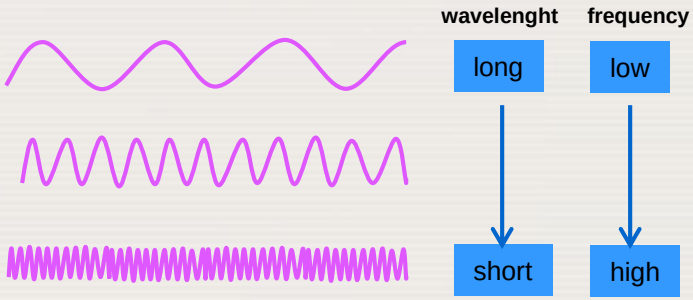


2.3. BIOLOGICAL PROPERTIES OF IONIZING RADIATION

2.3.1.1. Gamma radiation

Gamma radiation

- ❑ electromagnetic (**EM**) radiation of **high energy** (usually >25 keV)
- ❑ produced by **subatomic** particle interactions
- ❑ as a stream of **wave-like particle** bundles (photons) moving at the **speed of light**
- ❑ interaction **properties** governed mainly by their associated **wavelength**



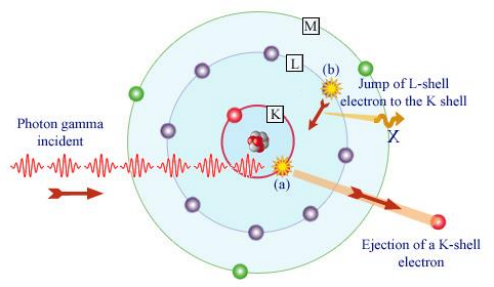
γ: very short wavelenght EM radiation

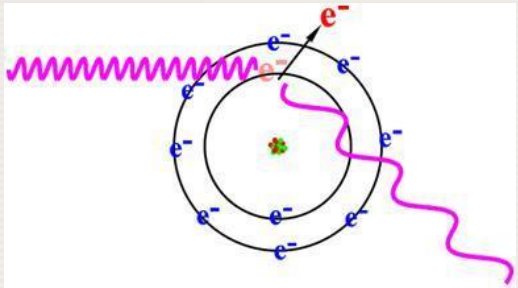
Ionization behaviour of **large numbers** of photons can be accurately **predicted**; **individual photon** interactions occur at random and, while passing through matter, a photon may interact one or **more times, or never**

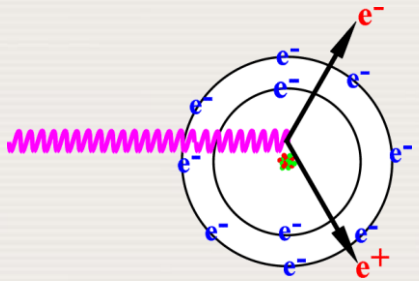
2.3. BIOLOGICAL PROPERTIES OF IONIZING RADIATION

2.3.1.1. Gamma radiation

In each interaction (normally involving a **photoelectric**, **Compton**, or **pair production** event), **secondary particles** are produced, usually **electrons** (directly ionizing) or another **photon** of reduced energy, which can undergo further interactions







secondary electrons undergo many ionizing events relatively close to the site of their creation → contribute mostly to the **locally absorbed dose**

secondary photons carry energy further away from the initial interaction site → following subsequent electron-producing interactions → responsible for the **dose deposition** at **more distant sites** from the original interaction

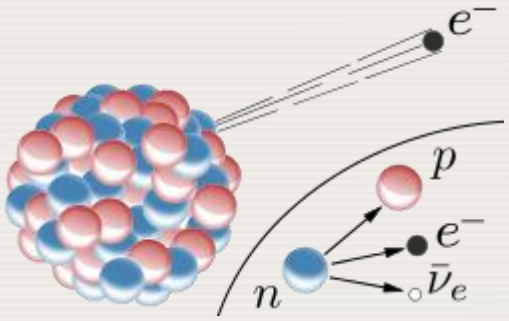
2.3. BIOLOGICAL PROPERTIES OF IONIZING RADIATION

2.3.1.2. Beta radiation

β radiation

Electrons emitted as a consequence of **β radionuclide decay**, occurring when there is a relative excess of **neutrons** (**β–**) or **protons** (**β+**) in the nucleus.

One of the excess neutrons is converted into a **proton**, with the subsequent excess of energy being released and shared between an emitted electron and an **anti-neutrino**.



Many radionuclides exhibit β decay; the emitted particle follows a **spectrum of possible energies** rather than being emitted with a fixed, discrete energy. In general, the average β energy is ~**1/3** of the **maximum energy**.

2.3. BIOLOGICAL PROPERTIES OF IONIZING RADIATION

2.3.1.2. Beta radiation

Most β **emitting** radionuclides also **emit** γ **photons** as a consequence of the initial β decay, leaving the daughter nucleus in an **excited, metastable state**.

Since β **particles** are electrons, once ejected from the host atom, they behave exactly as the electrons created following the passage of a γ ray, giving up their energy (usually of the order of several hundred keV) **to other atoms and molecules** through a series of **collisions**.

For radionuclides which emit both β particles and γ photons, it is usually the **particulate radiation** which delivers the **greatest fraction** of the radiation **dose** to the organ which has taken up the activity. E.g.:

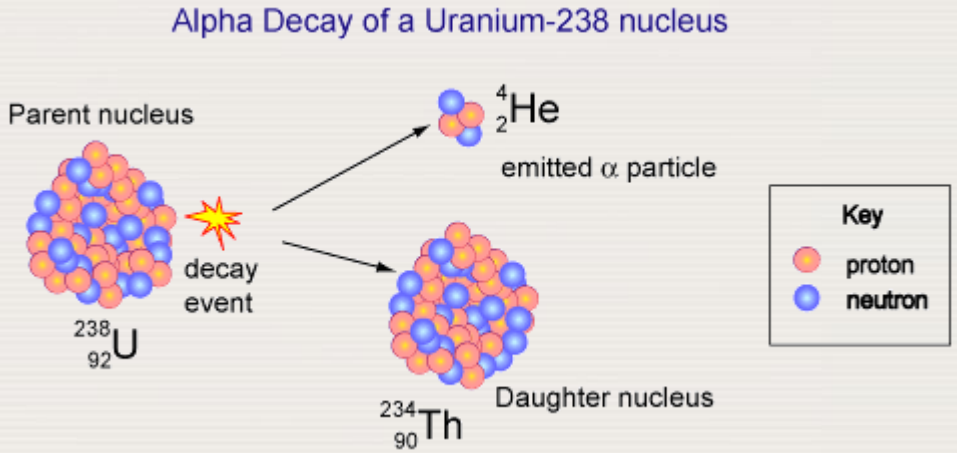
- about 90% of the dose delivered to the thyroid by ^{131}I is from the β component.
- emissions contribute more significantly to the overall whole body dose

2.3. BIOLOGICAL PROPERTIES OF IONIZING RADIATION

2.3.1.3. Alpha particles

α radiation

- emitted when **heavy, unstable** nuclides undergo decay.
- **helium nucleus** (2 n + 2 p) emitted in a nuclear decay
- $m_\alpha \cong 7000\ m_\beta$
- twice the electronic charge of β
- give up their **energy over a very short range (<100 μm)**.



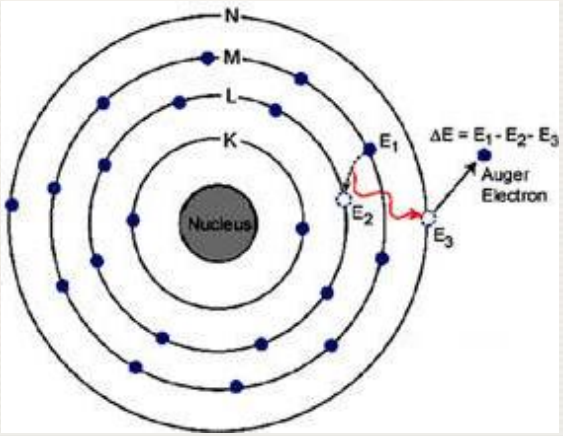
α particles usually possess energies in the **MeV range** and lose this energy in a short range making them **biologically very efficacious**, i.e. they possess a **high LET** (linear energy transfer; see Section 2.6.3) and are associated with **high RBE** (relative biological effectiveness; see Section 2.6.4).

2.3. BIOLOGICAL PROPERTIES OF IONIZING RADIATION

2.3.1.4. Auger electrons

Auger electrons

Radionuclides which decay by electron capture or internal conversion leave the atom in a highly excited state with a **vacancy** in one of the **inner shell electron orbitals**. This vacancy is rapidly filled by either a fluorescent transition (**characteristic X ray**) or a **non-radiative (Auger) transition**: the energy gained by the electron transition to the deeper orbital is used to **eject another electron** from the same atom.



Auger electrons are **very short range**, **low energy particles** often **emitted in cascades**, a consequence of the inner shell atomic vacancy that traverses up through the atom to the outermost orbital, ejecting additional electrons at each step. This cluster of very low energy electrons can produce **ionization densities comparable to those produced by an α particle track**.
→ Radionuclides which decay by electron capture and/or internal conversion can exhibit **high-LET-like behavior close (within 2 nm)** to the site of the decay.

2.4. MOLECULAR EFFECTS OF RADIATION AND THEIR MODIFIERS

Radiation induced damage to biological targets may result from:

Direct action

predominant with high LET radiation, e.g. α, neutrons

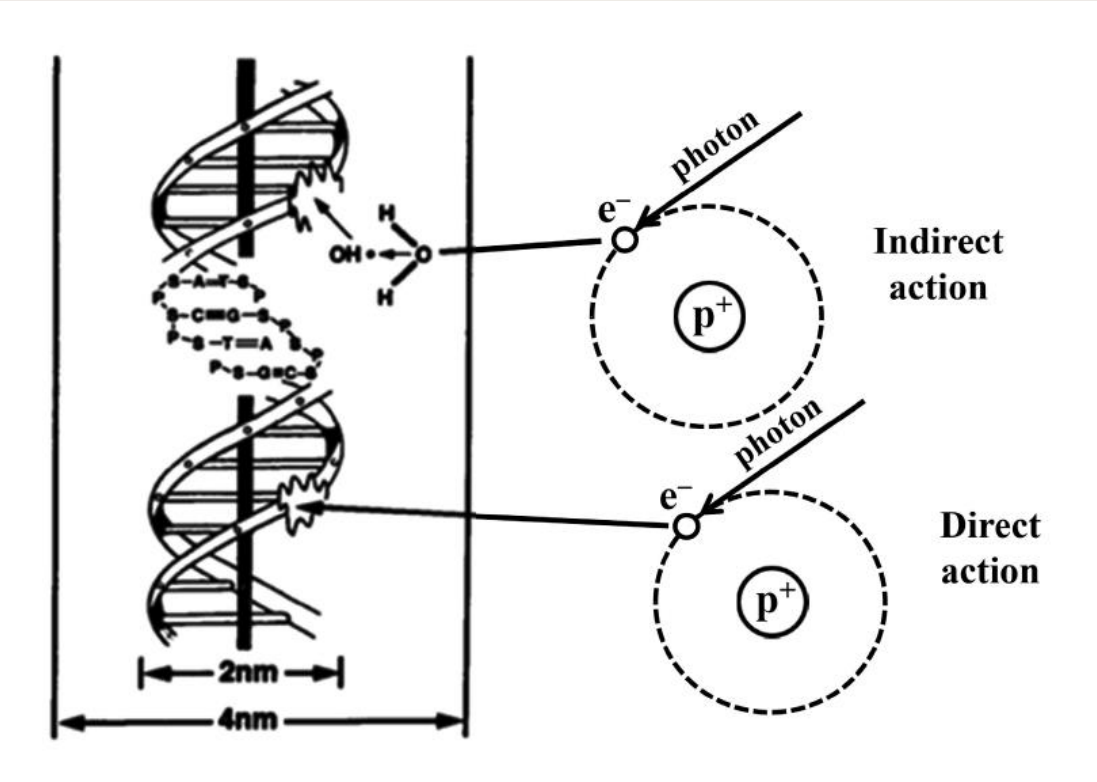
Ionization or excitation (via Coulomb interactions) of the atoms in the **biological target** → chain of events eventually leading to the observable (macroscopic) damage. In normally oxygenated mammalian cells, direct effects account for **~1/3 of the damage for low LET** radiations such as electrons and photons.

Indirect action

predominant with low LET radiation, e.g. X, γ rays

Radiation **effects on atoms or molecules** which are **not parts of the biological target**. Cells exist in a rich aqueous environment → the majority of indirect actions involve the **ionization or excitation of water molecules**. The **free radicals** created may then migrate and damage the adjacent biological targets. Indirect action is the **main cause of radiation damage** and, in normally normoxic cells, accounts for **~2/3** of the damage.

2.4. MOLECULAR EFFECTS OF RADIATION AND THEIR MODIFIERS



Difference between direct and indirect damage to cellular DNA

2.4. MOLECULAR EFFECTS OF RADIATION AND THEIR MODIFIERS

2.4.1. Role of oxygen

Radiation effects may be influenced especially by the presence/absence of oxygen.

The **free radicals** (**R**) produced as a result of direct or indirect effects are **very reactive** and seek to interact with other molecules which can share/donate electrons.

Molecular oxygen (**O_2**) has 2 unpaired electrons and readily reacts with free radicals, causing an increased likelihood that deoxyribonucleic acid (**DNA**) will be **damaged by indirect process**.

Important reactions via which oxygen can increase biological damage are:

$$R^{\bullet} + O_2 \rightarrow RO_2^{\bullet} \ (\text{highly toxic})$$

$$H^{\bullet} + O_2 \rightarrow HO_2^{\bullet}$$

$$HO_2^{\bullet} + HO_2^{\bullet} = H_2O_2 \ (\text{highly toxic}) + O_2$$

oxygen enhancement ratio (OER) to achieve equivalent biological effect

$$\text{OER} = \frac{D_{\text{hypoxia}}}{D_{\text{in air}}}$$

~ 3 for **low LET** radiation (as γ rays)

~ 1 for **high LET** radiation (as α particles)

2.4.2. Bystander effects

Bystander effects

- Occur when a **cell** which has **not been traversed by a charged particle** is **damaged** as a result of radiation interactions occurring in neighbouring cells
- Its discovery poses a challenge to the traditional view that all radiation damage stems from direct interactions of charged particles with critical cellular targets
- It still remains **controversial** in radiobiology
- A possible explanation is that **irradiated cells may send out a stress signal** to nearby cells → a **response**, e.g. the initiation of **apoptosis**, in those cells
- It is probably most significant in **radiation protection** involving **low doses** since it amplifies the overall radiation effect in situations where not all of the cells in a tissue are subjected to particle transversal, i.e. the overall radiation risk to that tissue is higher than would be expected

DNA damage

DNA damage is the primary cause of cell death caused by radiation. Radiation exposure produces a wide range of lesions in the DNA:

- **single strand breaks (SSBs)**
- **double strand breaks (DSBs)**
- **base damage**
- **protein–DNA cross-links**
- **protein–protein cross-links**

The number of DNA lesions generated by irradiation is large, but there are a number of mechanisms for DNA repair → the **percentage of lesions causing cell death is very small**

In the DNA of a cell, a dose of **1–2 Gy** leads to
- **base damages >1000**
- **SSBs ~1000**
- **DSBs ~40**

2.5. DNA DAMAGE AND REPAIR

2.5.1. DNA damage

DSBs play a critical role in **cell killing, carcinogenesis, hereditary effects**

Experimental evidence:

- the initially produced **DSBs** correlate with **radiosensitivity** and **survival** at lower dose
- unrepaired or **mis-repaired DSBs** also correlate with **survival** after higher doses
- there is causal link between the generation of **DSBs** and the **induction of chromosomal translocations** with carcinogenic potential

2.5. DNA DAMAGE AND REPAIR

2.5.2. DNA repair

DNA repair mechanisms

Important for the recovery of cells from radiation and other damaging agents.

There are multiple enzymatic mechanisms for detecting and repairing radiation induced DNA damage.

DNA repair mechanisms:	base excision repair, mismatch repair, nucleotide excision repair	respond to damages as:	base oxidation, alkylation, strand intercalation

Excision repair

cleavage of the damaged DNA strand by enzymes that cleave the polynucleotide chain on either side of the damage, and enzymes which cleave the end of a polynucleotide chain allowing removal of a short segment containing the damaged region. DNA polymerase can then fill in the resulting gap using the opposite undamaged strand as a template.

2.5. DNA DAMAGE AND REPAIR

2.5.2. DNA repair

For DSB, there are two primary repair pathways:

Non-homologous end joining (NHEJ)

Repair operates on blunt ended DNA fragments. This process involves the **repair proteins** recognizing lesion termini, cleaning up the broken ends of the DNA molecule, and the final ligation of the broken ends.
NHEJ operates throughout the cell cycle but **dominates in G1/S-phases**.
The process is **error-prone** because it does not rely on sequence homology.

Homologous recombination

DSB repair utilizes sequence homology with an undamaged copy of the broken region and, hence, **can only operate in late S- or G2-phases** of the cell cycle. Undamaged DNA from both strands is used as templates to repair the damage. In contrast to NHEJ, homologous recombination is **error-free**.

unrepaired or misrepaired damage to DNA → mutations and/or chromosome damage in the cell.

cancer or hereditary effects

cell death

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2.6. CELLULAR EFFECTS OF RADIATION

2.6.1. Concept of cell death

Radiation doses of the order of several Gy may lead to cell loss.
Cells are regarded as having been '**killed**' **by radiation** if they have **lost reproductive integrity**, which can occur by apoptosis, necrosis, mitotic catastrophe or by induced senescence and may take a significant time.

Apoptosis or programmed cell death can occur naturally or result from insult to the cell environment. It occurs in particular cell types after low doses of irradiation, e.g. lymphocytes, serous salivary gland cells, and certain cells in the stem cell zone in testis and intestinal crypts.

Necrosis is a form of cell death associated with loss of cellular membrane activity. Cellular necrosis generally occurs after high radiation doses.

Mitotic catastrophe cells attempt to divide without proper repair of DNA damage leading to a reproductive cell death which can occur in the first few cell divisions after irradiation, and with increasing frequency after increasing doses.

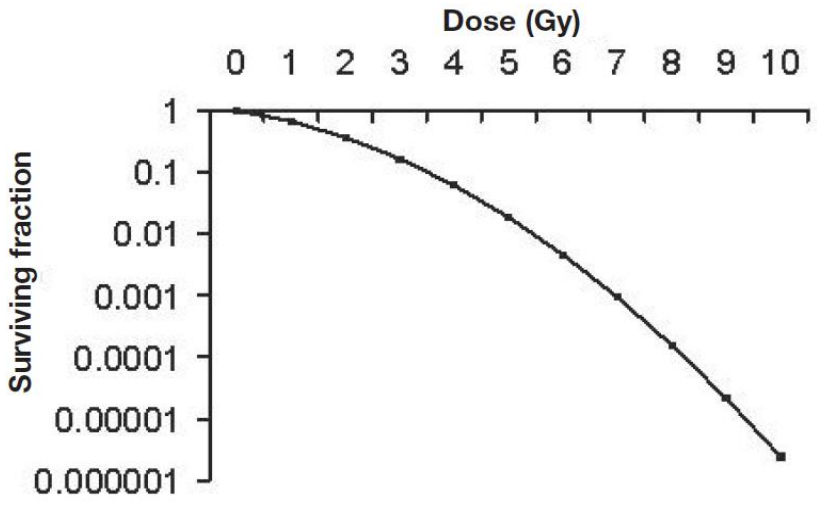
Senescence Senescent cells are metabolically active but have lost the ability to divide.

2.6. CELLULAR EFFECTS OF RADIATION

2.6.2. Cell survival curves

For quantitative understanding of biological responses to radiation:

behaviour of the cell survival (dose response) characteristics
structure and meaning of such curves
role played by the various factors which influence radiation response



Radiation cell survival curve:
Fraction of plated cells retaining colony forming ability vs. radiation absorbed dose.

Typical shape of a cell survival curve for mammalian tissue: fractional survival of cells resulting from delivery of single acute doses of the specified radiation (in this case γ). Acute dose to mean a dose delivered at high dose rate, i.e. near instantaneously.

Main characteristics: **a finite initial slope** (at zero dose) and a gradually **increasing slope** as dose increases

2.6. CELLULAR EFFECTS OF RADIATION

2.6.3. Dose deposition characteristics: linear energy transfer

The energy transfer to the absorbing medium is via secondary electrons created by the passage of the primary ionizing particle or ray.
LET is a measure of the **linear rate** at which **radiation is absorbed** in the absorbing medium by the secondary particles and is defined by ICRU:

$$LET = \frac{dE}{d\ell}$$

[LET] = keV/ μm

where dE is the average energy locally imparted to the medium by a charged particle of specified energy in traversing a distance dℓ.

TABLE 2.2. THE LINEAR ENERGY TRANSFER OF DIFFERENT RADIATIONS

Radiation type	Linear energy transfer (keV/μm)
^{60}Co γ rays	0.2
250 kVp X rays	2.0
10 MeV protons	4.7
2.5 MeV α particles	166
1 MeV electrons	0.25
10 keV electrons	2.3
1 keV electrons	12.3

2.6. CELLULAR EFFECTS OF RADIATION

2.6.3. Dose deposition characteristics: linear energy transfer

For radiobiological studies, the **concept of LET is problematic** since it relates to an average linear rate of energy deposition but, at the **microscopic level** (i.e. at dimensions comparable with the critical cellular targets), the **energy deposited per unit length** along different parts of a single track may **vary dramatically**.

As charged particles lose energy in their passage through a medium via the result of collision and ionizing processes, the LET rises steeply to its highest value towards the very end of their range. The change in LET value along the track length is one reason why **average LET** values **correlate poorly** with observed (i.e. macroscopic) **biological effects**.

The directly measured **RBE** is of much greater usefulness as an indicator of the differing **biological efficacies** of various radiation types.

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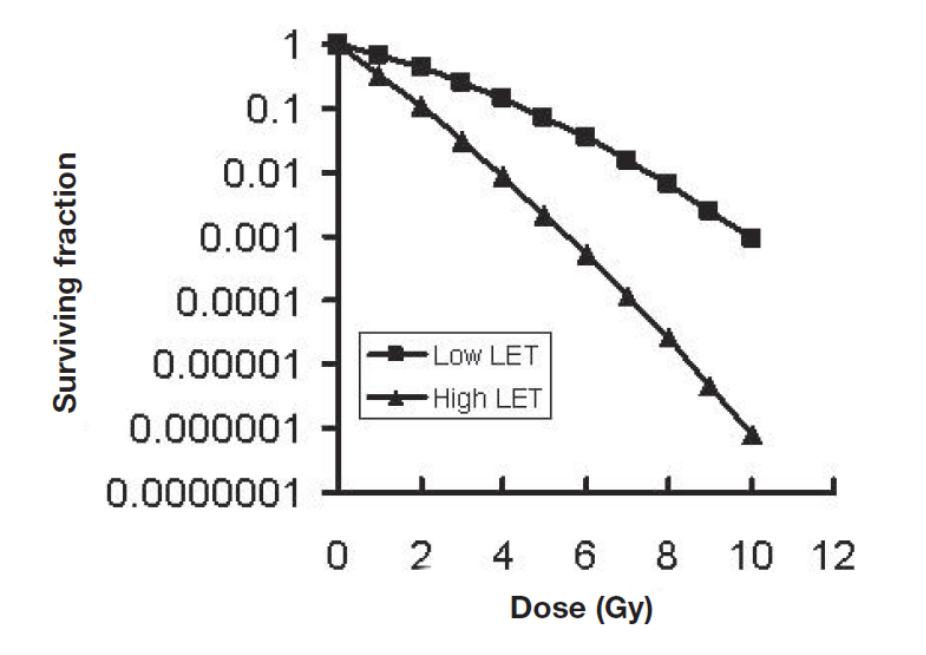
2.6. CELLULAR EFFECTS OF RADIATION

2.6.4. Determination of relative biological effectiveness

For a given biological end point, the RBE of the high LET radiation is defined as:

$$RBE = \frac{d_{\text{low LET}}}{d_{\text{high LET}}} = \frac{d_L}{d_H}$$

$d_{\text{low LET}}$ or d_L, $d_{\text{high LET}}$ or d_H: isoeffective doses for the reference (low LET, ^{60}Co γ rays or high energy (250 kVp) X rays) and high LET radiation.



In particular, the **RBE** of a radiation is defined as the **ratio of the dose required to produce the same reduction in cell survival** as a reference low LET radiation.

2.6. CELLULAR EFFECTS OF RADIATION

2.6.4. Determination of relative biological effectiveness

If the cell survival curves are described in terms of the linear–quadratic (LQ) model, the surviving fraction *S* as a function of acute doses at low- (L) high- (H) LET is:

$$S_{\mathrm{L}} = \exp\left(-\alpha_{\mathrm{L}} d_{\mathrm{L}} - \beta_{\mathrm{L}} d_{\mathrm{L}}^2\right)$$

$$S_{\mathrm{H}} = \exp\left(-\alpha_{\mathrm{H}} d_{\mathrm{H}} - \beta_{\mathrm{H}} d_{\mathrm{H}}^2\right)$$

RBEs determined at any particular end-point (cell surviving fraction) vary with changing dose for a given radiation fraction size for a low LET radiation.

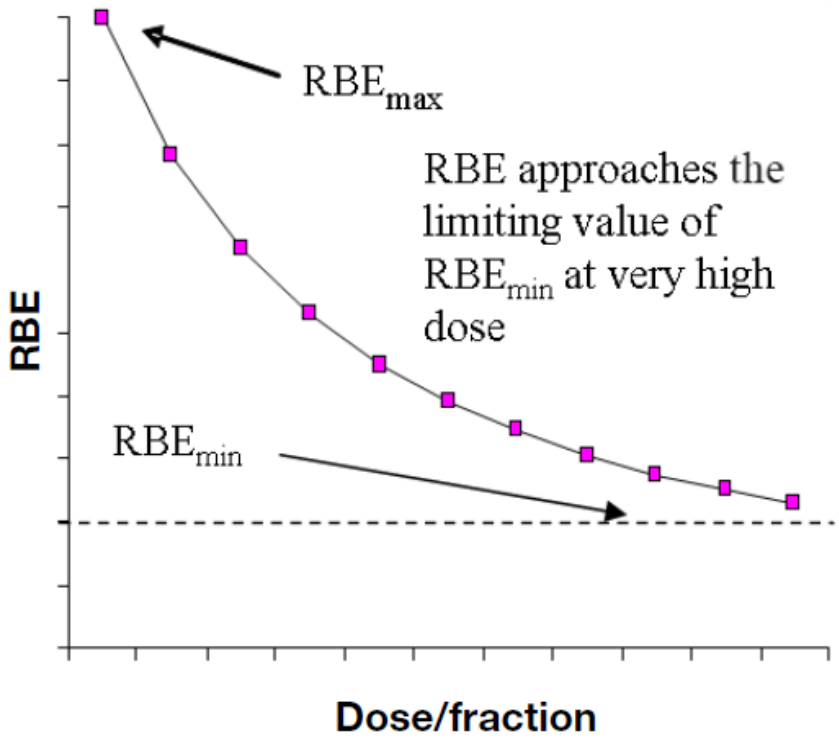
The maximum RBE (RBE_{max}) occurs at zero dose and, in terms of microdosimetric theory, corresponds to

$$\mathrm{RBE}_{\max} = \frac{\alpha_{\mathrm{H}}}{\alpha_{\mathrm{L}}}$$

(α_H and α_L are the high and low LET linear radio-sensitivity constants)

2.6. CELLULAR EFFECTS OF RADIATION

2.6.4. Determination of relative biological effectiveness



Relative biological effectiveness (RBE) as a function of the radiation dose per fraction, derived using:

$RBE_{max} = 5$,
$RBE_{min} = 1$
$(\alpha/\beta)_L = 3$ Gy,

The general trend of a steadily falling RBE with increasing dose per fraction is independent of the chosen values.

2.6. CELLULAR EFFECTS OF RADIATION

2.6.4. Determination of relative biological effectiveness

If the quadratic radiosensitivity coefficients (β_H and β_L) are unchanged with changing LET (i.e. $\beta_H = \beta_L$), at high doses, the **RBE tends to unity**. However, this constancy of β has been challenged and, if β does change with LET, then RBE will tend asymptotically to an alternative minimum value (**RBE_{min}**) given by:

$$RBE_{min} = \sqrt{\frac{\beta_H}{\beta_L}}$$

and the 'working' RBE at any given dose per fraction is given as

$$RBE = \frac{(\alpha/\beta)_L RBE_{max} + \sqrt{(\alpha/\beta)_L^2 RBE_{max}^2 + 4 d_L RBE_{min}^2 \left[(\alpha/\beta)_L + d_L\right]}}{2\left[(\alpha/\beta)_L + d_L\right]}$$

in terms of the low-LET dose per fraction d_L

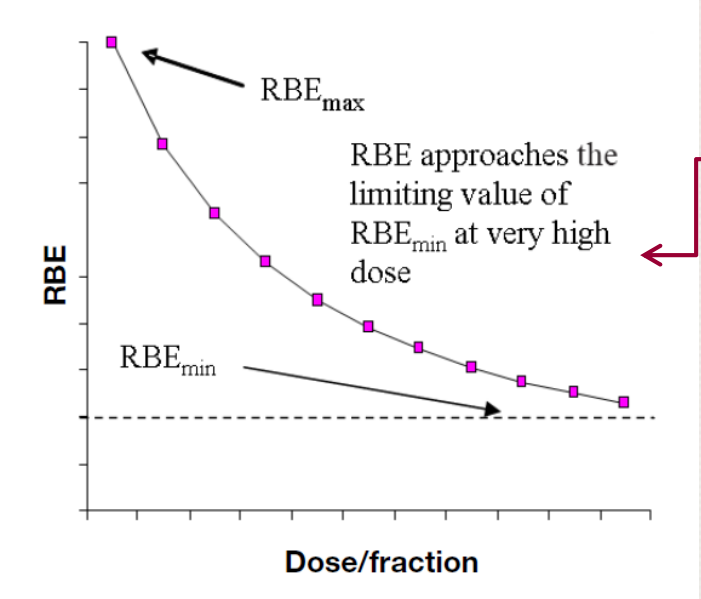
$$RBE = \frac{-(\alpha/\beta)_L + \sqrt{(\alpha/\beta)_L^2 + 4 d_H \left[(\alpha/\beta)_L RBE_{max} + RBE_{min}^2 d_H\right]}}{2 d_H}$$

in terms of the high-LET dose per fraction d_H

2.6. CELLULAR EFFECTS OF RADIATION

2.6.4. Determination of relative biological effectiveness

The **assumption of a fixed value of RBE**, if applied to all fraction sizes, could lead to **gross clinical errors**.
The previous equations point out that determination of **RBEs in a clinical setting is potentially complex** and will depend on accurate knowledge of RBE_{max} and RBE_{min} (if it is not unity).



The rate of change of RBE with dose/fraction is influenced by the existence of a non-unity RBE_{min} parameter.

Even for a fixed value of RBE_{max}, the potential uncertainty in RBE at the fraction sizes might be very large if RBE_{min} is erroneously assumed to be unity.

These uncertainties would be compounded if there were an additional linkage between RBE_{max} and the tissue α/β value.

2.6. CELLULAR EFFECTS OF RADIATION

2.6.4. Determination of relative biological effectiveness

The **RBE value** at any dose fraction size will also be governed by **the low-LET α/β ratio** (a tissue dependent parameter which provides a measure of how tissues respond to changes in dose fractionation) and the **dose fraction size** (a purely physical parameter) at the point under consideration.

The **RBE_{max}** value may itself be tissue dependent, likely being **higher for the dose-limiting normal tissues than for tumours** (as seen in clinical experience with neutron therapy, a variety of ion species as well as by theoretical microdosimetric studies).

This potentially deleterious effect may be offset by the fact that, in carbon-, helium- and argon-ion beams, **LET** (and, hence, RBE) will **vary along the track** in such a way that it is **low at the entry point** (adjacent to normal tissues) and **highest at the Bragg peak** located in the tumour.
Although this might be beneficial, it means that the local RBE is more spatially variable than is indicated by the low-LET dose per fraction d_L equation.

2.6. CELLULAR EFFECTS OF RADIATION

2.6.4. Determination of relative biological effectiveness

Difficulties in setting reference doses for clinical inter-comparisons

Wambersie: distinction between the 'reference' RBE and the 'clinical' RBE.

determined **at 2 Gy fractions** on a biological system representative end-point, (e.g. the overall late tolerance of normal tissues)

as more clinical experience becomes available, a more practical '**clinical' RBE evolves**, this being the reference RBE empirically weighted by collective clinical experience and by volume effects related to the beam characteristics, geometry or technical conditions

2.6. CELLULAR EFFECTS OF RADIATION

2.6.5. The dose rate effect and the concept of repeat treatments

When mammalian cells are irradiated, it is helpful to visualize their subsequent **death** as resulting from either of **two possible processes**:

1 The critical nuclear target (DNA) is subjected to a **large deposition of energy** which physically breaks both strands of the double helix structure and disrupts the code sufficiently to disallow any opportunity of repair. This process can be thought of as a **single-hit process** and the total amount of DNA damage is directly proportional ($\propto$) to the dose delivered.

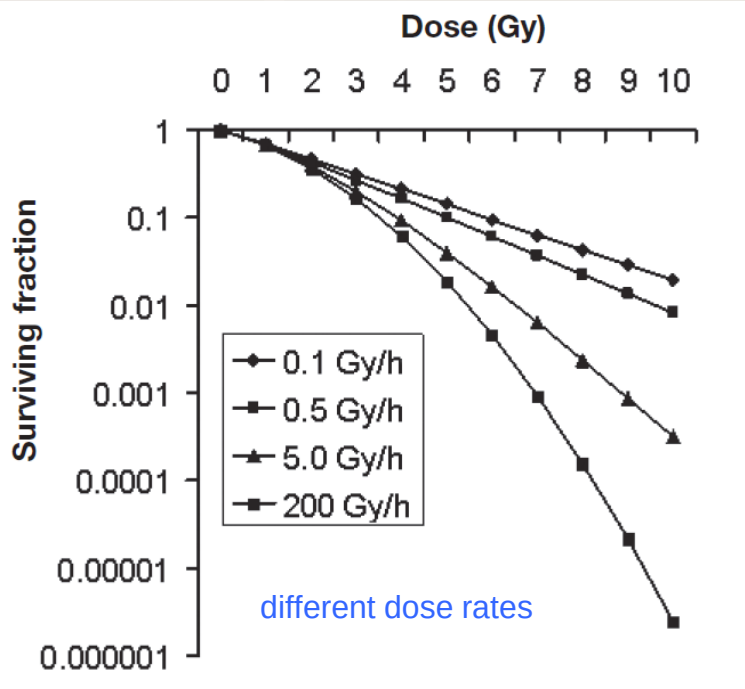
2 An ionizing event occurs and releases only sufficient energy to disrupt the coding carried by one strand of the DNA. If the irradiation continues, two outcomes are possible: either the broken strand will restore itself to its original state (no lethality) or, prior to full repair taking place, a second, independent radiation event may occur in the same location and damage the opposite strand of the DNA, a complementary action between the two damaged strands then leading to cell lethality in what is called a **two-hit process**.

2.6.5. The dose rate effect and the concept of repeat treatments

- This route depends on two independent events, each having a probability $\propto$ to dose $\rightarrow$ the number of damaged DNA targets is $\propto$ **to dose×dose: dose^2**
- Once created, the radiation damage due to these two routes is indistinguishable (i.e. **both processes are lethal**). The observed radiation response characterized in the cell survival curve consists of two components: one **linear ($\propto$ dose)** and the other **quadratic ($\propto$ dose^2)**.
- This phenomenological description qualitatively explains the shape of a radiation **survival curve**, with **a finite initial slope at low dose** followed by an increasingly downward **curvature as dose increases**.
- The amount of **damage created in the second process** is dependent on the ability of the second break to be induced before the first break has repaired itself, and, thus, **is dependent on the dose rate**.

2.6.5. The dose rate effect and the concept of repeat treatments

Range of response curves with doses delivered at different dose rates



Reducing the dose rate causes the shape of the response curve to become **less 'curvy'** than in the acute case, but the initial slope remains unchanged.

When the doses are all delivered at a very low dose rate, as for most radionuclide therapies (e.g. 0.1–0.5 Gy/h), **the response is essentially a straight line**, when the curves are plotted on a log–linear scale. This means that the low dose response is purely exponential.

2.6.6. The basic linear–quadratic model

The **basic equation of the LQ model** describes the shape of the cell survival curves and has a biophysical origin. Cell survival after delivery of an acute dose *d* is given is:

$$S = \exp\left(-\alpha d - \beta d^2\right)$$

with α (Gy^{-1}) and β (Gy^{-2}) being the linear and quadratic sensitivity coefficients

If the treatment is repeated in *N* spaced fractions, the net survival is S_N:

$$S_N = S^N = \exp\left(-N\alpha d - N\beta d^2\right)$$

$$\frac{\ln S_N}{\alpha} = -Nd - \frac{Nd^2}{(\alpha/\beta)}$$

2.6.7. Modification to the linear–quadratic model for radionuclide therapies

Targeted radionuclide therapy normally involves irradiation of the tumour/normal tissues at **a dose rate** which is not constant but which **reduces as treatment proceeds**, as a consequence of the combination of radionuclide decay and biological clearance of the radiopharmaceutical.

A more extensive formulation of the LQ model is required.

2.6.8. Quantitative intercomparison of different treatment types

In the LQ modelling, the term called the 'biological effective dose' (BED) is used to assess and inter-compare different treatment types. BED is defined as:

$$\mathrm{BED} = -\frac{\ln S_N}{\alpha} = Nd\left[1 + \frac{d}{(\alpha/\beta)}\right]$$

The parameters **α and β are rarely known** in detail for individual tumours or tissues, but values of the ratio **α/β** (Gy) are becoming **increasingly known** from clinical and experimental data.

In general, **α/β is systematically higher for tumours (5–20 Gy) than for critical, late-responding normal tissues (2–5 Gy)**.

This difference makes the BED concept useful in practice.

2.6.8. Quantitative intercomparison of different treatment types

For non-acute treatments (dose delivery is protracted over a long time period on account of a lower dose rate), the BED is re-written as:

$$\mathrm{BED} = Nd\left[1+\frac{d\,g(t)}{(\alpha/\beta)}\right]$$

where g(t) is a function of the time t taken for delivery

$$g(t)=\frac{2}{\mu}\left[1-\frac{1-\exp(-\mu t)}{\mu t}\right]$$

μ is the time constant relating to the repair of sublethal damage with tissue repair half-time $T_{1/2}$ ➡ $\mu = 0.693/ T_{1/2}$

2.6.8. Quantitative intercomparison of different treatment types

For a treatment delivery at **constant dose rate *R***, the delivered dose *d* is related to treatment time *t* via $d = R \times t$, thus:

$$\mathrm{BED} = Rt\left[1+\frac{2R}{\mu(\alpha/\beta)}\left\{1-\frac{1-\exp(-\mu t)}{\mu t}\right\}\right]$$

When $t > 12$ h the equation simplifies to:

$$\mathrm{BED} = Rt\left[1+\frac{2R}{\mu(\alpha/\beta)}\right]$$

2.6. CELLULAR EFFECTS OF RADIATION

2.6.9. Cellular recovery processes

At **lower doses and dose rates** (multiple exposures), **cellular recovery** may play an important role in the fixation of the radiation damage.

There are three broad types of cellular radiation damage:

Lethal damage	in which the cellular DNA is irreversibly damaged to such an extent that the cell dies or loses its proliferative capacity
Sublethal damage	in which partially damaged DNA is left with sufficient capacity to restore itself over a period of a few hours, provided there is no further damage during the repair period
Potentially lethal damage	in which repair of what would normally be a lethal event is made possible by manipulation of the post-irradiation cellular environment.

2.6. CELLULAR EFFECTS OF RADIATION

2.6.10. Consequence of radionuclide heterogeneity

The **effectiveness** per unit dose of a radiopharmaceutical depends on the heterogeneity of the **radionuclide distribution**

Global non-uniformity of a source distribution, which results in pockets of cells (tumour or normal tissue) receiving less than the average dose, almost always leads to a **greater fraction of cell survivors**, than if all cells receive a uniform dose

The one possible exception would be if a radiopharmaceutical would selectively localize at sensitive target cells, within an organ, that are key for organ regeneration or function, e.g. crypt cells in the colon.

The **cellular response** also depends on **microdosimetry**, especially if the radiopharmaceutical selectively localizes on the cell surface or internalizes within a certain cohort of cells within a tumour/normal organ. These radiolabels may exhibit geometric enhancement factors that modulate response (see ICRU Report 67)

2.7. GROSS RADIATION EFFECTS ON TUMOURS AND TISSUES/ORGANS

2.7.1. Classification of radiation damage (early versus late)

Cells lethally affected by radiation may continue to function, **only dying** when attempting to undergo subsequent cell division (**mitosis**).

Clinically observed radiation effects in whole tissues or organs reflect the damage inflicted to large numbers of constituent cells and, thus, appear on a **timescale** which is governed largely by the underlying **proliferation rates** of those cells.

Such **observable effects** are classified depending on the speed at which they manifest themselves following irradiation as:

Late effects	appear months or years after irradiation and appear in structures which proliferate very slowly, e.g. kidney.
Early (or acute) effects	appear within days, weeks or months of irradiation and are associated with fast-proliferating epithelial tissues, e.g. bone marrow, mucosa, intestinal tract, etc.

2.7. GROSS RADIATION EFFECTS ON TUMOURS AND TISSUES/ORGANS

2.7.1. Classification of radiation damage (early versus late)

- In most types of radiotherapy, **late effects** are considered to be **most critical** and generally limit the total dose which may be delivered to the tumour.

- If the tolerance of the **late-responding tissues** is exceeded, the subsequent reactions may seriously affect mobility, quality of life, even be life threatening. Such problems arise long after the treatment and are impossible to correct.

- **Acute reactions** in external beam radiotherapy (EBRT) are usually transient and easier to control by adjustment of the treatment dose delivery pattern and/or simple medication. In radionuclide therapies, acute radiation toxicities are generally possible to circumvent once they begin to occur (e.g. by accelerating clearance of the radiopharmaceutical).

- **Chronic toxicities** (e.g. to the kidney) usually occur at times which are long relative to the lifetime of the radionuclide. Safe activities of therapeutic radionuclides should be administered, taking into account dose limiting constraints.

2.7. GROSS RADIATION EFFECTS ON TUMOURS AND TISSUES/ORGANS

2.7.2. Determinants of tumour response

The potential advantage of **radionuclide therapy** over other forms of radiation therapy is its **ability to deliver dose to the local disease and to occult tumour deposits**. In nuclear medicine, the primary determinants of treatment effectiveness are:

- **tumour specificity** of the radionuclide carrier.
- **homogeneity of uptake** of the carrier within the targeted tumour(s).
- **intrinsic RBE** of the radiation used for the therapy, determined primarily by the nature of the radionuclide emissions (e.g. α, β, γ, Auger e^-…)
- **range of the particles**, as determined by their energies.
- **total dose** delivered.
- **responsiveness** of the targeted tumour cells to radiation.

radiobiological properties such as the cellular radiosensitivity, variations of sensitivity within the cell cycle, oxygen status of the cells (fully oxic, partially oxic or hypoxic), ability of the cells to recover from sublethal damage, degree to which tumour growth (re-population) may occur during therapy.

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2.7.2. Determinants of tumour response

These **factors are complementary and interactive**, and should not be considered in isolation from each other.

Thus, for example, significant non-uniformity of tumour uptake may result in activity/dose '**cold spots**', but the detrimental potential of these might be offset by the **selection of a radionuclide** which emits particles of sufficient range to produce a **cross-fire effect** within the cold spots from those adjacent cells which are properly targeted. The significance of cold spot and cross-fire effects is further dependent on the size of the tumour deposit under consideration.

2.7. GROSS RADIATION EFFECTS ON TUMOURS AND TISSUES/ORGANS

2.7.3. The concept of therapeutic index in radiation therapy and radionuclide therapy

The **therapeutic index** (or 'therapeutic ratio')* of a particular radiation treatment is a measure of the **damage to the tumour** vs. the **damage to critical normal** structures.

high therapeutic index → good tumour control, low normal tissue morbidity
low therapeutic index → low tumour control, high morbidity.

EBRT

normal tissues at risk are those immediately adjacent to the tumour. Doses to the normal tissues (and risk of toxicity) may be reduced by a good combination of physical and radiobiological factors.

Targeted radionuclide therapy

tumour may be single/discrete or may consist of distributed masses/ metastases within the body. Normal tissues at risk may be widely distributed and may be a reflection of the particular uptake pattern of the targeting compound used for the therapy.

(*) The therapeutic index can be considered as a qualitative concept, quantitative definitions are not necessary. Any new treatment improving tumour control and/or reducing morbidity is said to be associated with an improved therapeutic index.

2.7. GROSS RADIATION EFFECTS ON TUMOURS AND TISSUES/ORGANS

2.7.4. Long term concerns: stochastic and deterministic effects

The radiation detriment from radiation exposure may be classified as stochastic or deterministic in nature.

Stochastic effects (e.g. hereditary damage, cancer induction) are those for which the likelihood of them occurring is dose related, but the severity of the resultant condition is not related to the dose received.

Deterministic effects (e.g. cataract induction, general radiation syndromes, bone marrow ablation, etc.) manifest with a severity which is dose related.

From **diagnostic** uses of radionuclides predominantly **stochastic effects** need to be considered as potential side effects, although deterministic damage may result if the embryo or fetus is irradiated.

For **radionuclide therapy** applications, the concerns relate to both **stochastic** and **deterministic** effects.

2.8. SPECIAL RADIOBIOLOGICAL CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

2.8.1. Radionuclide targeting

Tumour targeted radiotherapy → very promising approach for the treatment of wide-spread metastasis and disseminated tumour cells to deliver therapeutic irradiation doses to the tumour while sparing normal tissues by targeting a structure that is abundant in tumour cells, but rare in normal tissues

antibodies labelled with a therapeutic radionuclide acting against a specific tumour target. (e.g. ^{131}I-tositumomab (Bexxar®) and ^{90}Y-ibritumomab tiuxetan (Zevalin® in the treatment of non-Hodgkin's lymphoma)

epidermal growth factor (EGF) labelled with ^{125}I which binds EGF receptors. EGF receptors are overexpressed on tumour cells in many malignancies such as highly malignant gliomas

At present, several other radiolabelled antibodies/molecules are being used in experimental models and in clinical trials to study their feasibility in other types of cancer.

2.8. SPECIAL RADIOBIOLOGICAL CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

2.8.2. Whole body irradiation

Conventional EBRT

involves controlled irradiation of a carefully delineated target volume. Normal structures adjacent to the tumour will likely receive a dose, in some cases moderately high, but the **volumes involved are relatively small**. The rest of the body receives only a minimal dose, mostly arising from radiation scattered within the patient from the target volume and from a small amount of leakage radiation emanating from the treatment machine outside the body.

Targeted radionuclide therapies

commonly administered intravenously, give rise to substantial **whole body** doses and doses to the radiation sensitive **bone marrow**. Once the untargeted activity is removed from the blood, it may give rise to substantial doses in normal structures, especially the kidneys. Furthermore, the activity taken up by the kidneys and targeted tumour deposits may (if γ ray emissions are involved) continue to irradiate the rest of the body.

2.8. SPECIAL RADIOBIOLOGICAL CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

2.8.3. Critical normal tissues for radiation and radionuclide therapies

Radiation doses used in radionuclide therapies are much higher than for diagnosis; systemic therapies → retention of the pharmaceuticals within the blood; increased accumulation of radionuclides in non-tumour cells

possible unwanted toxicities

main critical organs: bone marrow, kidney, liver, intestinal tract, lungs

Bone marrow

Very sensitive towards ionizing radiation. Exposure with high doses → rapid depression of **white blood cells** followed by **platelet** depression a few weeks later, and in a later stage (~1 month after exposure) also by depression of the **red blood cells**. Patients could suffer from infections, bleeding and anaemia.

2.8. SPECIAL RADIOBIOLOGICAL CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

2.8.3. Critical normal tissues for radiation and radionuclide therapies

GI tract	characterized by **de-population of the intestinal mucosa** (usually 3-10 days after) leading to prolonged diarrhoea, dehydration, loss of weight, etc.
Kidneys	radiation induced damage several months after exposure. A **reduction of proximal tubule cells** is observed. These pathological changes finally lead to **nephropathy**
Liver	Hepatocytes are the radiosensitive targets. The life-span of the cells is about a year → **deterioration of liver function** apparent 3 -9 months after exposure
Lungs	radiation induced damage several months after exposure. Pulmonary damage is observed as **acute pneumonitis** and **later fibrosis**

2.8. SPECIAL RADIOBIOLOGICAL CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

2.8.3. Critical normal tissues for radiation and radionuclide therapies

Radionuclide therapy: diversity of radiopharmaceuticals, with different pharmacokinetics and biodistribution → **different responses / tolerances.**

Determinants of normal tissue response:

radionuclide employed

E.g. isotopes of **iodine** localize in the thyroid, salivary glands, stomach, bladder. **Strontium, yttrium, samarium, fluorine, radium** concentrate in bone. Several **radiometals**, such as bismuth, can accumulate in the kidney

radiolabelled molecules

If radionuclides are tightly conjugated to a targeting molecule, then the biodistribution and clearance is determined by that molecule.
For **high** molecular weight targeting agents, such as an antibody injected intravenously, the slow plasma clearance results in **marrow toxicity.**
For **smaller** radiolabelled peptides, **renal toxicity** becomes of concern.

2.8.3. Critical normal tissues for radiation and radionuclide therapies

When studying a new radiopharmaceutical or molecular imaging agent it is

always important to **study** in **detail the biodistribution at trace doses**,

to ensure the absence of radionuclide sequestration within potentially sensitive tissue, such as the retina of the eye or the germ cells of the testes.

Meredith et al. (2008) offers a **review of normal tissue toxicities** resulting from radionuclide therapies.

2.8. SPECIAL RADIOBIOLOGICAL CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

2.8.4. Imaging the radiobiology of tumours

The development of molecular imaging using PET has given rise to new radiotracers which have the potential to assess radiobiological features of relevance for therapy planning.

Replicating cells, tumour response

A tracer that is becoming more widely available for PET imaging is fluorothymidine **(FLT)**. It is selectively entrapped within cells that are progressing through **S-phase (DNA replication)** of the cell cycle → signal ∝ to cell **proliferation**, minimizing the signal from cells in G0 or in cell cycle arrest.

Ability to identify **only replicating cells** separate from all tumour cells within the tumour volume identified by CT → more accurate measures of the initial viable tumour burden and **tumour response**.

2.8. SPECIAL RADIOBIOLOGICAL CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

2.8.4. Imaging the radiobiology of tumours

Selectively targeting cell death

Complementary to measuring tumour response is the measurement of therapeutic efficacy through **radiotracers that selectively target cell death**. Radiotracers such as **radiolabelled annexin V** are under development to selectively bind to receptors expressed on cells undergoing programmed cell death.

Hypoxia, resistance

Cells within a tumour microenvironmental region of low partial oxygen pressure (hypoxia), exhibit a great radio-resistance to radiation and chemotherapy relative to those under normoxic conditions. PET radiotracers under evaluation for imaging tumour hypoxia are, e.g. fluoromisonidazole (**^{18}F-FMISO**), fluoroazomycin arabinoside (**^{18}F-FAZA**) and copper-diacetyl-bis(N4-methylthiosemicarbazone) (**^{64}Cu-ATSM**).

The ability to measure the radiobiological attributes of a tumour prior to therapy may provide invaluable information about relative **resistance/ aggressiveness** of tumours → improved management of patients.

2.8. SPECIAL RADIOBIOLOGICAL CONSIDERATIONS IN TARGETED RADIONUCLIDE THERAPY

2.8.5. Choice of radionuclide to maximize therapeutic index

The choice of the **optimum radionuclide** to maximize the therapeutic index in clinical therapeutic applications depends on several factors:

1 **range of the emitted particles** from the radionuclide

It should **depend on the type of tumour** treated. For **leukaemia** or micro-metastatic deposits (individual/small clusters of tumour cells) → distinct advantage of radionuclides which emit very short range particles; α particle ranges <100 μm in tissue → advantage of **α particle** emitters, if the targeting molecule were able to reach all tumour cells.

However: α-emitting radionuclides are not widely available and extremely expensive, and the **short α range** can be a **disadvantage for bulk tumours**.

2.8.5. Choice of radionuclide to maximize therapeutic index

For these reasons almost all therapeutic radionuclides consist of **medium (^{131}I)** or **long range. (^{90}Y, ^{186}Re) β emitters**: advantageous for treating **solid tumours** for which target receptor (antigen) expression may be heterogeneous, or with non-uniform delivery, due to **greater cross-fire range** of their β emissions (up to a 1 cm range in unit density tissue)

2 **radiochemistry**

It is necessary to consider ease and **stability** of the radiolabelled end product radiochemistry.

3 **choice of radionuclide half-life ($T_{1/2}$)**

If the $T_{1/2}$ is too short, then the radiolabelled agent may have insufficient time to reach the tumor target → **minimal therapeutic index**.

Increasing $T_{1/2}$ increases the therapeutic index, but renders the patient radioactive for a longer period of time → prolonged confinement, greater expense and radiation risks to staff and family. Pure β emitting radionuclides (e.g. **^{90}Y**, **^{32}P**) have advantages in that they minimize the exposure to personnel assisting the patient.

The $T_{1/2}$ of the radionuclide should ideally match the biological uptake and retention kinetics of the tumour-targeting carrier. For **large protein** (e.g. antibodies), radionuclides with **$T_{1/2}$ of several days** are required to optimize the therapeutic index. For **smaller molecular** targeting agents (e.g. peptides), radionuclides with **short $T_{1/2}$** may be better suited to minimize radioactive waste.

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