Chapter 6: Radiobiology

NPRE441:Principles of Radiation Protection
Spring 2023, MW 12-1.50 pm
2018 Campus Instructional Facility

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Objective:

To familiarize the students with the basic principles of radiobiology.

Slides retrieved and adapted from:

- **Slide deck NPRE441 Spring 2021 by Prof.L.J. Meng (UIUC, USA)**
- **slide deck prepared in 2006 by Dr.E.B. Podgorsak (McGill University, Montreal)**
- **slide deck prepared in 2015 by Dr.M. Cremonesi (IEO European Institute of Oncology, Milano, Italy)**
- **slide deck prepared by Dr.E.Okuno (Institute of Physics of S. Paulo University, S. Paulo, Brazil)**

IAEA
International Atomic Energy Agency

環境省 Ministry of the Environment
Government of Japan

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Leaderboard

After 13 questions

1	12/13	1
2nd	10/13	1
=3rd	9/13	5
=8th	8/13	8
=16th	7/13	3
19th	6/13	1

FULL LIST

Average score	7.8
Participants	21

Most difficult question

> What of the following statements are TRUE:

Correct responses	2

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CHAPTER 6. PART 4

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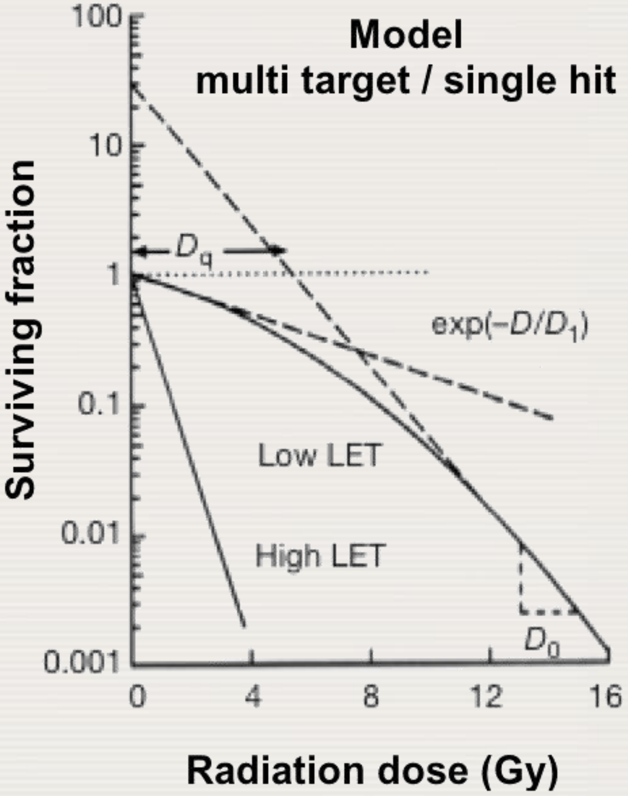
6.4.1 CELL SURVIVAL CURVES

- Cell survival curve (surviving fraction against absorbed dose) describes the relationship between:
  - **Surviving fraction of cells**, i.e., the fraction of irradiated cells that maintain their reproductive integrity (clonogenic cells)
  - **Absorbed dose.**

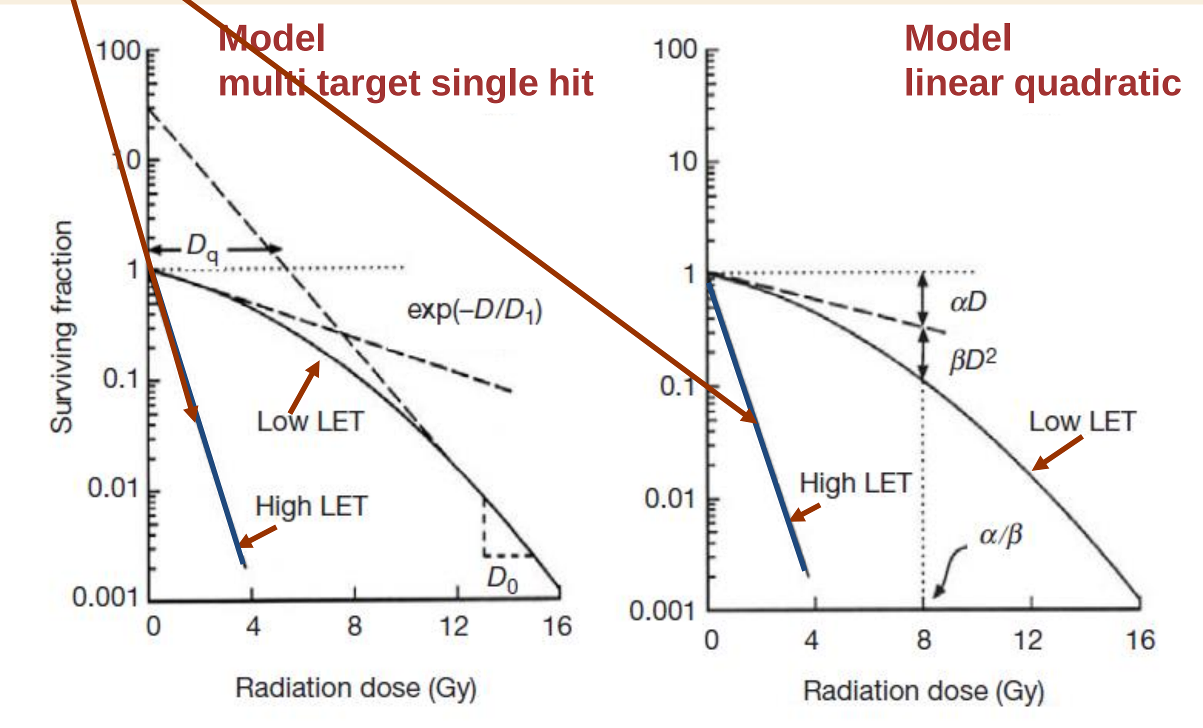
- Cell survival against dose is graphically represented by plotting the **surviving fraction *S*(*D*)** on a logarithmic scale on the ordinate against **dose *D*** on a linear scale on the abscissa.



6.4.1 CELL SURVIVAL CURVES

Typical survival curves for cells irradiated by densely ionizing radiation (high LET) and sparsely ionizing radiation (low LET)

For high LET radiation, the survival curve may be exponential, i.e. linear on a semi-logarithmic plot



6.4.1 CELL SURVIVAL CURVES

☐ Type of radiation influences the shape of the survival curve.

- For densely ionizing radiation (**high LET**) the cell survival curve is almost an exponential function of dose (shown by an almost straight line on a log-linear plot).

- For sparsely ionizing radiation (**low LET**) the survival curves show an initial slope followed by a shoulder region and then become nearly straight at high doses.

☐ Many mathematical models of varying degrees of complexity have been developed to describe the shape of the cell survival curve.

6.4.1 CELL SURVIVAL CURVES

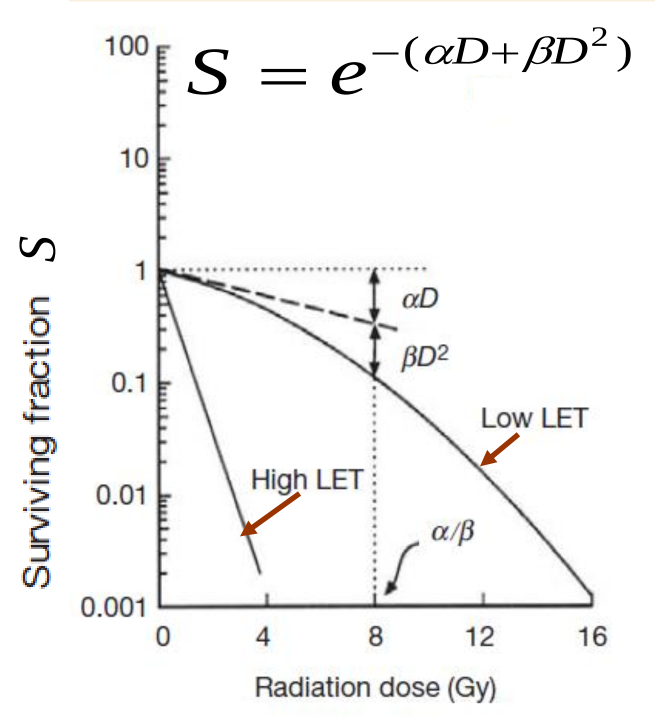
1. Linear-quadratic (LQ) model

- The most common model used today is the ***linear-quadratic model***, where cell death as a function of dose is described by a **second-order polynomial**

- This model assumes that there are two components to cell killing by radiation, commonly represented by two constants, α and β

- In this model, cell survival fraction S is described as a function of dose D by the following equation:

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

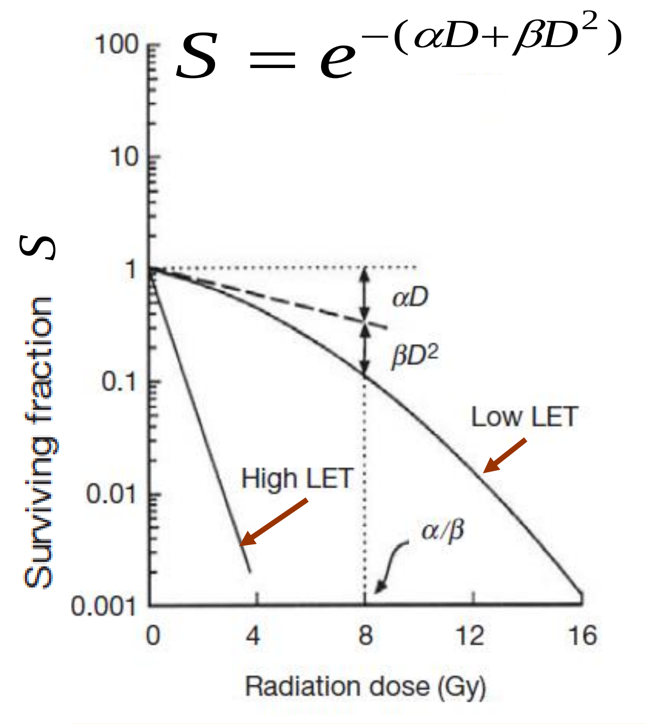


- α is a constant describing the initial slope of the cell survival curve.
- β describes the quadratic component.

6.4.1 CELL SURVIVAL CURVES

1. Linear-quadratic (LQ) model

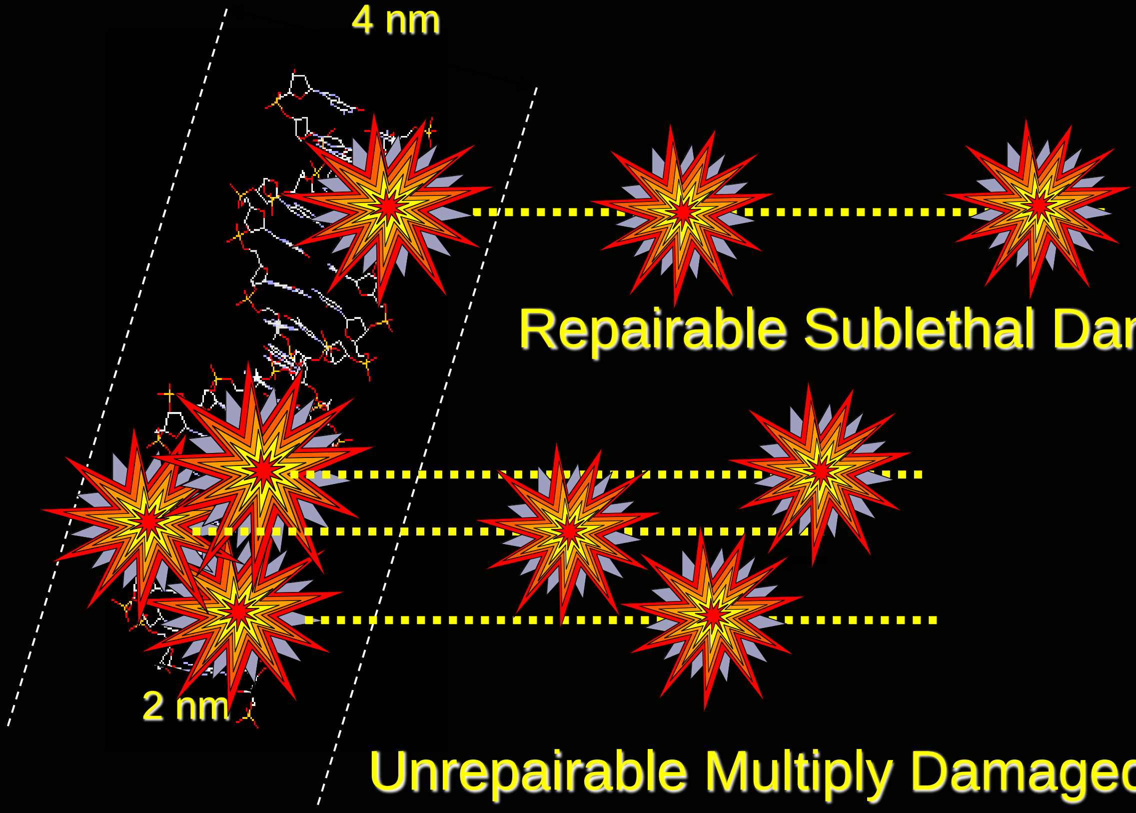
- A plausible explanation of the **linear component** is that the majority of DNA-interactions are single-radiation track events
- Under these circumstances, DNA damage can be effectively repaired before possible interaction with another single track when enough time is available and doses are relatively low
- As the dose or dose rate increases, multi-track events, reflecting the **quadratic component**, will predominate resulting in an increased probability of mis-repair and cell death
- Over 90% of radiation oncologists use the LQ model



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

- **Ratio α/β** gives the **dose** at which the linear and quadratic components of cell killing are equal.

Sub-lethal (or accumulated) damage results from accumulation of events that individually are incapable of killing a cell but that together can be lethal



Repairable Sublethal Damage

Unrepairable Multiply Damaged Site

6.4.1 CELL SURVIVAL CURVES

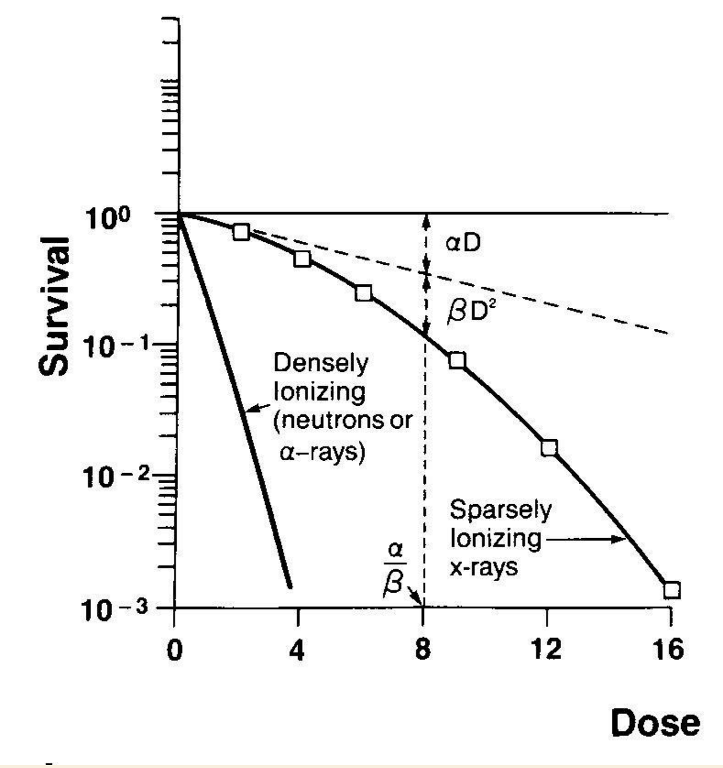
1. Linear-quadratic (LQ) model

α component

- **Linear variation with dose (Gy^{-1})**
- **Damage can be repaired**
- **SSB**

β component

- **Quadratic variation with dose (Gy^{-2})**
- **Lethal damage**
- **DSB**
- **Predominant for high LET radiation**



α/β ratio defines the bending of the survival curve

α/β ratio high (>10)

- **Lethal damage**
- **Curve linear at origin**
- **Early responding normal tissues**
- **Fast growing tumor**

α/β ratio low (~3)

- **Damage can be repaired**
- **Curve with shoulder at the beginning**
- **Late responding normal tissues**
- **Slow growing tumor**

6.4.1 CELL SURVIVAL CURVES

With regard to response time two types of tissue are known:

❑ **HIERARCHICAL OR EARLY-RESPONDING TISSUES**

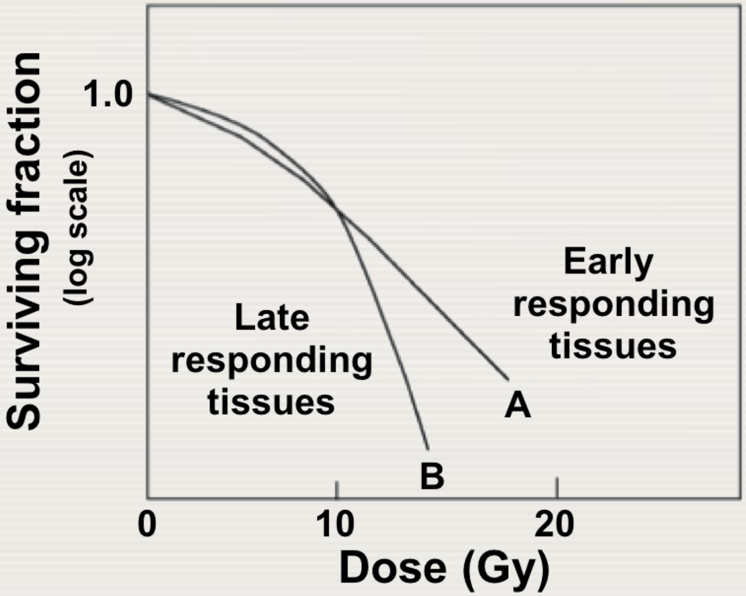
- **Rich in stem cells** and highly proliferative progenitor cells that differentiate into functional differentiated cells.
- They have a high turnover rate and a high rate of cell loss.
- They **respond rapidly to irradiation** and fail when the precursor pool fails to generate enough differentiated cells.
- Examples are Gut, Skin, Bone Marrow, Mucosa and TUMOR

❑ **FLEXIBLE OR SLOW-RESPONDING TISSUES**

- tissues with a **slow turnover rate** and **respond slowly to irradiation**.
- They fail when there is enough cell loss to induce regeneration, which triggers an avalanche of cell death, generally after a **long lag period**.
- Examples are Brain, Spinal Cord, Kidney, Lung, Bladder

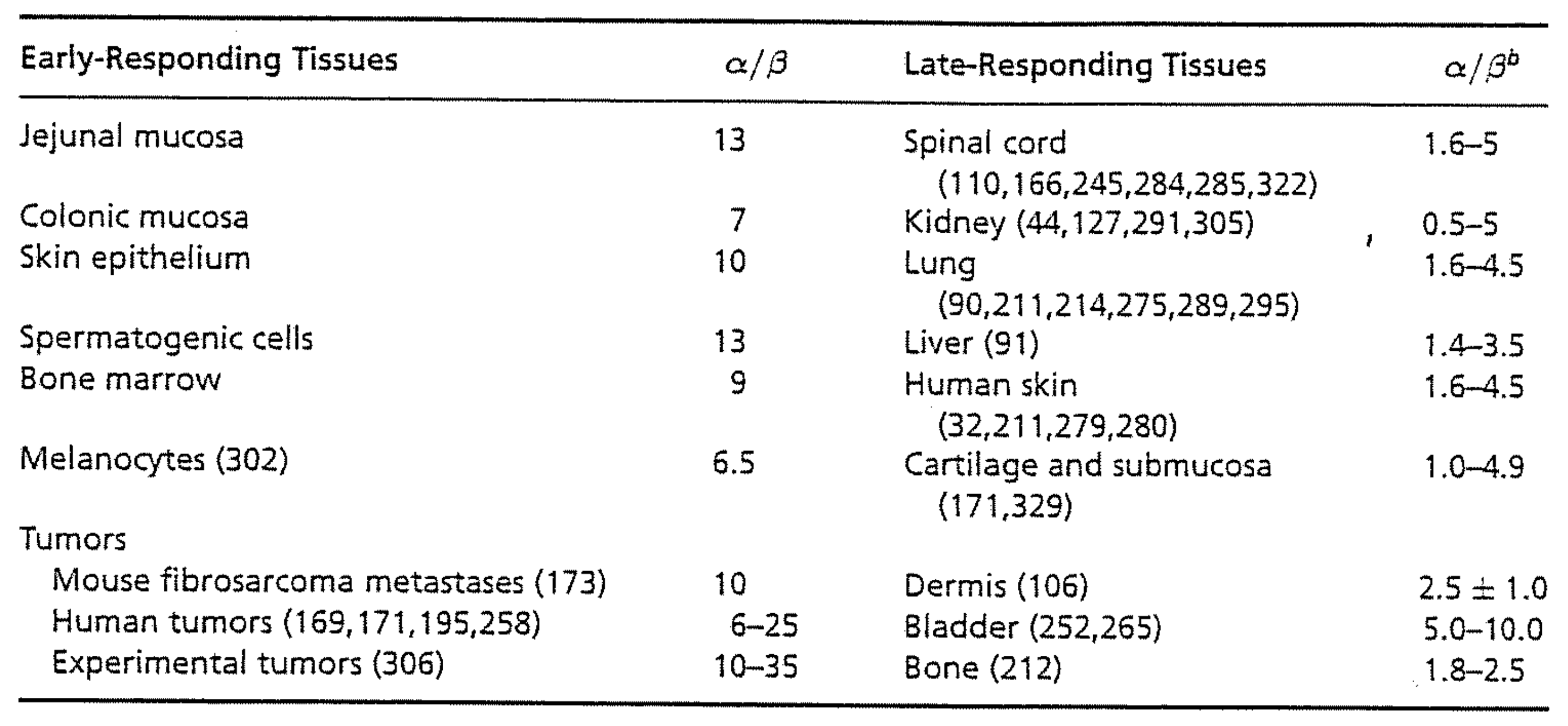
6.4.1 CELL SURVIVAL CURVES

- ☐ For late responding tissues the survival curves are more curved than those for early responding tissues.
- ☐ For **early effects the ratio α/β is large**; **for late effects it is small**.
- ☐ For early effects α dominates at low doses, for late effects β has an influence at doses lower than for early responding tissues.



6.4.1 CELL SURVIVAL CURVES

1. Linear-quadratic (LQ) model

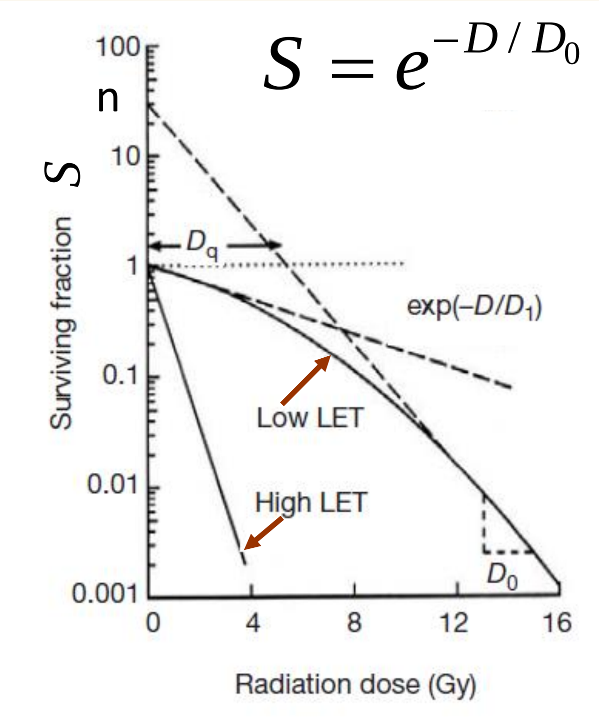


Early-Responding Tissues	α/β	Late-Responding Tissues	α/β^b
Jejunal mucosa	13	Spinal cord (110,166,245,284,285,322)	1.6–5
Colonic mucosa	7	Kidney (44,127,291,305)	0.5–5
Skin epithelium	10	Lung (90,211,214,275,289,295)	1.6–4.5
Spermatogenic cells	13	Liver (91)	1.4–3.5
Bone marrow	9	Human skin (32,211,279,280)	1.6–4.5
Melanocytes (302)	6.5	Cartilage and submucosa (171,329)	1.0–4.9
Tumors			
Mouse fibrosarcoma metastases (173)	10	Dermis (106)	2.5 ± 1.0
Human tumors (169,171,195,258)	6–25	Bladder (252,265)	5.0–10.0
Experimental tumors (306)	10–35	Bone (212)	1.8–2.5

- Both α and β vary with the cell cycle. At high doses, S phase and hypoxic cells become more important.
- The α/β ratio varies depending upon whether a cell is quiescent or proliferative
- The **LQ model best describes data in the range of 1 - 6Gy** and should not be used outside this range

6.4.1 CELL SURVIVAL CURVES

2. Single-hit single-target model



An alternative older model is the **single-hit single-target model** described by:

$$\boxed{S = e^{-D/D_0}}$$

D_0 is effectively the reciprocal of α (of LQ model) and **represents the dose which reduces survival to e^{-1} or 37 %**

The target theory is based upon the idea that there are n targets in a cell, all of which must be "hit" to kill the cell

Extrapolation number n (the point of intersection of the slope on the log survival axis).

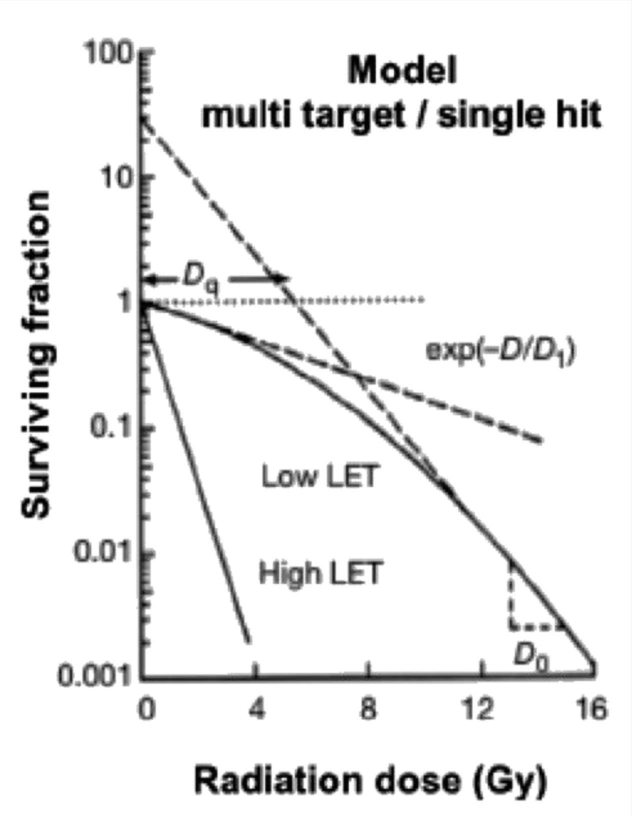
6.4.1 CELL SURVIVAL CURVES

3. Single-hit multi-target model

- The log-linear relationship is consistent with data from some bacteria (procaryotes) but it **does not apply in eukaryotic cells** (except at high LET), which show shouldered survival curves that can be accommodated by a *single-hit multi-target model* described by:

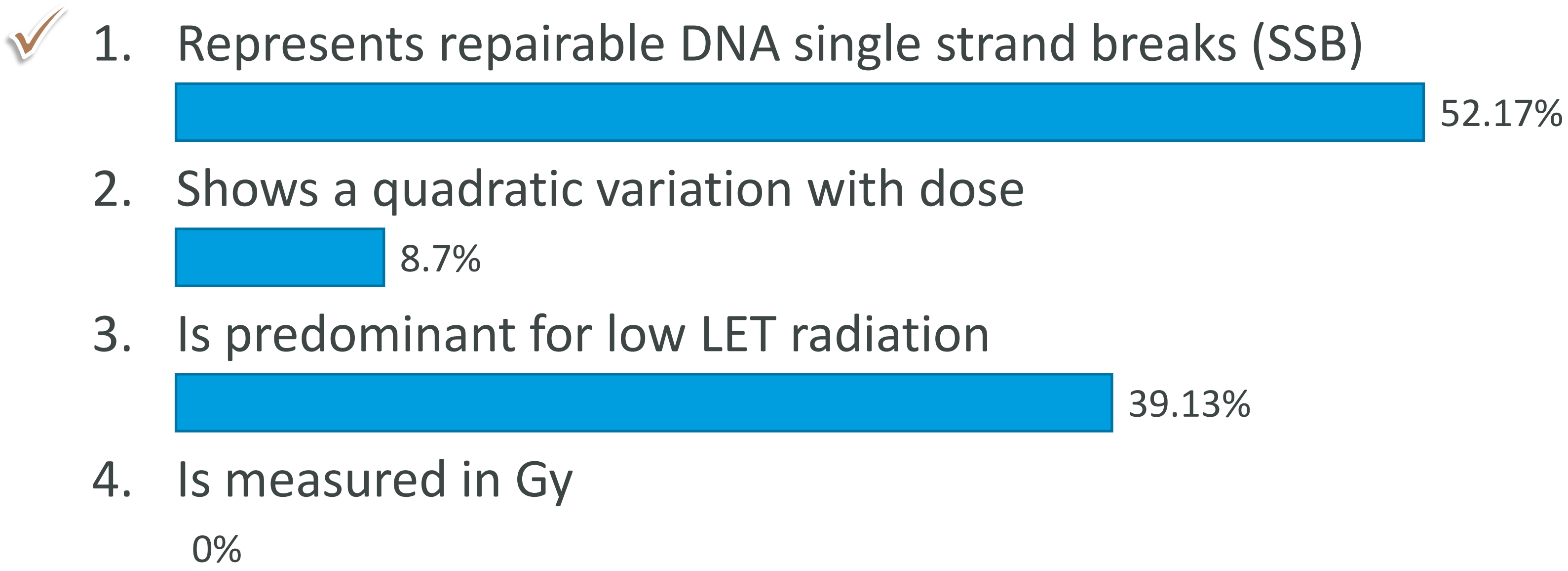
$$\boxed{S = 1 - (1 - e^{-D/D_0})^n}$$

n is the number of targets



- This is **reliable at high dose but not at low dose**, because it does not describe accurately the ‘shoulder’ region at low doses

The alpha parameter in the linear quadratic formula for a survival curve:



✓ 1. Represents repairable DNA single strand breaks (SSB)

2. Shows a quadratic variation with dose

3. Is predominant for low LET radiation

4. Is measured in Gy

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What is TRUE for the alpha/beta ratio

1. It is unitless

   4.55%

2. It is a measure of the shoulder of the survival curve

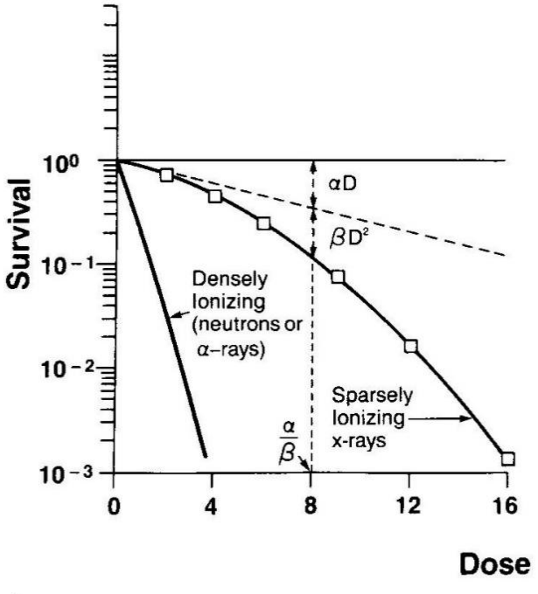
   31.82%

3. ✓ It is described in the linear-quadratic (LQ) model

   22.73%

4. It is the ratio where the number of non-repairable lesions equals that for repairable lesions

   40.91%



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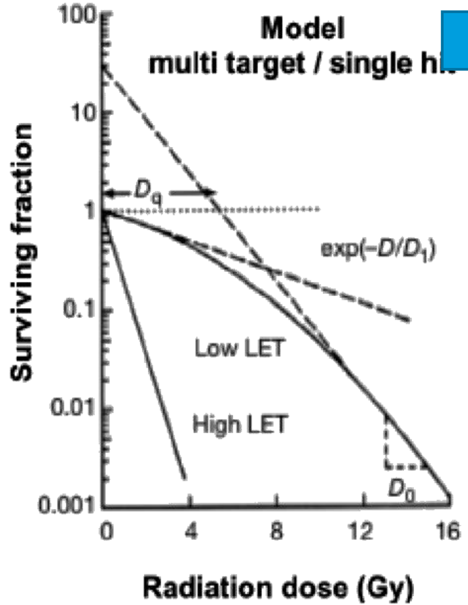
In the target theory/model, D0 :

1. Is a measure of the shoulder of a survival curve
16.67%

2. Is the mean lethal dose for the linear portion of the dose-response curve
29.17%

✓ 3. Represents the slope of the log linear survival curve
50%

4. Is constant at all levels of radiation effect
4.17%



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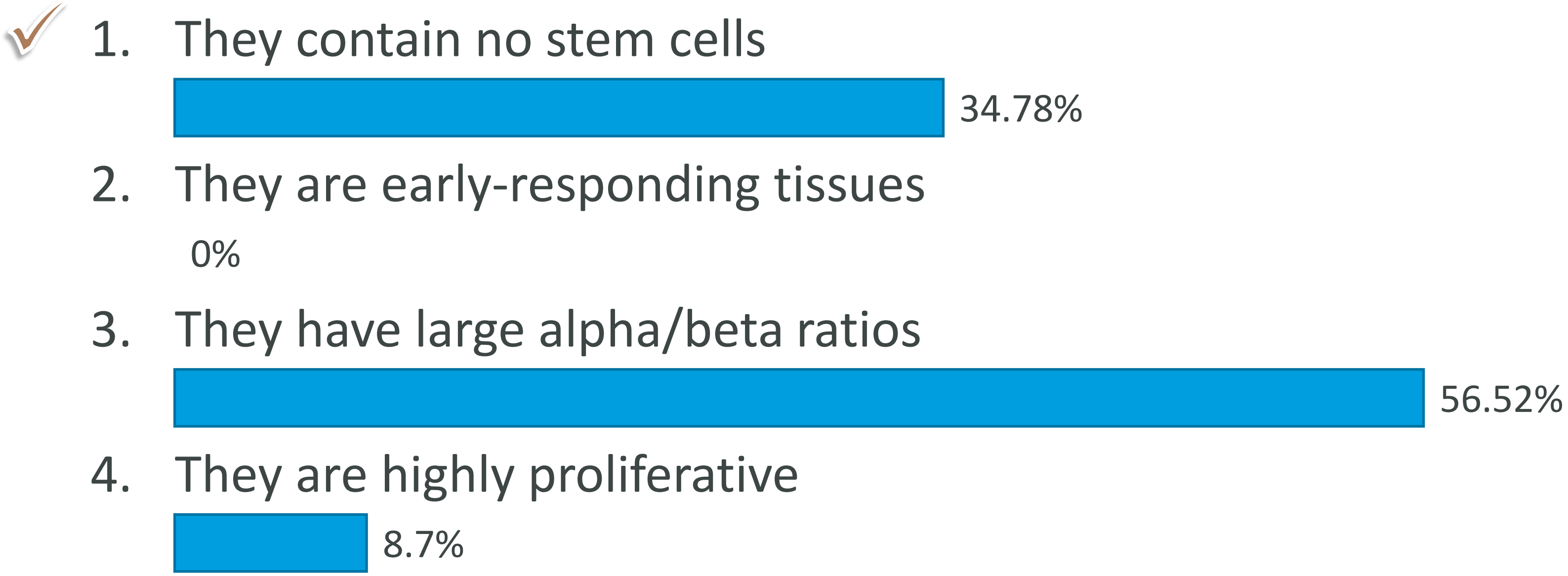
Which of the following is TRUE for slow-responding tissues:



✓ 1. They contain no stem cells 34.78%

2. They are early-responding tissues 0%

3. They have large alpha/beta ratios 56.52%

4. They are highly proliferative 8.7%

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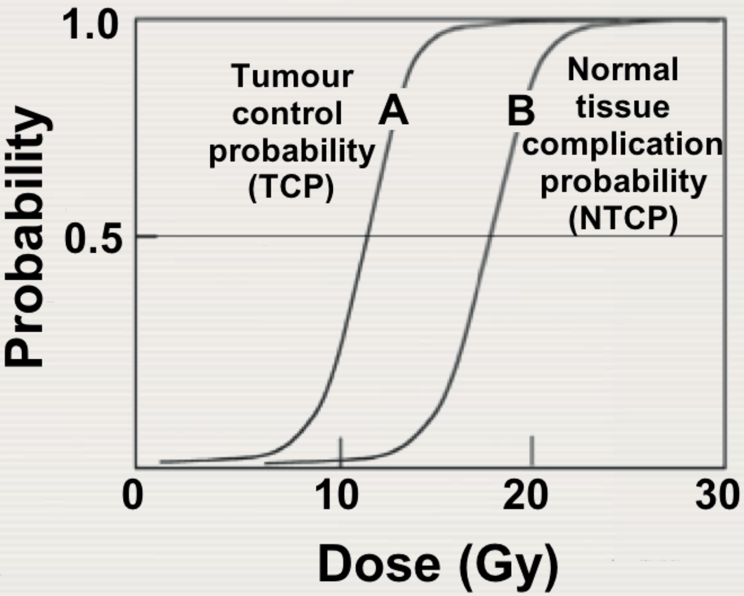
6.4.2 DOSE RESPONSE CURVES

- ❑ Plot of a biological effect observed (e.g., tumor induction or tissue response) against the dose given is called a dose response curve.

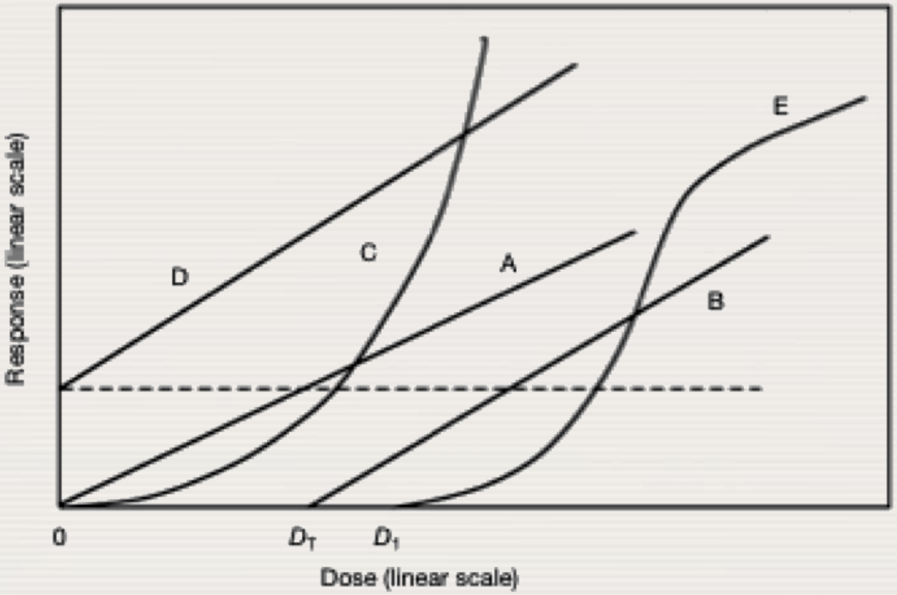
- ❑ Generally, **as the dose increases so does the effect.**

- ❑ Three types of dose response relationships are known:
  - Linear
  - Linear-quadratic
  - Sigmoid

- ❑ Threshold dose is the largest dose for a particular effect studied below which no such effect is observed.



6.4.2 DOSE RESPONSE CURVES



Dose response curves

(A) Linear relationship with no threshold.

(B) Linear relationship with threshold.

(C) Linear-quadratic relationship with no threshold (**stochastic effects** such as carcinogenesis).

(D) Linear relationship with no threshold and the area under the dashed line representing the **natural incidence** of the effect.

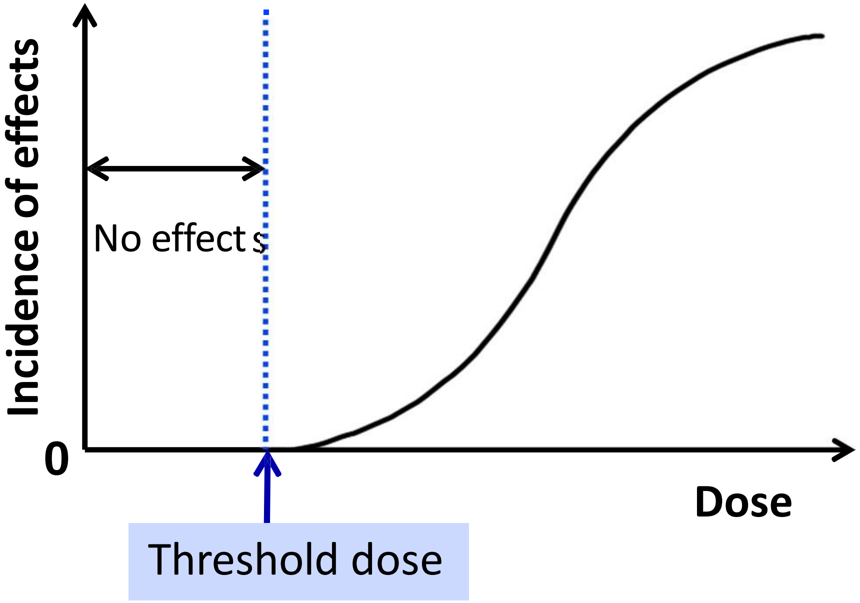
(E) Sigmoid relationship with threshold D1, as is common for **deterministic effects** in tissues.

Deterministic Effects and Stochastic Effects

Deterministic effects

(Hair loss, cataract, skin injury, etc.)

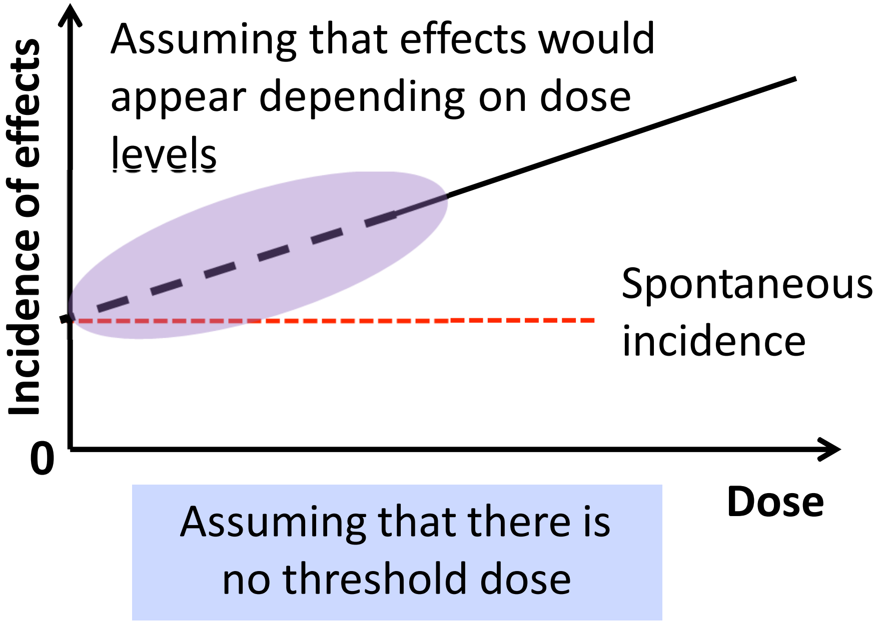
When a number of people were exposed to the same dose of radiation and certain symptoms appear in 1% of them, said dose is considered to be the threshold dose.
(2007 Recommendations of the International Commission on Radiological Protection (ICRP))



Stochastic effects

(Cancer, leukemia, hereditary effects, etc.)

Effects of radiation exposure under certain doses are not clear because effects of other cancer-promoting factors such as smoking and drinking habits are too large. However, the ICRP specifies the standards for radiological protection for such low-dose exposures, assuming that they may have some effects as well.



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6.4.3 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

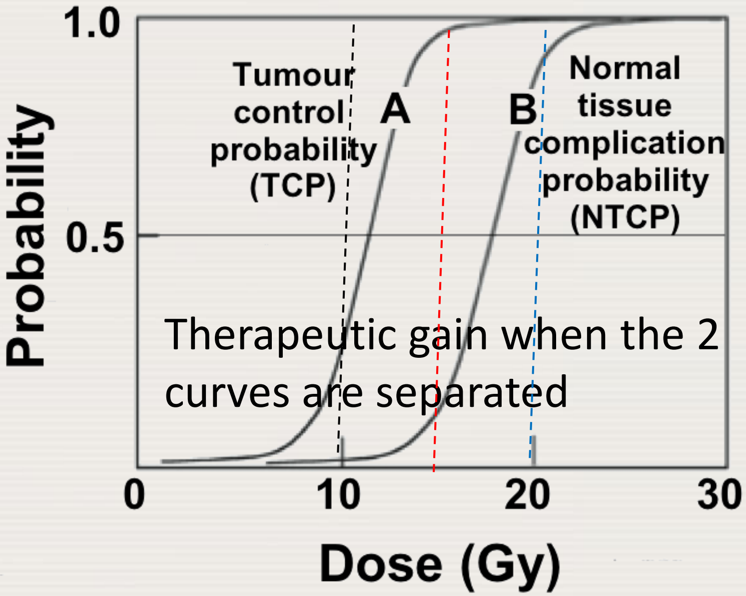
- ☐ Cancer is characterized by a **disorderly proliferation of cells** that can invade adjacent tissues and spread via the lymphatic system or blood vessels to other parts of the body.

- ☐ Aim of radiotherapy is to **deliver enough radiation to the tumor to destroy it without irradiating normal tissue** to a dose that will lead to serious complications (morbidity).

- ☐ It is imperative that the doses to normal tissues be kept lower than the doses to tumors in order to:
  - Minimize treatment complications.
  - Optimize treatment outcomes.

6.4.3 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

- ❑ Principle of radiotherapy is usually illustrated by plotting two sigmoid curves:
  - For tumor control probability (TCP).
  - For normal tissue complication probability (NTCP).



Therapeutic gain when the 2 curves are separated

- ❑ Optimum choice of radiation dose delivery technique in treatment of a given tumour is such that it maximizes the TCP and simultaneously minimizes the NTCP.

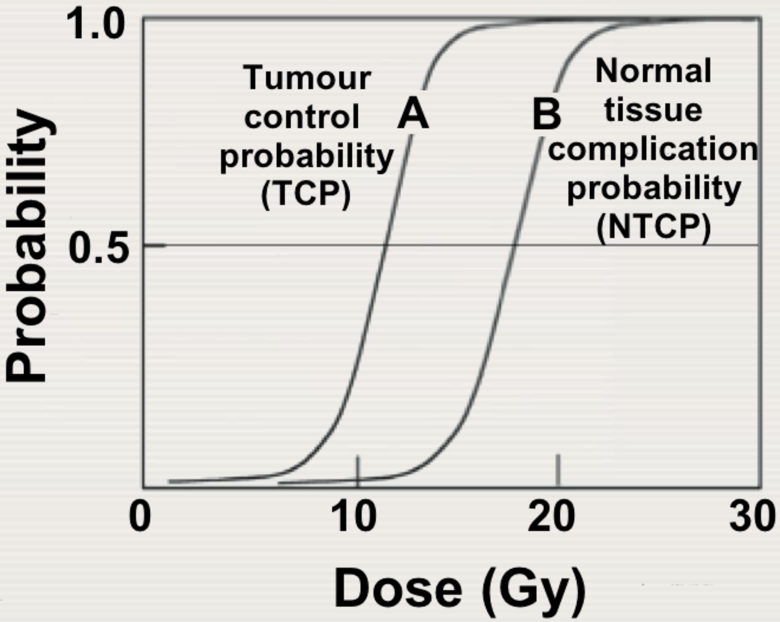
- ❑ For a typical good radiotherapy treatment:
  - TCP $\geq$ 0.5
  - NTCP $\geq$ 0.05

6.4.3 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

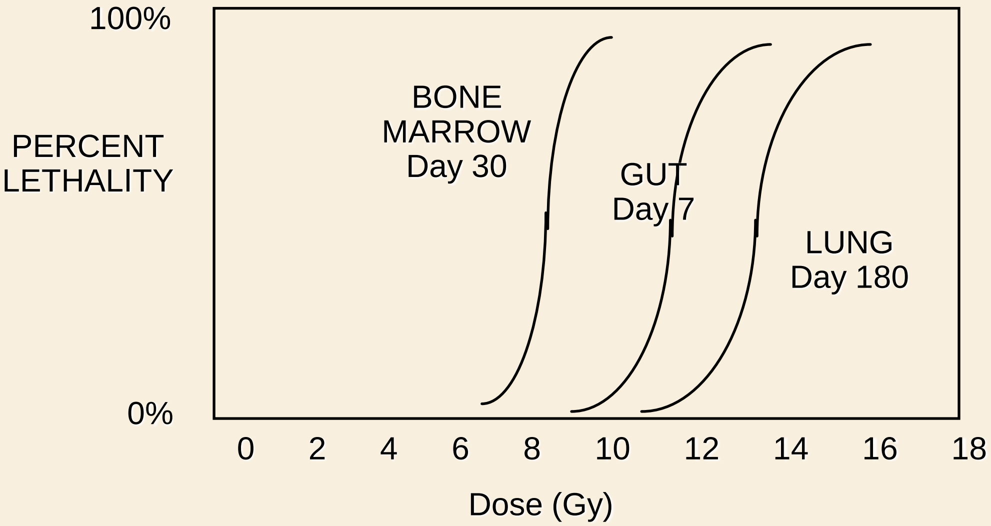
- ☐ Concept of the therapeutic ratio is often used to represent the optimal radiotherapy treatment.

- ☐ Therapeutic ratio generally **refers to the ratio of the TCP and NTCP at a specified level of response** (usually 0.05) for normal tissue.

- ☐ The further the NTCP curve is to the right of the TCP curve:
  - The easier it is to achieve the radiotherapeutic goal.
  - The larger is the therapeutic ratio.
  - The less likely are treatment complications.



6.4.3 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO



- Different tissues have different tolerances to irradiation and fail at different times after irradiation (intrinsic radiosensitivity)
- **LATENCY:** Different tissues take different times to express damage. This depends on their cell turnover time. → It is NOT an indicator of radiosensitivity.
- There is no relationship between latency and tolerance
- E.g. After moderate doses, gut fails first, then bone marrow, then lung, but the hematopoietic system is the most radiosensitive

6.4.3 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

Tumor Control Probability (TCP)

In order to cure a tumor, **the last surviving clonogen must be killed** → it is a probability function of dose.

$$TCP = e^{-x} = e^{-(m*S)} = e^{-m*e-(\alpha D+\beta D\text{^}2)} \text{ or } e^{-(m*e\ -(D/D0))}$$

where **x** is the number of surviving clonogenic stem cells
m is the initial number of clonogens

If there is an average of 1 cell surviving TCP=37%

6.4.3 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

☐ Several factors can make cells less radio-sensitive:

- Removal of oxygen to create a hypoxic state.
- Addition of radioprotectors or radiosensitizers.
- Use of low dose rates or multi-fractionated irradiation.
- Synchronization of cells in the late S phase of the cell cycle.

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The probability of tumor cure (TCP) in a series of tumors that have on average 1 cell surviving is

$$TCP = e^{-(m*S)}$$

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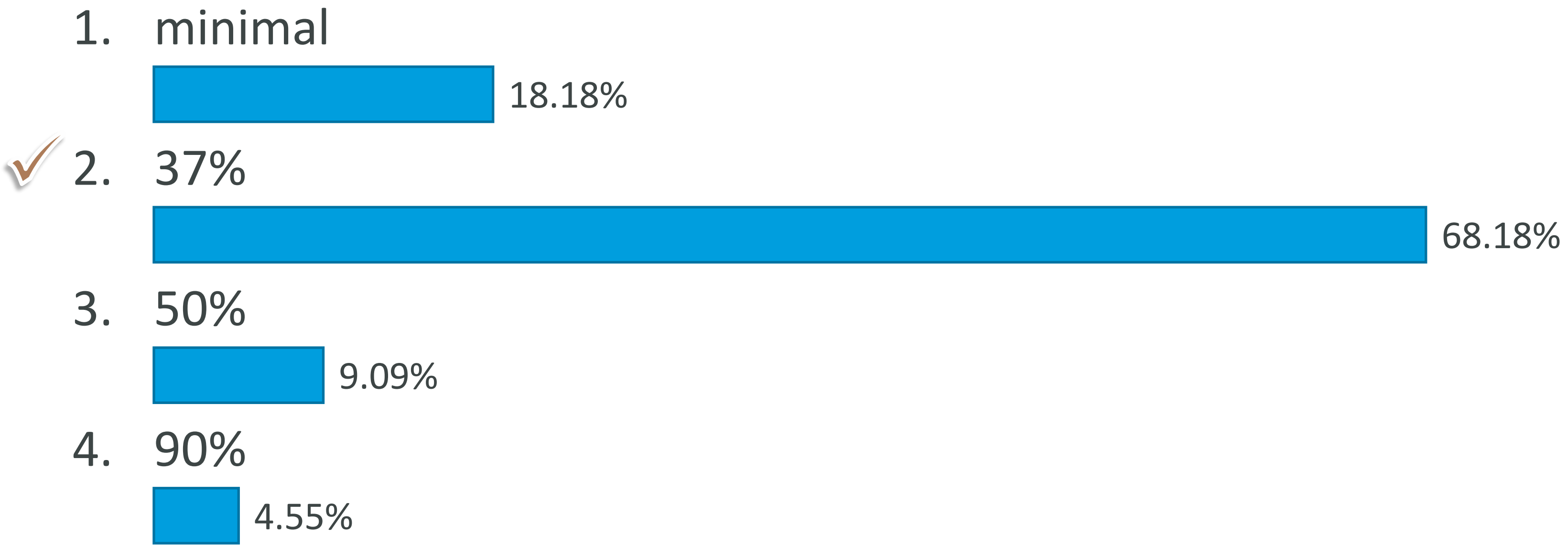
If a tumor contains 10^9 clonogenic cells and RT reduces survival by 10^-9, what is the probability of tumor cure?



1. minimal
2. ✓ 37%
3. 50%
4. 90%

$$TCP = e^{-(m*S)}$$

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If a tumor contains 10^9 clonogenic cells and RT reduces survival by 10^-10, what is the probability of tumor cure

1. 10%
   18.18%
2. 37%
   0%
3. 50%
   18.18%
4. ✓ 90%
   63.64%

$$TCP = e^{-(m*S)}$$

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6.4.4 RELATIVE BIOLOGICAL EFFECTIVENESS

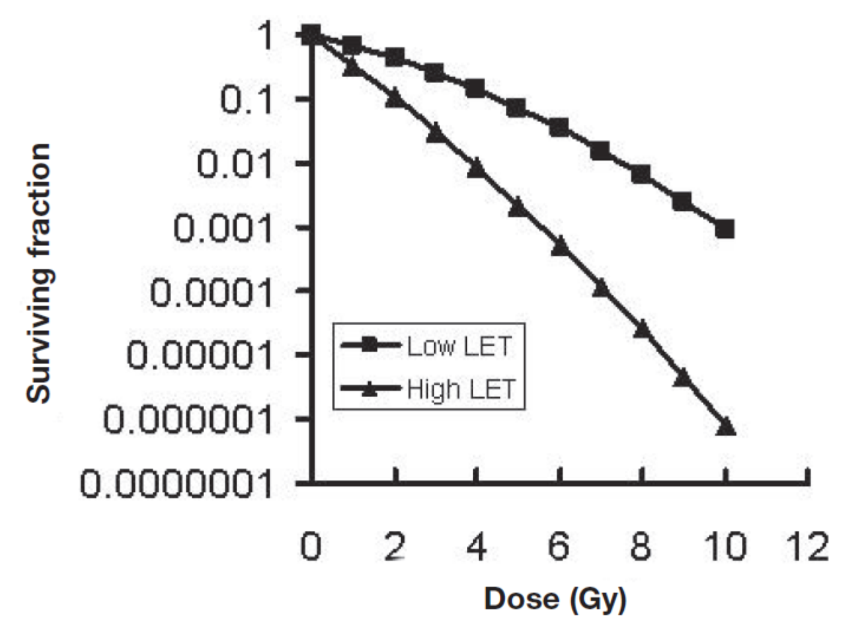
Assumption: **As the LET of radiation increases, the ability of the radiation to produce biological damage increases.**

The Relative biological effectiveness (RBE) is defined as:

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

Isoeffective doses for the reference:

- Historically, 250 kVp x rays were taken as standard radiation.
- Today cobalt-60 gamma rays are recommended for this purpose.



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

6.4.4 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 ($\mathrm{RBE}_{\mathrm{max}}$) occurs at zero dose and corresponds to

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

(α_{H} and α_{L} are the high and low LET linear radio-sensitivity constants)

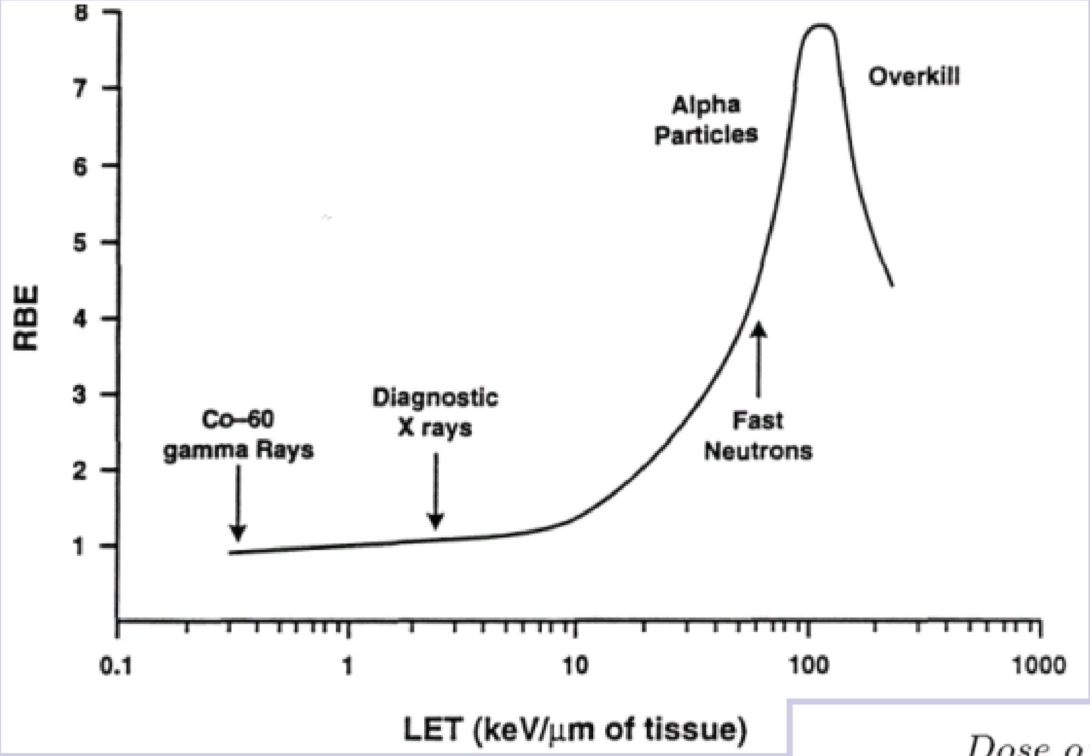
6.4.4 RELATIVE BIOLOGICAL EFFECTIVENESS

- 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 tumor

- The RBE varies with:
  - Type of radiation (high or low LET).
  - Type of cell or tissue (radiosensitive or radioresistant).
  - Dose.
  - Dose rate.
  - Oxygenation → **oxygen enhancement ratio (OER)**
  - Fractionation.
  - Cell cycle phase
  - Tissue/Tumor Type

Radiation Effect and Dose Delivery

For low LET radiation, $\Rightarrow$ RBE $\propto$ LET, for higher LET the RBE increases to a maximum, the subsequent drop is caused by the **overkill effect**.



$$RBE = \frac{Dose\ of\ 150\ V\ \ X-rays\ required\ to\ cause\ effect\ x}{Dose\ of\ radiation\ required\ to\ cause\ effect\ x}$$

These high energies are sufficient to kill more cells than actually available!

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The shape of the dose response curve for the induction of DETERMINISTIC effects is best described as:

1. Guassian

   0%

2. Linear

   4.35%

✓ 3. Sigmoidal with threshold

   60.87%

4. Linear-quadratic

   34.78%

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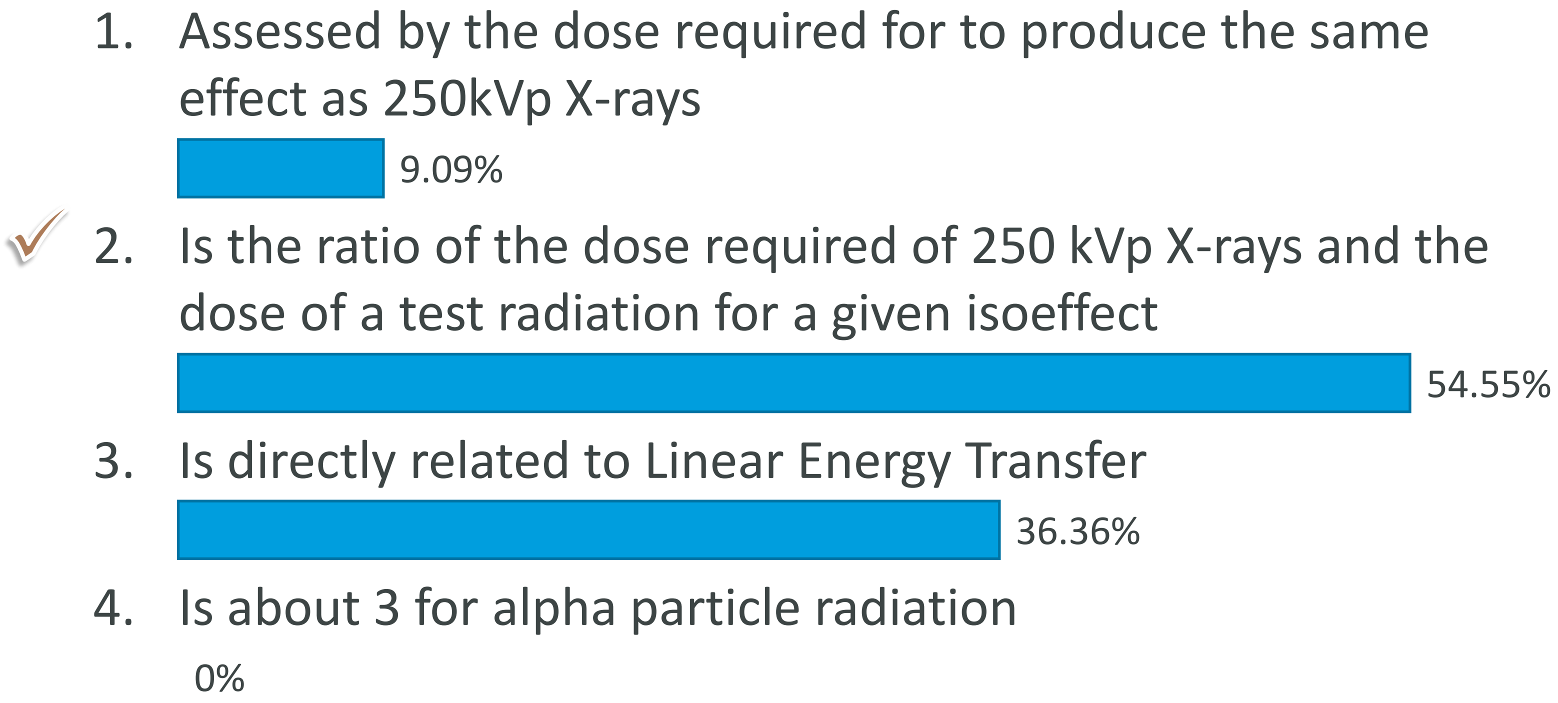
The Relative Biological Effectiveness (RBE) of a radiation is



1. Assessed by the dose required for to produce the same effect as 250kVp X-rays
   9.09%
2. ✓ Is the ratio of the dose required of 250 kVp X-rays and the dose of a test radiation for a given isoeffect
   54.55%
3. Is directly related to Linear Energy Transfer
   36.36%
4. Is about 3 for alpha particle radiation
   0%

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Which of the following statements is correct about Relative Biological Effect (RBE)?

✓ 1. RBE is the ratio of doses of two different radiations that produce the same biological endpoint, e.g. 50% survival

   39.13%

2. RBE is the ratio of survival fractions produced by the same doses of two different radiations

   43.48%

3. Beta-particles have higher RBE values than alpha-particles

   8.7%

4. High LET radiation have lower RBE values than low LET radiation

   8.7%

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6.4.5 OXYGEN EFFECT

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

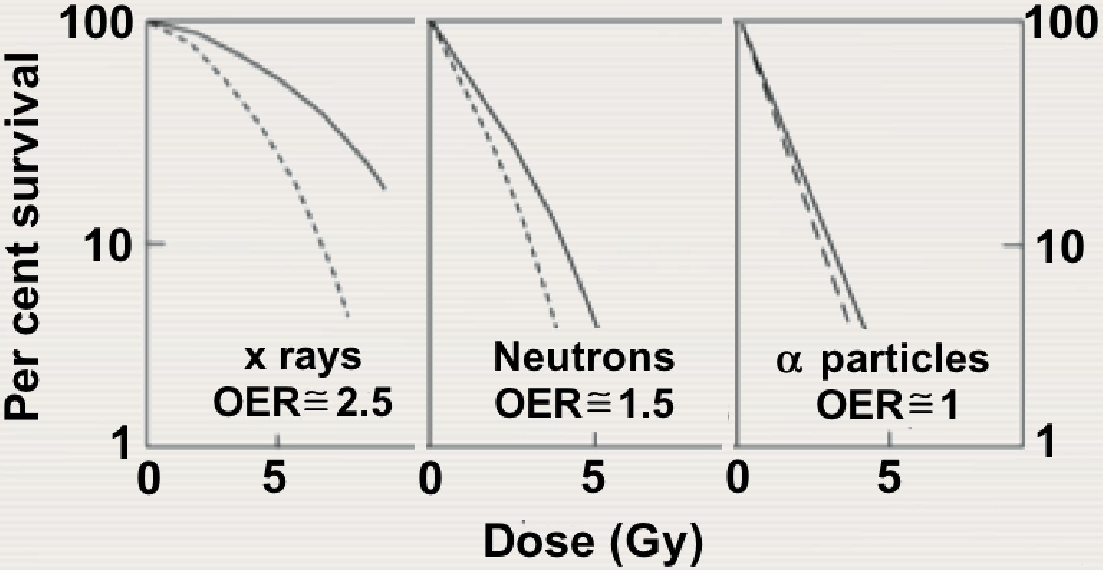
$$\boxed{\mathbf{OER} = \frac{D_{\text{hypoxia}}}{D_{\text{in air}}}}$$

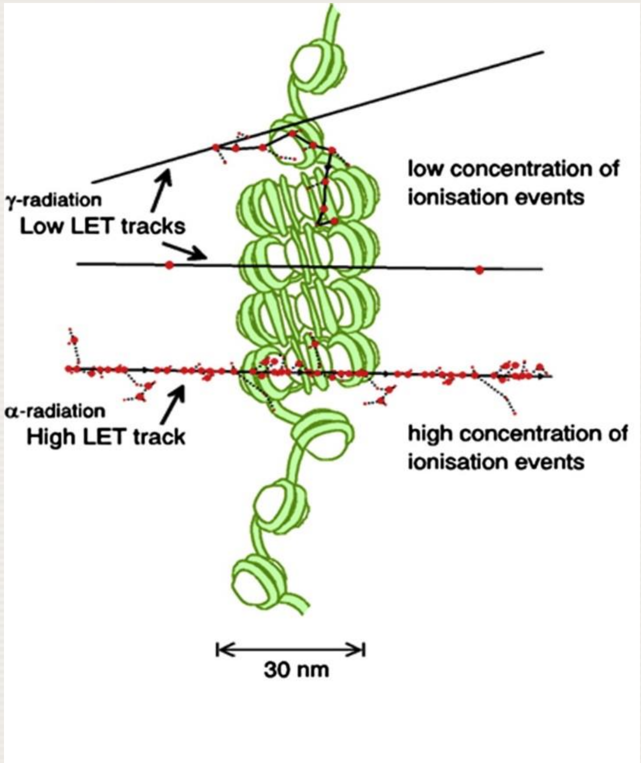
~ 3 for **low LET** radiation (as γ rays)

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

6.4.5 OXYGEN EFFECT

- Oxygen effect is quite dramatic for low LET (sparsely ionizing) radiation, while for high LET (densely ionizing) radiation it is much less pronounced.

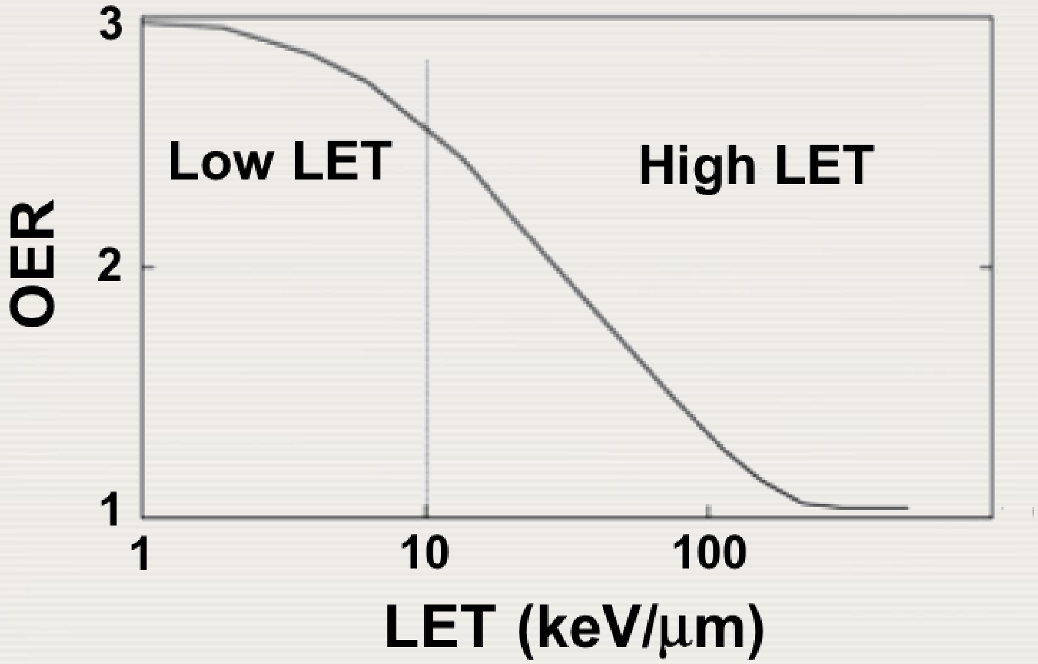


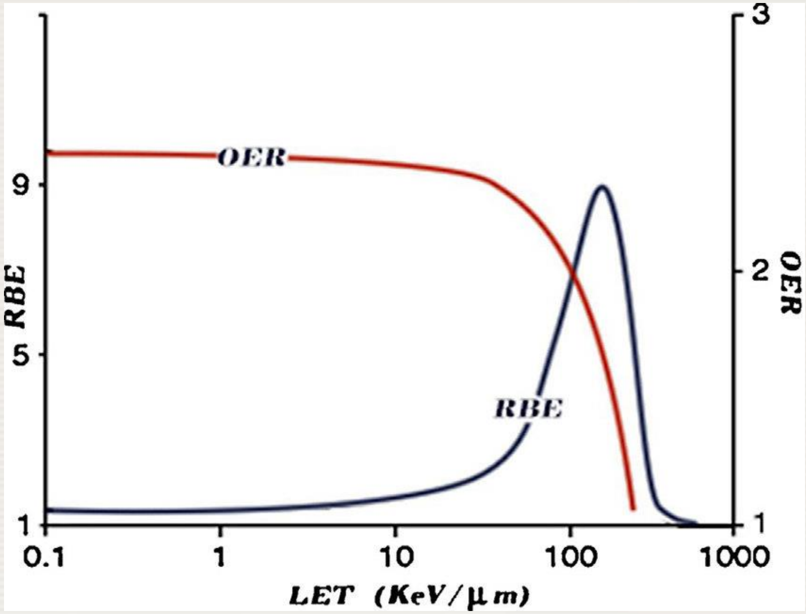


Solid survival curves are for hypoxic cells; dashed survival curves are for well oxygenated cells.

6.4.5 OXYGEN EFFECT

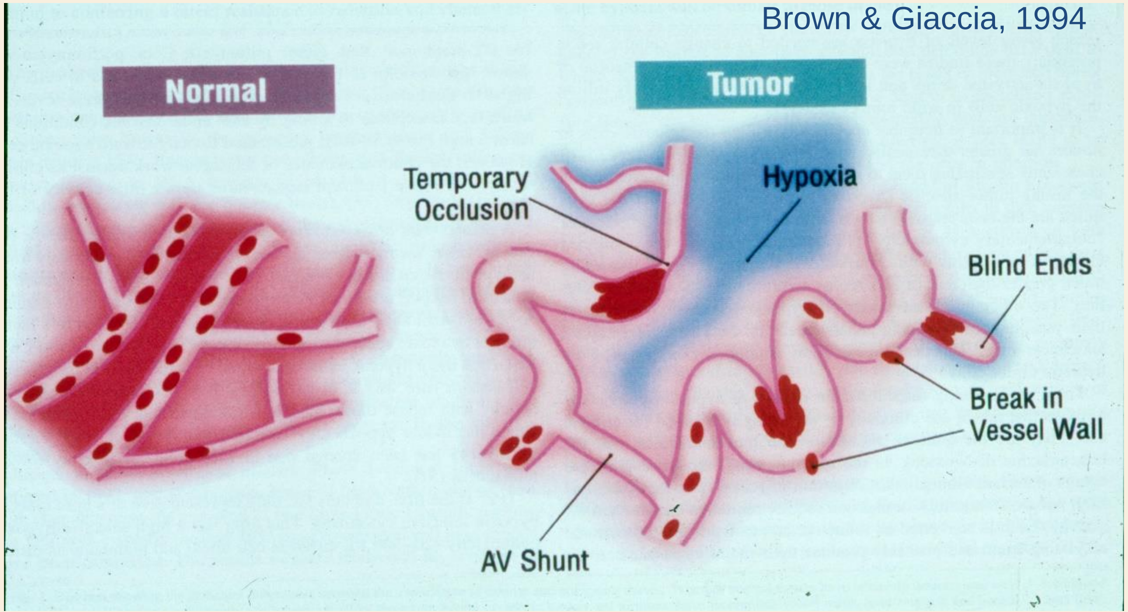
- The OER decreases as the LET increases and approaches OER = 1 at LET ≈ 150 keV/μm.



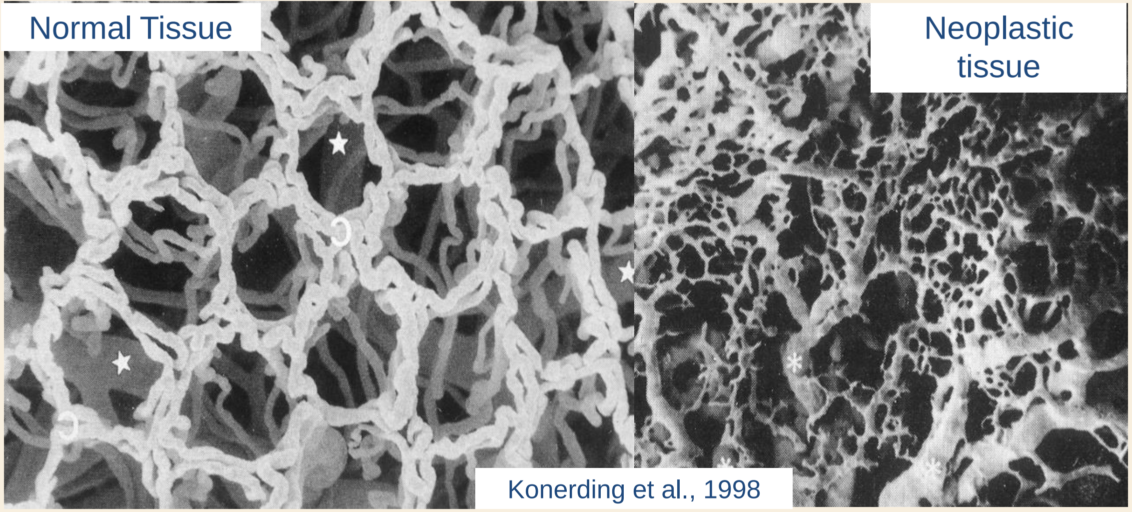


6.4.5 OXYGEN EFFECT

- The vascular network that develops in tumors is **structurally abnormal**
- Vessels are dilated, tortuous, elongated, with blind ends
- The abnormal vasculature results in spatial and temporal heterogeneity in blood flow that in turn produce regions of temporary or acute hypoxia, and nutrient depletion



Brown & Giaccia, 1994



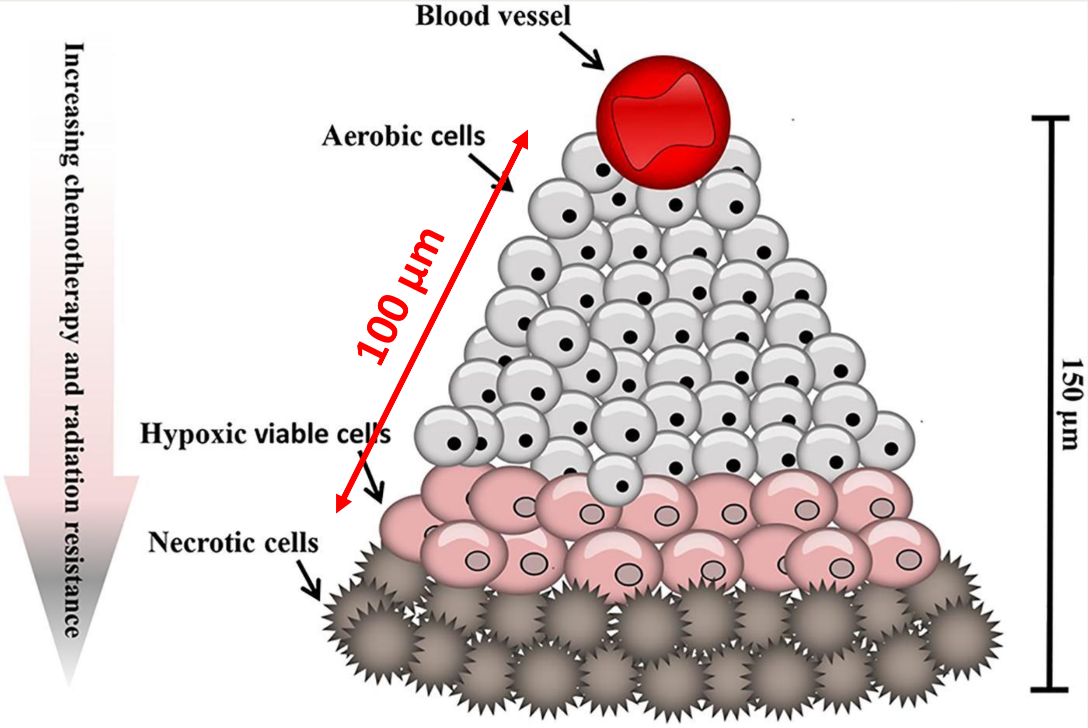
Normal Tissue

Neoplastic tissue

Konerding et al., 1998

6.4.5 OXYGEN EFFECT

- 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.



- Limited O2 diffusion due to high cell oxygen consumption and/or irregular vascular geometry

- Reoxygenation is process by which cells that are hypoxic become oxygenated after irradiation through the killing and removal of oxic radiosensitive cells from the tumor.

radiobiologically relevant hypoxia happens at **100 µm distance from a blood vessel**

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Which of the following is TRUE about the oxygen enhancement ratio (OER)

1. Is the same at all levels of cell survival

   0%

2. represents the increased likelihood that the DNA will be damaged by direct action of irradiation

   14.29%

✓ 3. Is the ratio of doses needed for an isoeffect in the absence to the presence of oxygen

   85.71%

4. Is low for cells in S cell cycle phase compared to cells in G2/M phase

   0%

Which of the following is true about Linear Energy Transfer (LET):

1. It is a measure of the relative biological effectiveness (RBE) of ionizing radiation
   17.39%
2. Shows a proportional correlation with the oxygen enhancement ratio (OER)
   34.78%
3. Is maximal at a relative biological effectiveness of 150 keV/micrometer
   4.35%
4. ✓ Is measured in keV/micrometer
   43.48%

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The OER is lowest at an LET closest to:

1. 1 keV/um

9.09%

2. 10 keV/um

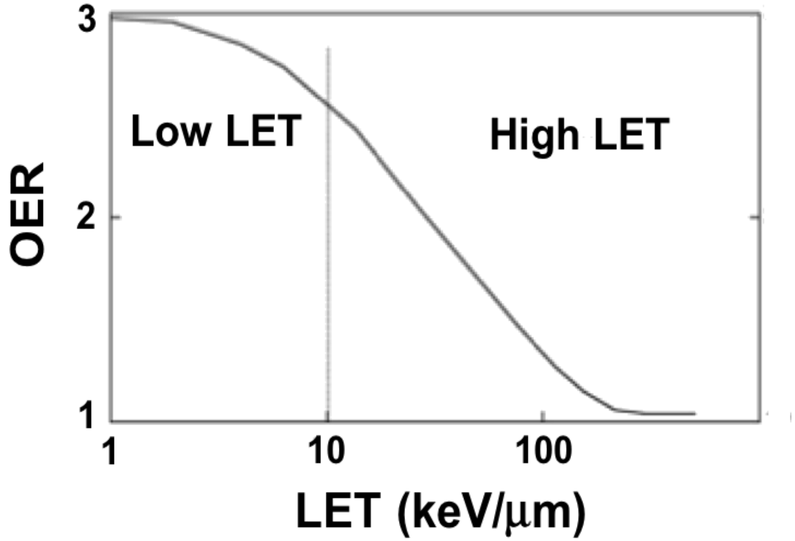
18.18%

3. 50 keV/um

13.64%

✓ 4. 100 keV/um

59.09%



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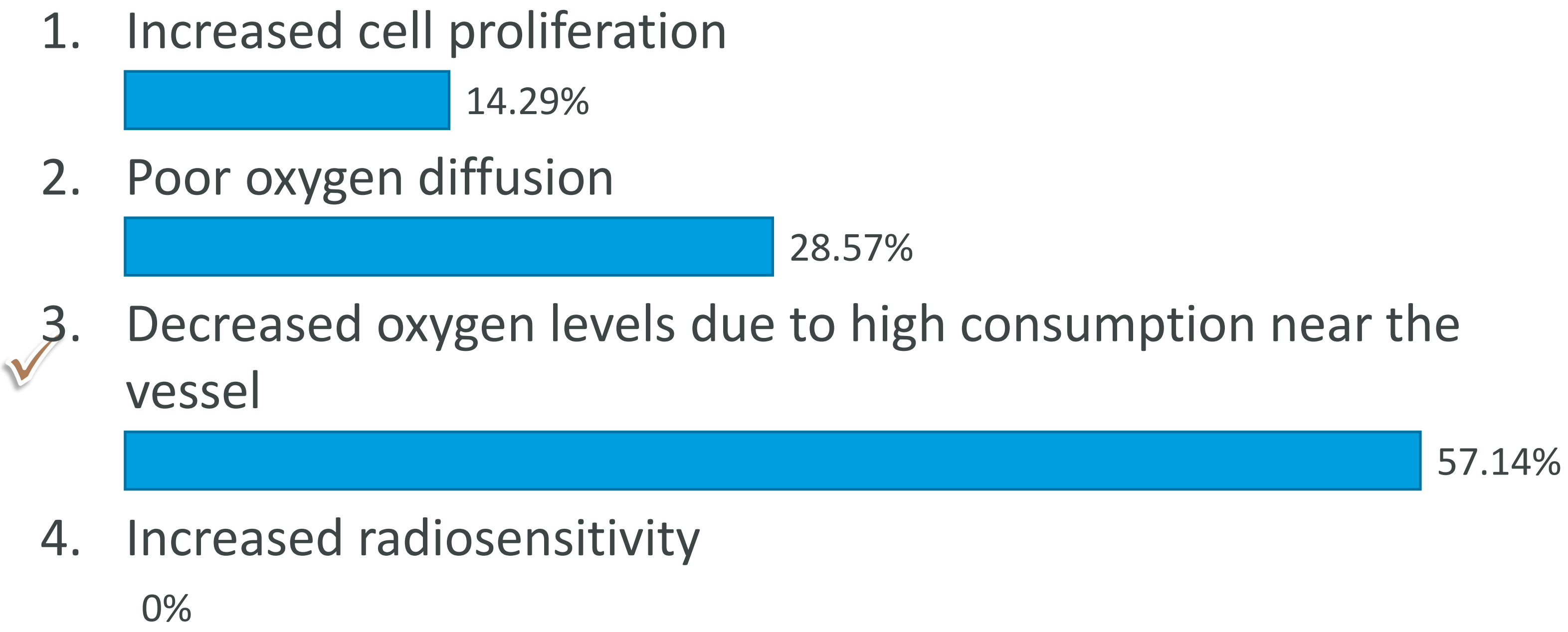
What occurs in tumors with distance from a blood vessel:

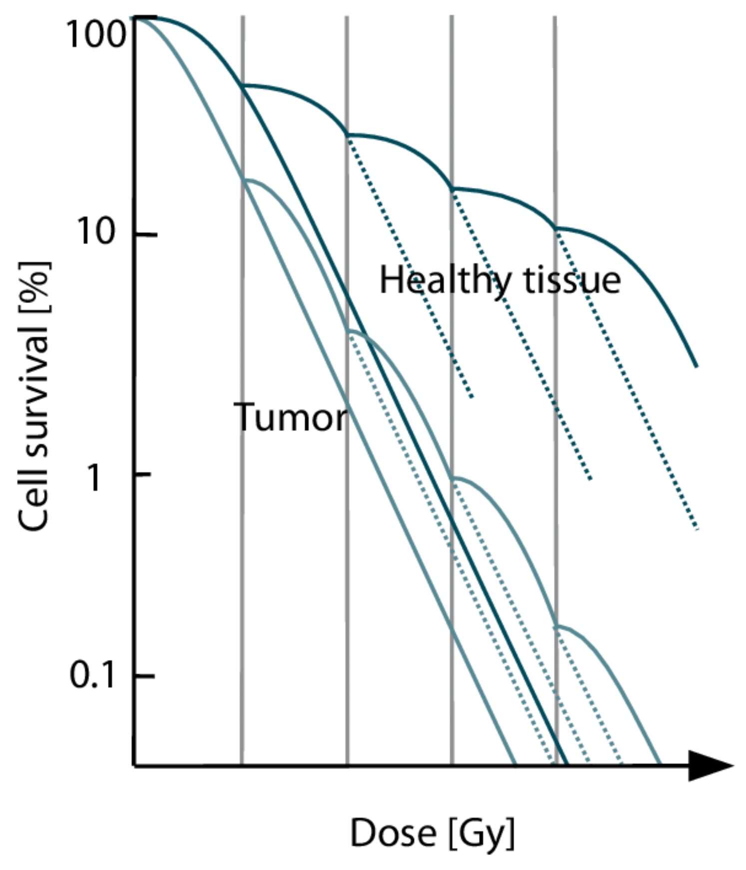


1. Increased cell proliferation
   14.29%
2. Poor oxygen diffusion
   28.57%
3. ✓ Decreased oxygen levels due to high consumption near the vessel
   57.14%
4. Increased radiosensitivity
   0%

CHAPTER 6. PART 4 TABLE OF CONTENTS

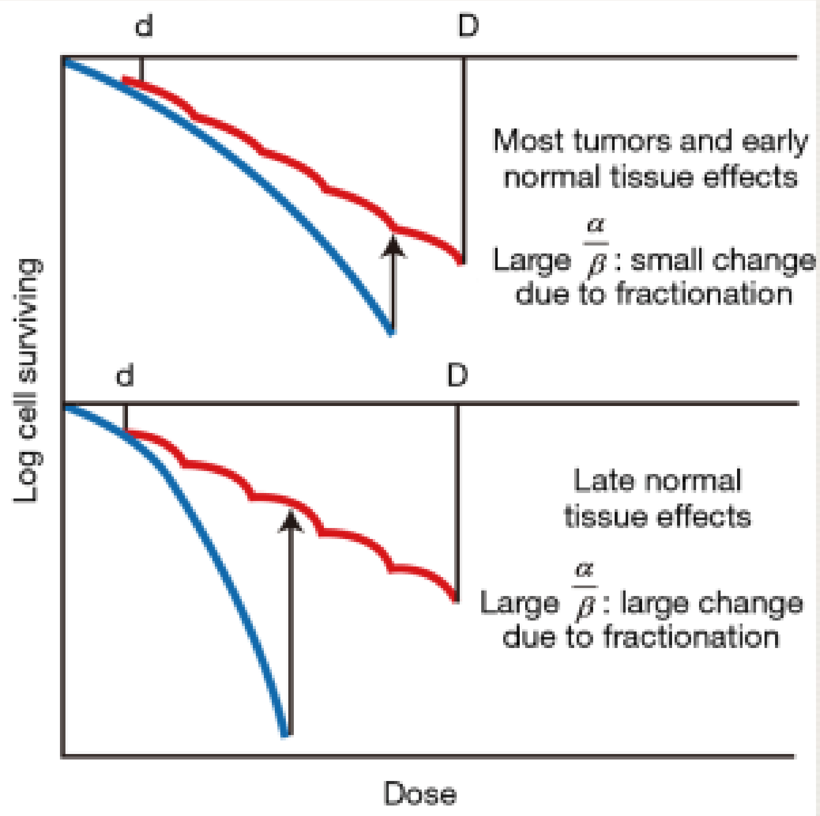
6.4.5 DOSE RATE AND FRACTIONATION

- ☐ **The dose delivered in radiation therapy is usually divided or "fractionated"** over a treatment course lasting multiple weeks (2 Gy dose/fraction over 6 weeks).
- ☐ Fractionation in the context of radiotherapy is the process of dividing a dose of radiation into multiple "fractions".
- ☐ This practice seeks to **maximize the destruction of malignant cells** while **minimizing damage to healthy tissues** → improve the therapeutic ratio
- ☐ 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.**



6.4.5 DOSE RATE AND FRACTIONATION

- Conventional fractionation is explained as follows:
  - Division of dose into multiple fractions allows for: (1) **repair** of sublethal damage between dose fractions and (2) **repopulation** of cells.
  - Repair of sublethal damage is greater for late responding (healthy) tissues, while cancer cells struggle to repair their (unstable) DNA
  - The repopulation of cells is greater for early responding tissues (tumors).
  - Fractionation increases tumor damage through **reoxygenation** and **redistribution** of tumor cells.

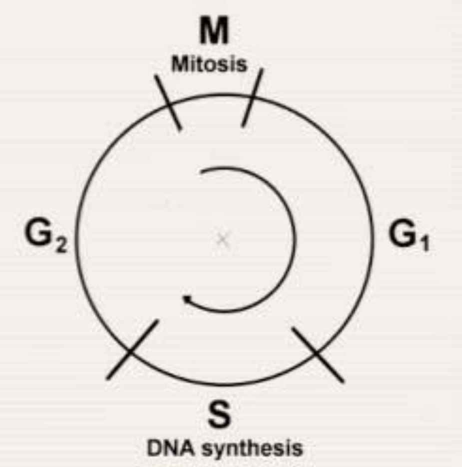


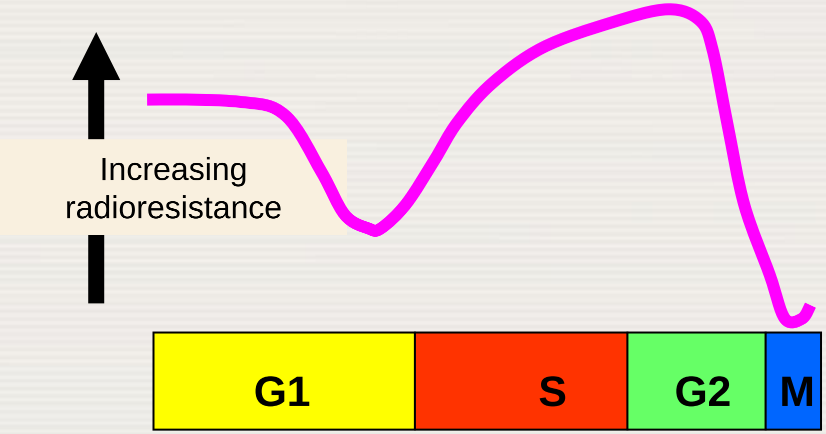
Large dose/fraction more toxic to tissues with low α/β ratio compared to tissues with high α/β ratio

6.2 IRRADIATION OF CELLS

Radiosensitivity differs throughout the cell cycle with, in general:

- late S phase being the most radioresistant
- G_2/M being the most radiosensitive (Cells going through the division phase)
- G_1 phase taking an intermediate position





- The greater proportion of DNA enzymatic repair during late S phase may explain the resistance of late S phase cells
- Poor repair competence (reduced enzyme access due to chromatin compaction) explains the high radiosensitivity in G_2/M phase
- Resting cells in G_0, not involved in the cell cycle, are more resistant to radiation when compared to late S-phase cells

6.4.5 DOSE RATE AND FRACTIONATION

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:

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

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:

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

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

$\mathrm{BED} = Nd(1+Nd/_{\alpha/\beta})$ Biologically Effective Dose

6.4.5 DOSE RATE AND FRACTIONATION

❑ Typical dose rates used in radiotherapy are of the order of:

- **1 Gy/min** in standard radiotherapy
- **0.1 Gy/min** in total body irradiation (TBI).
- **0.01 Gy/min** in brachytherapy

❑ Current standard fractionation is based on:

- 5 daily treatments per week.
- a total treatment time of several weeks.

❑ This regimen reflects:

- Practical aspects of dose delivery to a patient.
- Successful outcome of patient’s treatments.
- Convenience to staff delivering the treatment.

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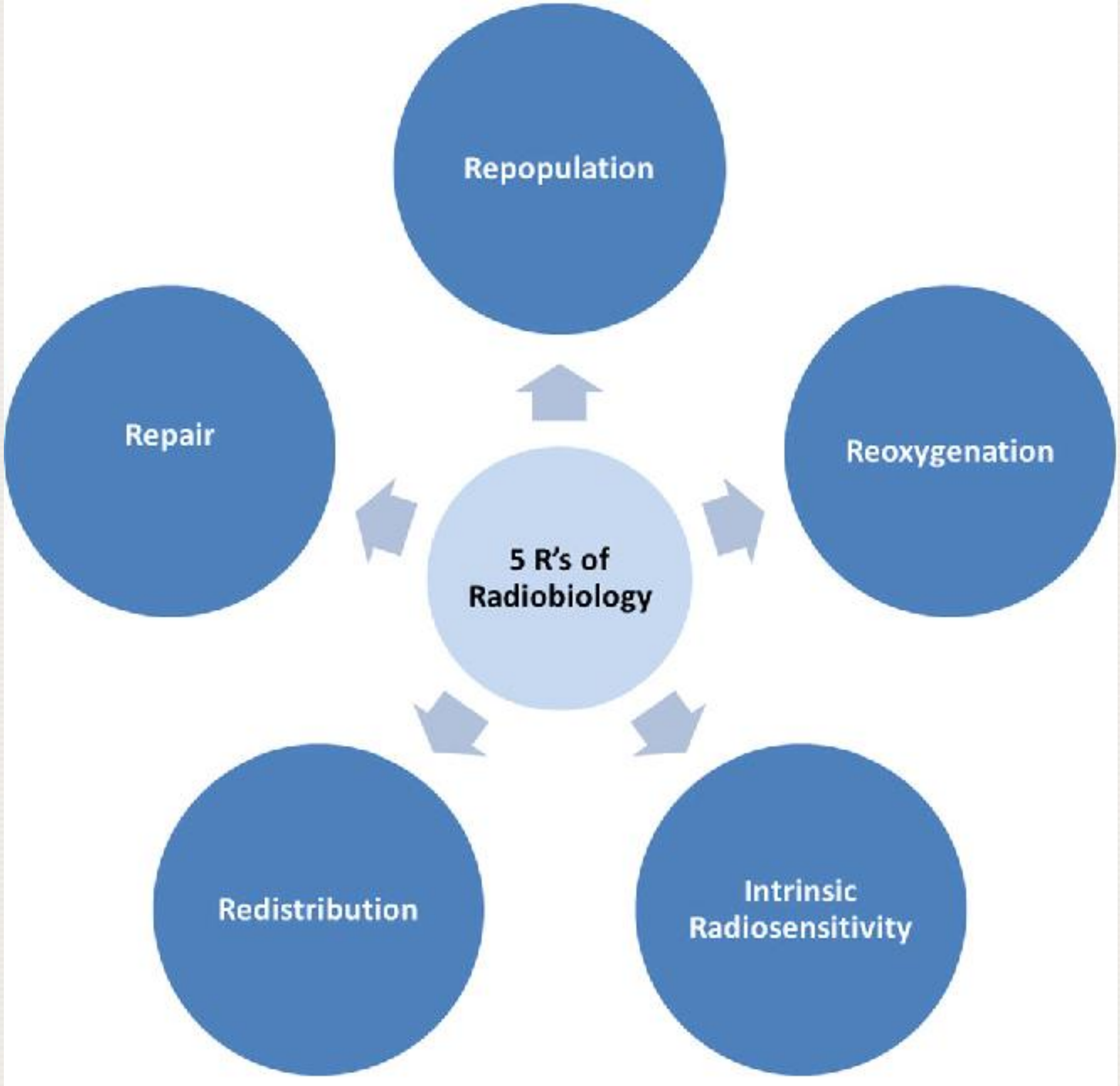
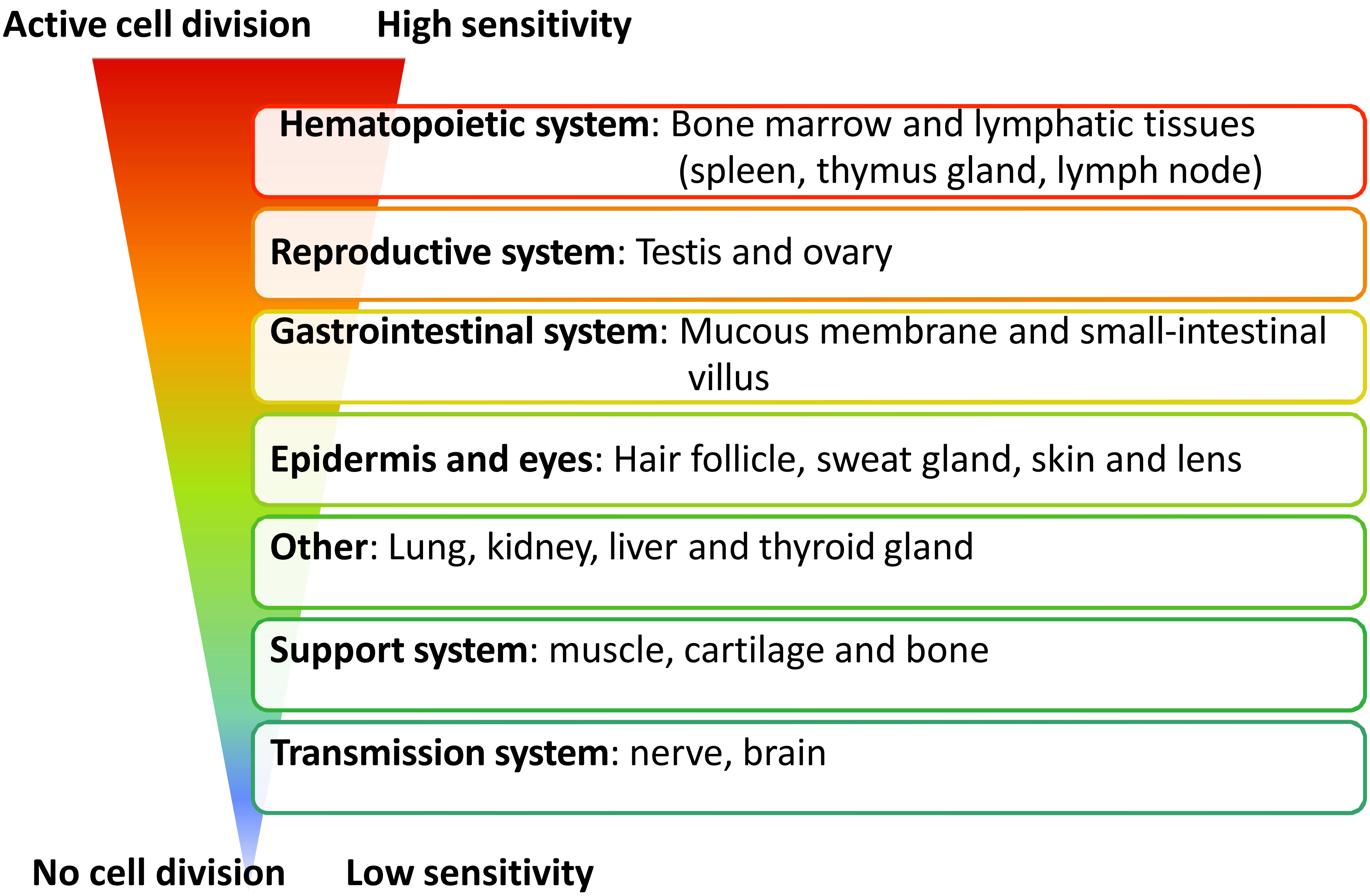


6.4.5 DOSE RATE AND FRACTIONATION

- ☐ Basis of fractionation is rooted in 5 primary biological factors called the **five Rs of radiobiology**:
  - Radiosensitivity. Eukaryotic cells have different radio-sensitivities (see next slide).
  - Redistribution: cells that survive a dose of radiation since in resistant phases of the division cycle, **redistribute into more sensitive phases** of the cell cycle during subsequent doses of radiation.
  - Repair. Healthy eukaryotic cells repair radiation damage easier than cancer cells due to their (unstable) DNA
  - Repopulation. Cells repopulate while receiving fractionated doses of radiation (visible in the shoulders).
  - Reoxygenation of hypoxic cells occurs during a fractionated course of treatment, making them more oxygenated and therefore radiosensitive to subsequent doses of radiation (the tumor cluster is “peeled” like an onion by removing the tumor layers that are oxic).

Radiosensitivity of Organs and Tissues



Active cell division **High sensitivity**

Hematopoietic system: Bone marrow and lymphatic tissues (spleen, thymus gland, lymph node)

Reproductive system: Testis and ovary

Gastrointestinal system: Mucous membrane and small-intestinal villus

Epidermis and eyes: Hair follicle, sweat gland, skin and lens

Other: Lung, kidney, liver and thyroid gland

Support system: muscle, cartilage and bone

Transmission system: nerve, brain

No cell division **Low sensitivity**

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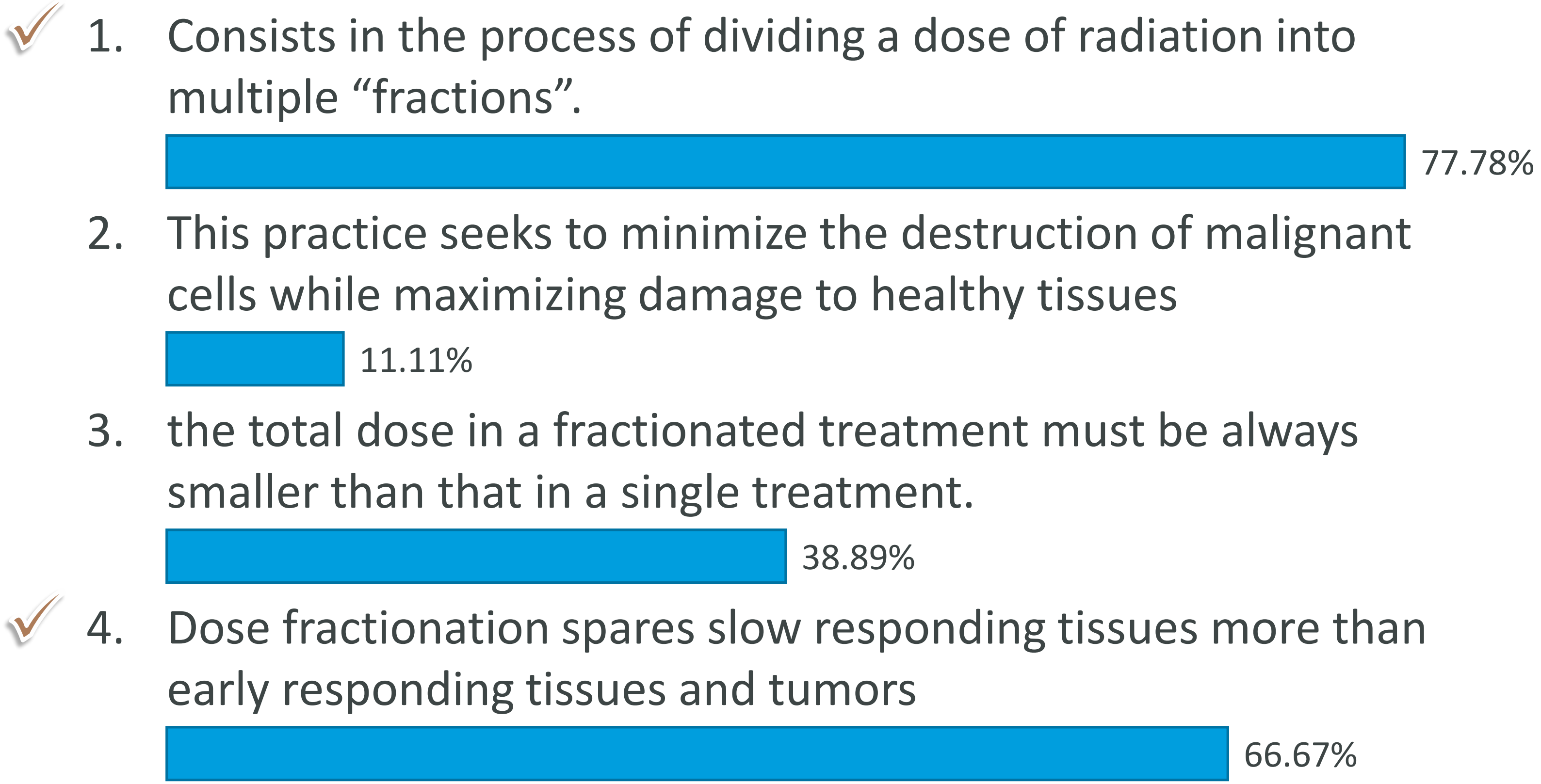
Which of the following statements are TRUE about fractionation

Vote for up to 2 choices



✓ 1. Consists in the process of dividing a dose of radiation into multiple “fractions”.

77.78%

2. This practice seeks to minimize the destruction of malignant cells while maximizing damage to healthy tissues

11.11%

3. the total dose in a fractionated treatment must be always smaller than that in a single treatment.

38.89%

✓ 4. Dose fractionation spares slow responding tissues more than early responding tissues and tumors

66.67%

(% = Percentage of Voters)

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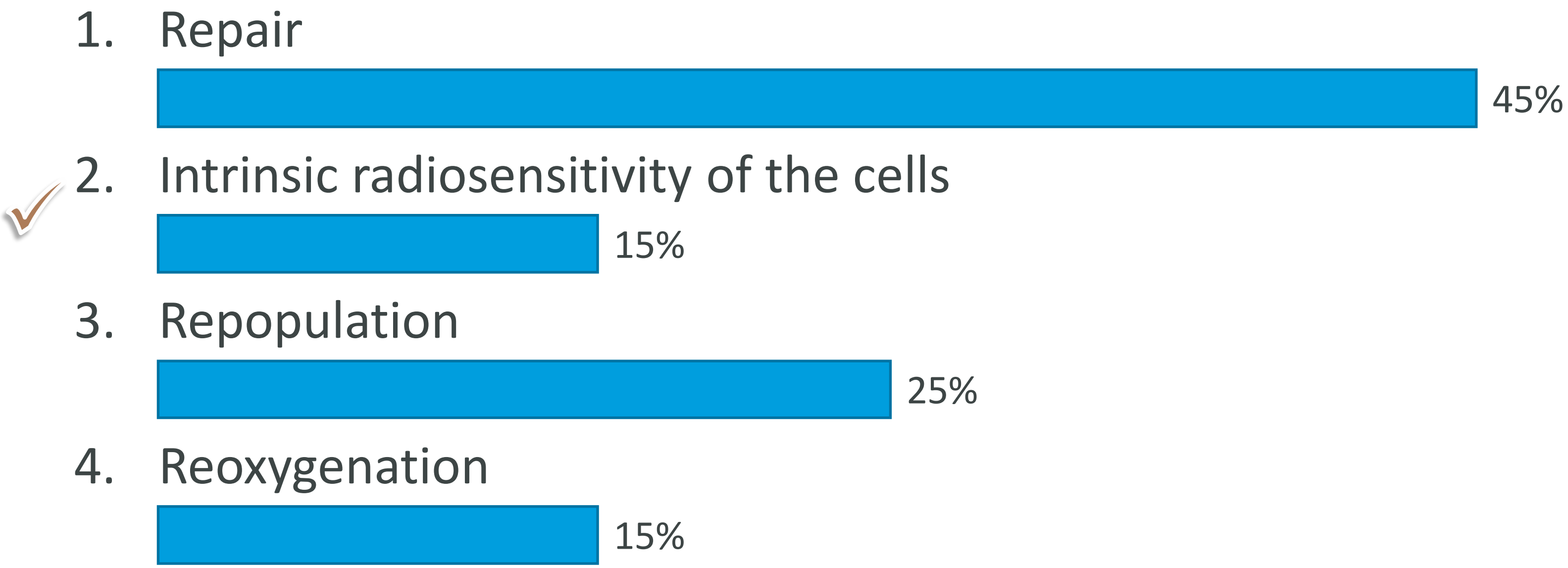
Which of the following radiobiological phenomena occurring between dose fractions has little or no effect on TUMOR TISSUE radiation responses?



1. Repair
   45%
2. ✓ Intrinsic radiosensitivity of the cells
   15%
3. Repopulation
   25%
4. Reoxygenation
   15%

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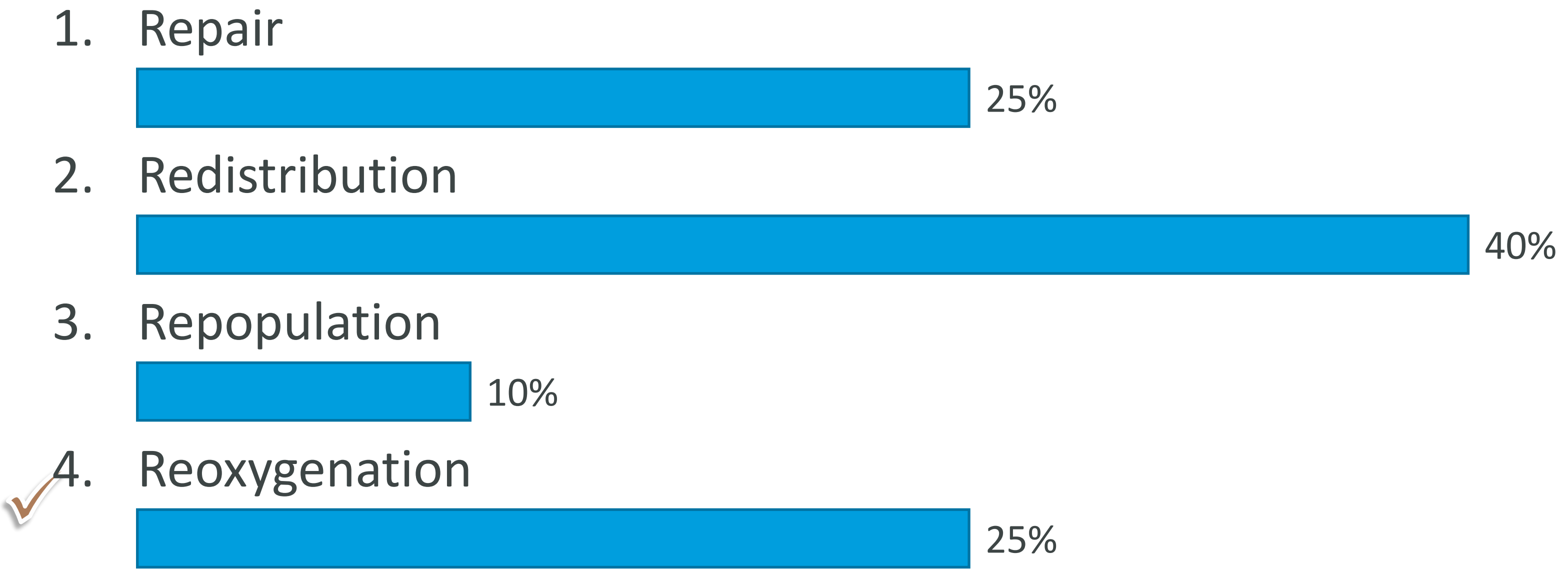
Which of the following radiobiological phenomena occurring between dose fractions has little or no effect on NORMAL TISSUE radiation responses?



1. Repair
2. Redistribution
3. Repopulation
4. ✓ Reoxygenation

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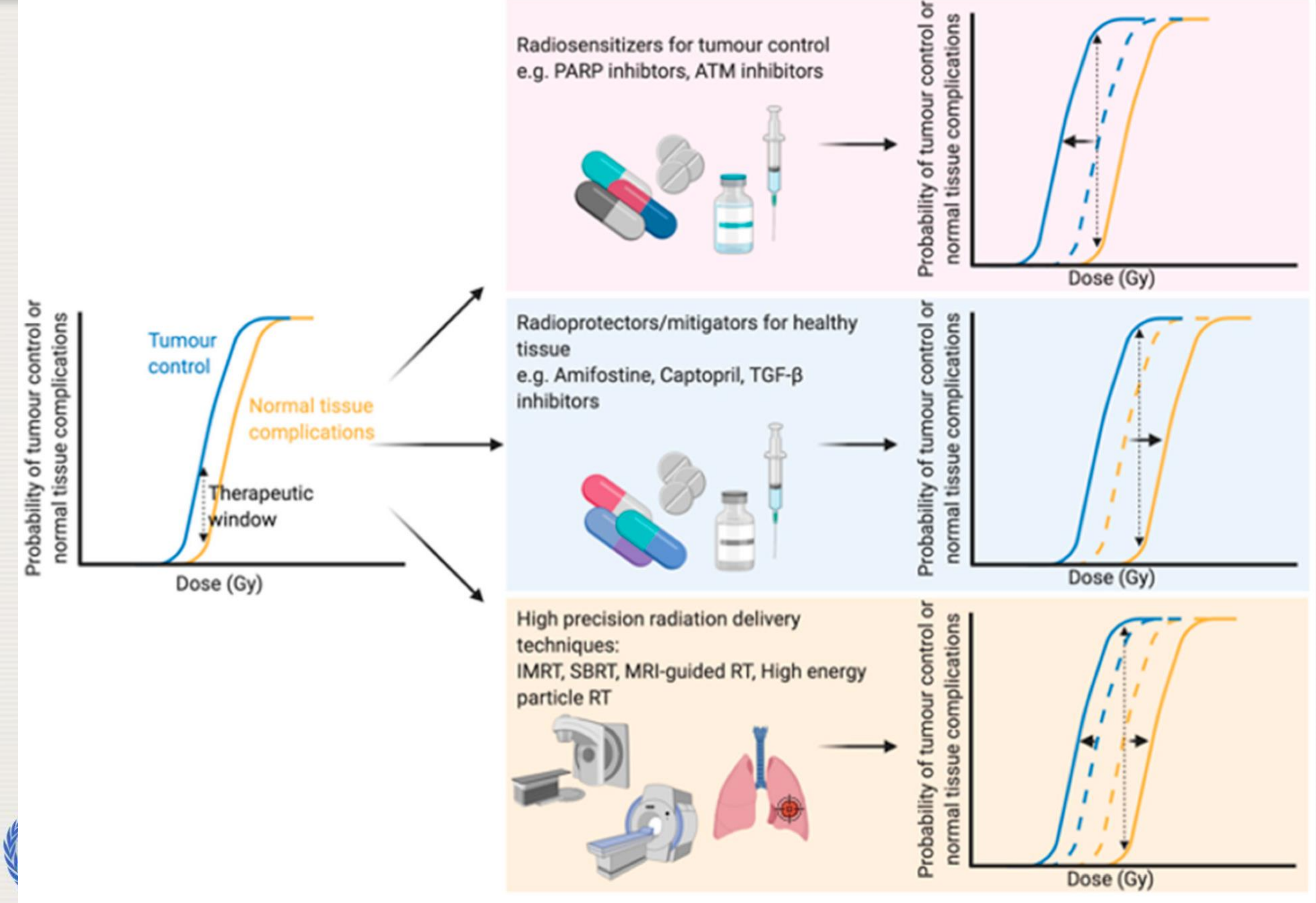
6.4.6 RADIOPROTECTORS AND RADIOSENSITIZERS

- Some chemical agents may alter the 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**.
  - Chemical agents that enhance cell response to radiation are called radiosensitizers. They generally **promote both the direct and indirect effects of radiation and OER.**
  - **Oxygen** is a powerful oxidizing agent and therefore acts as a radiosensitizer if it is present at the time of irradiation

6.4.6 RADIOPROTECTORS AND RADIOSENSITIZERS



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Leaderboard

After 17 questions

1	15/17	1
2nd	14/17	1
3rd	13/17	1
4th	11/17	1
=5th	10/17	3
=8th	9/17	3

FULL LIST ⋮

Average score 6.7

Participants 27

Most difficult question

> Which of the following radiobiological phenomena occurring between dose fractions has little or no effect on TUMOR TISSUE radiation responses?

Correct responses 3

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