Radiation biology

EBreast II

Co-funded by the
Erasmus+ Programme
of the European Union

Introduction

- What is radiation biology/radiobiology?
- Timeline of radiation effects
- Classification of radiation in radiobiology: The Linear Energy Transfer
- The DNA molecule
- Cells, cell cycle and cell death
- Direct and indirect effects of radiation

Introduction

- Effect on irradiated cells from radiation damages.
- Repair of DNA and factors affecting the repair of DNA.
- Mechanism behand early and late effects of radiation.
- Therapeutic Ratio
- The 5 Rs

What is radiobiology?

- A combination of radiation physics and biology.
- The science pertaining to the effects of ionising radiation on biological tissues and living organisms.

(1)

EBreast II

Timeline of radiation effects

Physics
Radiation absorbed, producing
- ions
- excited molecules
- free radicals

Chemistry
Secondary reactions, changes to
- DNA
- proteins
- other molecules

Biology
Biological effects, may cause
- cell death
- mutations
- cancer

Time

< nano-second

< seconds

Days or years

(2)

EBreast II

Classification of radiation in radiobiology: The Linear Energy Transfer

- Linear energy transfer (LET) is defined as the mean energy that a particle deposits per unit length when it passes through a substance.
- Unit of LET: keV/μm.
- High-LET radiation: LET >10 keV/μm
  - Energetic neutrons, protons, and heavy ions
- Low-LET radiation: LET <10 keV/μm
  - X-rays, γ-rays, high-energy electrons

(1)

EBreast II

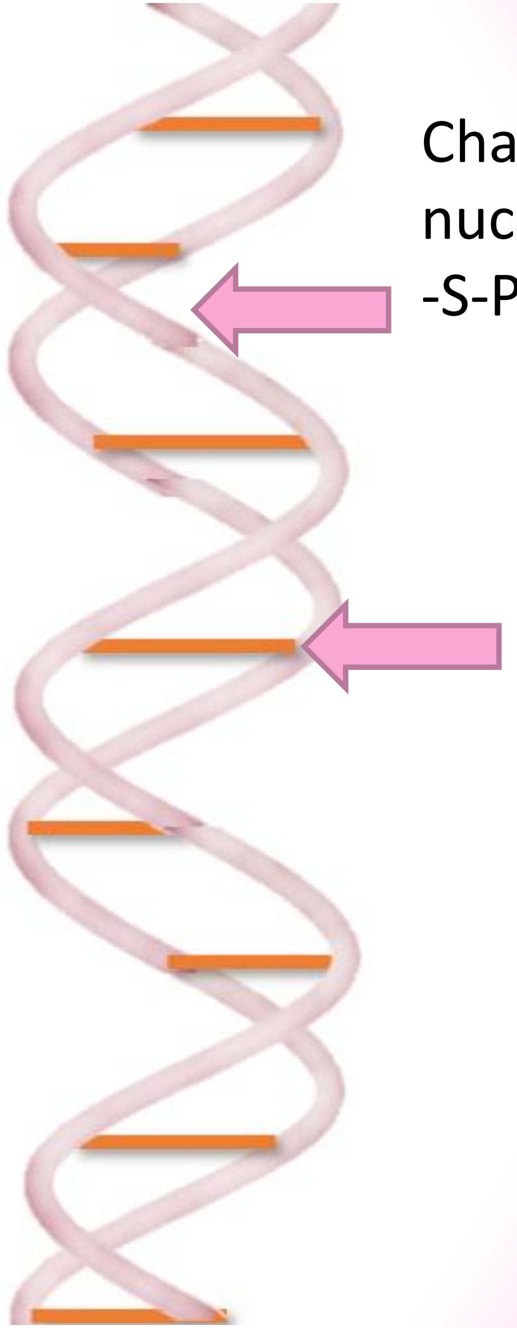
Classification of radiation in radiobiology: The Linear Energy Transfer

- LET values for radiation commonly used in radiation therapy:
  - 250 kV X-rays: 2 keV/μm.
  - Cobalt-60 γ-rays: 0.3 keV/μm.
  - 3 MV X-rays: 0.3 keV/μm.
  - 1 MeV electrons: 0.25 keV/μm.
- LET values for other, less commonly used radiations:
  - 14 MeV neutrons: 12 keV/μm.
  - Heavy ions: 100–200 keV/μm.
  - 1 keV electrons: 12.3 keV/μm.
  - 10 keV electrons: 2.3 keV/μm.

(1)

The DNA molecule

- 6 building blocks: The four bases adenine (A), thymine (T), guanine (G) and cytosine (C), deoxyribose which is a sugar molecule (S), and a phosphate group (P).
- Nucleotide: Phosphate, sugar and a base
- Helix: Chain of nucleotides -S-P-S-P-S-.
- Sugar and phosphate in adjacent nucleotides are bound together by covalent bonds.
- The two chains held together by hydrogen bonds between the bases A and T or the bases C and G.
- ≈ 2m stretched out



(2)

DNA, genes and chromosomes

- Chromosomes consist of genes, and genes consist of tightly packed DNA molecules.
- The genetic information is encoded in the DNA, and the gene consists of a specific sequence of the bases and has a fixed location on one of the chromosomes in the cell nucleus.

Cells

- Contain organic compounds (proteins, carbohydrates, nucleic acids and lipids), as well as inorganic compounds (water and minerals)
- Have two main constituents:
  - Cytoplasm (supports all metabolic functions within the cells)
  - Nucleus (contains the genetic information- DNA)
- Human cells are either
  - Somatic cells
  - Germ cells

(1)

Cells, tissues, organs, and organisms

- Somatic cells are classified as
  - Stem cells- self perpetuate and produce cells for a differentiated cell population
  - Transit cells- cells in movement to another cell population
  - Mature cells- fully differentiated and without mitotic activity
- Tissue:
  - A group of cells that perform one or more functions together
- Organ:
  - A group of tissues that perform one or more functions together
- Organism:
  - A group of organs that perform one or more functions together

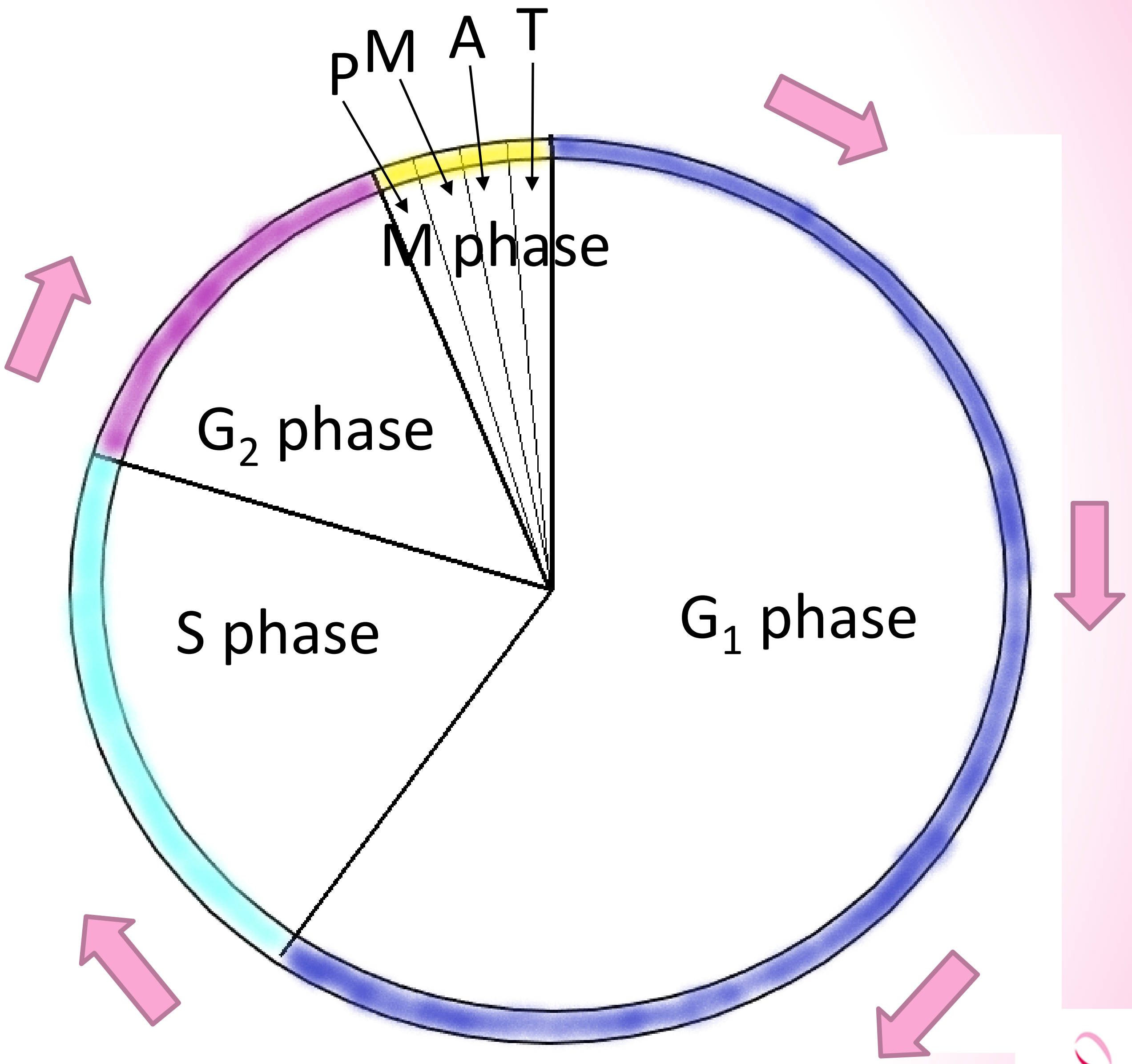
Cell division

- Somatic cells:
  - Mitosis- two identical cells, equal to the cell that divided, with the same number of chromosomes
  - The new cells may undergo further division, continuing the process
- Germ cells:
  - Meiosis- new cells that contain half of the chromosomes of the cell that divided, one pair of each chromosome pair is selected

(1)

Cell cycle

- G_1 phase: Resting phase after Mitosis, normal metabolism
- S phase: the period of DNA synthesising
- G_2 phase: the cell matures before Mitosis
- M phase: the Mitosis takes place
- ≈ 30 hours
- Some stem cell cycles take up to 10 days



(3, p. 142, 4)

EBreast II

Cell cycle and Cell death

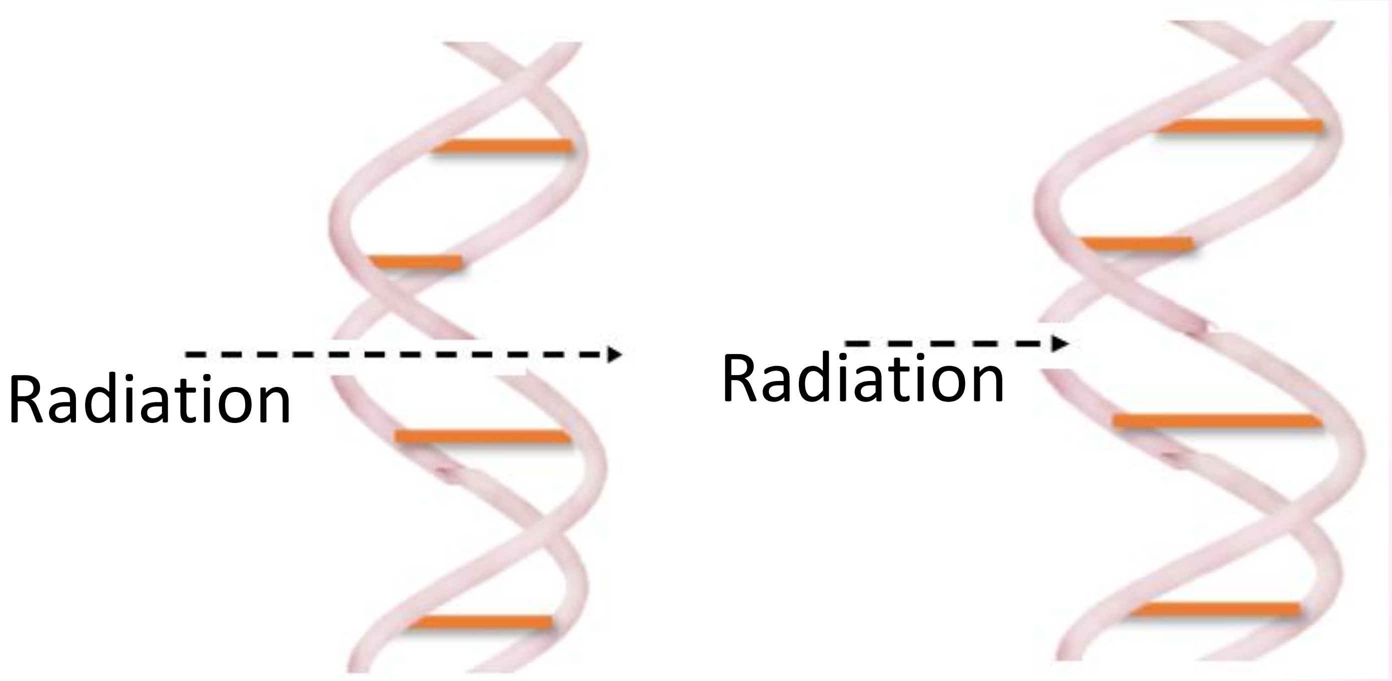
- The cells are most sensitive to radiation in the M phase and in the G_2 phase, and least sensitive to radiation in the latter part of the S phase.
- For cells that cannot divide, cell death is defined as the loss of a specific function.
- For stem cells or other cells that can divide, cell death is defined as the loss of the ability to reproduce.

(1)

Ionising radiation can cause DNA damages

- Double-strand breaks
- Single-strand breaks

- Direct effects
- Indirect effects

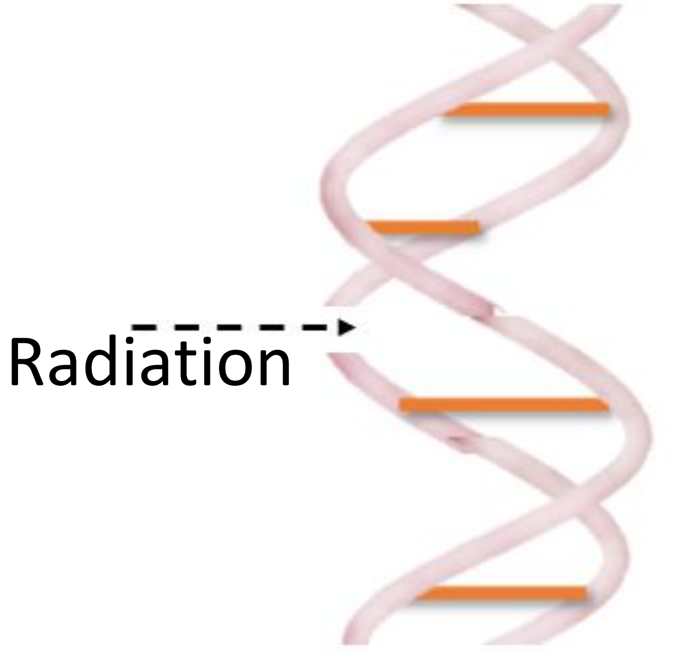


(3)

EBreast II

Direct effect

- Interaction between radiation and the DNA molecule.
- Ionisation and strand break.
- Dominant process for interaction between "high-LET" radiation and biological material

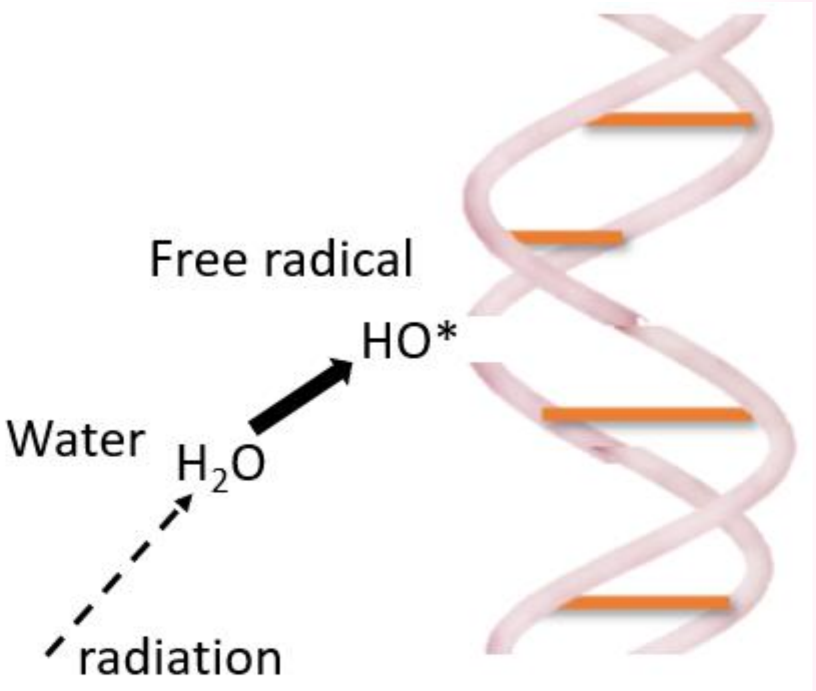


(3)

Indirect effect

- Interaction between radiation and water molecule in cell
- Ions and free radicals are formed
- Chemical reaction between radical and DNA which, in interaction with DNA, leads to ionisation and strand break.
- Dominant process for interaction between "low - LET" radiation (e.g. X-rays) and biological material

(3)



EBreast II

Formation of free radicals: radiolysis of water

- Radiolysis of water leads to the formation of an ion pair, H + and OH-, and the formation of two free radicals H * and OH *
- The ions can recombine and form water molecules, or react chemically with macromolecules like DNA
- The free radicals are very reactive and may create changes in the DNA through strand break.

H_2O + radiation -> $HOH^+ + e^-$

$H_2O + e^-$ -> HOH^-

HOH^+ -> H^+ + OH*

HOH^- -> OH^- + H*

OH* + OH* -> H_2O_2

(5)

EBreast II

Indirect effect- a 4 step process

1. Primary photon interaction -> a free high energy electron
2. High energy electron moves through tissue -> free radicals in water
3. Free radicals may produce changes in DNA from breakage of chemical bonds
4. Changes of chemical bonds result in biological effects

(1)

Effect on irradiated cells from radiation damages

- No effect.
- Division delay.
- Apoptosis.
- Reproductive failure.
- Genomic instability.
- Mutation.
- Transformation.
- Bystander effects.
- Adaptive responses.

(1)

EBreast II

Repair of DNA damages

- After irradiation, the damaged cell immediately begins to repair the damage to the DNA molecule
- Single-strand break: the DNA molecule is repaired using the undamaged strand as a template
- Double-strand break: there is no undamaged template, giving a higher probability of cell death

(2,3)

Repair of DNA damages

- After approximately half an hour, most damage to the cell is repaired.
- It takes at least 6 hours before the entire DNA molecule is repaired.
- Stop cell division -> avoid cell division that leads to cell death.

(3)

Factors affecting the probability of cell repair

- The "ability" to stop the division process to allow time for repair.
- The phase of cell division.
- Number of damages to the DNA.
- Tumour cells are more sensitive to radiation than normal cells.

(3)

Early and late effects of radiation

- Quicker cell division results in earlier occurrence of damage from radiation.
- Damage to tumour tissue occurs early
- Damage to healthy tissue occurs early or late; by hours, by days, by months or by years…
- The organs in the body are made up of three different types of cells:
    - Stem cells - produces cells for different cell groups
    - Flexible cells (cells that divide as needed)
    - Non-proliferating cells (cells that do not divide)

(3)

Early effects of radiation: tissues that originate from stem-cells

- Examples: Skin tissue, mucous membranes, blood-building organs, and reproductive organs
- Stem cells divide into mature cells and also into new stem cells.
- Organs that originate from stem cells develop acute radiation reactions which appear after a few days, when the mature cells are replaced).
- To compensate for the cell death among the stem cells, the cell division increases, and the time of the cell cycle decreases among the remaining stem cells.

(3)

Late effects of radiation

- Organs consisting of flexible cells, i.e. cells that divide as needed. Examples: Liver, kidney
- Injuries show up after several months and worsen with time
- The damage appears late as there is little need for cell division
- Often chronic.

(3)

Late effects of radiation

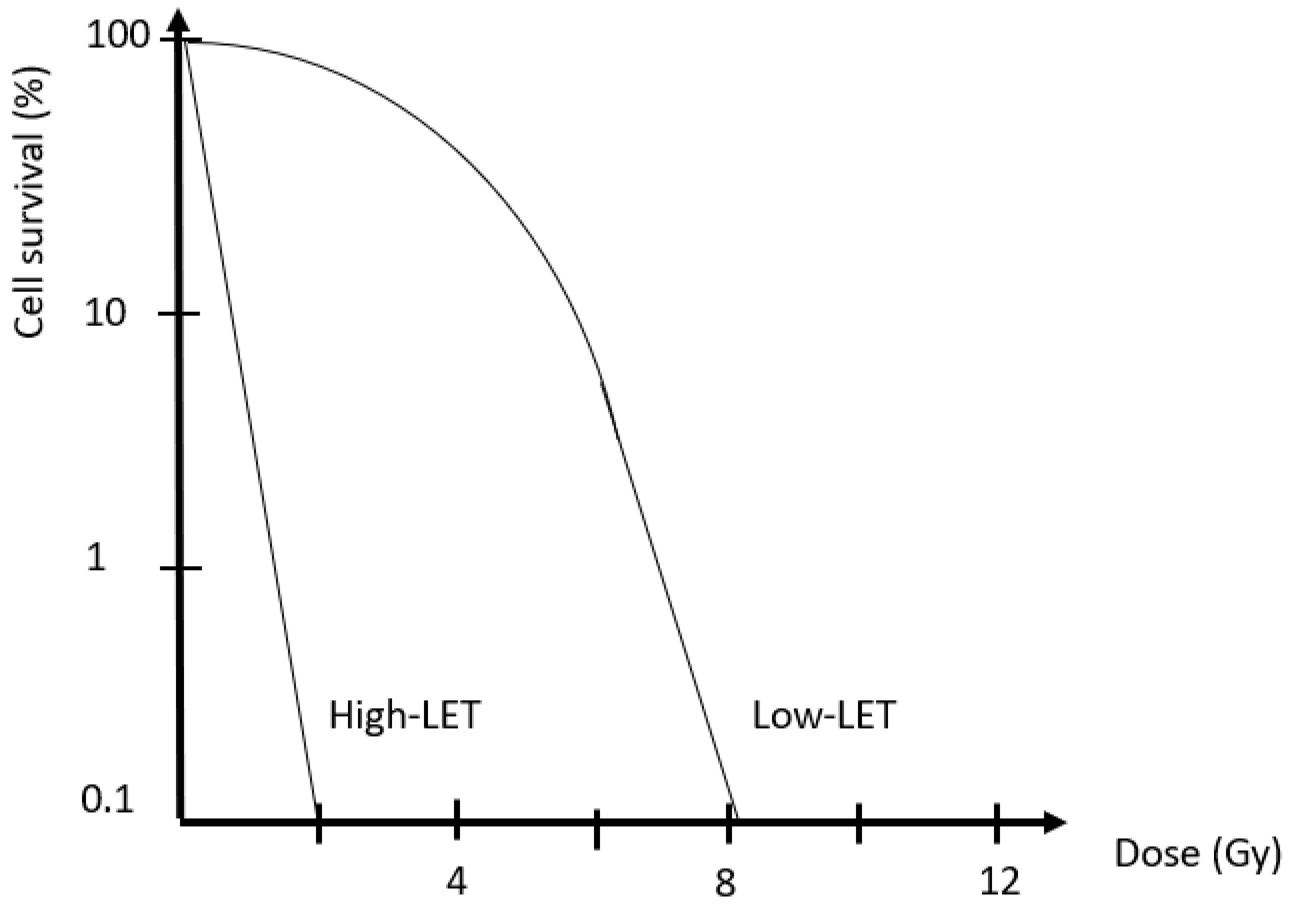
- Non-proliferating tissues (e.g. brain tissue and muscle tissue) do not undergo cell division, and thus can withstand relatively high doses.
- Cannot be replaced if damaged, and permanent damage to the organ occurs.

(3)

EBreast II

Cell survival curves

- Survival fraction as a function of absorbed dose
- High-LET versus Low-LET radiation (1)



EBreast II

Factors affecting the cell's sensitivity to radiation

- Oxygen concentration in the cell
- Protectors and sensitizers (medicines)
- Fractionation
- Different fractionation patterns
- Radiation sensitivity of the tumour
- Radiation therapy combined with medical oncology treatment

(3)

Oxygen concentration in the cells, fractionation, and sensitivity to radiation

- Production of free radicals increases when oxygen is present in the irradiated cells
- Cells with normal oxygen supply can be 2.5 to 3 times as sensitive to radiation as cells with poor oxygen supply (hypoxic cells)
- Healthy tissue has a good supply of oxygen
- There are hypoxic cells in the centre of the tumour (already in tumours of 0.1-0.2 mm, a core of necrotized cells is formed)

(3)

Oxygen concentration in the cells, fractionation, and sensitivity to radiation

- In the border area of the necrotized cells, the necrosis, there are hypoxic cells that are not particularly affected by the radiation.
- The tumour will decrease gradually during the treatment, and the oxygen concentration in this border area will increase; this is called **reoxygenation**.
- The dose is fractionated to give hypoxic tumour cells time to reoxygenate.
- The sensitivity to radiation of the cells varies during the cell cycle. Cells that were in a state less sensitive to radiation at one fraction may be in a phase more sensitive to radiation at the next fraction. This is called **redistribution.**

(3)

EBreast II

Therapeutic ratio (TR)

- The goal of radiation therapy is to achieve cell death in all tumour cells, while protecting healthy cells.
- In practice, it is not possible to protect all healthy cells from radiation.
- Cancer cells and healthy cells have different sensitivity to radiation, and this difference is related to the Therapeutic ratio (TR)

(3)

Therapeutic ratio (TR)

TCP: Tumor control probability

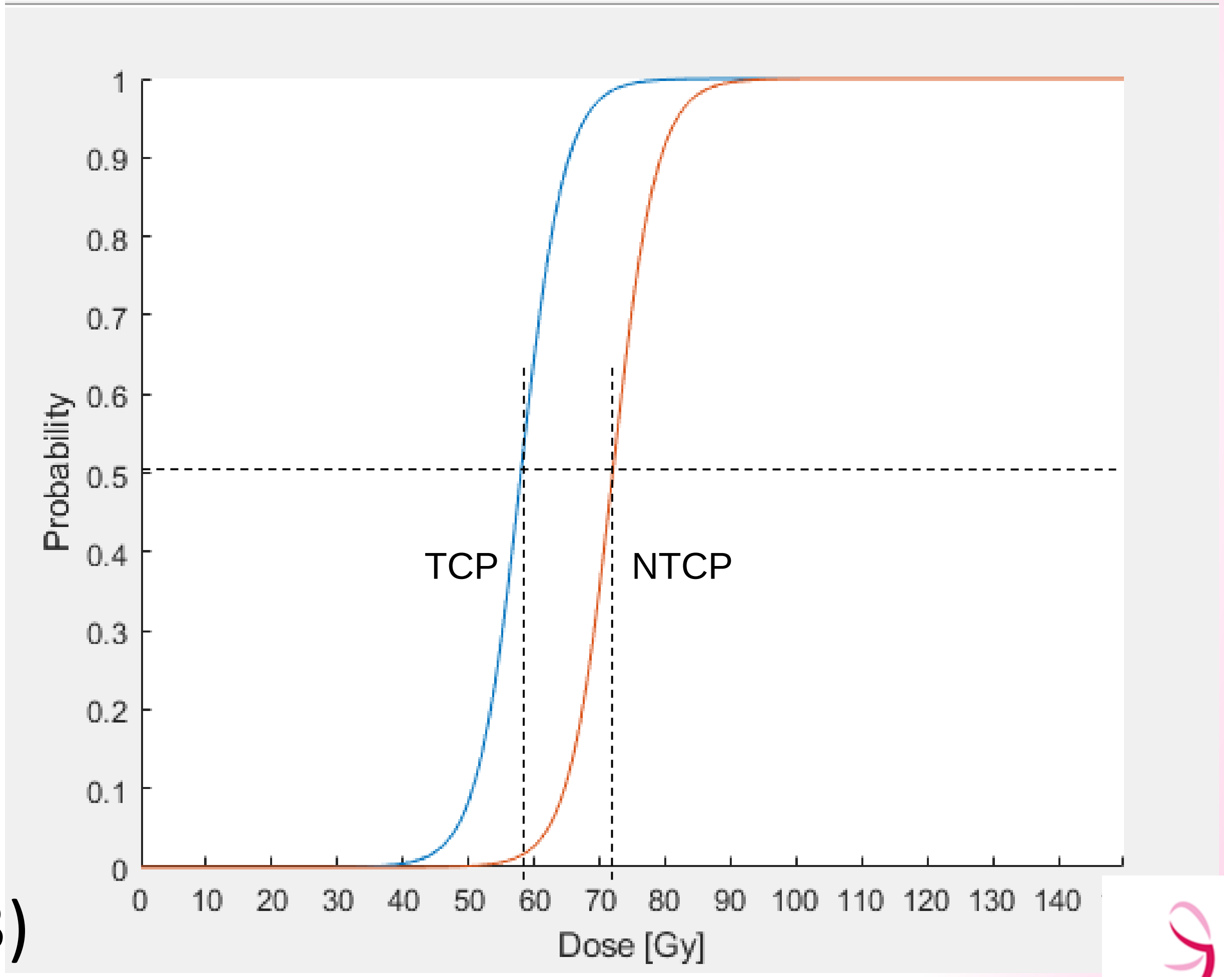
NPTC: Normal tissue complication probability

Example:

If TPC =0.5 for a dose of 58 Gy

and NTPC =0.5 for a dose of 72 Gy

TR = 72Gy/58Gy = 1.24 (3)

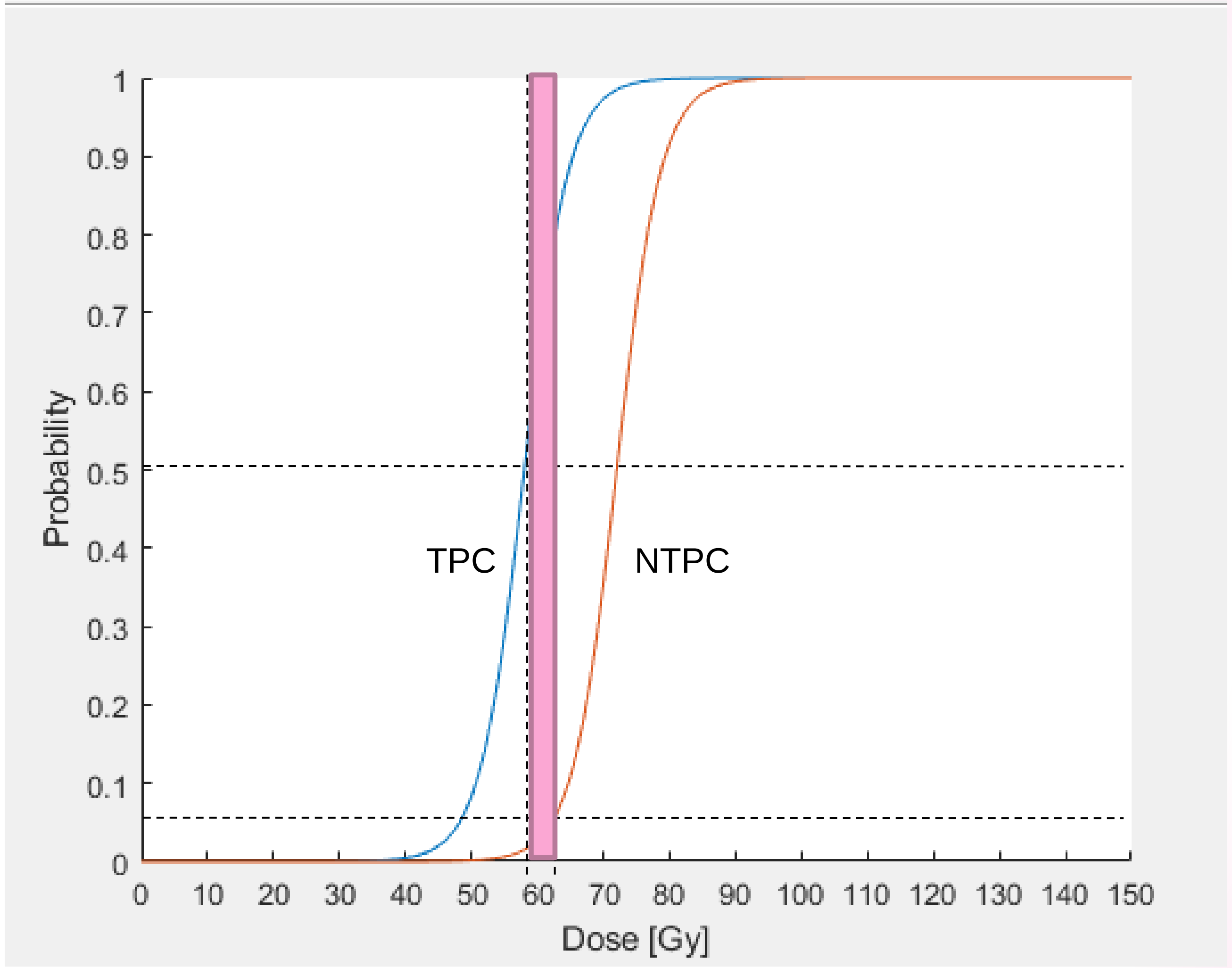


(3)

EBreast II

Therapeutic Ratio (TR)

- Optimal choice of dose maximises TCP and minimises NTCP. For a typical good radiation treatment, TCP ≥ 0.5 and NTCP ≤ 0.05 (2)
- Curves and TR varies
- Doses are fractionated



(3)

The basis of fractionation: The 5 Rs of radiation treatment

- Radiosensitivity
- Repair
- Repopulation
- Redistribution
- Reoxygenation

(1)

References

1. Suntharalingam N, Podgorsak EB, Hendry JH. Basic radiobiology. In: Podgorsak EB, editor. Radiation oncology physics: A handbook for teachers and students: IAEA; 2005. p. 485-504.
2. Henriksen T. Radiation and Health: University of Oslo; 2015
3. Degerfält J, Moegelin I-M, Sharp L. Strålbehandling: Studentlitteratur AB; 2008.
4. Bøhle K. Celledeling: mitose og meiose: NDLA; 2020 [updated 2020; cited 2023 Mar 27] Available from: https://ndla.no/article/23403
5. Forshier S. Essentials of radiation biology and protection. 2 ed. Albany, Delmar: Thomson Learning; 2008.

EBreast II

Author

Mona Øynes

Western Norway University of Applied Sciences

EBreast II

OAMK
OULU UNIVERSITY OF APPLIED SCIENCES

Metropolia
University of Applied Sciences

movetia
Austausch und Mobilität
Echanges et mobilité
Scambi e mobilità
Exchange and mobility

TARTU TERVISHOIU KÕRGKOOL
TARTU HEALTH CARE COLLEGE

EBreast II

Co-funded by the Erasmus+ Programme of the European Union

HESAV
HAUTE ÉCOLE DE SANTÉ VAUD

Hes·so
Haute Ecole Spécialisée de Suisse occidentale
Fachhochschule Westschweiz
University of Applied Sciences and Arts Western Switzerland

Tartu University Hospital

HELSE BERGEN
Haukeland University Hospital

Western Norway University of Applied Sciences