Radiation Therapy

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Introduction

- Radiation therapy (also called **radiotherapy**) is **a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors**.
- Based on the principles of radiobiology, the total dose of radiation prescribed to treat a particular tumor is divided into a number of **daily doses** or **fractions**.
- This aims to **protect** normal surrounding tissue while **maximizing** the radiation effect on the tumor.

Introduction

- Radiation therapy can be **external** beam therapy and **brachytherapy**.
- It can be with **curative** or **palliative** intent.
- A curative intent aim to **cure** a disease but a palliative treatment mainly aim to **reduce** and **manage** complications due to cancer such as **Pain management**.

Introduction

Introduction

- Radiobiology studies the interactions of ionizing radiation on atomic and molecular structures and consequently their induced effects on cells, tissues, and organs, both normal and diseased.
- As such, radiobiology **enhances the understanding of biological outcome (harm or benefit) from ionizing radiation exposure**.
- The knowledge of radiobiology is very important in radiation therapy as it enhance a better **control of a tumor** with **reduced complication** to normal tissues.

Fractionation

- Radiation therapy is delivered to your cancer in small doses called **fractions.**
- Radiation oncologist prescribe a **total dose** which is then divided into **smaller doses,** or fractions.
- The amount of radiation received is measured in **centigray** or **cGy.** A fraction (dose) is given each day and repeated over many days to add up to the total dose of radiation.
- Radiation is usually given 5 days a week, most often Monday-Friday, this gives your cells 2 days each week to repair themselves.

Fractionation

- Factors affecting the decision on the type and number of fraction a patient will receive includes

✓Type of cancer.

✓Size and location of the tumor.

✓General patient health.

✓How well the patient will be able to stick with treatment.

✓Other cancer treatments the patient is receiving.

Types of Fractionation

- **Conventional Fractionation**

✓ Doses ranging from 180cGy to 200cGy.

✓ Given once a day, 5 days a week.

✓ Given over 6-7 weeks.

✓ This is the most common type of fractionation and is used in many types of cancer.

Types of Fractionation

- **Hyperfractionation**

✓ Twice a day treatment (6 hours or more apart).

✓ Smaller doses per fraction.

✓ Given over the same number of days and weeks as conventional fractionation.

✓ Examples of cancer treated with hyperfractionation:

  - Breast cancer
  - Head and neck cancer

Types of Fractionation

- **Hypofractionation**
- ✓ Given over fewer days and weeks than conventional radiation.
- ✓ Treatment doses per fraction are higher.
- ✓ Treatment is sometimes not given every day.
- ✓ Can make the treatment course much shorter. This is not appropriate for all cancer types.
- ✓ Examples of cancers treated with hypofractionation:
    - Gynecological cancers
    - Palliative cancer cases
    - Any type of cancer treated with stereotactic radiation therapy (SBRT)

Types of Fractionation

- **Accelerated Fractionation**

✓ Given in smaller doses and more than once a day.

✓ The total dose of radiation is given over a shorter period of time (fewer days).

✓ Example of cancers treated with accelerated fractionation:

  - Breast
  - Head and neck cancers
  - Stem cell transplant patients (TBI or total body irradiation)

Types of Fractionation

- **Palliative Treatment Fractionation**

✓ A treatment used to manage symptoms in cancer that is not curable.

✓ The 1st to 3rd treatment fractions are delivered at a higher dose to relieve symptoms quickly.

✓ Between 350cgy-400cGy per fraction for doses 1-3.

✓ Doses then are reduced to around 200cGy per fraction.

✓ Palliative treatment fraction can be given for all disease types.

Types of Fractionation

Main characteristics of the conventional and altered fractionation schedules.

Fractionation regimen	Conventional	Hyperfractionated	Accelerated
Aim	To control the tumour through redistribution and reoxygenation at the same time as sparing normal tissue through repair and repopulation	To exploit the differences in radiosensitivity of tumour and healthy cells	To overcome tumour repopulation during treatment
Dose/fraction	2 Gy	<2 Gy	≥2 Gy
Number of fractions/day	1	2–3	1
Days of treatment/ week	5	5	6
Overall dose	70 Gy	≥70 Gy	<70 Gy
Overall treatment time	7 weeks	7 weeks	5 weeks

Four Rs

- The fundamental principles of radiobiology are **repair**, **redistribution**, **reoxygenation**, **and repopulation**.
- These are known as the "**Four Rs**" of radiobiology and they are of clinical importance in clinical radiation therapy.
- **Radiosensitivity (Radioresistance)** R is also on research to be added as the fifth R of radiobiology
- Radio sensitivity is **the relative susceptibility of cells, tissues, organs, organisms, or other substances to the injurious action of radiation**.
- Cell radio sensitivity is directly proportional to the rate of cell division and inversely proportional to the degree of cell differentiation.

Four Rs

- In general success or failure of standard clinical radiation treatment is determined by the 4 Rs of radiobiology.

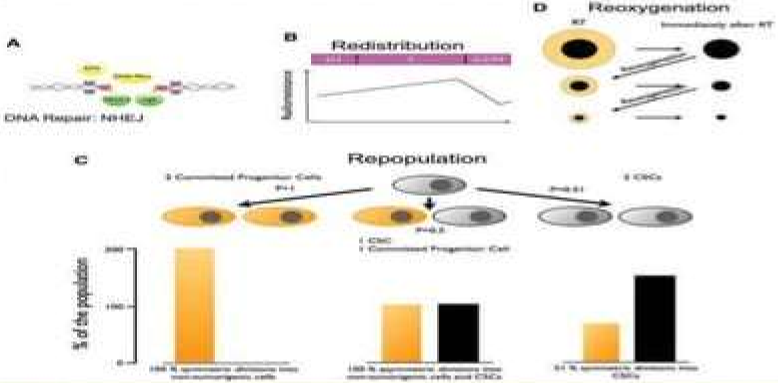
✓ Repair of DNA damage

✓ Redistribution of cells in the cell cycle

✓ Repopulation

✓ Reoxygenation of hypoxic tumor cells

Four Rs



A
DNA Repair: NHEJ
B
Redistribution
D
Reoxygenation
C
Repopulation
% of the population

Four Rs

Repair of DNA damage

- DNA repair occurs during two consecutive radiotherapy fractions
- Unrepaired sublethal DNA damage can be converted into lethal damage in the next fraction
- Ketogenic therapy improves DNA repair of normal cells and impairs DNA repair in tumor cells

Repopulation

- Tumor cell repopulation occurs between two consecutive radiotherapy fractions
- Tumors can exhibit accelerated repopulation when overall treatment duration gets too long
- Ketogenic therapy counters tumor cell repopulation

Redistribution in the cell cycle

- Cells exhibit different radiosensitivity depending on their cell cycle phase
- One single radiotherapy fraction predominantly kills proliferating cells in the radiosensitive late G2 and M phase
- Normal cells activate cell cycle checkpoints and remain in relatively radioresistant phases of the cell cycle; these checkpoints can be overridden by oncogene activation in tumor cells
- Ketogenic therapy favors a redistribution of normal cells into a non-dividing, more radioresistant state

Reoxygenation

- Oxygen acts as a radiosensitizer, and hypoxic tumor areas are up to three times more protected against ionizing radiation
- Reoxygenation of hypoxic tumor areas can occur after a radiotherapy fraction, increasing their radiosensitivity in the following fraction
- Ketogenic therapy puts pressure on hypoxic tumor cells by reducing blood glucose levels, eventually cutting these cells off their glucose supply
- Ketogenic therapy may affect tumor angiogenesis in a way that normalizes vascularization

Radioresistance

- This refers to the intrinsic radioresistance of a cell which is strongly connected to metabolism
- By upregulating glycolysis, tumor cells can become "anti-oxidative strongholds", producing large amounts of reducing substances against ROS and RNS
- Ketogenic therapy decreases glycolysis, forcing tumor cells to switch to inefficient mitochondrial metabolism, which leads to ATP depletion and additional ROS production
- Normal cells with functional mitochondria benefit from ketone body metabolism by decreasing the redox potential of the [NADP+]/[NADPH] couple, the most important anti-oxidant system in the body

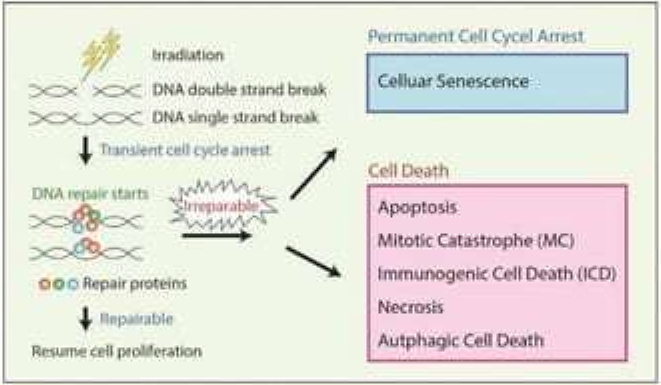
Repair

- Repair involves the fixing of sub lethal damage which are reversible.
- It involves fixing of normal cells hence improves cell survival. It is one of the reasons for fractionated radiation therapy.
- In irradiated cells, a number of DNA lesions are induced including single (SSB) and double-strand breaks (DSB). SSBs are corrected by the part of base excision repair (BER) known as single-strand break repair (SSBR).

Repair

- It involves
- ✓ Base excision repair
- ✓ Nucleotide excision repair
- ✓ Mismatch repair
- ✓ Cross links repair

Repair



Irradiation
DNA double strand break
DNA single strand break
Transient cell cycle arrest
DNA repair starts
Irreparable
Repair proteins
Repairable
Resume cell proliferation
Permanent Cell Cycel Arrest
Celluar Senescence
Cell Death
Apoptosis
Mitotic Catastrophe (MC)
Immunogenic Cell Death (ICD)
Necrosis
Autphagic Cell Death

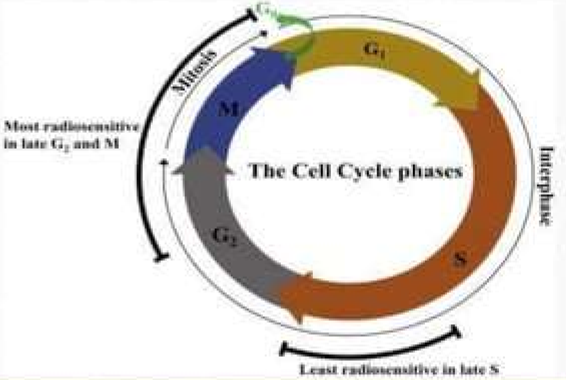
Redistribution

- Reassortment (redistribution) is progression of survived cells through the cell cycle during the interval between the split doses i.e.
- Cell in reassortment state are said to be synchronized and Movement of cells to sensitive phase reduce cell survival.
- **Cell synchronization** is a process by which cells in a culture at different stages of the cell cycle are brought to the same phase.

✓ S phase(Resistant phase)

✓ M phase(Sensitive phase)

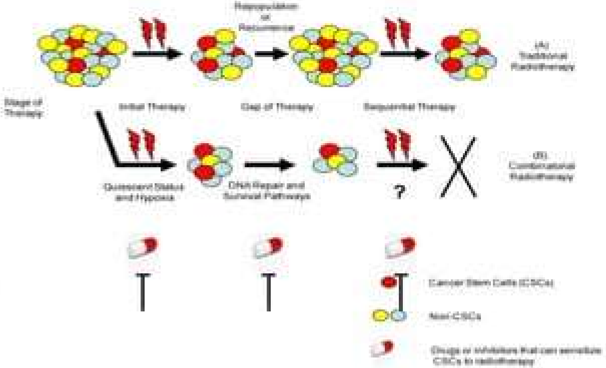
Redistribution



Repopulation

- Repopulation is the increase in cell division of normal and malignant cells at some point after irradiation.
- Repopulation is the **rapid proliferation of surviving tumor cells after radiation induced cell killing.**
- Significant tumor repopulation is common after the first 2 weeks of radiotherapy.

Repopulation

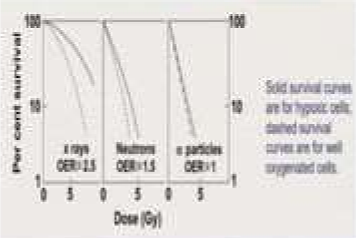


Oxygen effect

- Presence or absence of molecular oxygen within a cell influences the biological effect of radiation
- This is called the oxygen effect.
- The larger is the cell oxygenation above anoxia, the larger is the biological effect of ionizing radiation however a saturation of the effect eventually occurs.

Oxygen effect

- Oxygen effect is more pronounced for low LET (sparsely ionizing) radiation, while for high LET (densely ionizing) radiation it is much less pronounced.
- Oxygen is involved in formation of free radicals for LET radiation.



Oxygen effect

- Ratio of doses without and with oxygen (hypoxic versus well oxygenated cells) to produce the same biological effect is called the oxygen enhancement ratio (OER).
- The OER for x rays and electrons is

✓ About 3 at high doses.

✓ Falls to 2 for doses at 1 – 2 Gy.

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

Reoxygenation

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