

**Radiotherapy:**

Also called radiation therapy, is the branch of medicine that deals with the treatment of some medical conditions especially cancer disease by delivering high-energy radiation beams directly to a tumor, or intended target to destroy or weaken particular cells.

The interaction of radiation with a cell is a matter of chance [probability]. If an interaction occurs, the damage may not be expressed, in fact damage is more frequently repaired. The initial deposition of energy occurs very quickly, The radiation is deposited in the cell randomly and expression of damage occurs after a latent period, ranging from hours to years or even generations. The DNA is the sensitive target in the cell

**Type of radiation:**

1. *Ionizing radiation* → release electron from atom. All kinds of radiation (alpha, Beta particle , electron and gamma ray) except neutrons → (  $e^-$  )
2. *Non-Ionizing radiation* → ( neutrons ) →  $e^-$

In the late 1940, much higher radiation energy became available and started the trend toward megavoltage therapy. A **Betatron**, is a cyclic particle accelerator can accelerate electrons to energy of 45 MeV and produce high intensity and very penetrating X-rays.

**Radiation Dose:**

In the very early days of radiation therapy, the unit that used to measure the amount of radiation to the patient was erythematic dose where,

**Erythematic dose:** Is the quantity of X- rays that cause a reddening of the skin.

And,

**Radiation Dose:** is the change in the amount of radiation energy delivered per unit mass.

$$D (\text{Gy}) = \Delta E (\text{joul}) / \Delta m (\text{Kg})$$

$$D (\text{Rad}) = \Delta E (\text{erg}) / \Delta m (\text{g})$$

**1. Gray:** is a unit used for the absorption of one joule of radiation energy per one kilogram of matter and can be used for any type of radiation in any material (new unit).

**2. Rad (radiation absorbed dose):** it represents the amount of radiation absorbed in erg by an object or person per one gram of matter, it also can be used for any type of radiation in any material (old unit);

Where, **1 Gy = 100 rad**

$$1\text{Rad} = 0.87 \text{ Gy (D in air)}$$

**Exposure:** it is the quotient of  $\Delta Q$  by  $\Delta m$  where:

**$\Delta Q$ :** is the sum of both signs of the charge produced by Ionization of certain volume of air by X-ray &  $\gamma$  rays.

**$\Delta m$ :** is the mass of air.

$$X = \Delta Q / \Delta m = \text{Colum/Kg} \rightarrow \text{(Roentgen, R)}$$

$$X^\circ = X/T \rightarrow \text{R/Sec (exposure rate)}$$

**Roentgen (R):** is the unit that defined only for X-rays &  $\gamma$  rays in air (or defined in term of ionization in air).

$$1\text{R} = 0.87 \text{ Gray} = 87 \text{ Rad}$$

- At the energies used in diagnostic radiology the ratio of rads to roentgens in bone is about 4, that is, 1R exposure results is about 4 rads of absorbed dose.
- At the high energies used in modern radiotherapy the ratio of rads to roentgens is nearly 1 for bone and soft tissue.

## Cancer Treatments:

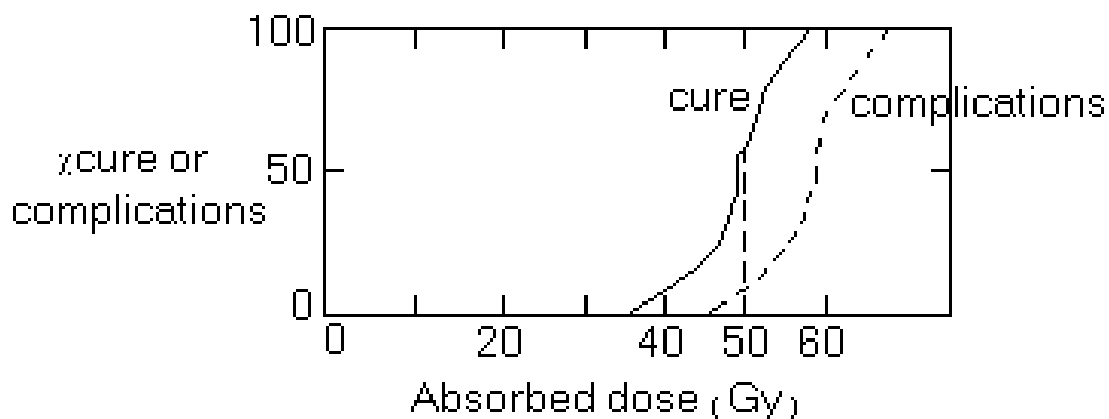
There are three major methods used alone or in combination to treat cancer, surgery, radiation therapy & chemotherapy (drugs).

Factors of significance to the success radiotherapy:

1. Skill of the radiotherapist.
2. Type and extent of the cancer.
3. The physician who specializes in the treatment of cancer with radiation.
4. The kind of radiation used in treatment.
5. Accuracy with which the radiation is administrated to the tumor.

Because of the possibility of radiation induced cancer, it is generally safer to use other types of treatment when it possible.

Small amounts of radiation does not kill the tumor, too much can produce serious complication in normal tissue therefore; the physician must take the exact measurements before exposing the patient to a radiation as shown in the figure below,



**Figure1. Local cure and severe complications depends on the dose in the treatment of the cancer with radiation therapy.**

The solid line shows the percentage of cure of the local tumor as a function of dose for a large number of patients with the same type of tumor while the dashed line shows the percentage of severe complication as a function of dose.

An error of 5% to 10% in the radiation dose to the tumor can have a significant effect on the results of the therapy.

## Principles of radiation therapy:

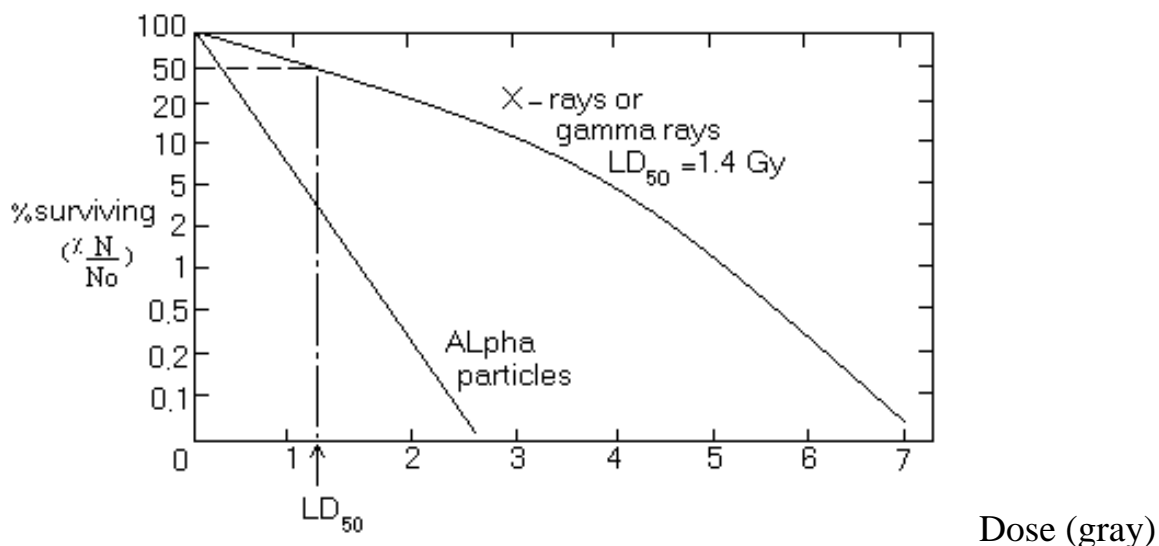
The basic principle of radiation therapy is to maximize damage to the tumor while minimizing damage to normal tissue.

### Factors that determine how much radiation is required:

1. The type of radiation used.
2. The type of cells.
3. The environment of the cells for example, its blood and oxygen supplies also the nucleus of the cell is more sensitive to the radiation than the surrounding cytoplasm.
4. The relative biological effect (RBE) of radiation.

### Lethal Dose (LD<sub>50</sub>)

The quantity of radiation that will kill half of the organisms in population is called lethal dose for 50% or LD<sub>50</sub>, figure (2) shows the surviving percentage for X-rays, gamma rays and Alpha particles.



**Figure2.** The percent of surviving heal cells as a function of the dose X-ray or gamma rays and alpha particles.

Where:

$$N/N_0 = e^{-KD}$$

$N_0$ : original number of survival cells prior Dose.

N: number of survival cells posterior Dose.

D: dose.

K: constant depend on cells type.

**Note:**

\* That the first grays of X-rays are not very lethal.

\* The alpha particles have a greater biological effect per Gray.

**Requirement for Radiotherapy:**

1. Determination of the tumor by accurate diagnosis.
2. Determination the quantity and quality of radiation required for radiotherapy.
3. Linear energy transfer of radiation.
4. Dose fractionating.
5. Dose diving.
6. Oxygen enhancement (or other sensitizers) to increase killing of tumor cells.
7. Prohibitive to reduce killing in the healthy cells.
8. Bragg peak calculation.

**Factors affecting radiosensitivity:****1. Biological factors:**

1. Proliferate state of the cells.
2. The phase of the cell cycle at irradiation.
3. The presence of biological repair capacity (some type of cells have greater capacity for repair than other).
4. The sex of the biological target (females, therefore are less radiosensitive).
5. The age (humans are most sensitivity before birth then decreases until maturity, in old age humans again become more radiosensitive).
6. The species differences (if the patient suffering from malignant disease or other type of tumor).

**2. Chemical Factors:**

1. **Rediosensitizers:** are agents that makes tumor cells more sensitive to radiation therapy for example, Halogenated pyrimidine and Oxygen.
2. **Radioprotectores:** are compounds used to protect against harmful effects of radiation in normal tissues for example Sulphdry1 group (sulfur and hydrogen bound together) such as cysteine and cysteamine.

**Chemical radiation protective agents:**

The addition of the chemical protective agents reduces the effectiveness of subsequent radiation effects, to be effective all protective agents need to be present at the time of radiation and they must be close to the critical site of radiation damage, post – irradiation treatment protection agents are ineffective. The protective agents normally combine with the damaging free radicals i.e. they act as a radical scavengers. These protective are sulphur – containing aminothids & their disulphide.

**3. Physical Factors:**

1. Dose and dose rate of radiation, if a dose of radiation is delivered over a long period of time rather than quickly, the effect of the dose will be less.
2. Dose fractionating, is less effective because tissue repair and recovery occur between the given doses.
3. Linear energy transfer of radiation. LET.

**LET**, is the most acceptable index to describe the average rate of energy an incident ionizing radiation transfers to soft tissue. It has units of keV of energy transferred per unit path length at micrometer level in soft tissue (keV/ $\mu\text{m}$ ). The ability of ionizing radiation to produce a biologic response increases as the LET of radiation increases.

<u>Type of radiation</u>	<u>LET(keV/<math>\mu</math>m)</u>
25 MeV X-rays	0.2
$^{60}\text{Co}$ rays	0.25
1 MeV electrons	0.3
Diagnostic X-rays	3.0
10 MeV protons	4.0
Fast neutrons	50.0
5 MeV alpha particles	100.0
Heavy nuclei	1000.0

Since the biological effectiveness of particle is related to amount of ionization, thus particle of high LET will be more damage than low LET.

### **The Oxygen enhancement of radiation effect:**

Gray noticed that cells irradiated in the presence of oxygen were much easier to kill than cells of the same type irradiated without oxygenation. The oxygen effect may play role in the recurrent of cancer.

- In the presence of molecular oxygen ( $\text{O}_2$ ), cells are more sensitive to X and  $\gamma$ -rays than when they are irradiated at very low levels of oxygen (hypoxia).
- Oxygen modifies the quantitative amount of radiation damage, but does not alter it qualitatively. It merely reduces the dose of radiation required to give certain radiobiological effect.
- The oxygen enhancement ratio (OER) is the ratio of the dose of radiation required to give an effect under hypoxia conditions to the dose needed to give the same effect under oxygenated conditions. OER is between 2 & 3 for most biological systems.

### **Relative biological effect( RBE) :**

Some types of radiation are more effective in killing cells i.e. have a higher relative biological effect.

**RBE:** is the ratio of the number of gray (Gy) of 250 KV<sub>P</sub> X – rays needed to produce a given biological effect to the number of grays of test radiation needed to produce the same effect.

<u>Particle</u>	<u>RBE</u>
e – or beta rays	1
X or $\gamma$ – rays	1
Fast neutrons	5
Alpha particles	>10.

Diagnostic X-rays have an RBE of 1 radiation with lower LET than diagnostic x-rays have an RBE less than 1, whereas radiation with higher LET have a higher RBE.

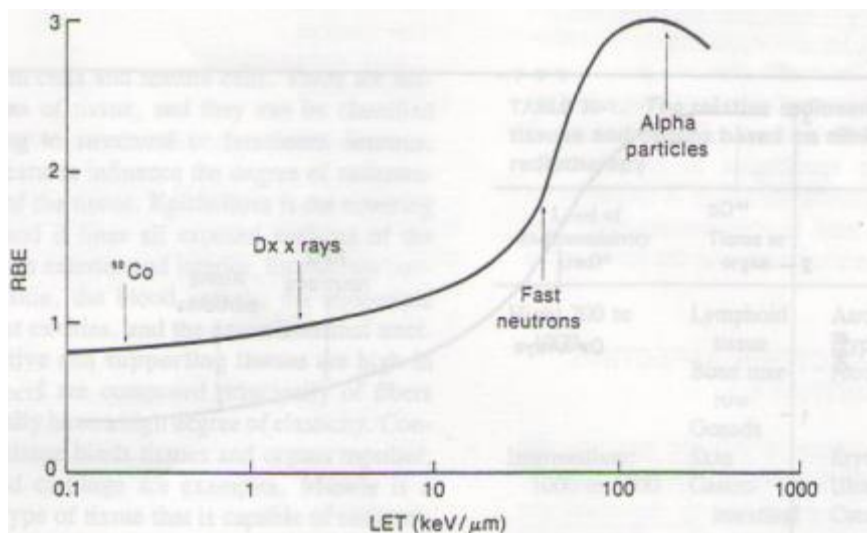


Fig. As LET increases, RBE increases also, but a maximum value is reached beyond which the RBE can increase no further.

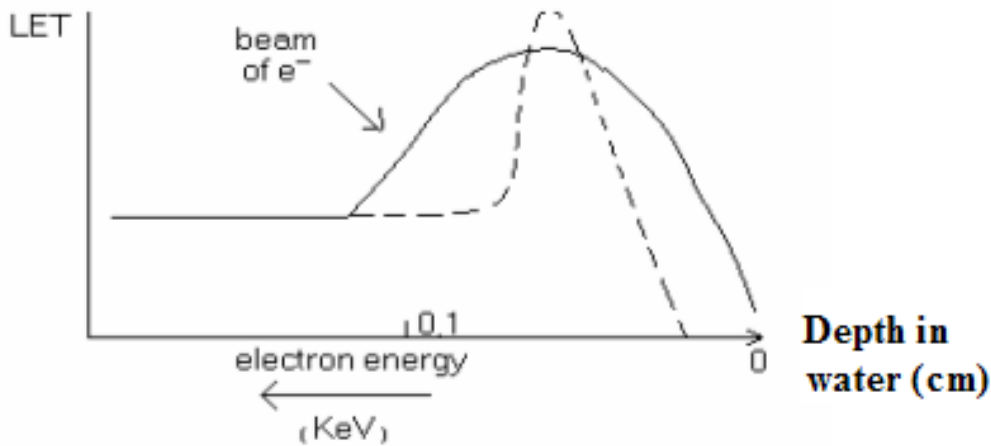


Figure 3: Relative energy deposited.

### Effect of Radiation on Cancer:

**Cancer (tumor):** is a group of cells that divides to give loosely organized mass of cells. Cancer cells are relatively independent of the normal control mechanisms of the body.

Cells can be divided into two types according to their response to radiation,

1. **Radiosensitive cells:** like skin and bone marrow.
2. **Radioresistive cells:** like brain, kidney muscle and liver.

Radiation can cure cancer but also can induce cancer. The cells near the center of large tumor have a poor blood supply. When the tumor irradiated the healthy cancer cells with a good blood supply are killed and many of the more poorly oxygenated, radio resistant tumor cells remain alive, that makes them more difficult to cure. Normal tissues are usually fully oxygenate means that a great number of normal cells than tumor cells will be killed . The aim in radiotherapy is to deliver the maximum possible radiation to the selected site while minimizing the energy deposited in healthy tissues.

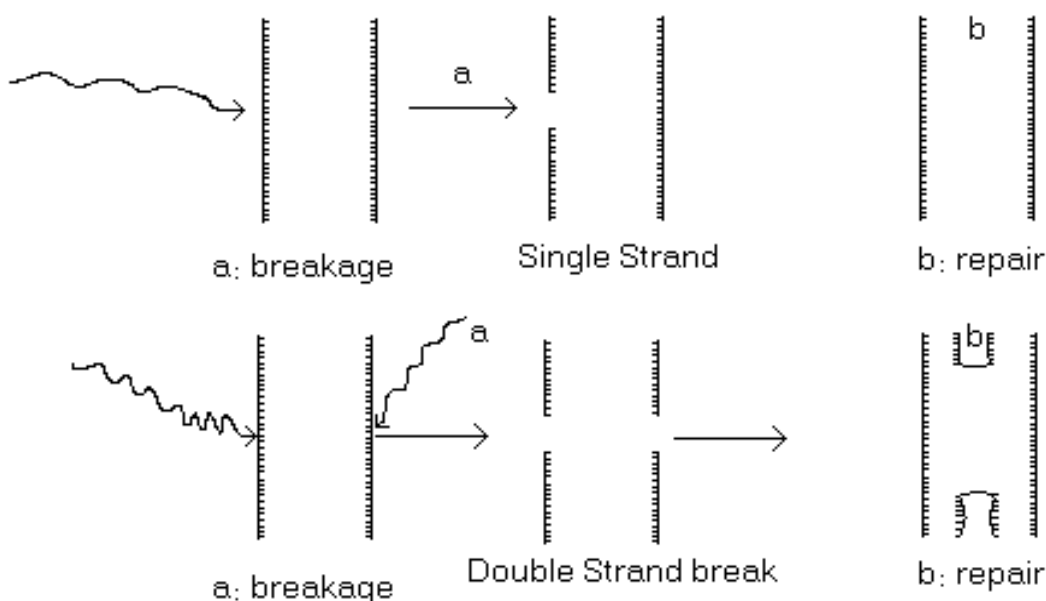
## Interaction of Radiation with the Biological Target:

The biological effects of radiation result mainly from damage to the DNA, which is the most critical target within the cell. When directly ionizing radiation is absorbed in biological material, the damage to the cell may occur in one of two ways: direct and indirect.

- 1. Direct interaction:** In direct action the radiation interacts directly with the critical target in the cell like protein and DNA. The atoms of the target itself may be ionized or excited through Coulomb interactions, leading to the chain of physical and chemical events that eventually produce the biological damage. □ Direct action is the dominant process in the interaction of high LET particles with biological material. The direct effects are responsible for about (~ 5%) of total radiation interaction.

### Effect of Ionizing Radiation on DNA:

1. Delay in DNA synthesis and cell division.
2. Reduction in the amount of DNA synthesis.
3. Strand breakage (single and double strand break) & nitrogenous base disruption.
4. Chromosomes damage and changes in the genetic material which leads to "mutations".
5. Killing of DNA i.e. killing the cell.

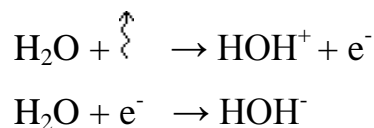


**Figure 4: Single and double strand break by direct interaction of ionizing radiation.**

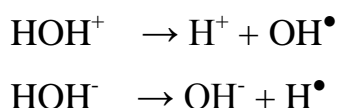
**2. Indirect interaction:** In indirect action the radiation interacts with other molecules and atoms (mainly water, since about 80% of a cell is composed of water) within the cell to produce free radicals, which can, through diffusion in the cell, damage the critical target within the cell. its contribution is about (~95%) of total radiation interaction. In interactions of radiation with water, short lived yet extremely reactive free radicals such as  $\text{H}_2\text{O}^+$  (water ion) and  $\text{OH}^\bullet$  (hydroxyl radical) are produced. The free radicals in turn can cause damage to the target within the cell.

### i. Formation of free radicals $\text{H}^+$ and $\text{OH}^\bullet$

Ionizing radiation breaks the covalent bonds that held the water molecule in its structure and leads to releasing of free radicals ( $\text{H}^+$  and  $\text{OH}^\bullet$ ) as shown by the following equation:



The  $\text{HOH}^+$  and  $\text{HOH}^-$  ions are relatively unstable and can dissociate into still smaller molecules as follows:



**A free radical** ( $\text{H}^\bullet$  and  $\text{OH}^\bullet$ ) is an uncharged molecule containing a single unpaired electron in the valence or outermost shell, and this causes them to be highly reactive.

\* **Free radicals** are unstable and therefore exist with a life time of less than 1 ms.

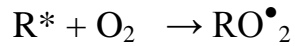
\* **Free radicals** contain excess energy that can be transferred to other molecules to disrupt bonds and produced point lesions at some distance from the initial ionizing event.

**ii. Formation of organic radicals R.**

Some organic molecules symbolized, RH, can become reactive free radical as follows:



When oxygen is present, yet another species of free radical is possible:



Free radicals are very reactive species. They seek for stability by losing or gaining an electron from a bio molecule in the cell. This process will affect the function of that bio molecule and hence the cell will be affected.