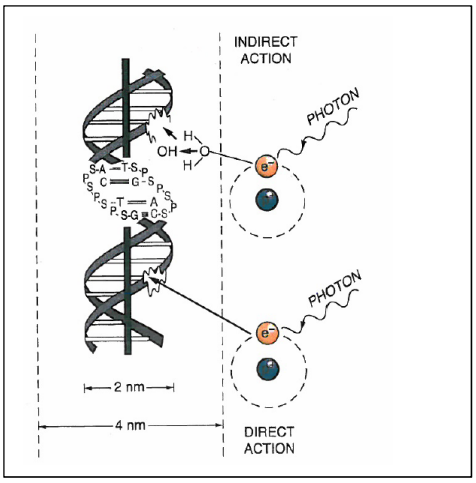
Solution exam TFY4315 Biophysics of Ionizing Radiation
May 2017

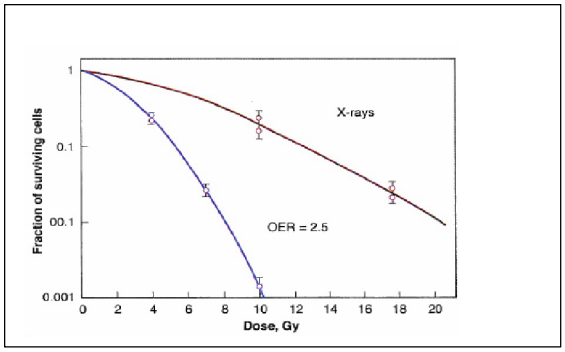
Exercise 1

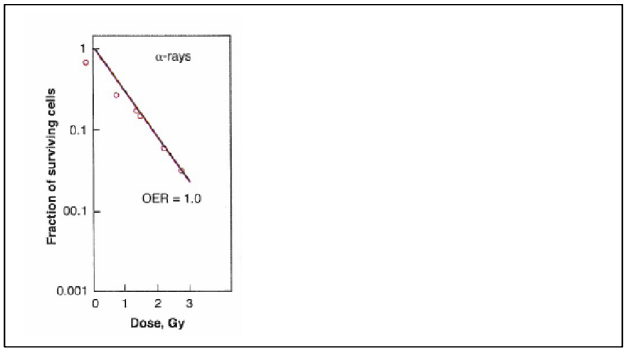
a) Direct and indirect action



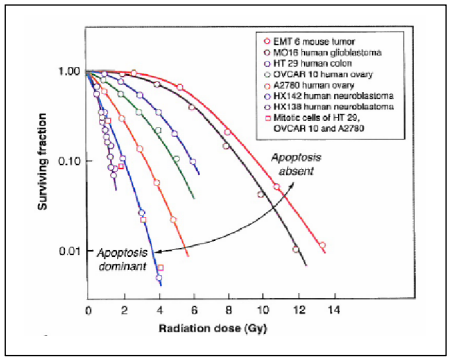
- **<u>Indirect action:</u>**
- Radiation interact with other atoms or molecules in the cell (particularly water) to produce free radicals which diffuse and damage critical targets.
- Caused by Low/medium x-ray LET
- **<u>Direct action</u>**:
- Radiation interact directly with the critical target
- Dominant for radiation with high **LET** (neutrons, α-particles)

b)





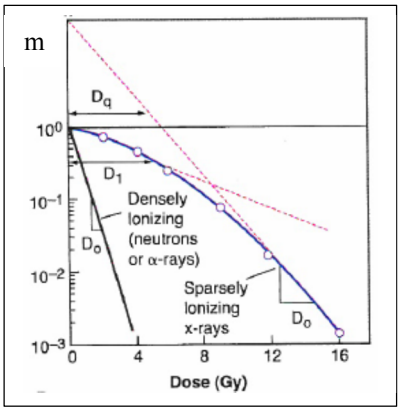
For x-ray the cell survival curves have a shoulder which represents the sub lethal damage repair and an exponential part (blue curve).
If oxygen is present, DNA will react with free radicals and form an irreparable damage.
Called fixation hypothesis.
In the absence of oxygen DNA damage can be repaired and cell survival increases.
i.e the slope decreases (red curve)
This occurs when DNA is damaged through indirect action.
In the case of direct action no sublethal damage repair takes place and the survival curve is purely exponential, no/very little shoulder.
No radicals is formed and there is no difference between cell survival for cell in the presence or absence of oxygen, i.e. the oxygen enhancement ratio=1.



DNA damage leading to mitotic cell death can be repaired. Thus survival cures will have a shoulder and an exponential part.
Apoptotic cell death cannot be repaired thus the cell survival cure is purely exponential.
The cell survival is given by:

$$S = e^{-(\alpha_M + \alpha_A)D - \beta_M D^2}$$

c) Multitarget model



Survival curve is described in terms of:

- $1/D_1$ Initial slope
- $1/D_0$ Final slope

i.e doses required to reduce the survival fraction to 0.37 for first log and exponential survival

- D_q Quasithreshold dose defines size of shoulder.

Extrapolation of exponential part of survival curve, gives dose at 100% survival

- m extrapolation number, Number of targets

$$S = ne^{-Dq/Do} = 1$$

$$D_q = D_o \ln \cdot n$$

The initial slope indicate a purely exponential survival curve, thus n=1

Exercise 2

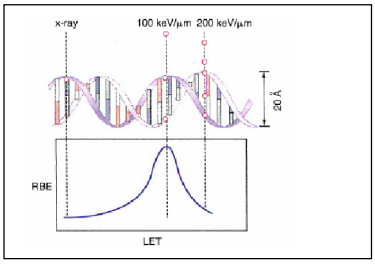
a) The RBE of a test radiation compared with a reference radiation is defined by:

$$RBE = \frac{Dose\ of\ reference\ radiation}{Dose\ of\ test\ radiation} = \frac{Dref}{Dtest}$$

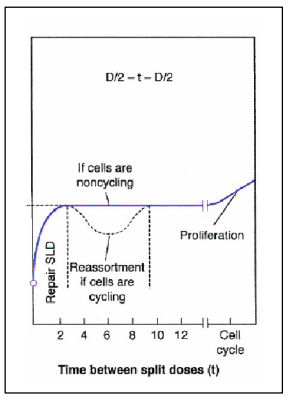
Where D_{ref} and D_{test} are the doses of reference and test radiation required for equal biological effect

X -rays of 250 kV is commonly used as a reference radiation =Dref
RBE= D250/Dtest

LET= 100 keV/µm:
- the average separation between ionizing events **coincides with the diameter of DNA double helix** (2 nm)

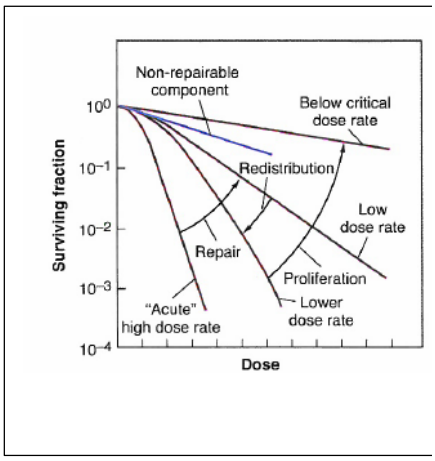


b)



The dose D is divided into two doses D/2 separated with time t. The figure shows the survival fraction as a function of the time t between the two doses. As t increases from 0 to approx 2 hr the survival fraction increases due to repair of sublethal damage that takes place before the second dose is given. Increasing the time further, cells that were in the radioresistant S-phase have reached the radiosensitive phase late G2/mitosis (due to redistribution) and the survival fraction decreases. If the time between the two doses is longer than the cell doubling time, the surviving fraction will increase due to cell division i.e. repopulation.

c)



- Acute exposure, HDR
  - Initial shoulder
- Lowering dose rate - Repair
  - Sublethal damage repair
  - A Broader shoulder, slope decreases
- Further lowering of the dose rate - Redistribution
  - Cells progress through the cycle and accumulate in G_2, the survival curve become steeper again
- A further reduction in dose rate - Reproliferation
  - to pass through the G_2 block and divide
  - If the dose rate is low enough and exposure time long compared with length of mitotic cycle
  - Further reduction in cell survival as the dose rate is progressively lowered because cell division offset cell death

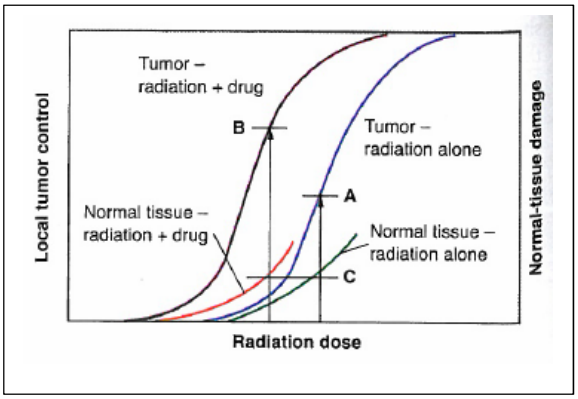
d) Reduction of amount of hypoxic cells caused by

1. Fractionated radiotherapy and reoxygenation between two fractions of radiation.
First dose causes significant killing of radiosensitive aerated cells and little killing of radioresistant hypoxic cells. In the period before the next dose the hypoxic cells becomes reoxygenated because they get closer to blood vessels and are then more radiosensitive when next dose is given.
2. Hyperthermia given at moderate temperature approx. 41 C and cause reoxygenation.
Moderate increase in temperature will increase the blood flow thus more oxygen is reached throughout the tumor .

3. Hypoxic cells can be killed by hypotoxic cytotoxins, i.e Drugs that selectively kills hypoxic cells.
4. Hypoxic cells can be made more radiosensitive by various drugs for instance by leaving cells in the radiosensitive state late G2/mitosis.
5. Using ionizing radiation with high LET the oxygen effect is not important
6. Previously beating O2 has been suggested and used to a limited extent.

Exercise 3

a)Therapeutic ratio = therapeutic index
= the ratio of tumor response for a fixed level of normal tissue damage.



In radiotherapy we are aiming to increase tumor control to a greater extent than increase in normal tissue damage. Various drugs and cytokines can be used to achieve this.

b) Hyperfraction

Use of doses / fraction less than 1.8 – 2.0 Gy.
Increased total number of fractions
Pure hyperfractionation:

- Keeping the same total dose as conventional
- The same overall time
- Twice fractions per day

Impure hyperfractionation: most used in clinical practice

- Increase in the total dose
- longer overall time
- Twice fractions per day

Aims:

- To further separate early and late effects
- Reduce late effects and maintain the same tumor control
- The same (or slightly increased) early effects

Has shown good effect for some head and neck cancers

Accelerated treatment

Pure accelerated treatment

- The same total dose as conventional

- Delivered in half the overall time
- Two or more fractions pr. day
  Aim: Reduce repopulation in rapidly proliferating tumors
- Acute effects limits this treatment.
  Must reduce the dose slightly or interpose a rest period
  - Little or no change in the late effects expected because the number of fractions and the dose pr. fraction are unaltered, however an increase in late effects has been observed..

  Used for Head and neck cancer:
  Pure accelerated treatment must be used with caution

Hypofraction

- Total number of fractions reduced
- Dose fractions much larger than 2 Gy
  Pallitative : Widely used
  Curative: tumors with low α/β
  - more similar to late responding normal tissue than other tumor
  - local control without increased normal tissue damage
    - External –beam regimen of smaler number of large doses
    - High dose rate brachytherapy in limited number of fractions
  - Advantage of acceleration (shortening the overall treatment time to improve local control)
  - Late responding normal tissue repair slow– limits the use of a larger number of treatments in short overall time.
- Prostate cancer
  - $\alpha/\beta = 2 – 3$
- Head and neck

c) Proton therapy

Advantages

Superior dose distribution compared to photon due to the Bragg peak, thus less damage to normal tissue.

– Sparsely ionizing, except for a very short region at the end of the particles' range, just before they stop

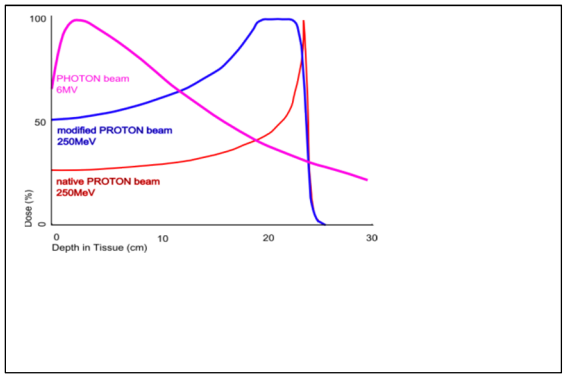
– precisely confine the high dose region to the tumor volume

– minimize the dose to surrounding normal tissue

- Somewhat Higher RBE, especially at the distal edge of the SOBP

Disavantages

- If the beam do not hit the tumor accurately but also hit normal tissue the damage to normal tissue can be severe.
- The equipment is very expensive



Exercise 4

$$BED = nd(1+\frac{d}{\alpha/\beta}) = 120Gy$$

a) $$= 60Gy(1+\frac{2}{\alpha/\beta}) = 120\,\text{Gy}$$

$$\frac{\alpha}{\beta} = 2Gy$$

New fractionation regimen, n fractions:

$$n3Gy(1+\frac{3}{2}) = 120Gy$$

$$n = 16$$

As this is a rapidly growing tumor I would give the 16 fractions in as short time as possible without damage normal tissue critically.

b)For the normal organ

Standard fractionation: $BED = 60Gy(1+\frac{2}{3}) = 100Gy$

New fractionation: $BED = 16 \cdot 3Gy(1+\frac{2}{3}) = 80Gy$

As the BED is reduced the effect of the treatment on normal tissue is reduced.

c) $$BED = EQD_2(1+\frac{2}{\alpha/\beta})$$

Due to proliferation the number of cells will increase exponentially:

$$N = N_0 e^{kt}$$

k is related to the potential doubling time T_{pot}:

$$2N_o = N_o e^{kT_{pot}}$$

$$k = \frac{\ln 2}{T_{pot}}$$

Due to proliferation of cells, the effectiveness of radiation is decrease with k.

The biological effect is now:

$$E = n(\alpha d + \beta d^2) - \frac{\ln 2}{T_{pot}} t$$

$$BED = \frac{E}{\alpha} = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\ln 2}{\alpha} \frac{t}{T_{pot}}$$

Exercise 5: Multiple choice (Credit 1)

You have 3 possible solutions. Mark the correct answer by setting x in front of the correct answer.

a) In the Compton process incoming photons interact with
   - The nucleus
   - bound electrons
   - **"free" electrons**

b) Charged particles causes
   - **Direct ionizing**
   - Indirect ionizing through the Compton process
   - Indirect ionizing through the photoelectric process

c) DNA double strand breaks can be repaired by homologous recombination repair. This takes place in
   - G1
   - **G2**
   - Mitosis

d) Which of the following statements is wrong for apoptosis
   - **Apoptosis is the most common mechanism of radiation-induced cell death**
   - Radiation-induced apoptosis is highly cell type dependent
   - Apoptosis causes fragmentation of the nucleus

e) Brachytherapy is characterized by
   - The dose rate is low close to the source
   - The is substantial repair of sublethal damage
   - **The dose is well defined around the source**

f) In clinical practice targeted radiotherapy is mainly based on
- Isotopes coupled to DNA
- **Isotopes coupled to antibodies**
- Isotopes coupled to nanoparticles

g) Deterministic effect is characterized by
- There is no threshold for the effect
- **Severity increases with the dose**
- The probability of occurrence is dose-independent

h) Normal tissue response to radiation is characterized by
- Proliferating cells having low radiosensitivity
- No threshold needs to be reached
- **Cell organization in the tissue**

i) Late effects on normal tissue depends mainly on
- **Size of fractionated dose**
- Overall treatment time
- Dose rate

j) Structurally defined functional units are characterized by
- Clonogenic cells can migrate from one functional structural units to another
- Having high radiation tolerance
- **Being independent of its neighbors**

k) Hypoxia-inducible factor in the presence of oxygen will
- **Be degraded**
- Promote angiogenesis (formation of new blood vessels)
- Promote cell proliferation

l) Advantages of chemotherapy is
- High specificity toward cancer cells
- **Reaches metastases**
- Can be repeated many times without inducing resistance toward cancer cells

m) The target for hyperthermia is
– DNA
– **Proteins**
– Both DNA and proteins

n) Hyperthermia is most sensitive to cells in
- G1
- **S-phase**
- Late G2/mitosis