Solution Exam TFY4315 Radiation biophysics
May 25, 2016

Exercise 1

A) Purely exponential curve represents radiation with high LET such as neutrons or α-particles.
No cellular repair takes place.
Such radiations damage the cells (DNA) through direct action.

The survival curve with a shoulder represents typical x-ray or γ-ray.
The shoulder is caused by sublethal damage repair.
Such radiation damage cells though indirect action.
The survival curve is described by the linear-quadratic equation

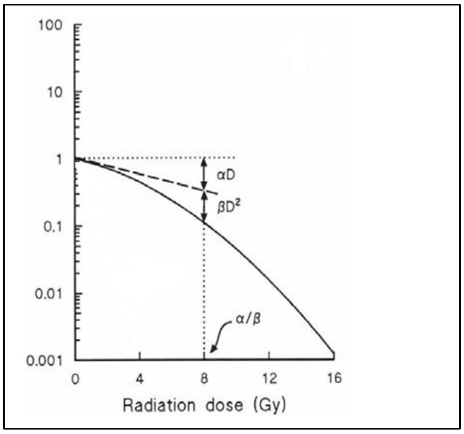
$$S = e^{-\alpha D - \beta D^2}$$

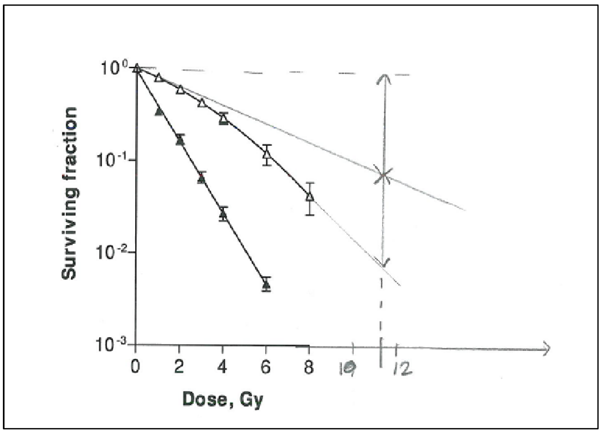
α is proportional to the dose D and is due to a single tack event and no sublethal damage repair takes place, i.e.the damage is lethal

β is proportional to the dose D^2 and is due to a two tracks that combined cause the damage. In this case sublethal damage repair can take place.

The dose D=α/β is defined when αD= βD^2

as shown on the figure below.





Estimate D=α/β:

For the purely exponential survival curve β=0 and the ratio has no meaning

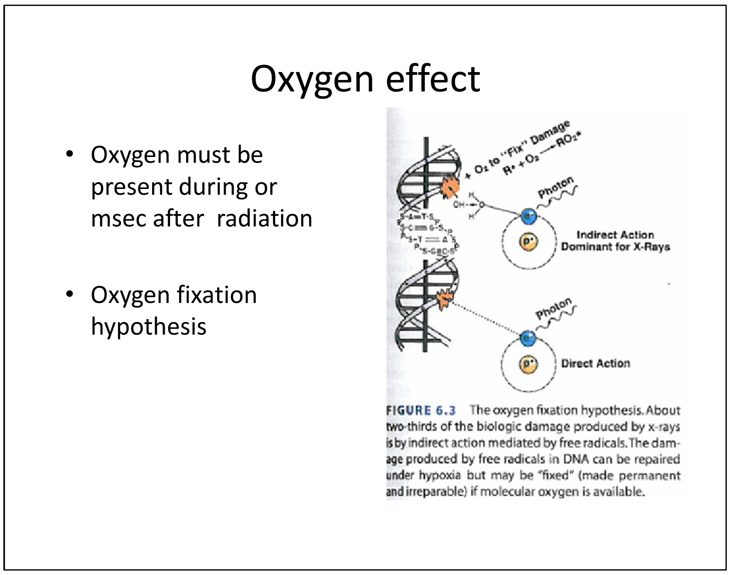
For the survival curve with a shoulder, from the figure one can estimate roughly D=11 Gy

b) OER=oxygen enhancement ratio= is the ratio between the doses given under hypoxic to aerated conditions needed to achieve the same biological effect.

The difference in OER is caused by the different action of radiation direct versus indirect.

For indirect action, the radiation interact with other atoms or molecules in the cell, particular water to produce free radical with diffuse and damage DNA. In the presence of oxygen these radicals are fixed, and no repair can take place. This gives a high OER.

For direct action, radiation interact directly with the critical target. Thus presence of oxygen or no oxygen does not play any role and OER=1.



Exercise 2:

a) Cell proliferation is the main properties determining radiosensitivity. Rapidly growing cells are more sensitive to radiation and their damage appear much faster than in tissue of slowly growing cells.

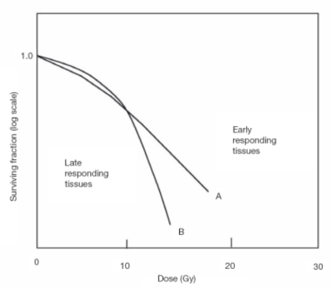


FIG. 14.3. Hypothetical target cell survival curves for (curve A) early responding tissues and (curve B) late responding tissues.

Early responding: High α/β (5 – 20 Gy)

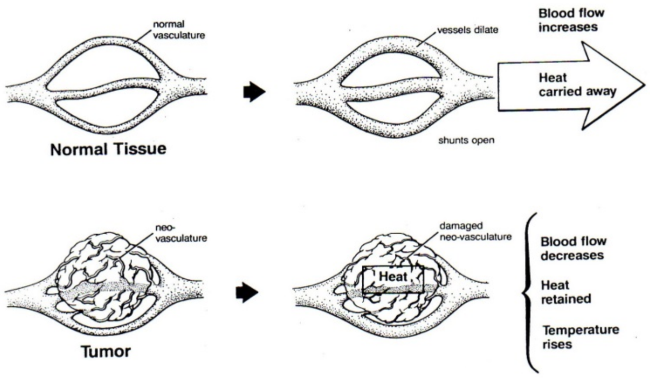
Late responding: Low α/β (1 – 4 Gy)

b) The kidney consist of millions of nephrons each being a FSU=Functional structural units .
The skin has much larger FSU, called structural undefined FSU.
The survival of a FSU depends on the survival of one or more clonogenic cells within the FSU. Tissue survival depends on the number and radiosensitivity of these clonogens.
Surviving clonogenic cells cannot migrate from one FSU to neighboring FSU. Thus survival of a FSU (nephron) in the kidney depends on the survival of at last one clonogenic cells within it.
For FSU in skin clonogenic cells can migrate between FSU, allowing repopulation of damaged cells.
Thus the radiosensitivity of FSU in kidney is much larger than in skin.

Exercise 3

a) 3 reasons for combining Radiotherapy (RT) and hyperthermia (HT):
  - Different targets, RT – DNA, HT-Protein
    This can lead to synergistic effects
    For example: HT denaturates proteins important for DNA repair or DNA replication, lead to increased effect of RT
  - Kills cells in different phases of the cell cycle. The most RT resistant cells (S-phase cells) are killed by HT.
  - Hypoxic cells being radioresistant are killed by HT

  Blood flow and structure of blood vessels are different in normal tissue and tumour tissue. Heat is removed faster away from normal tissue than form tumor tissue.



b) Targeted radiotherapy
  There are radioactive isotopes that has a high affinity towards certain tissue.

- Iodine-131 (**l**ong-range β emitters) accumulates in thyroida and can be used to treat thyroid cancer. Radium-223 (α-emitter) accumulates in bone (resemble Ca2+) and can be used to treat cancer patients with bone metastases.

Radioactive isotopes can be conjugated to monoclonal antibodies (Ab) or to nanoparticles (NPs). In the case of Ab, the Abs recognize receptors on the cell surface or intracellular in cancer cells that express a higher level of the receptors than normal tissue.
In the case of NPs, the leaky blood vessels in tumors allow NPs to enter into tumor tissue but into normal tissue thus the accumulation in tumors is higher than in normal tissue

Exercise 4: Fractionated radiotherapy

a) The 4 reasons for giving fractionated radiotherapy is the 4 R:

- **Repair** of subletal damage between the fractions. The aim is that normal tissues are repaired to a larger extent than cancer cells.
  The time between the fractions should be so long that repair can take place.This occurs for early responding tissue but not to the same extent for late responding tissue.

- **Reassortment,** Progression of cells through cell cycle causes redistribution. Cells that survive a first dose of radiation are in a resistant phase of the cell cycle and within a few hr they progress to the more sensitive phase G2, M. Thus rapidly dividing cancer cells will reach the sensitive phase, whereas slow proliferating normal cells will not. Early responding tissue consists of rapidly growing cells and reassortment might be an issue. It is not important for late responding tissue.
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- **Repopulation** due to cell division increases the number of cells if the time between the doses is sufficient long. This is important for sparing early responding tissue, but repopulation will not occur for late responding tissue. However also tumour cells might be repopulated.

- **Reoxygenation,** x-rays kills aerated cells more efficiently than hypoxic cells. Thus after the first dose the fraction of hyoxic cells increases. Part of the hypoxic cells becomes reoxygenated and sensitive to the next dose of x-rays.
  Reoxygenation is not important for normal tissue which will be well oxygenated.

b)A patients with a rapidly growing tumor should be given Hyperfractions or accelerated treatment:

Hyperfractioning:
Same total dose as in conventional treatment regimen in the same overall time. Each dose per fraction is reduced and the number of fraction increased. For instance deliver twice as many fractions by giving two fractions per day.
The aim of hyperfractioning is to reduce late effects without increasing significantly the early effects and maintain or improve local tumor control.

Accelerated treatment
Same total dose delivered in shorter time. Increasing the number of doses per day, not changing the number of fractions compared to conventional treatment. For instance the overall treatment time is half of what is used in conventional treatment and two fractions are given per day.
This treatment has been shown to give severe damage to normal tissue also late responding tissue.

Thus the fractionation regimen to suggest is normally hyperfractioning.

Exercise 5 Calculations

a) The standard fractionation regimen gives a BED:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) = 72GY$$

This is used to calculate the ratio α/β.

n=30
d=2 Gy
Gives α/β=10Gy

The new fractionation regimen has the same BED.
n is not known, d= 4Gy

$$n4Gy\left(1 + \frac{4Gy}{10Gy}\right) = 72Gy$$

n=12,8

Thus the treatment has to last 4 weeks and 1 treatment in week 5.

b) The tumor is growing exponentially with a rate constant k.

The rate constant k is thus:

$$N = Noe^{kt}$$

$$10^9 = 10^8 e^{kt}$$

$$k = \frac{ln10}{t}$$

The doubling time is given by: $2No = Noe^{kT_d}$

$$T_d = \frac{ln2}{ln10} t$$

The extra dose radiation that has to be given to compensate for the cell proliferation is:

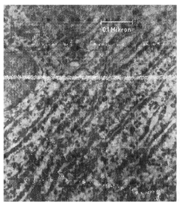
$$d = \frac{ln2}{\alpha} \frac{t}{T_d} = \frac{ln2}{0,3} \frac{t}{\frac{ln2 \cdot t}{ln10}} Gy = \frac{ln10}{0,3} Gy = 7,7Gy$$

<u>Extra dose d=7,7Gy</u>

Exercise 6: Multiple choice

You have 3 possible answers. Mark the correct answer by setting x in front of the correct answer. You have to hand in the two sheets with multiple choice questions together with the other answers. Write your candidate number on the sheets.

a) The figure below shows ionizing density for different types of radiation. The path with highets ionizing density is caused by
   - ***500 kev protons***
   - 1Mev electrons
   - 5 kev electrons



b) Which of the following chromosomal aberration can be repaired:
   - Anaphase bridge
   - Ring aberration
   - ***Symmetrical translocation***

c) Apoptosis contributes to:
   - ***Increased radiosensitivity***
   - Reduced radiosensitivity
   - No effect on radiosensitivity

d) Assume that the dose rate is reduced and the total exposure time increased. How does that affect the radiosensitivity?
   - Increase in radiosensitivity
   - ***Reduction in radiosensitivity***
   - No effect

e) What is the relationship between LET and the energy of ionizing radiation?
   - Increase with increasing energy
   - ***Decrease with increasing energy***
   - LET is constant when energy is increasing

f) What characterize stochastic effect?
- Has threshold
- ***Probability of the effect increases with increasing dose***
- The severity of the effect increases with increasing dose.

g) The total population is exposed to ionizing radiation due to natural background and medical diagnostic. How much larger is the contribution from medical diagnosis?
- Medical diagnostic exposure is 4 times higher
- Medical diagnostic exposure is 2 times higher
- ***The two contributions are equal in magnitude***

h) Radiotherapy is often combined with chemotherapy using a drug. Below is 3 proposed reasons for why combining radiotherapy and chemotherapy.
One is wrong, which?
- Drugs makes cells more sensitive to radiation
- Radiotherapy and chemotherapy kill different cell populations
- ***Chemotherapy is more specific towards tumours compared with radiotherapy.***

i) Which method is **not** used to spread the proton beam laterally
- ***Using a rotating wheel with variable thickness***
- Placing a scattering material (foil) in front of the proton source
- Scanning the proton beam across the tumour volume.

j) Multitarget model was earlier used to describe survival curves. Which of the following statements is correct for the multitarget model:
- It is a simple model with few parameters
- ***Gives a god fit for high doses***
- Gives a good fit for low doses

k) Which of the following statements is not correct for brachytherapy close to the radioactive source?
- ***The dose rate is low***
- No repair of sublethal damage takes place
- All cells will be killed independent of their radiosensitivity

l) Relative biologic effectiveness (RBE) for neutrons is:
– ***Biggest for low doses***
– Biggest for high doses
– Independent of the dose

m) Radiation weighting factor for neutrons is:
- 1
- 20
- ***Depending on the energy of the neutrons***