TFY4315 Biophysics of Ionizing Radiation
Exam 2019: Suggested Solutions

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Exercise 1: Radiation absorption, damage and repair

(a)
- Directly ionizing
  - Can disrupt the atomic structure of the absorber through which they pass directly and produce chemical and biological changes
  - Charged particles (the individual particles must have sufficient kinetic energy)
- Indirectly ionizing
  - Do not produce chemical and biological damage themselves, but give up their energy to produce fast moving charged particles that can produce damage (Compton process, photoelectric process)
  - Electromagnetic radiation (X and γ-rays) (with energy high enough to initiate the processes)

(b) A free radical is an atom or molecule carrying an unpaired orbital electron in the outer shell. In atoms / molecules with

- even number of electrons the spins are paired, leading to a high degree of chemical stability
- odd number of electrons one orbital electron have no other electron with opposing spin, leading to a high degree of chemical reactivity

The main water radicals are OH·, H· and and e^-_{aq}. 2/3 of the x-ray damage to DNA in mammalian cells is caused by the hydroxyl radical OH·.

(c) See the overview given in Figure 1.

Indirect action of x-rays – Chain of events

Time (sec)	Stage	Characteristics
$10^{-13} - 10^{-15}$	Physical	Initial ionization H_2O^+, e^-, H_2O^*
$10^{-9} - 10^{-10}$	Physical / Chemical	Radicals produced e^-_{aq}, $H^\bullet$, $OH^\bullet$
$10^{-5} - 10^{-7}$	Chemical	Reaction with bio-molecules, breaking of chemical bonds
Seconds – years	Biological	Effects on metabolism, gender cells, viability, genetic effects

- Cell killing is expressed hours to days after radiation
- Oncogenic damage may be delayed for up to 40 years
- Mutation damage may not be expressed for many generations

Figure 1: Exercise 1c

(d)
- Lethal damages
  - Irreversible
  - Irrepairable
  - Leads to cell death
- Potentially lethal damage (PLD)
  - Can be modified by postirradiation environmental conditions (causes cell death under normal circumstances, but survival can be stimulated due to manipulation of the postirradiation environment, PLD can therefore be repaired)
- Sublethal damage (SLD)
  - Can be repaired within hours if no additional SLD is added with which it can interact to form lethal damage

(e) In a split dose experiment a radiation dose to a cell population is split into two fractions with various time intervals between the two fractions. The survival is measured (see Figure 2).

- Sublethal damage (SLD) repair is seen as initial increase in survival if a radiation dose is split into two fractions by a time interval (the split dose survival curve increases when the split is within a few hours, before flattening).
- Reassortment can be seen as a dip in the split dose survival curve for rapidly growing cells (when the time interval between the split

doses is about 6 hours in the example shown). Explanation: In asynchronous populations more cells are killed in radiation sensitive than in radiation resistant phases. The surviving population therefore tends to be synchronized. After the first fraction most of the surviving cells are in S-phase. When the second fraction is delivered after 6 hours these cells are in G2/M phases (sensitive). If the increase in radiosensitivity moving from late S to G2/M exceed the repair of SLD the surviving fraction falls.

- Repopulation can be seen as an increase in the surviving fraction resulting from cell division (repopulation, proliferation) if the interval between the split doses is $>$ 10-12 hours (exceeding the cell cycling time of rapidly growing cells).

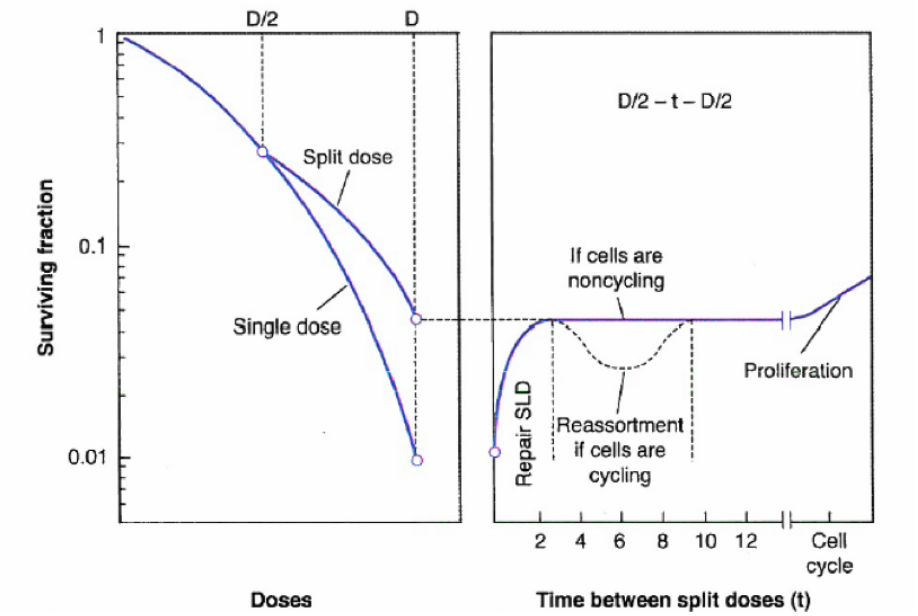


Figure 2: Exercise 1e

Exercise 2: Cell survival after radiation - calculations

(a) The plating efficiency (PE) is defined as

$$PE = \frac{\text{Number of colonies counted}}{\text{Number of cells seeded}}$$

and the surving fraction (SF) is obtained by

$$SF = \frac{\text{Number of colonies counted}}{\text{Number of cells seeded} \cdot PE}$$

The value of D_0 is obtained from

$$SF = e^{-D/D_0}$$

where D is the absorbed dose and D_0 is the dose that reduces the survival to 37% of the initial number of cells.

Data:
Unirradiated cells: number of cells seeded = 100, number of colonies = 75
Irradiated cells: number of cells seeded = 100, number of colonies = 20

Inserted, this gives a plating efficiency of

$$PE = \frac{75}{100} = 0.75$$

and a surviving fraction of

$$SF = \frac{20}{100 \cdot 0.75} = 0.267$$

Using these numbers and D = 2 Gy into the

$$SF = e^{-D/D_0}$$

gives

$$0.267 = e^{-2/D_0}$$

This results in $D_0 = 1.51$ Gy.

(b) With $D_{10} = 4$ Gy for oxygenated cells, then D_0 is obtained by

$$0.1 = e^{-4/D_0}$$

This gives $D_0 = -4/ln(0.1)$. Inserting this into

$$SF = e^{-D/D_0}$$

and setting D = 40 Gy gives

$$SF = e^{10ln(0.1)} = 10^{-10}$$

If the cells are hypoxic then D_{10} is twice as large as for oxygenated cells = 8 Gy. The relative survival is then given by

$$SF = e^{5ln(0.1)} = 10^{-5}$$

If 1% of a cell population is hypoxic the total survival is given by

$$SF = 0.99 \cdot 10^{-10} + 0.01 \cdot 10^{-5} = 10^{-7}$$

We see that the survival is dominated by the hypoxic cells.

The survival fraction is 10^{-10} for oxygenated cells and 10^{-7} for a population consisting of 99% oxygenated cells and 1% hypoxic cells.

(c)

- Neutrons: the cell survival when irradiating with neutrons will give an exponential curve as the survival follows the single-hit single-target model. Therefore;

  $$SF = e^{-D/D_0}$$

  With $D_0 = 1.7$ Gy the dose for 10% survival will be

  $$0.1 = e^{-D_{10}/1.7}$$

  This gives $D_{10} = 3.91$ Gy.

- Photons: the cell survival follows the linear quadratic model. Thus, the survival will be given by

  $$SF = e^{-(\alpha D + \beta D^2)}$$

  where $\alpha = 0.15$ Gy^{-1}, $\alpha/\beta = 3.0$ Gy and $\beta = 0.05$ Gy^{-2}. Inserted, this gives a dose for 10% survival of

  $$0.1 = e^{-(0.15D_{10} + 0.05D_{10}^2)}$$

  Solving the equation gives $D_{10} = 5.45$ Gy.

The RBE is defined as the ratio of doses for the same biologic effect or cell survival. Thus,

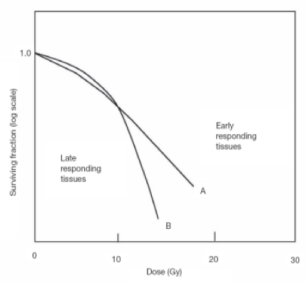
$$RBE_{10} = 5.45/3.91 = 1.39$$

The RBE for 10% survival is 1.39 (or 1.4).

Exercise 3: Normal tissue damage - theory and calculations

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

A simple sketch of survival curves for early- and late responding normal tissues is shown in Figure 3.



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

Late responding: Low α/β (1 – 4 Gy)

Figure 3: Exercise 3a

(b) The kidney consists of millions of nephrons each being an FSU (functional subunit). The skin has much larger FSUs, called structurally undefined FSUs. The survival of FSUs depends on the survival of one or more clonogenic cells within the FSUs, and tissue survival depends on the number and radiosensitivity of these clonogens.

Surviving clonogenic cells in the kidney cannot migrate from one FSU to neighbouring FSUs. Thus, survival of an FSU (nephron) in the kidney depends on the survival of at least one clonogenic cells within it. For FSUs in skin, clongenic cells can migrate between FSUs, allowing repopulation of damaged cells. Thus, the radiosensitivity of FSUs in kidney is much larger than in skin.

(c) Cell survival after one treatment for an absorbed dose D with the LQ model is given by

$$SF = e^{-(\alpha D + \beta D^2)}$$

After N treatment the survival is

$$SF_N = [e^{-(\alpha D + \beta D^2)}]^N$$

With D = 2.0 Gy and N = 30 treatments:

- Tumor cells: $\beta = 3.2 \cdot 10^{-2}$ Gy^{-2}, $\alpha/\beta = 10$ Gy $\rightarrow \alpha = 0.32$ Gy^{-1}
- Tumor cells: $\beta = 5.1 \cdot 10^{-2}$ Gy^{-2}, $\alpha/\beta = 3$ Gy $\rightarrow \alpha = 0.153$ Gy^{-1}

The surviving fractions for tumor and normal cells then become:

- Tumor cells:

$$SF_{30} = [e^{(-0.32 \cdot 2 - 3.2 \cdot 10^{-2} 2^2)}]^{30} = 9.860 \cdot 10^{-11}$$

- Normal cells:

$$SF_{30} = [e^{(-0.153 \cdot 2 - 5.1 \cdot 10^{-2} 2^2)}]^{30} = 2.266 \cdot 10^{-7}$$

The ratio of the surviving tumor cells to normal cells is:
$9.860 \cdot 10^{-11}/2.266 \cdot 10^{-7} = 4.35 \cdot 10^{-4}$

If the absorbed dose per fraction instead is 1.0 Gy, the number of treatments for the same survival for tumor cells is given by

$$9.860 \cdot 10^{-11} = [e^{-(0.32 \cdot 1 + 3.2 \cdot 10^{-2} 1^2)}]^N = [e^{-0.352}]^N$$

giving

$$N = \frac{ln(9.860 \cdot 10^{-11})}{-0.352} = 65.45$$

Thus, 65.45 treatments (65.45 Gy) are needed. This can be compared with the absorbed dose 30 x 2 Gy = 60 Gy that was needed with an absorbed dose of 2.0 Gy per treatment.

The survival fraction of normal cells will in this situation be

$$SF_{65} = [e^{-(0.153 \cdot 1 + 5.1 \cdot 10^{-2} 1^2)}]^{65.45} = 1.59 \cdot 10^{-6}$$

The ratio of the surviving tumor and normal cells will in this case be:
$9.860 \cdot 10^{-11}/1.59 \cdot 10^{-6} = 6.2 \cdot 10^{-5}$

This gives a better ratio than with 2.0 Gy per treatment as more normal cells will survive.

Summary: The ratio between the survival of tumor cells and normal cells is $4.35 \cdot 10^{-4}$ with 2.0 Gy per treatment. With 1.0 Gy per treatment a total absorbed dose of 65.45 Gy is needed and the ratio between the survival of tumor cells and normal cells is $6.2 \cdot 10^{-5}$.

A limitation is that repopulation is not included in the calculations.

Exercise 4: Lab and project work

(a) See poster in Figure 4 on low dose-rate irradiation. But clearly distinguish between low *dose* radiation and low *dose-rate* radiation, this is two different concepts.

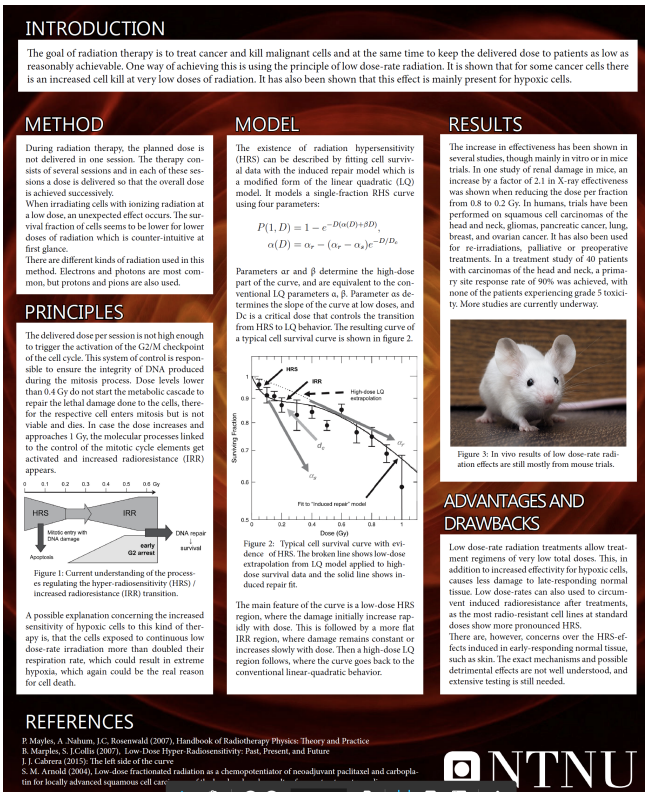


Figure 4: Exercise 4a

(b) See Figures 5 and 6 for typical depth dose curves for photons and electrons.

Electrons with energies 6-18 MeV will reach 2-5.5 cm into tissue. Superficial tumors are treated with electrons.

See Figures 7 and 8 for principles behind IMRT and VMAT. The dose profile with flatting filter free radiation is shown in Figure 9.

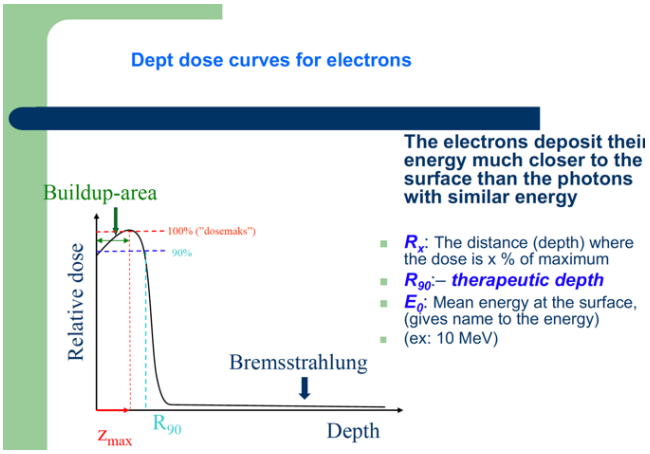


Figure 5: Exercise 4b

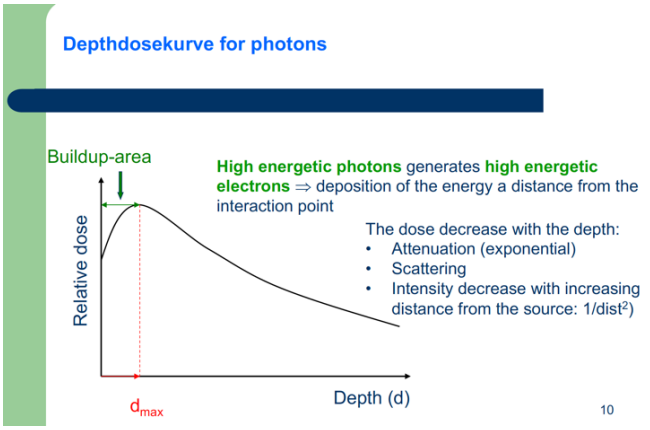


Figure 6: Exercise 4b

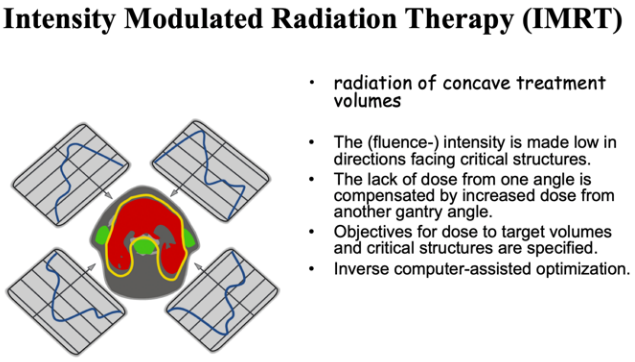


Figure 7: Exercise 4b

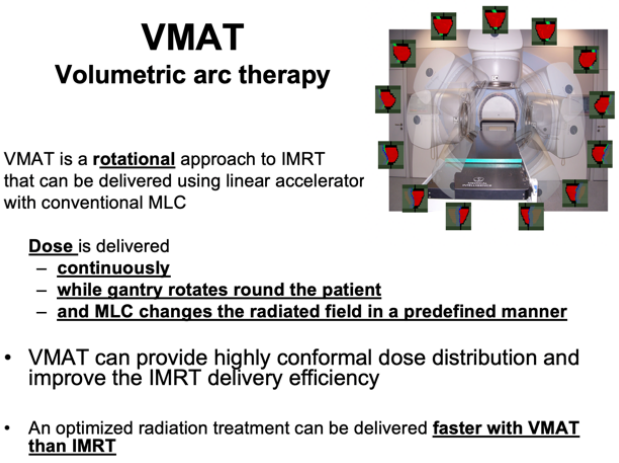


Figure 8: Exercise 4b

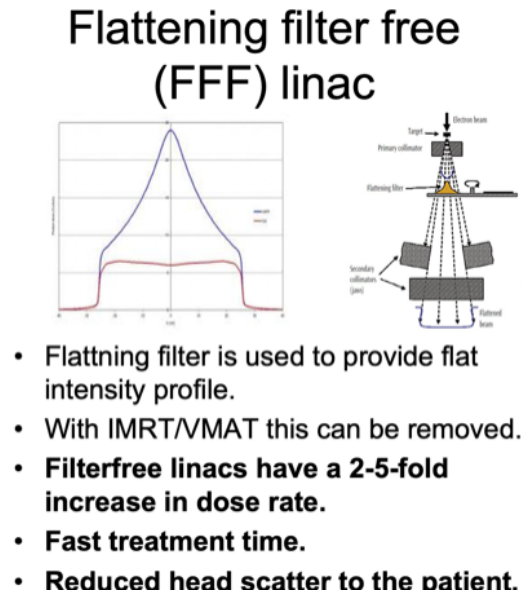


Figure 9: Exercise 4b

Exercise 5-24: Multiple choice

Correct answers given on request