TFY 4315
Biophysics of Ionizing Radiation

Examination paper 04.06.2013

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Solution proposal

Problem 1

a) Why does radiation with for example x-rays on a human have much higher biological effect than equal amount of energy given in form of heat or mechanical energy?

*The energy of x-rays absorbed in living material (humans) is **deposited unevenly** in discrete packets. The energy in a beam of x-rays is quantized into large individual packets, each of which is big enough to break a chemical bond (Double strand breaks in DNA) initiating a chain of events culminating in a biological change.*

The biological effect of radiation is determined <u>not by the total amount of energy</u> absorbed, but by the energy of each individual energy packet. Increasing the dose of x-rays will increase the number of high energy packets. For low doses of x-rays fewer energy packets are absorbed, but those absorbed may have enough energy to damage DNA locally.

Energy in the form of heat and mechanical energy is <u>absorbed uniformly and evenly</u>, and much greater quantities of energy are required to produce damage in living things.

Examples: Total body irradiation of x-rays with 4 Gy is lethal in 50% of individuals. The dose represents absorption of energy of about the same level as energy delivered in a sip of hot coffee, or lifting a person 0.4m.

b) Define what we mean by ***Linear energy transfer*** (LET)

Linear energy transfer (LET) is the energy transferred pr. unit length of the track. The LET (L) of a charged particle in medium is the quotient:

$$L = dE/dl$$

dE = average energy locally imparted to the medium by a charged particle of specified energy in traversing a distance of dl

Unit: eV / m

c)   For a given type of radiation; what happens to LET when the radiation energy increases?

*The density of ionization decreases, giving **lower LET**, as the radiation energy increase.*

Problem 2

a)   An individual is exposed to radiation. Define by introducing radiation and tissue weighting factors what is ment by:
- Absorbed dose
- Equivalent dose
- Effective dose

Indicate the units used for each type of dose.

Absorbed dose = Energy absorbed pr. unit mass of tissue
        Physical quantity
        Unit: Grey (Gy) (= J/kg)

Equivalent dose:
*The **same absorbed dose** of different types of radiation may have **different biological effects**. Adjusting the **absorbed dose** (for each tissue (organ) irradiated) with a **Radiation weighting factor (W_R)** (appropriate to the type and energy of the radiation) gives the **equivalent dose** with **comparable data for biological effects**: (A radiation weighting factor is an estimate of the effectiveness per unit dose of the given radiation relative to low-LET standard).*

$$\textbf{(Equivalent dose)}_T = \sum_R \textbf{(Absorbed doses)}_{RT} \, x \, W_R$$
        for each tissue (organ) (T)
         (Absorbed dose)$_{RT}$ = absorbed dose of radiation type R in tissue (organ) T
        *Unit: **Sievert (Sv)***

Effective dose = **The sum of all the weighted equivalent doses in all tissues or organs irradiated:**
$$\textbf{Effective dose} = \sum_T (\sum_R \textbf{(Absorbed dose)}_{RT} \, x \, W_R) \, x \, W_T$$
$$= \sum_T \textbf{(Equivalent dose)}_T \, x \, W_T$$

(Absorbed dose)$_{RT}$ = absorbed dose of radiation type R in tissue (organ) T

W_R = Radiation weighting factor
W_T = Tissue weighting factor
Unit: **Sievert**

The **effective dose is the whole body dose of X-rays** that would have to be delivered to produce the same stochastic risk as the partial body dose that actually was delivered.
- Provides an easy assessment of overall risk
- Makes comparison of risks simpler

Effective dose is in principle nonmeasurable

b)   What are the radiation weighting factors for
- Photons
- Electrons
- Protons
- α-particles
- Neutrons

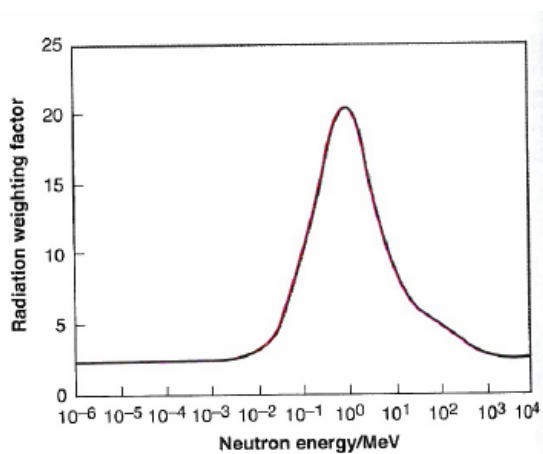Radiation weighting factors (W_R):

Photons: 1

Electrons: 1

Protons: 2

α-particles: 20

Neutrons: A continuous curve as a function of neutron energy.

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c) In radiation therapy patients can be given total doses which are much larger than lethal doses corresponding to acute radiation syndrome (ARS). Why is that tolerated? Give estimates of total doses associated with:
- curative external photon radiation therapy
- acute radiation syndrome

In radiotherapy generally smaller <u>parts of the body</u> are irradiated (not the whole body). When <u>fractionating</u> of the radiation, with enough time for repair of sublethal damage between each fraction, the total dose tolerated is much higher than corresponding tolerated dose given in one fraction.

*Acute radiation syndrome is associated with radiation of the <u>whole organism.</u>*

Common total doses corresponding to curative external photon radiation therapy:

*2 Gy x 25 – 35 = <u>**50 – 70 Gy**</u>*

*Total doses given to the whole body associated with acute radiation syndrome (lethal): <u>**3 – 5 Gy**</u>*

Problem 3

Delineate the dose-response relationships for tumor control probability and normal tissue damage for a situation favorable for radiation therapy. What do we mean by ***therapeutic ratio*** (therapeutic index)? Indicate in the figure a dose giving a favorable therapeutic ratio.
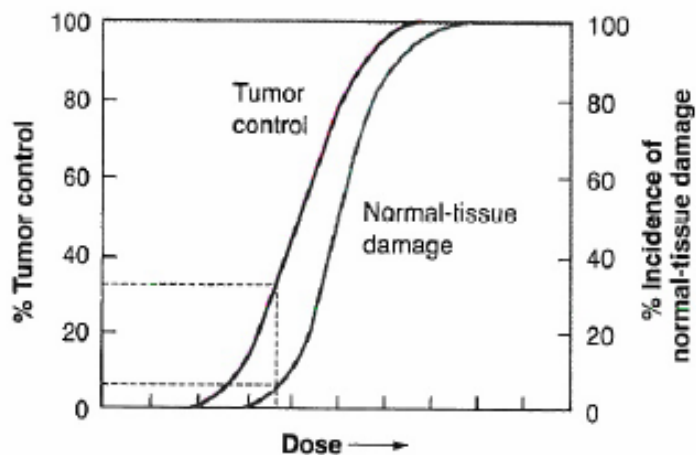
Therapeutic ratio (index) is the percent tumor control obtained for a fixed level of normal tissue damage.

The dose indicated in the figure gives a favorable therapeutic ratio with

How can the therapeutic ratio be manipulated to give a therapeutic gain?

Therapeutic ratio can be manipulated by:

- *Time – fractionation regimens*

- *Radiation sensitizers*

Therapeutic gain *is increase in tumor control to a greater extent than increase in normal tissue damage*

- *Moving the tumor control curve to the left farther than the normal tissue damage curve*

- *Consequently: an improved tumor control (B vs. A) is possible for the same probability of normal tissue injury (C):*

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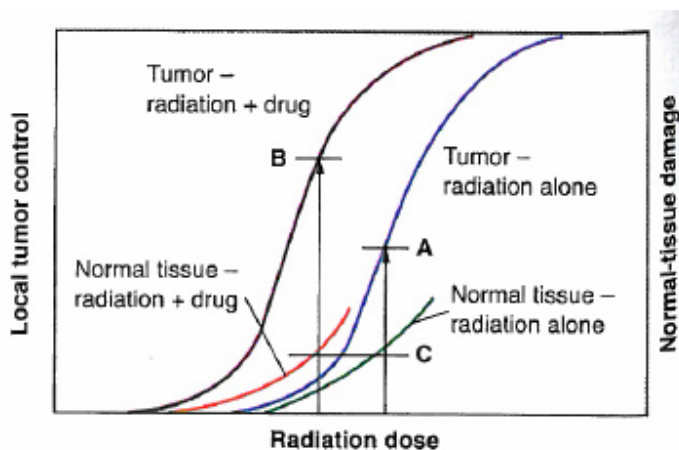
Problem 4

a) Two different mathematical models (the target theory and the linear-quadratic model) explain the shape of the dose survival curve for irradiated clonogenic cells in vitro. Explain the basis for the models, give adequate equations and define the different parameters used in each model.

Target theory: *Assuming there are specific sensitive regions (targets) in the cell. Survival after irradiation related to **number of targets** inactivated:*

- **_Single target – single hit_** _inactivation:_
  - _One hit by radiation on a single sensitive target would lead to cell death_
  - _Exponential survival curve (straight line in semilogarithmic plot (survival vs. dose))_

  Poisson statistics:

  $$P\ (survival) = P\ (0\ hits) = e^{(-D/D_0)}$$

  P (survival) = S = survival fraction of cells

  D= radiation dose

  D_0 _= dose given on average one hit pr. target_

- **_Multi target – single hit_** _inactivation_
  - **_n_** _independent targets must be inactivated (each by a single hit) for the cell to be inactivated_
  - _Survival curve with a shoulder in semilogarithmic plots (survival vs. dose)_

  Poisson statistics:

  P (0 hits on a specific target) = $e^{(-D/D_0)}$

  P (specific target inactivated) = 1- $e^{(-D/D_0)}$

  n targets in the cell:

  P (all n targets inactivated) = (1- $e^{(-D/D_0)}$)^n

  $$P\ (survival) = P\ (not\ all\ targets\ inactivated) = 1\text{-}(1\text{-}e^{(-D/D0)})^n$$

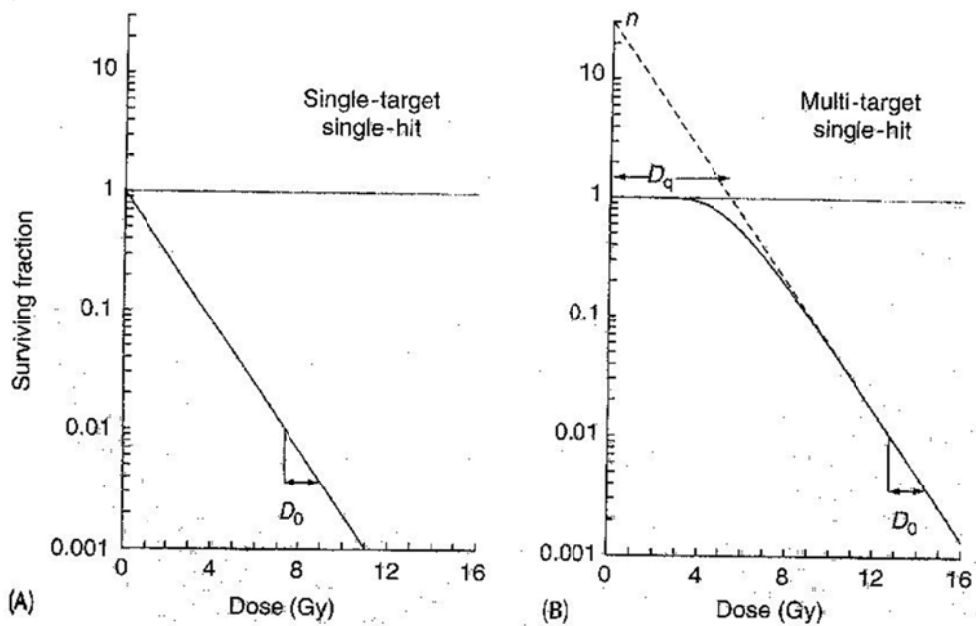_The equation for the tangent of the survival curve is dP/dD. The limit for large values of D is_

$$ne^{(-D/D0)} \qquad (stippled\ curve)$$

This curve crosses the D=0, at the «surviving fraction» n (see figure)

The quasithreshold dose D_q is the dose representing surviving fraction 1 on this tangent:

$$ln(n) = D_q/D_0$$

The theory can be expanded to multi hit inactivation

The linear quadratic theory

Cell survival can generally be described by:

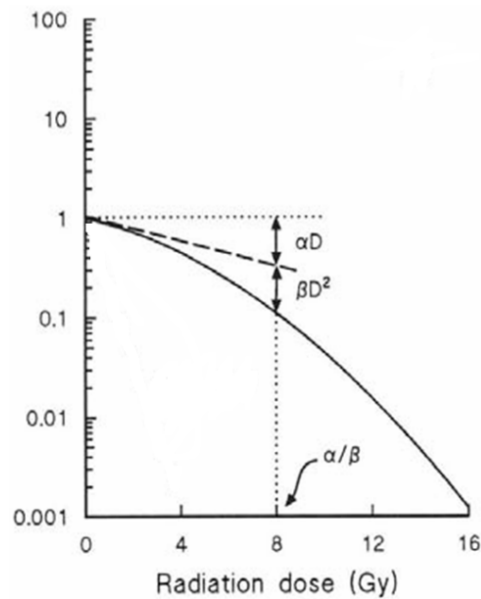$$S = e^{(-\alpha D - \beta D^2)}$$

S = survival fraction of cells

D = delivered dose

α and β are constants

Two components to cell killing by radiation:

- *α-component: Proportional to dose (irreparable – lethal)*

- *β-component: Proportional to the square of the dose (repairable – potentially lethal))*

  - *(dual radiation action – some chromosome aberrations are the result of two separate breaks)*

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The components of cell killing that are proportional to D and D² are equal when:

αD = βD² or D = α/β

The linear and quadratic contribution to cell killing are equal at a dose equal to the ratio α/β

The linear-quadratic model is most used the latest years. Why?

Problems with the target theory:

- **Specific radiation targets have not been identified for mammalian cells**

- *Predicts flat response for low radiation (not supported by experimental data)*

    - *The multi target model can be modified by adding an additional single target component. This type of curve predicts cell killing in the low dose region occurs almost linearly, implicating no sparing of damage should occur, which is usually not found experimentally.*
    - *A way of overcoming this limitation is to use a multi-target component as the initial slope, -* **making the model _very complicated_** *(with 4 parameters)……*

For exponential survival curves (straight line in semi logarithmic plot) the target theory (single hit – single target) is useful. For common survival curves with shoulders the target theory must be adjusted with extra parameters to give good fit to the observed shape of the curves. A biological explanation of the theory has not been well described.

b) α/β values in the linear-quadratic model are easily found from dose survival relationships in clonogenic assays. How can we infer α/β value from multifraction experiments in **non**clonogenic systems (as scoring of radiation effects on animal skin)?

Multifraction experiment with defined functional end points (example: Scoring of mouse foot or pig skin reactions). Doses that result in the same skin reaction delivered as single dose or fractionated regimens must be determined experimentally.

Assumptions:

- *The dose-response relationship is represented adequately by the LQ formula*

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

- *Each dose in the fractionated regimen produces the same biologic effect*
- *Full repair of sublethal damage takes place between dose fractions, but no cell proliferation occurs.*

The total dose D divided into n fractions of dose d:

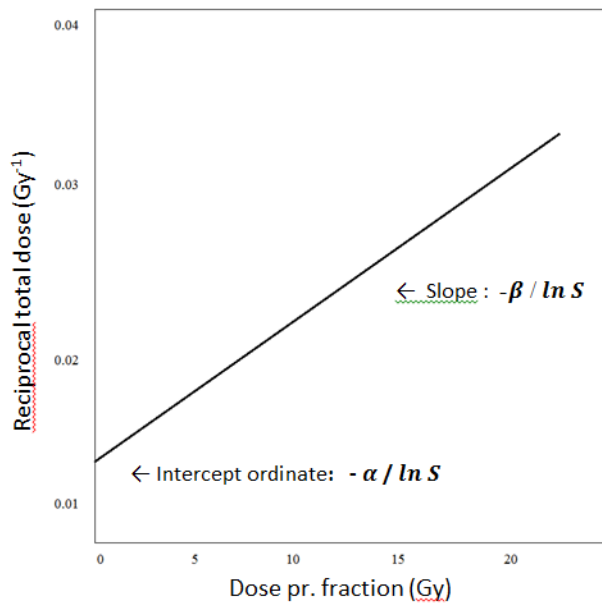$$S = (e^{-\alpha d - \beta d^2})^n$$

$$-\frac{\ln S}{nd} = \alpha + \beta d$$

For a given level of injury (equal S):

<u>Plotting (1/nd) against d:</u>

- *Straight line*
- *Intercept ordinate: $-\alpha / \ln S$*
- *Slope: $-\beta / \ln S$*

In general S is not known, but the <u>ratio of the intercept to slope gives estimate of α/β</u>

c) Give representative α/β values for early and late responding tissues.

Early responding tissue

- *α/β Larger ≈ **about 10 Gy (≈ 5 – 20 Gy)***

Late responding tissue

- *α/β Smaller ≈ **about 2 Gy (≈ 1 – 4 Gy)***

d) A patient receives external photon radiation therapy to a tumor with a known α/β value. A total dose D with fraction doses d is given. An equivalent total dose corresponding to fraction doses of 2 Gy (EQD$_2$) can be written:

$$\mathbf{EQD_2 = D\ (\frac{d+\ \alpha/\beta}{2+\alpha/\beta})}$$

Show how this equation is derived from the basic BED (biologically effective dose) formula.

Biologically effective dose (BED) for fractionated radiotherapy is defined by:

$$\boldsymbol{BED = D\ (1+\frac{d}{\alpha/\beta})}$$

*The BED of a radiation regimen with fraction dose d and total dose D can be converted to equivalent total dose in 2 Gy fractions (**EQD$_2$**) by:*

$$BED = D \left(1+ \frac{d}{\alpha/\beta}\right) = EQD_2 \left(1+ \frac{2}{\alpha/\beta}\right)$$

Rewritten:

$$EQD_2 = D \left(\frac{d+ \alpha/\beta}{2+\alpha/\beta}\right)$$

Problem 5

Radiation with photons is considered as standard therapy for cancer treatment. Neutrons, protons or heavier ions are alternative radiation modalities in cancer therapy. Give an overview of biological gains and disadvantages based on the individual radiation characteristics seen for each of these treatment modalities compared to the standard radiation therapy.

Neutrons

Characteristics:

- *High LET radiation*
- *Depth dose similar to photons*
- *Straighter dose survival curve than photons*

Advantages:

- *Reduced oxygen enhancement ratio (OER) vs. photons. May overcome the relative radioresistance of some tumors because of hypoxia (seen for photon radiation)*
- *Relative biologic effectiveness (RBE) larger for slow growing tumors*

Disadvantages:
   Straighter survival curve implies:
- *Loses the differential sparing effect between tumor and late responding normal tissue characteristic for photons*
    - *Little or no repair of sublethal damage and potentially lethal damage*
    - *Unacceptable late damage to normal tissue in many cases*
    - *Higher incidence of radiation induced secondary cancer*
- *Less variation of sensitivity through cell cycle*

    - *Cells in normal tissue spend less time in the radiosensitive phase (G_2/M) than do cycling tumor cells. The relative sparing of normal tissue is lost by use of neutrons*

There has been some use of neutrons for radiation therapy from 1930, but neutrons have never become mainstream in radiotherapy and are not in use today.

Protons

Characteristics:
- *Charged particles*
- *Dose delivered in an intense burst of ionization (the Bragg peak)*
- *Mostly low LET (High LET in the Bragg peak)*

Advantages
- **Superior physical dose distribution**
  - *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*
- **Radiobiological properties (RBE and OER) similar to photon radiation**
- *For the same tumor dose, protons will deliver a lower dose to a smaller volume of normal tissue than high energy photons.*

Proton therapy is a favorable treatment modality especially for tumors located near radiation sensitive critical organs.

Heavy ions

- *Charged particles (mostly used: carbon-ions)*
- *Dose delivered in an intense burst of ionization (the Bragg peak)*
- *Higher LET*

Advantages:

- *Lower OAR vs. photons. May overcome the relative radioresistance of some tumors because of hypoxia (seen for photon radiation)*

- **Favorable depth dose distribution**

- *High cell killing effectiveness*

Disadvantages;

- *Loss of repair capacity (due to higher LET)*

  - *Dose fractionation would no longer result in a differential sparing of normal tissue*

- *Smaller variation in radiosensitivity with phase of cell cycle*

Hypofractionated radiotherapy (one or two large fractions) is used
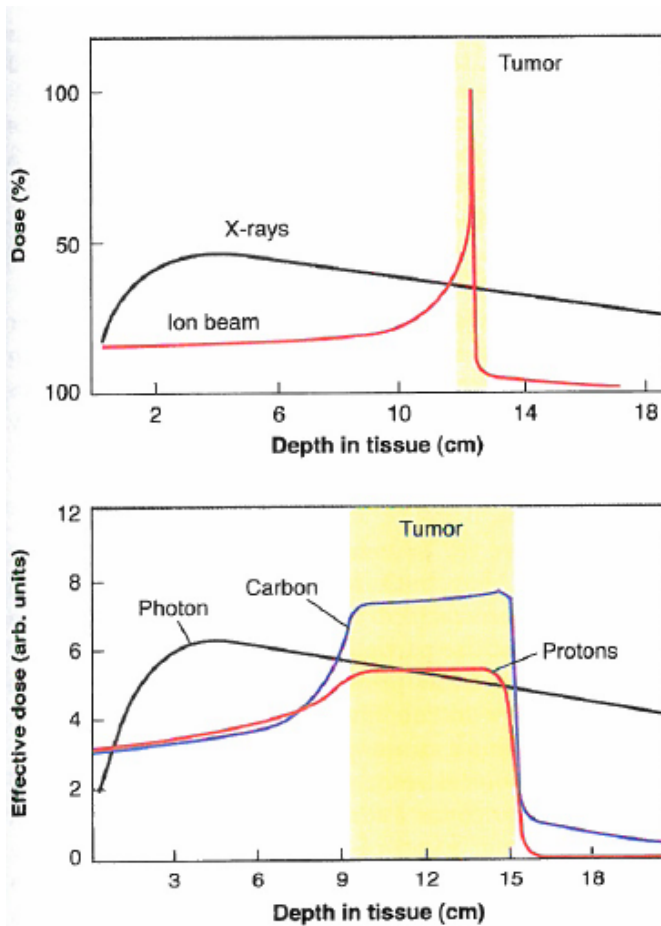
FIGURE 25.8 Illustrating the depth-dose profiles for protons and carbon ions compared with conventional high-energy photons. **Top panel:** Both protons and carbon ions are characterized by a sharp Bragg peak at the end of the particles' range, but it is too sharp and too narrow to encompass a tumor of realistic size. **Bottom panel:** By using a range shifter, or by varying the energy of the beam, the Bragg peak can be spread out to encompass a tumor of any size at any depth. For both protons and carbon ions, the dose to the tumor, located in the SOBP, is higher than in the normal tissue ahead of the SOBP, but the differential is greater for carbon ions because part of the radiation dose in the SOBP has a high LET and has a correspondingly higher RBE.