Solution Exam TFY5135 Biophysics of ionizing radiation
June 6, 2015

Exercise 1 Survival curves

a)

Linear quadratic model

Survival given by

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

Advantages

- In the first 1 – 2 decades of the surviving curve the model is well corresponding to experimental data and doses used in radiation therapy
- Can be characterized by only 2 parameters α and β and the α/β-ratio characterize the cell survival curve

Limitations

- The cell survival curve in the model is continuously bending. For higher doses this does not coincide with experiments when survival curves are determined down to 7 or more decades, showing a more straight line (exponential function of dose)

Multitarget model

Equation for n=1 hit and m= number of target

$S=1-(1-e^{(-D/D0)})^m$

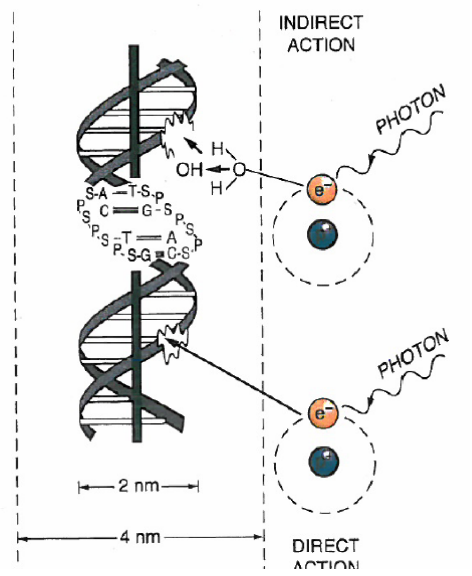
Advantages

- Exponential function toward straight line at very high doses which is more relevant than the LQM

Limitations

- Predicts flat response for low radiation (not supported by experimental data)
- Several parameters needed

b) Direct and indirect action



Indirect action:

-Radiation produces secondary electrons which interact with other atoms or molecules in the cell, particularly water, to produce free radicals which diffuse and damage critical targets such as DNA. The radicals have a very short half live of typical 10^{-9} s

-Radiation working through indirect action is primarily x-rays

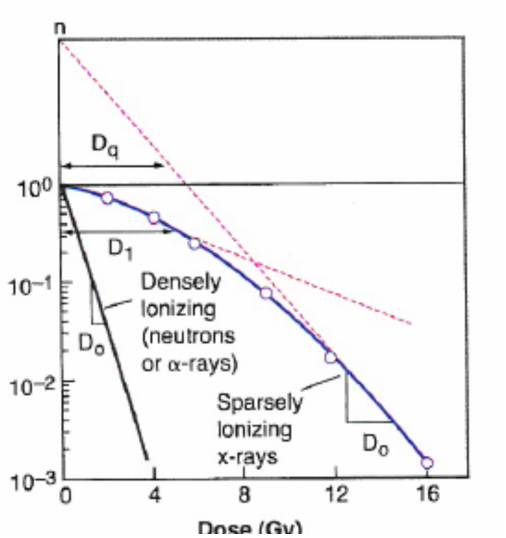
Direct action:

- Ionizing radiation produces secondary electrons that directly interact with the critical target DNA.

-Neutrons works by direct action. The neutrons do not produce electrons but recoil proteins that works through direct action.

-Heavy ions for instance α-particles –direct action

Survival curves:

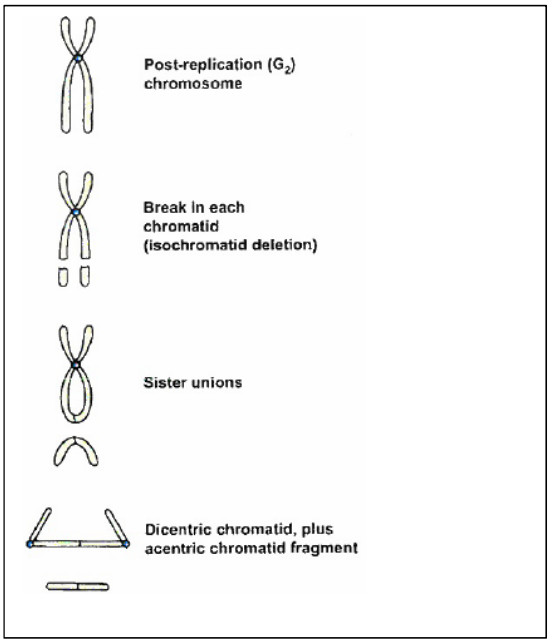


- Survival curve describing direct action is purely exponential. There is no repair of sublethal damage.
- Survival curves describing indirect action have a shoulder and the width of the shoulder represents the ability to repair sublethal damage.

c) Anaphase bridge

-Anaphase bridge is a chromatid aberration, and both chromatids are broken after DNA replication in S-phase, i.e.in late G2. The sticky ends formed at the break might rejoin incorrectly forming a sister unions. The two fragments of the chromatid may also rejoing forming a DNA sequence without any centromere. In mitosis the cells is dividing.

-The mitosis consists of 5 phases. In anaphase the two chromatids are supposed to be separated and dragged to each of the two spindle poles in the cell. However when the sister union is formed the two chromatids cannot be separated and the chromosome rather form a bridge between the two spindle poles. When the two chromatids are not separated properly the cells can not complete mitosis and the cell will die. When the half of the DNA has not reached each of the spindle poles the cells will be stopped in mitosis not being allowed to complete it and then die. The two small fragments of the chromatids having no centromere will be lost.



Exercise 2

a) Fractionated radiotherapy

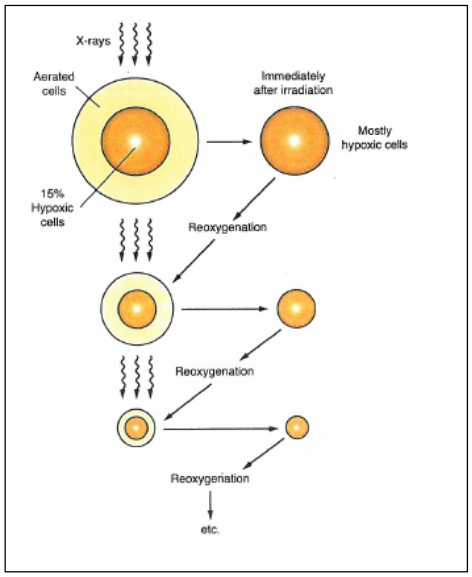
Normal tissue: fractions spare normal tissue through

-repair of sublethal damage between dose fractions. To have a benefit of sublethal repair the repair of normal cells has to be more effective than repair of tumour cells.

- *repopulation* of cells if the time between doses is sufficient long cells are deving forming new healthy cells. However the timing has to be choosen to avoid tumour cells also to repopulate.

Cancer tissue: fractions increases damage through

- ***Reoxygenation***..



Hypoxic cells become oxygenated after a dose of radiation. The aerated radiosensitive cells are killed by x-ray. Immediately after radiation radioresistent hypoxic cells are viable they will now have access to blood vessels and become reoxygenated and more radiosensitive

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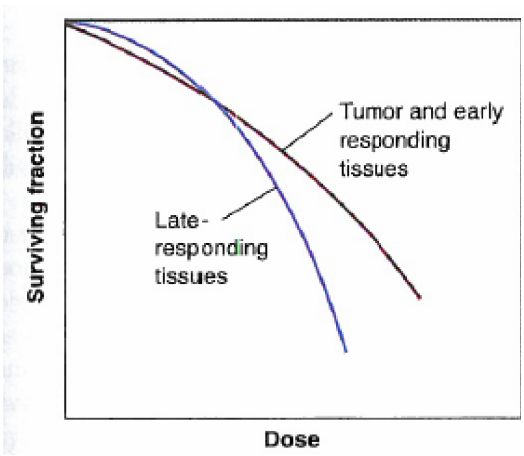
- Reassortment of cells into radiosensitive phases.

Radiation will kill the radiosensitive cells in G2 and mitosis. The surviving radioresitant S-phase cells will within some hours move into te radiosensitive G2+mitosis and if another fraction of radiation is the given the cells will dye.

b) Late and early responding tissue



Late responding tissue

- More curved for late responding tissue
  Larger shoulder, i.e more sublethal repair
  - Smaller α/β, Typical α/β=3Gy
  - Curved part more important, i.e. two and quadratic dose dependence
  -

Early responding tissue

- Less curved for early responding tissue
  Less shoulder, i.e less sublethal repair
  - Larger α/β, Typical α/β=10Gy
  - Linear part more important, i.e. one electron proportional to dose D

Late effects:

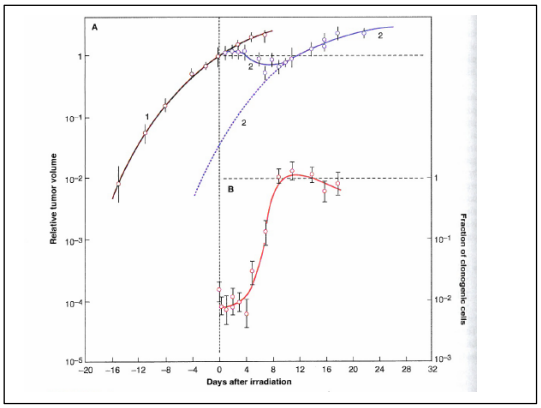
- Fraction size dominate factor
- Overall treatment time little influence

Early responding tissue:

- Both fraction size and overall treatment time determine the response

c) Accelerated repopulation

Radiation can trigger cells to divide faster. It has been found for tumour in rat that during the time the tumor is shrinking and regressing after radiation, the surviving clonogenic cells are dividing and increase in number more rapidly than before radiation. This leads to that the overall tumour growth is faster than for tumours not exposed to radiation. See figure



To account for accelerated repopulation the dose of radiation has to increase. The overall treatment time should not increase to avoid too much cell growth, thus the dose per fraction should be increased or number of fractions keeping the normal dose per fraction.

Exercise 3

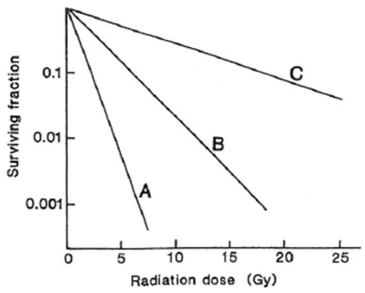
a) Brachytherapy

Implanting radioactive sources directly into tumor.

Sparing surrounding tissue compared to external radiation in some areas

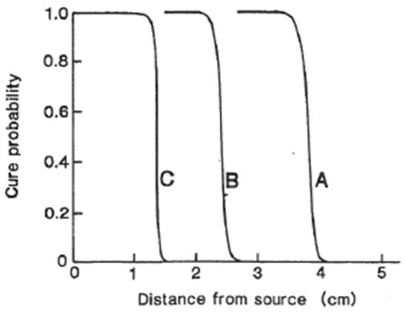
- *Intracavitary*
  - Using radioactive sources placed in body cavities in proximity to the tumor

- *Interstitial*
  - Radioactive wires or seeds implanted directly into the tumor volume



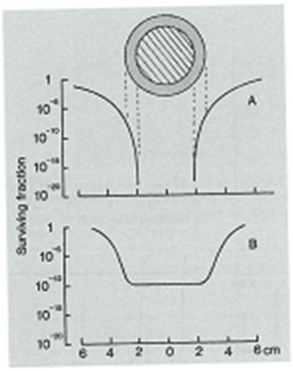
Close to the source

- High dose rate
- Survival curve pure exponential
- Cells of any radiosensitivity will be killed



Moving away from the source

- Cells will be less sensitive at the lower dose rates
- Cliff- like change from high to low local cure probability
- The distance of the cliff from the source is determined by the radiosensitivity of the cells at low dose rate
- Nearer for radioresistant cells
- Further away for radiosensitive cells



Between:

- Zone with differential cell killing
- Change from high to low survival over a radial distance of a few mm.
- A-B Compare brachytherapy and optimal external

b)Reasons for combing chemotherapy and radiotherapy

1.Drug make cancer cells more sensitive to radiotherapy through:
The drug kills cells in other phases than mitosis, kills cells in G1, S-phase and G2. Radiation kills then mitotic cells.

2.Spatial cooperation: Radiotherapy kills the primary tumour cells and metastases localized and often close to the primary tumour, and chemotherapy kills more distant and smaller metastases.

3.The drug make hypoxic cells more radiosensitive or actually kills hypoxic cells.

c)Proton therapy

Benefit of proton therapy

The dose deposited by beam of monoenergetic protons:

- increases slowly with depth
- reach a sharp maximum near the end of the particles' range **(Bragg peak)**
- falls to zero after the Bragg peak, at the end of the particles' range
- The Bragg peak occurs at a depth in tissue depending on the initial energy of the protons
- minimize the dose to surrounding normal tissue
- Proton therapy delivers a lower absorbed dose to normal tissues than high energy X-rays for the same dose to target volume
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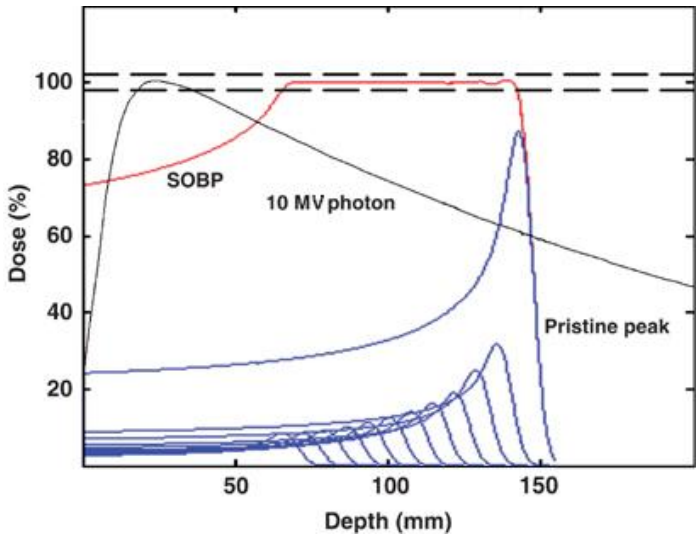
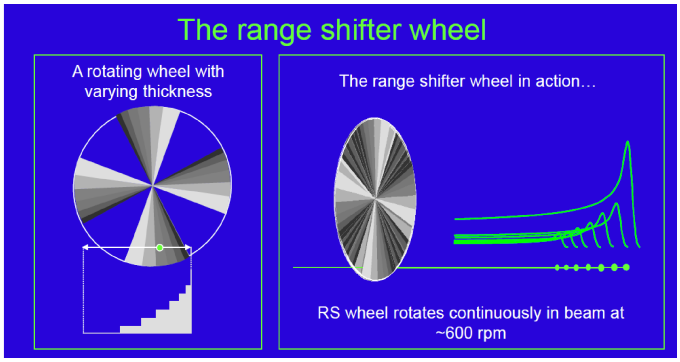


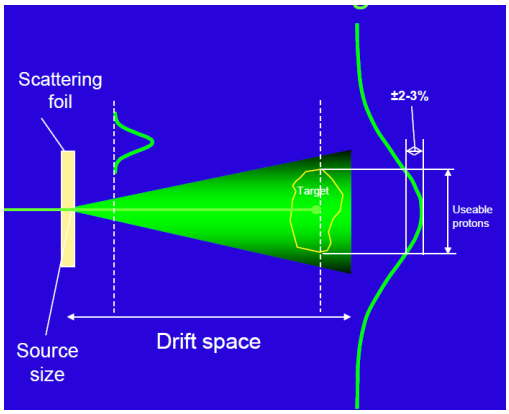
Red line: Spread out Bragg peak in a typically therapeutic radiation distribution.
The depth dose plot of a 10 MV photon beam is provided for comparison

Bragg peak is needed to be spread out to expose the whole tumour as seen as SOBP in the figure- This is done by passive scattering or active scanning

Passive scattering:
-Spreading the Bragg Peak in the depth of the tumour producing the SOBP dose distribution.
-Spreading the SOBP laterally

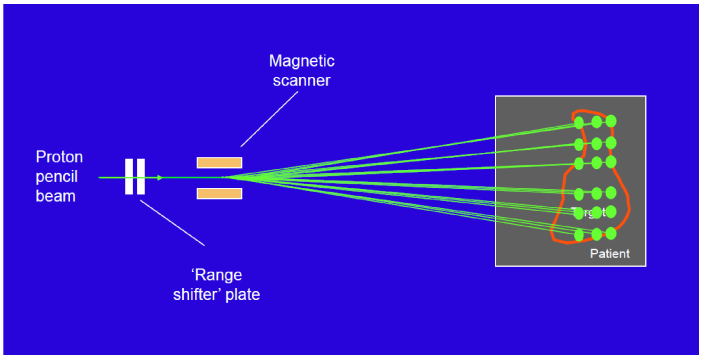


The Bragg peak is expanded in the depth of the tumour by using a rotating wheel with varying thickness to modulate the energy to obtain beams of lower intensity and shorter range producing the SOBP distribution



Spread out the beam laterally using a scattering foil. Broadening the beam Gaussian typically 20 cm

Active scanning: Spreading the proton beam laterally across the tumour, and deliver the Bragg peak also in depth of the tumour.



Lateral spreading:

- Spreading out the beam utilizing the charge of the proton to magnetically scan proton pencil beams across the target.
- Dose is confined to the target by actively steering the individual proton ”pencil”-beams such that only the Bragg peaks that stop in the target volume are delivered.

In depth scanning:

- ”Scanning” of beam is performed in depth through the use of Bragg peak specific energy modulation using a range shifter plate in the beamline
- Homogeneity and conformation of dose to target is achieved through mathematical optimisation of weights of individual proton beams.

Exercise 4 calculations

a) Pure exponential survival curve

$$N = N_o e^{-D/D_o}$$
$$1 = 10^8 e^{-D/3Gy}$$
$$\ln 10^{-8} = -D/3Gy$$
$$D = 3Gy \cdot 8 \cdot \ln 10 = \underline{\underline{55,3\,\text{Gy}}}$$

Alternative calculations using D_{10} =ln10·Do=ln10·3Gy=6,9Gy
8 log of cells has to be killed.
The dose is thus: D=8·6,9Gy=<u>55,3Gy</u>

b) BED for standard treatment:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) = 30 \cdot 2Gy(1 + \frac{2Gy}{3Gy}) = 100Gy$$

Hypofraction number of fractions:

$$BED = n4Gy(1 + \frac{4Gy}{3Gy}) = 100Gy$$
$$n = 10,7 \approx \underline{\underline{11}}$$

11 fractions should be given to maintain the same BED.

c) The increase in number of cells will result in a reduced biological effect.
The number of the exponentially growing tumour cells is given by:

$$N = N_o e^{kt}$$
$$2N_o = N_o e^{kT_d}$$
$$k = \ln 2/T_d$$

During 40 days of treatment the biological effect is reduced by:

$$E = \frac{\ln 2}{T_d} t$$

The biological effective dose is reduced by:

$$\frac{E}{\alpha} = \frac{\ln 2}{\alpha \cdot T_d} t = \frac{\ln 2}{0,3/\text{Gy} \cdot 4\,\text{d}} 40d = \underline{\underline{23,1Gy}}$$

Thus the additional dose to compensate for the cell growth is 23,10 Gy

Exercise 5. Multiple choice (Credit 1)

a) A charged particle is passing by an atom in the tissue. The probability for energy transfer increase with:
- Increasing the speed of the charged particle
- ***Increasing the charge of the particle***
- Increasing the mass of the particle

b) Radiosensitivity changes through the cell cycle. Rapidly growing cells is most radiosensitive in:
- G1
- S-phase
- ***Mitosis***

c) Sublethal damage occurs not for:
- x-rays
- ***Neutrons***
- γ-rays

d) A reduction in the dose rate and corresponding increased exposure time lead to:
– Slope of survival curve increases
– ***Slope of survival curve decreases***
– The shoulder of the survival curve increases

e)Which of the following statement is not correct?
Hypoxic cells become oxygenated due to:
- Angiogenesis
- Hyperthermia
- ***Synchronizing the cell population***

f)Which of the following is correct about hypoxic cells?
- They are dead cells
- ***They have a very low proliferating rate***
- They have a very high proliferating rate

g)Linear Energy Transfer (LET) indicates energy transferred per unit length of the track. With increasing energy for a given type of charged particle, LET will:
- Increase
- ***Decrease***
- Be unchanged

h)The relationship between LET and the relative biological effectiveness (RBE) when plotting RBE as a function of LET is:
- REB increases linearly with LET
- RBE decreases linearly with LET
- ***RBE reach a maximum for a certain value of LET***

i)When calculating effective dose you need to know the radiation weighting factor W_R. What is W_R. for α-particles?

- 1
- 5
- ***20***

j)Which diagnostic modality induces the highest radiation exposure to the patient?

- Conventional x-ray
- ***CT***
- PET

k)What are the two general classifications for ionizing radiation?

- Neutrons and α-particles
- X-rays and γ-rays
- ***Electromagnetic and particulate radiations***

l)Which of these tissues or cells respond late to ionizing radiation?

- Skin
- ***Lung***
- Blood cells

m)Which following particles have the shortest range?

- electrons
- neutrons
- ***α-particles***

n)In a rapidly growing cell line, which of the phases in the cell cycle have longest duration?

- G1
- ***S-phase***
- G2

o)Targeted radiotherapy is based on:

- ***A pure radioactive isotope with affinity towards the tumour tissue***
- Focus the x-ray toward the tumour
- Thermosensitive liposome carrying a drug

P)The Oxygen enhancement ratio for α-particles is?

- ***1***
- 2.5
- 10

q)What is the most common mechanism for death of normal cells?

- ***Mitotic death***
- Apoptosis
- Necrotic death

r)Normal cells are radiosensitive if:

- ***They have a high proliferating rate***
- They have a low proliferating rate
- They are well differentiated

s)Hyperthermia can be combined with radiotherapy. What is the target for hyperthermia?

- DNA
- ***Protein***
- Both DNA and protein