Chapter 3 – Lecture 2

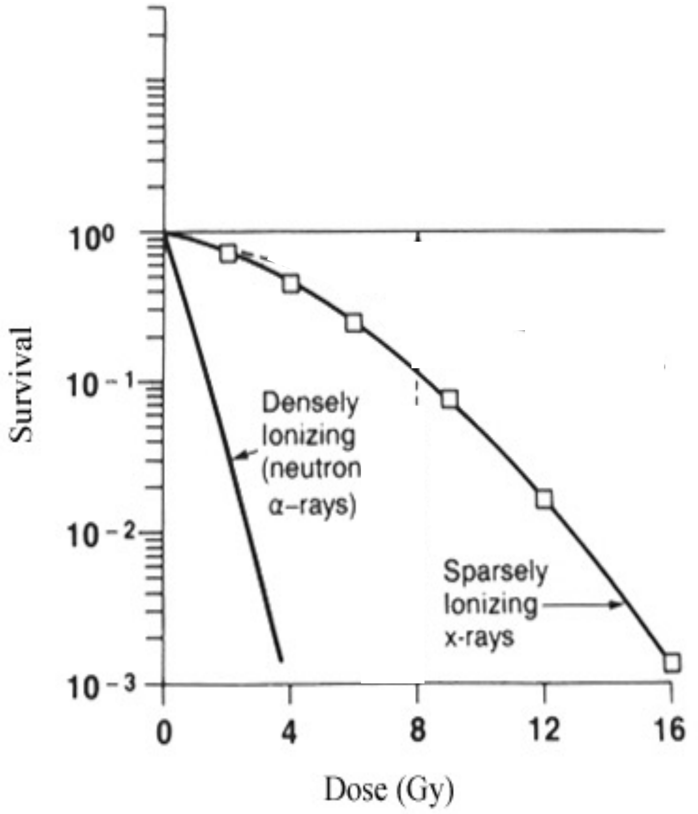
Cell Survival Curves
9/19/2024

Lecture Outline

- **Shape of the Survival Curve**
- Survival Curves for Various Mammalian Cells In Culture
- Survival Curve Shape and Mechanisms of Cell Death
- Oncogenes and Radioresistance
- Genetic Control of Radiosensitivity
- Intrinsic Radiosensitivity and Cancer Stem Cells
- Effective Survival Curve for a Multi-fraction Regimen
- Calculations of Tumor Cell Kill
- The Radiosensitivity of Mammalian Cells Compared with Microorganisms

Cell Survival Curves

- Survival curves are plotted on a log-linear scale
- **High LET** – survival curves are linear (i.e., the SF is an exponential function of dose)
- **Low LET** – curve starts out straight → bends → straighten again



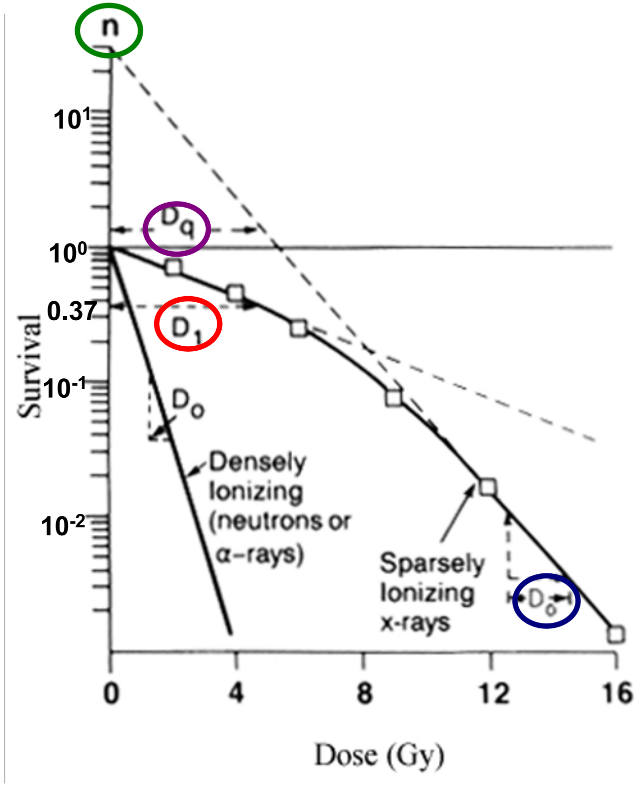
Qualitative Description

Shape of Cell Survival Curves

- The interpretation of the shape of the cell survival curve is still debated, as is the best way to fit these types of data **mathematically**

- 2 models will be discussed
  - **The Target Theory**
  - **The Linear-Quadratic Model**

Target Model



α-ray or neutron – D_0 is adequate

X-ray or γ-ray
Characterized by 4 parameters

Initial slope (D_1) – Dose to ↓ SF to 37% of its previous value on initial portion of the curve

Final slope (D_0) – Dose to ↓ SF to 37% of its previous value on straight line portion of the curve

Extrapolation number (n) – Estimate of width of the shoulder

Quasi-threshold dose (D_q) – *Almost* a threshold dose, dose below which radiation purportedly has no effect

Target Model

- Major problem with this model is that there are too many parameters
- Need a mathematically simpler model with fewer “unknown” parameters
- The **Linear-Quadratic Model** meets these needs and has taken over as the model of choice

Linear-Quadratic Model

- Based on the notion that lethal aberrations are the result of an interaction between 2 separate chromosomal DSBs

- Assumes that there are two components to radiation-induced cell killing (also called the dual radiation action theory)

Linear component

(*i.e.*, proportional to the dose)

Two chromosome breaks caused by the passage of a single charged particle

Quadratic component

(*i.e.*, proportional to the square of the dose)

Two separate chromosome breaks caused by separate charged particles

Dose Response – “2 Hits”

Exchange-type Rearrangements = “2 hits”

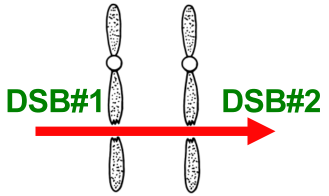
Dependent upon

SPACE = proximity

TIME = interaction

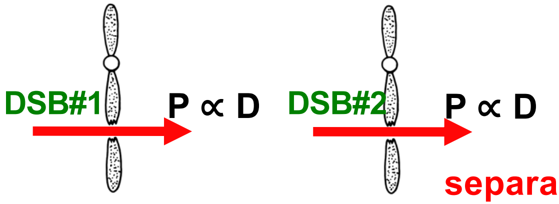
$Y = \alpha D + \beta D^2$

Linear component **Quadratic component**



single e⁻ track

$Y = \alpha D$



separate e⁻ tracks

$P = D \times D = D^2$

$Y = \beta D^2$

The Linear Component – α Type Damage

D is the radiation dose delivered

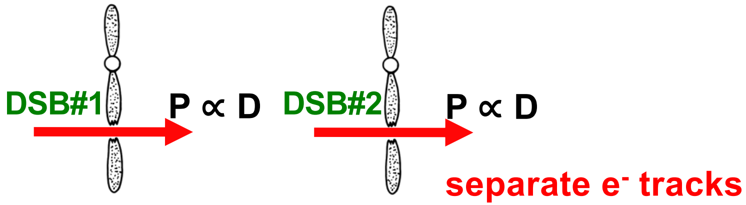
$$\textbf{Survival Fraction (SF)} = e^{-\alpha D}$$

α is the slope and a measure of the intrinsic radiation sensitivity

$$Y = \alpha D$$

The Quadratic Component – β-Type Damage

- Probability that one chromosome break will occur is linearly proportional to dose, D
- Probability that the other chromosome will be hit in an **independent** event is also proportional to dose, D
- Probability that both events will occur is, therefore, proportional to D^2, hence



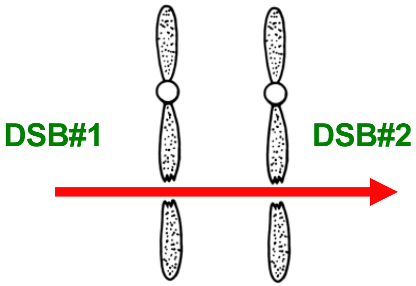
$$SF = e^{-\beta D^2}$$

$$P = D \times D = D^2$$
$$Y = \beta D^2$$

Linear-Quadratic Model

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

- α represents the probability of α damage, which is **irrepairable**

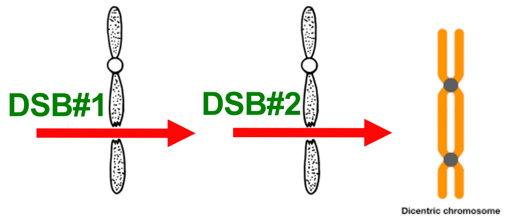


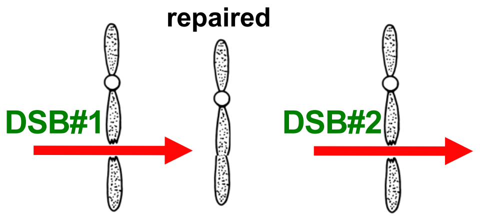
Temporally and spatially favorable for 2 DSBs to interact to form lethal aberrations

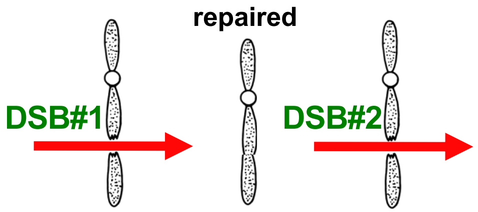
Linear-Quadratic Model

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

- β represents the probability that independent **repairable**, β-type events have combined to produce lethal events







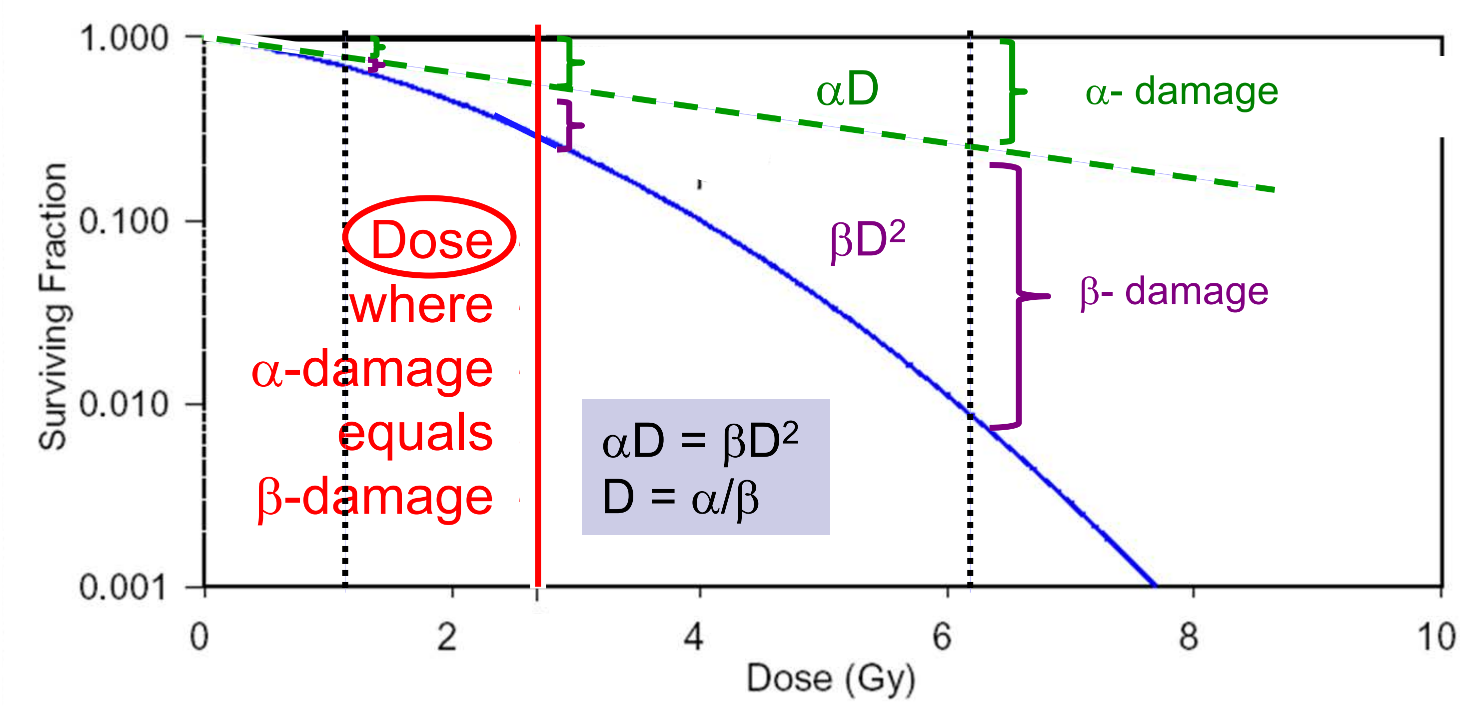
2 DSBs created during the same fraction of radiation, and spatially favorable to interact to form lethal aberration

- 2 DSBs created during the same fraction of radiation, but far apart
- DSB#1 is repaired before it can interact with DBSB#2

- DSB#1 was created during 1st fx
- DSB#2 was created during 2nd fx
- One or both repaired before they can interact

α/β Ratio

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

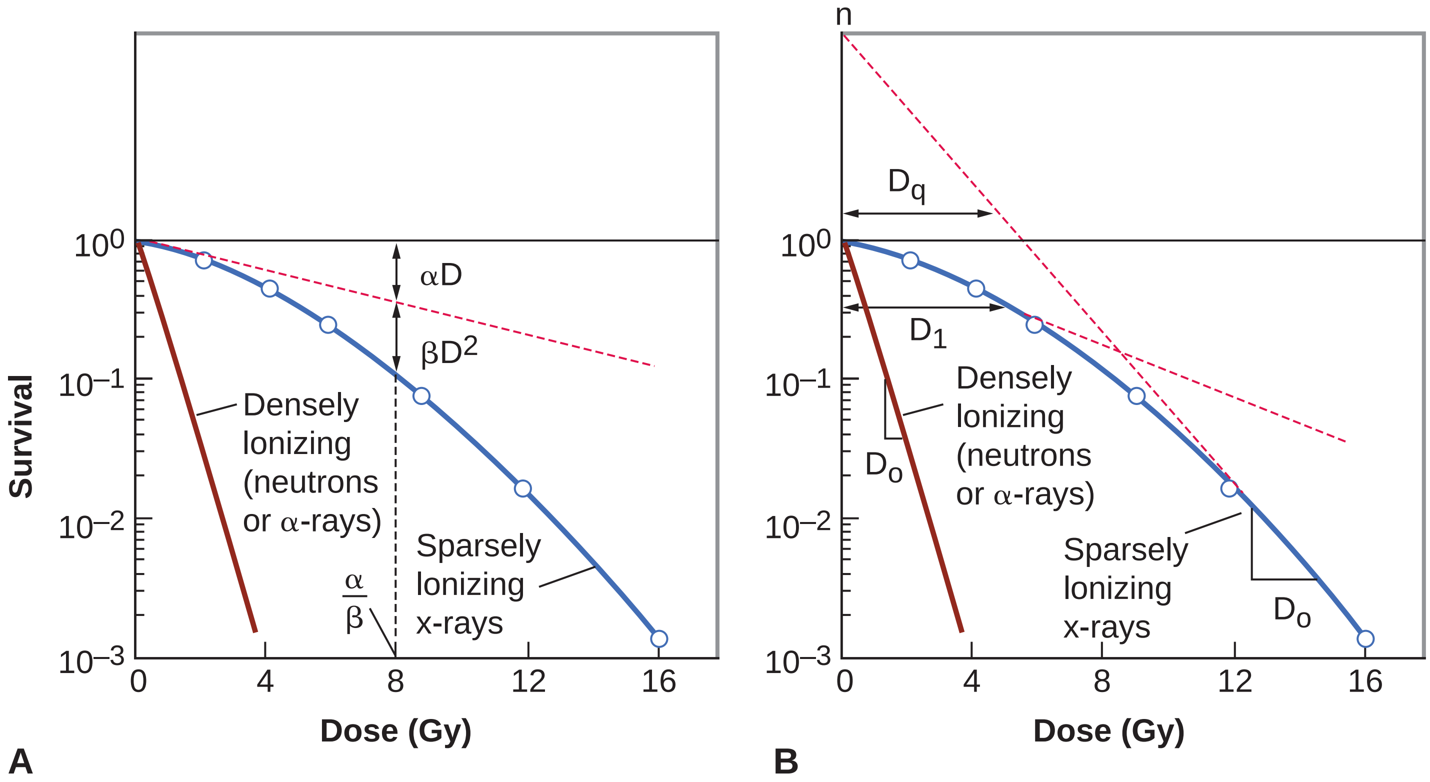


αD = βD²
D = α/β

Limitation of the Linear-Quadratic Model

- With L-Q model, survival curve is continuously bending, i.e., no final straight portion
- However, in the first decade or so of cell killing and up to any doses used as daily fractions in clinical radiotherapy, the L-Q model is an adequate representation of experimental data
- Simpler compared to multi-target model as there are only 2 parameters, α and β

Comparison of the L-Q and Target Theory Models



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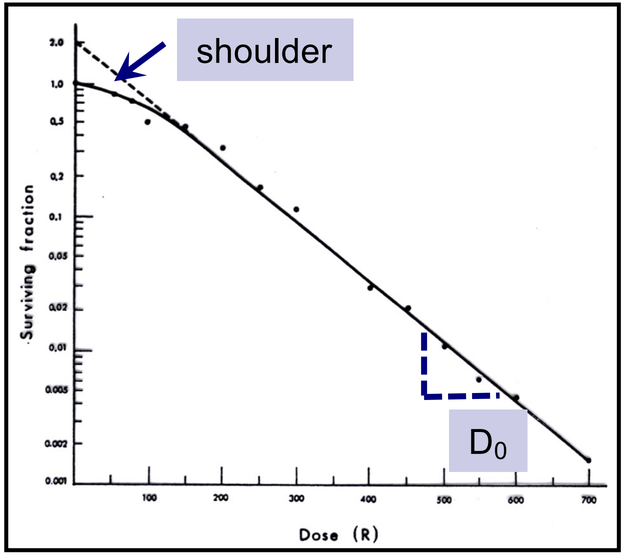
Survival Curve for Hela Cells

- The first *in vitro* survival curve for mammalian cells irradiated with x-rays was reported in 1956



Hela cell

All mammalian cells studied to date exhibit x-ray survival curve similar in shape, i.e., an initial shoulder followed by a portion that tends to become straight on a log-linear plot

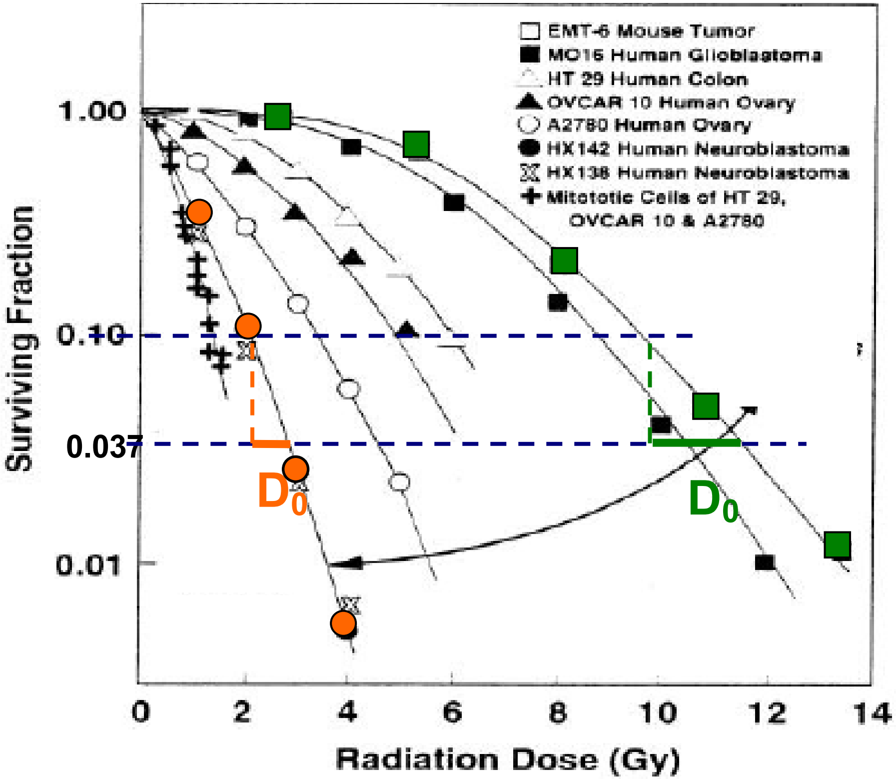
In vivo dose-response curves are similar

HeLa Cells

- The HeLa cell line was established in 1951 from a biopsy of a cervical tumor taken from **He**nrietta **La**cks, a working-class African-American woman living near Baltimore
- The cells were taken without the knowledge or permission of her or her family, and they became the first human cells to grow well in a lab
- They contributed to the development of a polio vaccine, the discovery of human telomerase and countless other advances
- Scientists have grown an estimated 50 tons of HeLa cells, and there are almost 11,000 patents involving these cells.

Henrietta Lacks with her husband David.

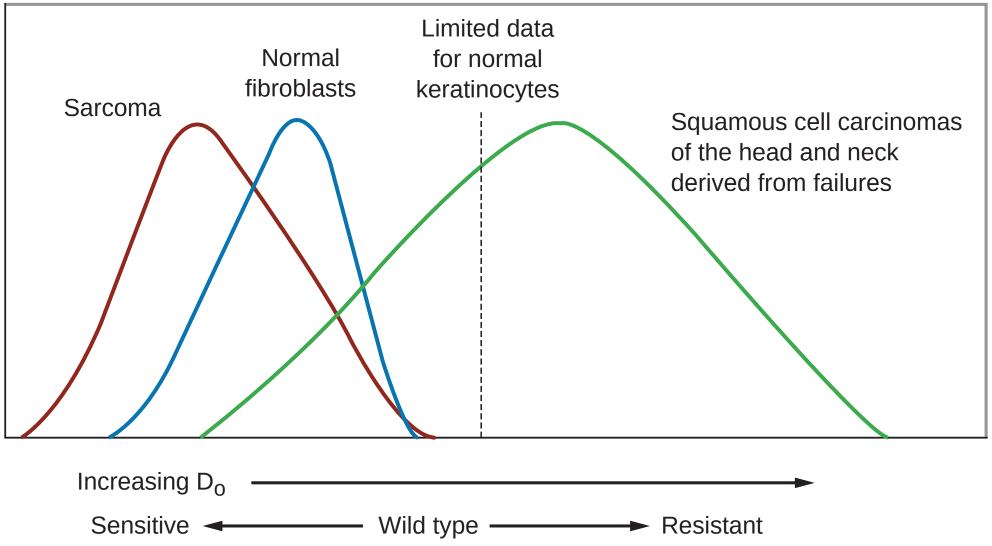
Cell Survival Curves for Various Cell Lines



- Mammalian cells culture *in vitro* vary considerably in their sensitivity to killing by radiation
- Note the difference in D_0 and extreme variability in the size of the shoulder

D_0 for Cells of **Human Origin**

- **D_0** is the dose required to reduce the SF to 37% of its previous value on the straight portion of survival curve
- It is a measure of radiosensitivity
- D_0 =**1-2 Gy** for most cells cultured *in vitro* (exception = AT Cells; D_0=**0.5 Gy**)



In general, cells from a given **normal tissue** show a narrow range of radiosensitivity

By contrast, cells from **human tumors** show a broad range of D_0 values, which brackets the radiosensitivity of normal human fibroblasts

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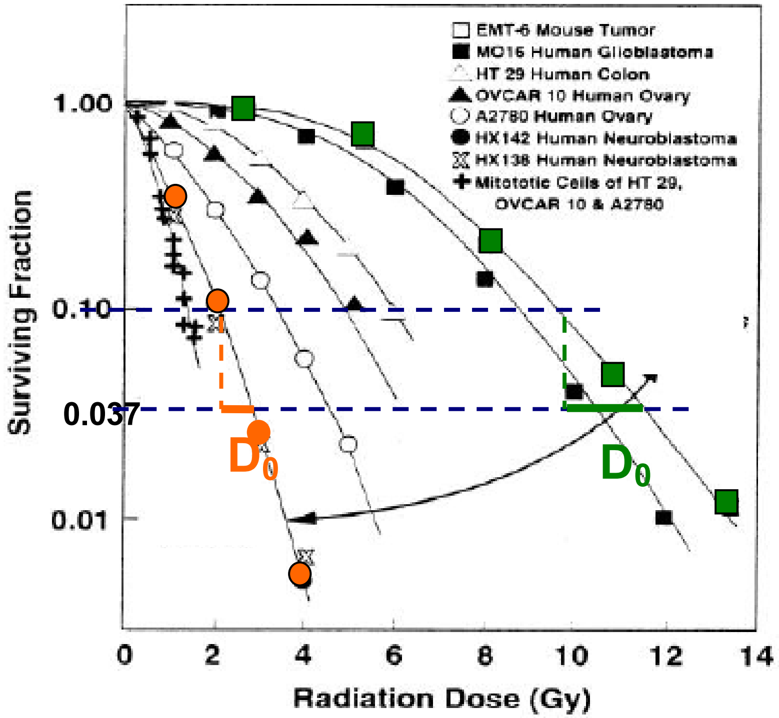
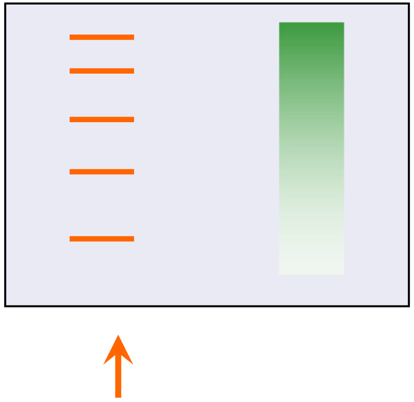
Survival Curve Shape and Mechanism of Cell Death



DNA Agarose Gel

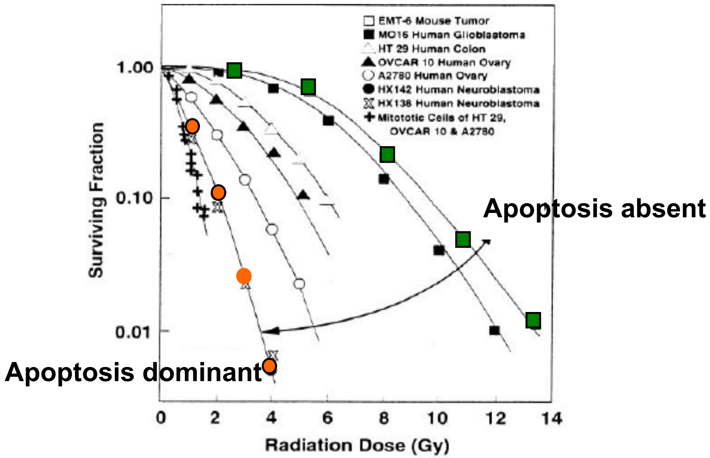


DNA laddering indicates apoptosis

Survival Curve Shape and Mechanism of Cell Death

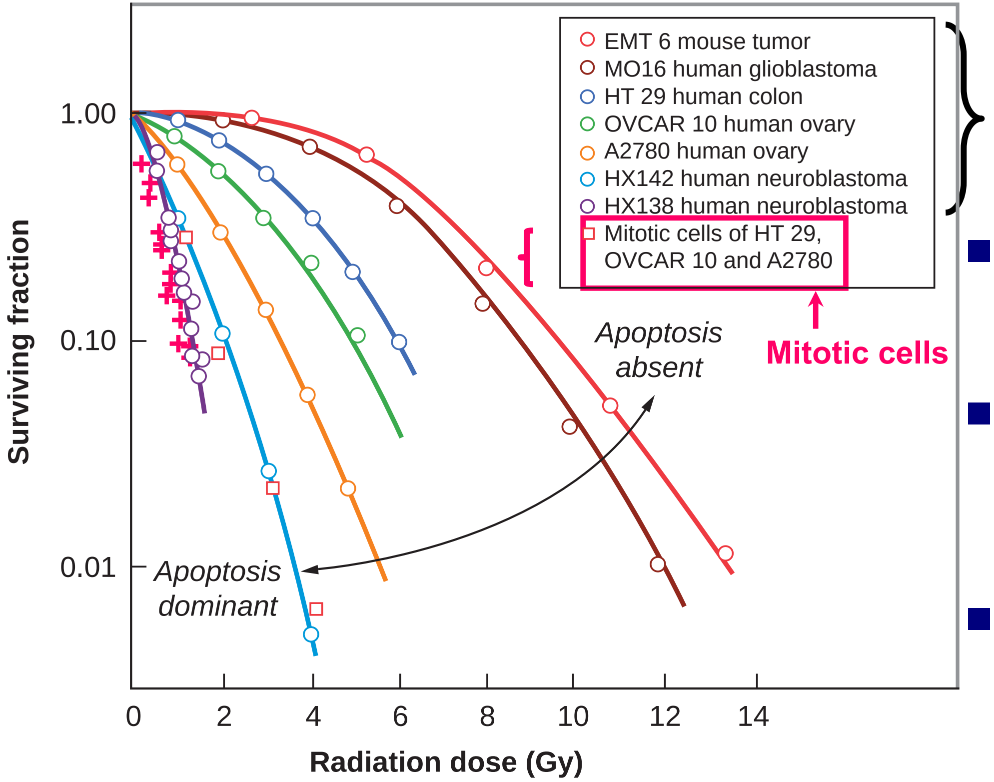
There is a close correlation b/w radiosensitivity and the importance of apoptosis

- **Apoptotic death** is a form of programmed cell death – the associated cell survival curve appears to be a straight line on a log-linear plot
- **Mitotic cell death** results from exchange-type chromosomal aberrations – the associated survival curve is curved in a log-linear plot, with a broad initial shoulder



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

Survival Curve Shape and Cell Cycle



Asynchronous cell

- Asynchronous cells show a wide range of radiosensitivity
- **Mitotic cells from all of the cell lines have essentially the same radiosensitivity**
- Implication – radiosensitivity is governed by DNA content and conformation

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Oncogene and Radioresistance

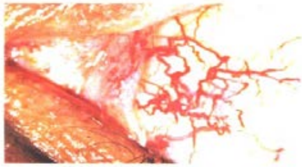
- Transfection of activated oncogenes into cell cultured *in vitro* increases their radioresistance
- Examples of oncogenes include activated N-*ras, raf*, or *ras* + *myc*
- It is unclear that oncogene expression is directly involved in the induction of radioresistance

Inherited Human Syndromes Associated with Radiosensitivity

- Ataxia telangiectasia (AT)
- Seckel syndrome
- AT-like disorder
- Nijmegen breakage syndrome
- Fanconi’s anemia
- Homologues of RecQ - Bloom syndrome, Werner syndrome and Rothmund-Thompson syndrome

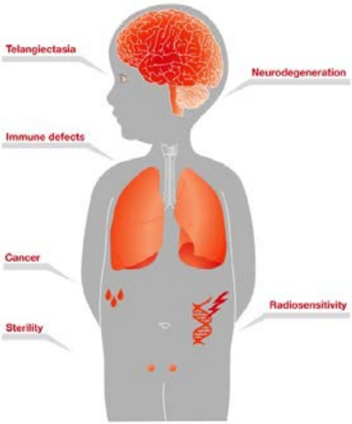
Ataxia -Telangiectasia Syndrome

- AT is a rare autosomal recessive disease
- AT patients exhibit a hypersensitivity skin reaction to IR and DNA breakage agents, but not UV light

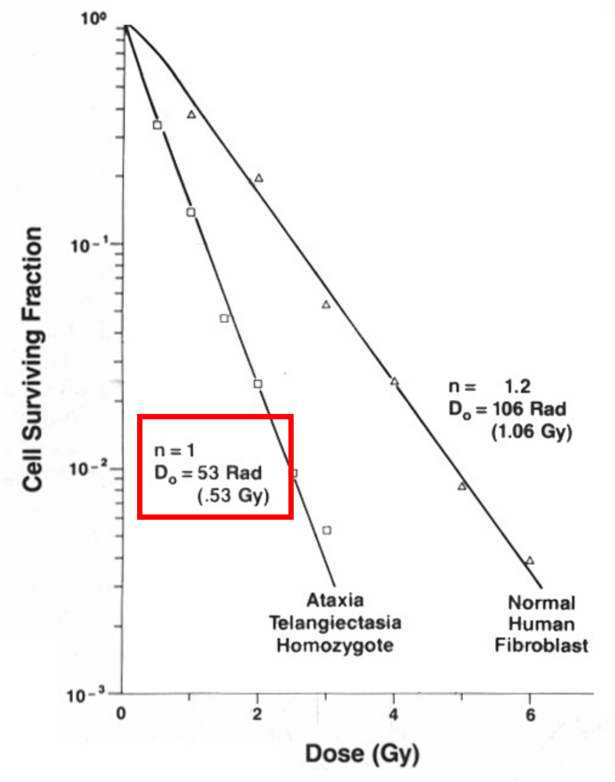


Oculocutaneous telangiectasia

Cerebellar ataxia



Survival Curve of AT Cells



- Fibroblasts from AT patients are 2-3x as radiosensitive as normal
- **$D_0 \approx 0.5$ Gy**
- This is at least in part due to **decreased ability to repair DSB**

- The gene associated with AT is called the **ATM** (AT-mutated)
- ATM protein is involved in many important DNA damage response

- Cells from AT heterozygoes are slightly more radiosensitive than normal

Heritable Syndromes That Affect Radiosensitivity, Genomic Instability and Cancer

Medical Residents Only

Syndrome	Gene	Comments
Ataxia-Telangiectasia	*ATM*	Heterozygotes may also be sensitive to radiation-induced cancer
Seckel Syndrome	*ATR*	Alterations in gene reduces quantity of ATR; individuals are not radiosensitive
Human Severe Combined Immunodeficiency (SCID)	*Artemis*	Mouse SCID is associated with mutation in *DNA-PKcs*
AT-Like Disorder (ATLD)	*MRE11*	Also defective in checkpoint response
Nijmegen Breakage Syndrome (NBS)	*NBS*	NBS is a direct phosphorylation target of ATM
Fanconi Anemia	*FANC*	At least 15 genes implicated
Homologues of RecQ – Bloom Syndrome, Werner Syndrome, and Rothmund-Thomson Syndrome	*RecQ Homologs*	RecQ genes encode for DNA helicases 3 of the 5 human RecQ Homologs are found mutated in cancer-prone syndromes

Genetic Control

Radiosensitivity

- Like AT cells, in many other radiosensitive cell lines, radiosensitivity has been related to their decreased ability to repair DSB
- Examples of genes affecting ability to repair DSB
  - *XRCC5 Ku80*
  - *XRCC6 Ku70*
  - *XRCC7* (DNA-PKcs)

Radioresistance

- It is unclear whether oncogene play a major role in radioresistance in human tumors

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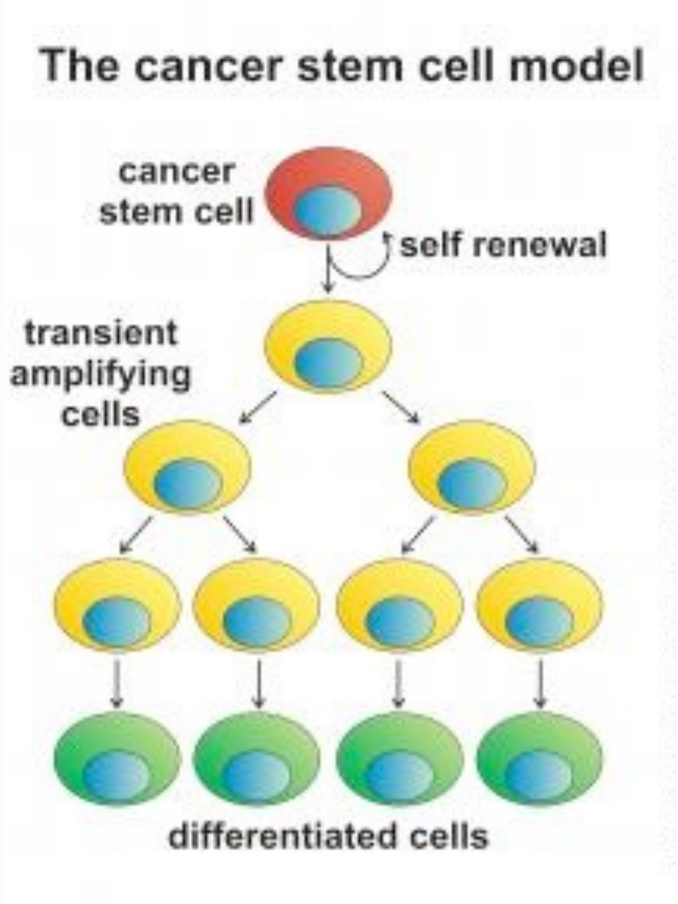
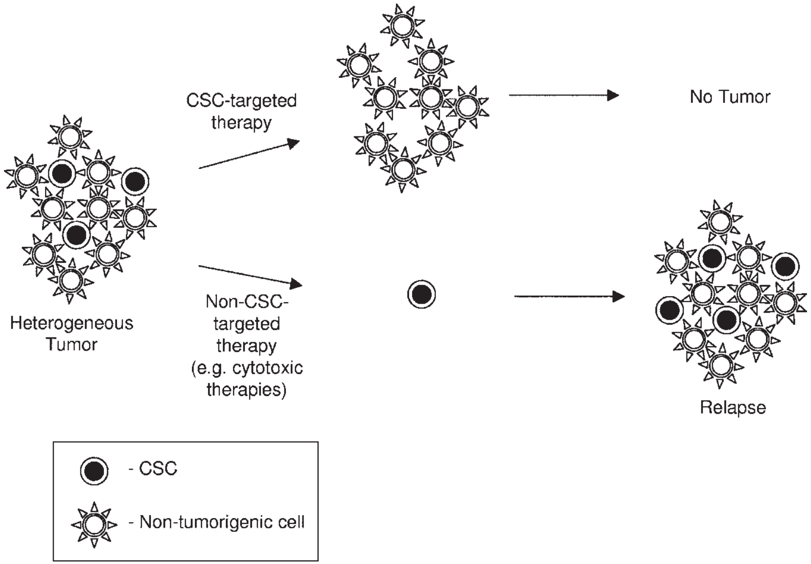
Cancer Stem Cells



- Cancer stem cells are cancer cells that possess characteristics associated with normal stem cells, specifically, self renewal and the ability to give rise to all cell types found in a particular cancer sample

- They are implicated in relapse and metastasis

Cancer Stem Cells



- Conventional cytotoxic therapies can shrink tumors but may preferentially spare some CSCs
- Because CSCs are left behind, tumors can eventually regrow

Clinical Implication

Cancer Stem Cell targeted therapies could remove the self-renewing tumor cells and thus lead to tumor stabilization and likely eventual regression

Cancer Stem Cells & Radiosensitivity

- Stem cells (normal tissue) are typically more radiosensitive than differentiated cells (To be discussed in Chapter 20)
- However, **cancer** stem cells are more resistant to radiation than their more differentiated counterparts
- This may be due to the increased level of free radical scavengers (hence low level of reactive oxygen species)

Clinical Implication

A potential means of radiosensitizing these stem cells is through targeting of free radical scavengers

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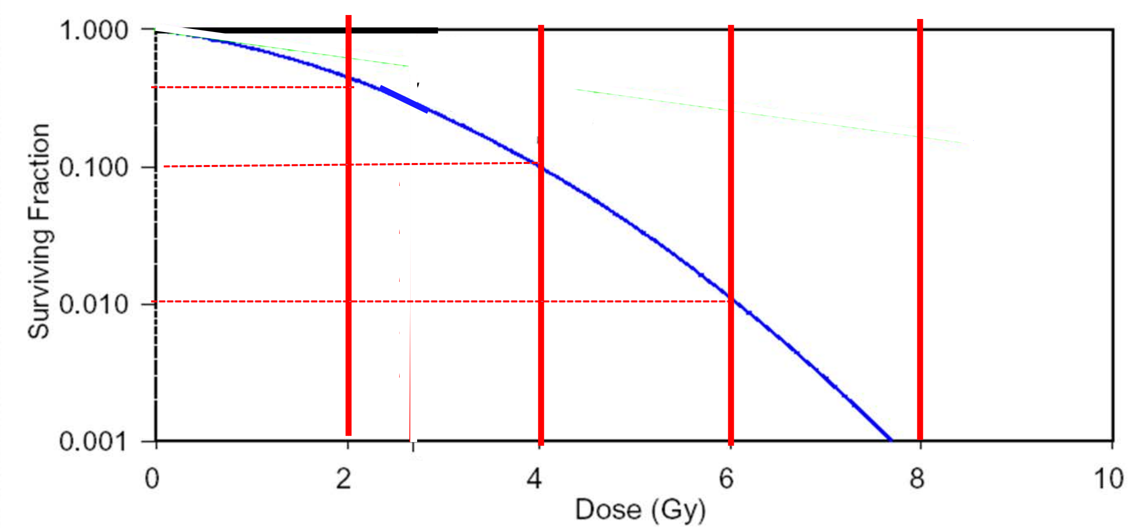
Linear-Quadratic Model

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

- α represents the probability of α damage, which is **irrepairable**
- β represents the probability that independent **repairable**, β-type events have combined to produce lethal events

Survival Curve to a Single Fraction

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



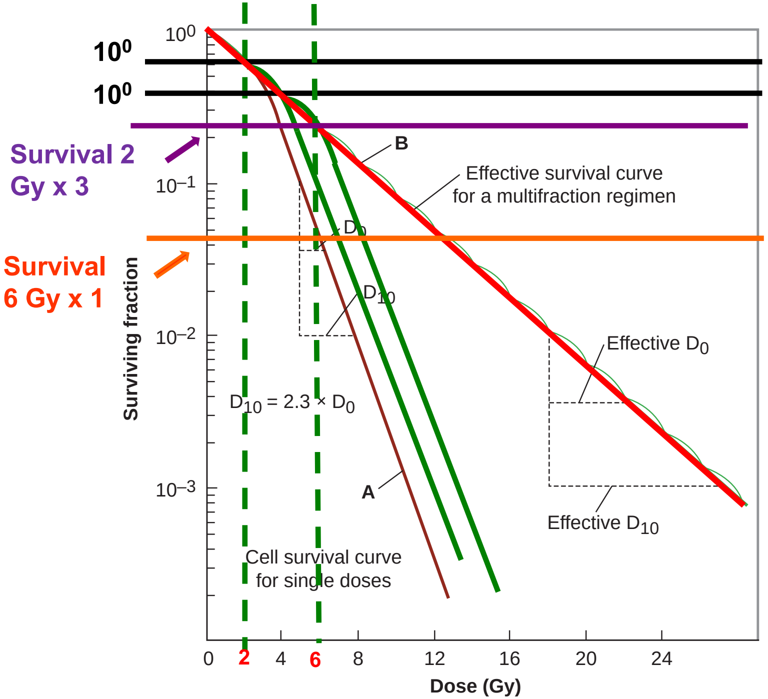
Survival curve gives the survival fraction to a **single dose** of 2 Gy, 4 Gy, 6 Gy, 8 Gy

What is the survival fraction if radiation is given by 2 Gy x 2, 2 Gy x 3, 2 Gy x 4, separated by 24 hours between fractions?

Fractionation

- Radiation therapy is not given in single high dose fractions, it is instead broken up into multiple small doses
- The effect that this has on the survival curve is to continuously repeat the shoulder portion thus making the survival curve an exponential function of dose

“Effective” Survival Curve



Suppose dose delivered per fraction is 2 Gy and equal fractions are separated by sufficient time interval for repair

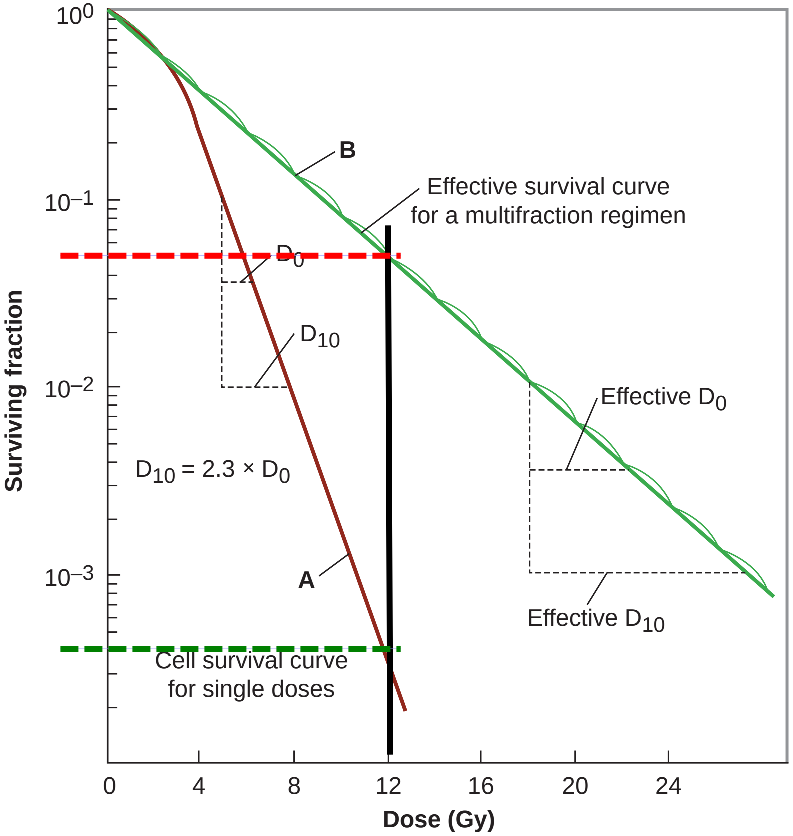
⇩

The **shoulder of the survival curve** is repeated many times

⇩

The effective dose-survival curve becomes an **exponential function of dose (Curve B)**

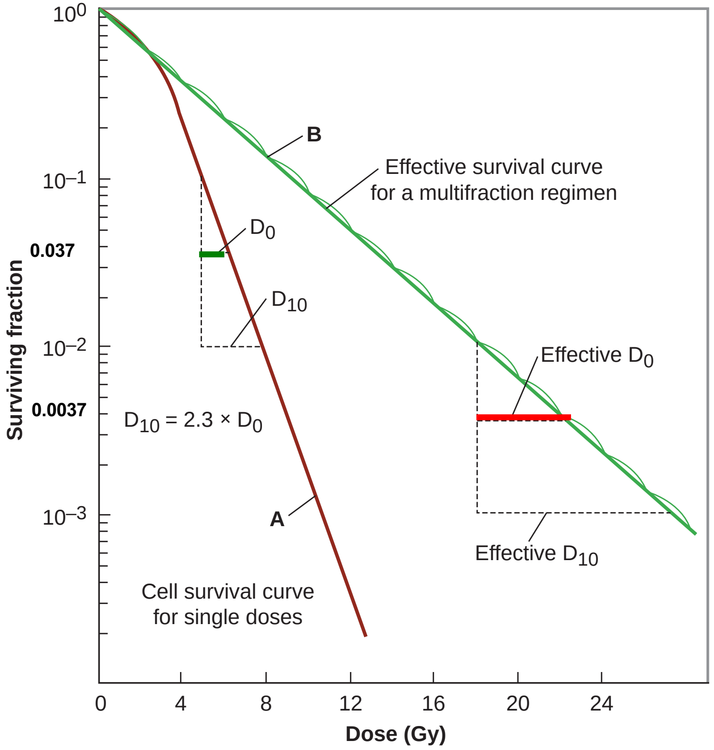
“Effective” Survival Curve



What is the SF to a single fraction of 12 Gy?

What is the SF to a fractionated regimen of 12 Gy given in 2 Gy fraction, i.e., 2 Gy x 6?

“Effective” Survival Curve



What is the D_0 for single dose survival curve?

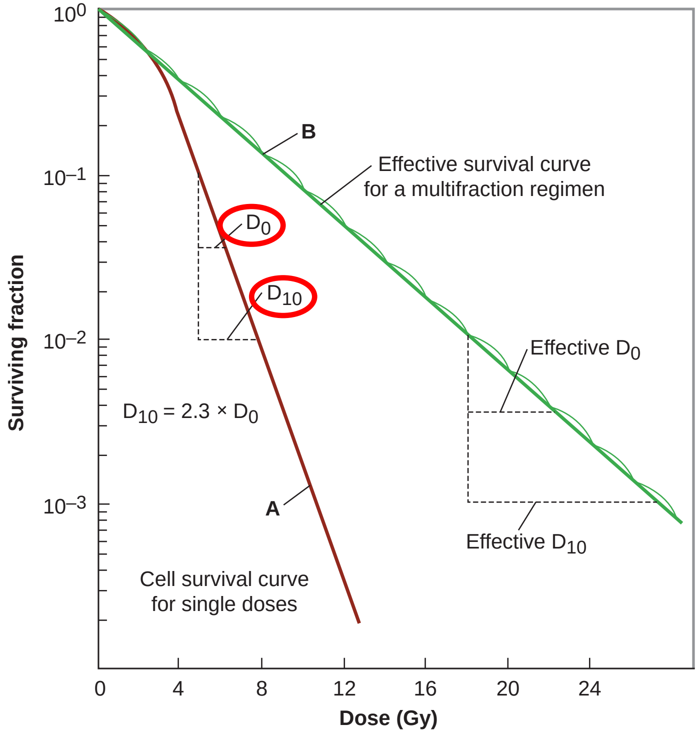
Final slope (D_0) – Dose to ↓ SF to 37% of its previous value on straight line portion of the curve

What is the D_0 for effective survival curve?

The effective survival curve is **shallower** than the single dose survival curve $D_{0Effective} > D_0$, and has a value of **~ 3 Gy** for cells of human origin

D_{10} and D_0

D_{10} – Dose to ↓ SF to **10%** of its previous value on straight line portion of the curve



On the straight portion of the single survival curve

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

D_0 – dose ↓ S to 37%
D_{10} – dose ↓ S to 10%

Thus,

$$10\% = e^{-D_{10}/D_0}$$

Solve for D_{10}, we have

$$\mathbf{D_{10} = 2.3 \times D_0}$$

Similarly, on the effective survival curve, we have

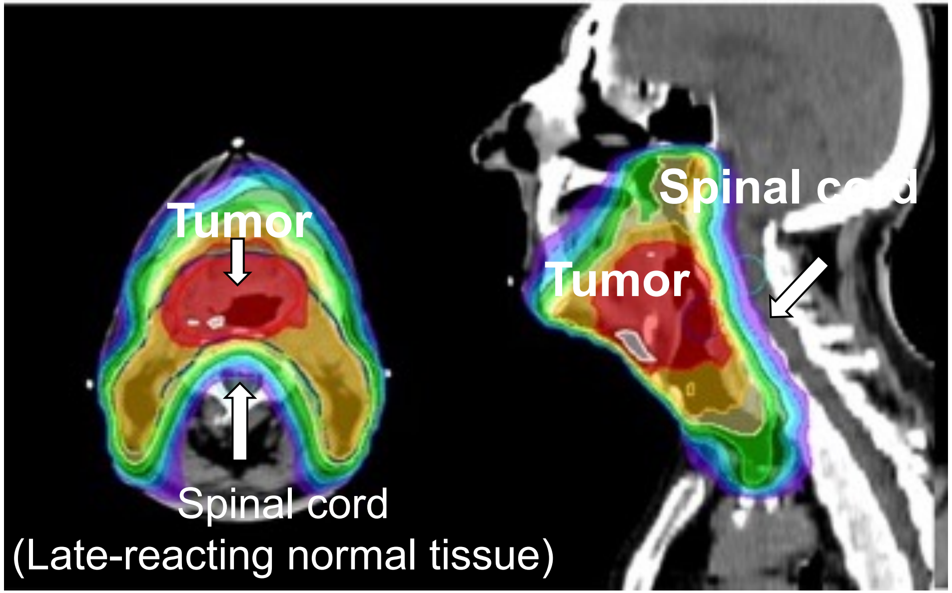
$$\mathbf{D_{10effecitve} = 2.3 \times D_{0effective}}$$

When survival is ↓ to 10% (ie, 10^{-1}), we call it **one decade of killing**
When survival is ↓ to 1% (ie, 10^{-2}), we call it **2 decades of killing**
…
When survival is ↓ to 10^{-n}, we call it n decades of killing

Head & Neck Radiotherapy

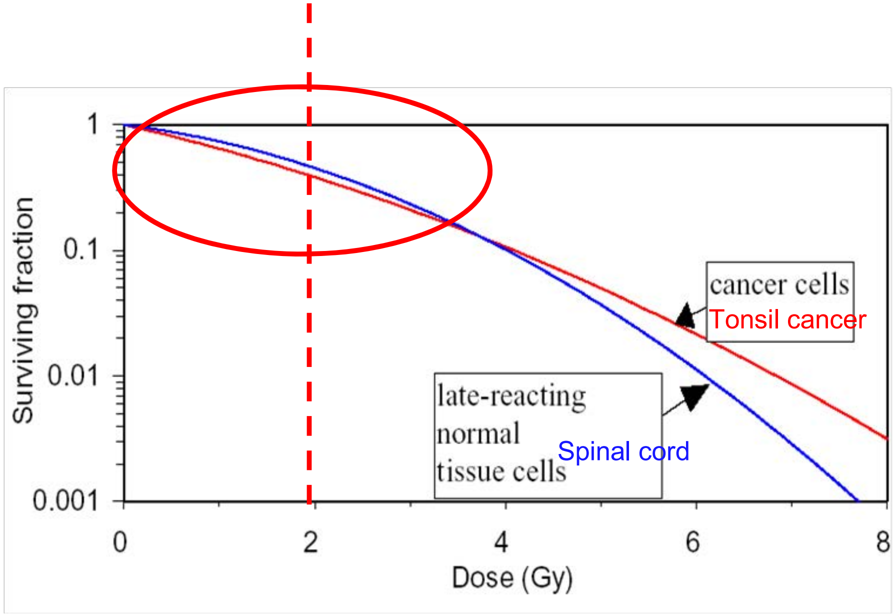
A typical course of H&N RT is delivered over 7 weeks

70 Gy / 35 fractions @ 2 Gy/fx



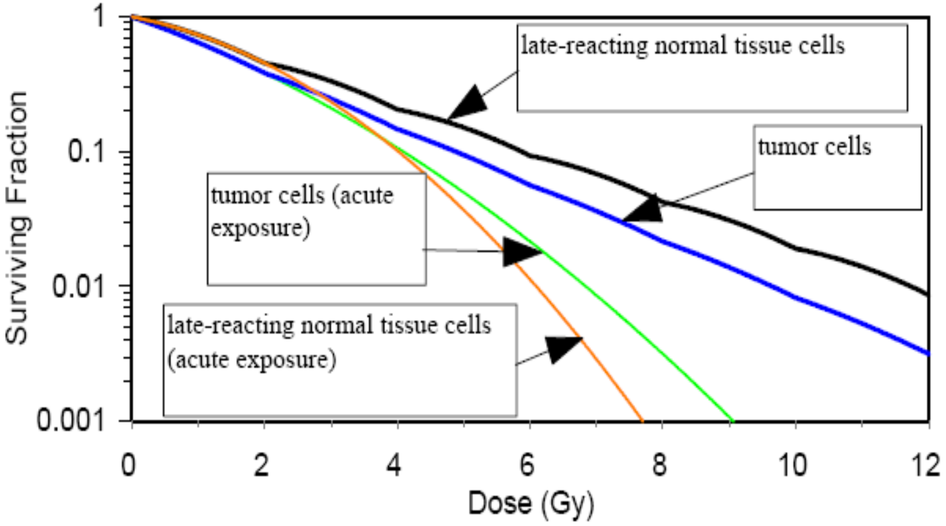
Why do we deliver such a small dose per fraction?

Single Cell Survival for Normal vs. Cancer Cells



- In general, cells of late-reacting normal tissues are better able to repair sublethal damage than are cancer cells
- Hence, cell-survival curves for late-reacting normal tissues are **“curvier”** than those for cancer cells

Multifraction Regimen



- In a multi-fractionated regimen, shoulder is repeated
- Fractionate at doses/fraction where survival of normal tissue exceeds that of tumor would therefore amplify this difference (“window of opportunity”)
- The fraction size is typically around **2 Gy/fraction**

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Problem 1

A tumor consists of 10^9 cancer cells with effective D_0 = 3 Gy for fractionated radiotherapy at 2 Gy/fraction. What total dose will result in 90% probability of local control?

Problem 1: Solution

- Employ Poisson statistics
- Probability that no cancer cells will survive, $P = e^{-m}$, where m is the mean number of cancer cells surviving (from the initial population of cells)
- For a 90% control probability, use $0.9 = e^{-m}$, so $\ln(0.9) = \ln(e^{-m}) = -m = -0.1054$,
  i.e. $m=0.1054$

Problem 1: Solution

- If $m = 0.1054$, then the surviving fraction must be SF = $0.1054/10^{9} = 1.054 \times 10^{-10}$
- Hence $1.054 \times 10^{-10} = e^{-D/Do} = e^{-D/3}$ where D is the total dose in Gy
- Therefore, $\ln(1.054 \times 10^{-10}) = -D/3 = 22.97$ Gy, so the total dose must be $3 \times 22.97 =$ <u>68.9 Gy</u>

Problem 1: Alternative Solution

- A SF of $0.1054/10^9$ ($\approx 1 \times 10^{-10}$) means 10 decades of killing is required
- $D_{10} = 2.3 \times D_0 = 2.3 \times 3 = 6.9$ Gy
- Since it is an exponential curve, 10 decades of killing thus requires 10 x 6.9 Gy = 69 Gy

Problem 2

- Repeat the same problem but for 70% chance of tumor control
- For a 70% control probability, $0.7 = e^{-m}$, so $\ln(0.7) = \ln(e^{-m}) = -m = -0.3567$, i.e. $m=0.3567$
- Hence, $SF = 3.567 \times 10^{-10} = e^{-D/3}$
- $\ln(3.567 \times 10^{-10}) = -D/3 = -21.75$ or $\underline{D=65.3\ Gy}$

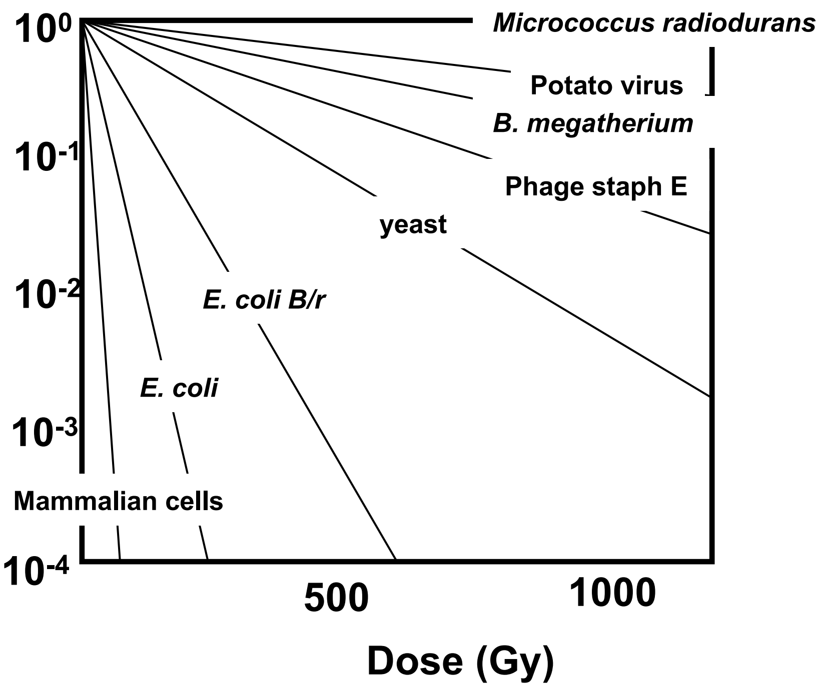
Clinical Implication

If a patient wishes to skip the last 2 treatments (i.e., 70 Gy to 66 Gy), the probably of tumor control decreased from 90% to 70%.

Lecture Outline

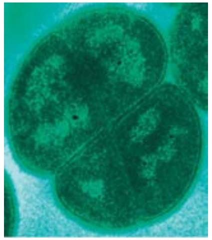
- Shape of the Survival Curve
- Survival Curves for Various Mammalian Cells In Culture
- Survival Curve Shape and Mechanisms of Cell Death
- Oncogenes and Radioresistance
- Genetic Control of Radiosensitivity
- Intrinsic Radiosensitivity and Cancer Stem Cells
- Effective Survival Curve for a Multi-fraction Regimen
- Calculations of Tumor Cell Kill
- **The Radiosensitivity of Mammalian Cells Compared with Microorganisms**

Radiosensitivity – Mammalian Cells vs. Microorganisms



- Mammalian cells are more radiosensitive compared with microorganisms
- The variations in radiosensitivity are due to differences in
  - DNA content
  - Efficiency of DNA repair
  - Mode of cell death (apoptosis vs. mitosis)

Deinococcus radiodurans (formerly known as *Micrococcus radiodurans*)



Deinococcus radiodurans

terrible grain/berry radiation surviving

- Discovered in 1956 by Arthur W. Anderson
- Experiments were being performed to determine if canned food could be sterilized using high doses of gamma radiation
- A tin of meat was exposed to a dose of radiation that was thought to kill all known forms of life, but the meat was subsequently spoiled, and *D. radiodurans* was isolated
- Capable of withstanding 5000 Gy of IR with almost no loss of viability, and an acute dose of **15,000 Gy with 37% viability**

- *D. radiodurans* is also extremely resistant to UV, dessication, and oxidizing and electrophilic agents

Deinococcus radiodurans

- *D. radiodurans* accomplishes its resistance to radiation by having multiple copies of its genome and rapid DNA repair mechanisms

- Usually repairs breaks in its chromosomes within 12-24 hours through a 2-step process
  - Single-stranded annealing
  - Homologous recombination

Deinococcus radiodurans

A Fun Trivia

In 2003, U.S. scientists demonstrated *D. radiodurans* could be used as a means of information storage that might survive a nuclear catastrophe. They translated the song "It's a Small World" into a series of DNA segments 150 base pairs long, inserted these into the bacteria, and were able to retrieve them without errors 100 bacterial generations later. However, since only a small portion of the information can be stored in DNA of *D. radiodurans*, several species had to be created, each holding a different part of the song and species needed to be kept segregated over time. If species are evolving together after a number of generations certain species will emerge dominant and others will become extinct and parts of the encoded message which were stored in extinct species will be lost.

Review Questions

Question 1

The α/β ratio is equal to the:

~~A.~~ surviving fraction at which the amount of cell killing caused by the induction of irreparable damage equals the amount of cell killing caused by the accumulation of sublethal damage
~~B.~~ optimal fraction size to use in a fractionated regimen
C. dose below which a further decrease in fraction size will not affect the surviving fraction for a particular total dose
~~D.~~ Dq
[✓ E.] dose at which the αD component of cell kill is equal to the βD^2 contribution to cell killing

The Linear Component – α Type Damage

D is the radiation dose delivered

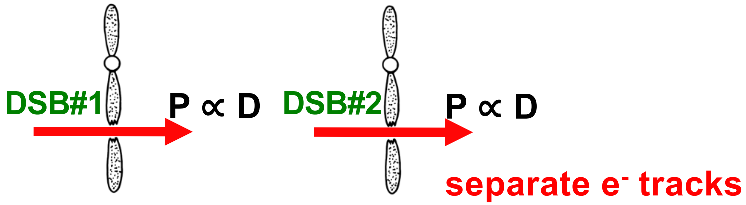
Survival Fraction (SF) = $e^{-\alpha D}$

α is the slope and a measure of the intrinsic radiation sensitivity

$Y = \alpha D$

The Quadratic Component – β-Type Damage

- Probability that one chromosome break will occur is linearly proportional to dose, D
- Probability that the other chromosome will be hit in an **independent** event is also proportional to dose, D
- Probability that both events will occur is, therefore, proportional to D^2, hence



DSB#1 $P \propto D$ **DSB#2** $P \propto D$

separate e⁻ tracks

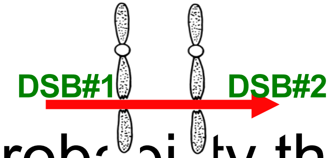
$$SF = e^{-\beta D^2}$$

$$P = D \times D = D^2$$
$$Y = \beta D^2$$

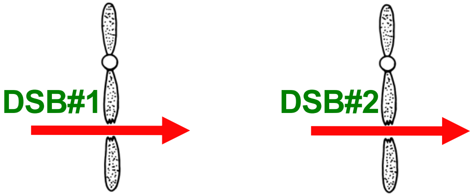
Linear-Quadratic Model

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

- α represents the probability of α damage, which is **irrepairable**

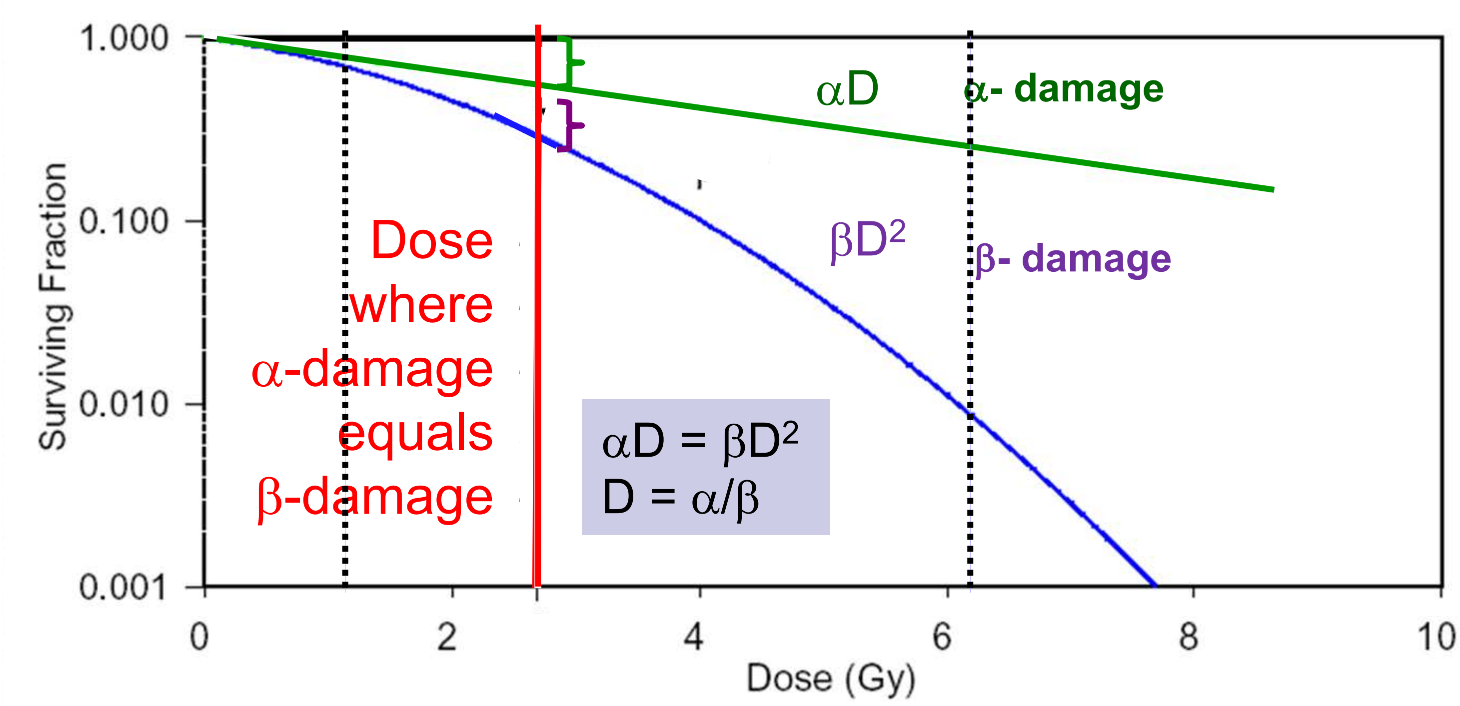


- β represents the probability that independent **repairable**, β-type events have combined to produce lethal events



α/β Ratio

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



Dose where α-damage equals β-damage

$\alpha D = \beta D^2$

$D = \alpha/\beta$

Question 2

The quasi-threshold dose Dq is an indicator of all of the following, EXCEPT:

A. the ability of the cell to accumulate sublethal radiation damage

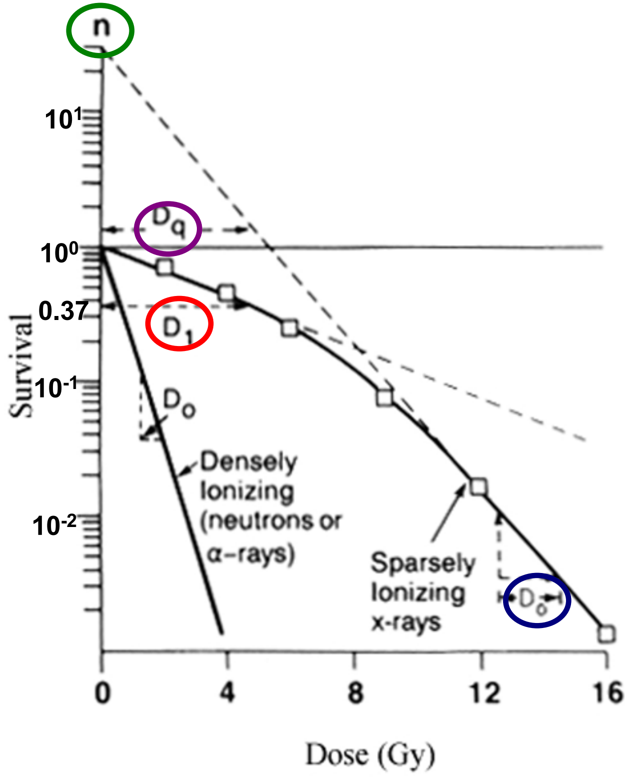
B. the width of the shoulder region of the cell survival curve

C. how much sparing will be obtained by dose fractionation

D. the cell’s sublethal damage repair capacity

[✓ E.] the duration of S phase of the cell cycle

Target Model



α-ray or neutron – D_0 is adequate

X-ray or γ-ray
Characterized by 4 parameters

Initial slope **(D_1)** – Dose to ↓ SF to 37% of its previous value on initial portion of the curve

Final slope **(D_0)** – Dose to ↓ SF to 37% of its previous value on straight line portion of the curve

Extrapolation number **(n)** – Estimate of width of the shoulder

Quasi-threshold dose **(D_q)** – *Almost* a threshold dose, dose below which radiation purportedly has no effect

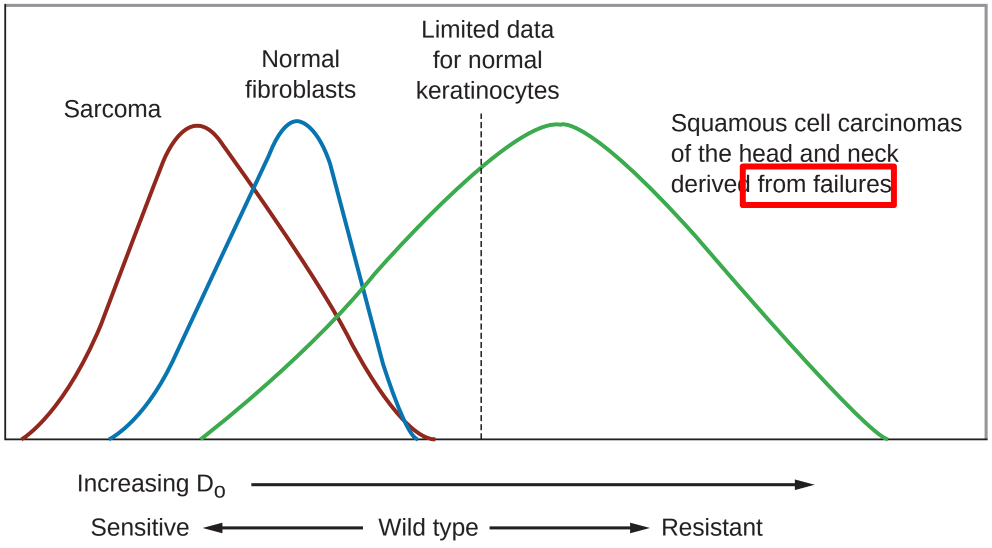
Question 3

The D_0 for most mammalian cells irradiated with X-rays *in vitro* under well-aerated conditions falls in the range of:

A. 0 - 0.2 Gy
B. 0.2 - 1 Gy
[✓ C.] 1 - 2 Gy
D. 2 - 4 Gy
E. 4 - 8 Gy

D_0 for Cells of **Human Origin**

- **D_0** is the dose required to reduce the SF to 37% of its previous value on the straight portion of survival curve
- It is a measure of radiosensitivity
- D_0 =**1-2 Gy** for most cells cultured *in vitro* (exception = AT Cells; D_0=0.5 **Gy**)



In general, cells from a given **normal tissue** show a narrow range of radiosensitivity

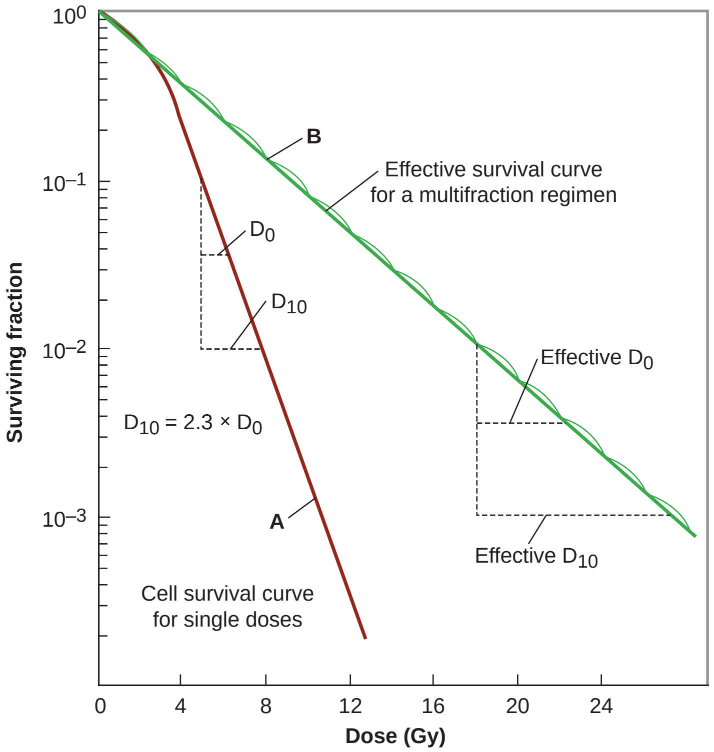
By contrast, cells from **human tumors** show a broad range of D_0 values, which brackets the radiosensitivity of normal human fibroblasts

Question 4

A multifraction protocol produces an effective survival curve that is:

A. linear-quadratic
B. bell-shaped
C. linear
D. parabolic
[✓ E.] exponential

“Effective” Survival Curve



Suppose dose delivered per fraction is 2 Gy and equal fractions are separated by sufficient time interval for repair

⇩

The **shoulder of the survival curve** is repeated many times

⇩

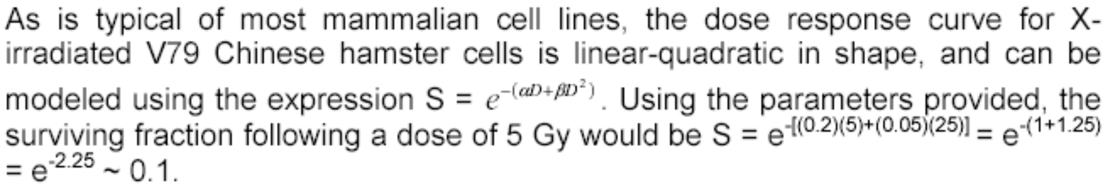
The effective dose-survival curve becomes an **exponential function of dose (Curve B)**

The effective survival curve is **shallower** than the single dose survival curve $D_{0Effective} > D_0$, and has a value of **~ 3 Gy** for cells of human origin

Question 5

What would be the estimated surviving fraction of Chinese hamster cells irradiated with an X-ray dose of 5 Gy delivered acutely? (Assume $\alpha=0.2\ Gy^{-1}$ and $\beta=0.05\ Gy^{-2}$)

A. 0.01
[✓ B.] 0.10
C. 0.37
D. 0.50
E. 0.90



As is typical of most mammalian cell lines, the dose response curve for X-irradiated V79 Chinese hamster cells is linear-quadratic in shape, and can be modeled using the expression $S = e^{-(\alpha D+\beta D^2)}$. Using the parameters provided, the surviving fraction following a dose of 5 Gy would be $S = e^{-[(0.2)(5)+(0.05)(25)]} = e^{-(1+1.25)} = e^{-2.25} \sim 0.1$.

Question 6

What is the approximate surviving fraction following 5 doses of 0.5 Gy of carbon ions, assuming that the surviving fraction following one dose is 0.4?

[✓ A.] 0.01
B. 0.10
C. 0.37
D. 0.50
E. 0.90

Since the survival curve for high LET carbon ions is exponential, the surviving fraction following 5 irradiations with a dose that results in a surviving fraction of 0.4 would be $(0.4)^5 = 0.01$.