Fundamental Radiobiology

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Topics to be discussed

- The 4 Rs of radiotherapy
  - *Repair*
  - *Repopulation*
  - *Reoxygenation*
  - *Redistribution*
- The effect of the LET of the radiation

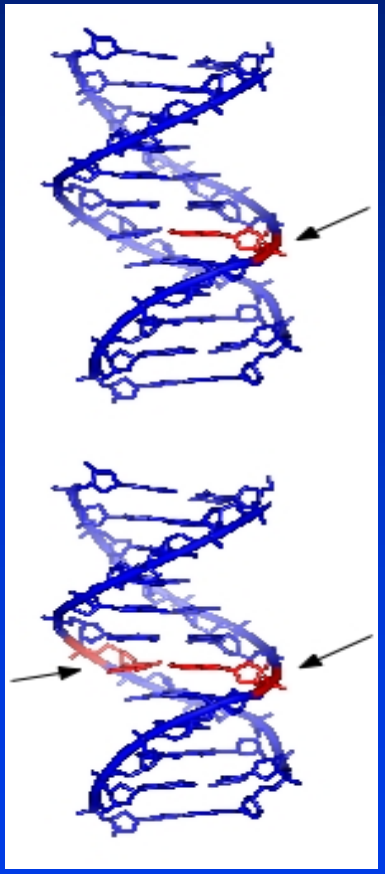
Which is the most important?

Repair!

Repair: Single strand and double strand damage

Single strand breaks (upper figure) are usually considered “repairable”

Double strand breaks (lower figure) are not usually “repairable” if the breaks are close together, since an intact 2nd strand of the DNA molecule is needed for the repair enzymes to be able to copy the genetic information

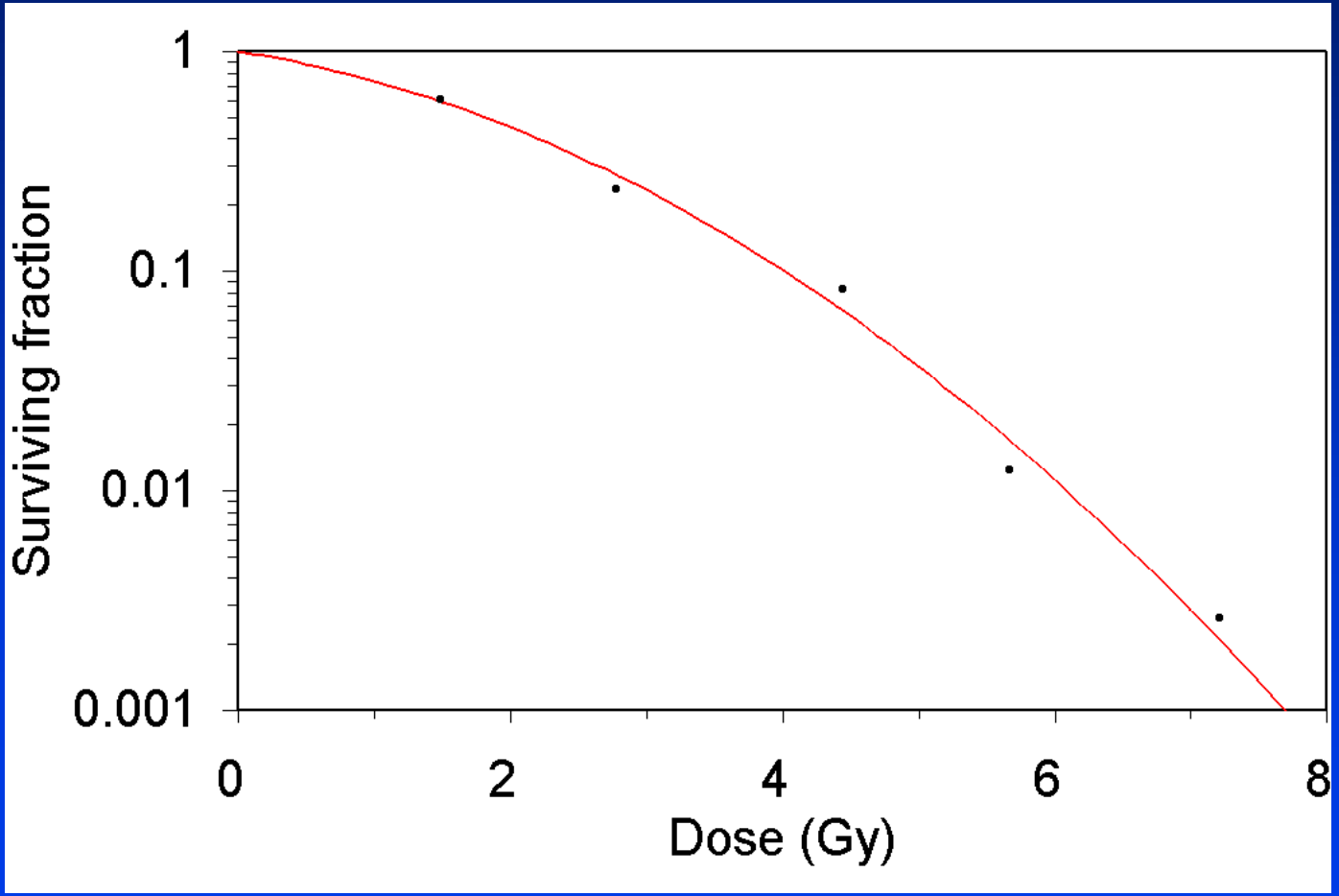


The effect of dose

- At low doses, both DNA strands are unlikely to be hit
  - *so single strand breaks will dominate i.e. repair is common*
- At high doses, double strand breaks will be common i.e. little repair
  - *consequently survival curves get steeper as dose increases*

As dose increases survival curves become steeper

For types of cells that have a high capacity for repair the less steep the curve will be at low doses and hence the curvier the survival curve



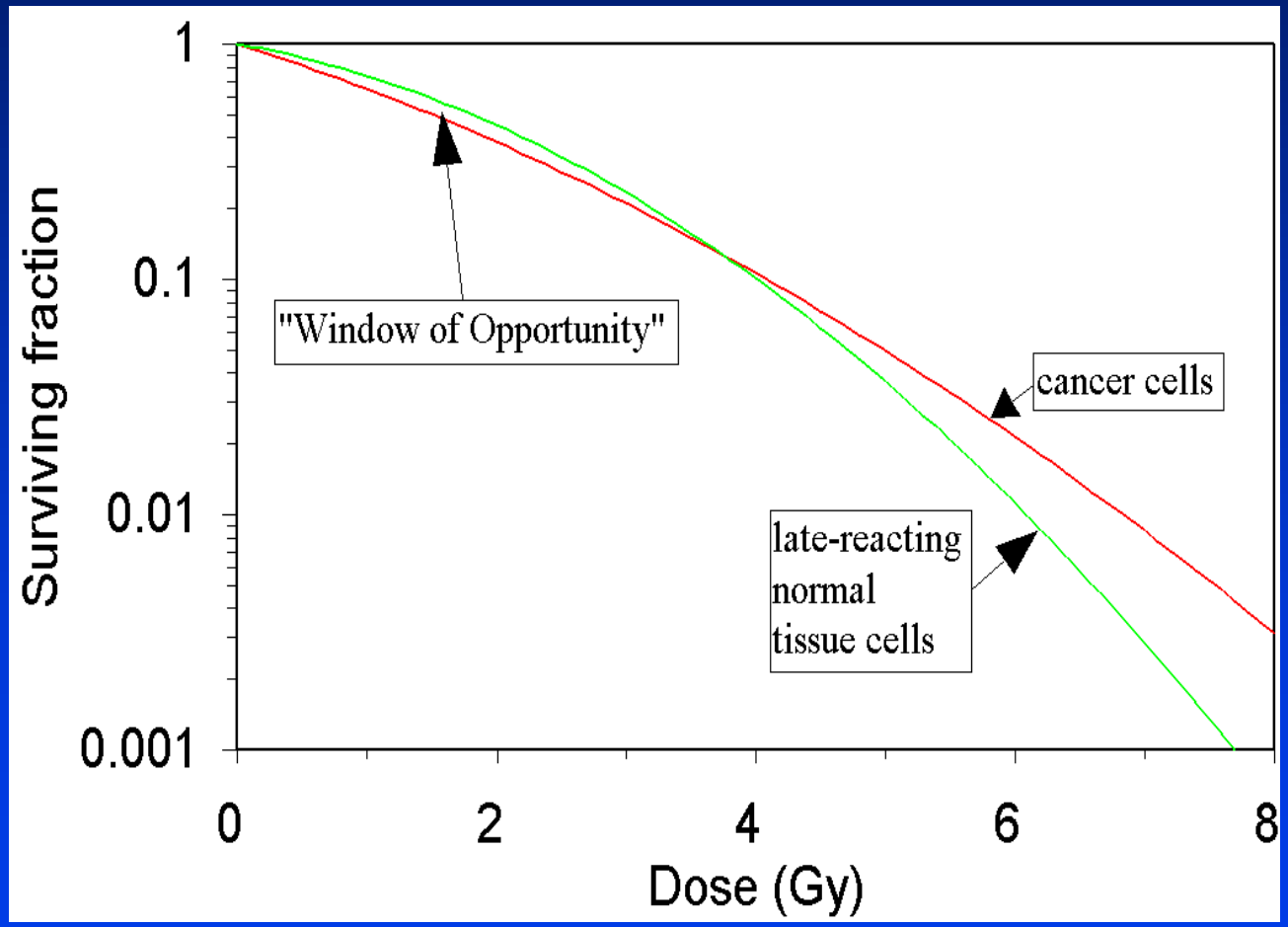
Survival curves: normal *vs* cancer cells

- Cancer cells do not "repair" damage at low doses as well as do normal tissue cells
  - *survival curves will be straighter*
- *There is a "Window of Opportunity" at low doses where the survival of late-reacting normal tissue cells exceeds that of cancer cells*

Cell survival curve comparison: the “Window of Opportunity”

At low doses, the survival of normal tissue cells (green curve) exceeds that of cancer cells

At high doses, the survival of cancer cells (red curve) exceeds that of normal tissues



Question!

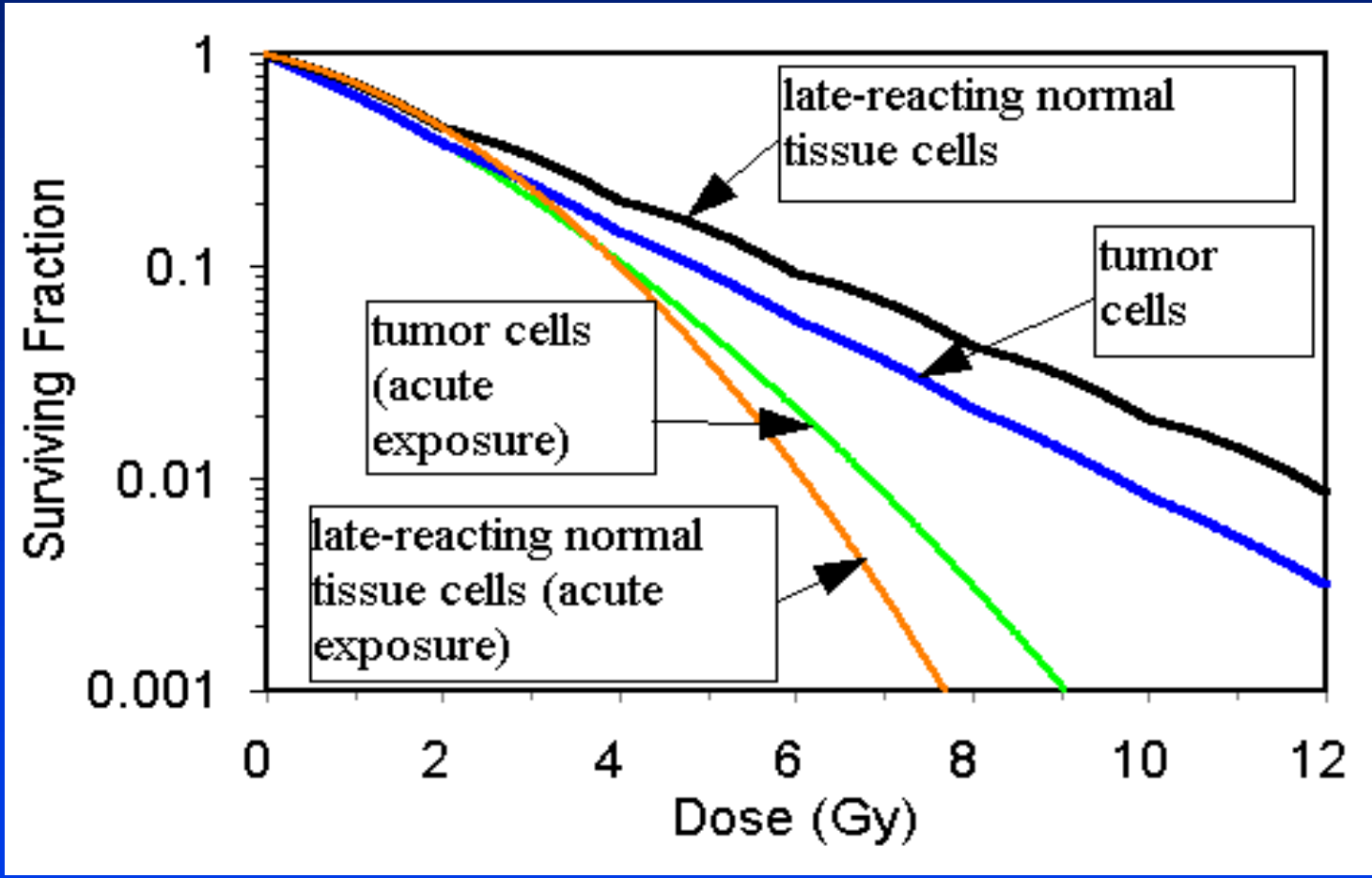
Does this mean that, since you cannot give more than about 4 Gy or you will kill more normal cells than cancer cells, and 4 Gy is not nearly enough dose to kill all the cancer cells in typical tumor, you can never cure cancers with radiation alone?

The solutuion is:

Fractionate!

- This is why we typically fractionate radiotherapy at low doses/fraction
- We need to fractionate at doses/fraction within this “Window of Opportunity” e.g. typically about 2 Gy/fraction

Normal *vs* cancer cells for fractionation at 2 Gy/fraction



Cell survival curve comparison: the "Window of Opportunity"

- Note that we have assumed that the dose to normal tissues is the same as the dose to the cancer cells
- Is this a reasonable assumption if we are using conformal teletherapy?

No!

- Because the major advantage of conformal radiotherapy is that the dose to normal tissues is kept less than the tumor dose
- Hence the *effective dose** to normal tissues will usually be less than the *effective dose* to tumor

**the effective dose is the dose which, if delivered uniformly to the organ or tumor, will give the same complication or cure rate as the actual inhomogeneous dose distribution. Sometimes called the Equivalent Uniform Dose (EUD)*

Geometrical sparing factor

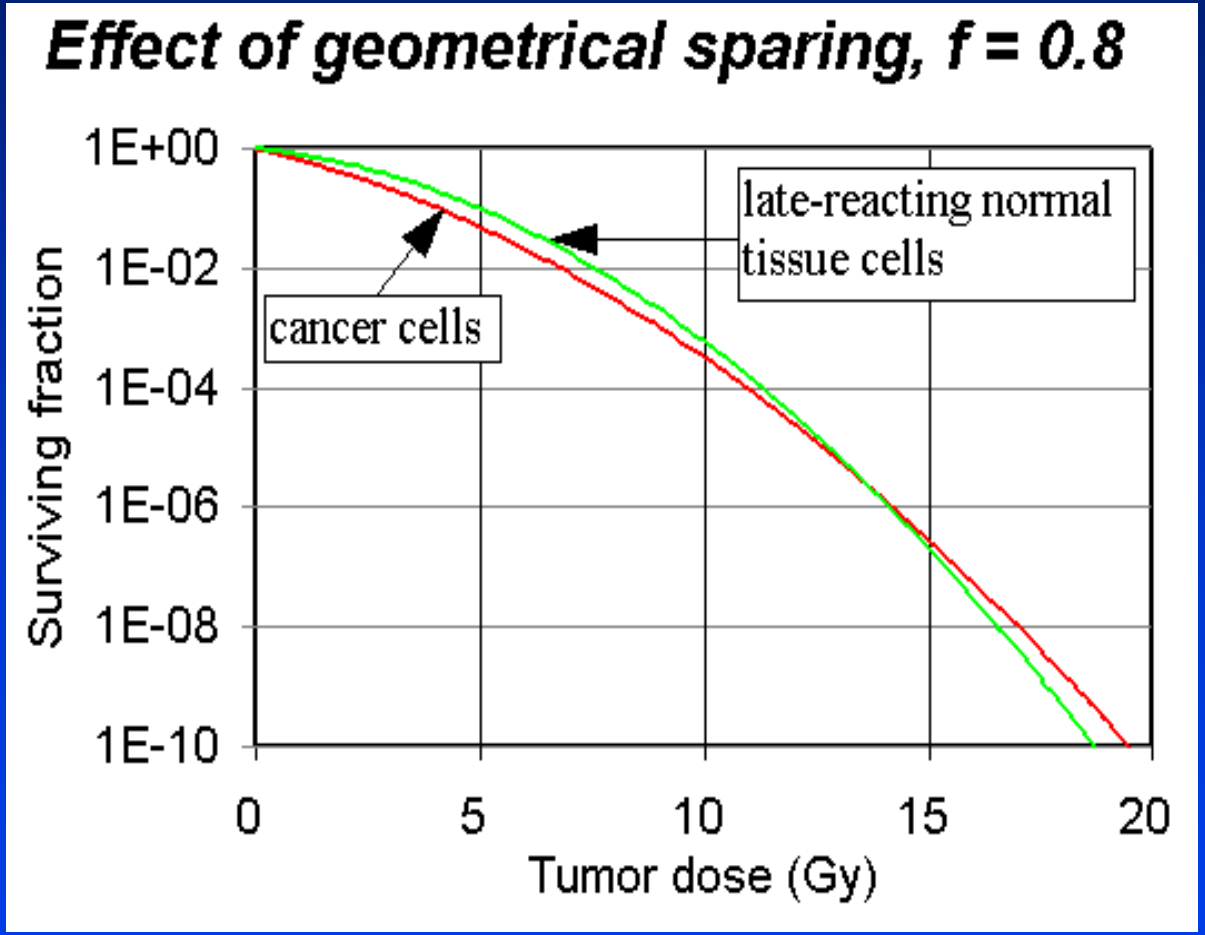
We can define a "geometrical sparing factor", *f*, such that:

$$f = \frac{\textit{effective dose to normal tissues}}{\textit{effective dose to tumor}}$$

For conformal radiotherapy $f < 1$

The “Window of Opportunity” widens with geometrical sparing

Even with a modest geometrical sparing of only 20%, the “Window of Opportunity” extends to over 10 Gy



This means that:

With highly conformal therapy we can safely use much higher doses per fraction

- *for teletherapy i.e. hypofractionation*
- *for brachytherapy i.e. High Dose Rate (HDR)*

What about dose rate and time between fractions?

- Repair takes time (half-time for repair typically 0.5 – 1.5 hours), hence repair decreases as
  - *time between fractions decreases*
  - *dose rate increases*

Importance of time between fractions

- Because repair is more important for normal tissues than for tumors, enough time must be left between fractions for full repair
  - *based on clinical results, this is assumed to be six hours*

Importance of dose rate

- Normal tissue cells repair better than cancer cells and low dose rate enhances repair
- This is the basis of low dose rate (LDR) brachytherapy and, especially, permanent implants at very low dose rate

Questions!

Does this mean that LDR brachytherapy will always be radiobiologically superior to HDR?

or

Might the advantage of geometrical sparing outweigh the disadvantage of high dose rate?

and

Can the best modality be determined by some type of modeling?

Radiobiological modeling

- We need a mathematical model that describes the effects of radiotherapy on cancer and normal tissue cells
  - *this is the linear-quadratic model*

The linear-quadratic model of cell survival: two components

- Linear component:
  - a double-strand break caused by the passage of a single charged particle e.g. electron, proton, heavy ion
- Quadratic component:
  - two separate single-strand breaks caused by different charged particles

So what is the equation for cell survival?

- This is based on Poisson statistics (the statistics of rare events), since the probability that any specific DNA molecule will be damaged is low
- According to Poisson statistics, the probability, P_0, that no event (DNA strand break) will occur is given by:

$$P_0 = e^{-m}$$

where m is the mean number of hits per target molecule

Single-particle events

- For single-particle events, *m* is a linear function of dose, *D*
  - *so the mean number of lethal events per DNA molecule can be expressed as αD and P_0 represents the probability that there are no single-particle lethal events, i.e. it is the surviving fraction of cells, S*
- Then

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

What causes these single-particle events

- For a single particle to damage both arms of the DNA at the same time it has to be highly ionizing
- Hence single-particle events are caused primarily by the high-LET component of the radiation
- For photon and electron beams, it is the very low-energy secondary ionizing radiations (i.e. slow electrons) that are high LET and hence give rise to these single-particle events

Two-particle events

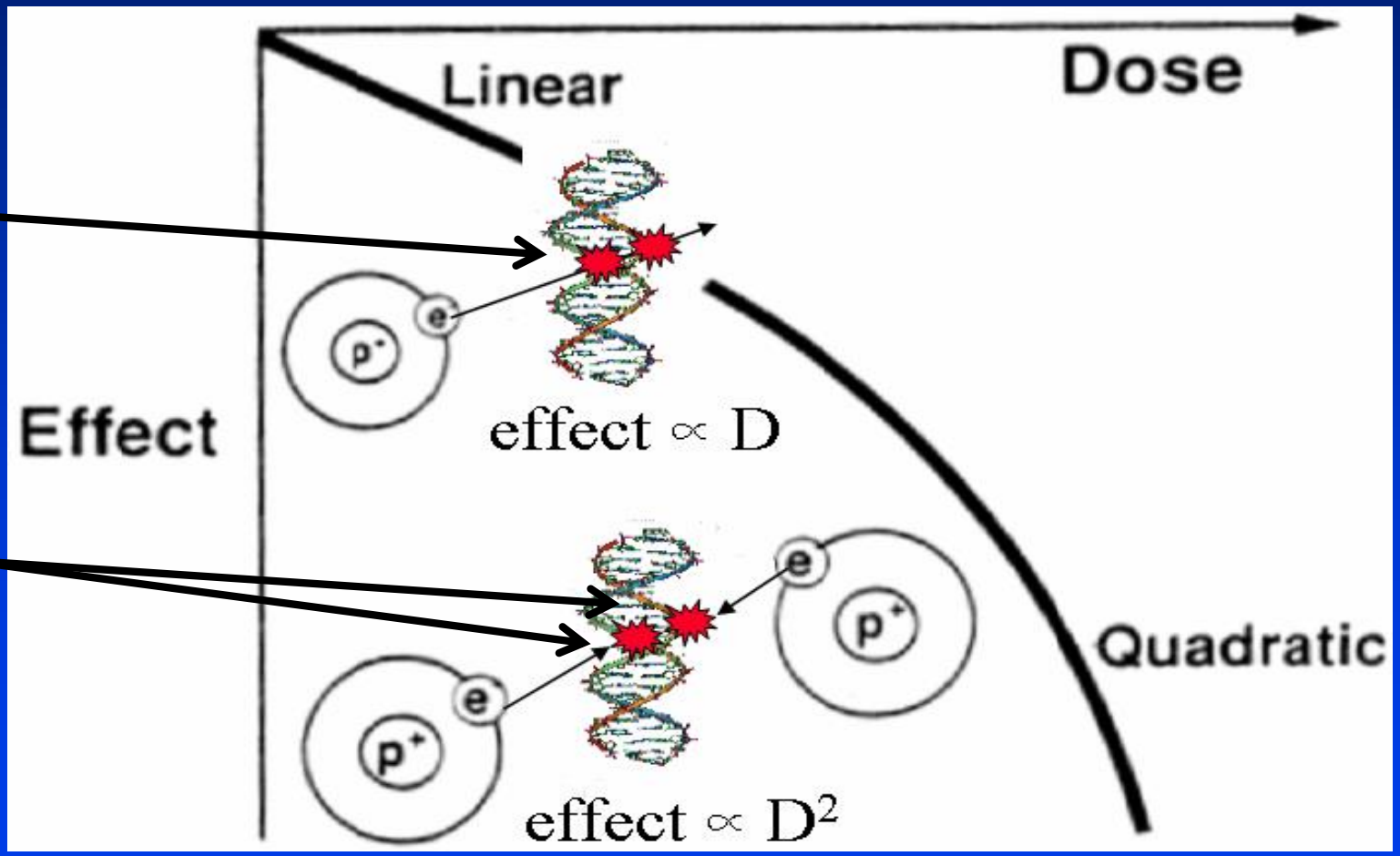
- With two-particle events, the probability that one arm of a DNA molecule will be damaged is a linear function of dose, *D*, and the probability of damage in an adjacent arm is also a linear function of dose, *D*
- Hence the probability that both arms are damaged by two different single-particle events is a function of D^2
- So the surviving fraction of cells due to single particle events is given by:

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

The linear-quadratic model

Single-particle event

Two different single-particle events



The L-Q Model Equation

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

or $\ln S = -(\alpha D + \beta D^2)$

where α represents the probability of lethal single-particle (α-type) damage

and β represents the probability that independent two-particle (β-type) events have combined to produce lethal damage

What about **R**epopulation

- Cancer cells and cells of acutely-reacting normal tissues proliferate during the course of therapy (called “repopulation”)
- Cells of late-reacting normal tissues proliferate little
- Hence the shorter the overall treatment time the better
  - *but should not be too short otherwise acute reactions will prevent completion of treatment*

Repopulation and the L-Q equation

- The basic L-Q model does not include the effect of repopulation during the course of therapy
- Hence, it does not take into account the effect of overall treatment time, T, or repopulation rate (represented by the potential doubling time, T_{pot})
- The L-Q model with repopulation correction assumes that increase in surviving fraction due to repopulation is an exponential function of time i.e. lnS increases linearly with time

The L-Q equation with repopulation

Hence:

$$lnS = -(\alpha D + \beta D^2) + 0.693T/T_{pot}$$

Where:

T = overall treatment time (days)

T_{pot} = potential doubling time (days)

What about Reoxygenation?

- Reoxygenation relates to the oxygen effect
- Oxygen is a powerful radiation sensitizer, so tumors that are poorly oxygenated (i.e. are hypoxic) tend to be resistant
- Hypoxic tumors can reoxygenate during a course of treatment and become more sensitive

The Oxygen Enhancement Ratio (OER)

- The degree of sensitization is expressed in terms of the Oxygen Enhancement Ratio, where:

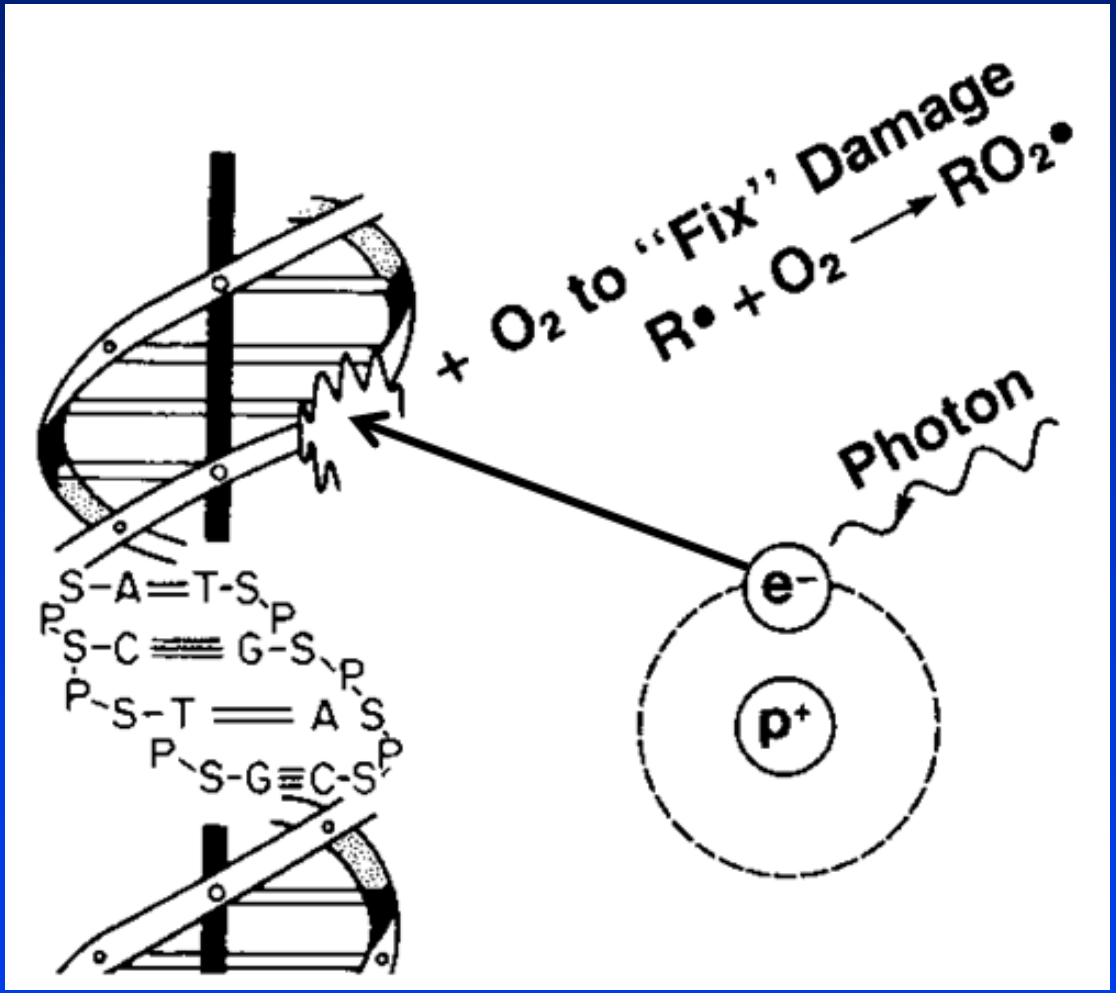
$$OER = \frac{dose\ under\ hypoxic\ conditions}{dose\ under\ aerobic\ conditions}$$

to produce the same biological effect

How the oxygen effect works

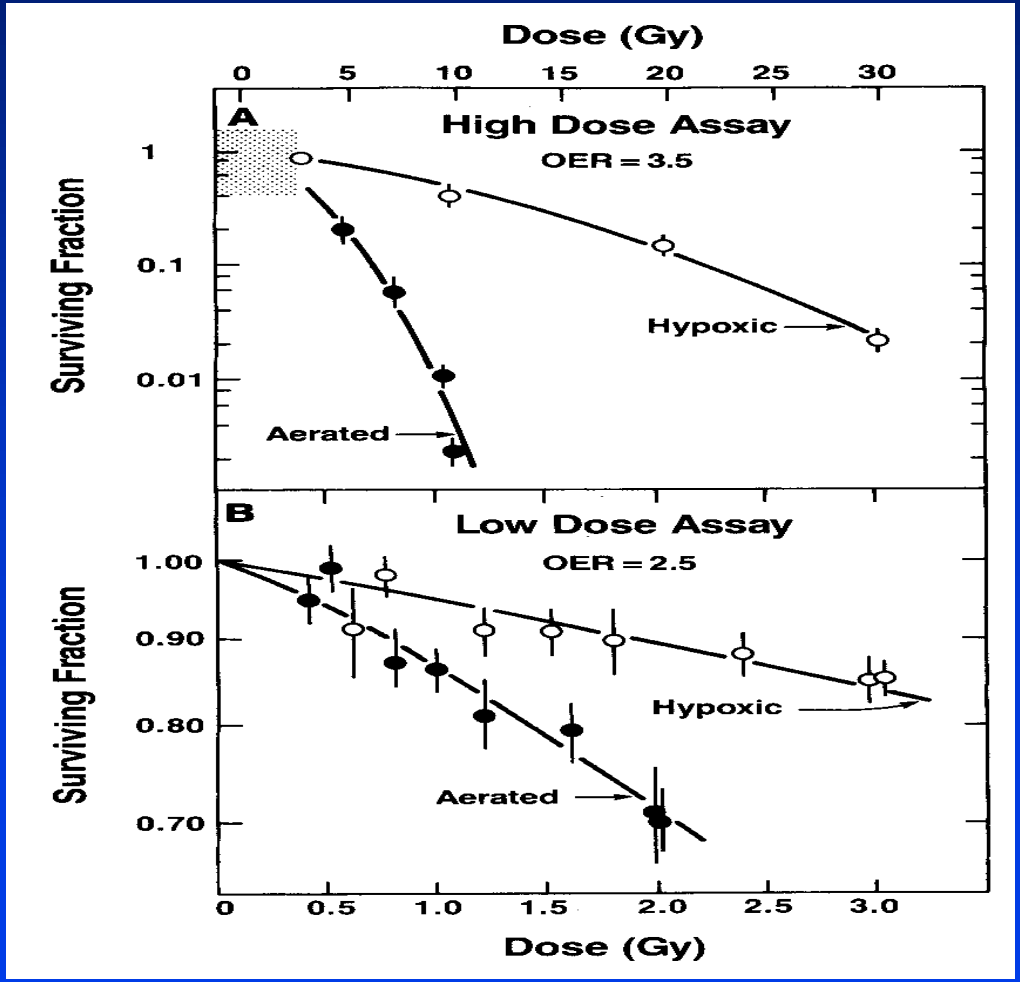
Oxygen reacts with the broken ends of the DNA molecule to make the damage permanent i.e. to “fix” the damage by preventing recombination of the broken ends

This is called the “oxygen fixation process”



OER is a function of dose and dose rate

OER at low doses (and dose rates) tends to be lower than the OER at high doses (and dose rates)



Why does OER decrease as dose decreases?

- O_2 sensitization relates to “fixing” of single-strand DNA breaks i.e. O_2 enhances β-type damage
- At low doses, α-type damage dominates, so the effect of O_2 sensitization is reduced
- Reduced effect of O_2 means lower OER

Might this be important in radiotherapy?

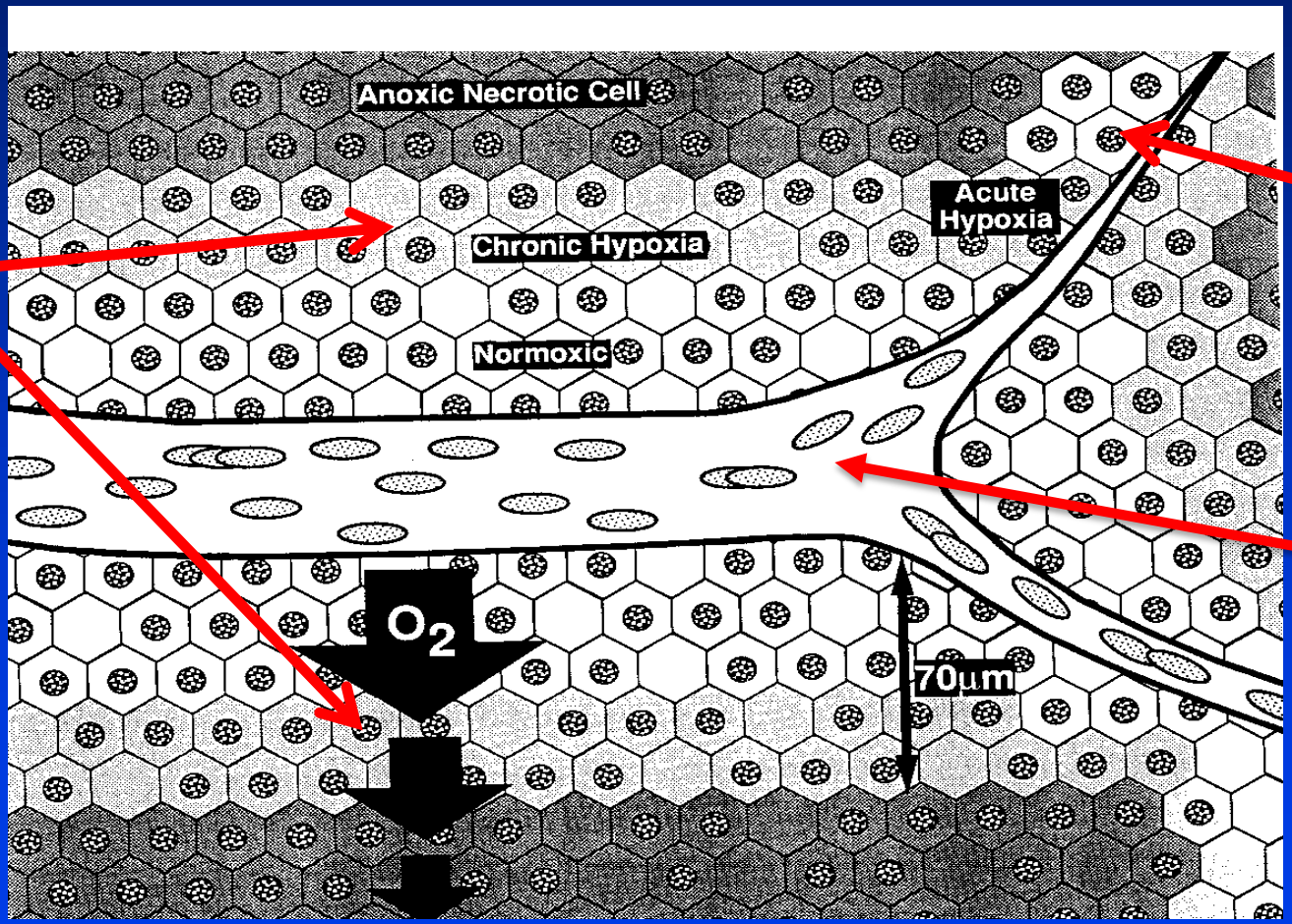
- Yes, because the protective effect of hypoxia in hypoxic cancers should be reduced by treating at low dose/fraction or low dose rate
  - *for teletherapy, this should be a benefit of hyperfractionation*
  - *for brachytherapy, this should be a benefit of permanent implants*

Two types of hypoxia in tumors: Chronic and acute

- Chronic hypoxia
  - *due to the limited diffusion distance of oxygen through tissue*
  - *cells may remain hypoxic for extended periods*
- Acute hypoxia
  - *due to temporary closing of a blood vessel*
  - *transient*

Chronic and acute hypoxia

Chronic hypoxia



Acute hypoxia

Blood vessel

Timing of reoxygenation

- Rapid component: reoxygenation of acutely hypoxic cells due to blood vessels reopening
- Slow components:
  - *as the tumor shrinks, cells previously beyond the range of oxygen diffusion (chronic hypoxia) find themselves closer to blood vessels and reoxygenate*
  - *revascularization of the tumor and killing of well-oxygenated cells might increase oxygen availability*

Reoxygenation in clinical practice

- Spreading irradiation over long periods of time by fractionation or very low dose rate brachytherapy (e.g. permanent implants) ought to be beneficial
- Modifications of the L-Q model to account for the oxygen effect and reoxygenation have been published but are not typically used in clinical practice

Finally, Redistribution

- Redistribution relates to the cell-cycle effect:
  - *Cells are most sensitive at or close to mitosis*
  - *Survival curves for cells in the M phase are linear, indicating the absence of any repair*
  - *Cells in late G_2 are usually sensitive, perhaps as sensitive as cells in M*
  - *Resistance is usually greatest in the latter part of the S phase*

What is Redistribution?

- Because of the cell cycle effect, immediately after a radiation exposure the majority of cells surviving will be those that were in a resistant phase of the cell cycle at the time of irradiation, such as late-S
- After exposure, cells are thus partially synchronized. This is known as *redistribution* (or *reassortment*)

Redistribution with fractionated radiotherapy

- The timing of the subsequent fraction will, therefore, make a difference in the response
- For example, if the next fraction is delivered at a time when the synchronized bolus of cells has reached a sensitive phase of the cell cycle, then the cells will be extra sensitive

Redistribution with daily fractionation

- Clearly, the effect of redistribution depends on both the length of the various phases of the cell cycle and the time between fractions
- Since 24 hours is much longer than the length of the G_2 phase of the cell cycle for most cells, it is unlikely that such sensitization will play a significant role for treatments delivered with daily fractionation

Redistribution in clinical practice

- With twice or three-times-a-day fractionation, sensitization by the redistribution effect is conceivable and could be significant
- However, we have not yet found a way of utilizing redistribution to our advantage
- Modifications of the L-Q model to account for the redistribution have been published but are not typically used in clinical practice

Effect of LET of the radiation

- Repair decreases as LET increases
- The OER decreases as LET increases
- The cell-cycle effect decreases as LET increases

So when might high-LET radiotherapy be most beneficial?

- For the treatment of cancers that have a high capacity for repair
- For the treatment of hypoxic cancers
- For the treatment of cancers that have cells trapped in a resistant phase of the cell cycle

Summary

- Radiotherapy is governed by the 4 Rs
  - ***R**epair, **R**epopulation, **R**eoxygenation, and **R**edistribution*
- Since normal tissue cells are better able to repair than are cancer cells, there is a “Window of Opportunity” at low dose/fraction or low dose rate
- With geometrical sparing of normal tissues, the “Window of Opportunity” widens making hypofractionation and HDR brachytherapy possible

Summary (cont'd.)

- The L-Q model can be used to calculate effects of dose/fraction, overall treatment time, and dose rate
- High-LET has potential biological advantages over conventional radiotherapy