

## Radiobiological Principles of Radiotherapy

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## Radiobiologically important parameters we can control

- ◆ Fractionation
  - *dose/fraction and number of fractions*
  - *time between fractions*
- ◆ Dose rate
- ◆ Overall treatment time
- ◆ LET of the radiation

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## Why are fractionation and dose rate important?

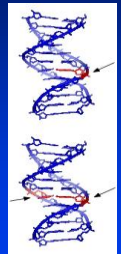
# Repair

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## 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 2<sup>nd</sup> strand of the DNA molecule is needed for the repair enzymes to be able to copy the genetic information



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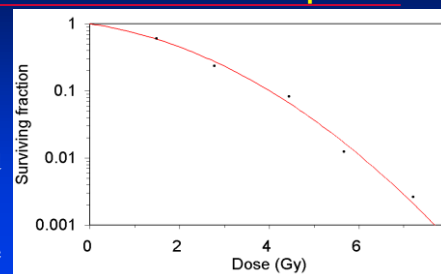
## The effect of dose

- ◆ At low doses, 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*

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## As dose increases survival curves become steeper

The more repair the less steep the curve is at low doses and hence the curvier the survival curve



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## Survival curves: normal vs cancer cells

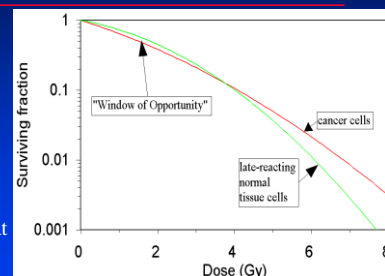
- ◆ Cancer cells do not “repair” damage at low doses as well as do normal tissue cells
  - *there is a “Window of Opportunity” at low doses where the survival of late-reacting normal tissue cells exceeds that of cancer cells*

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## 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



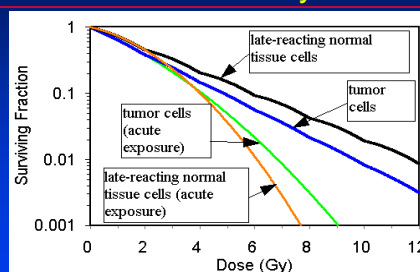
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## Fractionation

- ◆ 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

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



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## 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, but is this a reasonable assumption if we are using conformal teletherapy or brachytherapy?

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## Is this a reasonable assumption?

- ◆ 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

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## Geometrical sparing factor

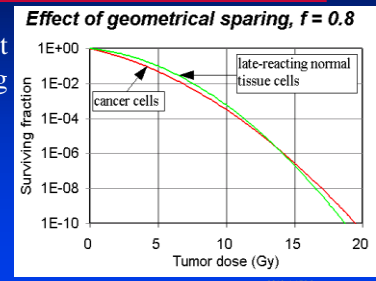
We can define a “geometrical sparing factor”,  $f$ , such that:

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

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## 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. HDR

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## 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

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## 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
  - *typically this is assumed to be six hours*

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## 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 brachytherapy and, especially, permanent implants at very low dose rate

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## What about overall treatment time?

- ◆ 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*

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## How can we determine the "best" fractionation to use?

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

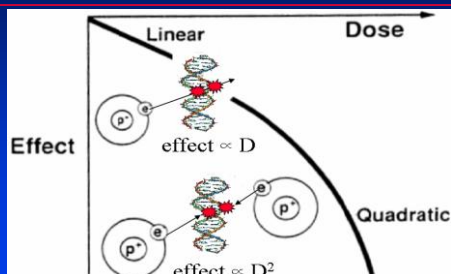
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## The linear-quadratic model of cell survival: two components

- ♦ 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

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## The linear-quadratic model



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## The L-Q Model Equation

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

$\alpha$  represents the probability of lethal  $\alpha$ -type damage

$\beta$  represents the probability that independent  $\beta$ -type events have combined to produce lethal events e.g. double-strand breaks

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## Problem with the L-Q model

- ♦ There are too many unknown biological parameters in the basic L-Q equation ( $\alpha$  and  $\beta$ ) for reliable values to be determined from analysis of clinical data
- ♦ These can be reduced to one parameter by dividing  $-\ln S$  by  $\alpha$

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The BED equation for fractionated radiotherapy in  $N$  fractions each of dose  $d$

$$- \ln S = N(\alpha d + \beta d^2)$$

Hence:

$$BED = \frac{-\ln S}{\alpha} = Nd \left( 1 + \frac{d}{\alpha / \beta} \right)$$

The remaining unknown biological parameter is  $\alpha/\beta$

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## Typical values for $\alpha/\beta$

The most common assumptions are:

for tumors and acute reactions:

$$\alpha/\beta = 10 \text{ Gy}$$

for late-reacting normal tissues:

$$\alpha/\beta = 2 - 3 \text{ Gy}$$

\* Note that some recent studies have reported that the  $\alpha/\beta$  value for prostate cancer may be as low as 1.5 Gy and for breast cancer as low as 4 Gy

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## What about repopulation?

Usually represented by  $T_{pot}$  which is the doubling time of the cells capable of continued proliferation

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It is assumed that repopulation increases cell survival exponentially with time

$$- \ln S = N(\alpha d + \beta d^2) - \frac{0.693T}{T_{pot}}$$

where  $T$  is the overall treatment time and  $T_{pot}$  is the doubling time of the cells capable of continued proliferation

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## BED equation with repopulation

$$BED = Nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693T}{\alpha T_{pot}}$$

where the tissue-specific radiobiological parameters are  $\alpha/\beta$ ,  $\alpha$ , and  $T_{pot}$

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## Problem with the BED equation with repopulation

- ♦ As before, there are too many unknown biological parameters in this L-Q equation ( $\alpha$ ,  $\alpha/\beta$  and  $T_{pot}$ ) for reliable values to be determined from analysis of clinical data
- ♦ These can be reduced to two parameters by replacing  $0.693/\alpha T_{pot}$  by  $k$

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## The BED equation with repopulation

$$BED = Nd\left(1 + \frac{d}{\alpha/\beta}\right) - kT$$

The remaining unknown biological parameters are  $\alpha/\beta$  and  $k$

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## Typical values for $k$ assumed for normal tissues

Acutely responding normal tissues:

- 0.2 - 0.3/day

♦ Late responding normal tissues:

- 0 - 0.1/day

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## Typical values for $k$ assumed for tumors

Growth rate of tumor	$k$ (day <sup>-1</sup> )
slow	about 0.1
average	about 0.3
rapid	about 0.6

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## Effect of LET

- ◆ High LET radiations are more biologically damaging and exhibit less repair than low LET radiations
- ◆ High-energy protons are not high LET

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## Why high-LET radiotherapy?

- ◆ Physical benefits
  - *the Bragg peak*
  - *reduced penumbra*
- ◆ Radiobiological benefits
  - *reduced effect of hypoxia*
  - *reduced cell cycle effect*

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## Summary

- ◆ Fractionation is important to allow normal tissues to repair (there is a “Window of Opportunity”)
- ◆ With highly-conformal therapy can use high doses/fraction
- ◆ The L-Q model is useful for determination of the “best” fractionation
- ◆ High-LET radiations have some advantages
  - *but they are very expensive*

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