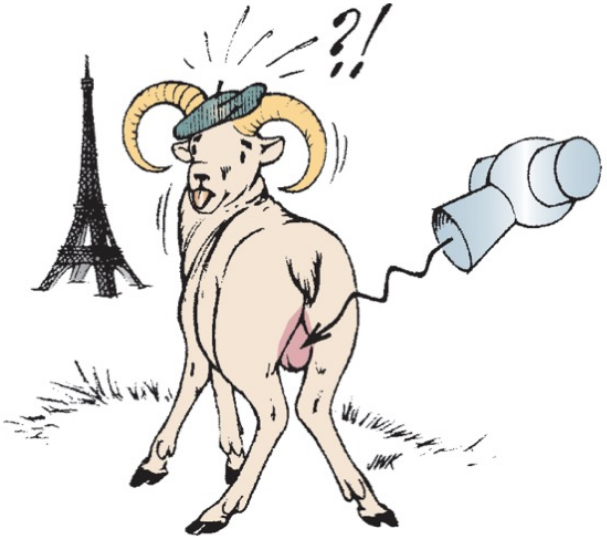
Chapter 23 – Time, Dose & Fractionation Lecture 1

12/2/2024

Outline

- **Historical Perspective of Fractionation**
- The Strandquist Plot and the Ellis NSD System
- Fraction Size – Early vs. Late-Responding Tissues
- Overall Treatment Time
  - Proliferation as a Factor in Normal Tissues
  - Accelerated Repopulation in Tumor
- Clinical Exploitation
  - Hyperfractionation
  - Accelerated Treatment
  - CHART
  - ARCON
  - Hypofractionation
- BED Calculation Based on Linear-Quadratic Model

Fractionation and Sterilization of Ram



Conventional multifraction radiotherapy was based on the radiobiolgoic experiments performed in the 1920s and 1930s

Single dose of x-ray – sterilization at the cost of severe skin damage to the scrotum

Multiple fractionation – sterilization without unacceptable skin damage

⇩

For a given level of normal-tissue toxicity, fractionation of the radiation dose produces, in most cases, better tumor control than a single large dose

Basis of Fractionation

4 Rs of Radiobiology

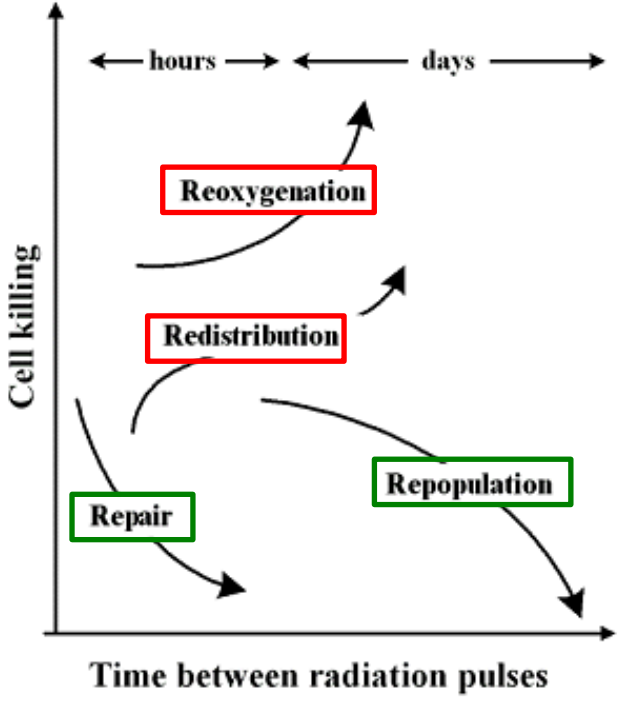
Repair of sublethal damage

Reassortment of cells within the cell cycle

Repopulation

Reoxygenation

Basis of Fractionation



Fractionation spares normal tissue

Repair of sublethal damage
Repopulation of normal cells (early-responding tissue)

Fractionation increases tumor kill

Reoxygenation
Reassortment of cells into more radiosensitive phase

There is a **fine balance** – excessive fractionation/prolongation of treatment allows surviving tumor cells to proliferate during the treatment!

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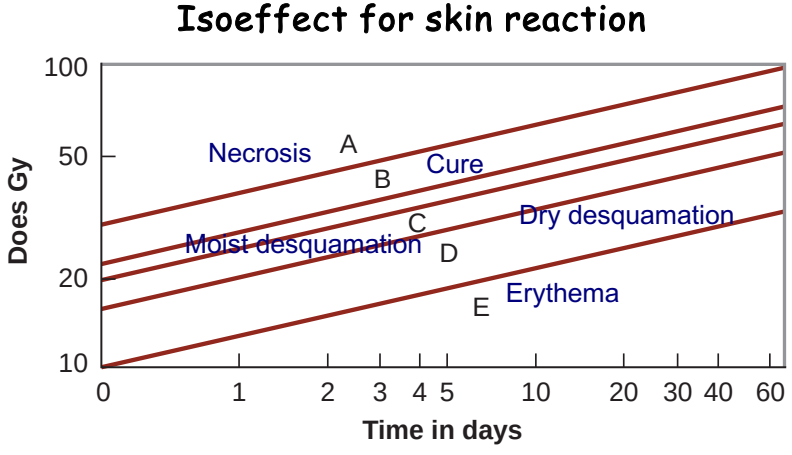
Strandquist Plot

Strandquist (1944) showed that **isoeffect doses** for various level of skin reactions in patients, plotted against **overall treatment time** for patients, produced straight lines on a log-log scale



The slopes was 0.33 → Total dose D (for an isoeffect) $\propto T^{0.33}$

or, $D \propto \sqrt[3]{T}$ which is known as the **cube root rule**

All treatments were given as 3 or 5 fractions per week → overall time contains by implication, the **number of fractions** as well

Strandquist and Contemporary Radiobiologists

The Strandquist plot gave direction to future work with isodose curves and today's computer generated linear quadratic equations, and to the varied research of contemporary radiation oncologists and biologists

The Nominal Standard Dose (NSD) Concept

Radiation oncologist **Frank Ellis** (1967), postulated that the time factor in the cube root rule was in part due to proliferation (function of **time**), and partly due to fractionation (function of number of **fractions**, N), with the latter more important, and proposed the equation

$$\text{Total Dose (D)} = (\text{NSD})\, T^{0.11} N^{0.24}$$

Note the separation of overall time from the number of fractions

NSD System

Example

What is the NSD for 60 Gy given 2 Gy/fraction over 6 weeks?

$60\ Gy = NSD \times 30^{0.24} \times 42^{0.11} \rightarrow 60\ Gy = 17.58\ NSD \rightarrow NSD = 3.41\ Gy$

Caveats

This formula has been used to equate different dose regimens, but because the formula is based on skin reactions, it cannot predict late effects

Another weakness is the single power function on T, which we now know is not accurate (to be discussed later)

The Linear-Quadratic Concept

We now use **linear-quadratic equation** to calculate biologically effective dose (**BED**)

$$BED = (nd) \times \left(1 + \frac{d}{\alpha/\beta}\right)$$

n = # of fraction
d = dose of each fraction

Before we learn how to calculate BED, let's take a closer look at the effect of **fraction size** and **time** on **normal tissue damage** as well as **tumor control**

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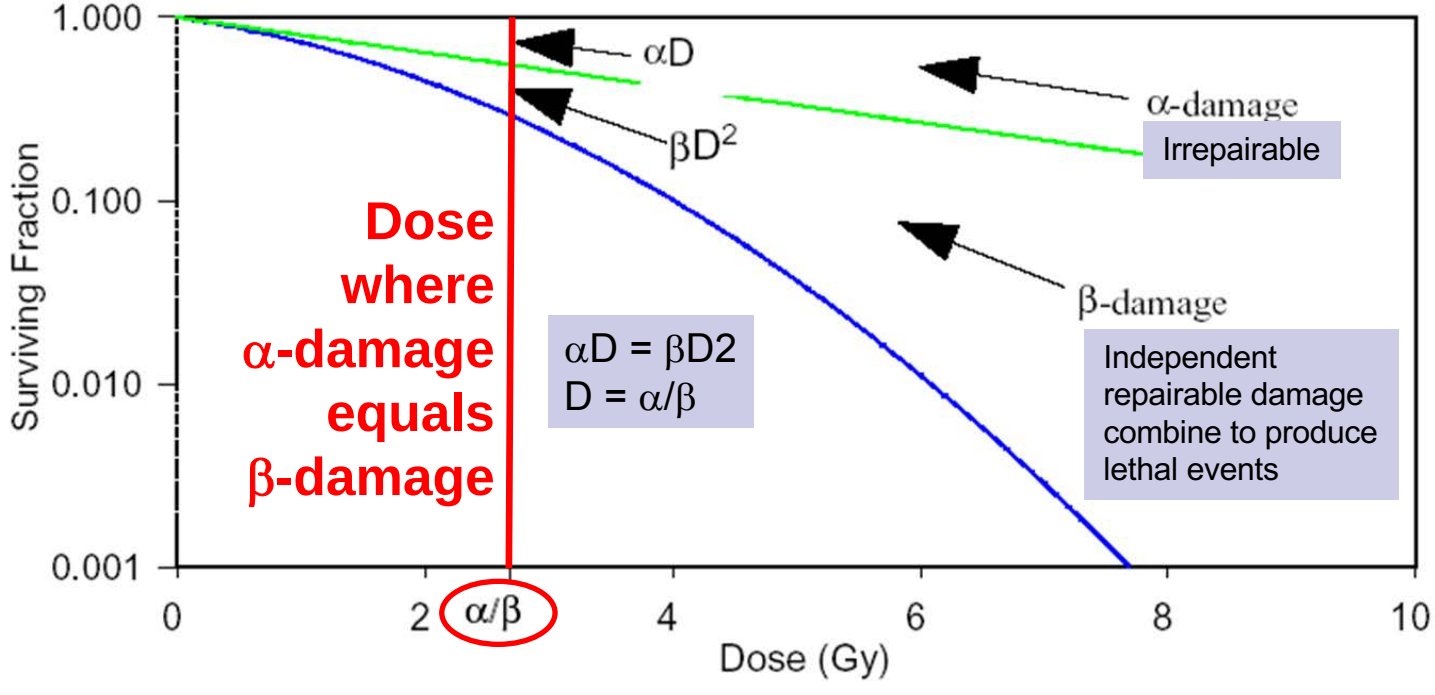
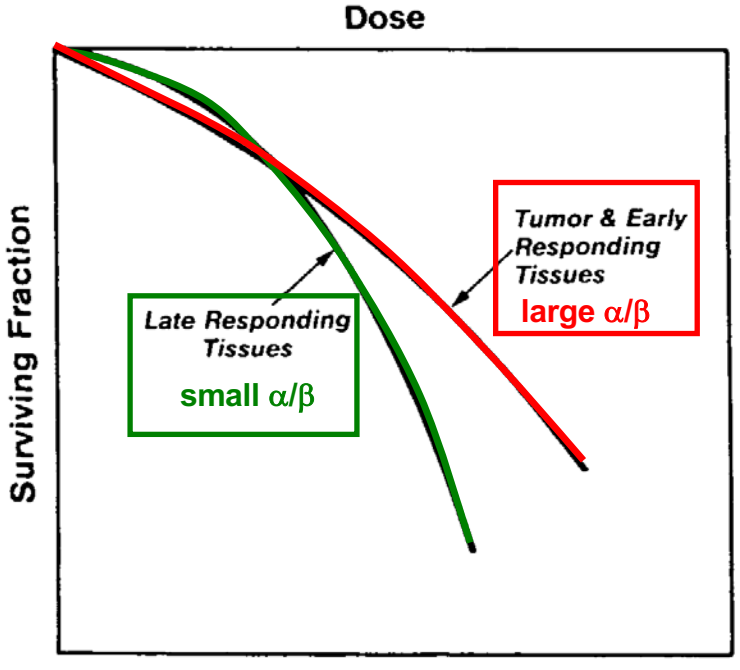
Linear-Quadratic Model Revisited

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



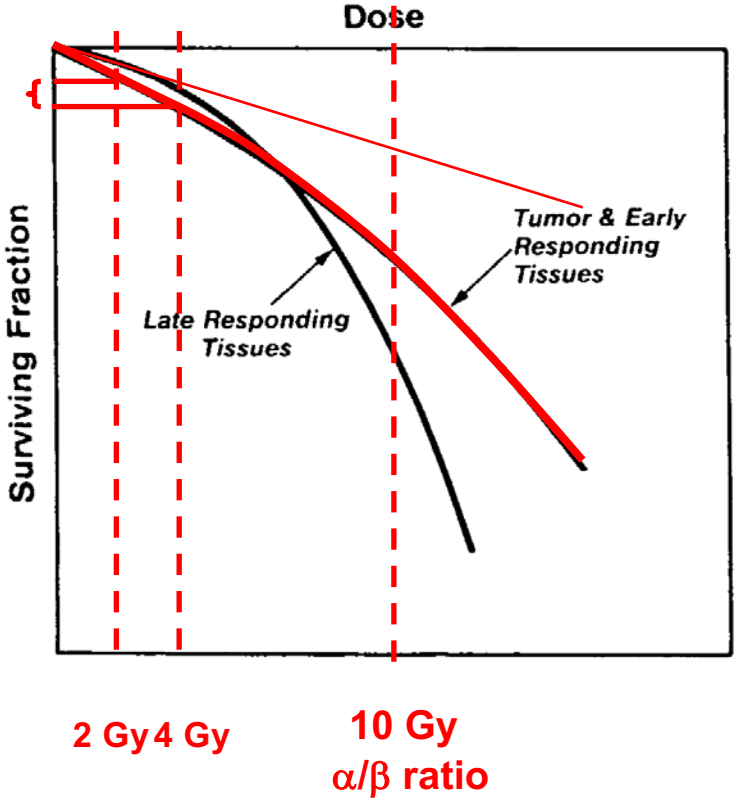
Dose-Response Curve – Early vs. Late-Responding Tissue



The dose-response relationship for late-responding tissue is **curvier** than for early-responding tissues

In the linear-quadratic formulation, this translates into a larger α/β ratio for early effects than for late effects

Early-Responding Tissue

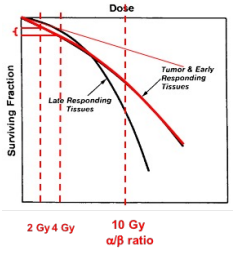


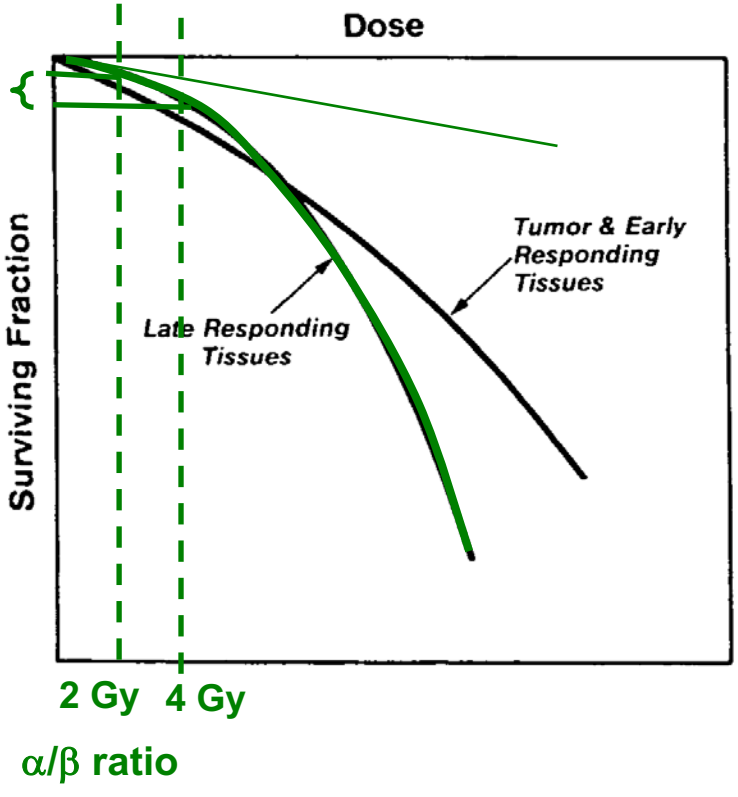
The α and β components of killing are not equal until about **10 Gy**

α component dominates at low doses, and the dose-response curve has a marked initial slope and does not bend until higher doses

Small β component (denominator) means little repair capacity → reduce the size of fraction results in little sparing, and the isoeffect curve tends to be flat

Late-Responding Tissue



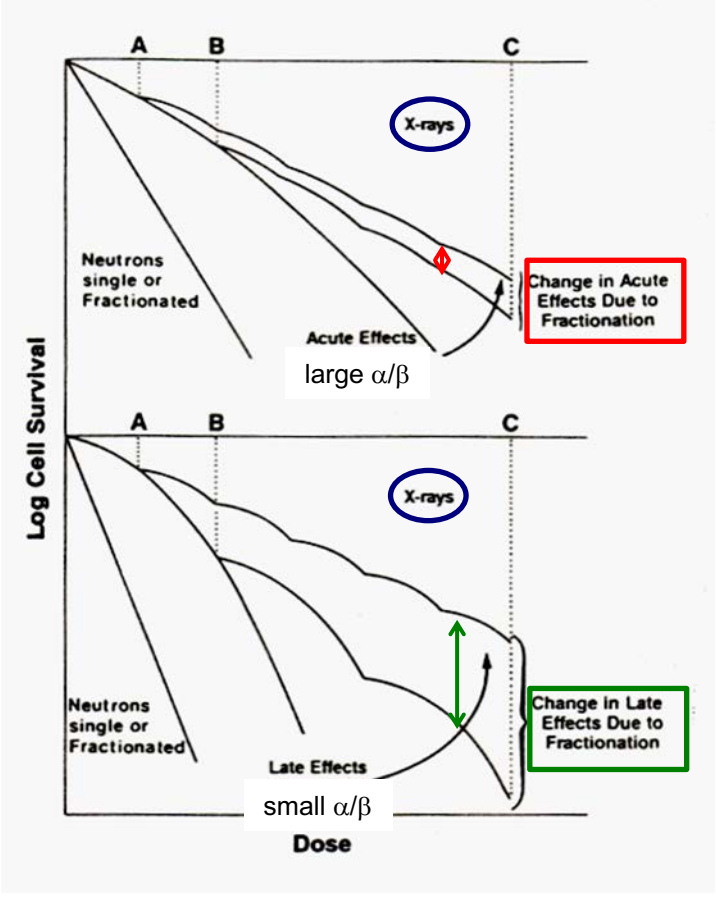


The α and β components of killing are equal by about **2 Gy**

The curve bends at lower doses to appear more curvy (broader shoulder)

Large β component (denominator) means large repair capacity $\rightarrow$ reduce the size of fraction results in significant sparing, and the isoeffect curve tends to be steep

Effect of Fractionation



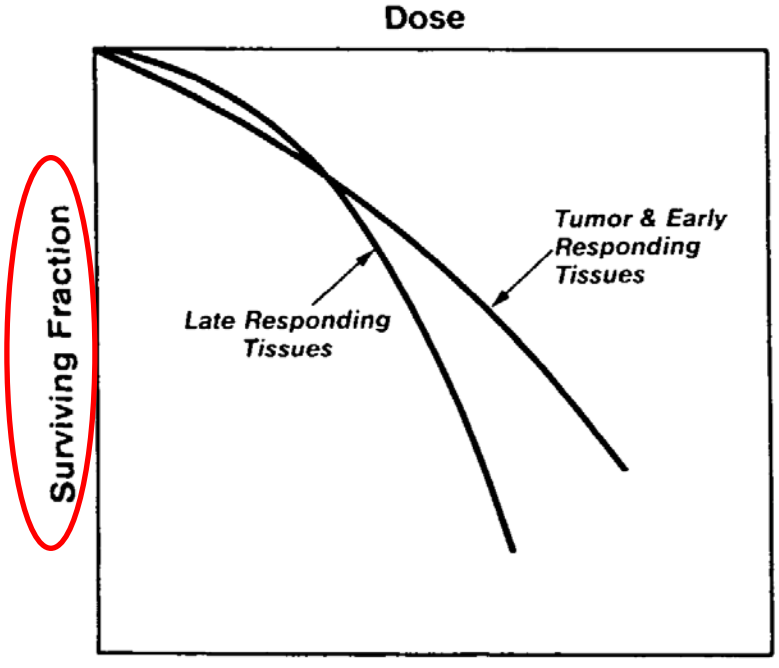
Shoulder has to be repeated with each fraction

Multifractionation leads to more sparing of the late effects than early effects

Fraction size is a dominant factor in determining late effects, more so than for early effects

What would the effect of fractionation be for therapy with high LET ?

Clinical Evidence



It is important to recognize that dose-response curve for **organ function ≠ clonogenic survival**

There are 3 pieces of information from clinical experience and animal studies that represent circumferential evidence for the conclusion that the shape of the dose-response relationship differs for early- and late-responding tissues

Clinical Evidence

Clinical Evidence – Large Fraction Size

If a fractionation scheme is changed in clinical practice from many small doses (e.g., 60 Gy in 30 fx of 2 Gy/fx) to a few large fractions (48 Gy in 5 fx of 9.6 Gy/fx) and the total dose is titrated to produce equal early effects, the treatment protocol involving a few large fractions results in more severe late effects

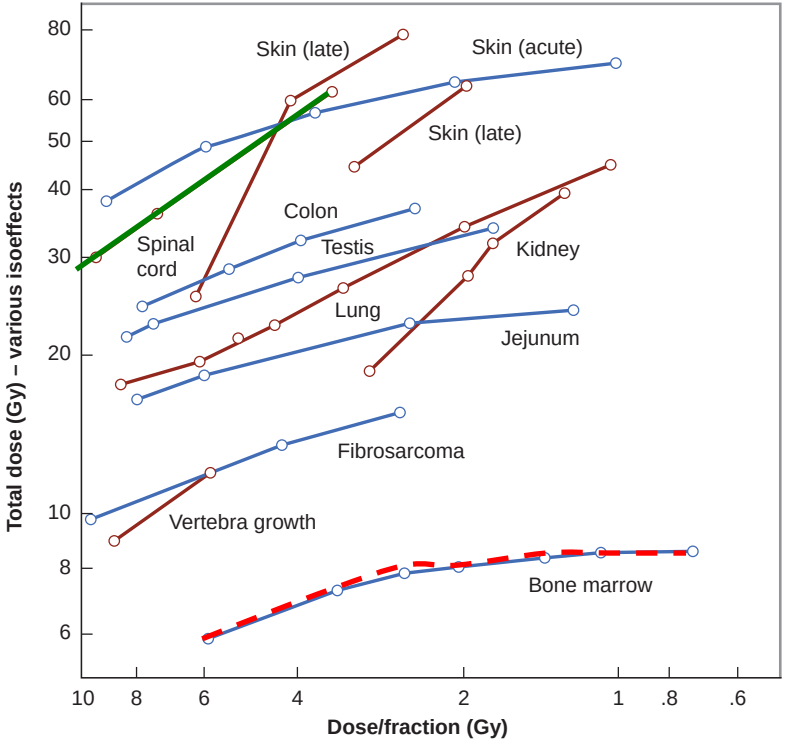
Clinical Evidence

Clinical Evidence – Small Fraction Size

Clinical trials of hyperfractionation, in which two **smaller doses** (e.g., 1.2 Gy/fx x 2) are delivered per day appear to result in **greatly reduced late effects** if the total dose is titrated to produce equal or possibly slightly more severe acute effects

This again is compatible with the difference in shape of dose-response curves between early- and late-responding tissues – late effect tissues are more sensitive to changes in fractionation patterns than are early-responding tissues

Clinical Evidence

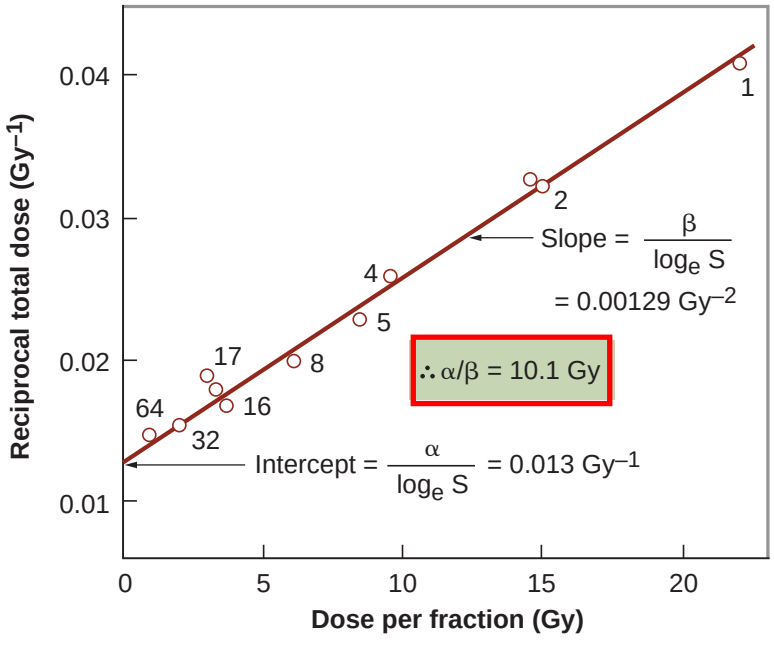


Clinical Evidence – Isoeffect Curve

In experiments with small laboratory animals, the isoeffect curves are **steeper** for a range of late effects than for a variety of acute effects

Inferring α/β Ratio from Multifraction Experiments

Skin reaction



Determine the total dose and dose per fraction for the same biologic endpoint (e.g., 50% moist desquamation) with single dose and various multifractionation regimen

↓

Plot 1/nd vs. d, and fit for a straight line

↓

Determine intercept and slope

↓

Calculate α/β

α/β Ratio from Multifraction Experiments

TABLE 23.1 Ratio of Linear to Quadratic Terms from Multifraction Experiments

Reactions	α/β, Gy
Early	
Skin	9–12
Jejunum	6–10
Colon	10–11
Testis	12–13
Callus	9–10
Late	
Spinal cord	1.7–4.9
Kidney	1.0–2.4
Lung	2.0–6.3
Bladder	3.1–7

α/β ratios are inferred from experiments where the effects of fractionation on **functional endpoints** are studied → data relevant to the tolerance dose in clinical radiotherapy

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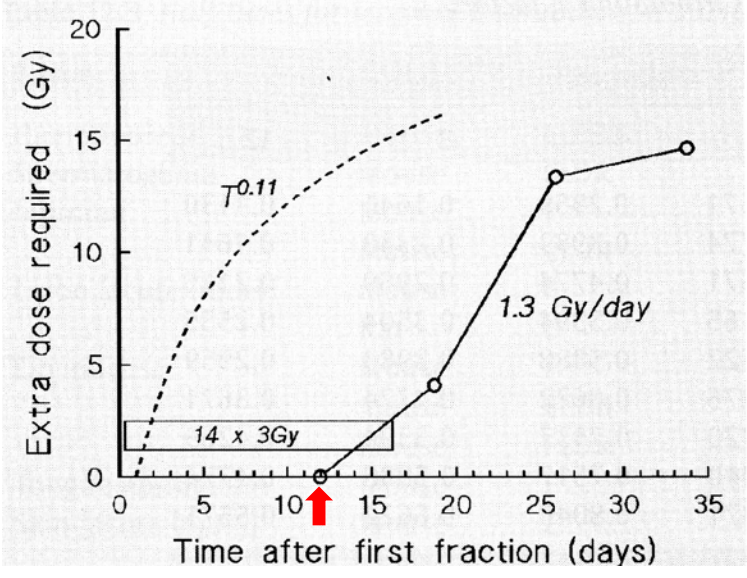
Proliferation Factor

Total Dose (D) = (NSD) $T^{0.11}N^{0.24}$

Mouse skin is irradiated with daily fraction of 3 Gy



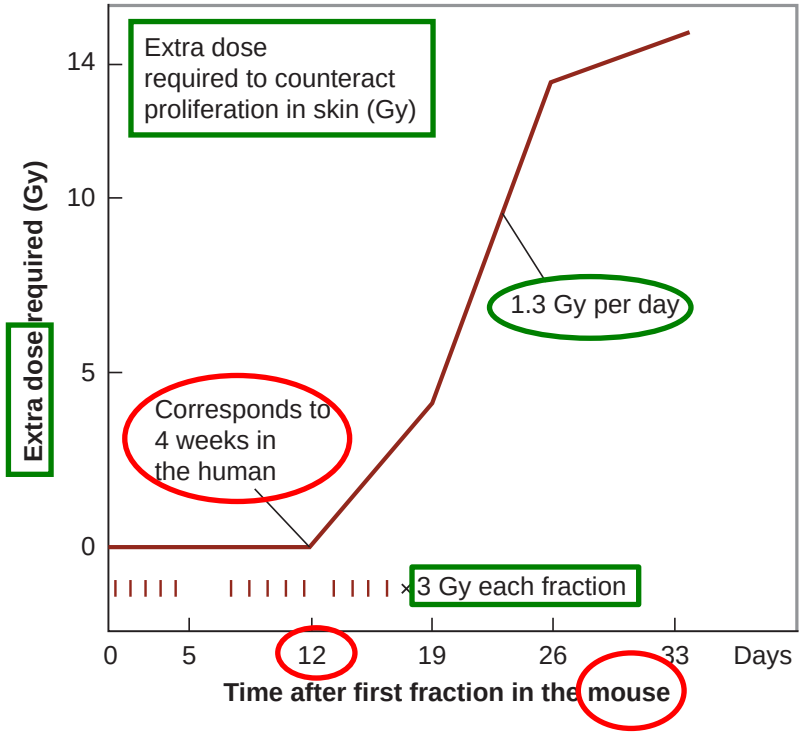
Ellis NSD system suggests that total dose to produce a given biologic effect is a power function of time

However, **experimental evidence** indicates that the extra dose required to counter proliferation and result in a given level of skin damage in mice does not increase until about **12 days** into a fractionated regimen

The method of allowing for overall time in the NSD system is incorrect

Related to lengthening of treatment time

Proliferation Factor

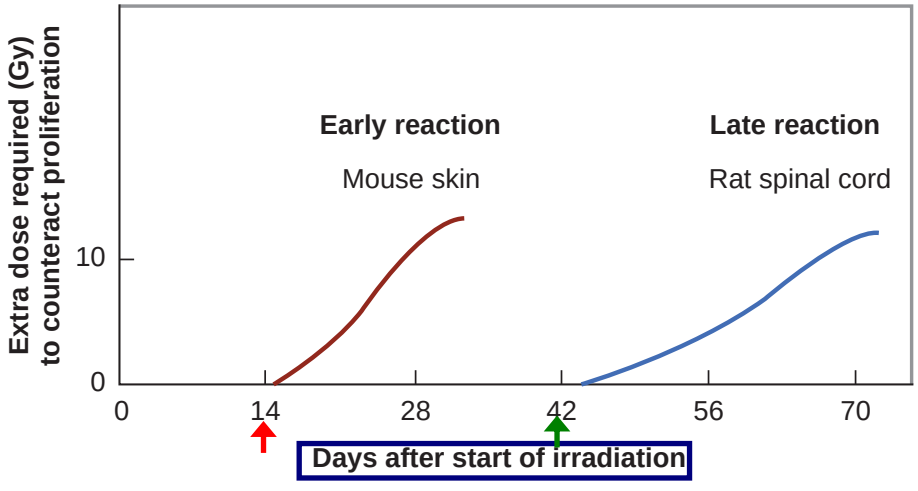


The shape of the curve is roughly **sigmoidal** – a delay followed by rapid increase (<u>at which point, skin is triggered to proliferate</u>)

In mouse, the delay is about 2 weeks

In **humans**, it is about **4 weeks** because of the slower response of the human skin and the longer cell cycle of the individual cells

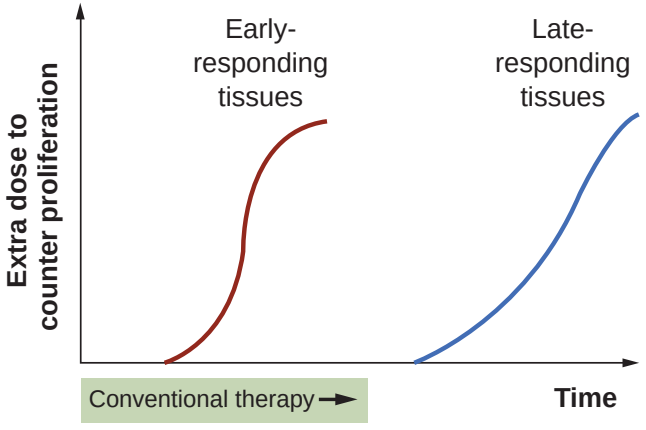
Proliferation – Early- vs. Late-Responding Tissue



Time after the start of a fractionated regimen at which extra dose required to compensate for cellular proliferation is quite different for late- vs. early-responding tissues

The time scale is likely to be **much longer** in humans

Extrapolation to Clinical Therapy



Fractionated regimen in 6-8 wks

Early-Responding Tissues

Triggered to proliferate within a few weeks of the start of a fractionated regimen

The extra dose required to counter proliferation occurs during the time course of conventional therapy

Late-Responding Tissues

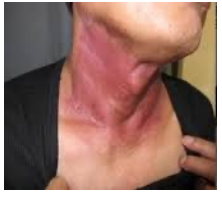
Conventional radiotherapy is never long enough to allow the triggering of proliferation in late responding tissues

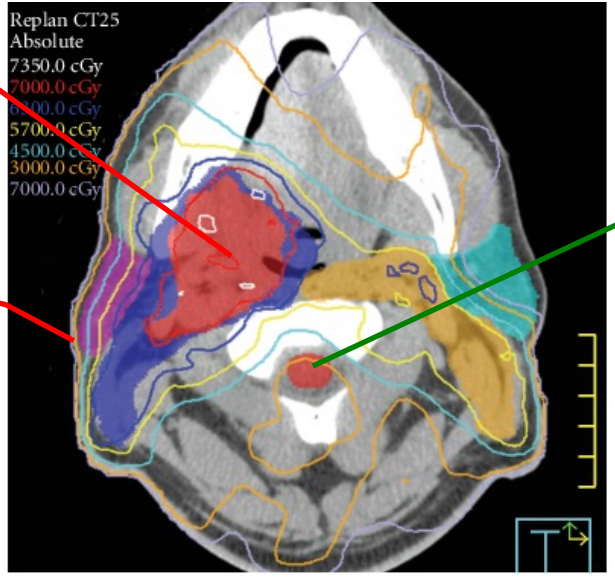
A Typical Head & Neck Treatment

Early Responding Tissue

Tumor receives 70 Gy in 35 fx over 7 weeks

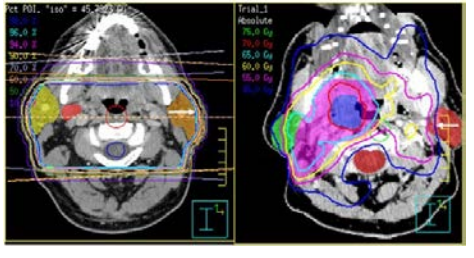
Skin receives a substantial radiation dose over 7 weeks





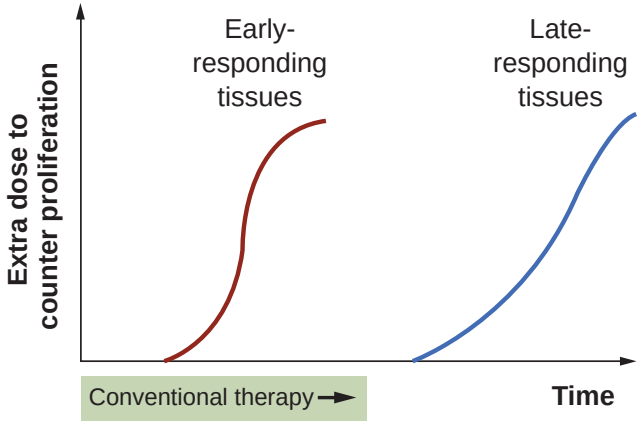
Late Responding Tissue

Spinal cord receives a lower dose over 7 weeks



Note that in old days with lateral beams, spinal cord would have received the full dose

Clinical Implication



"Prolonging overall treatment time spares **Early**- but not **Late**-responding tissues"

Early Effects

Protracting overall treatment time beyond the conventional 6-8 weeks may result in sparing of normal tissue (e.g., skin reaction, mucositis)

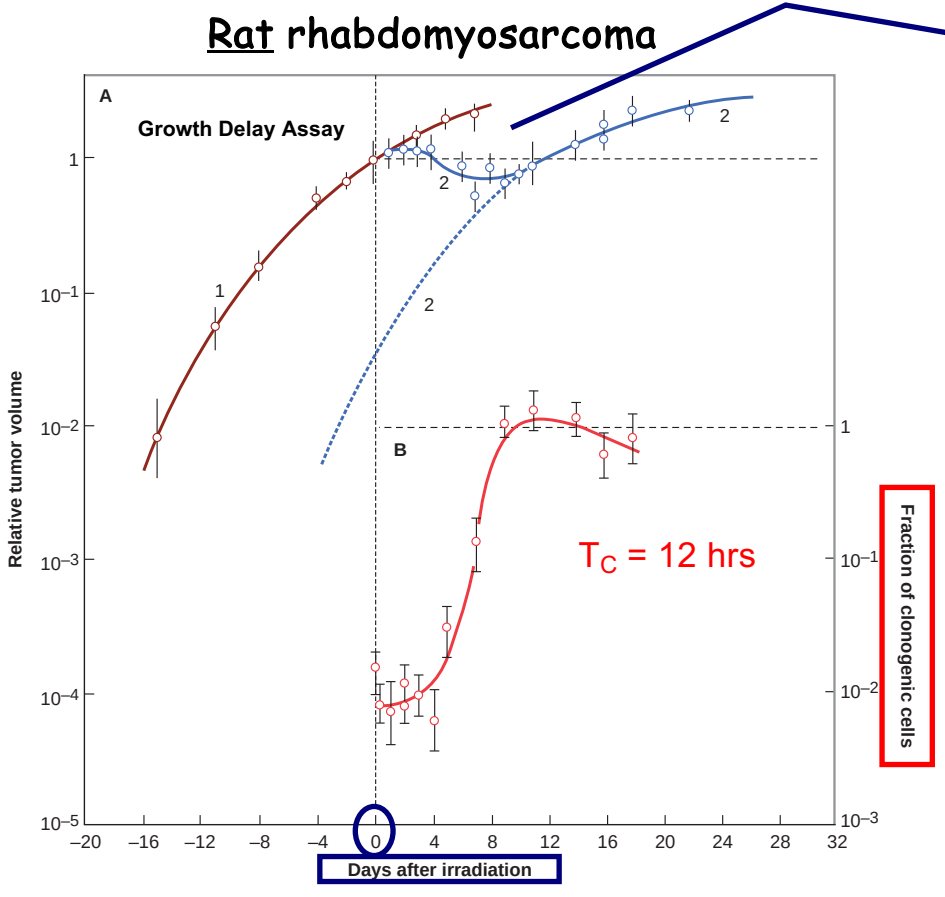
[But tumors may also be spared]

Decreasing overall treatment time to less than the conventional 6-8 weeks may result in more acute normal tissue reactions

Late Effects

Treatment time has relatively little effect on responses in late effects tissues

Accelerated Repopulation



Shrinkage and regrowth after a single dose of 20 Gy

Time to tumor recurrence after therapy is shorter than would be expected from the original growth rate

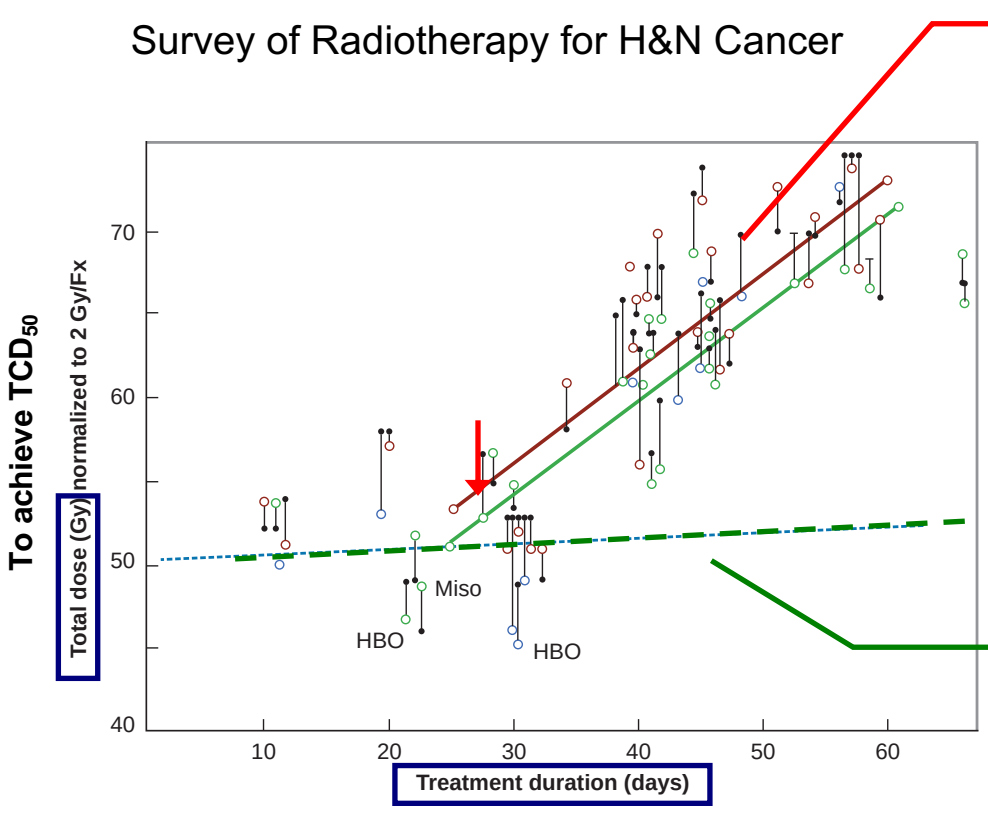
During the time that the tumor is overtly shrinking and regressing, the surviving clonogens are dividing and increase in number more rapidly than ever!!! This is known as **accelerated repopulation**

Tumor Cell Kinetics after Radiation

Immediately after irradiation their **cell cycle will ↑**, largely due to division delay

Subsequently, the loss of some cells in a tumor or non-growing normal tissue may cause the remaining cells to show **accelerated growth or repopulation;** this may result from shortening of the T_C, increased growth fraction, and/or decreased cell loss

Accelerated Repopulation in Human Tumors



Clonogen repopulation accelerates at about 28 days after the initiation of radiotherapy in a fractionated regimen

A dose increment of **0.6 Gy per day** is required to compensate for this repopulation

The dose increase predicted by T_D of 2 mo

Clinical Implication

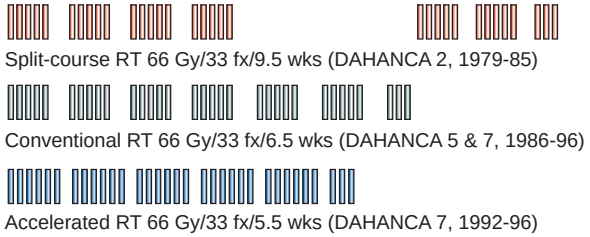
Radiotherapy, at least for head and neck cancer and probably in other instances also, should be completed as soon after it has begun as is practical

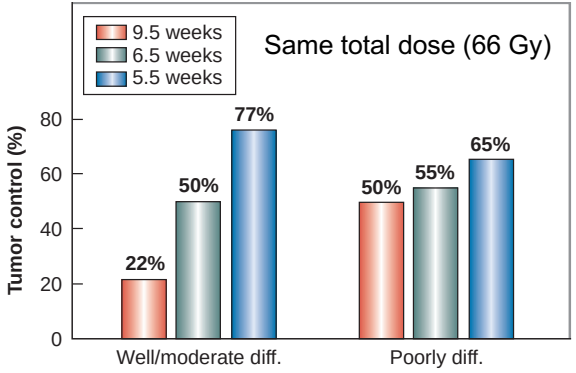
It may be better to delay initiation of treatment than to introduce delays during the treatment

If overall treatment time is too long, the effectiveness of later dose fraction is compromised because the surviving clonogens in the tumor have been triggered into rapid repopulation

Local Control and Overall Treatment Time

Retrospective analysis of 3 consecutive Danish H&N trials





Design	Overall Time, Weeks	3-Yr LC
Split course	9.5 wks	32%
5 fx/wk	6.5 wks	52%
6 fx/wk	5.5 wks	62%

In the case of relatively rapidly growing tumors, overall treatment time can be a dominant factor in determining outcome!

Importance of Overall Treatment Time vs. T_{pot}

Rapidly Proliferating Tumor

H&N cancer – T_{pot} as short as 4 days; local control is reduced by about **1.4%** (0.4-2.5%) for each day that the overall treatment time is prolonged
Cervical cancer – **0.5%** (0.3-1.1%) local control is lost for each day that the overall time is prolonged

Slowly Proliferating Tumor

Breast cancer – T_{pot} 14 days
Prostate cancer – T_{pot} 40 days
Rapid proliferation does not occur in these tumors, so overall treatment time is not so critical

Clinical Implication

In addition to radiotherapy, treatment with any cytotoxic agent, such as chemotherapy, can trigger accelerated repopulation

There is some evidence that in some human malignancies that radiotherapy produces poorer results if preceded by a course of chemotherapy (i.e., induction chemotherapy $\rightarrow$ radiotherapy)