The Linear-Quadratic Approach to Fractionation

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Disclosures

- **Licensing agreement with Modus Medical Devices**

Overview

- Importance of fractionation
- Development of models of the biological effect of varying fractionation
- Use of the linear-quadratic model to estimate biological effect

Learning Objectives

- To understand the importance of fractionation in radiation therapy
- To understand the use of α/β to describe the sensitivity of tissue to changes in fractionation
- To understand how to use the linear-quadratic model to estimate the biological effect of a fractionation change

Fractionation

- **Claudius Regaud**
  - **Noted rams could be sterilized without skin reaction if the radiation was delivered over multiple treatments**
- **Henri Coutard**
  - **"Coutard method" or "protracted-fractional" irradiation**

“Rich only in hope, possessing only incomplete information, incapable of offering precise techniques, adapted to diverse forms of cancer, radiotherapy has, however, obtained definite cures in cases incurable by surgery.”

Henri Coutard, 1936

Nominal Standard Dose

- **Based on observations of importance of dose, time, and fractionation**

$$NSD = \frac{D}{N^{0.24}\ T^{0.11}}$$

Ellis. Clin Radiol 1969;20:1-7

Nominal Standard Dose

- **Some problems**
  - **No tissue-specific factors**
  - **Requires comparison with known treatment**
  - **Limited ability to extrapolate**
  - **Time factor predicts opposite of observations**
  - **No insight to mechanisms of action**

$$\mathrm{NSD} = \frac{\mathrm{D}}{\mathrm{N}^{0.24}\ \mathrm{T}^{0.11}}$$

Ellis. Clin Radiol 1969;20:1-7

Linear-Quadratic Model

- First fitting of the linear-quadratic model by Douglas & Fowler
- Multi-fraction experiments of mouse skin reaction

Douglas & Fowler, Radiat Res 1976;66:401-426

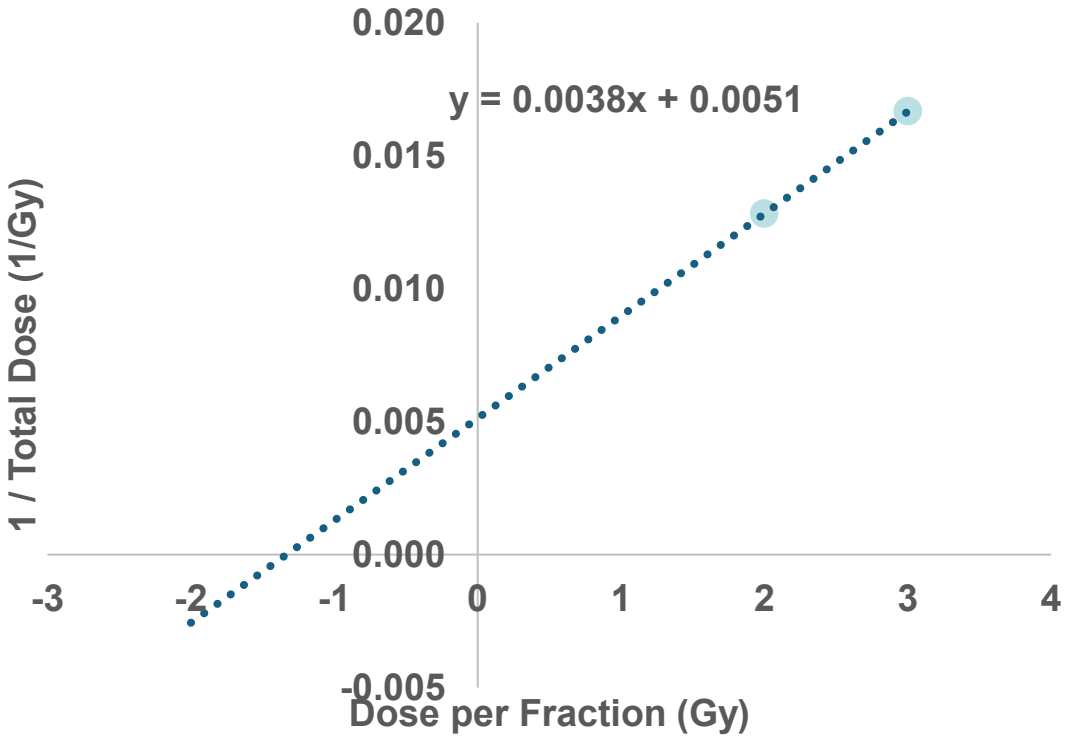
PROFIT

- PROstate Fractionated Irradiation Trial
- Is the shorter 60 Gy in 20 fractions equivalent to the standard 78 Gy in 39 fractions?
- Randomized 1206 men to those fractionation schedules
- Motivated by evidence that dose per fraction is important for prostate cancer

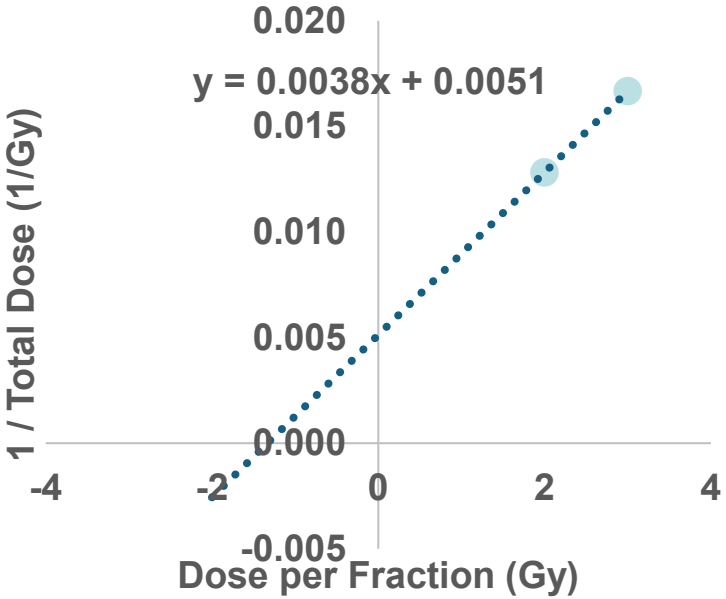
Catton et al, J Clin Oncol 2017;35:1884-1890

LQ-Fitting

	n	D (Gy)	.d (Gy)	1/D (1/Gy)
Arm 1	20	60	3	0.017
Arm 2	39	78	2	0.013



LQ-Fitting



$x = 0.0051 / 0.0038$

$x = 1.3$

$\alpha/\beta = 1.3$

Linear-Quadratic Development

- **"The cell survival curve derived here was well fitted by an equation of the form:"**
- **"…results are consistent with the postulate that cell death results from the formation of chromosome aberrations"**

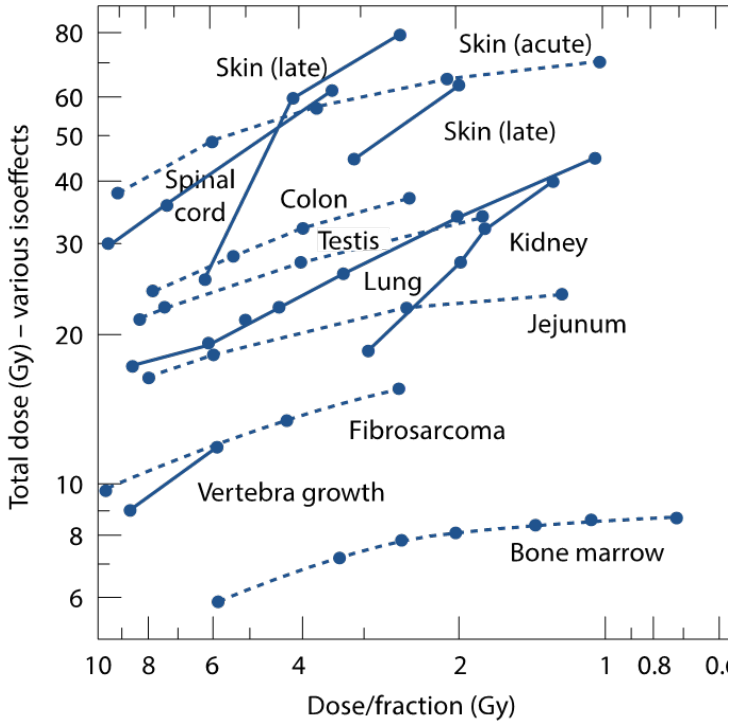
$$S = e^{-n(\alpha d + \beta d^2)}$$

S – Survival
n – Number of fractions
d – Dose per fraction
α - alpha
β - beta

Douglas & Fowler, Radiat Res 1976;66:401-426

Fraction Size

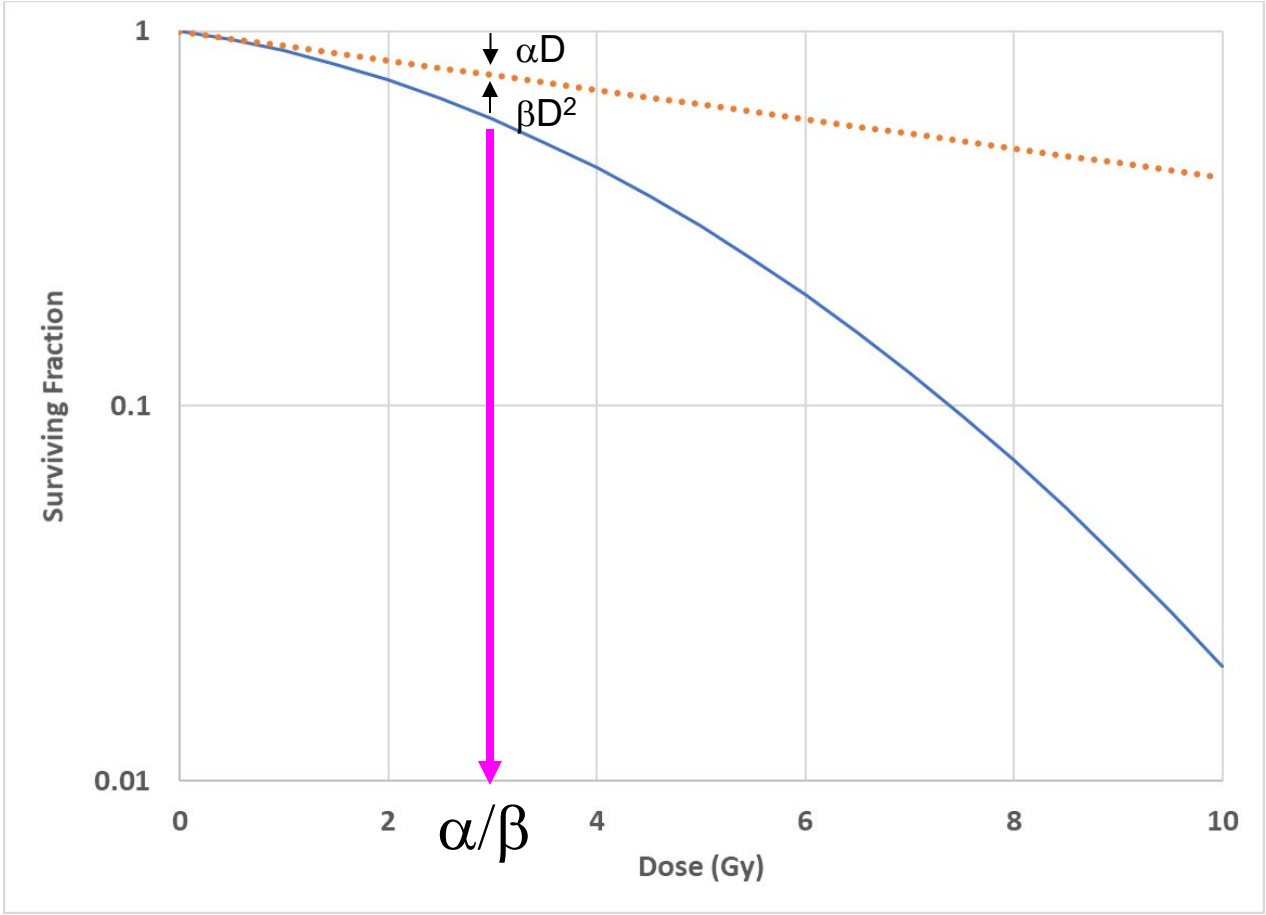
- Early effects have a shallow slope
- Late effects have a steep slope

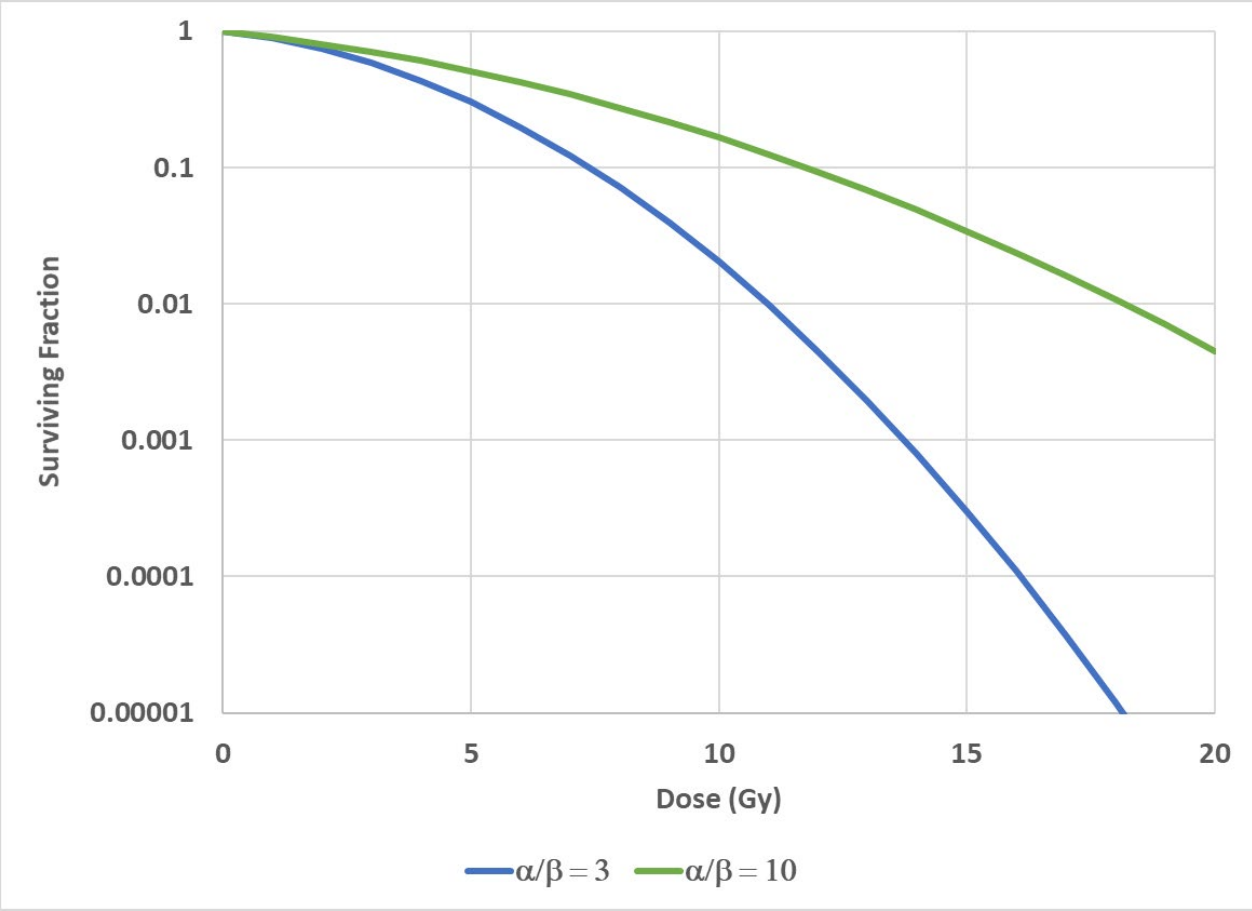


Thames et al. Int J Radiat Oncol Biol Phys 1982;8:219-226

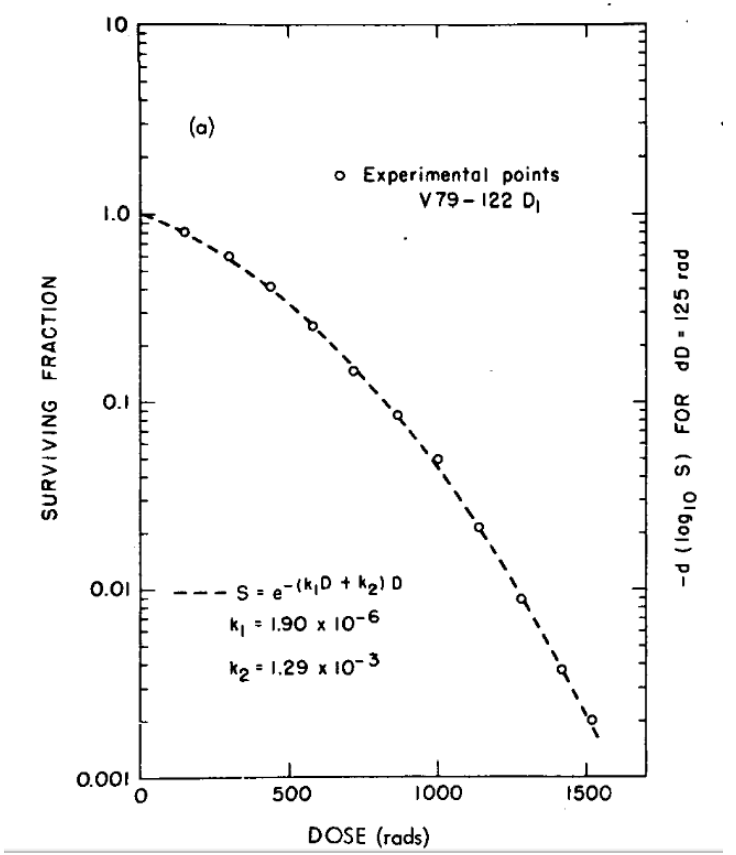
Dose per fraction is
not very important
for early effects

Dose per fraction is
very important
for late effects


1
0.1
0.01
Surviving Fraction
αD
βD²
0
2
α/β
4
6
8
10
Dose (Gy)

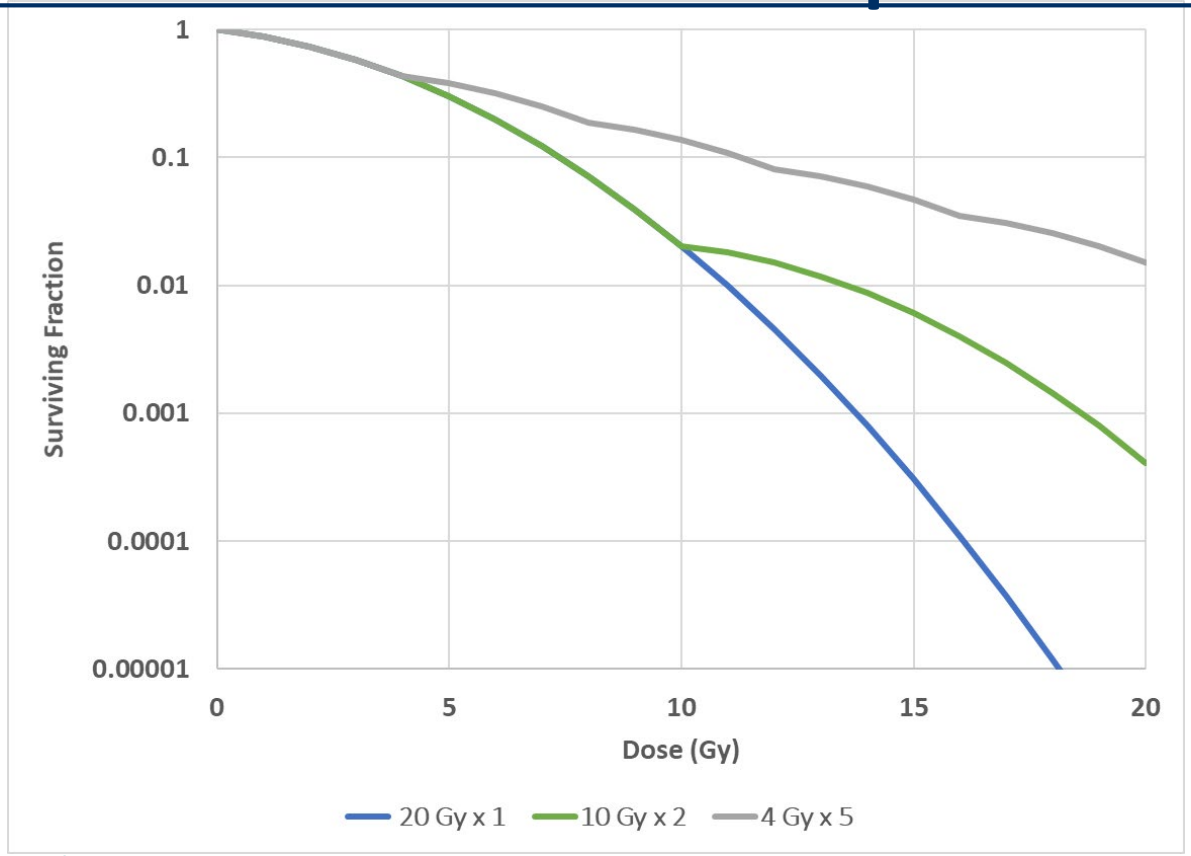

1
0.1
0.01
0.001
0.0001
0.00001
Surviving Fraction
0
5
10
15
20
Dose (Gy)
α/β = 3
α/β = 10

"The second or inverse approach is to fit a mathematical expression to the shape of the curve and see if the result can be interpreted in terms of a model"



Sinclair WK. IAEA TRS 58. 1966;21-43

LQ Survival Curves for Multiple Fractions

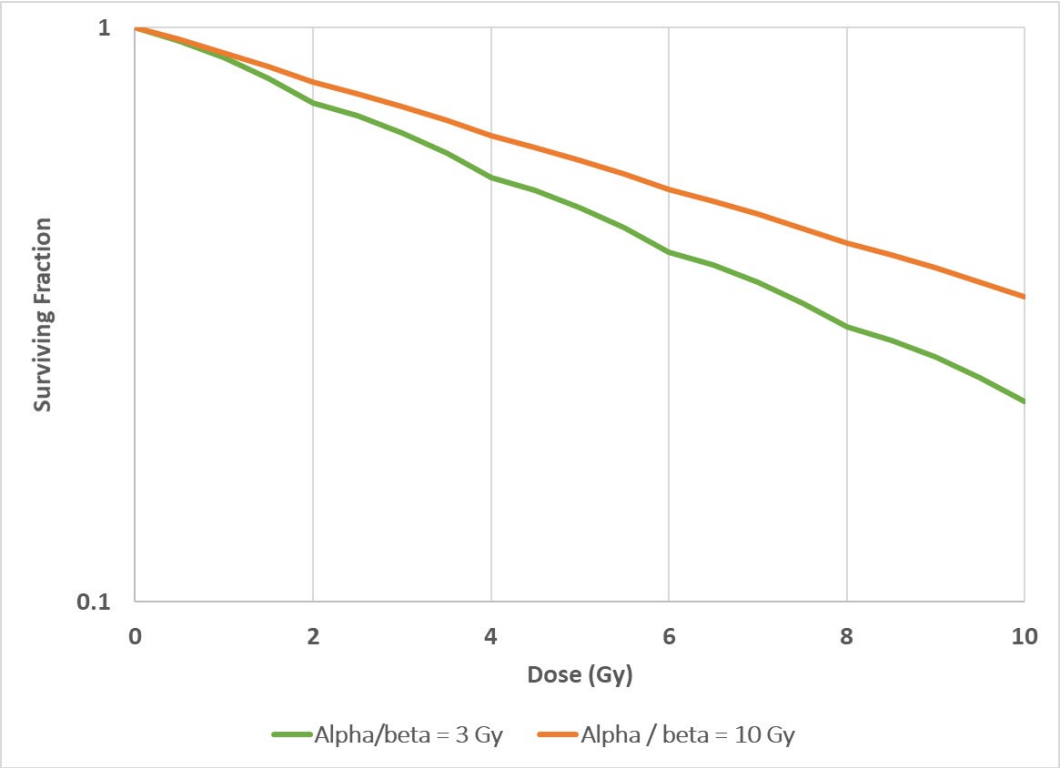


α/β for Some Human Tissues

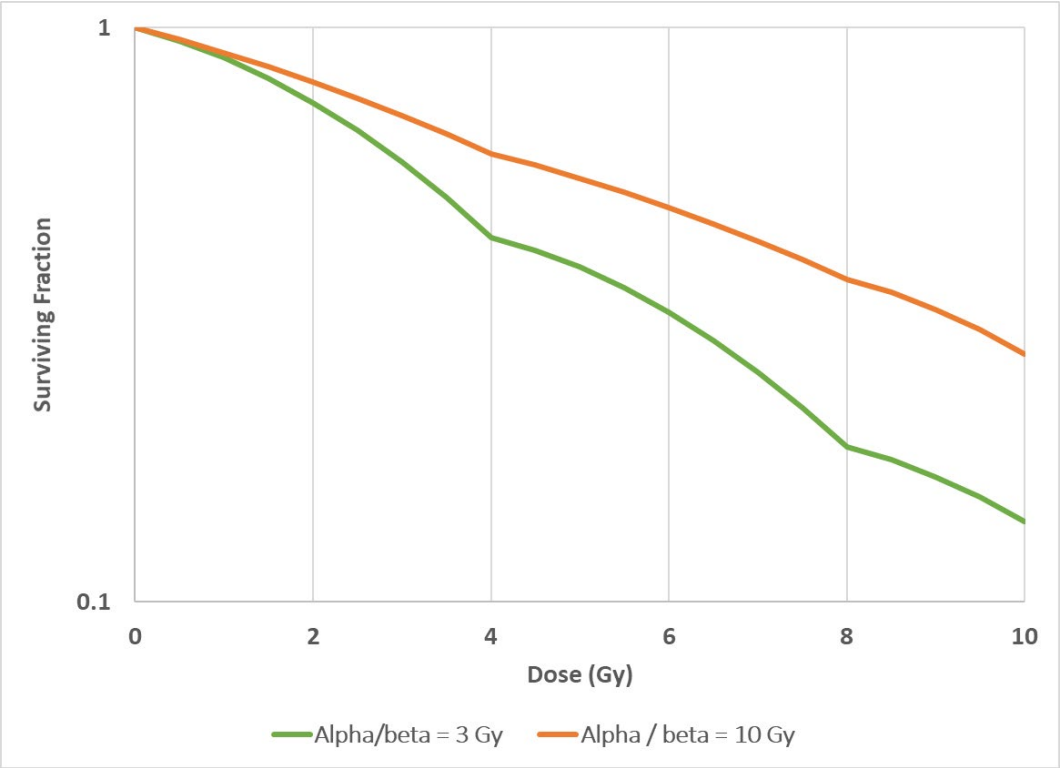
Tissue / Reaction	α/β (Gy)
Skin	9 – 13
Jejunum	9 – 11
Testis	12 – 13
Lung (pneumonitis)	4 – 7
Lung (fibrosis)	3 - 4
Spinal cord	2 – 5
Bone	2 – 3

Fowler, Brit J Radio, 1989; 62: 679-694

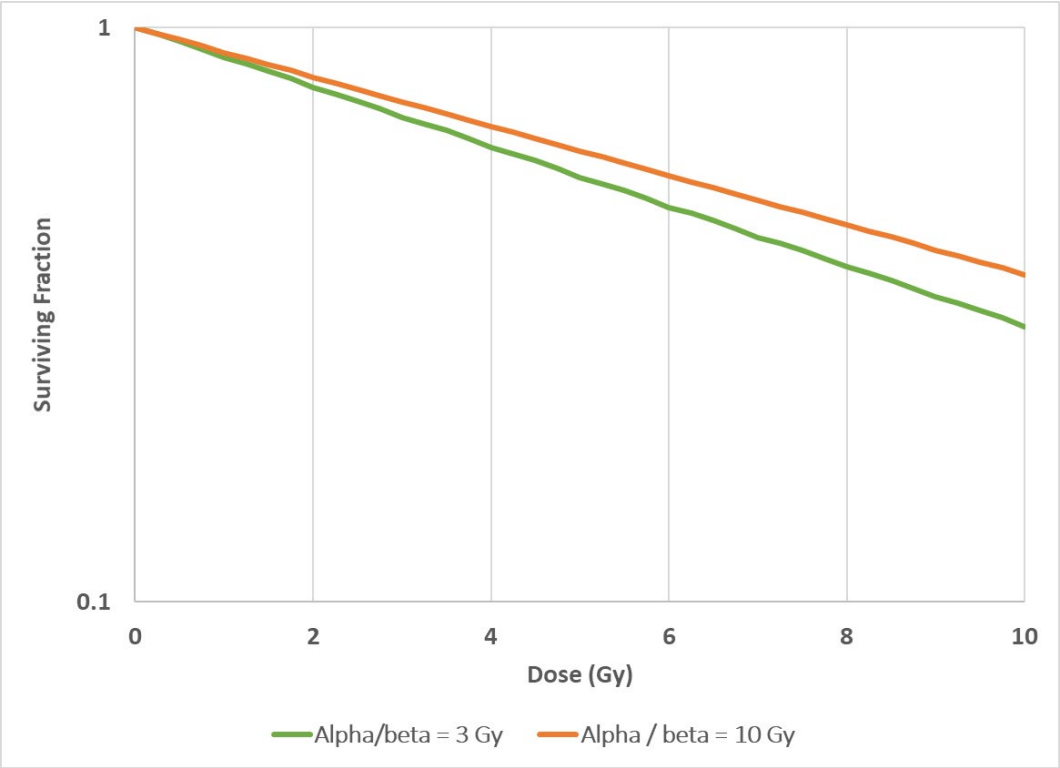
2 Gy per Fraction



4 Gy per Fraction



1 Gy per Fraction



Biologically Effective Dose

$$S = e^{-n(\alpha d + \beta d^2)}$$ Survival

$$E = D(\alpha + \beta d)$$ Effect

$$\frac{E}{\alpha} = D\left(1 + \frac{d}{\alpha/\beta}\right)$$ Biologically Effective Dose

Biologically Effective Dose

78 Gy / 39 fractions

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

$$BED = 78\left(1 + \frac{2}{1.3}\right)$$

$$BED = 198\ Gy_{1.3}$$

60 Gy / 20 fractions

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

$$BED = 60\left(1 + \frac{3}{1.3}\right)$$

$$BED = 198\ Gy_{1.3}$$

Biologically Effective Dose and Time

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

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

T – Total time
T_k – Time when accelerated repopulation begins
T_{pot} – Potential doubling time

Biologically Effective Dose and Time

70 Gy / 35 fractions, 47 days

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

$$BED = 70\left(1 + \frac{2}{10}\right) - \frac{ln(47 - 28)}{0.03x3}$$

$$BED = 84 - 32.7$$

$$BED = 51.3$$

Biologically Effective Dose and Time

70 Gy / 35 fractions, 61 days

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

$$BED = 70\left(1 + \frac{2}{10}\right) - \frac{ln(61 - 28)}{0.03x3}$$

$$BED = 84 - 38.9$$

$$BED = 45.1$$

“The LQ model, with the addition of the proliferation time factor, becomes more clumsy and dangerous than the simple LQ model to calculate late effects.”

Fowler, Brit J Radio, 1989; 62: 679-694

Continuous, hyperfractionated, accelerated radiotherapy (CHART) has given high levels of tumour control in advanced head and neck and bronchial carcinomas. In general, late changes have appeared less than after conventional radiotherapy but despite a prediction of reduced risk of spinal cord damage, two cases of radiation myelitis have presented.

Dische & Saunders. Radiother Oncol 1989; 16: 65-72

Incomplete Repair

- Application of the linear-quadratic model assumes identical effect per fraction
- This assumption can be violated if the time between fractions is short compared to the repair time of irradiated tissue
- Modern accelerated approaches typically require a minimum of 6 hours between fractions

Summary

- The dose per fraction tends to be very important for late responding tissues and less important for early responding tissues
- α/β tends to be high for tumours and early responding tissues and low for late responding tissues
- The linear-quadratic model and α/β allow estimation of the effect of dose per fraction

Questions?

Thank you!

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