

Quantitative Radiobiology for Treatment Planning

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The BED Equation

The L-Q equation for surviving fraction S after a dose D is:

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

or, for N fractions of dose/fraction d :

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

This could be used to calculate the biological effectiveness of a course of treatment

Problem with the L-Q model

- ◆ There are too many unknown biological parameters in this basic L-Q equation (α and β) for reliable values to be determined from analysis of clinical data
- ◆ These can be reduced to one parameter by dividing $-\ln S$ by α to give the Biologically Effective Dose (BED) equation

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 α/β

Typical values for α/β

The most common assumptions are:

for late-reacting normal tissues:

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

for tumors and acute reactions:

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

*

Note that some recent studies have reported that the α/β value for prostate cancer may be as low as 1.5 Gy and for breast cancer as low as 4 Gy

What about the effect of dose rate?

For low dose rate (LDR) brachytherapy at dose/rate R , where the time for each fraction, t , is long enough for some repair to take place but the time between fractions is long enough for complete repair:

$$BED = NRt \left\{ 1 + \frac{2R}{\mu(\alpha / \beta)} \left[1 - \frac{1 - e^{-\mu t}}{\mu t} \right] \right\}$$

where μ = repair rate constant ($= 0.693/t_{1/2}$ where $t_{1/2}$ is the half time for repair)

The approximate BED equation for LDR brachytherapy

If the treatment time t is long, typically greater than about 100 h, the BED equation reduces to:

$$BED = NRt \left(1 + \frac{2R}{\mu(\alpha / \beta)} \right)$$

What if the dose rate decreases due to decay during treatment?

$$BED = \frac{R_0}{A\lambda} \left[1 + \frac{2R_0\lambda}{(\mu - \lambda)\alpha / \beta} (A(B - C)) \right]$$

where:

$$A = \frac{1}{1 - e^{-\lambda t}}$$

$$B = \frac{1 - e^{-2\lambda t}}{2\lambda}$$

$$C = \frac{1 - e^{-(\mu + \lambda)t}}{\mu + \lambda}$$

Where R_0 is the initial dose rate and λ is the decay constant of the source

BED equation for permanent implants

By letting the treatment time t approach infinity in the LDR BED equation the equation for a permanent implant is obtained:

$$BED = \frac{R_0}{\lambda} \left[1 + \frac{R_0}{(\mu + \lambda)(\alpha / \beta)} \right]$$

What about the effect of time on the basic L-Q equation?

The effect of repopulation on the surviving fraction equation is:

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

So, for N fractions of dose/fraction d:

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

Where:

T = overall treatment time (days)

T_{pot} = potential doubling time (days)

The BED equation with repopulation

Hence, since $BED = -\ln S/\alpha$:

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

Problem!

- ◆ As before, there are too many parameters in this BED equation (α , α/β , 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

Then the BED equation with
repopulation becomes

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

The unknown biological parameters are α/β and k , where k is the “lost” BED/day due to repopulation

Typical values for k assumed for normal tissues

Acutely responding normal tissues:

- *0.2 - 0.3 BED units/day*

◆ Late responding normal tissues:

- *0 - 0.1 BED units/day*

◆ Note that this is not Gy/day, as you will see in some publications, because BED is not linear in dose (it's linear-quadratic)

Typical values for k assumed for tumors (assuming no accelerated repopulation)

Growth rate of tumor	k (BED units/day)
slow	about 0.1
average	about 0.3
rapid	about 0.6

What is accelerated repopulation?

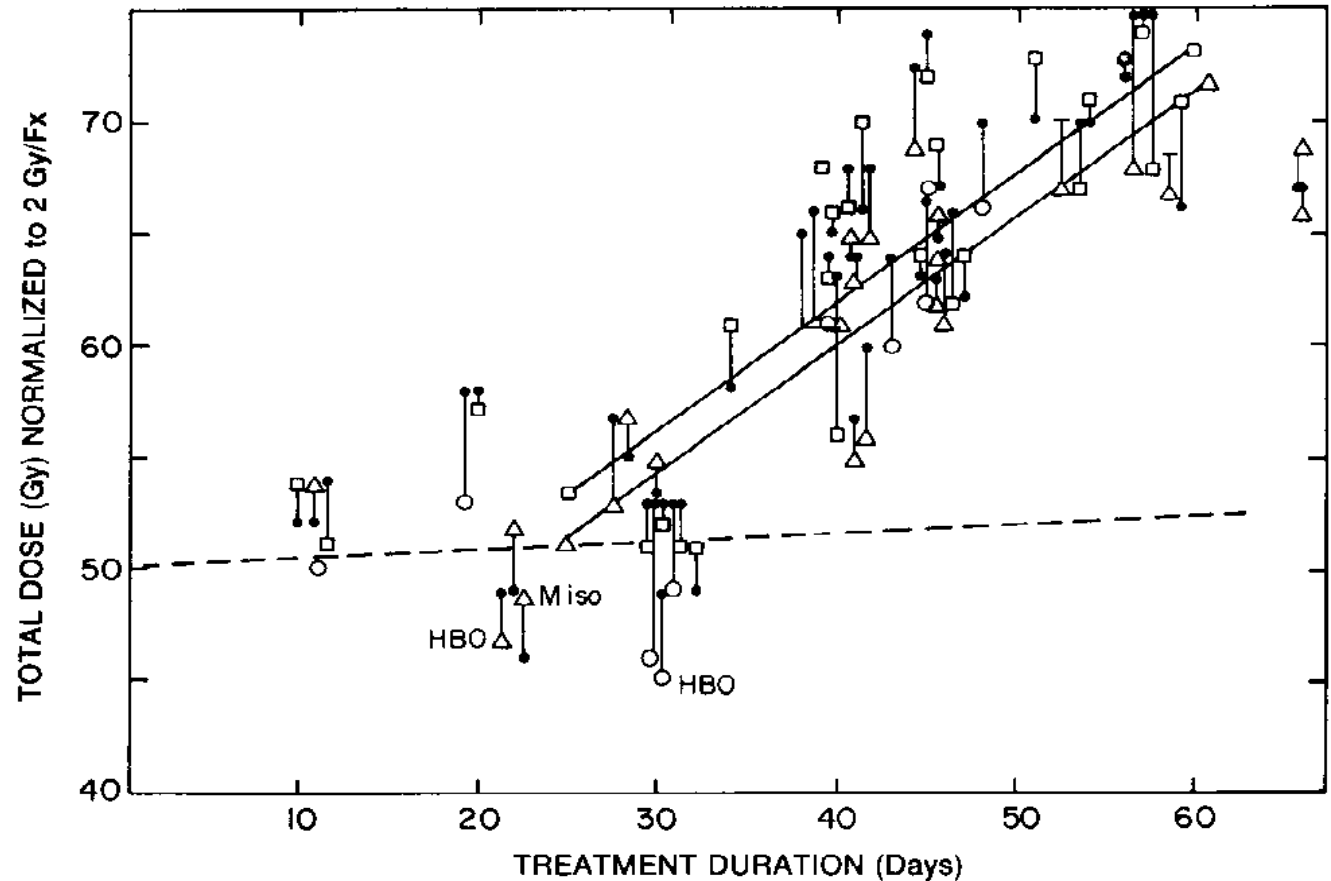
- ◆ Some believe that there is a delay between the start of treatment and the onset of “accelerated repopulation”
 - *there is no repopulation before the “kick-in” time T_k days for accelerated repopulation*
 - *there is significant repopulation after T_k days (the so-called “Withers’ hockey stick”)*
- ◆ The BED equation then becomes:

$$BED = NRt \left(1 + \frac{GRt}{\alpha/\beta} \right) - k(T - T_k)$$

where $k = 0$ for $T < T_k$

Withers' "hockey stick"

The iso-effect dose for local control of H & N cancers increases significantly after 3 - 4 weeks of treatment



Special applications of the BED equation

- ◆ Converting all total doses within the treated volume to their equivalent at 2 Gy/fraction
 - *Why? For biological treatment planning, since most of our knowledge of tumor and normal tissue effects has been obtained at about 2 Gy/fraction*
- ◆ Correcting for errors when you want the corrected course of therapy to be the same as originally planned as far as both normal tissue complication and tumor control probabilities are concerned
- ◆ Retreatments when previous treatment has failed and a region previously irradiated has to be retreated

The 2 Gy/fraction equivalent dose

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

$$-\frac{\ln S}{\alpha} = N \left(d + \frac{d^2}{\alpha/\beta} \right) = BED$$

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

$$D_i \left(1 + \frac{d_i}{\alpha/\beta} \right) = D_2 \left(1 + \frac{2}{\alpha/\beta} \right)$$

$$D_2 = D_i \left[\frac{\left(1 + \frac{d_i}{\alpha/\beta} \right)}{1 + \frac{2}{\alpha/\beta}} \right]$$

Using the L-Q model to correct for errors

**A SIMPLE α/β -INDEPENDENT METHOD TO DERIVE FULLY ISOEFFECTIVE
SCHEDULES FOLLOWING CHANGES IN DOSE PER FRACTION**

MICHAEL C. JOINER, M.A., PH.D.

Int. J. Radiat. Oncol. Phys. Biol., Vol. 58, No.3, pp. 871-875, 2004

The Mike Joiner method

- ◆ Joiner found that if several fractions are delivered at the wrong dose/fraction, you can derive a dose/fraction to use for the remainder of the course that will result in the planned BEDs being delivered to *all* tissues
 - *it is independent of the α/β of the tissue*

The Mike Joiner method: definitions

- ◆ The planned total dose is:

$$D_p \text{ Gy at } d_p \text{ Gy/fraction}$$

- ◆ The dose given erroneously is:

$$D_e \text{ Gy at } d_e \text{ Gy/fraction}$$

- ◆ The dose required to complete the course is:

$$D_c \text{ Gy at } d_c \text{ Gy/fraction in } N_c \text{ fractions}$$

The Joiner equations

$$D_c = D_p - D_e \quad \text{i.e. total dose is unchanged}$$

$$d_c = \frac{D_p d_p - D_e d_e}{D_p - D_e}$$

Example: dose below prescribed for 1st two fractions

Planned treatment: HDR brachytherapy to 42 Gy
at 7 Gy/fraction

Given in error: 2 fractions of 3 Gy

Then the dose/fraction needed to complete the
treatment is:

$$d_c = \frac{D_p d_p - D_e d_e}{D_p - D_e} = \frac{42 \times 7 - 6 \times 3}{42 - 6} = 7.67 \text{ Gy}$$

Example (cont'd.)

- ◆ The total dose remains unchanged so the extra dose required is:

$$D_c = 42 - 6 = 36 \text{ Gy}$$

- ◆ Hence the number of fractions required is:

$$N_c = 36/7.67 = 4.7$$

- ◆ Since we cannot deliver 0.7 of a fraction, complete the treatment with 5 fractions of $36/5 = 7.2 \text{ Gy/fraction}$
 - *always round out the number of fractions **up**, since increased fractionation spares normal tissues*


Additional benefit of the Joiner model

The solution is not only independent of α/β but it is also independent of any geometrical sparing of normal tissues

What about retreatments?

- ◆ Unfortunately, there is no simple solution, especially if normal tissues were taken to close to tolerance the first time around
- ◆ Best to change the field arrangement so as to minimize giving more dose to these tissues
- ◆ Need to discuss with the doctor
- ◆ There is a limited amount of literature on specific types of tumor or normal tissue
- ◆ **What would I do?**

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Thoracic cord could not be fit, but points were to the left of the cervical spine, suggesting higher tolerance; In terms of re-irradiation, using BED (a/b=2 Gy) ...

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A combined analysis of all published clinical data on spinal cord reirradiation was reported in 2005, providing a basis for radiation myelopathy risk estimation (1) ...

Summary

- ◆ The L-Q model can be used to calculate effects of dose/fraction, overall treatment time, and dose rate
- ◆ But Warning! The L-Q model is just a “model”
- ◆ By all means use it to as a guide in clinical practice
 - ◆ But don't fall in love with it!!!