Quantitative Radiobiology for Treatment Planning

Colin G. Orton, Ph.D.
Professor Emeritus,
Wayne State University,
Detroit, Michigan, USA

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 *-lnS* 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 tumors and acute reactions:

α/β = 10 Gy

for late-reacting normal tissues:

α/β = 2 - 3 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?

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

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:

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

Repopulation and the L-Q equation

- The basic L-Q model does not correct for repopulation during the course of therapy
- Hence, the basic L-Q equation does not take overall treatment time, *T*, into account
- The L-Q model with repopulation correction assumes that increase in surviving fraction due to repopulation is an exponential function of time

The L-Q equation with repopulation

Hence:

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

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 = -lnS/α:

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

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

Typical values for *k* assumed for normal tissues

Acutely responding normal tissues:

- *0.2 - 0.3 BED units/day*

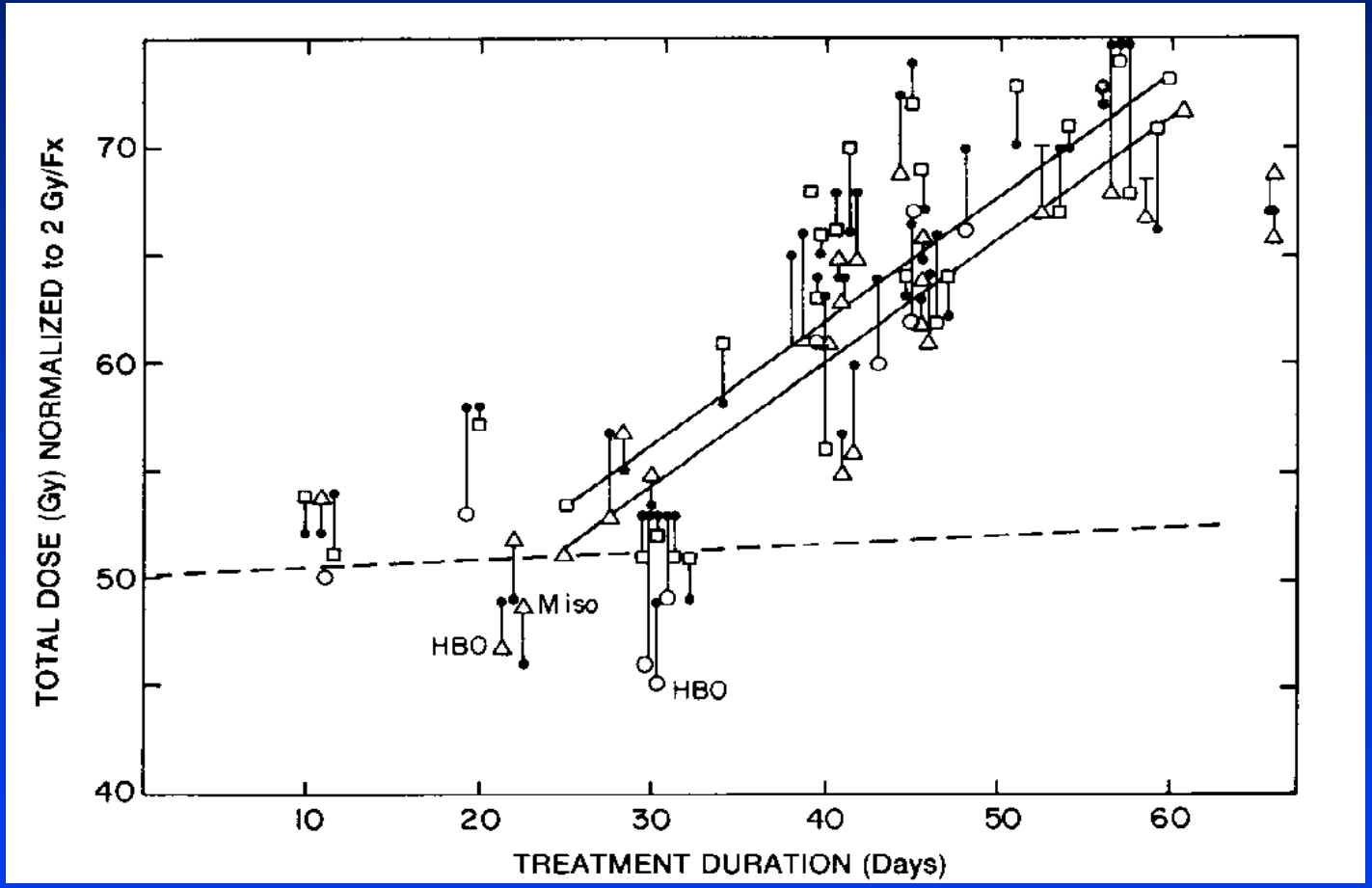
- Late responding normal tissues:
  - *0 - 0.1 BED units/day*
- Note that this is not Gy/day, as you will see in some publications, because BED is not linear in dose (it is linear-quadratic)

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

Withers' "hockey stick"

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

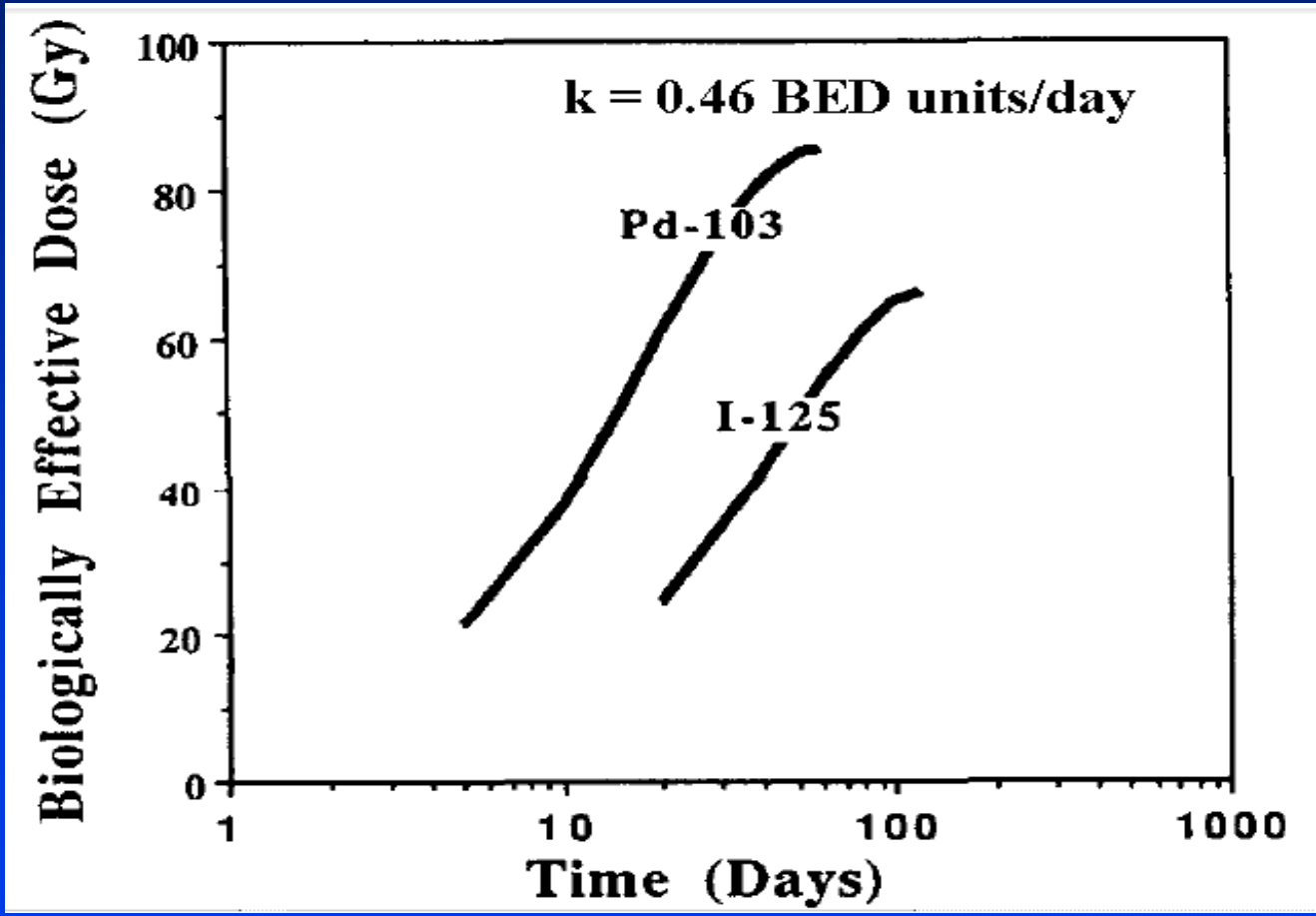


What about repopulation with permanent implants?

- With permanent implants for tumors that are repopulating during treatment, a time, T_{eff}, is reached at which the rate of repopulation equals the rate of decay
- At this time, the maximum BED has been reached
- It can be shown that, to a good approximation, assuming no accelerated repopulation, that

$$T_{eff} = 1/\lambda \ln(R_0/k)$$

BED reaches a maximum at T_{eff} days



Derived from Ling, 1992

The BED equation for permanent implants with repopulation

- This is obtained by substituting T_{eff} for t in the equations below, making sure to keep all the parameters R_0, α/β, μ, λ, and T_{eff}, in consistent units
- Then the maximum BED is given by:

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

where:

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

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

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

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 normal tissue complication and tumor control probabilities are concerned
- Retreatments when previous treatment has failed and a region previously irradiated has to be retreated

Conversion to 2 Gy/fraction equivalent dose

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

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

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 *Gy at* d_p *Gy/fraction*

- The dose given erroneously is:

  D_e *Gy at* d_e *Gy/fraction*

- The dose required to complete the course is:

  D_c *Gy at* d_c *Gy/fraction in* N_c *fractions*

The Joiner equations

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

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

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:

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

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 Gy/fraction
  - *always round out the number of fractions **up**, since increased fractionation spares normal tissues*

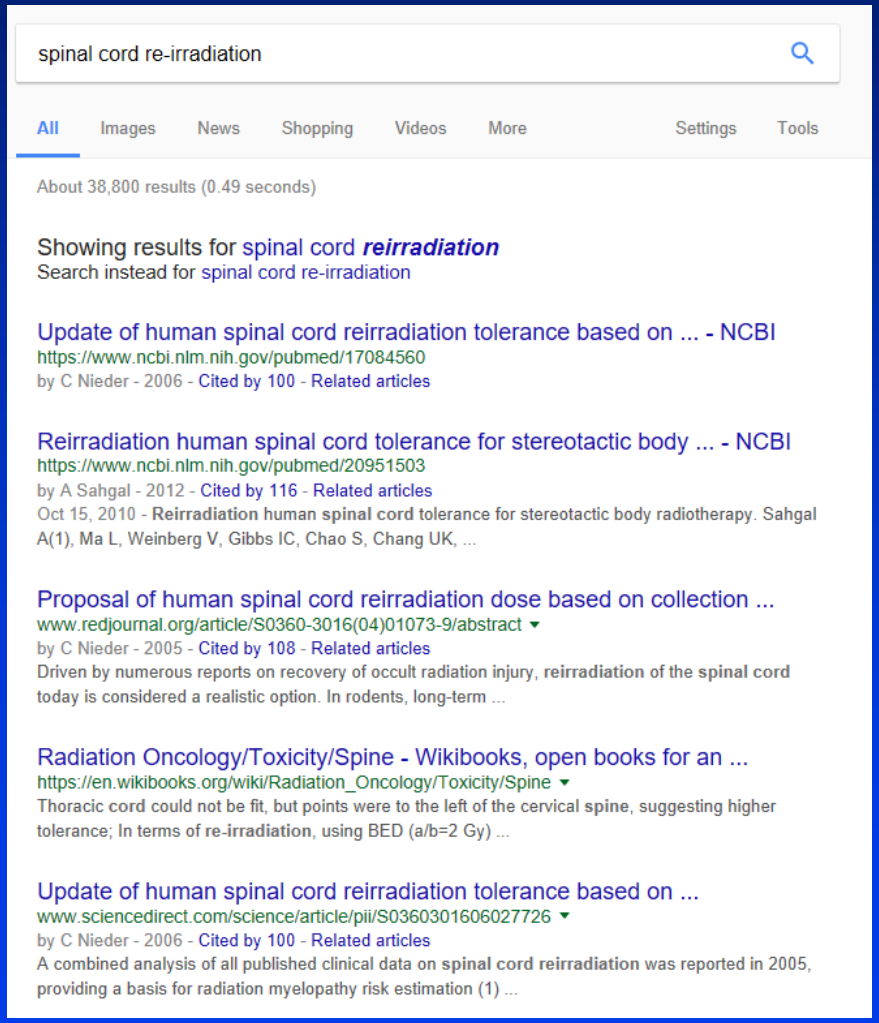
Additional benefit of the Joiner model

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?

Google Search!



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!!!