BED Applications in Practice

- The main application of the BED model is to design and/or compare different fractionation or dose-rate schemes
- It can also be used for correction for errors and for rest periods

Examples of the use of the BED model

- Simple fractionation changes
- Correction for errors
- Conversion to 2 Gy/fraction equivalent dose
- Effect of change in overall treatment time
- Correction for rest periods
- Change in dose rate
- Conversion from LDR to HDR
- Effect of half life on permanent implant doses

Example 1: simple change in fractionation

- Question: what dose/fraction delivered in 25 fractions will give the same probability of late normal tissue damage as 60 Gy delivered in 30 fractions at 2 Gy/fraction?
- The L-Q equation is:

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

Solution (cont'd)

Assuming α/β for late reacting normal tissues is 3 Gy, the BED for 60 Gy at 2 Gy/fraction is

$$60(1 + 2/3) = 100$$

Solution (cont'd)

Then the dose/fraction, *d*, is given by:

$$100 = 25d(1 + d/3)$$

Solving this quadratic equation for *d* gives:

$$d = 2.27 \text{ Gy/fraction}$$

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

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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

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

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

Example 2: 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 2 (cont'd.)

- 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

Conversion to 2 Gy/fraction equivalent dose

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

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

Example 3

What total dose given at 2 Gy/fraction is equivalent to 50 Gy delivered at 3 Gy/fraction for

(a) cancers with $\alpha/\beta = 10$ Gy?

(b) normal tissues with $\alpha/\beta = 3$ Gy?

Answers

(a) $D_2 = 50(1 + 3/10)/(1 + 2/10) = 54.2$ Gy

(b) $D_2 = 50(1 + 3/3)/(1 + 2/3) = 60.0$ Gy

Example 4: change in fractionation accounting for repopulation

- Problem: it is required to change a fractionation scheme of 60 Gy delivered in 30 fractions at 2 Gy/fraction over 42 days to 10 fractions delivered over 14 days
- What dose/fraction should be used to keep the same effect on cancer cells and will the new scheme have increased or decreased effect on late-reacting normal tissues?

Solution I: assume no repopulation and no geometrical sparing

Assuming the tumor α/β = 10 Gy, the tumor BED for 30 fractions of 2 Gy is:

$$BED_t = 30 \times 2(1 + 2/10) = 72$$

Then, for this same BED in 10 fractions of dose *d*/fraction:

$$72 = 10 \times d(1 + d/10)$$

The solution to this quadratic equation is:

$$d = 4.85 \text{ Gy}$$

Solution I (cont'd.): effect on late-reacting normal tissues

Assuming the late-reacting normal tissue α/β = 3 Gy, the normal tissue BED for 30 fractions of 2 Gy is:

$$BED_{late} = 30 \times 2(1 + 2/3) = 100$$

and the normal tissue BED for 10 fractions of 4.85 Gy is:

$$BED_{late} = 10 \times 4.85(1 + 4.85/3) = 127$$

It appears that the 10 fraction scheme is far more damaging to normal tissues (127 vs. 100)

Solution II: assume a geometrical sparing factor of 0.6

The dose to normal tissues will now be 2 x 0.6 = 1.2 Gy for the 30 fraction treatments and 4.85 x 0.6 = 2.91 Gy for the 10 fraction treatments

Then the BEDs for normal tissues will be:

$$BED_{late} = 30 \times 1.2(1 + 1.2/3) = 50$$

$$BED_{late} = 10 \times 2.91(1 + 2.91/3) = 57$$

It appears that the 10 fraction scheme is somewhat more damaging to normal tissues (57 vs. 50)

Solution III: assume geometrical sparing *and* repopulation (at $k = 0.3$/day)

Now we need to recalculate the tumor BEDs

The tumor BED for 30 fractions of 2 Gy is:

$$BED_t = 30 \times 2(1 + 2/10) - 0.3 \times 42 = 55.2$$

Then, for this same BED in 10 fractions of dose *d*/fraction:

$$55.2 = 10 \times d(1 + d/10) - 0.3 \times 14$$

The solution to this quadratic equation is:

$$d = 4.26 \text{ Gy}$$

Solution III (cont'd.): effect on late reactions

The dose to normal tissues will still be 2 x 0.6 = 1.2 Gy for the 30 fraction treatments but will become 4.26 x 0.6 = 2.56 Gy for the 10 fraction treatments

Then the BEDs for normal tissues will be:

$$BED_{late} = 30 \times 1.2(1 + 1.2/3) = 50$$

$$BED_{late} = 10 \times 2.56(1 + 2.56/3) = 47$$

It appears that the 10 fraction scheme is now somewhat less damaging to normal tissues (47 vs. 50)

What does this mean?

- Decreasing the number of fractions, i.e. hypofractionation, does not necessarily mean increasing the risk of normal tissue damage when keeping the effect on tumor constant
  - *This is why we may be using far more hypofractionation in the future, especially since it will be more cost-effective*

Example 5: Rest period during treatment

- Problem: a patient planned to receive 60 Gy at 2 Gy/fraction over 6 weeks is rested for 2 weeks after the first 20 fractions
- How should the course be completed at 2 Gy/fraction if the biological effectiveness is to be as planned?

Solution I: for late-reacting normal tissues

- Since late-reacting normal tissues probably do not repopulate during the break, they do not benefit from the rest period so the dose should not be increased
- Complete the course in 10 more fractions of 2 Gy

Solution II: for cancer cells

- Assume that the cancer is repopulating at an average rate, so k = 0.3 BED units/day and α/β = 10 Gy
- For a rest period of 14 days, the BED needs to be increased by 14 x 0.3 = 4.2
- The BED for the additional N fractions of 2 Gy is then:

$$2N(1 + 2/10) - (7/5)N \times (0.3) \text{ which must equal } 4.2$$

Solution is $N = 2.12$

i.e. instead of 10 fractions you need about 12 fractions of 2 Gy

But remember, the effect on normal tissues will increase

Example 6: change in dose rate

- A radiation oncologist wants to convert a 60 Gy implant at 0.5 Gy/h to a higher dose rate of 1 Gy/h, keeping the effect on the tumor the same
- What total dose is required?

The BED equation for LDR treatments

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

where

R = dose rate (in Gy h^{-1})

t = time for each fraction (in h)

μ = repair-rate constant (in h^{-1})

Simplified forms of the LDR BED equation

$$For\ 10h \le t \le 100h$$

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

$$For\ t \ge 100h$$

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

Solution

Assume that α/β (tumor) is 10 Gy, and μ (tumor) is 0.46 h^{-1} (i.e. repair half time is 0.693/0.46 = 1.5 h)

The approximate BED equation is:

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

Hence the BED for 60 Gy at 0.5 Gy/h is:

BED (tumor) = 60[1 + 2x0.5/(0.46x10)]

= 73.0

Solution (cont'd.)

To obtain this same BED of 73.0 at 1 Gy/h, the overall time *t* is given by:

$$73.0 = 1 \times t[1 + 2 \times 1/(0.46 \times 10)]$$

Hence:

$$t = 73.0/1.43$$

$$= 51.0 \text{ h}$$

Solution (cont'd.)

The total dose is thus 51.0 times the dose rate of 1 Gy/h

= 51.0 Gy

Solution (cont'd.)

- Actually, this is only an approximate solution since only the approximate expression for BED was used
- Calculation of *t* using the full BED equation would have been far more mathematically challenging and would have yielded a required dose of 51.3 Gy, not much different from the approximate solution of 51.0 Gy obtained here

Example 7: conversion of LDR to HDR

Problem:

It is required to replace an LDR implant of 60 Gy at 0.6 Gy h^{-1} by a 10-fraction HDR implant

What dose/fraction should be used to keep the effect on the tumor the same?

Solution

Since t = 100 h we can use the simplified version of the BED equation:

$$BED = Rt[1+2R/(\mu.\alpha/\beta)]$$

Assume: μ = 1.4 h^{-1} and α/β = 10 Gy for tumor

Then the BED for the LDR implant is:

$$\text{BED} = 60[1+1.2/(1.4 \times 10)]$$

$$= 65.1$$

Solution (cont'd.)

If d is the dose/fraction of HDR then:

$$65.1 = Nd[1+d/(\alpha/\beta)] = 10d[1+0.1d]$$

This is a quadratic equation in d the solution of which is

$$d = 4.49 \text{ Gy}$$

Is this better or worse as far as normal tissues are concerned?

For late-reacting normal tissues assume α/β = 3 Gy and μ = 0.46 h^{-1}

Then the BED for 60 Gy at 0.6 Gy h^{-1} is:

BED_{LDR} = 60[1+1.2/(0.46 x 3)] = 112.2

and the BED for 10 HDR fractions of 4.49 Gy is:

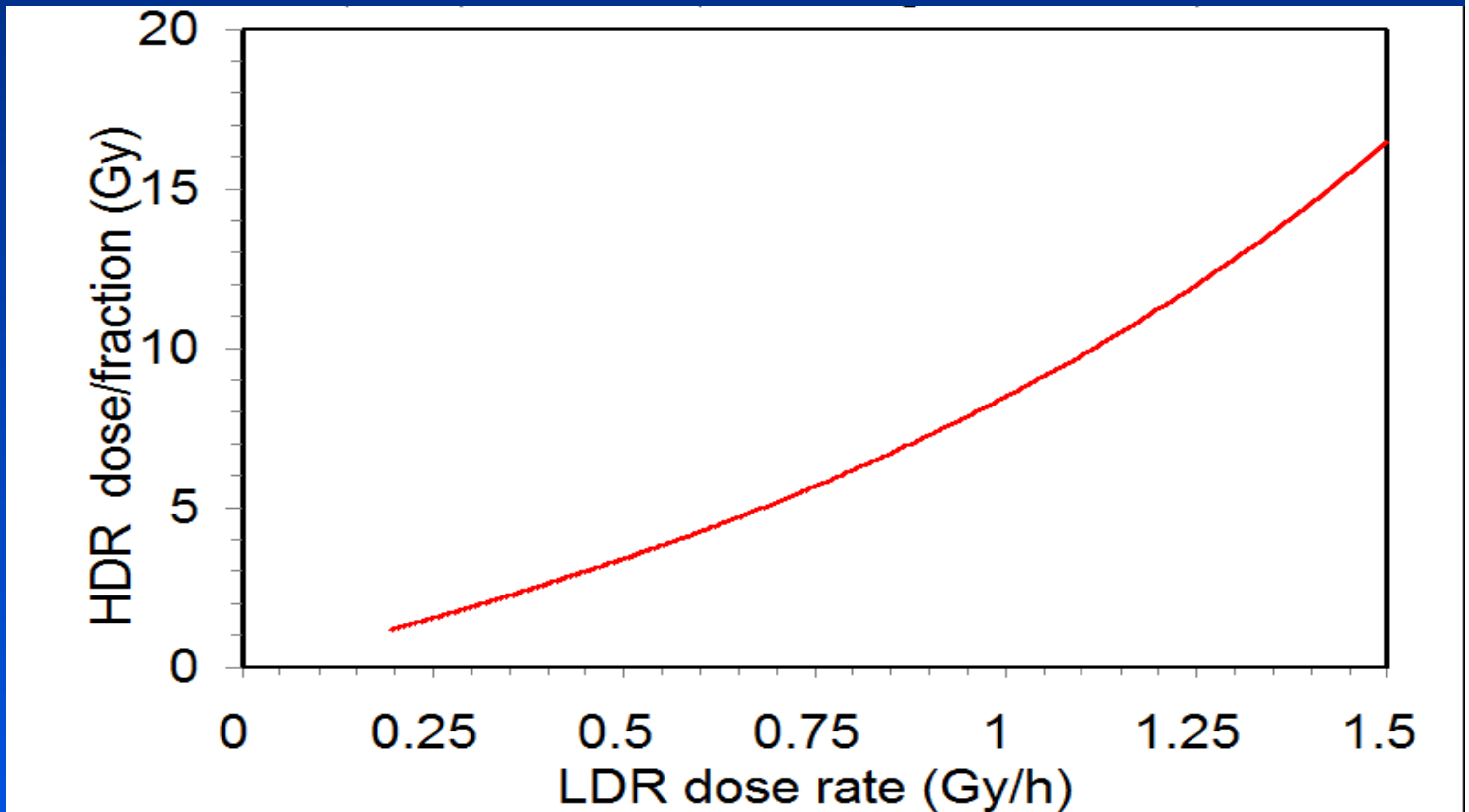
BED_{HDR} = 10 x 4.49[1+4.49/3] = 112.2

Is this better or worse as far as normal tissues are concerned?

- Amazing! By pure luck I selected a problem where the LDR and HDR implants are identical in terms of both tumor and normal tissue effects
- We will now demonstrate some general conditions for equivalence using the L-Q model

HDR equivalent to LDR for the same tumor and normal tissue effects

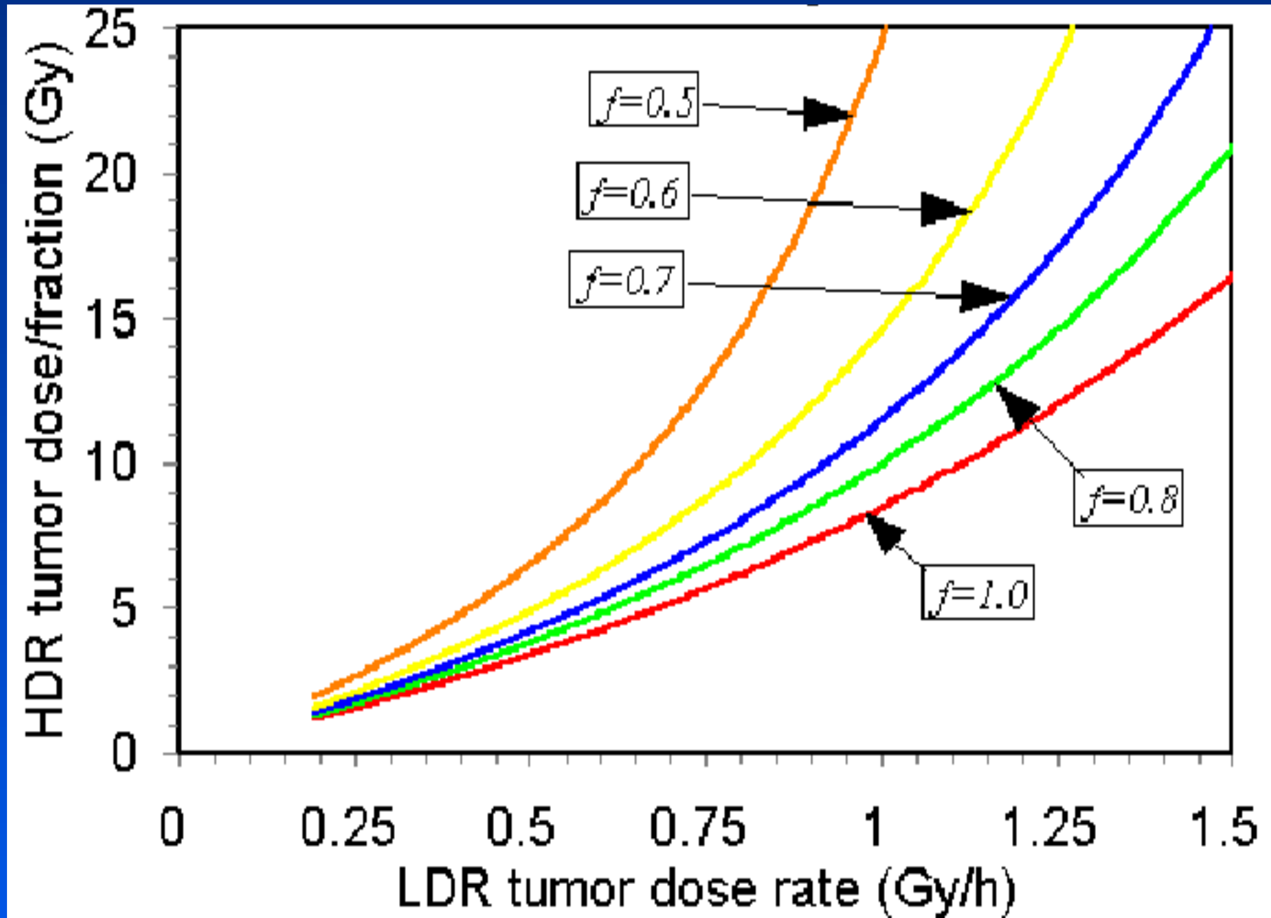
For equivalence to LDR at 0.6 Gy h^{-1} need to use about 4.5 Gy/ fraction with HDR (this was the example just shown)



Does geometrical sparing make any difference?

Yes, a big difference

Now HDR at about 6 Gy/fraction is equivalent to LDR at 0.6 Gy h^{-1} if the geometrical sparing factor is 0.6 (yellow line)



Example 8: permanent implants

What total dose for a ^{103}Pd permanent prostate implant will produce the same tumor control as a 145 Gy ^{125}I implant, assuming α/β for prostate cancer is 1.5 Gy and assuming that repopulation can be ignored?

BED equation for permanent implants

Ignoring repopulation, the BED equation for a permanent implant of a radionuclide with decay constant λ at initial dose rate R_0 is:

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

Solution

- R_0/λ is the total dose and λ for I-125, half life 60 days, is 0.693/(60 x 24) h^{-1} = 0.00048 h^{-1}
  - Hence, for a total dose of 145 Gy, the initial dose rate R_0 is 145 x 0.00048 = 0.0696 Gy/h

Solution (cont'd.)

Substituting this in the equation and assuming α/β for prostate cancer is 1.5 Gy and $\mu = 0.46\ h^{-1}$ gives:

$$BED = \frac{0.0696}{0.00048}\left[1 + \frac{0.0696}{(0.46)(1.5)}\right] = 159.6$$

Solution (cont'd.)

Now we need to substitute this in the BED equation in order to calculate the initial dose rate R_0 using the (17 day half life) Pd-103 λ of 0.693/(17 x 24) = 0.0017 h^{-1}

$$159.6 = \frac{R_0}{0.0017}\left[1 + \frac{R_0}{(0.462)(1.5)}\right]$$

The solution to this quadratic equation is

R_0 = 0.209 Gy/h

Hence the total dose of Pd-103 is 0.209/0.0017

= 122.9 Gy

Summary

- The BED model is useful for the solution of radiotherapy problems with changes in fractionation and/or dose rate
- But remember, this equation must be just an approximation for the highly complex biological changes that occur during radiotherapy
  - *the model is approximate*
  - *the parameters are approximate*

But the model is useful!