Monterrey, November, 2007

Review of the Radiobiological Principles of HDR Brachytherapy

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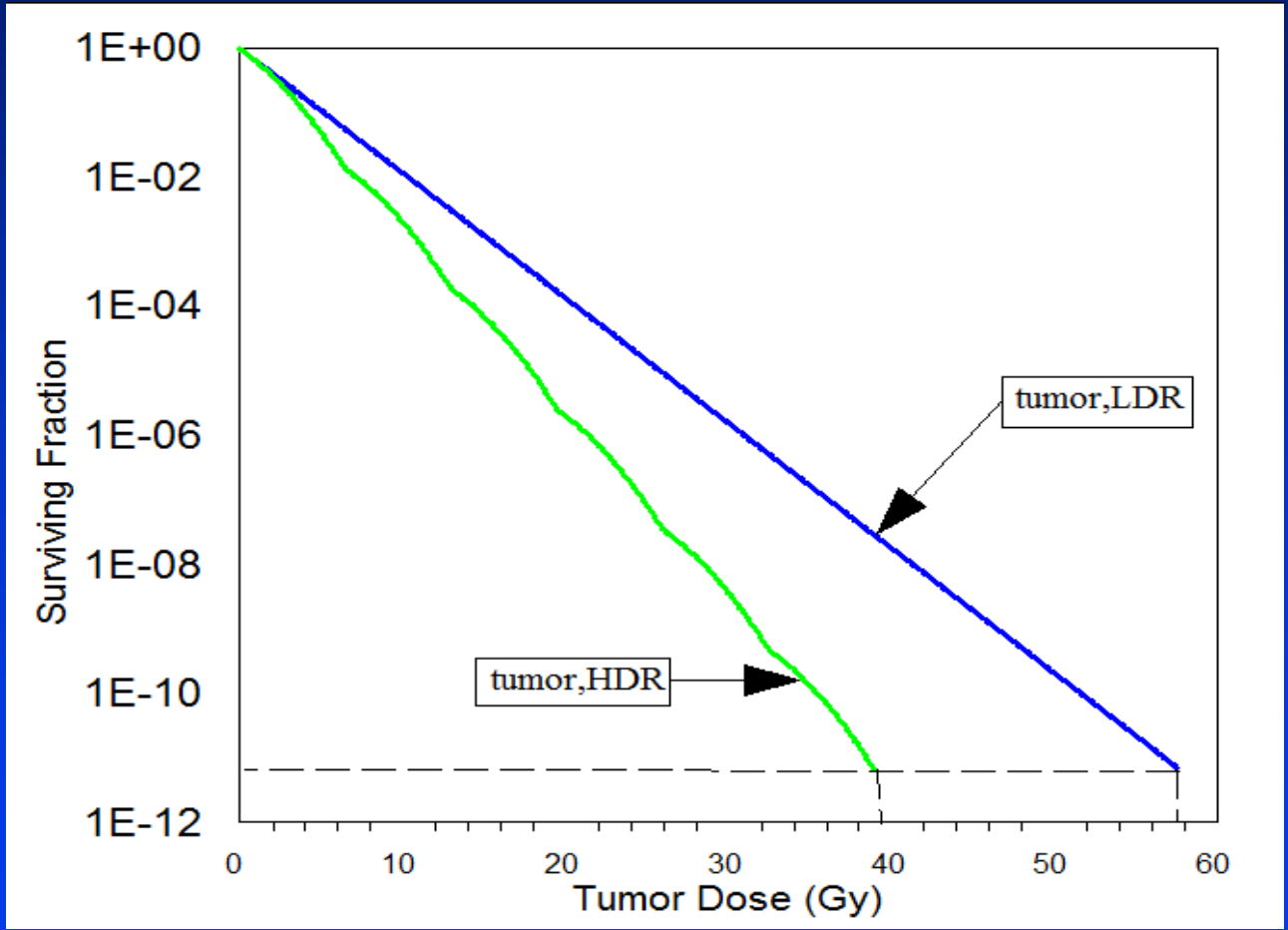
Can HDR be exactly equivalent to LDR?

- Yes, easily if the only object is to destroy all cancer cells
  - *simply make the cell surviving fractions the same*

Equivalent LDR (at 0.8 Gy h^{-1}) and HDR (at 6.5 Gy/fraction) regimes for tumor control

Six fractions of 6.5 Gy is equivalent to about 58 Gy at 0.8 Gy h^{-1} for these tumor cells



But what about normal tissues?

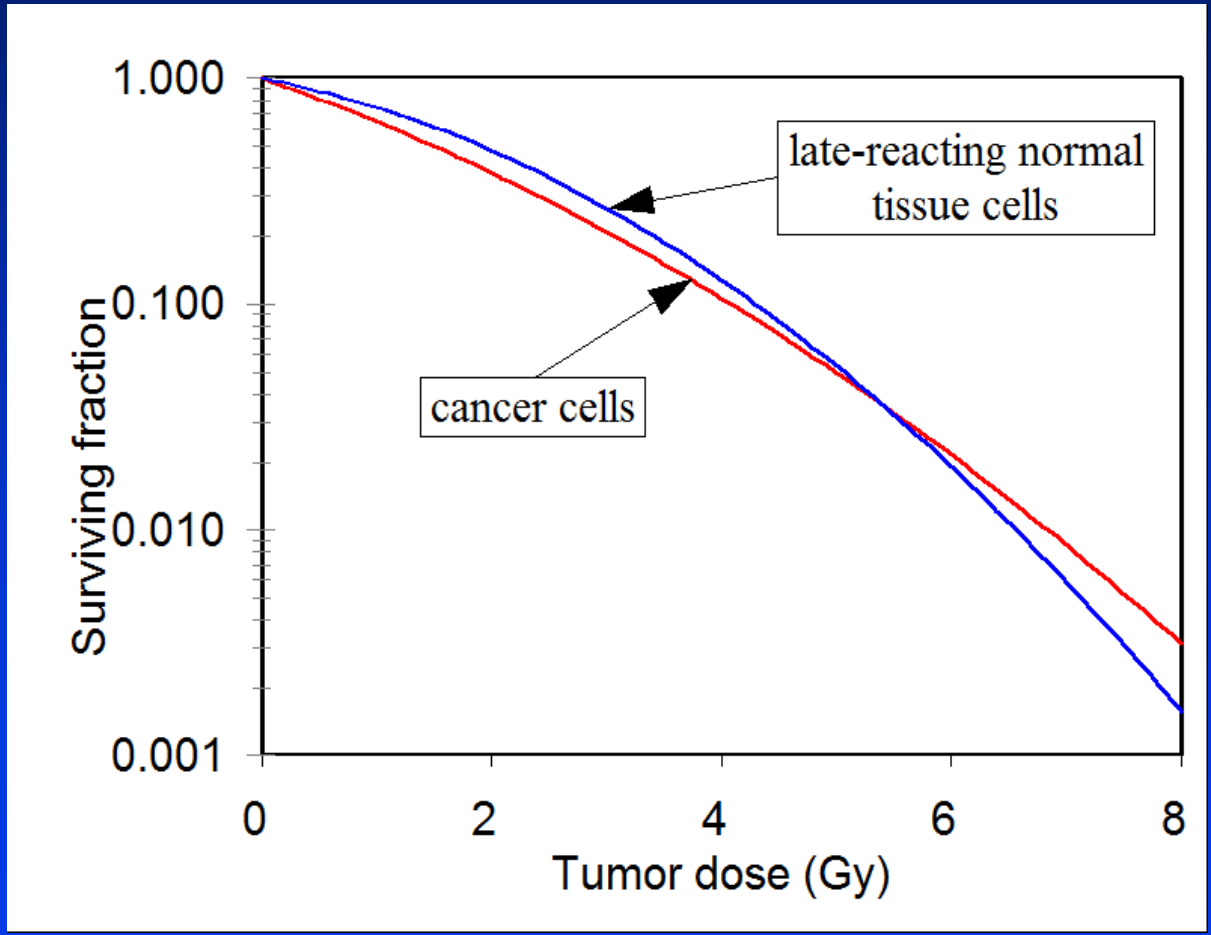
The main object of radiotherapy is to destroy all cancer cells without damaging too many normal tissue cells and thus exceeding normal tissue tolerance

Cell survival: normal *vs* cancer cells

- Survival curves for cancer cells and the cells of late reacting normal tissue (which typically limit the tolerance of normal tissues) are different
  - *this is mainly because these cells differ in radiation sensitivity and their ability to repair sublethal damage*

Cell survival: normal *vs* cancer cells

The survival curves for cancer cells are typically straighter than those for normal tissue cells



Why?

- This is because cancer cells do not "repair" damage at low doses as well as normal tissue cells
  - *this is probably due to damaged checkpoint genes in cancer cells*

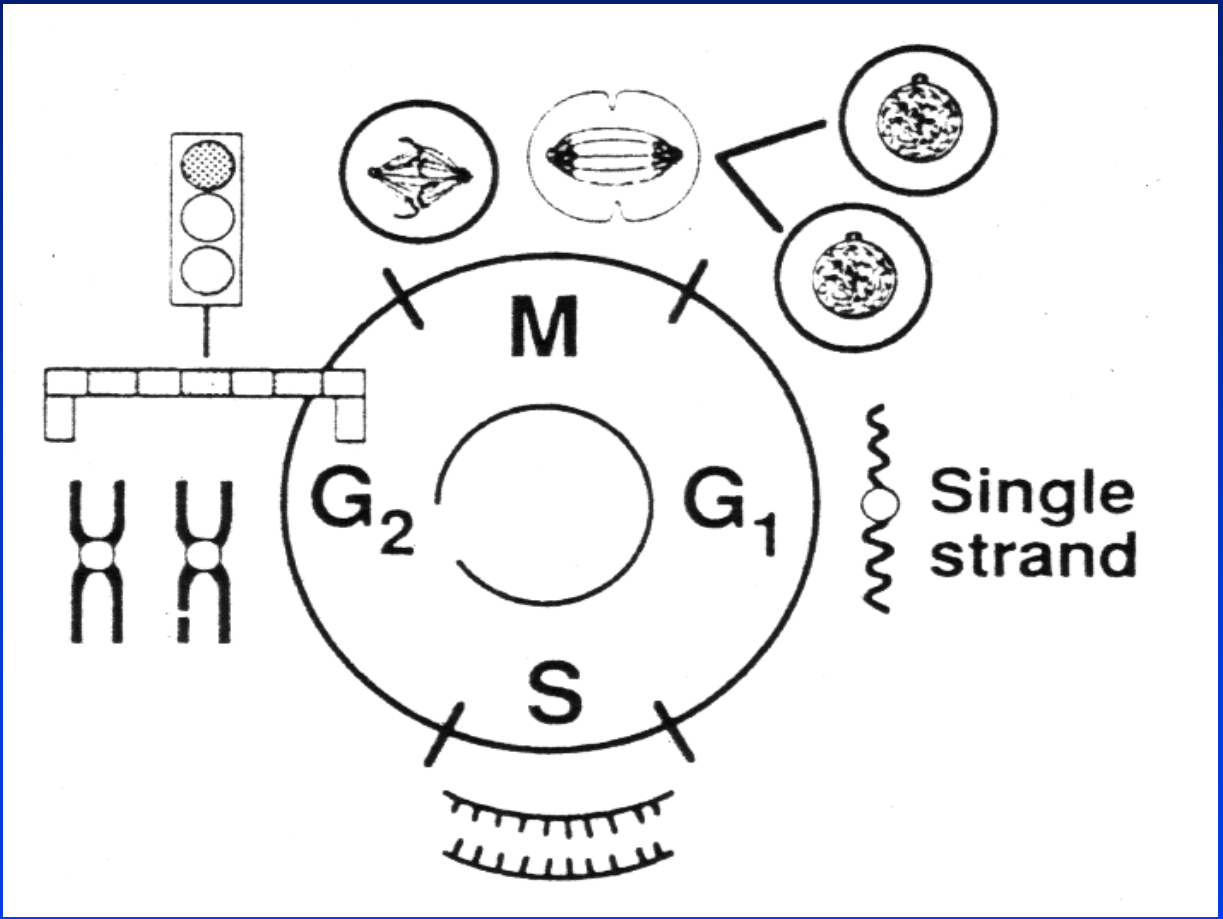
Checkpoint genes

- Cell-cycle progression is controlled by molecular checkpoint genes
- Checkpoint genes assure the correct order of cell-cycle events
  - *It is because these checkpoint genes are missing (or mutated) in cancer cells that they proliferate out of control*

Checkpoint genes

- The checkpoint gene responsible for the G_2 block is important in controlling radiation damage since it assures that time is given for repair of DNA damage before the complex task of mitosis is attempted
  - *if this gene is missing (or mutated) in a cancer cell it will often not have time to repair*
  - *typical repair half times are of the order of 0.5 – 1.5 hours*

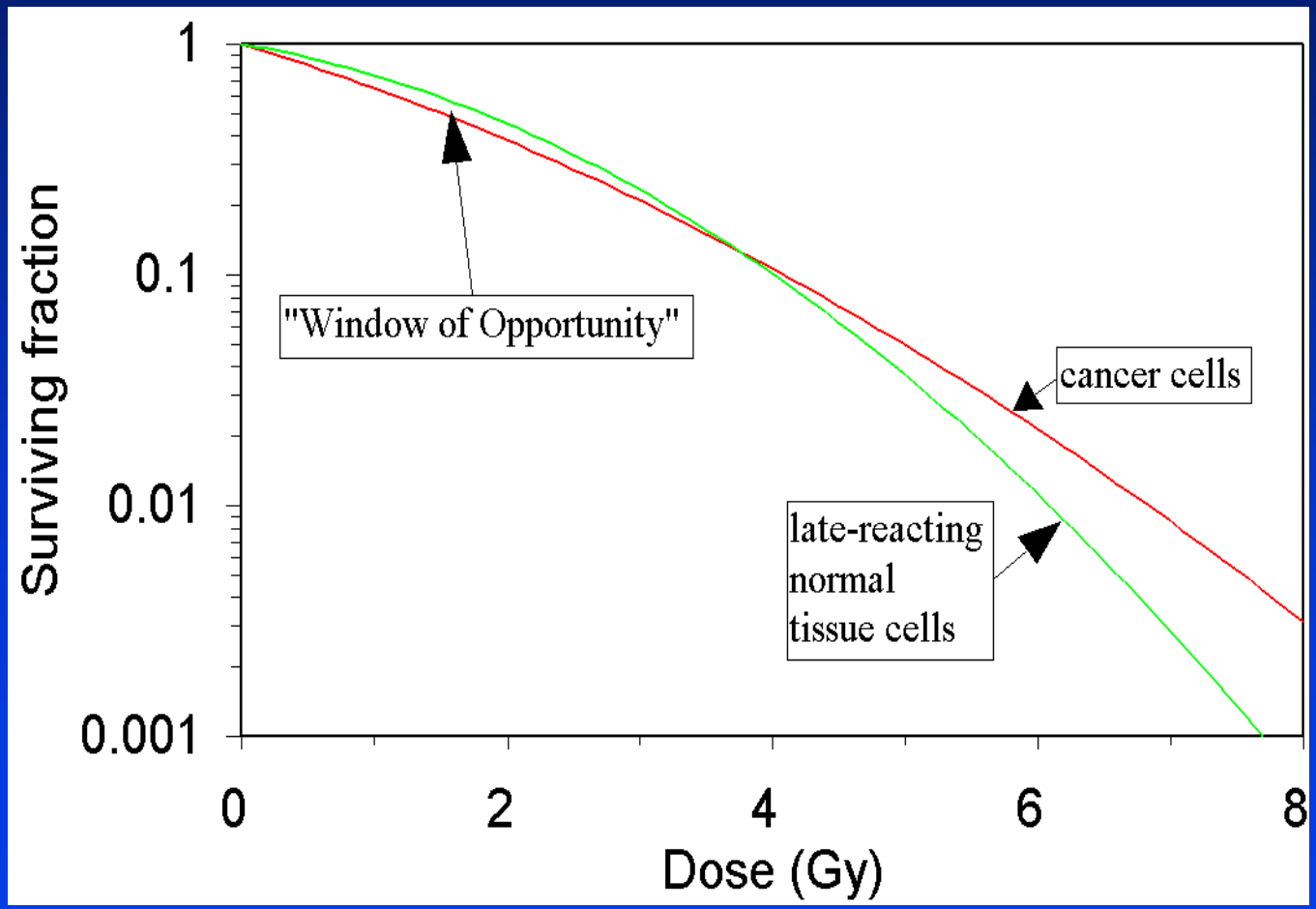
The G_2 checkpoint genes prevents progression through mitosis before repair takes place



Cell survival: normal *vs* cancer cells

Fortunately, because cancer cells do not “repair” damage at low doses as well as normal tissue cells, there is a “window of opportunity” at low doses where the survival of late-reacting normal tissue cells exceeds that of cancer cells

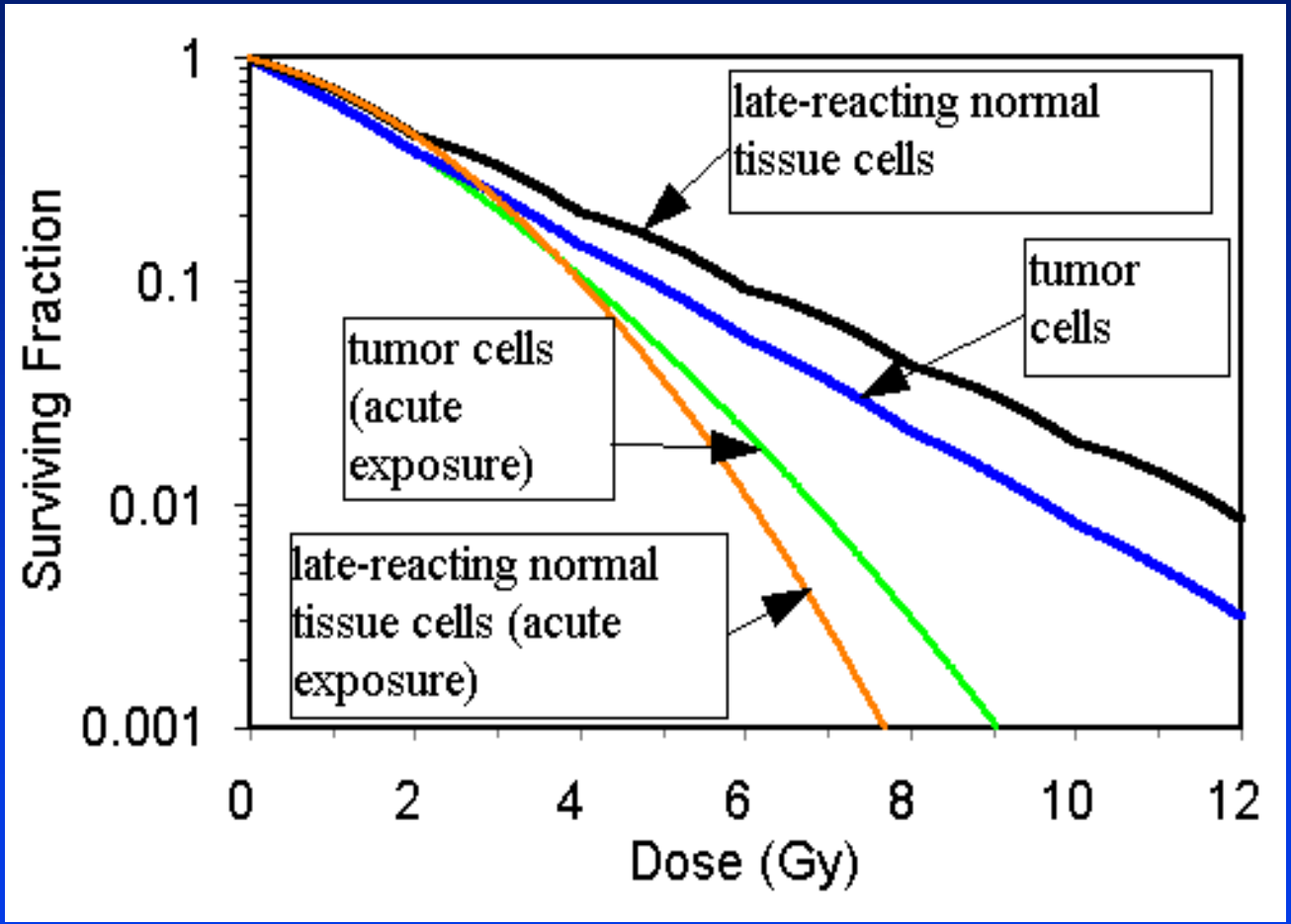
Cell survival curve comparison: the “Window of Opportunity”



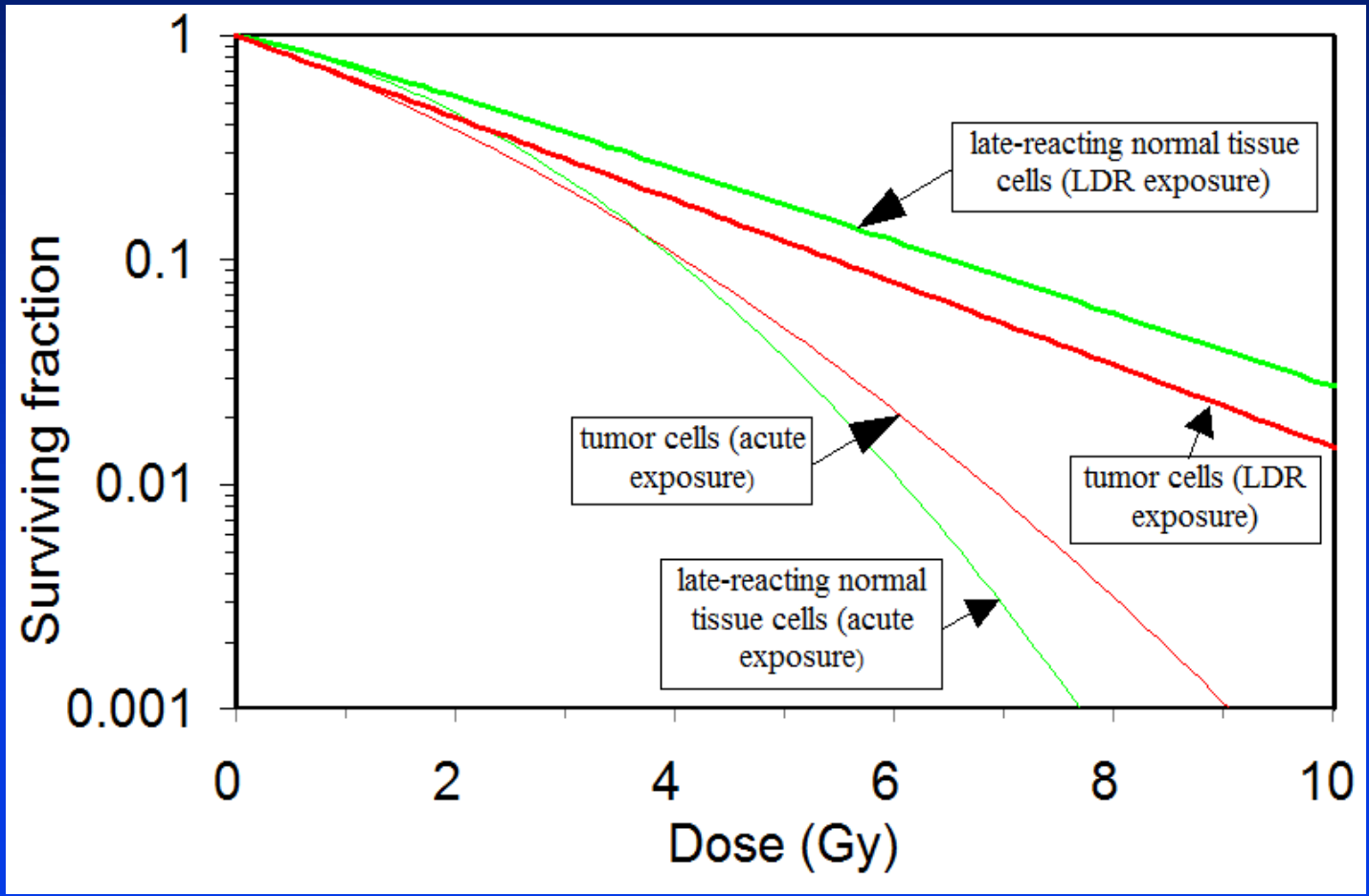
Fractionation and dose rate

- This is why we typically fractionate radiotherapy at low doses/fraction or treat at low dose rates
  - *fractionate at doses/fraction within this "window of opportunity" e.g. typically about 2 Gy/fraction*
  - *use dose rates below about 50 cGy/h for low dose rate brachytherapy (this allows ample time during irradiation for almost full repair)*

Normal *vs* cancer cells for fractionation at 2 Gy/fraction



Repair: normal *vs* cancer cells for low dose rate brachytherapy (LDR) at 0.4 Gy/h



Cell survival curve comparison: the “Window of Opportunity”

Note that we have assumed that the dose to normal tissues is the same as the dose to the cancer cells, but is this a reasonable assumption?

Geometrical sparing of normal tissues

- No, because the major advantage of brachytherapy is that the radiation is put where the cancer is, i.e. this is highly conformal radiotherapy
- Hence the *effective dose** to normal tissues will usually be less than the *effective dose* to tumor

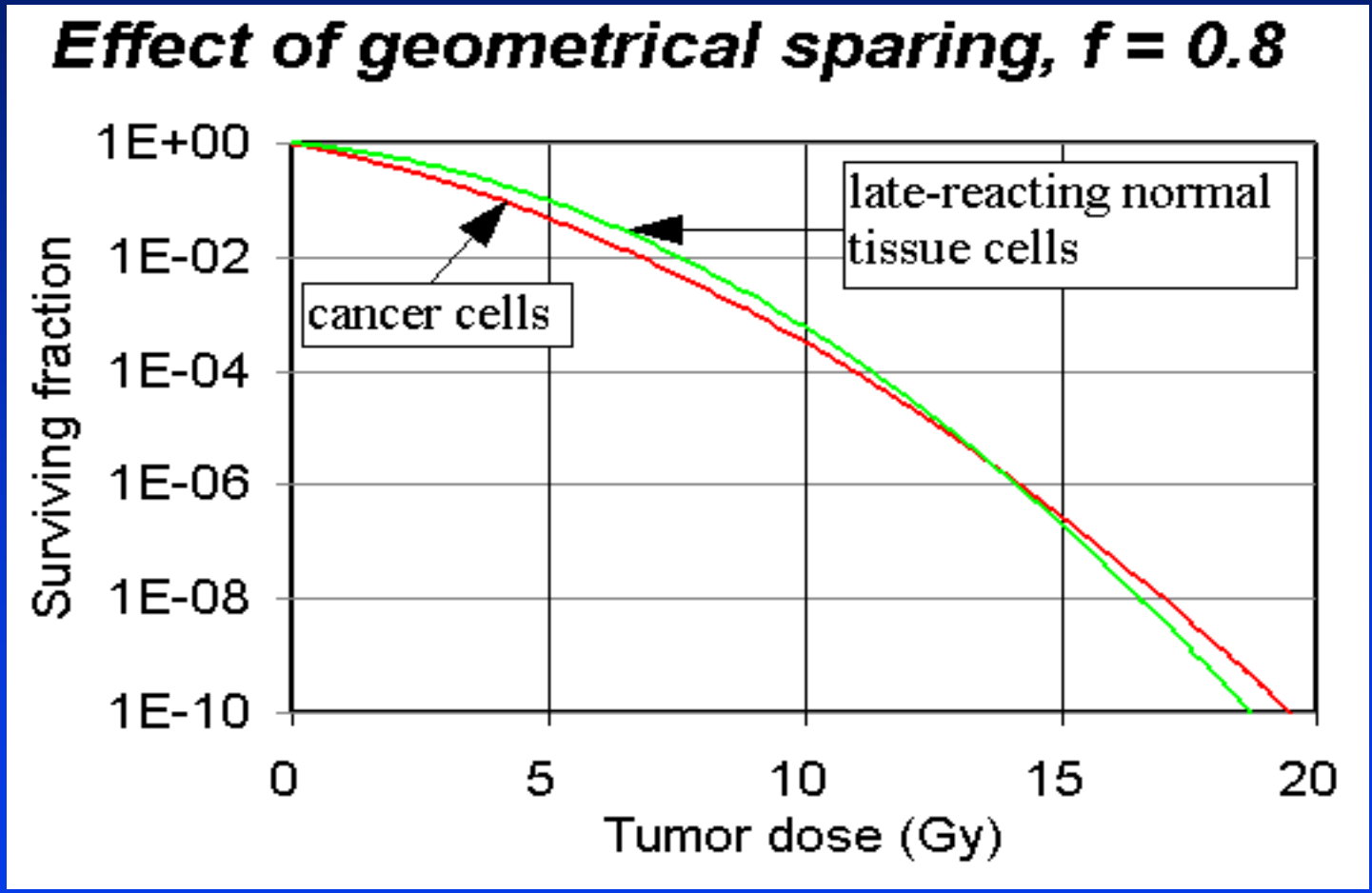
**the effective dose is the dose which, if delivered uniformly to the organ or tumor, will give the same complication or cure rate as the actual inhomogeneous dose distribution*

Geometrical sparing factor

We can define a “geometrical sparing factor”, *f*, such that:

$$f = \frac{effective\ dose\ to\ normal\ tissues}{effective\ dose\ to\ tumor}$$

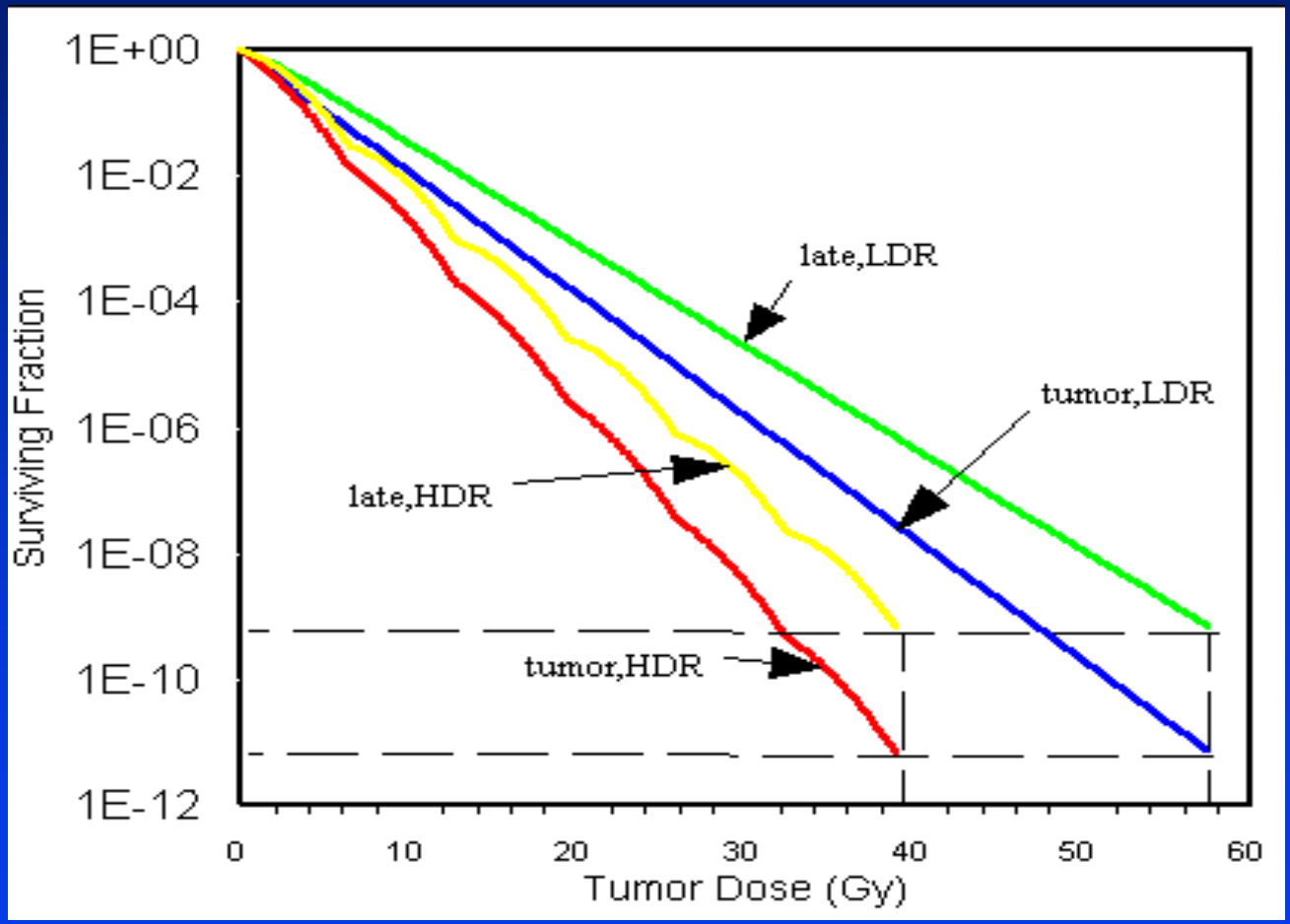
The “window of opportunity” widens with geometrical sparing



The “window of opportunity” widens with geometrical sparing

- This means that:
  - *we can safely use much higher doses per fraction*
  - *there is a wide range of doses per fraction that can be safely employed*

Equivalent LDR (at 0.8 Gy h^{-1}) and HDR (at 6.5 Gy/fraction) regimes assuming that normal tissues receive 80% of the tumor dose



What about dose rate?

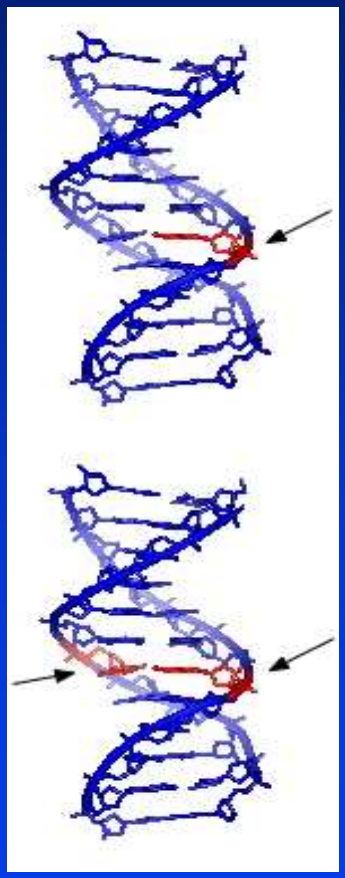
- There is a dose rate effect because it takes time for cells to repair sublethal damage
  - *at high dose rates a second break in a DNA molecule might occur before the 1st break has had enough time to be repaired (and double-strand breaks are usually lethal)*

DNA repair

- DNA repair enzymes search through DNA molecules to locate damaged regions
- These enzymes may then repair the damage by a sequence much like “cut-and-paste” in computers
  - *the damaged part of one strand of the DNA molecule is “cut” out and the genetic information (sequence of bases) is copied from the undamaged arm of the DNA by the repair enzyme and then “pasted” into the “gap” left in the damaged arm*
  - *this “repair” takes, on average, about one hour to be completed*

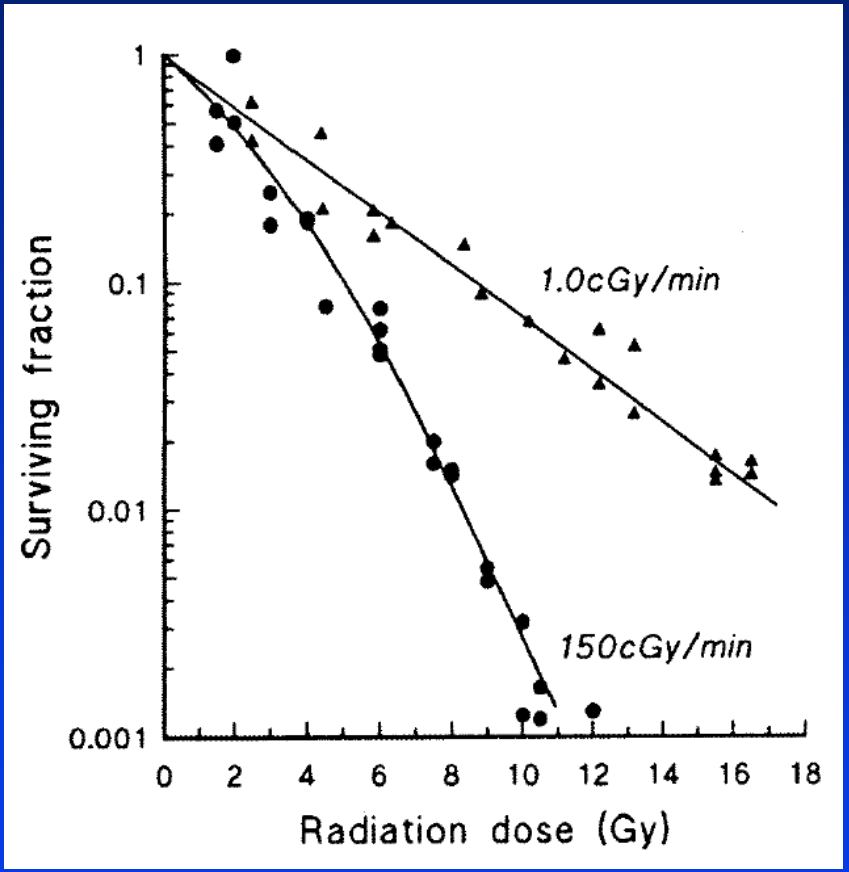
Single strand and double strand damage

Single strand breaks (upper figure) are usually considered “repairable”. Double strand breaks (lower figure) are not usually “repairable” if the breaks are close together, since an intact 2nd strand of the DNA molecule is needed for the repair enzymes to be able to copy the genetic information



The dose rate effect

Note that at low dose rates cell survival curves become linear because there is time during the irradiation for almost full repair of sublethal damage



The dose rate effect for cancer and normal tissue cells

- Cells which exhibit little repair (such as cancer cells) will therefore exhibit little dose rate effect
- Conversely, cells of late-reacting normal tissues will demonstrate a significant dose-rate effect

Clinical applications of the dose-rate effect

- Since low dose rate and fractionation benefit late-reacting normal tissues more than cancers, the lower the dose rate for LDR brachytherapy (or the lower the dose/fraction with HDR) used the better
- However, too low a dose rate or too many fractions may allow cancer cells to proliferate during treatment (*repopulation*)

Clinical applications of the dose-rate effect (cont'd)

- Brachytherapy
  - *low dose rate (LDR)*
  - *medium dose rate (MDR)*
  - *high dose rate (HDR)*
  - *permanent implants*

Brachytherapy: low dose rate

- The vast majority of interstitial and intracavitary brachytherapy experience has been with LDR
- Results have been excellent
- According to the Manchester experience, correction for the dose rate effect is necessary (Paterson)
- However, according to the original Paris System, dose rate is unimportant (Pierquin)

The Manchester dose-rate correction factor (normalized to 60 Gy in 7 days)

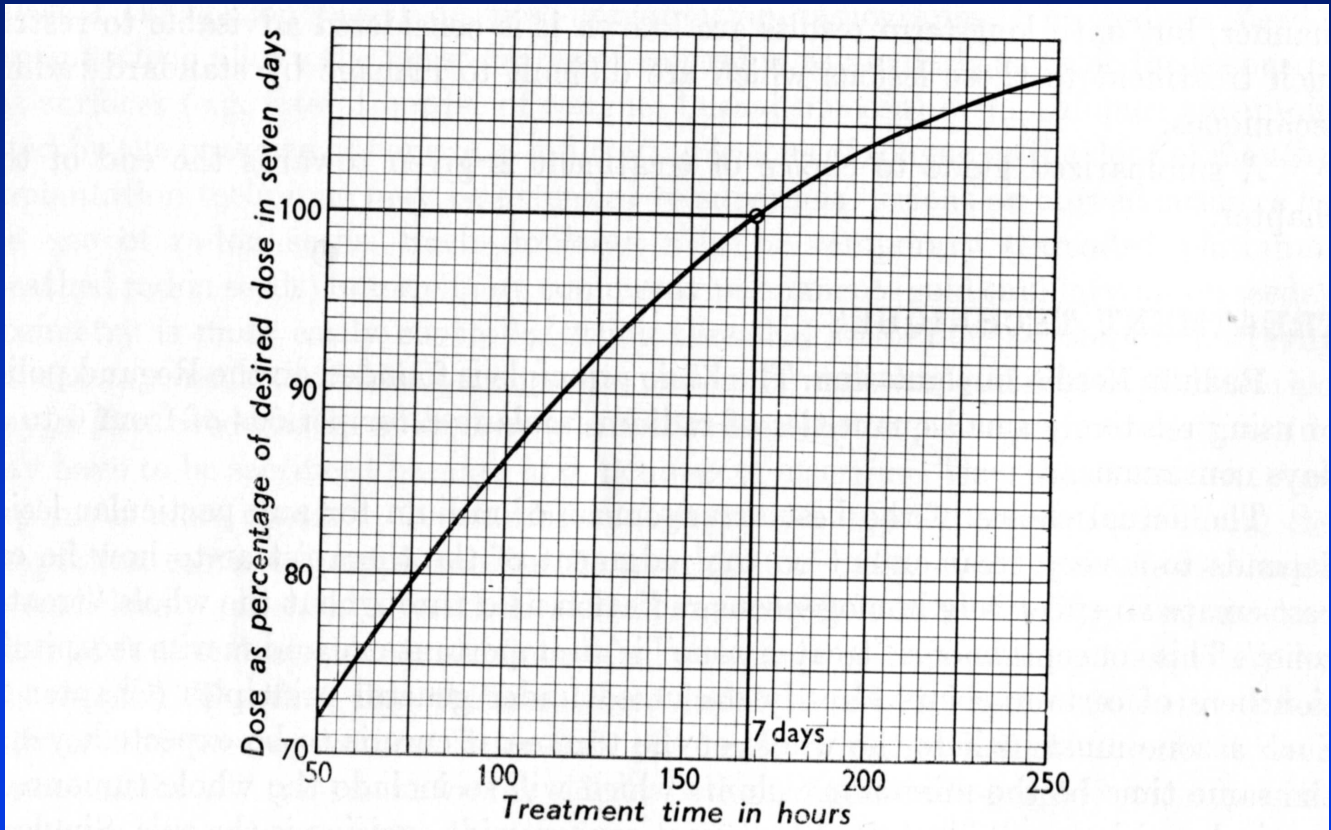
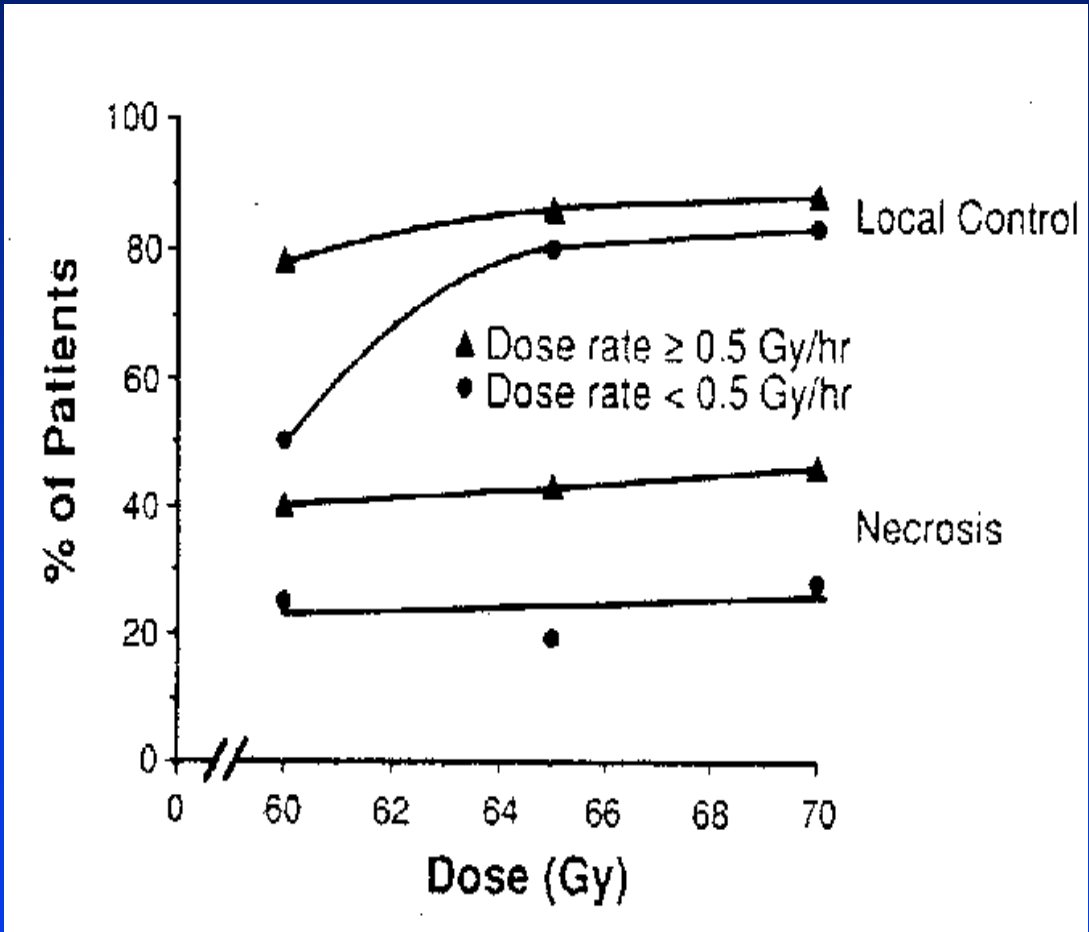


FIG. 13. 2.—EQUIVALENT DOSAGE FOR DIFFERING IMPLANT TIMES TAKING THE 7-DAY DOSE AS 100 PER CENT.

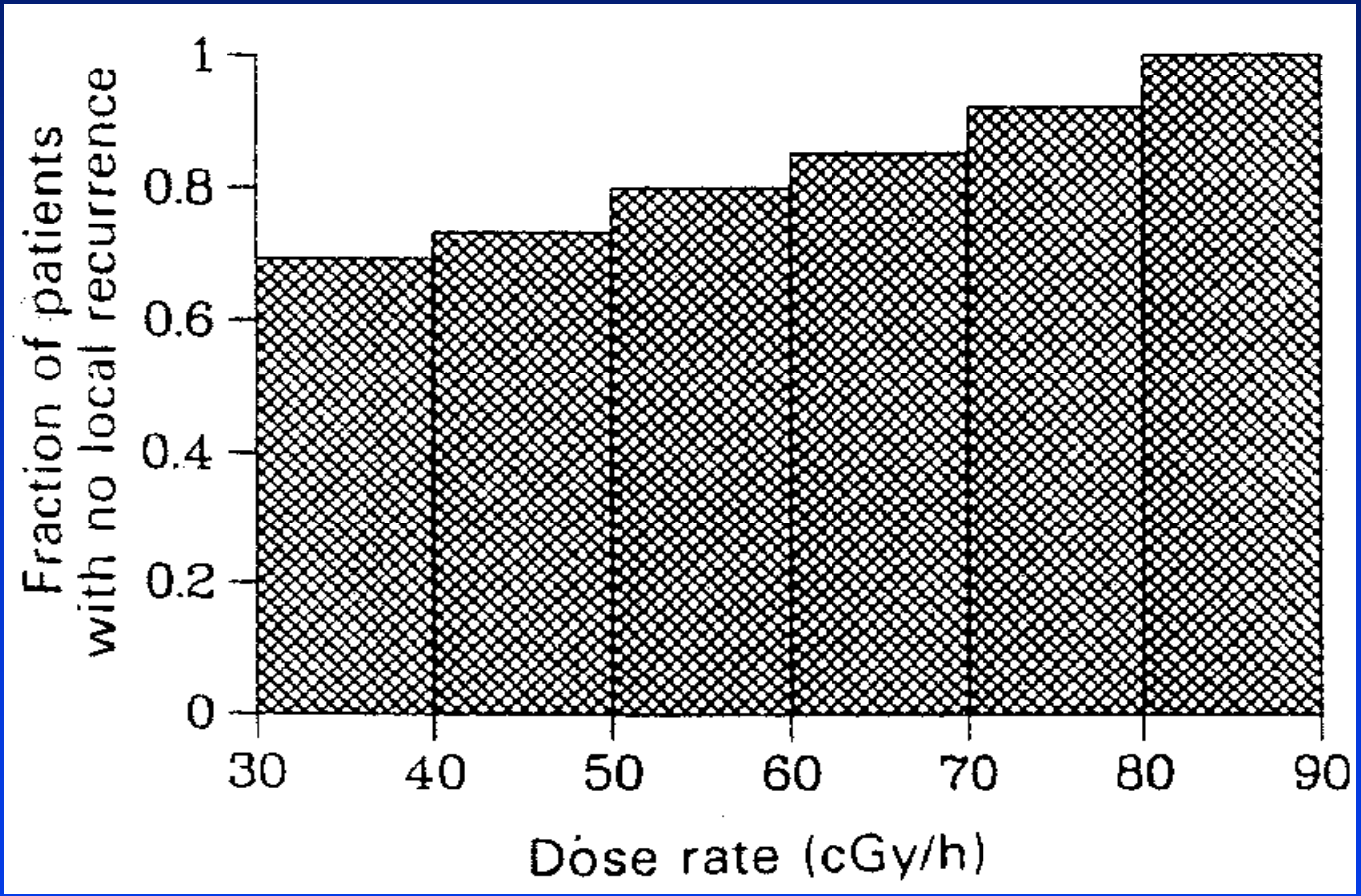
The Paris experience updated

- Pierquin, based on his tongue and floor-of-the-mouth implant experience, stated in the 1970s that there was no dose rate effect between 30 and 100 rads/hour
- However, recent updating of the same clinical data with far more patients shows this to be wrong: there is a significant dose rate effect for both normal tissue and tumor effects

The Paris experience updated in 1991: tongue and floor-of-the-mouth implants



The Paris experience updated: breast brachytherapy results (1991)



Brachytherapy: medium dose rate

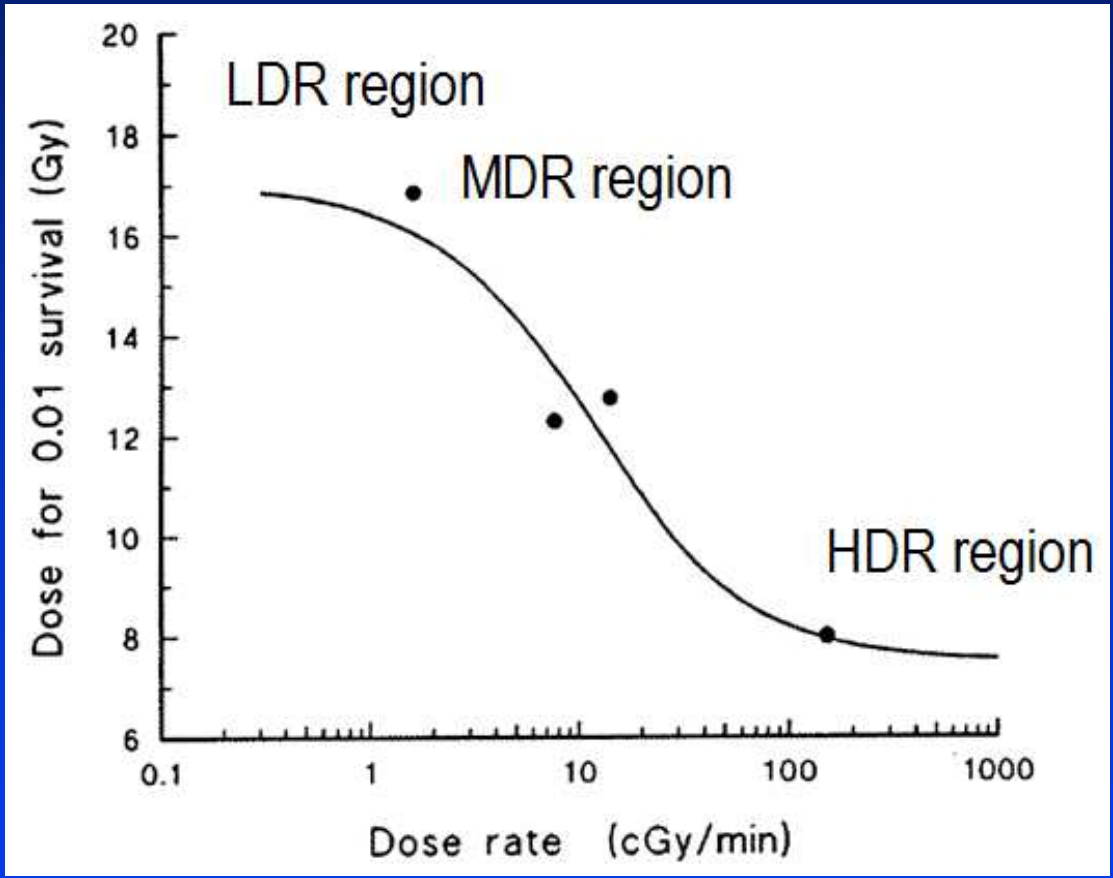
Because the classical LDR regimen of 60 Gy delivered in 7 days (35.7 cGy/h) is so inconvenient, attempts have been made to reduce the time by increasing the dose rate

Brachytherapy: medium dose rate

- Use of dose rates from 100 cGy/h to 400 cGy/h have generally failed due to increased complications, unless the treatments are fractionated, but this negates the convenience advantage of MDR
- The reason is that there is too little time during the course of therapy for adequate repair

Another reason to avoid MDR

In the LDR region there is a small dose rate effect
In the HDR region there is no dose rate effect
In the MDR region there is a considerable dose rate effect



Brachytherapy: high dose rate

- HDR is attractive because it can be performed on an outpatient basis
- It should be fractionated to allow for repair between fractions

HDR fractionation

- The time between fractions must be adequate for repair (usually considered as 6 hours or more)
- Experience has shown that properly fractionated HDR can be at least as good as LDR

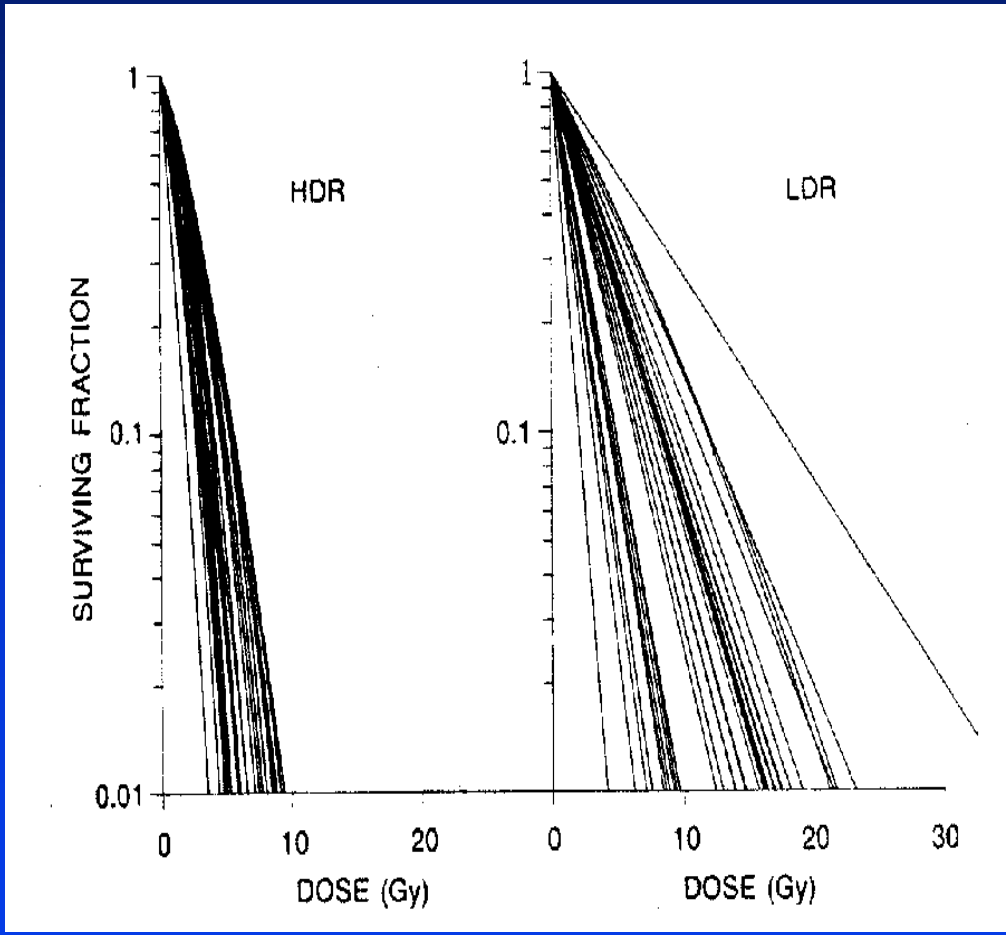
Might HDR be better than LDR?

- Yes, LDR survival curves vary more than those for HDR because:
  - *HDR survival curves vary only with cell sensitivity and the amount of repair between fractions*
  - *for LDR, survival curves vary not only with cell sensitivity and the amount of repair during irradiation, but also on the rate of repair*
- This might be considered an advantage of HDR (less variability in sensitivity between patients)

LDR and HDR survival curves compared: 40 different cell lines of human origin

The extra variability for the cells irradiated at low dose rate is due to variations in rates of repair

These are unimportant with HDR since there is no time for repair during the short irradiation times



LDR and HDR survival curves compared

- Note that some of these cells are very resistant to LDR irradiation (shallow survival curves) because the repair rate is slow
- Presumably this is why some cancers are more difficult to cure with LDR brachytherapy than others even though they look the same in other respects

Permanent implants

- Permanent implants have the advantage that only a single insertion is required (no removal)
- Dose rates are very low thus taking maximum advantage of the dose rate effect
- However, the dose rate effect is complicated due to the gradually decreasing dose rate

Permanent implants

- The half-life of the radionuclide sources used can be varied to change the dose-rate effect
  - *I-125 ($t_{1/2}$ = 60 days) and Pd-103 ($t_{1/2}$ = 17 days) are the most common sources*

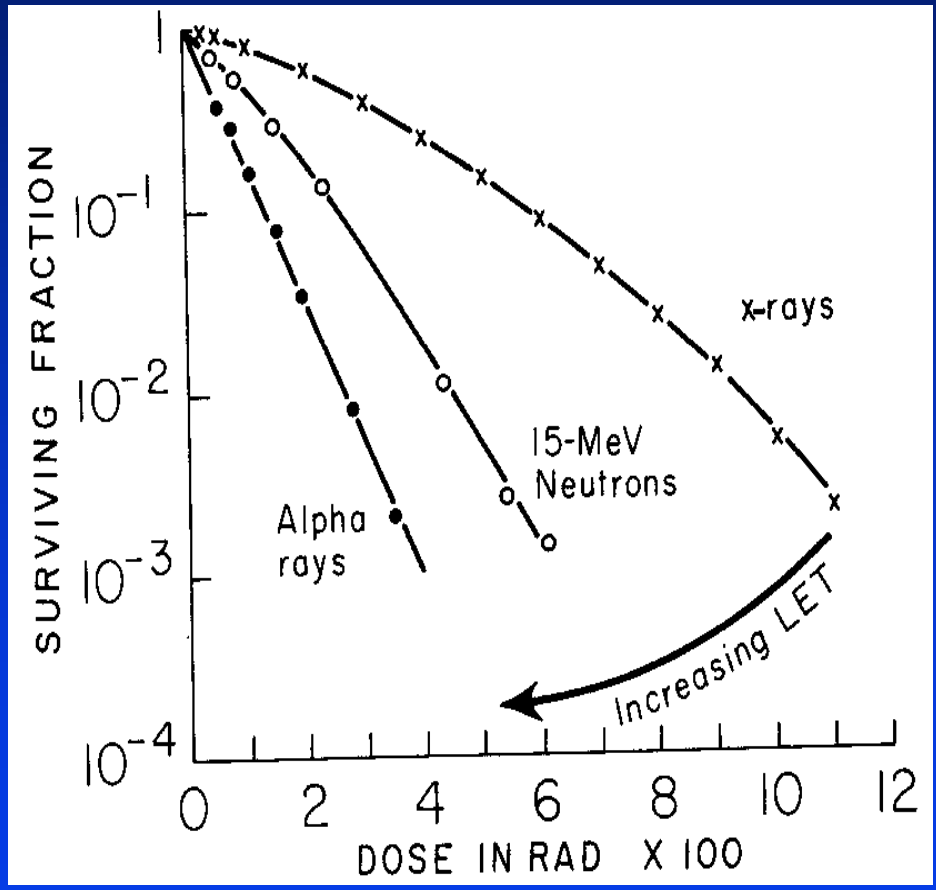
What about the low energy of these two isotopes?

- The photon energies are only 20 – 35 keV
  - *at these energies the LET is probably high enough to change the RBE and the effect on hypoxic cells*

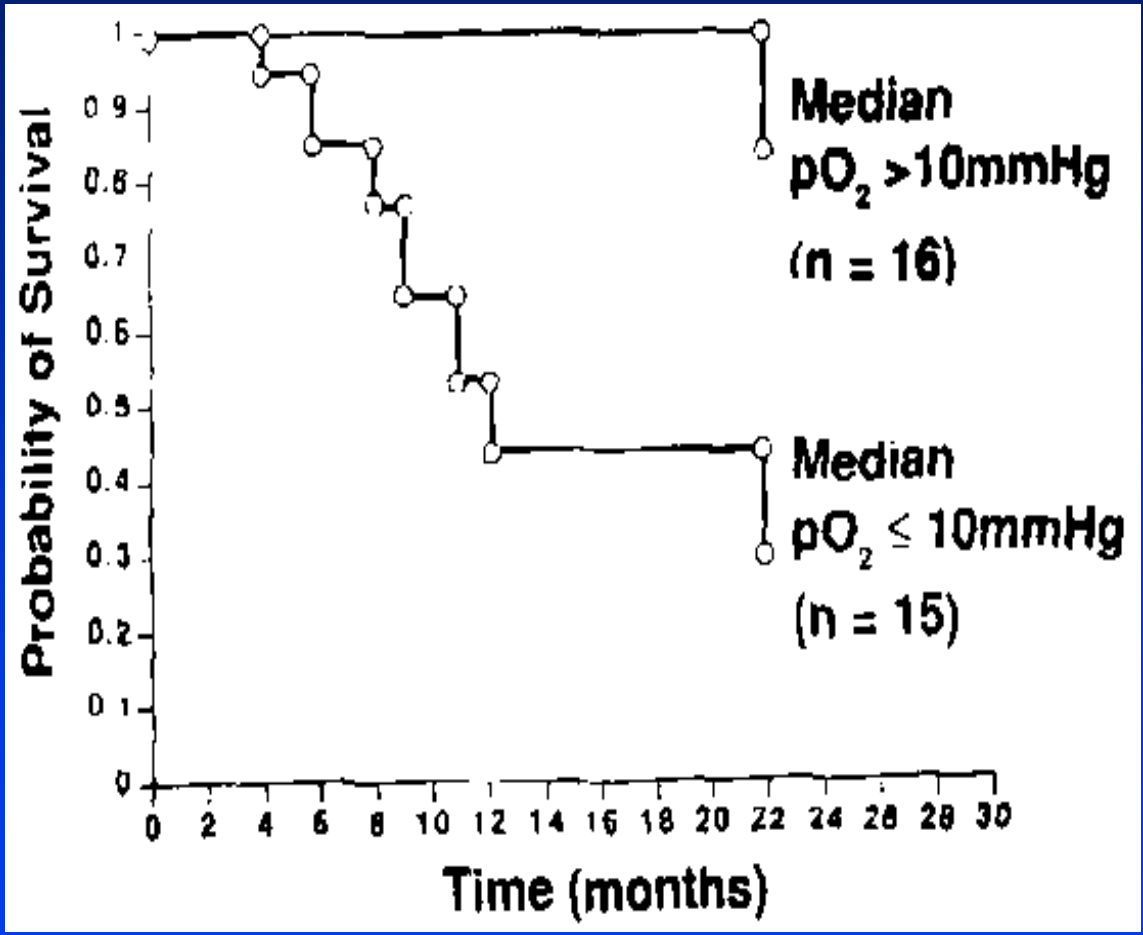
Effect of LET on cell survival curves

As LET increases the cell survival curves become straighter

This is because there is less repair as LET increases



O_2 probe measurements and survival of cervix cancer patients



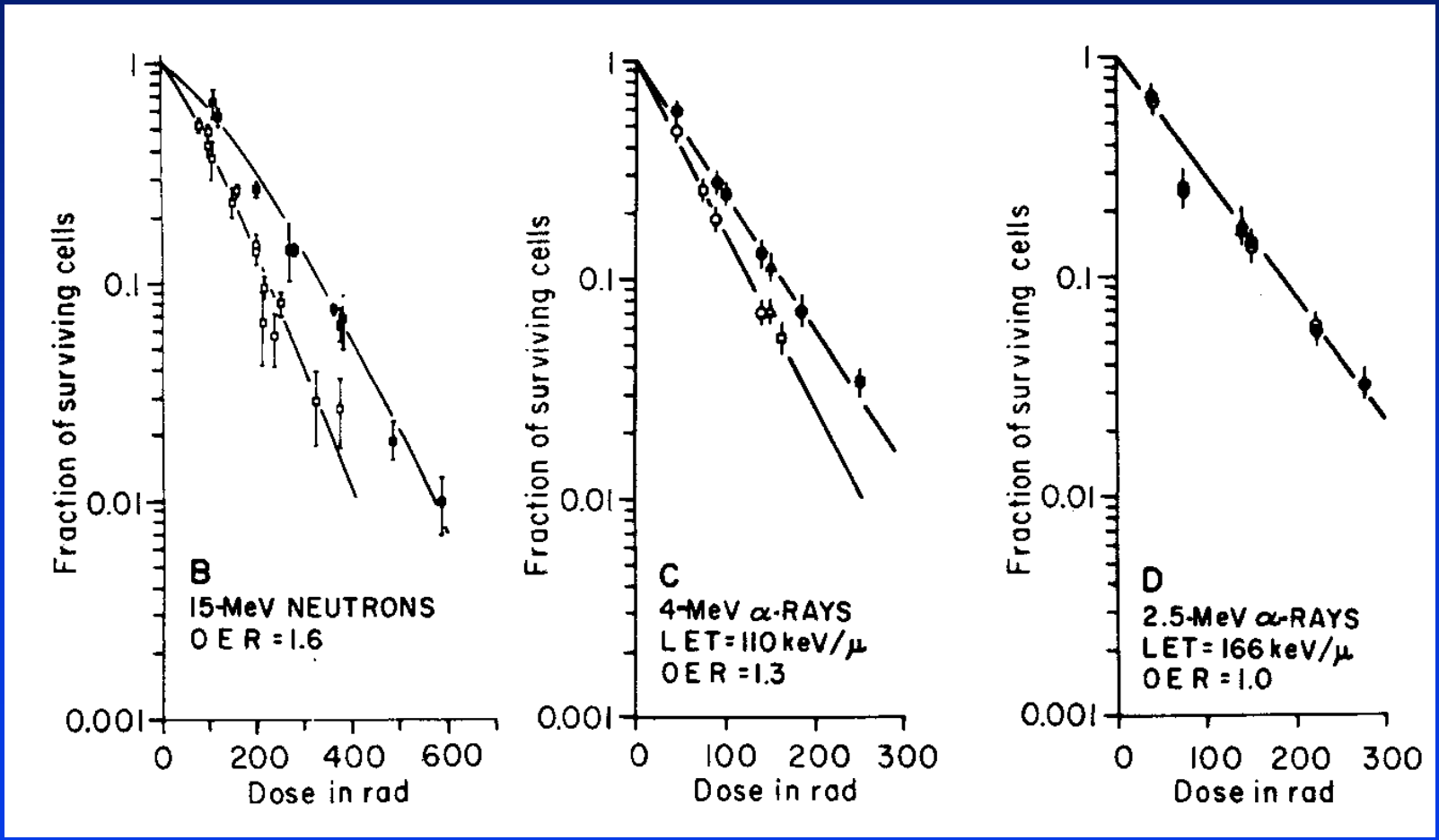
The Oxygen Effect

- Oxygen is a powerful radiation sensitizer
- The degree of sensitization is expressed in terms of the Oxygen Enhancement Ratio, where:

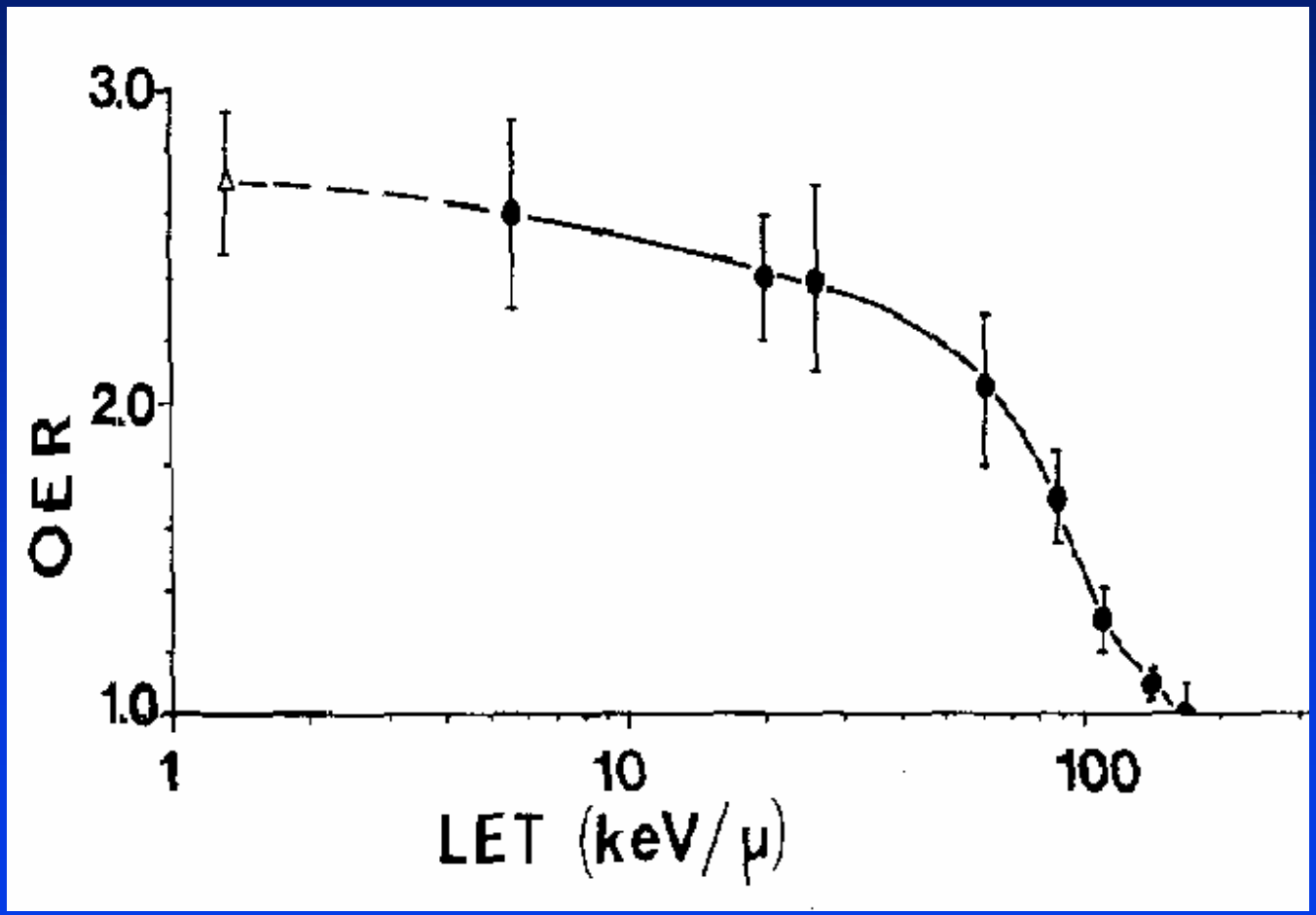
$$OER = \frac{dose\ under\ hypoxic\ conditions}{dose\ under\ aerobic\ conditions}$$

to produce the same biological effect

Effect of LET on the OER



As LET increases OER decreases



Is the low energy of these radiations an advantage?

- YES!
- And NO!
  - *Yes because a higher LET reduces the protective effect of hypoxia in tumors*
  - *No, because an increased LET means reduced repair and this reduces the beneficial difference in repair capacity of normal and cancer cells*

The LET and OER effects of low photon energy with permanent implants

Because the effects of these are both good and bad and because they are very difficult to predict, these are typically ignored when comparing permanent implants with other brachytherapy modalities

Summary

Repair describes the increase in survival that occurs when irradiations are fractionated or the dose rate is reduced

Summary (cont'd)

- Late reacting normal tissue cells are better able to repair sublethal damage than are cancer cells
- This gives us a "window of opportunity" at low doses (or low doses/fraction) and low dose rates

Summary (cont'd)

- Geometrical sparing of normal tissues widens the window of opportunity
- This allows us to use higher doses/fraction

Summary (cont'd)

- The half-time for repair is of the order of 0.5 – 1.5 hours
  - *but later we will show that this may be longer for late-responding normal tissue cells in vivo*
- Repair gives rise to the dose-rate effect

Summary (cont'd)

- LDR brachytherapy at dose rates 30 - 100 cGy/h has been shown to be effective
- MDR brachytherapy at dose rates > 100 cGy/h tends to exhibit higher than acceptable complication rates
- HDR, if adequately fractionated, can be at least as effective as LDR

Summary (cont'd)

Permanent implants with relatively short-lived radionuclides can take advantage of the dose rate effect with just a single procedure

What about repopulation?

Tumors

- *important for rapidly growing cancers*

Normal tissues

- *negligible for late-reacting tissues*
- *important for acutely-reacting tissues, especially for short courses of treatment*

Repopulation

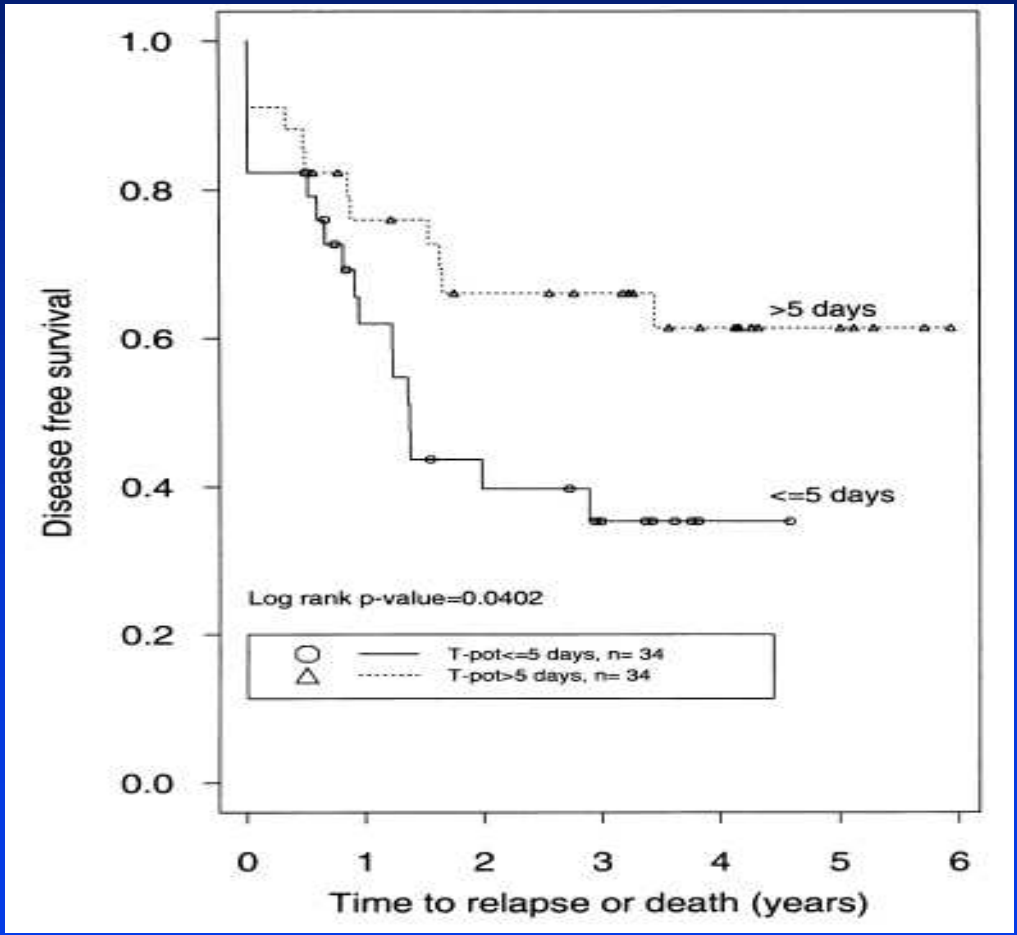
Usually represented by T_{pot} which is the doubling time of the cells capable of continued proliferation

Effect of T_{pot} on outcome

Tumor cells with short T_{pot} need to be treated with accelerated therapy otherwise they will repopulate faster than they can be treated

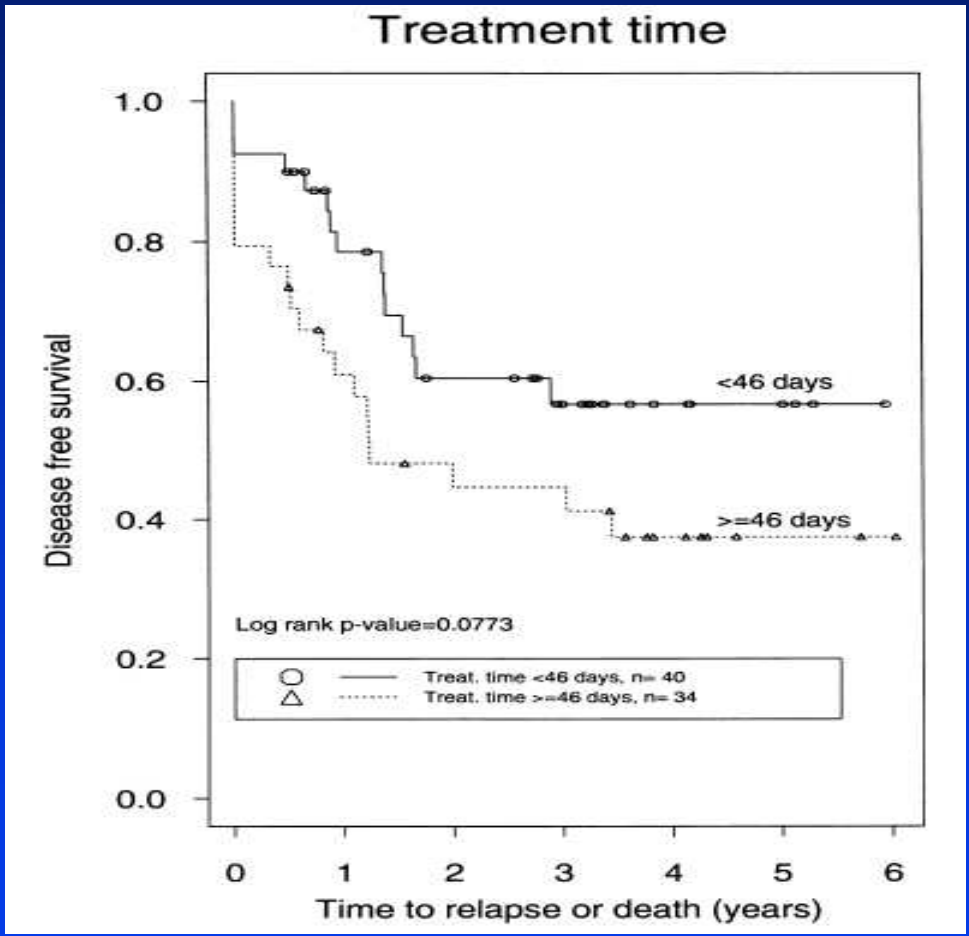
T_{pot} and survival for cervix cancer patients treated with radiation

Tsang, et el., Radiother. And Oncol. 50: 93-101, 1999.



Overall treatment time and survival for cervix cancer patients treated with radiation

Tsang, et el., Radiother. And Oncol. 50: 93-101, 1999.



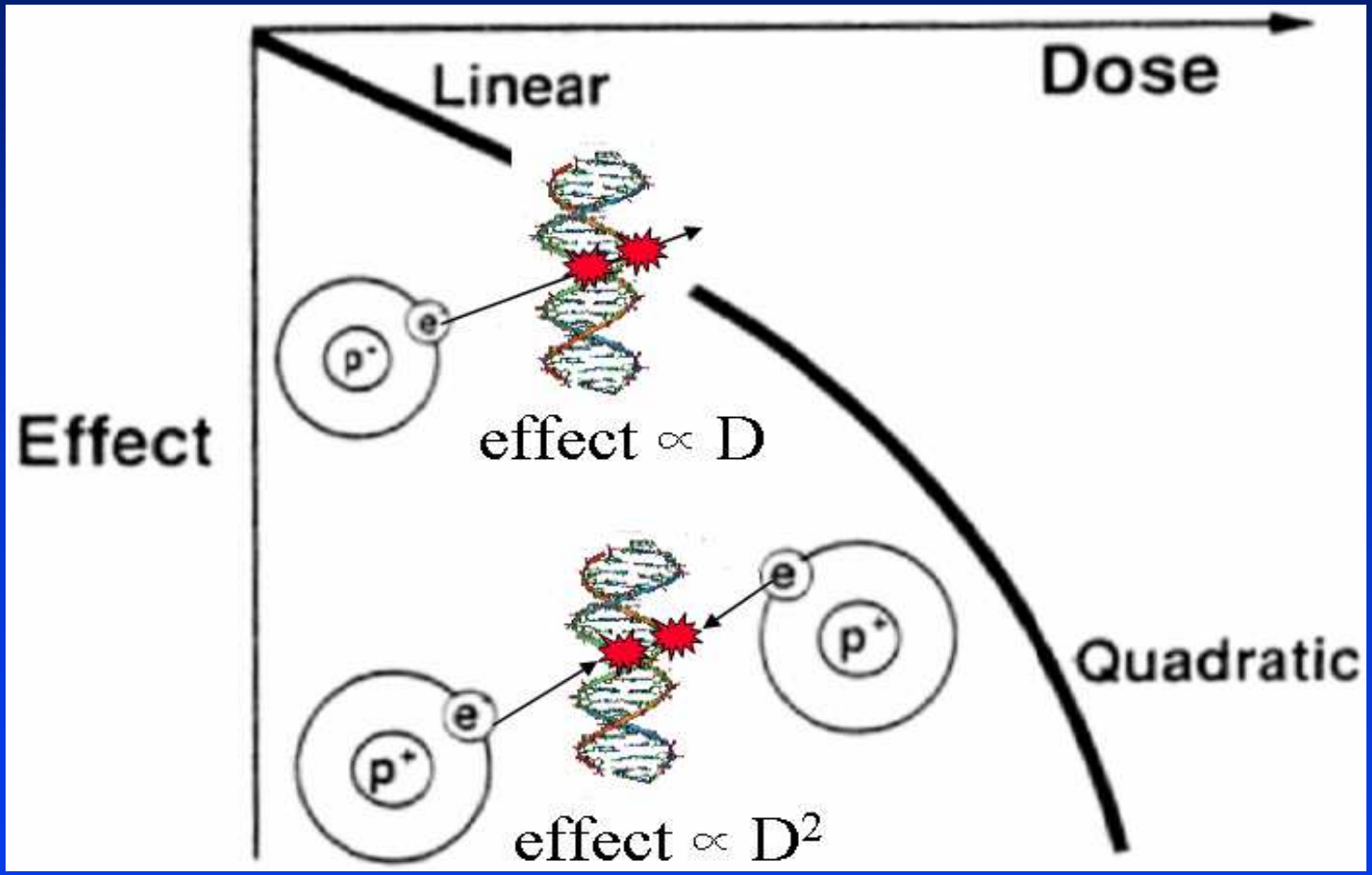
How can we determine the “best” fractionation or dose rate to use?

Need a mathematical model that describes the effects of radiotherapy on cancer and normal tissue cells

The linear-quadratic model of cell survival: two components

- Linear component:
  - a double-strand break caused by the passage of a single charged particle e.g. electron, proton, heavy ion
- Quadratic component:
  - two separate single-strand breaks caused by different charged particles

The linear-quadratic model



The L-Q model equation at high dose rate

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

- α represents the probability of lethal α-type damage
- β represents the probability that independent β-type events have combined to produce lethal events e.g. double-strand breaks

The L-Q model for fractionated treatments

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

where

N = number of fractions

d = dose/fraction

The L-Q model for fractionated treatments at low dose rate (LDR)

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

where

N = number of fractions

d = dose/fraction (= Rt)

R = dose rate

t = time for each fraction

G = dose-rate and repair-rate parameter

Dose rate and repair rate parameter, G

For conventional, fractionated treatments, when there is no time during each fraction for any repair, but sufficient time between fractions for complete repair:

$$G = 1$$

Dose rate and repair rate parameter, G

For brachytherapy where the time, *t*, for each fraction is long enough for some repair to take place:

$$G = \frac{2}{\mu t}\left[1 + \frac{1 - e^{-\mu t}}{\mu t}\right]$$

where μ = repair rate constant

The L-Q model for fractionated LDR treatments

$$-\ln S = NRt\left[\alpha + \frac{2\beta R}{\mu}\left\{1 + \frac{1-e^{-\mu t}}{\mu t}\right\}\right]$$

where

N = number of fractions

R = dose rate

t = time for each fraction

μ = repair-rate constant

The Biologically Effective Dose (BED) concept

- Problem: there are too many unknown biological parameters in the basic L-Q equations (α, β and μ) for reliable values to be determined from analysis of clinical data
- These can be reduced to one less parameter by dividing $-lnS$ by α

The BED equation for fractionated radiotherapy at d Gy/fraction

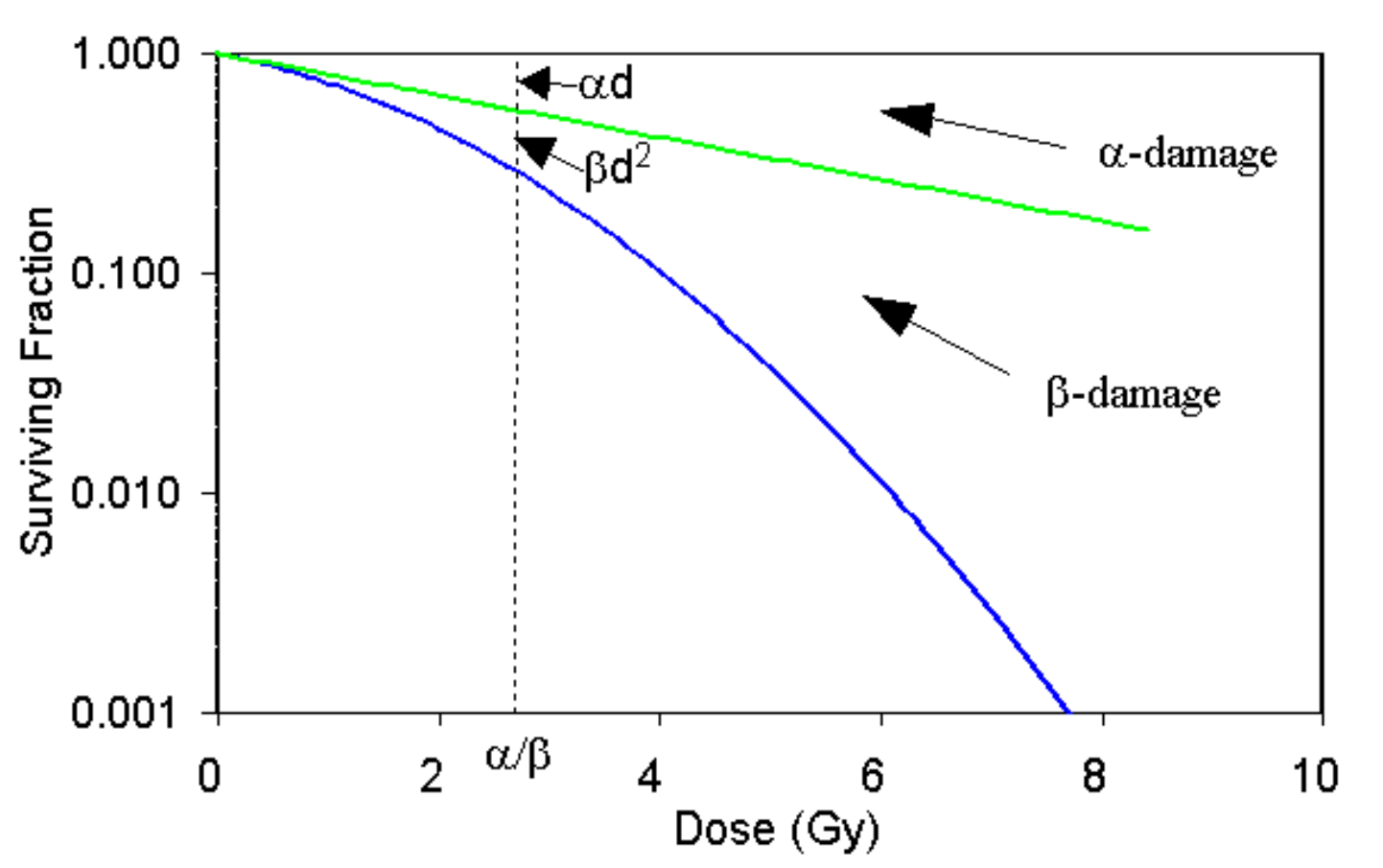
$$-\ln S = N(\alpha d + \beta d^2)$$

Hence:

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

The remaining unknown biological parameter is α/β

The L-Q Model: α/β is the dose where α-damage equals β-damage



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*

The BED equation for fractionated LDR treatments

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

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

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

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

$$For\ t \ge 100\ h$$

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

Typical values for μ

The most common assumptions are:

for tumors and acute reactions:

$$\mu = 0.46 - 1.4\ h^{-1*}$$

for late-reacting normal tissues:

$$\mu = 0.46\ h^{-1}$$

*Note: $\mu = 0.46 - 1.4\ h^{-1}$ corresponds to half times for repair ($t_{1/2}$) from 1.5 - 0.5 h, respectively

The BED equation for fractionated radiotherapy with insufficient time between fractions for full repair

$$BED = Nd\left[1+\frac{d}{N(\alpha/\beta)}\left\{\frac{N(1-K^2)-2K(1-K^N)}{(1-K)^2}\right\}\right]$$

where:

$K = e^{-\mu x}$

x is the time between fractions

μ = cellular repair rate constant (in h^{-1}) (half-time for repair = $0.693/\mu$)

BED equation when the initial dose rate R_0 decreases due to decay during treatment for an isotope with decay constant λ

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

where:

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

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

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

BED equation for permanent implants

For permanent implants *t* is infinite and this leads to the equation:

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

What about repopulation?
The BED equation with repopulation

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

where

T is the overall treatment time

and

T_{pot} is the doubling time of the cells capable of continued proliferation

Alternative form of the BED equation with repopulation

Some believe that there is a delay between the start of treatment and the onset of "accelerated repopulation". If T_k days is the "kick-in" time for accelerated repopulation, the LQ equation becomes:

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

where T_{pot} = infinity (i.e. no repopulation) for $T<T_k$

For simplicity we will usually assume that $T_k = 0$

Typical values for α and T_{pot} assumed for tumors

Growth rate of tumor	α (Gy^{-1})	T_{pot} (days)
slow	about 0.2	about 25
average	about 0.3	about 10
rapid	about 0.4	about 5

The BED equation with repopulation

- Problem: as before, there are too many unknown biological parameters in this 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

The BED equation with repopulation

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

The remaining unknown biological parameters are α/β and k

Typical values for *k* assumed for normal tissues

Acutely responding normal tissues:

- *0.2 - 0.3/day*

- Late responding normal tissues:
  - *0 - 0.1/day*

Typical values for *k* assumed for tumors

Growth rate of tumor	*k* (day^{-1})
slow	about 0.1
average	about 0.3
rapid	about 0.6

L-Q Model for Permanent Implants for cells that repopulate during treatment

Problem:

as *T* increases the dose rate decreases and hence a time (T_{eff} *in days or* t_{eff} *in hours*) is reached at which the rate of cell “killing” equals the rate of repopulation

L-Q Model for permanent implants with repopulation

At times longer than t_{eff} cell proliferation will dominate so that the maximum effectiveness in cell killing will be at time t_{eff}

t_{eff} can be approximated by the equation:

$$t_{eff} = (1/\lambda)\log_e(R_0/k)$$

where R_0 is the initial dose rate in Gy h^{-1}, λ is in h^{-1}, and k is in BED units per hour

Equation for permanent implants with repopulation

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

where:

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

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

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

Some clinical applications of the L-Q model in brachytherapy

- 1. Comparison of LDR and HDR
- 2. Change in dose rate
- 3. Comparison of I-125 and Pd-103 permanent implants with and without correction for repopulation

Some clinical applications of the L-Q model in brachytherapy

- 4. Comparison of permanent implants for prostate brachytherapy with other types of conformal radiotherapy
- 5. Comparison of HDR “balloon” brachytherapy with other types of conformal radiotherapy for partial breast irradiation

Some clinical applications of the L-Q model in brachytherapy (cont'd.)

- 6. Comparison of brachytherapy surface molds" with other types of skin radiotherapy treatments
- 7. Definitions of LDR, MDR (medium dose rate) and HDR
- 8. Dose rate corrections for LDR and fractionation corrections for HDR

1. Comparison of LDR and 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 = 100h 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:

$$BED = 60[1+1.2/(1.4 \times 10)] = 65.1$$

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:

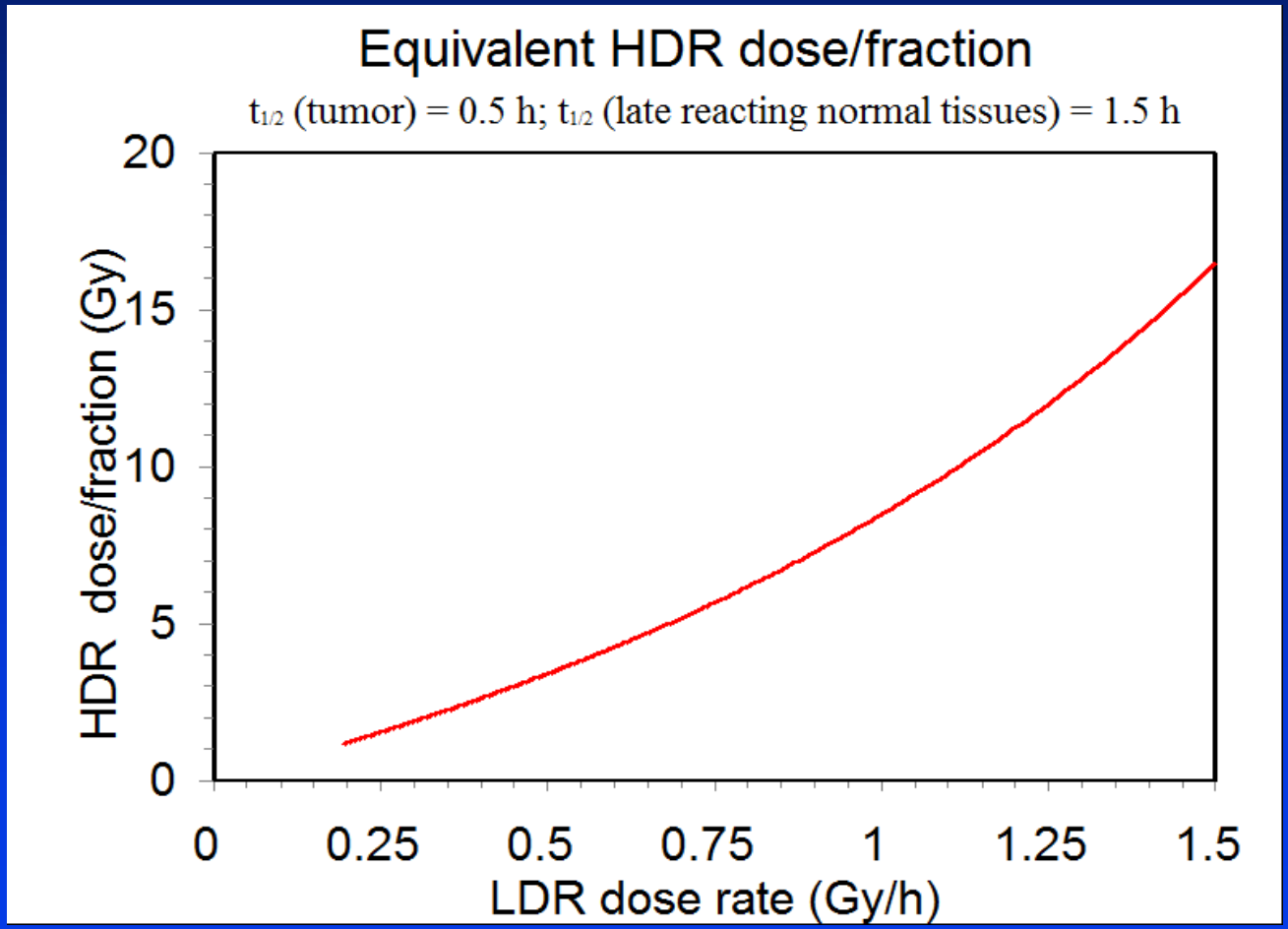
BED_{HDR} = 10 x 4.49[1+4.49/3] = 112.2

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

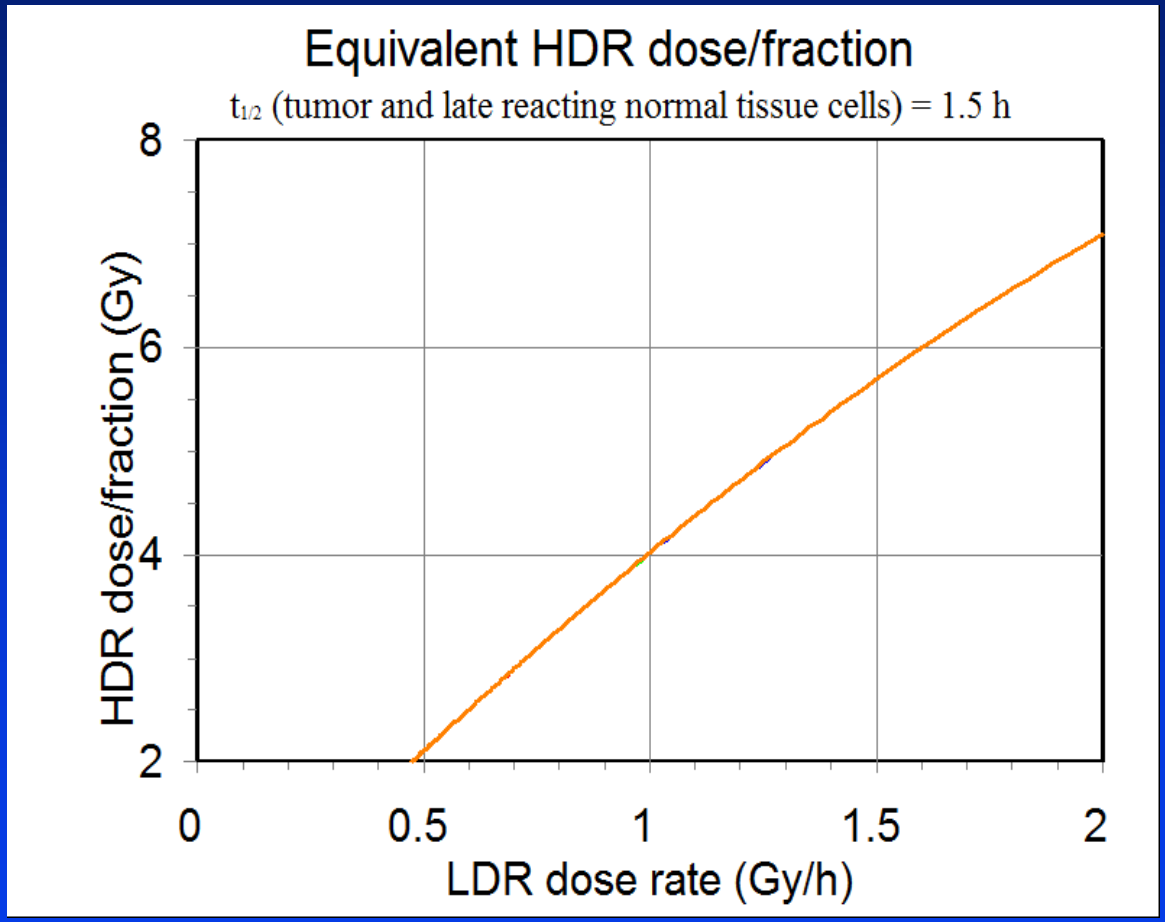
1 (cont'd.): HDR equivalent to LDR for the same tumor and normal tissue effects

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)



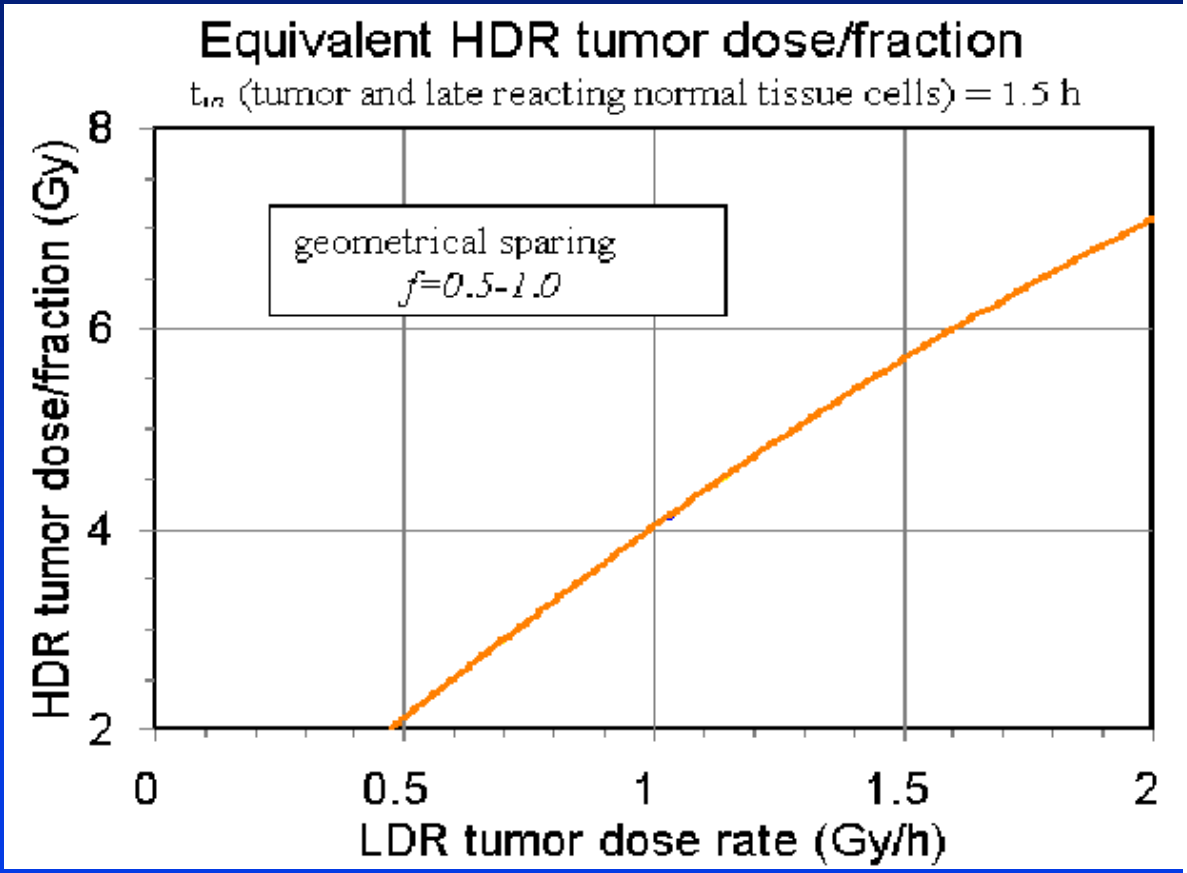
Comparison of LDR and HDR when tumor and normal tissue cells repair at the same rate

For equivalence to LDR at 0.6 Gy h^{-1} apparently need to use about 2.5 Gy/fraction with HDR for the same effect on both tumor and normal tissues



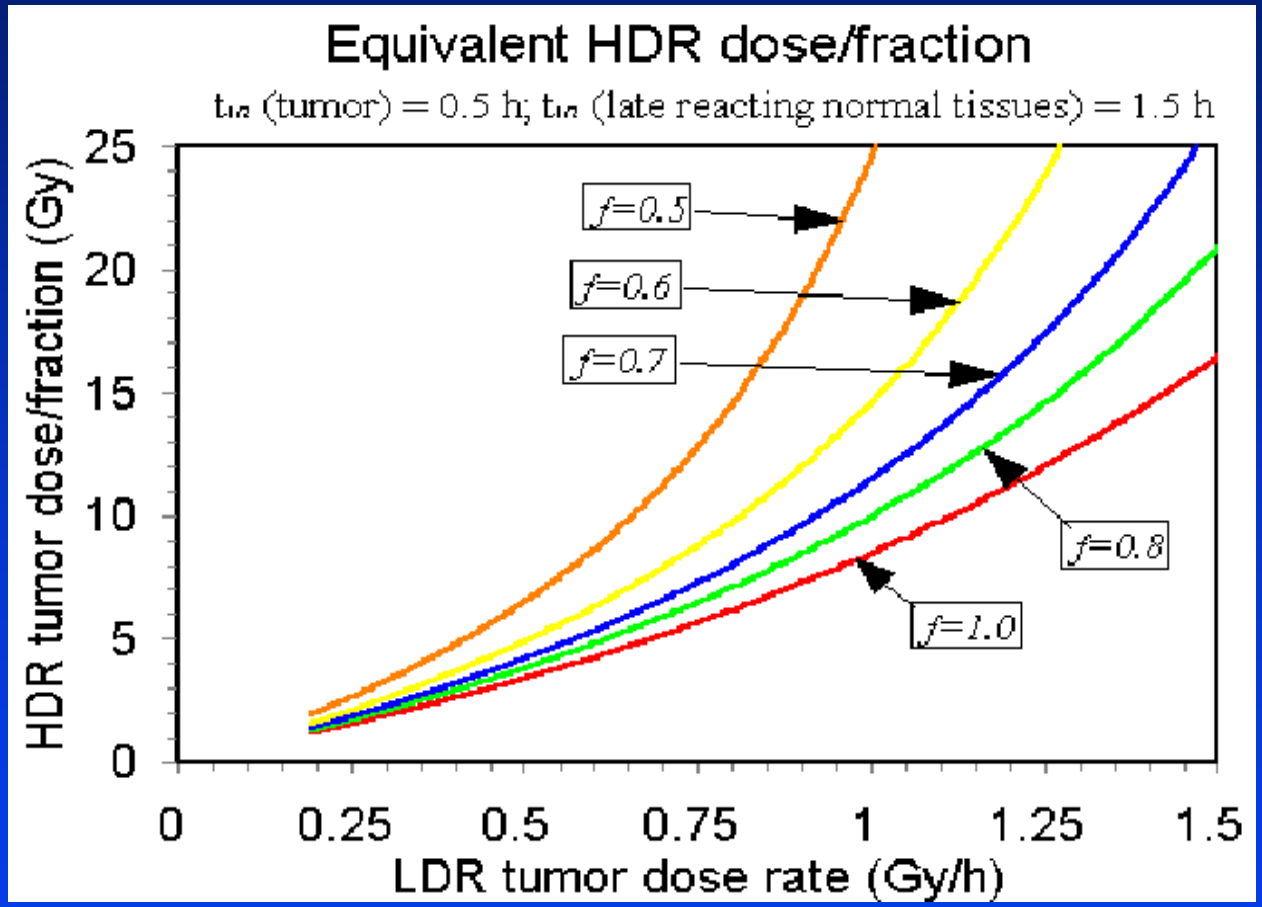
Does geometrical sparing make any difference?

No, not if the cancer and normal tissue cells repair at the same rate (HDR at 2 Gy/fraction is equivalent to LDR at 0.5 G h^{-1})



What if tumor cells repair faster than normal cells?

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)



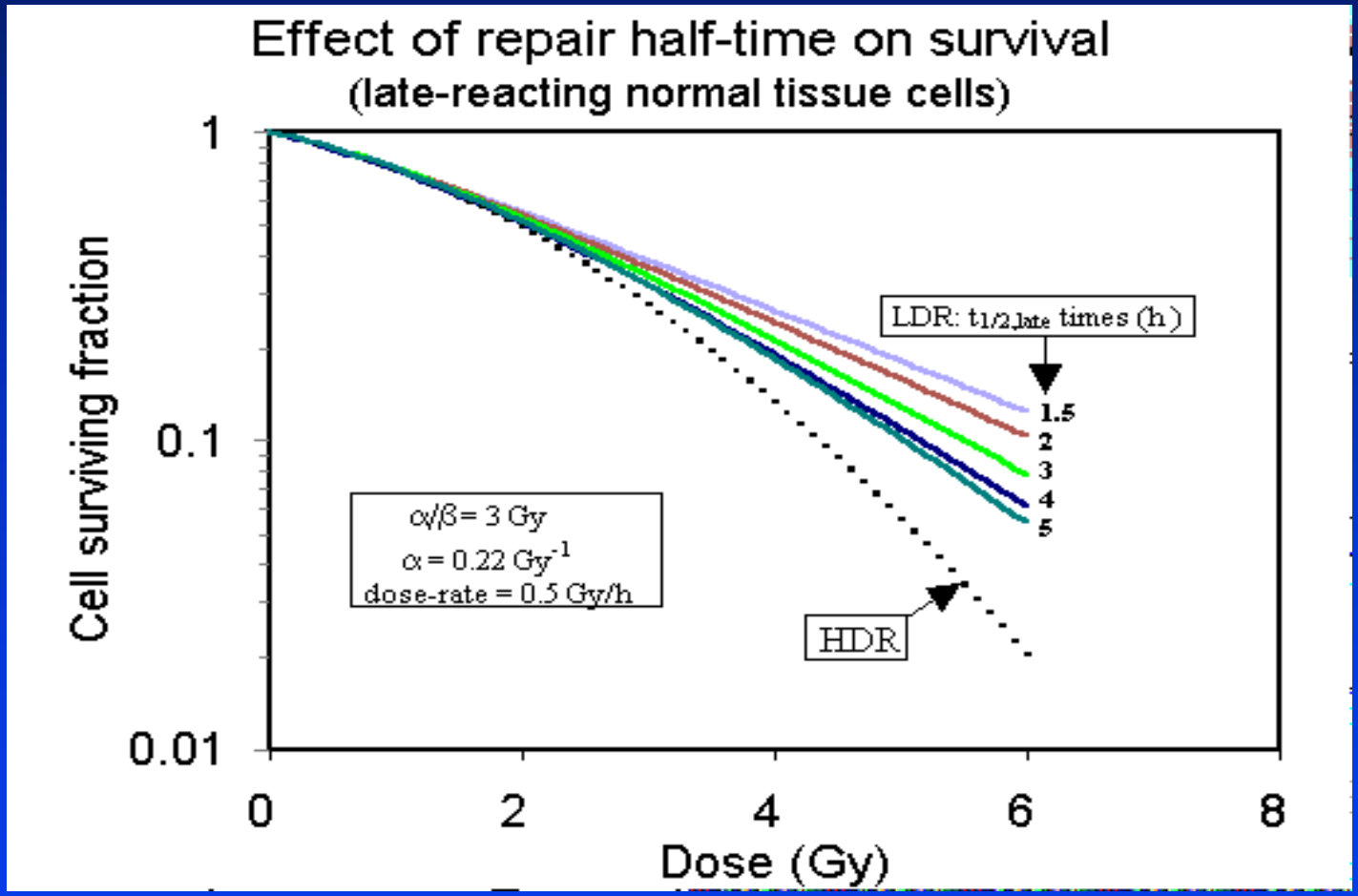
Effect of repair half time on comparison of LDR and HDR brachytherapy

Recent analysis of morbidity for patients treated with the CHART (Continuous Hyperfractionated Accelerated Radiation Therapy) regime demonstrates that repair half-times for late-reacting normal tissue cells are of the order of *4-5 hours*, which is considerably longer than previously believed.

Radiobiological significance of such long repair half-times

This would reduce cellular repair during a course of low dose rate (LDR) brachytherapy, but have no effect at high dose rate (HDR), where there is no repair during and full repair between fractions, regardless of repair half time.

Effect of repair half time on LDR cell survival

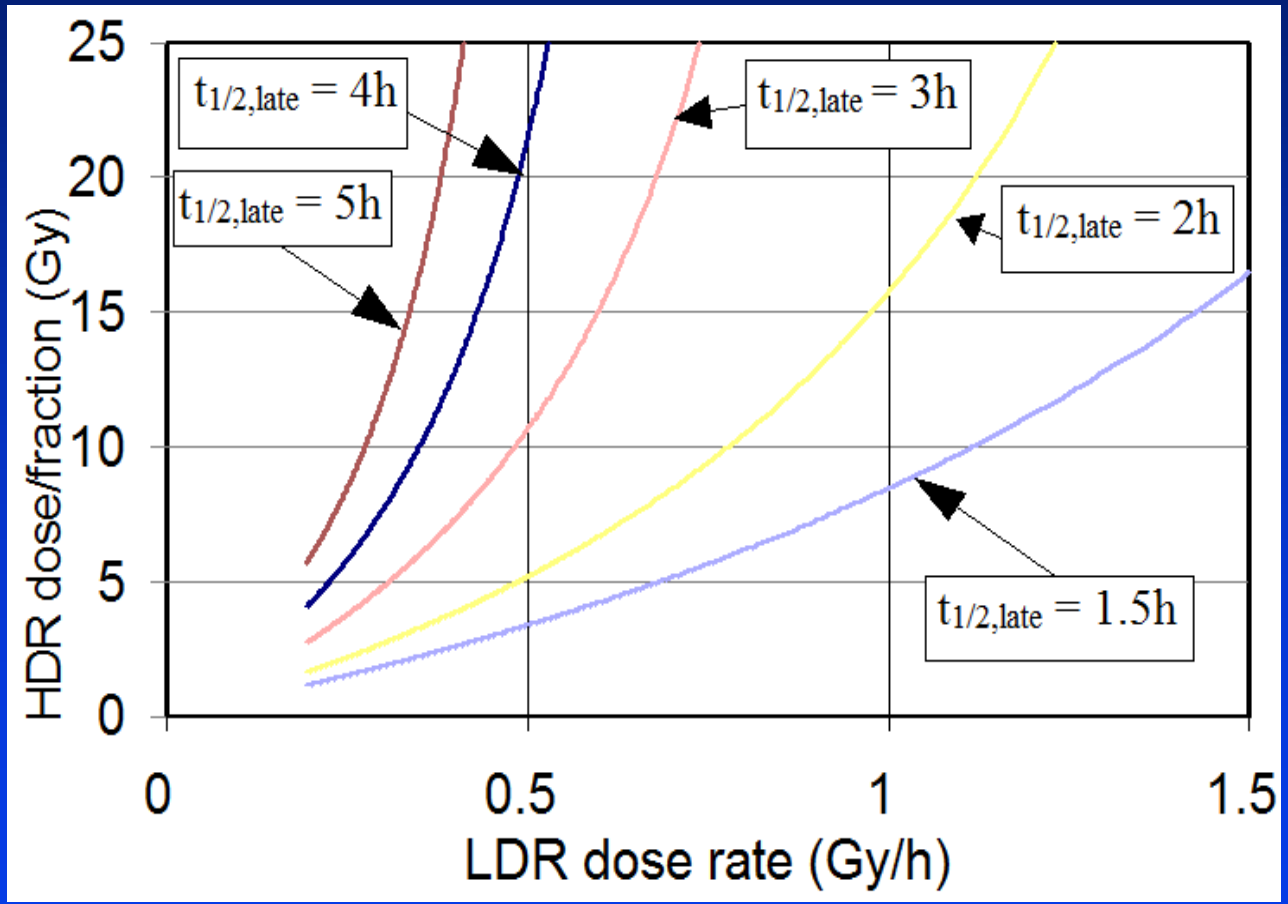


Is this a radiobiological advantage for HDR?

Yes, because the major advantage of LDR brachytherapy is *repair* during the treatment, and late-reacting normal tissue cells repair more effectively than tumor cells

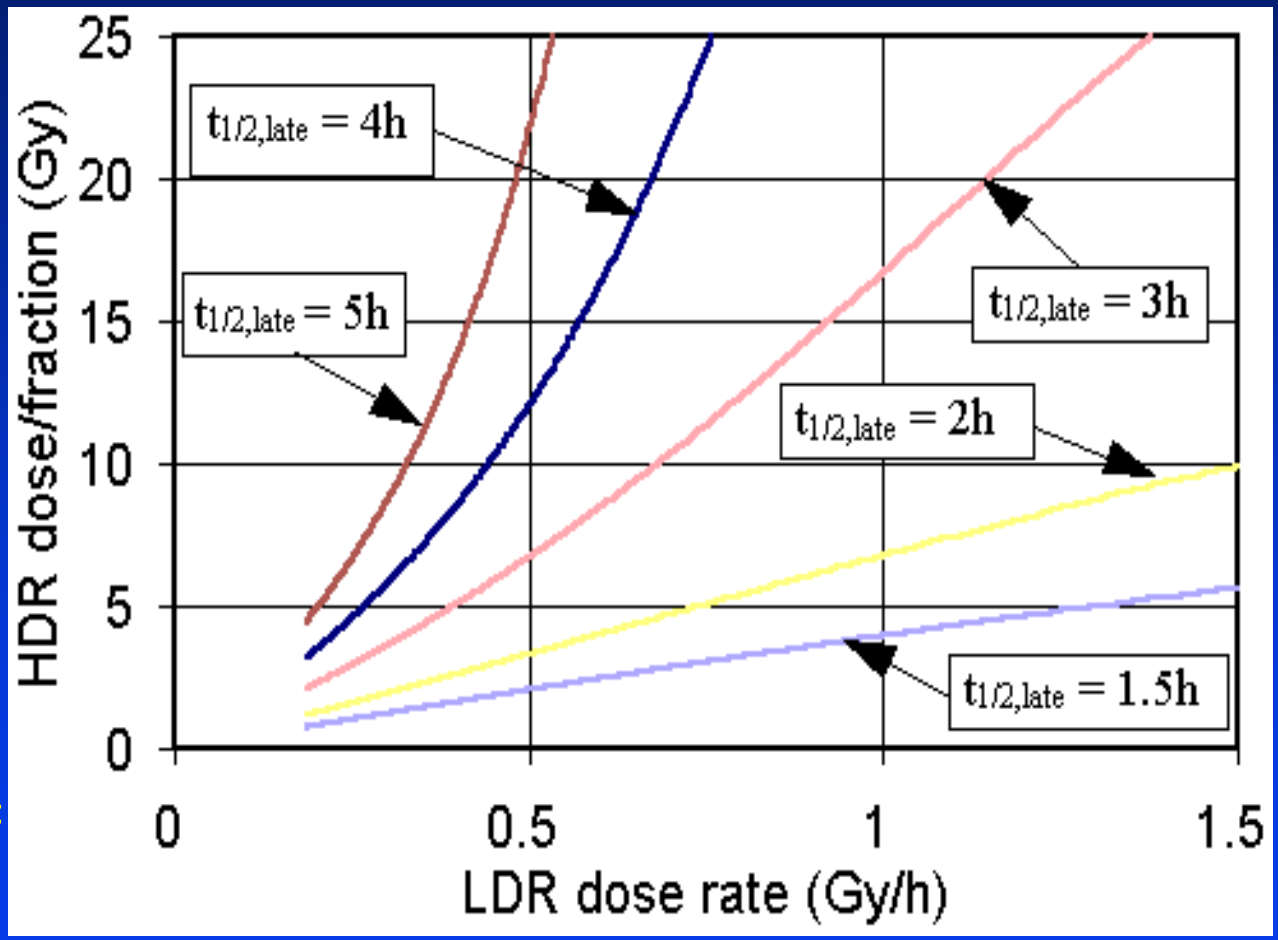
HDR dose/fraction required for equivalence to LDR with $t_{1/2,tumor}$ = 0.5 h and no geometrical sparing

As $t_{1/2,late}$ increases the HDR dose/fraction needed for equivalence increases dramatically



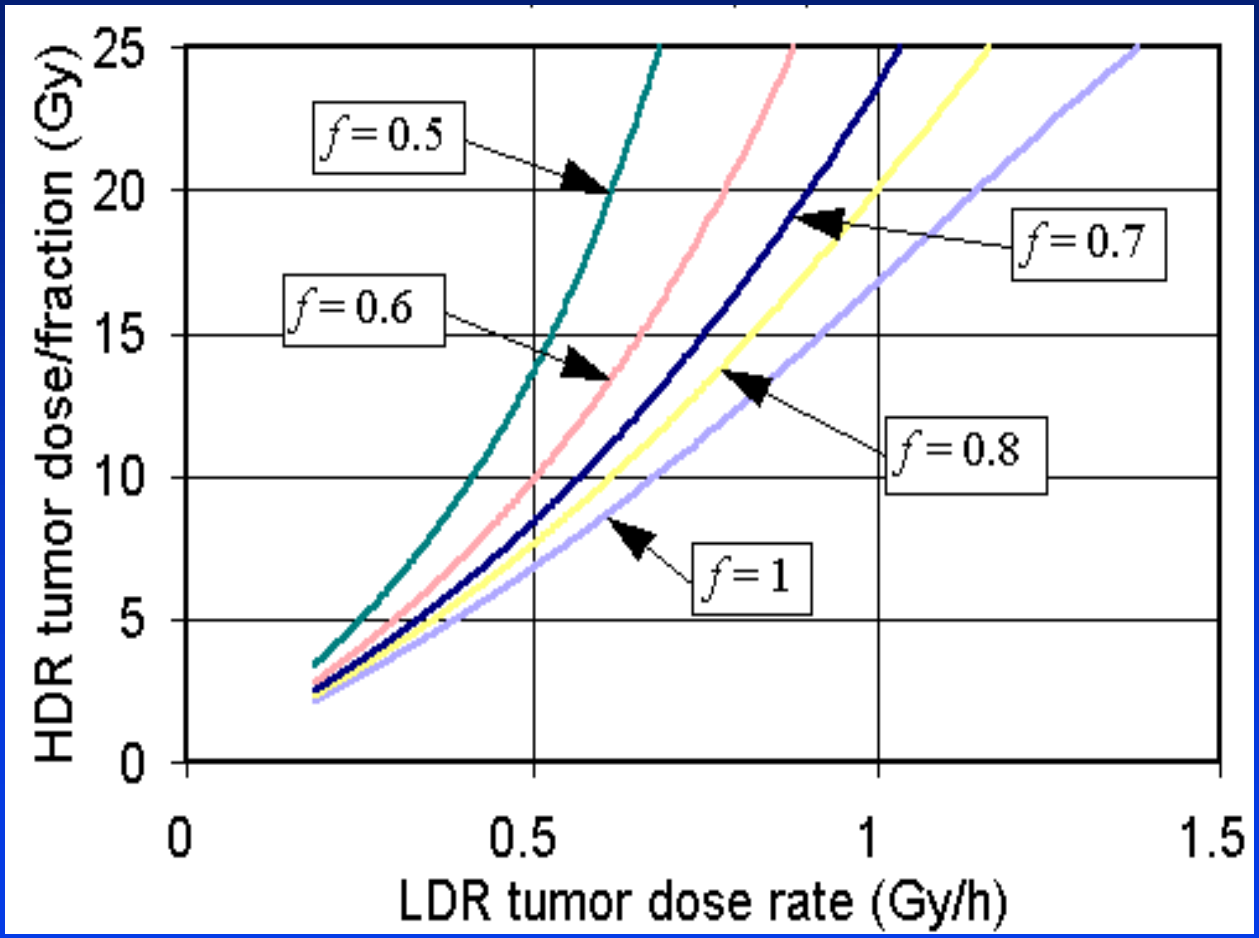
HDR dose/fraction required for equivalence to LDR with $t_{1/2,tumor}$ = 1.5 h

Even if $t_{1/2,tumor}$ is 1.5 h, the equivalent to LDR at 0.6 Gy h^{-1} is HDR at about 8 Gy/fraction with no geometrical sparing of normal tissues and $t_{1/2,late}$ = 3 h (pink line)



HDR equivalence: effect of geometrical sparing if $t_{1/2,tumor}$ = 1.5 h and $t_{1/2,late}$ = 3 h

With a geometrical sparing factor of 0.6, this equivalent HDR dose/fraction rises from8 Gy to about 12 Gy (pink line)



CONCLUSIONS

If the half-time for repair of late-reacting normal tissue cells exceeds about 2.5 hours, LDR becomes radiobiologically inferior to HDR if $t_{1/2,\ tumor}$ is 1.5h or less

CONCLUSIONS (continued)

The previously held belief that LDR must be radiobiologically superior to HDR is wrong if the long repair times demonstrated in the CHART study are applicable to other late-reacting normal tissue cells

2: Change in dose rate

- A radiation oncologist wants to reduce the treatment time by converting 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?

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, which is not appropriate for the new 51 h implant
- 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.

Solution using a table

- This is an example when a table could be used to solve a problem more accurately
- We will use Table 1 to solve this problem
  - 60 Gy at 0.5 Gy/h takes 120 hours
  - now looking down the 0.5 Gy/h column we see that the BED after 120 h is 72.8

Table 1: Tumor BEDs for LDR implants with $\alpha/\beta = 10$ Gy, repair half-time = 1.5 h.

	Dose rate (Gy/h)																			
time(h)	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2
10	1.0	2.1	3.3	4.5	5.9	7.2	8.7	10.2	11.8	13.4	15.1	16.9	18.8	20.7	22.7	24.7	26.9	29.1	31.3	33.6
20	2.1	4.3	6.7	9.2	11.9	14.8	17.8	21.0	24.3	27.8	31.4	35.2	39.1	43.2	47.4	51.8	56.4	61.1	66.0	71.0
30	3.1	6.5	10.1	13.9	18.0	22.4	26.9	31.7	36.8	42.1	47.6	53.4	59.4	65.7	72.2	79.0	86.0	93.2	100.7	108.4
40	4.2	8.7	13.5	18.6	24.1	29.9	36.1	42.5	49.3	56.4	63.9	71.7	79.8	88.2	97.0	106.1	115.5	125.3	135.4	145.8
50	5.2	10.8	16.9	23.3	30.2	37.5	45.2	53.3	61.8	70.8	80.2	89.9	100.1	110.8	121.8	133.2	145.1	157.4	170.1	183.2
60	6.3	13.0	20.3	28.0	36.3	45.1	54.3	64.1	74.4	85.1	96.4	108.2	120.5	133.3	146.6	160.4	174.7	189.5	204.8	220.6
70	7.3	15.2	23.7	32.7	42.4	52.6	63.5	74.9	86.9	99.5	112.7	126.5	140.8	155.8	171.4	187.5	204.2	221.6	239.5	258.0
80	8.3	17.4	27.0	37.4	48.5	60.2	72.6	85.7	99.4	113.8	128.9	144.7	161.2	178.3	196.1	214.6	233.8	253.6	274.2	295.4
90	9.4	19.5	30.4	42.1	54.5	67.7	81.7	96.4	111.9	128.2	145.2	163.0	181.5	200.8	220.9	241.8	263.4	285.7	308.9	332.7
100	10.4	21.7	33.8	46.8	60.6	75.3	90.8	107.2	124.5	142.5	161.5	181.3	201.9	223.4	245.7	268.9	292.9	317.8	343.6	370.1
110	11.5	23.9	37.2	51.5	66.7	82.9	100.0	118.0	137.0	156.9	177.7	199.5	222.2	245.9	270.5	296.0	322.5	349.9	378.2	407.5
120	12.5	26.0	40.6	56.2	72.8	90.4	109.1	128.8	149.5	171.2	194.0	217.8	242.6	268.4	295.3	323.2	352.1	382.0	412.9	444.9
130	13.6	28.2	44.0	60.9	78.9	98.0	118.2	139.6	162.0	185.6	210.3	236.0	262.9	290.9	320.1	350.3	381.6	414.1	447.6	482.3
140	14.6	30.4	47.4	65.6	85.0	105.6	127.4	150.4	174.5	199.9	226.5	254.3	283.3	313.5	344.8	377.4	411.2	446.2	482.3	519.7
150	15.6	32.6	50.8	70.3	91.1	113.1	136.5	161.1	187.1	214.3	242.8	272.6	303.6	336.0	369.6	404.5	440.8	478.3	517.0	557.1
160	16.7	34.7	54.2	75.0	97.2	120.7	145.6	171.9	199.6	228.6	259.0	290.8	324.0	358.5	394.4	431.7	470.3	510.3	551.7	594.5
170	17.7	36.9	57.6	79.7	103.2	128.3	154.8	182.7	212.1	243.0	275.3	309.1	344.3	381.0	419.2	458.8	499.9	542.4	586.4	631.9
180	18.8	39.1	61.0	84.4	109.3	135.8	163.9	193.5	224.6	257.3	291.6	327.3	364.7	403.5	444.0	485.9	529.5	574.5	621.1	669.3
190	19.8	41.3	64.4	89.1	115.4	143.4	173.0	204.3	237.2	271.7	307.8	345.6	385.0	426.1	468.8	513.1	559.0	606.6	655.8	706.7
200	20.9	43.4	67.7	93.8	121.5	151.0	182.1	215.0	249.7	286.0	324.1	363.9	405.4	448.6	493.5	540.2	588.6	638.7	690.5	744.1

Solution using the table (cont'd.)

- Now look for a BED of 72.8 down the 1.0 Gy/h column
  - after 50 h the BED is 70.8
  - after 60 h it is 85.1
  - interpolation between these gives the time for a BED of 72.8 which is 51.3 h and hence the dose at 1.0 Gy/h is 51.3 Gy

Table 1: Tumor BEDs for LDR implants with $\alpha/\beta = 10$ Gy, repair half-time = 1.5 h.

	Dose rate (Gy/h)																			
time(h)	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2
10	1.0	2.1	3.3	4.5	5.9	7.2	8.7	10.2	11.8	13.4	15.1	16.9	18.8	20.7	22.7	24.7	26.9	29.1	31.3	33.6
20	2.1	4.3	6.7	9.2	11.9	14.8	17.8	21.0	24.3	27.8	31.4	35.2	39.1	43.2	47.4	51.8	56.4	61.1	66.0	71.0
30	3.1	6.5	10.1	13.9	18.0	22.4	26.9	31.7	36.8	42.1	47.6	53.4	59.4	65.7	72.2	79.0	86.0	93.2	100.7	108.4
40	4.2	8.7	13.5	18.6	24.1	29.9	36.1	42.5	49.3	56.4	63.9	71.7	79.8	88.2	97.0	106.1	115.5	125.3	135.4	145.8
50	5.2	10.8	16.9	23.3	30.2	37.5	45.2	53.3	61.8	70.8	80.2	89.9	100.1	110.8	121.8	133.2	145.1	157.4	170.1	183.2
60	6.3	13.0	20.3	28.0	36.3	45.1	54.3	64.1	74.4	85.1	96.4	108.2	120.5	133.3	146.6	160.4	174.7	189.5	204.8	220.6
70	7.3	15.2	23.7	32.7	42.4	52.6	63.5	74.9	86.9	99.5	112.7	126.5	140.8	155.8	171.4	187.5	204.2	221.6	239.5	258.0
80	8.3	17.4	27.0	37.4	48.5	60.2	72.6	85.7	99.4	113.8	128.9	144.7	161.2	178.3	196.1	214.6	233.8	253.6	274.2	295.4
90	9.4	19.5	30.4	42.1	54.5	67.7	81.7	96.4	111.9	128.2	145.2	163.0	181.5	200.8	220.9	241.8	263.4	285.7	308.9	332.7
100	10.4	21.7	33.8	46.8	60.6	75.3	90.8	107.2	124.5	142.5	161.5	181.3	201.9	223.4	245.7	268.9	292.9	317.8	343.6	370.1
110	11.5	23.9	37.2	51.5	66.7	82.9	100.0	118.0	137.0	156.9	177.7	199.5	222.2	245.9	270.5	296.0	322.5	349.9	378.2	407.5
120	12.5	26.0	40.6	56.2	72.8	90.4	109.1	128.8	149.5	171.2	194.0	217.8	242.6	268.4	295.3	323.2	352.1	382.0	412.9	444.9
130	13.6	28.2	44.0	60.9	78.9	98.0	118.2	139.6	162.0	185.6	210.3	236.0	262.9	290.9	320.1	350.3	381.6	414.1	447.6	482.3
140	14.6	30.4	47.4	65.6	85.0	105.6	127.4	150.4	174.5	199.9	226.5	254.3	283.3	313.5	344.8	377.4	411.2	446.2	482.3	519.7
150	15.6	32.6	50.8	70.3	91.1	113.1	136.5	161.1	187.1	214.3	242.8	272.6	303.6	336.0	369.6	404.5	440.8	478.3	517.0	557.1
160	16.7	34.7	54.2	75.0	97.2	120.7	145.6	171.9	199.6	228.6	259.0	290.8	324.0	358.5	394.4	431.7	470.3	510.3	551.7	594.5
170	17.7	36.9	57.6	79.7	103.2	128.3	154.8	182.7	212.1	243.0	275.3	309.1	344.3	381.0	419.2	458.8	499.9	542.4	586.4	631.9
180	18.8	39.1	61.0	84.4	109.3	135.8	163.9	193.5	224.6	257.3	291.6	327.3	364.7	403.5	444.0	485.9	529.5	574.5	621.1	669.3
190	19.8	41.3	64.4	89.1	115.4	143.4	173.0	204.3	237.2	271.7	307.8	345.6	385.0	426.1	468.8	513.1	559.0	606.6	655.8	706.7
200	20.9	43.4	67.7	93.8	121.5	151.0	182.1	215.0	249.7	286.0	324.1	363.9	405.4	448.6	493.5	540.2	588.6	638.7	690.5	744.1

1 (cont'd.): now repeat this problem for late-reacting normal tissues

Assume that α/β (late) is 2.5 Gy, and μ (late) 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 (late) = 60[1 + 2x0.5/(0.46x2.5)] = 112

Solution (cont'd.)

To obtain this same BED of 112 at 1 Gy/h, the overall time t is given by:

$$112 = 1 \times t[1 + 2 \times 1/(0.46 \times 2.5)].$$

Hence:

$$t = 112/2.74 = 40.9 \text{ h}.$$

Solution (cont'd.)

The total dose is thus 40.9 times the dose rate of 1 Gy/h

= 40.9 Gy

Solution (cont'd.)

- As before, 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 yielded a required dose of 42.0 Gy instead of the approximate solution of 40.9 Gy obtained here.

Solution using a table

- We use table 2 for late-reacting normal tissues
- Looking down the 0.5 Gy/h column we see that a BED of 111.2 is reached after 120 h.
- We now look down the 1.0 Gy/h column to find the time for a BED of 111.2

Table 2: BEDs for late reacting normal tissues (or low α/β tumor) with α/β = 2.5 Gy and repair half-time = 1.5 h.

	Dose rate (Gy/h)																			
time(h)	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2
10	1.1	2.5	4.2	6.2	8.4	10.9	13.7	16.7	20.1	23.6	27.5	31.7	36.1	40.8	45.7	50.9	56.4	62.2	68.3	74.6
20	2.3	5.2	8.8	13.0	17.8	23.2	29.2	35.8	43.1	51.0	59.5	68.6	78.4	88.8	99.8	111.4	123.6	136.4	149.9	164.0
30	3.5	7.9	13.4	19.7	27.1	35.4	44.7	55.0	66.2	78.4	91.6	105.7	120.8	136.8	153.9	171.9	190.9	210.8	231.7	253.6
40	4.7	10.6	17.9	26.5	36.4	47.7	60.2	74.1	89.3	105.8	123.6	142.7	163.2	184.9	208.0	232.4	258.1	285.1	313.5	343.1
50	5.8	13.3	22.5	33.3	45.8	59.9	75.8	93.2	112.4	133.2	155.6	179.8	205.6	233.0	262.1	292.9	325.4	359.5	395.3	432.7
60	7.0	16.0	27.1	40.1	55.1	72.2	91.3	112.4	135.5	160.6	187.7	216.8	248.0	281.1	316.3	353.4	392.6	433.8	477.0	522.3
70	8.2	18.7	31.6	46.9	64.5	84.5	106.8	131.5	158.5	188.0	219.7	253.9	290.3	329.2	370.4	414.0	459.9	508.2	558.8	611.8
80	9.4	21.4	36.2	53.7	73.8	96.7	122.3	150.6	181.6	215.3	251.8	290.9	332.7	377.3	424.5	474.5	527.2	582.5	640.6	701.4
90	10.5	24.1	40.7	60.4	83.2	109.0	137.8	169.8	204.7	242.7	283.8	327.9	375.1	425.4	478.7	535.0	594.4	656.9	722.4	791.0
100	11.7	26.8	45.3	67.2	92.5	121.2	153.4	188.9	227.8	270.1	315.9	365.0	417.5	473.5	532.8	595.5	661.7	731.2	804.2	880.5
110	12.9	29.5	49.9	74.0	101.9	133.5	168.9	208.0	250.9	297.5	347.9	402.0	459.9	521.5	586.9	656.1	728.9	805.6	885.9	970.1
120	14.0	32.2	54.4	80.8	111.2	145.8	184.4	227.1	274.0	324.9	379.9	439.1	502.3	569.6	641.1	716.6	796.2	879.9	967.7	-
130	15.2	34.9	59.0	87.6	120.6	158.0	199.9	246.3	297.1	352.3	412.0	476.1	544.7	617.7	695.2	777.1	863.5	954.3	-	-
140	16.4	37.6	63.6	94.4	129.9	170.3	215.4	265.4	320.2	379.7	444.0	513.2	587.1	665.8	749.3	837.6	930.7	-	-	-
150	17.6	40.3	68.1	101.1	139.3	182.6	231.0	284.5	343.2	407.1	476.1	550.2	629.5	713.9	803.4	898.1	998.0	-	-	-
160	18.7	43.0	72.7	107.9	148.6	194.8	246.5	303.7	366.3	434.5	508.1	587.2	671.9	762.0	857.6	958.7	-	-	-	-
170	19.9	45.7	77.3	114.7	158.0	207.1	262.0	322.8	389.4	461.9	540.2	624.3	714.3	810.1	911.7	-	-	-	-	-
180	21.1	48.4	81.8	121.5	167.3	219.3	277.5	341.9	412.5	489.3	572.2	661.3	756.6	858.1	965.8	-	-	-	-	-
190	22.3	51.1	86.4	128.3	176.7	231.6	293.1	361.1	435.6	516.6	604.2	698.4	799.0	906.2	-	-	-	-	-	-
200	23.4	53.8	91.0	135.0	186.0	243.9	308.6	380.2	458.7	544.0	636.3	735.4	841.4	954.3	-	-	-	-	-	-

Solution (cont'd.)

- Looking for a BED of 111.2 down the 1.0 Gy/h column
  - after 40 h the BED is 105.8
  - after 50 h it is 133.2
  - interpolation between these gives the time for a BED of 111.2 which is 42.0 h and hence the dose at 1.0 Gy/h is 42.0 Gy

Table 2: BEDs for late reacting normal tissues (or low α/β tumor) with α/β = 2.5 Gy and repair half-time = 1.5 h.

	Dose rate (Gy/h)																		
time(h)	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2
10	1.1	2.5	4.2	6.2	8.4	10.9	13.7	16.7	20.1	23.6	27.5	31.7	36.1	40.8	45.7	50.9	56.4	62.2	68.3	74.6
20	2.3	5.2	8.8	13.0	17.8	23.2	29.2	35.8	43.1	51.0	59.5	68.6	78.4	88.8	99.8	111.4	123.6	136.4	149.9	164.0
30	3.5	7.9	13.4	19.7	27.1	35.4	44.7	55.0	66.2	78.4	91.6	105.7	120.8	136.8	153.9	171.9	190.9	210.8	231.7	253.6
40	4.7	10.6	17.9	26.5	36.4	47.7	60.2	74.1	89.3	105.8	123.6	142.7	163.2	184.9	208.0	232.4	258.1	285.1	313.5	343.1
50	5.8	13.3	22.5	33.3	45.8	59.9	75.8	93.2	112.4	133.2	155.6	179.8	205.6	233.0	262.1	292.9	325.4	359.5	395.3	432.7
60	7.0	16.0	27.1	40.1	55.1	72.2	91.3	112.4	135.5	160.6	187.7	216.8	248.0	281.1	316.3	353.4	392.6	433.8	477.0	522.3
70	8.2	18.7	31.6	46.9	64.5	84.5	106.8	131.5	158.5	188.0	219.7	253.9	290.3	329.2	370.4	414.0	459.9	508.2	558.8	611.8
80	9.4	21.4	36.2	53.7	73.8	96.7	122.3	150.6	181.6	215.3	251.8	290.9	332.7	377.3	424.5	474.5	527.2	582.5	640.6	701.4
90	10.5	24.1	40.7	60.4	83.2	109.0	137.8	169.8	204.7	242.7	283.8	327.9	375.1	425.4	478.7	535.0	594.4	656.9	722.4	791.0
100	11.7	26.8	45.3	67.2	92.5	121.2	153.4	188.9	227.8	270.1	315.9	365.0	417.5	473.5	532.8	595.5	661.7	731.2	804.2	880.5
110	12.9	29.5	49.9	74.0	101.9	133.5	168.9	208.0	250.9	297.5	347.9	402.0	459.9	521.5	586.9	656.1	728.9	805.6	885.9	970.1
120	14.0	32.2	54.4	80.8	111.2	145.8	184.4	227.1	274.0	324.9	379.9	439.1	502.3	569.6	641.1	716.6	796.2	879.9	967.7	-
130	15.2	34.9	59.0	87.6	120.6	158.0	199.9	246.3	297.1	352.3	412.0	476.1	544.7	617.7	695.2	777.1	863.5	954.3	-	-
140	16.4	37.6	63.6	94.4	129.9	170.3	215.4	265.4	320.2	379.7	444.0	513.2	587.1	665.8	749.3	837.6	930.7	-	-	-
150	17.6	40.3	68.1	101.1	139.3	182.6	231.0	284.5	343.2	407.1	476.1	550.2	629.5	713.9	803.4	898.1	998.0	-	-	-
160	18.7	43.0	72.7	107.9	148.6	194.8	246.5	303.7	366.3	434.5	508.1	587.2	671.9	762.0	857.6	958.7	-	-	-	-
170	19.9	45.7	77.3	114.7	158.0	207.1	262.0	322.8	389.4	461.9	540.2	624.3	714.3	810.1	911.7	-	-	-	-	-
180	21.1	48.4	81.8	121.5	167.3	219.3	277.5	341.9	412.5	489.3	572.2	661.3	756.6	858.1	965.8	-	-	-	-	-
190	22.3	51.1	86.4	128.3	176.7	231.6	293.1	361.1	435.6	516.6	604.2	698.4	799.0	906.2	-	-	-	-	-	-
200	23.4	53.8	91.0	135.0	186.0	243.9	308.6	380.2	458.7	544.0	636.3	735.4	841.4	954.3	-	-	-	-	-	-

Lesson learned

- For the same tumor effect we needed about 51 Gy at 1Gy h^{-1}
- For the same normal tissue effect we could only use about 42 Gy
- Hence, for the same effect on the tumor we have to put the normal tissues at increased risk of late damage when going from 0.5 Gy h^{-1} to 1 Gy h^{-1}

3: 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 $0.693/(60 \times 24)\ h^{-1} = 0.00048\ h^{-1}$
- Hence, for a total dose of 145 Gy, the initial dose rate R_0 is $145 \times 0.00048 = 0.0696$ 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

Solution using tables

- From Table 3, the BED for a 145 Gy ^{125}I implant, with α/β = 1.5 Gy, is 159.6
- Now reading down the ^{103}Pd column for α/β = 1.5 Gy, one sees that 159.6 is about half way between 155.2 (at 120 Gy) and 163.1 (at 125 Gy), so the total dose of ^{103}Pd required is about 122.5 Gy

Table 3: BEDs for permanent implants to complete decay with repair half-time = 1.5 h.

Total	Pd-103					I-125				
Dose (Gy)	α/β = 1.5Gy	α/β = 2.0Gy	α/β = 2.5Gy	α/β = 3.0Gy	α/β = 10Gy	α/β = 1.5Gy	α/β = 2.0Gy	α/β = 2.5Gy	α/β = 3.0Gy	α/β = 10Gy
10	10.2	10.2	10.1	10.1	10.0	10.1	10.1	10.0	10.0	10.0
15	15.5	15.4	15.3	15.3	15.1	15.2	15.1	15.1	15.1	15.0
20	21.0	20.7	20.6	20.5	20.1	20.3	20.2	20.2	20.1	20.0
25	26.5	26.1	25.9	25.8	25.2	25.4	25.3	25.3	25.2	25.1
30	32.2	31.6	31.3	31.1	30.3	30.6	30.5	30.4	30.3	30.1
35	38.0	37.2	36.8	36.5	35.4	35.8	35.6	35.5	35.4	35.1
40	43.9	42.9	42.3	42.0	40.6	41.1	40.8	40.7	40.6	40.2
45	49.9	48.7	48.0	47.5	45.7	46.4	46.1	45.8	45.7	45.2
50	56.1	54.6	53.7	53.1	50.9	51.7	51.3	51.0	50.9	50.3
55	62.4	60.5	59.4	58.7	56.1	57.1	56.6	56.3	56.0	55.3
60	68.8	66.6	65.3	64.4	61.3	62.5	61.9	61.5	61.2	60.4
65	75.3	72.7	71.2	70.2	66.5	67.9	67.2	66.8	66.5	65.4
70	82.0	79.0	77.2	76.0	71.8	73.4	72.5	72.0	71.7	70.5
75	88.7	85.3	83.2	81.9	77.1	78.9	77.9	77.3	76.9	75.6
80	95.6	91.7	89.4	87.8	82.3	84.4	83.3	82.7	82.2	80.7
85	102.6	98.2	95.6	93.8	87.6	90.0	88.8	88.0	87.5	85.8
90	109.8	104.8	101.9	99.9	93.0	95.6	94.2	93.4	92.8	90.8
95	117.0	111.5	108.2	106.0	98.3	101.2	99.7	98.7	98.1	95.9
100	124.4	118.3	114.6	112.2	103.7	106.9	105.2	104.2	103.5	101.0
105	131.9	125.2	121.1	118.5	109.0	112.6	110.7	109.6	108.8	106.1
110	139.5	132.2	127.7	124.8	114.4	118.4	116.3	115.0	114.2	111.3
115	147.3	139.2	134.4	131.1	119.8	124.2	121.9	120.5	119.6	116.4
120	155.2	146.4	141.1	137.6	125.3	130.0	127.5	126.0	125.0	121.5
125	163.1	153.6	147.9	144.1	130.7	135.8	133.1	131.5	130.4	126.6
130	171.3	160.9	154.8	150.6	136.2	141.7	138.8	137.0	135.9	131.8
135	179.5	168.4	161.7	157.2	141.7	147.6	144.5	142.6	141.3	136.9
140	187.8	175.9	168.7	163.9	147.2	153.6	150.2	148.1	146.8	142.0
145	196.3	183.5	175.8	170.7	152.7	159.6	155.9	153.7	152.3	147.2
150	204.9	191.2	183.0	177.5	158.2	165.6	161.7	159.3	157.8	152.3
155	213.6	199.0	190.2	184.3	163.8	171.6	167.5	165.0	163.3	157.5
160	222.5	206.9	197.5	191.2	169.4	177.7	173.3	170.6	168.9	162.7
165	231.5	214.8	204.9	198.2	175.0	183.8	179.1	176.3	174.4	167.8
170	240.5	222.9	212.3	205.3	180.6	190.0	185.0	182.0	180.0	173.0
175	249.8	231.1	219.9	212.4	186.2	196.2	190.9	187.7	185.6	178.2
180	259.1	239.3	227.5	219.5	191.9	202.4	196.8	193.5	191.2	183.4
185	268.5	247.7	235.1	226.8	197.5	208.7	202.8	199.2	196.8	188.6
190	278.1	256.1	242.9	234.1	203.2	215.0	208.7	205.0	202.5	193.7
195	287.8	264.6	250.7	241.4	208.9	221.3	214.7	210.8	208.2	198.9
200	297.6	273.2	258.6	248.8	214.6	227.7	220.8	216.6	213.8	204.2

Table 3: BEDs for permanent implants to complete decay with repair half-time = 1.5 h.

Total	Pd-103					I-125				
Dose (Gy)	α/β = 1.5Gy	α/β = 2.0Gy	α/β = 2.5Gy	α/β = 3.0Gy	α/β = 10Gy	α/β = 1.5Gy	α/β = 2.0Gy	α/β = 2.5Gy	α/β = 3.0Gy	α/β = 10Gy
10	10.2	10.2	10.1	10.1	10.0	10.1	10.1	10.0	10.0	10.0
15	15.5	15.4	15.3	15.3	15.1	15.2	15.1	15.1	15.1	15.0
20	21.0	20.7	20.6	20.5	20.1	20.3	20.2	20.2	20.1	20.0
25	26.5	26.1	25.9	25.8	25.2	25.4	25.3	25.3	25.2	25.1
30	32.2	31.6	31.3	31.1	30.3	30.6	30.5	30.4	30.3	30.1
35	38.0	37.2	36.8	36.5	35.4	35.8	35.6	35.5	35.4	35.1
40	43.9	42.9	42.3	42.0	40.6	41.1	40.8	40.7	40.6	40.2
45	49.9	48.7	48.0	47.5	45.7	46.4	46.1	45.8	45.7	45.2
50	56.1	54.6	53.7	53.1	50.9	51.7	51.3	51.0	50.9	50.3
55	62.4	60.5	59.4	58.7	56.1	57.1	56.6	56.3	56.0	55.3
60	68.8	66.6	65.3	64.4	61.3	62.5	61.9	61.5	61.2	60.4
65	75.3	72.7	71.2	70.2	66.5	67.9	67.2	66.8	66.5	65.4
70	82.0	79.0	77.2	76.0	71.8	73.4	72.5	72.0	71.7	70.5
75	88.7	85.3	83.2	81.9	77.1	78.9	77.9	77.3	76.9	75.6
80	95.6	91.7	89.4	87.8	82.3	84.4	83.3	82.7	82.2	80.7
85	102.6	98.2	95.6	93.8	87.6	90.0	88.8	88.0	87.5	85.8
90	109.8	104.8	101.9	99.9	93.0	95.6	94.2	93.4	92.8	90.8
95	117.0	111.5	108.2	106.0	98.3	101.2	99.7	98.7	98.1	95.9
100	124.4	118.3	114.6	112.2	103.7	106.9	105.2	104.2	103.5	101.0
105	131.9	125.2	121.1	118.5	109.0	112.6	110.7	109.6	108.8	106.1
110	139.5	132.2	127.7	124.8	114.4	118.4	116.3	115.0	114.2	111.3
115	147.3	139.2	134.4	131.1	119.8	124.2	121.9	120.5	119.6	116.4
120	155.2	146.4	141.1	137.6	125.3	130.0	127.5	126.0	125.0	121.5
125	163.1	153.6	147.9	144.1	130.7	135.8	133.1	131.5	130.4	126.6
130	171.3	160.9	154.8	150.6	136.2	141.7	138.8	137.0	135.9	131.8
135	179.5	168.4	161.7	157.2	141.7	147.6	144.5	142.6	141.3	136.9
140	187.8	175.9	168.7	163.9	147.2	153.6	150.2	148.1	146.8	142.0
145	196.3	183.5	175.8	170.7	152.7	159.6	155.9	153.7	152.3	147.2
150	204.9	191.2	183.0	177.5	158.2	165.6	161.7	159.3	157.8	152.3
155	213.6	199.0	190.2	184.3	163.8	171.6	167.5	165.0	163.3	157.5
160	222.5	206.9	197.5	191.2	169.4	177.7	173.3	170.6	168.9	162.7
165	231.5	214.8	204.9	198.2	175.0	183.8	179.1	176.3	174.4	167.8
170	240.5	222.9	212.3	205.3	180.6	190.0	185.0	182.0	180.0	173.0
175	249.8	231.1	219.9	212.4	186.2	196.2	190.9	187.7	185.6	178.2
180	259.1	239.3	227.5	219.5	191.9	202.4	196.8	193.5	191.2	183.4
185	268.5	247.7	235.1	226.8	197.5	208.7	202.8	199.2	196.8	188.6
190	278.1	256.1	242.9	234.1	203.2	215.0	208.7	205.0	202.5	193.7
195	287.8	264.6	250.7	241.4	208.9	221.3	214.7	210.8	208.2	198.9
200	297.6	273.2	258.6	248.8	214.6	227.7	220.8	216.6	213.8	204.2

3 (cont'd.): permanent implant with repopulation

What is the effective BED for a 145 Gy ^{125}I permanent implant for a moderately fast growing prostate cancer for which the repopulation rate is assumed to be k = 0.2 BED units/day and α/β = 1.5 Gy?

Solution by equation

- The solution to this problem is extremely complicated and involves solving complex exponential equations where the quantity that needs to be determined is in the exponent
- *It took me several hours to solve this problem using the equation!*
- Fortunately we have a table we can use

Table 4. BED_{eff} values for I-125 permanent implants for various values of the repopulation parameter k (BED units/day) and α/β = 1.5 Gy or 10 Gy.

Total dose (D_∞ Gy)	k = 0.2		k = 0.4		k = 0.6		k = 0.8		k = 1.0	
	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy
10										
15										
20	0.2	0.2								
25	1.5	1.3								
30	3.5	3.2								
35	6.1	5.6	0.0	0.0						
40	9.0	8.3	0.6	0.4						
45	12.3	11.3	1.8	1.4						
50	15.8	14.5	3.5	2.7						
55	19.5	17.9	5.5	4.5	0.3	0.1				
60	23.4	21.4	7.9	6.5	1.1	0.6				
65	27.4	25.1	10.6	8.8	2.4	1.5				
70	31.6	28.9	13.5	11.3	4.0	2.7	0.0	0.0		
75	35.9	32.8	16.6	14.0	5.9	4.2	0.8	0.3		
80	40.3	36.7	19.9	16.8	8.1	5.9	1.8	0.9		
85	44.8	40.8	23.3	19.8	10.5	7.9	3.2	1.8		
90	49.4	44.9	26.9	22.9	13.1	10.0	4.8	2.9	0.4	0.1
95	54.1	49.0	30.7	26.1	15.9	12.2	6.7	4.2	1.4	0.5
100	58.9	53.2	34.6	29.4	18.9	14.7	8.8	5.7	2.6	1.2
105	63.8	57.5	38.6	32.8	22.1	17.2	11.1	7.5	4.1	2.0
110	68.7	61.8	42.7	36.3	25.4	19.9	13.6	9.3	5.8	3.1
115	73.7	66.1	47.0	39.9	28.9	22.7	16.3	11.4	7.7	4.3
120	78.8	70.5	51.3	43.5	32.5	25.6	19.1	13.5	9.8	5.8
125	83.9	74.9	55.7	47.3	36.2	28.6	22.2	15.8	12.1	7.4
130	89.1	79.4	60.2	51.0	40.0	31.7	25.3	18.2	14.6	9.1
135	94.4	83.9	64.9	54.9	44.0	34.9	28.6	20.7	17.2	10.9
140	99.7	88.4	69.5	58.7	48.0	38.1	32.0	23.4	20.0	12.9
145	105.1	92.9	74.3	62.7	52.2	41.4	35.6	26.1	22.9	15.0
150	110.5	97.5	79.1	66.6	56.5	44.8	39.2	28.9	26.0	17.2
155	116.0	102.1	84.1	70.7	60.8	48.3	43.0	31.7	29.2	19.5
160	121.5	106.7	89.0	74.7	65.2	51.8	46.9	34.7	32.5	21.9
165	127.1	111.3	94.1	78.8	69.7	55.3	50.9	37.7	36.0	24.4
170	132.8	116.0	99.2	82.9	74.4	59.0	55.0	40.8	39.6	27.0
175	138.5	120.6	104.4	87.1	79.0	62.6	59.1	44.0	43.2	29.7
180	144.2	125.3	109.7	91.3	83.8	66.3	63.4	47.2	47.0	32.4
185	150.0	130.0	115.0	95.6	88.6	70.1	67.8	50.5	50.9	35.2
190	155.8	134.8	120.3	99.8	93.5	73.9	72.2	53.8	54.9	38.1
195	161.7	139.5	125.8	104.1	98.5	77.8	76.7	57.2	58.9	41.0
200	167.6	144.3	131.2	108.5	103.6	81.6	81.3	60.7	63.1	44.0

Permanent implant solution

From Table 4 reading from the k = 0.2, α/β = 1.5 Gy column,

BED_{eff} = 105.1

Table 4. BED_{eff} values for I-125 permanent implants for various values of the repopulation parameter k (BED units/day) and α/β = 1.5 Gy or 10 Gy.

Total dose (D_w Gy)	k = 0.2		k = 0.4		k = 0.6		k = 0.8		k = 1.0	
	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy
10										
15										
20	0.2	0.2								
25	1.5	1.3								
30	3.5	3.2								
35	6.1	5.6	0.0	0.0						
40	9.0	8.3	0.6	0.4						
45	12.3	11.3	1.8	1.4						
50	15.8	14.5	3.5	2.7						
55	19.5	17.9	5.5	4.5	0.3	0.1				
60	23.4	21.4	7.9	6.5	1.1	0.6				
65	27.4	25.1	10.6	8.8	2.4	1.5				
70	31.6	28.9	13.5	11.3	4.0	2.7	0.0	0.0		
75	35.9	32.8	16.6	14.0	5.9	4.2	0.8	0.3		
80	40.3	36.7	19.9	16.8	8.1	5.9	1.8	0.9		
85	44.8	40.8	23.3	19.8	10.5	7.9	3.2	1.8		
90	49.4	44.9	26.9	22.9	13.1	10.0	4.8	2.9	0.4	0.1
95	54.1	49.0	30.7	26.1	15.9	12.2	6.7	4.2	1.4	0.5
100	58.9	53.2	34.6	29.4	18.9	14.7	8.8	5.7	2.6	1.2
105	63.8	57.5	38.6	32.8	22.1	17.2	11.1	7.5	4.1	2.0
110	68.7	61.8	42.7	36.3	25.4	19.9	13.6	9.3	5.8	3.1
115	73.7	66.1	47.0	39.9	28.9	22.7	16.3	11.4	7.7	4.3
120	78.8	70.5	51.3	43.5	32.5	25.6	19.1	13.5	9.8	5.8
125	83.9	74.9	55.7	47.3	36.2	28.6	22.2	15.8	12.1	7.4
130	89.1	79.4	60.2	51.0	40.0	31.7	25.3	18.2	14.6	9.1
135	94.4	83.9	64.9	54.9	44.0	34.9	28.6	20.7	17.2	10.9
140	99.7	88.4	69.5	58.7	48.0	38.1	32.0	23.4	20.0	12.9
145	105.1	92.9	74.3	62.7	52.2	41.4	35.6	26.1	22.9	15.0
150	110.5	97.5	79.1	66.6	56.5	44.8	39.2	28.9	26.0	17.2
155	116.0	102.1	84.1	70.7	60.8	48.3	43.0	31.7	29.2	19.5
160	121.5	106.7	89.0	74.7	65.2	51.8	46.9	34.7	32.5	21.9
165	127.1	111.3	94.1	78.8	69.7	55.3	50.9	37.7	36.0	24.4
170	132.8	116.0	99.2	82.9	74.4	59.0	55.0	40.8	39.6	27.0
175	138.5	120.6	104.4	87.1	79.0	62.6	59.1	44.0	43.2	29.7
180	144.2	125.3	109.7	91.3	83.8	66.3	63.4	47.2	47.0	32.4
185	150.0	130.0	115.0	95.6	88.6	70.1	67.8	50.5	50.9	35.2
190	155.8	134.8	120.3	99.8	93.5	73.9	72.2	53.8	54.9	38.1
195	161.7	139.5	125.8	104.1	98.5	77.8	76.7	57.2	58.9	41.0
200	167.6	144.3	131.2	108.5	103.6	81.6	81.3	60.7	63.1	44.0

3 (cont'd.): equivalent permanent implants with repopulation

For this same patient, what ^{103}Pd permanent implant dose to complete decay (D_{∞}) will be equivalent to this 145 Gy ^{125}I implant i.e. a BED of 105.1?

Again, we can use a table

Table 5. BED_{eff} values for Pd-103 permanent implants for various values of the repopulation parameter k (BED units/day) and α/β = 1.5 Gy or 10 Gy.

Total dose (D_w, Gy)	k = 0.2		k = 0.4		k = 0.6		k = 0.8		k = 1.0	
	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy
10										
15										
20	9.1	8.3	3.9	3.3	1.2	0.8	0.0	0.0		
25	13.6	12.3	7.3	6.2	3.5	2.6	1.2	0.7	0.1	0.0
30	18.4	16.5	11.2	9.5	6.5	5.1	3.3	2.2	1.3	0.6
35	23.4	20.9	15.5	13.1	10.0	7.9	6.1	4.3	3.3	2.0
40	28.6	25.4	20.1	17.0	13.9	11.1	9.4	6.9	5.9	3.8
45	34.1	30.0	25.0	21.0	18.3	14.5	13.1	9.7	9.1	6.1
50	39.7	34.6	30.1	25.1	22.9	18.1	17.2	12.8	12.6	8.7
55	45.6	39.3	35.4	29.4	27.7	21.9	21.6	16.1	16.6	11.6
60	51.5	44.1	41.0	33.7	32.9	25.9	26.3	19.6	20.8	14.6
65	57.7	49.0	46.7	38.2	38.2	29.9	31.2	23.3	25.4	17.9
70	63.9	53.8	52.6	42.7	43.8	34.1	36.4	27.1	30.2	21.3
75	70.4	58.8	58.7	47.3	49.5	38.3	41.9	31.0	35.3	24.9
80	76.9	63.7	65.0	51.9	55.5	42.6	47.5	35.0	40.6	28.6
85	83.7	68.7	71.4	56.6	61.6	47.1	53.3	39.1	46.1	32.4
90	90.5	73.8	78.0	61.4	67.9	51.5	59.3	43.3	51.9	36.3
95	97.5	78.9	84.7	66.2	74.3	56.1	65.5	47.6	57.8	40.4
100	104.6	84.0	91.6	71.0	80.9	60.7	71.9	52.0	63.9	44.5
105	111.9	89.1	98.6	75.9	87.7	65.3	78.4	56.4	70.2	48.6
110	119.3	94.3	105.7	80.9	94.7	70.0	85.1	60.9	76.7	52.9
115	126.8	99.5	113.1	85.9	101.8	74.8	92.0	65.4	83.4	57.2
120	134.5	104.7	120.5	90.9	109.0	79.6	99.0	70.0	90.2	61.6
125	142.2	109.9	128.1	95.9	116.4	84.5	106.2	74.6	97.2	66.0
130	150.2	115.2	135.8	101.0	123.9	89.3	113.5	79.3	104.3	70.6
135	158.2	120.5	143.7	106.1	131.6	94.3	121.0	84.1	111.6	75.1
140	166.4	125.8	151.7	111.3	139.4	99.2	128.7	88.9	119.1	79.7
145	174.7	131.2	159.8	116.4	147.4	104.2	136.5	93.7	126.7	84.4
150	183.1	136.5	168.1	121.6	155.5	109.3	144.4	98.6	134.5	89.1
155	191.7	141.9	176.5	126.9	163.7	114.4	152.5	103.5	142.4	93.8
160	200.3	147.4	185.0	132.1	172.1	119.5	160.7	108.4	150.4	98.6
165	209.2	152.8	193.6	137.4	180.6	124.6	169.0	113.4	158.6	103.5
170	218.1	158.3	202.4	142.8	189.2	129.8	177.5	118.5	167.0	108.4
175	227.2	163.8	211.3	148.1	198.0	135.0	186.2	123.5	175.5	113.3
180	236.3	169.3	220.4	153.5	206.9	140.2	194.9	128.6	184.1	118.2
185	245.7	174.8	229.6	158.9	215.9	145.5	203.9	133.8	192.9	123.2
190	255.1	180.4	238.9	164.3	225.1	150.8	212.9	138.9	201.8	128.3
195	264.7	185.9	248.3	169.7	234.4	156.1	222.1	144.1	210.9	133.3
200	274.4	191.5	257.9	175.2	243.9	161.5	231.4	149.3	220.1	138.4

Solution

From Table 5, looking down the k = 0.2, α/β = 1.5 Gy column, a BED_{eff} of 105.1 is reached at a dose to complete decay of just over 100 Gy

Table 5. BED_{eff} values for Pd-103 permanent implants for various values of the repopulation parameter k (BED units/day) and α/β = 1.5 Gy or 10 Gy.

Total dose (D_{tot} Gy)	k = 0.2		k = 0.4		k = 0.6		k = 0.8		k = 1.0	
	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy	α/β=1.5 Gy	α/β=10 Gy
10										
15										
20	9.1	8.3	3.9	3.3	1.2	0.8	0.0	0.0		
25	13.6	12.3	7.3	6.2	3.5	2.6	1.2	0.7	0.1	0.0
30	18.4	16.5	11.2	9.5	6.5	5.1	3.3	2.2	1.3	0.6
35	23.4	20.9	15.5	13.1	10.0	7.9	6.1	4.3	3.3	2.0
40	28.6	25.4	20.1	17.0	13.9	11.1	9.4	6.9	5.9	3.8
45	34.1	30.0	25.0	21.0	18.3	14.5	13.1	9.7	9.1	6.1
50	39.7	34.6	30.1	25.1	22.9	18.1	17.2	12.8	12.6	8.7
55	45.6	39.3	35.4	29.4	27.7	21.9	21.6	16.1	16.6	11.6
60	51.5	44.1	41.0	33.7	32.9	25.9	26.3	19.6	20.8	14.6
65	57.7	49.0	46.7	38.2	38.2	29.9	31.2	23.3	25.4	17.9
70	63.9	53.8	52.6	42.7	43.8	34.1	36.4	27.1	30.2	21.3
75	70.4	58.8	58.7	47.3	49.5	38.3	41.9	31.0	35.3	24.9
80	76.9	63.7	65.0	51.9	55.5	42.6	47.5	35.0	40.6	28.6
85	83.7	68.7	71.4	56.6	61.6	47.1	53.3	39.1	46.1	32.4
90	90.5	73.8	78.0	61.4	67.9	51.5	59.3	43.3	51.9	36.3
95	97.5	78.9	84.7	66.2	74.3	56.1	65.5	47.6	57.8	40.4
100	104.6	84.0	91.6	71.0	80.9	60.7	71.9	52.0	63.9	44.5
105	111.9	89.1	98.6	75.9	87.7	65.3	78.4	56.4	70.2	48.6
110	119.3	94.3	105.7	80.9	94.7	70.0	85.1	60.9	76.7	52.9
115	126.8	99.5	113.1	85.9	101.8	74.8	92.0	65.4	83.4	57.2
120	134.5	104.7	120.5	90.9	109.0	79.6	99.0	70.0	90.2	61.6
125	142.2	109.9	128.1	95.9	116.4	84.5	106.2	74.6	97.2	66.0
130	150.2	115.2	135.8	101.0	123.9	89.3	113.5	79.3	104.3	70.6
135	158.2	120.5	143.7	106.1	131.6	94.3	121.0	84.1	111.6	75.1
140	166.4	125.8	151.7	111.3	139.4	99.2	128.7	88.9	119.1	79.7
145	174.7	131.2	159.8	116.4	147.4	104.2	136.5	93.7	126.7	84.4
150	183.1	136.5	168.1	121.6	155.5	109.3	144.4	98.6	134.5	89.1
155	191.7	141.9	176.5	126.9	163.7	114.4	152.5	103.5	142.4	93.8
160	200.3	147.4	185.0	132.1	172.1	119.5	160.7	108.4	150.4	98.6
165	209.2	152.8	193.6	137.4	180.6	124.6	169.0	113.4	158.6	103.5
170	218.1	158.3	202.4	142.8	189.2	129.8	177.5	118.5	167.0	108.4
175	227.2	163.8	211.3	148.1	198.0	135.0	186.2	123.5	175.5	113.3
180	236.3	169.3	220.4	153.5	206.9	140.2	194.9	128.6	184.1	118.2
185	245.7	174.8	229.6	158.9	215.9	145.5	203.9	133.8	192.9	123.2
190	255.1	180.4	238.9	164.3	225.1	150.8	212.9	138.9	201.8	128.3
195	264.7	185.9	248.3	169.7	234.4	156.1	222.1	144.1	210.9	133.3
200	274.4	191.5	257.9	175.2	243.9	161.5	231.4	149.3	220.1	138.4

Lesson

- When there was no repopulation of the tumor cells, the equivalent dose of ^{103}Pd was 122.5 Gy
- With repopulation this reduced to 100 Gy, hence, even a modest repopulation rate (k = 0.2 BED units/day) significantly effects the equivalence of ^{125}I and ^{103}Pd doses

4. Conformal Therapies of Prostate Cancer

Radiation therapy for prostate cancer is unique in that a wide variety of treatment techniques, differing enormously in dose rate and fractionation, all appear to be about equally effective

Conformal Therapies of Prostate Cancer

This provides an opportunity for study using the linear quadratic model, especially since the α/β for prostate cancer might be much lower that for most other types of cancer.

Conformal Therapies of Prostate Cancer

In this study we investigate the effect of α/β(tumor) on a variety of conformal treatment modalities:

- *monotherapy with I-125 permanent implants*
- *monotherapy with Pd-103 permanent implants*
- *monotherapy with HDR temporary implants (in four fractions)*
- *conformal teletherapy at low dose/fraction (in 40 fractions)*
- *conformal teletherapy at high dose/fraction (in 10 fractions)*

Confounding Variables

We will study how this α/β(tumor) effect varies with:

- *geometrical sparing of normal tissues*
- *repair rates for normal tissue cells*

Comparison of treatment regimes

For ease of comparison, since most experience has been with I-125, we will compare each of the treatment regimes against 144-Gy permanent I-125 implants

L-Q model parameters used

- α/β for late reacting normal tissues = 3 Gy
- α/β for prostate cancer cells ranging from 1 – 10 Gy
- repair half-time for prostate cancer cells ($t_{1/2,tumor}$) = 1.5 h
- repair half-times for late-reacting normal tissue cells ($t_{1/2,late}$) of 1.5 h, 3 h, and 4.5 h

Therapeutic Advantage

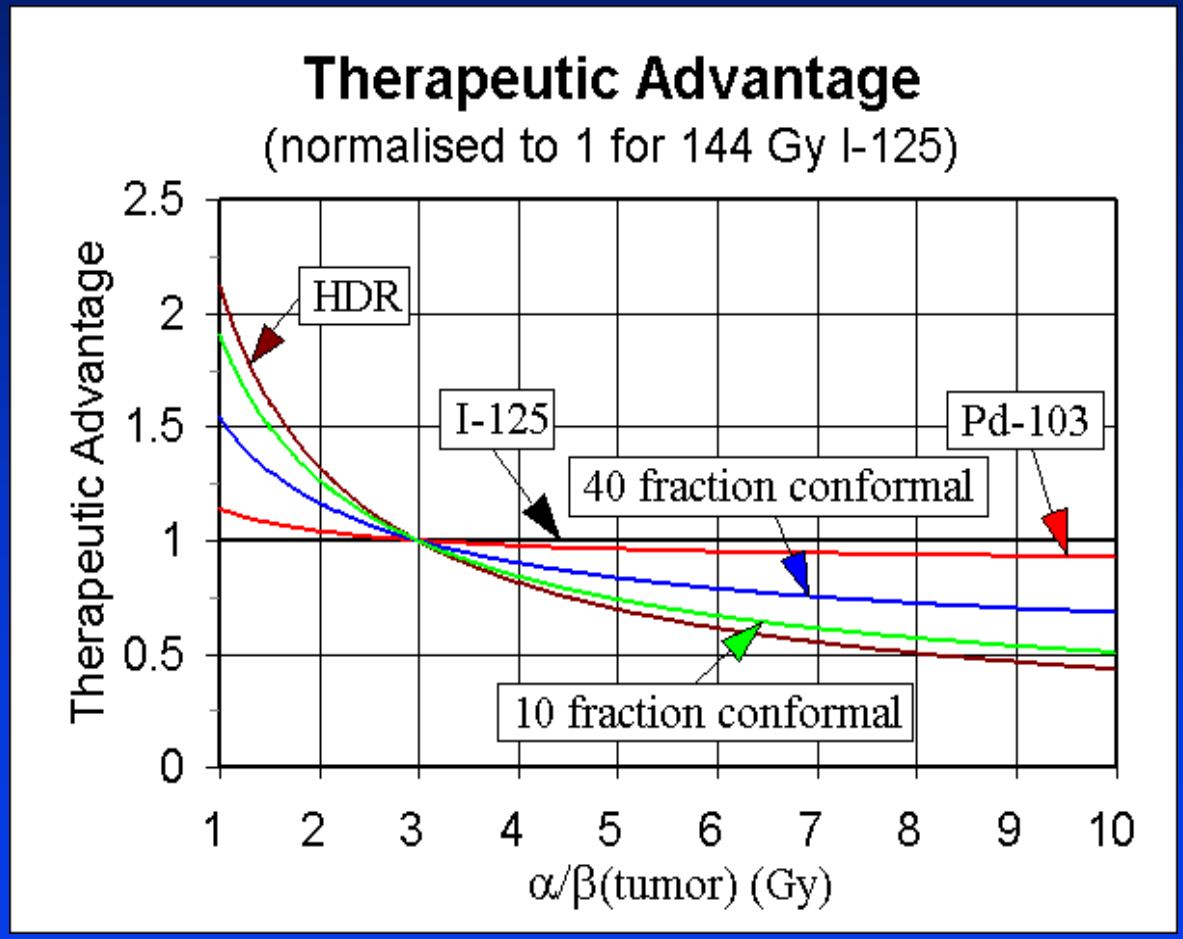
Define the Therapeutic Advantage (TA) of each treatment regime as:

$$TA = \frac{BED_{late,\ I-125}}{BED_{late,\ regime}}$$

for constant BED_{tumor}

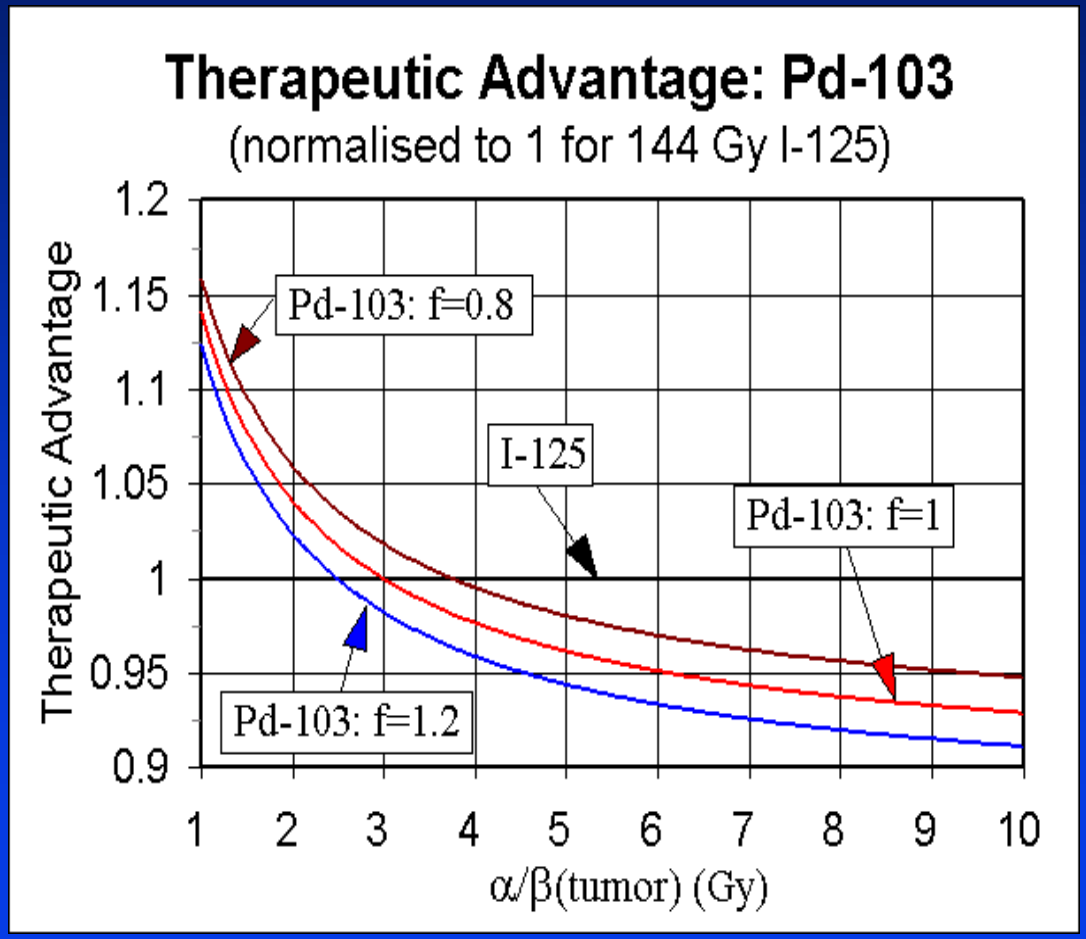
Therapeutic Advantage (compared to I-125) for the different treatment regimes as a function of α/β(tumor)

A low α/β(tumor) most favors those regimes which allow the least repair i.e. HDR and 10-fraction conformal



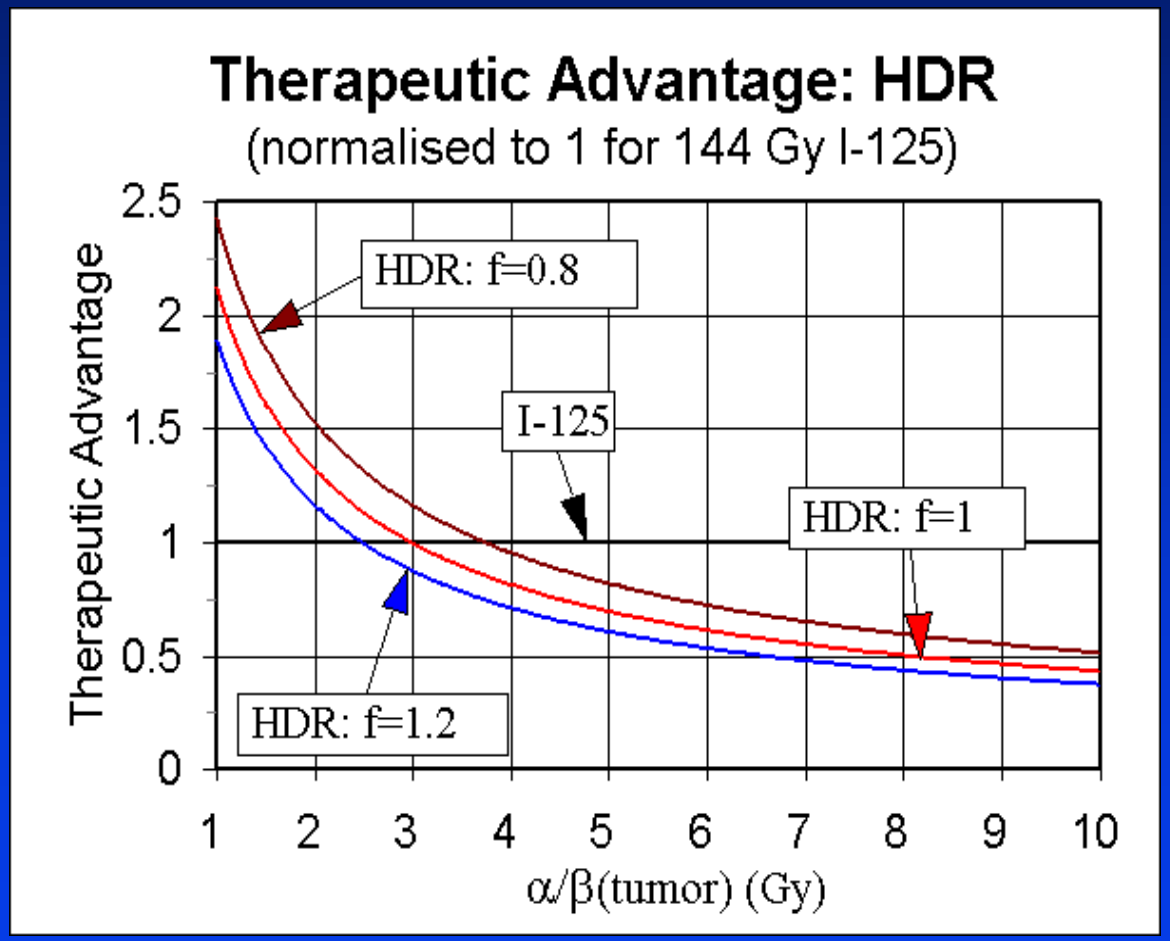
Confounding effect of geometrical sparing on the TA for Pd-103 permanent implants

A low *f* favors Pd-103 over I-125 and going from *f* = 1 to *f* = 0.8 raises the TA ~2% for α/β(tumor) = 1.5 Gy and moves the crossover point (TA = 1) from α/β(tumor) = 3 Gy up to 3/0.8 (=3.75 Gy)



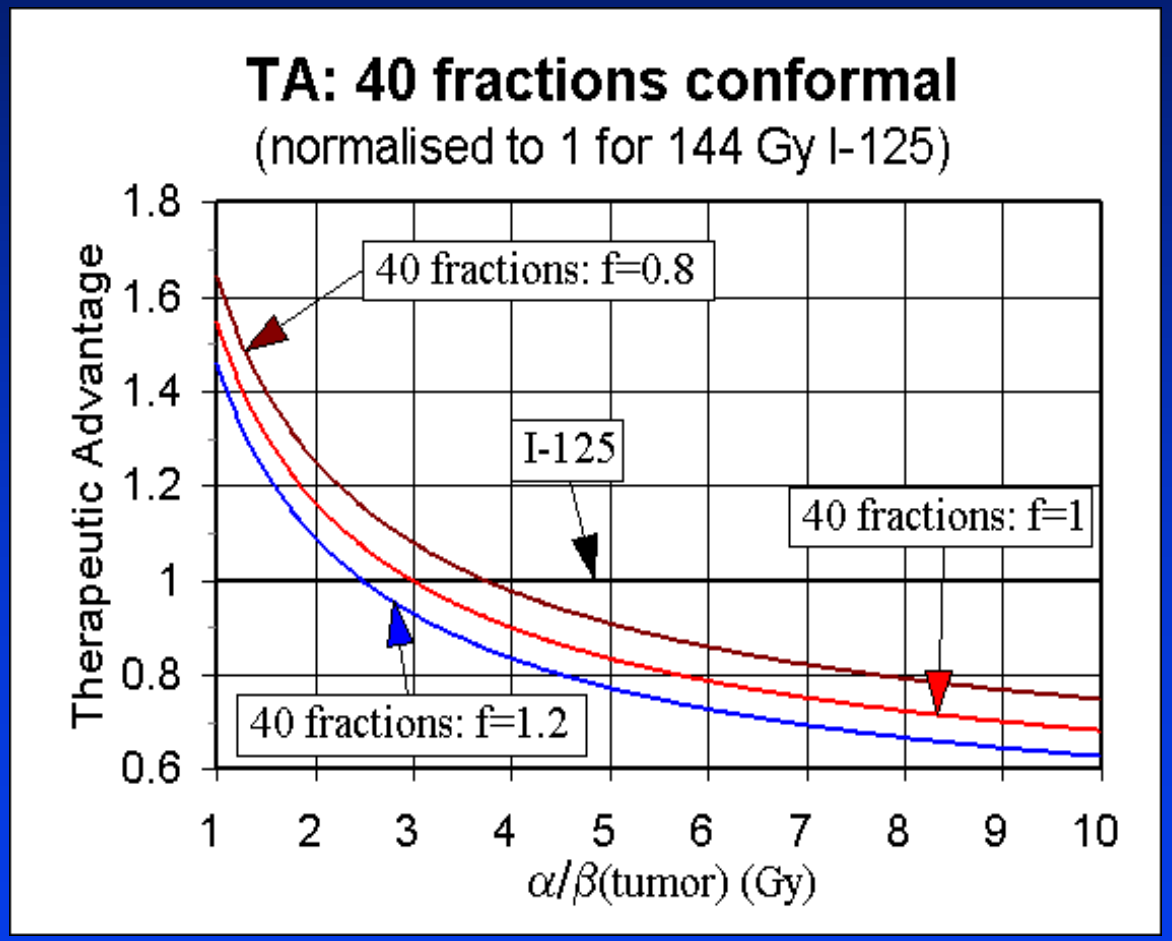
Confounding effect of geometrical sparing on the TA for four-fraction HDR implants

A low *f* favors HDR over I-125 and going from *f* = 1to *f* = 0.8 increases the TA ~15% (for α/β(tumor) = 1.5 Gy) and moves the crossover point up 3.75 Gy



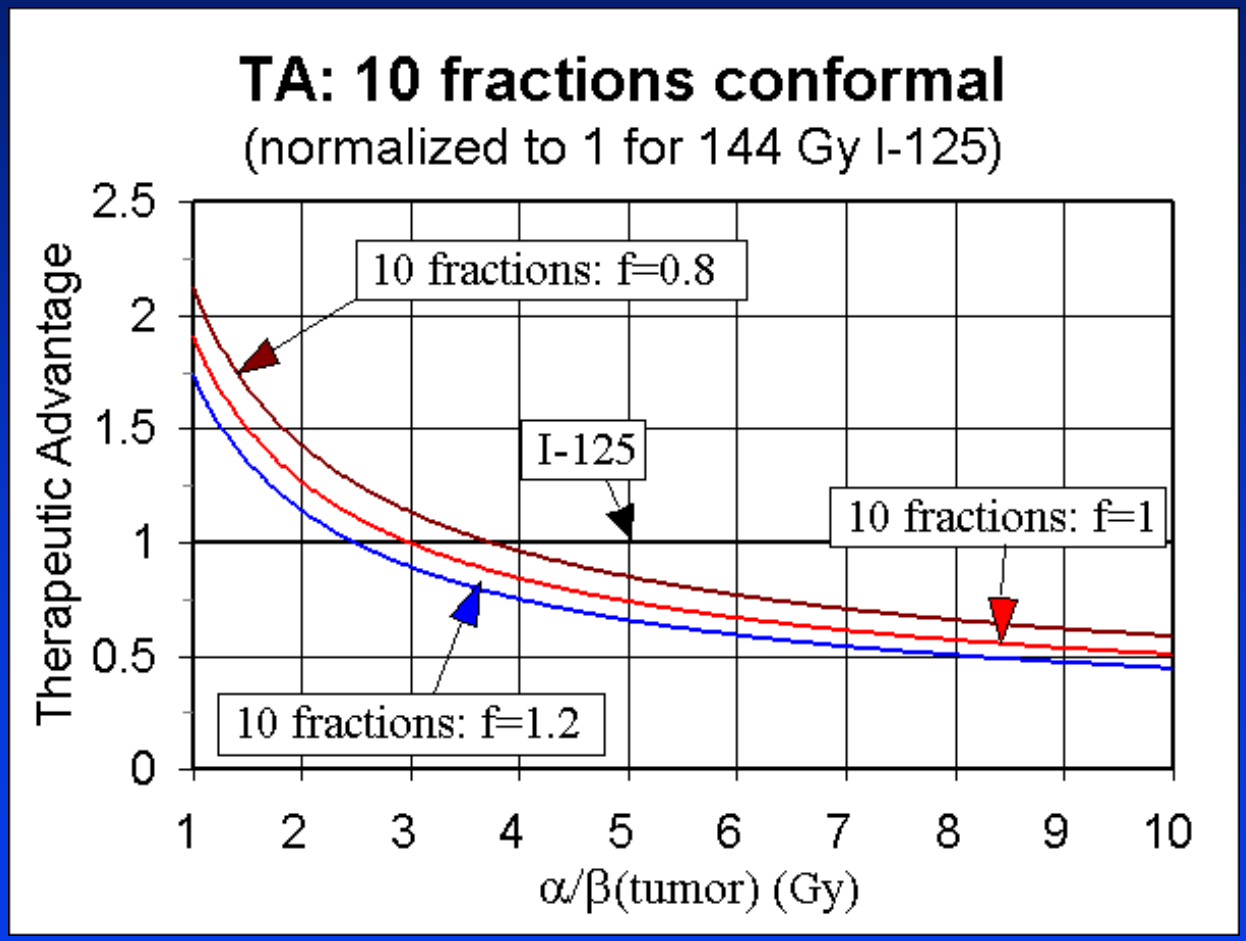
Confounding effect of geometrical sparing on the TA for 40-fraction conformal teletherapy

Again, the TA increases (~7% in this case) and the crossover point moves up to α/β(tumor) = 3.75 Gy



Confounding effect of geometrical sparing on the TA for 10-fraction conformal teletherapy

The TA increases ~12% and, again, the crossover point moves up to α/β(tumor) = 3.75 Gy

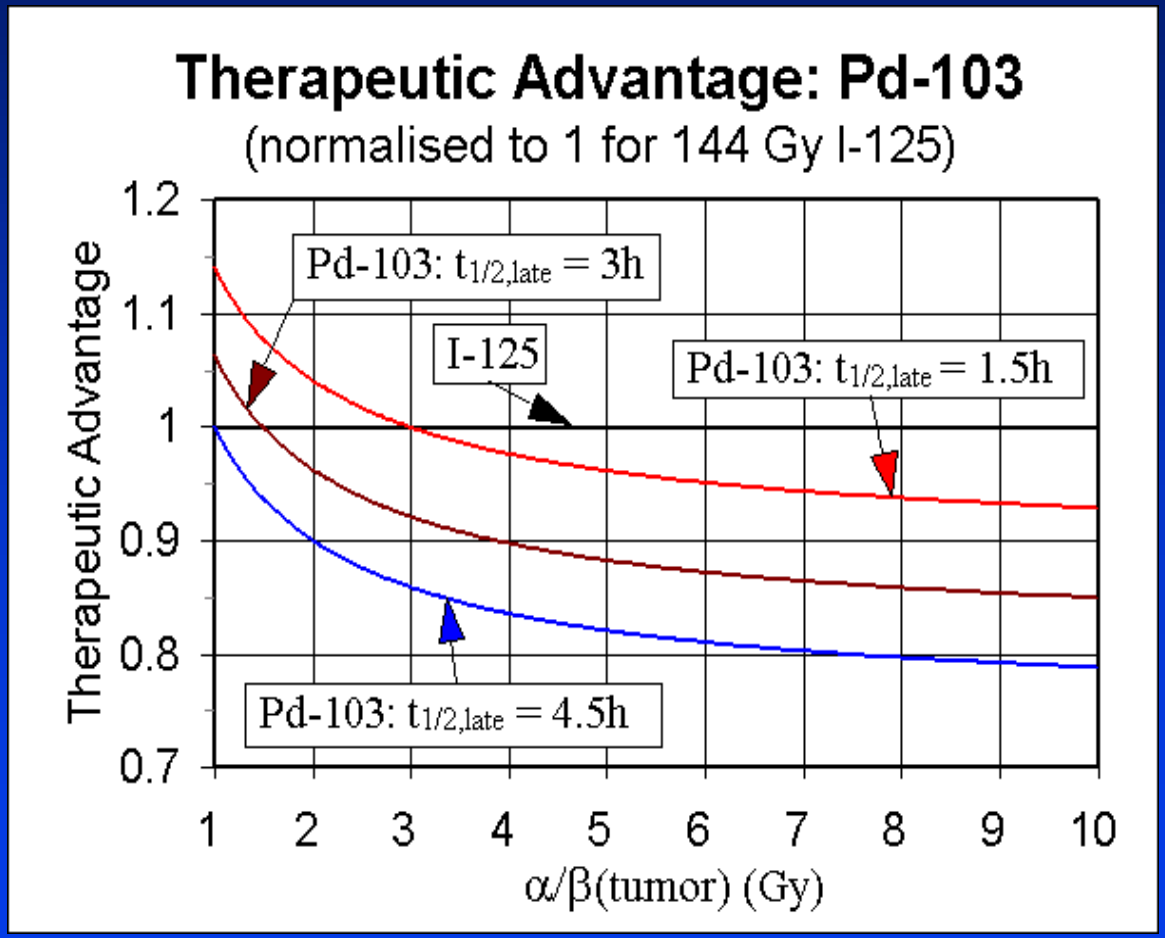


Effect of repair half-time for late-reacting normal tissue cells ($t_{1/2,late}$)

- Slow repair of late-reacting normal tissue cells should adversely affect those treatment regimes which allow insufficient time for repair
- HDR with only six hours between fractions should be affected most

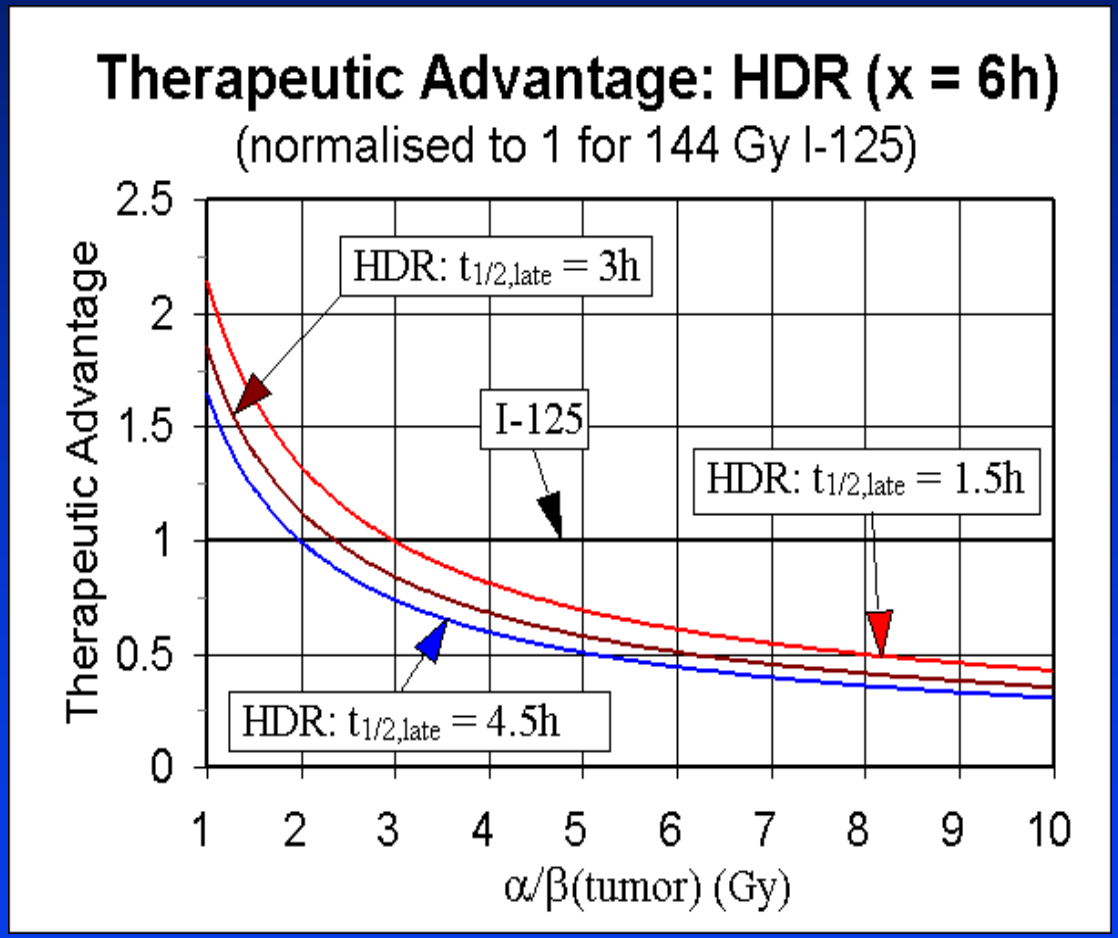
Effect of $t_{1/2,late}$ on the Therapeutic Advantage of Pd-103

Increasing $t_{1/2,late}$ from 1.5h up to 4.5h decreases the TA for Pd-103 about 13%



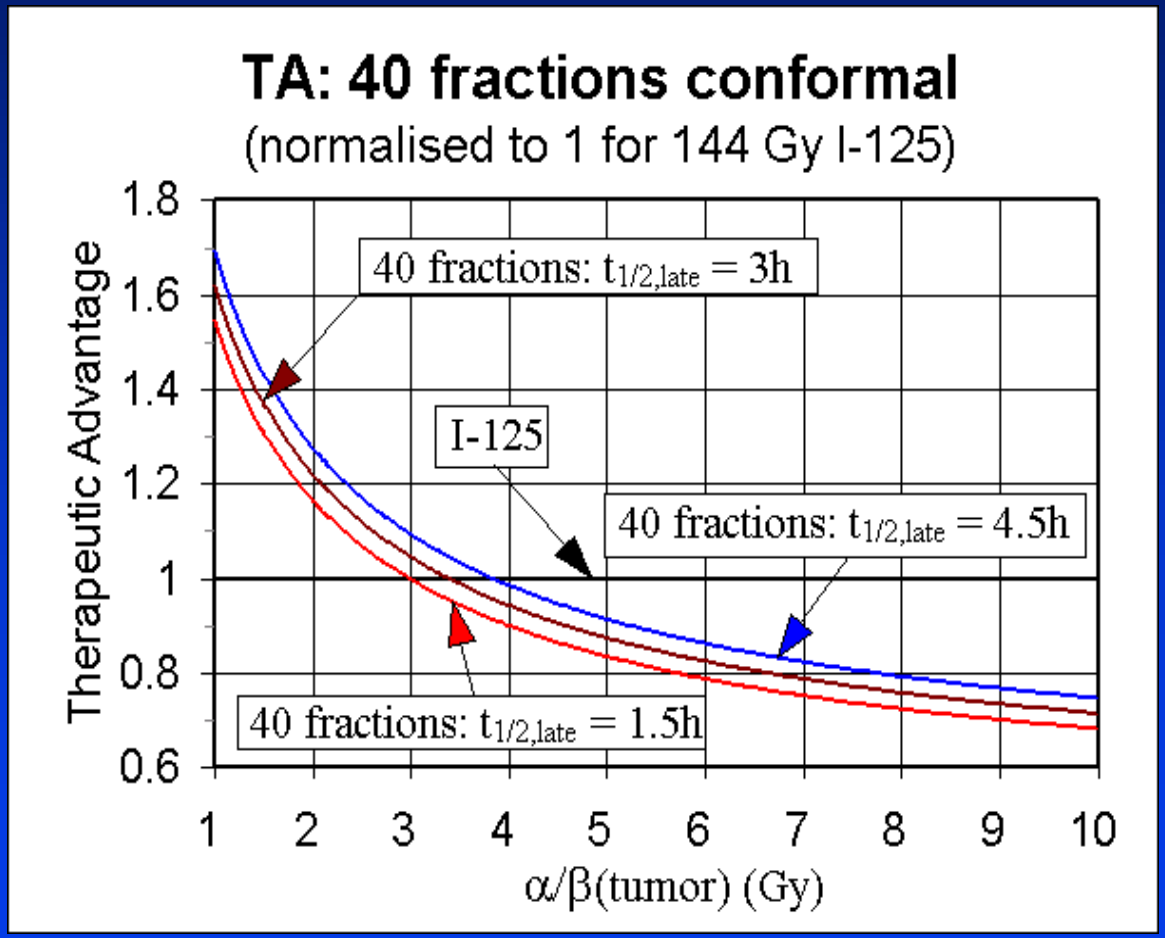
Effect of $t_{1/2,late}$ on the Therapeutic Advantage of HDR

With only 6h between HDR fractions, the TA for HDR may decrease as much as about 23% going from $t_{1/2,late}$ = 1.5h up to 4.5h, and the crossover point may fall from α/β(tumor) = 3 Gy down to 2 Gy.



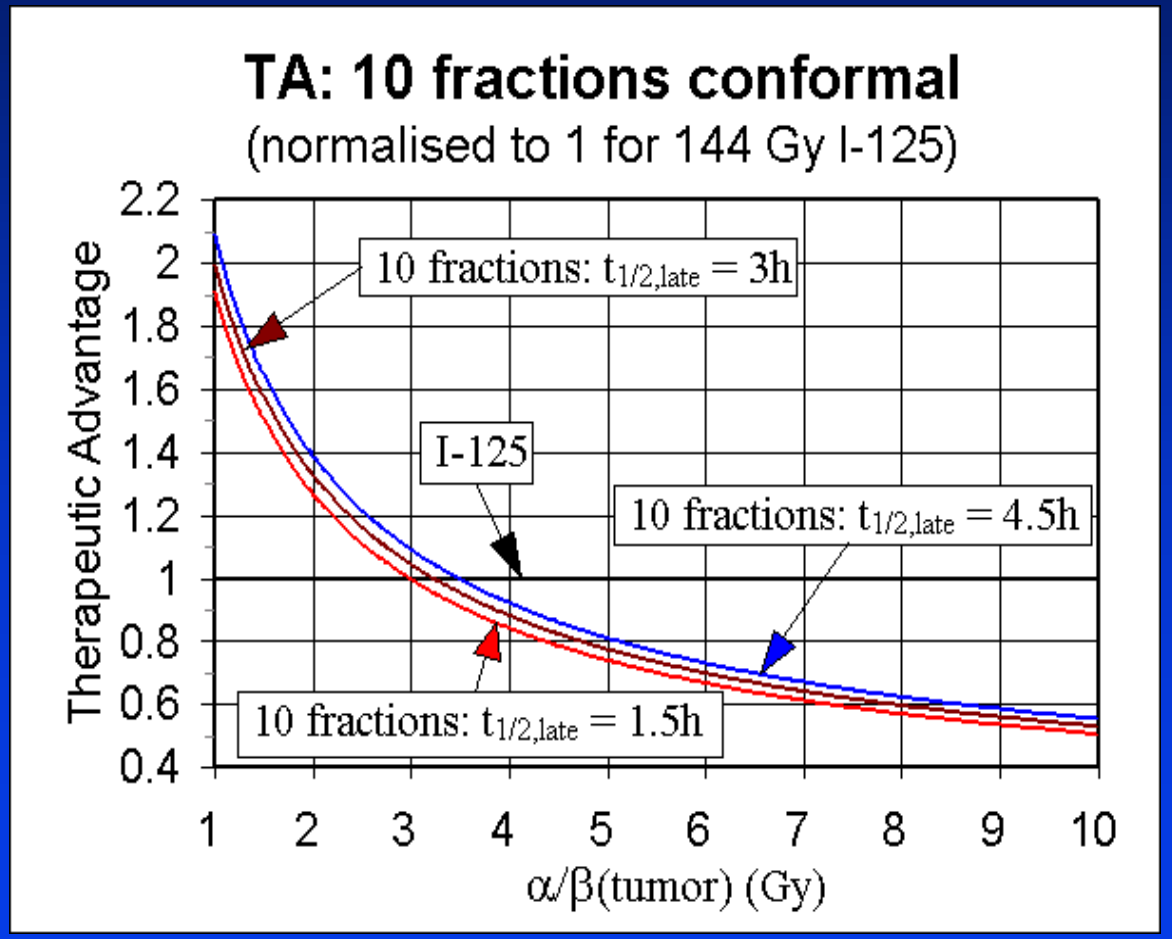
Effect of $t_{1/2,late}$ on the Therapeutic Advantage of 40 fraction conformal teletherapy

Due to the longer time between fractions, conformal therapy will always benefit from slow repair of the normal tissue cells.
In this case, the TA increases about 10% going from $t_{1/2,late}$ = 1.5h up to 4.5h, and the crossover point moves up to about 4 Gy.



Effect of $t_{1/2,late}$ on the Therapeutic Advantage of 10 fraction conformal teletherapy

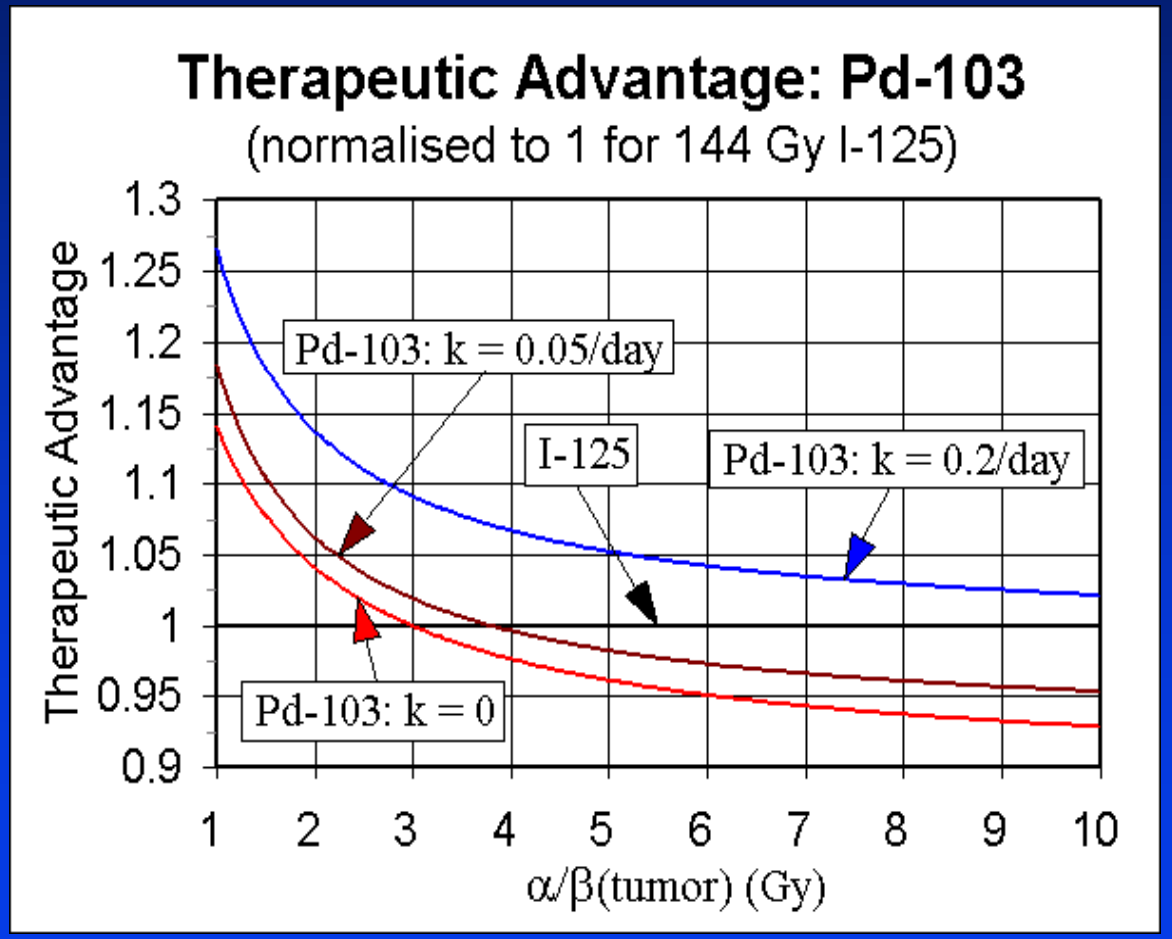
The 10-fraction conformal regime benefits about the same as for 40 fractions (~9%), although the crossover point moves up to only about 3.5 Gy.



Effect of repopulation rate on the Therapeutic Advantage of Pd-103

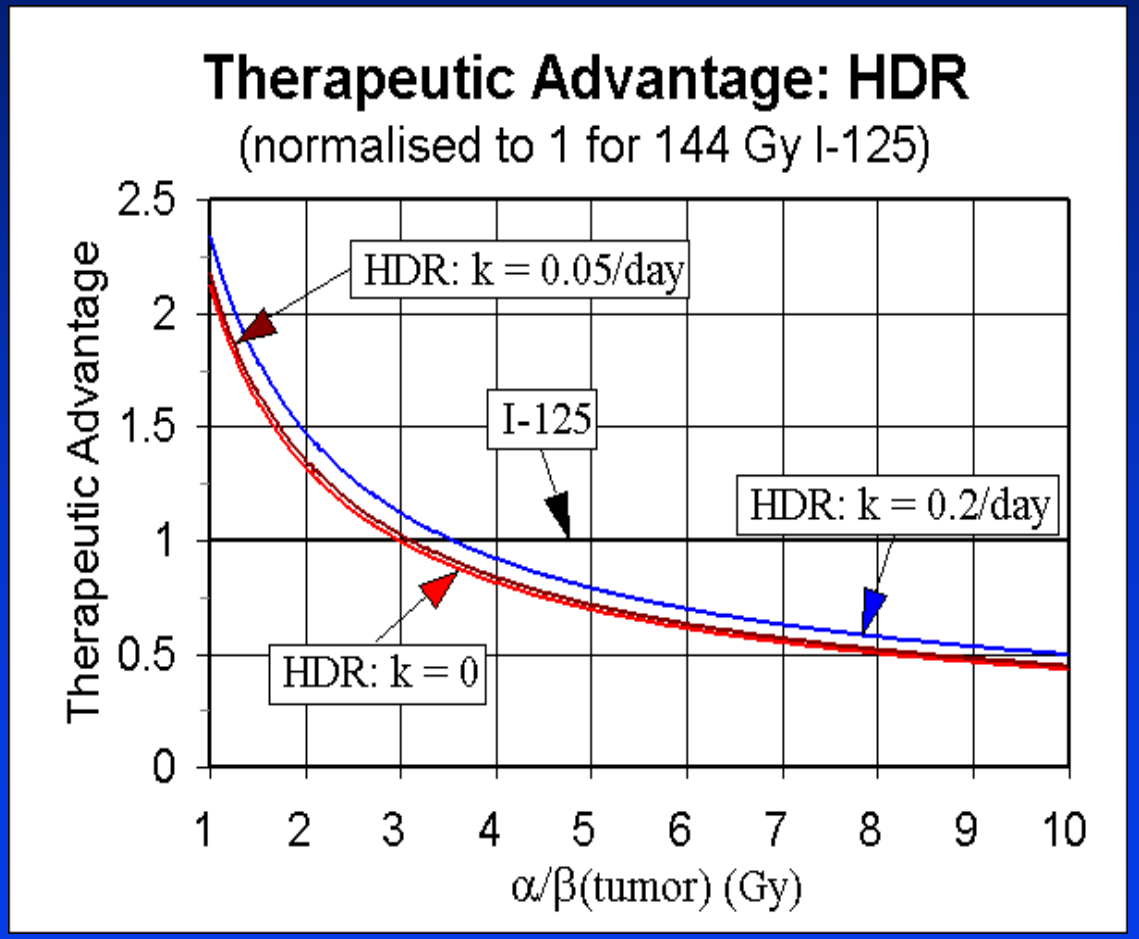
Due to more rapid delivery of dose, Pd-103 loses from repopulation less than does I-125.

Going from a BED loss of 0 up to 0.2/day increases the TA for Pd-103 about 9%, and increases the crossover point to beyond 10 Gy



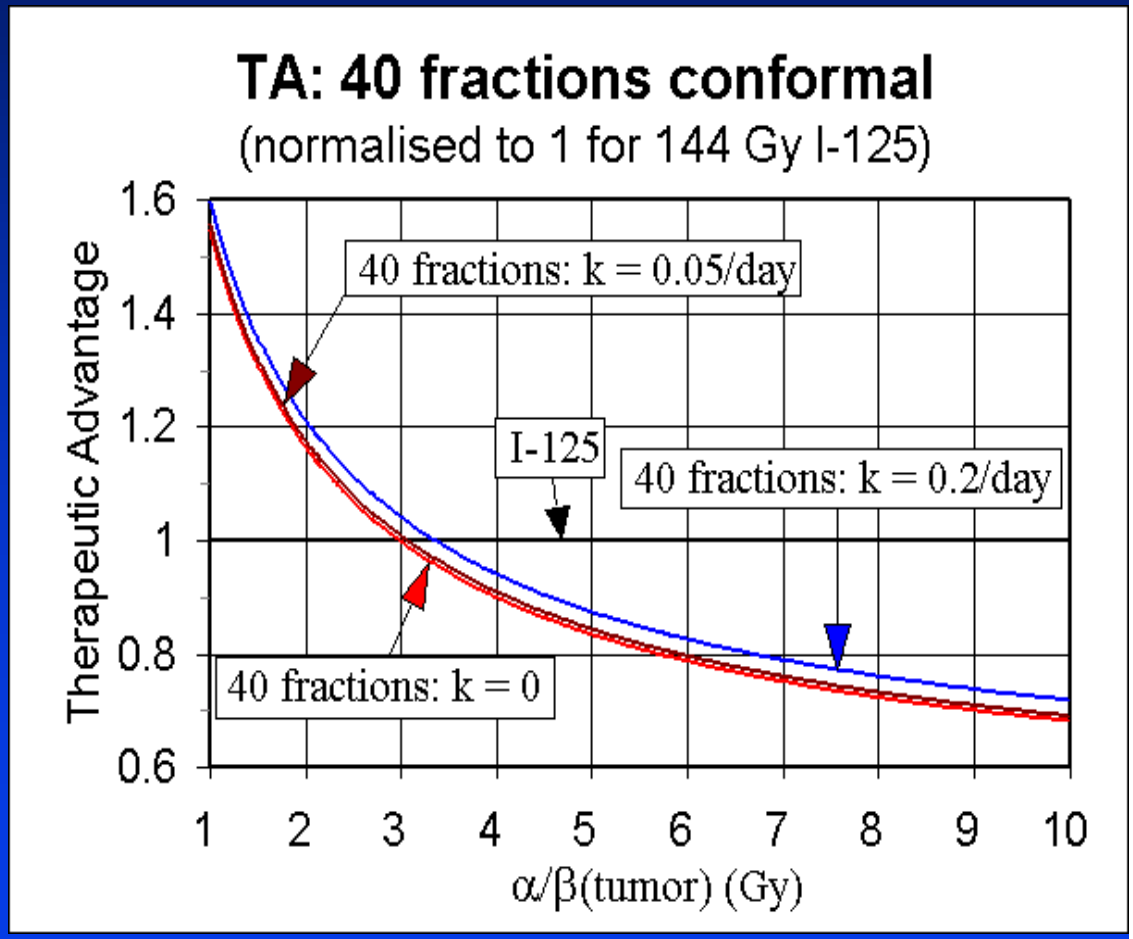
Effect of repopulation rate on the Therapeutic Advantage of HDR

Repopulation benefits the TA of HDR about 11% going from a BED loss of 0 up to 0.2/day and moves the crossover point up to about 3.5 Gy.



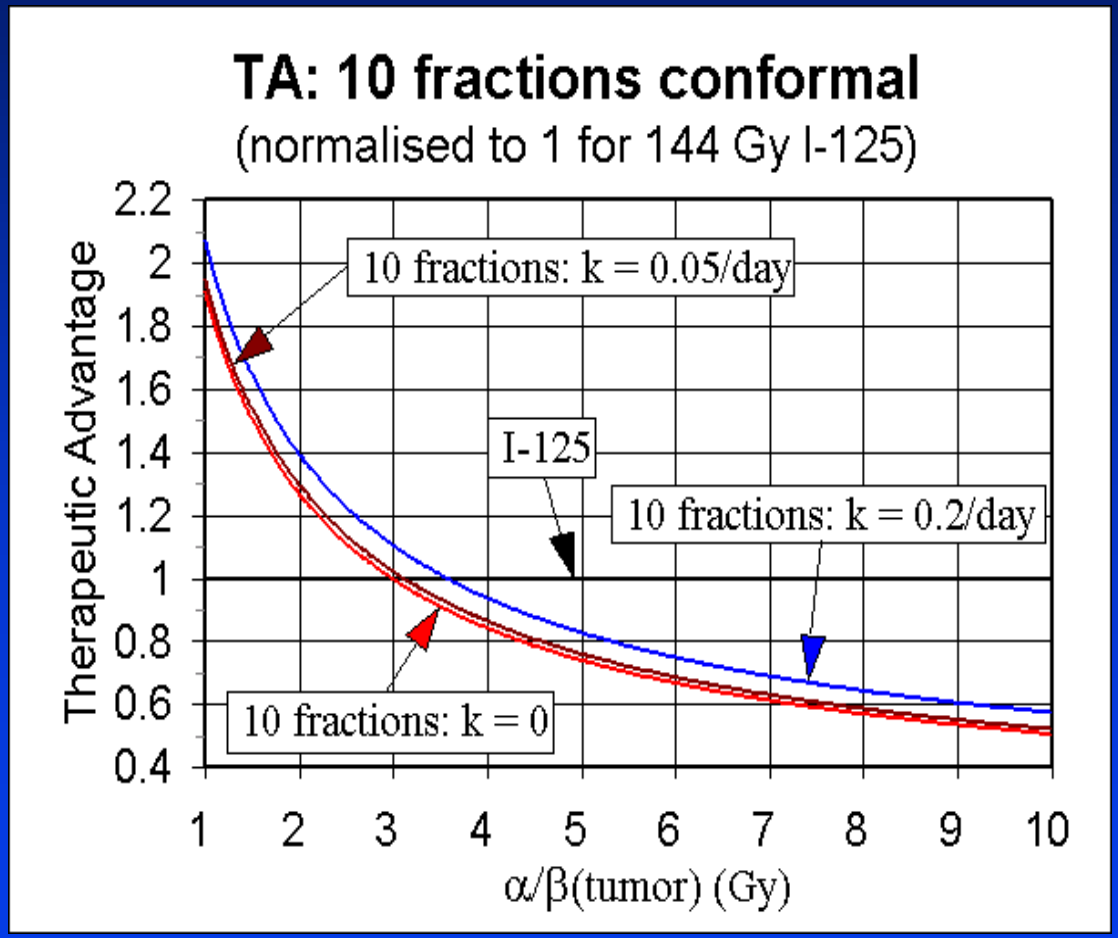
Effect of repopulation rate on the Therapeutic Advantage of 40-fraction conformal therapy

Repopulation benefits the TA of 40-fraction conformal therapy about 4% going from a BED loss of 0 up to 0.2/day and moves the crossover point up to about 3.4 Gy.



Effect of repopulation rate on the Therapeutic Advantage of 10-fraction conformal therapy

Repopulation benefits the TA of 10-fraction conformal therapy about 9% going from a BED loss of 0 up to 0.2/day and moves the crossover point up to about 3.6 Gy.



Conclusions: consequences of low prostate cancer α/β

- Low α/β means relatively more repair for cancer cells
  - *need higher doses*
  - *low dose/fraction and low dose rate protect cancer cells and hence should be avoided*
- This makes HDR and hypofractionated conformal teletherapy, very attractive

Conclusions (cont'd.): effect of geometrical sparing of normal tissues

- Geometrical sparing favors most those treatment regimes that allow the least repair
- HDR and hypofractionated conformal therapies benefit the most, I-125 the least

Conclusions (cont'd.): effect of slow repair of normal tissue cells

- Slow repair of late-reacting normal tissue cells is most detrimental to those regimes that allow the least time for repair
- Pd-103 and HDR with only 6h between fractions will be most affected

5. HDR “balloon” brachytherapy for partial breast irradiation

Objective:

use what we think we “know” about optimal doses with conformal teletherapy to estimate the optimal dose to use for HDR balloon brachytherapy

What we think we “know”

- Conformal teletherapy at 2 Gy/fraction in 25 – 30 fractions is appropriate to ensure good local control with few complications
- Conformal teletherapy at 3.85 Gy/fraction in 10 fractions is likely to be about as equivalent

Determination of optimal doses: what's involved?

- Best method:
  - *Clinical trials*
- Next best method:
  - *Calculate using the linear-quadratic model*

Most important radiobiological principles when comparing these different treatment regimes

- Repair of sublethal damage:
  - *effect of fractionation and dose rate*
- Repopulation of cancer cells:
  - *effect of the overall treatment time and the rate of repopulation*

So what is the optimal dose?

As far a tumor control is concerned, let us calculate what 10 fractions of 3.4 Gy with HDR balloon brachytherapy is equivalent to when compared with highly conformal teletherapy at specific doses/fraction (i.e. how many fractions?)

- *at 2 Gy/fraction (expect about 25 – 30)*
- *at 3.85 Gy/fraction (expect about 10)*

Simple approach

Assume that all the cancer cells receive the prescription dose of 3.4 Gy/fraction with the balloon and ignore repopulation.

Simple approach (2 Gy/fraction teletherapy)

Then, equating BEDs for equal tumor effect (α/β = 10 Gy) gives the equivalent number of 2 Gy fractions, N_{eq}:

$$BED = 34\left(1+\frac{3.4}{10}\right) = 2N_{eq}\left(1+\frac{2}{10}\right)$$

$$\rightarrow \; N_{eq} = 19.0$$

Simple approach (3.85 Gy/fraction teletherapy)

Equating BEDs for equal tumor effect gives the equivalent number of 3.85 Gy fractions, N_{eq}:

$$BED = 34\left(1+\frac{3.4}{10}\right) = 3.85N_{eq}\left(1+\frac{3.85}{10}\right)$$

$$\rightarrow \; N_{eq} = 8.54$$

Simple approach: summary

The equivalent number of fractions at 2 Gy/fraction is 19.0

- *we expected 25 – 30, so current balloon brachytherapy appears far less effective*

The equivalent number of fractions at 3.85 Gy/fraction is 8.54

- *we expected about 10, so current balloon brachytherapy appears slightly less effective*

Slightly more sophisticated approach

Assume that all the cancer cells receive the prescription dose of 3.4 Gy/fraction with the balloon but account for repopulation.

Assumptions

$\alpha = 0.3\ Gy^{-1}$

$T_{pot} = 10$ days

$T_k = 14$ days

Hence no account for repopulation is needed with balloon brachytherapy or teletherapy at 3.85 Gy/fraction since both these treatments take less than the accelerated repopulation "kick-in" time of 14 days

Solutions

The equivalent number of fractions at

2 Gy/fraction is 20.4

- *we expected 25 – 30, so current balloon brachytherapy still appears far less effective*

The equivalent number of fractions at 3.85 Gy/fraction is unchanged 8.54 (because T is less than T_k)

- *again, as before, we expected about 10, so current balloon brachytherapy appears slightly less effective*

Even more sophisticated approach

Account for repopulation *and* account for inverse square law fall off of dose from the balloon surface out to 1 cm away, where it reaches 3.4 Gy/fraction

How can this be achieved?

Calculate the cell surviving fraction (*S*) using the L-Q model by integrating the effect throughout the CTV (0 – 1 cm from the balloon surface) and equate this to the *S* calculated for the uniformly irradiated cells with the teletherapy treatments

Solution: compared to 2 Gy/fraction teletherapy

Balloon radius	N_{eq}
2.0 cm	24.4
2.5 cm	24.3
3.0 cm	24.1

We expected 25 – 30, so current balloon brachytherapy appears to be slightly less effective than 2 Gy/fraction teletherapy treatments

Solution: compared to 3.85 Gy/fraction teletherapy

Balloon radius	N_{eq}
2.0 cm	9.90
2.5 cm	9.83
3.0 cm	9.78

We expected about 10, so current balloon brachytherapy seems to be about as effective as 3.85Gy/fraction teletherapy treatments

Most sophisticated approach

Account for gradually decreasing cancer cell density *and* inverse square law fall off of dose from the balloon surface out to 1 cm away, *and* repopulation of cancer cells

How can we do this?

Assume that the density of cancer cells is a maximum at the balloon surface and falls linearly to zero at the distal edge of the CTV (at 1 cm away) and repeat integration throughout the CTV

Solutions: compared to 2 Gy/fraction teletherapy

Balloon radius	N_{eq}
2.0 cm	27.5
2.5 cm	27.1
3.0 cm	26.8

We expected 25 – 30, so current balloon brachytherapy appears to be as effective as the 2 Gy/fraction teletherapy treatments

Solutions: compared to 3.85 Gy/fraction teletherapy

Balloon radius	N_{eq}
2.0 cm	11.1
2.5 cm	10.9
3.0 cm	10.8

We expected about 10, so current balloon brachytherapy appears to be slightly more effective than 3.85Gy/fraction teletherapy treatments

What about late-reacting normal tissues?

Because the effect on late-reacting normal tissue cells increases with increase in dose/fraction (low α/β), and since the dose/fraction close to the cavity surface with balloon brachytherapy is much higher than 3.4 Gy, we need to be concerned about late reactions

Late reactions

Hence it is very important to follow all patients treated with balloon brachytherapy for several years to make sure that the incidence of severe morbidity, such as fat necrosis, remains “acceptable”

Conclusions

- In order to determine the optimal dose to use for partial breast irradiation one should account for:
  - *repair and repopulation of cancer cells*
  - *the inhomogeneous dose distributions inherent with brachytherapy*
  - *the expected decrease in cancer cell density as a function of distance from the cavity surface*
  - *the observed effect on late-reacting normal tissues*

6. Comparison of brachytherapy surface “molds” with other types of skin radiotherapy treatments

- External beam therapy
  - *low energy x rays*
  - *electrons*
- Brachytherapy
  - *radium and radon molds*
  - *HDR molds*

Publications Reviewed

- *low energy x rays: 10*
- *electrons: 5*
- *radium and radon molds: 3*
- *HDR molds or applicators: 9*

Ranges of fractions and doses

Modality	# fractions	Total dose reported (Gy)	# reports
Low energy x rays	1 - 21	20 - 60	21
electrons	1 - 32	20 - 65	12
HDR	1 - 36	18 - 65	19
Radium molds	1	60	1
Radon molds	1	40 - 60	2

Variations in dose specification

- surface dose
- minimum dose to tumor
- dose at 5 mm depth
- dose at depth of 67% DD
- dose at depth of 90% DD
- dose at depth of maximum dose (for electrons)
- not specified!

Corrections made to make dose specification consistent

- correct all doses to the minimum dose to tumor
  - assume 80% DD if not otherwise specified
- use RBE = 1.1 for low energy x rays i.e. increase x-ray doses by factor of 1.1
- use the linear-quadratic model to correct for fractionation and dose rate effects

Ranges of doses corrected to consistent specification

Modality	# fractions	Total minimum dose to tumor (Gy)
Low energy x rays	1 - 21	16 - 63
electrons	1 - 32	20 - 52
HDR	1 - 36	14 - 65
Radium molds	1	48
Radon molds	1	40 - 48

Minimum BED to tumor

Modality	Minimum BED to tumor (Gy)	Mean BED
Low energy x rays	42 - 88	63
electrons	48 - 63	56
HDR	30 - 132	56
Radium molds	54	54
Radon molds	47 - 54	51

What is the “correct” dose for HDR surface applicators?

- It appears from this study that we need to aim for a minimum BED to the tumor between 50 and 60
- Even though some have used a single fraction, it is probably better to fractionate in order to take advantage of the better repair capabilities of late reacting normal tissues compared with tumor
- *We must keep within skin tolerance*

What is the BED for skin tolerance?

- Without using conformal therapy, the tolerance dose for skin is about 64 Gy at 2 Gy/fraction
- Assuming an α/β of 3 Gy, this corresponds to a BED to late-reacting normal tissues of 107
- The volume of skin tissue irradiated to the tumor dose is less with the mold applicator than with more non-conformal therapies and a geometrical sparing factor of, say, 0.9, is probably reasonable when calculating BEDs to see if skin tolerance might be been exceeded

Suggested doses for tumor BEDs from 50 – 60

(late reaction BEDs calculated assuming α/β = 3 Gy and f = 0.9)

Number of fractions	Dose/fraction (Gy)	Total dose (Gy)	*Late-reaction BEDs*
1	18 - 20	18 - 20	*104 – 126**
2	11.6 - 13	23 - 26	*94 – 115**
3	8.8 - 10	26 - 30	*86 – 108**
4	7.3 - 8.2	29 - 33	*84 - 102*
5	6.2 - 7.0	31 - 35	*80 - 98*
6	5.4 - 6.2	32 - 37	*76 - 96*
8	4.4 - 5	35 - 40	*73 - 90*
10	3.7 - 4.2	37 - 42	*70 -85*
15	2.7 - 3.1	40 - 47	*66 - 81*
20	2.1 - 2.4	42 - 48	*62 - 74*

** possibly exceed skin tolerance BED of 107*

7. ICRU definitions of LDR, MDR, and HDR

Modality	Dose-rate range*
LDR	0.4 - 2 Gy h^{-1}
MDR	2 - 12 Gy h^{-1}
HDR	>12 Gy h^{-1} (0.2 Gy min^{-1})

**** It was stated in the ICRU Report that these dose-rate ranges were "arbitrary and debatable"***

Problems with these definitions

- They are "*arbitrary and debatable*"
- The upper limit for LDR (lower limit for MDR) is way too high: clinical evidence shows that complications increase significantly for LDR treatments at dose rates above about 1 Gy h^{-1}
- We ought to be able to specify these dose rate ranges in a more rational manner

Definitions of LDR, MDR, and HDR

Proposal:

In light of recent clinical and radiobiological evidence, it ought to be possible to devise more rational definitions of LDR, MDR, and HDR

New Definitions of LDR, MDR, and HDR: Proposed Basis

- Base lower limits for dose rate (for LDR) and dose/fraction (for HDR) on realistic limits of clinical practice
- Define upper limits of LDR dose rate and HDR dose/fraction such that the Therapeutic Ratio (TR) remains within $\pm$10% between lower and upper limits
- For MDR define lower limit of dose rate at upper limit for LDR, and upper limit as the dose rate at which five MDR fractions are needed in order to achieve the same TR

Dose Rate and Dose/Fraction Ranges for LDR, MDR, and HDR

Modality	Lower limit	Upper limit
LDR	0.35 Gy h^{-1}	1.3 Gy h^{-1}
MDR	1.30 Gy h^{-1}	3.0 Gy h^{-1}
HDR	4 Gy/fraction	11 Gy/fraction

MDR Fractionation

The number of fractions necessary at MDR dose rates in order to keep the TR the same as at the upper end of the LDR range (1.3 Gy h^{-1})

Dose rate (Gy h^{-1})	Number of fractions
1.30 - 1.40	2
1.41 - 1.60	3
1.61 - 2.00	4
2.00 - 3.00	5

Dose Rate Correction Factors

- ICRU 38
  - *"No correction factors for dose rate can be recommended"*
  - *This was based primarily on the early Paris experience (Pierquin, 1973)*
- Comment
  - *We now know that this was incorrect*
  - *It ought to be possible to devise appropriate dose-rate correction guidelines at this time*

Correction Factors for Dose Rate and Fractionation

Suggested basis

- use the linear-quadratic model to calculate correction factors
- normalize to center of LDR dose rate range
  - 0.7 Gy h^{-1} for LDR and MDR
  - 6.5 Gy/fraction for HDR
- below 0.7 Gy h^{-1} or 6.5 Gy/fraction use “tumor” parameters
- above 0.7 Gy h^{-1} (including MDR) or 6.5 Gy/fraction use late-reaction normal tissue parameters

Correction Factors for LDR (normalized to 1.00 for 0.7 Gy h^{-1})

Dose rate (Gy h^{-1})	Correction factor
0.31 - 0.40	1.13
0.41 - 0.50	1.09
0.51 - 0.60	1.05
0.61 - 0.70	1.02
0.71 - 0.80	0.97
0.81 - 0.90	0.92
0.91 - 1.00	0.88
1.01 - 1.10	0.84
1.11 - 1.20	0.80
1.21 - 1.30	0.77

Correction Factors for MDR (normalized to 1.00 for one fraction at 0.7 Gy h^{-1} (LDR)

Dose rate (Gy h^{-1})	Minimum number of fractions	Correction factor
1.30 - 1.40	2	0.77
1.41 - 1.60	3	0.77
1.61 - 2.00	4	0.76
2.01 - 3.00	5	0.74

*

Correction Factors for HDR

Dose/fraction	Correction factor (normalized to 6.5 Gy/fraction)	CF from LDR equivalent (at 0.7 Gy h^{-1})
4.0 - 5.0	1.14	0.74
5.1 - 6.0	1.06	0.69
6.1 - 7.0	1.00	0.65
7.1 - 8.0	0.92	0.60
8.1 - 9.0	0.84	0.55
9.1 - 10.0	0.78	0.51
10.1 - 11.0	0.73	0.47

Discussion and warning

- The L-Q model is useful for demonstrating radiobiological principles
- The quantitative results obtained are only approximations due to the uncertainty in the parameters and the oversimplicity of the L-Q model itself
- It is necessary to be aware of this uncertainty when using the L-Q model for patient calculations