

# Radiobiological principles of brachytherapy

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- ◆ Low dose rate (LDR)
- ◆ Medium dose rate (MDR)
- ◆ High dose rate (HDR)

# The effect of dose rate

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- ◆ As the dose rate is decreased, there is more time during irradiation for repair
  - *if the dose rate is low enough (e.g. with long-lived permanent implants) almost full repair of sublethal damage occurs*
  - *if the dose rate is high (e.g. HDR brachytherapy) there is almost no repair during irradiation (but almost full repair between fractions)*

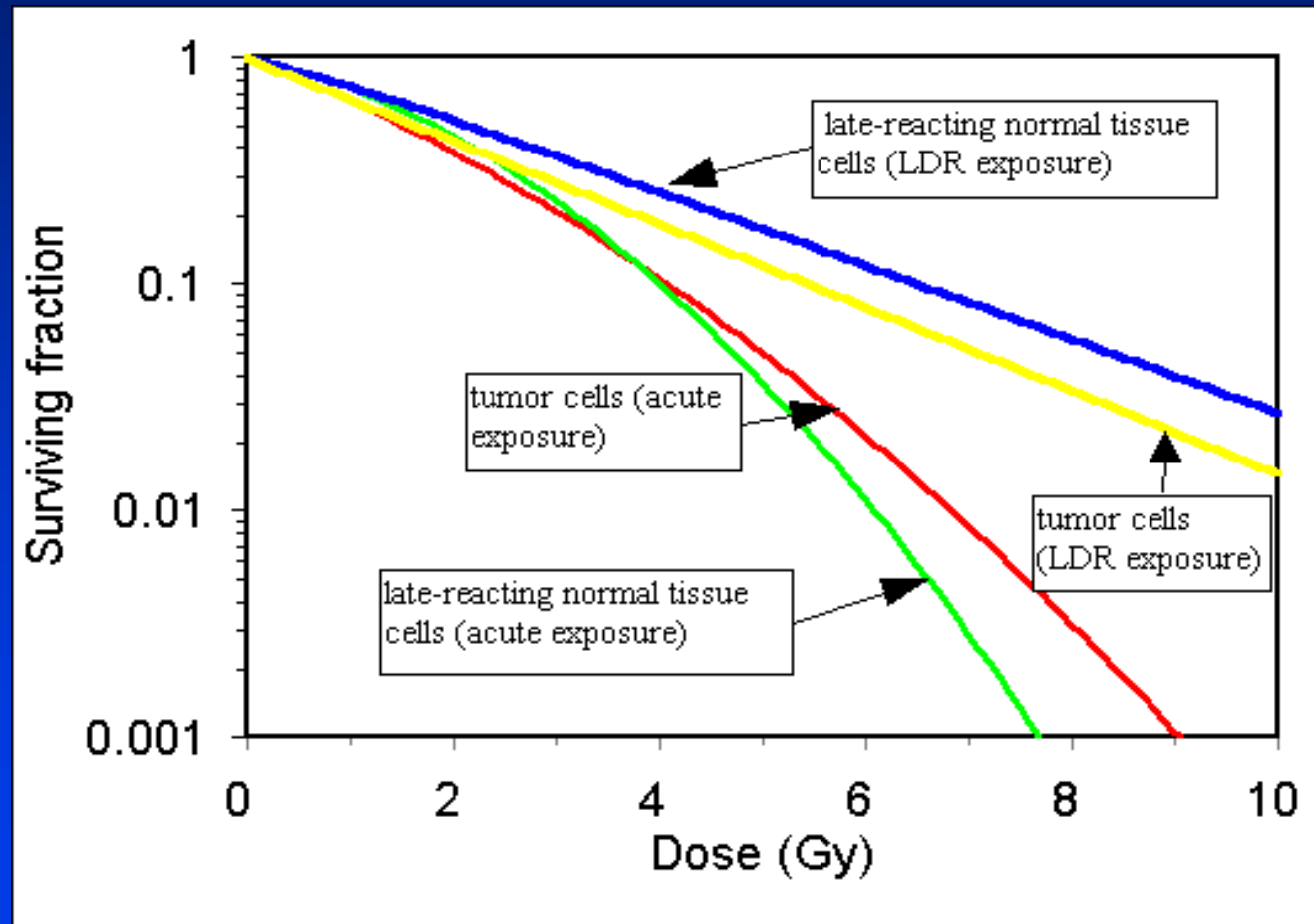
# The dose-rate effect for cancer and normal tissue cells

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- ◆ Cells which are not good at repairing sublethal damage repair (such as cancer cells) will exhibit little dose-rate effect
- ◆ Conversely, cells which are good at repairing (such as those of late-reacting normal tissues) will demonstrate a significant dose-rate effect

# Normal vs cancer cells for low dose rate (LDR) brachytherapy

At low dose rate (as at low doses/fraction), survival of normal tissue cells (blue curve) exceed that of cancer cells (yellow curve)



# Clinical applications of the dose-rate effect

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

# Brachytherapy: low dose rate

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- ◆ The vast majority of interstitial and intracavitary brachytherapy experience has been with LDR
- ◆ Results have been excellent

# Problem with LDR brachytherapy

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- ◆ LDR brachytherapy at about 50 cGy/h means that treatments last several days with the patient lying in a hospital bed
- ◆ This is so inconvenient that 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 treatment for adequate repair

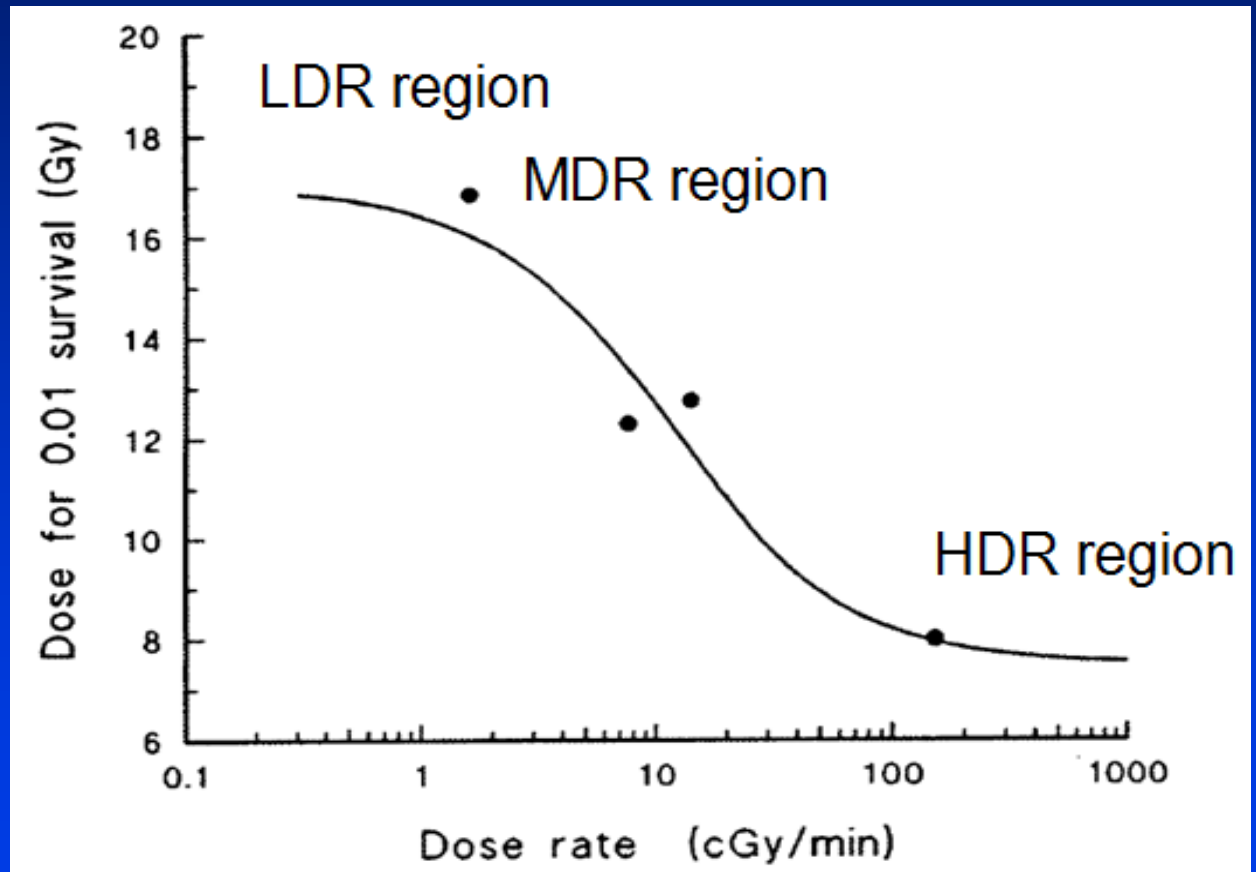


# Another reason to avoid MDR

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

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

# HDR fractionation

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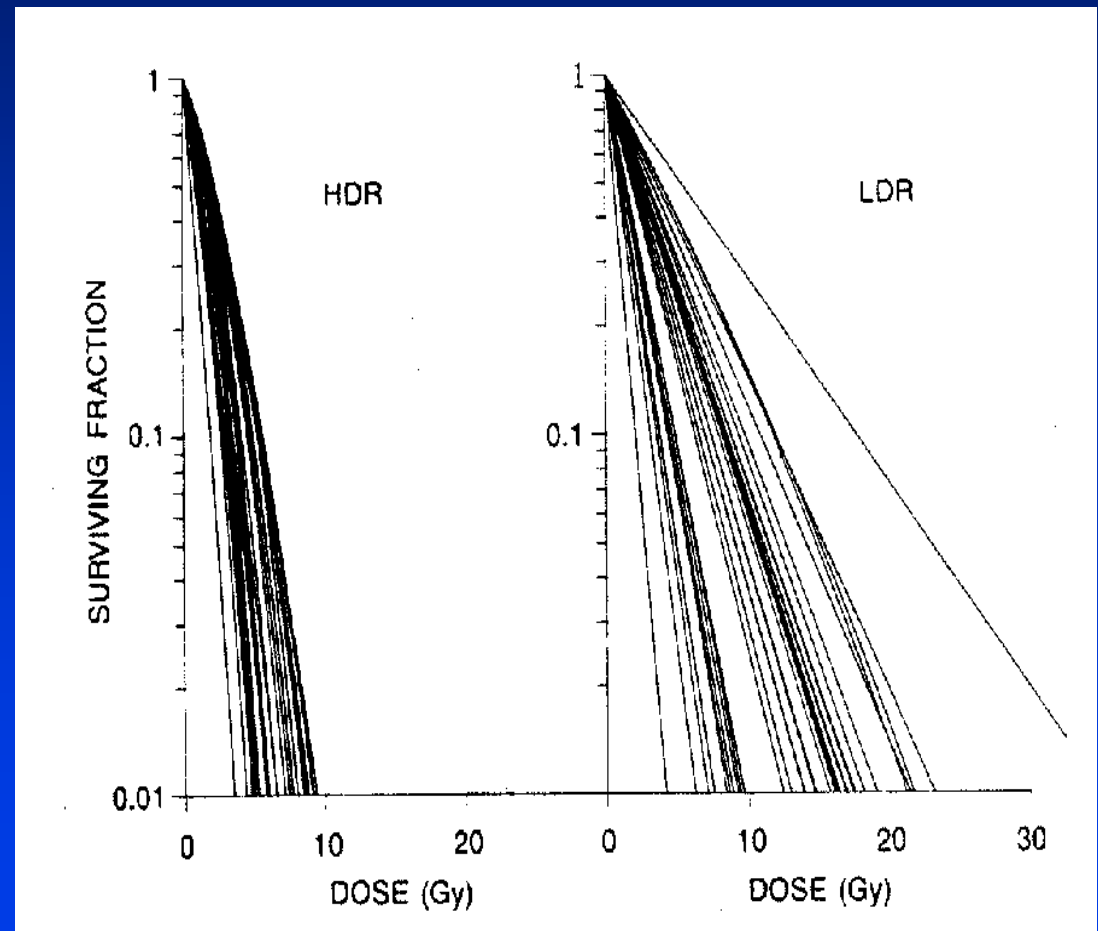
- ◆ The time between fractions must be adequate for repair
  - *need 6 hours or more*
- ◆ Experience has shown that properly fractionated HDR can be at least as good as LDR

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

Some of the variability is due to different values of  $\alpha/\beta$

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

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- ◆ Note that some of these cells are very resistant to LDR irradiation (shallow survival curves) because the repair rate is slow
  - *presumably this is one reason why some cancers are difficult to cure with LDR brachytherapy*

# Might HDR be better than LDR?

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- ◆ Yes, because LDR survival curves vary more than those for HDR:
  - *HDR survival curves vary only with cell sensitivity (i.e.  $\alpha/\beta$ )*
  - *for LDR, survival curves vary not only with cell sensitivity but also on the rate of repair*
- ◆ This might be considered an advantage of HDR (less variability in sensitivity between patients)

# The L-Q model for LDR treatments

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

*where*

$N$  = number of fractions

$R$  = dose rate

$t$  = time for each fraction

$\mu$  = repair-rate constant

# The BED equation for LDR treatments

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

where

$R =$  is in  $\text{Gy h}^{-1}$

$t =$  is in h

$\mu =$  is in  $\text{h}^{-1}$



# Simplified forms of the LDR BED equation

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*For*  $10h \leq t \leq 100h$

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

*For*  $t \geq 100h$

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

# Typical values for $\mu$

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The most common assumptions are:  
for tumors and acute reactions:

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

for late-reacting normal tissues:

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

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

# Example of application of the L-Q model: conversion from LDR to HDR

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Problem:

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

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

# Solution

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Since  $t = 100\text{h}$  we can use the simplified version of the BED equation:

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

Assume:  $\mu = 1.4 \text{ h}^{-1}$  and  $\alpha/\beta = 10 \text{ Gy}$  for tumor

Then the BED for the LDR implant is:

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

# Solution (cont'd.)

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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  $\alpha/\beta = 3$  Gy and  $\mu = 0.46$  h<sup>-1</sup>

Then the BED for 60 Gy at 0.6 Gy h<sup>-1</sup> is:

$$\text{BED}_{\text{LDR}} = 60[1 + 1.2 / (0.46 \times 3)] = 112.2$$

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

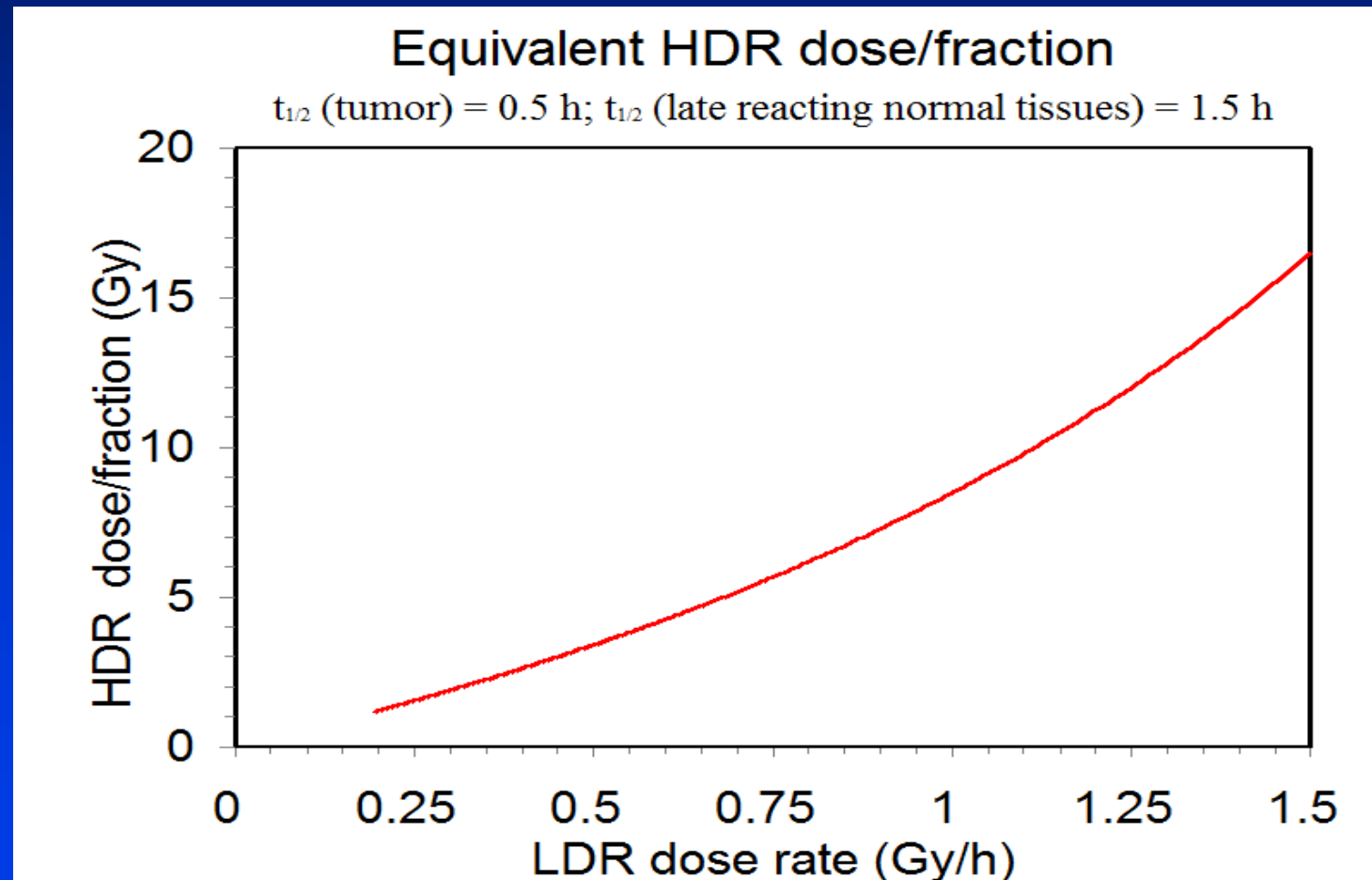
$$\text{BED}_{\text{HDR}} = 10 \times 4.49[1 + 4.49 / 3] = 112.2$$

# 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

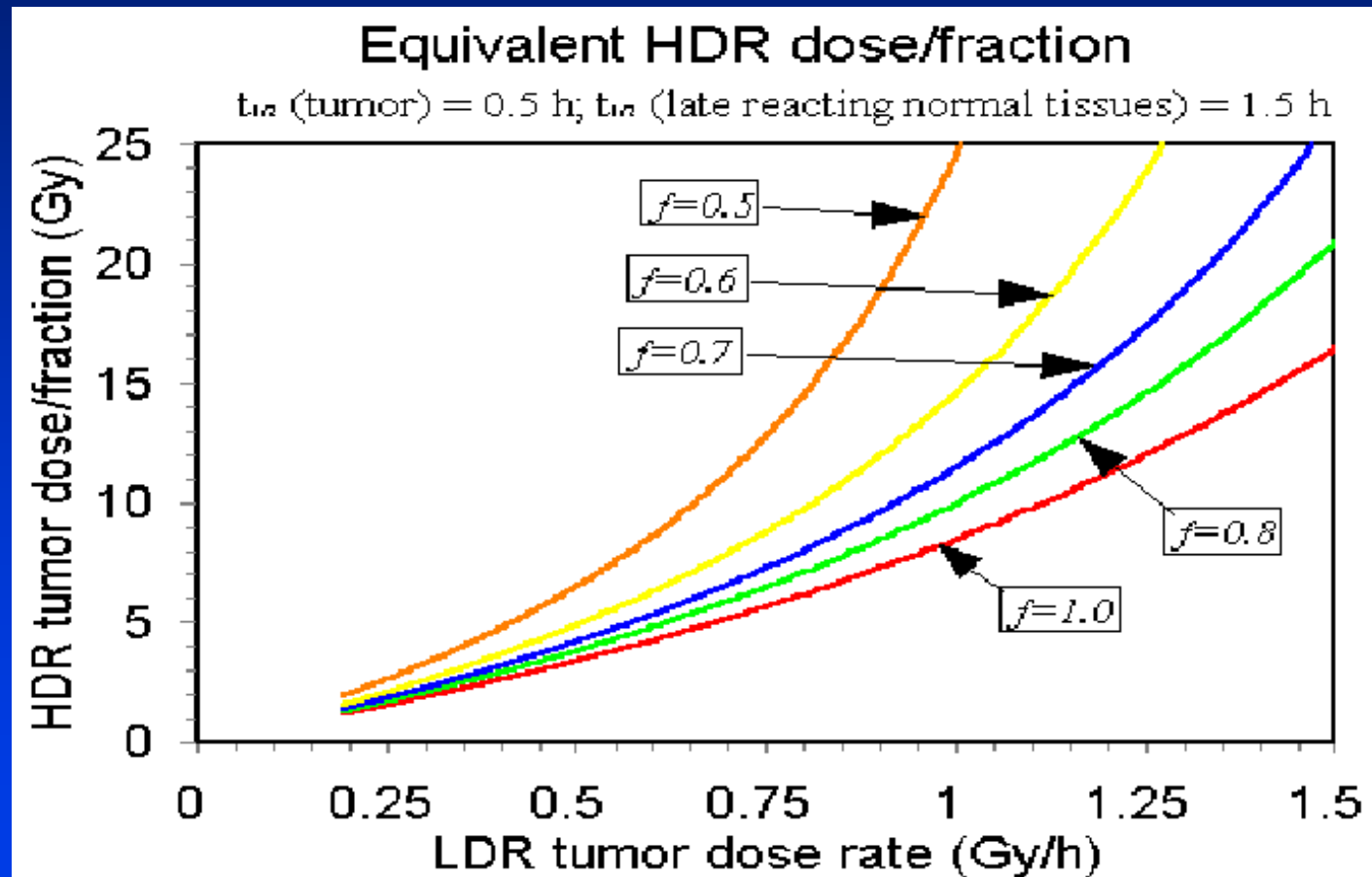
For equivalence to LDR at 0.6 Gy h<sup>-1</sup> need to use about 4.5 Gy/fraction with HDR (this was the example just shown)





# Does geometrical sparing make any difference?

Now if the geometrical sparing factor is 0.6 (yellow line), HDR at about 6 Gy/fraction is equivalent to LDR at 0.6 Gy h<sup>-1</sup>



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

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- ◆ 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*
  - *this is considerably longer than previously believed*

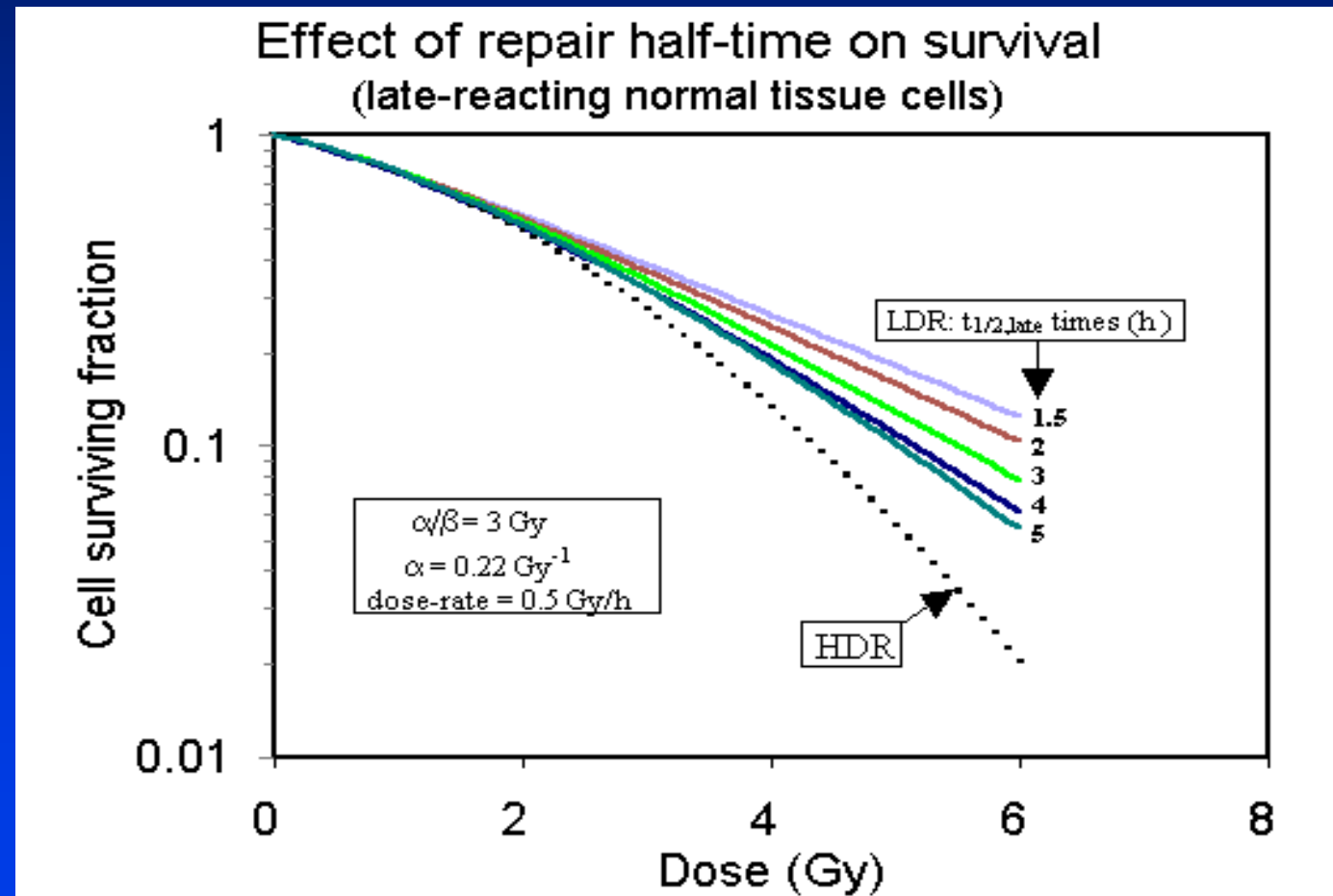
# Radiobiological significance of such long repair half-times

- ◆ This would reduce repair of normal tissue cells during a course of LDR brachytherapy, but have no effect at HDR if delivered with 24 h between fractions
  - *with HDR there is no repair during and full repair between fractions regardless of repair half time*

# Effect of repair half time on LDR cell survival

If cells repair fast,  $\beta$ -type damage is well repaired, leaving mainly  $\alpha$ -type damage

Hence survival curves for cells with a short  $t_{1/2}$  (top line) will be fairly shallow and straight



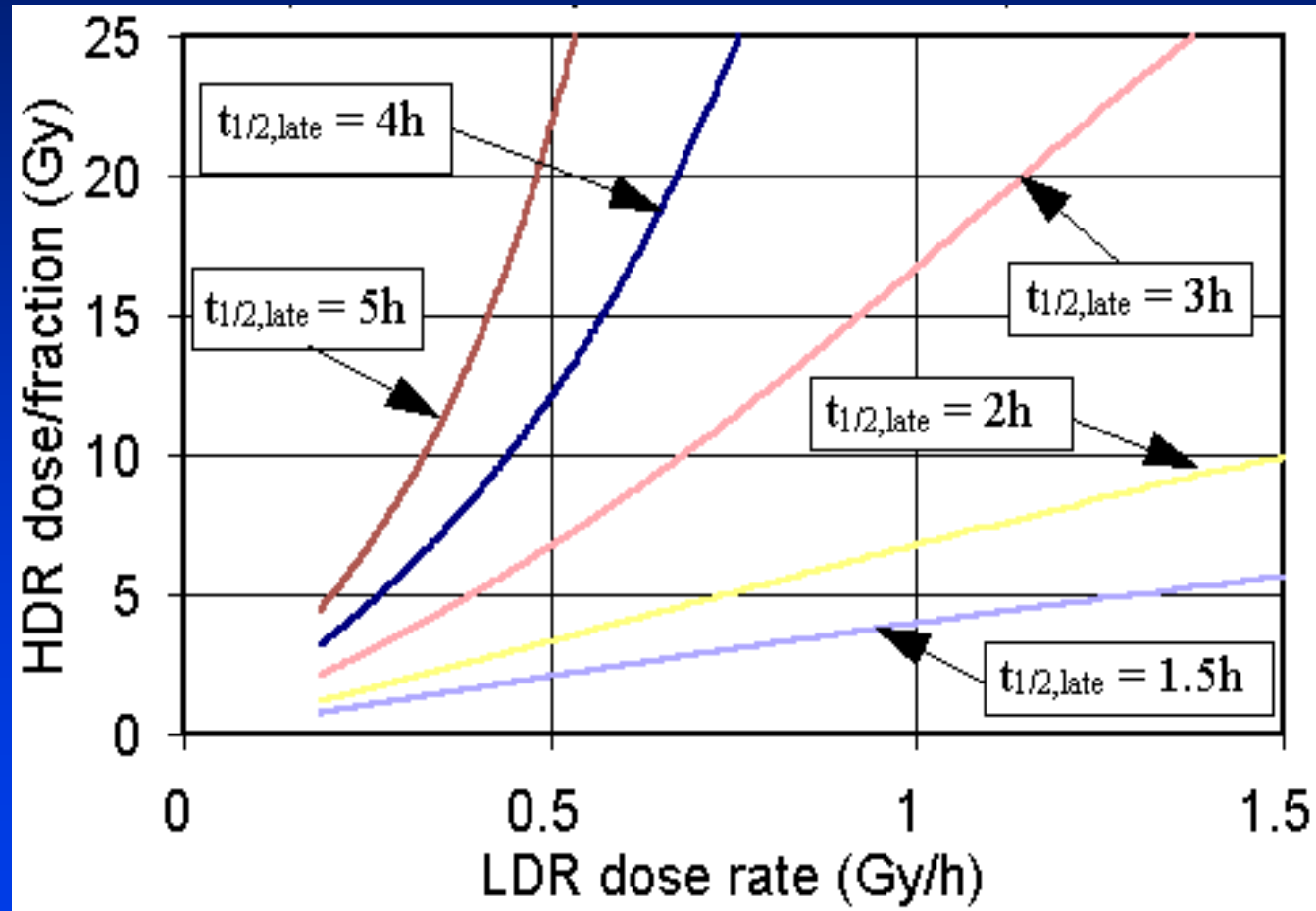
# Is this a radiobiological advantage for HDR?

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Yes, because the major advantage of LDR brachytherapy is *repair* during the treatment, and late-reacting normal tissue cells will repair less with LDR if they repair slowly

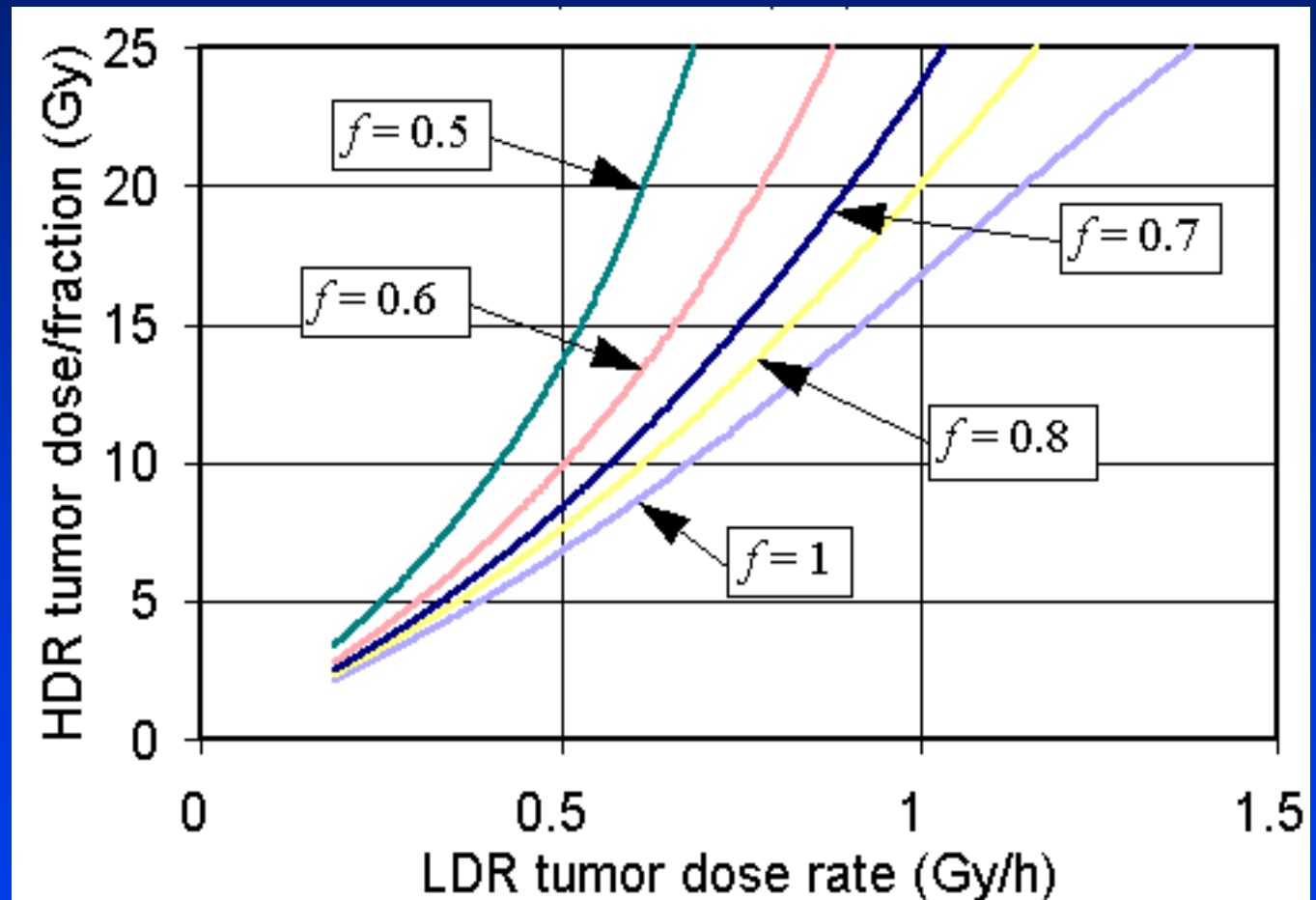
# HDR dose/fraction required for equivalence to LDR with $t_{1/2,tumor} = 1.5\text{ h}$

Even if  $t_{1/2,tumor}$  is 1.5 h, the equivalent to LDR at  $0.6\text{ Gy h}^{-1}$  is HDR at about 8 Gy/fraction with no geometrical sparing of normal tissues and  $t_{1/2,late} = 3\text{ h}$  (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, the equivalent HDR dose/fraction rises from 8 Gy to about 12 Gy (pink line)



# CONCLUSIONS

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



# CONCLUSIONS (continued)

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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

# Discussion and warning

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- ◆ 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

BED equation when the initial dose rate  $R_0$  decreases due to decay (with decay constant  $\lambda$ )

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

where:

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

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

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

# BED equation for permanent implants

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By letting the treatment time  $t$  approach infinity, the equation for a permanent implant of a radionuclide with decay constant  $\lambda$  at initial dose rate  $R_0$  is obtained:

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

# L-Q Model for permanent implants for cells that repopulate during treatment

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Problem:

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

# L-Q Model for permanent implants with repopulation

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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  $\text{Gy h}^{-1}$ ,  $\lambda$  is in  $\text{h}^{-1}$ , and  $k$  is in BED units per hour

# Equation for permanent implants with repopulation

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

where:

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

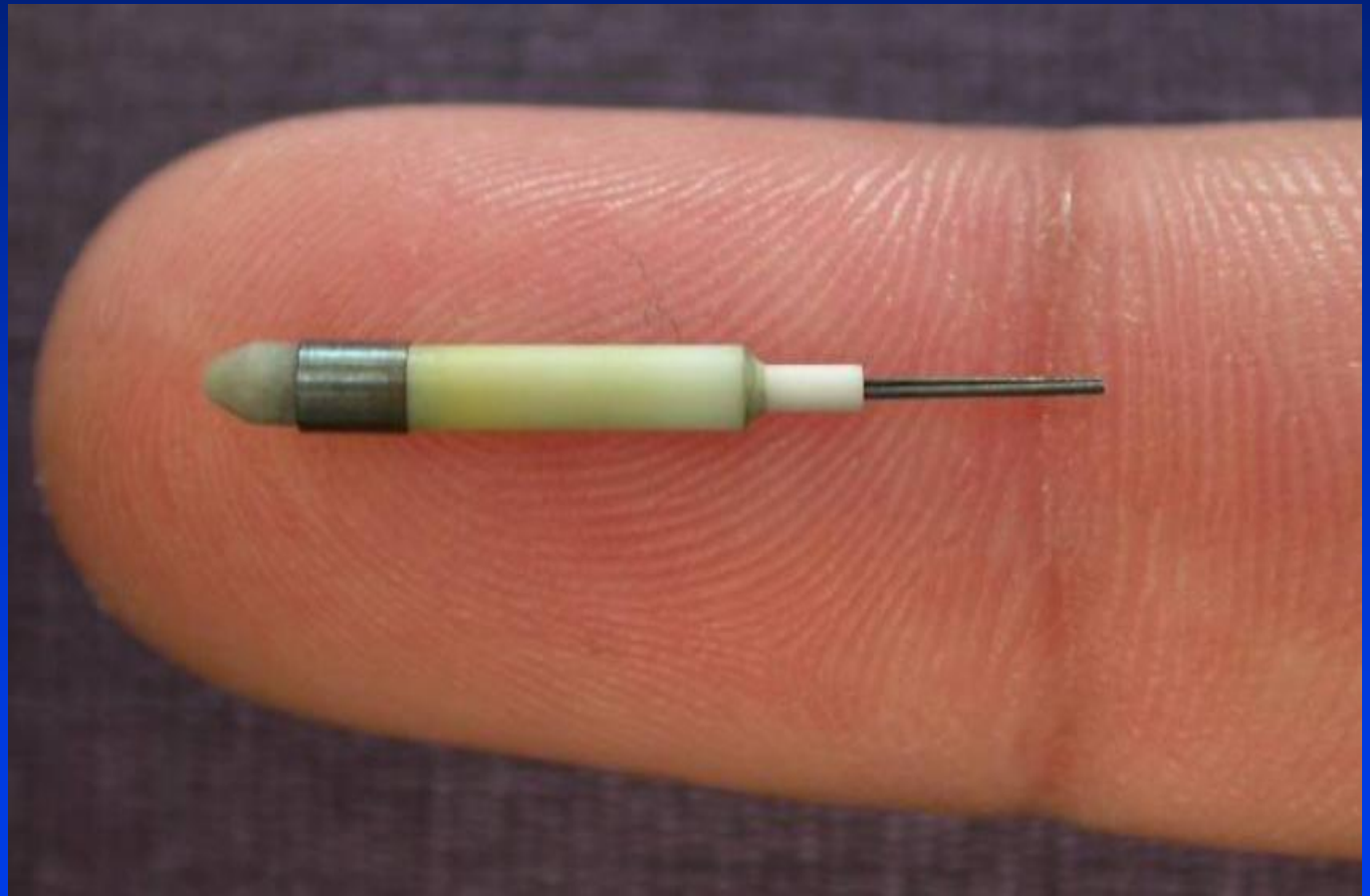
$$B = \frac{1 - e^{-2\lambda t_{eff}}}{2\lambda}$$

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

# The biology of 50kV electronic brachytherapy (EB) vs Ir-192 HDR

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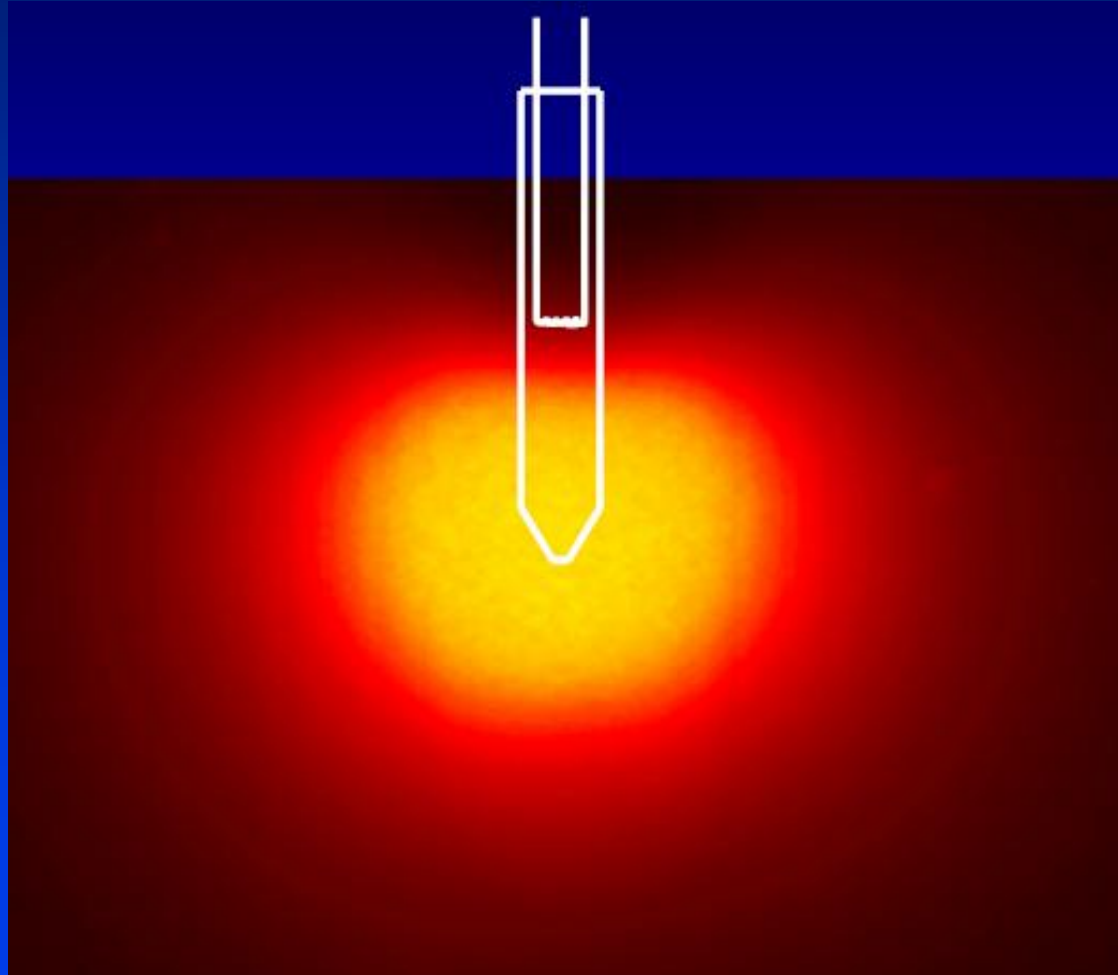
The Xoft Accent brachytherapy source is a miniature x-ray unit operating at 50 kV





# EB dose distribution on radiochromic film

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Phys. Med. Biol. **53** (2008) p. 7125

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**Title: “Calculation of relative biological effectiveness of a low-energy electronic brachytherapy source”**

**by: Reniers, Liu, Rusch and Verhaegen**

*The results indicate a substantially increased double strand break yield for the EB (electron brachytherapy) source compared to  $^{192}\text{Ir}$ , leading to an enhanced RBE by 40–50%*

# Conclusions (cont'd.)

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- ◆ *Our data do indicate...that a low-energy EB source may result in elevated biological effect compared to, for example, the commonly used high-energy brachytherapy isotope  $^{192}\text{Ir}$*
- ◆ *This may have an influence on prescription doses and toxicity criteria in brachytherapy*

# Objectives

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- ◆ Explain how these high RBEs were determined
- ◆ Demonstrate that increased biological effectiveness of EB radiations in clinical practice should be far less than the 40 – 50% “apparently” predicted in this article

# How were these RBEs determined?

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- ◆ The authors used Monte Carlo to follow the histories of electrons set in motion by the EB and  $^{192}\text{Ir}$  sources
- ◆ Microdosimetric deposition of energy was studied in DNA molecules and the probabilities of double-strand breaks (DSBs) were calculated
- ◆ The ratio of the dose/DSB for an  $^{192}\text{Ir}$  source to that for the EB source yielded the RBE

# What exactly is this “RBE”?

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- ◆ According to the linear-quadratic (L-Q) model of radiation effect, the yield of DSBs is directly related to the  $\alpha$  component of the damage
  - *this represents the initial slope of the cell survival curve at infinitely small dose*
- ◆ Hence the RBEs calculated are ratios of the  $\alpha$ 's for EB and  $^{192}\text{Ir}$  radiations

# Double-strand breaks calculated

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- ◆ The authors calculated that, for every billion DNA base pairs in muscle, the doses to produce a DSB were:
  - *0.068 Gy with EB*
  - *0.095 Gy with  $^{192}\text{Ir}$*
- ◆ Hence the  $\text{RBE} = 0.095/0.068 = 1.40$
- ◆ This is the maximum value of the RBE, often called  $\text{RBE}_{\text{max}}$

# How is $RBE_{max}$ related to the RBE in clinical practice?

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- ◆ RBE depends on dose (and dose/fraction)
- ◆ At extremely low doses,  $RBE = RBE_{max}$
- ◆ At doses used clinically,  $RBE < RBE_{max}$
- ◆ These clinical RBEs can be calculated using the L-Q model



# Calculation of clinical RBEs

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- ◆ RBEs are the ratios of doses that produce the same cell-surviving fractions,  $S$  (and hence the same values of  $-\ln S$ )
- ◆ But, for each fraction of dose  $d$ :
  - $\ln S = (\alpha d + \beta d^2)$
- ◆ Hence all we need to do is equate values of  $(\alpha d + \beta d^2)$  for EB and  $^{192}\text{Ir}$  at clinically relevant doses in order to calculate doses of each which are equivalent, and then take the ratio of these doses

# Sample calculation for tumors

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- ◆ Assume that we want to calculate the RBE for EB radiation for an  $^{192}\text{Ir}$  dose/fraction of 7 Gy
- ◆ We know that  $\alpha_{EB}/\alpha_{Ir} = 1.40$
- ◆ According to the L-Q model, the  $\beta$ 's are the same for both radiations
- ◆ Assume that  $(\alpha/\beta)_{Ir} = 10$  Gy for tumors

# Tumor RBE calculation, cont'd.

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- ◆ Then the dose/fraction of EB,  $d$ , that is equivalent to 7 Gy with  $^{192}\text{Ir}$  is given by:

$$7\alpha_{\text{Ir}} + 49\beta = d(1.4\alpha_{\text{Ir}}) + d^2\beta$$

- ◆ Dividing both sides of the equation by  $\beta$  and putting  $\alpha_{\text{Ir}}/\beta = 10$  Gy gives:

$$7 \times 10 + 49 = d(1.4 \times 10) + d^2$$

- ◆ This is a quadratic equation with solution:

$$d = 5.96 \text{ Gy and hence RBE} = 7/5.96 = 1.17$$

# What about the RBE for late-reacting normal tissues?

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- ◆ To calculate the RBE for late reacting normal tissues, we solve exactly the same equation but use, for example, 3 Gy for  $\alpha_{lr}/\beta$ :

$$7 \times 3 + 49 = d(1.4 \times 3) + d^2$$

- ◆ The solution is:

$$d = 6.53 \text{ Gy}$$

- ◆ Hence the RBE for late reactions is  $7/6.53$   
 $= 1.07$

# What does all this mean?

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- ◆ Because the clinical RBE for normal tissues is about 10% less than for tumors, EB has a therapeutic advantage over  $^{192}\text{Ir}$
- ◆ Since the clinical RBE for tumors is 1.17 for dose/fraction 7 Gy, we could reduce the dose by about 17% and still have the same effect on tumors

# So should we reduce the dose for EB?

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- ◆ Not necessarily, because, if late-reacting normal tissue tolerance is the limiting factor on dose, the increase in bioeffect dose would only be about 7% when changing from  $^{192}\text{Ir}$  to EB
  - *this is far less than the reduction in the physical dose to surrounding normal tissues with EB due to the lower energy (50 kV)*

# Warning!

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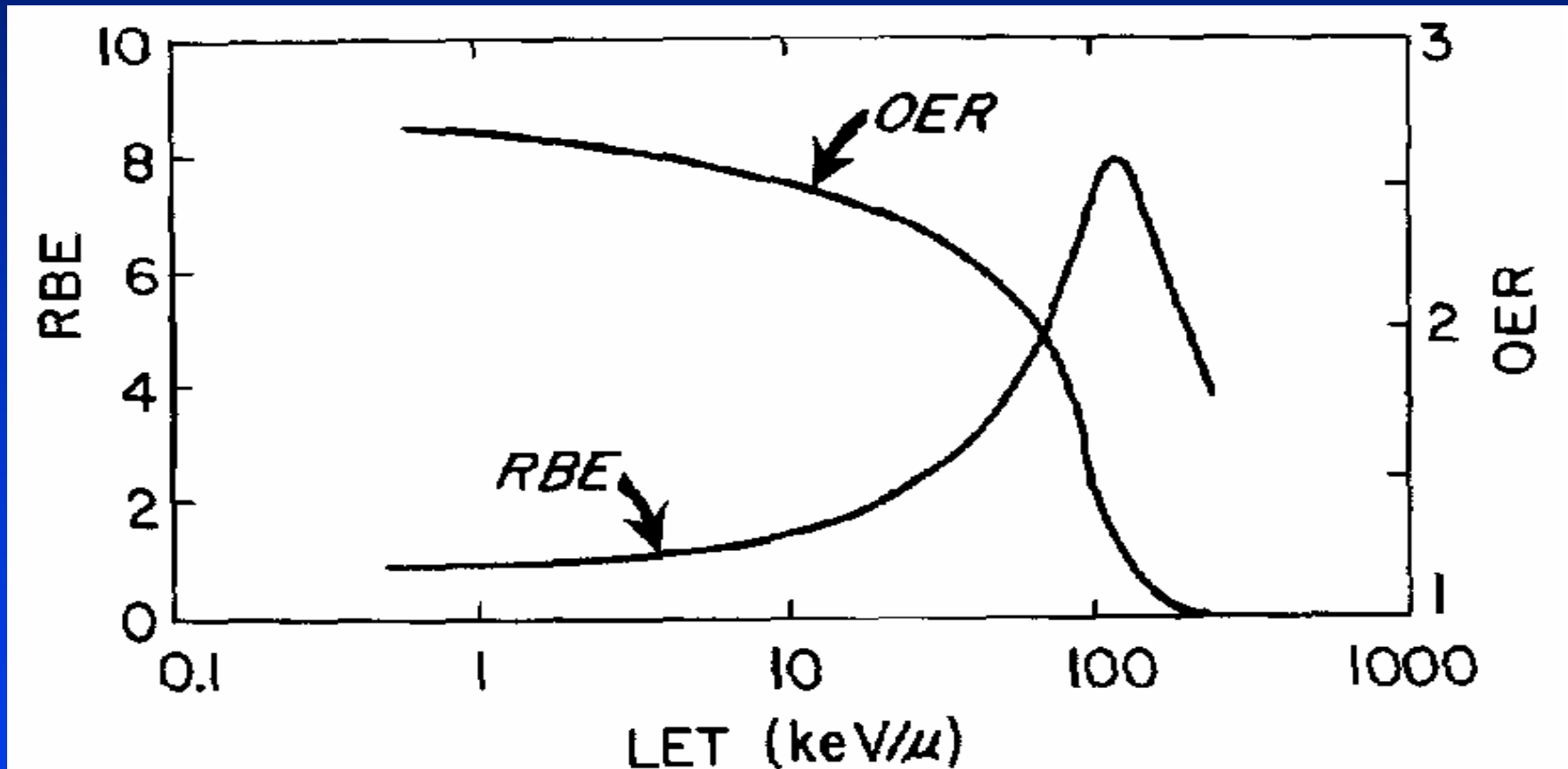
- ◆ We have made the “traditional” assumption that  $\beta$ 's are LET independent
  - *this might not be true*
- ◆ Also we have assumed that  $RBE_{\max}$  is the same for both tumors and late-reacting normal tissues
  - *this also may not be true*

# Might there be another biological advantage of EB?

- ◆ Yes, because the radiation from an EB source has a higher LET than that of the higher energy  $^{192}\text{Ir}$   $\gamma$  rays
  - *hence the relative effectiveness in killing hypoxic cells is greater*



# Variation of RBE and OER with LET



# Radiobiology of brachytherapy: Summary

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- ◆ Use either low dose rate at less than about 100 cGy/hour or fractionated HDR for maximum benefit
- ◆ Avoid medium dose rate if possible
- ◆ If the half time for repair of normal tissue cells is long, HDR might be better than LDR
- ◆ Electronic brachytherapy is a good alternative to conventional radionuclide brachytherapy