Therapy Educational Course (TH-C-108, 10:30-11:25 am):

# Radiobiological Models in Brachytherapy Planning and Evaluation

*Zhe (Jay) Chen, PhD & David J. Carlson, PhD*

Department of Therapeutic Radiology

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# Session at a Glance

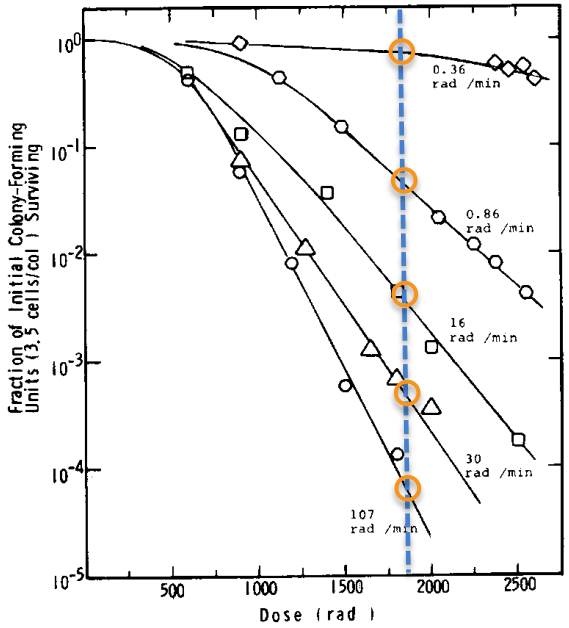
- General introduction
  - *Zhe (Jay) Chen, Ph.D.*
- Basic concepts and relevant radiobiological models
  - *David J. Carlson, Ph.D.*
- Clinical applications in brachytherapy
  - *Zhe (Jay) Chen, Ph.D.*
- Questions & answers
  - *David J. Carlson, Ph.D. & Zhe (Jay) Chen, Ph.D.*
- Session ends promptly at 11:25 am

# Rationale for this course

- Brachytherapy is just a little bit **more complex** than EBRT
  - Brachytherapy utilizes a multitude of radioactive sources & dose delivery techniques:
    - Photon energies: 20 keV to 660 keV (e.g., $^{103}$Pd, $^{125}$I, $^{192}$Ir, $^{137}$Cs)
    - Decay half-lives: ~10 days to 30 years (e.g., $^{131}$Cs, $^{137}$Cs)
    - Temporary continuous LDR irradiation lasting hours to days (e.g., conventional intracavitary GYN)
    - Permanent LDR irradiation with exponentially decaying dose rates (e.g., permanent interstitial implants for prostate and head & neck cancers)
    - Multi-fraction HDR irradiations with different dose fractionations (e.g., intracavitary GYN/Cervix, interstitial prostate implant)
  - The spatial & temporal dose delivery patterns can be drastically different from one another and from EBRT
    - Dose/dose rate can differ easily by a factor of 2 or more among techniques, or over the same target volume for a given technique

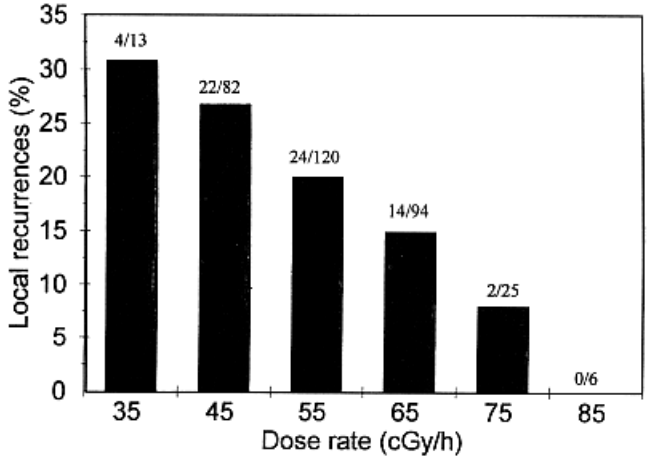
# Rationale for this course

- The clinical impact of such diverse spatial & temporal variations is **difficult to assess** using traditional dose-based metrics
  - The biological effects depend **not only** on the total dose given **but also** on how the dose is delivered
    - *in vitro* Chinese Hamster cells




(Bedford et al., *Radiat Res*, 1973)

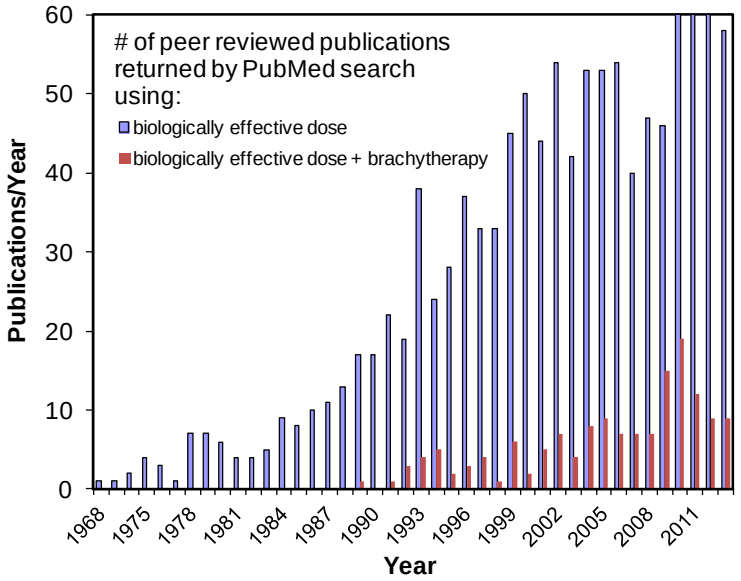
- Breast cancer: EBRT (45 Gy) + $^{192}$Ir boost (37 Gy)




(Mazeron et al., *IJROBP* 1991)

# Rationale for this course

- Radiobiological models can be a potentially useful tool for **relative comparison** of different spatial & temporal dose delivery patterns
  - Many models, purely empirical or based on high-level modeling of key cellular processes, have been developed
  - They are being used increasingly by medical physicists in comparing different treatment techniques and in deriving equivalent treatment regimes




- A good understanding of their potential, limitations, and intended use is critical for safe and beneficial use of the models in clinics

# Goal & Objectives:

- **Goal**: Review existing models and their use in selected brachytherapy modalities to facilitate meaningful and consistent use

- **Objectives**: Help clinical medical physicists to
  - Gain a better understanding of the rationale for using radiobiological models in brachytherapy treatment planning and evaluation
  - Recognize the assumptions and limitations of the models and their intended use in relative comparison of competing brachytherapy modalities
  - Be aware of the potential pitfalls regarding the selection, use, and interpretation of radiobiological models

# Radiobiological Models in Brachytherapy Planning and Evaluation

## Part I: Basic Concepts and Relevant Models

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*Dept. of Therapeutic Radiology*
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***Therapy Educational Course** at the **55th Annual Meeting of the AAPM***

***Date and Time:** August 8, 2013 from 10:30-11:25 AM*
***Location:** Room 108*
***Conflict of interest:** None*

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# Background and Motivation

## Biologically Guided Radiation Therapy (BGRT)

- Systematic method to derive prescription doses that integrate patient-specific information about tumor and normal tissue biology
- ***Problem*:** derived prescriptions may have large uncertainties
  - Uncertainties in physical and biological factors (experimental and clinical) that influence tumor and normal-tissue radiation response
  - Incomplete understanding of molecular and cellular mechanisms

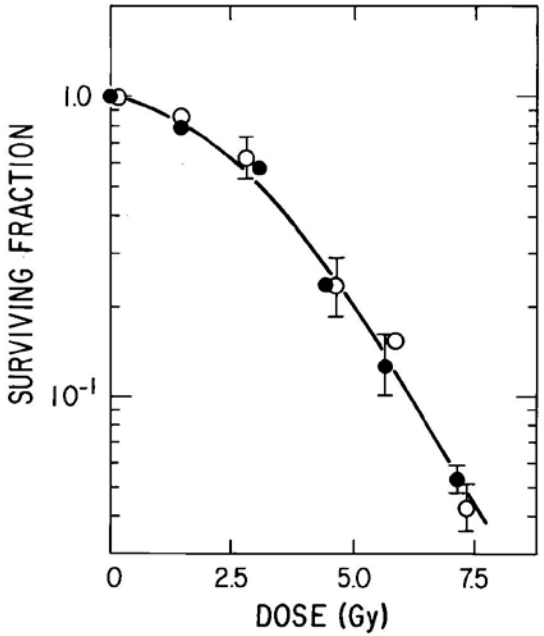
- **Dose-Based TP** → ***Physical objective functions***
  - Minimize dose gradients across tumor (uniformity), deliver prescribed isodose contours to target, minimize max. dose to critical structures, etc.
  - Uniform dose may not be most desirable

- **BGRT** → ***Biological objective functions***
  - More direct approach to optimization instead of relying on dose-based surrogates
    - ✦ Maximize tumor cell killing (LQ) and tumor control probability (TCP)
    - ✦ Minimize normal tissue complication probability (NTCP)

# Classical description of survival curves

- **Low doses**: shoulder region, survival falls slowly w/ dose
- **Intermediate doses**: region where survival curve bends and survival shows greater change with increasing dose
- **High doses**: region where survival falls rapidly with dose (curved? exponential?)

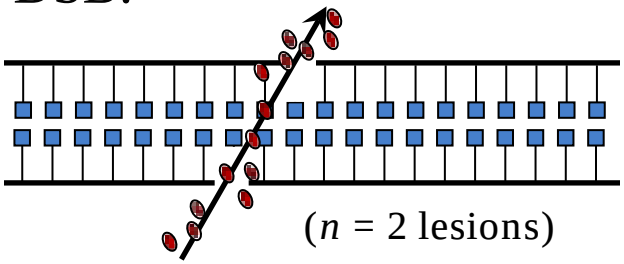
- Most models used to fit survival curves are based this shape
  - Models based on target theory
    - Single target, single hit
    - Multi-target, single hit
    - Composite curves
  - Linear-quadratic (LQ) model



# The double strand break (DSB)

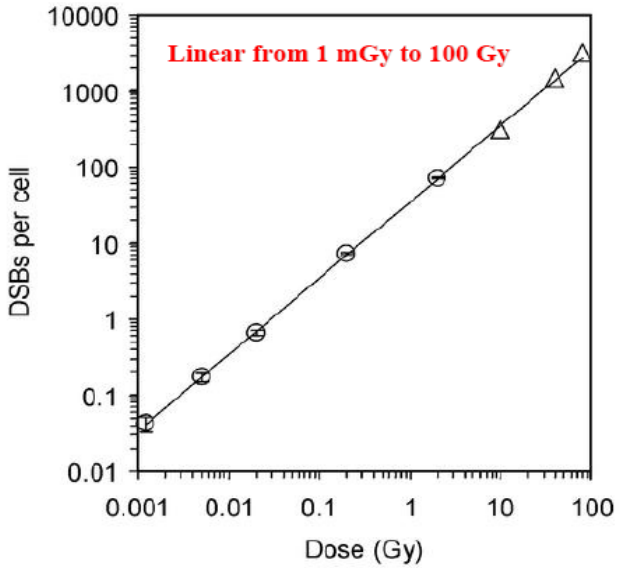
- A DSB is formed when two breaks in the sugar-phosphate backbone occur on opposite sides of DNA helix within **~10 base pairs**

- Simple DSB:




- Many experiments for all types of DNA damage, including DSB, show that damage formation is proportional to absorbed dose up to hundreds of Gy

***DSBs are formed through one-track mechanisms***

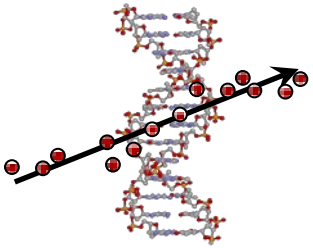



DSB induction in human fibroblasts (MRC-5) irradiated by 90 kVp x-rays (Rothkamm and Lobrich 2003)

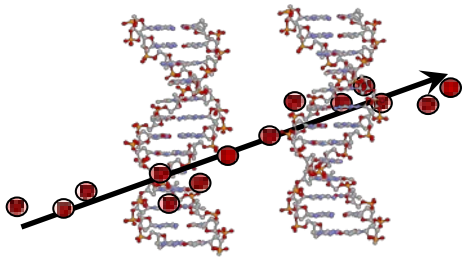
# One- and two-track radiation damage

Lethal lesions are created by the actions of one or two radiation tracks

**1 track damage**
**($\propto D$)**

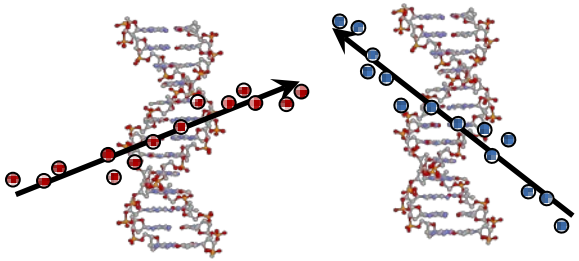


**Lethal DSB misrepair, unrepairable damage**



**Pairwise interaction of two DSBs**

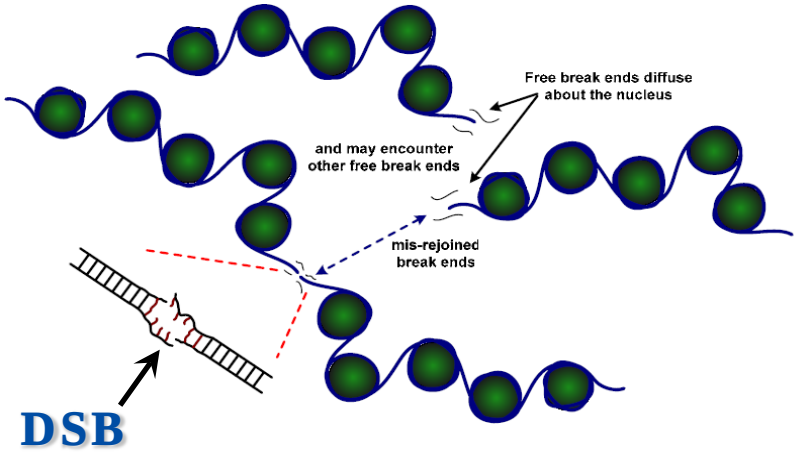
**2 track damage**
**($\propto D^2$)**



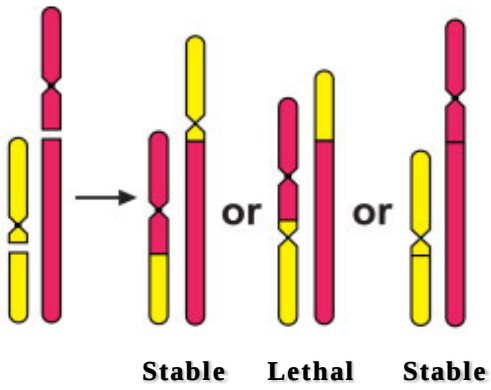
**Pairwise interaction of two DSBs**

# Exchange-type aberrations

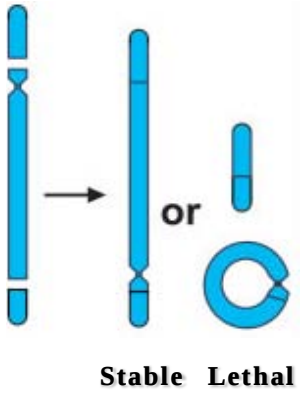
## Pairwise damage interaction (binary misrepair)




**2 chromosomes:**




**1 chromosome:**



# Linear-quadratic (LQ) cell survival model

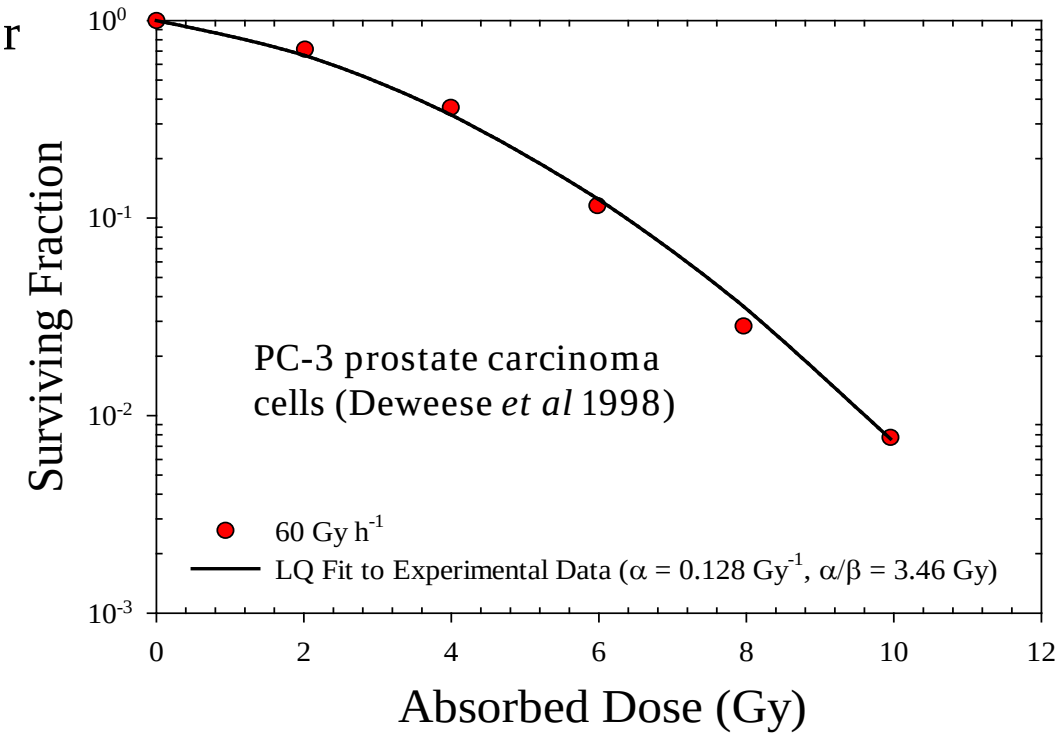
$$S(D) = \exp\left[-\left(\alpha D + \beta D^2\right)\right]$$

($\alpha D + \beta D^2$) = expected number of lethal lesions per cell

$\alpha$ = one-track lethal damage [$Gy^{-1}$]

$\beta$ = two-track lethal damage [$Gy^{-2}$]

**$\alpha/\beta$ [Gy] is clinically used descriptor of intrinsic radiosensitivity**

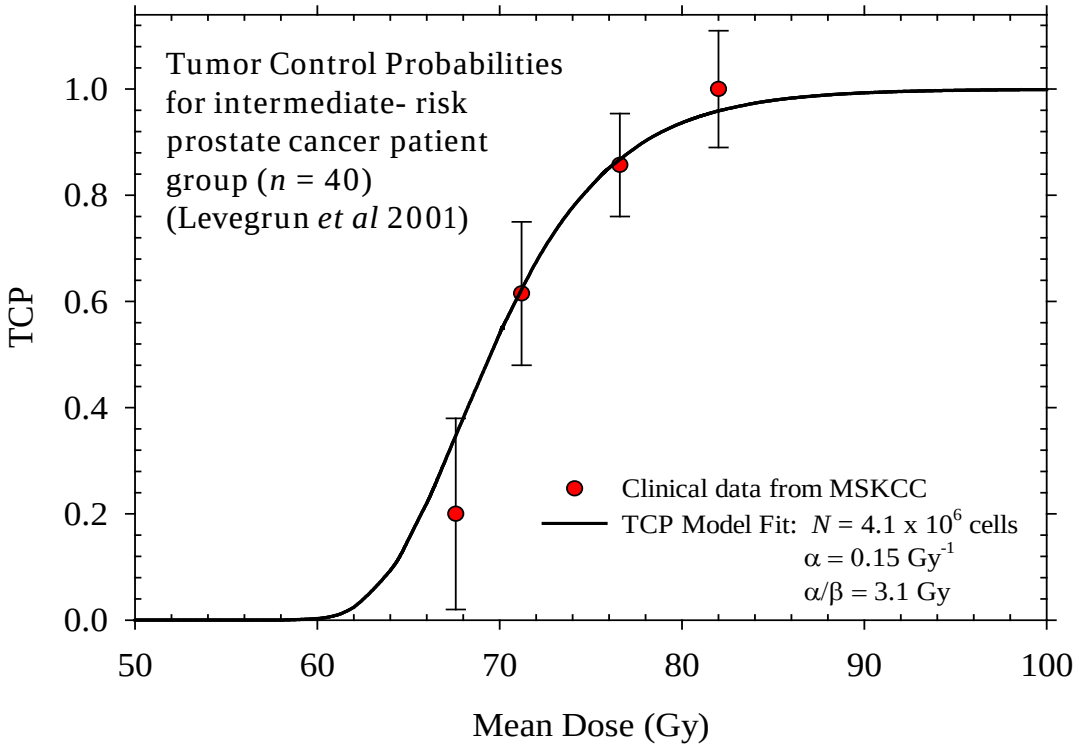


# Tumor Control Probability (TCP) Model

**TCP → relates tumor size and radiation dose to the prob. of tumor control (i.e., no tumor cells survive)**

$$TCP = \exp\left[-N \cdot S(D)\right]$$

$$= \exp\left[-N \cdot \left(e^{-\alpha D - \beta D^2}\right)\right]$$




***N* = initial # of tumor clonogens**

# Inter-patient variability in radiosensitivity

- Heterogeneity of human tumour radiation response is well known
- Many groups have accounted for variations in interpatient tumour heterogeneity by assuming that radiosensitivity values are normally distributed across the population
- If interpatient heterogeneity is ignored, TCP model generally results in an unrealistically steep dose-response curve

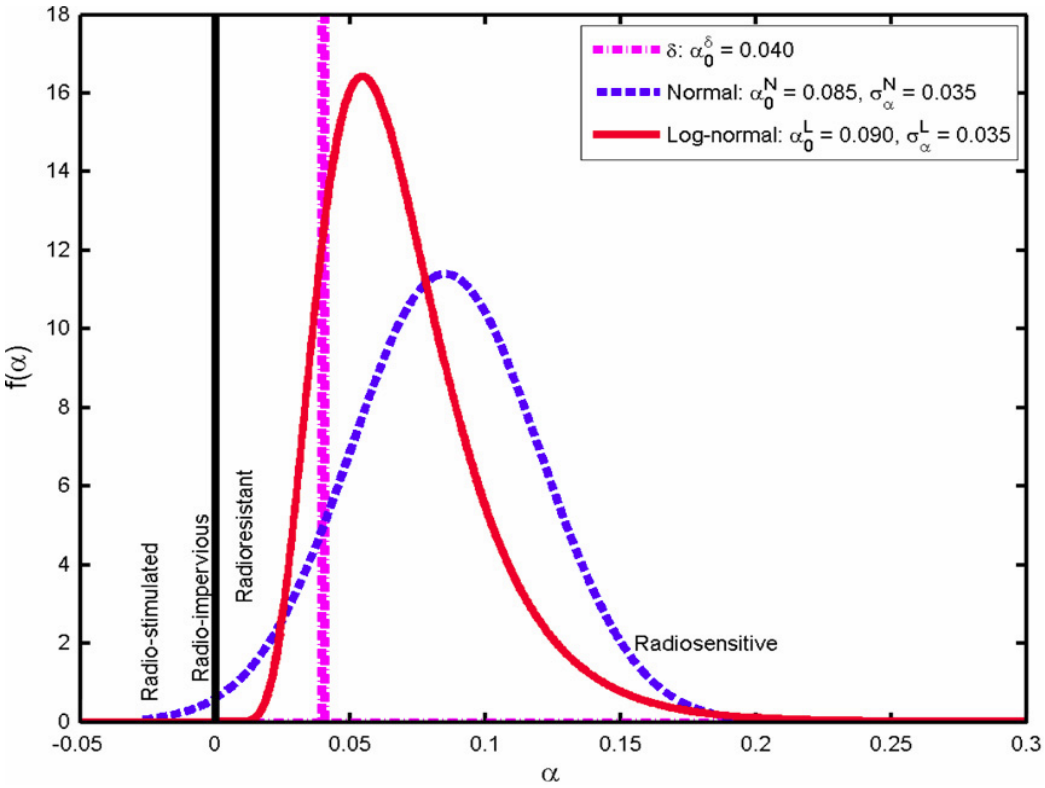
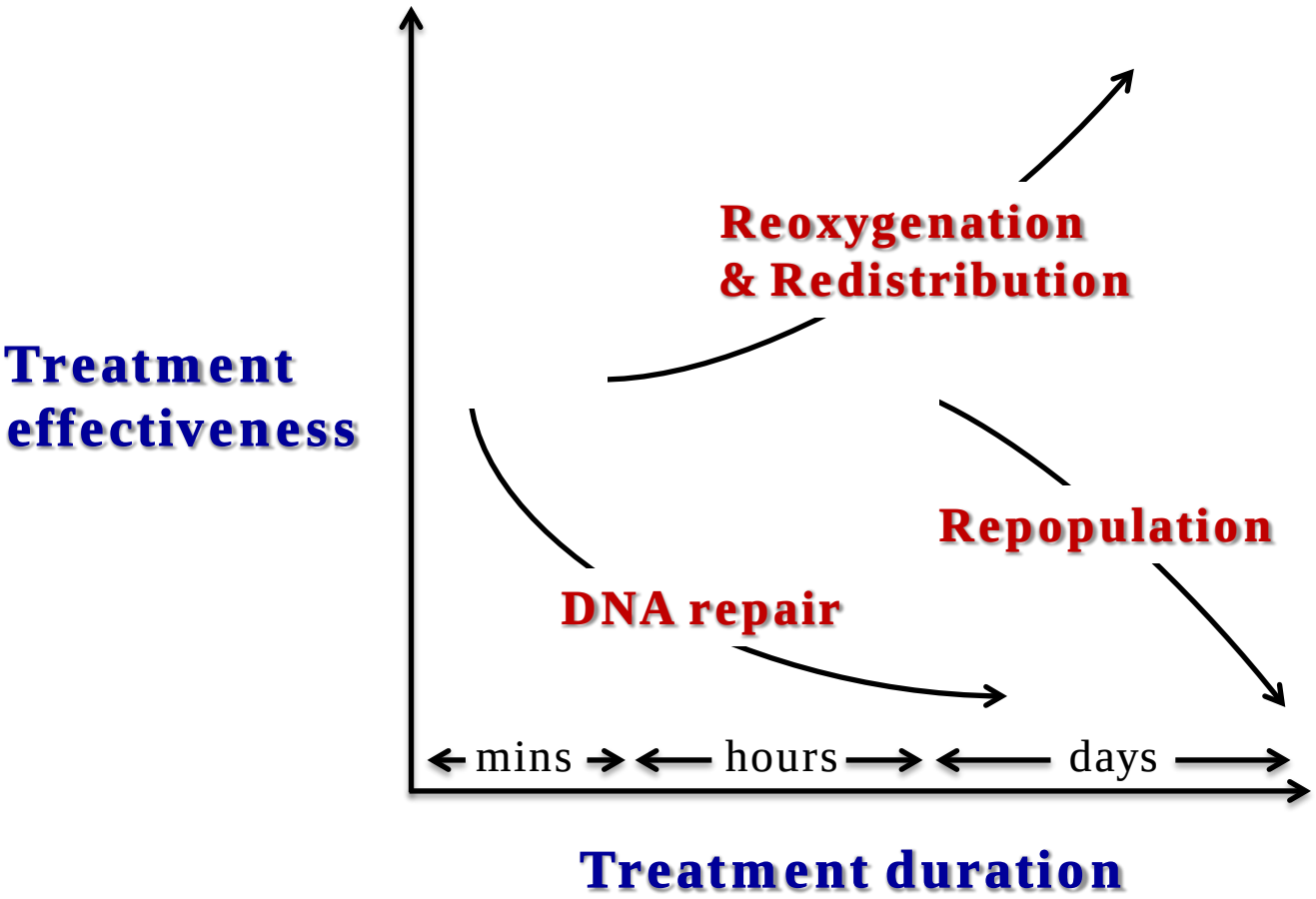



Figure from: Keall PJ, Webb S. Optimum parameters in a model for tumour control probability, including interpatient heterogeneity: evaluation of the log-normal distribution. *Phys. Med. Biol.* 2007; 52: 291–302.

# Factors that alter treatment effectiveness

**4 R's of Radiobiology give rise to "dose rate" effects:**



# Factors that alter treatment effectiveness

Divide a tumor into voxels with radiosensitivity $\alpha_i$ and $\beta_i$. Correct SF for dose heterogeneity, inter- and intra-tumor variability in radiosensitivity and the R's of radiobiology:

$$\mathrm{TCP} = \prod_i \mathrm{TCP}_i$$

$$\mathrm{TCP}_i = \exp\left\{-N_0 f_i \exp\left[-D\left(\alpha_i + \beta_i G_i D_i\right) + \gamma_i T\right]\right\}$$

**Oxygen and LET effects ($\alpha$ and $\beta$)**

**Repair effects ($\mu$ or $\tau$)**

**$N_0 f_i$ is initial # of cells in the *i*th tissue region**

**Repopulation rate in *i*th tissue region**

# DNA damage repair in the LQ model

$$S(D) = \exp\left[-\left(\alpha D + \beta G[\mu,t] D^2\right)\right]$$

$(\alpha D + \beta G[\mu,t] D^2)$ = expected number of lethal lesions per cell

$\alpha$ = one-track lethal damage coefficient [$Gy^{-1}$]

$\beta$ = two-track lethal damage coefficient [$Gy^{-2}$]

**G[$\mu$,$t$] is the Lea-Catcheside dose protraction factor**

$\mu = \ln 2 / \tau$ = rate of DSB rejoining [$h^{-1}$]

**Limiting cases:**

$\lim_{t \to 0} G = 1$ ← **Instantaneous dose delivery**

$\lim_{t \to \infty} G = 0$ ← **Infinitely protracted dose**

Sachs RK, Hahnfeld P, Brenner DJ. The link between low-LET dose-response relations and the underlying kinetics of damage production/repair/misrepair. *Int. J. Radiat. Biol.* 72(4): 351–74 (1997).

# General form of the protraction factor

**Most general form of the protraction factor:**

**Instantaneous absorbed dose rate (e.g., Gy/h) at time *t***

$$G = \frac{2}{D^2} \int_{-\infty}^{\infty} dt\, \dot{D}(t) \int_{-\infty}^{t} dt'\, \dot{D}(t') \exp\left\{-\mu(t-t')\right\}$$

**Absorbed dose (Gy)**

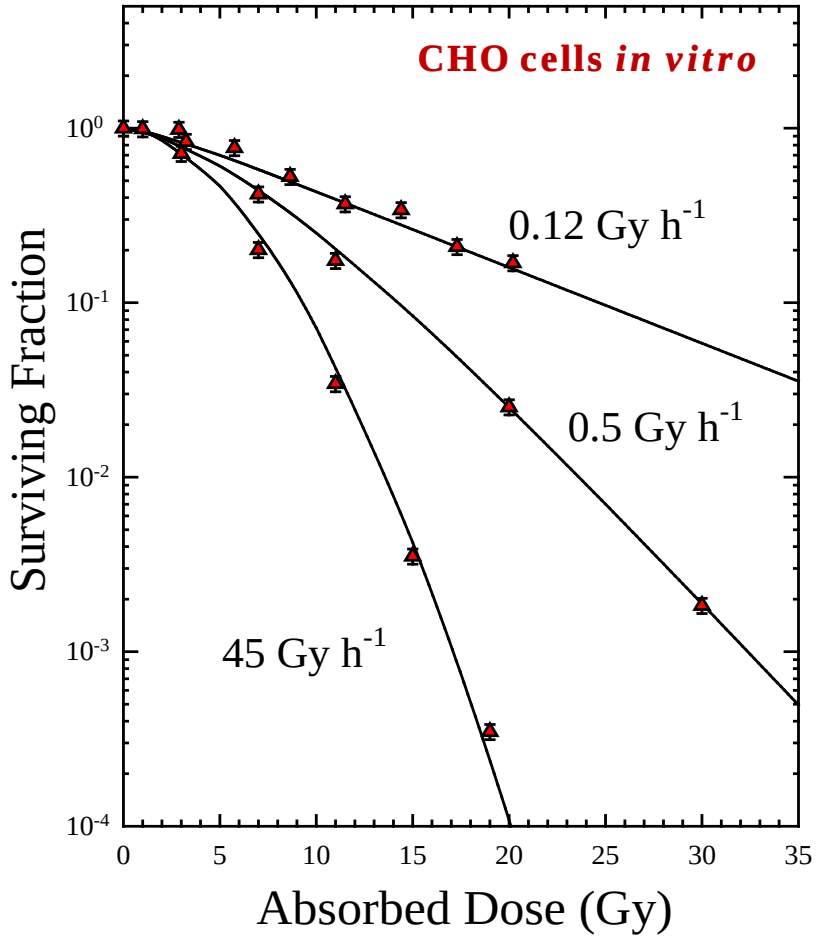
**Probability per unit time sub-lethal damage (DSBs) is rejoined**

$$\mu = \frac{\ln 2}{\tau}$$

$\tau$ ← **Half-time for sub-lethal damage (DSB) repair**

**For most mammalian cells, $\tau$ ~ 0.1 h to 10 h**

# Dose rate effects and DNA damage repair




- Cell killing decreases with decreasing dose rate
- If $G(\mu,t)$ included, unique set of parameters can predict the data:

  $\alpha = 0.04$ Gy$^{-1}$ , $\beta = 0.02$ Gy$^{-2}$, $\tau = 6.4$ h
- Repair of DNA damage occurs between fractions *and* during treatment delivery
- Effect increases with increase in delivery time

→ **Critical for brachytherapy**

Measured data from Stackhouse M.A. and Bedford J.S. *Radiat. Res.* **136**, 250-254 (1993) and Wells R.L. and Bedford J.S. *Radiat. Res.* **94**(1), 105-134 (1983).

# Biologically Effective Dose (BED)

- BED is an **LQ based** estimate of the *effective* biological dose that accounts for delivered **total dose**, the **dose fractionation**, and the **radiosensitivity** of tissue
- Commonly used for isoeffect calculations

**Recall** $S(D) = \exp\left[-\alpha D - \beta G D^2 + \gamma T\right]$

**Take the negative logarithm of *S* and divide by $\alpha$:**

$$\text{BED} \equiv \frac{-\ln S(D)}{\alpha} = D\left[1 + \frac{GD}{\alpha/\beta}\right] - \frac{\gamma T}{\alpha}$$

Physical dose

Relative effectiveness

"Lost" dose due to repopulation effect

# Biologically Effective Dose (BED)

This expression is more general than the commonly used BED formalism

$$\mathrm{BED} = -\ln S(D)/\alpha = D\left[1+\frac{GD}{\alpha/\beta}\right]-\frac{\gamma T}{\alpha}$$

($G \to 1/n$; $\gamma T \to 0$)

Repopulation effects are often neglected and $G$ is set equal to $\sim 1/n$ (daily fractions), where $n$ = # of fractions.

$$\mathrm{BED} = D\left[1+\frac{d}{\alpha/\beta}\right]$$

where $d$ = dose per fraction (Gy) and $D = nd$

HR Withers, HD Thames, LJ Peters. A new isoeffect curve for change in dose per fraction. *Radiother. Oncol.* **1**, 187-191 (1983).

# Isoeffect Example for Prostate Cancer

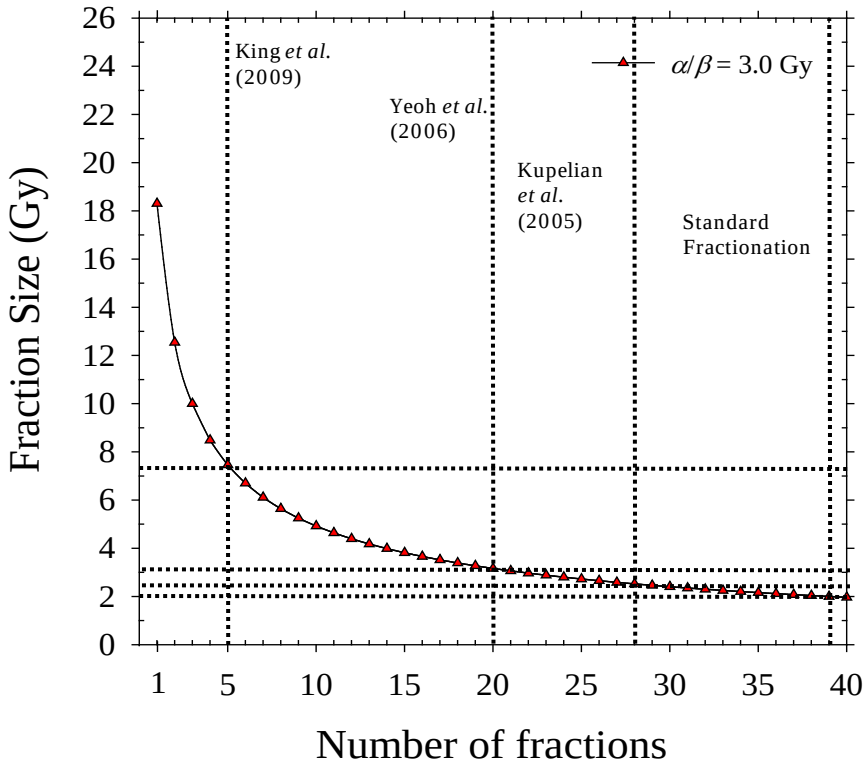
- Assume $\alpha/\beta = 3$ Gy, for a standard EBRT fractionation of 39 fractions of 2 Gy:

$$\text{BED} = 78\ \text{Gy}\left[1+\frac{2\ \text{Gy}}{3\ \text{Gy}}\right] = 130\ \text{Gy}$$

- Rearrange simplified BED equation:

$$d = \frac{\alpha/\beta}{2n}\left(-n+\sqrt{n^2+\frac{4nBED}{\alpha/\beta}}\right)$$

$$= \frac{3\text{Gy}}{2n}\left(-n+\sqrt{n^2+\frac{4n\times 130\ \text{Gy}}{3\ \text{Gy}}}\right)$$



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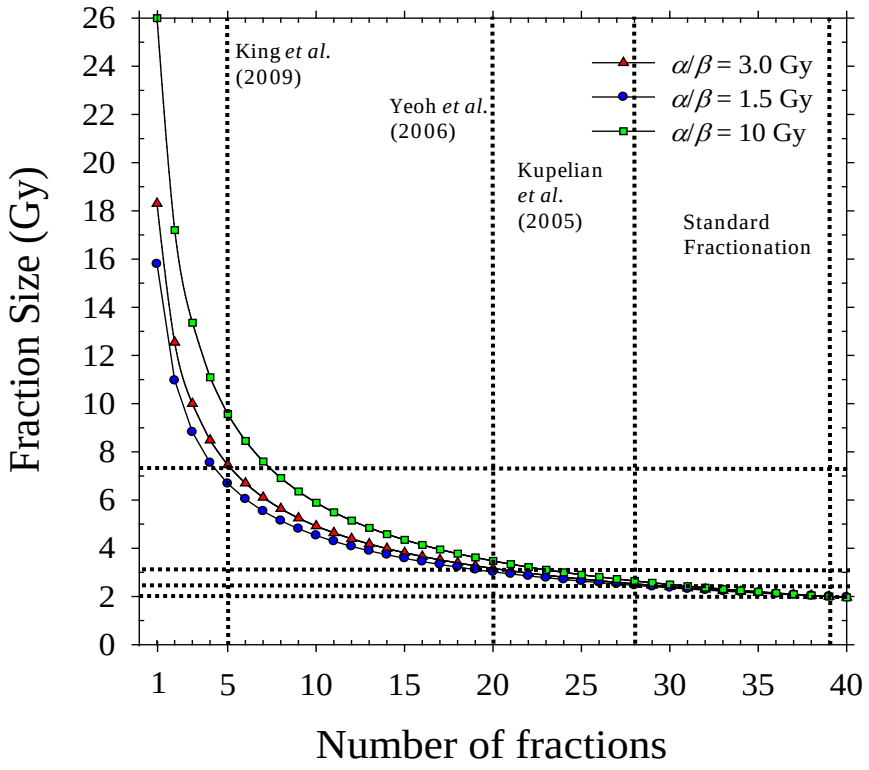

# General Isoeffect Calculations with BED

Two radiotherapy regimens are equally effective when

**Biological effect for Treatment #1** → $BED_1 = BED_2$ ← **Biological effect for Treatment #2**

↓

$$D_1\left[1+\frac{d_1}{\alpha/\beta}\right] = D_2\left[1+\frac{d_2}{\alpha/\beta}\right]$$

↓

**Total dose required for treatment #2 to be equally effective** →

$$D_2 = D_1\frac{\left[d_1+\alpha/\beta\right]}{\left[d_2+\alpha/\beta\right]}$$

**Fraction size (treatment 1)**

**Fraction size (treatment 2)**

# Equivalent Dose in 2 Gy Fractions (EQD2)

- The total dose in 2-Gy fractions that would give the same log cell kill as the given schedule
- Often considered a more practical alternative than BED for the clinic
  - Familiar and intuitive quantity for physicians
  - Can be compared with clinical experience – decades of experience administering 2 Gy fractions

**Fraction size (treatment 1)**

**Equivalent dose in 2-Gy fractions** $\rightarrow EQD2 = D_1 \dfrac{[d_1 + \alpha/\beta]}{[2 + \alpha/\beta]}$

**$d_2$ = 2 Gy**

**Assumptions:**
1. **No change in treatment time**
2. **Repair negligible**

- Note: also commonly written as $EQD2 = \dfrac{\text{BED}}{1 + 2/(\alpha/\beta)}$

# Effective BED

- Brachytherapy dose distributions are inherently nonuniform

- An **Effective BED** can be calculated from individual $BED_i$ for all tumor subvolumes:

$$\mathrm{BED} = -\frac{1}{\alpha}\ln\left(\sum_i v_i e^{-\alpha \cdot BED_i}\right)$$

$v_i \equiv$ fractional volume receiving dose $D_i$ or initial dose rate $\dot{D}_{0i}$

- Information on 3D variation of BED over entire volume of clinical interest
- Evaluate and address biological significance of "hot" or "cold" dose regions
- Can be used to calculate and analyze BED-volume histograms

- **Note**: formulation above implicitly assumes that the (1) initial tumor burden and radiosensitivity are spatially uniform and that (2) RBE is unity

# Equivalent Uniform Dose (EUD)

- EUD is defined as the uniform dose that, if delivered over the same number of fractions as the non-uniform dose distribution of interest, yields the same radiobiological effect
  - Assumes two dose distributions are equivalent if they cause same biological effect
  - Accounts for non-uniform dose throughout tissue of interest
- To extend the concept to normal tissues, Niemierko (1999) proposed a phenomenological formula referred to as the generalized EUD:

$$\mathrm{gEUD} = \left( \sum_i v_i D_i^a \right)^{1/a}$$

**$v_i$ is the fractional organ volume receiving a dose $D_i$**
**$a$ is a tissue-specific parameter for volume effect**

**gEUD often used in plan optimization and evaluation because same model can be applied to both targets and OARs with a single biological parameter**

Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Med Phys.* 24(1):103-10 (1997).
Niemierko A. A generalized concept of equivalent uniform dose (EUD). *Med Phys.* 26: 1101 (1999).

# Model assumptions and limitations

- **Limitations of the LQ model**
  - Does not explicitly capture many important biological factors, e.g., low dose hyper-radiosensitivity, bystander effects, possibility of other biological targets (e.g., endothelial cell apoptosis in vasculature)
  - High dose controversy (approximation for low dose rates and low doses, predictive up to ~10 Gy or higher?)
- **Uncertainties in radiosensitivity parameters**
  - Assumed values not meant to be interpreted as only biologically plausible parameters (inter- and intra-patient variability in radiosensitivity)
  - Lack of adequate data for many tumor sites and normal tissue
- **Best to practice evidence-based medicine**
  - Clinical data is the gold standard → must be skeptical of simplified models and understand limitations
  - Value of models highest in absence of good data → guide treatment decisions instead of relying on trial and error

# Radiobiological Models in Brachytherapy Planning and Evaluation

## II. Clinical Applications and Discussions

*Zhe (Jay) Chen, Ph.D.*
*Professor*
*Dept. of Therapeutic Radiology*
*zhe.chen@yale.edu*

***Therapy Educational Course** at the **55th Annual Meeting of the AAPM***

***Date and Time:*** *August 8, 2013 from 10:30-11:25 AM*
***Location:*** *Room 108*
***Conflict of Interest:*** *None*

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# What are the models good for?

- Predicting absolute response – **No** (at least, not yet)
- Relative comparison – Yes (in most of the current applications)

**Comparing the relative effectiveness of a given technique on different biological systems**

(**same** dose/dose delivery pattern on **different** model parameters)

- fast/slow growing tumors
- early/late reacting tissues
- aerobic/hypoxic cells
- impact of model parameters uncertainties
- …

**Comparing the relative effectiveness of different treatment techniques on a given biological system**

(**different** dose/dose delivery patterns on the **same** set of model parameters)

- $^{125}I/^{103}Pd/^{131}Cs$
- LDR/HDR/PDR
- impact of technique variation
- optimization of dose delivery techniques
- …

# Protracted irradiation with constant dose rates

- Relevant clinical scenarios:
  - Intracavitary LDR brachytherapy using $^{137}Cs$ source ($T_{1/2}$ of 30 yrs) for cervical cancer
    - e.g., total dose: 80 Gy to Point-A in two fractions
    - Dose rate at Point-A: ~ 0.53 Gy/hr, total treatment last 144 hrs
    - Dose rate: ~constant per fraction due to long $T_{1/2}$
  - Intracavitary HDR using $^{192}Ir$ source ($T_{1/2}$ of 74 days) for GYN malignances, breast cancer, and interstitial HDR for prostate cancer, ...
    - Total dose: variable in multiple fractions
    - Dose rate at prescription point: ~ 12 – 50 Gy/hr, treatment last from minutes to < 1 hr per fraction
    - Dose rate: ~constant per fraction due to short treatment time
- How is the biological effectiveness of a prescribed dose affected by the rate of dose delivery?

# Protracted irradiation with constant dose rate

- The BED model

$G(T)$ – dose protraction factor

$$BED = D\left[1 + \frac{D}{(\alpha/\beta)}\frac{2}{(\mu T)^2}(e^{-\mu T} + \mu T - 1)\right] - \gamma\frac{T - T_k}{\alpha}$$

RE – relative effectiveness

**Recall the basic assumptions:**

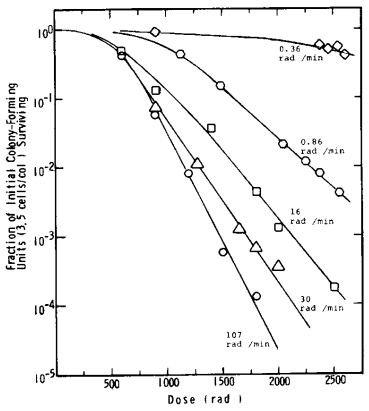
- Constant dose rate = $D/T$
- For uniform dose distribution or dose at a point of interest
- Radiobiological properties by five parameters ($\alpha$, $\beta$, $\mu$, $\gamma$, $T_k$)
- Mono-exponential repair kinetics
- Uniform proliferation rate

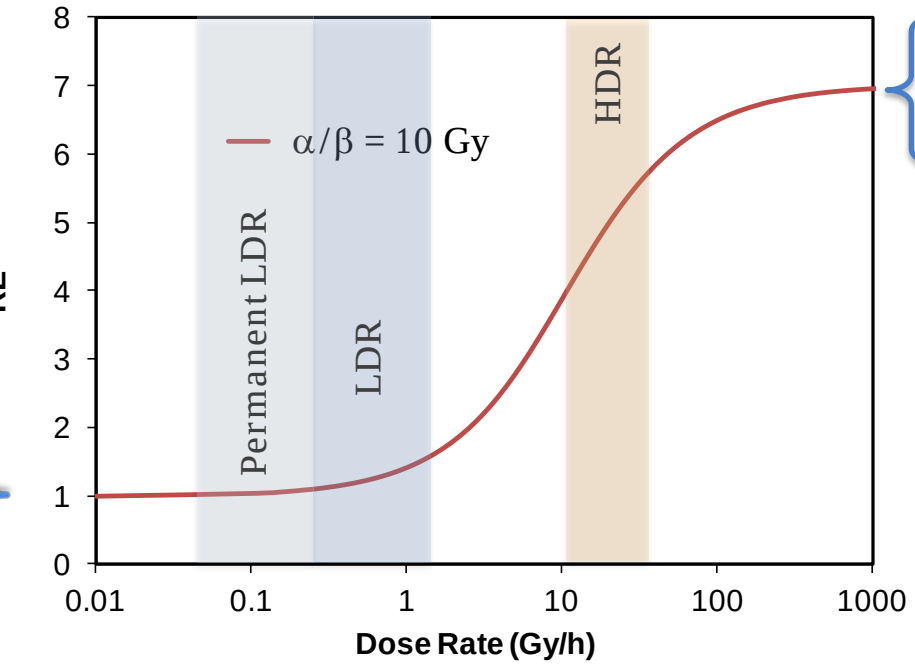
– This model captures the influence of only 2 "R"s of radiobiology, i.e., repair & repopulation, on the dose rate effect

– In absence of these 2 "R"s, $BED = D\left[1 + \frac{D}{(\alpha/\beta)}\right]$, no dose rate effect

# Single fraction LDR/HDR: Influence of dose rate

$$RE = 1 + \frac{D}{(\alpha/\beta)} \frac{2}{(\mu T)^2} (e^{-\mu T} + \mu T - 1)$$




$RE = 1$

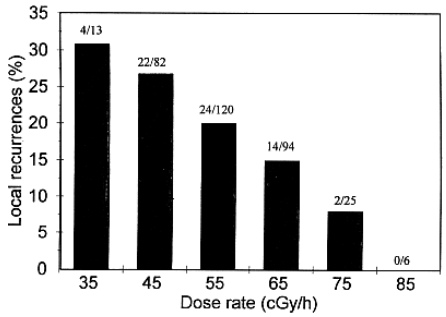
$T \rightarrow \infty$

Instant repair ($\mu \rightarrow \infty$)

$RE = 1 + \frac{D}{(\alpha/\beta)}$

$T \rightarrow 0$

No repair ($\mu \rightarrow 0$):

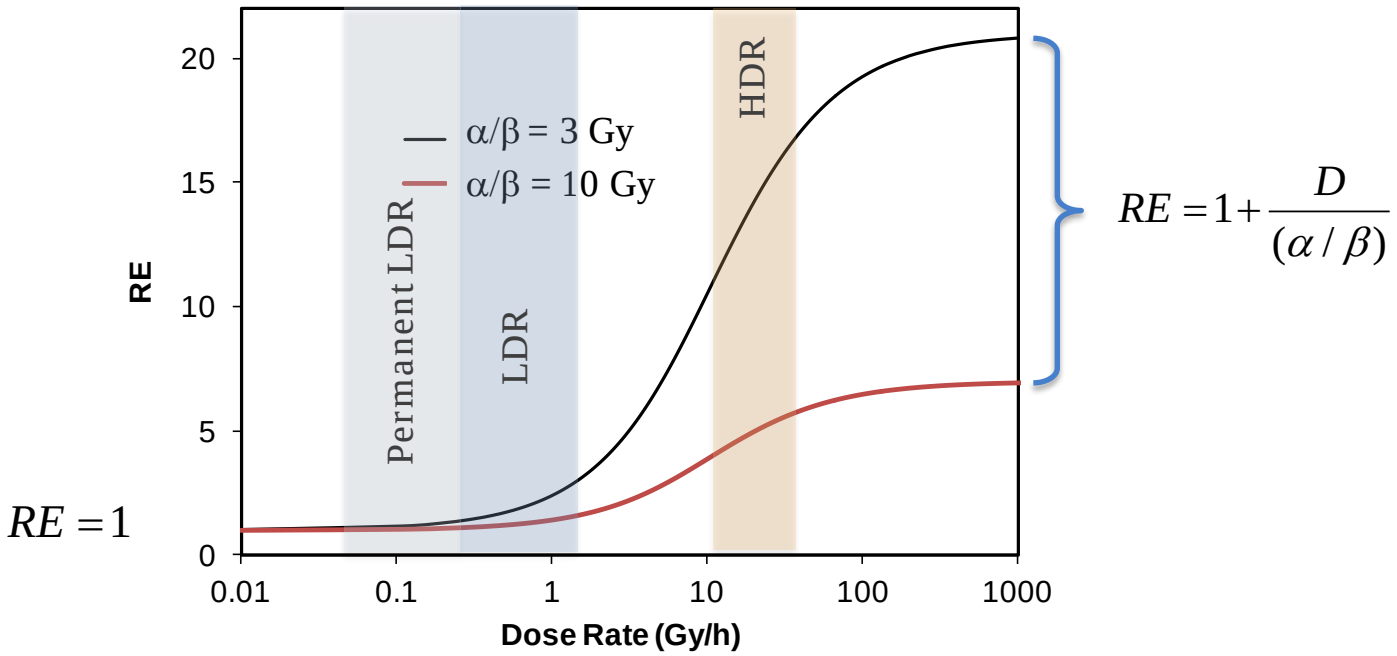



(repair half-time ($t_{1/2}$) = 1.5 hr, $\gamma$ = 0.0, $D$ = 60 Gy)

– The relative effectiveness of a given dose increases with increasing dose rate

# Single fraction LDR/HDR: Influence of dose rate
## - dependence on tissue type

$$RE = 1 + \frac{D}{(\alpha/\beta)} \frac{2}{(\mu T)^2} (e^{-\mu T} + \mu T - 1)$$




($t_{1/2}$ = 1.5 hr, γ = 0.0, $D$ = 60 Gy)

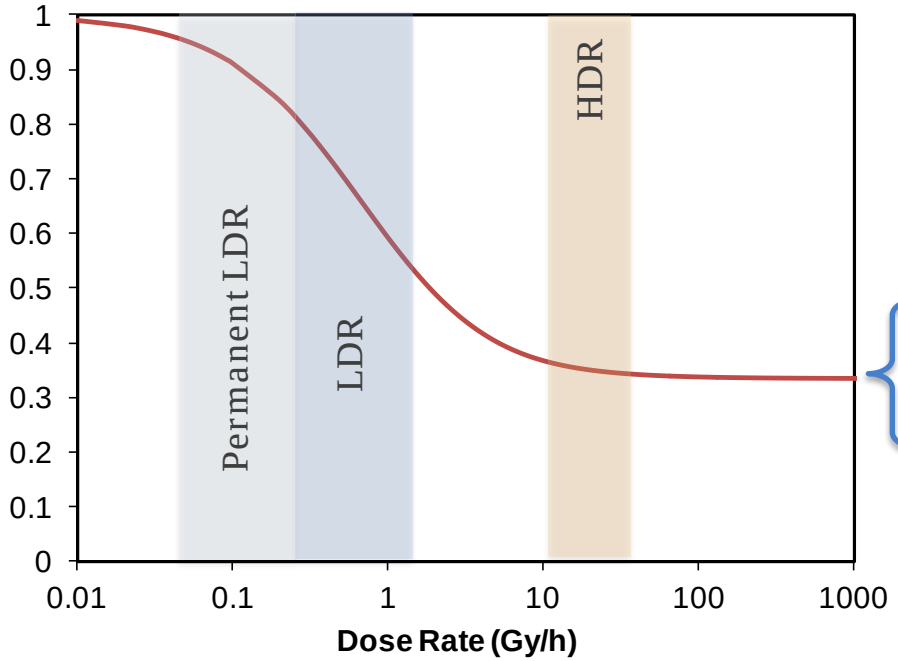
– Altering dose rate has a greater influence on late-reacting (e.g., typical normal) tissues than for early reacting tissues (e.g. typical tumors)

# Single fraction LDR/HDR: Influence of dose rate
## - impact on therapeutic gain

$$RE = 1 + \frac{D}{(\alpha/\beta)} \frac{2}{(\mu T)^2} (e^{-\mu T} + \mu T - 1)$$

Surrogate for potential therapeutic gain

$$\frac{RE(\alpha/\beta = 10\ Gy)}{RE(\alpha/\beta = 3\ Gy)}$$




$T \rightarrow 0$:

$= (1 + 60/10)/(1 + 60/3)$

$= 1/3$

($t_{1/2}$ = 1.5 hr, $\gamma$ = 0.0, $D$ = 60 Gy)

– Consistent with the general philosophy favoring dose protraction while cautioning against using small number of high doses/dose rate

# Single fraction LDR/HDR: Influence of dose rate
## - interplay with other factors

- The observations made so far are based on three key assumptions:

  1) The $\alpha/\beta$ of tumor is greater than irradiated normal tissues
  2) There is no cell proliferation
  3) Normal tissues receives the same dose as the tumor

- A change in these assumed conditions may lead to a different conclusion, for example
  - The advantage of dose protraction on therapeutic gain diminishes for tumors with $\alpha/\beta \leq$ those of normal tissues (e.g., prostate Ca)
  - Additional normal tissue sparing achievable in a HDR treatment could potentially improve the therapeutic ratio of the HDR technique to the level of LDR treatment

# Multi-fraction HDR vs. LDR for cervix
## - influence of normal tissue sparing

- An illustrative sample by Dale:
  - LDR reference treatment
    - 60 Gy in 72 hrs
    - $\alpha/\beta$ = 10 Gy for tumor & 3 Gy for rectum, $t_{1/2}$ = 1.5 hr, no repopulaiton
    - Rectum receive 80% of prescription dose ($f$ = 0.8)

--> $$BED = f \cdot D\left[1+\frac{f \cdot D}{(\alpha/\beta)}\frac{2}{(\mu T)^2}(e^{-\mu T}+\mu T-1)\right]$$

    - $BED_{tumor}$ (LDR) = 81.0 Gy
    - $BED_{rectum}$ (LDR) = 92.8Gy
  - HDR using 6 fractions with matching tumor BED

$$BED = 6 \cdot f \cdot d\left[1+\frac{f \cdot d}{(\alpha/\beta)}\right] = 81.0$$

    - $d$ = 7.6 Gy ($f$ = 1.0)
    - $BED_{rectum}$ = 111.6 Gy ($f$ = 0.8)
  - Additional sparing needed to achieve LDR $BED_{rectum}$

$$BED = 6 \cdot f \cdot d\left[1+\frac{f \cdot d}{(\alpha/\beta)}\right] = 92.8$$

    - $f$ = 0.72

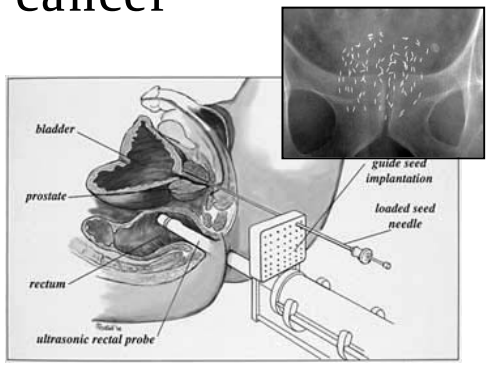
- An extensive analysis by Brenner & Hall for fractionated HDR and LDR brachytherapy of the cervix also reached a similar conclusion

Dale RG, *BJR* **63**, 290-294; Brenner D, et al., **64**, 133-141

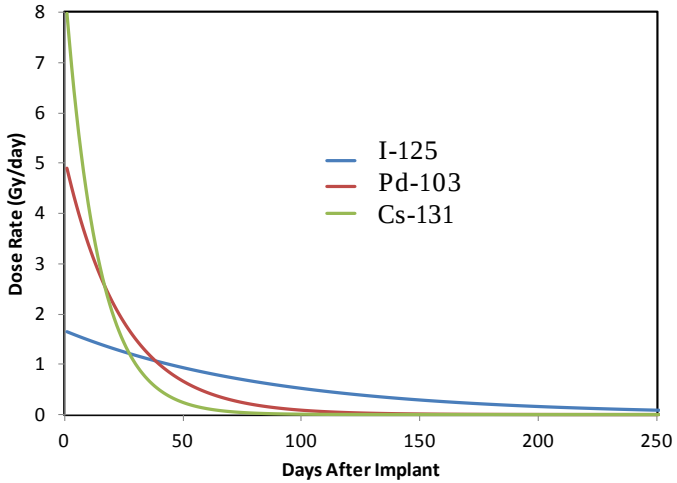
# Permanent interstitial brachytherapy (PIB)
## - Protracted irradiation with declining dose rate

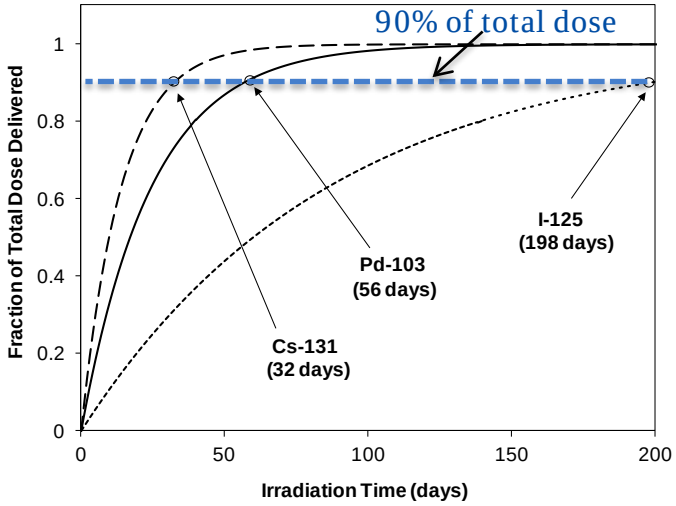
- For example, PIB for early-stage prostate cancer

| Radionuclide | <Energy> (keV) | HVL (mm Pb) | Half-Life (days) |
|---|---|---|---|
| $^{125}$I | 28.5 | ~0.03 | 60 |
| $^{103}$Pd | 21 | ~0.01 | 17 |
| $^{131}$Cs | 30.4 | ~0.03 | 9.7 |




– With unique dose delivery patterns



# BED for PIB: The Dale Formalism

- Recall the equation: $BED = D(T_{eff})RE(T_{eff}) - \dfrac{\ln 2 \cdot (T_{eff} - T_k)}{\alpha T_d}$

$$\mathrm{RE(T)} = 1 + \frac{D(T)}{(\alpha/\beta)} \times \underbrace{\frac{\lambda}{\mu - \lambda} \frac{2}{(1 - e^{-\lambda T})^2} \left\{ \frac{1}{2\lambda}(1 - e^{-2\lambda T}) - \frac{1}{\lambda + \mu}(1 - e^{-(\mu+\lambda)T}) \right\}}_{G(T)}$$

$G(T)$ – dose protraction factor

  - It captures the interacting effects of changing dose rate during dose delivery with sublethal damage repair and cell repopulation

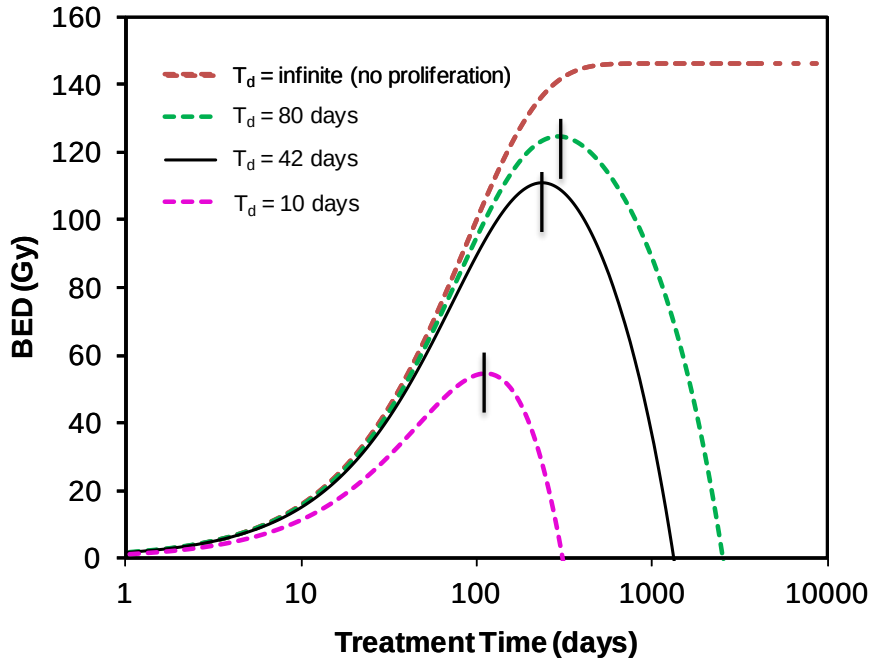
**Basic assumptions:**

- For uniform dose distribution or dose at a point of interest
- Radiobiological properties by five parameters ($\alpha$, $\beta$, $\mu$, $\gamma$, $T_k$)
- Mono-exponential repair kinetics
- Uniform proliferation rate
- BED evaluated at the "effective treatment time", $T_{eff}$, is adequately representative of biological effects produced by the implant

(Dale RG, *BJR* **62**, 241-244, 1989; & **58**, 515-528, 1985)

# BED for PIB: The Dale Formalism

- Definition of "effective treatment time", $T_{eff}$




($^{125}$I, D=145 Gy, $t_{1/2}$=0.27 hr, α=0.15 Gy$^{-1}$, α/β=3Gy, $T_k$=0)

– In absence of cell proliferation:

$$\mathrm{BED}\big|_{T=\infty} = D \times \left\{ 1 + \frac{\lambda}{\lambda + \mu} \frac{D}{\alpha / \beta} \right\}$$

– In presence of cell proliferation:

- BED becomes negative at $T = \infty$
- *A* $T_{eff}$ is defined as the time at which

  *the rate of cell kill equal the rate of cell repopulation*

$$T_{eff} = T_{avg} \ln\left( \alpha D \frac{T_d}{T_{1/2}} \right)$$

# PIB for prostate cancer: Influence of radioactive source

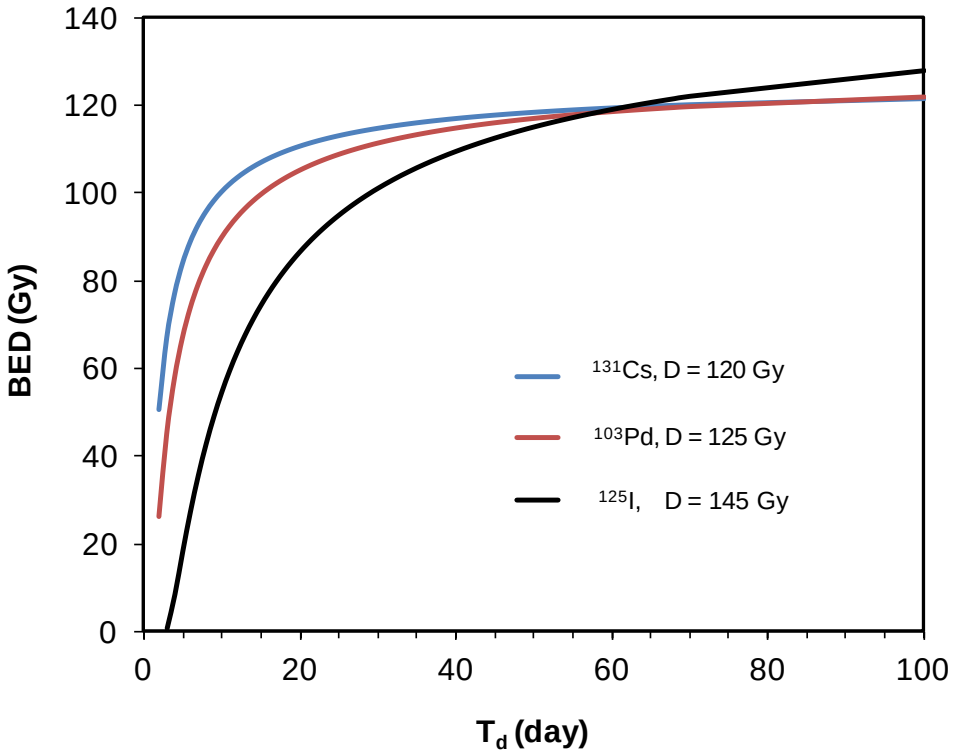
- For monotherapy, the prescribed dose for different sources are usually different
  - Why using different doses? Are they biologically equivalent?

| Radionuclide | <Energy> (keV) | Half-Life (day) | Total Dose (Gy) | Initial DR (cGy/h) | $T_{eff}$ (day) | BED (Gy) |
|---|---|---|---|---|---|---|
| $^{125}$I | 28.5 | 60 | 145 | 7 | 236 | 111 |
| $^{103}$Pd | 21 | 17 | 125 | 21 | 94 | 115 |
| $^{131}$Cs | 30.4 | 9.7 | 120 | 36 | 61 | 117 |
| | | | 110 | | | 107 |

  - Let's perform BED calculation using the AAPM TG-137 recommended parameter set ($\alpha$=0.15 Gy$^{-1}$, $\alpha/\beta$=3 Gy, $t_{1/2}$=0.27 hr, $T_d$ = 42 days, $T_k$=0)
  - It seems the BEDs are reasonably similar for this particular set of radiobiological parameters

# PIB for prostate cancer: Influence of radioactive source
## - dependence on tumor growth rate

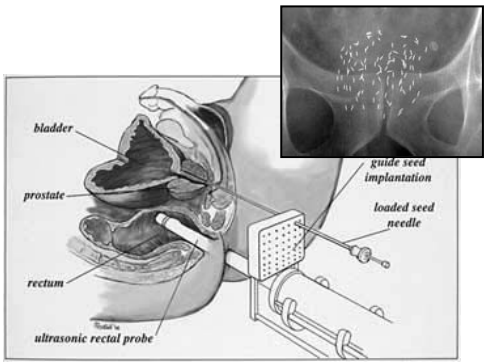
– What happens if some tumors grow at different rates?



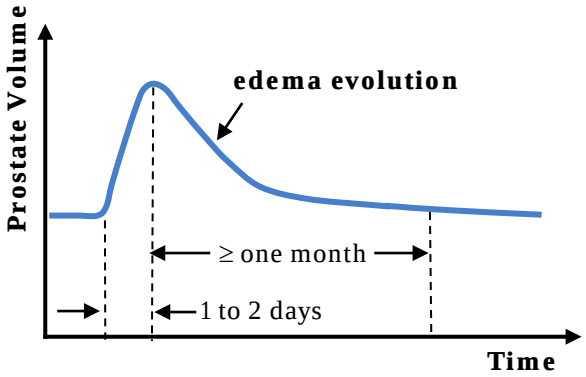

⇒ Relative effectiveness depends on tumor growth rate: $^{125}$I relative more effective for slow growing tumor, $^{103}$Pd and $^{131}$Cs are better for fast growing tumors

# PIB for prostate cancer: Influence of radioactive source
## - interplay with treatment-induced temporal variations

- Is the source with shorter decay half-life always better in practice?
  - "Yes", for static implants
  - "?", when tumor/source position varies during treatment




Procedure-induced
Prostate edema




  - Severity & time-to-resolution vary widely from patient to patient
    (magnitude: 30 to 100%; resolution half-life: 4 to 25 days)*
  - Edema forces the sources to deviate from their planned locations
  - It can have a significant impact on the actual dose delivered to patient**

*e..g., Waterman F, et al., *IJROBP 1998;* **e.g., Yue N, et al., *IJROBP 1999* & Chen Z, et al., *IJROBP*, 2000

# PIB for prostate cancer: Influence of radioactive source
## - interplay with procedure-induced prostate edema

- Edema-induced reduction in BED as a function of edema magnitude and resolution hale-life for pre-planned prostate implant

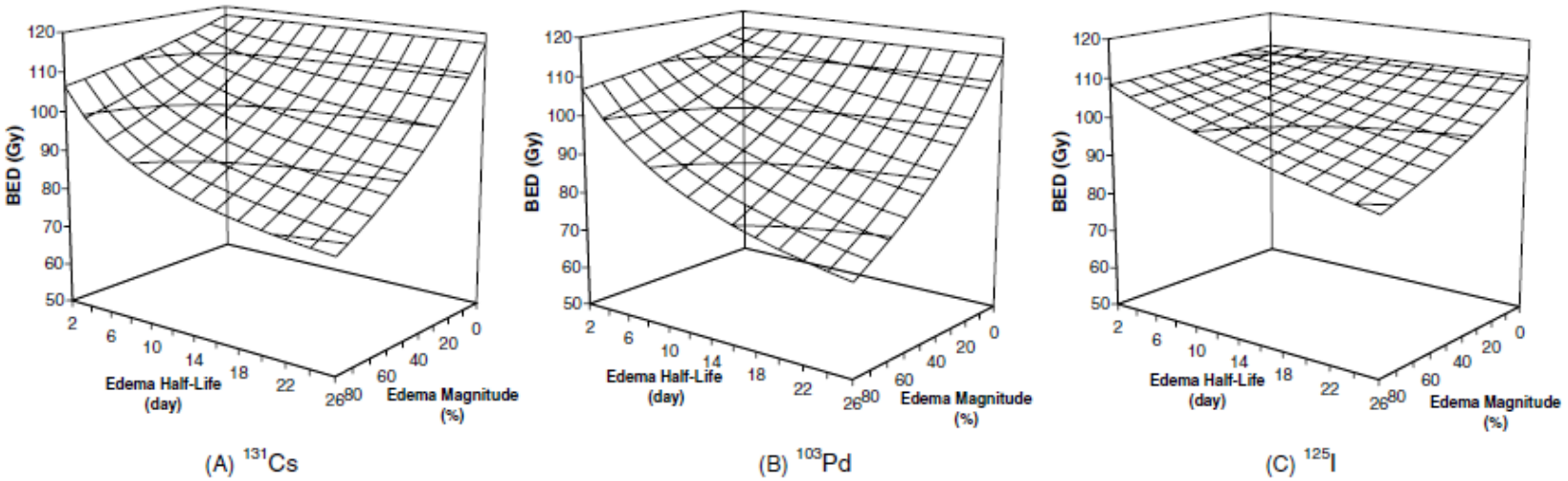



**Figure 1.** Edema-induced variations in the BED for prostate brachytherapy using $^{131}$Cs, $^{125}$I and $^{103}$Pd sources ($\alpha = 0.15$ Gy$^{-1}$, $\alpha/\beta = 3.0$ Gy, $T_p = 42$ days and repair half-time = 0.27 h).

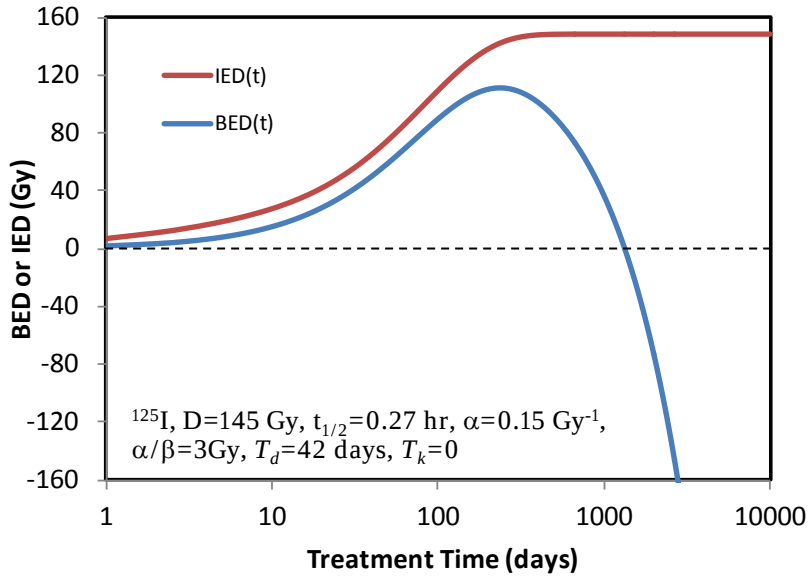
⇒ Source with shorter decay half-life and lower photon energy is more sensitive to edema induced reduction in BED

(Chen Z, et al, *PMB*, 2011; 56:4895-4912; *IJROBP, 2008;* **70**:303-310)

# BED for PIB: Concerns for *proliferating* tumors (?)

- Zaider et al. introduced an iso-effective dose (IED) formalism that is mathematically well behaved in the limit of $t \to \infty$

$$IED(t) = -\frac{1}{\alpha}\log\left[\frac{S_0(t)e^{(b-d)t}}{1+bS_0(t)e^{(b-d)t}\int_0^t \frac{du}{S_0(u)e^{(b-d)u}}}\right]$$



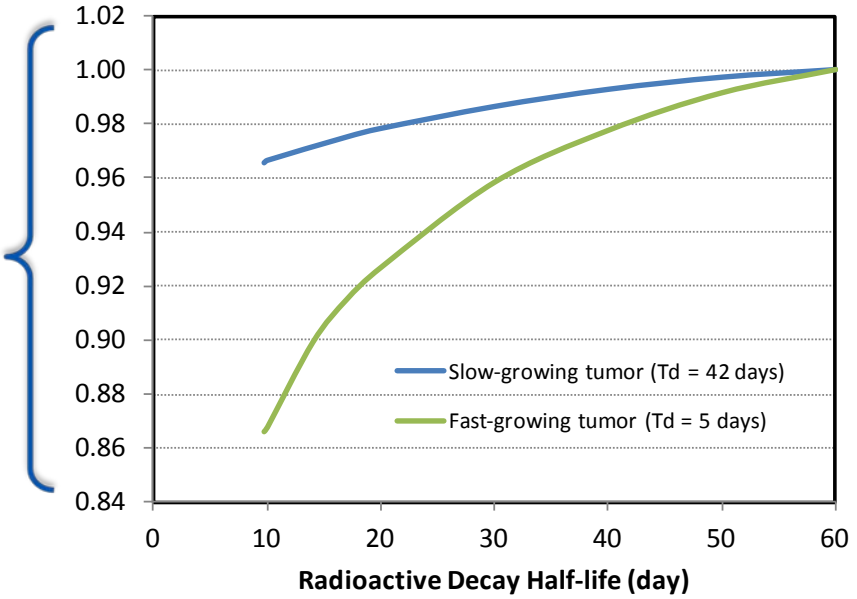

- $S_0(t)$: cell survival probability at time $t$, in absence of cell proliferation
- $b$: cell birth rate
- $d$: spontaneous cell death rate
- $b$-$d$: $= \ln(2)/T_d$

(Zaider M et al., *PMB*, 2000; **45**:279-293 & 2007; **52**:6355-6362)

# BED vs. IED: Permanent prostate brachytherapy

- Impact on deriving iso-effective prescription dose for new sources:
  - e.g., using $^{125}$I implant with 145 Gy as a reference:

$$\frac{\text{Prescription dose derived using BED}}{\text{Prescription dose derived using IED}}$$




  - BED model produces lower iso-effect prescription dose than IED model
  - The difference becomes greater for faster-growing tumors using source of shorter half-life
    - For $T_d$ = 42 days: the difference is 2.7% & 3.5% lower for $^{103}$Pd and $^{131}$Cs, respectively
    - For $T_d$ = 5 days: the difference is 8.4% & 13.4% lower for $^{103}$Pd and $^{131}$Cs, respectively

(Chen Z and Nath R, *IJROBP*, 2012; **84**:S755)

# Concluding Remarks

- "Essentially, all models are wrong, but some are useful"

  - 1987, George E.P. Box


- When **used properly**, radiobiological modeling in brachytherapy can provide a potentially useful tool for
  - performing efficient pre-clinical evaluation of the relative clinical effects of different dose delivery patterns
  - conducting meaningful comparison of the treatment outcomes of different techniques and their efficacy relative to EBRT
  - optimizing the treatment efficacy of brachytherapy in either mono-therapy or combined modality settings.

# Thank You!