Biologically Guided Radiation Therapy (BGRT)

Effects Inter-Patient and Intra-Tumor Heterogeneity

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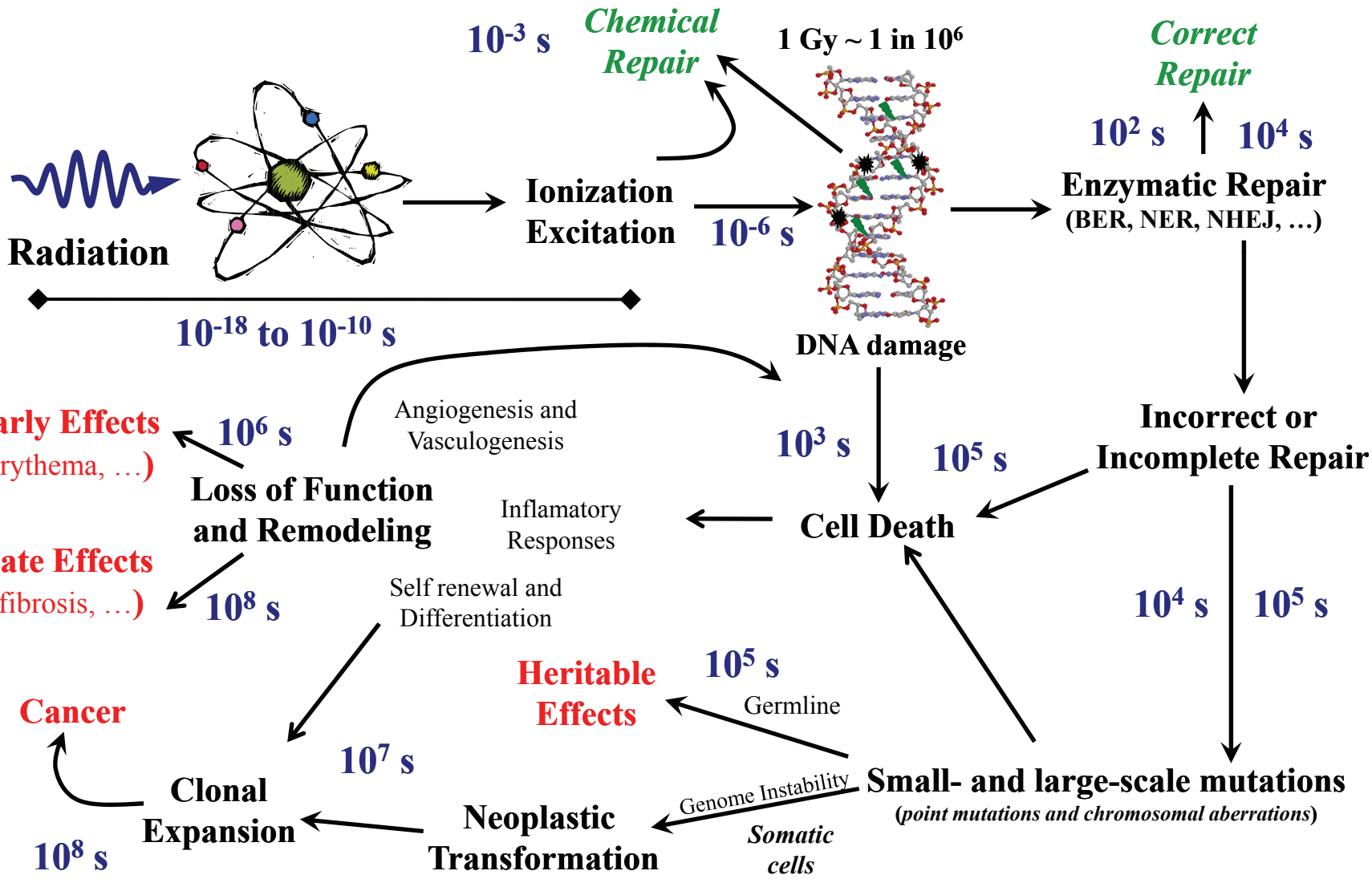
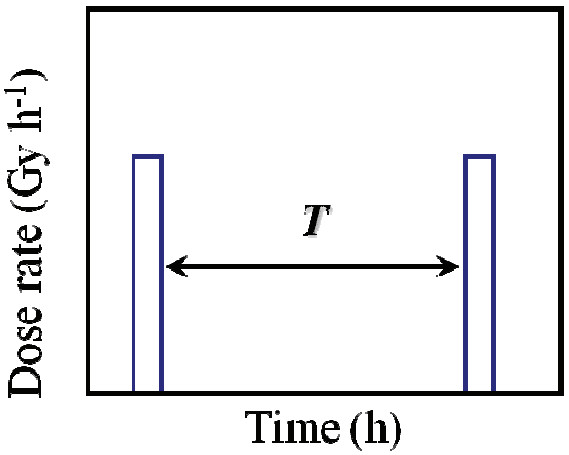
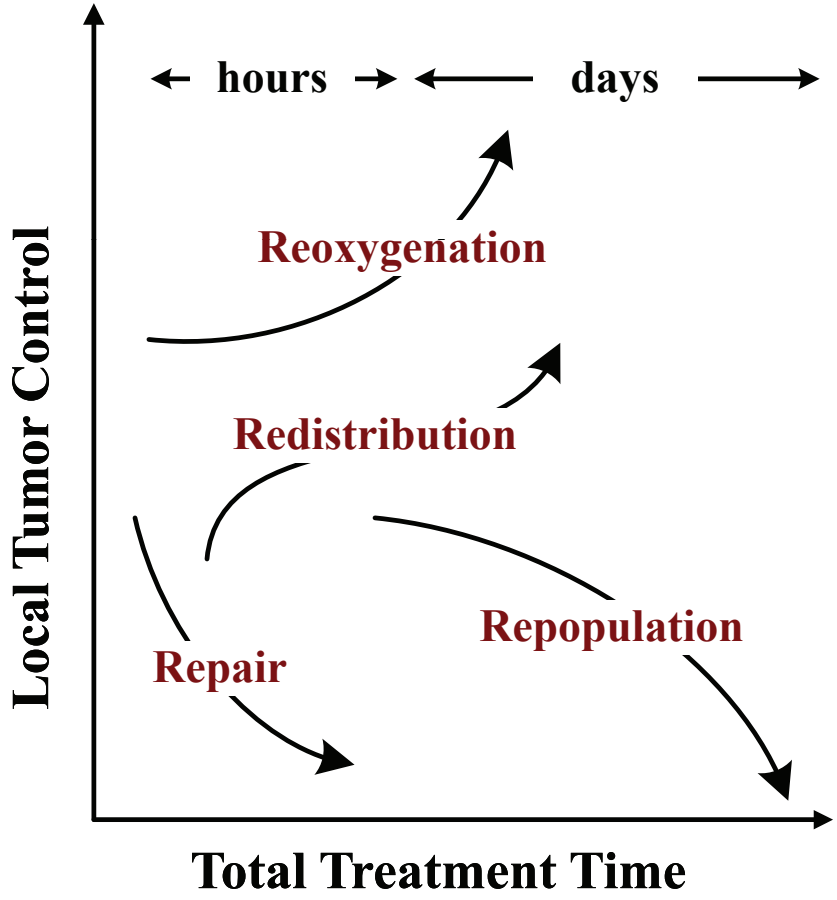
Physics → Chemistry → Biology → Clinic



Four R's of Radiobiology in RT

- **R**epair (↓)
- **R**epopulation (↓)
- **R**edistribution (↑)
- **R**eoxygenation (↑)





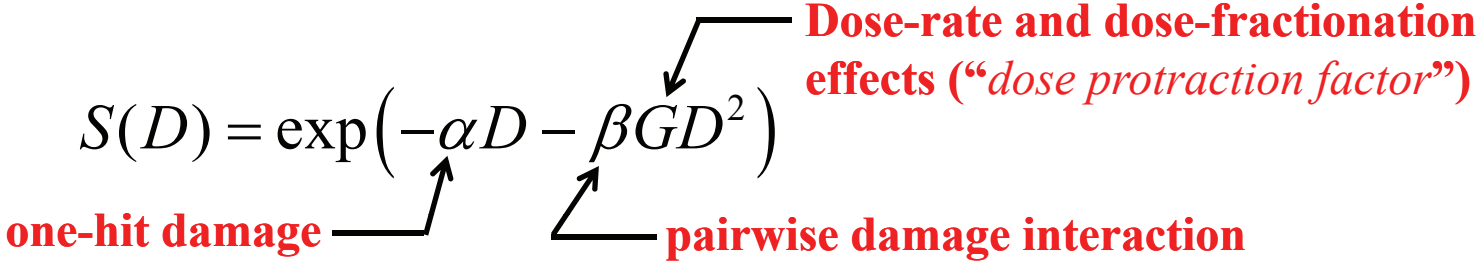
Outline

- **Local tumor control**
  - Models, methods and issues
  - Feasibility of predicting outcomes for individual patients
  - Feasibility of predicting outcomes for patient populations
- **Strategies to guide the design alternate and refined treatments**
  - Fractionated external beam radiation therapy (EBRT)
  - Brachytherapy

RD Stewart, JH Park, DJ Carlson, Isoeffect Calculations in Adaptive Radiation Therapy and Treatment Individualization, In *Adaptive Radiation Therapy*, X.A. Li, Editor. Taylor and Francis Group, *in press* (2010)

The LQ in Radiation Therapy

Inaccurate and too simplistic (*compared to known biology*)



Parameters (e.g., α and β**) derived from analysis of clinical outcomes are uncertain and averaged over a heterogeneous patient population**

JF Fowler, R Chappell, M Ritter,
IJROBP **50**, 1021-1031 (2001)

α = 0.039 Gy^{-1}

α/β = 1.49 Gy

***S* = 1.159 × 10^{-3} (**37 × 2 Gy**)**

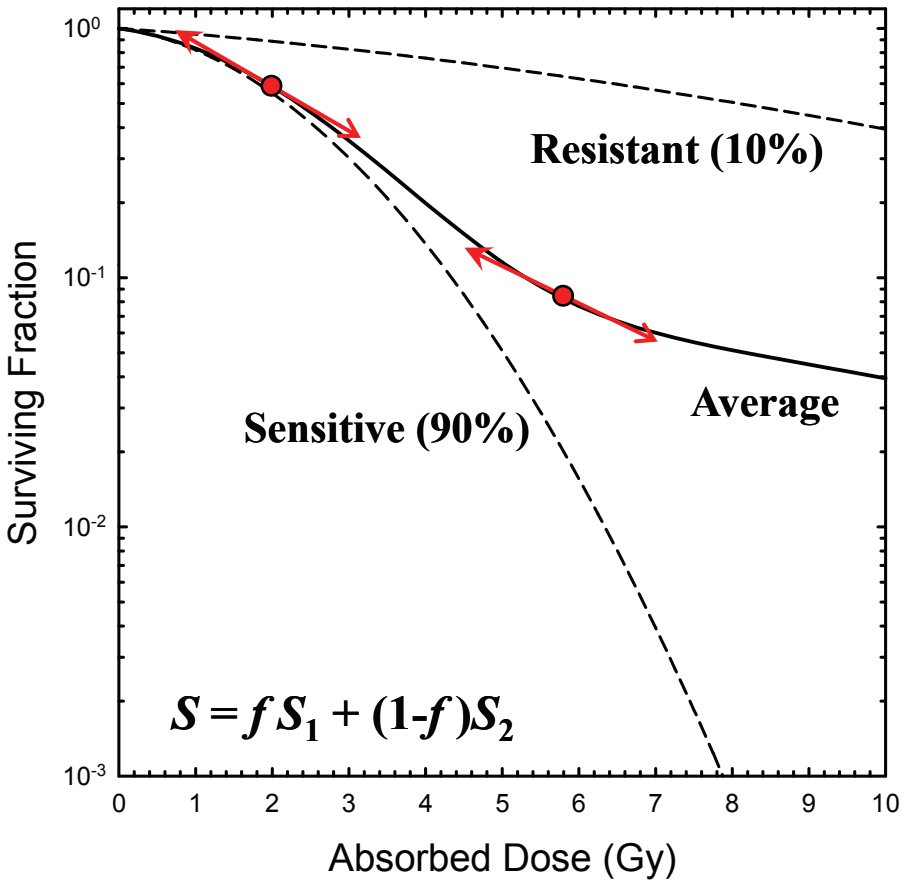
JZ Wang, M Guerrero, XA Li,
IJROBP **55**, 194-203 (2003)

α = 0.15 Gy^{-1} (*4X higher*)

α/β = 3.1 Gy (*2X higher*)

***S* = 2.677 × 10^{-8}** (*10^4 smaller*)

SF for a Heterogeneous Cell Population

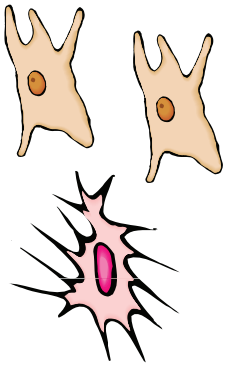


Can't use a single (*average*) set of LQ radiation sensitivity parameters (α, α/β) to predict overall shape of dose-response curve

$$S \neq \exp(-\alpha D - \beta G D^2)$$

Five Reasons (*many others possible*)

- **Genomic Instability**
- **Repair**
- **Repopulation**
- **Reassortment**
- **Reoxygenation**



But maybe we could extrapolate from a known point?

Poisson Tumor control probability (TCP)

Most widely used model assumes that the distribution of the *number* of tumor cells surviving a treatment is adequately described by a Poisson distribution

$$TCP = \exp\{-\rho V S(D)\}$$

Chance no tumor cells survive a treatment that delivers total dose *D*

ρ = number of tumor cells per unit volume ($< 10^9$ cells cm^{-3})

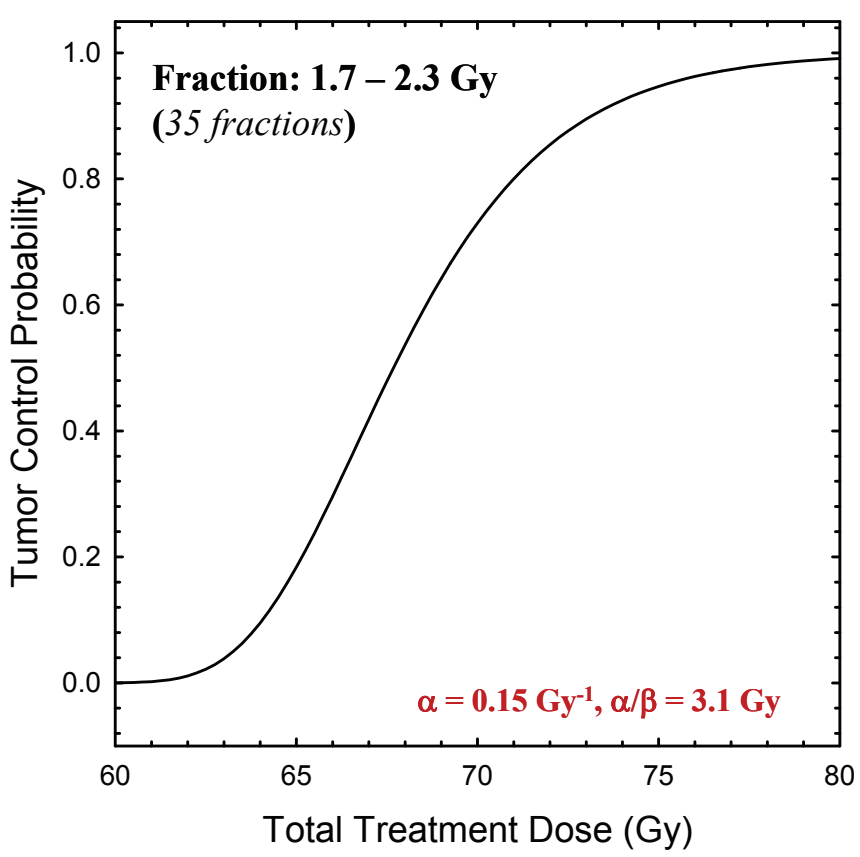
V **= tumor volume** (GTV? PTV?)

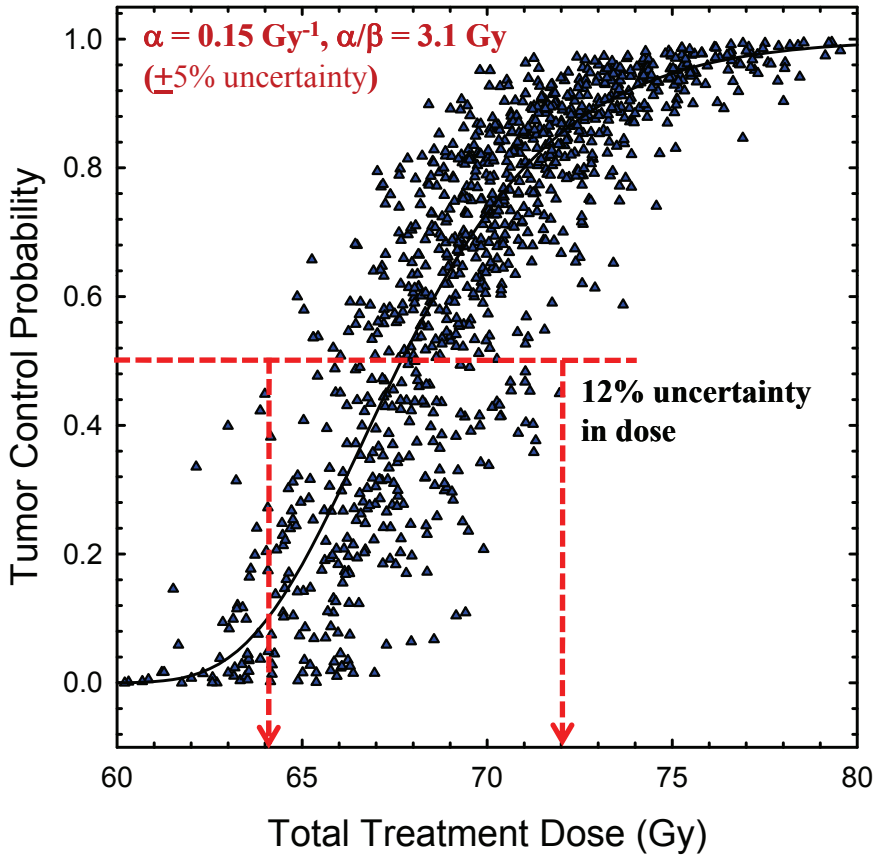
product ρV = pre-treatment number of tumor cells

Typical uncertainty? Factors as large as 10^3 to 10^6!

Eradication of some cells, such as cancer stem cells, may be far more important than the eradication of others (effective $\rho << 10^9$ cells cm^{-3}?)

Prediction of Local Tumor Control





Accurate prediction of local tumor control for individual patients seems rather unlikely, no?

Outcomes for a Patient Population?

http://www.cartoonaday.com/images/cartoons/2010/03/Crowd-of-Cartoon-Sports-FansA-598x429.jpg

Equivalent Tumor Doses

What dose should be delivered to achieve the same level of biological damage as another treatment?

Reference Treatment *Alternate Treatment*

$$TCP(D_R) = TCP(D)$$

$$\exp\left(-\rho VS(D_R)\right) = \exp\left(-\rho VS(D)\right) \quad \textit{Poisson TCP model}$$

ρ = *cell density* (# cm^{-3}) V = *tumor volume* (cm^3)

When considering radiation effects in the *same patient*, ρ and V may be considered *treatment independent* constants.

$$S(D_R) = S(D)$$

Two biological parameters (ρ and V) eliminated from modeling process (*uncertainty in ρV doesn't matter!*)

For individual patients, iso-TCP = iso-survival

Equivalent dose derived from the LQ

Reference Treatment = Alternate Treatment

$$S(D_R) = S(D)$$

$$\exp\left(-\alpha D_R - \beta G D_R^{\,2}\right) = \exp\left(-\alpha D - \beta G D^2\right)$$

α and β (or α/β) characterize *intrinsic radiation sensitivity*

G* is the *dose protraction factor

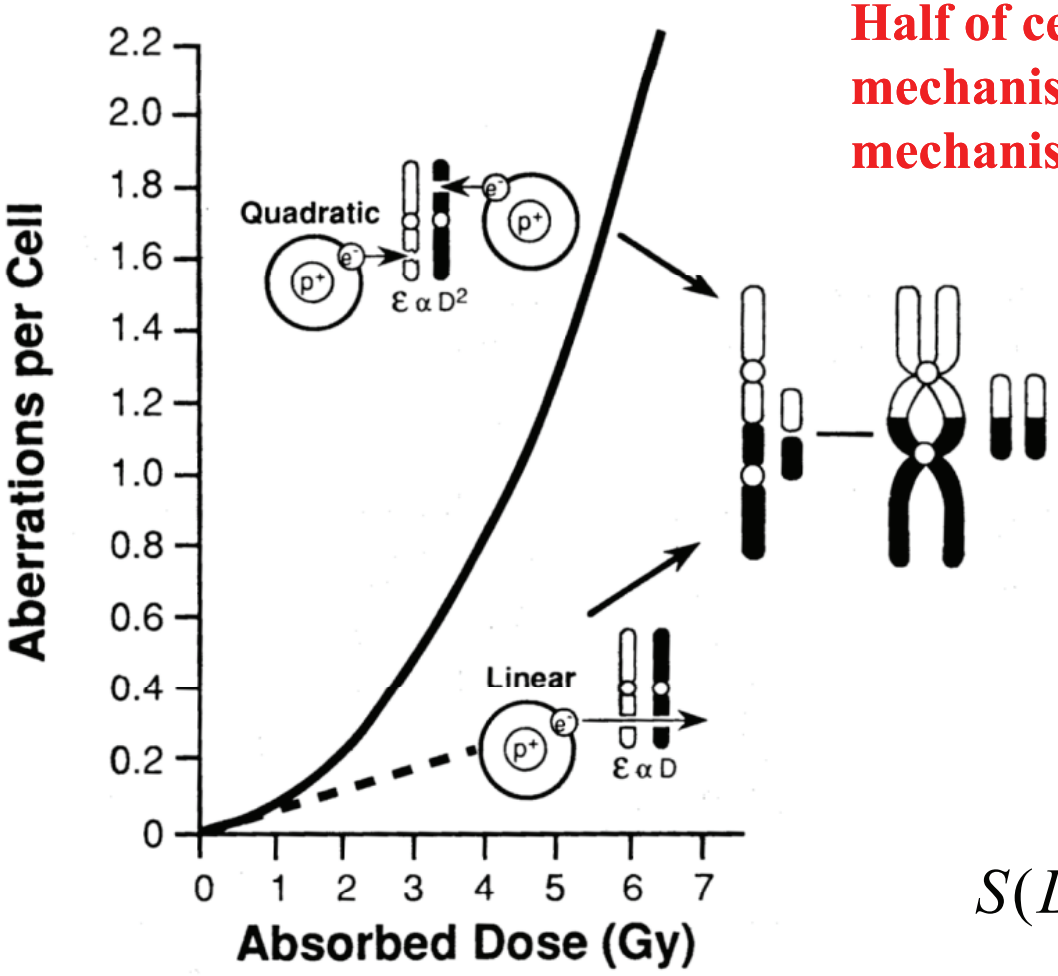
Take logarithm, apply quadratic formula and rearrange terms

$$D = \frac{\alpha/\beta}{2G}\left\{-1 + \sqrt{1 - \frac{4G\ln S(D_R)}{\alpha(\alpha/\beta)}}\right\} = \frac{\alpha/\beta}{2G}\left\{-1 + \sqrt{1 + \frac{4GD_R}{(\alpha/\beta)}\left(1 + \frac{G_R D_R}{\alpha/\beta}\right)}\right\}$$

***D* is the total treatment dose needed to achieve same biological effect as a reference treatment that delivers total dose D_R**

Determined by the value of α/β and the dose protraction factor for the reference and alternate treatments (G_R and G)

One-Hit and Two-Hit Damage?



EJ Hall and AJ Giaccia, Radiobiology for the Radiologist, 6th Edition, Lippincott Williams & Wilkins (2006)

Half of cell killing due to one-track mechanism and half due to two-track mechanism

$$D = \frac{\alpha}{\beta}$$

≅ lethal aberrations

$$S(D) = \exp\left\{-\left(\alpha D + \beta G D^2\right)\right\}$$

($G = 1$ for an acute dose)

Conceptual Basis for G (*protraction factor*)?

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

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

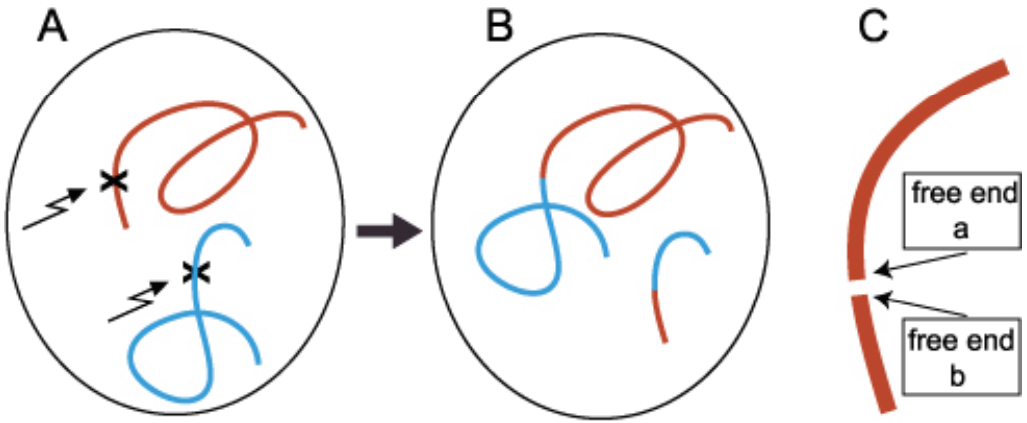
Repair half-time

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

Absorbed dose (Gy)

Probability per unit time sub-lethal damage (= DSB) is rejoined

$$S(D) = \exp\left\{-\left(\alpha D + \beta G D^2\right)\right\}$$



R.K. Sachs and D.J. Brenner, Chromosome Aberrations Produced by Ionizing Radiation: Quantitative Studies
http://web.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=mono_002

Protraction Factor – *n* daily fractions

Series of *n* daily fractions

$$G = \frac{g}{n} \cong \frac{1}{n} \quad \textit{if } \Delta t \ll \tau$$

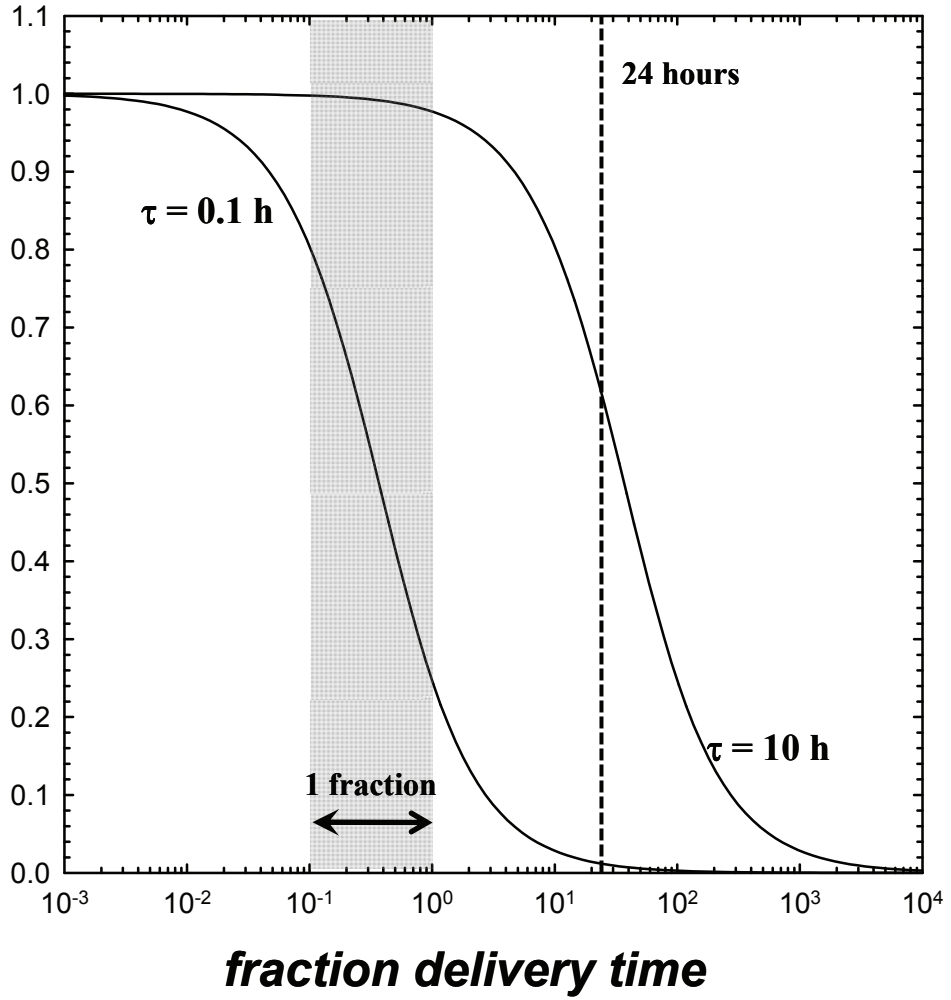
(*assumes repair complete between fractions*)

$$S(D) = \exp\left\{-\left(\alpha D + \beta G D^2\right)\right\}$$

Dose *d* (*fraction size*) delivered during time interval Δ*t* (*fraction delivery time*)

$$g = 2(e^{-x} + x - 1) / x^2$$

$$x \equiv \lambda \Delta t = \Delta t \ln 2 / \tau$$



***g* is *always* between 0 (*large delivery time*) and 1 (*short delivery times*)**

Equivalent Fractionation Schedules?

$$D = \frac{\alpha/\beta}{2G}\left\{-1+\sqrt{1+\frac{4GD_R}{(\alpha/\beta)}\left(1+\frac{G_R D_R}{\alpha/\beta}\right)}\right\} \qquad \begin{array}{l} G \cong 1/n \\ G \cong 1/n_R \end{array}$$

Determine biologically equivalent dose *D* by adjusting the *physical* parameter *n*

$$D = \frac{n}{2}(\alpha/\beta)\left\{-1+\sqrt{1+\frac{4D_R}{n(\alpha/\beta)}\left(1+\frac{D_R}{n_R(\alpha/\beta)}\right)}\right\}$$

Reference Treatment
(“*clinical experience*”)

D_R = total dose (Gy)

n_R = number fractions

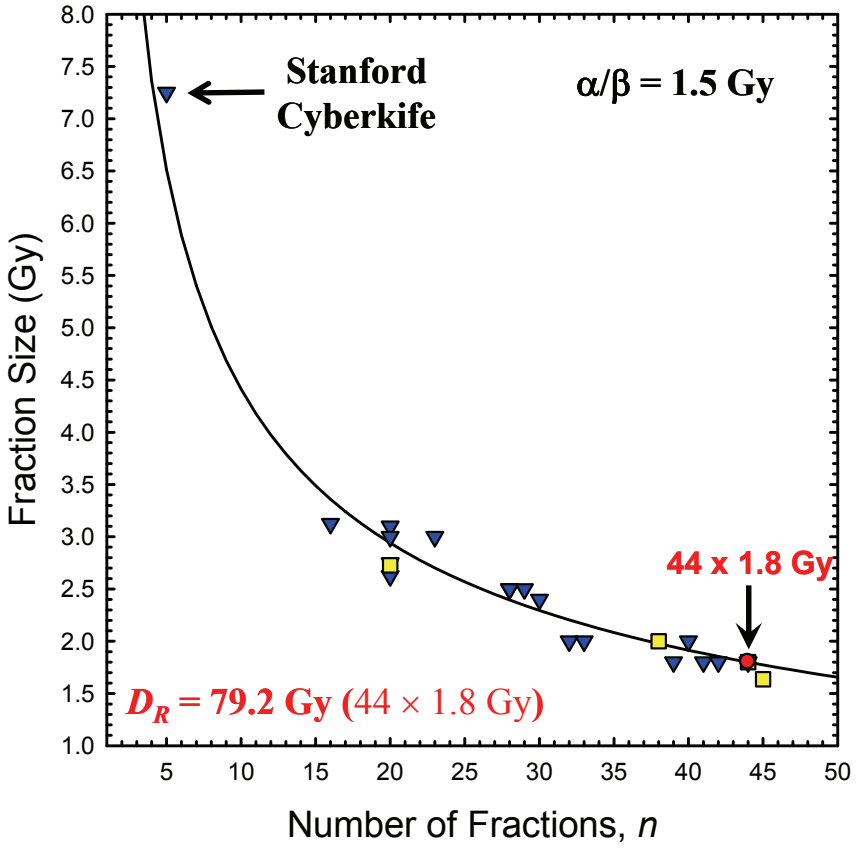
$d_R = D_R/n_r$ (*fraction size*)

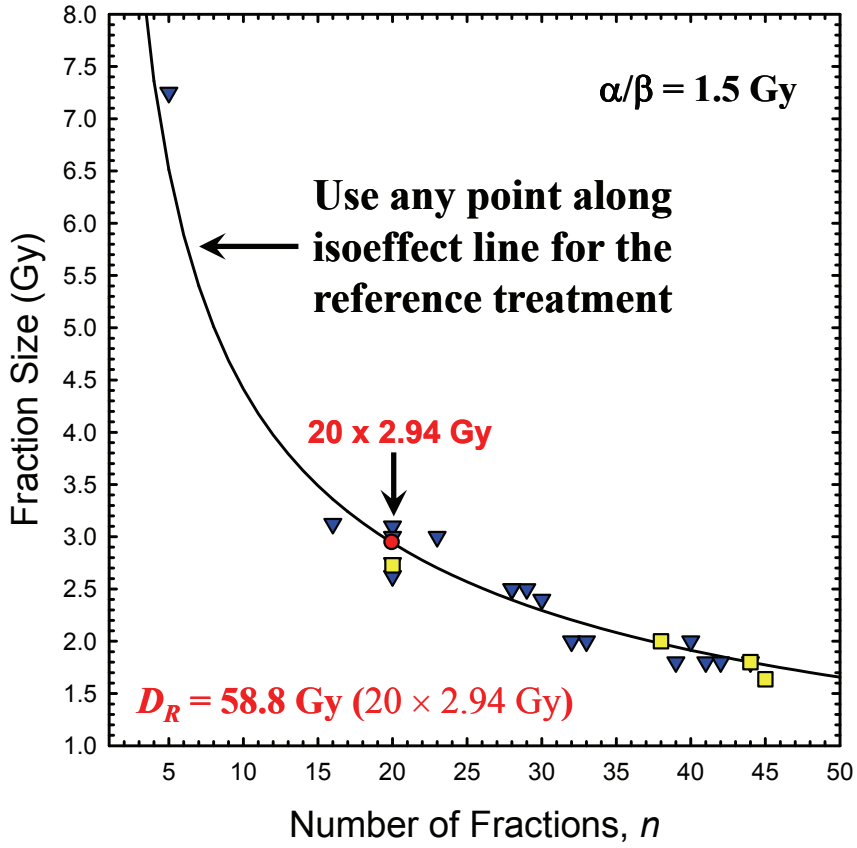
New (alternate) Treatment

n = desired number fractions

Uncertainty in *D* mainly arises from uncertainties associated with α/β.

Equivalent Treatments (*prostate cancer*)





$$D = \frac{n}{2}(\alpha/\beta)\left\{-1+\sqrt{1+\frac{4D_R}{n(\alpha/\beta)}\left(1+\frac{D_R}{n_R(\alpha/\beta)}\right)}\right\}$$

Inter-Patient Heterogeneity

$$D = \frac{n}{2}(\alpha/\beta)\left\{-1+\sqrt{1+\frac{4D_R}{n(\alpha/\beta)}\left(1+\frac{D_R}{n_R(\alpha/\beta)}\right)}\right\}$$

When applied to a patient population, we are implicitly assuming that α/β is the same for *all patients* for the reference *and* alternate treatment – an assumption that is *surely* incorrect!

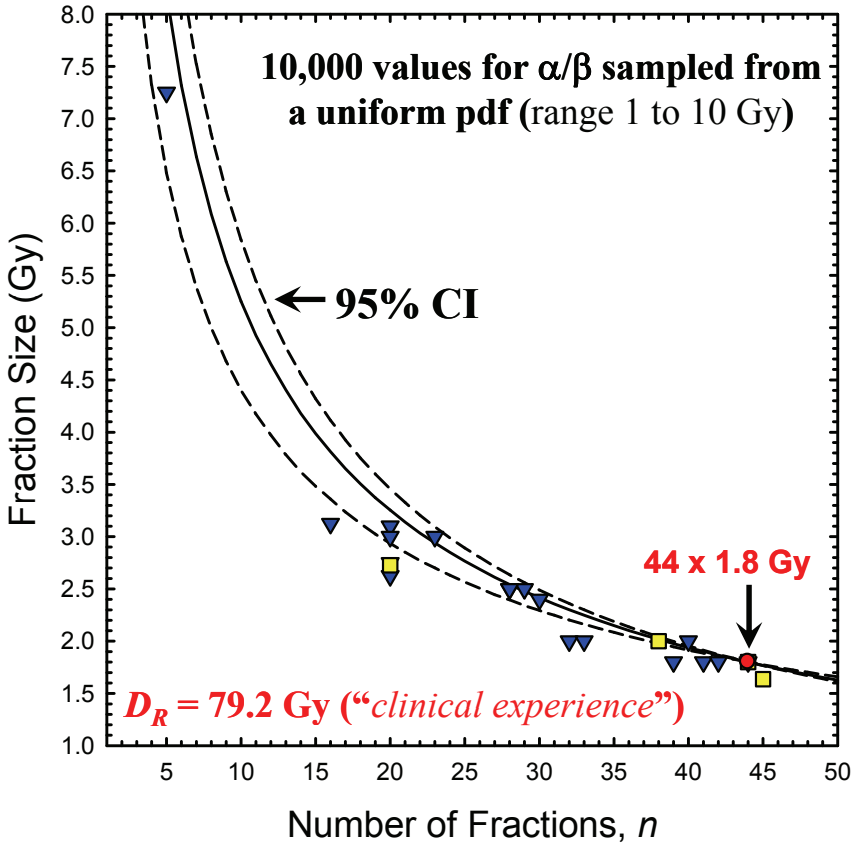
Inter-Patient Heterogeneity

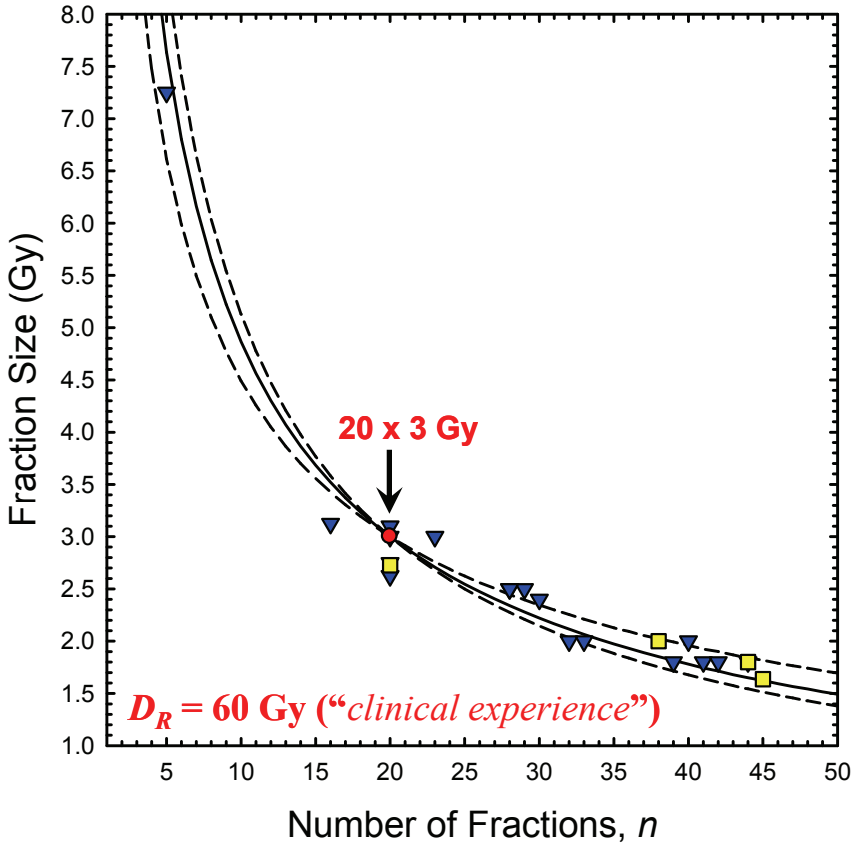
Hypothesis: All patients have a different α/β (*unknown distribution*). BUT… same value of α/β is appropriate (*as a first approximation*) for all treatments in the same patient.

How does inter-patient heterogeneity influence our ability to determine equivalent prescription doses?

How sensitive are estimates of *D* to uncertainties in α/β?

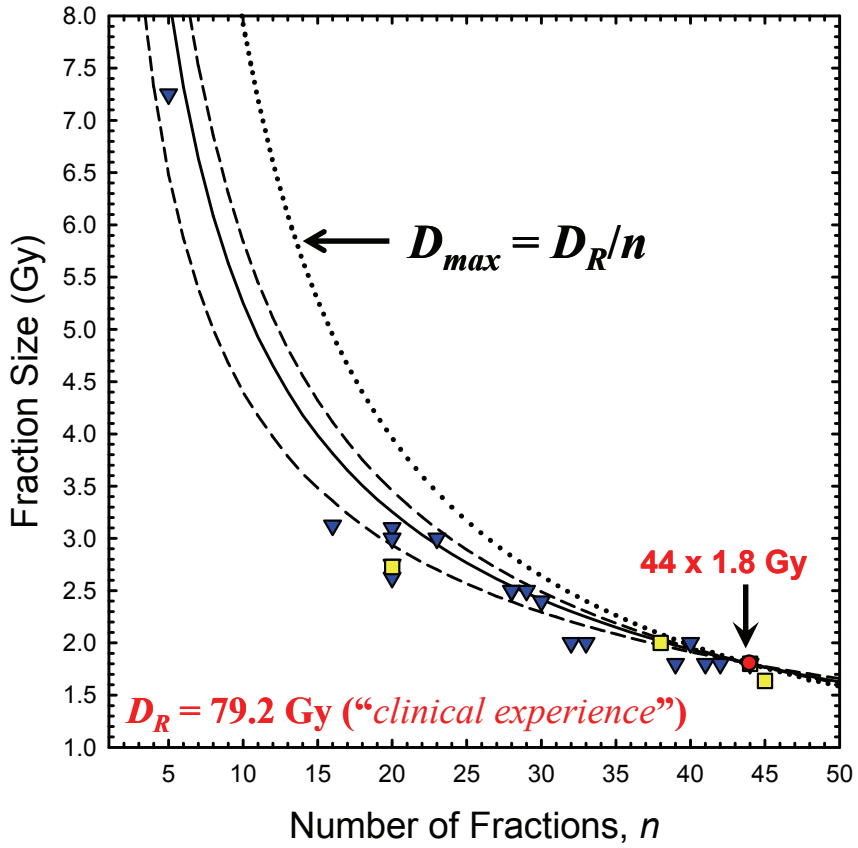
Effects of Inter-Patient Heterogeneity





Key Point #1: Small changes from an accepted fractionation schedule quite reasonable – even for a *very* heterogeneous patient population

Special Case – Fraction Size $d << \alpha/\beta$



For the special case when $d << \alpha/\beta$, $S \cong \exp(-\alpha D)$ and

$$S(D_R) = S(D)$$
$$exp(\alpha n_R d_R) \cong exp(\alpha n d)$$

Maximum fraction size required for biological equivalence (iso-TCP)
$d \cong D_R/n$

$$n = 44 \rightarrow 40 \ (3.48\%)$$
$$n = 44 \rightarrow 35 \ (8.60\%)$$

Uncertainty comparable to differences in prescription dose among institutions *and* to uncertainties arising from treatment delivery…

Repopulation Effects

When radiation is protracted over time intervals comparable to or longer than the doubling time (T_d) additional cell killing is required to eradicate the tumor

$$S(D) = e^{\gamma T} S(D) = e^{\gamma T} \times \exp\left[-\alpha D\left(1 + \frac{GD}{\alpha / \beta}\right)\right]$$

$$\gamma \equiv \frac{\ln 2}{T_d} \qquad = \exp\left[-\alpha D\left(1 + \frac{GD}{\alpha / \beta}\right) + \gamma T\right]$$

Correction for cell division over time interval *T*

(γT must be dimensionless)

Total treatment time

$$T = (n - 1) + 2\text{int}[(n - 1)/5]$$

Assume treatment starts on Monday

Equivalent dose – repair and repopulation

Reference Treatment = Alternate Treatment

$$S(D_R) = S(D)$$

$$\exp\left(-\alpha D_R - \beta G D_R^{\,2} + \gamma T_R\right) = \exp\left(-\alpha D - \beta G D^2 + \gamma T\right)$$

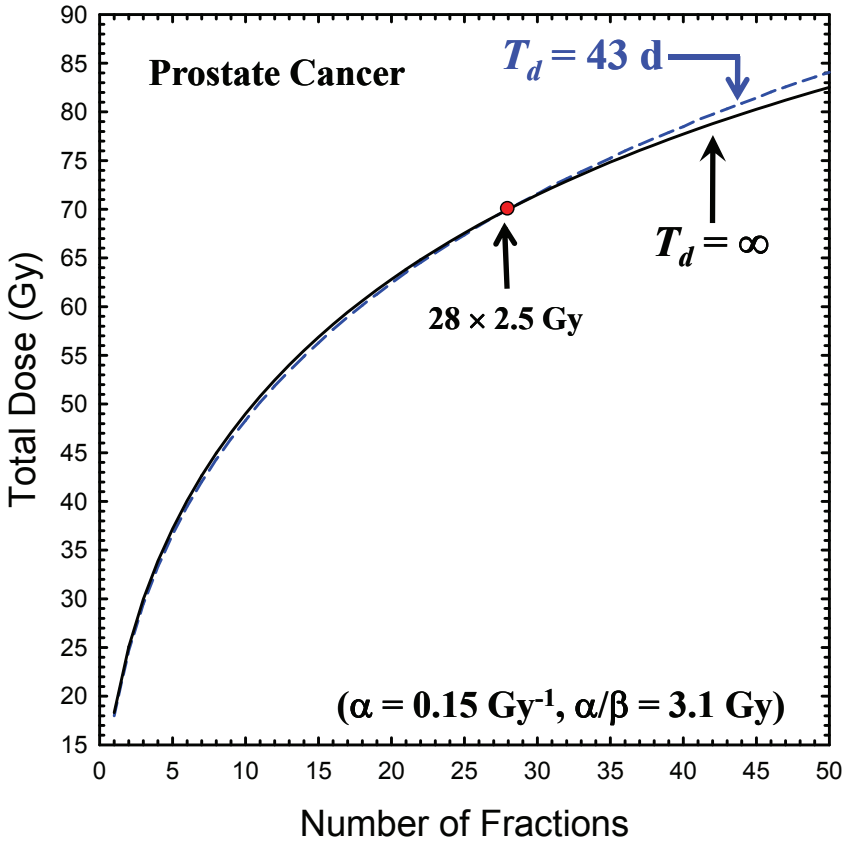
Take logarithm, apply quadratic formula and rearrange terms

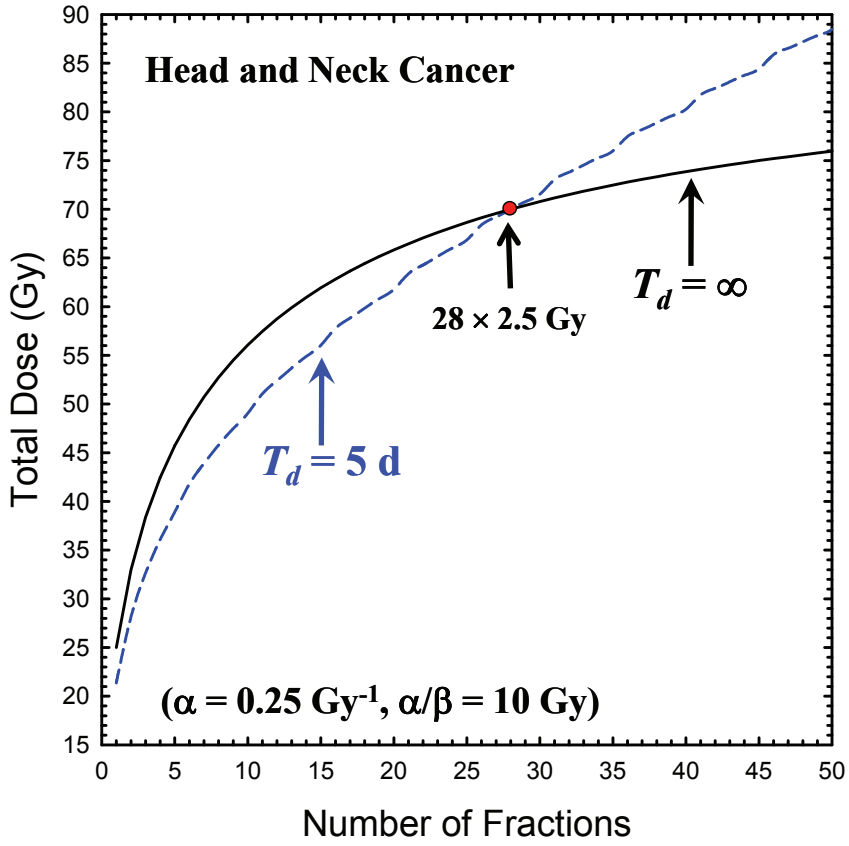
$$D = \frac{\alpha/\beta}{2G}\left\{-1 + \sqrt{1 + \frac{4GD_R}{\alpha/\beta}\left[1 + \frac{G_R D_R}{\alpha/\beta} - \frac{\gamma(T_R - T)}{\alpha D_R}\right]}\right\}$$

D **is the total treatment dose needed to achieve same biological effect as a reference treatment that delivers total dose** D_R

Determined by the value of α/β **(in Gy),** γ/α **(in Gy/day) and the dose protraction factor for the reference and alternate treatments (*G* and** G_R**)**

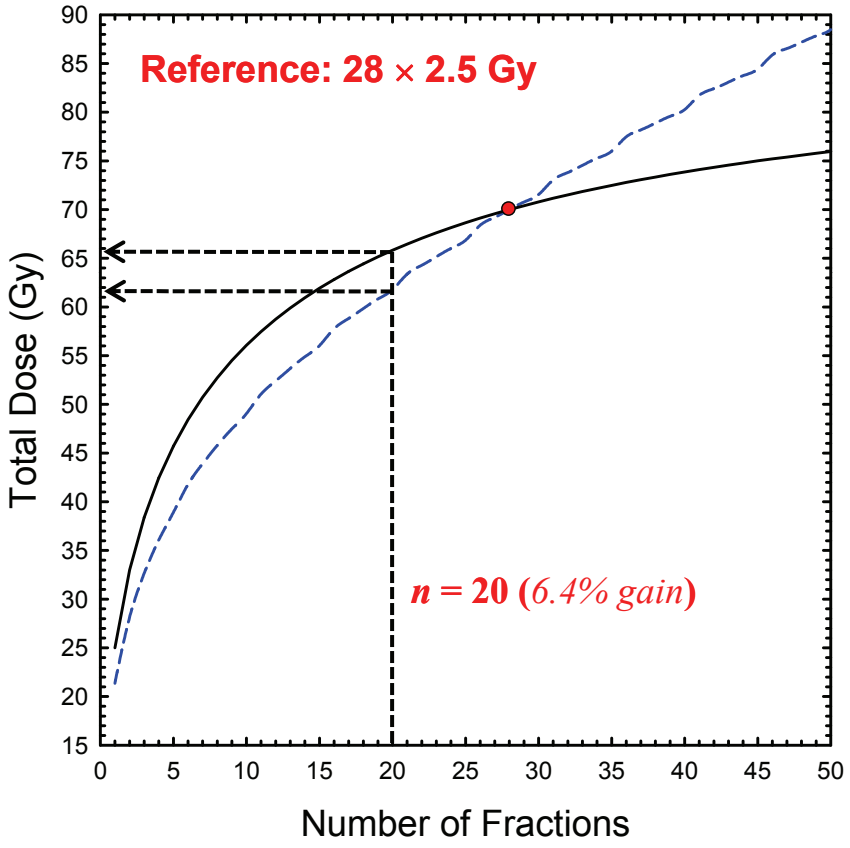
Repopulation Effects – Fast and Slow Growing Tumors

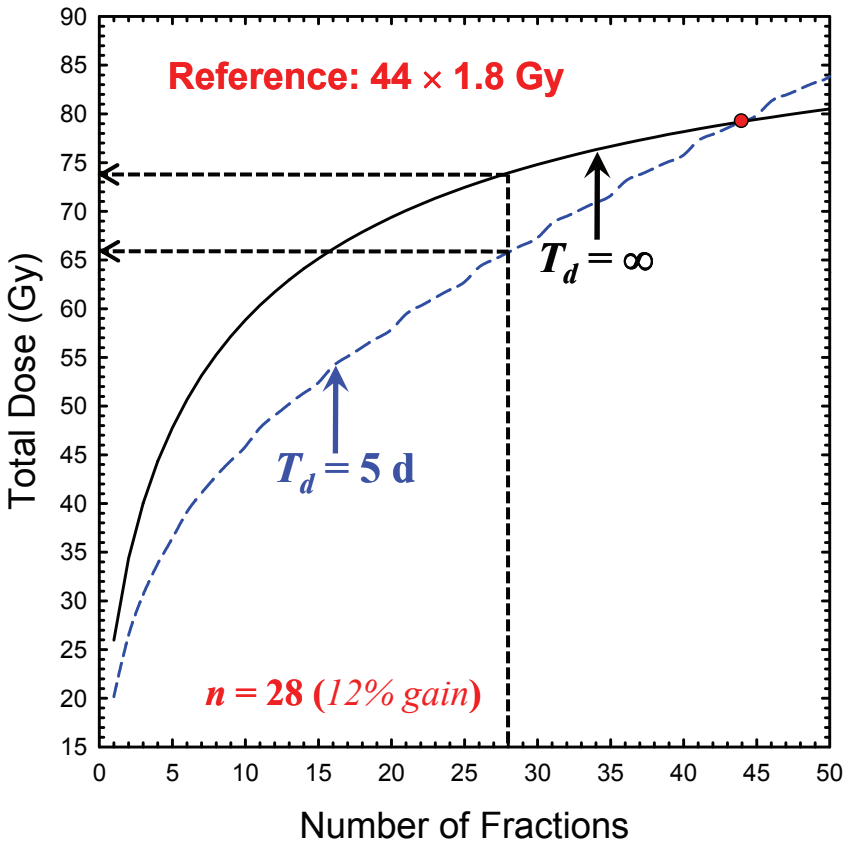




Repopulation effects are negligible for slow growing tumors but potentially very significant for fast growing tumors

Are gains in tumor control significant?

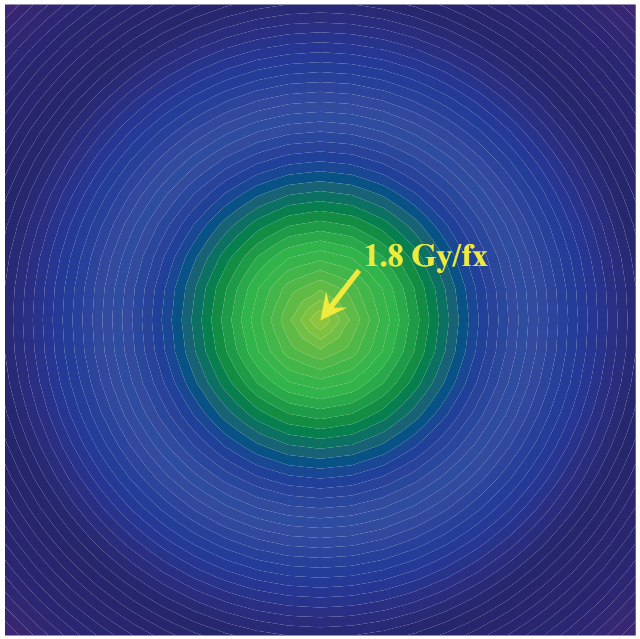




Key Point #2: Clinical significance of potential gains (*or losses*) are easily judged when expressed in terms of physical dose.

Isoeffective Dose Distributions

Absolute dose distributions (*in Gy*) typically determined through application of a calibration factor (Gy/MU**) at a reference location**

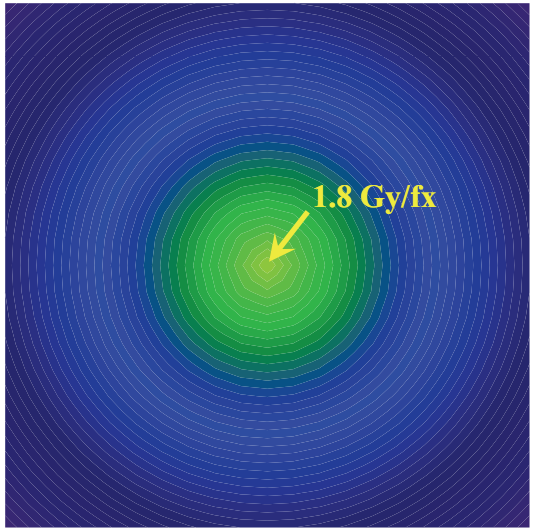


44 fractions

Prescription dose specified at center (44 x 1.8 Gy = 79.2 Gy**)**

Equivalent dose distributions?

Scale the dose distribution by a ratio of biologically equivalent prescription doses ($n = 44 \rightarrow n = 20$)



44 fractions

$$D = \frac{n}{2}(\alpha/\beta)\left\{-1+\sqrt{1+\frac{4D_R}{n(\alpha/\beta)}\left(1+\frac{D_R}{n_R(\alpha/\beta)}\right)}\right\}$$

α/β = 1.5 Gy

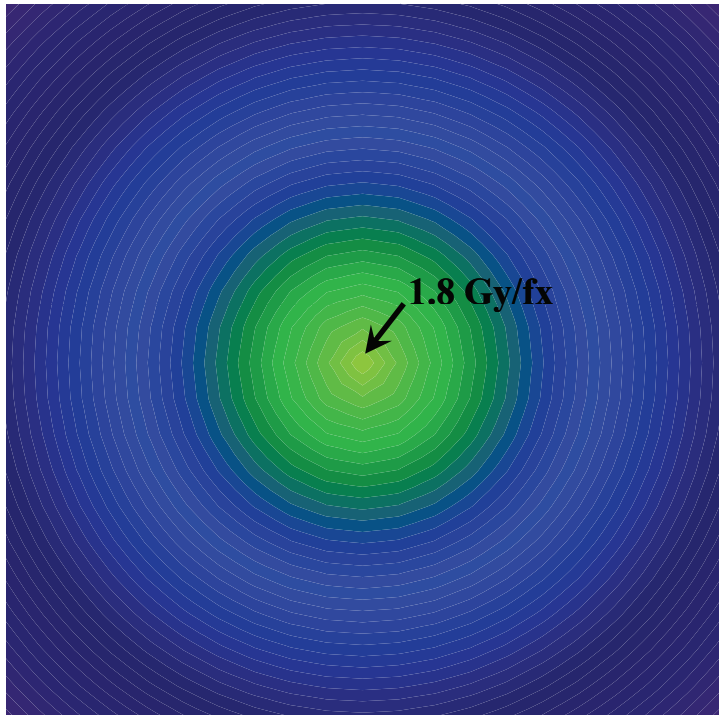
n_R = 44 D_R = 79.2 Gy (d_R = 1.8 Gy)

n = 20 (*new*) D = 58.8 Gy (d_R = 2.94 Gy)

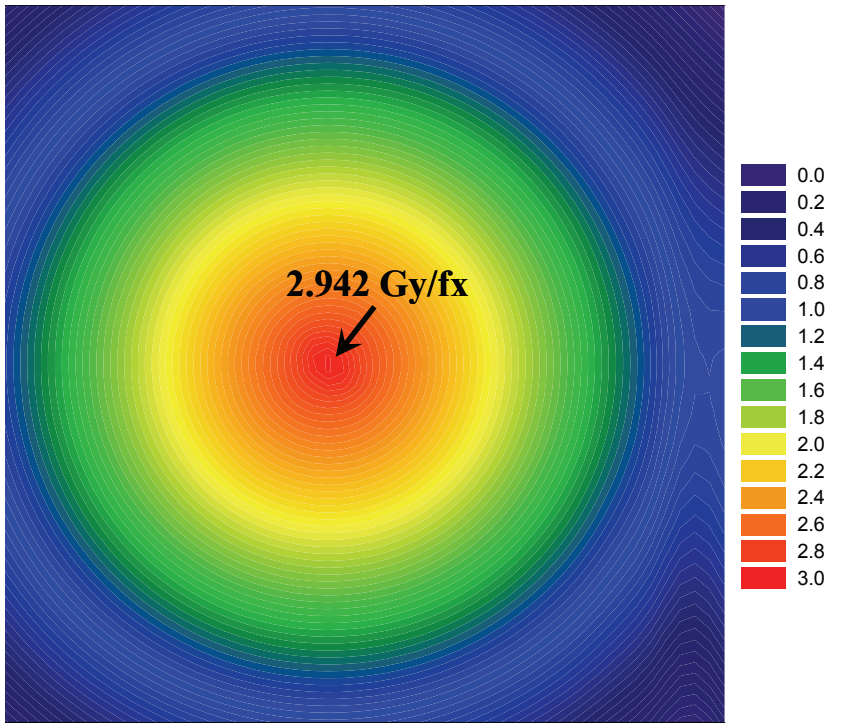
Dose to i^{th} voxel in new treatment

$$d^i = \frac{d}{d_R} d_{R,i} = \frac{2.94\ \text{Gy}}{1.8\ \text{Gy}} d_R^i = 1.6333 d_R^i$$

Dose Distribution ($n = 44 \rightarrow 20$) – MU scaling



44 fractions



20 fractions

Same biological effect at center ($n = 44$ and 20).

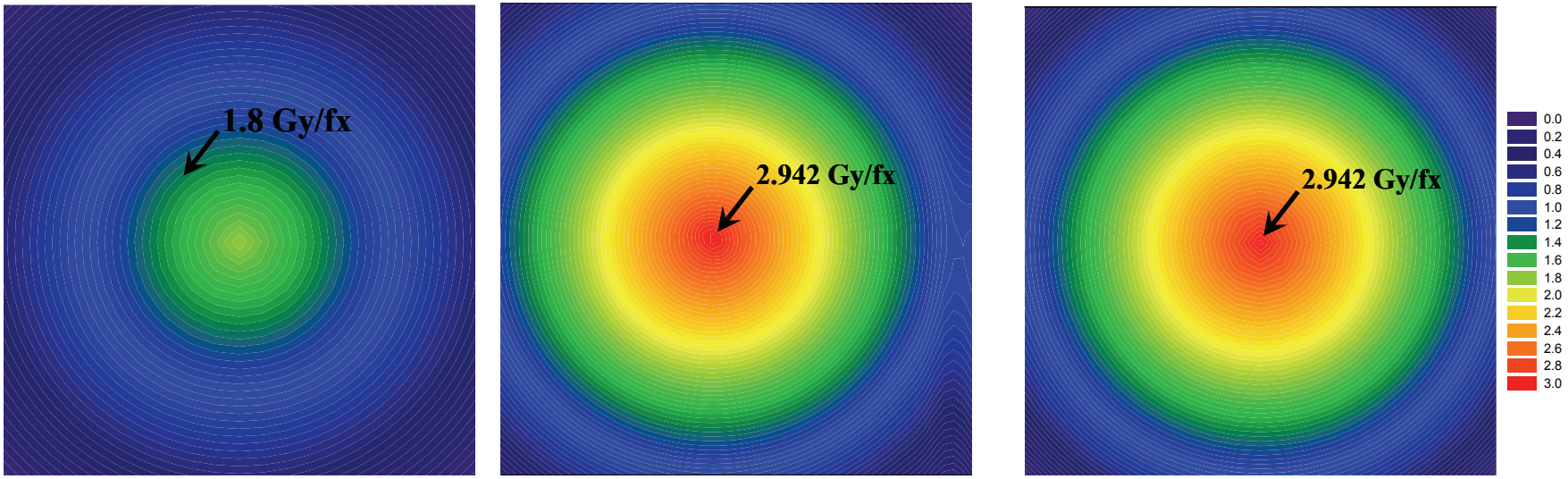
But same biological effect at other locations??

Biologically Equivalent Dose Distributions

dose to i^{th} voxel

$$D^i = \frac{n}{2}(\alpha/\beta)\left\{-1+\sqrt{1+\frac{4D_R^i}{n(\alpha/\beta)}\left(1+\frac{D_R^i}{n_R(\alpha/\beta)}\right)}\right\}$$

α/β = 1.5 Gy



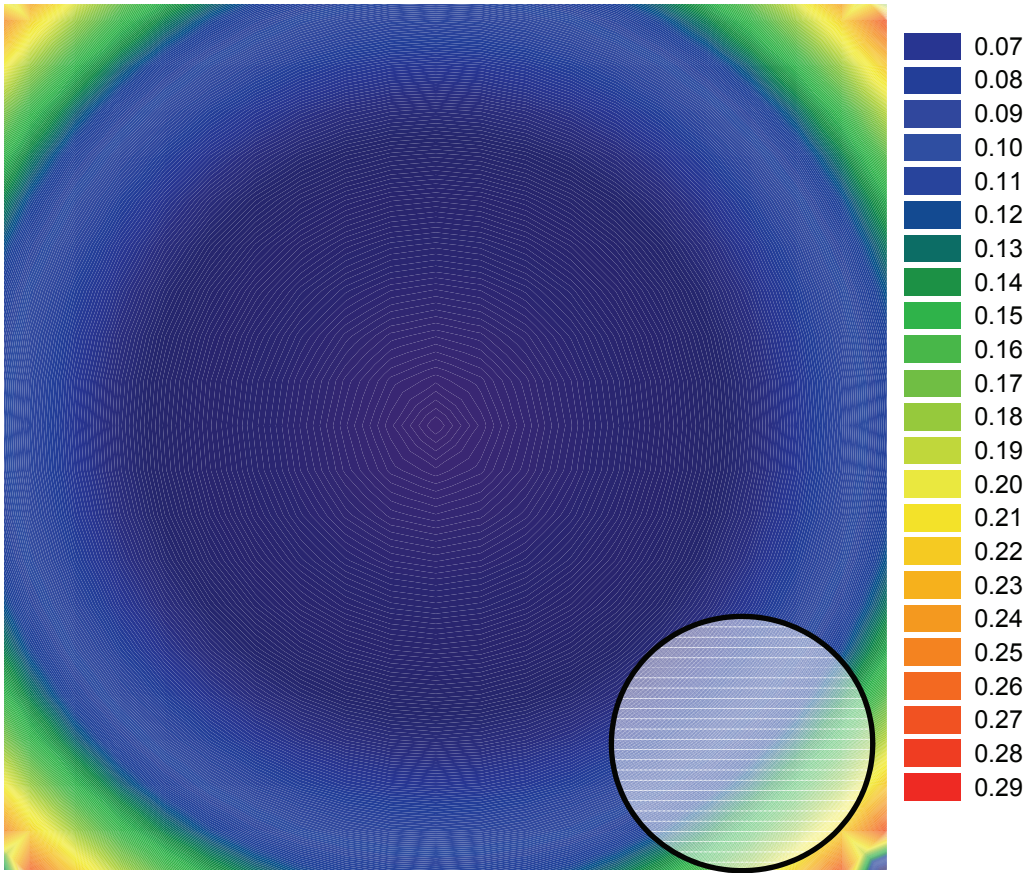
44 fractions (*original*)

20 fractions (*scaled using dose at center*)

20 fractions (*isoeffect*)

Isoeffect dose is up to 27% larger than the distribution scaled by dose (*or MU or fluence*)

Dose Distribution Difference ($n = 20$)

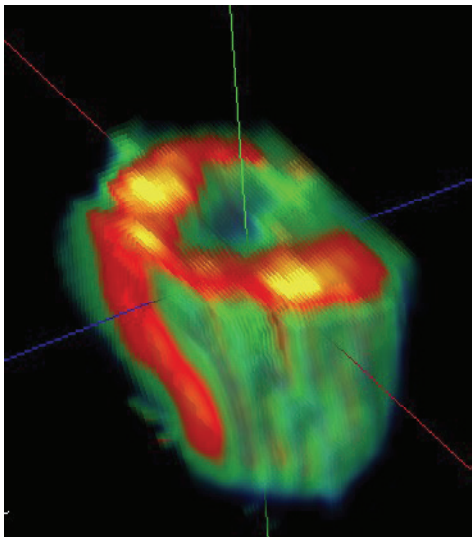


Scaling by physical quantities *underestimates* isoeffect dose by up to 27% ($n = 44 \rightarrow 20$)

Dose "scaling" effects become more important as fraction size increases (*because of* βD^2 *term*)

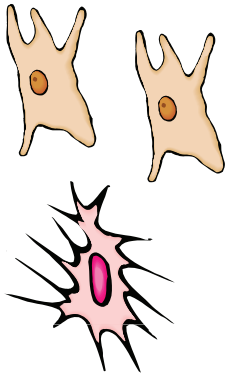
Key Point #3: Scaling dose distributions by maximum dose (*or fluence or monitor units*) at a point may *underestimate* tolerance dose for normal tissues

Intra-Tumor Heterogeneity



Representative DCE-CT image of a tumor
(Courtesy Minsong Cao, IUSM)

- Genomic Instability
- Repair
- Repopulation
- Reassortment
- Reoxygenation



How does intra-tumor heterogeneity influence our ability to determine biologically equivalent *dose distributions*?

Imagine that…

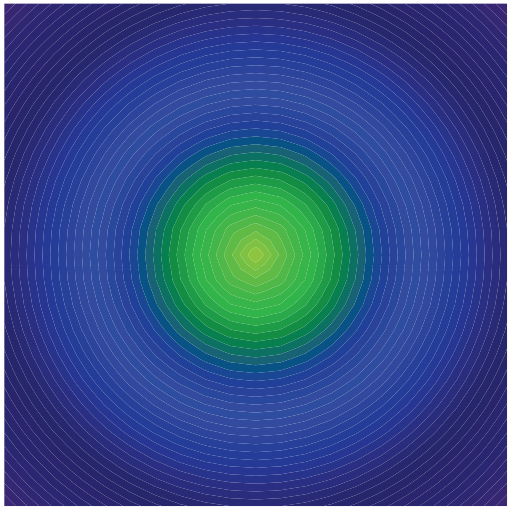
Individual cells have different values of α/β (*unknown distribution*). But, again, same for all treatments as a *first approximation*

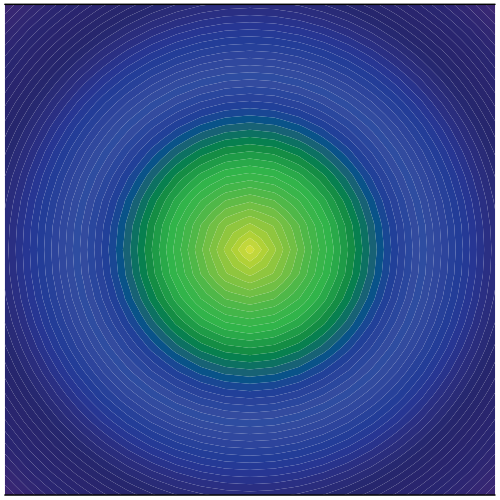
Effect of intra-tumor heterogeneity

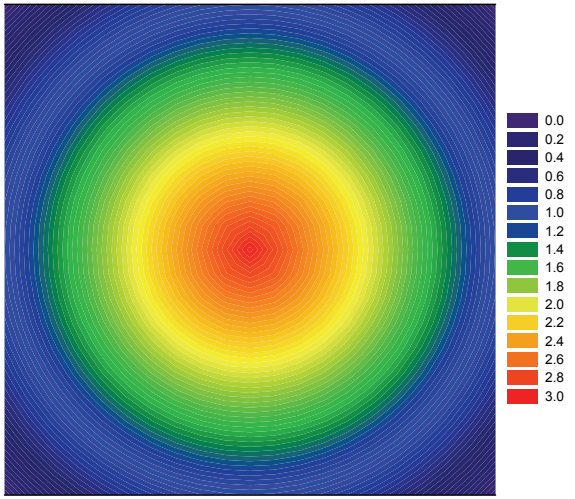
44 × 1.80 Gy (*original*)

39 × 1.95 Gy (α/β = 1.5 Gy)

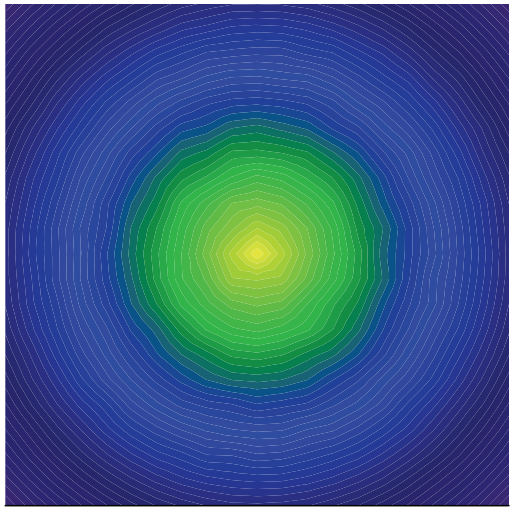
20 × 2.94 Gy (α/β = 1.5 Gy)

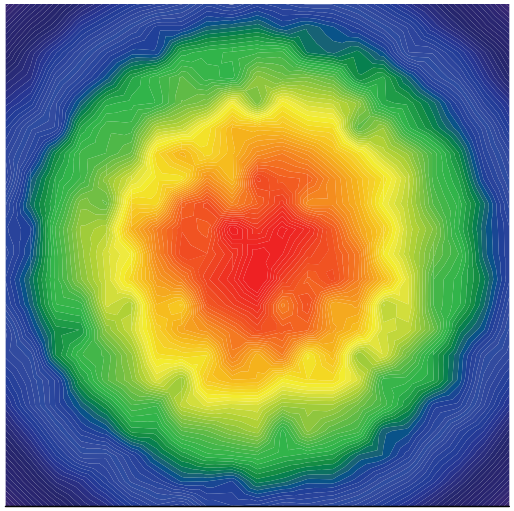






α/β sampled from a uniform pdf (range 1 to 10 Gy**) on a voxel by voxel basis**





Fractionated EBRT → Brachytherapy

Dose for a brachytherapy procedure (*again*) determined by

$$D = \frac{\alpha / \beta}{2G}\left\{-1 + \sqrt{1 + \frac{4GD_R}{\alpha / \beta}\left[1 + \frac{G_R D_R}{\alpha / \beta} - \frac{\gamma(T_R - T)}{\alpha D_R}\right]}\right\}$$

Reference Treatment
(“*clinical experience*”)

D_R = total dose (Gy)

n_R = number fractions

$d_R = D_R/n_r$ (*fraction size*)

$T_R = (n_R - 1) + 2\text{int}[(n_R - 1)/5]$

Brachytherapy Procedure

$$G = G_\infty\left\{\frac{(1+x)}{(1-x)} - \frac{yx^2}{(1-x)^2}\left[1 - e^{-(\lambda-\mu)T}\right]\right\}$$

$$G_\infty \equiv \mu / (\mu + \lambda) \qquad x \equiv \exp(-\mu T)$$

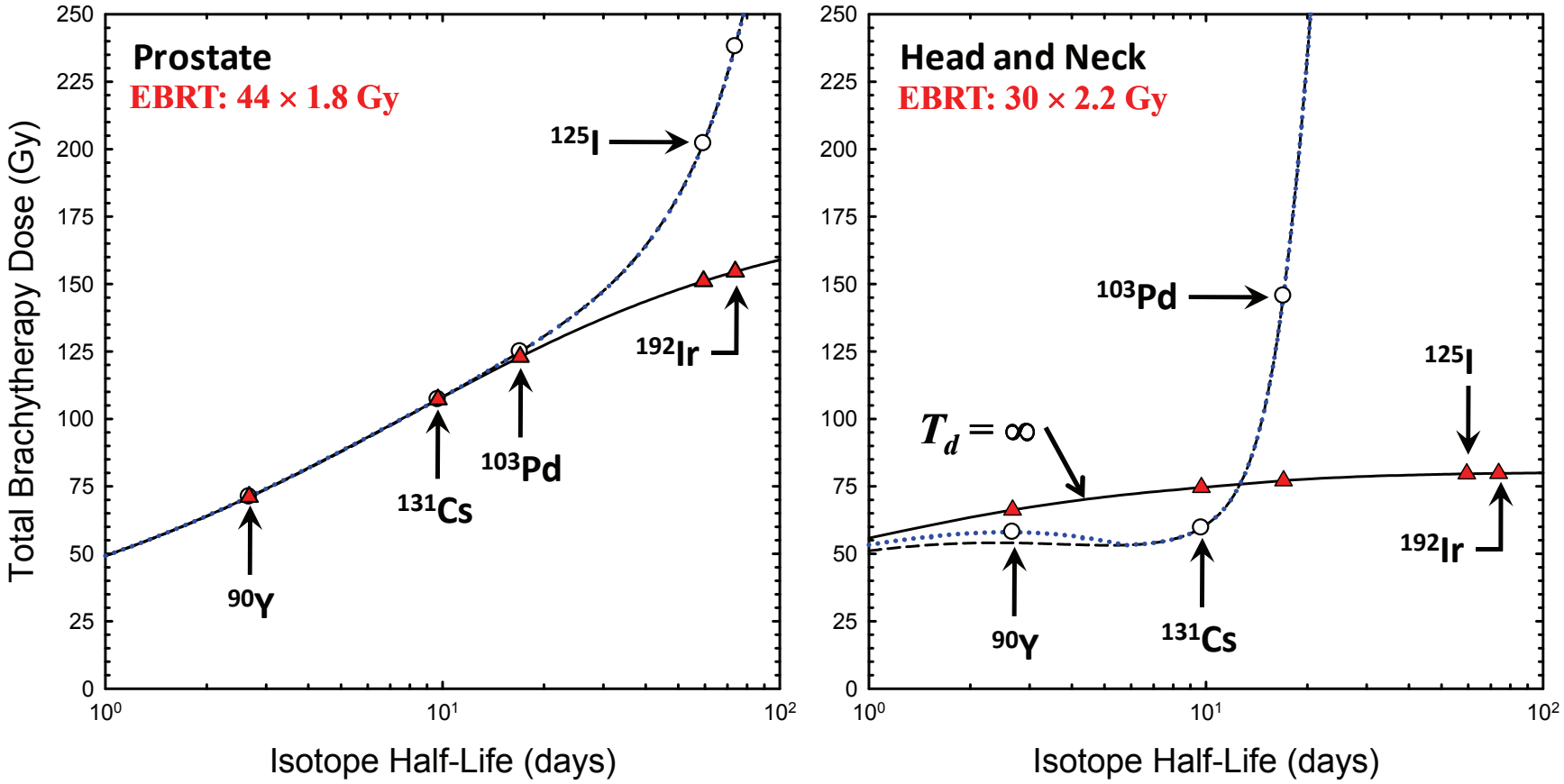
$$y \equiv 2\mu / (\lambda - \mu)$$

relates to

Isotope Half-life **Repair Half-time**

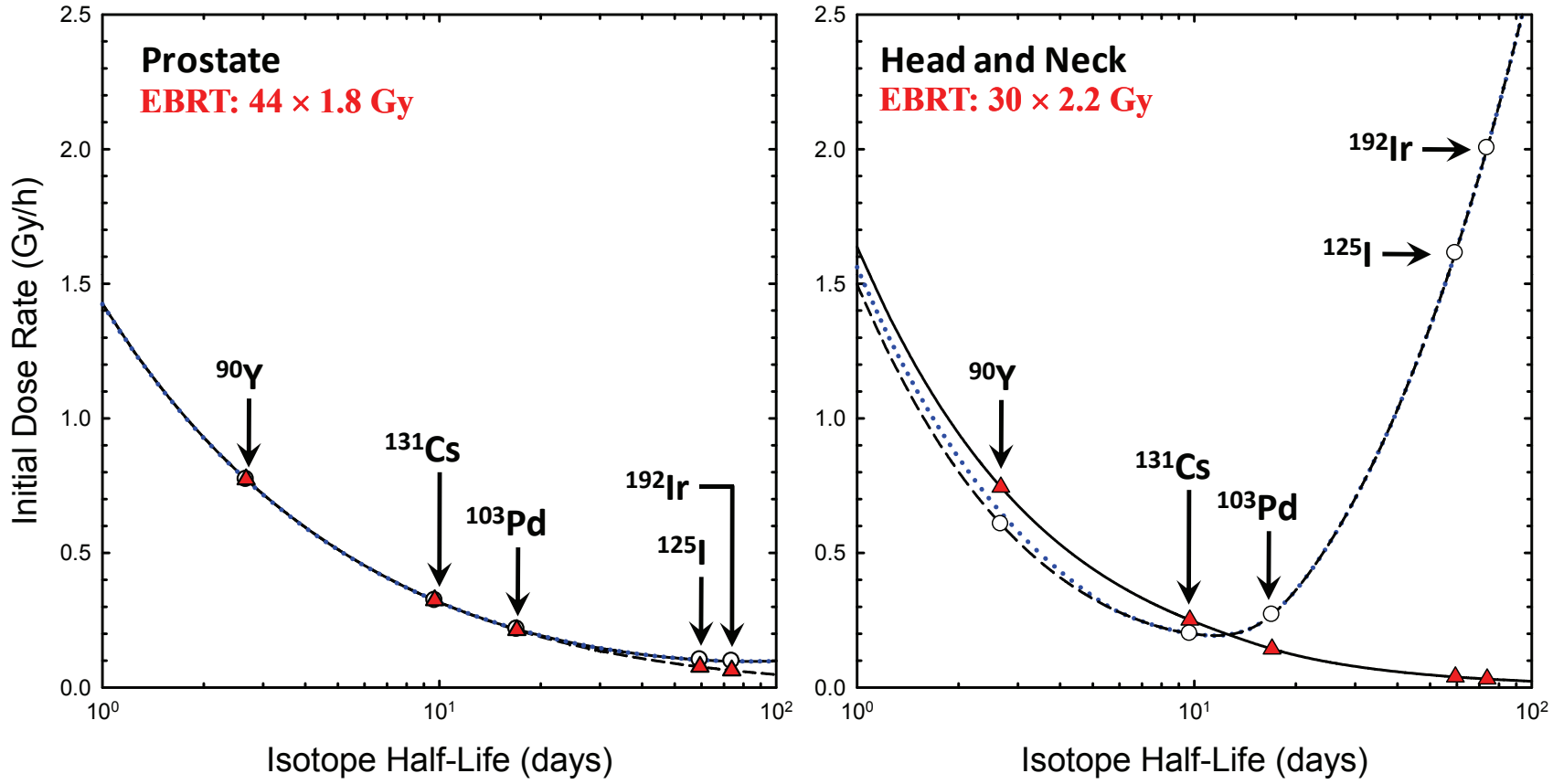
***T* = *effective* treatment time**

Brachytherapy – Isotope Selection and Dose



Biologically equivalent brachytherapy doses for **prostate cancer** (**left panel**) and **head and neck cancer** (**right panel**). **Prostate** (T_d = 43 days): T_k = 0 days (**black dashed line**) or T_k = 60 days (**blue dotted line**). **Head and Neck** (T_d = 5 days): T_k = 0 days (**black dashed line**) or T_k = 21 days (**blue dotted line**). **Solid black lines**: not corrected for repopulation effects ($T_d = \infty$).

Brachytherapy – Initial Dose Rate



Initial brachytherapy dose rates for **prostate cancer** (**left panel**) and **head and neck cancer** (**right panel**). **Prostate** (**T_d** = 43 days): T_k = 0 days (**black dashed line**) or T_k = 60 days (**blue dotted line**). **Head and Neck** (T_d = 5 days): T_k = 0 days (**black dashed line**) or T_k = 21 days (**blue dotted line**). **Solid black lines**: not corrected for repopulation effects ($T_d = \infty$).

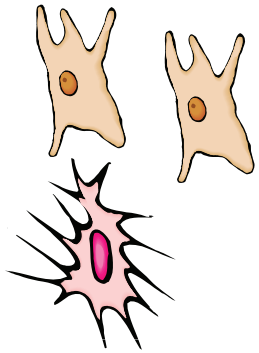
Summary and Conclusions

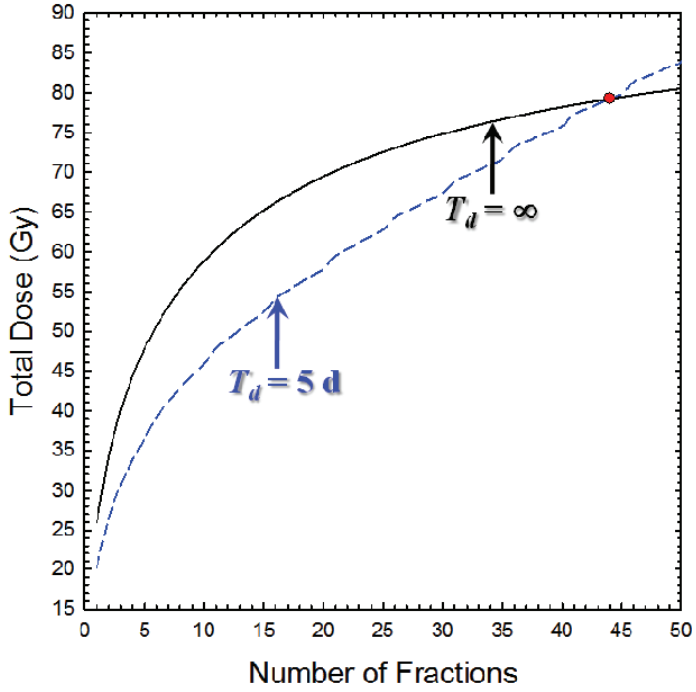
- **Direct application of TCP (**and NTCP**) modeling may result in the selection of inappropriate or suboptimal treatment parameters or modalities**
  - Too many parameters – very challenging to estimate from clinical data
  - Predictions very sensitive to parameter uncertainties
  - Prediction of individual outcomes unlikely (*foreseeable future*)
  - *But* general trends in dose-response behavior of a patient population can be predicted despite inter-patient and intra-tumor heterogeneity
- **Isoeffect calculations are a useful alternative**
  - Uncertainties and limitations mitigated through use of prior clinical experience ("*dose or dose distribution for an accepted treatment*")
  - Focus on most important parameters, such as α/β (Gy) and γ/α (Gy/day)
  - Easy to judge potential gains and losses in treatment effectiveness in terms of *physical dose* (< 3-5% change in dose not significant)
  - Guide design of dose escalation studies, compare effectiveness of EBRT and brachytherapy, isotope selection and initial dose rate, …

A Path to Treatment Individualization

Develop distributions of parameters for sub-populations
(*biomarkers, functional imaging, …*)

- **Repair**
- **Repopulation**
- **Reassortment**
- **Reoxygenation**





Group 1	Group 2
$\alpha/\beta \cong$ 2-5 Gy	$\alpha/\beta \cong$ 3-8 Gy
$\gamma/\alpha <$ 10 Gy/day	$\gamma/\alpha >$ 50 Gy/day

α/β relates to fraction-size sensitivity (*repair, oxygen effects, genetic factors, cell kinetics*)

γ/α related to cell loss, growth fraction, hypoxia, tumor responsiveness (*shrinkage?*), …

Estimating Parameters from Clinical Data

Don't we need TCP and NTCP models to estimate biological parameters?

Group 1	Group 2
$\alpha/\beta \cong$ 2-5 Gy	$\alpha/\beta \cong$ 3-8 Gy
$\gamma/\alpha <$ 10 Gy/day	$\gamma/\alpha >$ 50 Gy/day

If so, what about uncertainties in ρV? Inter-patient heterogeneity? Intra-tumor heterogeneity?