Effective Treatment Planning with Imperfect Models and Uncertain Biological Parameters

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Translating Physics and Biology into the Clinic
Tuesday September 23, 2008
2:30 to 4:30 pm

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From whence the biological parameters?

Random and systematic patient setup errors

Inter-patient heterogeneity

Intra-tumor heterogeneity

Dosimetry

Combined treatments

Interpretation of clinical outcomes

Biological Parameters

α, α/β

Repair rate (τ)

Cell and tissue kinetics

Tolerance Dose (TD_{50})

Analysis

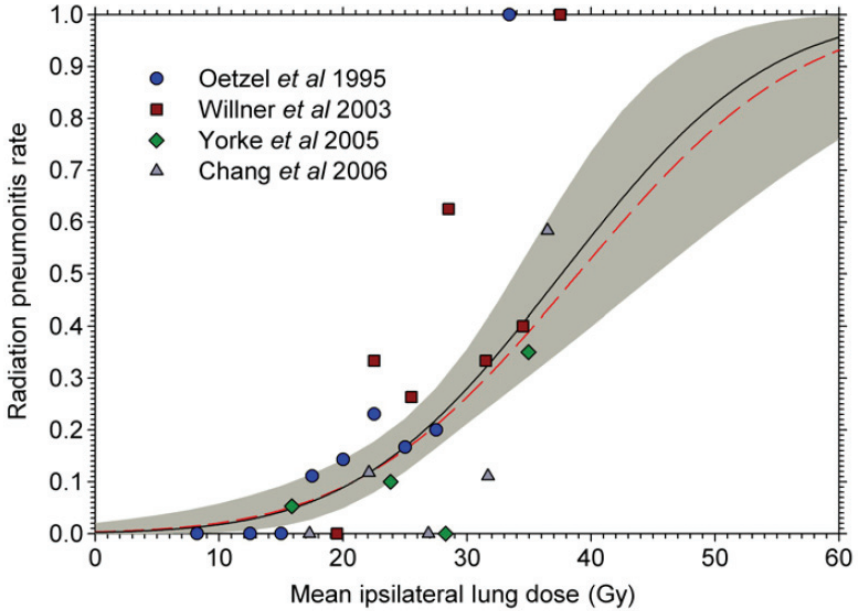
LQ model

Poisson TCP

Imperfect and *highly* non-linear models

LKB-NTCP model

Clinical Outcomes



VA Semenenko and XA Li, *Phys. Med. Biol.* **53**, 737-755 (2008)

Biologically Guided Treatment Planning?

Temporal Alterations in Dose Delivery
(e.g., external beam vs brachytherapy implants)

New treatment technologies

Altered dose distributions

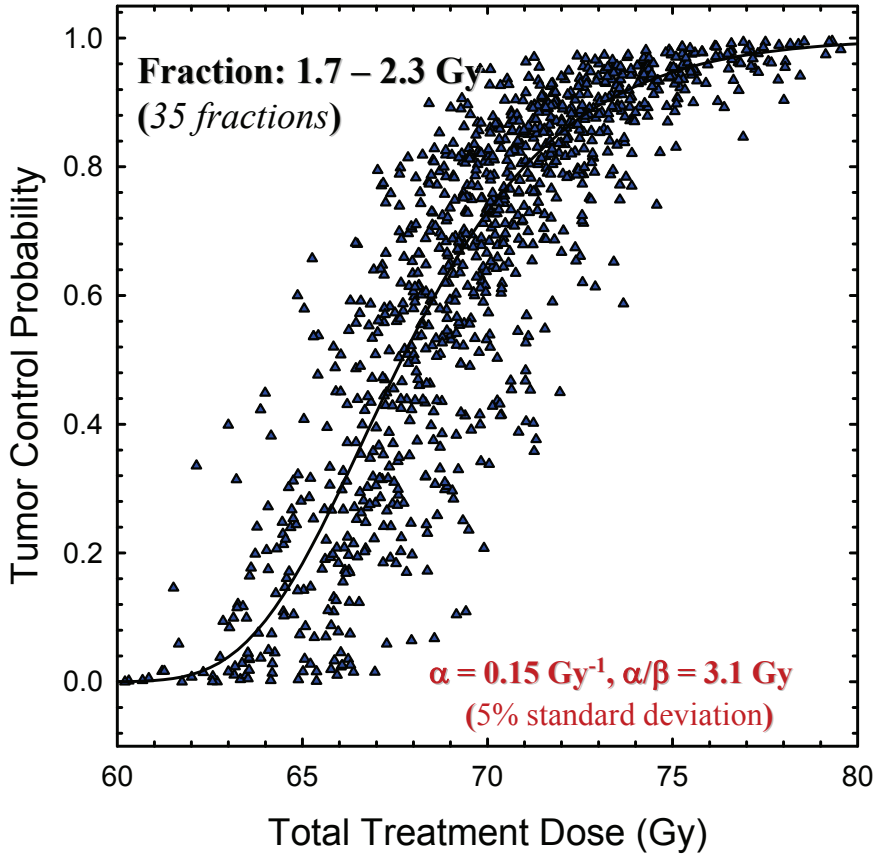
Altered radiation quality

Clinical Outcome
(Better?, Same? Worse?)

Imperfect and *highly* non-linear models

Uncertain Biological Parameters

Current Treatment



Equivalent Dose to a Tumor Target

What dose must 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

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 and G_R)

Lea-Catcheside Dose Protraction Factor

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

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

τ ← **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

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

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

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

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)

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

Effect of Fraction Delivery Time

Assume the fraction delivery time for the *reference treatment* is very short compared to the repair half-time ($\Delta t \ll \tau$)

$$G_R = \frac{1}{n_R}$$

Reference Treatment

$$G = \frac{g}{n}$$

Alternate Treatment

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

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

fraction delivery time

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

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

Fraction Size

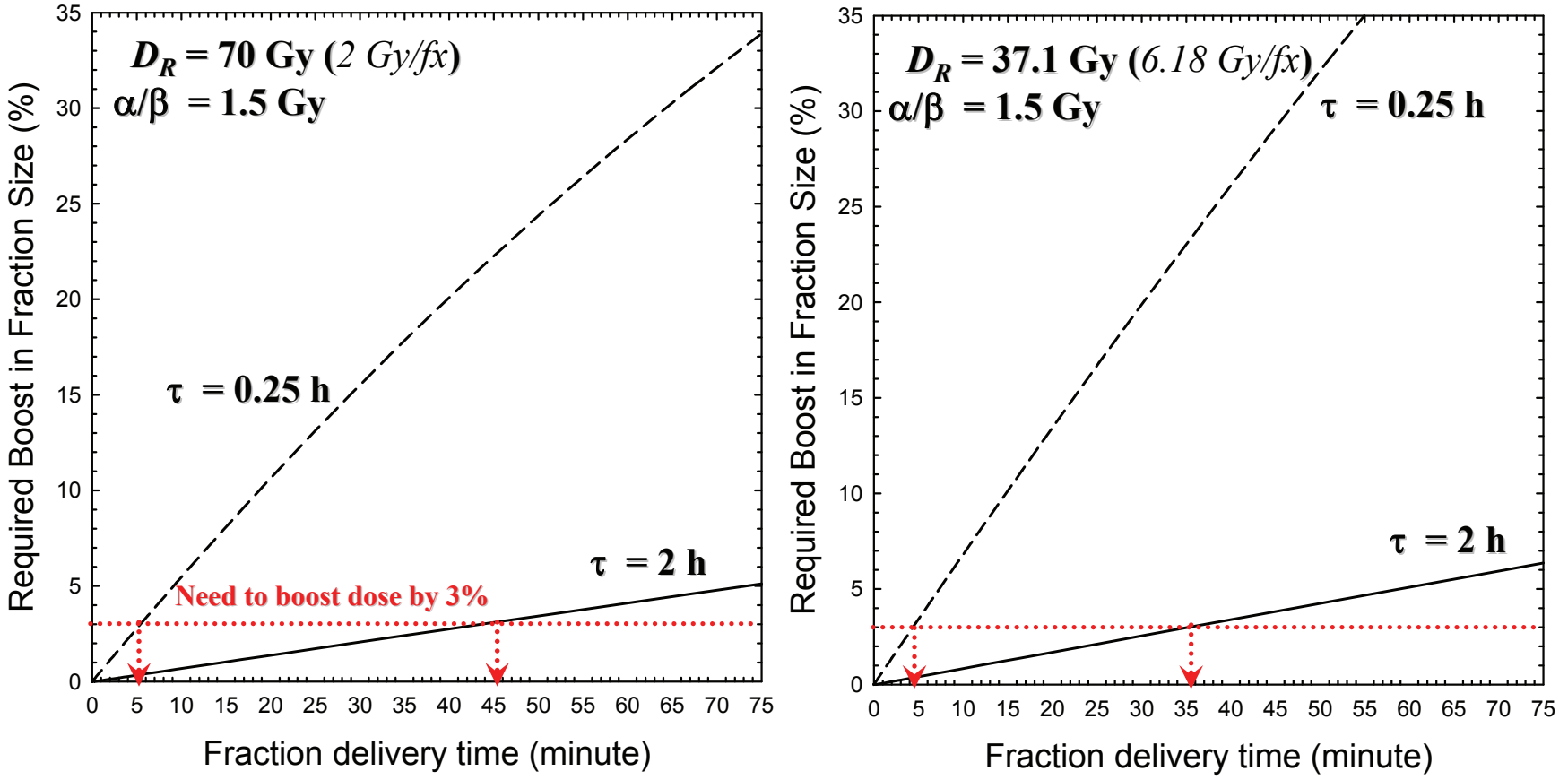
$$d = \frac{D}{n} \text{ and } d_R = \frac{D_R}{n_R}$$

Alternate *Reference*

Physical Parameters: n, n_R, Δt, D_R (*small or no uncertainty*)

Biological Parameters: α/β and τ (*large uncertainty*)

Effect of fraction delivery time



Keep fraction delivery time < 5-10 minutes to maximize local tumor control

Nominal impact on normal tissues as long as dose small compared to α/β

Equivalent Fractionation Schedules

An equivalent treatment dose *D* can be determined by adjusting the *physical* parameter *n*

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

$$g = 2(e^{-x}+x-1)/x^2 \qquad x = \Delta t \ln 2/\tau$$

Reference Treatment
("*clinical experience*")

D_R = total dose (Gy)

n_R = number fractions

$\Delta t \ll \tau$ ("short" fraction delivery time)

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

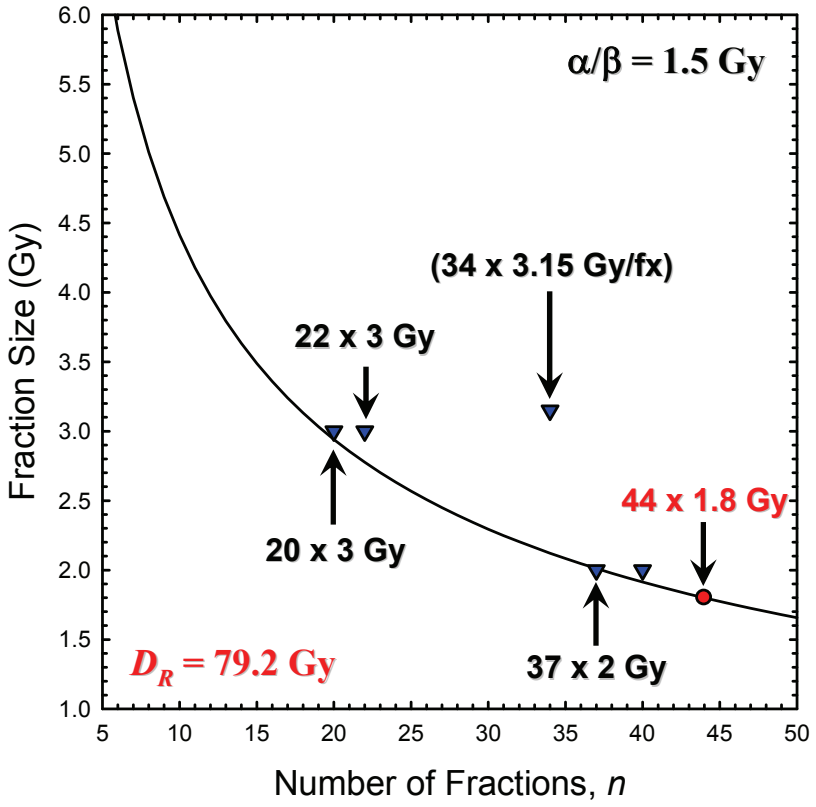
New Treatment

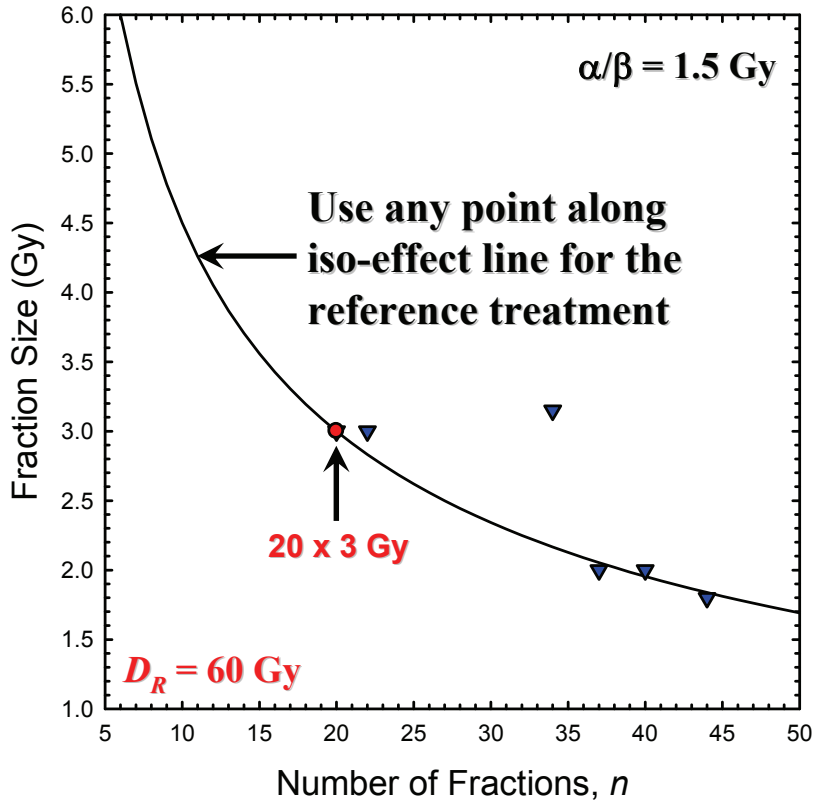
n = desired number fractions

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

$g \cong 1$ when $\Delta t \ll \tau$

Equivalent Treatments (*local tumor control*)





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

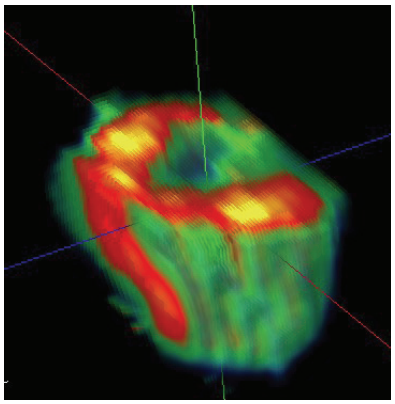
Intra-Tumor and Inter-Patient Heterogeneity

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

Formula premised on the idea that α/β (and τ) are the same for the reference and alternate treatments.

Inter-Patient Heterogeneity

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



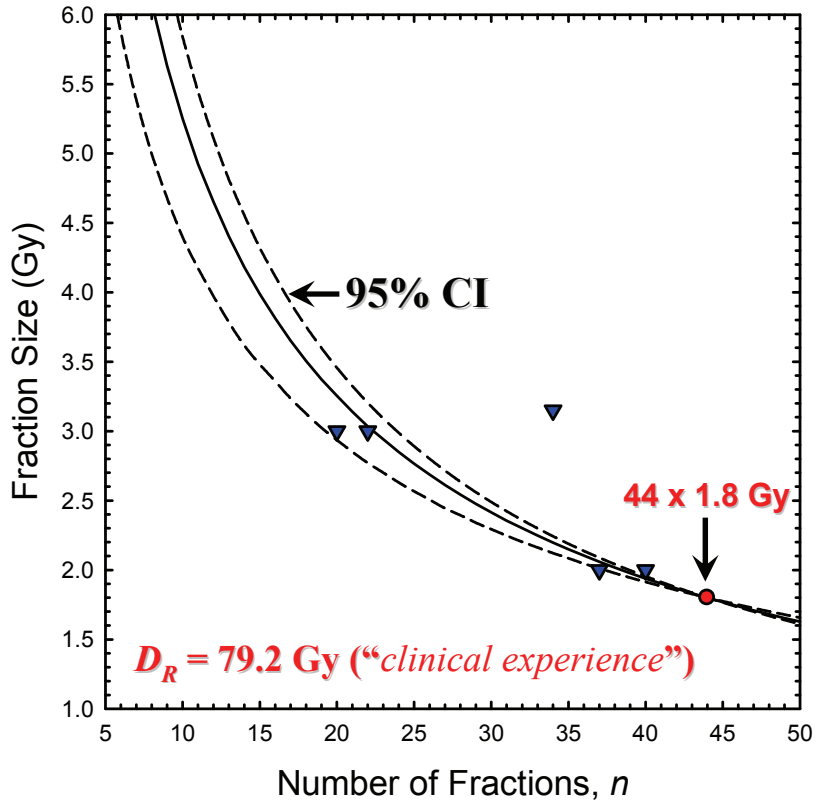
Representative DCE-CT image of a tumor (Courtesy Minsong Cao, IUSM)

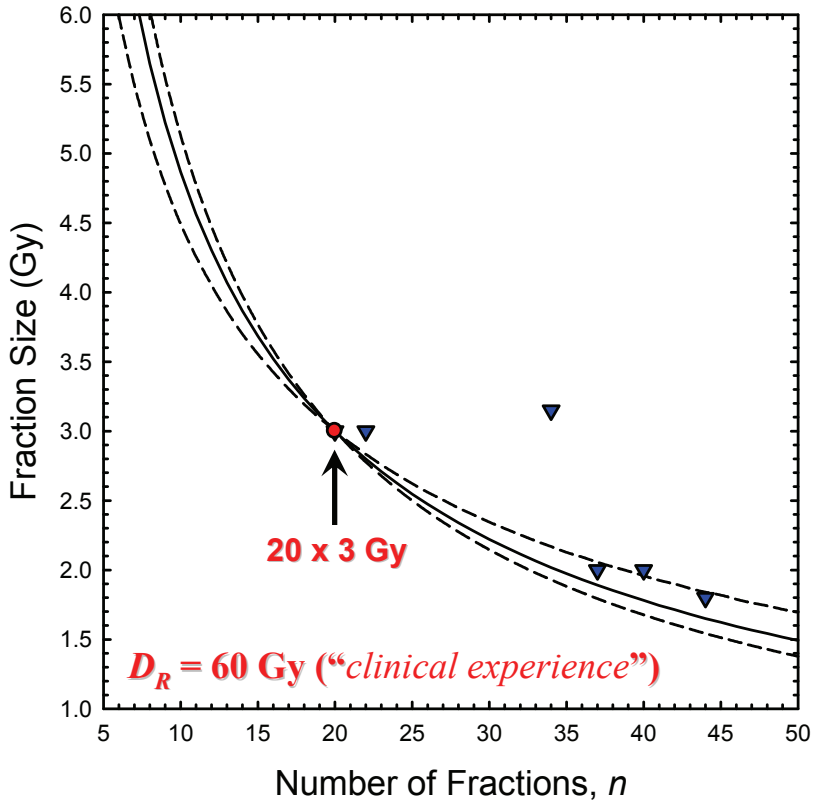
Intra-Tumor Heterogeneity

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

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

Sensitivity to α/β



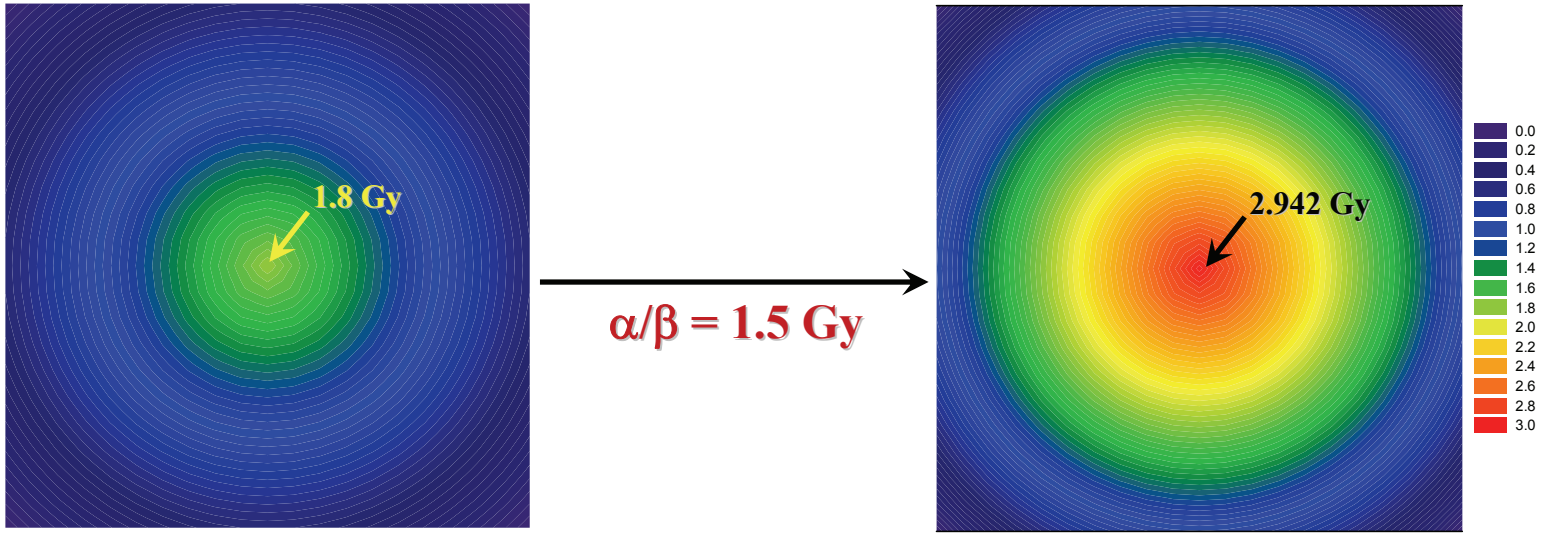


10,000 values for α/β sampled from a uniform pdf
(range 1 to 10 Gy)

Non-Uniform Dose Distributions

Apply formula on a voxel-by-voxel basis to determine biologically equivalent 3D dose distributions.

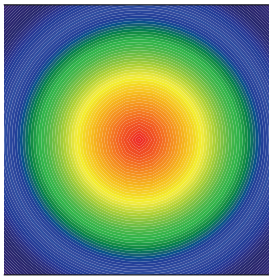
$$\text{dose to } i^{\text{th}} \text{ voxel } D_i = \frac{n(\alpha/\beta)}{2g}\left\{-1+\sqrt{1+\frac{4gD_{R,i}}{n(\alpha/\beta)}\left(1+\frac{D_{R,i}}{n_R(\alpha/\beta)}\right)}\right\}$$



44 fractions **20 fractions**

Extrapolation is *non-linear* and not overly sensitive to value of α/β

Ranking and Comparing 3D Distributions



Same basic approach can be used to convert 3D dose distributions into an equivalent uniform dose (EUD)

$$S(EUD) = S_{avg}$$ **Surviving fraction averaged over target volume**

$$S_{avg} \equiv \frac{1}{\sum_i \rho_i V_i} \sum_i \rho_i V_i \exp\left(-\alpha D_i - \beta G D_i^2\right)$$

$$EUD = \frac{\alpha/\beta}{2G}\left\{-1 + \sqrt{1 - \frac{4G \ln S_{avg}}{\alpha(\alpha/\beta)}}\right\}$$ Niemierko *Med Phys* **24**(1), 103-110 (1997)

Niemierko, *Med Phys* **26**, 1100 (1999)

$$gEUD = \left(\frac{1}{N}\sum_{i=1}^{N} D_i^a\right)^{1/a}$$

$$D_i = \frac{\alpha/\beta}{2G}\left\{-1 + \sqrt{1 - \frac{4G \ln S(D_{R,i})}{\alpha(\alpha/\beta)}}\right\}$$

voxel-by-voxel **corrections for dose rate, fraction size, …**

Effects of Radiation Quality

Outcome Low LET = Outcome High LET

$$S(D_L) = S(D_H)$$

$$\exp\left(-\alpha_L D_L - \beta_L G_L D_L^{\,2}\right) = \exp\left(-\alpha_L D_L - \beta_L G_L D_L^2\right)$$

$$RBE \equiv \frac{D_L}{D_H}$$

Take logarithm, apply quadratic formula and rearrange terms

$$D_H = \frac{n_H(\alpha/\beta)_H}{2g_H}\left\{-1+\sqrt{1+\frac{4g_H D_L}{n_H(\alpha/\beta)_H}\cdot\frac{\alpha_L}{\alpha_H}\left(1+\frac{g_L D_L}{n_L(\alpha/\beta)_L}\right)}\right\}$$

Formula has *explicit* corrections for total dose, fraction size, and dose rate effects – the effects of radiation quality are *implicit* in the biological parameters.

α_H, $(\alpha/\beta)_H$, $(\alpha/\beta)_L$, α_L

τ_H **and** τ_L (*expect* $\tau_L \leq \tau_H$)

Effects of LET on α and α/β

RADIATION RESEARCH 169, 447–459 (2008)
0033-7587/08 $15.00

Combined Use of Monte Carlo DNA Damage Simulations and Deterministic Repair Models to Examine Putative Mechanisms of Cell Killing

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$$\alpha = \theta\Sigma + \kappa\bar{z}_F\Sigma^2$$

$$\bar{z}_F \cong 0.204\frac{LET}{d^2}$$

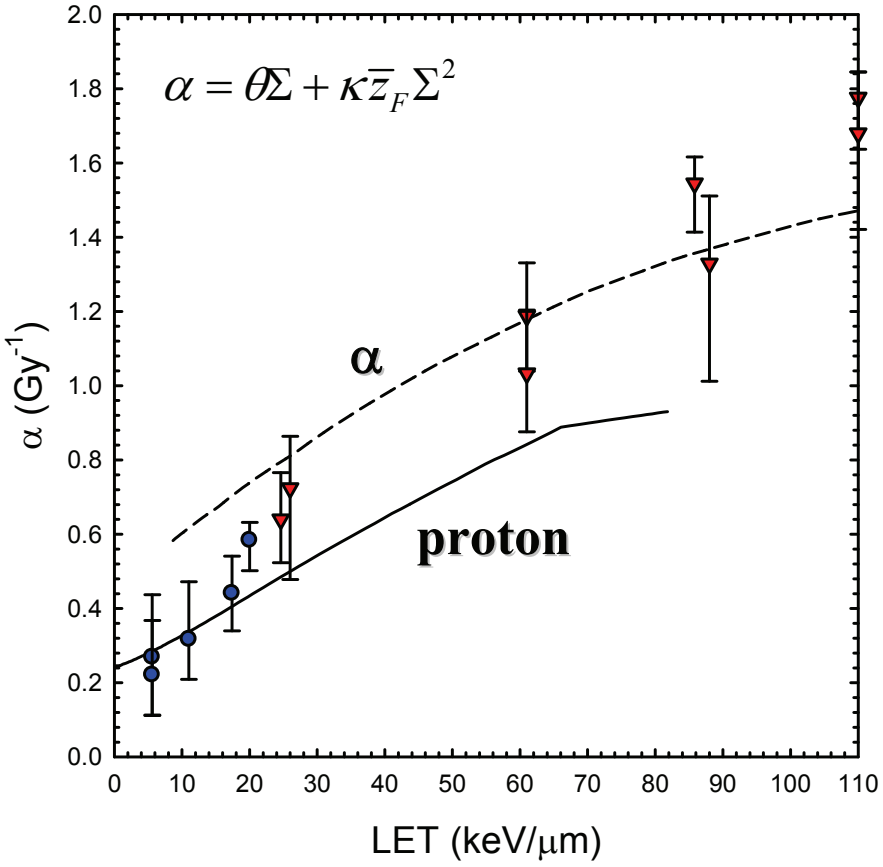
$$\alpha/\beta = \frac{2}{\Sigma}\left(\frac{\theta}{\kappa} + \bar{z}_F\Sigma\right)$$

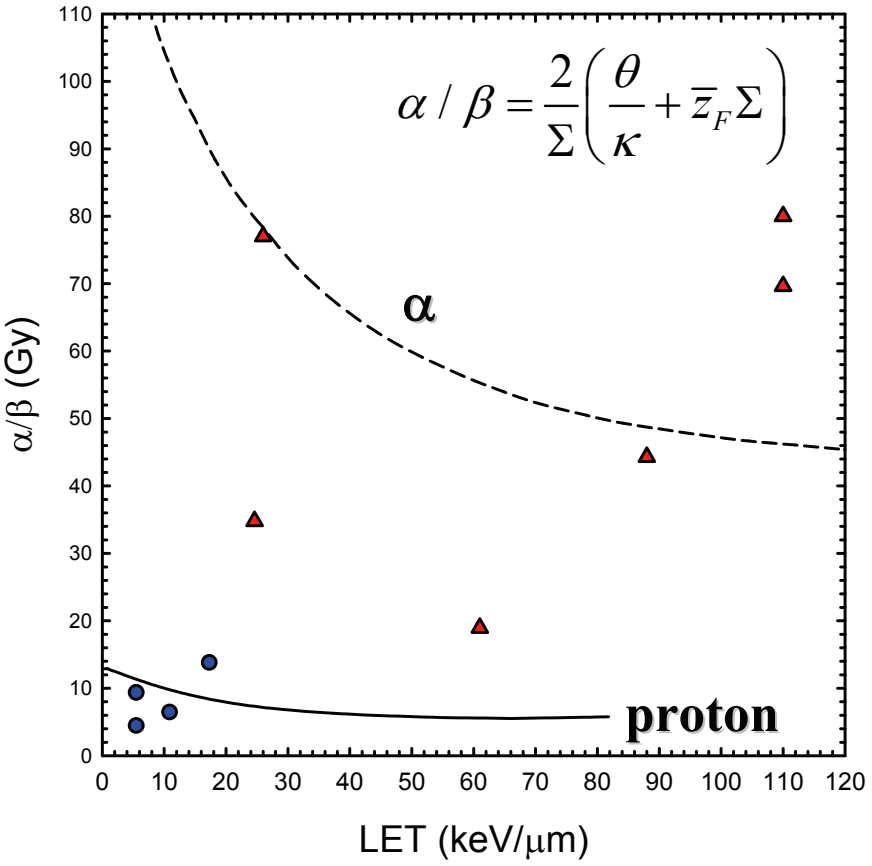
θ and κ are biological parameters that are independent of LET up to ~ 100 keV/μm

Σ = number of DSB Gy^{-1} cell^{-1} (*estimated using Monte Carlo simulations*)

Isoeffect calculations with two adjustable parameters (θ and κ) instead of four [$(\alpha/\beta)_H$, $(\alpha/\beta)_L$, α_L, and α_H] – effects of LET *explicit*

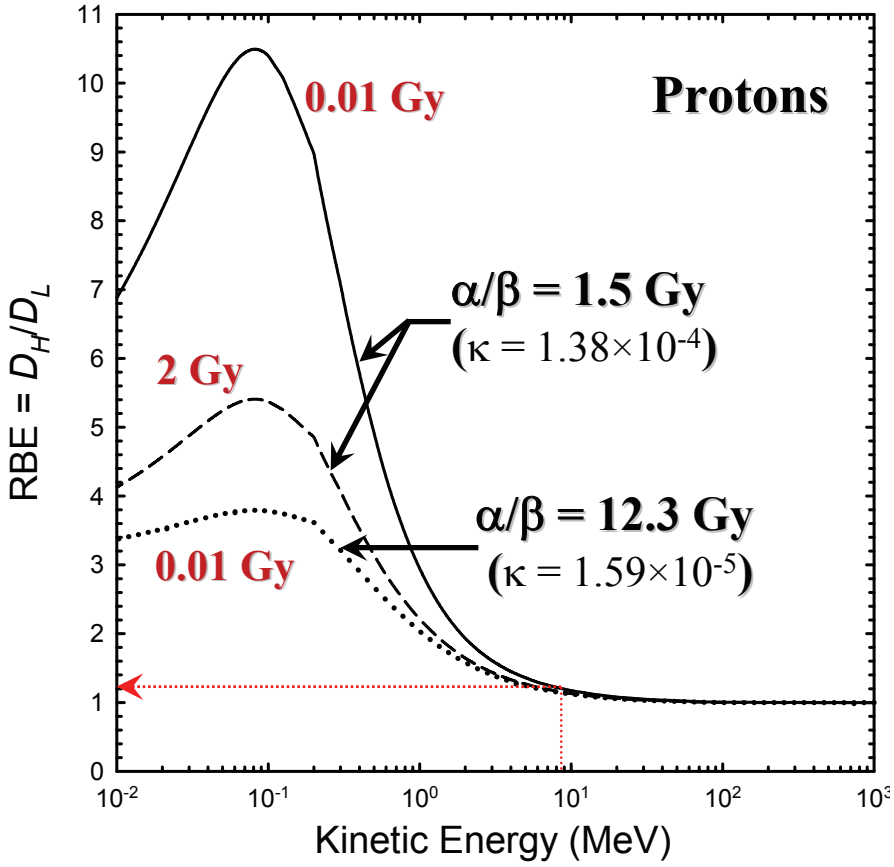
Effect of LET on α and α/β (*Human Kidney T1 cells*)

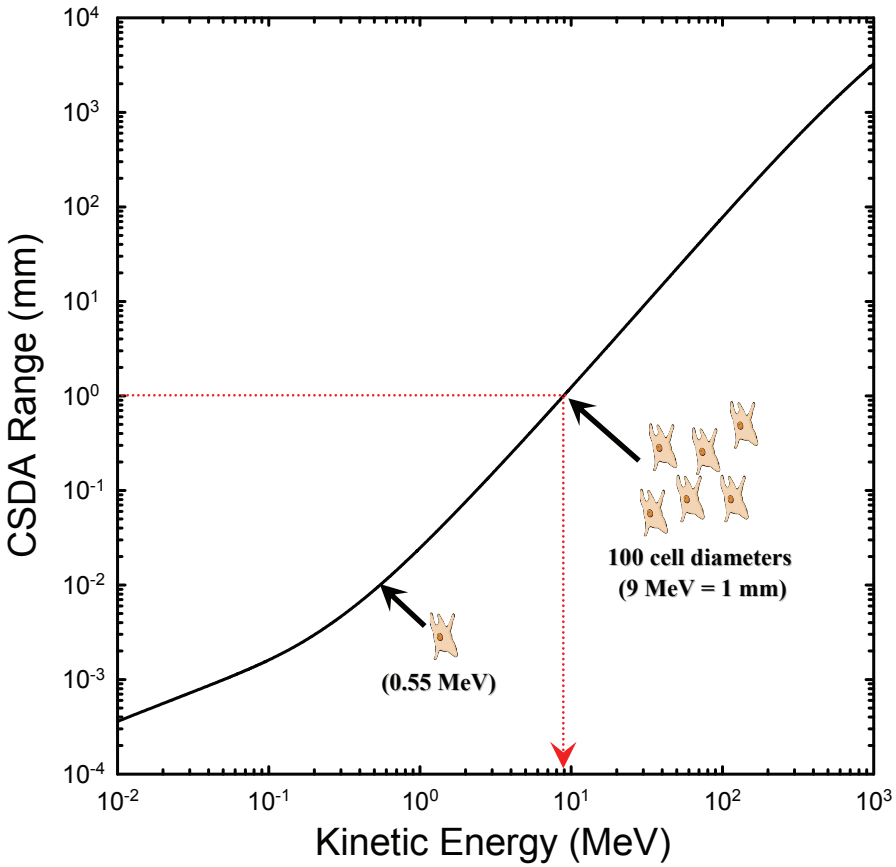




$^{2}H^{+}$	$^{4}He^{2+}$
$\theta = 5.025\times10^{-3}$	$\theta = 1.003\times10^{-2}$
$\kappa = 1.593\times10^{-5}$	$\kappa = 3.204\times10^{-6}$

Relative Biological Effectiveness (RBE)





Predicted RBE in distal end (*last mm*) of Bragg peak > 1.1
(compare to generic clinical RBE of ~ 1.1 for the SOBP)

Isoeffect Calculations – A Summary

- ***Easy-to-use*** method to guide the selection of equivalent fractionation schedules and 3D dose distributions
  - Corrections for fraction delivery time ("dose rate effects"), fraction size, radiation quality, repopulation effects, oxygen effects, …
  - Small number of biological parameters (**α/β most critical one**)
  - *Potential* to use Monte Carlo DNA damage simulations to account for oxygen and LET effects with 2 adjust parameters (**θ and κ**) instead of $(\alpha/\beta)_H$, $(\alpha/\beta)_L$, α_L, α_H

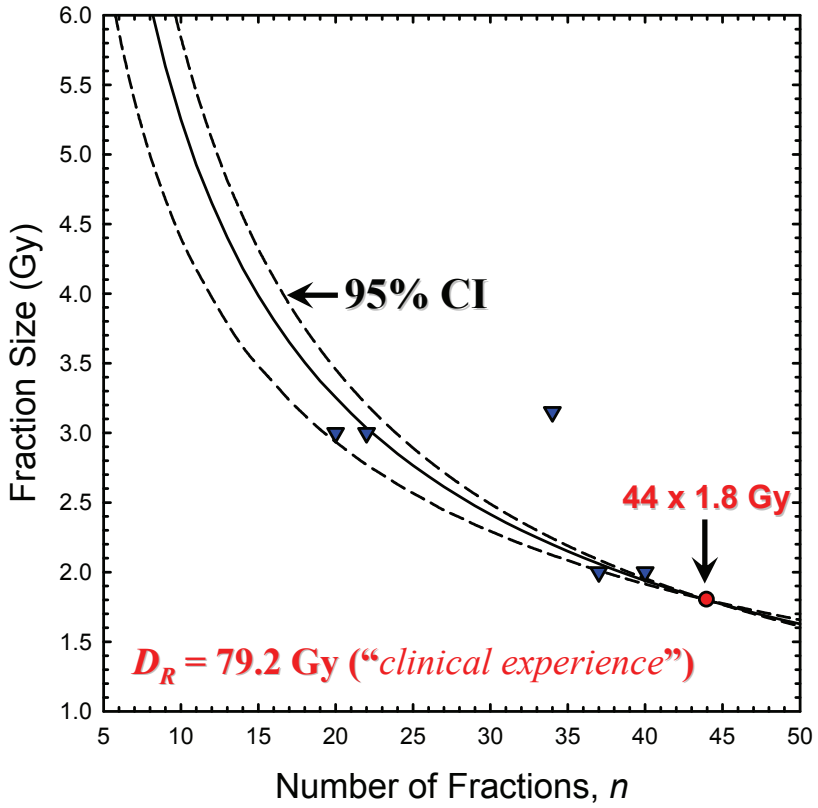
$$D = \frac{n(\alpha/\beta)}{2g}\left\{-1+\sqrt{1+\frac{4gD_R}{n(\alpha/\beta)}\left(1+\frac{D_R}{n_R(\alpha/\beta)}\right)}\right\}$$

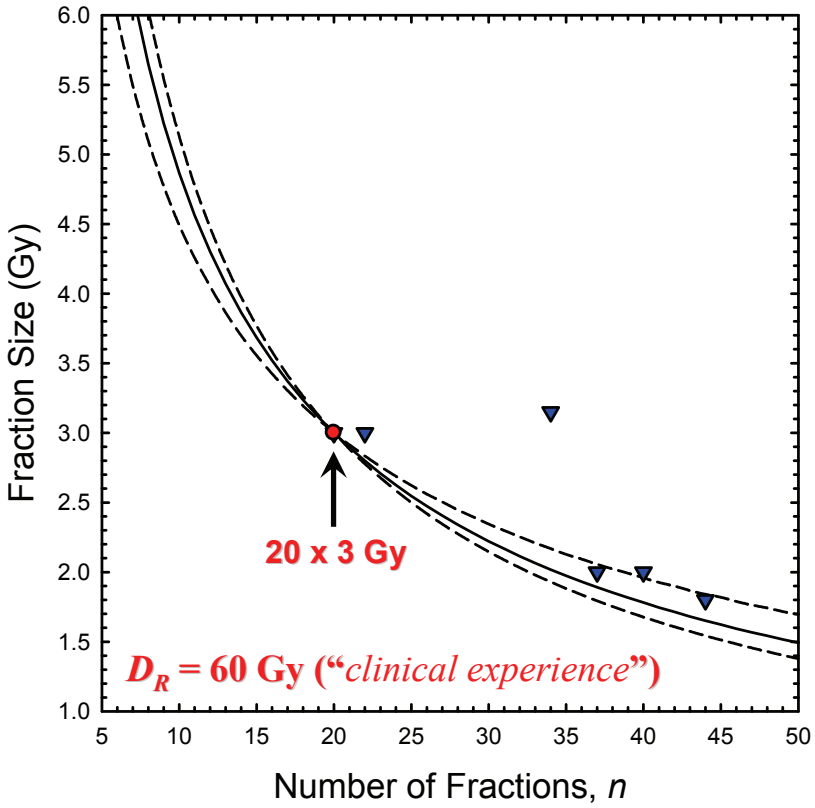
Need approximate value for (α/β) and τ (to compute *g***)**

$$\alpha = \theta\Sigma + \kappa\bar{z}_F\Sigma^2 \qquad \alpha/\beta = \frac{2}{\Sigma}\left(\frac{\theta}{\kappa}+\bar{z}_F\Sigma\right)$$

Inter-patient and Intra-tumor Heterogeniety

Small changes in a fractionation schedule quite reasonable *despite* uncertainties in biological parameters





Treatment Individualization?

Outcome Reference Patient = Outcome *i*th (*specific*) Patient

$$S(D_R) = S(D_i)$$

$$\exp\left(-\alpha_R D_R - \beta_R G_R D_R^{\,2}\right) = \exp\left(-\alpha_i D_i - \beta_i G_i D_i^2\right)$$

↓ **Take logarithm, apply quadratic formula and rearrange terms**

$$D_i = \frac{(\alpha/\beta)_i}{2G_i}\left\{-1 + \sqrt{1 + \frac{4G_i D_R}{(\alpha/\beta)_i}\cdot\frac{\alpha_R}{\alpha_i}\left(1 + \frac{G_R D_R}{(\alpha/\beta)_R}\right)}\right\}$$

Analysis of clinical outcomes for patient population: $(\alpha/\beta)_R$, α_R, τ_R (G_R)

Use, for example, predictive assays or functional imaging to estimate patient-specific parameters $(\alpha/\beta)_i$, α_i, and/or τ_i (G_i)

$$\frac{\alpha_i}{\alpha_R} \propto \{\text{measured quantity}\} \qquad \frac{(\alpha/\beta)_i}{(\alpha/\beta)_R} \propto \{\text{measured quantity}\}$$

Hypothetical Patient Groups

An analysis of clinical outcomes suggests that the overall tumor response for a patient population can be characterized by

$$\alpha_R = 0.15 \text{ Gy}^{-1} \qquad (\alpha/\beta)_R = 3 \text{ Gy}$$

A dose limiting normal tissue (α/β = 4 Gy) can tolerate 15 Gy over 20 fractions.

Now imagine that a new technique allows us to separate the patient population into two tumor response groups…

Group 1:

$$\frac{\alpha_1}{\alpha_R} = 2 \pm 0.4$$

$$\frac{(\alpha/\beta)_1}{(\alpha/\beta)_R} = 20 \pm 4$$

$$\alpha_1 = 0.3 \pm 0.06 \text{ Gy}^{-1}$$

$$(\alpha/\beta)_1 = 60 \pm 12 \text{ Gy}$$

Group 2:

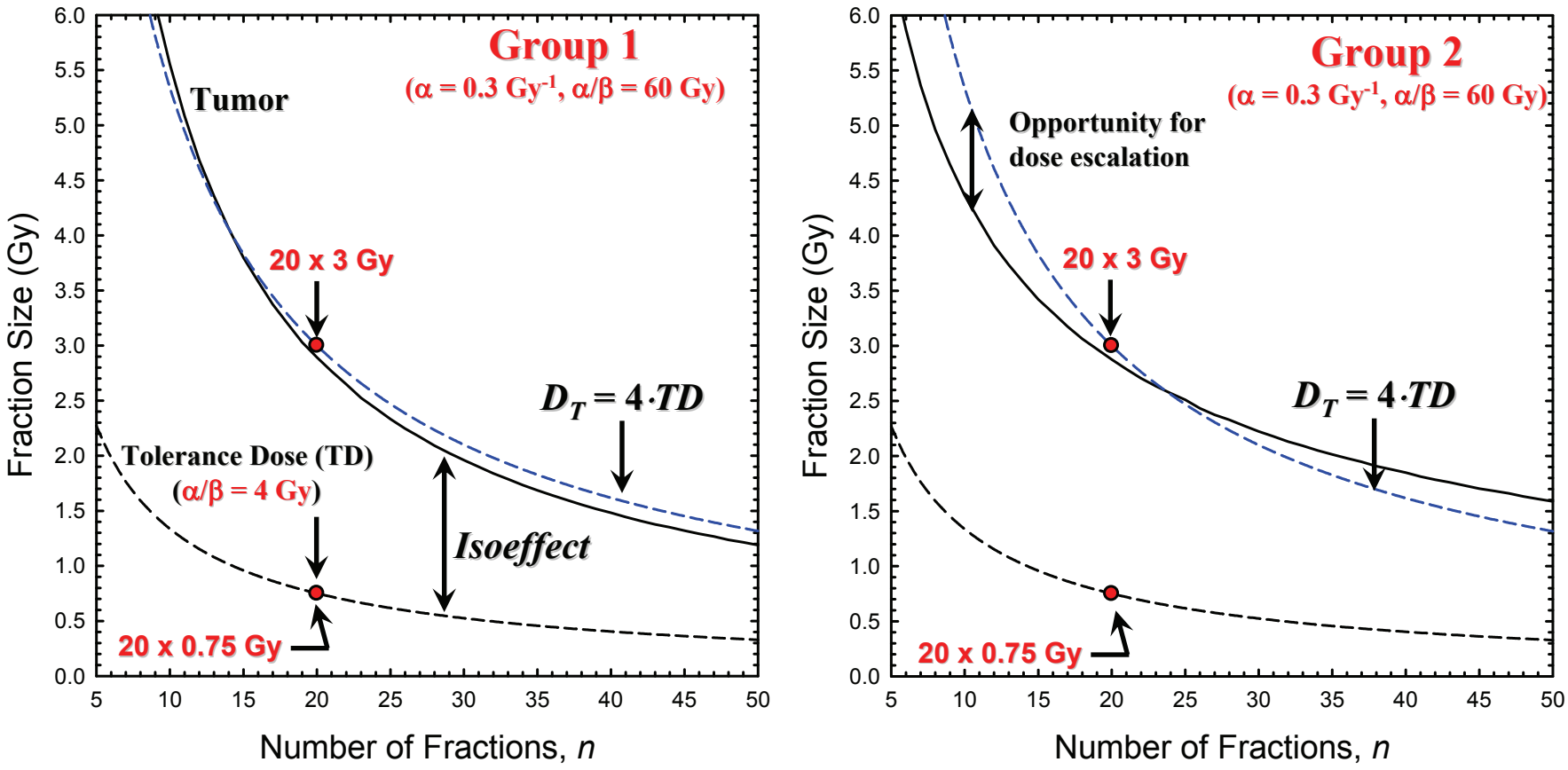
$$\frac{\alpha_2}{\alpha_R} = 0.8 \pm 0.2$$

$$\frac{(\alpha/\beta)_2}{(\alpha/\beta)_R} = 0.6 \pm 0.3$$

$$\alpha_2 = 0.12 \pm 0.03 \text{ Gy}^{-1}$$

$$(\alpha/\beta)_2 = 1.8 \pm 0.9 \text{ Gy}$$

Potential for Dose Escalation (Groups 1 and 2)



Might increase number of fractions for group 1 ($n > 20$)

Very desirable to decrease number of fractions for group 2 ($n < 20$)

Concluding Remarks

Isoeffect calculations are the preferred way to tackle many treatment-related activities

- **Assess, design and compare dose escalation studies**
  - Studies from multiple clinics
  - Optimal number of fractions (fraction size and total dose)
- **Assess and correct for deviations from a planned treatment**
  - Patient setup errors and organ motion
  - Missed treatment days or interrupted treatments
- **Leverage existing clinical experience with low LET radiation when introducing new techniques and dose delivery technologies**
  - Proton therapy, new brachytherapy sources and procedures
  - Combined treatments (e.g., brachytherapy with an IMRT boost)
  - Compare and rank 3D dose distributions (EUD)
  - Alterations in the temporal pattern of radiation delivery (fraction delivery time, shortened overall treatment time)
- **Aid in the analysis of clinical outcomes**
- **Aid in the implementation of individualized treatments**

Research still needed to develop and, *especially*, validate models and methods – but the future looks promising!

Thank You

Translating Physics and Biology into the Clinic

Tuesday September 23, 2008

2:30 to 4:30 pm

- **X. Allen Li**, Medical College of Wisconsin Department of Radiation Oncology
- **Joseph O. Deasy**, Washington University School of Medicine, Department of Radiation Oncology
- **Yue Cao**, University of Michigan Health System, Department of Radiation Oncology
- **Robert Jeraj**, University of Wisconsin Medical School, Department of Medical Physics
- **Rob Stewart**, Purdue University, School of Health Sciences