Robust Biologically Guided Radiation Therapy (BGRT)

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Location: Hotel Grand Chancellor, 65 Hindley Street, Adelaide, South Australia

Website: *http://www.rah.sa.gov.au/cancer/mot.php*

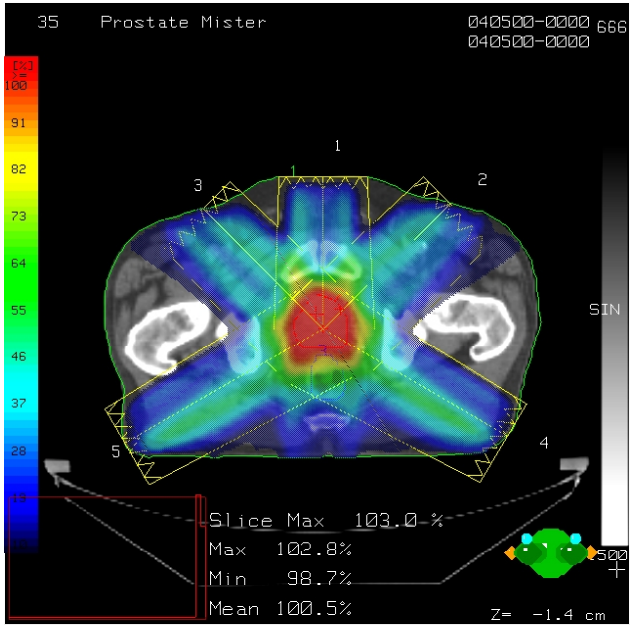
Learning Objectives

- **Rationale for BGRT**
- **Are existing biological models "good enough" for clinical applications?**
  - Some of the challenges
  - Limitations and applicability of BED and EUD concepts with a focus on intra- and inter-patient heterogeneity
- **Examples**
  - Equivalent prescriptions
  - Plan ranking and comparison with EUD
- **This Presentation and Supplemental Slides**
  - http://faculty.washington.edu/trawets/

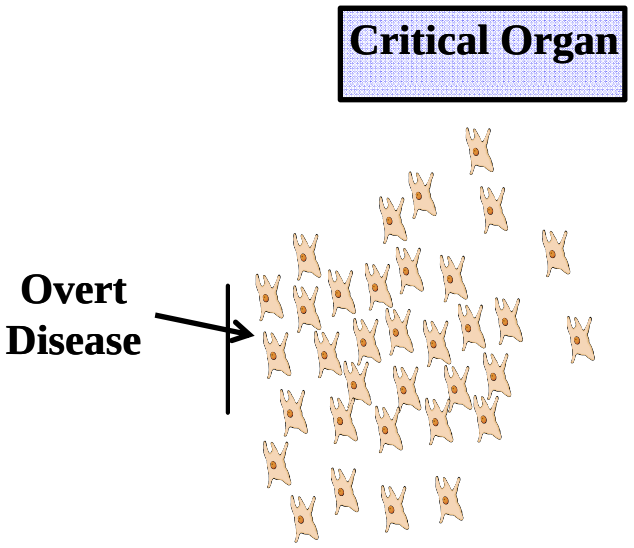
Presenter has no conflicts of interest to disclose

Why isn't EBRT more successful?

- Uncertainty in boundary of primary tumor
- Inability to delivery a tumoricidal dose
- Migration of diseased cells to other body parts



Dose escalation not always possible



Motivation for BGRT

How do we get the most bang for our buck (*dose*)?

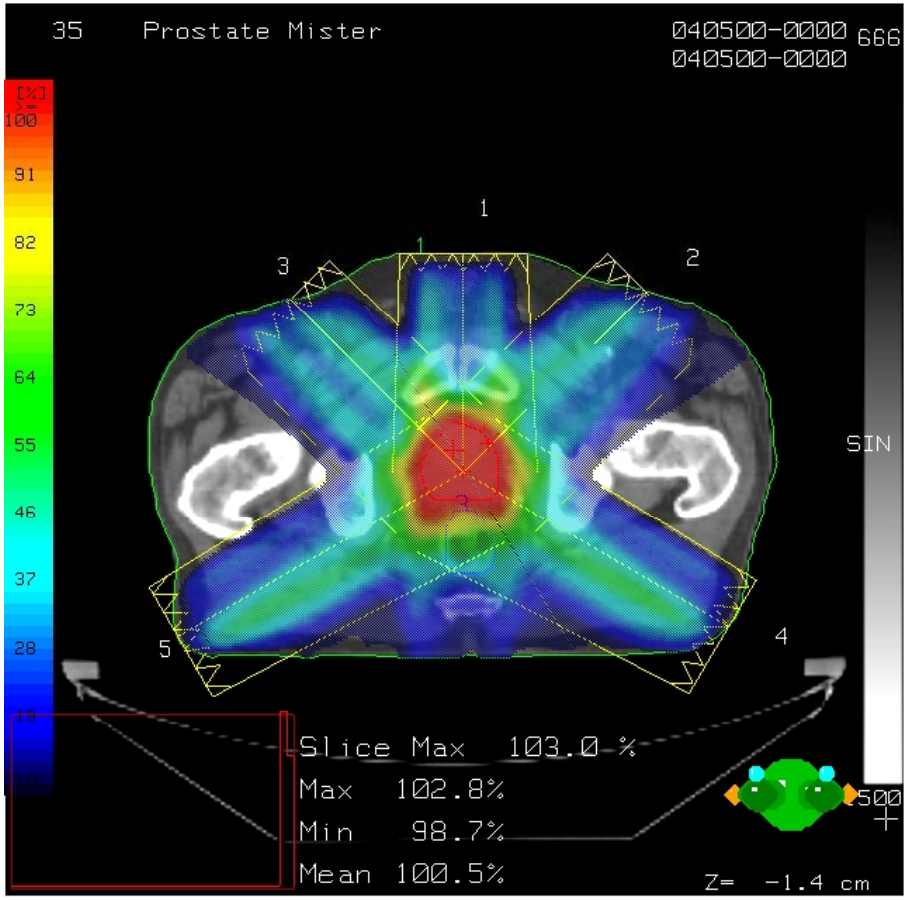
↓

Outcome Prediction

or

"Biological Metrics"

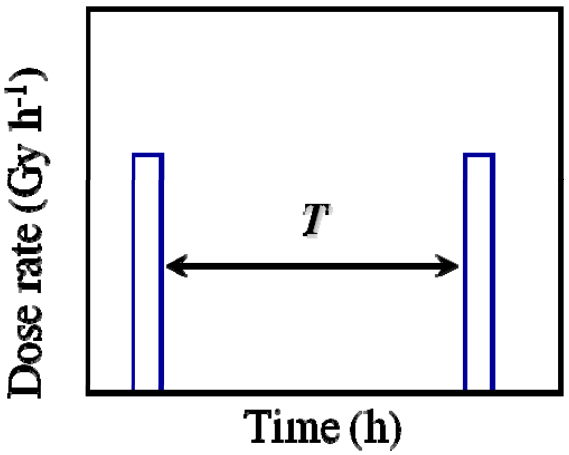
A way to rank the *relative* efficacy of alternate and competing treatments

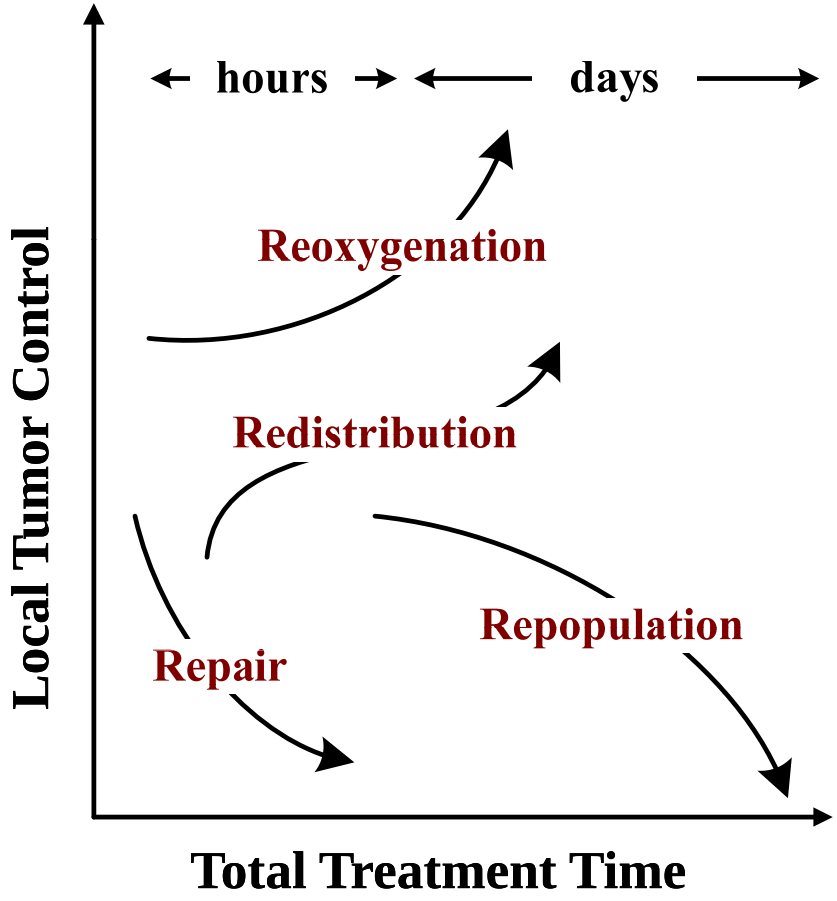


When local control cannot be achieved through dose escalation, only RT option is to move the dose around in space *and/or* time.

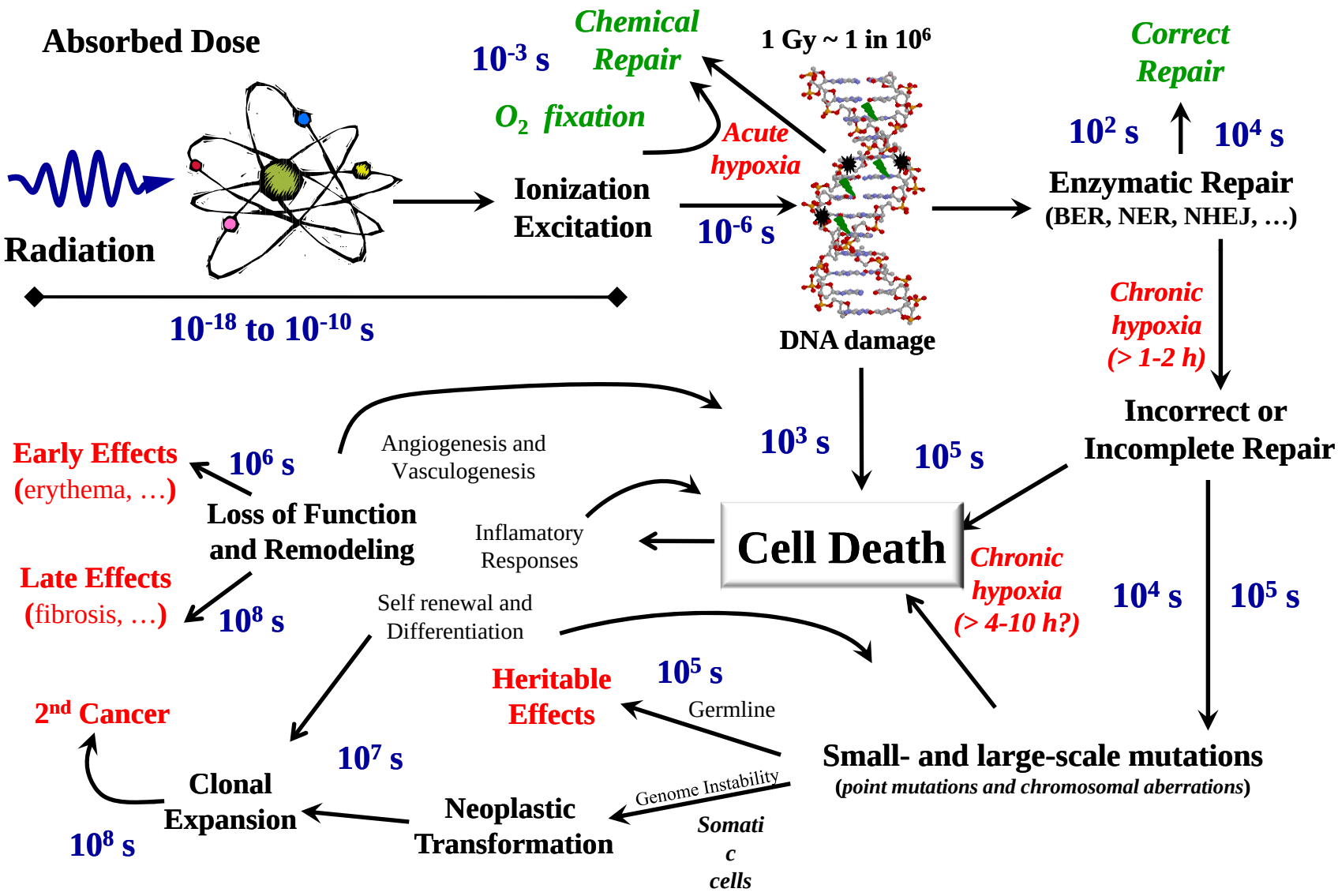
Four R's of Radiobiology (*conventional wisdom*)

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





Physics → Chemistry → Biology → Clinic



The LQ in Radiation Therapy

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

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

Dose-rate and dose-fractionation effects ("*dose protraction factor*")

one-hit damage

inter-track damage interaction

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

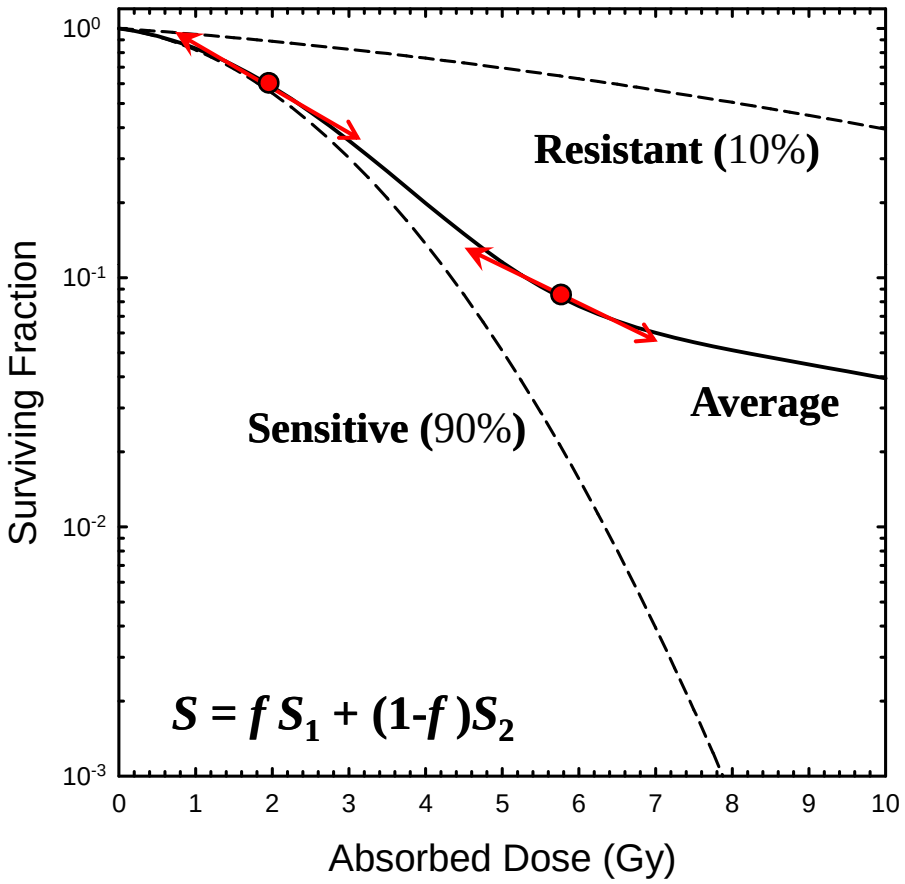
JZ Wang, M Guerrero, XA Li, IJROBP **55**, 194-203 (2003)

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

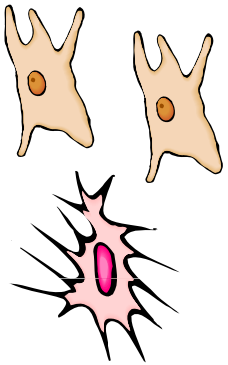


Can't use a single (*average*) set of LQ radiation sensitivity parameters (α, α/β) to predict overall shape of dose-response curve

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

Five Reasons (*many others possible*)

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



But may be reasonable to 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})

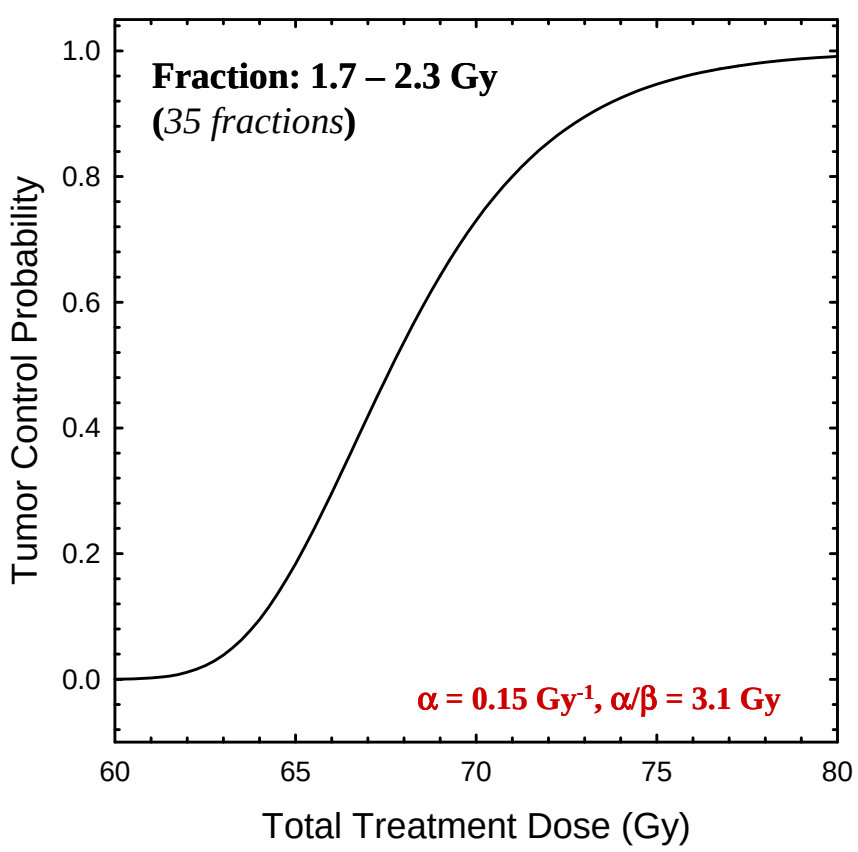
***V* = tumor volume** (GTV? CTV? PTV?)

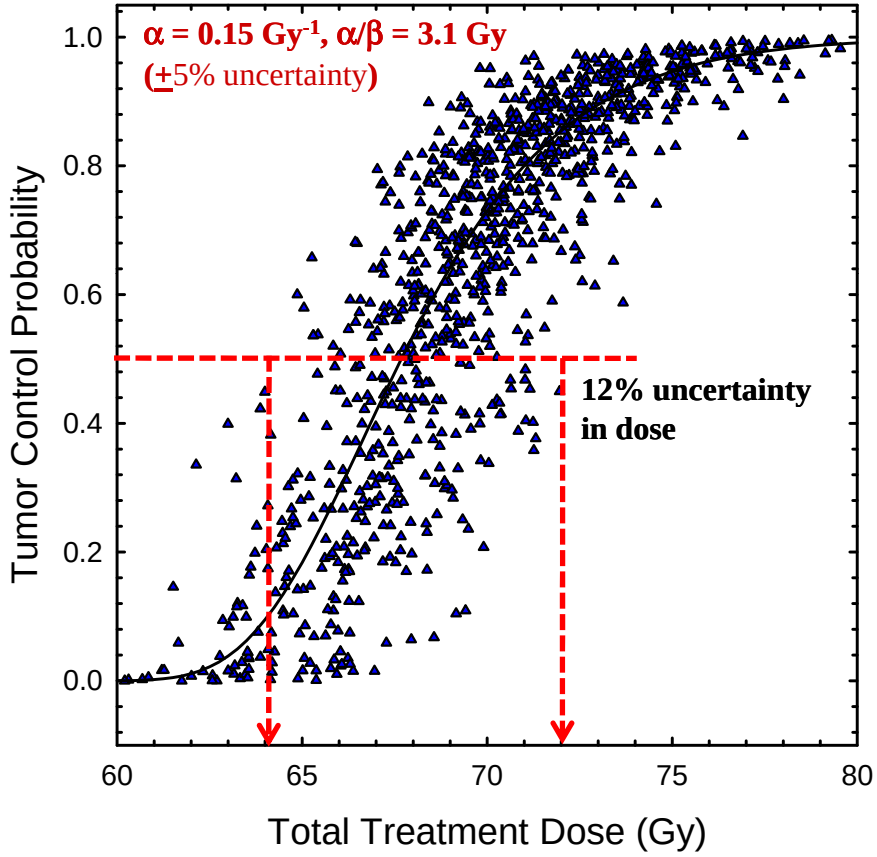
product ρ*V* = pre-treatment number of tumor cells

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 ρ << 10^9 cells cm^{-3}?**)**

Prediction of Local Tumor Control





Even small levels of uncertainty in the biological parameters (α and α/β) have a big impact on our ability to predict the chance we achieve tumor control

Outcomes for a Patient Population?

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

Equivalent Prescriptions (*tumor*)

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 comparing or ranking plans in the *same patient*, ρ and V may be considered *modality and plan independent* constants (*same number of diseased cells regardless of modality and plan***).**

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

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)

Equivalent Treatment 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.

Biologically Effective Dose (BED)

How is an iso-effective physical dose related to BED?

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

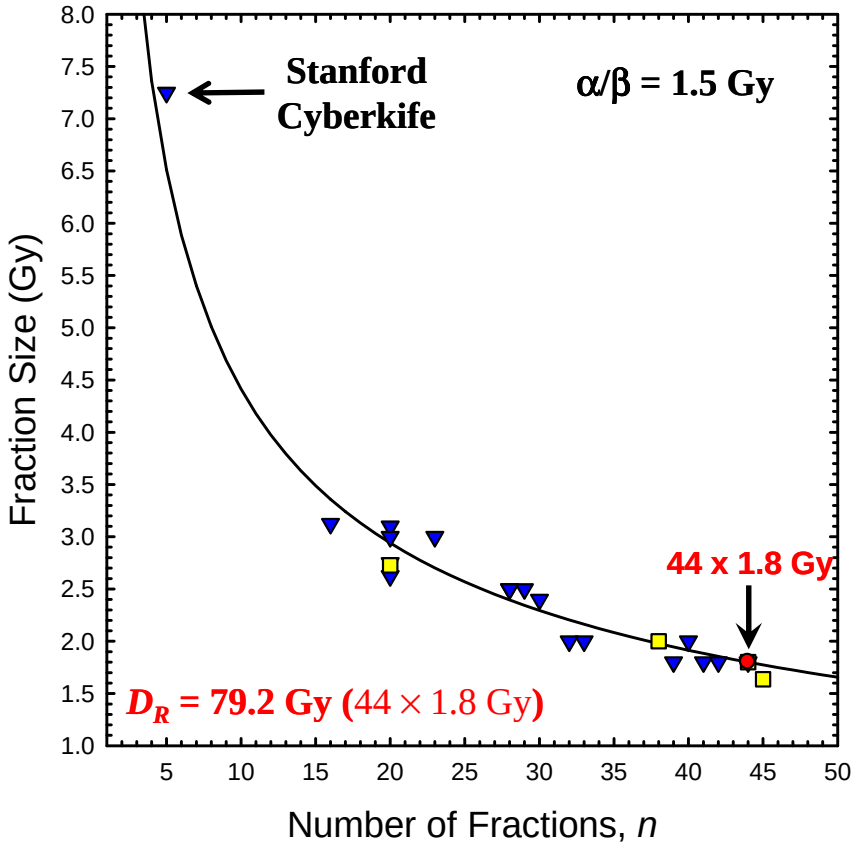
$$= \frac{\alpha/\beta}{2G}\left\{-1+\sqrt{1+\frac{4G}{(\alpha/\beta)}D_R\left(1+\frac{d_R}{\alpha/\beta}\right)}\right\}$$

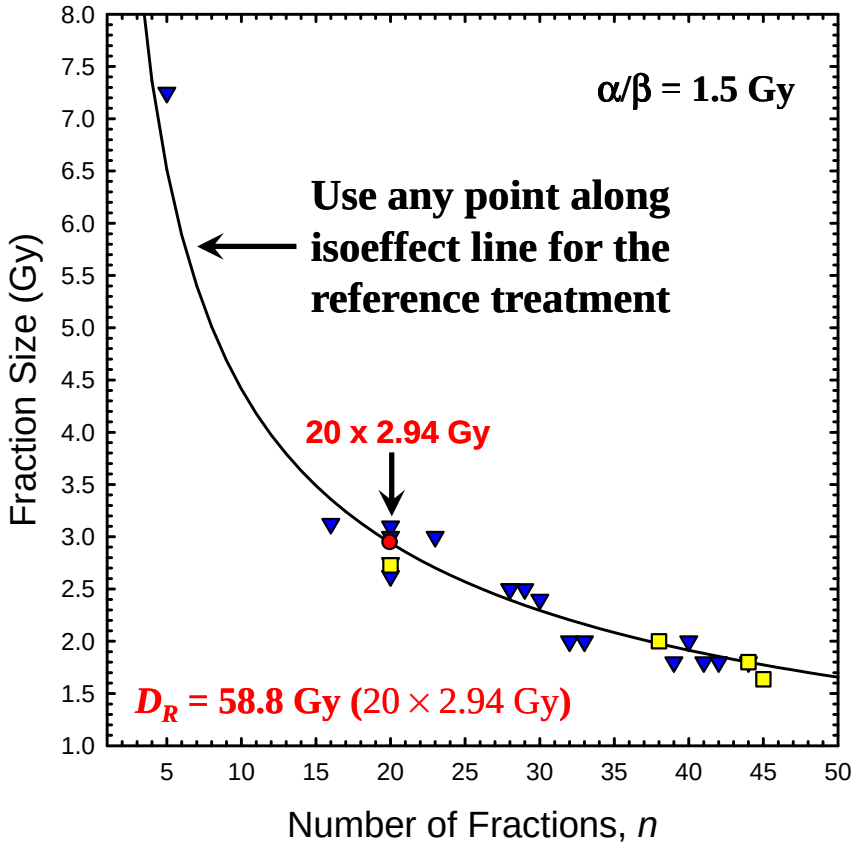
No repopulation effects

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

Correction for exponential repopulation without time lag

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!

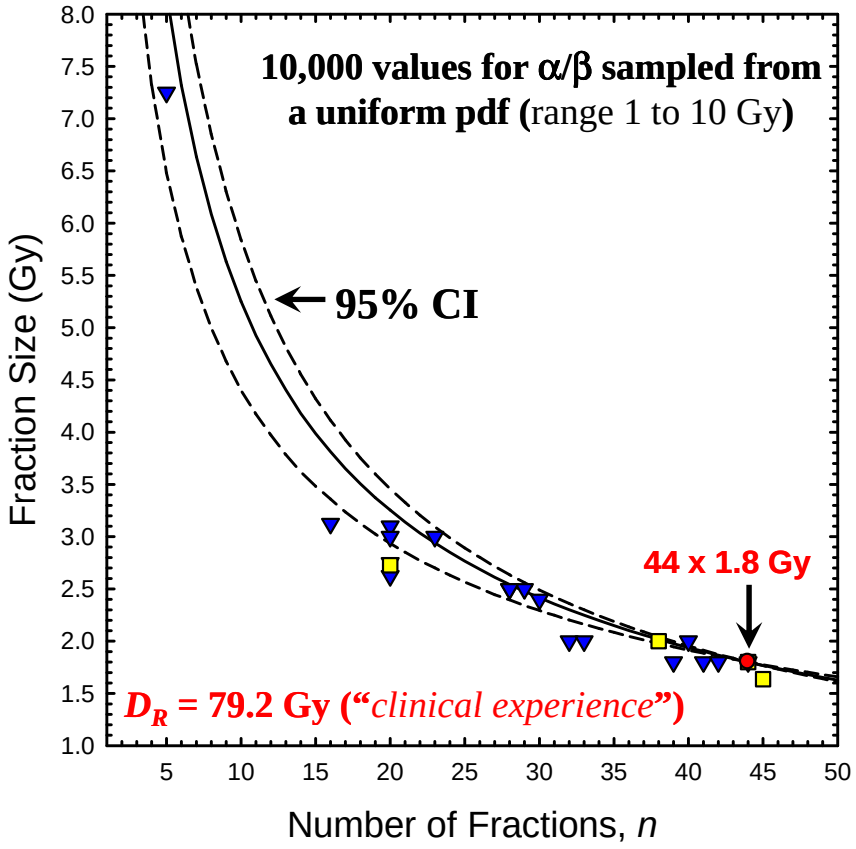
Inter-Patient Heterogeneity

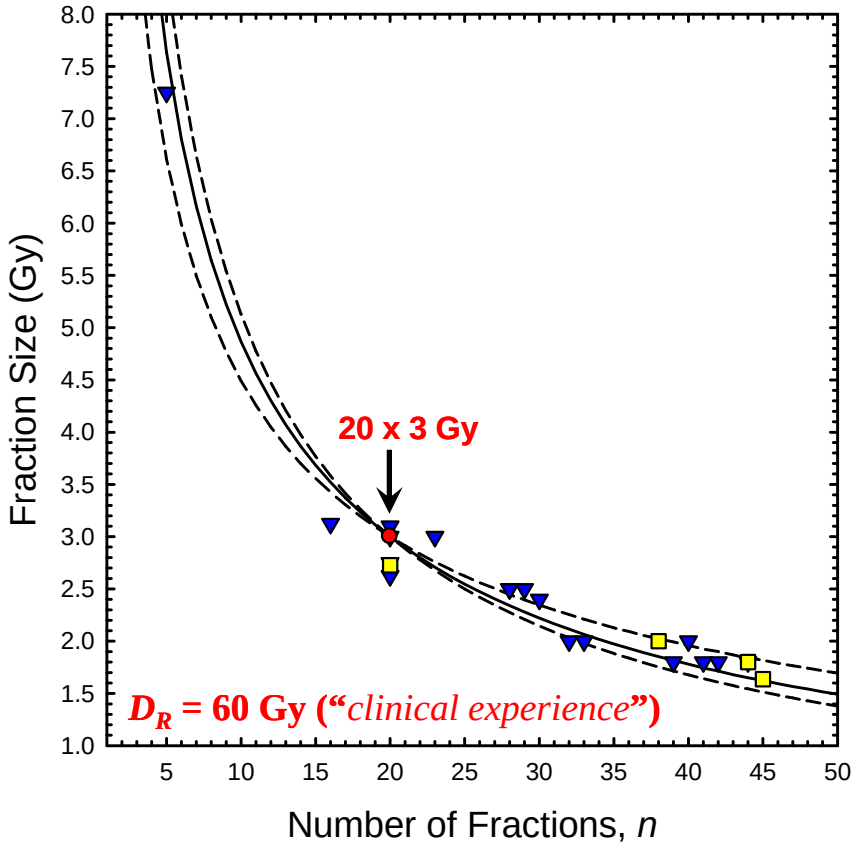
Thought Experiment: All patients (*tumors*) have a different effective α/β (*unknown distribution*). BUT… same value of α/β is appropriate (*as a first approximation*) in the same patient for competing plans and modalities

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

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

Equivalent Uniform Dose (EUD)

Concept of an EUD introduced by A. Niemierko in 1997

"It is intuitively logical that, for any inhomogeneous dose distribution delivered to a volume of interest (VOI) according to a certain fractionation scheme, there exists a unique uniform dose distribution delivered in the same number of fractions, over the same total time, which causes the same radiobiological effect.

The important feature of this equivalent dose distribution would be its uniformity, which allows one to use a *single number to describe the entire VOI dose distribution*. Of course, the equivalent dose depends on the considered effect."

A. Niemierko, Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Med Phys.* 24(1), 103-110 (1997).

EUD for tumor control and cell survival

$$\exp\left(-\alpha EUD - \beta EUD^2\right) = \frac{1}{\rho V}\sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^{\,2}\right)$$

To solve for EUD, take logarithm and apply quadratic formula

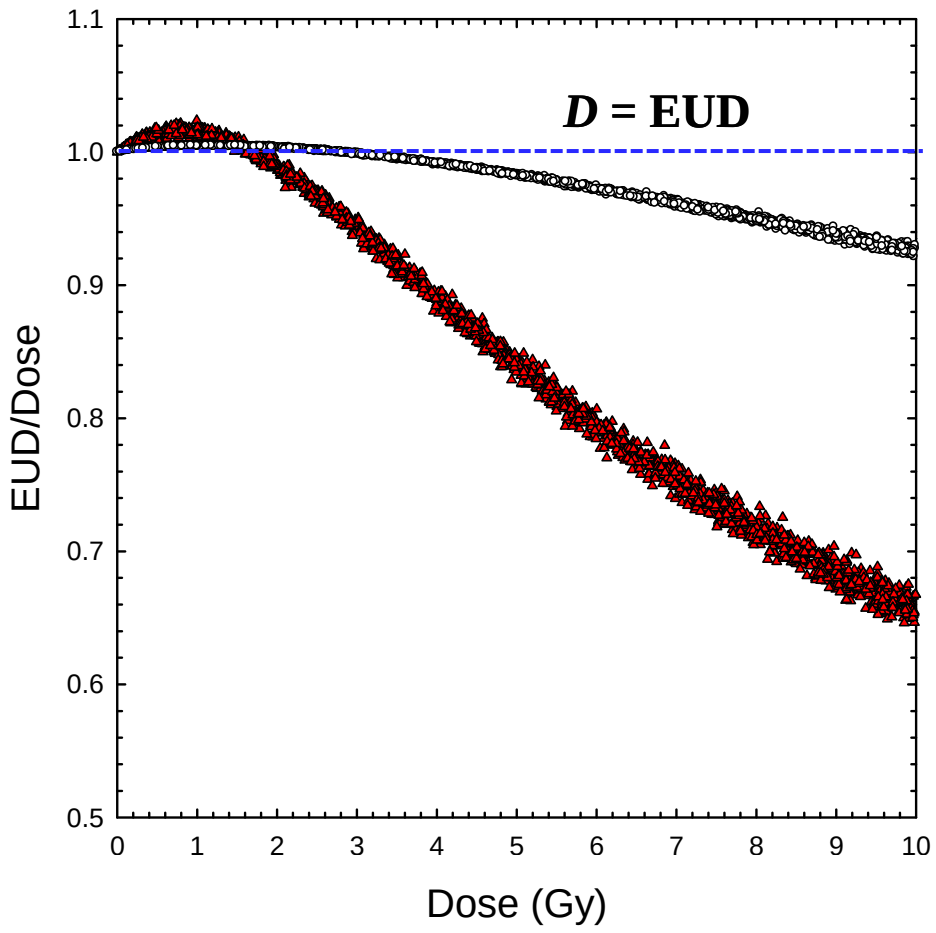
$$\downarrow$$

$$EUD = \frac{1}{2}\alpha/\beta\left(-1+\sqrt{1-\frac{4\ln \bar{S}}{\alpha(\alpha/\beta)}}\right) = \frac{1}{2}\alpha/\beta\left(-1+\sqrt{1+\frac{4\overline{BED}_{het}}{(\alpha/\beta)}}\right)$$

$$\bar{S} \equiv \frac{1}{\rho V}\sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^{\,2}\right)$$

Delivery of dose = EUD to all *i* regions will produce same surviving fraction and level of tumor control as heterogeneous dose distribution (array of D_i values)

EUD for a heterogeneous cell population



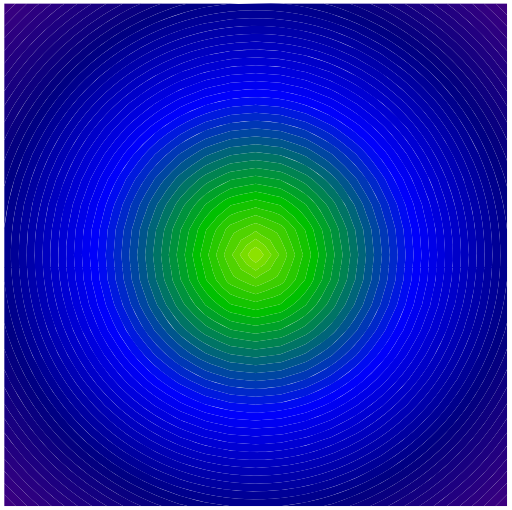
Individual filled symbols denote Monte Carlo sampling of the radiation response characteristics of 1000 cells given a uniform dose of radiation (*x*-axis).

Open circles: α_i sampled from 0.1 Gy^{-1} to 0.2 Gy^{-1}; $(\alpha/\beta)_i$ sampled 2 to 4 Gy (population-average: α = 0.15 Gy^{-1}, α/β = 3 Gy).

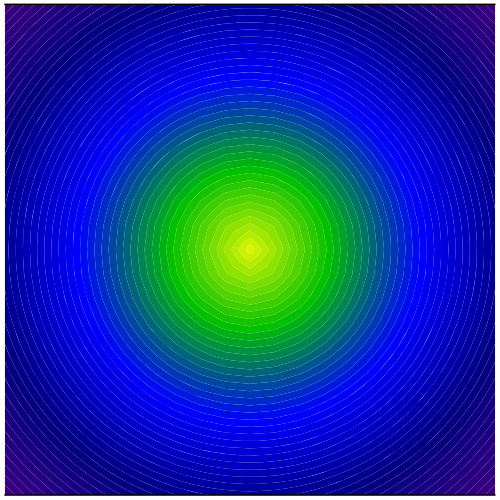
Filled Triangles: α_i sampled from 0.05 Gy^{-1} to 0.5 Gy^{-1} and $(\alpha/\beta)_i$ sampled from 1 to 10 Gy (α = 0.275 Gy^{-1}, α/β = 5.5 Gy).

Effects of intra-tumor heterogeneity

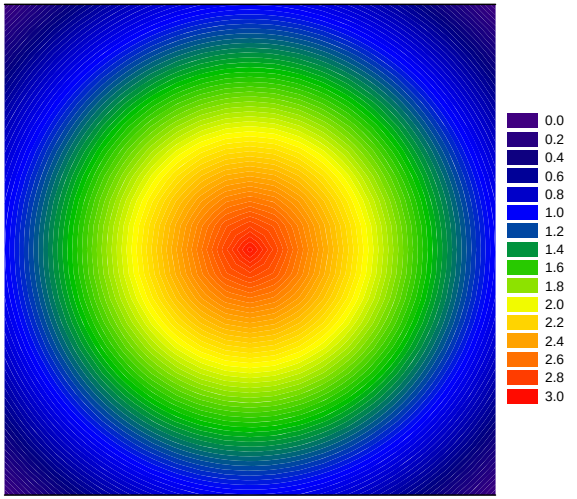
44 × 1.80 Gy (*original*)



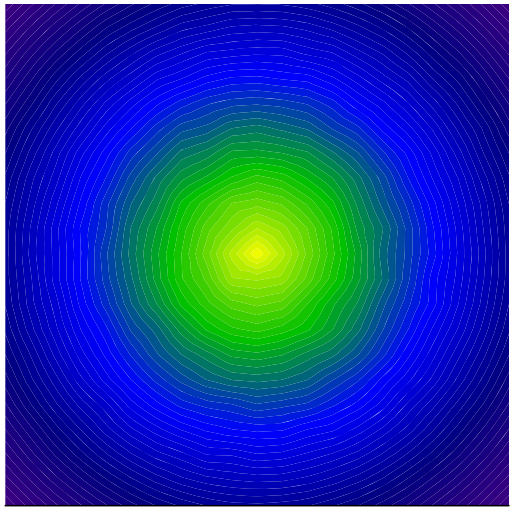
39 × 1.95 Gy (α/β = 1.5 Gy)

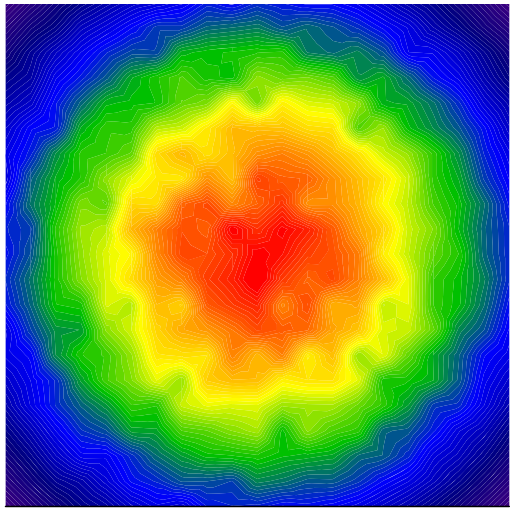


20 × 2.94 Gy (α/β = 1.5 Gy)



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





EUD for large dose per fraction

- **So-called "generalized" gEUD neglects the βGD^2 component of cell killing**
  - Most of our knowledge of the effects of radiation on normal tissues comes from conventional (*low dose*) fractionation

Step 1. Convert 3D dose distribution for hypofractionated (n_R < 3-5) treatment into equivalent conventional (n < 30-45) 3D dose distribution

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

Apply on voxel by voxel basis

Step 2. Convert 3D dose distribution for conventional treatment into gEUD

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

a = 1 (*average dose*), $a \rightarrow +\infty$ (*maximum dose*), $a \rightarrow -\infty$ (*minimum dose*)

Summary

- **Absolute quantitative prediction of tumor control, complication rates and cell survival very sensitive to even small uncertainties in biological parameters**
  - Such models are (*and always will be*) a highly non-linear function of dose
- **For a heterogeneous patient (*or cell*) population, shapes of dose-response curve cannot be accurately modeled using the LQ and a single set of (*average*) radiosensitivity parameters**
  - Usefulness of alternate mathematical models usually offset by introduction of additional *ad hoc* biological parameters into modeling process
- **Direct use of TCP, NTCP models to compare and rank alternate plans and modalities may result in the selection of inappropriate or suboptimal treatments**
  - Also need to specify large number of biological inputs

Robust BGRT – Key Points

- ***Many*** **(all?) clinical questions *can* be usefully tackled using biological metrics (*doses*) derived from existing models**
  - Semi-quantitative *relative* plan ranking and comparison
- **Biological metrics derived by equating *acceptable treatments* to *alternate ones***
  - Need to incorporate corrections for relevant biology into biological metrics (repopulation effects, LET effects, oxygen effects, low-dose hyper-radiation sensitivity, bystander effects, …)
- **Isoeffect calculation are remarkably *insensitive* to uncertainties in biology parameters**
  - Assess the impact of uncertainties associated with biological parameters through Monte Carlo sampling (or other methods)
  - Uncertainties in biology offset by clinical judgment (i.e., the use of a "*reference treatment*")

Future of BGRT – Individualize and Adapt

- **Patient imaging first part of treatment**
  - Estimate of *one or two* key biological parameters from patient imaging
- **Individualized isoeffect calculations**
  - Sample *other* biological parameters from probability distributions for an appropriate patient population
- **Individualize and adapt 2nd stage of treatment**
  - Compare and rank alternate plans and modalities for individual patients
    - Boost, alter modality (e.g., protons), re-size GTV or PTV, …
  - Patient-specific cost-benefit analysis of adapted treatment
    - Is it worthwhile to alter the original plan?

Supplemental Slides

- Repopulation Effects in External Beam Therapy
- Brachytherapy Isoeffect Calculations
- Derivation of EUD formula

This presentation along with the supplemental slides available at

http://faculty.washington.edu/trawets/

Equivalent dose – repair and repopulation

Reference Treatment = Alternate Treatment

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

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

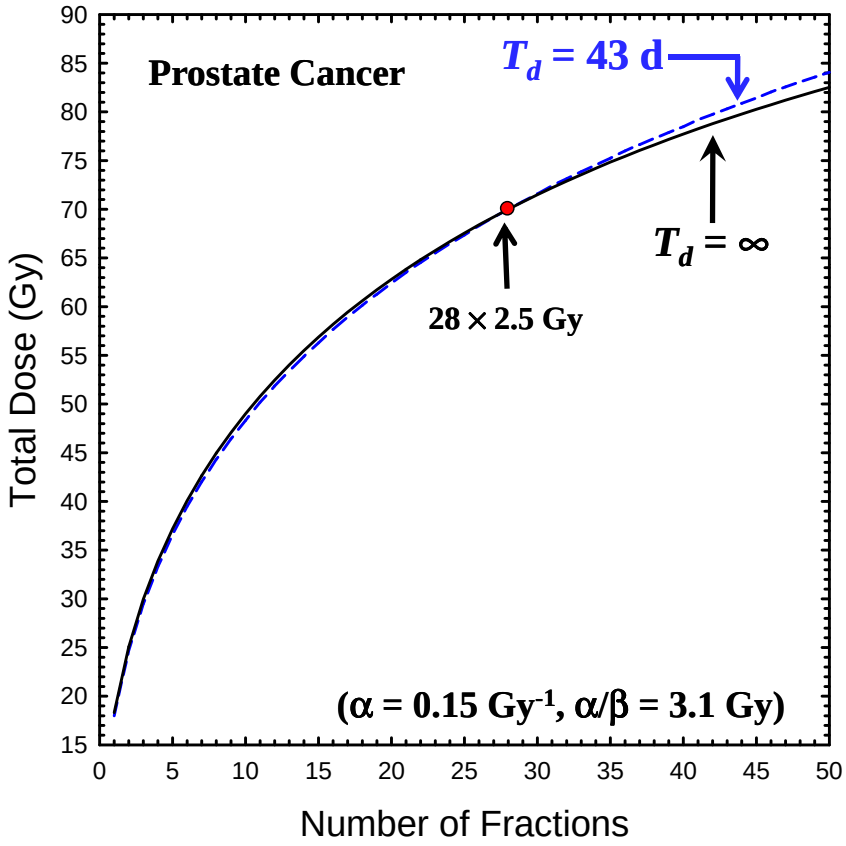
Take logarithm, apply quadratic formula and rearrange terms

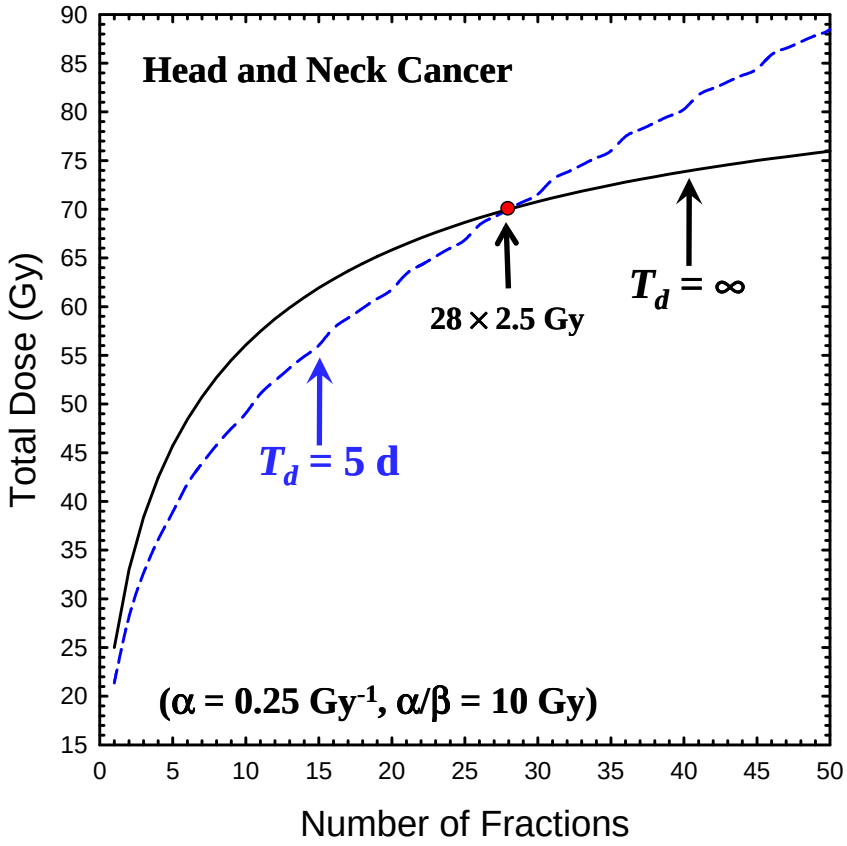
$$D = \frac{\alpha/\beta}{2G}\left\{-1 + \sqrt{1 + \frac{4GD_R}{\alpha/\beta}\left[1 + \frac{G_R D_R}{\alpha/\beta} - \frac{\gamma(T_R - T)}{\alpha D_R}\right]}\right\}$$

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**)**

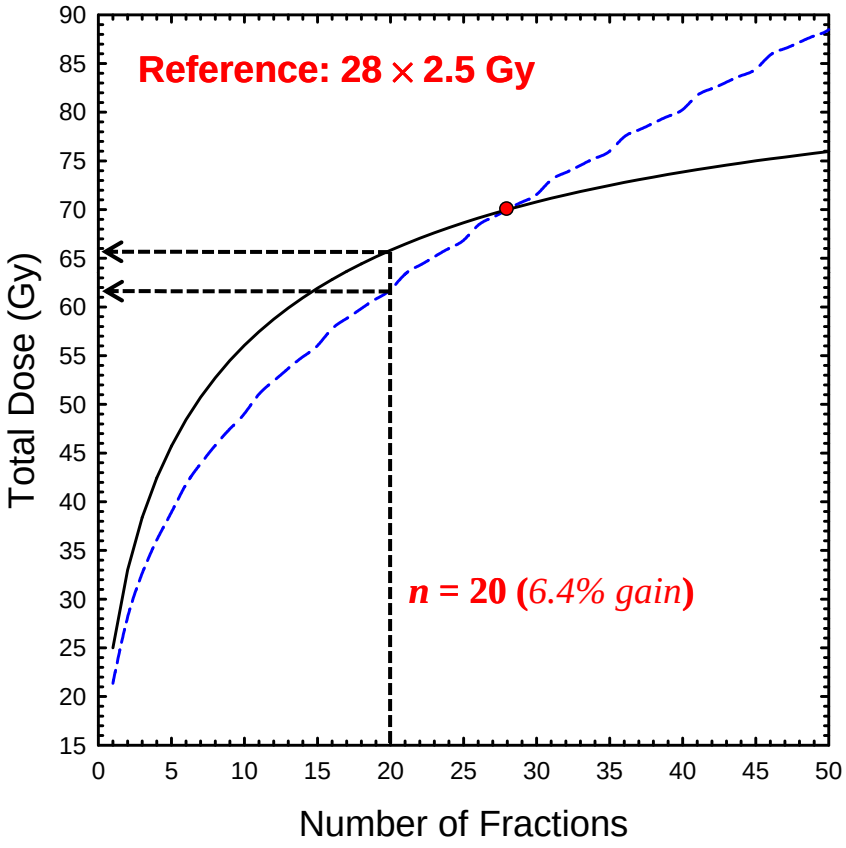
Repopulation Effects – Fast and Slow Growing Tumors

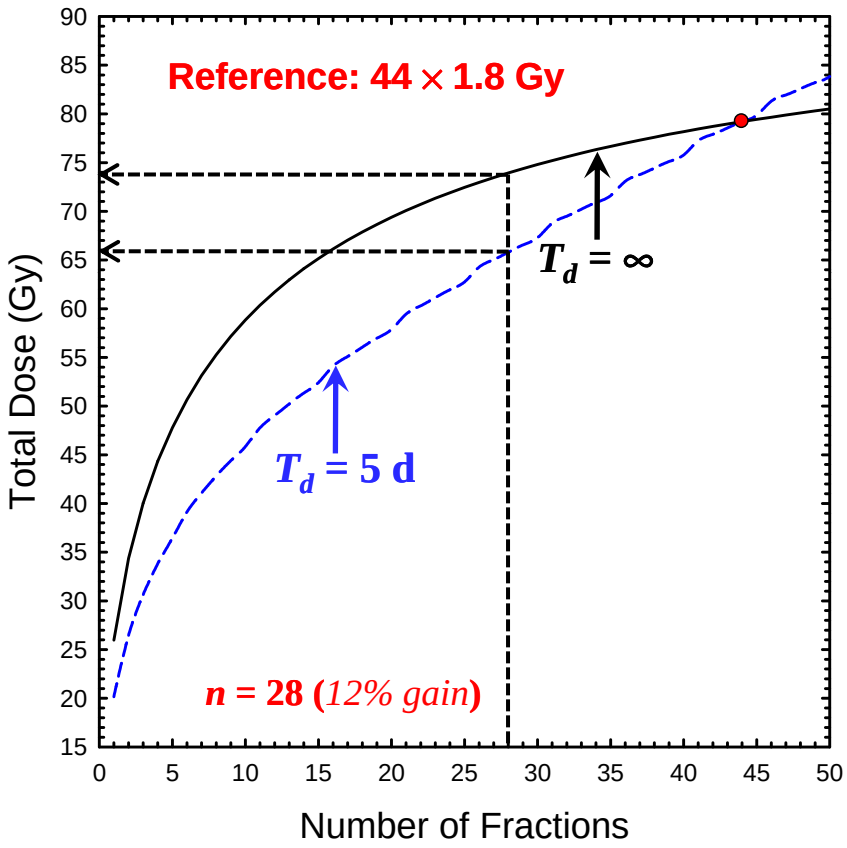




Repopulation effects are negligible for slow growing tumors but potentially very significant for fast growing tumors

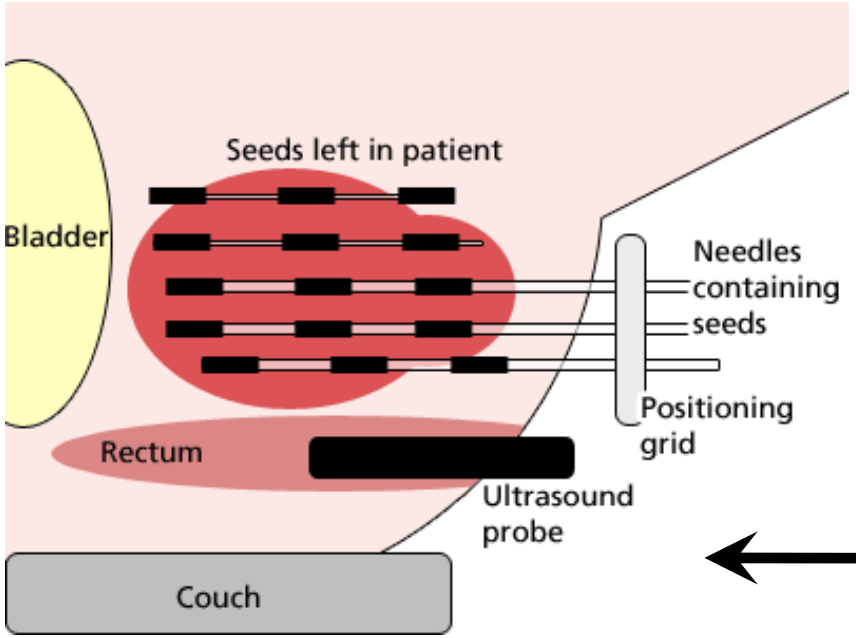
Are gains in tumor control significant?



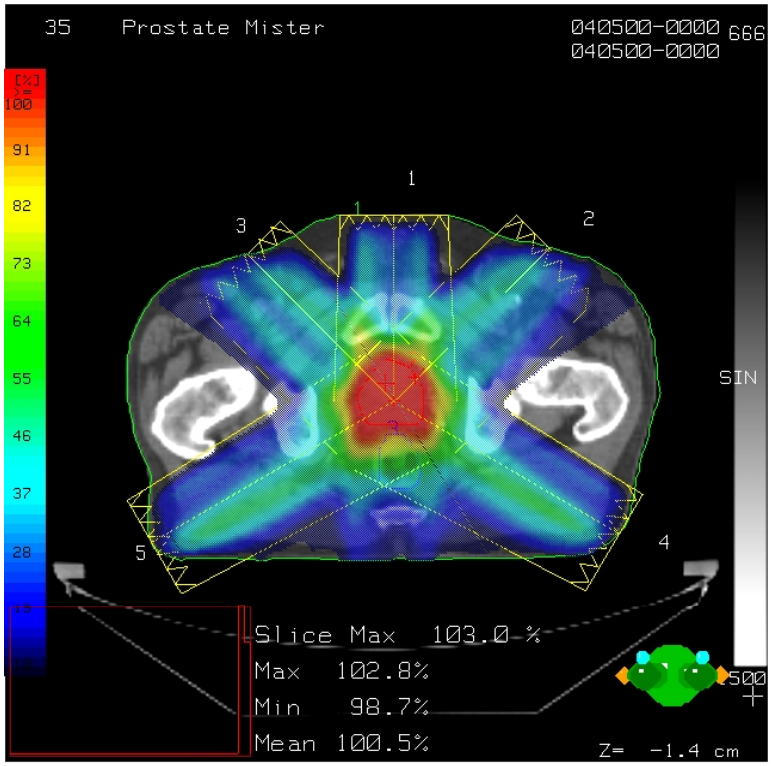


Key Point #2: Clinical significance of potential gains (*or losses*) are easily judged when expressed in terms of physical dose.

Prescription dose for competing modalities?



Temporary or permanent brachytherapy implants



Fractionated External Beam Radiation Therapy

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

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

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

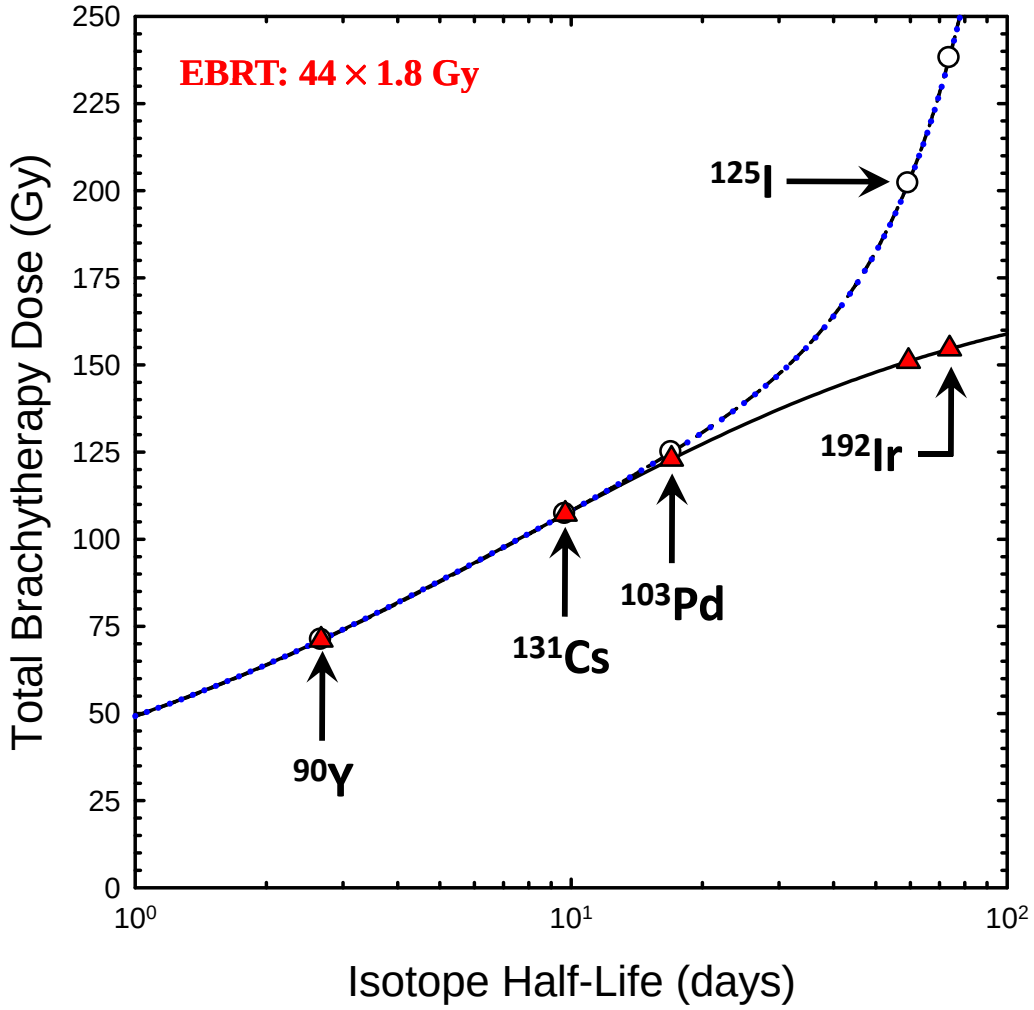
$$y \equiv 2\mu/(\lambda-\mu)$$

relates to

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

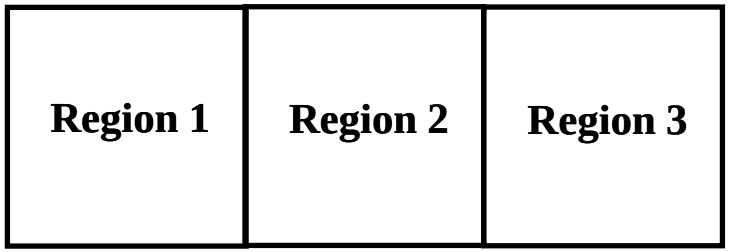
***T* = *effective* treatment time**

Brachytherapy – Isotope Selection and Dose



Brachytherapy dose equivalent to 44 × 1.8 Gy fractions EBRT

EUD Motivation – which is better?



Distribution 1

D_1 = 74 Gy
D_2 = 78 Gy
D_3 = 76 Gy
D_{avg} = 76 Gy

⟶ EUD_1

Distribution 2

EUD_2 ⟵

D_1 = 73 Gy
D_2 = 75 Gy
D_3 = 80 Gy
D_{avg} = 76 Gy

EUD = the dose applied to all three regions that would produce the same overall level of biological damage

In general, EUD ≠ D_{avg} (*because cell killing is a non-linear function of dose*)

Biological damage increases with increasing EUD

EUD for tumor control (3)

$$\exp\left(-\alpha EUD - \beta EUD^2\right) = \frac{1}{\rho V}\sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^2\right)$$

To solve for EUD, take logarithm and apply quadratic

$$\downarrow$$

$$EUD = \frac{1}{2}\alpha/\beta\left(-1+\sqrt{1-\frac{4\ln \bar{S}}{\alpha(\alpha/\beta)}}\right) = \frac{1}{2}\alpha/\beta\left(-1+\sqrt{1+\frac{4\overline{BED}}{(\alpha/\beta)}}\right)$$

$$\bar{S} \equiv \frac{1}{\rho V}\sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^2\right)$$

Delivery of dose = EUD to all *i* regions will produce same surviving fraction *and* level of tumor control as heterogeneous dose distribution (array of D_i values)

EUD for tumor control (1)

$$TCP(EUD) = \prod_{i=1}^{N} TCP_i$$

$$\exp\left[-\sum_{i=1}^{N} v_i \rho_i S(EUD)\right] = \exp\left[-\sum_{i=1}^{N} v_i \rho_i S(D_i)\right]$$

Neglect repopulation effects

$$\sum_{i=1}^{N} v_i \rho_i \left[\exp\left(-\alpha_i EUD - \beta_i EUD^2\right)\right] = \sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^{\,2}\right)$$

EUD for tumor control (2)

$$\sum_{i=1}^{N} v_i \rho_i \left[\exp\left(-\alpha_i EUD - \beta_i EUD^2\right) \right] = \sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^2\right)$$

Solve for EUD – in principle, formula applicable to *any* dose distribution

Assume ok to replace α_i and β_i on the left-hand-side (LHS) with tumor-averaged parameters α and β

↓

$$\exp\left(-\alpha EUD - \beta EUD^2\right) = \frac{1}{\rho V} \sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^2\right)$$

$$V \equiv \sum_{i=1}^{N} v_i \text{ and } \rho \equiv \frac{1}{V} \sum_{i=1}^{N} v_i \rho_i$$

EUD for tumor control (3)

$$\exp\left(-\alpha EUD - \beta EUD^2\right) = \frac{1}{\rho V}\sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^{\,2}\right)$$

To solve for EUD, take logarithm and apply quadratic ↓

$$EUD = \frac{1}{2}\alpha / \beta\left(-1 + \sqrt{1 - \frac{4\ln \bar{S}}{\alpha(\alpha/\beta)}}\right)$$

$$\bar{S} \equiv \frac{1}{\rho V}\sum_{i=1}^{N} v_i \rho_i \exp\left(-\alpha_i D_i - \beta_i D_i^{\,2}\right)$$

Delivery of dose = EUD to all *i* regions will produce same surviving fraction and level of tumor control as heterogeneous dose distribution (array of D_i values)