Biologically Related Models for Treatment Planning

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Reference list as additional handout

- All treatment planning is biological in nature
  - What is a “biological” or “biologically related” model?
- An equation or algorithm that combines dosimetric and other factors to predict treatment outcome
  - “Other”: medical factors (type of cancer, chemo, age), ‘biological’ factors (FDG uptake, hypoxia, genomics)
  - Model may be
    - Descriptive (algorithmic reformulation of outcomes data)
    - Mechanistic (built on physiological or cellular data)

- Are biological models more reliable predictors of outcomes than dose/dose-volume plan features?
  - Especially when applied to **your patients**?
- Are optimizers based on biological models better?

  Better=More efficiently generated

  Better=plans the MD prefers

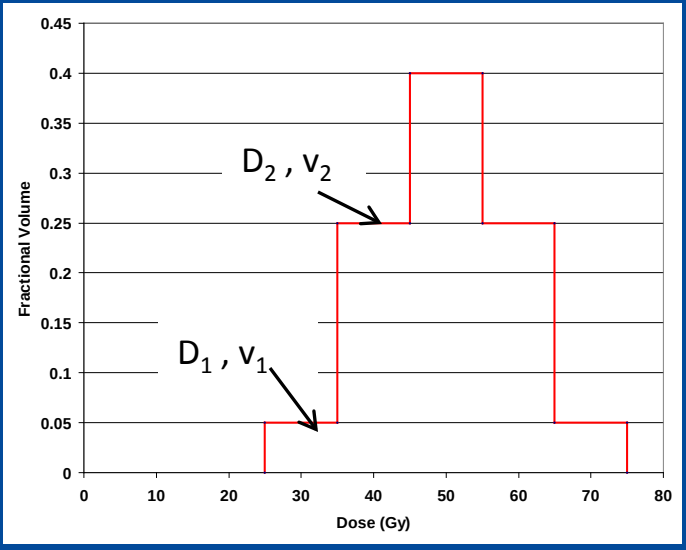
  Better= Plans with better outcomes
- Several commercial TPS have plan evaluation and optimization modules based on biological models
  - TG 166: biologically based treatment planning (BBTP)

    http://www.aapm.org/pubs/reports/RPT_166.pdf

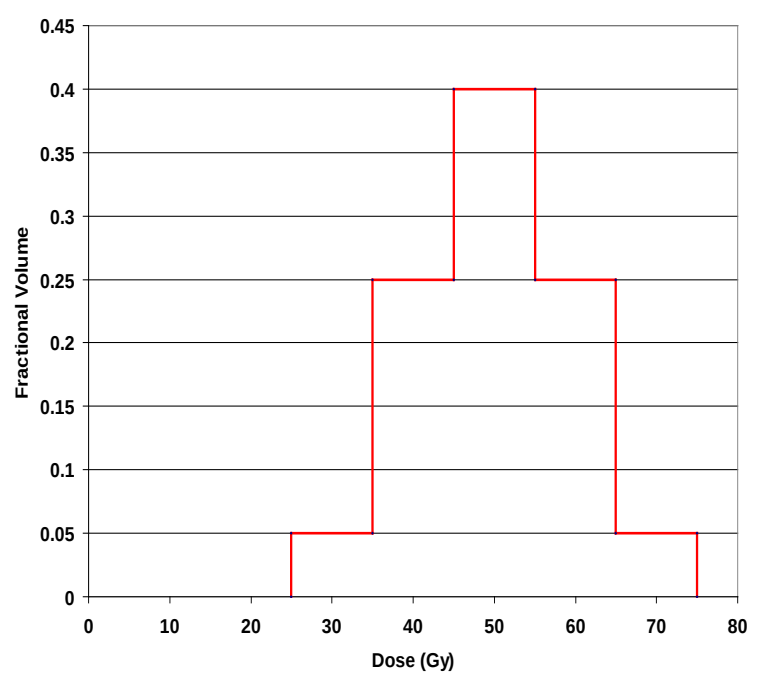
- Endpoints of successful treatment planning
  - High tumor control (eradicate the irradiated tumor)
    - High Tumor Control Probability (TCP)
  - Low incidence of complications
    - Low Normal Tissue Complication Probability (NTCP)
- This talk will discuss several popular biological models
  - Generalized Equivalent Uniform Dose (gEUD)
    - Optimize and evaluate dose distributions for tumors and normal tissues
  - Linear-Quadratic (LQ) Model
    - Dose/fraction effects for tumors and normal tissues
  - TCP models- general nature
    - Predict TCP for given irradiation pattern; used for optimization and evaluation
  - NTCP models- general nature
    - Predict complication rates for given irradiation pattern; used for optimization and evaluation

gEUD (Generalized Uniform Dose)

- *"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"* (TG 166, Niemierko 1999)
- $gEUD = (\sum v_i (D_i)^a)^{1/a}$
- 'a': user-chosen parameter
- Convenient optimization term



gEUD dependence on “a”



a	gEUD (Gy)
-20	34.8
0.2	49.3
1	50
20	60.9
100	67.9

- a <0: cold spots dominate (use negative a for tumors)
- a=1: gEUD= mean dose
- a large positive : hot spots dominate (use for normal tissues like spinal cord)

Linear-Quadratic (LQ) Model

- Observed: Same total dose delivered at high dose/fraction is more potent than at low dose/fraction
  - SBRT (hypofractionation) vs conventional fractionation (~ 2 Gy/fx)
- Radiobiology experiments:

  Surviving fraction (SF) of cells vs single dose D fits well to

  $$SF=\exp(-\alpha D (1+ D/[\alpha/\beta])$$
- α (units Gy^{-1}) and β (units Gy^{-2}) are independent of D
  - Depend on type of cell or organ response and irradiation conditions
  - RBE, dose rate, hypoxia
- More complex versions of LQ not discussed here- see references

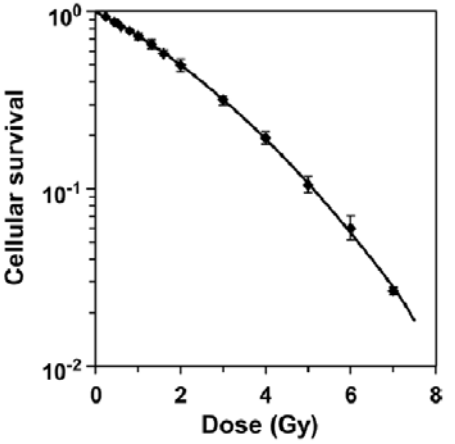


Figure 2 Survival of x-irradiated CHO cells, determined by flow cytometry population counting, 5 days after treatment.[22] The curve is the corresponding LQ model fit.

LQ Model: fractionated RT

- Dose D delivered in n fractions (d=D/n)

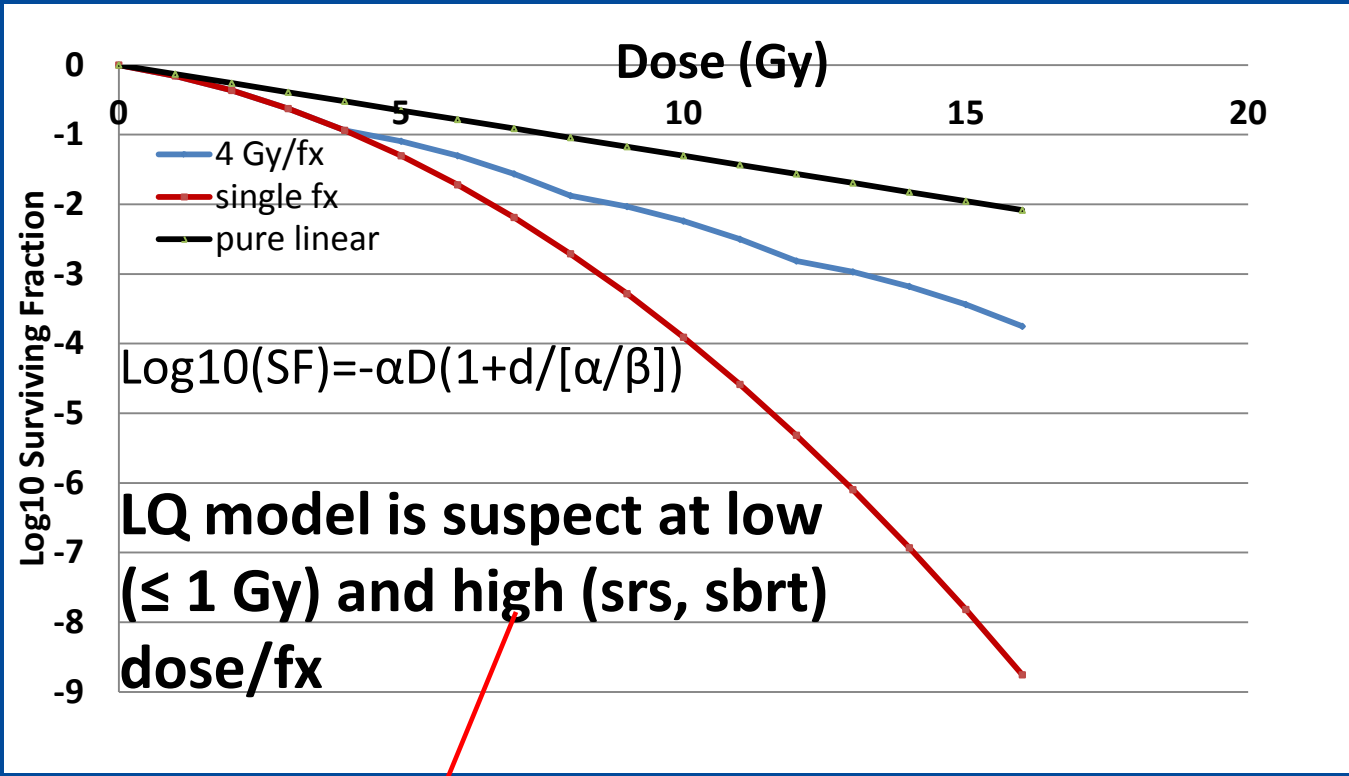
$$SF=\exp(-\alpha D\ (1+d/[\alpha/\beta]))$$

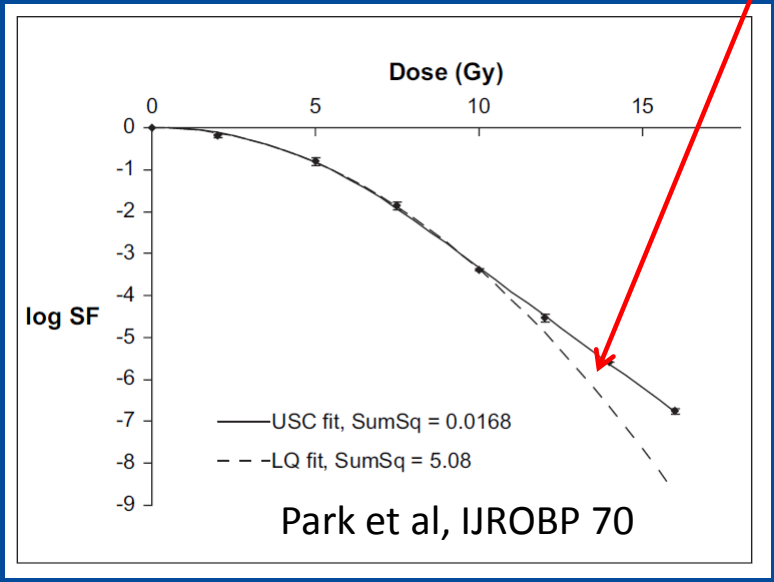
- $D\ (1+d/[\alpha/\beta])$=Biologically Effective Dose (BED)
- Hypothesis: Regimens with the same LQ model BED have the same biological effect (isoeffective) on living tissues to which they are applied
  - In vitro, same BED means same SF
- D1 in fractions d1 is isoeffective to D2 in fractions d2 if

$$D1(1+d1/[\alpha/\beta])=D2\ (1+d2/[\alpha/\beta])$$

- LQED2 = dose in 2 Gy fractions that is isoeffective to (D,d)

$$LQED2=D(1+d/[\alpha/\beta]))/(1+2/[\alpha/\beta])$$

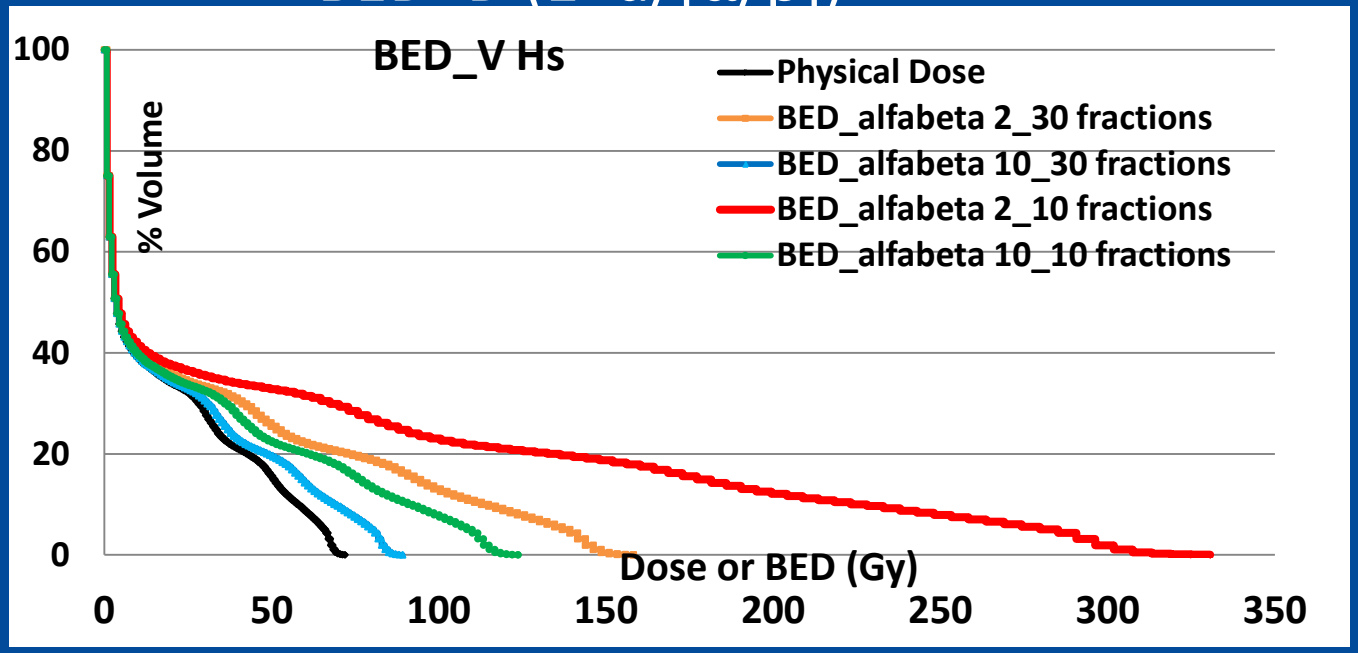




- There are other models but LQ is most commonly used because:
  - LQ fits decently over much of the clinical dose range
  - LQ is mathematically simple

BED=D (1+d/[α/β])

- For fixed D
- BED> D
- Different α/β's
  α/β↓ , BED↑

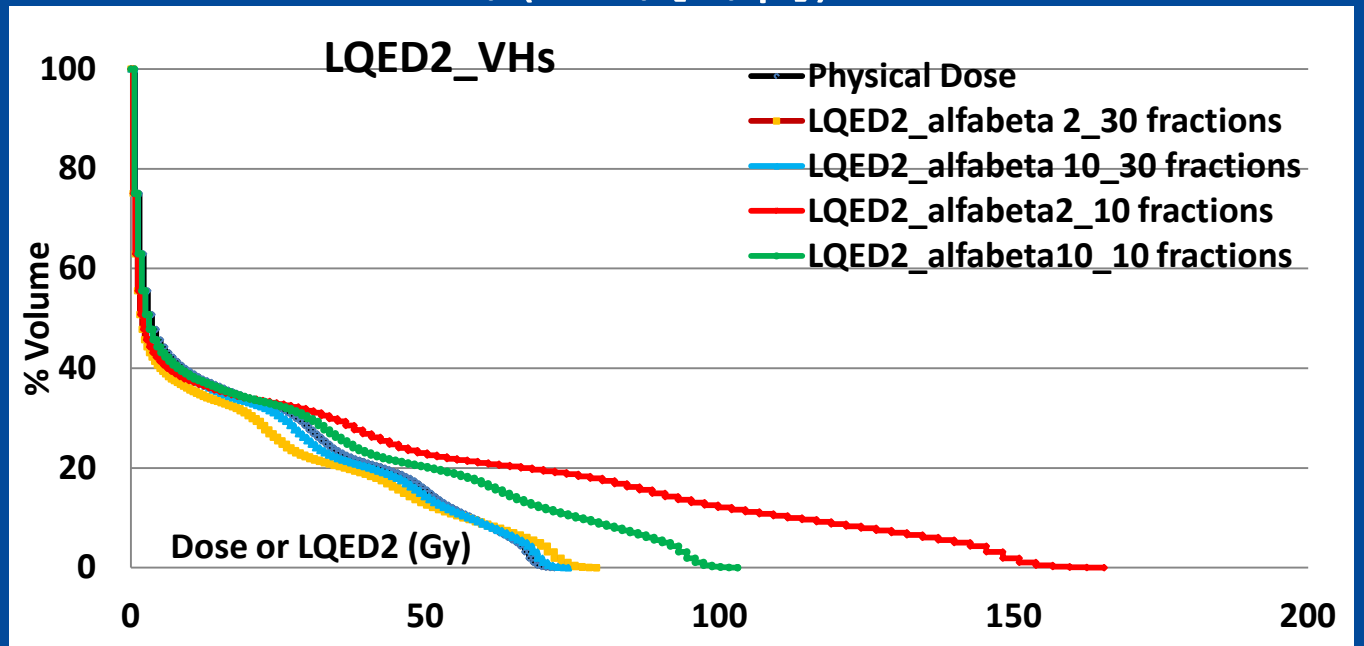


- Same α/β
- # fx↓ , BED↑
  because
- # fx↓ , d↑

- d<2, LQED2<D

- Rx/fx ~ 2 Gy, LQED2_VH similar to DVH

LQED2=BED/(1+2/[α/β])



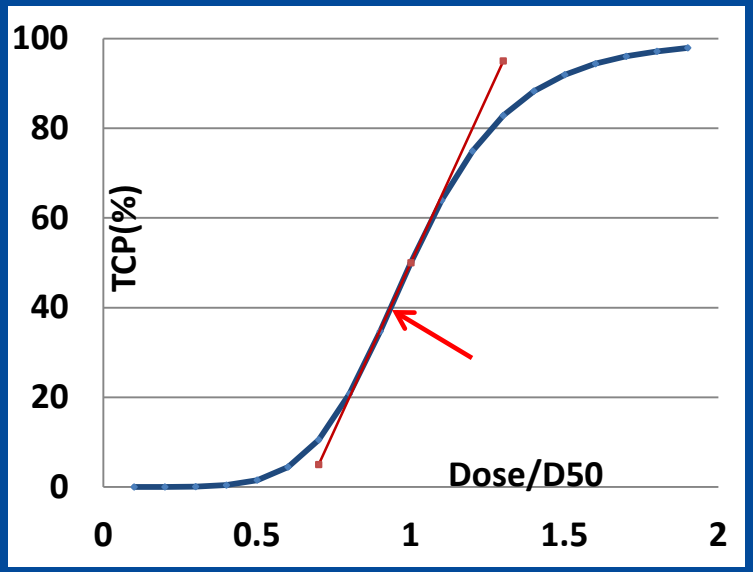
- For MV photon and electron radiation, α ranges from ~ 0.1 Gy^{-1} [radioresistant] to ~ 0.7 Gy^{-1} [radiosensitive]

- α/β ranges from ~ 1 Gy [effect depends strongly on the dose per fraction] to 15 Gy [effect depends only weakly on dose per fraction]

- The LQ model is semi-mechanistic; related to DNA damage mechanisms
  - Model refinements account for repair during the delivery time and proliferation between fractions
    - See Hall & Giaccia, Joiner & van der Kogel (good references and good source of LQ parameters)
- Stay tuned for a future ICRU Report (#25) which aims to bring order to the LQ-model terminology wilderness

Tumor Control Probability (TCP)

- Tumor control: irradiated tumor doesn't grow after radiation treatment course ends
- TCP is sigmoidally increasing function of dose.
- For given tumor type and irradiation conditions
  - **D50**=dose for 50% TCP of uniformly irradiated tumors
  - γ50=% ΔTCP /% Δ(d/D50) evaluated at d/D50=1
    - Typical γ50 range: 1 (shallow curve) – 5 (steep curve)



- Many equations are used for TCP
- Some have no mechanistic basis- just approximately right shape
- For example _ the Log Logistic

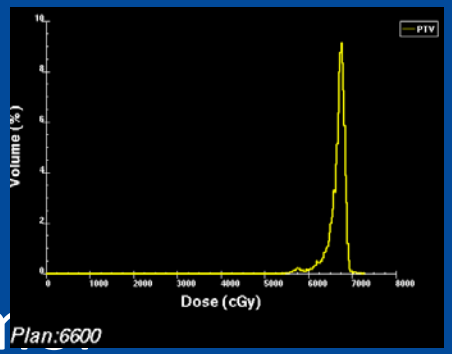
$$TCP=100/(1+(D50/D)^{4\gamma 50})$$

Poisson-LQ cell kill TCP model

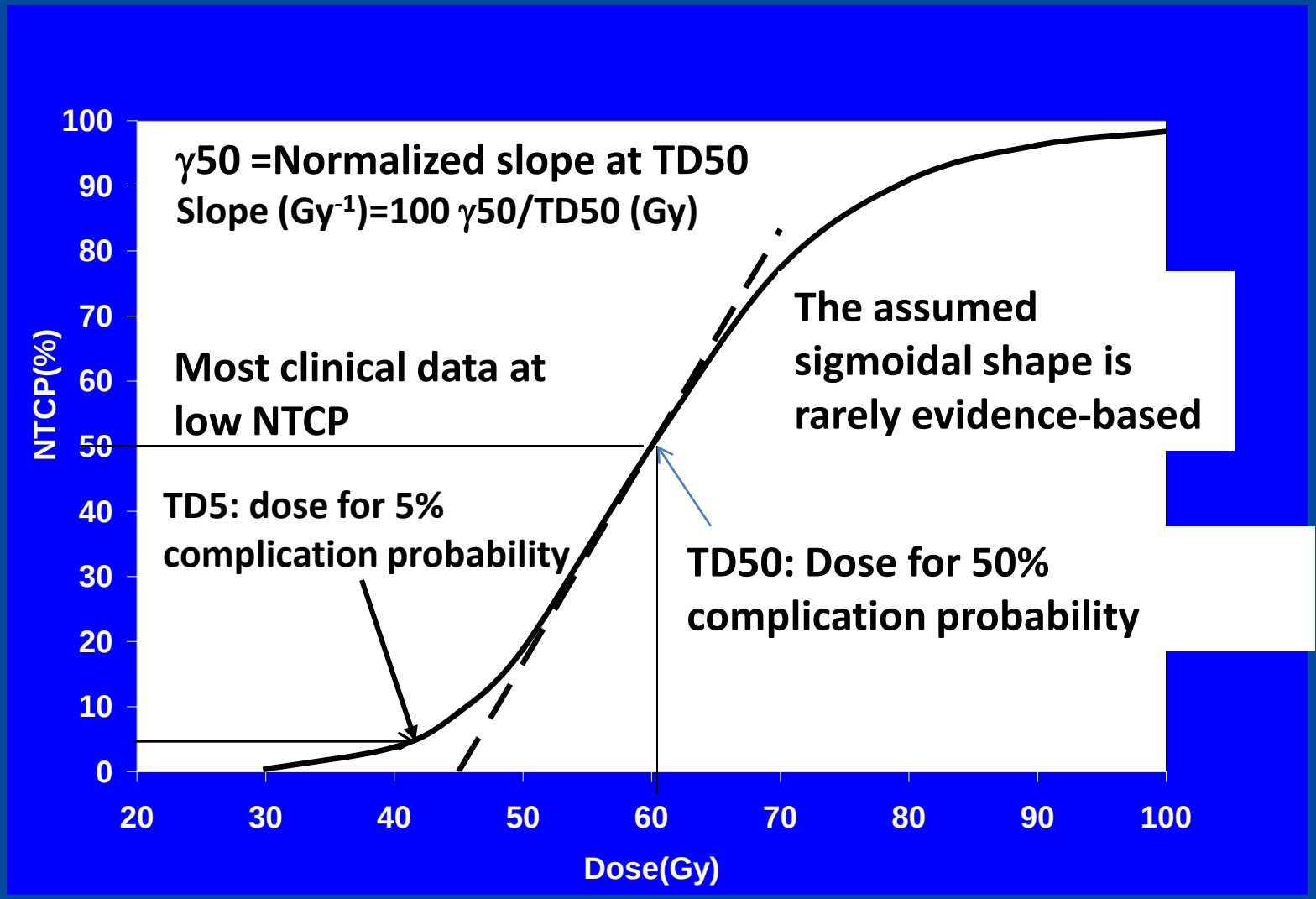
- Assume N clonogenic cells (cells that can regrow tumor)
  - Assume LQ: $SF=\exp(-\alpha D(1+d/[\alpha/\beta])$
  - Assume the number of clonogens that survive treatment is Poisson distributed
  - Assume TCP=probability of no surviving clonogens
- $TCP= \exp(-N \exp(-\alpha D(1+d/[\alpha/\beta])))$
- N can be calculated from γ50; with these assumptions, N is very small for observed γ50's
  - <~100 cells, independent of tumor size
- Two different approaches to this puzzle:
  - There really are very few clonogens – just carry on
  - There are many clonogens (~ 10^7/cc) but observed TCP is a population average over a range of sensitivities (α's); averaging smears out the slope (Niemierko & Goitein 1993; Webb & Nahum, 1993)

TCP for non-uniform radiation

- Break tumor into 'tumorlets', each with uniform dose
  - Which structure to use: PTV? CTV? GTV?
- Start from differential DVH $\{D_i, v_i\}$
- $TCP = \Pi_i (TCP(D_i, d_i))^{vi}$
- This approach can model non-uniform tum… characteristics as well as non-uniform doses
  - (D50's, clonogen densities, etc)
  - Can we use information from molecular imaging?
    - Location? LQ parameters? Relevant cell density?
    - Dose-painting guided by PET, etc?
- For tumors, given current knowledge are fancier models (TCP) than dose or BED/volume metrics or gEUD with consistent 'a' useful for tx planning?



Normal Tissue Complication Probability (NTCP)



Complications are Complicated

- Most organs have more than one complication, each with different dosimetric correlates
  - Lung: pneumonitis, fibrosis
  - Rectum: bleeding, incontinence, fistula
- Acute complications: during or soon after treatment
- Late complications: many months-years latency
- A complication can be mild, intermediate, or severe
  - Toxicity grading: 1 (mild, asymptomatic) – 5 (fatal)
  - CTCAE 4.03*, RTOG, SWOG
- 'Tolerable' complication rate depends on impact of toxicity on quality of life and on treatment tradeoffs
  - Serious risk more acceptable in last-chance scenarios

* http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

NTCP: Tolerance Doses

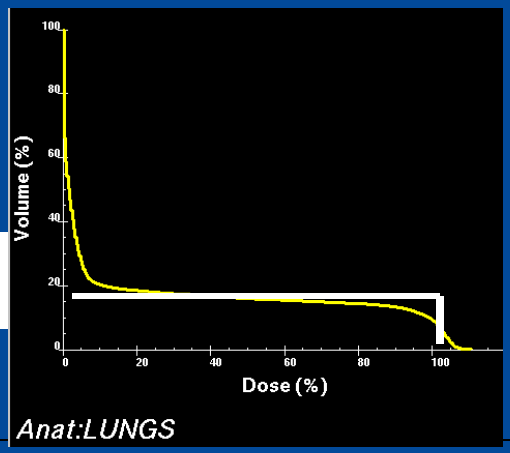
Tolerance dose (or dose/volume metric) depends on:

- The complication
- The dose/fraction
  - LQ model generally used
  - Acute complications: α/β typically large (~ 10 Gy)
    - Weak dependence on dose/fx
  - Late complications: α/β typically small (< 5 Gy)
    - Strong dependence on dose/fx
- The dose distribution
- And other things which we won't handle here
  - Dose rate (external beam vs LDR)
  - Medical factors (chemo, smoking, co-morbidities)
  - RBE (protons, heavy ions)

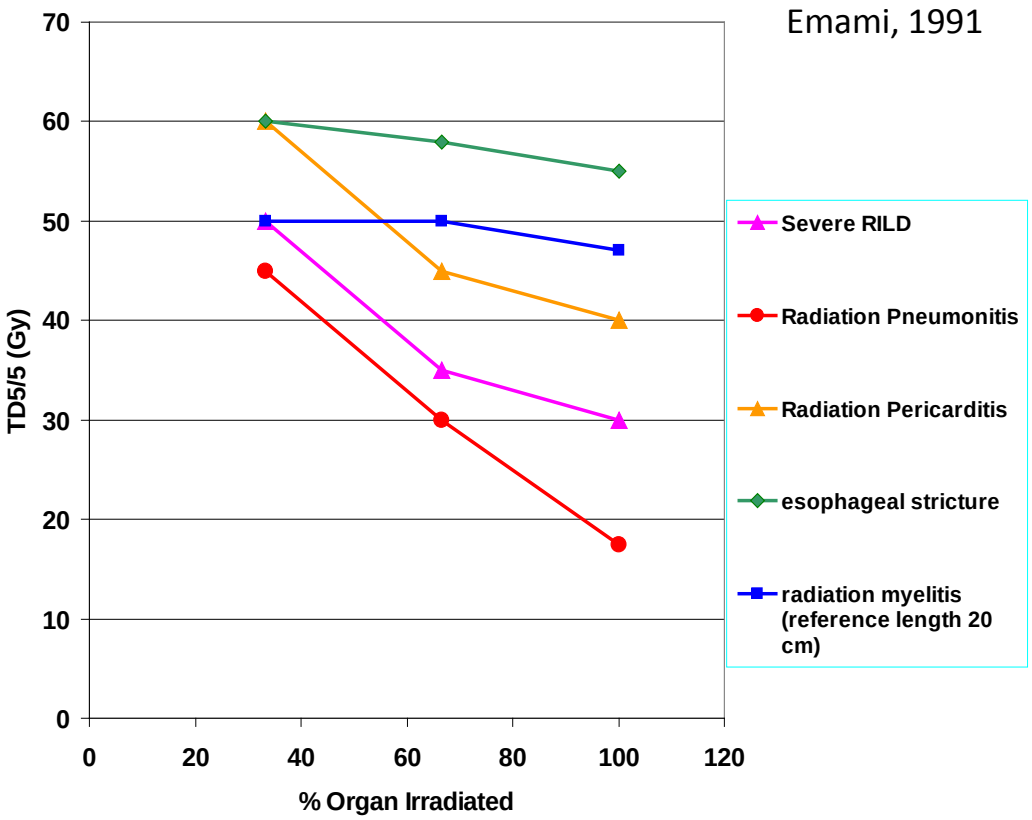
Tolerance dose-volume dependence

Partial organ irradiation (see Emami 1991)

Zero dose Volume fraction=1-v	Uniform Dose D Volume fraction=v



5% complication vs irradiated volume fraction

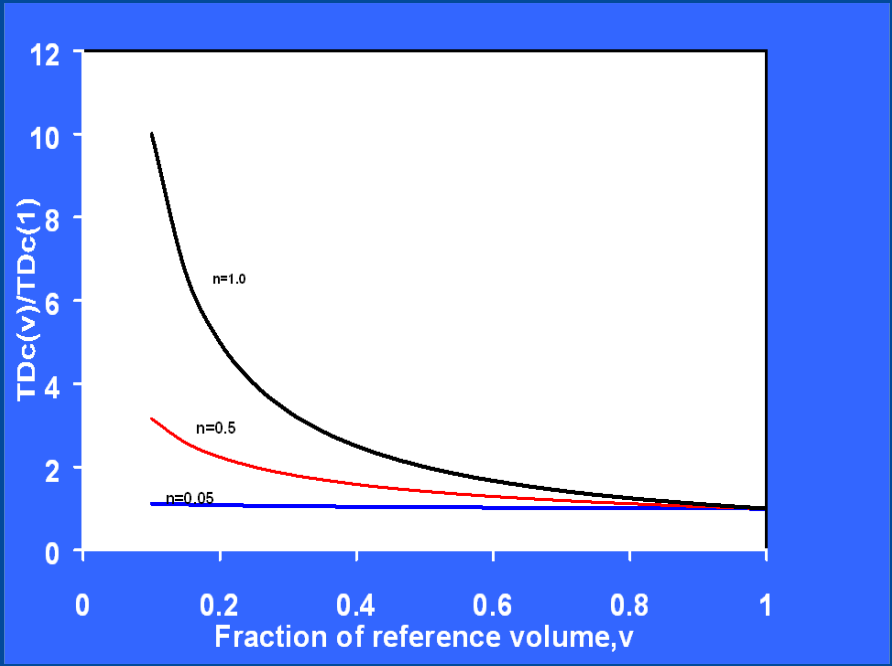


Observed

- **Iso-complication dose increases as irradiated volume fraction decreases**
- **Weak vs strong volume effects**

Power Law 'Fit' to Volume Dependence

TDc vs volume fraction in partial organ irradiation



Low n-> myelitis, brainstem necrosis

High n-> pneumonitis, xerostomia, RILD

Mid n-> rectal bleeding, pericarditis

Inverse relationship between tolerance dose TDc% and irradiated volume fraction, v

$$\mathbf{TDc(v)=TDc(1)/v^n}$$

Descriptive (not mechanistic)

Serial-type response

Low n-> weak volume dependence,

D_{max} dominates

Parallel-type response

High n-> strong volume dependence

n=1: mean dose dependence

NTCP: Lyman Model

Most popular in USA

- Power law volume dependence
- 4 complication-specific parameters: n, TD50(1), slope parameter m, reference volume for v=1

$$NTCP = (2\pi)^{-1/2} \int_{-\infty}^{(D - TD50(v))/(m\ TD50(v))} \exp(-t^2/2)dt$$

- Also called Lyman-Kutcher or LKB (Lyman-Kutcher-Burman) Model
- Histogram reduction converts general DVH, $\{D_i, v_i\}$, to an equivalent uniform or partial irradiation
  - $D_{eff} = (\Sigma\ v_i\ (D_i)^{1/n})^n$, $v = 1$ (whole organ)
    - Use D_{eff} for D and 1 for v in upper limit of integral
  - or $v_{eff} = \Sigma v_i\ (D_i/D_{ref})^{1/n}$
    - Use V_{eff} for V and D_{ref} for D in upper limit of integral

Lyman Model D_{eff} is gEUD

- Lyman $D_{eff} = (\sum v_i (D_i)^{1/n})^n$
- gEUD= $(\sum v_i (D_i)^a)^{1/a}$

- a=1/n
  - Serial-type response: large a, small n (n<1)
  - Parallel-type response: small a, large n (n≥1)

- There are Lyman model parameters in the literature for many complications
  - Classical: Burman et al, IJROBP 21 (1991) p 123-135
  - QUANTEC: IJROBP 76. Vp; 3S (2010)
  - Watch for ongoing research

NTCP: Källman s-model (Relative seriality)

Källman et al, Int J Rad Biol 62, 249-62

- Popular in Europe – implemented on some commercial TPS
- Organ responds to radiation damage in combined serial and parallel fashion
- 4 parameters (and α/β if use LQ)
  - D50 and $\gamma 50$ for whole organ response to uniform dose
  - s ='seriality parameter'; s=1 for weak volume dependence, small s for strong dependence
- With proper parameters, NTCP curves similar to Lyman

- Planners routinely include volume dependences as planning goals for many organs
  - This is not new!
  - Cord: Dmax<50 Gy (avoid myelitis)
  - Parotid: Mean dose < 26 Gy (avoid xerostomia)
  - Lung: Mean dose< 20 Gy (avoid pneumonitis)
- Where do these numbers come from?
  - Literature
    - Emami, QUANTEC, subsequent publications
- Red and Green Journals and meetings are good sources of updates

Pitfalls and cautions

- To use models for plan evaluation
  - Use reliable sources of parameters
    - Cautiously update as knowledge evolves
  - Your patients may be different so…..
  - Test carefully against your clinic's outcomes before changing your plan acceptance criteria
- Hypofractionation is a vast unknown
  - TG101 and floods of peer-reviewed literature
- To use models to drive optimization
  - If you get qualitatively similar, 'good' plans faster with biological optimizations, that's great but….
  - Watch out for unusual distributions
    - For example, gEUD may steer hot or cold spots to odd places
- Clinical outcomes still the best criteria for 'good' plans

- **General References on Biological Models**

1. TG166 Report: http://www.aapm.org/pubs/reports/RPT_166.pdf (full report); short form in Medical Physics (http://www.aapm.org/pubs/reports/RPT_166ShortReport.pdf)
2. QUANTEC supplement to Int Jnl of Radiat Oncol Biol Phys http://www.aapm.org/pubs/QUANTEC.asp
3. The "Emami paper" (NTCP)
    1. B. Emami, J. Lyman, A. Brown, L. Coia, M. Goitein, J. E. Munzenrider, B. Shank, L. J. Solin, and M. Wesson, "Tolerance of normal tissue to therapeutic irradiation," Int. J. Radiat. Oncol. Biol. Phys. **21**, 109–122 (1991).
    2. Companion paper on Lyman model: Burman C., G.J. Kutcher, B. Emami, M. Goitein. (1991). "Fitting of normal tissue tolerance data to an analytic function." *Int J Radiat Oncol Biol Phys* 21: 123-135.
4. "Basic Clinical Radiobiology, 4th Edition" edited by Joiner and van der Kogel, Hodder Arnold, London (2009)
5. "Radiobiology for the Radiologist, 7th edition", Hall and Giaccia, Lippincott, Williams and Wilkins, Philadelphia (2012)
6. Interesting view on TCP: Zaider M and Hanin L, Tumor control probability in radiation treatment, Med Phys 38, 574-583 (2011)
7. Interesting view of NTCP: Trott, Doerr, Facoetti, Hopewell et al, "Biological mechanisms of normal tissue damage: Importance for the design of NTCP models", Radiother and Oncol in press, 2012
8. Normal tissue guidelines for SBRT: Table III of the report of TG 101 (http://www.aapm.org/pubs/reports/RPT_101.pdf). It is very important to note that the TG itself says "The doses are mostly unvalidated, and while most are based on toxicity observation and theory, there is a measure of educated guessing involved as well."
9. TCP-Population averaging
    1. Niemierko A , Goitein M, "Implementation of a model for estimating tumor control probability for an inhomogeneously irradiated tumor", Radiother and Oncol 29, 140-147 (1993)
    2. Webb S, Nahum AE "A model for calculating tumor control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density", Phys Med Biol 38, 653-66 (1993)
10. Brachytherapy (especially LDR brachy) is quite different and is not covered by TG166: In addition to the radiobiology text references, look at the report of AAPM TG 137 (http://www.aapm.org/pubs/reports/RPT_137ExecSummary.pdf)

NTCP since QUANTEC

- QUANTEC cites consensus-selected NTCP references, up to ~ 2009, covering mostly conventional fractionation. Here are a few standard-fractionation NTCP modeling studies published **since QUANTEC** that look interesting (PubMed search). Hypofractionation (sbrt) is in such vigorous flux that I don't dare make suggestions!
- **Rectal toxicity:**

1. Guilliford SL, et al, "Parameters for the Lyman Kutcher Burman (LKB) model of Normal Tissue Complication Probaiblity (NTCP) for specific rectal complications observed in clinical practise", Radiother and Oncol 102, p 347 - (2012)
2. Prior P, Devisetty K et al, "Consolidating risk estimates for radiation-induced complications in individual patient: late rectal toxicity", Int J Radiat Oncol Biol Phys 83, p 53- (2012) {also has many references to literature}
3. Defraene G, Van Den Bergh L, et al "The benefits of including clinical factors in rectal normal tissue complication probability modeling after radiotherapy for prostate cancer", Int J Radiat Oncol Biol Phys 83, p 53- (2012)
4. Liu M, Moiseenko V, et al "Normal Tissue Complication probabioity (NTCP) modeling of late rectal bleeding following external beam radiotherapy for prostate cancer: A test of the QUANTEC-recommended NTCP model." Acta Oncol 49, 1040-4 (2010).

- **Lung toxicity:**

  Palma DA, Senan S et al, "Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis." Int J Radiat Oncol Biol Phys 2012 (check epubs)