2014 AAPM SUMMER SCHOOL
University of Vermont • Burlington, VT • June 22–26, 2014
SRS/SBRT/SABR:
Safely and Accurately Delivering
High-Precision, Hypofractionated Treatments

Radiobiological Effects of Hypofractionation: Unique Aspects of Tumor Response to High Dose Per Fraction Radiotherapy— SBRT as Ablative Therapy

Dr. Jimm Grimm, PhD

Holy Redeemer Hospital

with the support of 74 other physicians, physicists, and radiobiologists

Part 1 of 2

Conflict of Interest

- Dr. Grimm founded www.DiversiLabs.com and developed the DVH Evaluator (This conflict has been disclosed on the AAPM website since 2011)

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WGSBRT

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Outline of Presentation

- Part 1
  - Introductory & definitions
- Part 2
  - Tumor Control Probability (TCP)
  - Normal Tissue Complication Probability (NTCP)
  - A few hints about possible radiobiological explanations

Learning Objectives

1. Common SBRT fractionation schemes and current evidence for efficacy
2. Evidence for normal tissue tolerances in hypofractionated treatments
3. Clinically relevant radiobiological effects at large fraction sizes

Working Group on Biological Effects of Hypofractionated Radiotherapy/SBRT

WGSBRT Organization

- Five top-level groups:
  1. Tumor Control Probability (TCP)
  2. Normal Tissue Complication Probability (NTCP)
  3. Radiobiology
  4. Rationale for Prescription Schemes
  5. Reporting Standards

WGSBRT Subgroups

- The TCP and NTCP groups have each divided into six anatomical subgroups
  1. Cranial
  2. Head & Neck
  3. Thoracic
  4. Abdominal
  5. Pelvic
  6. Spinal

Preliminary Results Will Be Presented at AAPM 2014

- TCP for lung and liver
- NTCP for thoracic organs
- Radiobiological foundations

- Part 2 of this Summer School lecture is a brief review of this published data, but not of the new analysis which will be presented at AAPM 2014

Linear Quadratic (LQ) Model

$$BED_{LQ} = Nd\left(1+\frac{d}{\alpha/\beta}\right)$$

- N = number of fractions
- d = dose per fraction
- α/β = tissue-specific parameter

- The LQ model is hotly debated for SBRT, but easy and useful as long as caveats are heeded

If α/β=10Gy, what is the LQ BED of 50Gy in 5 fractions?

5% 1. 50Gy

13% 2. 60Gy

55% 3. 100Gy

11% 4. 108.14Gy

17% 5. 150Gy

$$BED_{LQ} = Nd\left(1+\frac{d}{\alpha/\beta}\right)$$

If α/β=10Gy, what is the LQ BED of 50Gy in 5 fractions?

- Correct answer:
- 3. **100Gy**
- Ref: Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010 Jul;83(991):554-68.

$$BED_{LQ} = 5*10\left(1+\frac{10}{10}\right) = 50*2 = 100Gy$$

If α/β=10Gy, which prescription schemes have LQ BED less than 100Gy?

5% 1. 50Gy in 5 fractions

42% 2. 40Gy in 4 fractions

18% 3. 48Gy in 4 fractions

6% 4. 42Gy in 3 fractions

29% 5. 34Gy in 1 fraction

$$BED_{LQ} = Nd\left(1+\frac{d}{\alpha/\beta}\right)$$

If α/β=10Gy, which prescription schemes have LQ BED less than 100Gy?

- Correct answer:
- 2. **40Gy in 4 fractions**
- Ref: Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010 Jul;83(991):554-68.

$$BED_{LQ} = 4*10\left(1+\frac{10}{10}\right) = 40*2 = 80Gy$$

The other answers…

1. 50Gy in 5 fractions = 50*(1+1)=100Gy
2. 40Gy in 4 fractions = 40*(1+1)=80Gy
3. 48Gy in 4 fractions = 48*(1+1.2)=105.6Gy
4. 42Gy in 3 fractions = 42*(1+1.4)=100.8Gy
5. 34Gy in 1 fraction = 34*(1+3.4)=149.6Gy

Physical Dose

- BED can be converted back to physical dose in any other fractionation scheme
- Examples:
- 2 Gy Equivalent Dose (2Gy Equiv, or EQD2)
- 3-Fraction Equivalent Dose (3fxED)
- Single Fraction Equivalent Dose (SFED)

Many BED Models are Being Studied

- Linear Quadratic (LQ)
- Linear Quadratic Cubic (LQC)
- Universal Survival Curve (USC)
- Linear Quadratic – Linear (LQ-L)
- Tome 2008
- McKenna & Ahmad 2009
- Many others…

Tomé WA. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy: in regard to Parks et al. (Int J Radiat Oncol Biol Phys 2008;70:847-852). Int J Radiat Oncol Biol Phys. 2008 Dec 1;72(5):1620

McKenna FW, Ahmad S. Fitting techniques of cell survival curves in high-dose region for use in stereotactic body radiation therapy. Phys Med Biol. 2009 Mar 21;54(6):1593-608.

Which of the following is ***not*** a way of calculating biological effective dose (BED)?

0%	1. LQ
1%	2. LQC
19%	3. USC
2%	4. LQ-L
78%	5. 2Gy Equiv (EQD2)

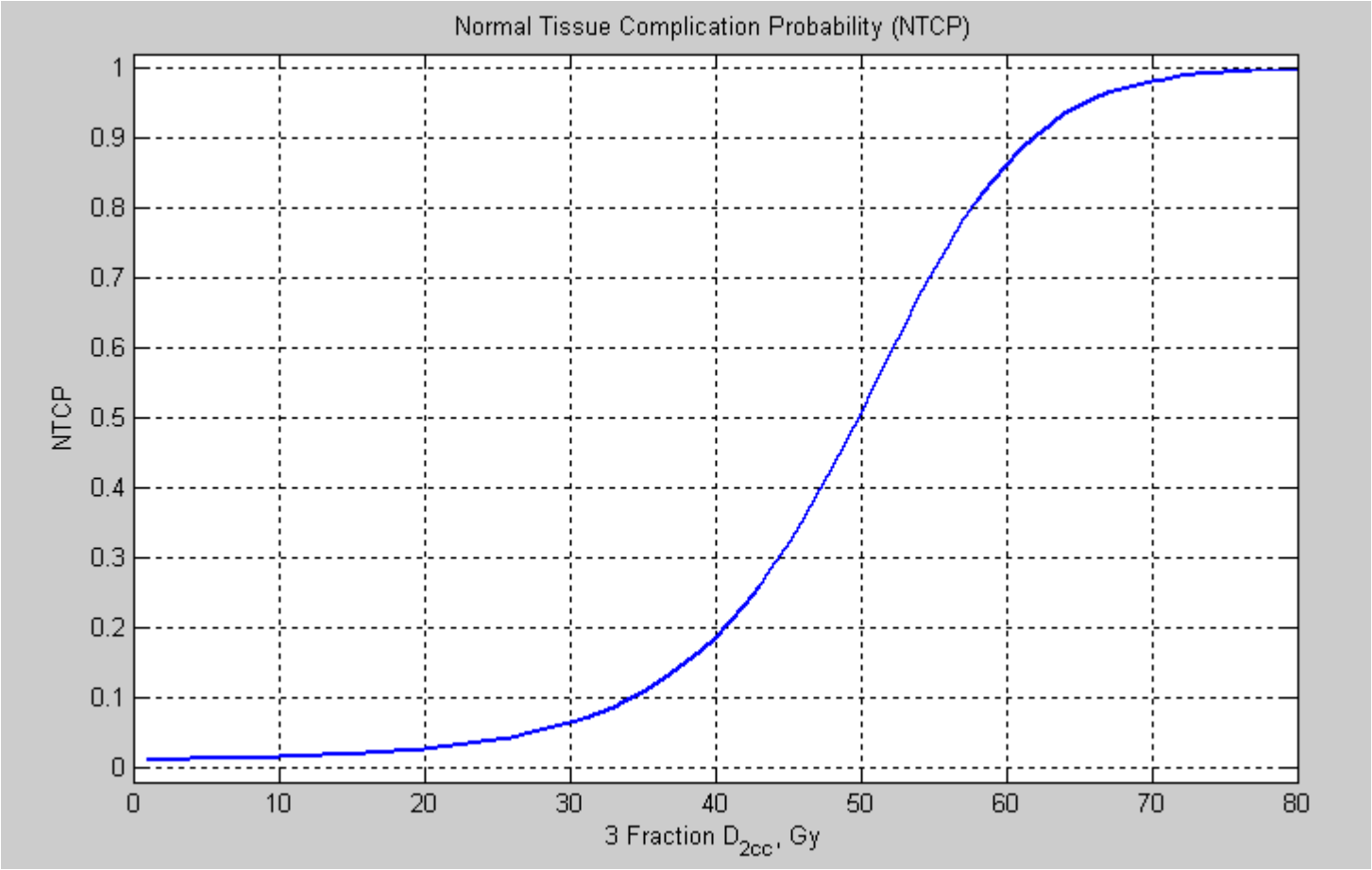
Which of the following is *not* a way of calculating biological effective dose (BED)?

- Correct answer:
- 5. **2Gy Equiv (EQD2)**
- Ref: Fowler JF, Dale RG. When Is a "BED" not a "BED"?-When it is an EQD2: In regard to Buyyounouski et al. (Int J Radiat Oncol Biol Phys 2010;76:1297-1304). Int J Radiat Oncol Biol Phys. 2010 Oct 1;78(2):640-1.
- **Note: EQD2, 3fxED, and other physical dose estimates can be made from any of the BED methods, but are not actually BED**

Dose Response Modeling

- To statistically estimate a continuum of outcomes, as a function of
  - Dose
  - Volume, and
  - Other key parameters

Example Dose Response Model



Radiobiologist Approach

1. Study cell lines, animal models, human data
2. Consider response of cells to incoming photons
3. Derive mechanistic models
4. Compare models to data

- Clinical modelers may think this is too theoretical

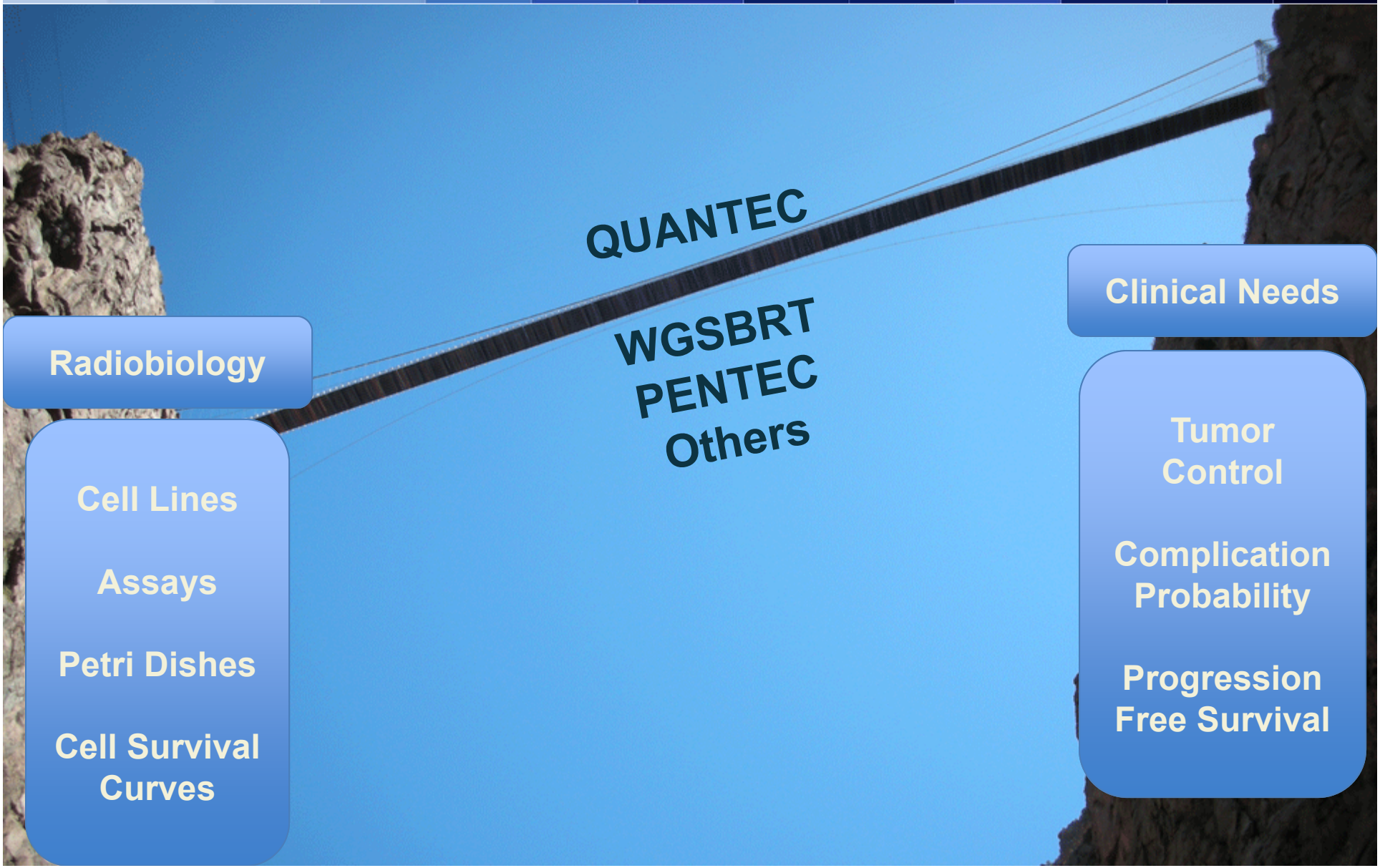
Model Fitting Approach

1. Convert doses to an equivalent basis (BED)
2. Fit clinical data to dose response models
3. Compare goodness of fit metrics, choose the model that fits the data
4. Convert results to physical dose in desired fractionation scheme

- Radiobiologists may think this is heresy

Both approaches are needed; In WGSBRT we work together in harmony

- We need radiobiologists to study the underlying mechanisms and explain the results
  - Animal models are a bridge between pure radiobiology and clinical studies
- We need clinical modelers to apply practical models to real world data
- We need physicians to guide, interpret, and implement clinically


QUANTEC
WGSBRT
PENTEC
Others
Radiobiology
Cell Lines
Assays
Petri Dishes
Cell Survival Curves
Clinical Needs
Tumor Control
Complication Probability
Progression Free Survival

After a while it might even seem easy

Why convert all doses to BED prior to dose-response modeling?

10% 1. To improve TCP

8% 2. To improve NTCP

1% 3. To eliminate hypoxia

80% 4. To compare alternate fractionations

1% 5. To increase vascular damage

Why convert all doses to BED prior to dose-response modeling?

- Correct answer:

- 4. **To compare alternate fractionations**

- Ref: Mehta N, King CR, Agazaryan N, Steinberg M, Hua A, Lee P. Stereotactic body radiation therapy and 3-dimensional conformal radiotherapy for stage I non-small cell lung cancer: A pooled analysis of biological equivalent dose and local control. Prac Radiat Oncol. 2012 Oct; 2(4):288-295.
- **Note: Converting to BED doesn't change the outcomes, but we cannot construct a model until all inputs are in matching units**

Dose Volume Histogram (DVH)

- True patient anatomy is a moving target: 4D
- A 4D or 3D dose distribution is challenging to analyze
- A DVH is a distillation of this data
  - Purely physical conversion
- Can be further reduced to 1D for analysis
  - This conversion may be based on biology…
- Some people do the BED conversion first, others do the DVH distillation first – BED is nonlinear so order matters…

DVH Reduction Techniques / Dose Descriptors

- To consolidate anatomic and dosimetric information into a 1D quantity for analysis:
  - Equivalent Uniform Dose (EUD)
  - Generalized Equivalent Uniform Dose (gEUD)
  - Effective Volume (Veff)
  - Effective Dose (Deff)
  - V20Gy, V10Gy, V95%, V90%, etc. (multimetric)
  - Dmax, D0.1cc, D1cc, D10%, D50%, etc.
  - D95%, D90%, for GTV, CTV, ITV, or PTV coverage
- These are methods to condense DVH for analysis

Which of the following is not a Dose Descriptor?

1% 1. EUD

2% 2. gEUD

2% 3. V20Gy

20% 4. Dmax

76% 5. TCP

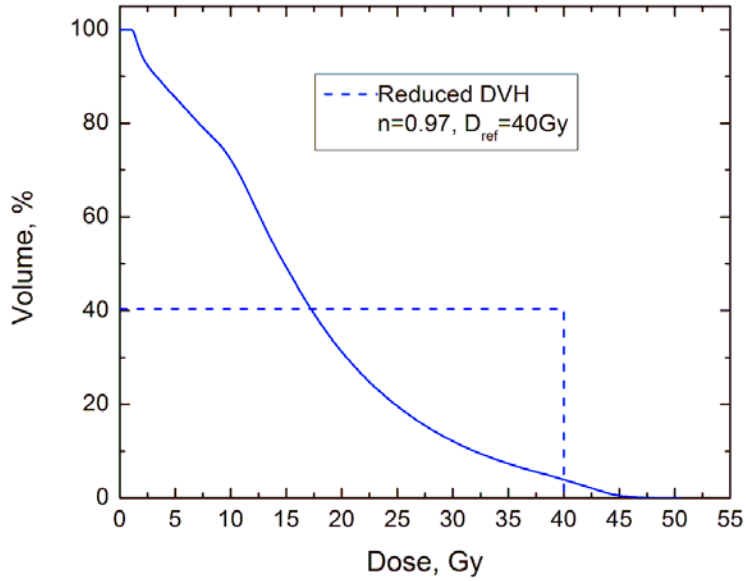
Which of the following is not a Dose Descriptor?

- Correct answer:
- 5. **TCP**
- Ref: **Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, Bentzen SM, Nam J, Deasy JO. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S10-9.**

Order matters for nonlinear BED operations

especially at high dose per fraction

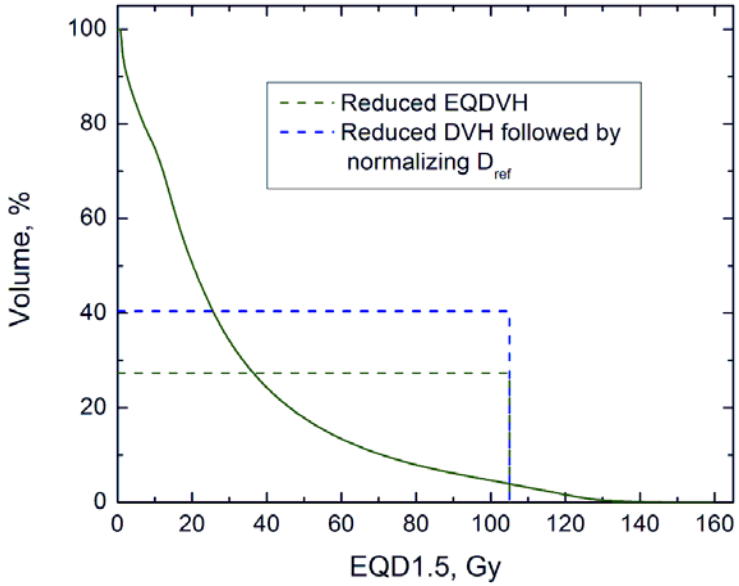
A) V_{eff} first, then EQD



5-Fraction SBRT Liver Example

Same DVH in both methods

B) EQD first, then V_{eff}



V_{eff}=40.4%, D_{ref} is in 5 fx

D_{ref}(1.5Gy/fx)=40(1+8/2.5)/(1+1.5/2.5)=105Gy

NTCP(D=105Gy, V=40.4%) = 34.2%

V_{eff}=27.3%, D_{ref} is 105Gy (LQ, α/β=2.5Gy)

NTCP(D=105Gy, V=27.3%) = 0.2%

Liver LKB (1.5Gy/fx) : D_{50}=45.8 Gy, n=0.97, m=0.12 - Dawson 2006 Acta Onc

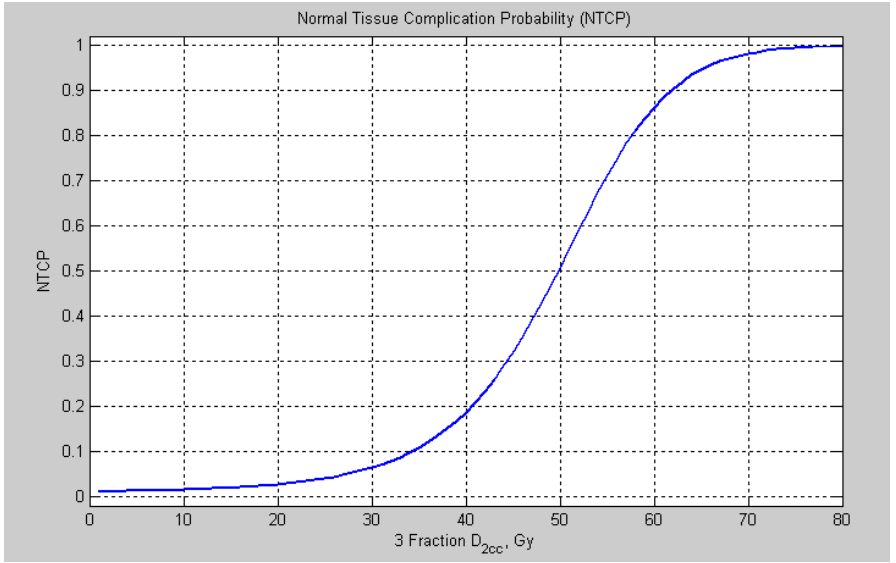
Slide provided by Dr. Vitali Moiseenko, PhD

Order matters for nonlinear BED operations *especially at high dose per fraction*

- Phase I/II trials at least need some starting point – there are several options:
  - Use D_{eff}/EUD instead of V_{eff}
  - Use alternate LKB parameters
- All these options could give different estimates – outside of trials you can't just arbitrarily try existing models
- Morals of the story:
  - Ensure your model has been optimized for SBRT, in the dose-volume range you are treating!
  - Validate these models with clinical data as soon as we can!

Dose Response Models

- Clinical dose response models have a sigmoidal shape, approach 0% at 0 dose, approach 100% at high dose
  - Probit
  - Lyman Kutcher Burman (LKB)
  - Logistic
  - Poisson
  - More complex models involving parallel architecture, functional subunits, mechanistic aspects, etc.



Parameter Fitting

- Least Squares
- Weighted Least Squares
- Maximum Likelihood

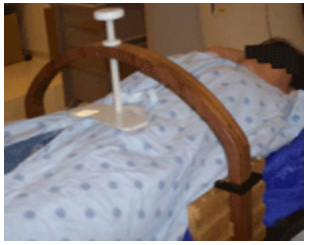
- Goodness of fit:
  - Confidence intervals
  - AIC, LLmax, p-value, etc.
  - Heterogeneity assessment

20+ Years of Clinical Use

Leksell Lars. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand. 1951 Dec 13;102(4):316-9.

Lutz W, Winston KR, Maleki N. A system for stereotactic radiosurgery with a linear accelerator. IJROBP. 1988 Feb;14(2):373-81.

Lax I, Blomgren H, Näslund I, Svanström R. Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. Acta Oncol. 1994 Jan;33(6):677-83.



Adler J R. (2009) Accuray, Inc. A Neurosurgical Business Case Study. Cureus 1(9):e1.doi:10.7759/cureus.1

("first CyberKnife patient treatment on June 8, 1994")

Which of the following SRS/SBRT treatment systems have been used clinically for at least 20 years?

5% 1. Gamma Knife

1% 2. Stereotactic Linac

1% 3. CyberKnife

81% 4. All of the Above

13% 5. 1 and 2 only

Which of the following SRS/SBRT treatment systems have been used clinically for at least 20 years?

- Correct answer:

- 4. **All of the above**

- Refs: **Leksell L. Acta Chir Scand. 1951 Dec 13;102(4):316-9.**
  Lutz W, Winston KR, Maleki N. IJROBP. 1988 Feb;14(2):373-81.
  Lax I, Blomgren H, et al. Acta Oncol. 1994 Jan;33(6):677-83.
  Adler J R. (2009) Cureus 1(9):e1.doi:10.7759/cureus.1

Summary | Conclusion

- 30 minute coffee break, let the concepts soak in…
- Then we are ready to start looking at the data!

Acknowledgements

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Holy Redeemer Hospital