University of Michigan
Medical School

Cranial TCP/NTCP Modeling
Insights and Caveats

Issam El Naqa, MA, PhD

The Department of Radiation Oncology
University of Michigan

University of Michigan Medical School

Acknowledgements

Jimm Grimm and Ellen Yorke

Andy Jackson, Randy Ten Haken and the WGSBRT

Cranial TCP team

- ***Scott G. Soltys, MD***
- Jinyu Xue, PhD
- Michael T. Milano, MD, PhD
- Wolfgang A. Tomé, PhD
- Andrew Jackson, PhD
- George Ding, PhD
- Arjun Sahgal, MD
- Lijun Ma, PhD
- Timothy Solberg, PhD
- John P. Kirkpatrick, MD PhD
- Lawrence B. Marks, MD
- John Adler, MD
- JP Sheehan , MD

Cranial NTCP team

- ***Michael T. Milano, MD, PhD***
- Wolfgang A. Tomé, PhD
- Vitali Moiseenko, PhD
- Jinyu Xue, PhD
- Arjun Sahgal, MD
- Lijun Ma, PhD
- Scott G. Soltys, MD
- Timothy Solberg, PhD
- John P. Kirkpatrick, MD PhD
- Lawrence B. Marks, MD
- John C. Flickinger, MD

University of Michigan Medical School

What is "Computational" Modeling?

- Definition:
  - The use of mathematics, physics and computer science to study the behavior of complex systems by computer simulation
- Objective:
  - To make predictions about what will happen in the real system that is being studied in response to changing conditions

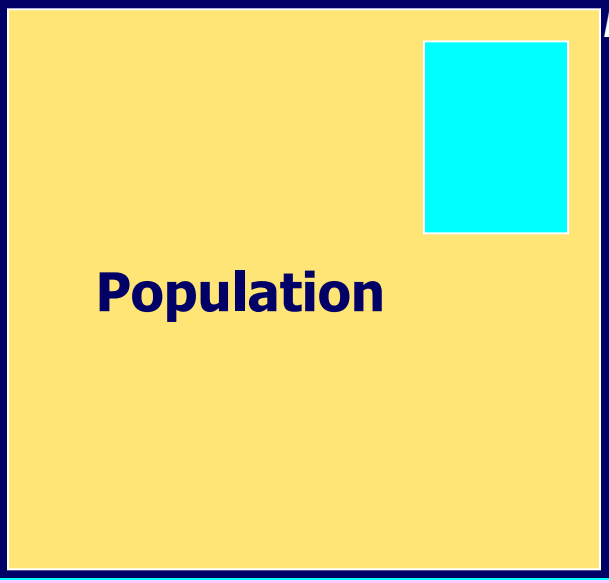
Source: www.nibib.nih.gov

University of Michigan Medical School

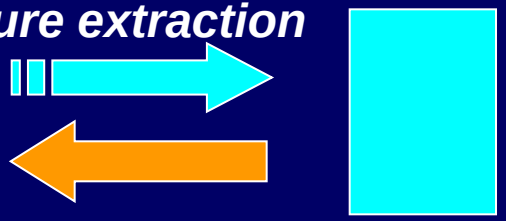
What is "Radiobiological" Modeling?

- Definition:
  - The use of mathematics, physics, biology, and computer science to study the behavior of tissue response to irradiation by computer simulation
- Objective:
  - To make predictions about what will happen in the patient that is being treated in response to changing irradiation conditions

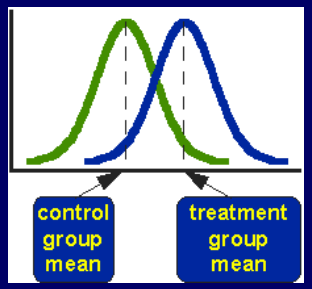
Computational modeling vs. Statistics



Feature extraction



Sample

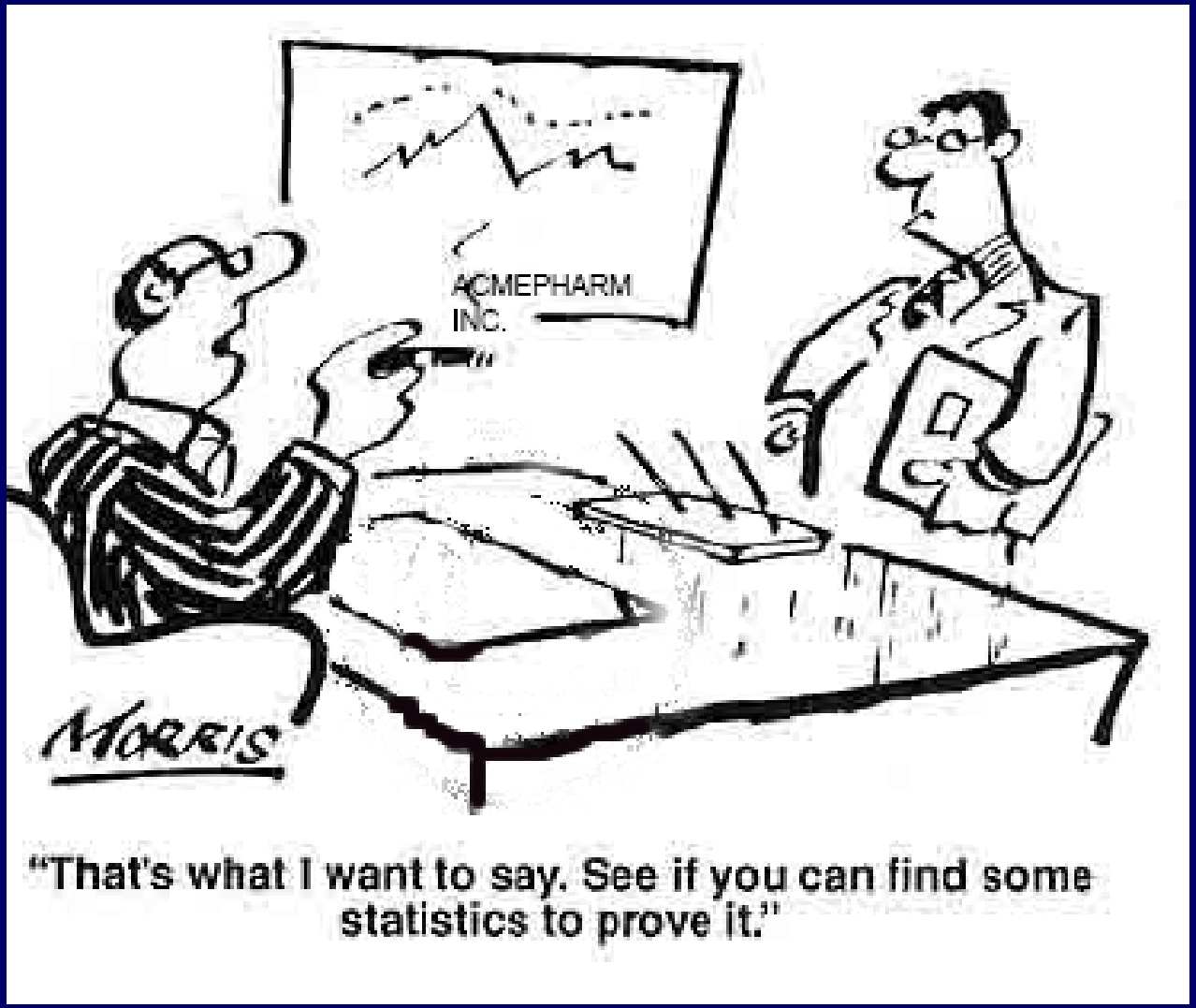


Use statistics to describe data and infer on population

Hypothesis Testing

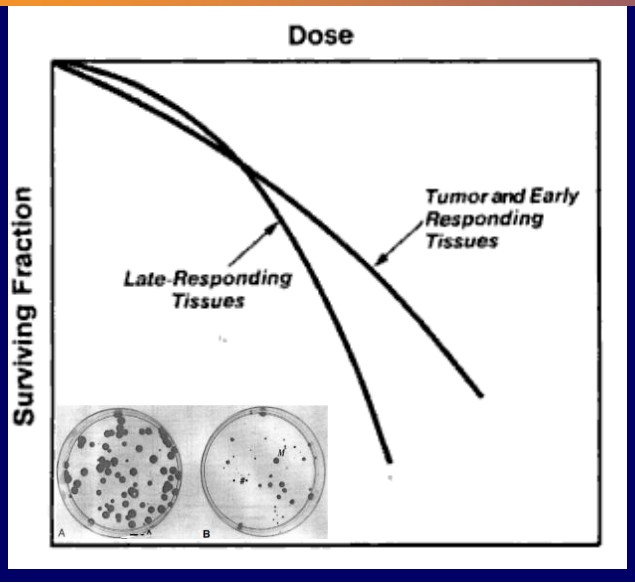
Use computational modeling to describe data and summarize features

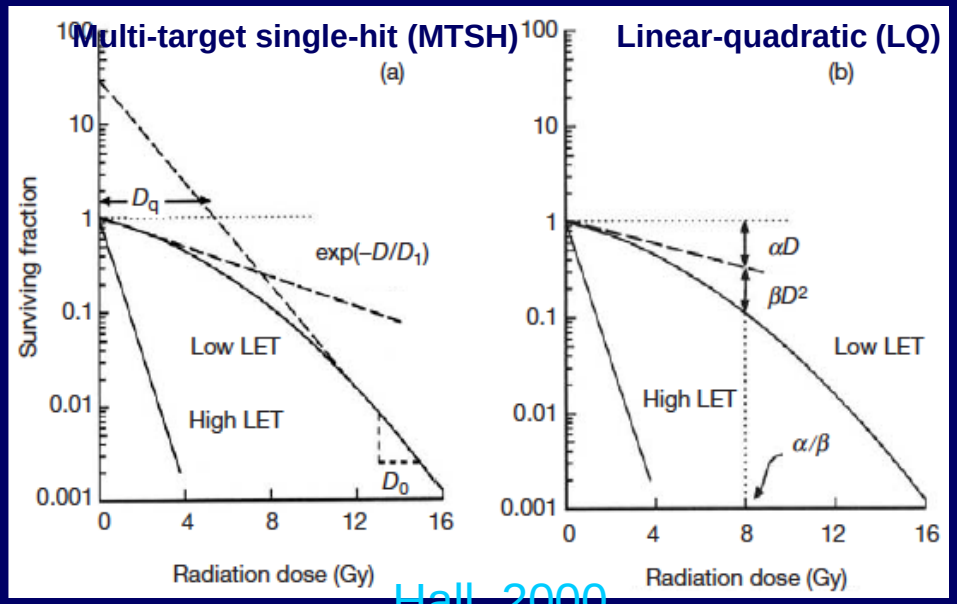
Hypothesis Generation



"That's what I want to say. See if you can find some statistics to prove it."

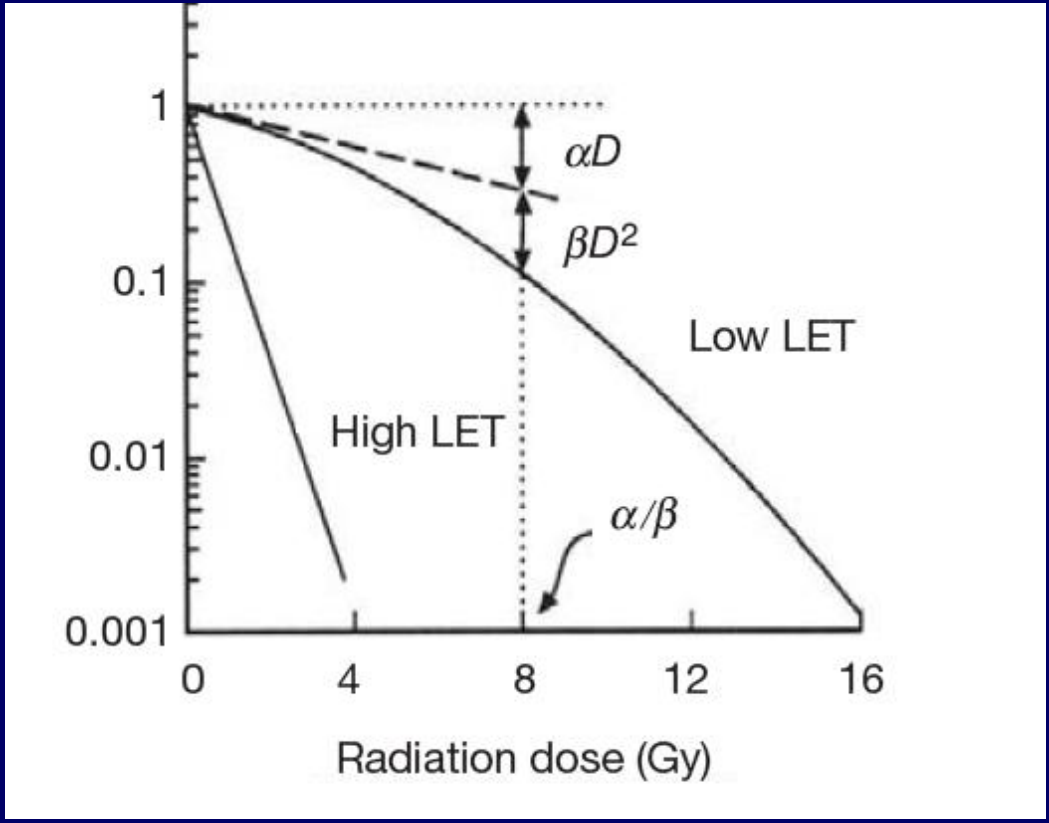
Radiobiology Background





Hall, 2000

Linear-quadratic (LQ) model

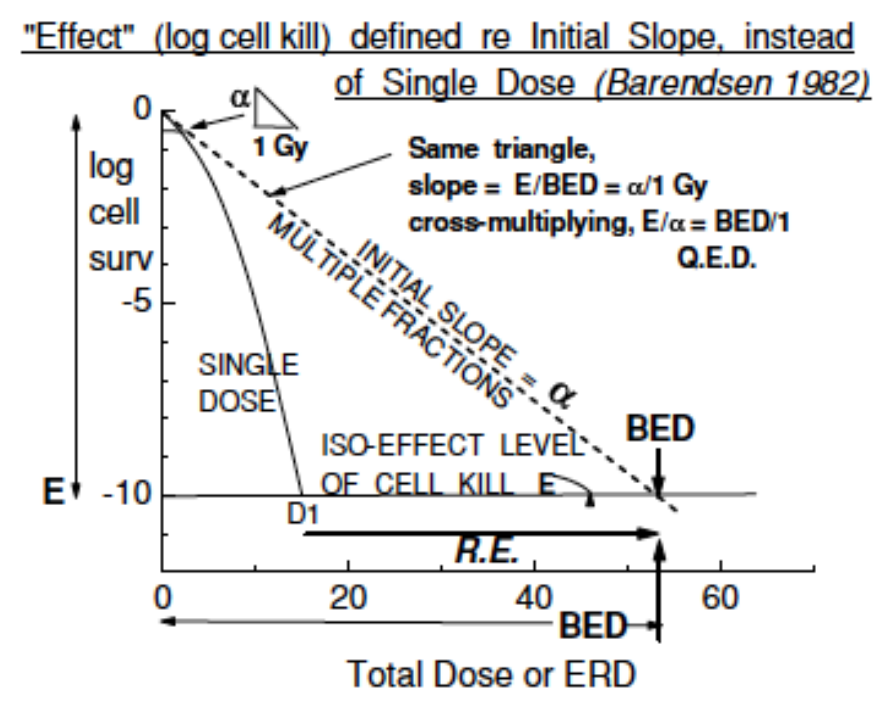


$$S = \exp(-\alpha D - \beta G D^2)$$

$$TCP = \exp(-SN)$$

Douglas & Fowler, 1972

Biological effective dose (BED)

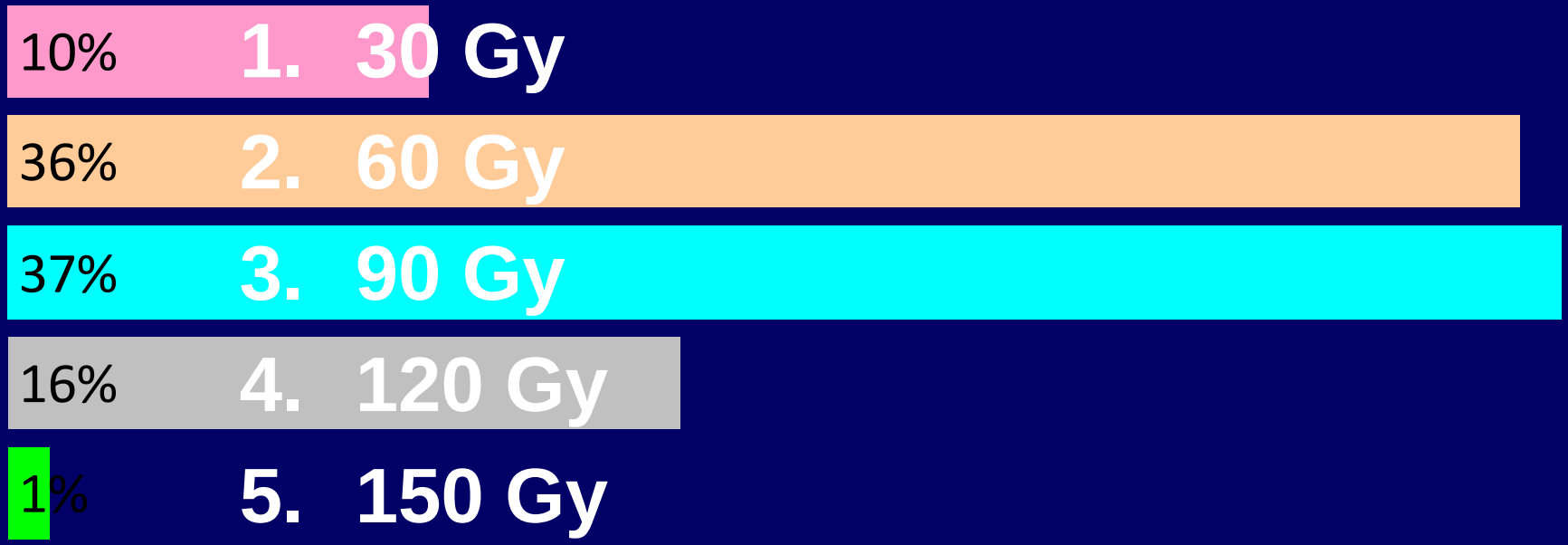


$$BED = (nd)\left(1 + \frac{d}{(\alpha/\beta)}\right)$$

University of Michigan Medical School

SAM Questions#1:

The BED for a treatment of 60 Gy in 30 fractions for an organ that has α/β=2 Gy is:



University of Michigan Medical School

The BED for a treatment of 60 Gy in 30 fractions for an organ that has α/β=2 Gy is:

1. 30 Gy
2. 60 Gy
3. 90 Gy
4. *120 Gy*
5. 150 Gy

Reference: Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010 Jul;83(991):554-68.

University of Michigan Medical School

Some BED examples

Schedule type	Total dose (Gy)	BED	
		Gy_{10} (early effect, tumor)	Gy_3 (late)
30fx2 Gy/6 wks	60	72	100
70f x 1.15 Gy BID/ 7 wks	80.5	89.8	111.4
35f x 2 Gy/7 wks	70	84	116.7
([30f x1.8 Gy] + [12f x1.5 Gy])/6 wks	72	84.4	113.4
3f x 20 Gy	60	180	460

ICRU Bioeffect Modelling and Equieffective Dose Concepts in Radiation Therapy

Definition: Two radiation treatment regimens having different dose–time–fractionation schedules or dose rate patterns, and/or different spatial distributions and/or different radiation qualities are said to be *equieffective* with respect to a specific clinical (biological) endpoint, if they produce the same probability of reaching this endpoint when delivered under the carefully specified conditions.

$$EQDX_{\alpha/\beta} = D \cdot \frac{d+\alpha/\beta}{X+\alpha/\beta} \quad \textbf{Gy}$$

The total absorbed dose delivered by the reference treatment plan (fraction size *X*) that leads to the same biological effect as a test treatment plan that is conducted with absorbed dose per fraction d and total absorbed dose *D* expressed in units of Gy.

University of Michigan Medical School

SAM Question#2:

The correct ICRU recommendation for equieffective dose nomenclature of equivalent 2 Gy per fraction with an α/β=10 Gy is:

29% 1. $EQD2\ Gy_{10}$

22% 2. $EQD10\ Gy_{2}$

32% 3. $EQD2_{10}\ Gy$

12% 4. $EQD10_{2}\ Gy$

5% 5. None of the above.

University of Michigan Medical School

The correct ICRU recommendation for equieffective dose nomenclature of equivalent 2 Gy per fraction with an α/β=10 Gy is

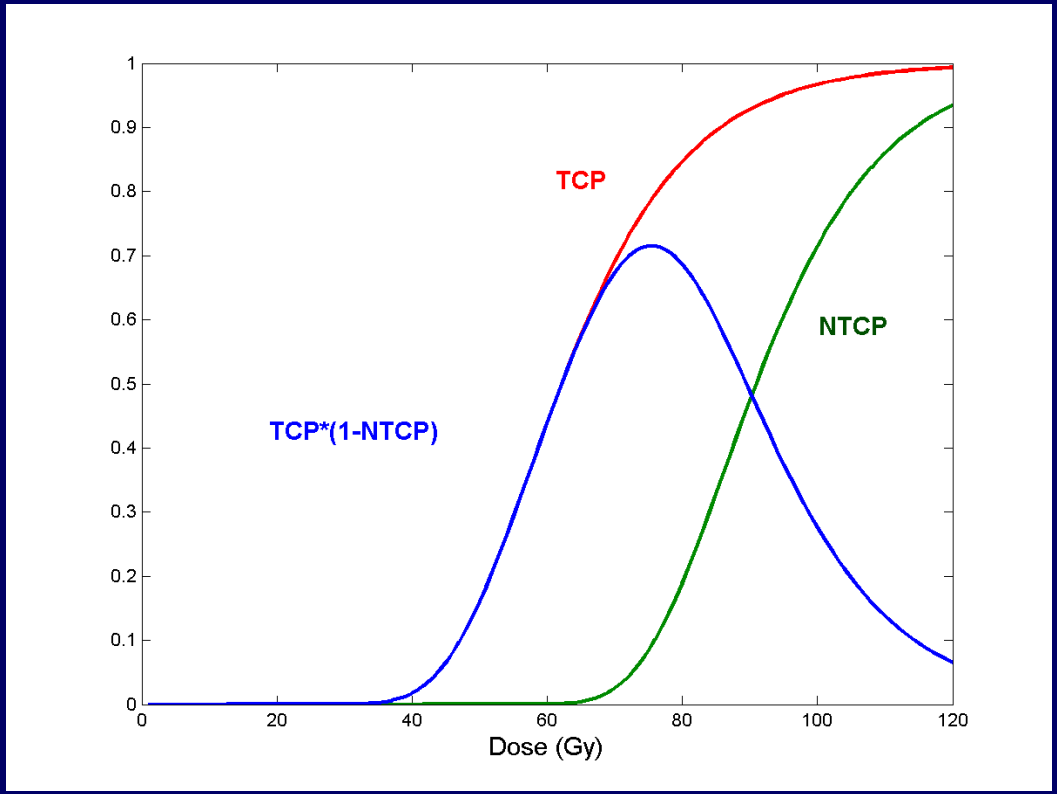
1. EQD2 Gy_{10}
2. EQD10 Gy_{2}
3. *$EQD2_{10}$ Gy*
4. $EQD10_{2}$ Gy
5. None of the above.

Reference:Bentzen SM, Dörr W, Gahbauer R, Howell RW, Joiner MC, Jones B, Jones DT, van der Kogel AJ, Wambersie A, Whitmore G. Bioeffect modeling and equieffective dose concepts in radiation oncology--terminology, quantities and units. Radiother Oncol. 2012 Nov;105(2):266-8.

Radiotherapy Dogma (TCP↑, NTCP↓)

- ***Tumor control probability (TCP):*** **The probability of local control given the planned dose distribution.**

- ***Normal Tissue Complication Probability (NTCP):*** **The probability of some defined undesirable effect on the patient due to the irradiation.**



Courtesy Joseph Deasy

Holthusen (1936)

University of Michigan Medical School

LQ modifications for SBRT

- **Modified LQ (MLQ) or Lq-Linear (LQL) (Guerrero, 2004):**

$$SF = \exp(-aD - bG(dD)D^2)$$

$$G = \frac{2}{(dD)^2}\left(\exp(-dD) + dD - 1\right)$$

- **LQ cubic (LQC) (Joiner and Kogel, 2009):**

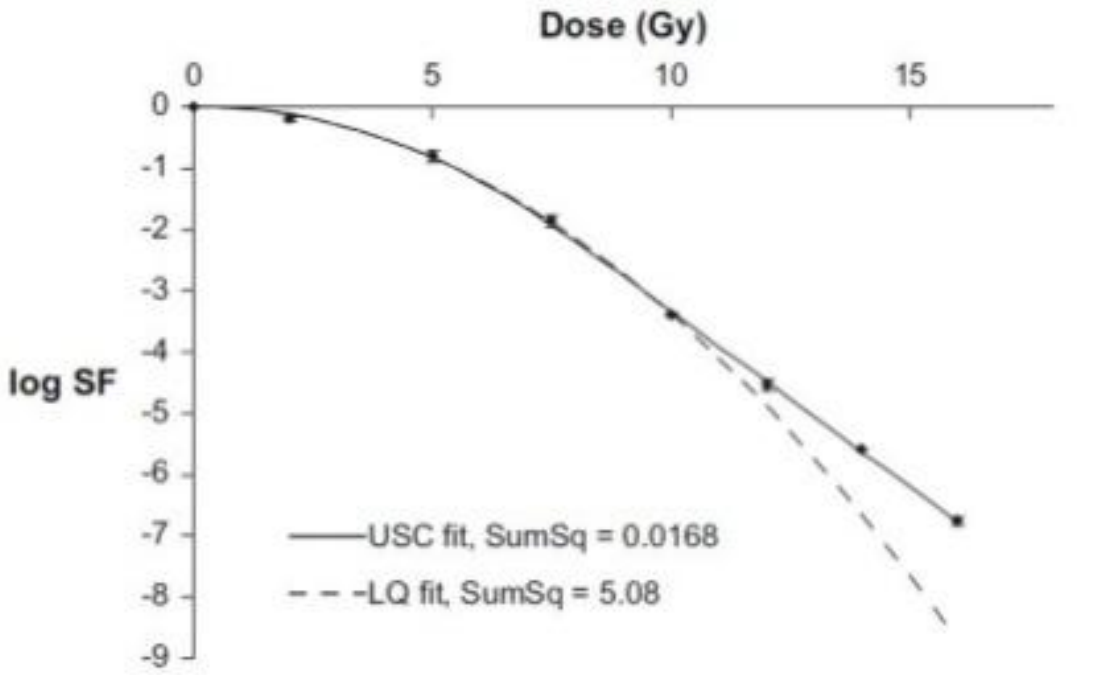
$$SF = \exp(-\alpha D - \beta D^2 + \gamma D^3)$$

- **Universal survival curve (USC) (Park, 2008):**

$$\ln SF = \begin{cases} -n(\alpha d + \beta G d^2), d \le D_T \\ -n\left(\frac{d}{D_0} - \frac{D_q}{D_0}\right), d \ge D_T \end{cases}$$

University of Michigan Medical School

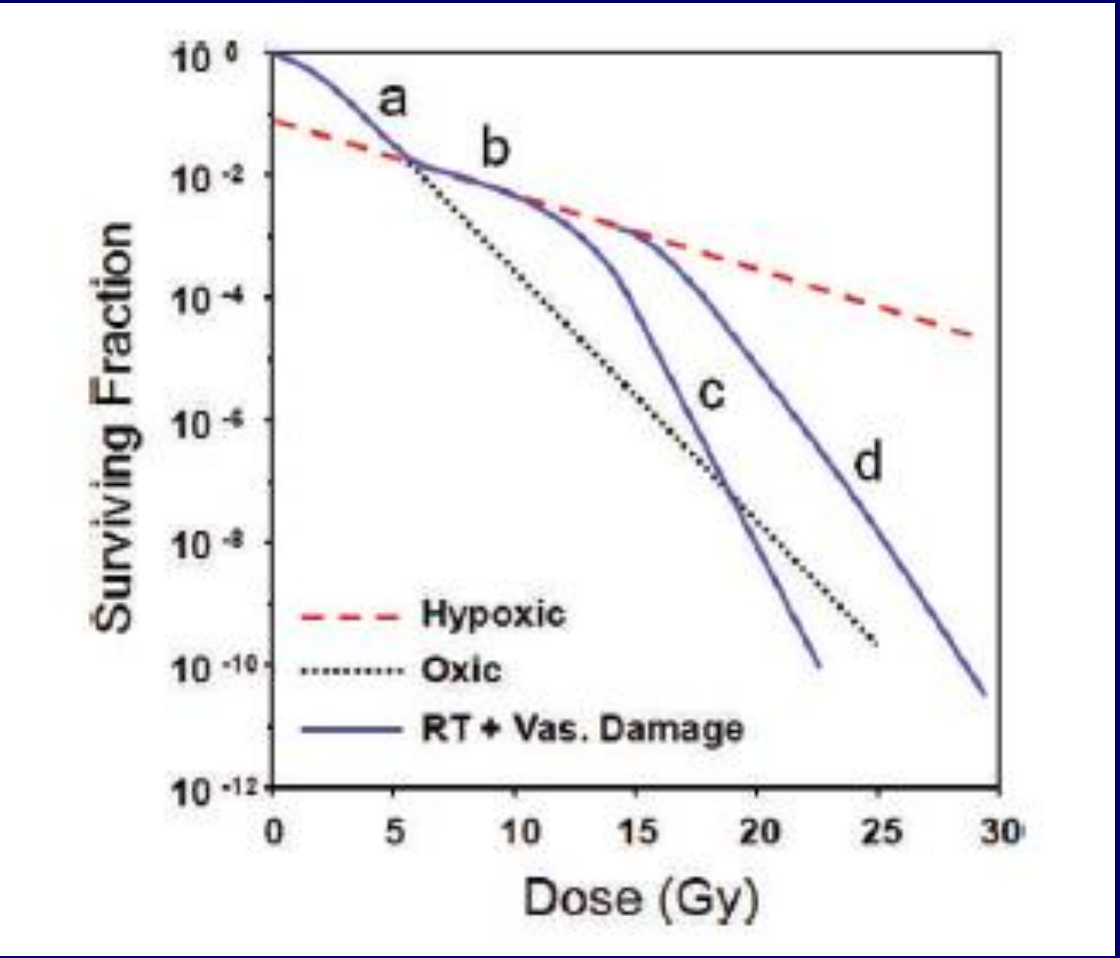
SBRT Survival curves



Park et al., IJROBP, 2008

University of Michigan Medical School

SBRT Survival curves



 Park et al., RR, 2012

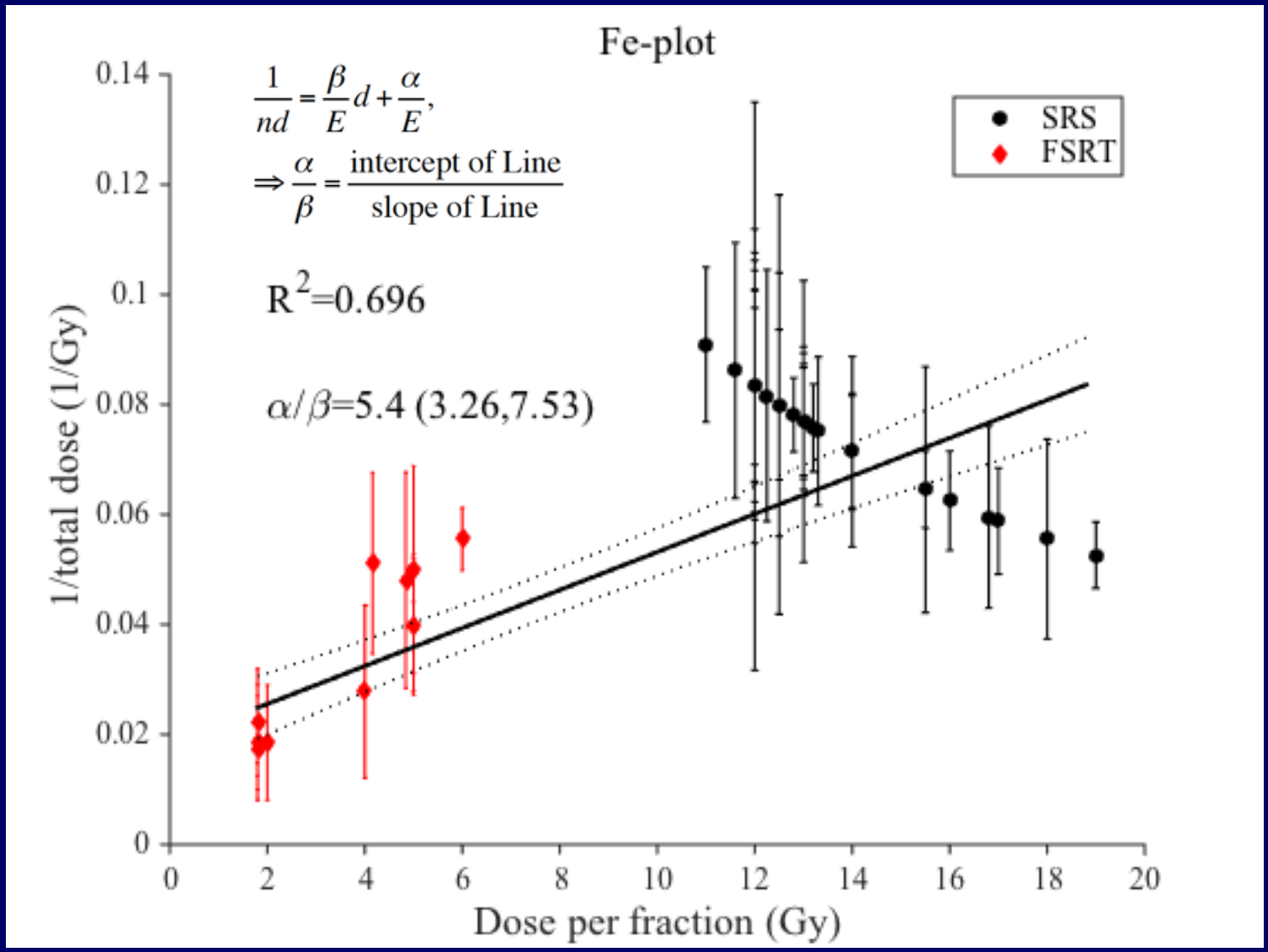
University of Michigan Medical School

TCP for Vestibular Schwannoma

- **Estimation of alpha/beta ratio**
  - **Fe-plot**
  - **dD-D plot**
- **Modeling of TCP**
  - **Biological dose correction (LQ, LQL, LQC, EQD2)**
  - **Model form: *Poisson***

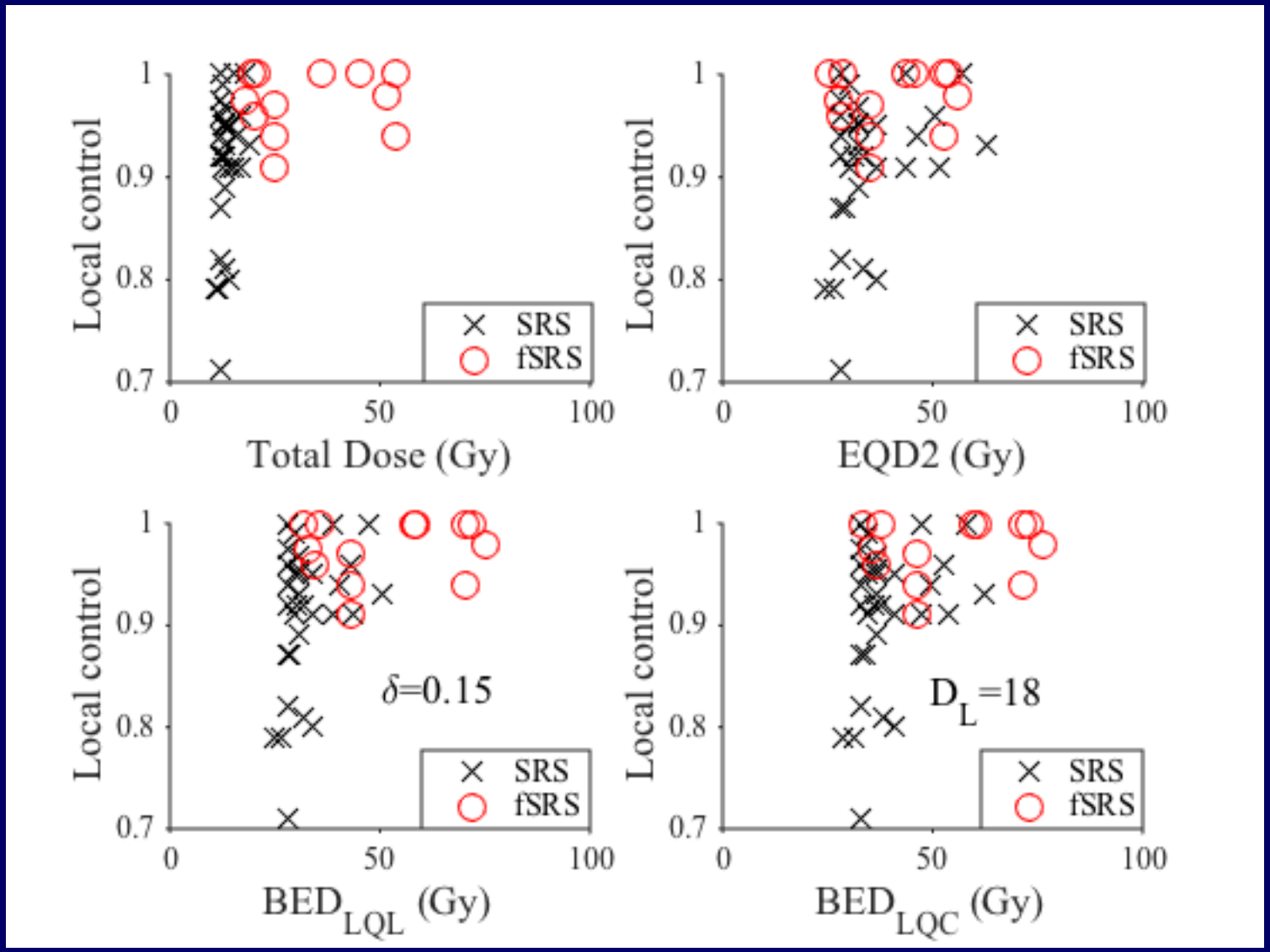
University of Michigan
Medical School

Alpha/Beta estimation (Fe-Plot)

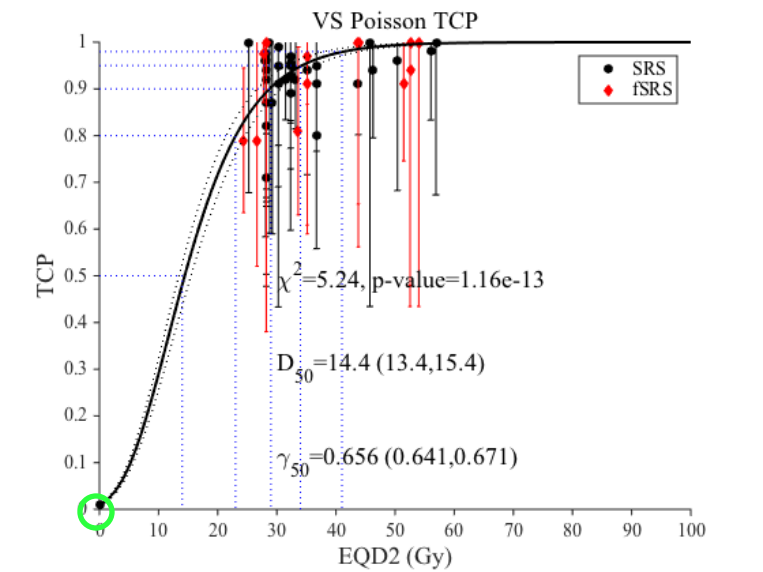


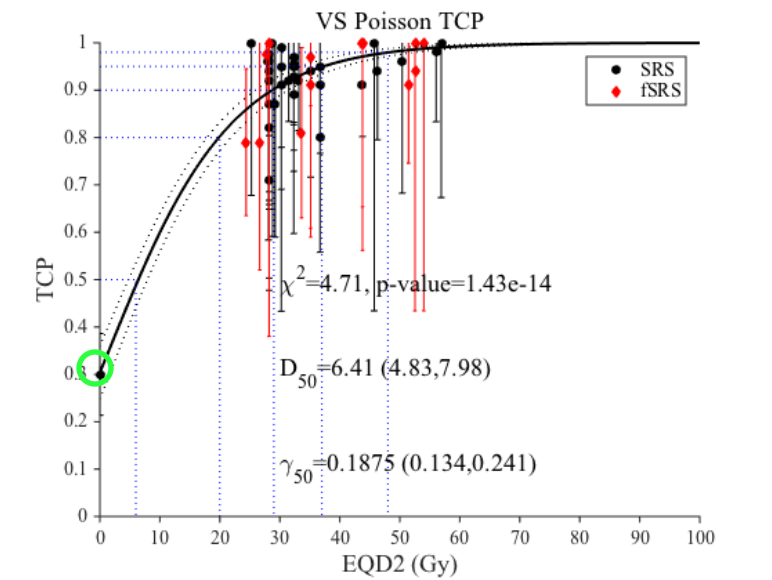
University of Michigan
Medical School

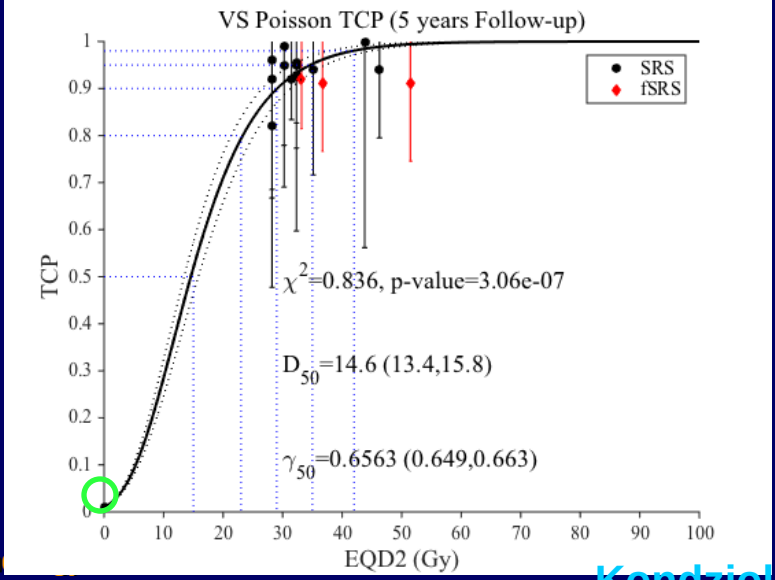
alpha/beta=5.4 Gy

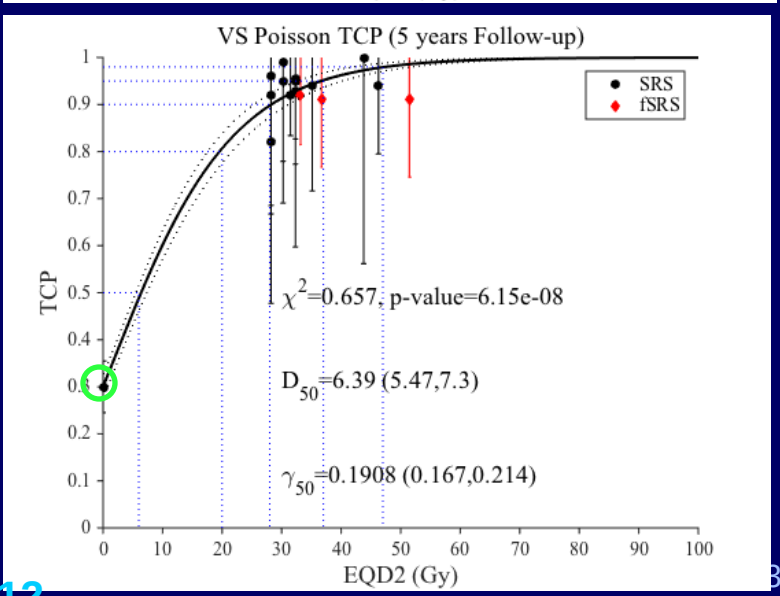


Observational point effect









Kondziolka, 2012

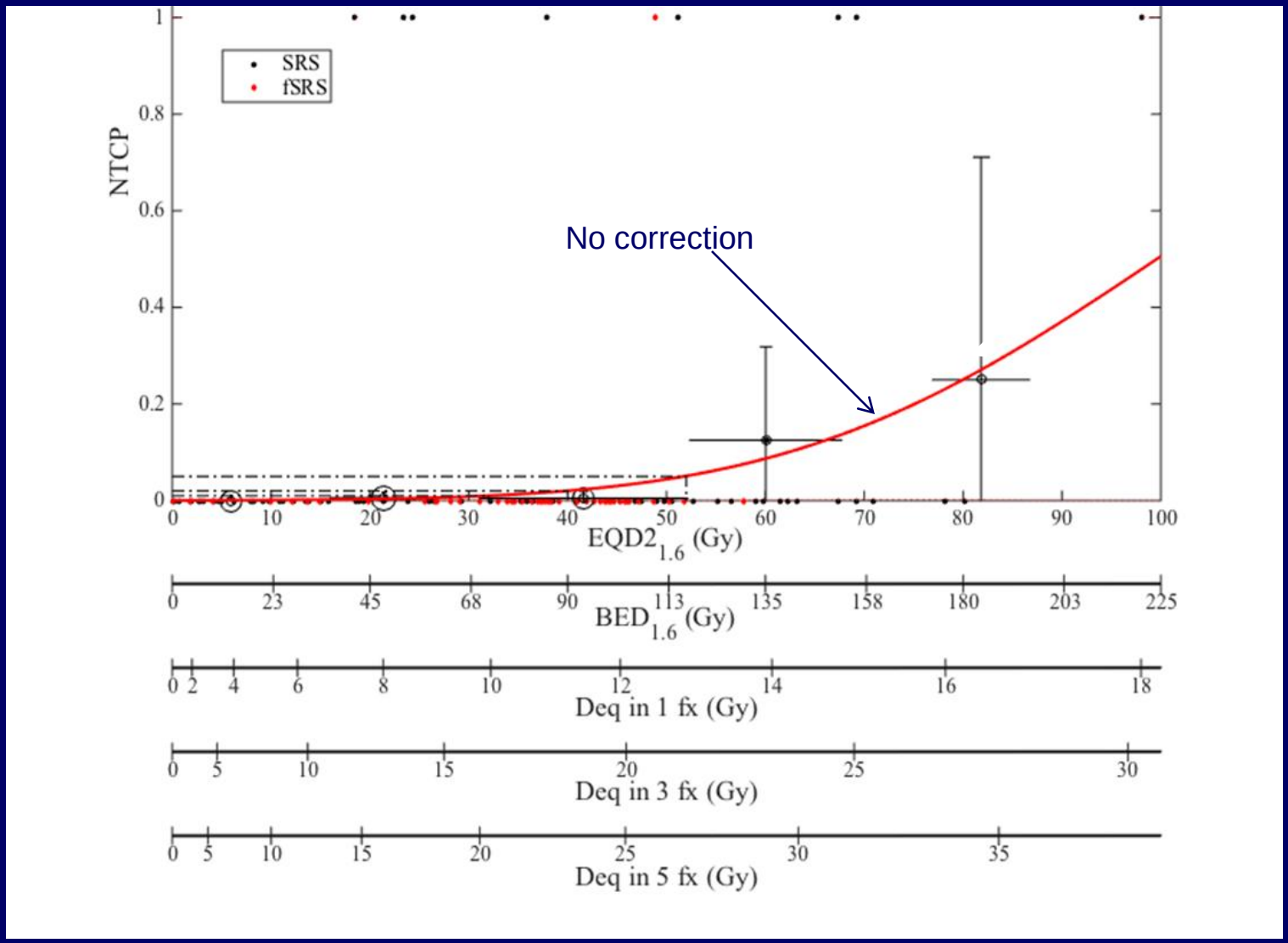
University of Michigan Medical School

NTCP for Optic nerve

- **Actuarial analysis (Kaplan Meier)**
- **Modeling of NTCP**
  - **Biological dose correction (BED, EQD2, conversion to different fractions)**
  - **Model form: *Probit***

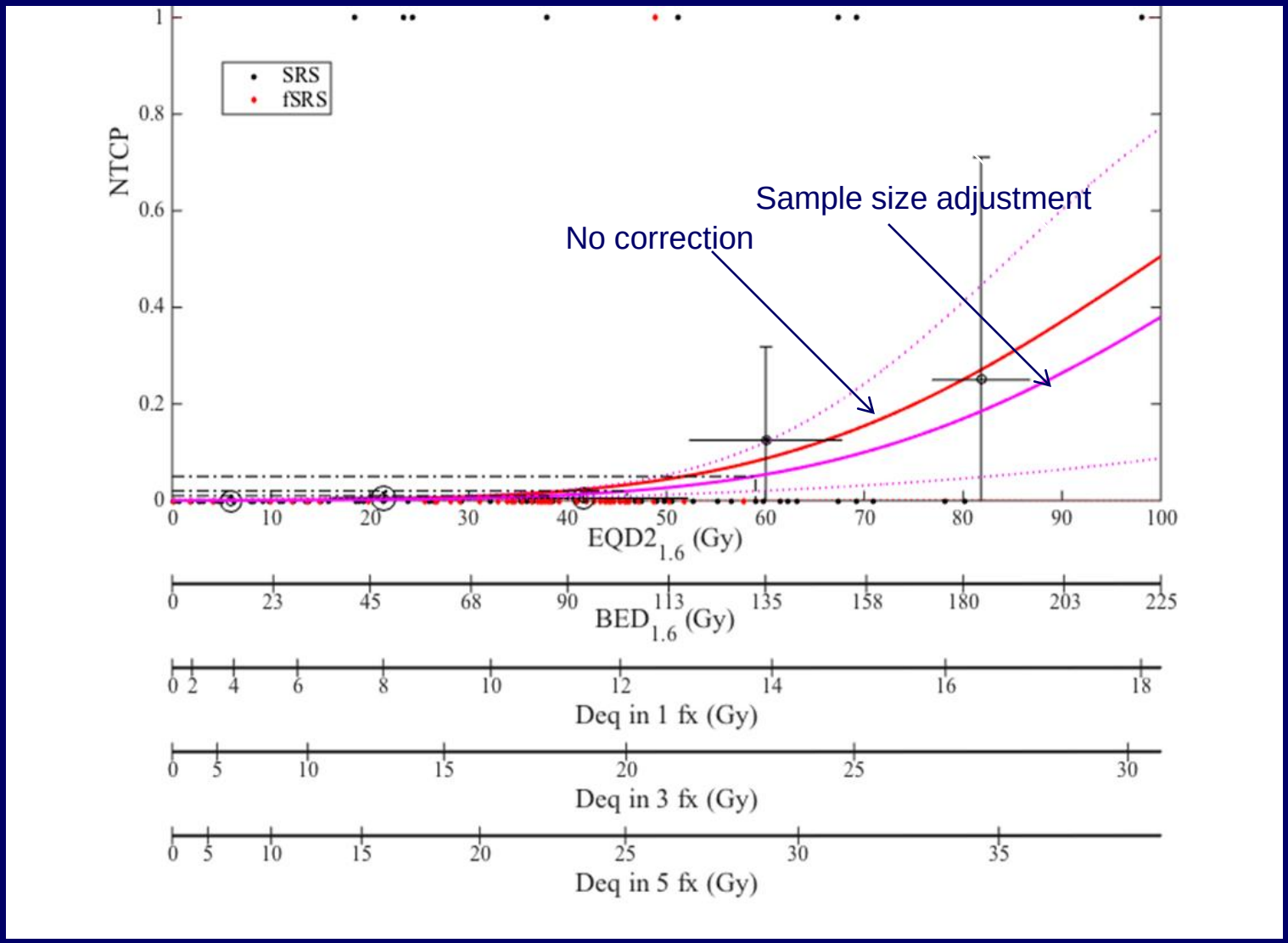
University of Michigan
Medical School

NTCP model (alpha/beta=1.6)



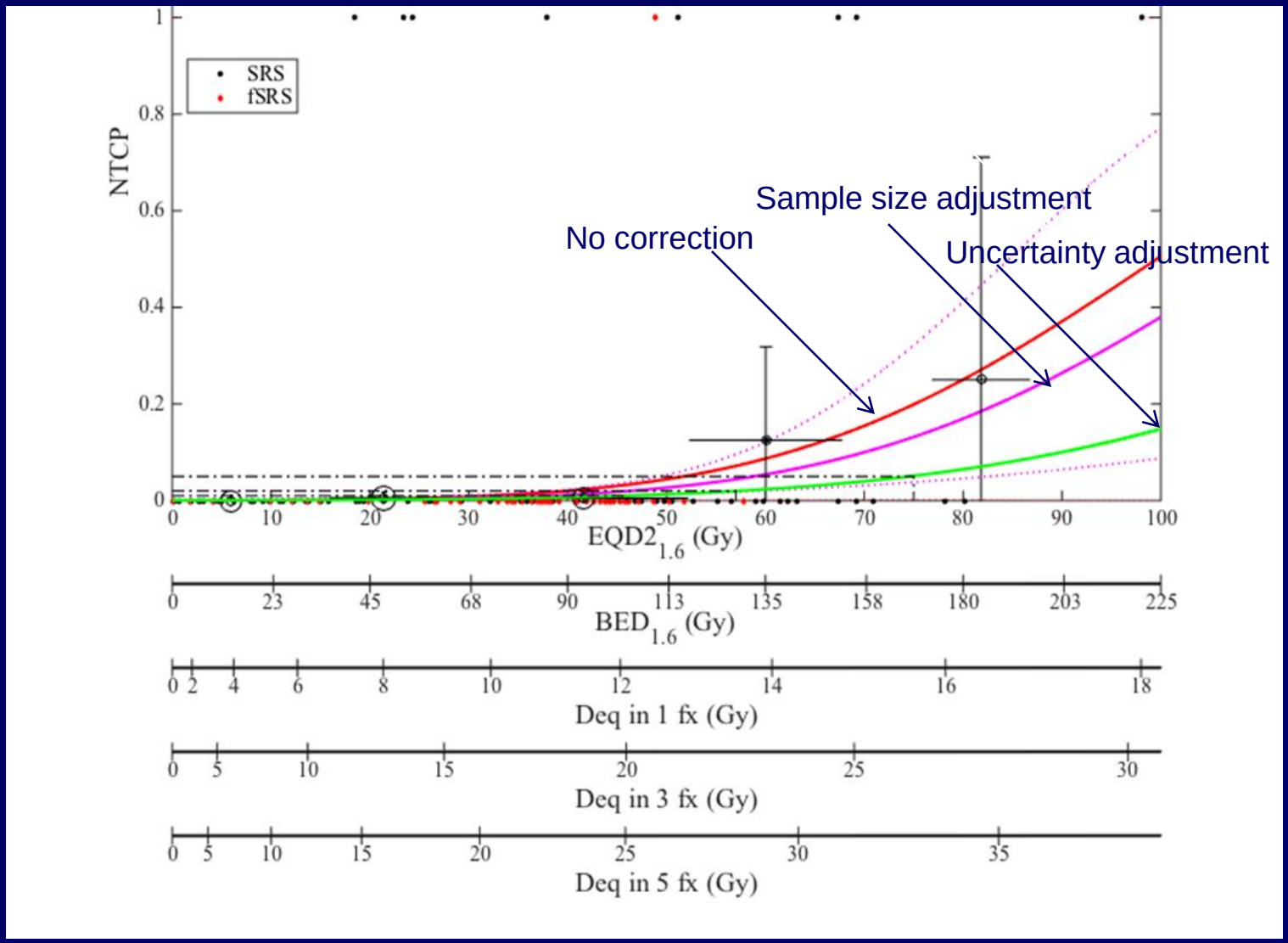
University of Michigan
Medical School

NTCP model (alpha/beta=1.6)



University of Michigan
Medical School

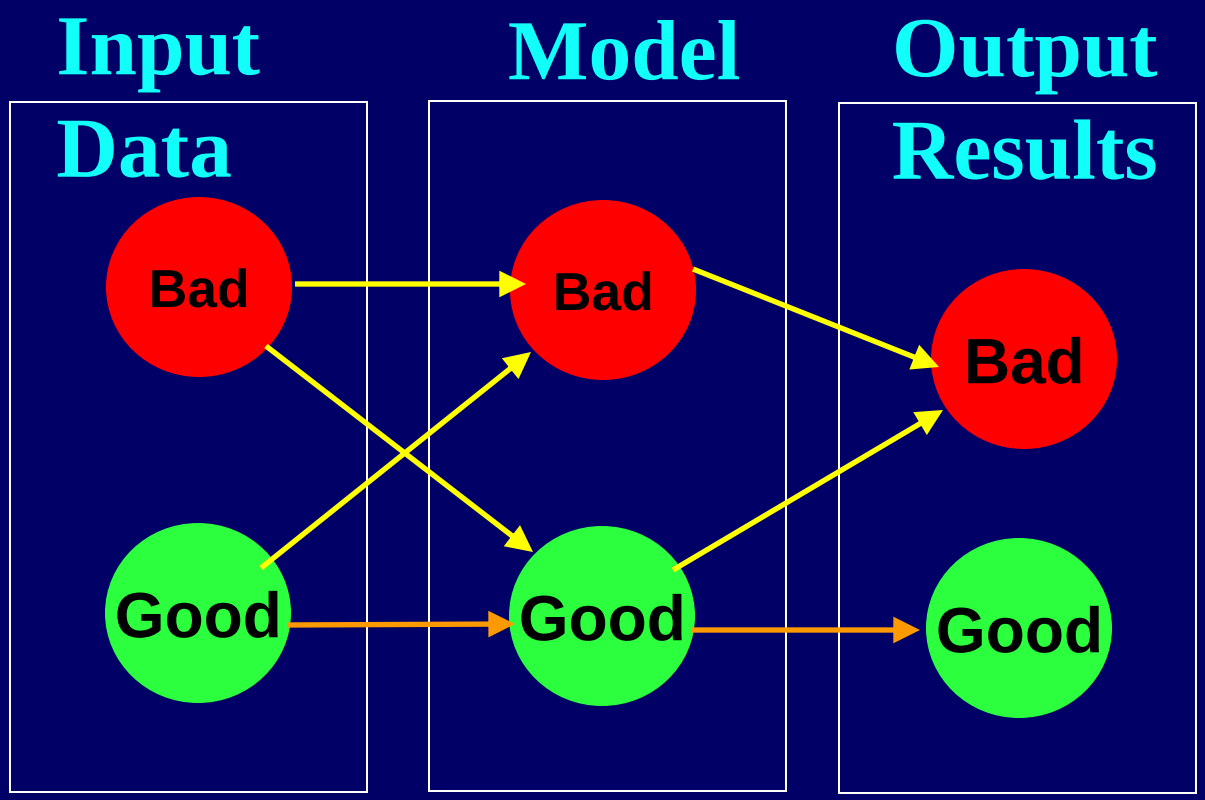
NTCP model (alpha/beta=1.6)



University of Michigan
Medical School

Take home message

Modeling is a marriage between Mr. Data and Miss Model



Data is the cornerstone of modeling

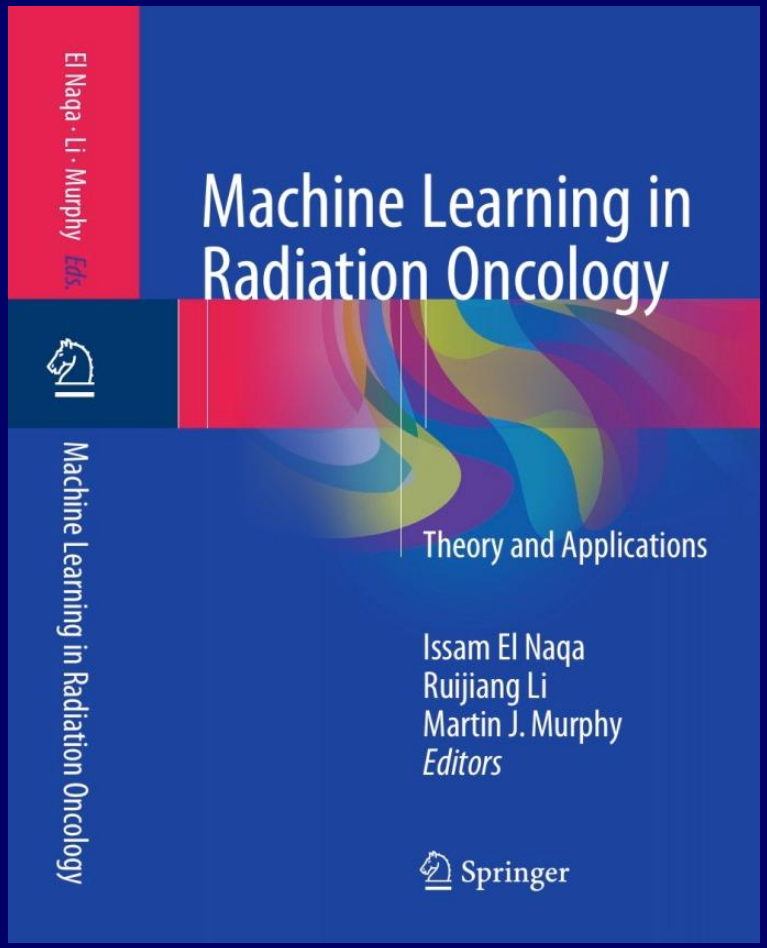
University of Michigan Medical School

- **GIGO paradigm**
  - **TWEEDIE, R.L., MENGERSEN , K.L., ECCLESTON, J.A. (1994) Garbage in, garbage out: can statisticians quantify the effects of poor data? Chance 7 , 20-27.**

University of Michigan
Medical School

Not all models are created equal

There are models and there are 'super'-models



University of Michigan Medical School

Acknowledgements

Jimm Grimm and Ellen Yorke

Andy Jackson, Randy Ten Haken and the WGSBRT

Cranial TCP team

- ***Scott G. Soltys, MD***
- Jinyu Xue, PhD
- Michael T. Milano, MD, PhD
- Wolfgang A. Tomé, PhD
- Andrew Jackson, PhD
- George Ding, PhD
- Arjun Sahgal, MD
- Lijun Ma, PhD
- Timothy Solberg, PhD
- John P. Kirkpatrick, MD PhD
- Lawrence B. Marks, MD
- John Adler, MD
- JP Sheehan , MD

Cranial NTCP team

- ***Michael T. Milano, MD, PhD***
- Wolfgang A. Tomé, PhD
- Vitali Moiseenko, PhD
- Jinyu Xue, PhD
- Arjun Sahgal, MD
- Lijun Ma, PhD
- Scott G. Soltys, MD
- Timothy Solberg, PhD
- John P. Kirkpatrick, MD PhD
- Lawrence B. Marks, MD
- John C. Flickinger, MD